STRATEGIES TOWARDS MODULAR SYNTHESES OF FLUOROORGANICS

by

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ABSTRACT

STRATEGIES TOWARDS MODULAR SYNTHESES OF FLUOROORGANICS

by

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Synthesis of TMS-protected fluoropropargyl benzothiazolyl sulfone, a bifunctional fluoro-Julia-Kocienski reagent, was achieved by metalation-electrophilic fluorination of benzothiazolyl propargyl sulfone. Reactions of the fluoro-Julia-Kocienski reagent with carbonyl compounds produced fluoroenynes in high yields and with high *E*-selectivity. Olefinations proceeded with LHMDS, or the milder base, DBU. A one-pot deprotection-copper-catalyzed azide alkyne cycloaddition (CuAAC) to the alkyne moiety in the Julia-Kocienski reagent provided a new class of triazole-derived fluorinated and unfluorinated Julia-Kocienski reagents. Competitive experiments showed higher reactivity of the fluorinated reagent in the CuAAC than the protio analog. Computational analysis of electron densities in fluoro and protio propargyl sulfones showed that fluorine lowers electron density at the terminal alkynyl carbon, which can contribute to its higher reactivity. These triazole-derived "second generation" Julia-Kocienski reagents reacted smoothly with aldehydes and ketones, and olefinations could be tuned towards *E*- or *Z*-stereoselectivity by change in reaction conditions. The CuAAC-Julia olefination sequence was also used for the synthesis of triazole-derived analogs of biologically relevant combretastatin A-4. Biological testing of these compounds against HeLa cancer cell lines showed that two analogs displayed modest activity.

Putative fjord region dihydrodiol and diol epoxide metabolites of 5-

fluorobenzo[*c*]phenanthrene (5-FB*c*Ph), arising by the oxidation of the angular ring remote to the fluorinated ring, were synthesized. A key step in the chemistry was fluoro-Julia-Kocienski olefination, followed by photocyclization. Deoxyadenosine adducts of the (±)-series 2 diol epoxide of 5-FB*c*Ph were synthesized. *Trans* opening of this epoxide by azide, followed by reduction, furnished (±)-aminotriol. $\mathrm{S_NAr}$ reaction of the aminotriol with silyl protected 6-fluoro-9-(2'-deoxy-*b*-D-ribofuranosyl)purine gave two diastereomeric deoxyadenosine adducts. Unequivocal stereochemical assignment to the individual adduct diastereomers came via conversion of the racemic *trans* dihydrodiol to the bis(–)-menthoxy acetate ester, and chromatographic separation of the diastereomers. Resolved enantiomers were converted to bis-*p*-(*N*,*N*)-dimethylaminobenzoates of a *trans* tetrahydrodiol. Absolute configuration was determined by CD spectroscopy. *R,R*-dihydrodiol enantiomer was converted to the *R,S,S,R* diol epoxide of 5-FB*c*Ph, which was used for the synthesis of a single diastereomer of the 2'-deoxyadenosine adduct, whose CD spectrum and optical rotation were recorded. This allowed configurational assignment to the adenosine adducts, obtained from the racemic diol epoxides.

To
My Brother,
Shri Hans Raj Guleria

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CHAPTER 1

METHODS DEVELOPMENT FOR SYNTHESIS OF DIVERSE FLUOROOLEFINS USING BIFUNCTIONAL OLEFINATION REAGENT

GENERAL INTRODUCTION

In the 21st century, organofluorine chemistry has grown remarkably because of unique properties of fluorine and wide range of applications of fluoroorganic compounds. The fluorocarbon systems have become an important area of research not only in chemistry but also in all other sciences. Due to several distinctive properties that fluorine possesses it is very attractive to the researchers. Some of these properties are highest electronegativity (3.98 on Pauling scale) in the periodic table, smaller van der Waals radius (147 pm) that is comparable to H (120 pm) and O (150 pm), low polarizability, strong bonding to three non-bonding pairs of electrons and high probability of overlap between 2s and 2p orbitals of fluorine and the corresponding orbitals of second period elements, e.g. carbon.[1-4] These properties of fluorine give rise to the enhanced thermal stability of fluorocarbons where the C-F and C-H bond energies are 116 kcal/mol and 99 kcal/mol respectively.[1-4]

Introduction of fluorine in the organic molecules dramatically changes their physical, chemical and biological properties. [1-4] These changes may include the changes in properties of the biologically active compounds, influence on the metabolism and distribution of drug molecules in the body, effect on the hydrophobicity and lipophilicity of compounds, and change in the molecular conformation.[1-4] Taking advantage of the changes that fluorine brings about in the molecules, researchers have explored numerous areas of applications of fluoroorganic compounds.

1 APPLICATIONS OF FLUOROCARBONS

In the modern time, fluoroorganics have become an integral part of our day-to-day life. The diverse areas of their applications include polymer industry, pharmaceuticals, agrochemicals and electronic industry.[1,2,5-18] Some of the applications of fluorocarbons are described below:

1.1 Fluoropolymers

Fluoropolymers constitute a major part of the polymer industry. Fluoropolymers contain either perfluorinated or partially fluorinated monomer units. Use of fluoropolymers ranges from the home appliances to materials used in industries. Polytetrafluoroethylene (PTFE) and perflouoroalkoxy resin (PFA) (**1** and **2** shown in Figure 1), also known by their brand names *Teflon* and *PFA Teflon*, are examples of very useful members of fluoropolymer family of a large number of such compounds.[1]

Polytetrafluoroethylene(PTFE)

1

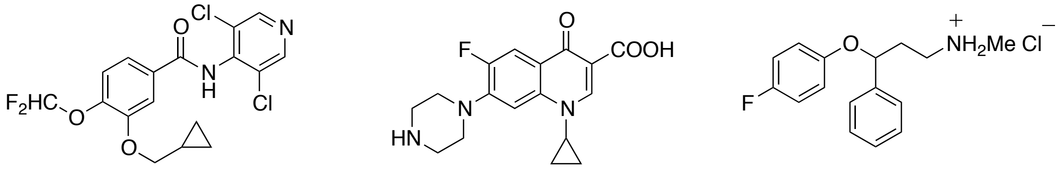
Perflouoroalkoxy resin(PFA)

2

Figure 1. Examples of fluoropolymers.

1.2 Pharmaceuticals

In special reference to medicinal applications, fluoroorganics are used as anticancer, antiviral and central nervous system agents, antibacterial and antifungal agents, and artificial blood substitutes.[1,6-10] A large number of drugs with fluorine substituents are in the market and many are in the clinical trials.[1,6-10] Some of the commonly used drugs are shown in Figure 2.



Roflumilast
(Anti-inflamatory)

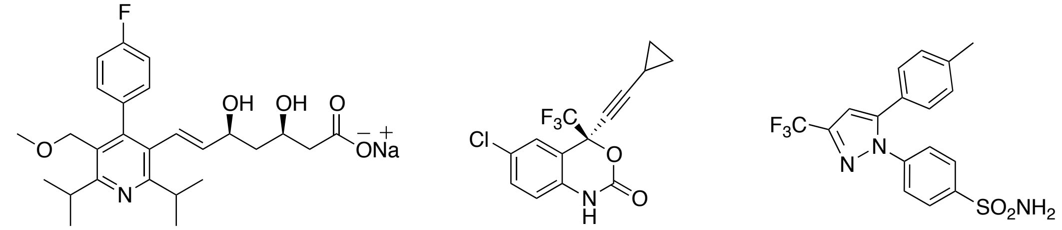
3

Ciprofloxacin
(Antibiotic)

4

Fluoxetine hydrochloride
(Anti-depressant)

5



Cerivastatin
(Modulator of cholesterol metabolism)
6

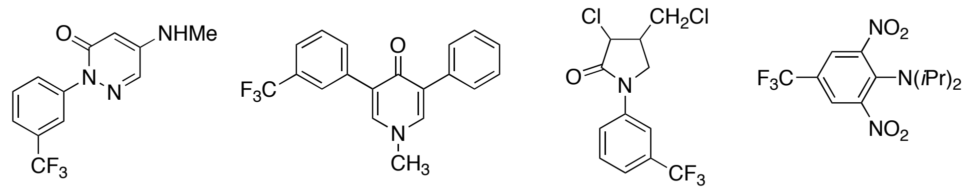
Efavirenz
(Anti-viral)
7

Celebrex
(Anti-inflamatory)
8

Figure 2. Examples of fluorine-containing pharmaceuticals and their uses.

1.3 Agrochemicals

Use of fluorocarbons in agriculture is growing very rapidly, due to their increased effectiveness compared to the unfluorinated drugs. These are used as herbicides, insecticides and fungicides.[1,11] Some typical herbicides, containing fluorine substituent, are shown in Figure 3.



Norflurazon
9

Fluoridone
10

Flurochoridone
11

Trifluralin
12

Figure 3. Examples of fluorine-containing herbicides.

A few examples of fluoroorganics used as insecticides and fungicides are shown in Figure 4.

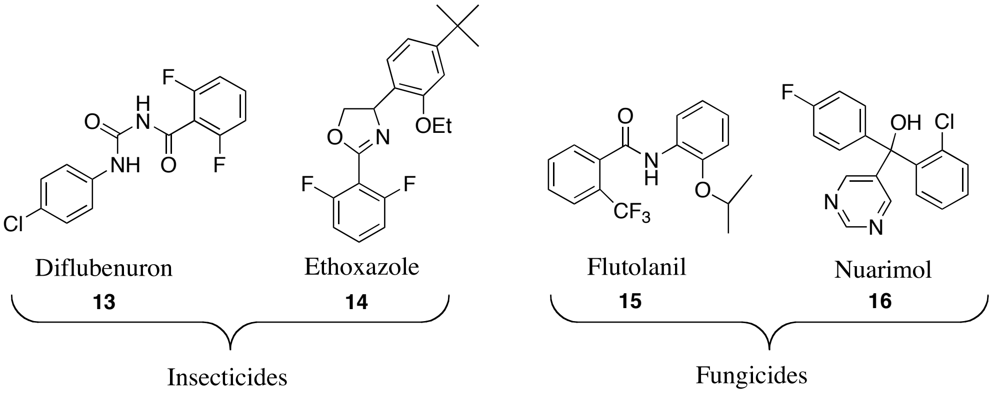


Figure 4. Examples of fluorinated insecticides and fungicides.

1.4 Electronic Industry

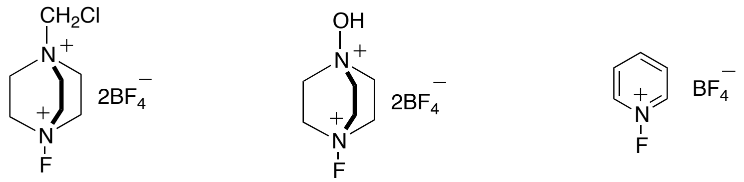
In addition, fluorocarbons have found great applications in electronic industry. Flat panel LCD-TV, PC monitors, notebook computers, and cellular phones are the result of use of fluorine containing liquid crystals.[1, 5,12]

In addition to the applications described above, fluoroorganic compounds are also useful as radiopharmaceuticals. Positron emission tomography (PET), a powerful imaging technique used in the clinical diagnostics, uses ^{18}F labeled organic compounds.[6,13-18] Interestingly, 2-deoxy-2-[^{18}F]fluoro-D-glucose, which is a commonly used PET agent, has also been found to be a therapeutic agent against breast cancer.[14]

2 SYNTHETIC STRATEGIES FOR FLUOROCARBONS

Selective introduction of fluorine in the organic molecules has been challenging, as well as interesting. In general, two main strategies are used for the synthesis of fluorocarbons: direct fluorination and the building block approach.[19] Direct fluorination involves the transformation of a C-H bond or a suitable functional group in the target molecule to a C-F bond, using an appropriate fluorinating reagent. This method sometimes lacks regio- and stereoselectivity. The building block approach involves the appropriate transformations of fluorinated small molecules to the target molecule. These fluoro-building blocks are either commercially available, or can be synthesized relatively easily. This method is widely used in modern fluoroorganic chemistry; however, the presence of fluorine in the molecules can change their reactivity as well as the selectivity of the reaction to be carried out.[1,2,20,21]

Different methods and reagents for fluorination of organic molecules have been used.[1] Use of fluorine gas and electrochemical fluorination; nucleophilic fluorination by Finkelstein exchange, Halex reaction, use of fluorides with larger cations, e.g. tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF); hydrofluorination and halofluorination of multiple bonds; transition metal assisted oxidative fluorination; electrophilic fluorinations using XeF_2, perchloryl fluoride ($FClO_3$), hypofluorites and NF- reagents, are among the general methods of fluorination.[1]



F-TEDA-BF_4 (Selectfluor)

17

NFTh (Accufluor)

18

N-Fluoropyridinium tetrafluoroborate

19

N-Fluorobenzenesulfonimide (NFSI)

20

N-Fluoro-*o*-benzenedisulfonimide (NFOBS)

21

Figure 5. Examples of NF-reagents for electrophilic fluorination.

In modern fluoroorganic chemistry, use of the NF-reagents for electrophilic fluorination is getting popularity due to the advantages associated with these reagents.[1,22] They are less hazardous and most of them are solid, non-volatile compounds that are not explosive.[1] A few examples of these reagents are given in Figure 5.

3 FLUOROOLEFINS

Among the various classes of fluorinated compounds, fluoroolefins are of particular interest because of their well-known applications in material sciences[12] and medicinal chemistry.[23-26] With particular regard to medicinal chemistry, fluoroolefins are used as peptide bond isosteres, since they mimic the amide functional group (see Figure 6).[23-26] They have been found to act as anticancer, antimicrobial, anti-HIV, anti-diabetic agents.[26] Some examples of such fluoroolefins are shown in Figure 7.

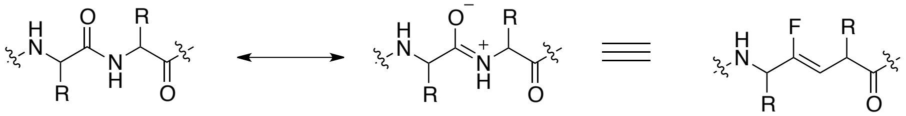
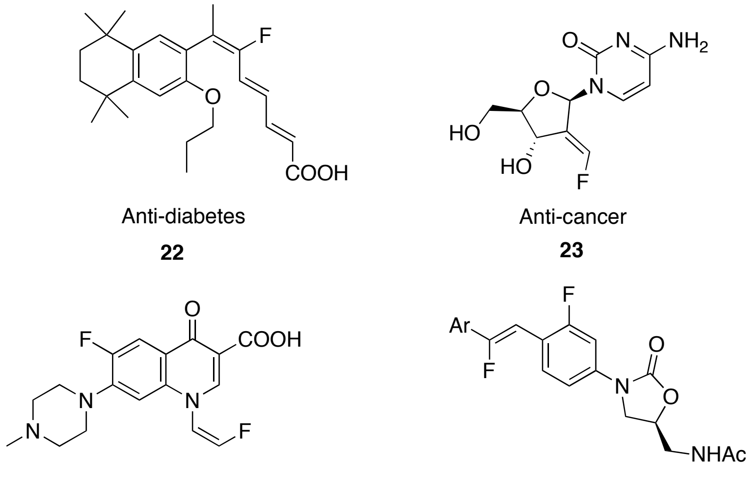


Figure 6. Fluoroolefins as peptide bond isosteres.

Additionally, fluoroolefins are very useful fluorinated intermediates in synthetic organic chemistry.[23-27]



Anti-diabetes

22

Anti-cancer

23

Anti-bacterial agent

24

Antimicrobial agent

25

Figure 7. Examples of biologically relevant fluoroolefins.

3.1 Methods for Synthesis of Fluoroolefins

In the recent years, a large number of methods for the synthesis of fluoroolefins have been developed.[26,27] Some of the commonly used methods are summarized here:

1. Olefination reactions
    1. Horner-Wadsworth-Emmons (HWE) olefination
    2. Peterson olefination
    3. Julia-Kocienski olefination
2. Cross-coupling reactions
3. Fluorination of vinyl metallic species
4. Fluorination of alkynes
5. Elimination reactions
6. Defluorinative functionalization of alkyl difluorides

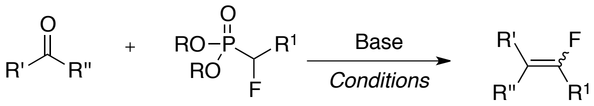
3.1.1 Olefination Reactions

Olefination reactions involve condensations of carbonyl compounds (aldehydes and ketones) with suitable fluorinated reagents, in the presence of a base to produce α-fluoroolefins. There are many olefination methods for the syntheses of unfluorinated olefins, but only a few of these have been studied for the syntheses of fluoroolefins.[26-28]

i. Horner-Wadsworth-Emmons (HWE) Olefination

HWE-reaction involves the reaction of a carbonyl compound with α-fluorophosphonate derivative to produce fluoroolefins (see Scheme 1). [26,27]

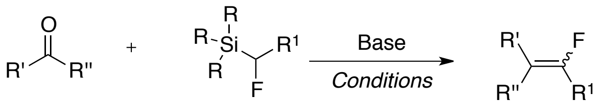
Scheme 1. Horner-Wadsworth-Emmons Olefination for Fluoroolefin Synthesis



ii. Peterson Olefination:

This method uses α-fluoro-α-trialkylsilyl derivatives in the condensation reactions with carbonyl compounds to produce fluoroolefins (see Scheme 2).[26,27]

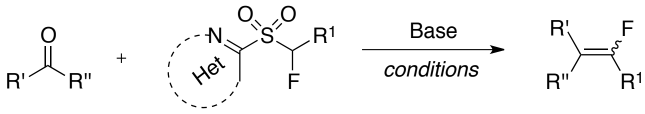
Scheme 2. Peterson Olefination for Fluoroolefin Synthesis



iii. Modified Julia-Kocienski Olefination:

α-Fluoromethyl heteroaryl or aryl sulfones react with carbonyl compounds to produce fluoroolefins (Scheme 3).[26-28]

Scheme 3. Modified Julia Olefination for Fluoroolefin Synthesis



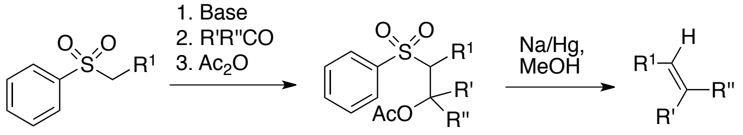
3.1.1.1 Modified Julia-Kocienski Olefination for Syntheses of Fluoroolefins

In the recent years, Julia-Kocienski olefination[29-34] has emerged as a versatile approach for the syntheses of variously functionalized fluoroolefins.[26-28]

In general, Julia-Kocienski olefination is a modification of the classical Julia olefination for synthesis of olefins and hence is also known as modified Julia olefination.

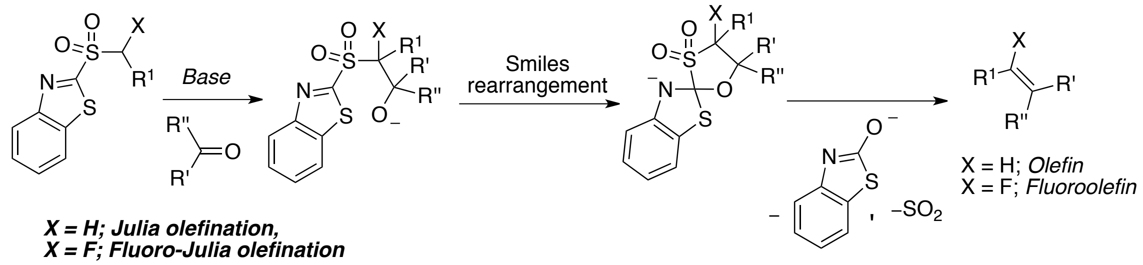
Classical Julia olefination, also known as the Julia-Lythgoe olefination, involves addition of an α-metalated phenyl sulfone to an aldehyde or ketone, acylation of the resulting β-alkoxy sulfone, followed by its reductive elimination with a single electron donor to yield the desired alkene (Scheme 4).[32,33]

Scheme 4. Classical Julia Olefination



Modified Julia olefination uses heteroaryl sulfones instead of phenyl. A brief mechanism of Julia-Kocienski olefination with benzothiazolyl sulfone is shown in Scheme 5.[28-34]

Scheme 5. Modified Julia Olefination and Fluoro-Julia Olefination



Upon addition of metalated sulfone to carbonyl, the initial β-alkoxy heteroaryl sulfone is formed that is very labile. It quickly undergoes Smiles rearrangement via spirocyclic intermediate to afford another unstable intermediate, a sulfinate salt, which immediately eliminates sulfur dioxide and salt of benzothiazol-2-ol to give the alkene.

Aryl or heteroaryl sulfones containing an α-fluoromethylene unit to sulfone (X = F in Scheme 5) lead to formation of fluoroolefins in a so-called fluoro-Julia olefination.[28] Various aryl- and heteroaryl-derived reagents that are used in modified Julia olefination are shown in Figure 8.[28-34] In fluoro-Julia olefination, use of pyrimidyl, pentachlorophenyl, and nitrophenyl derivatives has not yet been explored.

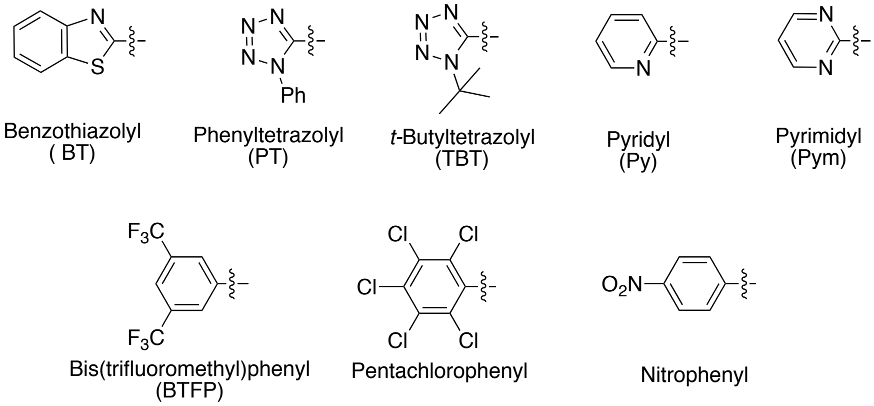


Figure 8. The heteroaryl and aryl moities used in modified Julia olefnation.

The stereochemical outcomes of these reactions depend upon many factors and have been studied by many research groups.[28,30-34] The detailed mechanism of modified Julia olefination in the reaction of an aldehyde is shown in Figure 9.[28,30-34]

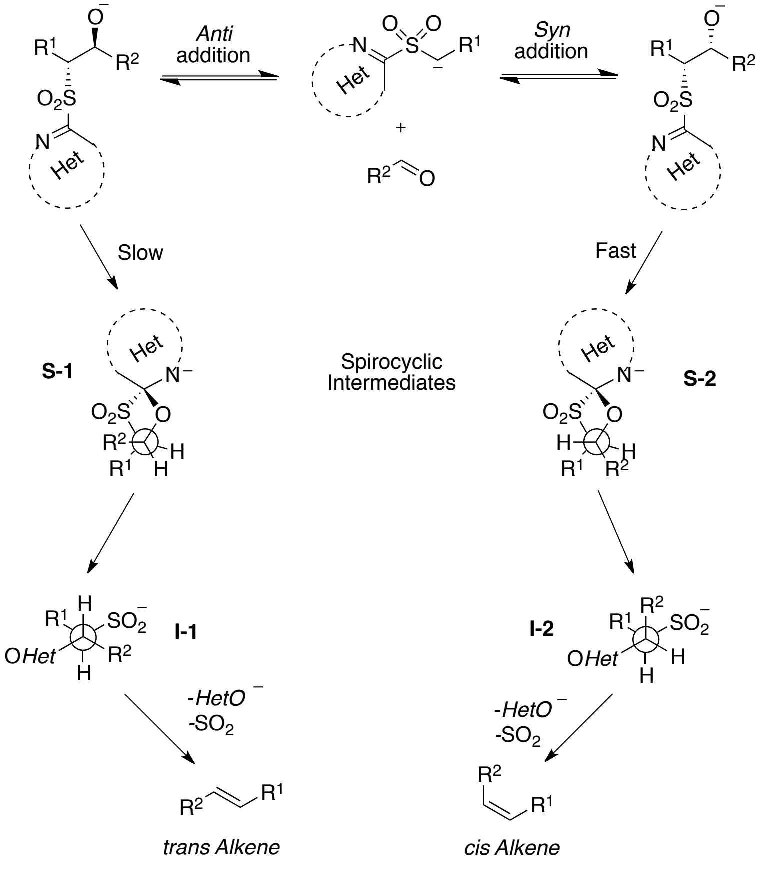


Figure 9. Mechanism of Julia-Kocienski olefination.

The first step is the addition of carbanion to the carbonyl compound. This addition can be *syn* or *anti* thus leading to adducts **S-1** and **S-2**. These adducts are not stable and undergo Smiles rearrangement to spirocyclic intermediates **I-1** and **I-2**. The rates of formation of these intermediates are different and *syn* adducts undergoes faster spirocyclization. These spirocyclic intermediates then ring open to produce the *E*- and *Z*-olefins, after elimination of sulfur dioxide and heteroaryl alkoxide.

Another pathway suggested by Julia in case of aromatic aldehydes, is the formation of zwitterionic species by elimination of heteroaryl alkoxide (see Figure 10). These species can be stabilized by the aromatic group of the aldehyde via conjugation. The equilibration in these species, followed by elimination of sulfur dioxide, leads predominantly to *trans*-alkenes.[28,30-34]

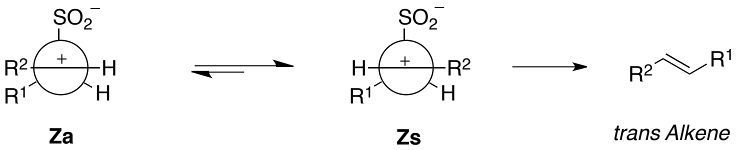


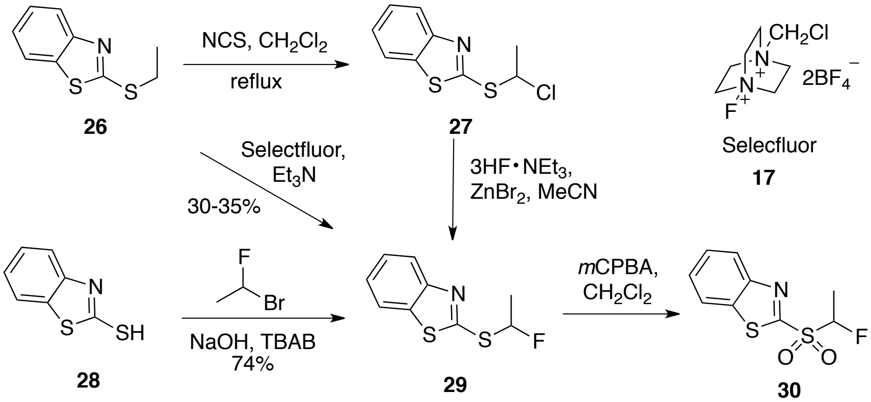
Figure 10. Alternative mechanism for *trans* stereoselectivity.

In the case of α- fluorosulfones, the possibility of zwitterionic pathway is diminished, due to the destabilizing effect that β-fluorine substituent exerts on the carbocation.[28]

4. LITERATURE REPORTS ON SYNTHESES OF FLUOROOLEFINS USING JULIA-KOCIENSKI OLEFINATION

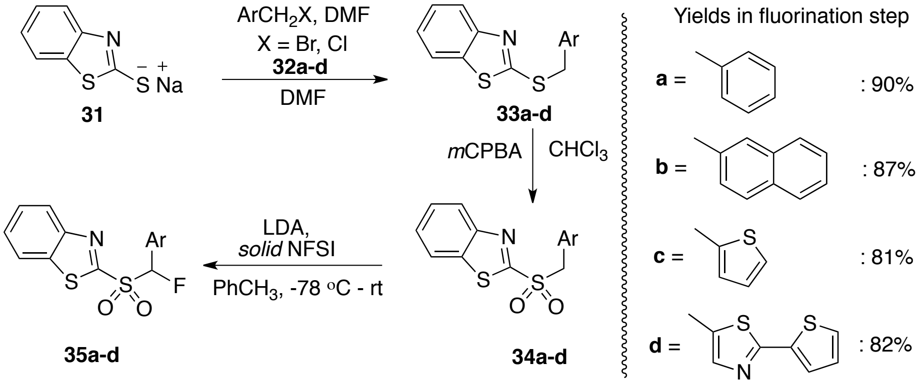
The use of Julia-Kocienski olefination was first reported by Lequeux et al.[35] The required benzothiazol-2-yl 1-fluoroethylsulfone **30** was obtained by the oxidation of benzothiazol-2-yl 1-fluoroethylsulfide **29** (see Scheme 6), whereas direct fluorination of the sulfone derivative with *N*-fluorobenzenesulfonimide **20** gave multiple fluorinated products. The fluorinated sulfide **29** was obtained by different methods (Scheme 6). When benzothiazol-2-yl ethyl sulfide **26** was subjected to direct fluorination using 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis(tetrafluoroborate) (Selectfluor) **17**, only 30-35% yield of the fluorinated sulfide **29** was obtained. Benzothiazol-2-yl 1-fluoroethylsulfide **29** was therefore synthesized via reaction of BT-thiol **28** with commercially available bromofluoroethane or via chlorination of BT-sulfide, followed by Cl-F exchange (Scheme 6). In the latter case a side product was obtained by partial chlorination of the benzothiazole ring, but did not have any effect on the olefination reaction.[35]

Scheme 6. First Synthesis of a Fluoro-Julia-Kocienski Reagent



The first general method for the synthesis of fluoro-Julia-Kocienski reagents involved metalation-electrophilic fluorination of sulfons and was developed by Zajc et al.[36] Various α-fluoromethylaryl BT-sulfones **35a-d** were synthesized by deprotonation of sulfones **34a-d**, using LDA at low temperature and heterogeneous electrophilic fluorination using NFSI (**20**) in toluene (Scheme 7).

Scheme 7. General Route to (Aryl)-α-fluoromethyl BT-Sulfones via Metalation-Fluorination



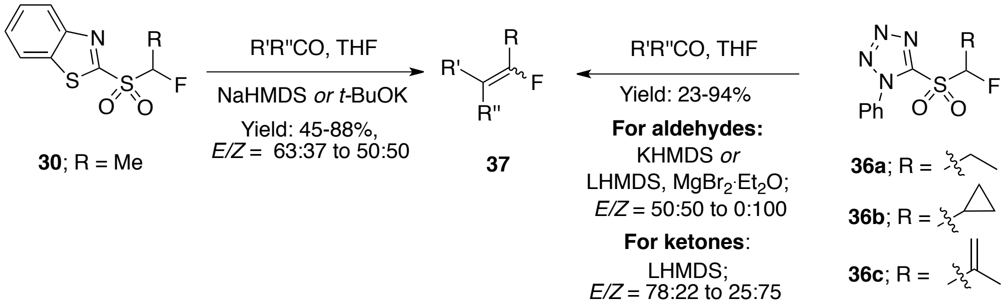
The selection of solvent and addition of solid NFSI were critical for the success of the reaction.[36] When the reactions were performed under homogeneous conditions in tetrahydrofuran solvent, no fluorination was observed and only starting unfluorinated sulfones were recovered due to possible competing single electron transfer process.[37,38]

Variously functionalized fluoro-Julia reagents have been synthesized using this approach of metalation-electrophilic fluorination and successfully used in the olefination reactions.[28] Synthesis of fluoroolefins using Julia reagents synthesized by this approach or obtained via other methods is described below.

4.1 Synthesis of Fluoroalkylidenes

Synthesis of fluoroalkylidenes using Julia-Kocienski olefination was reported by Lequeux et al.[35] and Zajc et al (Scheme 8).[39] Benzothiazole-based fluoro-Julia reagent **30** used by Lequeux et al.[35] was synthesized as shown in Scheme 6, whereas some other Julia reagents were synthesized by de-ethoxycarbonylation method[40] and Michael reaction.[41] Phenyltetrazole-based reagents **36a-c** reported by Zajc et al.[39] were obtained by metalation-electrophilic fluorination using LDA and NFSI in toluene (solid addition of NFSI) or THF (NFSI added as solution in THF).[39]

Scheme 8. Synthesis of Fluoroalkylidenes

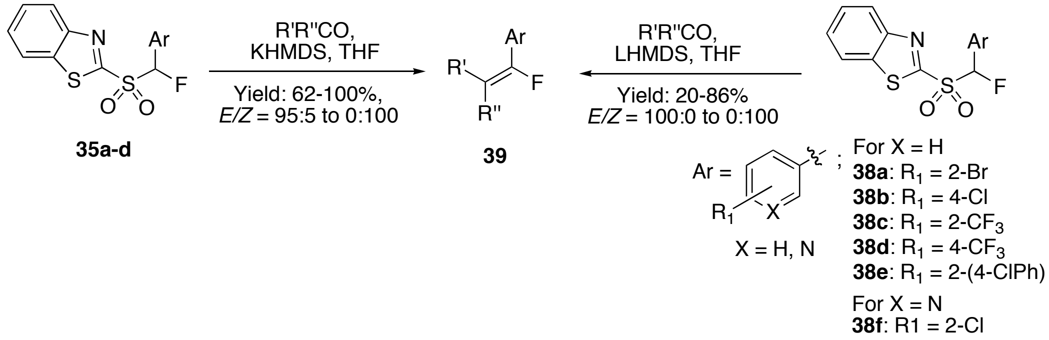


Olefination reactions of **30** with aldehydes and ketones were performed using either NaHMDS or *t*-BuOK in THF. Reactions were unselective to moderately *E*-selective and moderate to high yields of products were obtained.[35] *E/Z* ratios of products from reactions with ketones were not determined.[35] Condensations of PT-sulfones **36a-c** with aldehydes under KHMDS/THF or LHMDS/ $MgBr_2{\cdot}Et_2O$ were mostly *Z*-selective, except for a few cases where either no selectivity, or reversal of selectivity was observed.[39] Ketones were also reactive under LHMDS/THF conditions and in the case of unsymmetrical ketones, the isomeric ratio of products depended on the structure of the ketone.[39]

4.2 Synthesis of Fluorostilbene-like and Fluorostyrene-Like Derivatives

Synthesis of fluorostilbenes and fluorostyrene-like compounds by fluoro-Julia olefination was first reported by Zajc et al.[36] and later by Allendörfer et al.[42] The fluoro-Julia reagents **35a-d** were obtained by metalation-electrophilic fluorination using LDA/NFSI in toluene in the first report[36] (shown in Scheme 7); whereas **38a-f** were obtained by NaH/NFSI mediated fluorination in CH_3CN in the latter case.[42] Moderate yields in fluorination step were obtained when NaH/NFSI in CH_3CN was used,[42] compared to LDA/NFSI in toluene.[36] The fluoroolefins **39** were obtained as shown in Scheme 9.

Scheme 9. Synthesis of Fluorostilbenes and Fluorostyrenes



Condensation reactions of these reagents were performed using LHMDS in THF at 0 °C. Excellent yields of products were obtained in reactions of **35a-d**, with an exception in olefination of 1-indanone with **35d** that gave a moderate yield of 62%.[36] The stereochemical outcome of the reactions depended on the structure of the carbonyl compound and the Julia reagent.[36]

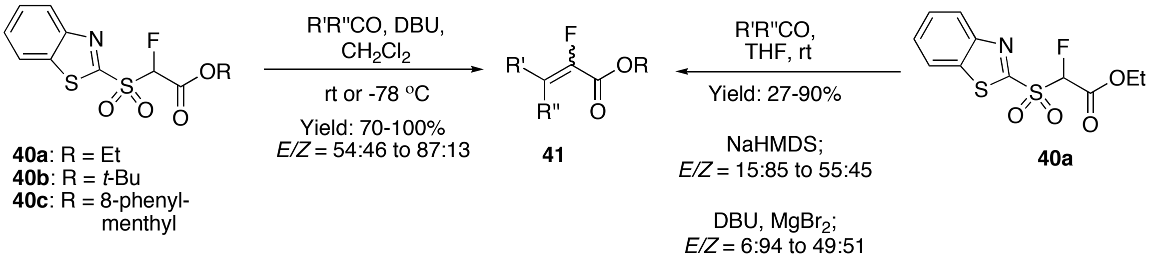
Similarly, reactions of reagents **38a-f** were conducted with various aldehydes and stereoselectivity again depended upon both, the aldehyde as well as the sulfone.[42] The fluorostilbenes were however obtained in moderate yields in most examples reported,[42] compared to very high yields obtained in olefinations with reagents **35a-d**.[36] Olefination reactions of ketones with reagents **38a-f** were not tested.[42]

4.3 Synthesis of α-Fluoroacrylates

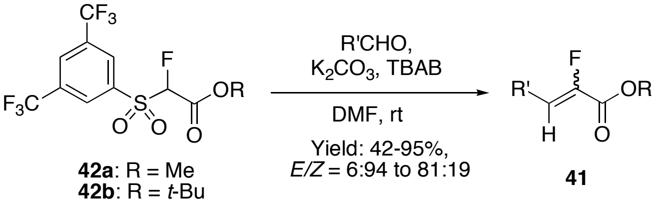
Synthesis of α-fluoroacrylates by Julia-Kocienski olefination was reported by various groups (Schemes 10).[43-45] A series of benzothiazole-based fluoro-Julia reagents **40a-c**,[43] and subsequently bis(trifluoromethyl)phenyl (BTFP)-derived **42a,b**[45] were obtained by metalation-electrophilic fluorination of protio analogs using NaH and Selectfluor in THF by Zajc et al.[43] and Nájera et al.[45] Lequeux et al.[44] synthesized BT-sulfonyl derivative **40a** by the uses of commercially available ethyl 2-bromo-2-fluoroacetate.[44]

Scheme 10. Synthesis of Fluoroacrylates

Using BT-Sulfone reagents



Using BTFP-Sulfone Reagents



Olefination reactions of BT-sulfones **40a-c** were *E*-selective under DBU/CH_2Cl_2 conditions,[43] whereas *Z*-selectivity of olefinations with **40a** was reported[44] when NaHMDS/ THF or DBU/ $MgBr_2$ in THF were used[44] (Scheme 10, top part). 4-*tert*-Butylcyclohexanone was also reacted with **40a** using DBU in THF to yield 83% of the product.[44]

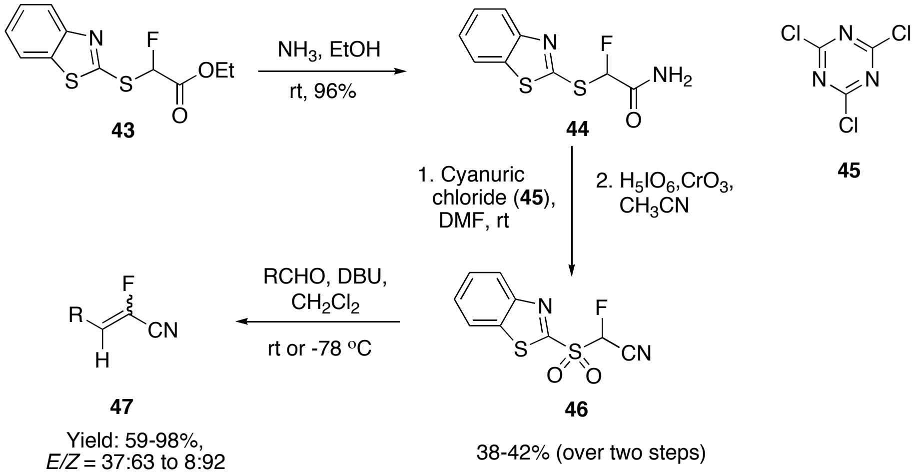
Condensations of bis(trifluoromethyl)phenyl sulfones were mainly *Z*-selective, except for a few cases where a reversal of selectivity was obtained (Scheme 10. bottom part).[45] Reactions of ketones with bis(trifluoromethyl)phenyl sulfone reagents were not studied.

4.4 Synthesis of α-Fluoroacrylonitriles

Fluoro-Julia olefination for synthesis of α-fluoroacrylonitriles was studied by Zajc et al.[46] The benzothiazole-derived sulfone **46** was obtained from ester precursor **43** in two steps, as shown in Scheme 11. Sulfone **46** was reacted with various aldehydes under mild DBU-mediated conditions to obtain α-fluoroacrylonitriles **47** in moderate to very high yields (Scheme 11).

Reactions were *Z*-selective and selectivity was improved when reactions were performed at lower temperature.[46]

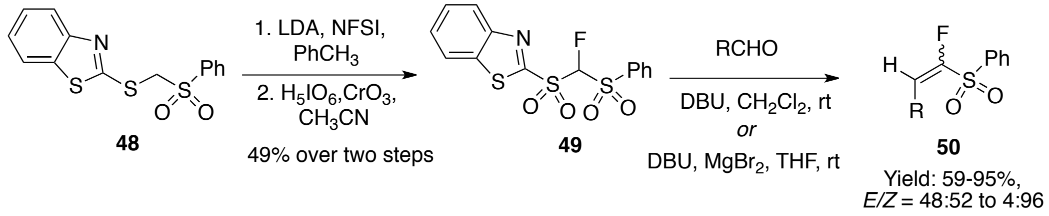
Scheme 11. Synthesis of α-Fluoroacetonitrile BT-Sulfone and α-Fluoroacrylonitriles



4.5 Synthesis of α-Fluorovinyl Phenyl Sulfones

Julia-Kocienski olefination has also been used for the synthesis of α-fluorovinyl sulfones.[47] The requisite bis-sulfone fluoro-Julia reagent **49** (Scheme 12) was obtained by metalation-fluorination of precursor **48**, followed by oxidation (Scheme 12).[47]

Scheme 12. Synthesis and Olefinations of α-(Phenylsulfonyl)-α-fluoromethyl BT- Sulfone



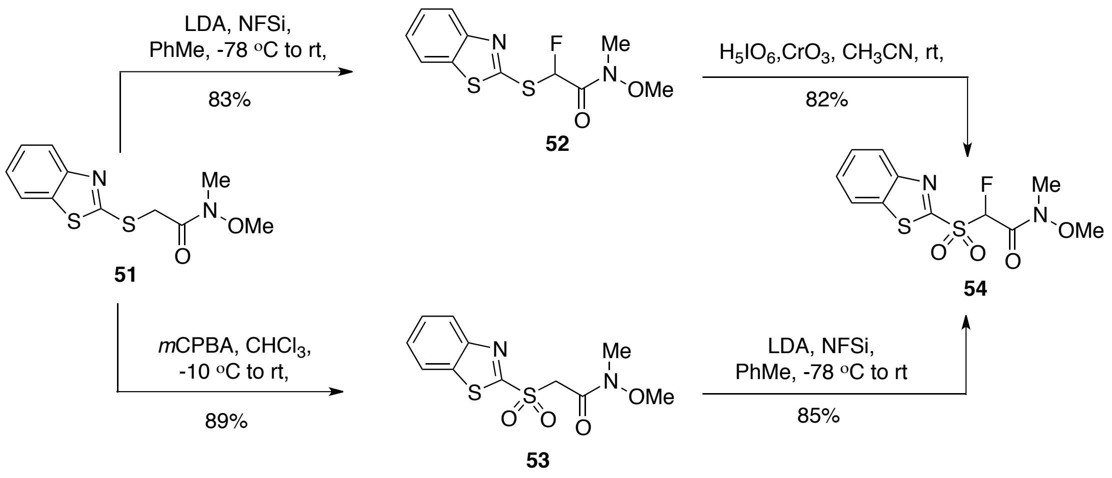
Condensation reactions of bis-sulfone **49** with aldehydes were performed under mild DBU-mediated conditions, in CH_2Cl_2 at rt. Reactions with most of the aldehydes produced the fluorovinyl sulfones **50** in high yields and in good to excellent *Z*-selectivity, with a few exceptions. The *Z*-selectivity was higher when $MgBr_2$ was used as an additive. Reaction of 1-benzylpiperidin-4-one under LHMDS/THF/0 °C yielded 70% of the olefin product.[47]

4.6 Synthesis of α-Fluorovinyl Weinreb Amides

Synthesis of α-fluorovinyl Weinreb Amides has been reported using benzothiazole-derived sulfone by Zajc et al.[48] and BTFP- derived sulfone by Nájera et al.[45] In the first case, benzothiazole-derived fluoro-Julia reagent **54** was prepared from sulfide **51** by metalation-fluorination, followed by oxidation. Alternatively, the order of the reactions could be reversed with initial addition to **53**, followed by metalation-fluorination (Scheme 13).[48]

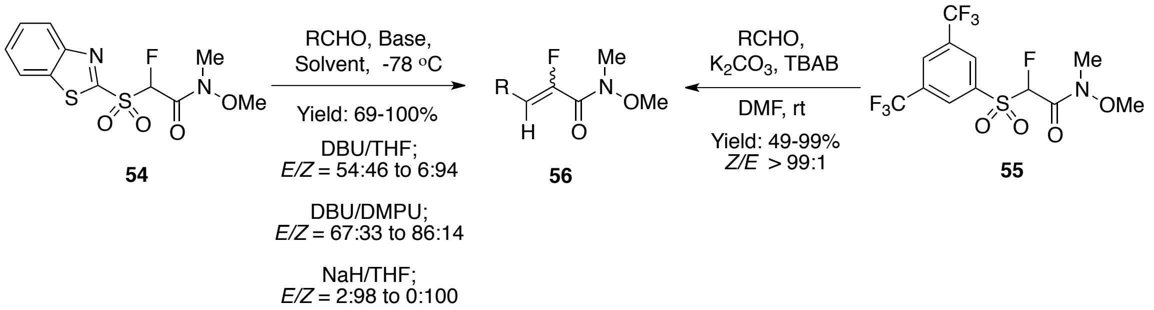
Stereoselectivity in the condensations reactions of **54** with aldehydes could be tuned by variation of solvent and base.[48] The stereoselectivity of reactions with DBU in THF depended upon the structure of the aldehyde, whereas in DMPU all reactions were *E*-selective (Scheme 14).

Scheme 13. Synthesis of Fluoro-Julia Weinreb Amide Reagent



NaH mediated reactions in THF were highly *Z*-selective, producing ≥ 98% of *Z*-isomer (Scheme 14).[48] Fluorosulfone **54** could also be reacted with cyclohexanone and 1-benzylpiperidin-4-one using Cs_2CO_3/DMF to yield 42% and 59% of fluoroolefins, respectively.[48]

Scheme 14. Synthesis of α-Fluorovinyl Weinreb Amides

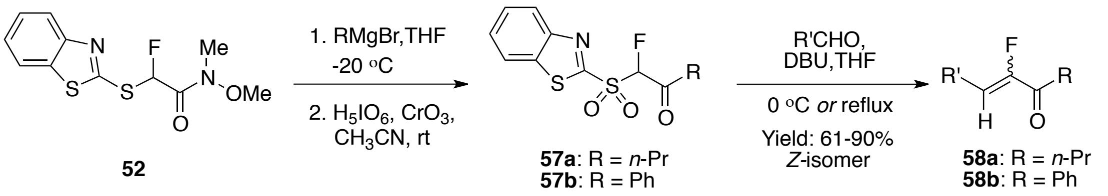


BTFP-derived fluoro-Julia reagent **55** was obtained in 74% yield, by fluorination of the protio precursor using NaH/Selectfluor in THF at 0°C in 74% yield.[45] Condensations of **55** with aldehydes were performed under mild K_2CO_3 mediated conditions, with high *Z/E* ≥ 99/1 selectivity of reactions (Scheme 14).[45]

4.7 Synthesis of α-Fluoroenones

Fluorinated benzothiazolyl sulfide **52** (synthesis shown in Scheme 13) was reacted with *n*-propyl and phenyl magnesium bromide, followed by oxidation to yield the fluoro-Julia reagents **57a** and **57b**, respectively.[48] These reagents, when reacted with various aldehydes using DBU/THF at 0 °C or under reflux, produced *Z*-fluoroenones in 61-90% yield (Scheme 15).[48]

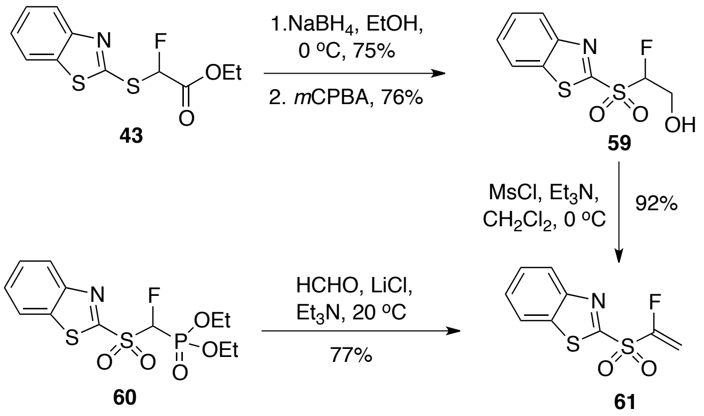
Scheme 15. Julia Reagents for α-Fluoroenones; Synthesis and Condensations with Aldehydes



4.8 Synthesis of Fluoroallylamines

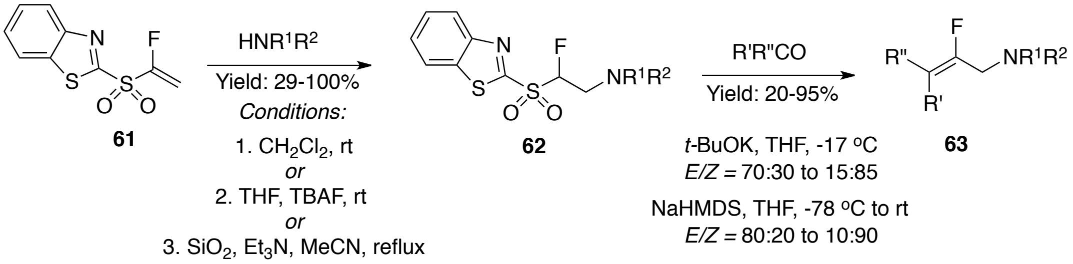
Calata et al. reported the synthesis of various fluoro-Julia reagents for the synthesis of fluoroallylamines uisng aza-Michael addition.[41] α-Fluorovinyl BT-sulfone **61**, the Michael acceptor, was obtained either from fluoro ester derivative **43** via reduction-elimination sequence, or the Horner–Wadsworth–Emmons reaction using phosphonate derivative **60** (Scheme 16).[41]

Scheme 16. Synthesis of α-Fluorovinyl BT-Sulfone



Compound **61** was reacted with various aliphatic and aryl amines, and esters of amino acids, to obtain the Julia-Kocienski reagents **62** (Scheme 17).[41] Condensation reactions were performed under two conditions that provided fluoroallyamines in 20-95% yields.[41,49] Reactions with aldehydes using NaHMDS in THF at -78 °C were *Z*-selective, whereas stereoselectivity was moderate when under *t*-BuOK in THF at -17 °C was used, and the isomeric ratio depended on the structure of the aldehyde as well as the amine moiety (Scheme 17).[41,49] A ketone 4-*tert*-butylcyclohexanone gave high yields of products using NaHMDS/THF/-78 °C conditions but lower yields under *t*-BuOK/THF/-17 °C conditions.[49]

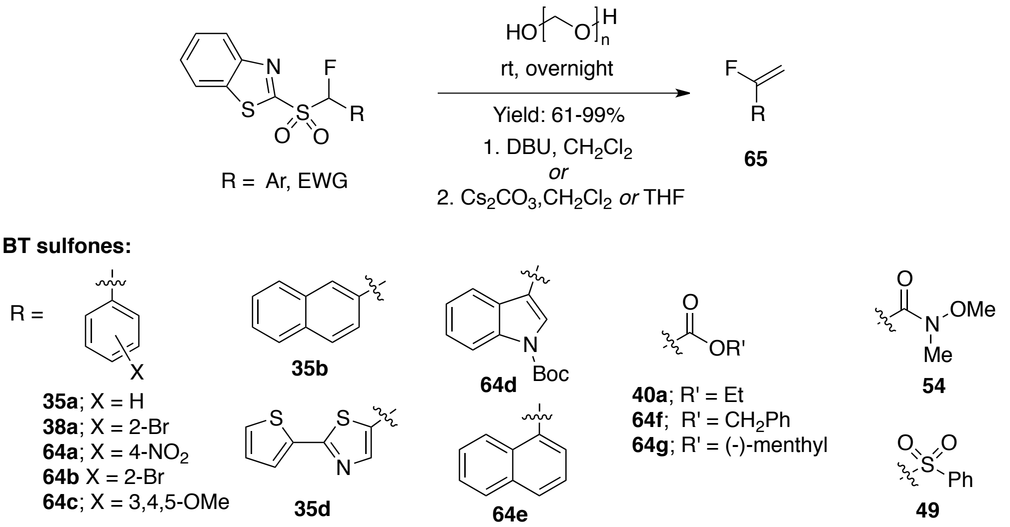
Scheme 17. Aza-Michael Addition-Julia Olefination Sequence for Synthesis of Fluoroallylamines



4.9 Synthesis of α-Substituted Fluoroethenes:

Synthesis of various α-substituted fluoroethenes by fluoro-Julia olefination was recently reported by Zajc et al.[50] Synthesis involved the reactions of paraformaldehyde with BT (aryl)fluoromethyl sulfones and (EWG)fluoromethyl sulfones, where EWG is an electron-withdrawing group, under mild DBU or Cs_2CO_3-mediated conditions. α-Substituted fluoroethenes were obtained in yields ranging from 61-99% (Scheme 18).[50]

Scheme 18. Synthesis of α-Substituted Fluoroethenes by Fluoro-Julia Olefination

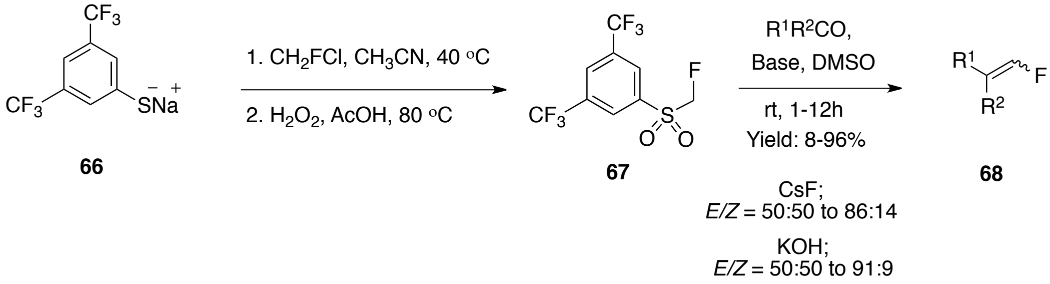


The benzothiazole sulfones derived by (aryl)fluoromethyl, phenylsulfonyl-substituted and Weinreb amide-substituted were synthesized by metalation-electrophilic fluorination as reported previously and as shown in Schemes 7, 12 and 13, respectively; Benzothiazole sulfones derived by substituted fluoromethyl ethyl, benzyl, and (–)-menthyl ester were obtained via transesterification of the ethyl ester derivative **43**.[50]

4.10 Synthesis of Terminal Monofluoroethenes

Prakash et al. recently reported the synthesis of terminal fluoroethene derivatives by using BTFP-based fluoro-Julia reagent.[51] The fluoro-Julia reagent **67** was obtained from commercially available chlorofluoromethane by reaction with sodium salt of BTFP thiol **66**, followed by oxidation of the sulfide precursor (Scheme 19).[51] Condensation reactions were performed using either CsF or KOH. Reactions of aldehydes were *E*-selective and selectivity was higher with KOH than with CsF as base. Ketones also reacted using either KOH or CsF as base. Reactions with unsymmetrical ketones were non-stereoselective.[51]

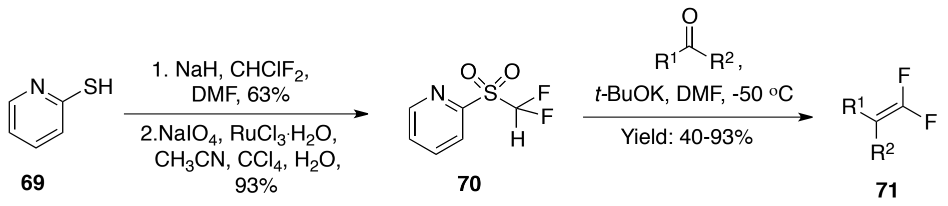
Scheme 19. Synthesis of Fluoromethyl BTFP-Sulfone and Terminal Monofluoroethenes



4.11 Synthesis of 1,1-Difluoroalkenes

In addition to its use for synthesis of monofluoroolefins, fluoro-Julia olefination has also been used for synthesis of terminal difluoroolefins using a 2-pyridyl sulfone.[52] The requisite Julia reagent, difluoromethyl 2-pyridyl sulfone was obtained in two steps, by reaction of 2-mercaptopyridine with chlorodifluoromethane and then oxidation as shown in Scheme 20.[52] Olefination reactions with aldehydes and ketones in the presence of *t*-BuOK in DMF at -50 °C produced 1,1-difluoroalkenes in moderate to very high yields (Scheme 20).

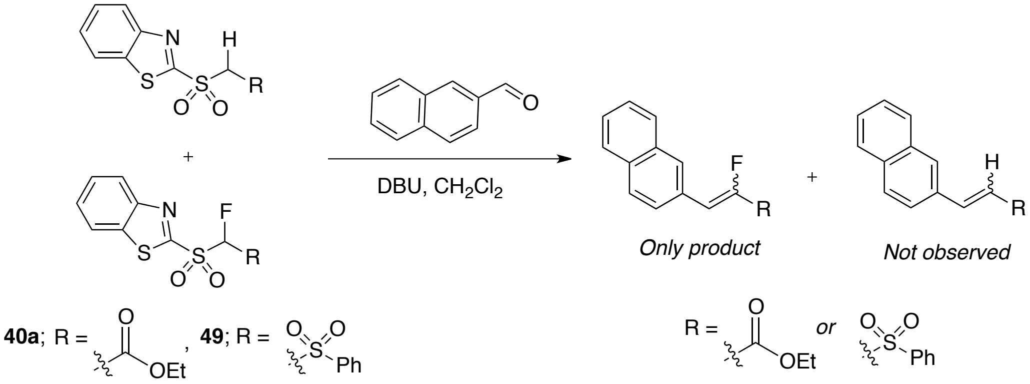
Scheme 20. Synthesis of Difluoromethyl 2-Pyridyl Sulfone and 1,1-Difluoroalkenes



Interestingly, other difluoromethyl heteroaryl sulfones (BT, PT and TBT) either gave low yields or traces of olefin products.[52]

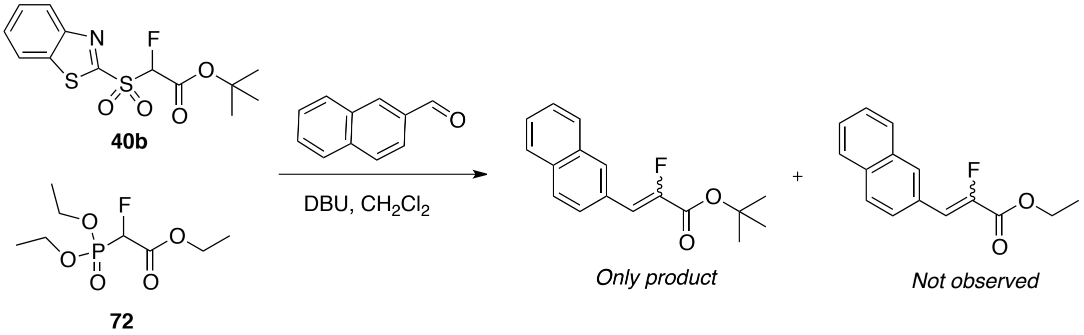
Effect of fluorine substitution on the reactivity of fluoro-Julia reagents has been studied and wherever tested, fluoro-Julia reagents were found to be more reactive than their protio analogs. In independent studies, the competitive DBU-mediated olefination reactions of ethyl(BT-sulfonyl)fluoroacetate **40a**[43] and fluorometheny(phenylsulfonyl) BT- sulfone **49**[47] were performed in the presence of their corresponding unfluorinated analogs to give fluoroolefins products only (Scheme 21).

Scheme 21. Higher Reactivity of Fluoro-Julia Reagents than Protio Analogs



Fluoro-Julia reagents also showed higher reactivity in olefination reactions than their HWE-analogs. In a competitive experiment, a mixture of *t*-butyl(BT-sulfonyl)fluoroacetate **40b** and HWE-analog **72** (as shown in Scheme 22) was reacted with 2-naphthaldehyde, using DBU.[43] Analysis of the crude reaction mixture showed the presence of the olefin product resulting from Julia reagent **40b** and no product from **72**. However, when reacted independently with 2-naphthaldehyde in the presence of DBU, **72** yielded 78% of fluoroolefin, with stereoselectivity opposite to that obtained in Julia olefination.[43]

Scheme 22. Higher Reactivity of Fluoro-Julia Regent Compared to the HWE-Reagent



5 RESEARCH GOALS

From the above discussion it can be concluded that fluoro-Julia-Kocienski olefination is a versatile tool for synthesis of fluoroolefins. The requisite fluoro-Julia-Kocienski reagents can be obtained either by fluorination of appropriate precursors or from commercially available fluorinated building blocks. Whereas introduction of fluorine can be challenging, the limited availability of commercially available fluorinated precursors narrows the scope of this approach. Therefore, a modular approach that can provide access to diverse fluoro-Julia-Kocienski reagents from a common fluorinated precursor is desirable. In this direction, we decided to explore synthesis of a bifunctional fluorinated building block. That is, a fluorinated molecule containing a Julia-olefination unit combined with another functionality that can be subjected to modifications, leading to '*second generation*' Julia-Kocienski reagents. This chapter describes the synthesis of such a bifunctional Julia reagent, its modifications to a new class of a '*second generation*' Julia reagents, and applications of these reagents for synthesis of biologically relevant compounds.

REFERENCES

1. Kirsch, P. *Modern Fluoroorganic Chemistry. Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004.

2. *Current Fluoroorganic Chemistry: New Synthetic Directions, Technologies, Materials, and Biological Applications;* Soloshonok, V. A.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J. F., Eds.; American Chemical Society: Washington DC, 2007.

3. Smart, B. E.: Fluorine Substituent Effect (On Bioactivity), *J. Fluorine Chem.* **2001**, *109*, 3-11.

4. O'Hagan, D.: Understanding Organofluorine Chemistry. An Introduction to the C–F Bond, *Chem. Soc. Rev.* **2008**, *37,* 308–319.

5. Berger, R.; Resnati, G.; Metrangolo, P.; Weberd, E.; Hulliger, J.: Organic Fluorine Compounds: A Great Opportunity for Enhanced Materials Properties, *Chem. Soc. Rev.* **2011**, *40*, 3496–3508.

6. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V.: Fluorine in Medicinal Chemistry, *Chem. Soc. Rev.* **2008**, *37*, 320-330.

7. Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst- Sander, U.; Stahl, M.: Fluorine In Medicinal Chemistry, *Chembiochem* **2004**, *5*, 637-643.

8. Ismail, F. M. D.: Important Fluorinated Drugs in Experimental and Clinical Use, *J. Fluorine Chem.* **2002**, *118*, 27-33.

9. Bégué, J.-P.; Bonnet-Delpon, D.: Recent Advances (1995–2005) in Fluorinated Pharmaceuticals Based on Natural Products, *J. Fluorine Chem.* **2006**, *127*, 992-1012.

10. Kirk, L. K.: Fluorine in Medicinal Chemistry: Recent Therapeutic Applications of Fluorinated Small Molecules, *J. Fluorine Chem.* **2006**, *127*, 1013-1029.

11. Jeschke, P.: The Unique Role of Fluorine in the Design of Active Ingredients for Modern Crop Protection, *ChemBioChem* **2004**, *5*, 570-589.

12. Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R.: Fluorinated Organic Materials for Electronic and Optoelectronic Applications: The Role of the Fluorine Atom, *Chem. Commun.* **2007**, 1003-1022.

13. Ding, Y.-S.: ^{18}F-Labeled Biomolecules for PET Studies in the Neurosciences, *J. Fluorine Chem.* **2000**, *101*, 291-295.

14. Moadel, R. M.; Nguyen, A. V.; Lin, E. Y.; Lu, P.; Mani, J.; Blaufox, M. D.; Pollard, J.

W.; Dadachova, E.: Positron Emission Tomography Agent 2-Deoxy-2-[^{18}F]fluoro-D-glucose has a Therapeutic Potential in Breast Cancer, *Breast Cancer Research* **2003**, *5*, R199-R205.

15. Hausner, S. H.; Marik, J.; Gagnon, M. K. J.; Sutcliffe, J. L.: In Vivo Positron Emission Tomography (PET) Imaging with an $\alpha_v\beta_6$ Specific Peptide Radiolabeled using ^{18}F-"Click " Chemistry: Evaluation and Comparison with the Corresponding 4-[^{18}F]Fluorobenzoyl- and 2-[^{18}F]Fluoropropionyl-Peptides, *J. Med. Chem.* **2008**, *51,* 5901–5904.

16. Pisaneschi, F.; Nguyen, Q.-D.; Shamsaei, E.; Glaser, M.; Robins, E.; Kaliszczak, M.; Smith, G.; Spivey, A. C.; Aboagye, E. O: Development of a New Epidermal Growth Factor Receptor Positron Emission Tomography Imaging Agent Based on the 3-Cyanoquinoline Core: Synthesis and Biological Evaluation, *Bioorg. Med. Chem*. **2010**, *18*, 6634–6645.

17. Michel, K.; Büther, K.; Law, M. P.; Wagner, S.; Schober, O.; Hermann, S.; Schäfers, M.; Riemann, B.; Höltke, C.; Kopka, K.: Development and Evaluation of Endothelin-A Receptor (Radio) Ligands for Positron Emission Tomography, *J. Med. Chem*. **2011**, *54*, 939–948.

18. Fujinaga, M.; Maeda' J.; Yui, J.; Hatori, A.; Yamasaki, T.; Kawamura, K.; Kumata, K.; Yoshida, Y.; Nagai, Y.; Higuchi, M.; Suhara, T.; Fukumura, T.; Zhang, M.-R.: Characterization of 1-(2-[^{18}F]Fluoro-3-pyridyl)-4-(2-isopropyl-1-oxo- isoindoline-5-yl)-5-methyl-1*H*-1,2,3-triazole, a PET Ligand for Imaging the Metabotropic Glutamate Receptor Type 1 in Rat and Monkey Brains, *J. Neurochem*. **2012**, *121*, 115–124.

19. DINOIU, V.: Chemical Fluorination of Organic Compounds, *Revue Roumaine de Chimie* **2007**, *52*, 219–234.

20. *Modern Organofluorine Chemistry – Synthetic Aspects*, ed. K. K. Laali, Bentham Science Publishers, Hilversum, The Netherlands, 2006, vol. 2.

21. *Fluorine-Containing Synthons*, ed. V. A. Soloshonok, American Chemical Society, Washington, DC, 2005.

22. Lal, G. S.; Pez, G. P.; Syvret, R. G.: Electrophilic NF Fluorinating Agents, *Chem. Rev*. **1996**, 96, 1737−1755.

23. Dutheuil, G.; Couve-Bonnaire, S.; Pannecoucke, X.: Diastereomeric Fluoroolefins as Peptide Bond Mimics Prepared by Asymmetric Reductive Amination of α-Fluoroenones, *Angew. Chem. Int. Ed*. **2007**, *46*, 1290-1292.

24. Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X.: Chiral Dipeptide Mimics Possessing a Fluoroolefin Moiety: A Relevant Tool for Conformational and Medicinal Studies, *Org. Biomol. Chem*. **2007**, *5*, 1151-1157.

25. Veken, P. V.; Senten, K.; Kertesz, I.; De Meester, I.; Lambeir, A. M.; Maes, M. B.;

Scharpe, S.; Haemers, A.; Augustyns, K.: Fluoroolefins as Peptidomimetic Inhibitors of Dipeptidyl Peptidases, *J. Med. Chem*. **2005**, *48*, 1768-1780.

26. Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F.: Synthetic Approaches to Monofluoroalkenes, *Chem. Soc. Rev*. **2011**, *40*, 2867–2908.

27. Yanai, H.; Taguchi, T.: Synthetic Methods for Fluorinated Olefins, *Eur. J. Org. Chem.* **2011**, 5939–5954.

28. Zajc, B.; Kumar, R.: Synthesis of Fluoroolefins via Julia–Kocienski Olefination, *Synthesis*, **2010**, 1822-1836.

29. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O.: A Direct Synthesis of Olefins by Reaction of Carbonyl Compounds with Lithio Derivatives of 2-[Alkyl- or (2′-Alkenyl)- or Benzyl-Sulfonyl]-Benzothiazoles, *Tetrahedron Lett*. **1991**, *32*, 1175–1178.

30. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O.: Stereochemistry of the Olefin Formation From *Anti* And *Syn* Heterocyclic β-Hydroxy Sulfones, *Bull. Soc. Chim. Fr.* **1993**, *130*, 336-357.

31. Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O.: Stereochemistry of Direct Olefin Formation From Carbonyl Compounds and Lithiated Heterocyclic Sulfones, *Bull. Soc. Chim. Fr.* **1993**, *130*, 856-878.

32. Blakemore, P. R.: The Modified Julia Olefination: Alkene Synthesis *via* the Condensation of Metallated Heteroarylalkylsulfones with Carbonyl Compounds, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.

33. Plesniak, K.; Zarecki, A.; Wicha, J.: The Smiles Rearrangement and the Julia–Kocienski Olefination Reaction, *Top. Curr. Chem*. **2007**, *275*, 163–250.

34. Aissa, C.: Mechanistic Manifold and New Developments of the Julia–Kocienski Reaction, *Eur. J. Org. Chem*. **2009**, 1831–1844.

35. Chevrie, D.; Lequeux, T.; Demoute, J. P.; Pazenok, S.: A Convenient One-Step Synthesis of Fluoroethylidene Derivatives, *Tetrahedron Lett.* **2003**, *44*, 8127-8130.

36. Ghosh, A. K.; Zajc, B.: High-Yield Synthesis of Fluorinated Benzothiazolyl Sulfones: General Synthons for Fluoro-Julia Olefinations, *Org. Lett*. **2006**, *8*, 1553-1556.

37. Differding, E.; Rüegg, G. M.: Nucleophilic Substitution Versus Electron Transfer: 1. On the Mechanism of Electrophilic Fluorinations, *Tetrahedron Lett.* **1991**, *32*, 3815-3818.

38. Differding, E.; Wehrli, M.: Nucleophilic Substitution Versus Electron Transfer: 2. SN^2 at Flouride and Electron Transfer are Competing and Different Pathways in Electrophilic Flourinations, *Tetrahedron Lett.* **1991**, *32*, 3819-3822.

39. Ghosh, A. K.; Zajc, B.: Fluorinated 1-Phenyl-1*H*-tetrazol-5-yl Sulfone Derivatives as

General Reagents for Fluoroalkylidene Synthesis, *J. Org. Chem***. 2009**, *74,* 8531–8540.

40. Calata, C.; Catel, J.-M.; Pfund, E.; Lequeux, T.: Scope and Limitations of the Julia–Kocienski, Reaction with Fluorinated Sulfonylesters, *Tetrahedron* **2009**, *65*, 3967-3973.

41. Calata, C.; Pfund, E.; Lequeux, T.: Toward the Synthesis of Benzothiazolyl Fluoroaminosulfones, *J. Org. Chem.* **2009**, *74*, 9399-9405.

42. Allendörfer, N.; Es-Sayed, M.; Nieger, M.; Bräse, S.: Novel Aromatic Fluoroolefins via Fluoro-Julia–Kocienski Olefination, *Synthesis* **2010**, 3439-3448.

43. Kake, S.; Zajc, B.: Exceptionally Mild, High-Yield Synthesis of α-Fluoro Acrylates, *Org. Lett*. **2006**, *8*, 4457-4460.

44. Pfund, E.; Lebargy, C.; Rouden, J.; Lequeux, T.: Modified Julia Fluoroolefination: Selective Preparation of Fluoroalkenoates, *J. Org. Chem*. **2007**, *72*, 7871-7877.

45. Alonso, D. A.; Fuensanta, M.; Gómez-Bengoa, E.; Nájera, C. Highly Efficient and Stereoselective Julia–Kocienski Protocol for the Synthesis of α-Fluoro-α,β-unsaturated Esters and Weinreb Amides Employing 3,5-Bis(trifluoromethyl)phenyl (BTFP) Sulfones, *Adv. Synth. Catal.* **2008**, *350*, 1823-1829.

46. del Solar, M.; Ghosh, A. K.; Zajc, B.: Fluoro-Julia Olefination as a Mild, High-Yielding Route to α-Fluoro Acrylonitriles, *J. Org. Chem.* **2008**, *73*, 8206-8211.

47. He, M.; Ghosh, A. K.; Zajc, B.: Julia Olefination as a General Route to Phenyl (α-Fluoro)vinyl Sulfones, *Synlett* **2008**, 999-1004.

48. Ghosh, A. K.; Banerjee, S.; Sinha, S.; Kang, S. B.; Zajc, B.: α-Fluorovinyl Weinreb Amides and α-Fluoroenones From a Common Fluorinated Building Block, *J. Org. Chem.* **2009**, *74*, 3689-3697.

49. Calata, C.; Pfund, E.; Lequeux, T.: Convergent Synthesis of Functionalized Fluoroallylamines by the Julia-Kocienski Reaction, *Tetrahedron* **2011**, *67*, 1398-1405.

50. Mandal, S. K.; Ghosh, A. K.; Kumar, R.; Zajc, B.: Expedient Synthesis of α-Substituted Fluoroethenes, *Org. Biomol. Chem.* **2012**, *10*, 3164-3167.

51. Prakash, G. K. S.; Shakhmin, A.; Zibinsky, M.; Ledneczki, I.; Chacko, S.; Olah, G. A.: Synthesis of Monofluoroalkenes via Julia–Kocienski Reaction, *J. Fluorine Chem.* **2010**, *131*, 1192-1197.

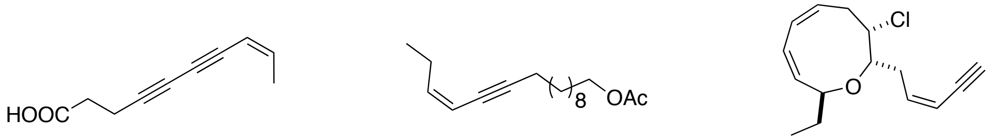
52. Zhao, Y.; Huang, W.; Zhu, L.; Hu, J.; Difluoromethyl 2-Pyridyl Sulfone: A New *gem*-Difluoroolefination Reagent for Aldehydes and Ketones, *Org. Lett.* **2010**, *12*, 1444-1447.

PART 1

SYNTHESIS OF A NEW BIFUNCTIONAL FLUORO-JULIA-KOCIENSKI REAGENT AND ITS REACTIVITY FOR THE SYNTHESIS OF 2-FLUOROENYNES

1.1 INTRODUCTION

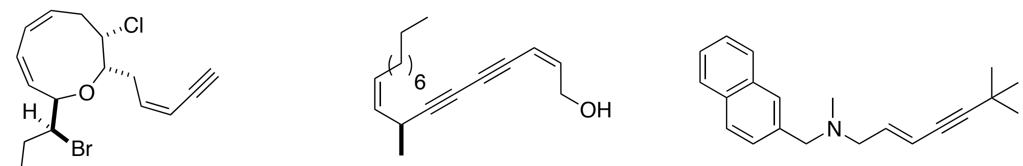
Conjugated enynes are useful synthetic intermediates, where chemistry of the two functionalities i.e. a double bond and a triple bond, can be utilized for diversity oriented synthesis.[1-3] Compounds containing 1,3-enyne structural unit are not only synthetically useful but are also part of important natural products[4-10] and pharmaceutical agents.[11-13] Some examples of such compounds are shown in Figure 1.



1
Dihydromatricaria acid

2
(*Z*)-13-Hexadecen-11-ynyl acetate

3
(+)-Brasilenyne



4
(+)-*cis*-Dihydrodophytin

5
(2*Z*, 8*S*, 9*Z*)-Heptadeca-2,9-dien-4,6-diyn-1,8-diol

6
Tabinafine (Lamisil)

Figure 1. Examples of natural products and a pharmaceutical agent containing conjugated enyne unit.

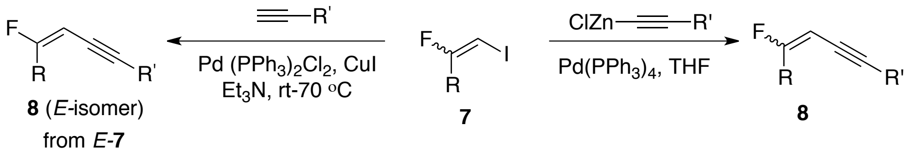
Compound **1** is secreted by soldier beetles (Cantharidae) for defense,[4,5] compound **2** is a sex pheromone of the processionary moth *Thaumetopoea pityocampa*,[6,7] compounds **3** and **4** are antifeedants from a sea hare,[8] compound **5** was isolated from *Bupleurum salicifolium* and possesses an antibiotic activity,[9,10] Terbinafine, also known as Lamisil, is a well known antifungal agent.[11-13]

Due to a wide range of applications of fluoroorganic compounds,[14-17] there is an increased demand for their synthetic methods. The building block approach is one of the convenient methods for obtaining regio- and stereospecifically fluorinated compounds.[18] Fluoroenynes can be such diversely functionalizable building blocks. Although there are several methods known in the literature for the synthesis of conjugated enynes,[1-3,19-24] only limited reports on the synthesis of fluorinated 1,3-enynes are available. Some of the literature reports on synthesis of fluorinated 1,3-enynes are as described below

1.1.1 Metal Mediated Synthesis of Fluoroenynes

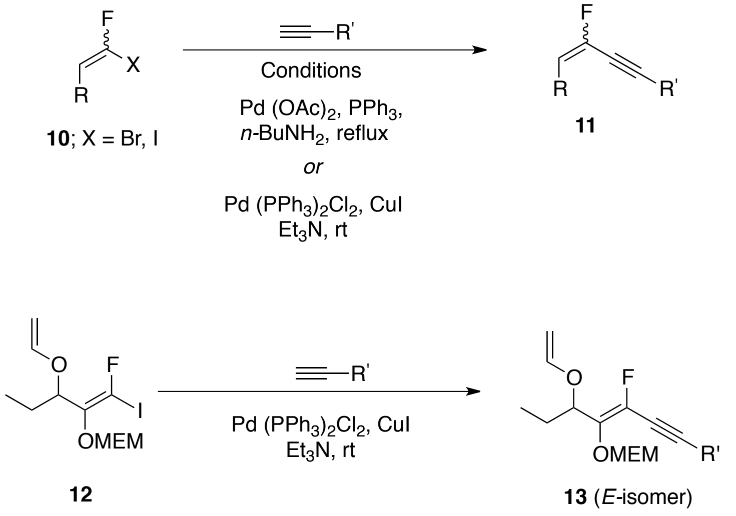
***1-Fluoroenynes*:** Tellier et al.[25] and Yoshida et al.[26] have utilized palladium chemistry for the synthesis of 1-fluoroenynes using fluorovinyl iodides. Tellier et al.[25] used zinc reagents in the presence of $Pd(PPh_3)_4$, whereas Yoshida et al.[26] used Sonogashira cross-coupling conditions (Scheme 1).

Scheme 1. Synthesis of 1-Fluoroenynes



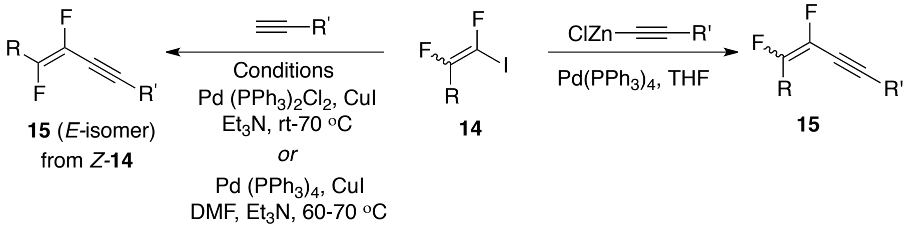
***2-Fluoroenynes*:** Synthesis of 2-fluoroenynes by the use of Sonogashia cross-coupling has also been reported by Eddarir et al.,[27] Percy et al.[28] and Burton et al.[29-31] Fluorovinyl iodides and bromides were reacted with alkynes using Pd(0) or Pd(II) catalysts (Scheme 2).

Scheme 2. Synthesis of 2-Fluoroenynes

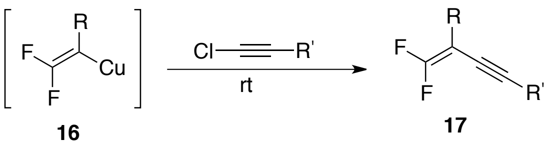


Difluoro- and trifluoroenynes: Tellier et al.[25] and Burton et al.[32,33] have also used palladium-catalyzed reactions for synthesis of 1,2-difluoroenynes (Scheme 3). Use of vinyl copper reagents for synthesis of 1,1-difluoroenynes was reported by Ichikawa et al. (Scheme 4).[34]

Scheme 3. Synthesis of 1,2-Difluoroenynes

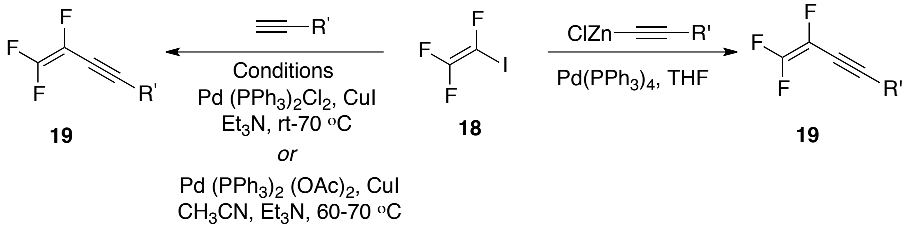


Scheme 4. Synthesis of 1,1-Difluoroenynes



Synthesis of trifluoroenynes has also been reported using similar conditions as in the case of difluoroeyne synthesis (Scheme 5).[25,33]

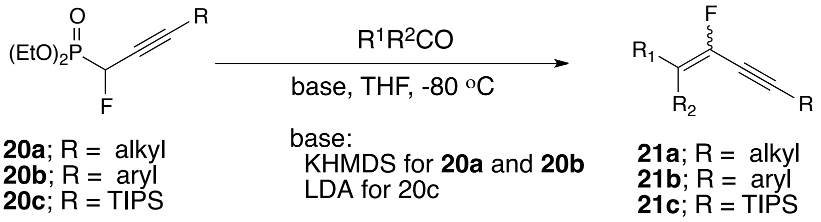
Scheme 5. Synthesis of Trifluoroenynes



1.1.2 Synthesis of Fluoroenynes by Horner-Wadsworth-Emmons Olefination

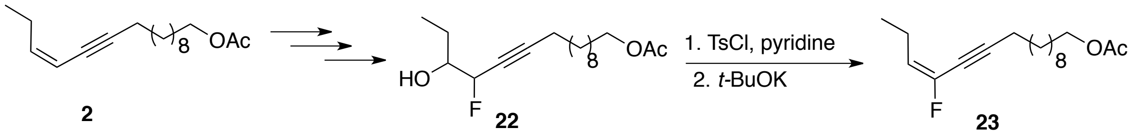
Hammond et al. reported synthesis of 2-fluoroenynes using HWE olefination.[35-37] Variously substituted α-fluoropropargyl phosphonates were reacted with aldehydes and ketones at low temperature using NaH, LDA or KHMDS bases. In the case of alkyl or aryl-derived fluoropropargyl phosphonate (**20a** and **20b**, Scheme 6), moderate to low yields of products were obtained.[36] Also, a moderate *E*-selectivity in the case of reactions with benzaldehyde and acetophenone was observed, whereas reactions with aliphatic aldehydes were either moderately *Z*-selective or non-selective.[36] When the alkyne functionality was protected with TIPS group, the yields improved significantly, however selectivity remained low to moderate. but reaction selectivity did not change much.[37]

Scheme 6. Synthesis of 2-Fluoroenynes by HWE Olefination



Synthesis of fluoroenynes, synthesis of (*E*)-13-fluoro-13-hexadecen-11-ynyl acetate **23**, a fluorinated analog of a sex pheromone **2**, was also reported via dehydration of fluorohydrin intermediate **22** (Scheme 7).[38-39] The effect of fluorine substitution on biological activity was exemplified in this case as well where the presence of fluorine in **23** (analog of **2**) induced the antipheromone activity.[40]

Scheme 7. Synthesis of Fluoroenyne **23**, Fluorinated analog of Sex Pheromone **2** of *Thaumetopoea Pityocampa*



Julia-Kocienski olefination[41-43] is a versatile tool for synthesis of functionalized olefins and has been explored in the recent years for the synthesis of fluoroolefins.[44] The requisite fluorinated Julia-Kocienski reagents can be obtained by metalation-fluorination approach, developed by Zajc et al.[45-51] Although Julia-Kocienski olefination has been used for the synthesis of 1,3-enynes,[52] its use for the synthesis of conjugated fluoroenynes is not known in the literature. Part 1 describes synthesis of a bifunctional fluoro-Julia-Kocienski reagent, TMS-protected propargyl benzothiazolyl sulfone, by metaltion-fluorination approach. Utility of the reagent in the modular synthesis of conjugated fluoroenynes is presented. Further conversion of fluoroenynes to stereoisomeric fluorodienes is also demonstrated.

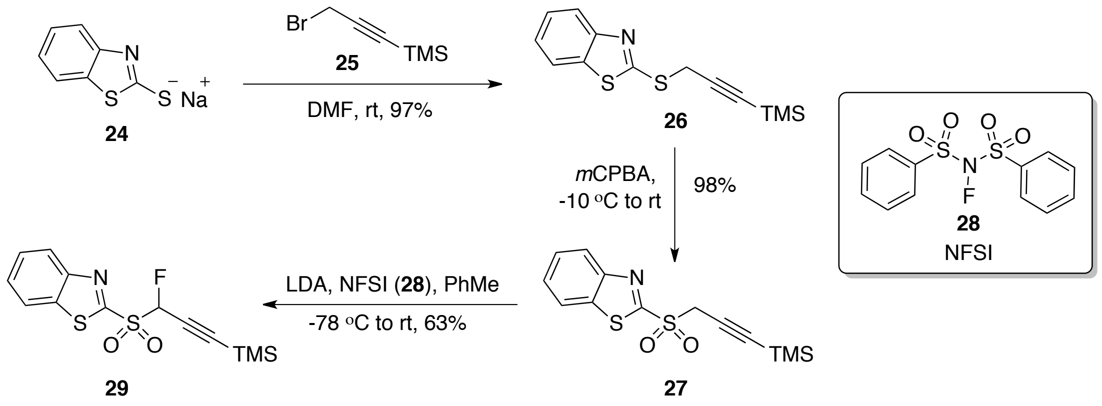
1.2 RESULTS AND DISCUSSION

1.2.1 Synthesis of Fluoro-Julia-Kocienski Reagent

Synthesis of TMS protected 1,3-benzothiazol-2-yl (BT) propargyl sulfone has previously been reported by Bonini et al.[53] Using their method, compound **27** was obtained in two steps. Reaction of sodium salt of 2-mercaptobenzothiazole **24** with TMS-protected propargyl bromide

25 provided sulfide **26** that was subjected to *m*CPBA oxidation to obtain sulfone derivative **27** (Scheme 8). Metalation of **27** by LDA followed by fluorination using NFSI (**28**) under heterogeneous conditions in toluene gave TMS fluoropropargyl BT-sulfone **29** (Scheme 8). Use of toluene as solvent and solid addition of NFSI has been reported to be critical for the success of fluorination reaction in the case of (aryl)fluoromethyl BT-sulfones.[45]

Scheme 8. Synthesis of TMS-protected 1,3-Benzothiazol-2-yl Fluoropropargyl Sulfone **29**



It is important to mention that in order to obtain the consistent yields of **29**, it is critical to remove any residual fluoride salts from the crude reaction mixture immediately. Therefore, following the workup, the reaction mixture was suspended in toluene and filtered through a short silica gel plug and eluted with toluene. The filtrate was then subjected to purification using silica gel column chromatography.

Fluoropropargyl sulfone **29** was crystallized from hexanes and analyzed by X-ray diffraction. X-ray structure of **29** is shown in Figure 2. A slight bend of the triple bond from the linearity was observed where Si-C1-C2 and C1-C2-C-3 angles are 177.0° and 176.7°, respectively.

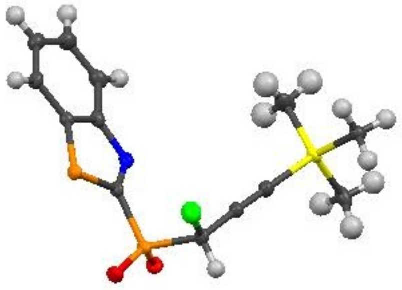


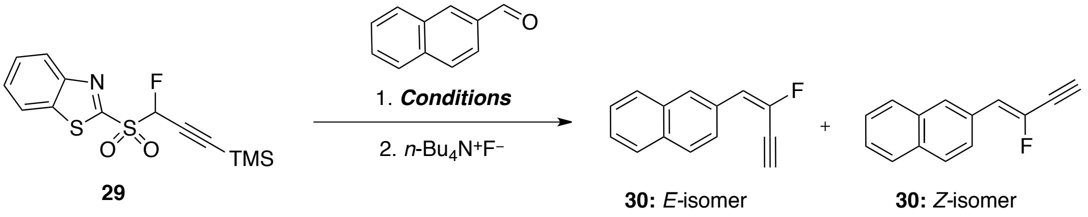
Figure 2. Crystal structure of fluoropropargyl sulfone **29** (C: black, H: grey, F: green, N: blue, O: red, S: orange, Si: yellow).

1.2.2 Synthesis of Fluoroenynes

For the screening of conditions for condensations, fluoropropargyl BT-sulfone **29** was reacted with 2-naphthaldehyde under different conditions. KHMDS, LHMDS, and Cs_2CO_3-mediated reactions were conducted using Barbier conditions, where the base was added to 2-naphthaldehyde (1 molar equiv), BT-sulfone **29 (**2.0-2.5 molar equiv) and additive, in cases where additive was used. In DBU-mediated reactions, sulfone **29** (2.5 molar equiv) was added to solution of aldehyde and base. A partial loss of the TMS group from the condensation products was observed under these reaction conditions. Therefore, when all of the aldehyde was consumed, tetrabutylammonium fluoride was added to the reaction mixture. Thus, the deprotected fluoroenyne **30** was obtained in a two-step, one-pot operation. The results from these experiments are shown in Table 1.

In the synthesis of conjugated enynes via Julia-Kocienski olefination using TMS-protected propargyl BT-sulfone **27**,[52] KHMDS-mediated reactions at –55˚C produced the enynes in yields that were typically moderate, but high *Z*-selectivity was obtained under these conditions.[52]

Table 1. Screening of Olefination Conditions



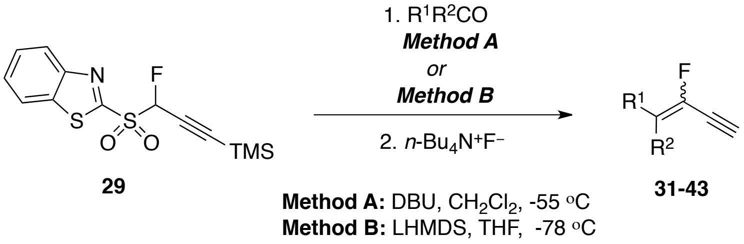
Entry	Base (molar equiv)	Solvent	Additive (molar equiv)	T (˚C); time	(%) E/Z;[a] (%) yield [b]
1[c]	KHMDS (2.4)	THF	--	–55; 10 min	82/18; 86
2[c]	LHMDS (2.4)	THF	--	–78; 10 min	88/12; 97
3[c]	LHMDS (2.4)	THF	$MgBr_2 \cdot Et_2O$ (3.0)	rt; 4 h	89/11; 78
4[c]	LHMDS (2.4)	DMF	DMPU[d]	–78; 10 min	63/37; 74
5[c]	LHMDS (2.4)	DMPU	--	0; 10 min	58/42; NA[e]
6[f]	DBU (4.0)	CH_2Cl_2	--	rt; 10 min	69/31; 91
7[f]	DBU (4.0)	CH_2Cl_2	--	0; 10 min	70/30; 92
8[f]	DBU (4.0)	CH_2Cl_2	--	–55; 10 min	74/26; 95
9[f]	DBU (4.0)	CH_2Cl_2	--	–78; 10 min	74/26; NA[e]
10[f]	DBU (4.0)	CH_2Cl_2	$MgBr_2 \cdot Et_2O$ (3.0)	rt; 30 h	60/40; Inc[g]
11[f]	DBU (4.0)	THF	$MgBr_2 \cdot Et_2O$ (3.0)	rt; 30 h	90/10; Inc[g]
12[f]	Cs_2CO_3 (3.0)	CH_2Cl_2	--	rt; 6 h	74/26; NA[e]

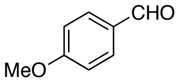
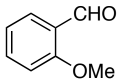
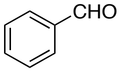
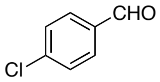
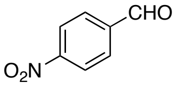
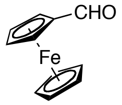
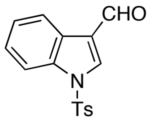
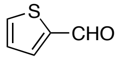
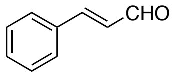
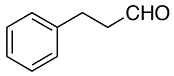
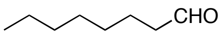
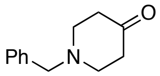
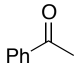
[a] E/Z ratio of diastereomers in the crude reaction mixture was determined by ^{19}F NMR, prior to isolation. [b] Yields are of isolated and purified products. [c] Sulfone **29**, 2.0 molar equiv. [d] Cosolvent, ratio of DMF/DMPU 1:1 (v/v). [e] Products were not isolated. [f] Sulfone **29**, 2.5 molar equiv. [g] Reaction was incomplete after 30 h.

In the case of fluoro analog **29**, KHMDS-mediated reaction of **29** with 2-naphthaldehyde at –55˚C gave product **30** in 82/18 *E*/*Z* ratio and high yield (86%, entry 1). When LHMDS was used at –78˚C an increase in *E*/*Z* ratio (88/12) and product yield (97%) was observed (entry 2).

Similarly high *E*/*Z* ratio was obtained when the reaction was performed in the presence of $MgBr_2 \cdot Et_2O$ and at rt, but the yield was significantly lower (entry 3). The use of polar and/or complexing solvents substantially decreased both the selectivity and the yield (entries 4, 5). We were interested in knowing if the reactions proceed in the presence of a milder base. Therefore, olefination in presence of DBU at room temperature was performed which resulted in a high yield of **30**, but with lowered selectivity (*E*/*Z* 69/31, entry 6). Lowering the temperature to –55˚C marginally increased both the *E*-selectivity and yield (entry 8). No improvement in the selectivity was observed upon further lowering of temperature to –78˚C (entry 9). The effect of $MgBr_2 \cdot Et_2O$ on *E/Z* ratio of fluoroeynes in DBU-mediated olefinations depended on the solvent used. A high 90/10 *E*/*Z* ratio was observed in THF (entry 11), whereas in CH_2Cl_2 the ratio was substantially lowered to 60/40 (entry 10). Reactions in these two solvents were comparatively very slow and did not go to completion even after 30 h. Condensation could also be conducted with Cs_2CO_3 as base and at room temperature (entry 12), where similar *E/Z* ratio was obtained as in the case of DBU at –55˚C but, the reaction was much slower (entries 8 and 12).

Table 2. Condensation Reactions of **29** with Aldehydes and Ketones



Entry	Carbonyl	Product: yield,[a] E/Z ratio[b]	
		Method A[c]	Method B[d]
1		**31**: 92%, 81/19	**31**: 97%, 95/5
2		**32**: 92%, 78/22	**32**: 87%, 90/10
3		**33**: 90%, 76/24	**33** 59%, 94/6
4		**34**: 81%, 70/30	**34**: 95%, 94/6
5		**35**: 59%, 51/49	**35**: 81%, 72/28
6		**36**: 95%, 83/17	**36**: 98%, 90/10
7		**37**: 95%, 75/25	**37**: 92%, 91/9
8		**38**: 78%, 75/25	**38**: 78%, 91/9
9		**39**: 95%, 72/28	**39**: 96%, 80/20
10		**40**: 54% (63%[e]), 80/20	**40**: 63%, 70/30
11		**41**: 79% (91%[e]), 85/15	--
12		--	**42**: 77%
13		--	**43**: 88%, *E* only[f]

[a]Yields of isolated and purified products. [b]*E/Z* ratio of diastereomers in the crude reaction mixture was determined by ^{19}F NMR, prior to isolation. No change in ratio was observed after purification. [c]Method A: sulfone **29**, 2.0-2.5 molar equiv; DBU, 4.0 molar equiv; TBAF, 0.20 molar equiv. For **37** and **39**, 3.0 molar equiv of **29** was used. Sulfone was added to solution of aldehyde and base. [d]Method B for aldehydes: sulfone **29**, 2.0 molar equiv; LHMDS, 2.4 molar equiv; TBAF, 2.0 molar equiv. Method B for ketones: sulfone **29**, 3.0 molar equiv; LHMDS, 5.0 molar equiv; TBAF, 3.0 molar equiv. LHMDS was added to a solution of sulfone and aldehyde. [e]Yield was calculated using octafluoronaphthalene as an internal standard. [f]Determined by NOESY experiment on the diene **44** obtained by Lindlar reduction of **43** (see Figure 3).

To test the scope of the condensation reactions of fluoropropargyl BT-sulfone **29**, it was reacted with various carbonyl compounds. Eleven aldehydes were reacted under mild DBU-mediated conditions (Method A), and LHMDS-mediated conditions (Method B), whereas two ketones were reacted under LHMDS-mediated conditions (Method B). The results of the condensation reactions are displayed in Table 2. High yields of fluoroenynes were obtained under both conditions and were generally comparable for all substrates, except for entries 3 and 5, where there is no obvious reason for the differences observed. Also, *E*-isomer (*cis* arrangement of bulkier groups at the double bond) was obtained as the major isomer in both methods. In DBU-mediated condensations with substituted benzaldehydes, electron-donating substituents increased the *E*-selectivity (entries 1, 2 and 3), whereas electron-withdrawing groups decreased the selectivity (entries 3, 4 and 5).

Reactions of ketones with sulfone **29** under LHMDS-mediated conditions also produced high yields of fluoroenynes (entries 12 and 13), and a single isomer was formed in reaction with acetophenone (**43**, entry 13). For determination of stereochemistry in **43**, the triple bond was subjected to partial hydrogenation with Lindlar catalyst to obtain fluorodiene **44**. The 2D NOESY data showed a correlation between the *ortho* protons in the phenyl ring and the internal olefinic proton, supporting the assignment of *E*-configuration in **43**.

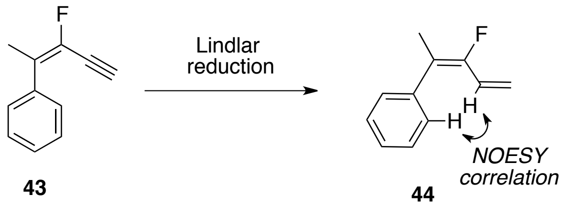
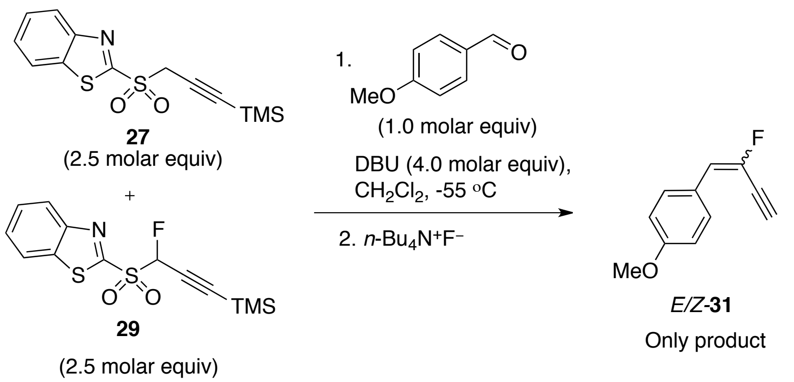


Figure 3. Determination of stereochemistry in **43**.

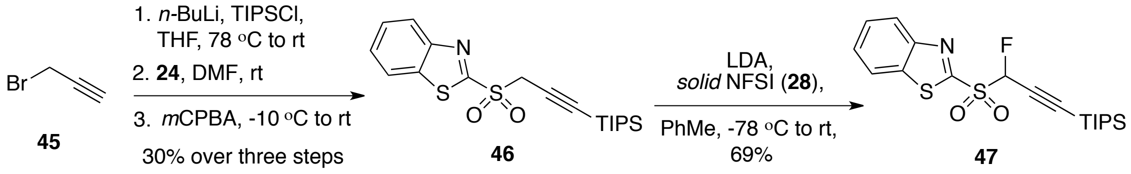
We have previously demonstrated the higher reactivity of α-fluoro substituted Julia-Kocienski reagents in olefination reactions, compared to their protio analogs. To test the relative reactivities of the protio and fluoro analogs **27** and **29**, respectively, a competitive experiment was performed under DBU-mediated conditions (Scheme 9). A one-pot reaction of 4-methoxybenzaldehyde with 2.5 molar equiv of each, **27** and **29**, gave fluoroenyne (*E*/*Z*)-**31** as the only product. Thus, the higher reactivity of Julia reagents upon fluorine substitution was again supported.

Scheme 9. Competitive Reactivity of the Fluoro and Protio Julia-Kocienski Analogs



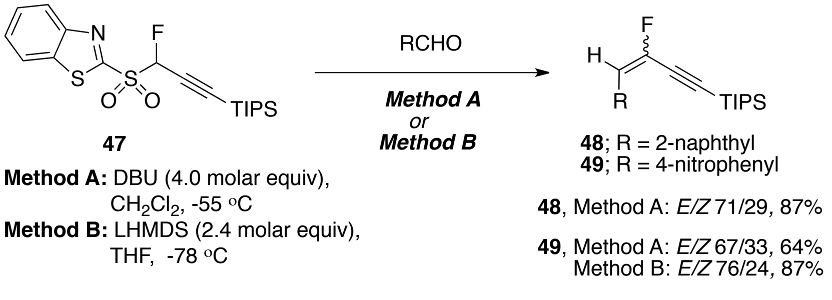
To assess whether size of the silyl protecting group would influence the stereoselectivity of the condensation reactions, triisopropylsilyl (TIPS) protected fluoropropargyl BT-sulfone **47** was synthesized as shown in Scheme 10. Briefly, TIPS-protected propargyl bromide[54] (that was obtained from propagyl bromide **45**) was reacted with the sodium salt of 2-mercaptobenzothiazole **24**, followed by *m*CPBA oxidation to furnish TIPS-protected BT-sulfone **46** (30% yield over three steps, Scheme 10). Metalation-electrophilic fluorination of **46** under heterogeneous conditions provided TIPS-protected fluoropropargyl BT-sulfone **47** in 69% yield. TIPS-protected fluoropropargyl sulfone **47** was found to be more stable as compared to the TMS-derivative **29**, and after workup the crude reaction mixture could be directly loaded to a silica gel column for purification. Also, the higher stability of **47** compared to **29**, was also reflected in the condensation reactions, where a lower molar excess of sulfone **47** was required for complete conversion of the aldehyde in the condensation reaction, compared to **29** (1.3 versus 2.0-2.5 molar equiv).

Scheme 10. Synthesis of TIPS-protected Fluoropropargyl BT-Sulfone



Fluoropropargyl BT-sulfone **47** was subjected to condensation reactions with 2-naphthaldehyde and 4-nitrobenzaldehyde using Method A and/or Method B (Scheme 11). Since no partial removal of the TIPS-group was observed in the condensation reactions, products were isolated as the TIPS-protected enynes. In all cases tested, both TIPS-protected reagent **47** and the TMS-protected **29** gave comparable yields of products. Similarly, stereoselectivities were also comparable for LHMDS-mediated reactions and for the DBU-mediated reaction with 2-naphthaldehyde. However, DBU-mediated reaction of sulfone **47** with 4-nitrobenzaldehyde gave moderate *E*-selectivity, whereas no selectivity was observed with **29** (compare to Table 2, entry 5).

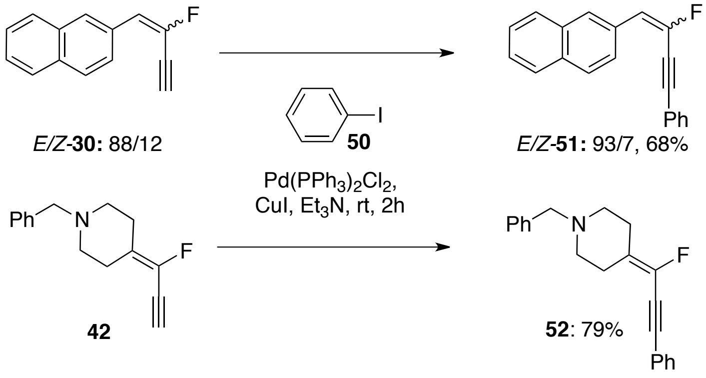
Scheme 11. Condensation Reactions of TIPS-protected Fluoropropargyl BT-Sulfone **47**



It is plausible that the steric bulk of triisopropylsilyl group decreases the rate of spirocyclization of the adducts (obtained upon addition of the carbanion from **47** to the aldehyde) as compared to spirocyclization of adducts resulting from **29**. If the addition is reversible, the slow rate of spirocyclization would allow for some equilibration between *syn*/*anti* adducts of the less stable[55] 4-nitrobenzaldehyde. Since *syn* adduct undergoes spirocylization faster than *anti*, the higher *cis* selectivity (*E*-isomer of fluoroenyne*)* would be obtained.

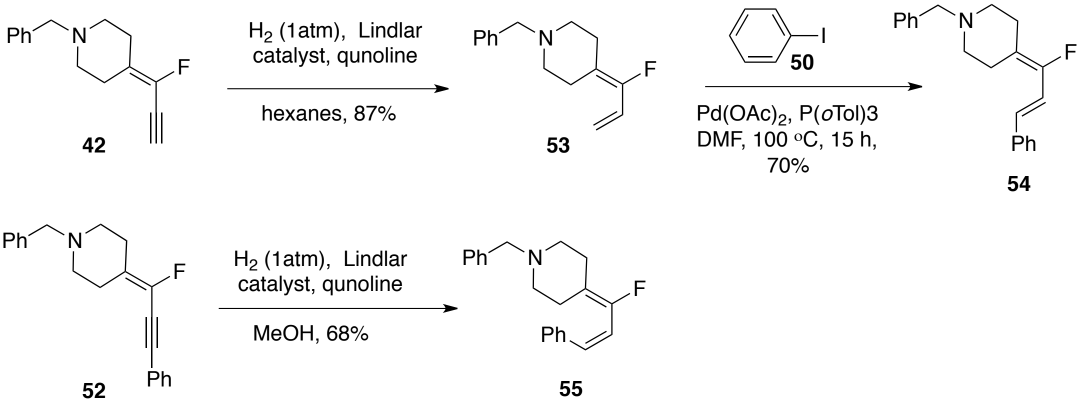
HWE olefination for the synthesis of internal fluoroenynes containing phenyl and alkyl-substituted alkynes, gave poor yields of products and no selectivity.[35,36] Since in the present case, the terminal fluoroenynes were obtained with high *E*-selectivity, we were interested in exploring the possibility of converting them to internal fluoroenynes using Sonogashira coupling reaction. For this, compounds **30** and **42** were subjected to Sonogashira couplings with phenyl iodide **50** and phenyl-derived fluoroenynes **51** and **52**, respectively, were obtained in good yields (Scheme 12). In the reaction of *E*/*Z*-**30**, some minor change in the *E*/*Z* ratio was observed that might be due to the loss of the minor isomer in the workup or purification.

Scheme 12. Sonogashira Coupling of Terminal Fluoroenynes



Further, utility of the terminal fluoroenynes for the synthesis of regiospecifically fluorinated dienes was also demonstrated. Lindlar reduction of compound **42** produced terminal fluorodiene **53** in high yield of 87% (Scheme 13). Heck reaction[56-58] of this fluorodiene with phenyl iodide under the conditions reported by Lakshman et al.[58] gave fluorodiene **54** in good 70% yield and with *trans* geometry at the newly formed double bond (Scheme 13). On the other hand, fluorodiene **55**, with *cis* geometry at the new olefinic bond, was obtained by Lindlar reduction of internal fluoroenyne **52** (Scheme 13).

Scheme 13. Synthesis of Isomeric Fluorodienes



1.3 CONCLUSION

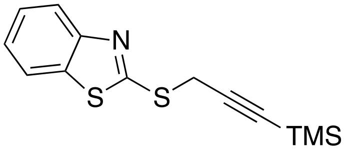
Synthesis of conjugated 2-fluoroenynes was achieved by fluoro-Julia-Kocienski olefination. The requisite reagents, TMS- and TIPS-protected fluoropropargyl BT-sulfones were synthesized from the corresponding sulfones via heterogeneous metalation-electrophilic fluorination using *N*-fluorobenzenesulfonimide. Both reagents reacted with aldehydes under mild, DBU-mediated conditions, or with LHMDS. High yields of conjugated 2-fluoroenynes were obtained under both conditions, with moderate to excellent *E*-stereoselectivity. TMS-protected fluoroenynes were deprotected in situ, due to lability of the TMS group. This was not the case with the TIPS-protected products, which were isolated with the silyl group present. Higher *E*-stereoselectivity was obtained when LHMDS was used as base. Ketones were shown to react as well.

To demonstrate the synthetic utility of terminal fluoroenynes, two were converted to internal fluorenynes via Sonogashira reaction. Further, the use of fluoroenynes for the preparation of stereoisomeric fluorodienes was also shown. For this, 1-benzyl-4-(1-fluoroprop-2-ynylidene)piperidine was subjected to Sonogashira coupling and partial reduction of the alkyne, to yield the (*Z*)-1-benzyl-4-(1-fluoro-3-phenylallylidene)piperidine. The *E*-isomer was synthesized by conversion of 1-benzyl-4-(1-fluoroprop-2-ynylidene)piperidine to diene via partial reduction of the triple bond, followed by Heck reaction at the terminal alkene.

EXPERIMENTAL SECTION

THF was distilled over $LiAlH_4$ and then over sodium, toluene was distilled over sodium, and CH_2Cl_2 was distilled over $CaCl_2$. For reactions performed under a nitrogen atmosphere, glassware was dried with heat gun under vacuum. LDA (2.0 M solution in heptane/THF/EtPh) and LHMDS (1.0 M in THF) were obtained from commercial sources. All other reagents were obtained from commercial sources and used without further purification. *N*-fluorobenzenesulfonimide (NFSI) is commercially available. Thin layer chromatography was performed either on aluminum foil-backed silica gel plates (200 μm), or glass-backed silica gel plates (250 μm). Column chromatographic purifications were performed on 200–300 mesh silica gel. ^{1}H NMR spectra were recorded at 500 MHz and were referenced to residual solvent. ^{13}C NMR spectra were recorded at 125 MHz and are referenced to the carbon resonance of the deuterated solvent. ^{19}F NMR spectra were recorded at 282 MHz with $CFCl_3$ as internal standard. Chemical shifts (δ) are reported in parts per million and coupling constants (J) are in hertz (Hz).

Synthesis of 2-[3-(trimethylsilyl)prop-2-ynylthio]benzo[*d*]thiazole (26)[52]



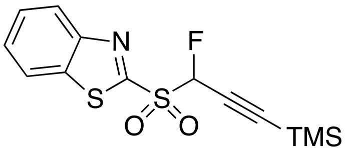
To a solution of (3-bromoprop-1-ynyl)trimethylsilane **25** (2.00 g, 10.5 mmol, 1 molar equiv) in DMF (40.0 mL) at room temperature, the sodium salt of 2-mercapto-1,3-benzothiazole **24** (2.57 g, 13.6 mmol, 1.3 molar equiv) was added and the reaction mixture was stirred for 5 h. The reaction mixture was diluted with water and extracted with EtOAc (3x). The combined organic layer was thoroughly washed with water and then with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield 2.81 g (97%) of crude 2-[3-

(trimethylsilyl)prop-2-ynylthio]benzo[*d*]thiazole **26** as a light yellow solid, that was subjected to oxidation without further purification. R_f (10% EtOAc in hexanes) = 0.51. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, 1H, Ar-H, J = 8.0 Hz), 7.78 (d, 1H, Ar-H, J = 8.0 Hz), 7.43 (t, 1H, Ar-H, J = 7.5 Hz), 7.32 (t, 1H, Ar-H, J = 7.5 Hz), 4.16 (s, 2H, CH_2), 0.15 (s, 9H, $SiMe_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 153.2, 135.6, 126.3, 124.6, 121.9, 121.2, 99.6, 89.9, 23.1, –0.05.

Synthesis of 2-[3-(Trimethylsilyl)prop-2-ynylsulfonyl]benzo[*d*]thiazole (27)

To a stirring solution of 2-[3-(trimethylsilyl)prop-2-ynylthio]benzo[*d*]thiazole **26** (2.00 g, 7.22 mmol) in $CHCl_3$ (30.0 mL) at –10 °C (ice-salt) a solution of *m*-CPBA (3.74 g, 21.7 mmol, 3 molar equiv) in $CHCl_3$ (55.0 mL) was added dropwise. After complete addition, the mixture was stirred for an additional 10 min at –10 °C, allowed to warm to room temperature and stirred for 15 h. The reaction was quenched with 35 mL of saturated aqueous $NaHCO_3$ solution, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layer was thoroughly washed with water and finally with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield 2.19 g (98%) of 2-[3-(trimethylsilyl)prop-2-ynylsulfonyl]benzo[*d*]thiazole (**27**) of crude product as an off-white solid that was subjected to fluorination without further purification. R_f (10% EtOAc in hexanes) = 0.30. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (d, 1H, Ar-H, J = 8.0 Hz), 8.04 (d, 1H, Ar-H, J = 8.0 Hz), 7.68-7.60 (m, 2H, Ar-H), 4.39 (s, 2H, CH_2), 0.03 (s, 9H, $SiMe_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 152.7, 137.4, 128.4, 127.9, 125.8, 122.4, 95.8, 90.8, 48.7, –0.05.

Synthesis of 2-[1-Fluoro-3-(trimethylsilyl)prop-2-ynylsulfonyl]benzo[d]thiazole (29)



A stirring solution of sulfone **27** (2.00 g, 6.46 mmol, 1 molar equiv) in dry toluene (45.0 mL) was cooled to –78 ˚C (dry ice/*iso*PrOH) under nitrogen. LDA (3.23 mL, 6.46 mmol, 1.0 molar equiv) was added and after 12 min, solid NFSI **28** (2.24 g, 7.11 mmol, 1.1 molar equiv) was added. The reaction mixture was allowed to stir at –78 ˚C for 50 min, then warmed to room temperature and the stirring was continued for an additional 50 min. Saturated aq NH_4Cl (20 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with EtOAc (25–30 mL, 3 x) and the combined organic layer was washed with saturated aq $NaHCO_3$, water, and brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude reaction mixture (brown oil) was suspended in toluene (7 mL) and passed through a short silica column (100–200 mesh, 6 cm x 3 cm) using toluene (100 mL) as eluent. The solvent was removed under reduced pressure and the crude product (colorless oil) was purified by column chromatography (19 cm x 2.8 cm, 10% EtOAc in hexanes) to yield 1.32 g (62%) of **29** as an off-white solid. R_f (10% EtOAc in hexanes) = 0.30. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (d, 1H, Ar-H, J = 8.3 Hz), 8.05 (d, 1H, Ar-H, J = 7.8 Hz), 7.69-7.63 (m, 2H, Ar-H), 6.12 (d, 1H, CHF, $^2J_{FH}$ = 48.8 Hz), 0.17 (s, 9H, SiMe3). ^{13}CNMR (125 MHz, $CDCl_3$): δ 160.9, 152.6, 137.6, 128.8, 128.0, 125.9, 122.3, 104.5 (d, $3J_{CF}$ = 8.2 Hz), 91.8 (d, $^1J_{CF}$ = 222.0 Hz), 89.6 (d, 2JCF = 23.4 Hz), 0.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ –164.6 (d, $^2J_{FH}$ = 48.8 Hz). HRMS (ESI) calcd. for $C_{13}H_{15}FNO_2S_2Si$ $[M + H]^+$ 328.0292, found 328.0296.

General procedures for condensations of sulfone 29 with aldehydes

Method A. A solution of aldehyde (0.500 mmol, 1.0 molar equiv) and DBU (2.00 mmol, 4.0 molar equiv) in CH_2Cl_2 (6.8 mL per mmol of aldehyde) was cooled under nitrogen to –55 °C (dry ice/*iso*PrOH). A solution of fluoropropargyl sulfone **29** (1.00 mmol, 2.0 molar equiv) in

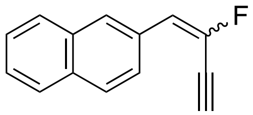
CH_2Cl_2 (2.0 mL per mmol of sulfone) was added via a syringe and the reaction mixture turned dark. The reaction mixture was stirred for 5 min and checked by TLC (10% EtOAc in hexanes). If TLC showed unreacted aldehyde, fluoropropargyl sulfone **29** (0.25 or 0.50 mmol, 0.5 or 1.0 molar equiv) in CH_2Cl_2 (2.0 mL per mmol of sulfone) was added via a syringe and the reaction mixture was stirred for another 5 min. TBAF (1.0 M solution in THF, 0.100 mL, 0.20 molar equiv; for *E*/*Z*-**31**, 0.090 mL, 0.18 molar equiv was used) was added and the reaction mixture was concentrated under reduced pressure. The crude reaction mixture was analyzed by ^{19}F NMR, and the combined *E*/*Z* product mixture was isolated by column chromatography (10% EtOAc in hexanes, unless stated otherwise).

Method B. A solution of aldehyde (0.500 mmol, 1.0 molar equiv) and sulfone **29** (1.00 mmol, 2.0 molar equiv) in dry THF (26.0 mL per mmol of aldehyde) was cooled under nitrogen to –78 °C (dry ice/*iso*PrOH). LHMDS (1.0 M solution in THF, 1.2 mL, 2.4 molar equiv) was added and upon addition, the reaction mixture turned intense orange. The reaction mixture was stirred at –78 °C for 5 min and checked by TLC (10% EtOAc in hexanes), which showed disappearance of the aldehyde. TBAF (1.0 M solution in THF, 1.0 mL, 2.0 molar equiv) was added and the reaction mixture was allowed to stir for another 5 min. Saturated aq NH_4Cl was added and the mixture was poured into EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude reaction mixture was analyzed by ^{19}F NMR, and the combined *E*/*Z* product mixture was isolated by column chromatography (10% EtOAc in hexanes, unless stated otherwise).

General procedure for condensations of sulfone 29 with ketones

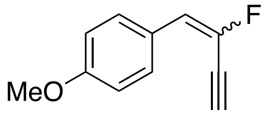
A stirred solution of ketone (0.300 mmol, 1.0 molar equiv) and sulfone **29** (294 mg, 0.900 mmol, 3.0 molar equiv) in dry THF (2.5 mL) was cooled under nitrogen to –78 °C (dry ice/*iso*PrOH). LHMDS (1.0 M solution in THF, 1.5 mL, 5.0 molar equiv) was added, the reaction mixture was stirred at –78 °C for 2 h and checked by TLC (20% EtOAc in hexanes for **42** and 10% EtOAc in hexanes for **43**), which showed disappearance of the ketone. TBAF (1.0 M solution in THF, 0.900 mL, 3.0 molar equiv) was added, and the reaction mixture was allowed to stir for another 5 min. Saturated aq NH_4Cl was added and the mixture was poured into EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude reaction mixture was analyzed by ^{19}F NMR, and the combined *E*/*Z* product mixture was isolated by column chromatography (10% EtOAc in hexanes).

Synthesis of (*E*/*Z*)-2-(2-Fluorobut-1-en-3-ynyl)naphthalene (*E*/*Z*-30)



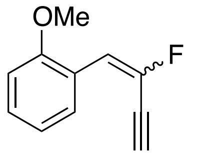
Method B: 2-Naphthaldehyde: 78.0 mg (0.500 mmol, 1.0 molar equiv);sulfone **29**: 327 mg (1.00 mmol, 2.0 molar equiv); LHMDS: 1.2 mL (1 M, 1.2 mmol, 2.4 molar equiv); THF (13.0 mL); TBAF (1.0 M solution in THF, 1.0 mL, 2.0 molar equiv). Eluting solvent for column chromatography: 10% EtOAc in hexanes. Yield of *E*/*Z*-**30**: 95.2 mg (97%), as a white solid, *E*/*Z* ratio: 88/12. R_f (10% EtOAc in hexanes) = 0.41. ^1H NMR (500 MHz, $CDCl_3$): δ 8.01 (s, 1H, Ar-H, *E*-isomer), 7.95 (s, 1H, Ar-H, *Z*-isomer), 7.85-7.80 (m, 3H, Ar-H, both *E* and *Z*-isomers and 1H, Ar-H, *E*-isomer), 7.66 (d, 1H, Ar-H, J = 8.5 Hz, *Z*-isomer), 7.49-7.48 (m, 2H, Ar-H, both *E* and *Z*-isomer), 6.84 (d, 1H, =CH, $^3J_{\mathrm{FH}}$ = 17.4 Hz, *E*-isomer), 6.27 (d, 1H, =CH, $^3J_{\mathrm{FH}}$ = 35.1 Hz, *Z*-isomer), 3.67 (d, 1H, ≡CH, $^4J_{\mathrm{FH}}$ = 4.3 Hz, *E*-isomer), 3.34 (d, 1H, ≡CH, $^4J_{\mathrm{FH}}$ = 3.7 Hz, *Z*-isomer). ^{19}F NMR (282 MHz, CDCl$_3$): δ –104.69 (d, $^3J_{\mathrm{FH}}$ = 15.3 Hz, *E*-isomer), –107.17 (d, $^3J_{\mathrm{FH}}$ = 36.6 Hz, *Z*-isomer). HRMS (APPI) calcd for $C_{14}H_9F$ $[M]^+$ 196.0683, found 196.0682.

Synthesis of 1-(2-Fluorobut-1-en-3-ynyl)-4-methoxybenzene (*E*/*Z*-31)



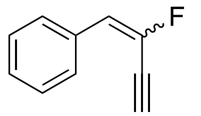
Method A: 4-Methoxybenzaldehyde: 68.0 mg (0.500 mmol); sulfone **29**: 409 mg (1.25 mmol, 2.5 molar equiv); DBU: 305 mg (2.0 mmol, 4.0 molar equiv); CH_2Cl_2: 5.9 mL; TBAF (1.0 M solution in THF, 0.090 mL, 0.18 molar equiv). Eluting solvent for column chromatography: 10% EtOAc in hexanes. Yield of *E*/*Z*-**31**: 80.5 mg (92%), as a light-yellow liquid), *E*/*Z* ratio: 81/19. R_f (10% EtOAc in hexanes) = 0.47. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.58 (d, 2H, Ar-H, J = 8.5 Hz, *E*-isomer), 7.46 (d, 2H, Ar-H, J = 8.0 Hz, *Z*-isomer), 6.89-6.88 (m, 2H, Ar-H, both *E* and *Z*-isomers), 6.63 (d, 1H, =CH, $^3J_{\mathrm{FH}}$ = 17.5 Hz, *E*-isomer), 6.06 (d, 1H, ArCH, $^3J_{\mathrm{FH}}$ = 35.5 Hz, *Z*-isomer), 3.82 (s, 3H, OCH$_3$, both *E* and *Z*-isomers), 3.63 (d, 1H, ≡CH, $^4J_{\mathrm{FH}}$ = 3.7 Hz, *E*-isomer), 3.29 (d, 1H, ≡CH, $^4J_{\mathrm{FH}}$ = 2.8 Hz, *Z*-isomer). ^{19}F NMR (282 MHz, CDCl$_3$): δ –108.90 (d, $^3J_{\mathrm{FH}}$ = 18.3 Hz, *E*-isomer), –110.93 (d, $^3J_{\mathrm{FH}}$ = 33.6 Hz, *Z*-isomer). HRMS (APPI) calcd for $C_{11}H_9FO$ $[M]^+$ 176.0632, found 176.0629.

Synthesis of 1-(2-Fluorobut-1-en-3-ynyl)-2-methoxybenzene (*E*/*Z*-32*)*



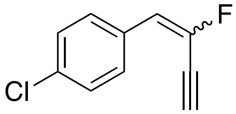
Method B: 2-Methoxybenzaldehyde: 68.0 mg (0.500 mmol); sulfone **29**: 327 mg (1.00 mmol, 2.0 molar equiv); LHMDS: 1.2 mL (1 M, 1.2 mmol, 2.4 molar equiv); THF (13.0 mL); TBAF (1.0 M solution in THF, 1.0 mL, 2.0 molar equiv). Eluting solvent for column chromatography: 10% EtOAc in hexanes. Yield of *E*/*Z*-**32**: 76.7 mg (87%), as a colorless liquid, *E*/*Z* ratio: 90/10. R_f (10% EtOAc in hexanes) = 0.47. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.94 (d, 1H, Ar-H, J = 7.4 Hz, *E*-isomer), 7.79 (d, 1H, Ar-H, J = 7.4 Hz, *Z*-isomer), 7.29-7.28 (m, 1H, Ar-H, both *E* and *Z*-isomers), 7.05 (d, 1H, =CH, $^3J_{FH}$ = 18.0 Hz, *E*-isomer), 6.98-6.94 (m, 1H, Ar-H, both *E* and *Z*-isomers), 6.89-6.88 (m, 1H, Ar-H, both *E* and *Z*-isomers), 6.62 (d, 1H, =CH, $^3J_{FH}$ = 36.8 Hz, *Z*-isomer), 3.85 (s, 3H, OCH$_3$, both *E* and *Z*-isomers), 3.52 (d, 1H, ≡CH, $^4J_{FH}$ = 4.1 Hz), 3.28 (d, 1H, ≡CH, $^4J_{FH}$ = 3.7 Hz). ^{19}F NMR (282 MHz, CDCl$_3$): δ –105.33 (d, $^3J_{FH}$ = 18.3 Hz, *E*-isomer), –109.16 (d, $^3J_{FH}$ = 36.6 Hz, *Z*-isomer). HRMS (APPI) calcd for $C_{11}H_9FO$ $[M]^+$ 176.0632, found 176.0635.

Synthesis of (2-Fluorobut-1-en-3-ynyl)benzene (*E*/*Z*-33)



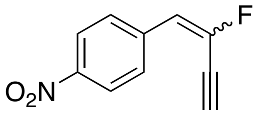
Method B: Benzaldehyde: 53.0 mg (0.500 mmol); sulfone **29**: 327 mg (1.00 mmol, 2 molar equiv); LHMDS: 1.2 mL (1.0 M, 1.2 mmol, 2.4 molar equiv); THF (13.0 mL); TBAF (1.0 M solution in THF, 1.00 mL, 2.0 molar equiv). Eluting solvent for column chromatography: 10% EtOAc in hexanes. Yield of *E*/*Z*-**33**: 43.0 mg (59%), as a colorless liquid, *E*/*Z* ratio: 94/6. R_f (10% EtOAc in hexanes) = 0.54. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.63 (d, 2H, Ar-H, J = 7.4 Hz, *E*-isomer), 7.51 (d, 2H, Ar-H, *J* = 7.4 Hz, *Z*-isomer), 7.37-7.34 (m, 2H, Ar-H, both *E* and *Z*-isomers), 7.32-7.28 (m, 1H, Ar-H, both *E* and *Z*-isomers), 6.68 (d, 1H, =CH, $^3J_{FH}$ = 17.0 Hz, *E*-isomer), 6.11 (d, 1H, =CH, $^3J_{FH}$ = 35.0 Hz, *Z*-isomer), 3.61 (d, 1H, ≡CH, $^4J_{FH}$ = 4.6 Hz, *E*-isomer), 3.29 (d, 1H, ≡CH, $^4J_{FH}$ = 3.7 Hz, *Z*-isomer). ^{19}F NMR (282 MHz, CDCl$_3$): δ –105.32 (d, $^3J_{FH}$ = 15.3 Hz, *E*-isomer), –107.42 (d, $^3J_{FH}$ = 33.6 Hz, *Z*-isomer). HRMS (APPI) calcd for $C_{10}H_7F$ [M]$^+$ 146.0526, found 146.0525.

Synthesis of 1-Chloro-4-(2-fluorobut-1-en-3-ynyl)benzene (*E*/*Z*-34)



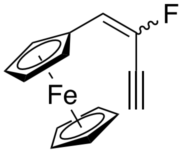
Method A: 4-Chlorobenzaldehyde: 70.3 mg (0.500 mmol); sulfone **29**: 327 mg (1.00 mmol, 2.0 molar equiv); DBU: 305 mg (2.00 mmol, 4.0 molar equiv); CH$_2$Cl$_2$: 5.4 mL; TBAF (1.0 M solution in THF, 0.100 mL, 0.20 molar equiv). Eluting solvent for column chromatography: 10% EtOAc in hexanes. Yield of *E*/*Z*-**34**: 73.4 mg (81%), as an orange liquid, *E*/*Z* ratio: 70/30. R_f (10% EtOAc in hexanes) = 0.47. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.56 (d, 2H, Ar-H, *J* = 8.8 Hz, *E*-isomer), 7.44 (d, 2H, Ar-H, *J* = 8.3 Hz, *Z*-isomer), 7.33-7.31 (m, 2H, Ar-H, both *E* and *Z*-isomers), 6.62 (d, 1H, =CH, $^3J_{FH}$ = 17.1 Hz, *E*-isomer), 6.06 (d, 1H, =CH, $^3J_{FH}$ = 34.2 Hz, *Z*-isomer), 3.63 (d, 1H, ≡CH, $^4J_{FH}$ = 3.9 Hz, *E*-isomer), 3.31 (d, 1H, ≡CH, $^4J_{FH}$ = 3.9 Hz, *Z*-isomer). ^{19}F NMR (282 MHz, CDCl$_3$): δ –104.25 (d, $^3J_{FH}$ = 15.3 Hz, *E*-isomer), –106.45 (d, $^3J_{FH}$ = 33.6 Hz, *Z*-isomer). HRMS (APPI) calcd for $C_{10}H_6ClF$ [M]$^+$ 180.0137, found 180.0139.

Synthesis of 1-(2-Fluorobut-1-en-3-ynyl)-4-nitrobenzene (*E*/*Z*-35)



Method A: 4-Nitrobenzaldehyde: 75.6 mg (0.500 mmol); sulfone **29**: 409 mg (1.25 mmol, 2.5 molar equiv); DBU: 305 mg (2.0 mmol, 4.0 molar equiv); CH_2Cl_2: 5.9 mL; TBAF (1.0 M solution in THF, 0.100 mL, 0.20 molar equiv). Eluting solvent for column chromatography: 10% EtOAc in hexanes. Yield of *E*/*Z*-**35**: 56.8 mg (59%), as a yellow solid, *E*/*Z* ratio: 51/49. R_f (20% EtOAc in hexanes) = 0.53. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, 2H, Ar-H, J = 8.6 Hz, both *E* and *Z*-isomers), 7.79 (d, 2H, Ar-H, J = 8.9 Hz, *E*-isomer), 7.65 (d, 2H, Ar-H, J = 8.8 Hz, *Z*-isomer), 6.72 (d, 1H, =CH, $^3J_{FH}$ = 15.9 Hz, *E*-isomer), 6.18 (d, 1H, =CH, $^3J_{FH}$ = 33.6 Hz, *Z*-isomer), 3.70 (d, 1H, ≡CH, $^4J_{FH}$ = 4.3 Hz, *E*-isomer), 3.38 (d, 1H, ≡CH, $^4J_{FH}$ = 4.0 Hz, *Z*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$): δ –97.63 (d, $^3J_{FH}$ = 15.3 Hz, *E*-isomer), –100.80 (d, $^3J_{FH}$ = 33.6 Hz, *Z*-isomer). HRMS (ESI) calcd for $C_{10}H_7FNO_2$ $[M+H]^+$ 192.0455, found 192.0462.

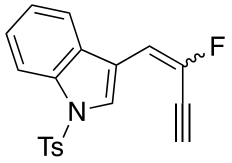
Synthesis of (2-Fluorobut-1-en-3-ynyl)ferrocene (*E*/*Z*-36)



Method A: Ferrocenecarboxaldehyde: 107 mg (0.500 mmol); sulfone **29**: 409 mg (1.25 mmol, 2.5 molar equiv); DBU: 305 mg (2.0 mmol, 4.0 molar equiv); CH_2Cl_2: 5.9 mL; TBAF (1.0 M solution in THF, 0.100 mL, 0.20 molar equiv). Eluting solvent for column chromatography: 10% EtOAc in hexanes. Yield of *E*/*Z*-**36**: 121 mg (95%), as an orange solid, *E*/*Z* ratio: 83/17. R_f (10% EtOAc in hexanes) = 0.53. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.41 (d, 1H, =CH, $^3J_{FH}$ = 15.6 Hz, *E*-isomer), 5.94 (d, 1H, =CH, $^3J_{FH}$ = 35.1 Hz, *Z*-isomer), 4.62 (s, 2H, Ar-H, *E*-isomer), 4.49 (d, 2H, Ar-H, J = 1.5 Hz, *Z*-isomer), 4.30-4.29 (m, 2H, Ar-H, both *E* and *Z*-isomers), 4.17 (s, 5H, Ar-H, *E*-isomer), 4.16 (s, 5H, Ar-H, *Z*-isomer), 3.66 (d, 1H, ≡CH, $^4J_{FH}$ = 4.0 Hz), 3.34 (d, 1H, ≡CH, $^4J_{FH}$ = 3.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ –111.06 (d, $^3J_{FH}$ = 15.3 Hz, *E*-isomer), –

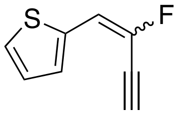
111.97 (d, $^3J_{FH}$ = 33.6 Hz, *Z*-isomer). HRMS (ESI) calcd for $C_{14}H_{11}FFe$ $[M]^+$ 254.0189, found 254.0191.

Synthesis of 3-(2-Fluorobut-1-en-3-ynyl)-1-Tosyl-1*H*-Indole (*E*/*Z*-37)



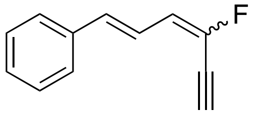
Method A: 1-Tosyl-1*H*-indole-3-carboxaldehyde: 150 mg (0.500 mmol); sulfone **29**: 490 mg (1.50 mmol, 3.0 molar equiv); DBU: 305 mg (2.0 mmol, 4.0 molar equiv); CH_2Cl_2: 6.4 mL; TBAF (1.0 M solution in THF, 0100 mL, 0.20 molar equiv). Eluting solvent for column chromatography: CH_2Cl_2. Yield of *E*/*Z*-**37**: 162 mg (95%), as an off-white solid, *E*/*Z* ratio: 75/25. R_f (CH_2Cl_2) = 0.74. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (s, 1H, Ar-H, *E*-isomer), 8.00-7.97 (m, 1H, Ar-H, both *E* and *Z*-isomers), 7.94 (s, 1H, Ar-H, *Z*-isomer), 7.80-7.77 (m, 2H, Ar-H, both *E* and *Z*-isomers), 7.55 (d, 1H, Ar-H, *J* = 8.0 Hz, *Z*-isomer), 7.51 (d, 1H, Ar-H, *J* = 7.5 Hz, *E*-isomer), 7.36-7.33 (m, 1H, Ar-H, both *E* and *Z*-isomers), 7.29-7.23 (m, 3H, Ar-H, both *E* and *Z*-isomers), 6.75 (d, 1H, =CH, $^3J_{FH}$ = 14.3 Hz, *E*-isomer), 6.31 (d, 1H, =CH, $^3J_{FH}$ = 35.0 Hz, *Z*-isomer), 3.83 (d, 1H, ≡CH, $^4J_{FH}$ = 3.7 Hz, *E*-isomer), 3.39 (d, 1H, ≡CH, $^4J_{FH}$ = 3.7 Hz, *Z*-isomer), 2.35 (s, 3H, CH_3, both *E* and *Z*-isomers). ^{19}F NMR (282 MHz, $CDCl_3$): δ –106.89 (d, $^3J_{FH}$ = 15.3 Hz, *E*-isomer), –100.96 (d, $^3J_{FH}$ = 33.6 Hz, *Z*-isomer). HRMS (ESI) calcd for $C_{19}H_{15}FNO_2S$ $[M+H]^+$ 340.0802, found 340.0806.

Synthesis of (*E*/*Z*)-2-(2-Fluorobut-1-en-3-ynyl)thiophene (*E*/*Z*-38)



Method A: 2-Thiophenecarboxaldehyde 56.1 mg (0.500 mmol), sulfone **29**: 409 mg, (1.25 mmol, 2.5 molar equiv); DBU: 305 mg (2.00 mmol, 4.0 molar equiv), CH_2Cl_2: 5.90 mL; TBAF (1.0 M solution in THF, 0.100 mL, 0.20 molar equiv). Eluting solvent for column chromatography: 10% EtOAc in hexanes. Yield of *E*/*Z*-**38**: 59.0 mg (78%), as a light-brown liquid, *E*/*Z* ratio: 75/25. R_f (10% EtOAc in hexanes) = 0.42. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, 1H, Ar-H, J = 4.6 Hz, *Z*-isomer), 7.31(d, 1H, Ar-H, J = 5.1 Hz, *E*-isomer), 7.24 (d, 1H, Ar-H, J = 2.8 Hz, *E*-isomer), 7.15 (d, 1H, Ar-H, J = 3.2 Hz, *Z*-isomer), 7.04-7.02 (m, 1H, Ar-H, *E* and *Z*-isomer), 6.89 (d, 1H, =CH, $^3J_{FH}$ = 14.3 Hz, *E*-isomer), 6.42 (d, 1H, =CH, $^3J_{FH}$ = 33.6 Hz, *Z*-isomer), 3.85 (d, 1H, ≡CH, $^4J_{FH}$ = 4.1 Hz, *E*-isomer), 3.38 (d, 1H, ≡CH, $^4J_{FH}$ = 3.7 Hz, *Z*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$): δ –111.82 (d, $^3J_{FH}$ = 15.3 Hz, *E* isomer), –106.40 (d, $^3J_{FH}$ = 33.6 Hz, *Z*-isomer). HRMS (APPI) calcd for C_8H_5FS $[M]^+$ 152.0091, found 152.0089.

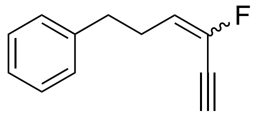
Synthesis of (4-Fluorohexa-1,3-dien-5-ynyl)benzene (*E*/*Z*-39)



Method A: Cinnamaldehyde: 66.1 mg (0.500 mmol); sulfone **29**: 490 mg (1.50 mmol, 3.0 molar equiv); DBU: 305 mg (2.0 mmol, 4.0 molar equiv); CH_2Cl_2: 6.4 mL; TBAF (1.0 M solution in THF, 0.100 mL, 0.20 molar equiv). Eluting solvent for column chromatography: 10% EtOAc in hexanes. Yield of *E*/*Z*-**39**: 82.1 mg (95%), as a deep-orange liquid, *E*/*Z* ratio: 72/28. R_f (30% EtOAc in hexanes) = 0.60. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.43 (m, 2H, Ar-H, both *E* and *Z*-isomers), 7.35-7.32 (m, 2H, Ar-H, both *E* and *Z*-isomers), 7.28-7.26 (m, 1H, Ar-H, both *E* and *Z*-isomers), 7.07 (dd, 1H, =CH, J = 15.7; 11.1 Hz, *Z*-isomer), 6.88 (dd, 1H, =CH, J = 15.7; 11.5 Hz, *E*-isomer), 6.68 (d, 1H, ArCH, J = 15.7 Hz, *E*-isomer), 6.63 (d, 1H, ArCH, J = 15.7 Hz, *Z*-

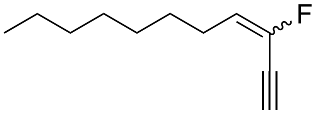
isomer), 6.47 (t, 1H, =CH, ${}^3J_{FH}$, ${}^3J_{HH}$ = 12.0 Hz, *E*-isomer), 6.04 (dd, 1H, =CH, ${}^3J_{FH}$ = 30.9 Hz; ${}^3J_{HH}$ = 11.1, *Z*-isomer), 3.68 (d, 1H, ≡CH, ${}^4J_{FH}$ = 3.2 Hz, *E*-isomer), 3.35 (d, 1H, ≡CH, ${}^4J_{FH}$ = 3.2 Hz, *Z*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$): δ –110.55 (d, ${}^3J_{FH}$ = 12.2, *E*-isomer), –111.43 (d, ${}^3J_{FH}$ = 30.5, *Z*-isomer). HRMS (APPI) calcd for $C_{12}H_9F$ $[M]^+$ 172.0683, found 172.0683.

Synthesis of (4-Fluorohex-3-en-5-ynyl)benzene (*E*/*Z*-40)



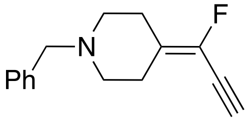
Method A: 3-Phenylpropanal: 67.1 mg (0.500 mmol); sulfone **29**: 327 mg (1.0 mmol, 2.0 molar equiv); DBU: 305 mg (2.0 mmol, 4.0 molar equiv); CH_2Cl_2: 5.4 mL; TBAF (1.0 M solution in THF, 0.100 mL, 0.20 molar equiv). Eluting solvent for column chromatography: 10% EtOAc in hexanes. Yield of *E*/*Z*-**40**: 46.6 mg (54%), as a light-greenish liquid, *E*/*Z* ratio: 80/20. R_f (10% EtOAc in hexanes) = 0.59. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.18 (m, 5H, Ar-H, both *E* and *Z*-isomers), 5.69 (dt, 1H, =CH, ${}^3J_{FH}$ = 14.3 Hz, ${}^3J_{HH}$ = 8.3 Hz, *E*-isomer), 5.31 (dt, 1H, =CH, ${}^3J_{FH}$ = 33.6 Hz, ${}^3J_{HH}$ = 7.8 Hz, *Z*-isomer), 3.34 (d, 1H, ≡CH, ${}^4J_{FH}$ = 3.2 Hz, *E*-isomer), 3.08 (d, 1H, ≡CH, ${}^4J_{FH}$ = 3.7 Hz, *Z*-isomer), 2.74-2.69 (m, 2H, CH_2, both *E* and *Z*-isomers), 2.53-2.45 (m, 2H, CH_2, both *E* and *Z*-isomers). ^{19}F NMR (282 MHz, $CDCl_3$): δ –110.43 (d, ${}^3J_{FH}$ = 12.2 Hz, *E*-isomer), –112.51 (d, ${}^3J_{FH}$ = 33.6 Hz, *Z*-isomer). HRMS (CI) calcd for $C_{12}H_{11}F$ $[M]^+$ 174.0839, found 174.0860.

Synthesis of 3-Fluoroundec-3-en-1-yne (*E*/*Z*-41)



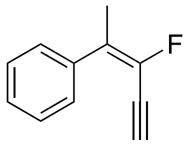
Method B. Octanal: 64.1 mg (0.500 mmol); sulfone **29**: 327 mg (1.00 mmol, 2.0 molar equiv); DBU: 305 mg (2.0 mmol, 4.0 molar equiv); CH_2Cl_2: 5.4 mL; TBAF (1.0 M solution in THF, 0.100 mL, 0.20 molar equiv). Eluting solvent for column chromatography: 10% EtOAc in hexanes. Yield of *E*/*Z*-**41**: 66.6 mg (79%), as a colorless liquid, *E*/*Z* ratio: 85/15. R_f (10% EtOAc in hexanes) = 0.73. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.67 (dt, 1H, =CH, $^3J_{FH}$ = 15.7 Hz, $^3J_{HH}$ = 8.3 Hz, *E*-isomer), 5.29 (dt, 1H, =CH, $^3J_{FH}$ = 33.2 Hz, $^3J_{HH}$ = 7.8 Hz, *Z*-isomer), 3.34 (d, 1H, ≡CH, $^4J_{FH}$ = 3.2 Hz, *E*-isomer), 3.09 (d, 1H, ≡CH, $^4J_{FH}$ = 3.7 Hz, *Z*-isomer), 2.19-2.11 (m, 2H, CH_2, both *E* and *Z*-isomers), 1.42-1.29 (m, 10H, 5CH_2, both *E* and *Z*-isomers), 0.86 (m, 3H, CH_3, both *E* and *Z*-isomers). ^{19}F NMR (282 MHz, $CDCl_3$): δ –111.45 (d, $^3J_{FH}$ = 15.3 Hz, *E*-isomer), –114.05 (d, $^3J_{FH}$ = 33.6 Hz, *Z*-isomer). HRMS (CI) calcd for $C_{11}H_{17}F$ $[M]^+$ 168.1309, found 168.1302.

1-Benzyl-4-(1-fluoroprop-2-ynylidene)piperidine (42)



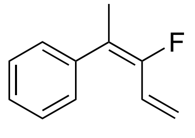
N-benzylpiperidin-4-one: 57.0 mg, (0.300 mmol, 1.0 molar equiv); sulfone **29**: 294 mg (0.900 mmol, 3.0 molar equiv); LHMDS: 1.5 mL (1.0 M, 1.5 mmol, 5.0 molar equiv); THF (2.5 mL); TBAF (1.0 M solution in THF, 0.900 mL, 3.0 molar equiv). Eluting solvent for column chromatography: 10% EtOAc in hexanes. Yield of **42**: 52.7 mg (77%), as a colorless liquid. R_f (20% EtOAc in hexanes) = 0.52. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.25 (m, 5H, Ar-H), 3.53 (s, 2H, CH_2), 3.35 (d, 1H, ≡CH, $^4J_{FH}$ = 3.7 Hz), 2.50 (t, 2H, CH_2, $^4J_{FH}$ = 5.5 Hz), 2.45 (s, 4H, 2CH_2), 2.40 (t, 2H, CH_2, $^4J_{FH}$ = 5.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 134.9 (d, $^1J_{CF}$ = 227.0 Hz), 129.2 (2C), 128.4 (2C), 127.3, 127.0 (d, $^2J_{CF}$ = 18.3 Hz), 83.4 (d, $^3J_{CF}$ = 7.8 Hz), 74.7 (d, $^2J_{CF}$ = 44.4 Hz), 62.9, 53.8 (d, $^4J_{CF}$ = 1.8 Hz), 53.3 (d, $^4J_{CF}$ = 1.4 Hz), 29.0 (d, $^3J_{CF}$ = 1.8 Hz), 26.0 (d, ${}^3J_{CF}$ = 3.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ –121.4 (s). HRMS (EI) calcd for $C_{15}H_{16}FN$ $[M]^+$ 229.1261, found 229.1250.

(3*E*)-(3-Fluoropent-2-en-4-yn-2-yl)benzene (43)



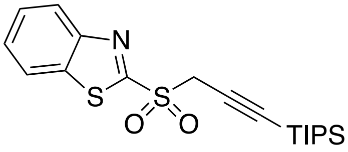
Acetophenone: 36.0 mg (0.300 mmol); sulfone **29**: 294 mg (0.900 mmol, 3.0 molar equiv); LHMDS: 1.5 mL (1.0 M, 1.5 mmol, 5.0 molar equiv); THF (2.5 mL); TBAF (1.0 M solution in THF, 0.900 mL, 3.0 molar equiv). Eluting solvent for column chromatography: 10% EtOAc in hexanes. Yield of **43**: 42.3 mg (88%), as a colorless liquid. R_f (10% EtOAc in hexanes) = 0.76. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, 2H, Ar-H, J = 7.4 Hz), 7.37 (t, 2H, Ar-H, J = 7.4 Hz), 7.32 (t, 1H, Ar-H, J = 7.4 Hz), 3.18 (d, 1H, ≡CH, ${}^4J_{FH}$ = 3.7 Hz), 2.14 (d, 3H, CH_3, ${}^4J_{FH}$ = 4.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4 (d, ${}^1J_{CF}$ = 232.1 Hz), 137.6 (d, ${}^3J_{CF}$ = 4.7 Hz), 128.4 (2C), three resonances: 128.27, 128.25, 128.23 (2C, one d and one s), 127.4 (d, ${}^2J_{CF}$ = 22.4 Hz), 82.5 (d, ${}^3J_{CF}$ = 7.3 Hz), 75.9 (d, ${}^2J_{CF}$ = 42.1 Hz), 16.3 (d, ${}^3J_{CF}$ = 4.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ –110.0 (s). HRMS (EI) calcd for $C_{11}H_9F$ $[M]^+$ 160.0683, found 160.0667.

Stereochemistry assignment to enyne 43 by reduction to (*E*)-(3-fluoropenta-2,4-dien-2-yl)benzene to 44.



Fluoroenyne **43** (7.0 mg, 0.044 mmol) and Lindlar catalyst (5% Pd on $CaCO_3$ poisoned with lead, 2.5 mg) were suspended in anhydrous hexanes (0.600 mL) in a dry vial and one small drop of quinoline was added. The vial was evacuated, filled with hydrogen gas via a hydrogen balloon, and the reaction was conducted at atmospheric pressure for 2 h. The mixture was filtered through Celite and the residue was washed with EtOAc (10.0 mL). The filtrate was evaporated under reduced pressure and the crude mixture was purified by column chromatography (20% EtOAc in hexanes). Yield of (*E*)-(3-fluoropenta-2,4-dien-2-yl)benzene **44**: 3.0 mg (42%), as a colorless liquid. R_f (10% EtOAc in hexanes) = 0.78. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.35 (t, 2H, Ar-H, J = 7.3 Hz), 7.28 (t, 1H, Ar-H, J = 7.3 Hz), 7.23 (d, 2H, Ar-H, J = 7.6 Hz), 6.25 (ddd, 1H, =CH, J = 28.3, 17.1, 11.2 Hz), 5.51 (d, 1H, =CH$_2$, J = 17.1 Hz), 5.07 (d, 1H, =CH$_2$, J = 10.7 Hz), 2.10 (d, 3H J = 3.4 Hz). ^{19}F NMR (282 MHz, CDCl$_3$): δ –124.4 (d, $^3J_{HF}$ = 27.5 Hz). HRMS (ESI) calcd for $C_{11}H_{12}F$ $[M + H]^+$ 163.0918, found 163.0910. NOESY correlation between the vinylic proton at the C-2 and the ortho protons in the phenyl ring confirmed the *E* stereochemistry of the double bond in fluoroenyne **43**.

Synthesis of 2-[3-(Triisopropylsilyl)prop-2-ynylsulfonyl]benzo[*d*]thiazole (46)



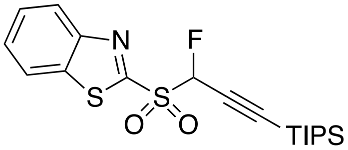
Step 1: A solution of 1.00 g of propargyl bromide **45** (80 wt% in toluene: 6.72 mmol) in THF (20.0 ml) was cooled to –78 °C (dry ice/*iso*PrOH) and 4.20 mL (6.72 mmol, 1.0 molar equiv) of *n*-BuLi (1.6 M in hexane) was added dropwise. After stirring the mixture at –78 °C for 10 min, 1.42 mL (6.72 mmol, 1.0 molar equiv) of TIPS-Cl was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for another 2 h. The reaction was quenched by addition of saturated aq NH$_4$Cl and the mixture was poured into EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with water and brine, and dried over anhydrous Na$_2$SO$_4$.

The solvent was evaporated under reduced pressure and the crude product was used in the next step without purification.

Step 2: The yellow oil obtained in step 1 was diluted with DMF (10.0 mL) and the sodium salt of 2-mercapto-1,3-benzothiazole **24** (1.65 g, 8.74 mmol) was added. After stirring for 2 h at room temperature, 10.0 mL of water was added and the mixture was poured into EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure.

Step 3: The crude product obtained in step 2 (1.23 g) was dissolved in $CHCl_3$ (15.0 mL) and cooled to –10 °C (ice/salt). A solution of *m*CPBA (1.85 g, 10.7 mmol) in $CHCl_3$ (28 mL) was slowly added via an addition funnel. After the addition was complete, the mixture was allowed to warm to room temperature and the stirring was continued for 12 h. Saturated aq $NaHCO_3$ (10.0 mL) was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc in hexanes). Yield of **46**: 800 mg (30% over three steps), as a white solid. R_f (10% EtOAc in hexanes) = 0.23. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, 1H, Ar-H, J = 8.3 Hz), 8.00 (d, 1H, Ar-H, J = 7.8 Hz), 7.65-7.58 (m, 2H, Ar-H), 4.48 (s, 2H, CH_2), 0.878-0.873 (m, 21H, Si(*iso*-Pr)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.3, 152.8, 137.3, 128.3, 127.8, 125.8, 122.3, 92.4, 92.3, 48.5, 18.5, 11.1. HRMS (ESI) calcd for $C_{19}H_{27}NO_2S_2Si$ $[M + H]^+$ 394.1325, found 394.1330.

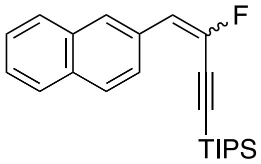
Synthesis of 2-[1-Fluoro-3-(triisopropylsilyl)prop-2-ynylsulfonyl]benzo[*d*]thiazole (47)



A stirring solution of sulfone **46** (500 mg, 1.27 mmol, 1.0 molar equiv) in dry toluene (10.0 mL) was cooled under nitrogen to –78 °C (dry ice/*iso*PrOH). LDA (0.700 mL, 1.1 molar equiv of a 2.0 M solution in heptane/THF/EtPh) was added and after 15 min, solid NFSI **28** (479 mg, 1.52 mmol, 1.2 molar equiv) was added. The reaction mixture was allowed to stir at –78 °C for 50 min then warmed to room temperature, and stirring was continued for an additional 50 min. Saturated aq NH_4Cl was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with EtOAc (3 x), and the combined organic layer was washed with water, saturated aq $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (10% EtOAc in hexanes). Yield of **47**: 359 mg (69%), as a white solid. R_f (20% EtOAc in hexanes) = 0.50. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, 1H, Ar-H, J = 8.2 Hz), 8.02 (d, 1H, Ar-H, J = 7.6 Hz), 7.66-7.60 (m, 2H, Ar-H), 6.19 (d, 1H, CHF, $^2J_{FH}$ = 48.5 Hz), 1.04-1.01 (m, 21H, Si(*iso*-Pr)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4, 152.9, 137.7, 128.7, 128.0, 126.1, 122.4, 101.9 (d, $^3J_{CF}$ = 8.2 Hz), 91.9 (d, $^1J_{CF}$ = 222.5 Hz), 91.6 (d, $^2J_{CF}$ = 23.3 Hz), 18.48, 18.47, 11.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ –164.46 (d, $^2J_{FH}$ = 48.8 Hz). HRMS (ESI) calcd for $C_{19}H_{27}FNO_2S_2Si$ $[M + H]^+$ 412.1231, found 412.1204.

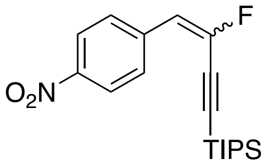
Condensations of sulfone 47 with aldehydes

Synthesis of (3-Fluoro-4-(naphthalen-2-yl)but-3-en-1-ynyl)triisopropylsilane (*E*/*Z*-48)



Method A: A solution of 2-naphthaldehyde (15.0 mg, 0.096 mmol) and DBU (58.5 mg, 0.385 mmol, 4.0 molar equiv) in CH_2Cl_2 (0.600 mL) was cooled under nitrogen to –55 °C (dry ice/*iso*PrOH). A solution of fluoropropargyl sulfone **47** (51.5 mg, 0.125 mmol, 1.3 molar equiv) in CH_2Cl_2 (0.300 mL) was added via a syringe. The dark reaction mixture was stirred for 15 min and checked by TLC (10% EtOAc in hexanes), which showed disappearance of the aldehyde. Reaction mixture was analyzed by ^{19}F NMR, and the combined *E*/*Z* product mixture was isolated by column chromatography (10% EtOAc in hexanes). Yield of *E*/*Z*-**48**: 29.4 mg (87%), as a white solid, *E*/*Z* ratio: 71/29. R_f (10% EtOAc in hexanes) = 0.81. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (s, 1H, Ar-H, *E*-isomer), 7.94 (s, 1H, Ar-H, *Z*-isomer), 7.91 (d, 1H, Ar-H, J = 8.5 Hz, *E*-isomer), 7.82-7.76 (m, 3H, Ar-H, both *E* and *Z*-isomers), 7.66 (d, 1H, Ar-H, J = 8.5 Hz, *Z*-isomer), 7.48-7.46 (m, 2H, Ar-H, both *E* and *Z*-isomers), 6.74 (d, 1H, =CH, $^3J_{FH}$ = 17.4, *E*-isomer), 6.23 (d, 1H, =CH, $^3J_{FH}$ = 35.1 Hz, *Z*-isomer), 1.17-1.14 (m, 21H, both *E* and *Z*-isomers). ^{19}F NMR (282 MHz, $CDCl_3$): δ –101.66 (d, $^3J_{FH}$ = 18.3 Hz, *E*-isomer), –104.65 (d, $^3J_{FH}$ = 33.6 Hz, *Z*-isomer). HRMS (ESI) calcd for $C_{23}H_{30}FSi$ $[M+H]^+$ 353.2095, found 353.2070.

Synthesis of (*E*/*Z*)-(3-Fluoro-4-(4-nitrophenyl)but-3-en-1-ynyl)triisopropylsilane (*E*/*Z*-49)

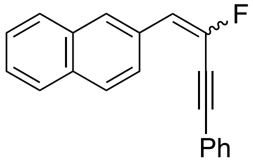


Method A: A solution of 4-nitrobenzaldehyde (20.0 mg, 0.132 mmol) and DBU (80.4 mg, 0.528 mmol, 4.0 molar equiv) in CH_2Cl_2 (0.900 mL) was cooled under nitrogen to –55 °C (dry ice/*iso*PrOH). A solution of fluoropropargyl sulfone **47** (70.8 mg, 0.172 mmol, 1.3 molar equiv) in CH_2Cl_2 (0.400 mL) was added via a syringe. The dark reaction mixture was stirred for 5 min and checked by TLC (10% EtOAc in hexanes), which showed disappearance of the aldehyde. The reaction mixture was analyzed by ^{19}F NMR, then loaded onto a silica gel column and the combined *E*/*Z* olefin mixture was eluted with 10% EtOAc in hexanes. Yield of *E*/*Z*-**49**: 29.2 mg (64%), as a light-yellow solid, *E*/*Z* ratio: 67/33. R_f (10% EtOAc in hexanes) = 0.58. ^1H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, 2H, Ar-H, J = 8.8 Hz, *Z*-isomer), 8.17 (d, 2H, Ar-H, J = 8.8 Hz, *E*-isomer), 7.86 (d, 2H, Ar-H, J = 8.8 Hz, *E*-isomer), 7.64 (d, 2H, Ar-H, J = 8.8 Hz, *Z*-isomer), 6.63 (d, 1H, =CH, $^3J_{FH}$ = 15.6 Hz, *E*-isomer), 6.13 (d, 1H, =CH, $^3J_{FH}$ = 33.2 Hz, *Z*-isomer), 1.15-1.12 (m, 21H, *E* and *Z*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$): δ –94.43 (d, $^3J_{FH}$ = 15.3 Hz, *E* isomer), –98.03 (d, $^3J_{FH}$ = 33.6 Hz, *Z* isomer). HRMS (ESI) calcd for $C_{19}H_{27}FNO_2Si$ $[M+H]^+$ 348.1790, found 348.1774.

Method B: A solution of 4-nitrobenzaldehyde (20.0 mg, 0.132 mmol, 1.0 molar equiv) and sulfone **47** (70.8 mg, 0.172 mmol, 1.3 molar equiv) in dry THF (3.4 mL) was cooled under nitrogen to –78 °C (dry ice/*iso*PrOH). LHMDS (1.0 M solution in THF, 0.317 mL, 2.4 molar equiv) was added, the reaction mixture was stirred at –78 °C for 10 min and checked by TLC (10% EtOAc in hexanes), which showed disappearance of the aldehyde. Saturated aq NH_4Cl was added and the mixture was poured into EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude reaction mixture was analyzed by ^{19}F NMR, and the combined *E*/*Z* product mixture was then isolated by column chromatography (10% EtOAc in hexanes). Yield of *E*/*Z*-**49**: 39.7 mg (87%), as a light-yellow solid, *E*/*Z* ratio: 76/24.

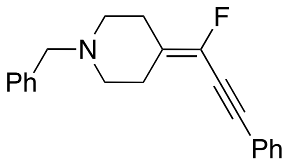
Sonogashira Cross-Coupling of Fluoroenynes

Synthesis of 2-(2-Fluoro-4-phenylbut-1-en-3-yn-1-yl)naphthalene (*E*/*Z*-51)



A solution of fluoroenyne (*E*/*Z*)-**30** (*E*/*Z* 88/12, 17.0 mg, 0.09 mmol, 1.00 molar equiv), iodobenzene (**50**) (35.5 mg, 0.18 mmol, 2.0 molar equiv), [$PdCl_2(PPh_3)_2$] (3.2 mg, 5 mol%) and CuI (1.7 mg, 10 mol%) in Et_3N (0.30 mL) was stirred at room temperature. After 2 h, TLC (hexanes) showed complete disappearance of fluoroenyne **30**. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude reaction mixture was analyzed by ^{19}F NMR, and then purified by column chromatography (hexanes). Yield of *E*/*Z*-**51**: 16.0 mg (68%), as a white solid, *E*/*Z* ratio: 93/7. R_f (hexanes) = 0.28. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (s, 1H, Ar-H, *E*-isomer), 7.91 (s, 1H, Ar-H, *Z*-isomer), 7.90 (dd, 1H, Ar-H, J= 8.5, 1.5 Hz, *E*-isomer), 7.85-7.82 (m, 3H, Ar-H, both *E* and *Z*-isomers), 7.72 (dd, 1H, Ar-H, J= 8.5, 1.5 Hz, *Z*-isomer), 7.61-7.55 (m, 2H, Ar-H, both *E* and *Z*-isomers), 7.51-7.39 (m, 5H, Ar-H, both *E* and *Z*-isomers), 6.82 (d, 1H, =CH, $^3J_{FH}$= 16.5 Hz, *E*-isomer), 6.27 (d, 1H, =CH, $^3J_{FH}$= 35.1 Hz, *Z*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$): δ –102.43 (d, $^3J_{FH}$ = 15.3 Hz, *E*-isomer), –104.41 (d, $^3J_{FH}$ = 36.6 Hz, *Z*-isomer). HRMS (ESI) calcd for $C_{20}H_{14}F$ $[M+H]^+$ 273.1074, found 273.1065.

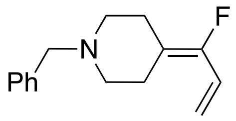
Synthesis of 1-benzyl-4-(1-fluoro-3-phenylprop-2-ynylidene)piperidine (52



A solution of fluoroenyne **42** (50.0 mg, 0.220 mmol, 1.00 molar equiv), iodobenzene (**50**) (90.0 mg, 0.440 mmols, 2.0 molar equiv), [$PdCl_2(PPh_3)_2$] (7.7 mg, 5 mol%) and CuI (4.0 mg, 10 mol%) in Et_3N (0.750 mL) was stirred at room temperature. After 2 h, TLC (20% EtOAc in hexanes) showed complete disappearance of fluoroenyne **42**. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude reaction mixture was analyzed by ^{19}F NMR, and then purified by column chromatography (20% EtOAc in hexanes). Yield of **52**: 53.0 mg (79%), as a pale-yellow oil. R_f (SiO_2, 20% EtOAc in hexanes) = 0.34. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48-7.46 (m, 2H, Ar-H), 7.34-7.27 (m, 8H, Ar-H), 3.54 (s, 2H), 2.55-2.47 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 135.6 (d, $^1J_{CF}$ = 227.0 Hz), 131.7 (2C, d, $^5J_{CF}$ = 1.8 Hz), 129.3 (2C), 129.1, 128.6 (2C), 128.4 (2C), 127.3, 125.8 (d, $^2J_{CF}$ = 19.7 Hz), 122.1 (d, $^4J_{CF}$ = 2.3 Hz), 94.9 (d, $^3J_{CF}$ = 7.8 Hz), 80.2 (d, $^2J_{CF}$ = 43.5 Hz), 63.0, 54.0 (d, $^4J_{CF}$ = 1.8 Hz), 53.4 (d, $^4J_{CF}$ = 1.4 Hz), 29.3 (d, $^3J_{CF}$ = 1.3 Hz), 26.2 (d, $^3J_{CF}$ = 3.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ –118.85 (s). HRMS (ESI) calcd for $C_{21}H_{21}FN$ $[M + H]^+$ 306.1653, found 306.1626.

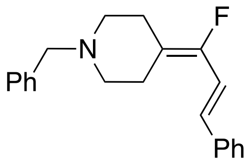
Synthesis of stereoisomeric fluorodienes

Synthesis of 1-benzyl-4-(1-fluoroallylidene)piperidine (53)



Fluoroenyne **42** (25.0 mg, 0.110 mmol) and Lindlar catalyst (5% Pd on $CaCO_3$ poisoned with lead, 5.0 mg) were suspended in anhydrous hexanes (1.0 mL) in a dry vial and one drop of quinoline was added. The vial was evacuated and filled with hydrogen gas via a hydrogen balloon, and the reaction was conducted at atmospheric pressure for 2 h. The mixture was filtered through Celite and the residue was washed with EtOAc (10.0 mL). The filtrate was evaporated under reduced pressure and the crude mixture was purified by column chromatography (20% EtOAc in hexanes). Yield of **53**: 22.0 mg (87%), as a pale-yellow oil. R_f (20% EtOAc in hexanes) = 0.40. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.24 (m, 5H, Ar-H), 6.44 (ddd, 1H, =CH, J = 28.1, 17.0, 11.1 Hz), 5.47 (d, 1H, =CH_2, J = 17.0 Hz), 5.13 (d, 1H, =CH_2, J = 11.1 Hz), 3.52 (s, 2H), 2.46 (br s, 6H), 2.31 (t, 2H J = 5.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.9 (d, $^1J_{CF}$ = 238.9 Hz), 138.6, 129.3 (2C), 128.4 (2C), 127.2, 124.9 (d, $^2J_{CF}$ = 27.5 Hz), 117.8 (d, $^2J_{CF}$ = 17.9 Hz), 113.5 (d, $^3J_{CF}$ = 6.0 Hz), 63.1, 54.1 (d, $^4J_{CF}$ = 1.8 Hz), 53.8 (d, $^4J_{CF}$ = 1.4 Hz), 27.5 (d, $^3J_{CF}$ = 5.0 Hz), 26.0 (d, $^3J_{CF}$ = 7.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ –130.47 (d, $^3J_{HF}$ = 27.5 Hz). HRMS (ESI) calcd for $C_{15}H_{19}FN$ $[M + H]^+$ 232.1496, found 232.1519.

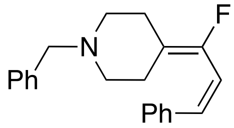
(*E*)-1-Benzyl-4-(1-fluoro-3-phenylallylidene)piperidine (54) via Heck coupling of 53[58]



Et_3N (0.045 mL, 5 molar equiv) was added to a solution of fluorodiene **53** (15 mg, 0.065 mmol), iodobenzene (26.5 mg, 0.130 mmol, 2 molar equiv), $Pd(OAc)_2$ (1.5 mg, 10 mol%), and

P(o-tol)$_3$ (4.0 mg, 20 mol%) in anhydrous DMF (0.650 mL), in a dry vial. The vial was flushed with nitrogen gas and sealed with a Teflon-lined cap. The reaction mixture was stirred at 100 °C for 15 h, then diluted with EtOAc (10 mL), and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude reaction mixture was analyzed by ^{19}F NMR and then purified by column chromatography (10% EtOAc in hexanes). Yield of **54**: 14.0 mg (70%), as a brown oil. R_f (20% EtOAc in hexanes) = 0.33. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, 2H, J = 7.8 Hz, Ar-H), 7.35-7.23 (m, 8H, Ar-H), 6.84-6.75 (m, 2H), 3.54 (s, 2H), 2.52-2.40 (m, 6H), 2.42 (t, 2H, J = 5.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.2 (d, $^1J_{CF}$ = 238.0 Hz), 138.5, 137.0, 129.3 (2C), 128.9 (2C), 128.4 (2C), 128.1 (d, $^3J_{CF}$ = 5.5 Hz), 128.0, 127.3, 126.8 (2C), 118.4 (d, $^2J_{CF}$ = 18.8 Hz), 116.5 (d, $^2J_{CF}$ = 25.2 Hz), 63.1, 54.2 (d, $^4J_{CF}$ = 1.8 Hz), 53.9 (d, $^4J_{CF}$ = 1.5 Hz), 27.8 (d, $^3J_{CF}$ = 5.0 Hz), 26.3 (d, $^3J_{CF}$ = 8.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ –128.10 to –128.20 (m). HRMS (ESI) calcd for $C_{21}H_{23}FN$ $[M + H]^+$ 308.1809, found 308.1794.

Synthesis of (*Z*)-1-Benzyl-4-(1-fluoro-3-phenylallylidene)piperidine (55)



Fluoroenyne **52** (10 mg, 0.033 mmol) and Lindlar catalyst (5% Pd on $CaCO_3$ poisoned with lead, 2.5 mg) were suspended in CH_3OH (0.80 mL) in a dry vial and one drop of quinoline was added. The vial was evacuated, filled with hydrogen gas via a hydrogen balloon, and the reaction was conducted at atmospheric pressure for 10 h. The mixture was filtered through Celite and the residue was washed with EtOAc (10.0 mL). The filtrate was evaporated under reduced pressure and the crude mixture was purified by column chromatography (20% EtOAc in hexanes). Yield of **55**: 6.8 mg (68%), as a pale-yellow oil. R_f (20% EtOAc in hexanes) = 0.32. ^{1}H NMR (500

MHz, $CDCl_3$): δ 7.34-7.21 (m, 10H, Ar-H), 6.49 (d, 1H, =CH, J = 12.2 Hz), 6.12 (dd, 1H, =CH, J = 23.7, 12.5 Hz), 3.50 (s, 2H) 2.45-2.43 (m, 4H), 2.37 (t, 2H, J = 5.1 Hz), 2.21 (t, 2H, J = 5.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.2 (d, $^1J_{CF}$ = 240.8 Hz), 138.6, 137.3, 131.4, 129.3 (2C), 129.2 (d, $^3J_{CF}$ = 6.0 Hz), 128.4 (2C), 128.0 (2C), 127.6 (2C), 127.2, 118.9 (d, $^2J_{CF}$ = 18.0 Hz), 117.8 (d, $^2J_{CF}$ = 26.1 Hz), 63.2, 53.9 (d, $^4J_{CF}$ = 1.7 Hz), 53.8 (d, $^4J_{CF}$ = 1.9 Hz), 28.1 (d, $^3J_{CF}$ = 4.6 Hz), 25.9 (d, $^3J_{CF}$ = 7.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ –115.90 (d, $^3J_{HF}$ = 24.4 Hz). HRMS (ESI) calcd for $C_{21}H_{23}FN$ $[M + H]^+$ 308.1809, found 308.1812.

Single-Crystal X-ray Diffraction for 29. The intensity data for **29** were measured on a Bruker-Nonius KappaCCD diffractometer (graphite-monochromated Mo *Ka* radiation, $\lambda = 0.71073$ Å, *f*-*w* scans) at 100 (1) K. The data were corrected for absorption. Details of the solution and refinements for $C_{13}H_{14}FNO_2S_2Si$ (**29**) are as follows. The crystals of **29**, with approximate dimensions 0.060 x 0.24 x 0.40 mm, were triclinic with space group *P*-1. The final unit-cell constants of 3 were $a = 6.9930(14)$ $b = 8.7110(17)$, $c = 13.512(3)$ Å, $\alpha = 74.66(3)$, $\beta = 75.88(3)$, $\gamma = 85.75(3)^\circ$, $V = 769.8(3)$ Å^3, $Z = 2$, $\rho = 1.413$ g cm^{-1}, $\mu = 0.433$ mm^{-1}, formula weight = 327.46. The structure of **3** was solved with SHELXS-97 and refined by full-matrix least squares on F^2 with SHELXL-97. The hydrogen atoms were calculated with the riding model in the structure-factor calculations, but their parameters were not refined. The final discrepancy indices, $3.00 < q < 27.62^\circ$, were $R = 0.0487$ (calculated on F for 2681 reflections) and R_W = 0.1215 (calculated on F^2 for all 3520 reflections) with 184 parameters varied. The major peaks of the final difference map are – 0.46 and + 0.64 e Å^3.

REFERENCES

1. Thirsk, C.; Whiting, A.: Polyene Natural Products, *J. Chem. Soc., Perkin Trans 1* **2002**, 999-1023.

2. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D.: Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489.

3. Shi Shun, A. L. K.; Tykwinski, R. R.: Synthesis of Naturally Occurring Polyynes, *Angew. Chem. Int. Ed.* **2006**, *45*, 1034-1057.

4. Meinwald, J.; Meinwald, Y. C.; Chalmers, A. M.; Eisner, T.: Dihydromatricaria Acid: Acetylenic Acid Secreted by Soldier Beetle, *Science* **1968**, *160*, 890-892.

5. Eisner, T.; Hill, D.; Goetz, M.; Jain, S.; Alsop, D.; Camazine, S.; Meinwald, J.: Antifeedant Action of *Z*-Dihydromatricaria Acid From Soldier Beetles, *J. Chem. Ecol.* **1981**, *7*, 1149-1158.

6. Guerrero, A.; Camps, F.; Coll, J.; Riba, M.; Einhorn, J.; Descoins, Ch.; Lallemand, J. Y.: Identification of a Potential Sex Pheromone of the Processionary Moth, Thaumetopoea Pityocampa (Lepidoptera, Notodontidae), *Tetrahedron Lett.* **1981**, *22*, 2013-2016.

7. Quero, C.; Malo, E. A.; Fabriàs, G.; Camps, F.; Lucas, P.; Renou, M.; Guerrero, A.: Reinvestigation of Female Sex Pheromone of Processionary Moth *(Thaumetopoea Pityocampa):* No Evidence for Minor Components, *J. Chem. Ecol.* **1997**, *23*, 713-726.

8. Kinnel, R. B.; Dieter, R. K.; Meinwald, J.; Van Engen, D.; Clardy, J.; Eisner, T.; Stallard, M. O.; Fenical, W.: Brasilenyne and Cis-Dihydrorhodophytin: Antifeedant Medium-Ring Haloethers From a Sea Hare (*Aplysia Brasiliana*), *Proc. Natl. Acad. Sci. USA* **1979**, *76*, 3576-3579.

9. Estevez-Braun, A.; Estevez-Reyes, R.; Moujir, L. M.; Ravelo, A. G.; Gonzalez, A. G.: Antibiotic Activity and Absolute Configuration of 8*S*-Heptadeca-2(*Z*),9(*Z*)-diene-4,6-diyne-1,8-diol From *Bupleurum Salicifolium*, *J. Nat. Prod.* **1994**, *57*, 1178-1182.

10. Ashour, M. L.; Wink, M.: Genus *Bupleurum*: a Review of its Phytochemistry, Pharmacology and Modes of Action, *J. Pharm. Pharmacol.* **2011**, *63*, 305-321.

11. Gupta, A. K.; Shear, N. H.: Terbinafine: An Update, *J. Am. Acad. Dermatol.* **1997**, *37*, 979-988.

12. Abdel-Rahman, S. M.; Nahata, M. C.: Oral Terbinafine: a New Antifungal Agent, *Ann. Pharmacother.* **1997**, *31*, 445-456.

13. Iverson, S. L.; Uetrecht, J. P.: Identification of a Reactive Metabolite of Terbinafine: Insights into Terbinafine-Induced Hepatotoxicity, *Chem. Res. Toxicol.* **2001**, *14*, 175-181.

14. Kirsch, P. *Modern Fluoroorganic Chemistry. Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004.

15. *Current Fluoroorganic Chemistry: New Synthetic Directions, Technologies, Materials, and Biological Applications;* Soloshonok, V. A.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J. F., Eds.; American Chemical Society: Washington DC, 2007.

16. Berger, R.; Resnati, G.; Metrangolo, P.; Weberd, E.; Hulliger, J.: Organic Fluorine Compounds: A Great Opportunity for Enhanced Materials Properties, *Chem. Soc. Rev.* **2011**, *40*, 3496–3508.

17. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V.: Fluorine in Medicinal Chemistry, *Chem. Soc. Rev.* **2008**, *37*, 320-330.

18. Fluorine-Containing Synthons, ed. V. A. Soloshonok, American Chemical Society, Washington, DC, 2005.

19. Negishi, E.-i.; Anastasia, L.: Palladium-Catalyzed Alkynylation, *Chem. Rev.* **2003**, *103*, 1979-2017.

20. Doucet, H.; Hierso, J.-C.: Palladium-Based Catalytic Systems for the Synthesis of Conjugated Enynes by Sonogashira Reactions and Related Alkynylations, *Angew. Chem. Int. Ed.* **2007**, *46*, 834-871.

21. Chinchilla, R.; Nájera, C.: The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry, *Chem. Rev.* **2007**, *107*, 874-922.

22. Weibel, J.-M.; Blanc, A.; Pale, P.: Ag-Mediated Reactions: Coupling and Heterocyclization Reactions, *Chem. Rev.* **2008**, *108*, 3149-3173.

23. Yamamoto, Y.: Silver-Catalyzed C_{sp}-H and C_{sp}-Si Bond Transformations and Related Processes, *Chem. Rev.* **2008**, *108*, 3199-3222.

24. Satoh, T.; Tsurugi, H.; Miura, M.: Catalytic Synthesis of Oligoene and Enyne Derivatives Through Carbometalation of Internal Alkynes, *The Chemical Record* **2008**, *8*, 326-336.

25. Tellier, F.; Sauvêtre, R.; Normant, J.-F.: Preparation Et Reactivite De Quelques Enynes Fluores, *Tetrahedron Lett.* **1986**, *27*, 3147-3148.

26. Yoshida, M.; Yoshikawa, S.; Fukuhara, T.; Yoneda, N.; Hara, S.: Stereoselective Synthesis of (*E*)-1-Fluoro-1,3-enynes, *Tetrahedron* **2001**, *57*, 7143-7148.

27. Eddarir, S.; Francesch, C.; Mestdagh, H.; Rolando, C.: Synthesis of Fluorinated Enynes via 1-Bromo 1-Fluoro Alkenes, *Tetrahedron Lett.* **1990**, *31*, 4449-4452.

28. Percy, J. M.; Wilkes, R. D.: A Rapid and Convenient Approach to Functionally Diverse Monofluorinated Vinylic Compounds, *Tetrahedron* **1997**, *53*, 14749-14762.

29. Zhang, X.; Burton, D. J.: A Kinetic Separation Method for the Stereoselective Preparation of (*Z*)- and (*E*)-Monofluoroenynes From *E*/*Z* Mixtures of 1-Bromo-1-fluoroolefins, *J. Fluorine Chem.* **2001**, *112*, 317-324.

30. Xu, J.; Wang, Y.; Burton, D. J.: Site-Specific Preparation of 3-Fluoro-1-substituted-naphthalenes via a Novel Base-Catalyzed Cyclization Reaction from (*E*)-Monofluoroenynes, *Org. Lett.* **2006**, *8*, 2555-2558.

31. Wang, Y.; Xu, J.; Burton, D. J.: A Simple, Two-Step, Site-Specific Preparation of Fluorinated Naphthalene and Phenanthrene Derivatives From Fluorobromo-Substituted Alkenes, *J. Org. Chem.* **2006**, *71*, 7780-7784.

32. Yang, Z.-Y.; Burton, D. J.: A Facile, General Method for the Preparation of Fluorinated Enynes, *Tetrahedron Lett.* **1990**, *31*, 1369-1372.

33. Yang, Z.-Y.; Burton, D. J.: Palladium-Catalyzed Reaction of Fluorinated Vinyl Iodides With Terminal Alkynes: A New and General Route To Fluorinated Enynes, *J. Fluorine Chem.* **1991**, *53*, 307-326.

34. Ichikawa, J.; Ikeura, C.; Minami, T.: A One-Pot Synthesis of Conjugated Fluoroenynes via 2,2-Difluorovinylcopper Intermediates, *J. Fluorine Chem.* **1993**, *63*, 281-285.

35. Sanders, T. C.; Golen, J. A.; Williard, P. G.; Hammond, G. B.: The Crystal Structure of 2-Fluoro-1-(*p*-methoxyphenyl)-1-penten-3-yne, A Fluorinated Vinylacetylene Prepared via Horner-Wadsworth-Emmon Condensation, *J. Fluorine Chem.* **1997**, *85*, 173-175.

36. Benayoud, F.; Chen, L.; Moniz, G. A.; Zapata, A. J.; Hammond, G. B.: Synthesis of α-Fluoro-β,γ-alkenylphosphonates and Conjugated Fluoroenynes From a Common Intermediate (α-Fluoropropargyl)phosphonate, *Tetrahedron* **1998**, *54*, 15541-15554.

37. Zapata, A. J.; Gu, Y.; Hammond, G. B.: The First α-Fluoroallenylphosphonate, the Synthesis of Conjugated Fluoroenynes, and the Stereoselective Synthesis of Vinylfluorophosphonates Using a New Multifunctional Fluorine-Containing Building Block, *J. Org. Chem.* **2000**, *65*, 227-234.

38. Camps, F.; Coll, J.; Fabriàs, G.; Guerrero, A.; Riba, M.: Fluorinated Analogs of Insect Sex Pheromones, *Experientia* **1984,** *40*, 933-934.

39. Camps, F.; Fabriàs, G.; Guerrero, A.: Synthesis of a Fluorinated Analog of the Sex Pheromone of the Processionary Moth *Thaumetopoea Pityocampa*, *Tetrahedron*, **1986**, *42*, 3623-3629.

40. Camps, F.; Fabriàs, G.; Gasol, V.; Guerrero, A.; Hernández, R.; Montoya, R.: Analogs of Sex Pheromone of the Processionary Moth, *Thaumetopoea Pityocampa*: Synthesis and Biological Activity*, J. Chem. Ecol.* **1988**, *14*, 1331-1346.

41. Blakemore, P. R.: The Modified Julia Olefination: Alkene Synthesis *via* the Condensation of Metallated Heteroarylalkylsulfones with Carbonyl Compounds, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.

42. Plesniak, K.; Zarecki, A.; Wicha, J.: The Smiles Rearrangement and the Julia–Kocienski Olefination Reaction, *Top. Curr. Chem*. **2007**, *275*, 163–250.

43. Aissa, C.: Mechanistic Manifold and New Developments of the Julia–Kocienski Reaction, *Eur. J. Org. Chem*. **2009**, 1831–1844.

44. Zajc, B.; Kumar, R.: Synthesis of Fluoroolefins via Julia–Kocienski Olefination, *Synthesis*, **2010**, 1822-1836.

45. Ghosh, A. K.; Zajc, B.: High-Yield Synthesis of Fluorinated Benzothiazolyl Sulfones: General Synthons for Fluoro-Julia Olefinations, *Org. Lett*. **2006**, *8*, 1553-1556.

46. Ghosh, A. K.; Zajc, B.: Fluorinated 1-Phenyl-1*H*-tetrazol-5-yl Sulfone Derivatives as General Reagents for Fluoroalkylidene Synthesis, *J. Org. Chem***. 2009**, *74,* 8531–8540.

47. Kake, S.; Zajc, B.: Exceptionally Mild, High-Yield Synthesis of α-Fluoro Acrylates, *Org. Lett*. **2006**, *8*, 4457-4460.

48. del Solar, M.; Ghosh, A. K.; Zajc, B.: Fluoro-Julia Olefination as a Mild, High-Yielding Route to α-Fluoro Acrylonitriles, *J. Org. Chem.* **2008**, *73*, 8206-8211.

49. He, M.; Ghosh, A. K.; Zajc, B.: Julia Olefination as a General Route to Phenyl (α-Fluoro)vinyl Sulfones, *Synlett* **2008**, 999-1004.

50. Ghosh, A. K.; Banerjee, S.; Sinha, S.; Kang, S. B.; Zajc, B.: α-Fluorovinyl Weinreb Amides and α-Fluoroenones From a Common Fluorinated Building Block, *J. Org. Chem.* **2009**, *74*, 3689-3697.

51. Mandal, S. K.; Ghosh, A. K.; Kumar, R.; Zajc, B.: Expedient Synthesis of α-Substituted Fluoroethenes, *Org. Biomol. Chem.* **2012**, *10*, 3164-3167.

52. Bonini, C.; Chiummiento, L.; Videtta, V.: Direct Preparation of *Z*-1,3-Enyne Systems with a TMS-Propargylic Sulfone: Application of a One-Pot Julia Olefination, *Synlett* **2006**, 2079-2082.

53. Bonini, C.; Chiummiento, L.; Videtta, V.: One-Pot Practical Preparation of Novel Propargylic Aryl and Heteroaryl Sulfides and Sulfones, *Synlett* **2005**, 3067-3070.

54. Hoogboom, J.; Swager, T. M.: Increased Alignment of Electronic Polymers in Liquid

Crystals via Hydrogen Bonding Extension, *J. Am. Chem. Soc.* **2006**, *128*, 15058-15059.

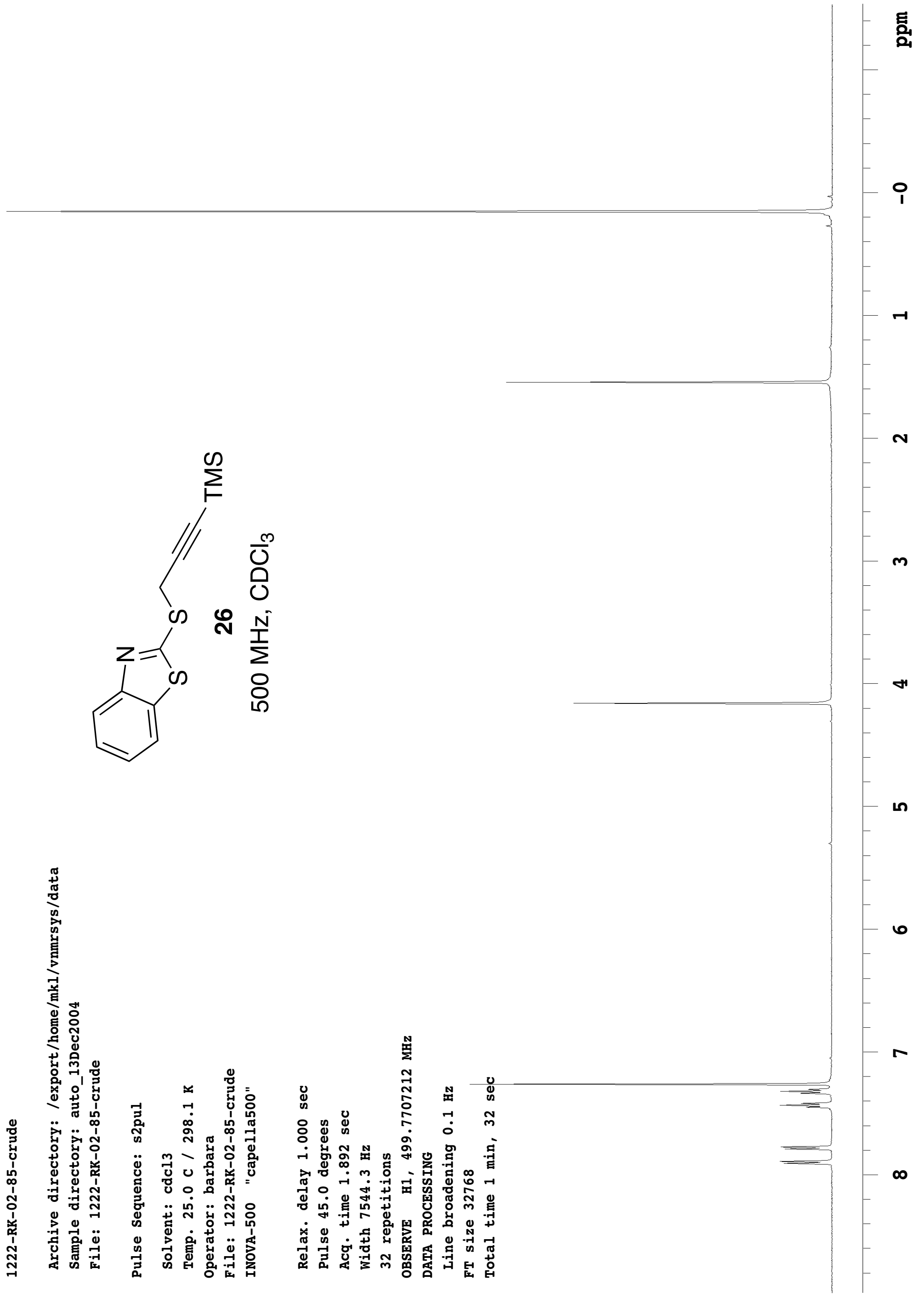
55. Neuvonen, H.; Neuvonen, K.; Koch, A.; Kleinpeter, E.; Pasanen, P.: Electron-Withdrawing Substituents Decrease the Electrophilicity of the Carbonyl Carbon. An Investigation with the Aid of ^{13}C NMR Chemical Shifts, ν(C=O) Frequency Values, Charge Densities, and Isodesmic Reactions To Interprete Substituent Effects on Reactivity, *J. Org. Chem.* **2002**, *67*, 6995-7003.

56. Ziegler, C. B., Jr.; Heck, R. F.: Palladium-Catalyzed Vinylic Substitution with Highly Activated Aryl Halides, *J. Org. Chem.* **1978**, *43*, 2941-2946.

57. Beletskaya, I. P.; Cheprakov, A. V.: The Heck Reaction as a Sharpening Stone of Palladium Catalysis, *Chem. Rev.* **2000**, *100*, 3009-3066.

58. Lagisetty, P.; Zhang, L.; Lakshman, M. K.: Simple Methodology for Heck Arylation at C- 8 of Adenine Nucleosides, *Adv. Synth. Catal.* **2008**, *350*, 602-608.

APPENDIX



26

500 MHz, $CDCl_3$

```
1222-RK-02-85-crude

Archive directory: /export/home/mk1/vnmrsys/data
Sample directory: auto_13Dec2004
File: 1222-RK-02-85-crude

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
 Operator: barbara
 File: 1222-RK-02-85-crude
 INOVA-500  "capella500"

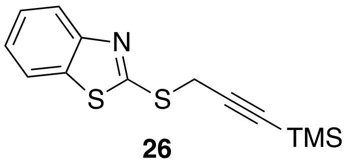
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 32 repetitions
 OBSERVE   H1, 499.7707212 MHz
 DATA PROCESSING
 Line broadening 0.1 Hz
 FT size 32768
 Total time 1 min, 32 sec
```

1231-RK-02-85-13C

Pulse Sequence: s2pul

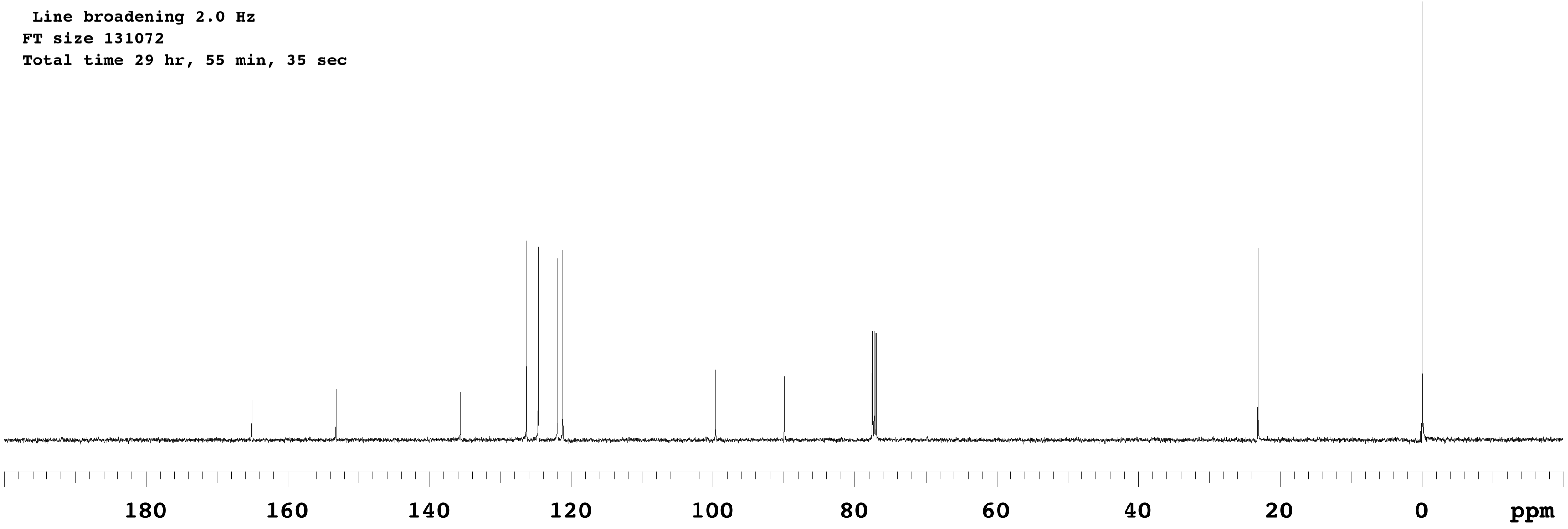
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: Raghu
INOVA-500 "capella500"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
270 repetitions
OBSERVE C13, 125.6674287 MHz
DECOUPLE H1, 499.7730084 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 29 hr, 55 min, 35 sec



26

125 MHz, $CDCl_3$



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1222-RK-02-139-pure

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 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-02-139-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 24 repetitions
OBSERVE   H1, 499.7707221 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 3 min, 5 sec
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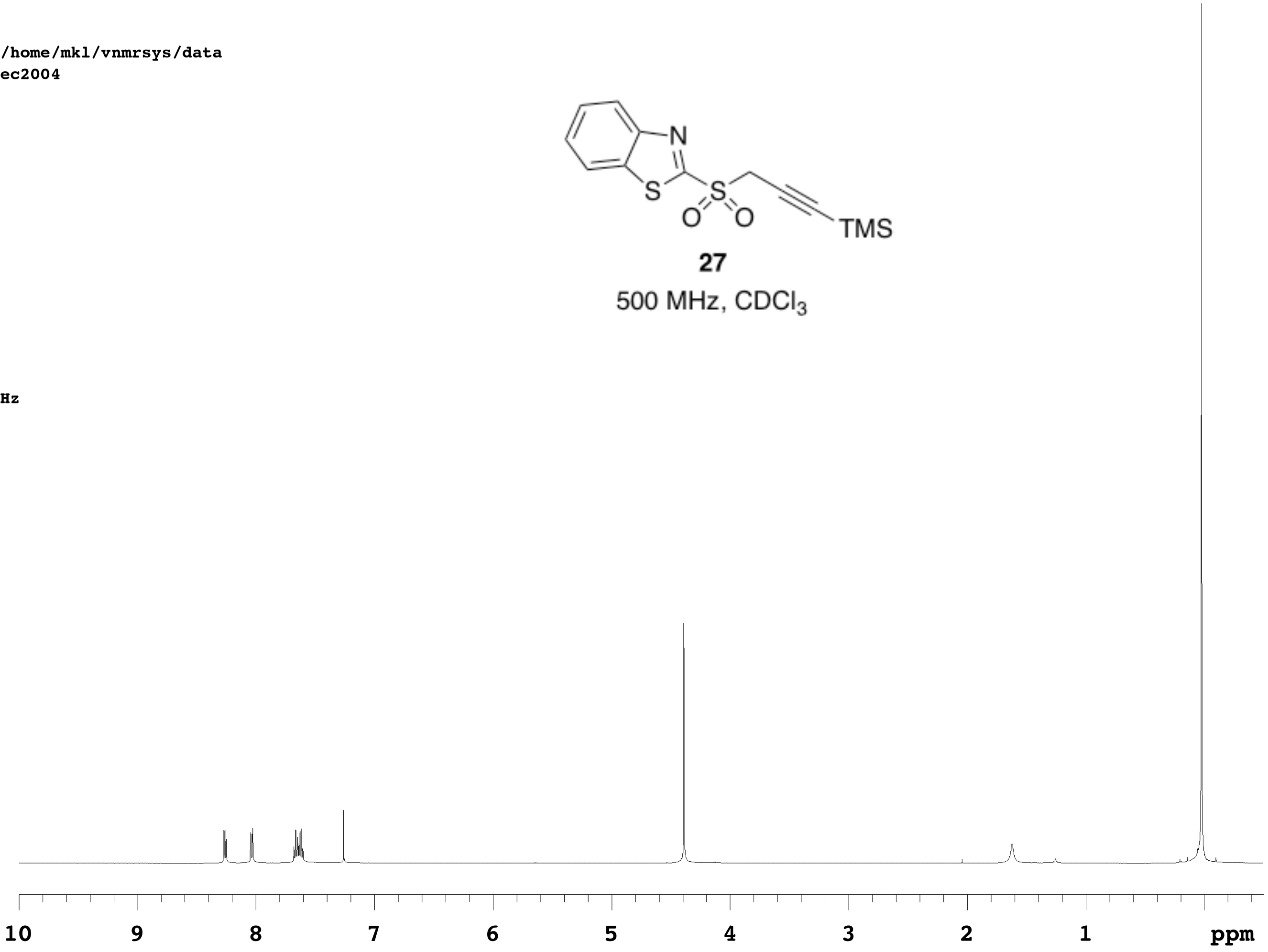


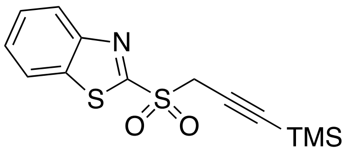
27

500 MHz, $CDCl_3$

```
1222-RK-02-139-13C

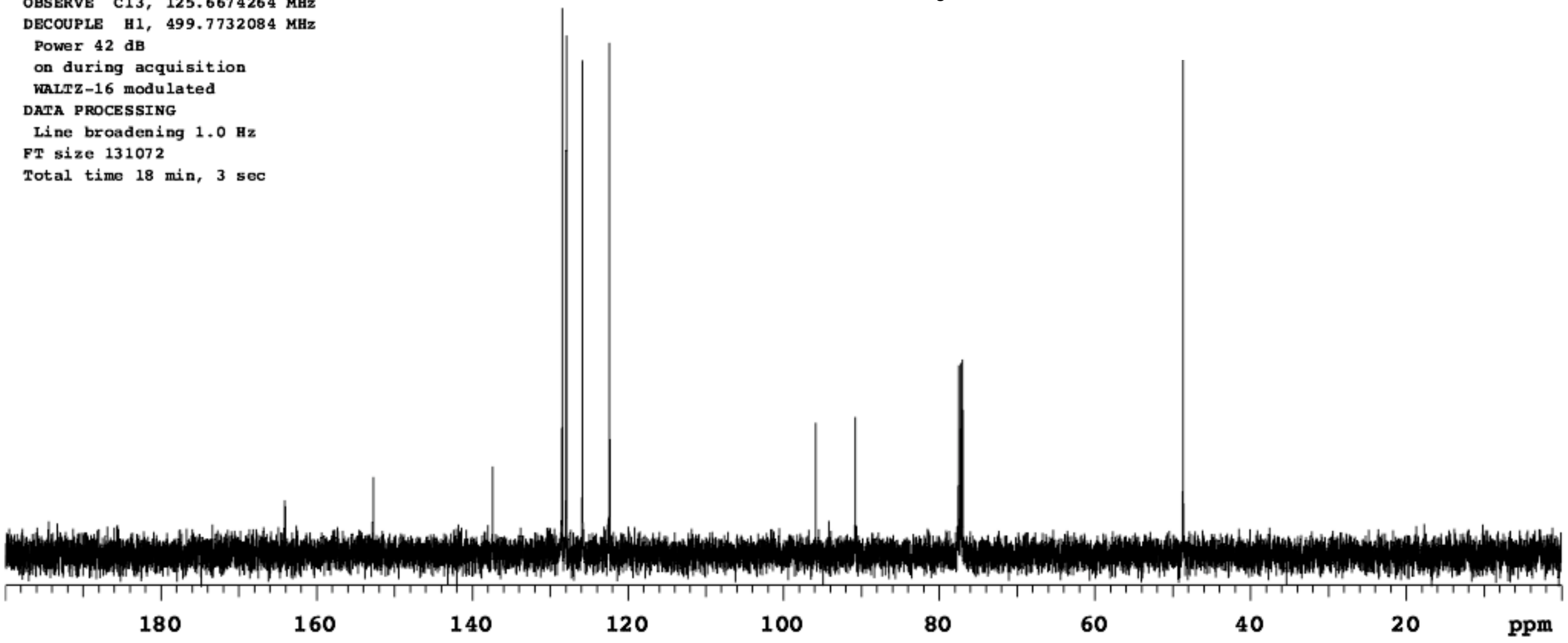
Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
INOVA-500  "capella500"

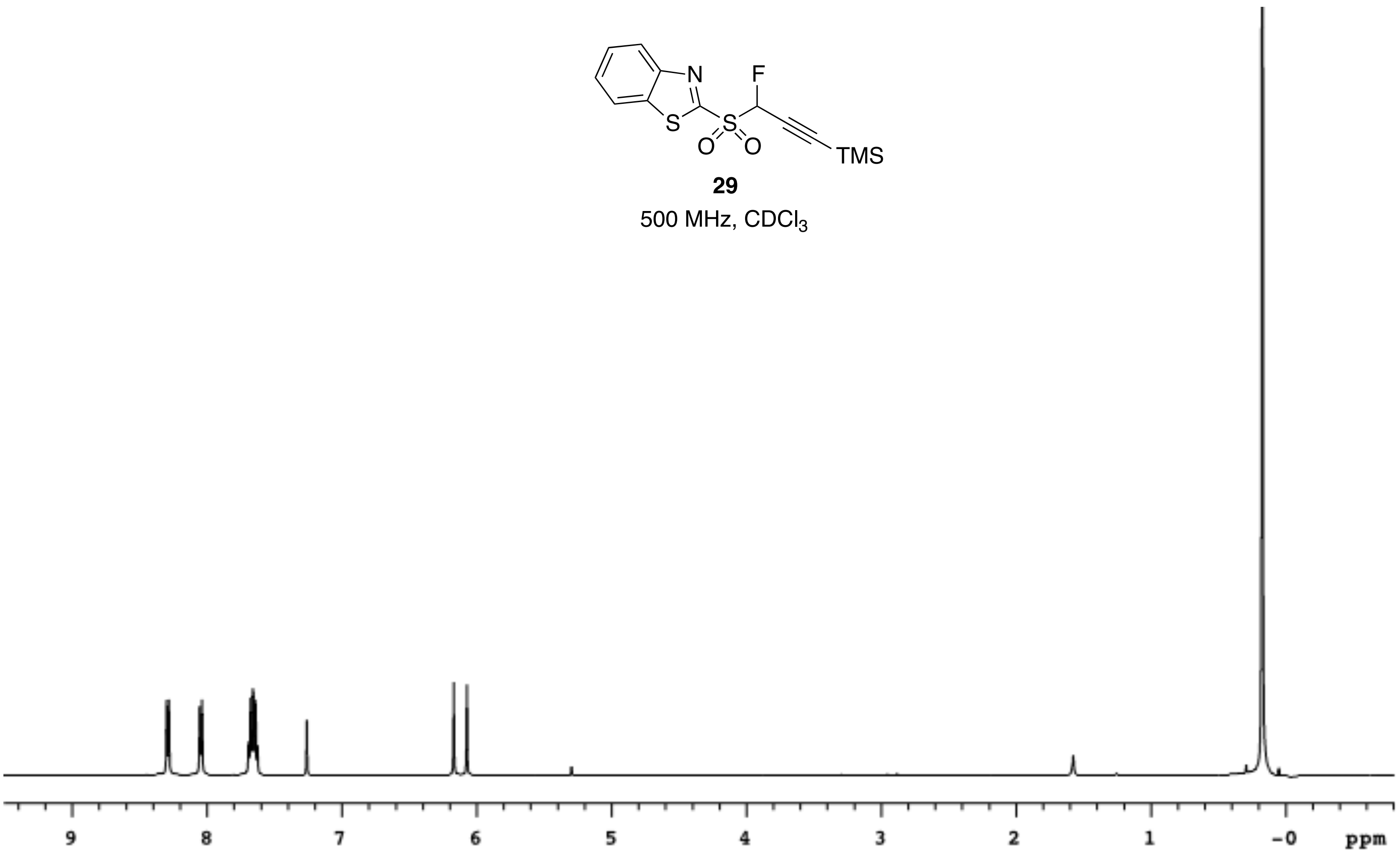
 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 52 repetitions
OBSERVE  C13, 125.6674264 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 18 min, 3 sec
```



27

125 MHz, $CDCl_3$





29

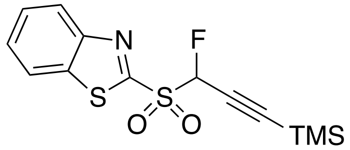
500 MHz, $CDCl_3$

```
1222-RK-02-144-13C

Pulse Sequence: s2pul

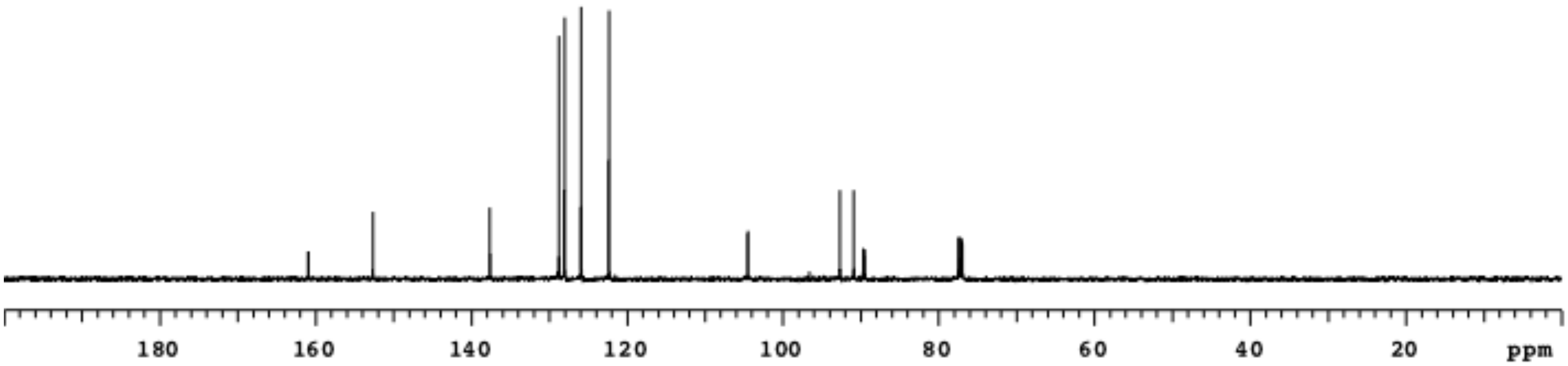
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-02-144-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 100 repetitions
OBSERVE  C13, 125.6674411 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 9 min, 12 sec
```



29

125 MHz, $CDCl_3$

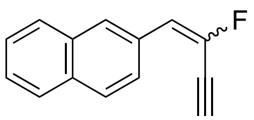


```
1231-RK-14-33-pure

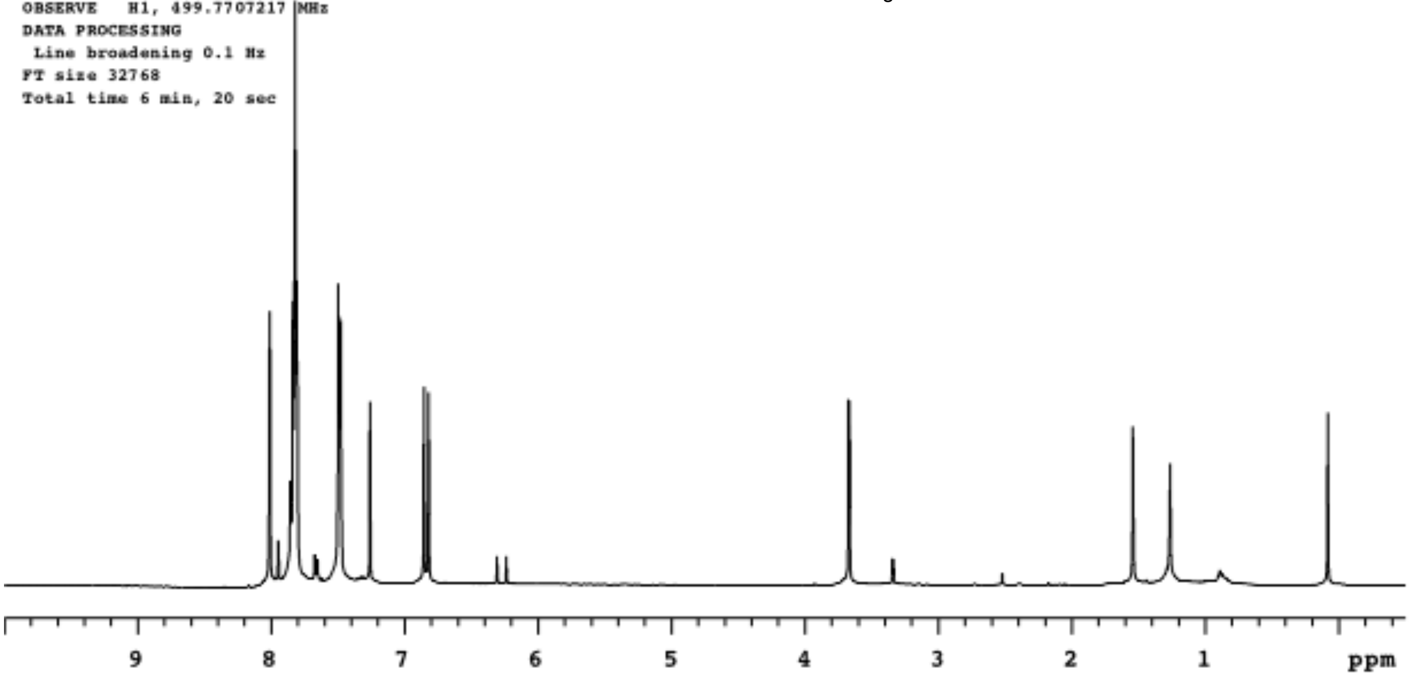
Pulse Sequence: s2pul

 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-14-33-pure
INOVA-500  "riga"

 Pulse 48.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 28 repetitions
OBSERVE   H1, 499.7707217 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec
```



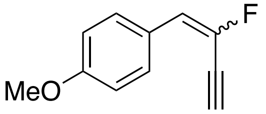
30: *E/Z* 88/12
500 MHz, $CDCl_3$



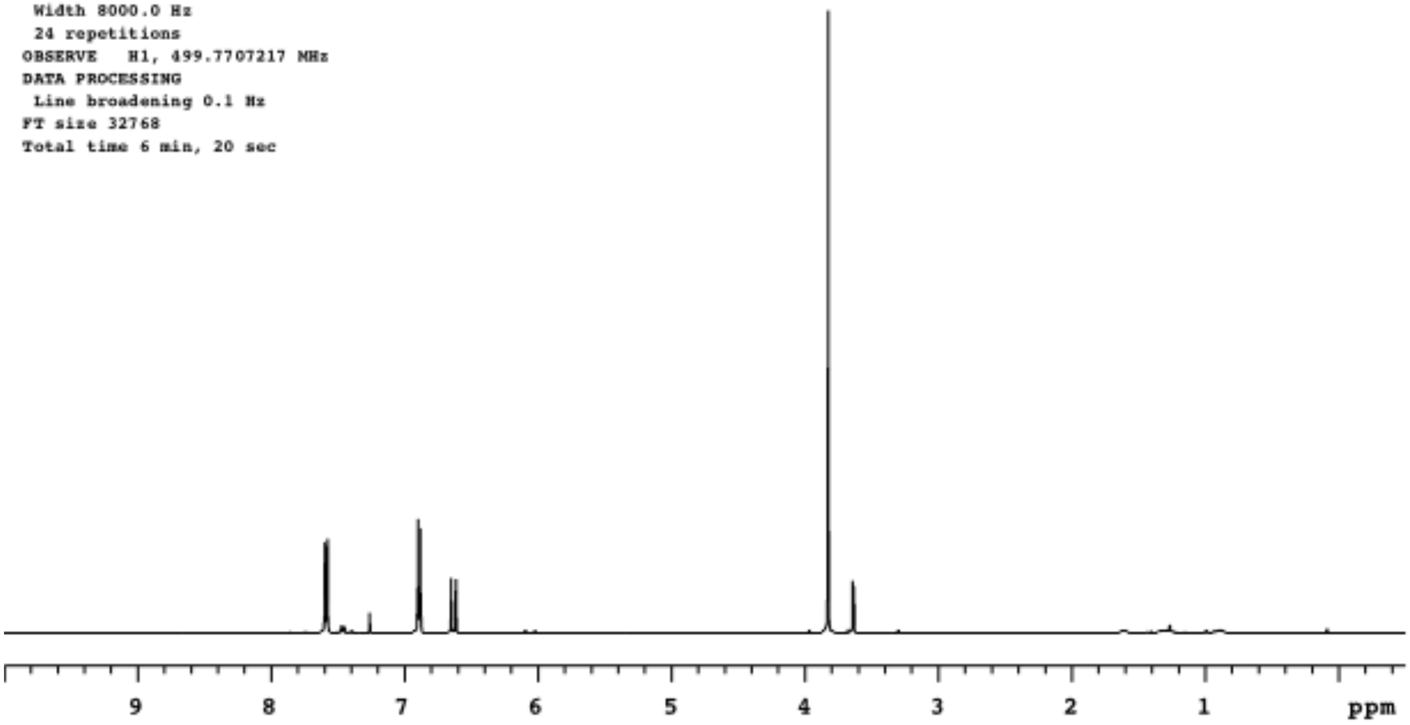
```
1222-RK-10-755-pure

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: barbara
File: 1222-RK-10-755-pure
INOVA-500  "riga"

 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 24 repetitions
OBSERVE   H1, 499.7707217 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec
```



31: *E/Z* 95/5
500 MHz, $CDCl_3$



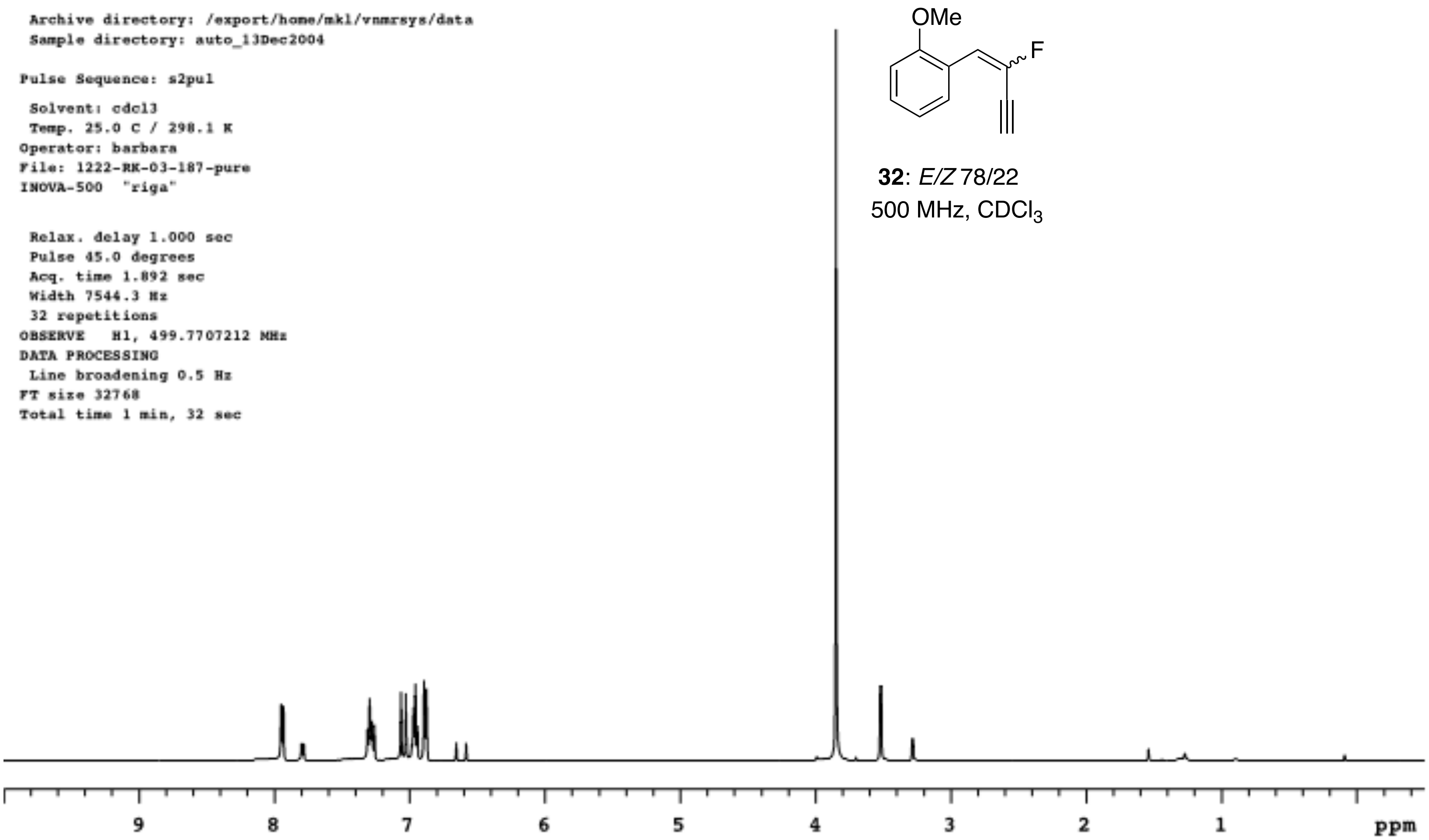
```
1222-RK-03-187-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-03-187-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 32 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 32768
Total time 1 min, 32 sec
```



32: *E/Z* 78/22
500 MHz, $CDCl_3$

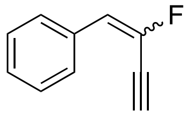
```
1222-RK-03-198-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

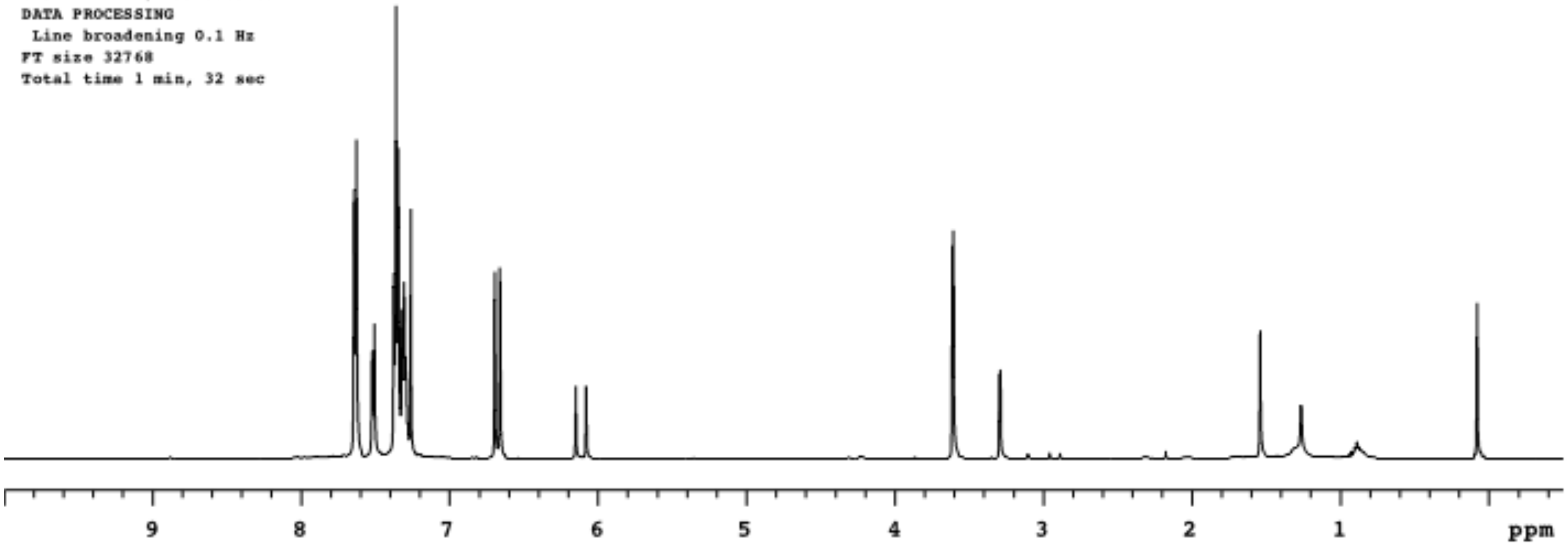
Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-03-198-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 32 repetitions
OBSERVE   H1, 499.7707207 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 32 sec
```



33: *E/Z* 76/24
500 MHz, $CDCl_3$



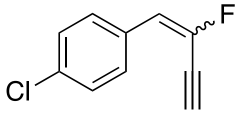
```
1222-RK-03-196-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

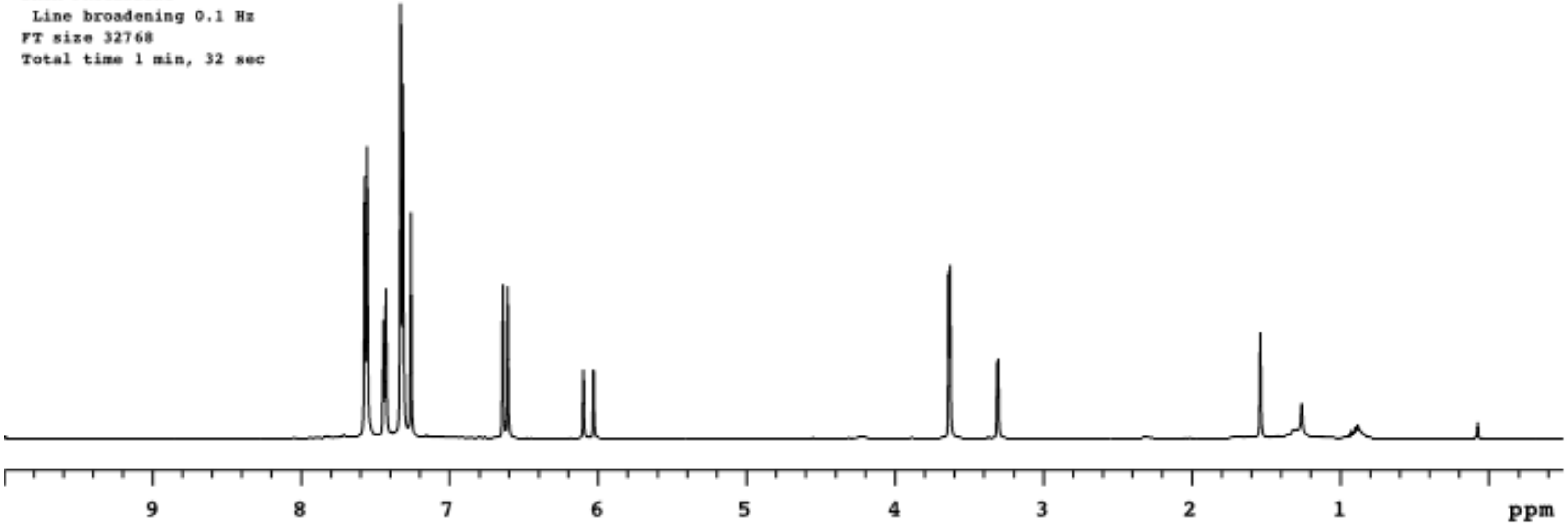
Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-03-196-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 28 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 32 sec
```



34: *E/Z* 70/30
500 MHz, $CDCl_3$



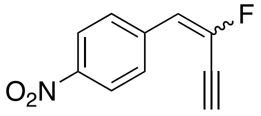
```
1222-RK-03-223-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

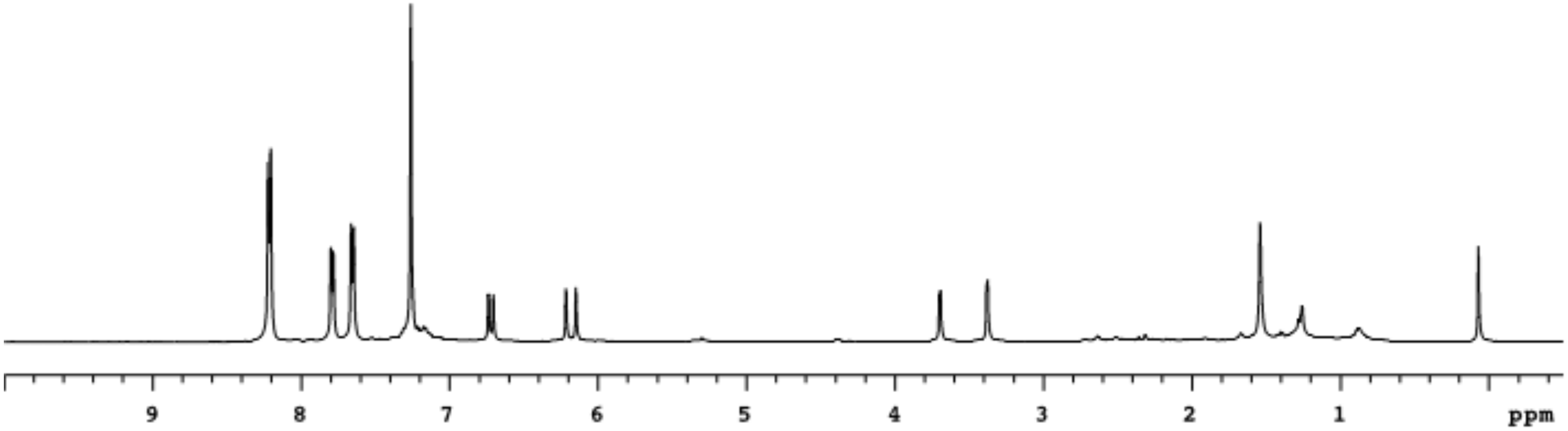
Pulse Sequence: s2pul

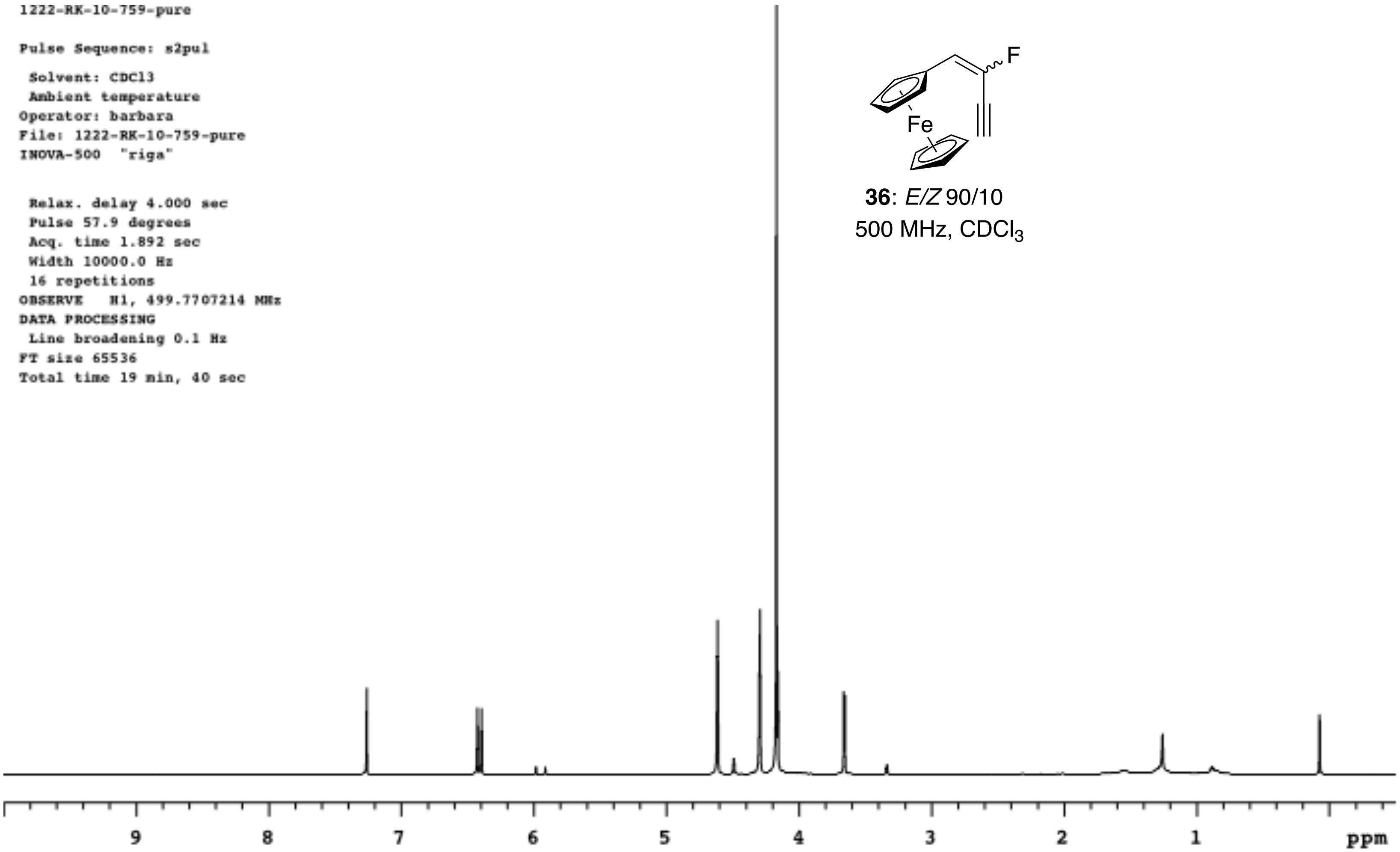
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-03-223-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 20 repetitions
OBSERVE   H1, 499.7707207 MHz
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 32768
Total time 1 min, 32 sec
```



35: *E/Z* 51/49
500 MHz, $CDCl_3$





```
1222-RK-10-759-pure

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: barbara
File: 1222-RK-10-759-pure
INOVA-500  "riga"

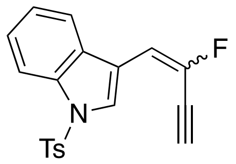
 Relax. delay 4.000 sec
 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 16 repetitions
OBSERVE   H1, 499.7707214 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 19 min, 40 sec
```

36: *E/Z* 90/10
500 MHz, $CDCl_3$

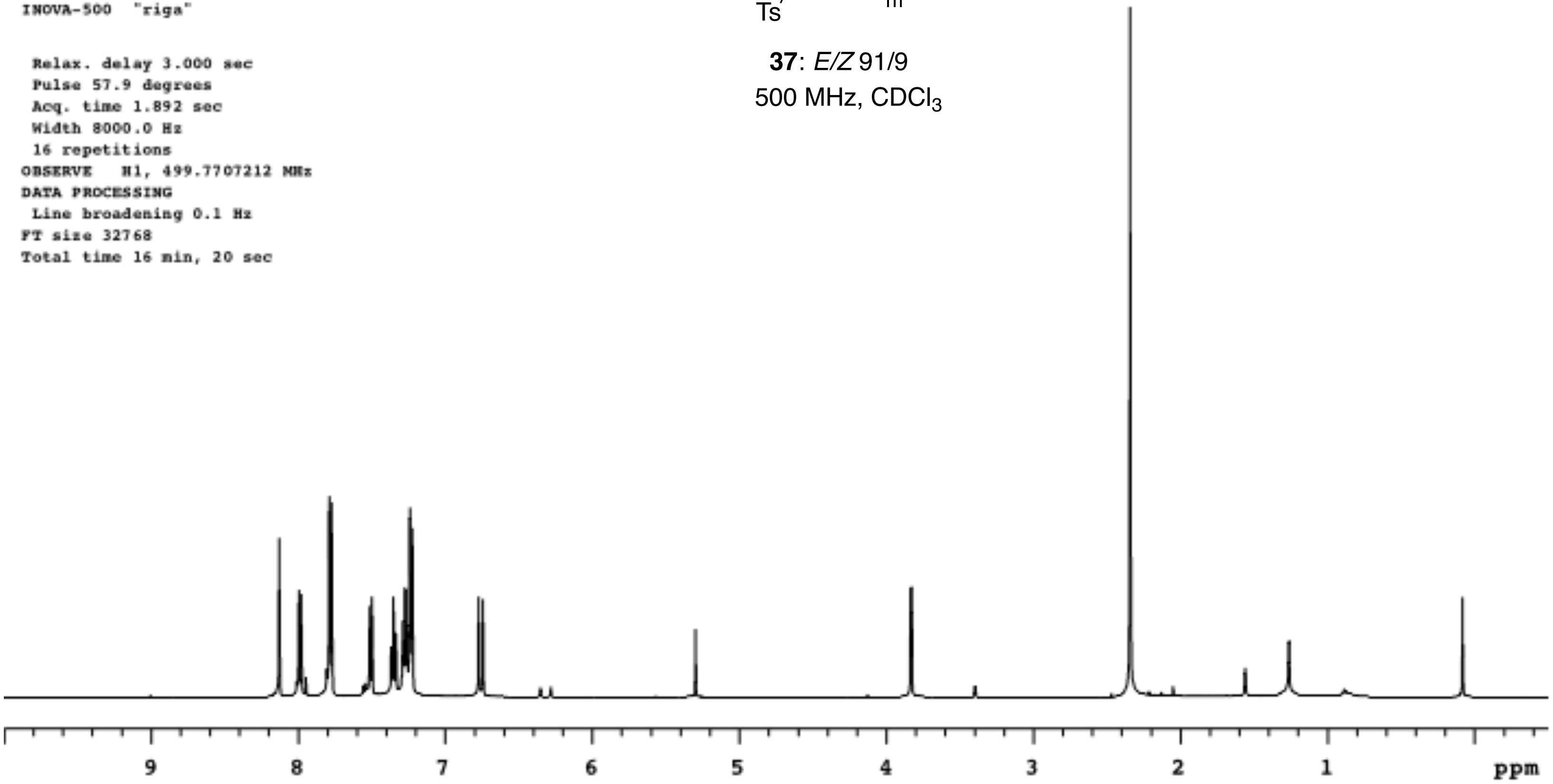
```
1222-RK-10-750

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-10-750
INOVA-500  "riga"

 Relax. delay 3.000 sec
 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 16 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 16 min, 20 sec
```



37: *E/Z* 91/9
500 MHz, $CDCl_3$

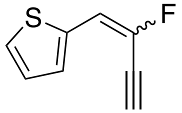


```
1231-RK-14-43-pure-rxn2

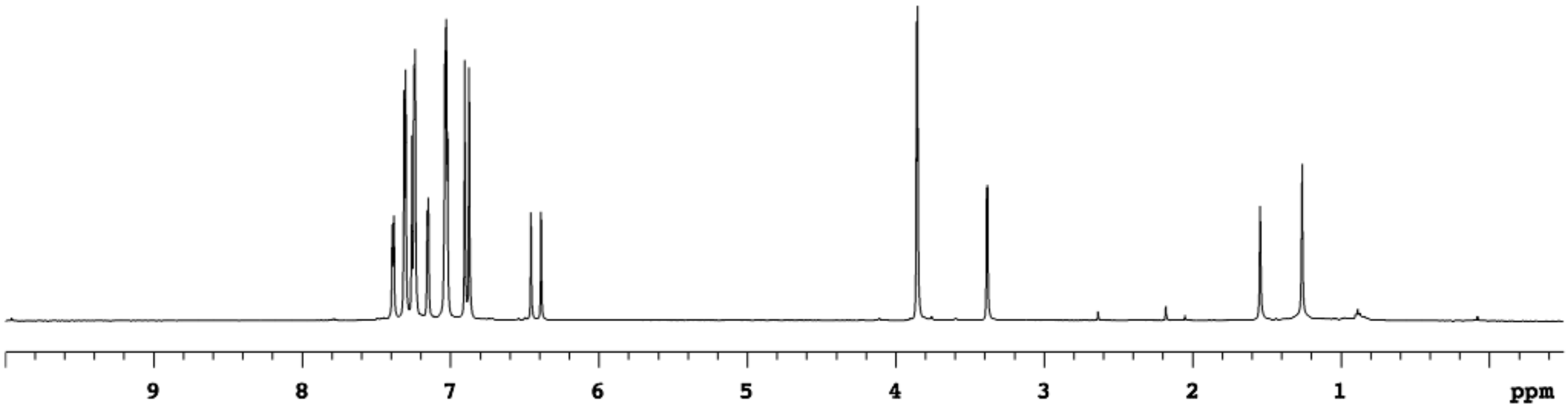
 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 24.0 C / 297.1 K
Operator: barbara
File: 1231-RK-14-43-pure-rxn2
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 32 repetitions
OBSERVE   H1, 499.7707216 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



38: *E/Z* 75/25
500 MHz, $CDCl_3$



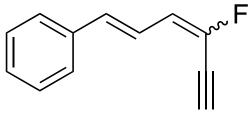
```
1222-RK-03-199-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

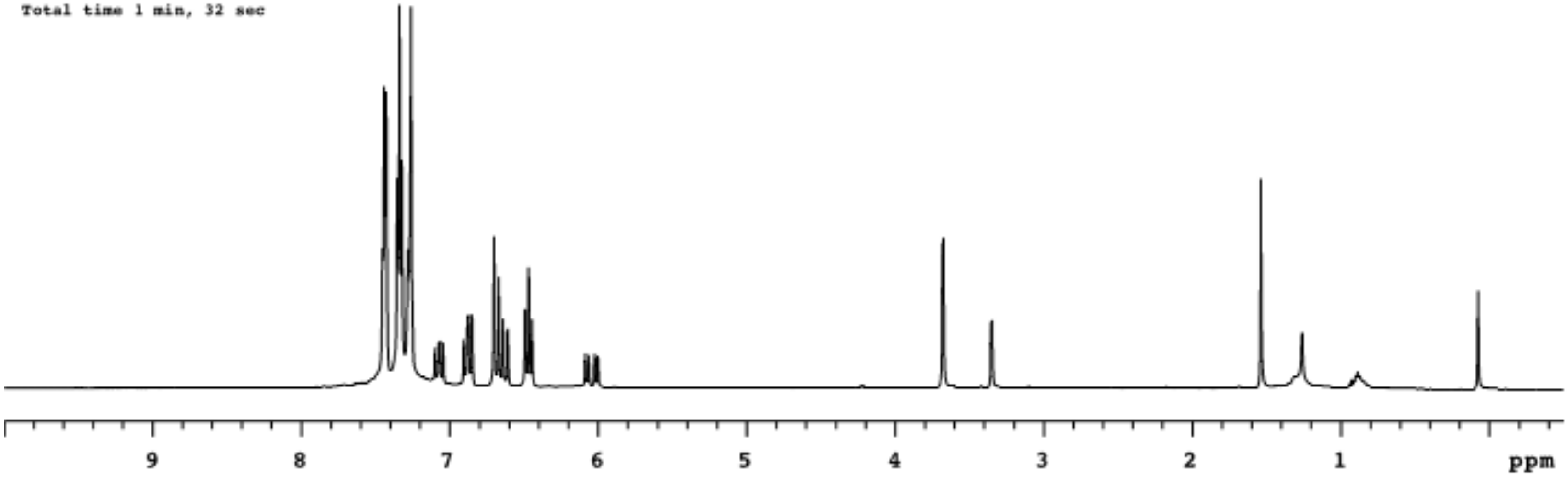
Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-03-199-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 16 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 32768
Total time 1 min, 32 sec
```



39: *E/Z* 72/28
500 MHz, $CDCl_3$



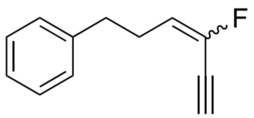
```
1222-RK-03-207

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

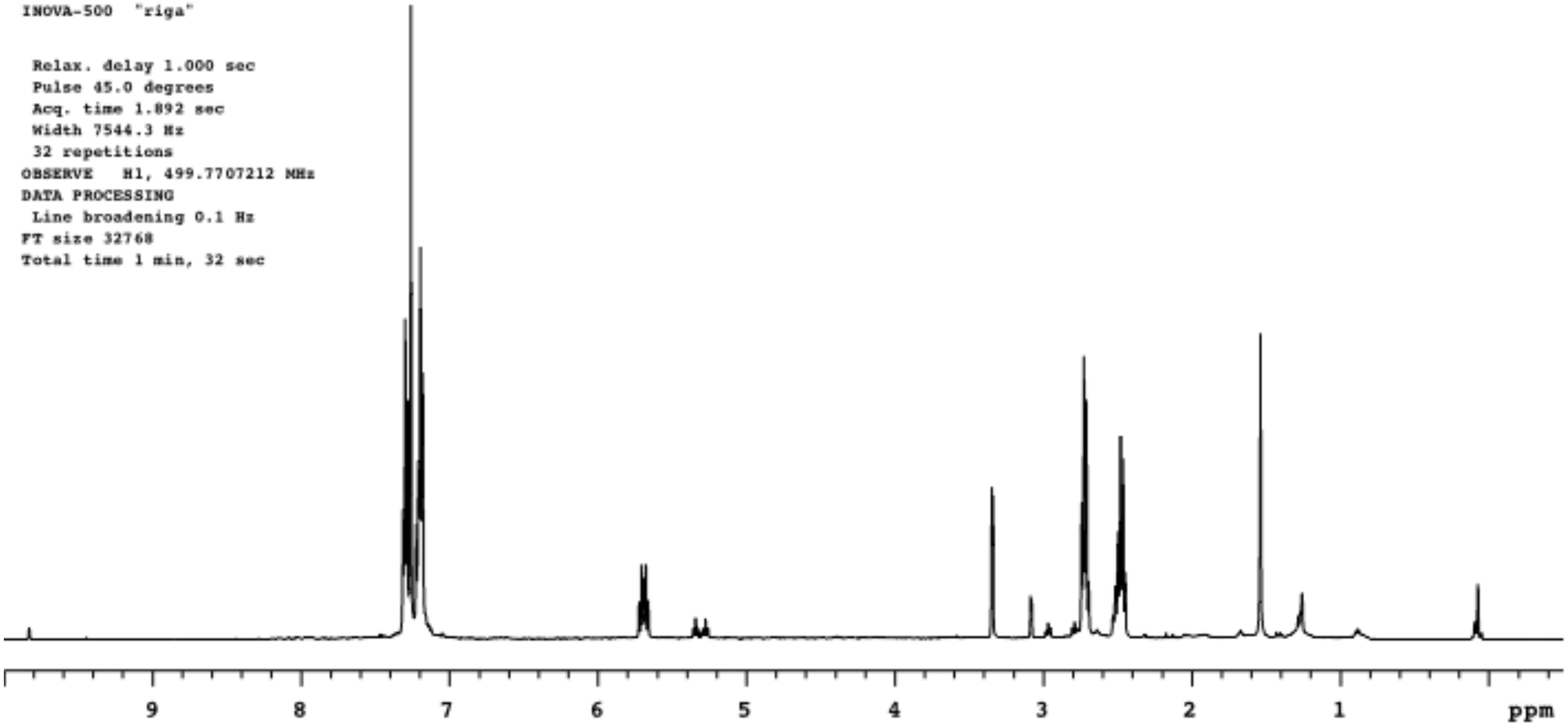
Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-03-207
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 32 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 32 sec
```



40: *E/Z* 80/20
500 MHz, $CDCl_3$



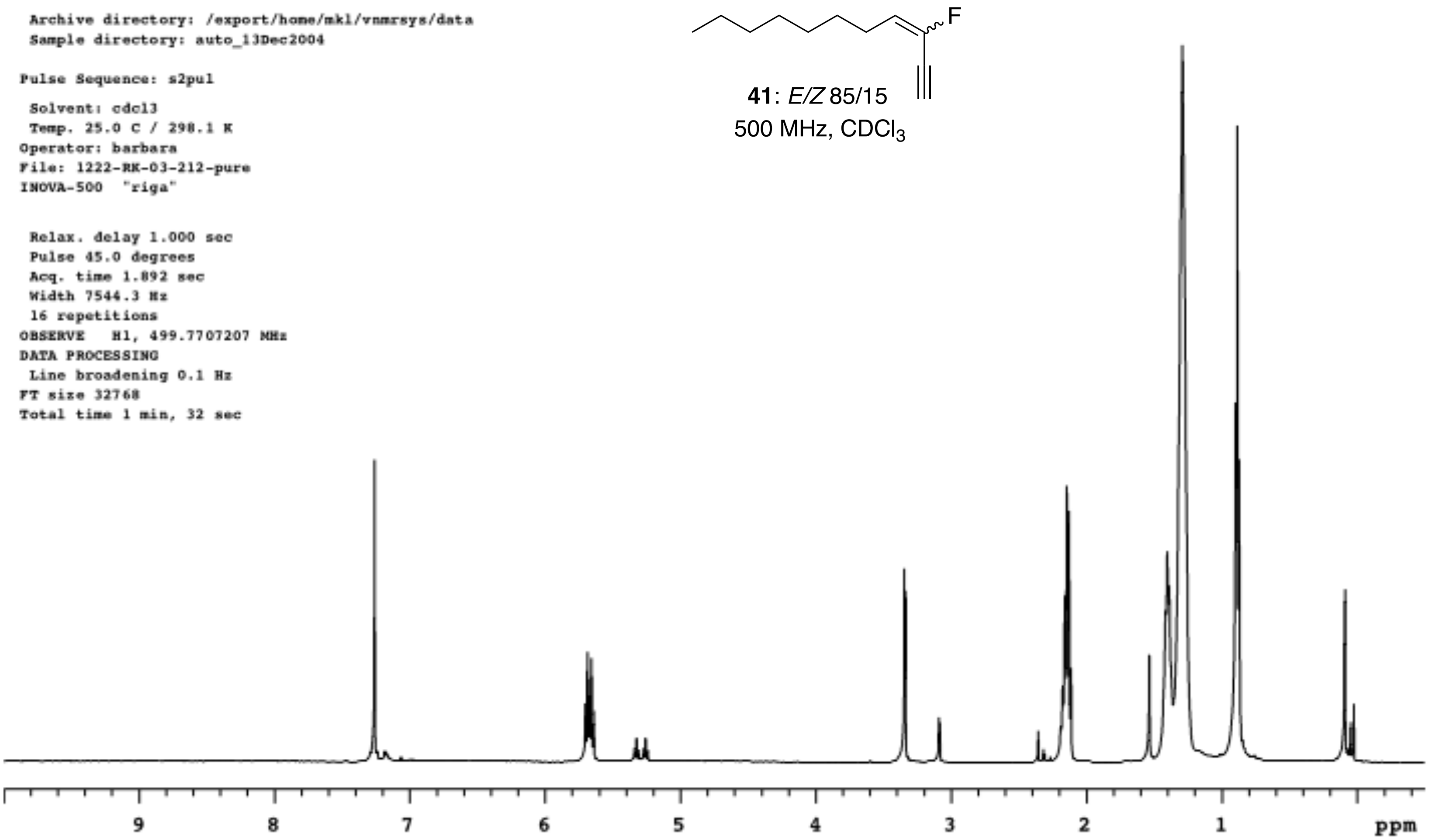
```
1222-RK-03-212-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

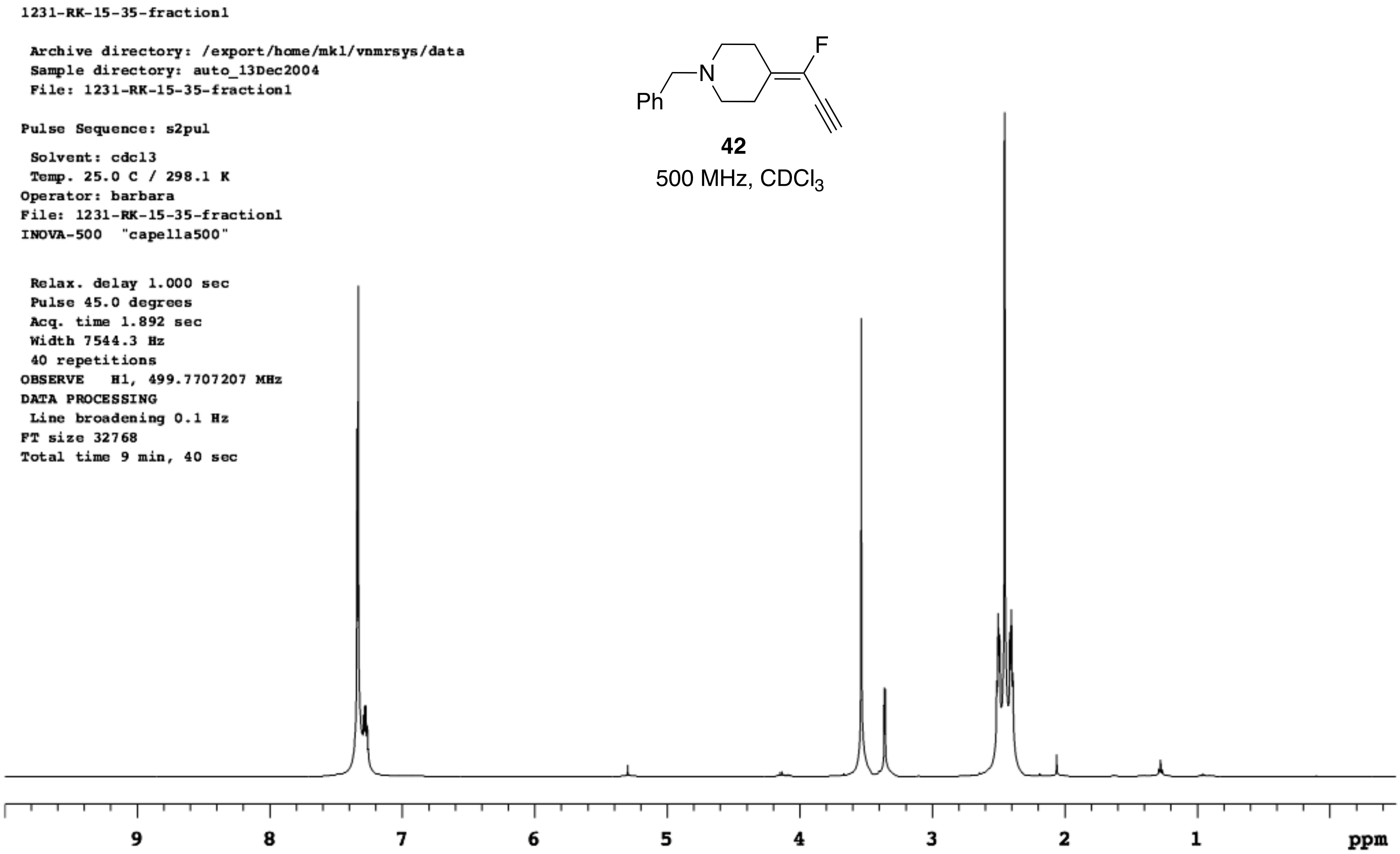
Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-03-212-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 16 repetitions
OBSERVE   H1, 499.7707207 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 32 sec
```



41: *E/Z* 85/15
500 MHz, $CDCl_3$



```
1231-RK-15-35-fraction1

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004
 File: 1231-RK-15-35-fraction1

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-35-fraction1
INOVA-500  "capella500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 40 repetitions
OBSERVE   H1, 499.7707207 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```

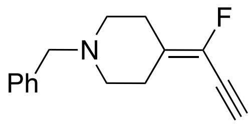
42

500 MHz, $CDCl_3$

```
1231-RK-15-35-fractioin1-13C

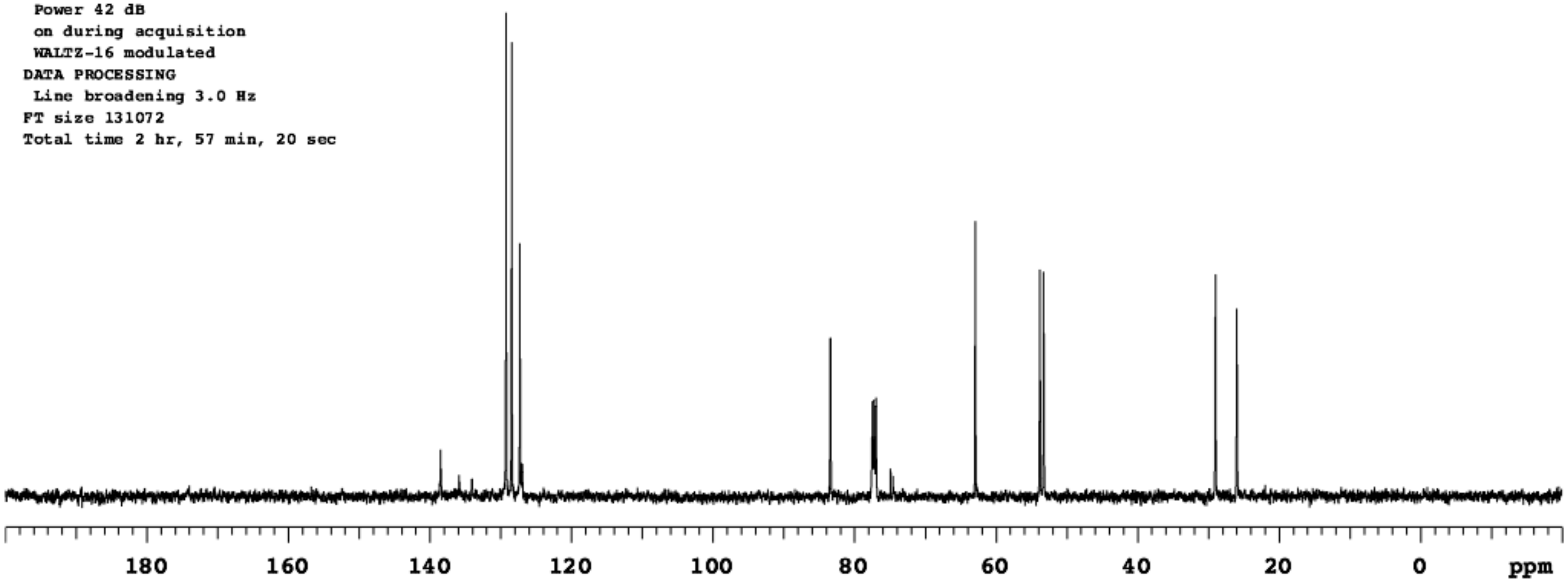
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-35-fractioin1-13C
INOVA-500  "capella500"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 132 repetitions
OBSERVE  C13, 125.6674241 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 3.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec
```



42

125 MHz, $CDCl_3$



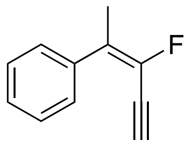
```
1231-RK-15-21-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004
 File: 1231-RK-15-21-pure

Pulse Sequence: s2pul

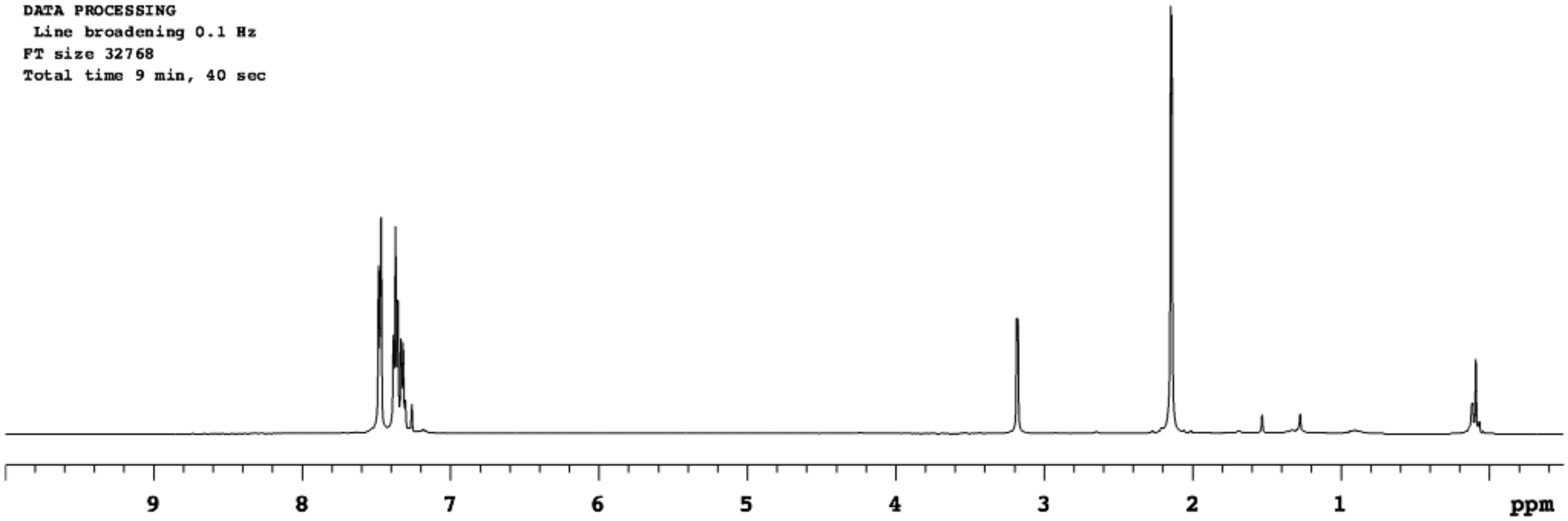
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-21-pure
INOVA-500  "capella500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 24 repetitions
OBSERVE   H1, 499.7707216 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



E-**43**

500 MHz, $CDCl_3$

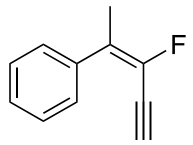


1231-RK-15-21-13C

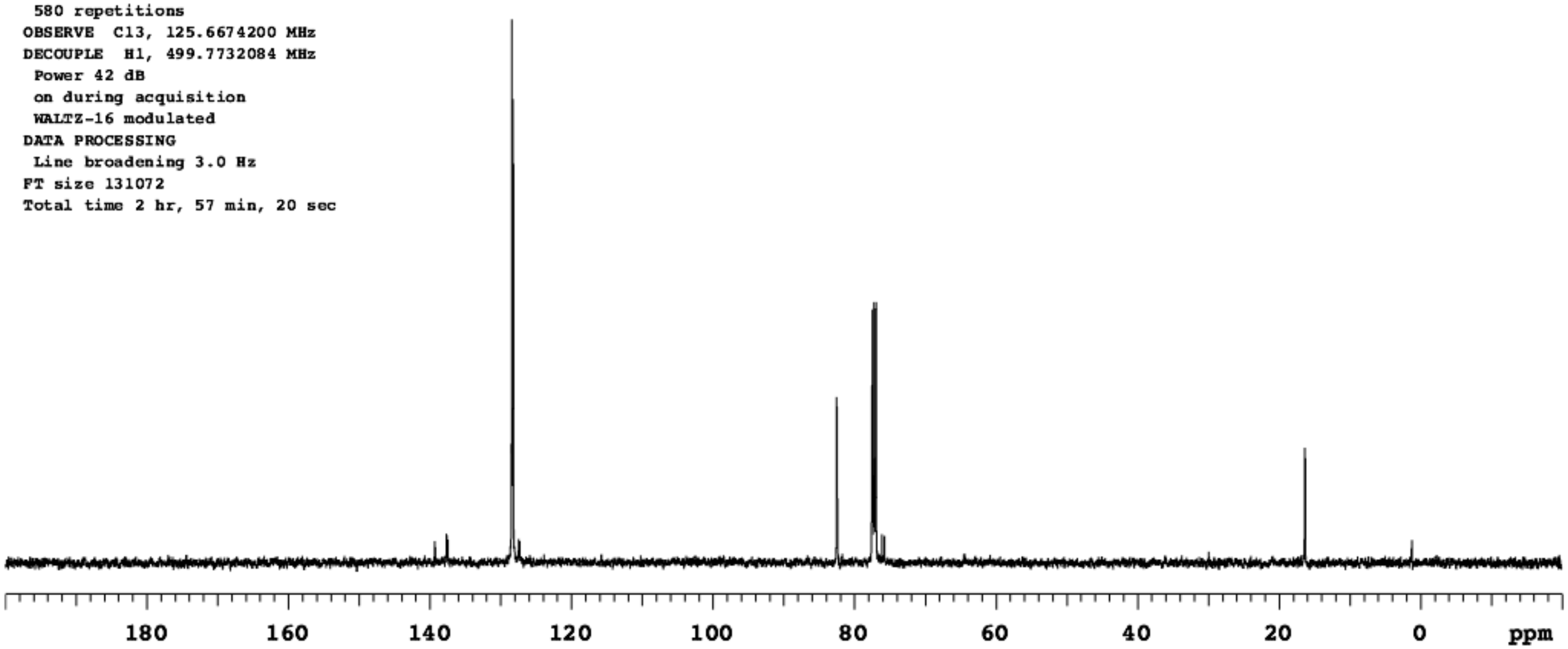
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-21-13C
INOVA-500 "capella500"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
580 repetitions
OBSERVE C13, 125.6674200 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec



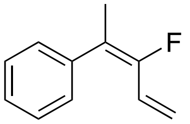
E-**43**
125 MHz, $CDCl_3$



```
1231-RK-15-80-pure

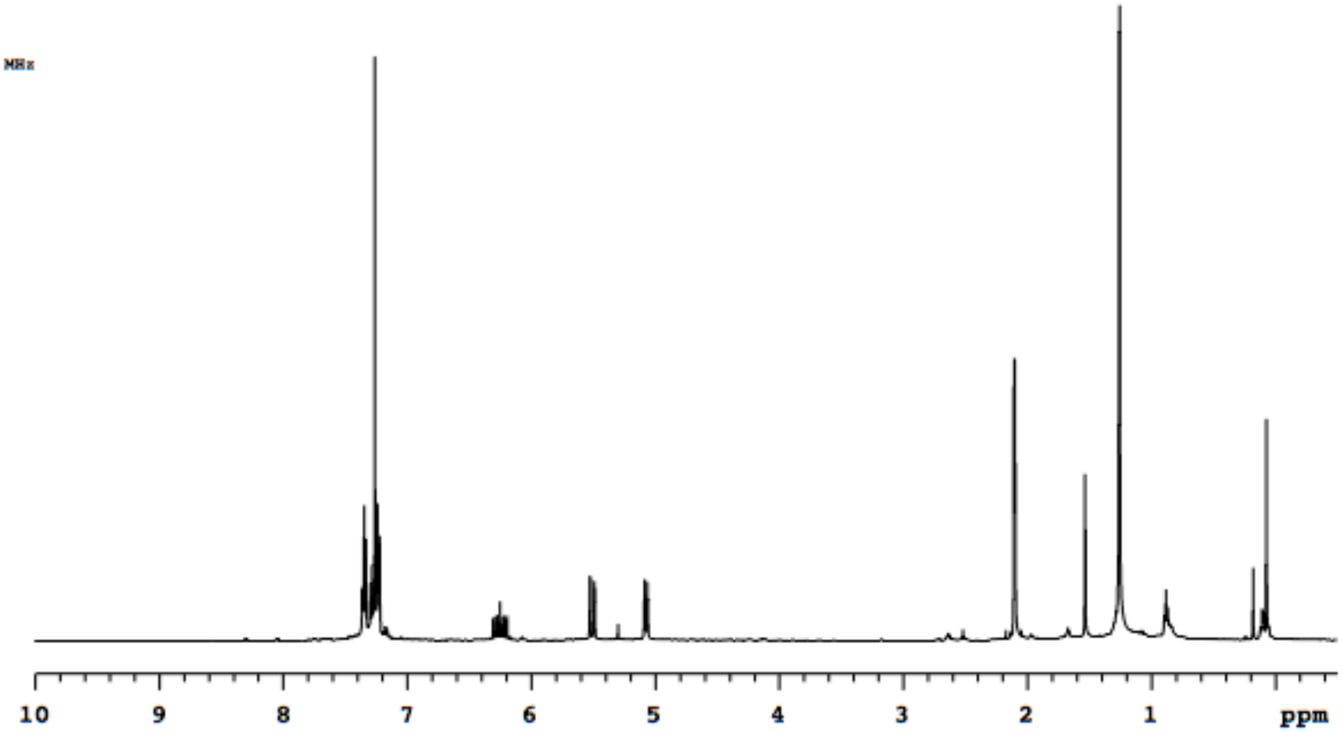
Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-80-pure
INOVA-500  "riga"

 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 24 repetitions
OBSERVE   H1, 499.7707217 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec
```



E-**44**

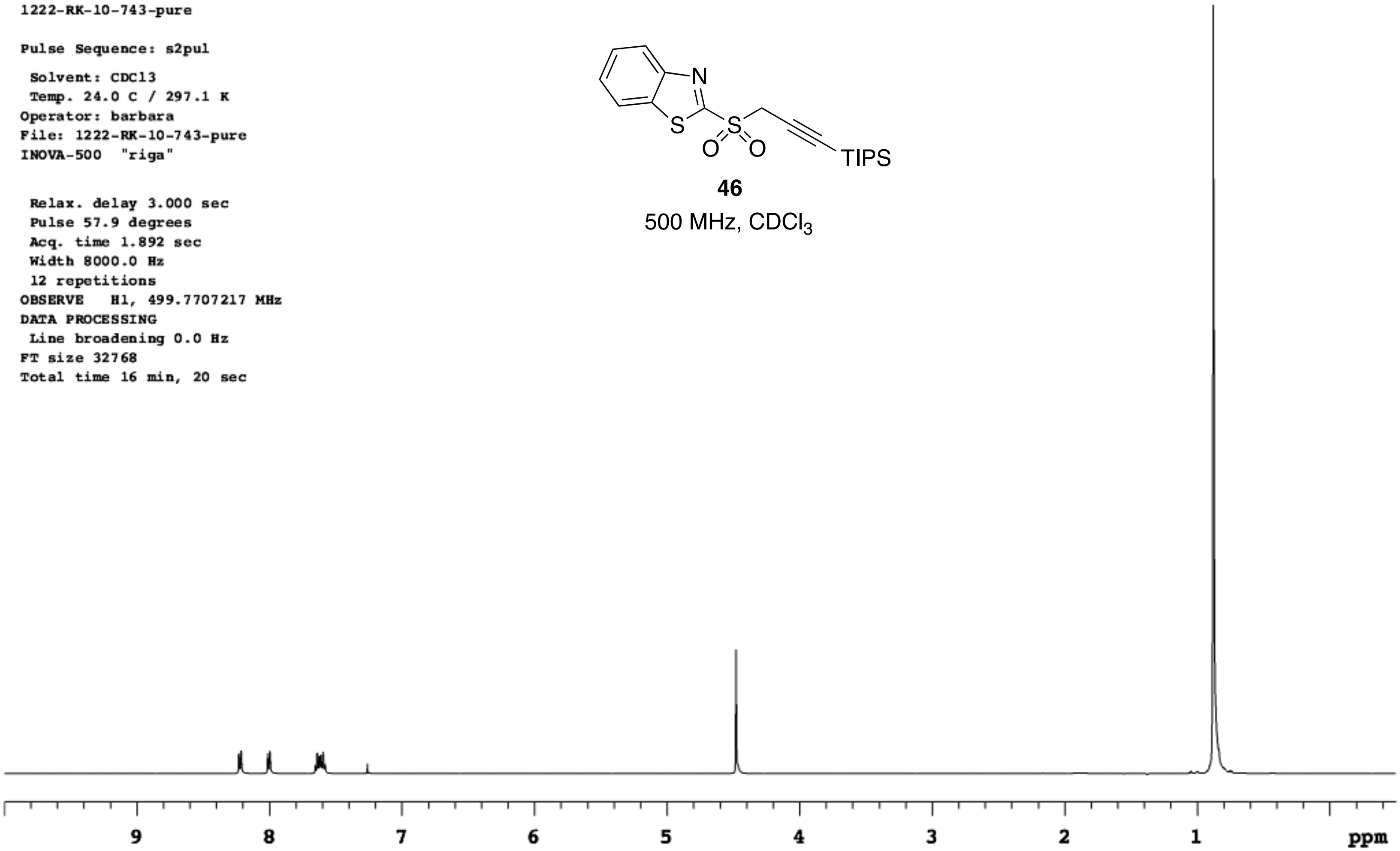
500 MHz, $CDCl_3$



```
1222-RK-10-743-pure

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 24.0 C / 297.1 K
Operator: barbara
File: 1222-RK-10-743-pure
INOVA-500  "riga"

 Relax. delay 3.000 sec
 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 12 repetitions
OBSERVE   H1, 499.7707217 MHz
DATA PROCESSING
 Line broadening 0.0 Hz
FT size 32768
Total time 16 min, 20 sec
```



46

500 MHz, $CDCl_3$

1222-RK-10-743-13C

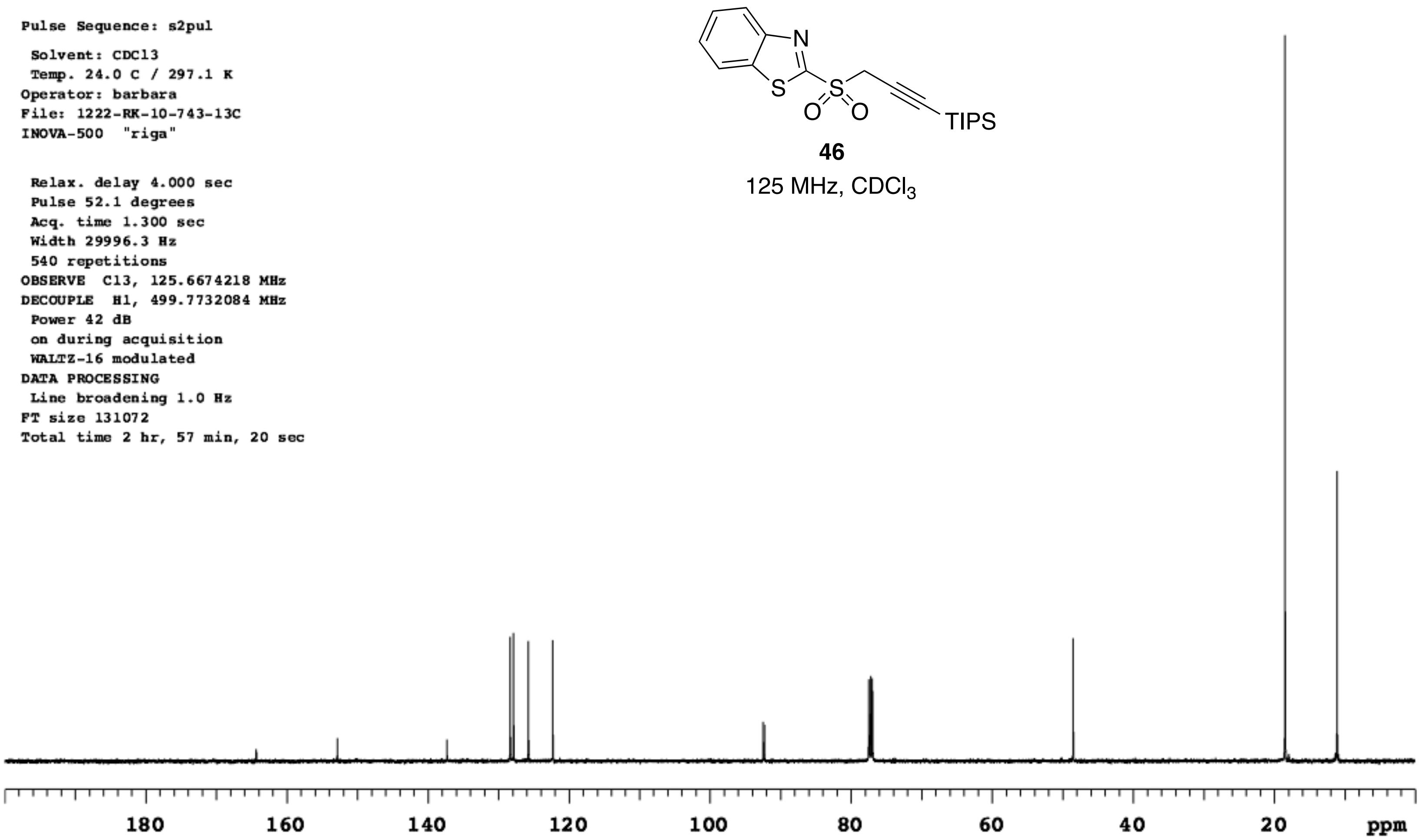
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: barbara
File: 1222-RK-10-743-13C
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
540 repetitions
OBSERVE C13, 125.6674218 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec

46

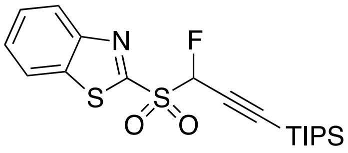
125 MHz, $CDCl_3$



```
1222-RK-10-756-pure

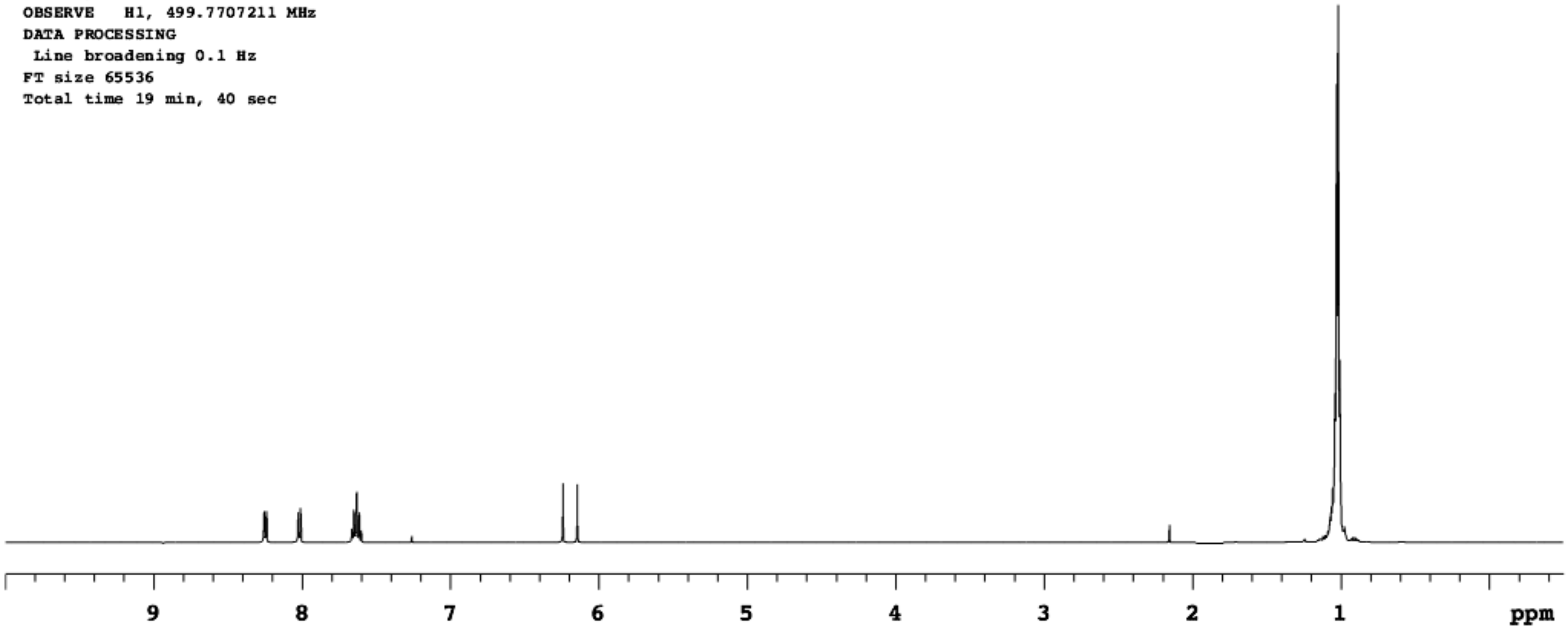
Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: barbara
File: 1222-RK-10-756-pure
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 12 repetitions
OBSERVE   H1, 499.7707211 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 19 min, 40 sec
```



47

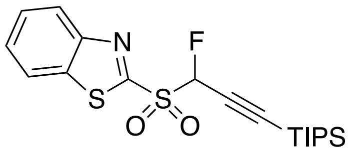
500 MHz, $CDCl_3$



```
1222-RK-10-756-13C

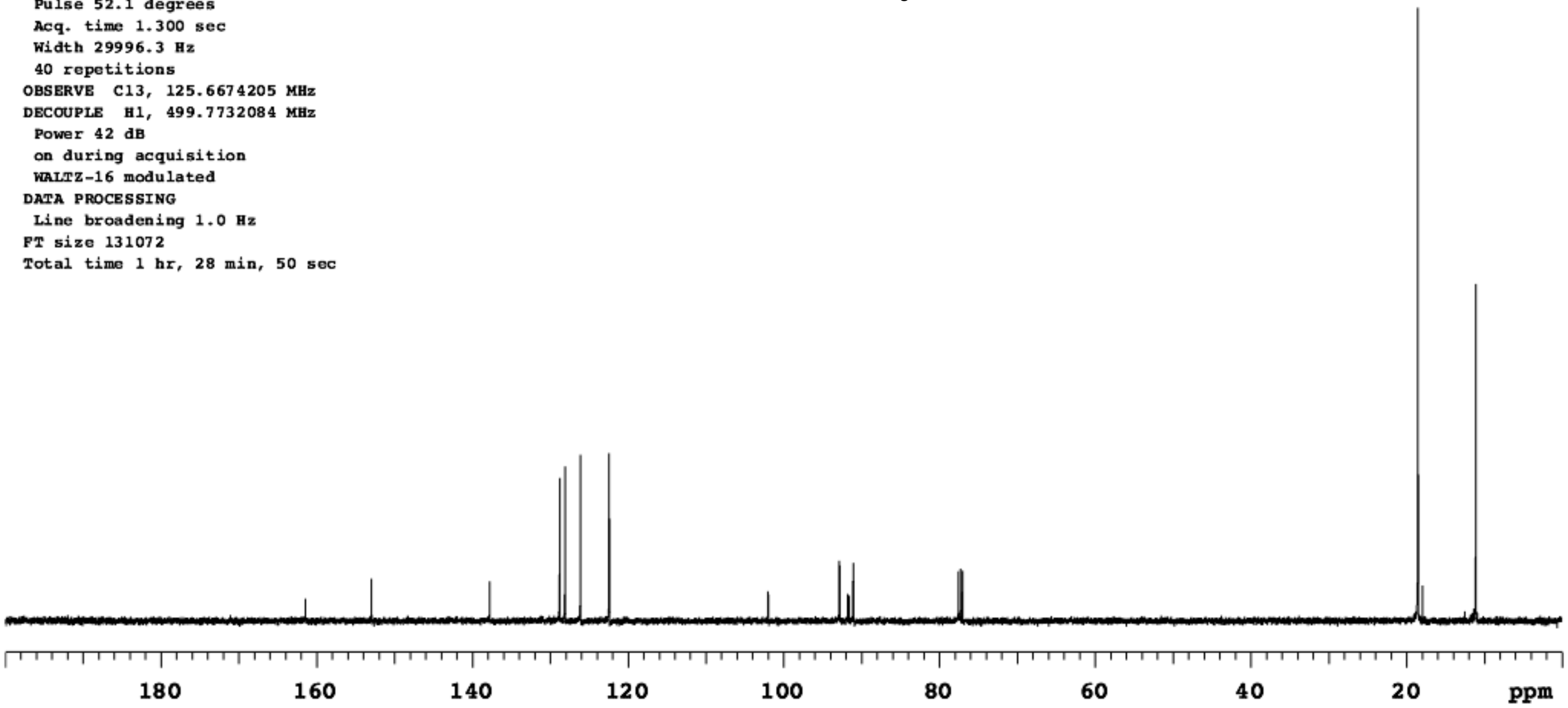
Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-10-756-13C
INOVA-500  "riga"

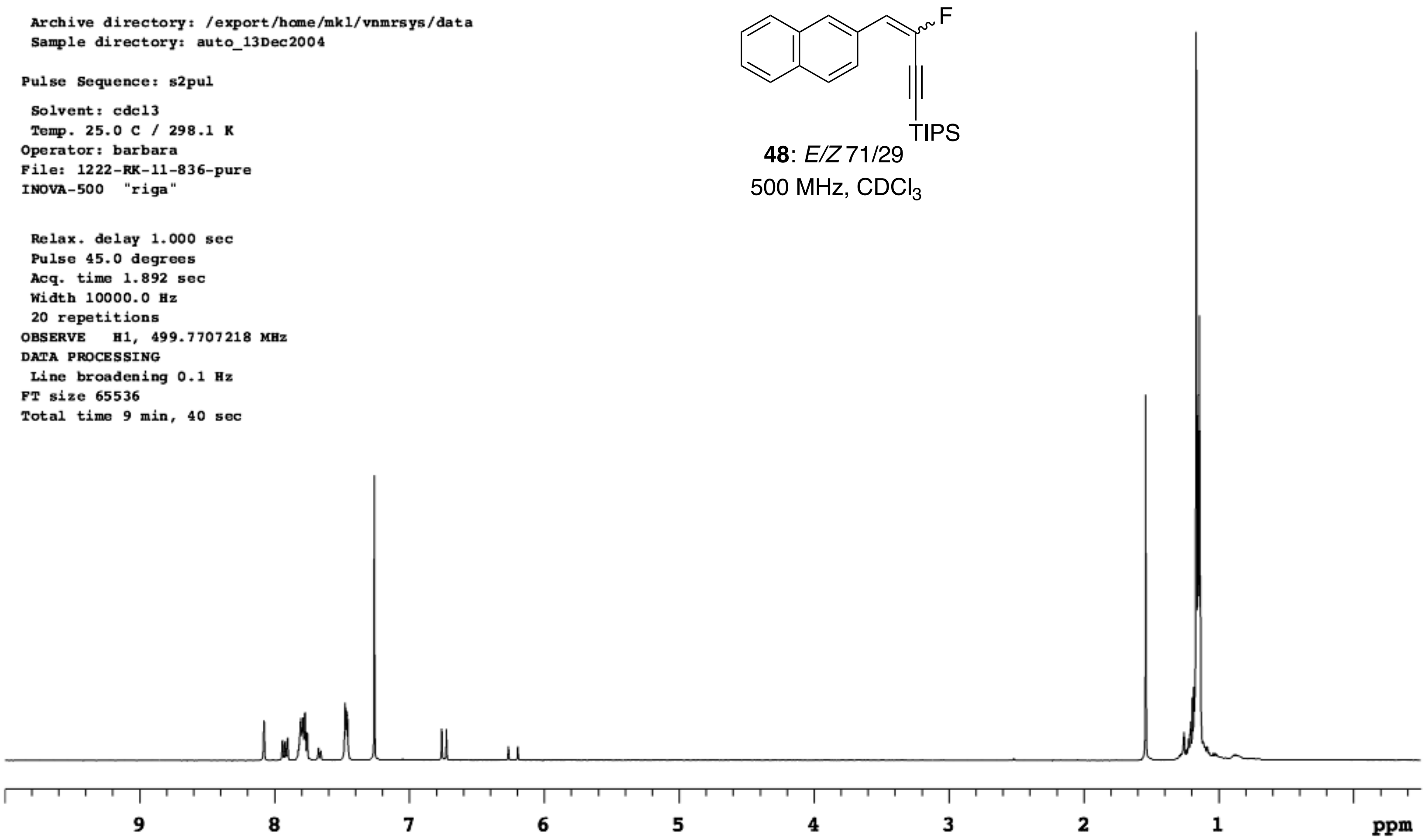
 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 40 repetitions
OBSERVE  C13, 125.6674205 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 28 min, 50 sec
```



47

125 MHz, $CDCl_3$





```
1222-RK-11-836-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-11-836-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 20 repetitions
OBSERVE   H1, 499.7707218 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
```

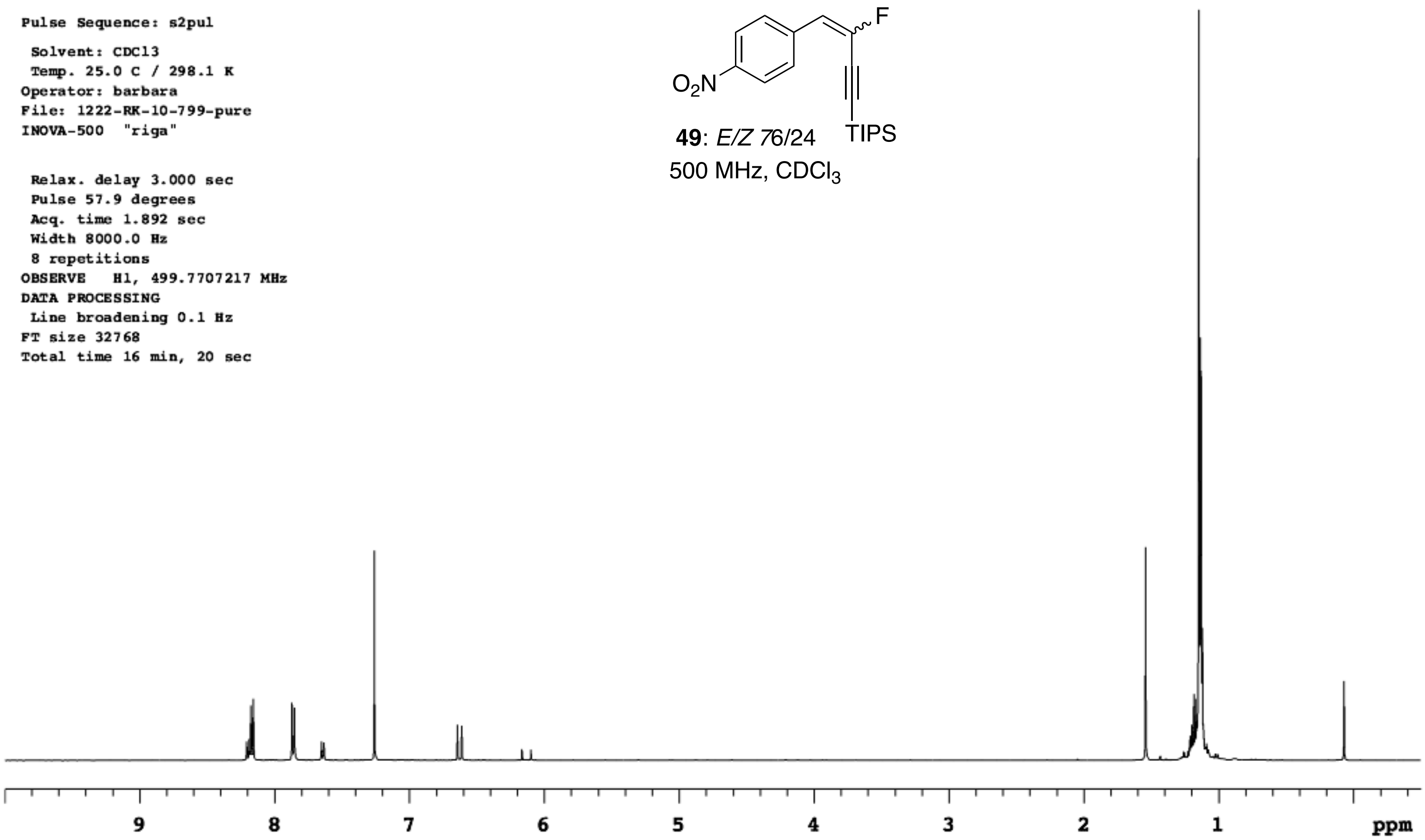
48: *E/Z* 71/29

500 MHz, $CDCl_3$

```
1222-RK-10-799-pure

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-10-799-pure
INOVA-500  "riga"

 Relax. delay 3.000 sec
 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 8 repetitions
OBSERVE   H1, 499.7707217 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 16 min, 20 sec
```



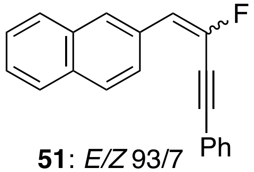
49: *E/Z* 76/24

500 MHz, $CDCl_3$

```
1222-RK-10-760-pure

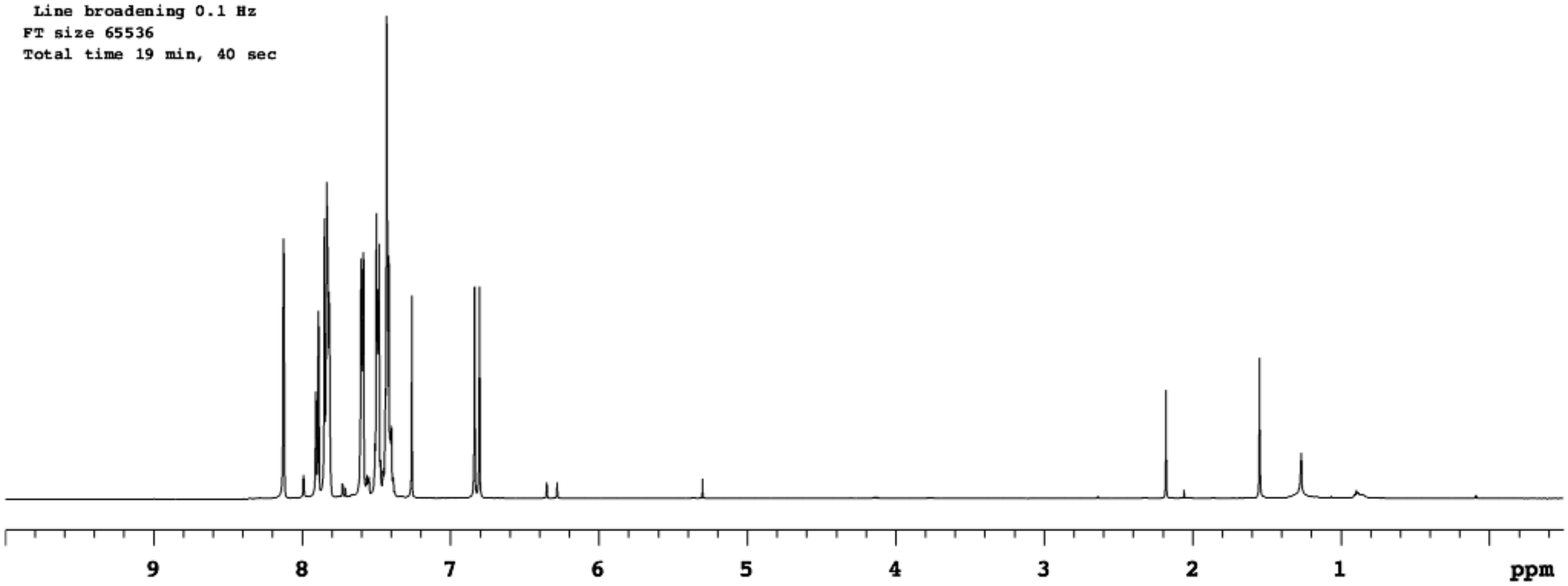
Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: barbara
File: 1222-RK-10-760-pure
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 8 repetitions
OBSERVE   H1, 499.7707214 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 19 min, 40 sec
```



51: *E*/*Z* 93/7

500 MHz, $CDCl_3$



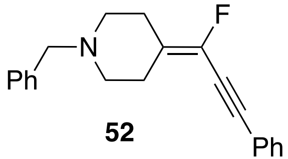
```
1231-RK-15-57-pure

 Archive directory: /export/home/mk1/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

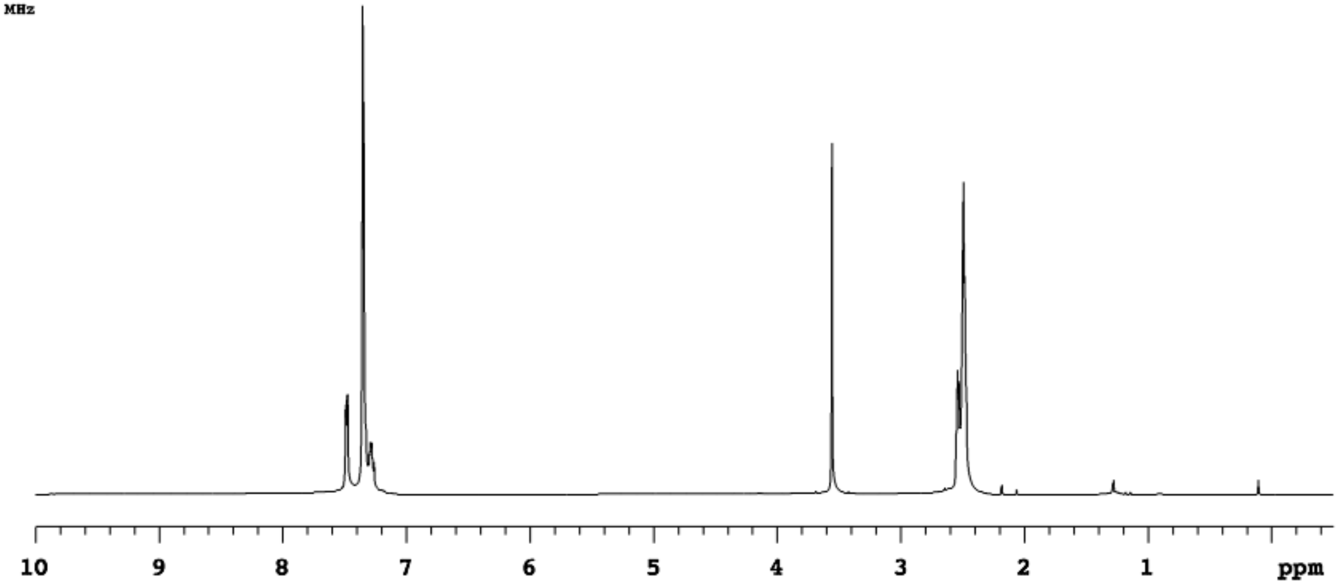
 Solvent: cdcl3
 Temp. 24.0 C / 297.1 K
Operator: barbara
File: 1231-RK-15-57-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 76 repetitions
OBSERVE   H1, 499.7707216 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



52

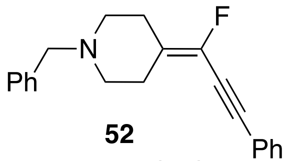
500 MHz, $CDCl_3$



```
1231-RK-15-57-13C

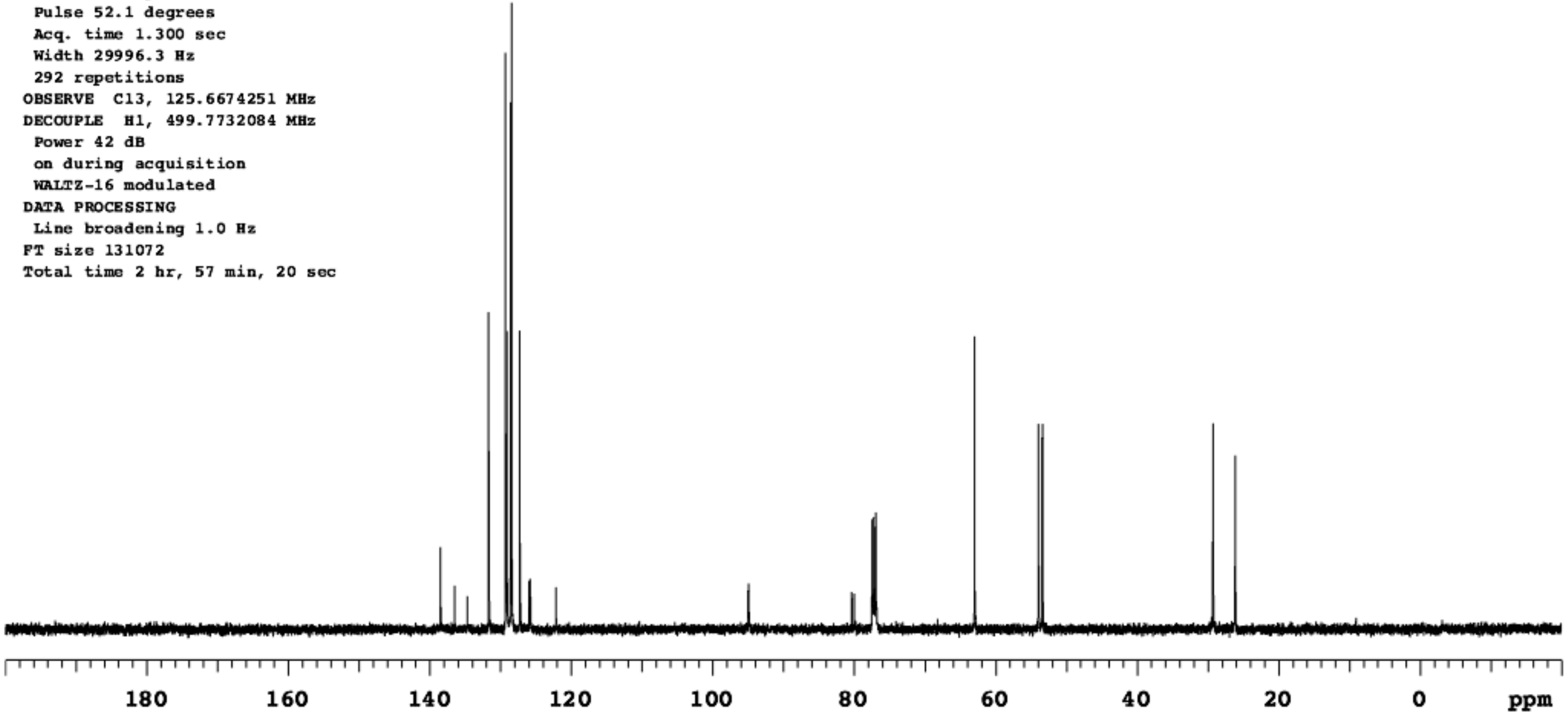
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-57-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 292 repetitions
OBSERVE  C13, 125.6674251 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec
```



52

125 MHz, $CDCl_3$



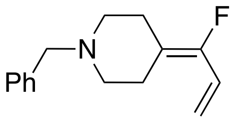
```
1231-RK-15-27-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

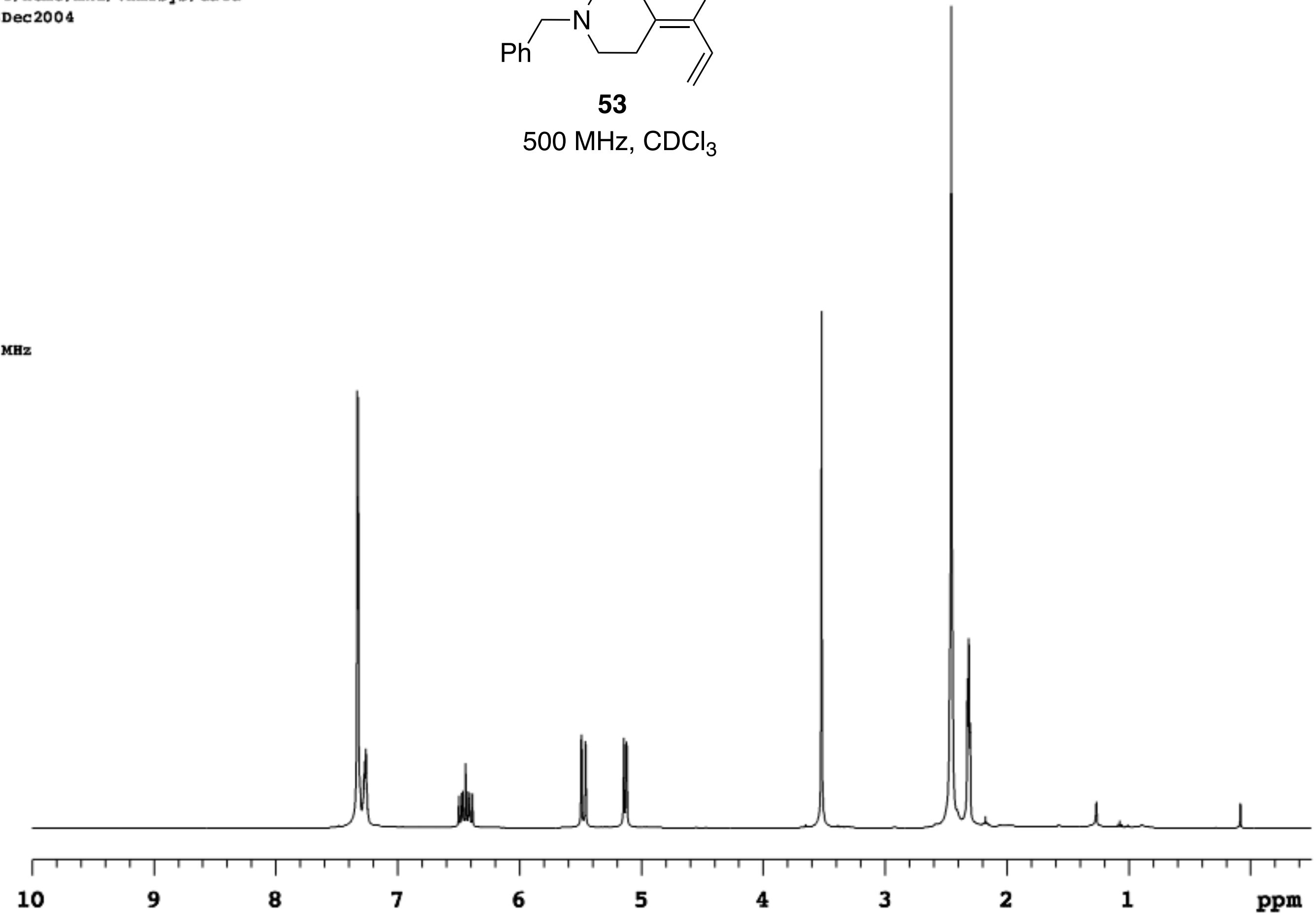
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-27-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 20 repetitions
OBSERVE   H1, 499.7707226 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



53

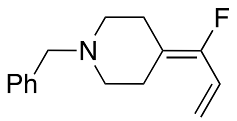
500 MHz, $CDCl_3$



```
1231-RK-15-27-13C

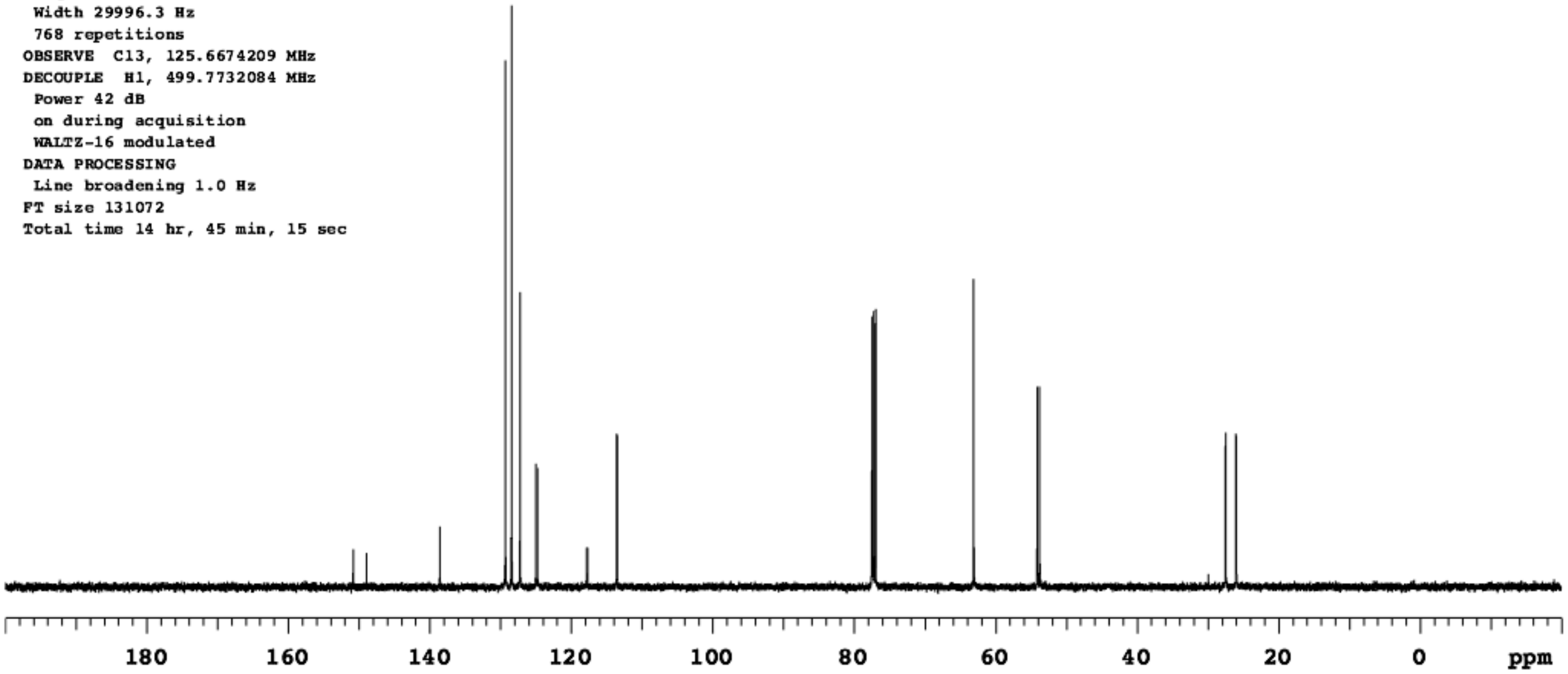
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-27-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 768 repetitions
OBSERVE  C13, 125.6674209 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 14 hr, 45 min, 15 sec
```



53

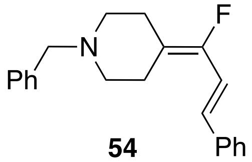
125 MHz, $CDCl_3$



```
1231-RK-15-65-pure

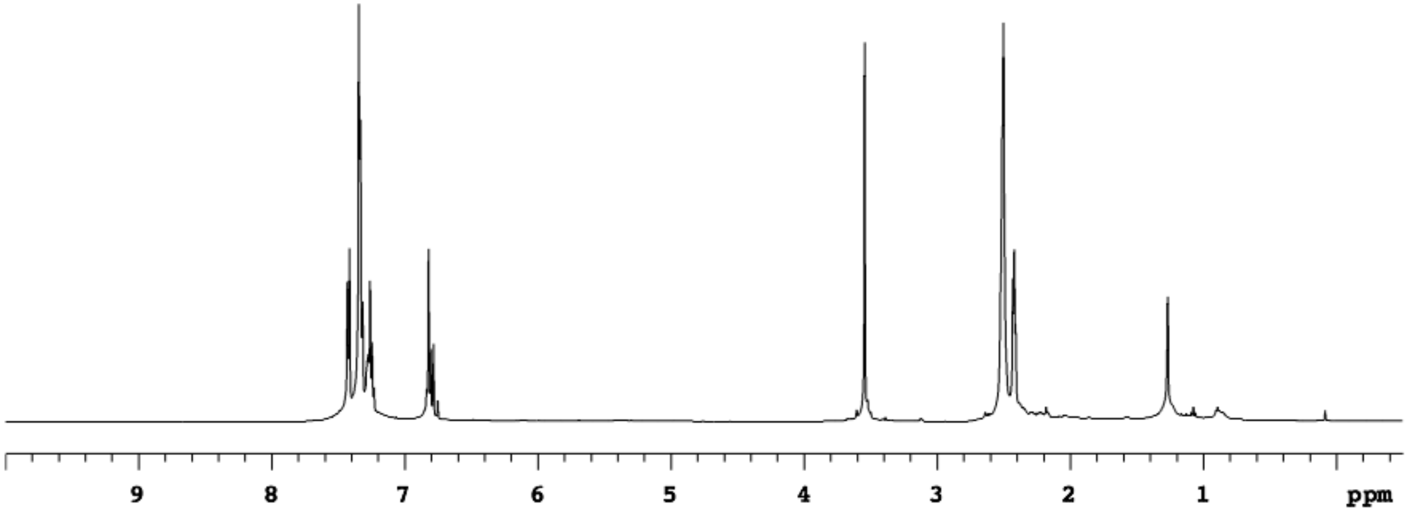
Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-65-pure
INOVA-500  "riga"

 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 108 repetitions
OBSERVE   H1, 499.7707222 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec
```



54

500 MHz, $CDCl_3$



```
1231-RK-15-65-13C

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-65-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 2120 repetitions
OBSERVE  C13, 125.6674200 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 131072
Total time 29 hr, 30 min, 9 sec
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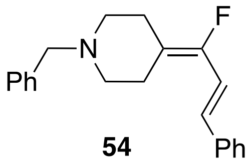
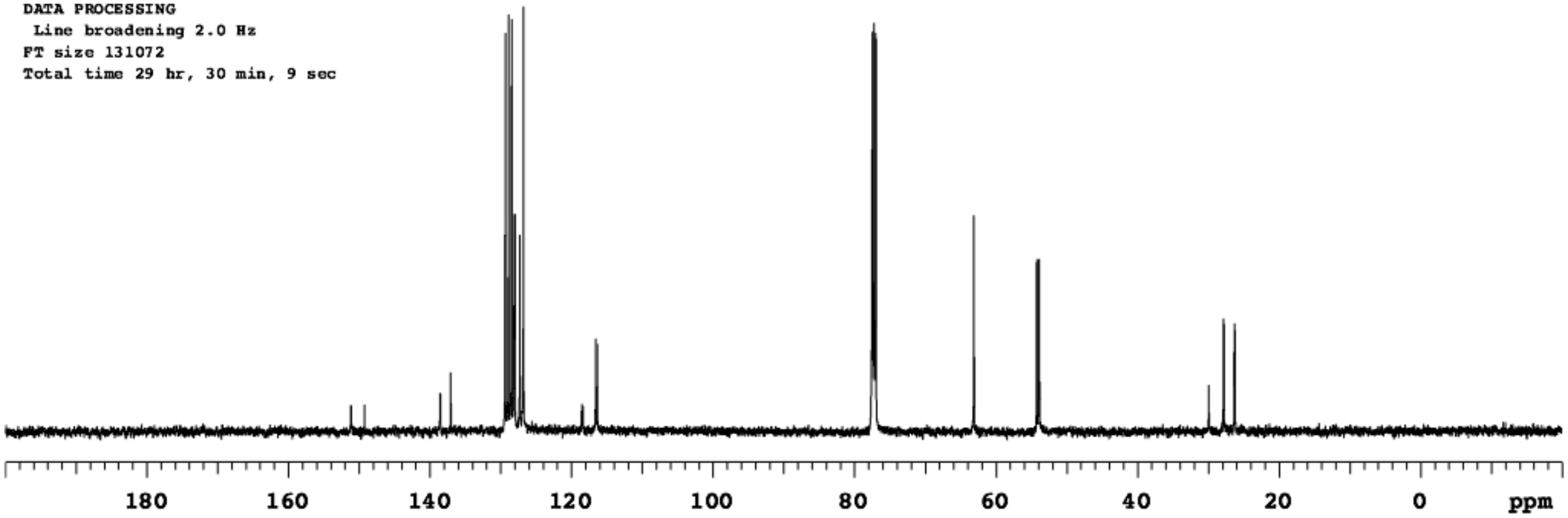


54

125 MHz, $CDCl_3$



```
1231-RK-16-68-pure

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-16-68-pure
INOVA-500  "riga"

 Relax. delay 2.500 sec
 Pulse 38.6 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 16 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 14 min, 40 sec
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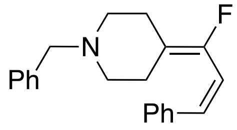
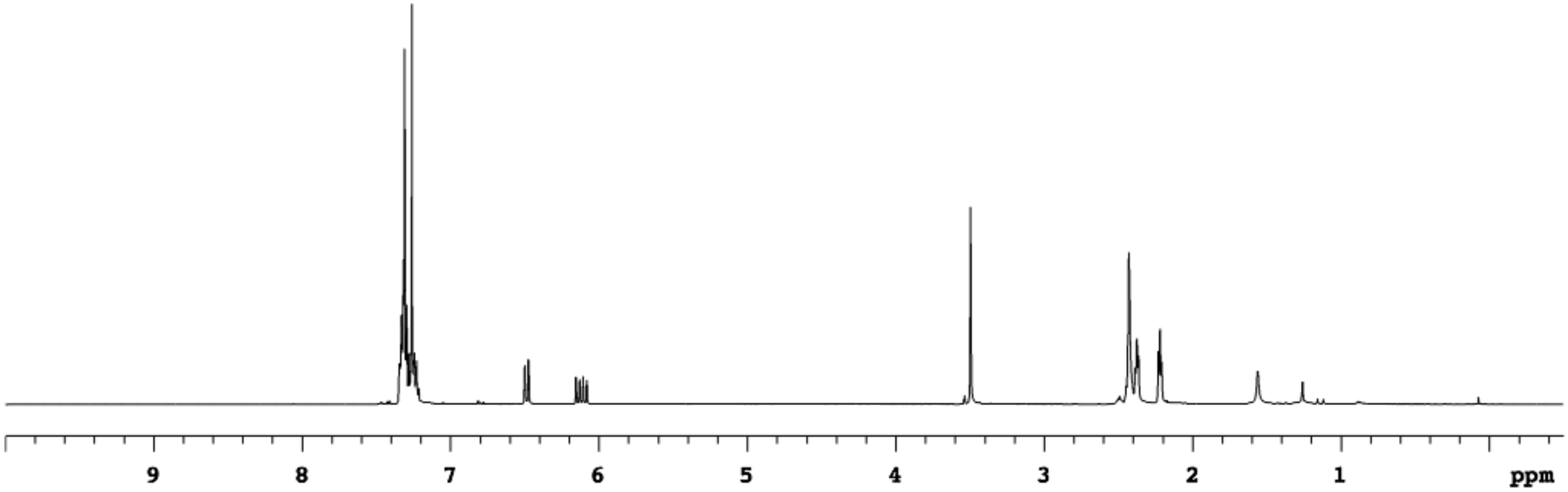


55

500 MHz, $CDCl_3$

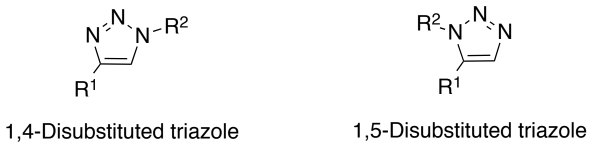


PART 2

MODULAR SYNTHESIS OF FLUOROVINYL AND VINYL 1,2,3-TRIAZOLES VIA CLICK REACTION- JULIA-KOCIENSKI OLEFINATION

2.1 INTRODUCTION

The heterocyclic compounds are widely used as pharmaceutical agents and development of novel methods for their synthesis represent the major part of research in organic chemistry.[1] Among various classes of heterocyclic compounds, 1,2,3-triazoles are of high importance, due to the wide range of their applications.[2-10] 1,2,3-Triazoles are of two types, depending upon the position of the substituents, i.e. 1,4-disubstituted and 1,5-disubstituted, as shown in Figure 1.

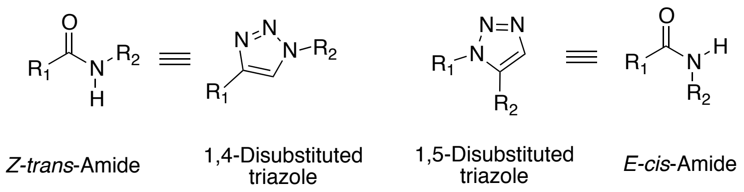


1,4-Disubstituted triazole

1,5-Disubstituted triazole

Figure 1. 1,4- and 1,5-disubstituted 1,2,3-triazoles.

1,2,3-Triazoles mimic the electronic properties of the amide bond very well (see Figure 2) and hence are very good peptide bond isosteres with additional hydrolytic stability.[2-4]



Z-trans-Amide

1,4-Disubstituted triazole

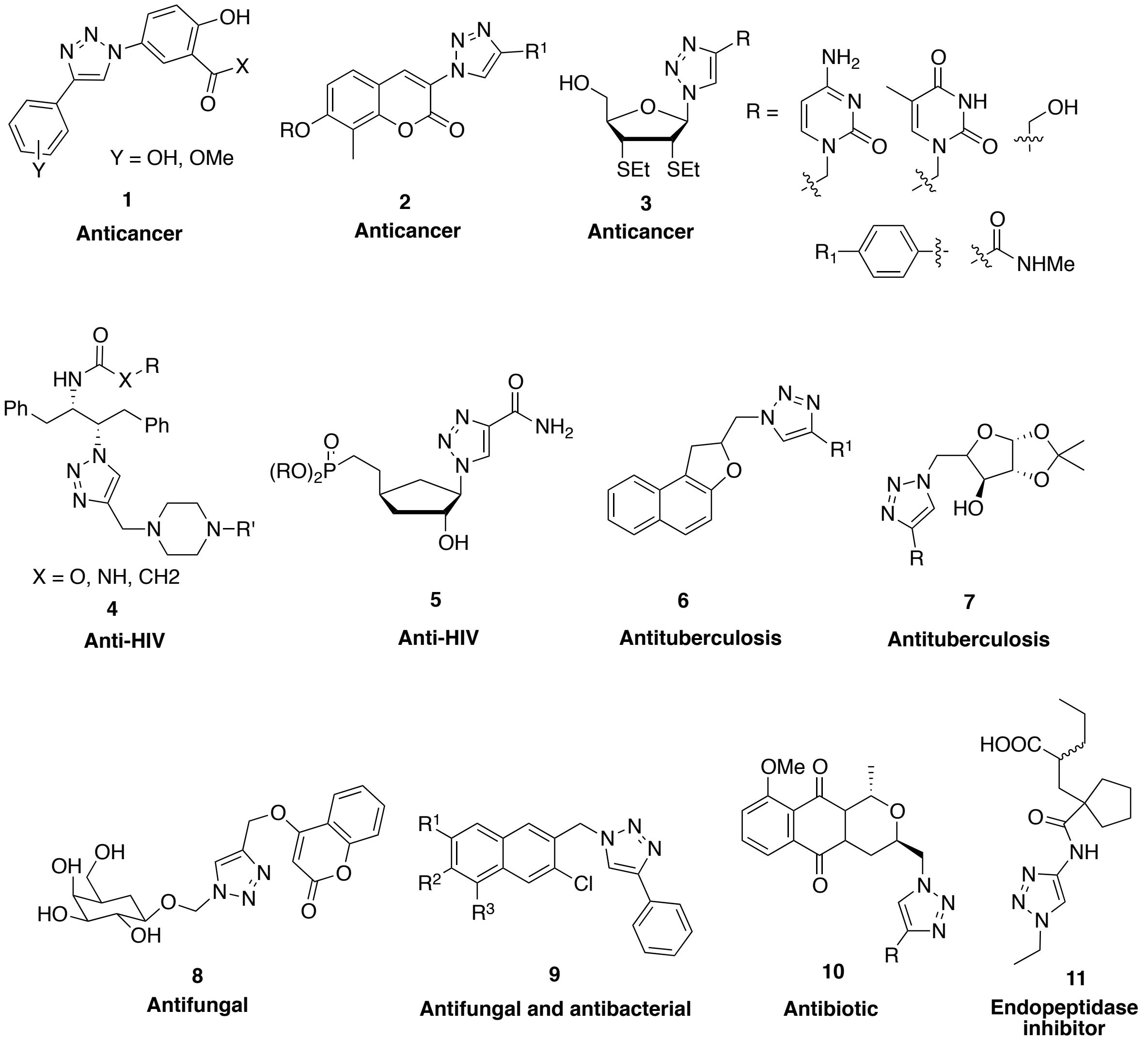
1,5-Disubstituted triazole

E-cis-Amide

Figure 2. 1,2,3-triazoles as amide bond isosteres.

1,4-Disubstituted derivatives are the focus of much of modern research, due to the wide range of their applications.[5-10] These compounds are well-known pharmaceutical agents and have been used as antibiotics, antibacterial, and anti-HIV agents.[5-8] Some representative biologically important triazole compounds are shown in Figure 3.

In addition to their numerous applications as pharmaceutical agents, these compounds are also useful in polymer and materials sciences.[9,10]



1 **Anticancer**

2 **Anticancer**

3 **Anticancer**

4 **Anti-HIV**

5 **Anti-HIV**

6 **Antituberculosis**

7 **Antituberculosis**

8 **Antifungal**

9 **Antifungal and antibacterial**

10 **Antibiotic**

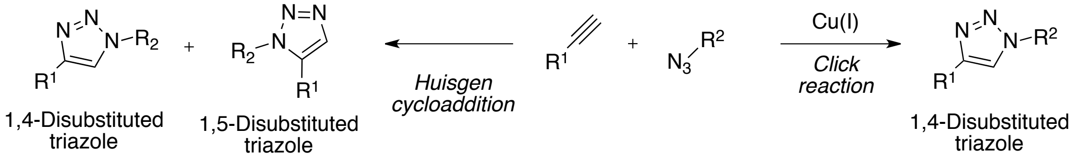
11 **Endopeptidase inhibitor**

Figure 3. 1,4-Disubstituted triazoles as pharmaceutical agents.

Original method for the synthesis of 1,2,3-triazoles involved the alkyne-azide cycloaddition reaction developed by Rolf Huisgen.[11] This method requires high temperature and longer reaction times, and produces mixtures of 1,4- and 1,5-disubsituted triazole derivatives

(Scheme 1). This approach was modified in 2002 by Meldal[12] and Sharpless,[13] where the use of copper(I) catalysts produced exclusively 1,4-disubstituted triazoles. These reactions generally require milder conditions and shorter reaction times than the classical Huisgen cycloaddition reactions. The modified version is also known as azide-alkyne click reaction.[2-10, 14,15]

Scheme 1. Huisgen Cycloaddition and Cu(I)-Catalyzed Click Reaction



In the past decade, a large number of research groups have used azide-alkyne click reaction for the syntheses of triazoles and it still is an integral part of modern research.[14,15] One major disadvantage of this reaction is that internal alkynes are not suitable reactants under these conditions. The original mechanism of Cu(I) catalyzed click reaction proposed by Sharpless is shown in Figure 4.[13,16] This mechanism has also been supported by computational and kinetic studies by Sharpless and Fokin.[16-18]

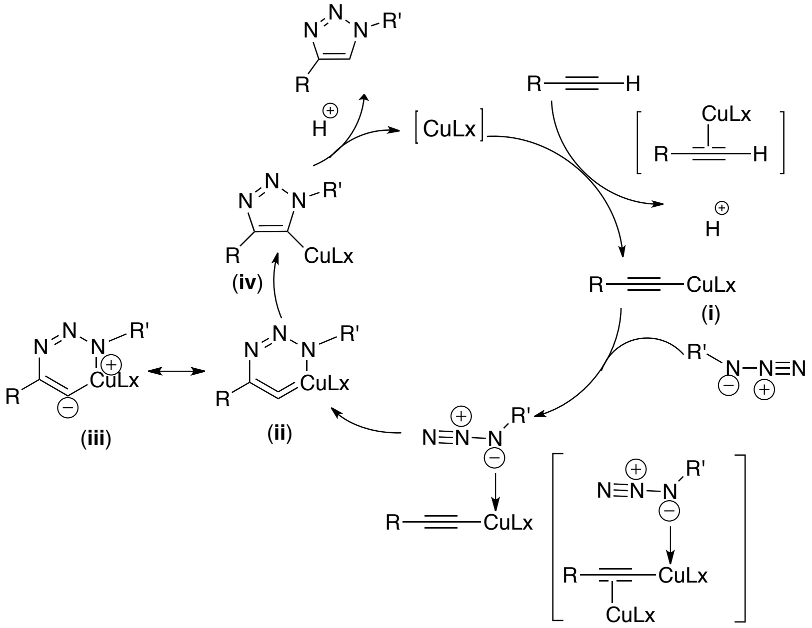
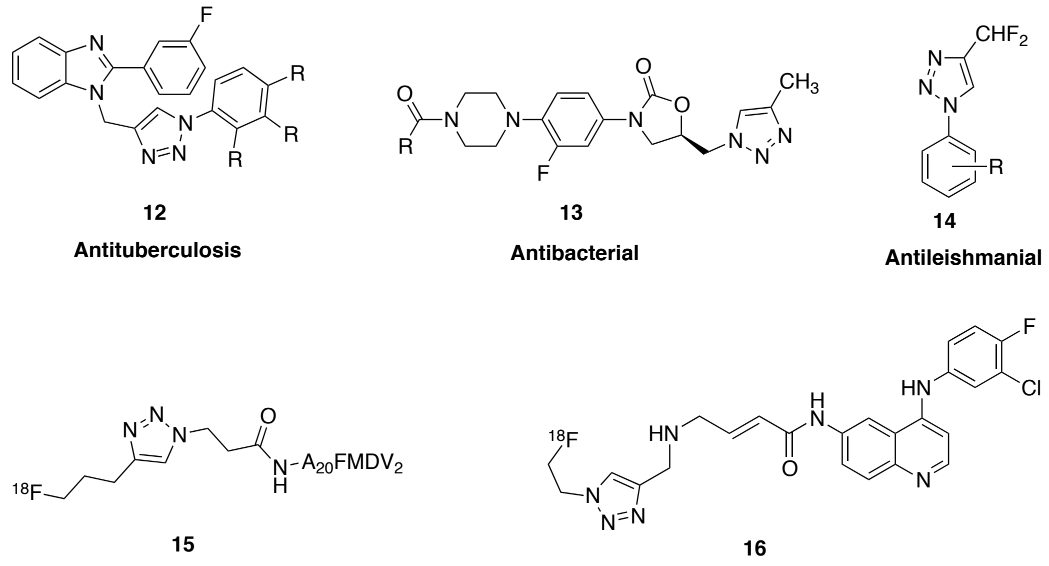


Figure 4. Mechanism of the azide-alkyne click reaction.

Introduction of fluorine into organic molecules changes their chemical, physical and biological properties.[19-21] As a result of this, fluoroorganics are useful as drugs, agrochemicals and polymers.[19-22] The applications of such compounds have been described in the General Introduction. Fluorine containing triazoles have also been recognized as a biologically useful class of compounds.[5,23-25] Some representative examples are shown in Figure 5. Also, in the recent years, ^{18}F-labeled triazoles have been used for positron emission tomography (PET) imaging technique.[15, 26-29] Compounds **15** and **16** are two examples of such 1,2,3-triazole compounds.



12
Antituberculosis

13
Antibacterial

14
Antileishmanial

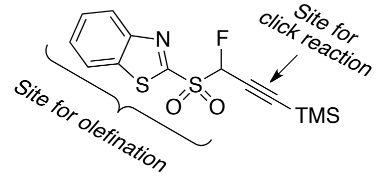
15

16

Figure 5. Biologically relevant fluorine containing 1,2,3-triazoles.

Fluoroolefins are highly useful synthetic precursors and also a known class of biologically relevant compounds.[30-33] Assembly of a triazole moiety with fluorovinyl unit can therefore lead to a synthetically and biologically versatile class of compounds. There are no reports in literature on the synthesis of such compounds. The unavailability of methods for the synthesis of fluorovinyl triazoles, prompted our interest in exploring a modular approach towards the synthesis of 4-fluorovinyl-1,2,3-triazoles. Fluoro-Julia olefination is a convenient approach for the synthesis of fluoroolefins and has emerged in the recent years.[34]

Synthesis of fluorovinyl triazoles by Julia-Kocienski olefination, requires availability of (triazolyl)fluoromethyl heteroaryl sulfones, Julia-Kocienski reagents. In Part 1, we have reported synthesis of TMS-protected fluoropropargyl benzothiazolyl sulfone, a bifunctional building block **17** (shown in Figure 6).



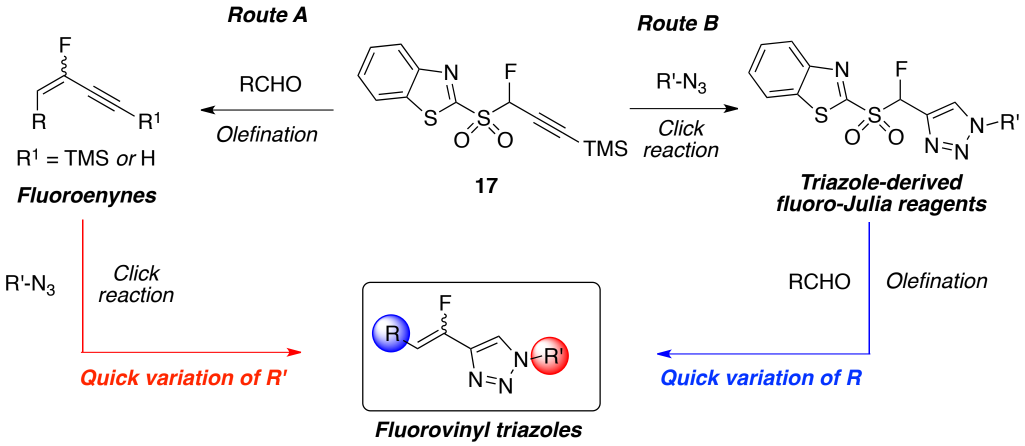
17

Figure 6. Bifunctional fluoro-Julia-Kocienski reagent.

Azide-alkyne ligation with fluoro-Julia reagent **17** can result in 'second generation' Julia-Kocienski reagents for synthesis of fluorovinyl triazoles. Alternatively, these can be synthesized via click reaction from fluoroenynes. Synthesis of fluorovinyl triazoles from our *key building block* **17** using two the routes is shown in Scheme 2. In route A, the initial condensation of compound **17** provides fluoroenynes that can be subjected to click reactions with various azides. In route B, by performing click reactions with various azides, compound **17** can be converted to a new class of "Second Generation" fluoro-Julia reagents. These triazole-derived Julia-Kocienski reagents, upon condensations with carbonyl compounds, can be converted to fluorovinyl triazoles. Depending upon what part of the molecule requires variation, either of the two routes can be used. However, limitation of route A is that fluoroenynes can be obtained only with *E*-selectivity as described in Part 1. So the methodology using route A is limited to *E*-selective synthesis of fluorovinyl triazoles. We were interested to see whether route B can overcome this limitation, and if the variation of olefination conditions of triazole-derived fluoro-Julia reagents would provide an access to fluorovinyl triazoles with *Z*-selectivity.

Part 2 describes synthesis of triazole-derived fluoro-Julia reagents by click reactions of fluoropropargyl BT sulfone. The effect of α-fluorine on the reactivity of alkyne in click reactions is also studied. The reactivity of unfluorinated propragyl BT-sulfone in click reactions, and vinyl triazoles in condensation reactions of the resulting triazole-derived Julia reagents is presented.

Scheme 2. Possible Routes for Synthesis of Fluorovinyl Triazoles from Building Block **17**



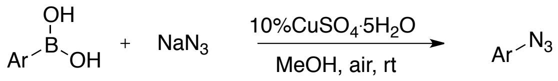
2.2 RESULTS AND DISCUSSION

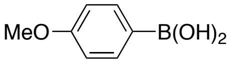
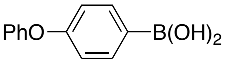
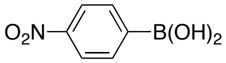
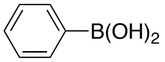
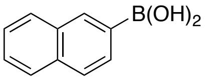
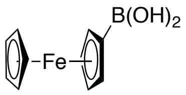
2.2.1 Synthesis of Azides

There are various methods reported in the literature for the synthesis of azides. Syntheses of aryl azides from boron reagents were reported by Tao et al.[35] and Grimes et al.[36] In the first case,[35] boronic acids, were reacted with sodium azide in the presence of copper sulfate ($CuSO_4$), to produce aryl azides in high yields.[35] Grimes et al.[36] reported that boronic acids, boronates and trifluoroborates reacted with sodium azide in the presence of $Cu(OAc)_2$ to produce aryl as well as heteroaryl azides.[36] Whereas aryl azides were obtained in high yields, low yields of heteroaryl azides were reported.[36] The method was not suitable for conversions of alkyl boronic acids, that did not react under these conditions.

Various aryl azides and a ferrocenyl azide were synthesized from the corresponding boronic acids and sodium azide in the presence of $CuSO_4$ (see Table 1). Electron rich as well as electron deficient aryl boronic acids reacted efficiently to give high yields of the azides. Ferrocenyl azide was also synthesized in high yield.

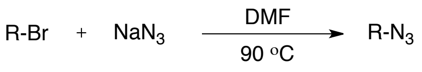
Table 1. Synthesis of Aryl Azides From Boronic Acids



Entry	Ar-B(OH)$_2$	Product	%Yield
1		**18**	98
2		**19**	97
3		**20**	90
4		**21**	70
5		**22**	98
6		**23**	89

Two alkyl azides, i.e. 3-phenylpropyl azide **24** and *n*-decyl azide **25** were also synthesized by nucleophilic substitution reactions of corresponding alkyl bromides, as shown in Scheme 3.[37] Adamantyl azide **26** (Table was obtained from the commercial source.

Scheme 3. Synthesis of Alkyl Azides From Alkyl Bromides

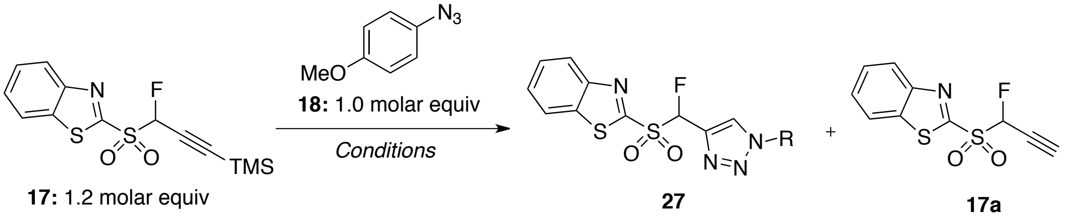


24; R = 3-Phenylpropyl (87%)
25; R = 1-Decyl (42%)

2.2.2 Synthesis of Triazole-Derived Fluoro-Julia-Kocienski Reagents

As discussed earlier, for click reactions terminal alkynes are required and internal alkynes are not suitable candidates. In the present case, since the alkyne partner, i.e. the TMS-fluoropropargyl benzothiazolyl sulfone, contains a TMS-protected triple bond, the removal of TMS group was necessary. The use of $AgBF_4$ provided the TMS-free alkyne functionality, but the column chromatographic purification gave a mixture of alkyne and the rearranged fluoroallene product. A one-pot synthesis of triazoles by deprotection-click reaction of TMS-protected alkynes was reported by Aucagne et al.,[38] where the use of a copper catalyst, $Cu(CH_3CN)_4PF_6$ in the presence of $AgBF_4$ in 4:1 CH_2Cl_2/MeOH produced high yields of triazoles. Using these conditions, i.e. TMS-fluoropropargyl benzothiazolyl sulfone **17** was reacted with *p*-methoxyphenyl azide **18**, and the triazole product **27** was obtained in 93% yield in 2 h (Table 2).

Table 2. Screening of Conditions for Deprotection-Click Reaction

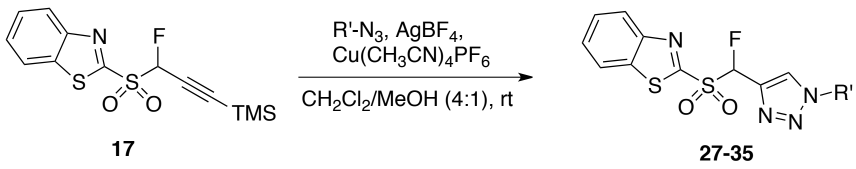


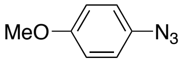
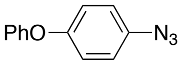
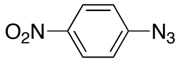
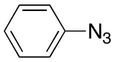
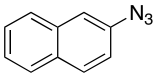
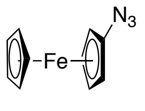
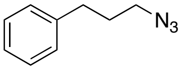
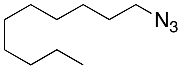
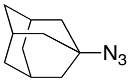
Entry	Click catalyst (molar equiv)	$AgBF_4$ (molar equiv)	Solvent; temp (°C); time (h)	%Yield[a] or % ratio of **27**: **17**: **17a**[b]
1	$Cu(CH_3CN)_4PF_6$ (0.2)	0.2	CH_2Cl_2/MeOH (4 :1); rt; 2	93
2	$CuSO_4 \cdot 5H_2O$ (0.1); sodium ascorbate (0.2)	0.2	*t*-BuOH/H_2O (9.5 : 0.5); 35; 72	16 : 0 : 84[b]
3	$CuSO_4 \cdot 5H_2O$ (0.05); sodium ascorbate (0.1)	0.2	CH_2Cl_2/H_2O (1.7 : 1); rt; 72	5 : 77: 18[b]

[a]Yield of purified product **27**. [b]Relative ratio of **27** : **17** : **17a** determined by ^{19}F NMR. Molar excess of **17** was considered while calculating the ratio.

Use of $CuSO_4$/sodium ascorbate catalyst system in *t*-BuOH/H_2O[13,38] resulted in a sluggish reaction, and after 72 hours only 16% conversion to triazole was observed. Similarly, $CuSO_4$/sodium ascorbate in a biphasic solvent system CH_2Cl_2/H_2O[39] gave only 5% conversion to the triazole, even after 72 hours (Table 2).

Table 3. Synthesis of Triazole-Derived Fluoro-Julia-Kocienski Reagents by Click Reaction



Entry	R'-N_3	Product	%Yield[a]
1	**18**; 	**27**	93
2	**19**; 	**28**	90
3	**20**; 	**29**	82
4	**21**; 	**30**	79
5	**22**; 	**31**	92
6	**23**; 	**32**	66
7	**24**; 	**33**	68
8	**25**; 	**34**	81
9	**26**; 	**35**	85

[a]Yields of purified products.

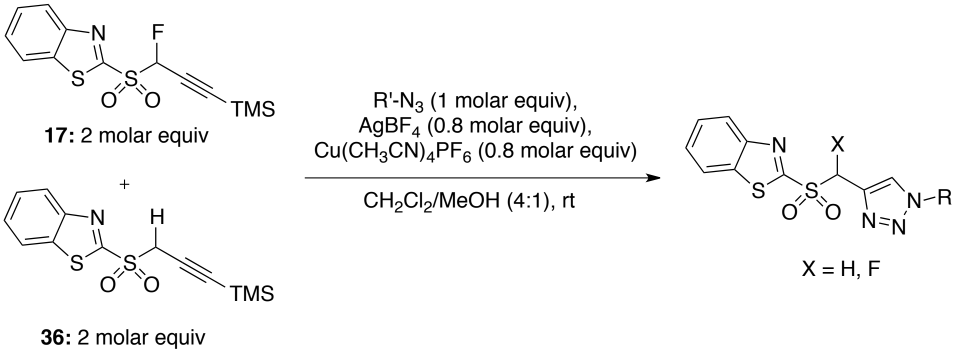
No further conditions for deprotection-click reaction were tested and using $Cu(CH_3CN)_4PF_6/AgBF_4$, TMS-fluoropropargyl benzothiazolyl sulfone **17** was reacted with aryl and alkyl azides. The triazole-derived fluoro-Julia-Kocienski reagents were obtained in good to high yields, as shown in Table 3. Yields were high in reactions with electron rich aryl azides (entries 1, 2 and 5). Electron deficient aryl azide **20** also reacted efficiently to give a very good yield of a triazole product **29** (82%, entry 3), and the yield was similar to that obtained with phenyl azide **21** (79%, entry 4). Reaction with organometallic, ferrocenyl azide was also successful, giving 66% yield of the click product **32** (entry 6). Among alkyl azides, 3-phenylpropyl azide **24** furnished product **33** in 68% yield (entry 7), whereas *n*-decyl azide **25** as well as adamantyl azide **26** gave triazoles in 81% and 85% yield, respectively (entries 8 and 9).

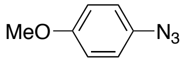
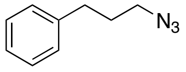
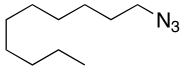
2.2.3 Effect of Fluorine Substitution on Reactivity of Alkyne in Click Reactions

It has been shown previously that the presence of fluorine atoms at the α-carbon to the triple bond in difluorinated cyclooctynes increases reactivity in uncatalyzed click reactions.[40-45] Such an effect was also observed in Cu(I)-catalyzed azide-alkyne ligation reactions of monofluorinated diynes.[46] We were interested to assess the effect of fluorine in fluoropropargyl sulfone **17** on the reactivity of alkyne in Cu(I)-catalyzed ligation reactions. In competitive experiments, equimolar mixtures of fluoro reagent **17** (2.0 molar equiv) and its protio analog **36** (2.0 molar equiv) were reacted with three different azides (Table 4). In all cases studied, fluoroalkyne showed higher reactivity than the protio analog. A very high fluoro/protio ratio (11.5) of click products was obtained in the reaction with 4-methoxyphenyl azide **18** (entry 1). Similarly, 3-phenylpropyl azide **24** and *n*-decyl azide **25** also gave 4.9 and 2.6 ratios of fluoro/protio triazole derivatives, respectively (entries 2 and 3).

To get an insight into the basis of higher reactivity of **17** compared to **36** in click reactions, computational studies were performed. Preliminary DFT calculations were performed on silyl free alkyne derivatives **17a** and **36a** respectively, using B3LYP/6-311++G(2d,2p) method (see Tables 5 and 6). A very small difference in the HOMO energies of **17a** and **36a** was observed, whereas the LUMO of **17a** was lower in energy than that of **36a** by 3.7 kcal mol^{-1} (Table 5).

Table 4. Competitive Click Reactions of **17** and **36**

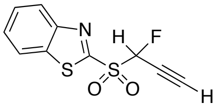
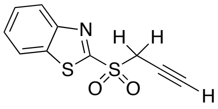


Entry	R′-N$_3$	% Ratio of products[a]	
		X = F to	X = H
1	**18**; 	**27**; 92	**37**; 8
2	**24**; 	**33**; 83	**38**; 17
3	**25**; 	**34**; 72	**39**; 28

[a]Relative ratios of products determined by ^{1}H NMR

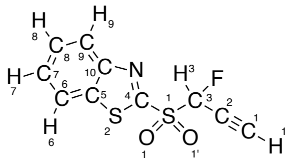
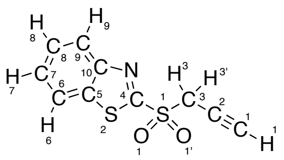
Also, the NBO bond order of triple bond in **17a** (1.926) was nearly equal to that in **36a** (1.932). The NBO analyzed natural charges at the triple bonds revealed interesting differences (see Table 6).

Table 5. Calculated LUMO and HOMO Energies of **17a** and **36a**

Entry	Molecular orbitals	 **17a**	 **36a**
		Energy (kcal mol^{-1})	Energy (kcal mol^{-1})
1	LUMO	-56.8	-53.1
2	HOMO	-167.8	-167.6

The terminal carbon C1 in **17a** showed a lower electron density than **36a**, whereas the internal carbon C2 in **17a** had a higher electron density than **36a**. This indicates that in the ligation reactions of **17a**, the accumulating negative charge at the terminal alkynyl carbon can be stabilized by the presence of fluorine. The stepwise mechanism of Cu(I)-catalyzed azide-alkyne ligation reactions is shown in Figure 4. In the catalytic cycle, formation of copper-metallacycle (**ii**) is proposed to be the rate- limiting step that results in the accumulation of negative charge on the terminal carbon of the alkyne (intermediate **iii**). [13,16,17] The involvement of the second copper atom stabilizes the transition state.[17,18] In the case of reactions of **17** an additional stabilization of the accumulating negative charge by fluorine substituent can be the major factor responsible for the higher reactivity of **17** compared to **36**.

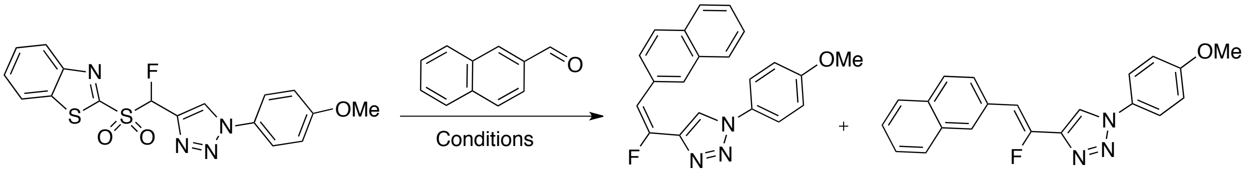
Table 6. Calculated NBO Analyzed Natural Charges of **17a** and **36a**

 **17a**		 **36a**	
Atom number	**NBO analyzed natural charges**	**Atom number**	**NBO analyzed natural charges**
H1	0.232	H1	0.230
C1	-0.110	C1	-0.162
C2	-0.101	C2	-0.050
C3	-0.004	C3	-0.636
H3	0.228	H3	0.252
F	-0.353	H3’	0.266
S1	2.027	S1	2.063
O1	-0.878	O1	-0.881
O1’	-0.889	O1’	-0.908
C4	-0.191	C4	-0.186
N	-0.436	N	-0.444
S2	0.474	S2	0.464
C5	0.102	C5	0.101
C6	-0.173	C6	-0.175
H6	0.223	H6	0.223
C7	-0.199	C7	-0.200
H7	0.211	H7	0.211
C8	-0.180	C8	-0.182
H8	0.211	H8	0.211
C9	-0.211	C9	-0.211
H9	0.218	H9	0.218
C10	-0.203	C10	-0.205

2.2.4 Condensations of Triazole-Derived Fluoro-Julia-Kocienski Reagents

Next, we wanted to test the triazole-derived fluoro-Julia reagents in the olefination reactions. For optimization of olefination reactions, compound **27** (1-1.6 molar equiv) was reacted with 2-naphthaldehyde (1.0 molar equiv) under different conditions (Table 7). Use of LHMDS in a mixed solvent 1:1 DMF/DMPU at -78 °C gave very high *Z*-selectivity and a good yield of fluorovinyl triazole **40** in a short reaction time of 3 min (entry 1). Use of $MgBr_2$ and THF as a solvent gave no olefin product after 51 h (entry 2). We were interested to see if the olefination reactions of compound **27** could be performed using milder bases. In fact, the use of DBU in DMF at -55 °C produced the olefins, but with lower *Z*-selectivity than the LHMDS-mediated reaction (compare entries 3 and 1). Change of solvent to DMF/DMPU 1:1 and lowering of temperature to -78 °C increased the reaction time and decreased the *Z*-selectivity (entry 4).

Table 7. Optimization of Olefination Conditions in Reactions of **27** with 2-Naphthaldehyde



27 **40**; *E*-isomer **40**; *Z*-isomer

Entry	Base (molar equiv)	Additive (molar equiv)	Solvent; temp; time	% *E/Z*[b]; %yield[c]
1	LHMDS (2.4)		DMF-DMPU[a]; -78 ºC; 3 min	7/93; 76
2	LHMDS (2.4)	$MgBr_2$ (1.8)	THF; -78 ºC; 51 h	NR[d]
3	DBU (4.0)		DMF; -55 ºC; 3.5 h	22/78; NA[e]
4	DBU (4.0)		DMF-DMPU[a]; -78 ºC; 24 h	27/73; Inc[f]
5	DBU (4.0)		THF; -78 ºC; 50 h	63/37; Inc[f]
6	DBU (4.0)		THF; rt; 10 h	77/23; 77
7	DBU (4.0)		THF; 50 ºC; 6 h	77/23; NA[e]
8	DBU (4.0)		THF; reflux; 2.5 h	78/22; 74
9	DBU (4.0)	$MgBr_2$ (1.8)	THF; reflux; 40 min	69/31; NA[e]
10	DBU (4.0)		$CHCl_3$; reflux; 4.5 h	75/25; NA[e]

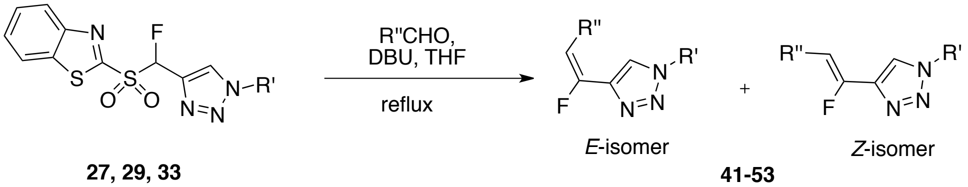
[a] 1:1 v/v mixture of solvents used. [b] *E/Z* ratio of diastereomers determined in the crude mixture by ^{19}F NMR. [c] Yields of purified products. [d] No product observed. [e] Products werenot isolated. [f] Incomplete reaction and products not isolated.

Interestingly, reversal of the stereoselectivity occurred in reaction with DBU, when performed in THF at -78 °C (entry 5). The reaction was very slow and did not go to completion even after 50 h. Increase in temperature to room temperature resulted in completion of reaction in 10 h, and a significant increase in *E/Z* ratio (compare entries 5 and 6). Further increase in temperature to 50 °C decreased the reaction time, but did not have an effect on *E/Z* ratio (entry 7). Under reflux, a marginal improvement in the *E/Z* ratio was observed, but the reaction was decreased to 2.5 h (entry 8). Addition of $MgBr_2$, or change of solvent to $CHCl_3$, marginally decreased the *E/Z* ratio (entries 9 and 10). With conditions that allowed tenability of olfinations determined, we decided to perform the reactions using two sets of conditions that give complementary stereoselectivity, i.e. LHMDS/ DMF-DMPU/-78 °C for high *Z*-selectivity and mild DBU/THF/reflux for high *E*-selectivity. To show the generality of this methodology as well as the scope of tenability of olefinations for the synthesis of fluorovinyl triazoles, three triazole-derived fluoro-Julia reagents were reacted with aryl as well as aliphatic aldehydes under both conditions. The fluoro-Julia reagents that were chosen for the study were two *N*-aryl and one *N*-alkyl-derived reagents, i.e. electron rich *N*-(*p*-methoxyphenyl) and electron deficient *N*-(*p*-nitrophenyl) substituted derivatives (**27** and **29**, respectively), and *N*-(3-phenylpropyl)-derived reagent **33**.

2.2.4.1 DBU-Mediated Condensations

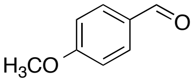
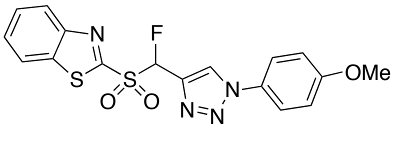
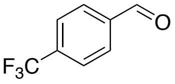
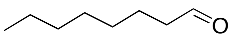
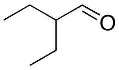
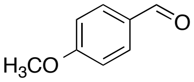
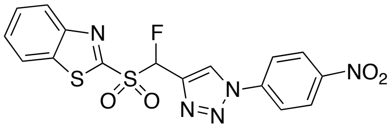
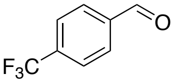
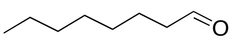
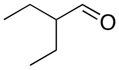
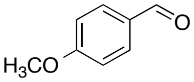
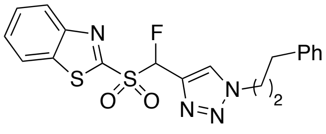
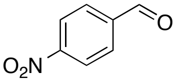
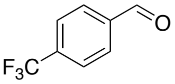
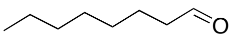
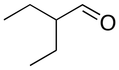
Compounds **27**, **29** and **33** were reacted with three aromatic and two aliphatic aldehydes using DBU in refluxing THF. The *E*-isomer was obtained as major isomer in all reactions. Whereas the *E*-selectivity depends on the nature of the aldehyde, it varies to a much lesser extent with the structure of triazoles reagent.

Table 8. DBU-Mediated Condensations of Triazole-derived Fluoro-Julia Reagents



27, 29, 33

41-53

Entry	R″CHO	Triazole-derived Julia reagent	Product	%Yield[a]; *E/Z* ratio[b]
1		 **27**	**41**	80; 81/19
2			**42**	52; 64/36
3			**43**	61; 57/43
4			**44**	47; 54/46
5		 **29**	**45**	82; 87/13
6			**46**	66; 60/40
7			**47**	33; 58/42
8			**48**	3; 54/46
9		 **33**	**49**	75; 76/24
10			**50**	85; 57/43
11			**51**	80; 63/37
12			**52**	56; 61/39
13			**53**	5; 61/39

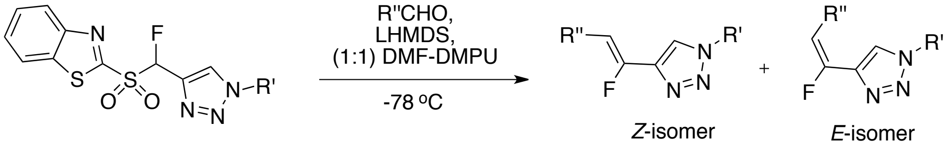
[a] Yield of the purified product. [b] *E/Z* ratio of products in the crude mixture determined by ^{19}F NMR.

Higher *E*-selectivity was observed with electron rich aldehydes, and moderate to poor *E*-selectivity was observed with electron deficient aldehydes and alkanals. For aromatic aldehydes, yields were in the range of 85%-52%. Yields in the case of octanal were moderate with **27** and **33** (entries 3 and 12), and poor with **29** (entry 7). Whereas in the case of 2-ethylbutanal, products were isolated in 47% yield (reagent **27**, entry 4) and only traces of products were obtained with reagents **29** and **33** (3% and 5% respectively, entries 8 and 13). It is likely that in the case of enolizable aldehydes, yields are low due to a competing aldol reaction under refluxing, DBU-mediated conditions. This would be consistent with the lower yields in the case of 2-ethylbutanal compared to octanal, where steric hindrance not only decreases the rate of addition of Julia reagent to the aldehyde, but the rate of spirocyclization as well.

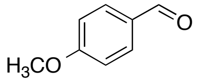
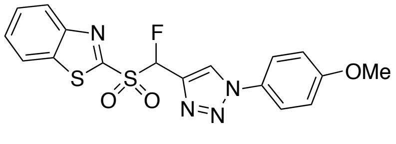
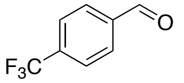
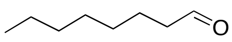
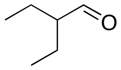
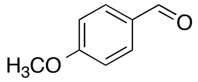
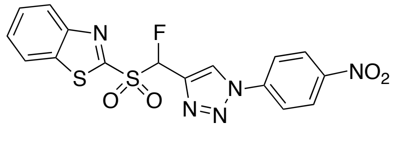
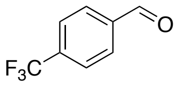
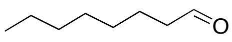
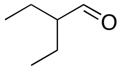
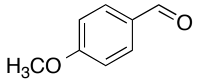
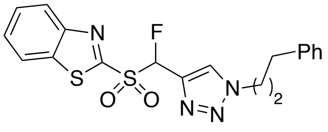
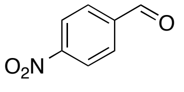
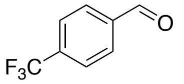
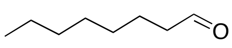
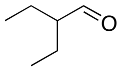
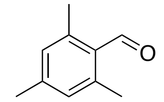
2.2.4.2 LHMDS-Mediated Condensations

Triazole-derived fluoro-Julia reagents **27, 29** and **33** were also reacted with various aromatic as well as aliphatic aldehydes using LHMDS in 1:1 DMF-DMPU solvent at -78 °C (Table 9). In all the cases, *Z*-isomer was obtained as major isomer. As can be seen from Table 9, good to excellent *Z*-selectivity was obtained in the reactions of electron rich aldehydes with all three reagents (entries 1, 5, 9 and 14) as well as in the case of sterically hindered 2-ethylbutanal (entries 4, 8 and 13). Moderate to good stereoselectivity was observed for electron deficient aromatic aldehydes (entries 2, 6, 10 and 11) and *n*-octanal (entries 3, 7 and 12). Yields were typically in the range of high 90% in reaction of *p*-methoxybenzaldehyde with reagent **33** (entry 9) to moderate 57% for reaction of **33** and 2-ethylbutanal (entry 13). An exception was reaction of **33** with highly sterically hindered 2,4,6-trimethylbenzaldehyde (entry 14), where 47% of the product was isolated.

Table 9. LHMDS-Mediated Condensations of Triazole-derived Fluoro-Julia Reagents



27, 29, 33 **41-54**

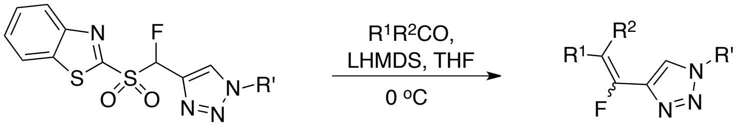
Entry	R″CHO	Triazole-derived Julia reagent	Product	%Yield[a]; *E/Z* ratio[b]
1		 **27**	**41**	72; 14/86
2			**42**	77; 30/70
3			**43**	68; 34/66
4			**44**	60; 15/85
5		 **29**	**45**	62; 19/81
6			**46**	73; 15/85
7			**47**	61; 32/68
8			**48**	68; 12/88
9		 **33**	**49**	90; 7/93
10			**50**	76; 38/62
11			**51**	72; 20/80
12			**52**	63; 36/64
13			**53**	57; 19/81
14			**54**	47; 26/74

[a]Yields of the purified product. [b]*E/Z* ratio of products in the crude mixture determined by ^{19}F NMR. [c]Yields calculated by the use of internal standard method.

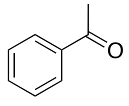
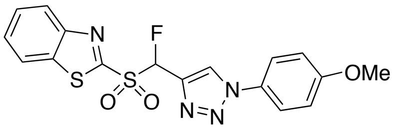
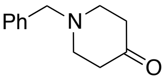
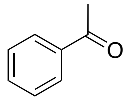
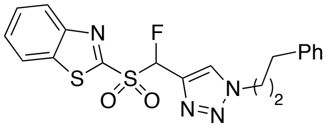
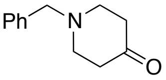
2.2.4.3 Condensation Reactions with Ketones

Olefinations of the fluoro-Julia reagents **27** and **33** were conducted with two ketones as well, using LHMDS in THF at 0 °C (Table 10). Acetophenone reacted with **27** and **33** to give products in moderate and good yields, respectively (entries 1 and 3). Olefinations of acetophenone with reagent **27** gave product with higher isomeric ratio (28/72, entry 1) compared to that obtained in reaction with reagent **33** (20/80, entry 3). A higher isomeric ratio of products was obtained in reaction with **27** than **33** (compare entries 1 and 3). The stereochemistry of the product **57** was determined by X-ray crystallography and the major isomer was found to be the *Z*-olefin.

Table 10. Condensation Reactions of Ketones with **27** and **33**



27,33 **55-58**

Entry	R^1R^2CO	Triazole-derived Julia reagent	Product	%Yield[a]; *E*/*Z* ratio[b]
1		 **27**	**55**	64; 28/72[c]
2			**56**	87; NA
3		 **33**	**57**	77; 20/80[d]
4			**58**	58; NA

[a]Yields of the purified product. [b] Isomeric ratio of products in the crude mixture determined by ^{19}F NMR. [c]*E*/*Z* ratio not determined. [d]Stereochemistry assigned by X-ray crystallography.

The X-ray structure of compound **57** is shown in Figure 7. Reaction of *N*-benzyl-4-piperidone with **27** gave a high yield of product, whereas a moderate yield was obtained in reaction with **33**.

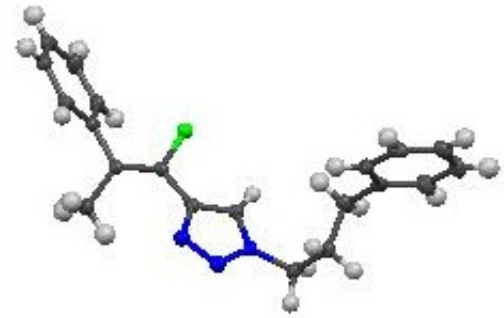
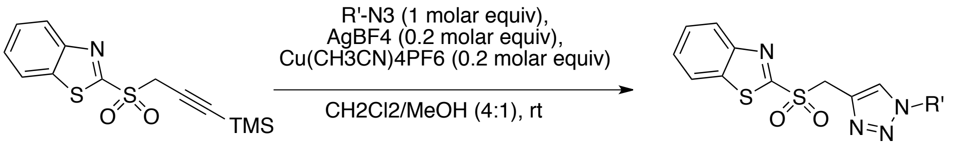


Figure 7. X-ray structure of compound **57**.

2.2.4.4 Synthesis of Unfluorinated Vinyl Triazoles

Although Julia-Kocienski olefination has been explored to a great extent for synthesis of alkenes, interestingly, its use for vinyl triazole synthesis is unprecedented.[47-49] Also, it has been previously shown that fluoro-Julia reagents are more reactive than their unfluorinated anlaogs in condensation reactions.[50,51] We were interested to see if the unfluorinated triazole-derived Julia-Kocienski reagents would be suitable candidates for the synthesis of vinyl triazoles as well.

Scheme 4. Synthesis of Unfluorinated Triazole-Derived Julia-Kocienski Reagents

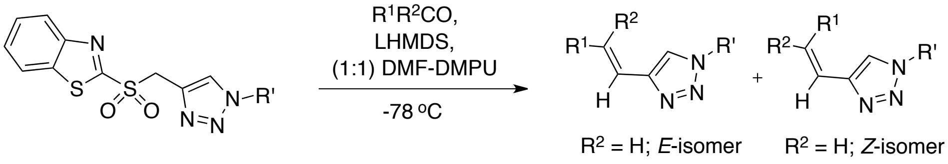


36

37; R' = p-methoxyphenyl; 74%
38; R' = 3-phenylpropyl; 84%
39; R' = n-decyl; 81%

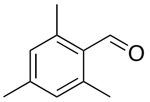
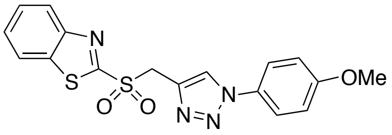
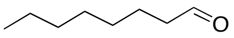
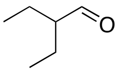
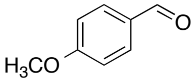
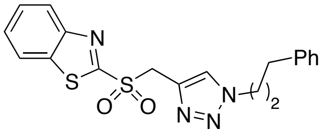
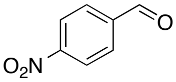
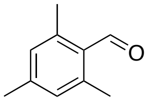
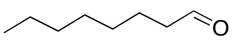
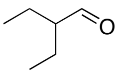
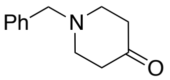
For this, the unfluorinated propargyl BT sulfone **36** was reacted with azides **18**, **24** and **25** to obtain the Julia-Kocienski reagents **37**, **38** and **39** respectively (Scheme 4). Compounds **37** and **38** were subjected to olefinations with various aldehydes using LHDMS (DMF-DMPU solvent mixture at -78 °C) and a ketone (LHMDS in THF at 0 °C) to obtain vinyl triazoles (Table 11). In reactions with aldehydes stereoselectivities of olefinations varied and depended upon both the aldehyde as well as the triazole reagent. The yields of olefin products ranged from low (entries 5, 7 and 8) to high (entry 7). Reactions of *p*-anisaldehyde with **38** (entry 4), and 2-ethylbutanal with both **37** and **38** gave *E*-isomer as major (entries 3 and 8). On the other hand, *Z*-isomer was obtained as the major one in reactions of mesitaldehyde (entries 1 and 6).

Table 11. Condensation Reactions of Unfluorinated Triazole-Derived Julia Reagents



37, 38

59-67

Entry	R^1R^2CO	Triazole-derived Julia reagent	Product	%Yield[a]; *E/Z* ratio[b]
1		 **37**	**59**	73; 33/67
2			**60**	71; 72/28
3			**61**	67; 86/14
4		 **38**	**62**	65; 72/28
5			**63**	44; 83/17
6			**64**	85; 15/85
7			**65**	31; 7/93
8			**66**	41; 77/23
9			**67**[c]	59; NA

[a]Yields of the purified product. [b]*E/Z* ratio of products in the crude mixture was determined by ^{1}H NMR. [c]Reaction performed in THF at 0 °C

Octanal reacted with moderate *E*-selectivity with **37**, but with high *Z*-selectivity with **38** (entries 2 and 7). Olefinations of *p*-nitrobenzaldehyde with **38** proceeded with good *E*-selectivity (entry

5). *N*-benzyl-4-piperidone also reacted with **38** to produce a trisubstituted olefin in 59% yield (entry 9).

2.3 CONCLUSION

A modular approach consisting of click reaction-Julia-olefination sequence was developed for synthesis of vinyl and fluorovinyl triazoles. One-pot TMS-deprotection followed by click reactions of bifunctional TMS-protected fluoropropargyl BT sulfone with azides provided access to a series of triazole-derived fluoro-Julia-Kocienski reagents. The unfluorinated triazole-derived Julia-Kocienski reagents were also obtained from protio analog, TMS-protected propargyl BT-sulfone. The presence of fluorine at the α-position to alkyne increased the reactivity of the propargyl BT-sulfone in click reactions, where a higher fluoro/protio triazole product ratio was observed in the competitive click reactions of fluoro and protio propargyl BT-sulfones with azides. DFT calculations showed a lower electron density on the terminal alkynyl carbon in the fluorosulfone than in its protio analog. Stereoselectivity of olefinations using fluorinated triazole-derived Julia-Kocienski reagents could be tuned. Olefinations with aldehydes were *E*-selective when DBU in refluxing THF was used, whereas LHMDS-mediated olefinations in DMF/DMPU and at -78 °C were *Z*-selective. The unfluorinated triazole-derived Julia-Kocienski reagents also reacted with aldehydes under LHMDS-mediated conditions, however an irregular trend in stereoselectivity was observed. Ketones reacted using LHMDS in THF with both, fluorinated and unfluorinated triazole-derived Julia-Kocienski reagents.

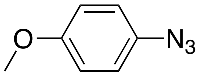
EXPERIMENTAL SECTION

THF was distilled over $LiAlH_4$, and then over sodium. DMF and DMPU were obtained from commercial sources and were used without further purification. LHMDS (1.0 M in THF) was also obtained from commercial sources. For reactions, which were performed under a nitrogen atmosphere, glassware was dried with hot gun under vacuum. Thin layer chromatography was performed on 250 µm silica plates and column chromatographic purifications were performed on silica gel. The mesh size of silica gel and the eluting solvents are reported for each compound separately. All other reagents were obtained from commercial sources and used without further purification. ^1H NMR spectra were recorded at 500 MHz in $CDCl_3$, acetone-*d₆* and C_6D_6. ^{13}C specta were recorded at 125 MHz using $CDCl_3$, acetone-d_6 and C_6D_6. ^{19}F NMR spectra were recorded at 282 MHz using $CFCl_3$ as internal standard. Chemical shifts (δ) are reported in parts per million and coupling constants (J) are in hertz.

General Procedure for synthesis of aryl azides[35]

In a round bottom flask, boronic acid (1 molar equiv) was dissolved in MeOH (2 mL per mmol of boronic acid). NaN_3 (1.2 molar equiv) and $CuSO_4{\cdot}5H_2O$ (0.1 molar equiv) were added and the reaction mixture was stirred at room temp in open flask. After 5-6 h reaction was stopped and crude reaction mixture was filtered through a short silica gel column (silica gel mesh size 200-300). The eluting solvents for each azide are given below.

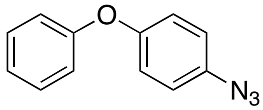
1-Azido-4-methoxybenzene (18)



4-Methoxyphenyl boronic acid: 200 mg (1.32 mmol); NaN_3: 102.7 mg (1.58 mmol); $CuSO_4{\cdot}5H_2O$: 33.0 mg (0.13 mmols). Eluting solvent: methylene chloride. Yield: 194.2 mg

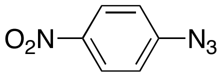
(98%) of light orange oil. *R*$_f$ (methylene chloride) = 0.68. ^{1}H NMR (500 MHz): δ 6.95 (d, 2H, Ar-H, *J* = 9.2 Hz), 6.89 (d, 2H, Ar-H, *J* = 8.8 Hz), 3.80 (s, 3H, CH_3).

1-Azido-4-phenoxybenzene (19)



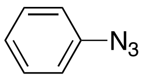
4-Phenoxyphenyl boronic acid: 107.0 mg (0.50 mmol); NaN_3: 39.0 mg (0.60 mmol); $CuSO_4{\cdot}5H_2O$: 12.5 mg (0.05 mmol). Eluting solvent: methylene chloride. Yield: 102.4 mg (97%) of dark brown oil. *R*$_f$ (methylene chloride) = 0.77. ^{1}H NMR (500 MHz): δ 7.34 (t, 2H, Ar-H, *J* = 7.4 Hz), 7.11 (t, 1H, Ar-H, *J* = 7.4 Hz), 6.98-7.02 (m, 6H, Ar-H).

1-Azido-4-nitrobenzene (20)



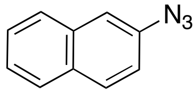
4-Nitrophenyl boronic acid: 500 mg (3.00 mmol); NaN_3: 234.0 mg (3.60 mmol); $CuSO_4{\cdot}5H_2O$: 74.9 mg (0.30 mmol). Eluting solvent: 50% EtOAc in hexanes. Yield: 442.0 mg (90%) of yellow solid. *R*$_f$ (20% EtOAc in hexanes) = 0.47. ^{1}H NMR (500 MHz): δ 8.24 (d, 2H, Ar-H, *J* = 8.6 Hz), 7.14 (d, 2H, Ar-H, *J* = 8.8 Hz).

Azidobenzene (21)



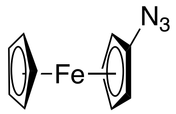
Phenyl boronic acid: 300 mg (2.46 mmol); NaN_3: 191.8 mg (2.95 mmol); $CuSO_4{\cdot}5H_2O$: 62.4 mg (0.25 mmols). Eluting solvent 10% EtOAc in hexanes. Yield: 205 mg (70%) of colorless oil. *R*$_f$ (20% EtOAc in hexanes) = 0.53. ^{1}H NMR (500 MHz): *δ* 7.36 (t, 2H, Ar-H, *J* = 7.8 Hz), 7.14 (t, 1H, Ar-H, *J* = 7.6 Hz), 7.04 (d, 2H, Ar-H, *J* = 8.3 Hz).

2-Azidonaphthalene (22)



Naphthalen-2-ylboronic acid: 344.0 mg (2.0 mmol); NaN_3: 156.0 mg (2.4 mmol); $CuSO_4{\cdot}5H_2O$: 50.0 mg (0.20 mmols). Eluting solvent: methylene chloride. Yield: 330.6 mg (98%) of brown soild. R_f (methylene chloride) = 0.89. ^{1}H NMR (500 MHz): δ 7.82 (t, 2H, Ar-H, *J* = 9.4 Hz), 7.76 (d, 1H, Ar-H, *J* = 8.3 Hz), 7.50 (t, 1H, Ar-H, *J* = 7.1 Hz), 7.42-7.45 (m, 2H, Ar-H), 7.16 (dd, 1H, Ar-H *J* = 8.7, 2.3 Hz).

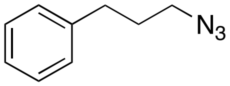
Azidoferrocene (23)



Ferrocenyl boronic acid: 114.9 mg (0.50 mmol); NaN_3: 39.0 mg (0.60 mmol); $CuSO_4{\cdot}5H_2O$: 12.5 mg (0.05 mmols). Eluting solvent: methylene chloride. Yield: 100 mg (89%) of brown soild. R_f (methylene chloride) = 0.66. ^{1}H NMR (500 MHz): δ 4.26-4.35 (m, 5H, Ar-H), 4.16 (br s, 2H, Ar-H), 4.0-4.04 (m, 2H, Ar-H).

General Procedure for synthesis of alkyl azides.[37] To a stirring solution of alkyl halide (1 molar equiv) in DMF (70.0 mL), was added NaN_3 (2 molar equiv). The reaction mixture was stirred at 80 °C for 7 h, cooled to room temperature, 20 mL of water was added and the mixture was poured into separatory funnel containing EtOAc. Organic layer was separated and the aqueous layer was extracted with EtOAc (3x), combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The alkyl azide obtained was used without further purification.

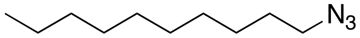
3-Phenylpropyl Azide (24)



3-Phenylpropyl bromide: 1.00 g (5.02 mmol); NaN_3: 0.650 g (10.0 mmol). Yield: 700 mg (87%) of 3-phenylpropyl azide as a colorless oil. R_f (10% EtOAc in hexanes) = 0.66.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (t, 2H, Ar-H, J = 7.6 Hz), 7.23-7.19 (m, 3H, Ar-H), 3.29 (t, 2H, CH_2, J = 6.9 Hz), 2.72 (t, 2H, CH_2, J = 7.6 Hz), 1.96-1.90 (m, 2H, CH_2).

Decyl Azide (25)

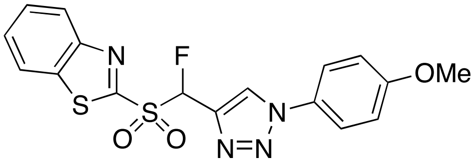


Decyl bromide: 0.500 g (2.26 mmol); NaN_3: 0.294 g (4.52 mmol). Yield: 172 mg (42%) of decyl azide as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.25 (t, 2H, CH_2, J = 6.9 Hz), 1.60 (m, 2H, CH_2, J = 7.4 Hz) 1.27-1.63 (m, 14H, $7CH_2$), 0.88 (t, 3H, CH_3, J = 7.4 Hz).

General procedure for synthesis of triazoles[38]

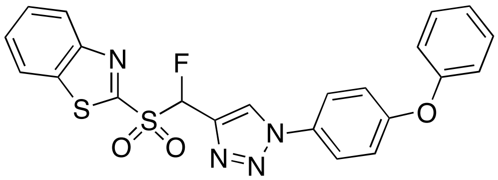
To a stirring solution of azide (1 molar equiv) in 4:1 (v/v) CH_2Cl_2/MeOH (28.0 mL per mmol of azide), sulfone **17** or **36** (1 to 1.25 molar equiv), $Cu(CH_3CN)_4PF_6$ (0.20 molar equiv) and $AgBF_4$ (0.20 molar equiv) were added sequentially. The stirring was continued at room temperature until TLC showed disappearance of the azide. The solvents were evaporated under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel (mesh 200-300). Eluting solvents for chromatography are indicated under the specific compound headings.

2-{Fluoro[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methylsulfonyl}benzo[*d*]-thiazole (27)



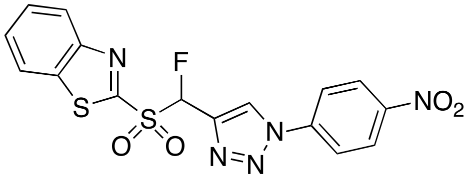
4-Methoxyphenyl azide (**18**) : 300 mg (2.01 mmol); sulfone **17**: 723 mg (2.21 mmol). Column chromatography: eluting solvent 20% EtOAc in hexanes. Yield: 756 mg (93%) of white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (d, 1H, Ar-H, J = 1.4 Hz), 8.32 (d, 1H, Ar-H, J = 8.3 Hz), 8.06 (d, 1H, Ar-H, J = 7.8 Hz), 7.71-7.64 (m, 4H, Ar-H), 7.05 (d, 2H, Ar-H, J = 8.7 Hz), 7.01 (d, 1H, CHF, $^2J_{FH}$ = 46.1 Hz), 3.88 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0, 160.6, 153.0, 137.8, 135.7 (d, $^2J_{CF}$ = 24.0 Hz), 129.9, 128.8, 128.2, 126.1, 124.1, 122.7, 122.5, 115.1, 96.1 (d, $^1J_{CF}$ = 220.1 Hz), 55.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ –165.3 (d, $^2J_{FH}$ = 45.8 Hz). HRMS (ESI) calcd. for $C_{17}H_{14}FN_4O_3S_2$ $[M + H]^+$ 405.0486, found 405.0489.

2-{Fluoro[1-(4-phenoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl]sulfonyl}benzo[*d*]thiazole (28)



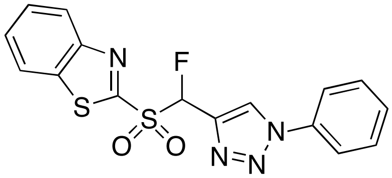
4-Phenoxyphenyl azide (**19**): 20.0 mg (0.095 mmol); sulfone **17**: 46.6 mg (0.143 mmol). Column chromatography: eluting solvent methylene chloride. Yield: 39.7 mg (90%) of white solid ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.48 (d, 1H, Ar-H, J = 1.9 Hz), 8.33 (d, 1H, Ar-H, J = 8.3 Hz), 8.07 (d, 1H, Ar-H, J = 7.8 Hz), 7.72 -7.65 (m, 4H, Ar-H), 7.41 (t, 2H, Ar-H, J = 8.1 Hz), 7.21 (t, 1H, Ar-H, J = 7.4 Hz), 7.16 (d, 2H, Ar-H, J = 8.8 Hz), 7.09 (d, 2H, Ar-H, J = 7.8 Hz), 7.01 (d, 1H, CHF, $^2J_{FH}$ = 46.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.9, 158.9, 156.2, 153.1 137.8, 135.9 (d, $^2J_{CF}$ = 23.8 Hz), 131.6, 130.3 128.9, 128.2, 126.2, 124.6, 124.1, 122.9, 122.6, 119.9, 119.4, 96.0 (d, $^1J_{CF}$ = 220.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ -165.7 (d, $^2J_{FH}$ = 45.8 Hz). HRMS (ESI) calcd. for $C_{22}H_{16}FN_4O_3S_2$ $[M + H]^+$ 467.0642, found 467.0646.

2-{[Fluoro(1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl]sulfonyl}benzo[*d*]thiazole (29)



4-Nitrophenyl azide (**20**): 425 mg (2.59 mmol); sulfone **17**: 932 mg (2.85 mmol). Column chromatography: eluting solvent 40% EtOAc in hexanes. Yield: 819 mg (82%) of yellow solid. ^{1}H NMR (500 MHz, dmso-d_6): δ 9.57 (s, 1H, Ar-H), 8.47 (d, 2H, Ar-H, J = 8.8 Hz), 8.41 (d, 1H, Ar-H, J = 8.3 Hz), 8.36 (d, 1H, Ar-H, J = 7.4 Hz), 8.30 (d, 2H, Ar-H, J = 8.8 Hz), 7.81-7.76 (m, 2H, Ar-H), 7.72 (d, 1H, CHF, $^2J_{FH}$ = 43.3 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.8, 152.2, 147.2, 140.2, 137.3s, 136.4 (d, $^2J_{CF}$ = 23.8 Hz), 128.8, 128.3, 126.1, 125.5, 125.3, 123.6, 121.3, 95.9 (d, $^1J_{CF}$ = 217.4 Hz). ^{19}F NMR (282 MHz, DMSO-d_6): δ -172.0 (d, $^2J_{FH}$ = 42.7 Hz). HRMS (ESI) calcd. for $C_{16}H_{11}FN_5O_4S_2$ $[M + H]^+$ 420.0231, found 420.0223.

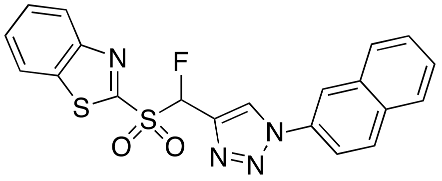
2-{[Fluoro(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl]sulfonyl}benzo[*d*]thiazole (30)



Phenyl azide (**21**): 60.0 mg (0.500 mmol); sulfone **17**: 206 mg (0.630 mmol). Column chromatography: eluting solvent 20% EtOAc in hexanes. Yield: 148 mg (79%) of off white solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.54 (d, 1H, Ar-H, J = 1.4 Hz), 8.32 (d, 1H, Ar-H, J = 8.3 Hz), 8.07 (d, 1H, Ar-H, J = 8.3 Hz), 7.78 (d, 2H, Ar-H, J = 7.4 Hz), 7.71 (t, 1H, Ar-H, J = 7.5 Hz), 7.66 (t, 1H, Ar-H, J = 7.6 Hz), 7.58 (t, 2H, Ar-H, J = 7.6 Hz), 7.52 (t, 1H, Ar-H, J = 7.4 Hz), 7.02 (d, 1H, CHF, $^2J_{FH}$ = 46.5 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): δ 162.0, 153.1, 137.8, 136.6, 136.0 (d, $^2J_{CF}$ = 24.3 Hz), 130.2 129.9, 128.9, 128.3, 126.2, 124.0, 122.6, 121.2, 96.0 (d,

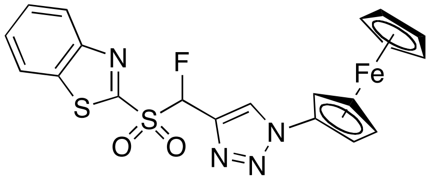
$^{1}J_{\mathrm{CF}}$ = 219.7 Hz). ^{19}F NMR (282 MHz, CDCl$_3$): δ -165.6 (d, $^{2}J_{\mathrm{FH}}$ = 45.8). HRMS (ESI) calcd. for $C_{16}H_{12}FN_4O_2S_2$ [M + H]$^+$ 375.380, found 375.379.

2-{[Fluoro(1-(naphthalen-2-yl)-1*H*-1,2,3-triazol-4-yl)methyl]sulfonyl}benzo[*d*]thiazole (31)



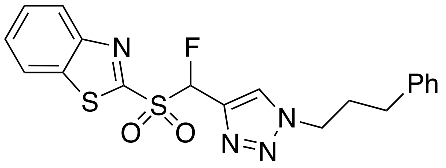
2-Azidonaphthalene (**22**): 85.0 mg (0.500 mmol); sulfone **17**: 206 mg (0.630 mmol). Column chromatography: eluting solvent 20% EtOAc in hexanes. Yield: 367 mg (92%) of off white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.67 (d, 1H, Ar-H, *J* = 1.8 Hz), 8.32 (d, 1H, Ar-H, *J* = 8.3 Hz), 8.22 (d, 1H, Ar-H, *J* = 1.9 Hz), 8.06 (d, 1H, Ar-H, *J* = 8.3 Hz), 8.04 (d, 1H, Ar-H, *J* = 8.8 Hz), 7.96-7.93 (m, 2H, Ar-H), 7.90 (dd, 1H, Ar-H, *J* = 8.8, 2.3 Hz), 7.72 -7.59 (m, 4H, Ar-H), 7.06 (d, 1H, CHF, $^{2}J_{\mathrm{FH}}$ = 46.5 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): *δ* 162.0, 153.1, 137.8, 136.1 (d, $^{2}J_{\mathrm{CF}}$ = 24.3 Hz), 133.9, 133.4, 133.3, 130.5 128.9, 128.6, 128.2, 127.9, 127.7, 126.6, 126.2,124.2, 122.6, 119.4, 119.0, 96.1 (d, $^{1}J_{\mathrm{CF}}$ = 220.2 Hz). ^{19}F NMR (282 MHz, CDCl$_3$): δ -165.5 (d, $^{2}J_{\mathrm{FH}}$ = 54.2 Hz). HRMS (ESI) calcd. for $C_{20}H_{14}FN_4O_2S_2$ [M + H]$^+$ 425.0537, found 425.0541.

2-{[Fluoro(1-(ferrocenyl)-1*H*-1,2,3-triazol-4-yl]methyl}sulfonyl)benzo[*d*]thiazole (32)



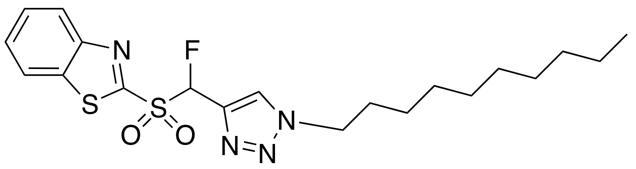
Azidoferrocene (**23**): 160 mg (0.710 mmol); sulfone 17**2**: 279 mg (0.850 mmol). Column chromatography: eluting solvent 20% EtOAc in hexanes. Yield: 226 mg (66%) of yellowish solid. ^{1}H NMR (500 MHz, CDCl$_3$) *δ* 8.33-8.32 (m, 2H, Ar-H), 8.07 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.72-7.63 (m, 2H, Ar-H), 6.97 (d, 1H, CHF, $^{2}J_{\mathrm{FH}}$ = 46.5 Hz), 4.88-4.879 (m, 2H, Ar-H), 4.33 (t, 2H, Ar-H, J = 1.8 Hz), 4.25 (s, 5H, Ar-H). ^{13}C NMR (125 MHz, $\mathrm{CDCl_3}$): δ 162.0, 153.1, 137.8, 135.2 (d, $^{2}J_{\mathrm{CF}}$ = 24.3 Hz), 128.9, 128.2, 126.2, 125.5, 122.6, 96.1 (d, $^{1}J_{\mathrm{CF}}$ = 219.7 Hz), 93.3, 70.6, 67.4, 62.8. ^{19}F NMR (282 MHz, $\mathrm{CDCl_3}$): δ -165.7 (d, $^{2}J_{\mathrm{FH}}$ = 45.8 Hz). HRMS (ESI) calcd. for $\mathrm{C_{20}H_{16}FFeN_4O_2S_2}$ $[\mathrm{M+H}]^+$ 483.0043, found 483.0048.

2-{Fluoro[1-(3-phenylpropyl)-1*H*-1,2,3-triazol-4-yl]methylsulfonyl}benzo[*d*]-thiazole (33)



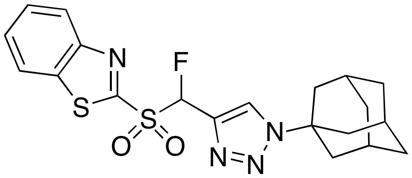
3-Phenylpropyl azide (**24**): 500 mg (3.10 mmol); sulfone **17**: 1.01 g (3.10 mmol). Column chromatography: eluting solvent 20% EtOAC in hexanes. Yield: 879 mg (68%) of white solid. ^{1}H NMR (500 MHz, $\mathrm{CDCl_3}$): δ 8.27 (d, 1H, Ar-H, J = 8.3 Hz), 8.08 (d, 1H, Ar-H, J = 1.8 Hz), 8.01 (d, 1H, Ar-H, J = 7.8 Hz), 7.68-7.61 (m, 2H, Ar-H), 7.30 (t, 2H, Ar-H, J = 7.6 Hz), 7.22 (t, 1H, Ar-H, J = 7.4 Hz), 7.17 (d, 2H, Ar-H, J = 7.4 Hz), 6.94 (d, 1H, CHF, $^{2}J_{\mathrm{FH}}$ = 46.5 Hz), 4.42 (t, 2H, $\mathrm{CH_2}$, J = 7.4 Hz), 2.67 (t, 2H, $\mathrm{CH_2}$, J = 7.4 Hz), 2.29 (quint, 2H, $\mathrm{CH_2}$, J = 7.4 Hz). ^{13}C NMR (125 MHz, $\mathrm{CDCl_3}$): δ 162.0, 153.0, 139.9, 137.7, 135.1 (d, $^{2}J_{\mathrm{CF}}$ = 24.2 Hz), 128.9, 128.8, 128.6, 128.2, 126.7, 126.1, 125.8, 122.5, 96.2 (d, $^{1}J_{\mathrm{CF}}$ = 219.7 Hz), 50.2, 32.5, 31.5. ^{19}F NMR (282 MHz, $\mathrm{CDCl_3}$): δ –165.4 (d, $^{2}J_{\mathrm{FH}}$ = 45.8 Hz). HRMS (ESI) calcd. for $\mathrm{C_{19}H_{18}FN_4O_2S_2}$ $[\mathrm{M+H}]^+$ 417.0850, found 417.0852.

2-[(1-Decyl-1*H*-1,2,3-triazol-4-yl)fluoromethylsulfonyl]benzo[*d*]thiazole (34)



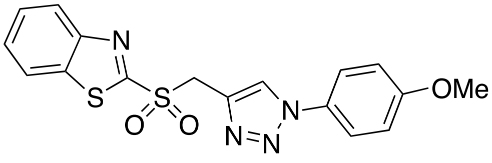
Decyl azide (**25**): 91.6 mg (0.500 mmol); sulfone **17**: 164 mg (0.500 mmol). Column chromatography: eluting solvent 20% EtOAc in hexanes. Yield: 178 mg (81%) of white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, 1H, Ar-H, J = 8.3 Hz), 8.09 (d, 1H, Ar-H, J = 1.8 Hz), 8.05 (d, 1H, Ar-H, J = 7.8 Hz), 7.70-7.63 (m, 2H, Ar-H), 6.93 (d, 1H, CHF, $^2J_{FH}$ = 46.5 Hz), 4.48-4.38 (m, 2H, CH_2), 1.98-1.93 (m, 2H, CH_2), 1.34-1.26 (m, 14H, $(CH_2)_7$), 0.88 (t, 3H, CH_3, J = 6.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0, 153.0, 137.7, 135.1 (d, $^2J_{CF}$ = 24.3 Hz), 128.8, 128.2, 126.1, 125.6, 122.5, 96.2 (d, $^1J_{CF}$ = 219.7 Hz), 51.2, 32.0, 30.3, 29.6, 29.5, 29.4, 29.1, 26.6, 22.8, 14.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ –165.0 (d, $^2J_{FH}$ = 46.1 Hz). HRMS (ESI) calcd. for $C_{20}H_{28}FN_4O_2S_2$ $[M + H]^+$ 439.1632, found 439.1635.

2-{[(1-(adamantan-1-yl)-1*H*-1,2,3-triazol-4-yl)fluoromethyl]sulfonyl}benzo[*d*]thiazole (35)



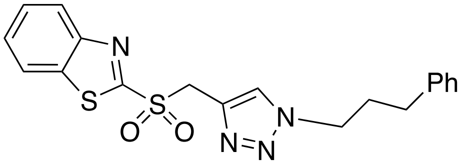
Adamentyl azide (**26**): 177 mg (1.00 mmol); sulfone **17**: 409 mg (1.25 mmol). Column chromatography: eluting solvent methylene chloride. Yield: 367 mg (85%) of white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, 1H, Ar-H, J = 8.3 Hz), 8.12 (s, 1H, Ar-H), 8.02 (d, 1H, Ar-H, J = 7.8 Hz), 7.66-7.59 (m, 2H, Ar-H), 6.93 (d, 1H, CHF, $^2J_{FH}$ = 46.5 Hz), 2-51-2.23 (m, 9H), 1.80-1.74 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.2, 153.0, 137.7, 134.1 (d, $^2J_{CF}$ = 21.5 Hz), 128.7, 128.1, 126.1, 122.5, 122.3, 96.4 (d, $^1J_{CF}$ = 219.2 Hz), 61.0, 43.0, 35.9, 29.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ -163.8 (d, $^2J_{FH}$ = 45.8 Hz). HRMS (ESI) calcd. for $C_{20}H_{22}FN_4O_2S_2$ $[M+H]^+$ 433.1163, found 433.1169.

2-{[1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methylsulfonyl}benzo[*d*]thiazole (37)



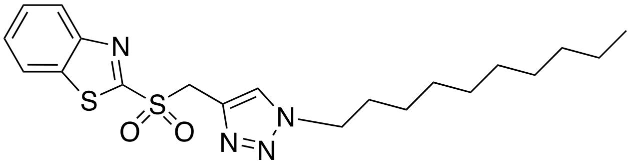
4-Methoxyphenyl azide (**18**): 250 mg (1.68 mmol); sulfone **36**: 624 mg (2.02 mmol). Column chromatography: eluting solvent 20% acetone in hexanes. Yield: 481 mg (74%) of off white solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.25 (d, 1H, Ar-H, J = 7.8 Hz), 8.14 (s, 1H), 7.97 (d, 1H, Ar-H, J = 7.8 Hz), 7.65 (t, 1H, Ar-H, J = 7.8 Hz), 7.61-7.58 (m, 3H, Ar-H), 7.02 (d, 2H, Ar-H, J = 8.8 Hz), 5.03 (s, 2H, CH$_2$), 3.87 (s, 3H, CH$_3$). ^{13}C NMR (125 MHz, CDCl$_3$): δ 164.4, 160.4, 152.8, 137.3, 135.1, 130.3, 128.4, 128.0, 126.0, 123.3, 122.52, 122.47, 115.1, 55.9, 52.9. HRMS (ESI) calcd. for $C_{17}H_{15}N_4O_3S_2$ [M + H]$^+$ 387.0580, found 387.0582.

2-{[1-(3-Phenylpropyl)-1*H*-1,2,3-triazol-4-yl]methylsulfonyl}benzo[*d*]thiazole (38)



3-Phenylpropyl azide (**24**): 300 mg (1.86 mmol); sulfone **36**: 689 mg (2.23 mmol). Column chromatography: eluting solvent 40% EtOAc in hexanes. Yield: 623 mg (84%) of white solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.22 (d, 1H, Ar-H, J = 8.3 Hz), 7.92 (d, 1H, Ar-H, J = 7.8 Hz), 7.73 (s, 1H, Ar-H), 7.62 (t, 1H, Ar-H, J = 7.6 Hz), 7.57 (t, 1H, Ar-H, J = 7.8 Hz), 7.30 (t, 2H, Ar-H, J = 7.6 Hz), 7.23 (t, 1H, Ar-H, J = 7.4 Hz), 7.14 (d, 1H, Ar-H, J = 7.8 Hz), 4.96 (s, 2H, CH$_2$), 4.34 (t, 2H, CH$_2$, J = 7.1 Hz), 2.60 (t, 2H, CH$_2$, J = 7.6 Hz), 2.23 (quint, 2H, CH$_2$, J = 7.4 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): δ 164.3, 152.8, 140.1, 137.2, 134.5, 128.8, 128.6, 128.3, 127.9, 126.6, 125.9, 125.0, 122.4, 52.9, 49.9, 32.5, 31.6. HRMS (ESI) calcd. for $C_{19}H_{19}N_4O_2S_2$ [M+H]$^+$ 399.0944, found 399.0943.

2-[(1-Decyl-1*H*-1,2,3-triazol-4-yl)methylsulfonyl]benzo[*d*]thiazole (39)



Decyl azide (**25**):: 300 mg (1.64 mmol); sulfone **36**: 609 mg (1.97 mmol). Column chromatography: eluting solvent 20% EtOAc in hexanes. Yield: 555 mg (81%) of white solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.22 (d, 1H, Ar-H, J = 8.2 Hz), 7.95 (d, 1H, Ar-H, J = 8.2 Hz), 7.75 (s, 1H, Ar-H), 7.63 (t, 1H, Ar-H, J = 7.2 Hz), 7.57 (t, 1H, Ar-H, J = 7.4 Hz), 4.95 (s, 2H, CH$_2$), 4.32 (t, 2H, CH$_2$, J = 7.2 Hz), 1.89-1.83 (m, 2H, CH$_2$), 1.28-1.25 (m, 14H, (CH$_2$)$_7$), 0.87 (t, 3H, CH$_2$, J = 6.9 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): δ 164.4, 152.8, 137.3, 134.4, 128.4, 127.9, 125.9, 124.8, 122.4, 52.9, 50.8, 32.0, 30.3, 29.64, 29.6, 29.4, 29.1, 26.6, 22.8, 14.3. HRMS (ESI) calcd. for $C_{20}H_{29}N_4O_2S_2$ $[M + H]^+$ 421.1726, found 421.173.

General procedures for synthesis of vinyl- and fluorovinyl triazoles

DBU-mediated condensations (Method A) of sulfones 27, 29 and 33:

In a dry flask, aldehyde (1 molar equiv) and sulfone (1.2-2.1 molar equiv) were dissolved in THF (20 mL per mmol of aldehyde). DBU (4 molar equiv) was weighed in a vial, diluted with THF (8 mL per mmol of aldehyde) and added to reaction mixture that was then stirred with reflux until all the aldehyde was consumed. Then the solvent was removed under reduced pressure and the crude mixture was purified by column chromatography using silica gel. The product *E*/*Z* ratio for fluorovinyl derivatives was determined by ^{19}F NMR, prior to column chromatography purification.

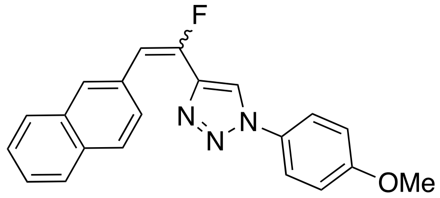
LHMDS-mediated condensations (Method B) of fluorinated sulfones 27, 29 and 33, and unfluorinated sulfones 37 and 38 with aldehydes:

In a dry flask, a stirring solution of aldehyde (1 molar equiv) and triazole (1.2 molar equiv) in DMF (7.6 mL per mmol of aldehyde) and DMPU (7.6 mL per mmol of aldehyde) was cooled to –78 °C (dry ice/*iso*-PrOH) and under nitrogen LHMDS (2.4 molar equiv) was added to the reaction mixture. The reaction mixture was stirred at –78 °C for 5 min. Then saturated aq NH4Cl was added and the mixture was poured into EtOAc. Organic layer was separated and the aqueous layer was extracted with EtOAc three times. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the combined *E*/*Z* product mixture was isolated by column chromatography using silica gel (mesh 200-300). The product *E*/*Z* ratio was determined by ^{19}F NMR for fluorovinyl and ^{1}H NMR for vinyl triazole derivatives, prior to column chromatography purification.

LHMDS-mediated condensations (Method C) of fluorinated sulfones 27 and 33, and unfluorinated sulfone 38 with ketones:

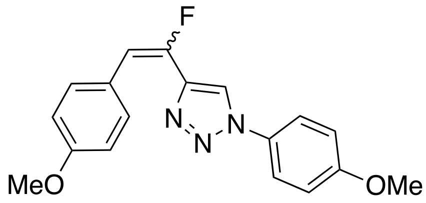
In a dry, round bottom flask, ketone (1 molar equiv) and sulfone (1.2-1.3 molar equiv) were dissolved in THF (12 mL per mmol of ketone) under nitrogen. Flask was cooled to 0 ˚C using an ice bath. LHMDS (2.4 molar equiv) added to reaction mixture using a syringe. The reaction mixture was the stirred for at 0 ˚C until all ketone was consumed. Then reaction was quenched with saturated NH_4Cl solution. Organic layer was separated in ethyl acetate. Aqueous layer was extracted with ethyl acetate. Combined organic layer was washed with water and brine solution, and then dried over sodium sulfate. Solvent was removed under reduced pressure. The crude mixture was purified by chromatography using silica gel chromatography (silica gel mesh 200-300).

4-[1-Fluoro-2-(naphthalen-2-yl)vinyl]-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (40)



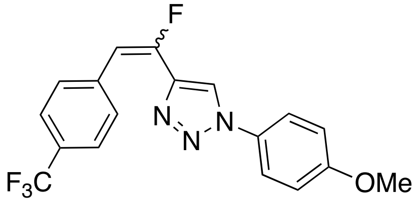
Method B: 2-Naphthaldehyde: 20.0 mg (0.128 mmol); sulfone **27**: 62.3 mg (0.154 mmol, 1.2 molar equiv); LHMDS: 0.307 mL (1 M, 0.307 mmol, 2.4 molar equiv); DMF (1.0 mL), DMPU (1.0 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**40** 33.4 mg (76%), as a white solid, *E*/*Z* ratio: 7/93. R_f (20% EtOAc in hexanes) = 0.23. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.09 (s, 1H, Ar-H, *Z*-isomer), 8.05 (s, 1H, Ar-H, *Z*-isomer), 7.96 (s, 1H, Ar-H, *E*-isomer), 7.87-7.78 (m, Ar-H, both *E* and *Z*-isomers), 7.68 (d, 2H, Ar-H, J = 8.5 Hz, *Z*-isomer), 7.59 (d, 1H, Ar-H, J = 8.5 Hz, *E*-isomer), 7.55 (d, 2H, Ar-H, J = 8.6 Hz, *E*-isomer), 7.50-7.46 (m, 2H, Ar-H, both *E* and *Z*-isomers), 7.05 (d, 2H, Ar-H, J = 8.2 Hz, *Z*-isomer), 6.99 (d, 2H, Ar-H, J = 8.9 Hz, *E*-isomer), 6.98 (d, 1H, CHF, $^3J_{FH}$ = 41.2 Hz, *Z*-isomer), 6.78 (d, 1H, CHF, $^3J_{FH}$ = 22.3 Hz, *E*-isomer), 3.89 (s, 3H, CH$_3$, *Z*-isomer), 3.85 (s, 3H, CH$_3$, *E*-isomer). ^{19}F NMR (282 MHz, CDCl$_3$): δ –105.98 (d, $^3J_{FH}$ = 24.4 Hz, *E*-isomer), –118.47 (d, $^3J_{FH}$ = 39.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{21}H_{17}FN_3O$ [M+H]$^+$ 346.1350, found 346.1334.

4-[1-Fluoro-2-(4-methoxyphenyl)vinyl]-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (41)



Method A: 4-Methoxybenzaldehyde: 68.1 mg (0.500 mmol); sulfone **27**: 242.7 mg (0.600 mmol, 1.2 molar equiv); DBU: 304.5 mg (2.00 mmol, 4.0 molar equiv); THF (14 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**41**: 130.1 mg (80%), as a white solid, *E*/*Z* ratio: 81/19. R_f (20% EtOAc in hexanes) = 0.22. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H, Ar-H, *Z*-isomer), 7.81 (s, 1H, Ar-H, *E*-isomer), 7.66 (d, 2H, Ar-H, J = 8.3 Hz, *Z*-isomer), 7.61-7.57 (m, 2H, Ar-H, both *E* and *Z*-isomers), 7.46 (d, 2H, Ar-H, J = 7.8 Hz, *E*-isomer), 7.04 (d, 2H, Ar-H, J = 7.4 Hz, *Z*-isomer), 7.01 (d, 2H, Ar-H, J = 8.8 Hz, *E*-isomer), 6.92 (d, 2H, Ar-H, J = 9.2 Hz, *Z*-isomer), 6.87 (d, 2H, Ar-H, J = 9.2 Hz, *E*-isomer), 6.75 (d, 1H, CHF, $^3J_{FH}$ = 40.5 Hz, *Z*-isomer), 6.57 (d, 1H, CHF, $^3J_{FH}$ = 23.0 Hz, *E*-isomer), 3.88 (s, 3H, CH_3, *Z*-isomer), 3.86 (s, 3H, CH_3, *E*-isomer), 3.84 (s, 3H, CH_3, *Z*-isomer), 3.81 (s, 3H, CH_3, *E*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$): δ –108.51 (d, $^3J_{FH}$ = 21.4 Hz, *E*-isomer), –121.54 (d, $^3J_{FH}$ = 42.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{18}H_{17}FN_3O_2$ $[M+H]^+$ 326.1299, found 326.1304.

4-{1-Fluoro-2-[4-(trifluoromethyl)phenyl]vinyl}-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (42)

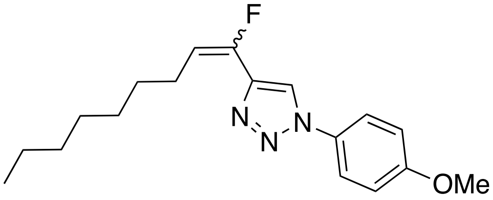


Method A: 4-(Trifluoromethyl)benzaldehyde: 20.0 mg (0.115 mmol); sulfone **27**: 55.8 mg (0.138 mmol, 1.2 molar equiv); DBU: 70.0 mg (0.460 mmol, 4.0 molar equiv); THF (3.2 mL). Eluting solvent for column chromatography: 10% EtOAc in hexanes. Yield of *E*/*Z*-**42**: 21.6 mg (52%), as a white solid, *E*/*Z* ratio: 64/36. R_f (10% EtOAc in hexanes) = 0.21.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H, Ar-H, *Z*-isomer), 7.94 (s, 1H, Ar-H, *E*-isomer), 7.75 (d, 2H, Ar-H, J = 8.3 Hz, *Z*-isomer), 7.68 (d, 2H, Ar-H, J = 7.8 Hz, *E*-isomer), 7.65 (d, 1H, Ar-H, J = 7.4 Hz, *Z*-isomer), 7.62-7.58 (m, Ar-H, 4H *E*-isomer and 2H *Z*-isomer), 7.05 (d, 2H, Ar-H, J = 8.8 Hz, *Z*-isomer), 7.03 (d, 2H, Ar-H, J = 9.2 Hz, *E*-isomer), 6.86 (d, 1H, CHF, $^3J_{FH}$ = 40.5 Hz, *Z*-isomer), 6.61 (d, 1H, CHF, $^3J_{FH}$ = 23.0, *E*-isomer), 3.89 (s, 3H, CH_3, *Z*-isomer), 3.87

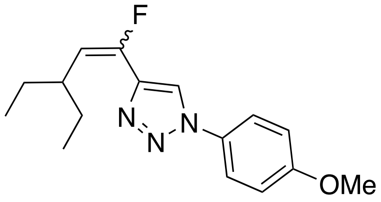
(s, 3H, CH_3, *E*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$): δ -63.17 (CF_3, both *E* and *Z*-isomers), –103.52 (d, $^3J_{FH}$ = 21.4 Hz, *E*-isomer), –116.10 (d, $^3J_{FH}$ = 39.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{18}H_{14}FN_3O$ $[M+H]^+$ 364.1068, found 364.1068.

4-(1-Fluoronon-1-en-1-yl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (43)



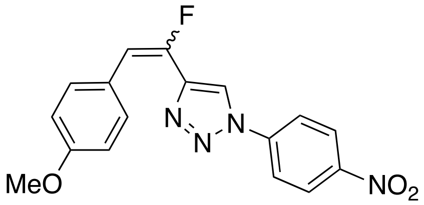
Method B: Octanal: 20.0 mg (0.160 mmol); sulfone **27**: 76.8 mg (0.190 mmol, 1.2 molar equiv); LHMDS: 0.384 mL (1 M, 0.384 mmol, 2.4 molar equiv); DMF (1.2 mL), DMPU (1.2 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**43**: 34.7 mg (68%), as a colorless semi solid, *E*/*Z* ratio: 34/66. R_f (20% EtOAc in hexanes) = 0.40. ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H, Ar-H, *E*-isomer), 7.86 (s, 1H, Ar-H, *Z*-isomer), 7.65-7.62 (m, 2H, Ar-H, both *E* and *Z*-isomers), 7.04-702 (m, 2H, Ar-H, both *E* and *Z*-isomers), 5.89 (dt, 1H, CHF, $^3J_{FH}$ = 39.1, $^3J_{HH}$ = 7.8 Hz, *Z*-isomer), 5.81 (dt, 1H, CHF, $^3J_{FH}$ = 22.6, $^3J_{HH}$ = 8.3 Hz, *E*-isomer), 3.87 (s, 3H, both *E* and *Z*-isomers), 2.30 (q, 2H, *J* = 7.4 Hz, *E*-isomer), 2.32 (q, 2H, *J* = 7.2v, *Z*-isomer), 1.50 (quint, 2H, *J* = 7.4 Hz, both *E*- and *Z*-isomers), 1.40-1.26 (m, 8H, both *E*- and *Z*-isomers) 0.90-0.86 (m, 3H, *J* = 6.8, both *E*- and *Z*-isomers). ^{19}F NMR (282 MHz, $CDCl_3$): δ –115.56 (d, $^3J_{FH}$ = 21.4 Hz, *E* isomer), –124.67 (d, $^3J_{FH}$ = 39.7 Hz, *Z* isomer). HRMS (ESI) calcd. for $C_{18}H_{25}FN_3O$ $[M+H]^+$ 318.1976, found 318.1983.

4-(3-Ethyl-1-fluoropent-1-en-1-yl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (44)



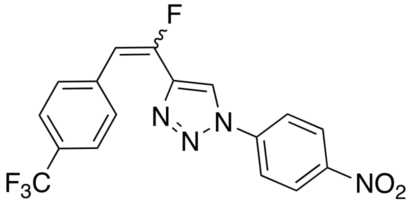
Method B: 2-Ethylbutanal: 15.0 mg (0.15 mmol); sulfone **27**: 76.8 mg (0.18 mmol, 1.2 molar equiv); LHMDS: 0.360 mL (1 M, 0.360 mmol, 2.4 molar equiv); DMF (1.1 mL), DMPU (1.1 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**44**: 25.7 mg (60%), as a colorless semi solid, *E*/*Z* ratio: 15/85. R_f (20% EtOAc in hexanes) = 0.39. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.94 (s, 1H, Ar-H, *E*-isomer), 7.87 (s, 1H, Ar-H, *Z*-isomer), 7.66-7.62 (m, 2H, Ar-H, both *E* and *Z*-isomers), 7.03 (d, 2H, Ar-H, J = 7.4 Hz, both *E* and *Z*-isomers), 5.61 (dd, 1H, CHF, $^3J_{FH}$ = 39.1 Hz, $^3J_{HH}$ = 10.6 Hz, *Z*-isomer), 5.27 (dd, 1H, CHF, $^3J_{FH}$ = 24.0 Hz, $^3J_{HH}$ = 11.0 Hz, *E*-isomer), 3.87 (s, 3H, both *E*-and *Z*-isomers), 3.31-3.23 (m, 1H, *E*-isomer), 2.57-2.49 (m, 1H, *Z*-isomer), 1.60-1.52 (m, 4H, *E*-isomer), 1.40-1.30 (m, 4H, *Z*-isomer), 0.93 (t, 6H, J = 7.6 Hz, both *E* and *Z*-isomers). ^{19}F NMR (282 MHz, CDCl$_3$): δ –114.37 (d, $^3J_{FH}$ = 21.4 Hz, *E* isomer), –124.68 (d, $^3J_{FH}$ = 39.7 Hz, *Z* isomer). HRMS (ESI) calcd. for $C_{16}H_{21}FN_3O$ $[M+H]^+$ 290.1663, found 290.1666

4-[1-Fluoro-2-(4-methoxyphenyl)vinyl]-1-(4-nitrophenyl)-1*H*-1,2,3-triazole (45)



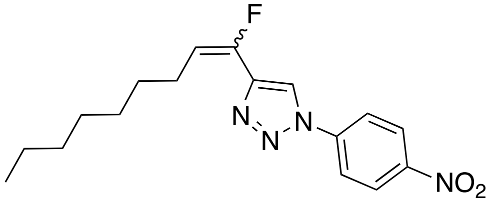
Method A: 4-Methoxybenzaldehyde: 20.5 mg (0.150 mmol); sulfone **29**: 75.5 mg (0.180 mmol, 1.2 molar equiv); DBU: 91.3 mg (0.600 mmol, 4.0 molar equiv); THF (4.3 mL). Eluting solvent for column chromatography: methylene chloride. Yield of *E*/*Z*-**45**: 41.9 mg (82%), as a pale yellow solid, *E*/*Z* ratio: 87/13. R_f (20% EtOAc in hexanes) = 0.29. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.34 (s, 1H, Ar-H, *Z*-isomer), 9.31 (s, 1H, Ar-H, *E*-isomer), 8.49-8.46 (m, Ar-H, 2H, both *E* and *Z*-isomers), 8.30-8.27 (m, Ar-H, 2H, both *E* and *Z*-isomers), 7.64 (d, 2H, Ar-H, J = 8.8 Hz, *Z*-isomer), 7.46 (d, 2H, Ar-H, J = 8.8, *E*-isomer), 7.01 (d, 2H, Ar-H, J = 7.8 Hz, *Z*-isomer), 6.90 (d, 2H, Ar-H, J = 7.8 Hz, *E*-isomer), 6.783 (d, 1H, CHF, $^3J_{FH}$ = 23.0 Hz, *E*-isomer), 6.778 (d, 1H, CHF, $^3J_{FH}$ = 40.1 Hz, *Z*-isomer), 3.80 (s, 3H, *Z*-isomer), 3.75 (s, 3H, *E*-isomer). ^{19}F NMR (282 MHz, CDCl$_3$): δ –109.57 (d, $^3J_{FH}$ = 21.4 Hz, *E*-isomer), –122.23 (d, $^3J_{FH}$ = 39.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{17}H_{14}FN_4O_3$ [M +H]$^+$ 341.1044, found 341.1043.

4-{1-Fluoro-2-[4-(trifluoromethyl)phenyl]vinyl}-1-(4-nitrophenyl)-1*H*-1,2,3-triazole (46)



Method B: 4-(Trifluoromethyl)benzaldehyde: 20.0 mg (0.115 mmol); sulfone **29**: 58.0 mg (0.138 mmol, 1.2 molar equiv); LHMDS: 0.280 mL (1 M, 0.280 mmol, 2.4 molar equiv); DMF (0.900 mL), DMPU (0.900 mL). Eluting solvent for column chromatography: 50% methylene chloride in hexanes. Yield of *E*/*Z*-**46**: 31.6 mg (73%), as a pale yellow solid, *E*/*Z* ratio: 15/85. R_f (10% EtOAc in hexanes) = 0.19. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.48-8.44 (m, Ar-H, 2H, both *E* and *Z*-isomers), 8.26 (s, 1H, Ar-H, *Z*-isomer), 8.17 (s, 1H, Ar-H, *E*-isomer), 8.03 (d, 2H, Ar-H, J = 8.8 Hz, *Z*-isomer), 7.97 (d, 2H, Ar-H, J = 8.8 Hz, *E*-isomer), 7.77 (d, 2H, Ar-H, J = 7.8 Hz, *Z*-isomer), 7.66-7.60 (m, Ar-H, 4H *E*-isomer and 2H *Z*-isomer), 6.92 (d, 1H, CHF, $^3J_{FH}$ = 40.1 Hz, *Z*-isomer), 6.69 (d, 1H, CHF, $^3J_{FH}$ = 23.0 Hz, *E*-isomer). ^{19}F NMR (282 MHz, CDCl$_3$): δ -63.20 (CF$_3$, both *E* and *Z*-isomers), –104.80 (d, $^3J_{FH}$ = 21.4 Hz, *E*-isomer), –116.81 (d, $^3J_{FH}$ = 39.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{17}H_{10}F_4N_4NaO_2$ [M + H]$^+$ 401.0632, found 401.0616.

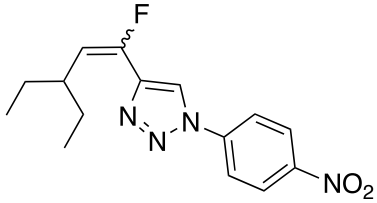
4-(1-Fluoronon-1-en-1-yl)-1-(4-nitrophenyl)-1*H*-1,2,3-triazole (47)



Method B: Octanal: 20.0 mg (0.160 mmol); sulfone **29**: 79.7 mg (0.19 mmol, 1.2 molar equiv); LHMDS: 0.380 mL (1 M, 0.380 mmol, 2.4 molar equiv); DMF (1.1 mL), DMPU (1.1 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**47**: 32.5 mg (61%), as a pale yellow solid, *E*/*Z* ratio: 32/68. R_f (20% EtOAc in hexanes) = 0.48.

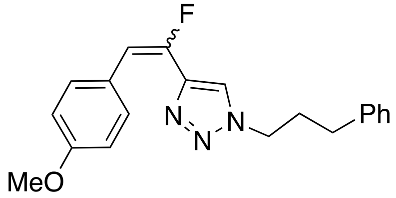
^{1}H NMR (500 MHz, CDCl$_3$) δ 8.45-8.42 (m, 2H, Ar-H, both *E* and *Z*-isomers), 8.14 (s, 1H, Ar-H, *E*-isomer), 8.05 (s, 1H, Ar-H, *Z*-isomer), 8.01-7.97 (m, 2H, Ar-H, both *E* and *Z*-isomers), 5.93 (dt, 1H, CHF, $^3J_{FH}$ = 39.0 Hz, $^3J_{HH}$ = 7.8 Hz, *Z*-isomer), 5.62 (dt, 1H, CHF, $^3J_{FH}$ = 22.9 Hz, $^3J_{HH}$ = 8.3 Hz, *E*-isomer), 2.68 (q, 2H, CH$_2$, J = 7.7 Hz, *E*-isomer), 2.32 (q, 2H, CH$_2$, J = 7.5 Hz, *Z*-isomer), 1.50 (quint, 2H, CH$_2$, J = 7.2 Hz, both *E*- and *Z*-isomers), 1.41-1.29 (m, 8 H, both *E*- and *Z*-isomers), 0.88 (app q, 3H, CH$_3$, J = 6.8 Hz, both *E*- and *Z*-isomers). ^{19}F NMR (282 MHz, CDCl$_3$): δ –116.23 (d, $^3J_{FH}$ = 21.4 Hz, *E* isomer), –125.21 (d, $^3J_{FH}$ = 39.7 Hz, *Z* isomer). HRMS (ESI) calcd. for $C_{17}H_{22}FN_4O_2$ [M +H]$^+$ 333.1721, found 333.1719.

4-(3-Ethyl-1-fluoropent-1-en-1-yl)-1-(4-nitrophenyl)-1*H*-1,2,3-triazole (48)



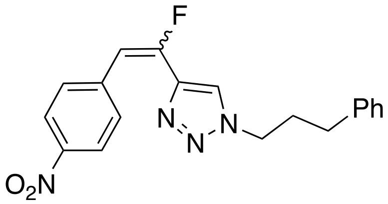
Method B: 2-Ethylbutanal: 15.0 mg (0.15 mmol); sulfone **29**: 75.5 mg (0.18 mmol, 1.2 molar equiv); LHMDS: 0.360 mL (1 M, 0.360 mmol, 2.4 molar equiv); DMF (1.0 mL), DMPU (1.0 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**48**: 31.0 mg (68%), as a pale yellow solid, *E*/*Z* ratio: 12/88. R_f (20% EtOAc in hexanes) = 0.53. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, 2H, Ar-H, J = 8.9, both *E* and *Z*-isomers), 8.14 (s, 1H, Ar-H, *E*-isomer), 8.05 (s, 1H, Ar-H, *Z*-isomer), 8.01-7.98 (m, 2H, Ar-H, both *E* and *Z*-isomers), 5.70 (dd, 1H, CHF, $^3J_{FH}$ = 39.4 Hz, $^3J_{HH}$ = 10.4 Hz, *Z*-isomer), 5.35 (dd, 1H, CHF, $^3J_{FH}$ = 24.0 Hz, $^3J_{HH}$ = 11.1 Hz, *E*-isomer), 3.34-3.24 (m, 1H, *E*-isomer), 2.59-2.51 (m, 1H, *Z*-isomer), 1.64-1.54 (m, 4H, *E*-isomers), 1.41-1.32 (m, 4H, *Z*-isomer), 0.93 (t, 6H, J = 7.5 Hz, both *E* and *Z*-isomers). ^{19}F NMR (282 MHz, $CDCl_3$): δ –114.94 (d, $^3J_{FH}$ = 24.4 Hz, *E* isomer), –125.07 (d, $^3J_{FH}$ = 39.7 Hz, *Z* isomer). HRMS (ESI) calcd. for $C_{15}H_{18}FN_4O_2$ [M +H]$^+$ 305.1408, found 305. 1414.

4-[1-Fluoro-2-(4-methoxyphenyl)vinyl]-1-(3-phenylpropyl)-1*H*-1,2,3-triazole (49)



Method A: 4-Methoxybenzaldehyde: 20 mg (0.15 mmol); sulfone **33**: 87.5 mg (0.26 mmol, 1.7 molar equiv); DBU: 91.3 mg (0.60 mmol, 4.0 molar equiv); THF (4.2 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**49**: 38.2 mg (75%), as a white solid, *E*/*Z* ratio: 76/24. R_f (20% EtOAc in hexanes) = 0.29. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H, Ar-H, *Z*-isomer), 7.58 (d, 2H, Ar-H, J = 8.8 Hz, *Z*-isomer), 7.39 (d, 2H, Ar-H, J = 8.8 Hz, *E*-isomer), 7.38 (s, 1H, *E*-isomer), 7.33-7.18 (m, Ar-H, 3H *E*-isomer and 5H *Z*-isomer), 7.14 (d, 2H, Ar-H, J = 7.8 Hz, *E*-isomer), 6.91 (d, 2H, Ar-H, J = 8.8 Hz, *Z*-isomer), 6.85 (d, 2H, Ar-H, J = 8.3 Hz, *E*-isomer), 6.67 (d, 1H, CHF, $^3J_{FH}$ = 41.4 Hz, *Z*-isomer), 6.52 (d, 1H, CHF, $^3J_{FH}$ = 22.6 Hz, *E*-isomer), 4.39 (t, 2H, CH_2, J = 6.9 Hz, *Z*-isomer), 4.32 (t, 2H, CH_2, J = 6.9 Hz, *E*-isomer), 3.83 (s, 3H, CH_3, *Z*-isomer), 3.80 (s, 3H, CH_3, *E*-isomer), 2.69 (t, 2H, CH_2, J = 7.4 Hz, *Z*-isomer), 2.63 (t, 2H, CH_2, J = 7.4 Hz, *E*-isomer), 2.29 (quint, 2H, CH_2, J = 7.2 Hz, *Z*-isomer), 2.23 (quint, 2H, CH_2, J = 7.4 Hz, *E*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$): δ –108.20 (d, $^3J_{FH}$ = 21.4 Hz, *E*-isomer), –121.30 (d, $^3J_{FH}$ = 42.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{20}H_{21}FN_3O$ $[M + H]^+$ 338.1663, found 338.1667.

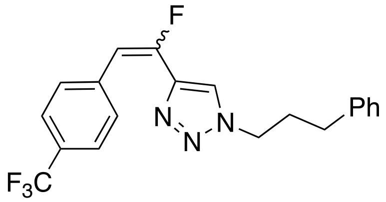
4-(1-Fluoro-2-[4-nitrophenyl]vinyl)-1-(3-phenylpropyl)-1*H*-1,2,3-triazole (50)



Method B: 4-Nitrobenzaldehyde: 75.6 mg (0.50 mmol); sulfone **33**: 249.9 mg (0.60 mmol, 1.2 molar equiv); LHMDS: 1.20 mL (1 M, 1.20 mmol, 2.4 molar equiv); DMF (3.8 mL), DMPU (3.8 mL). Eluting solvent for column chromatography: 40% EtOAc in hexanes. Yield of *E*/*Z*-**50**: 133.9 mg (76%), as a white solid, *E*/*Z* ratio: 38/62. R_f (20% EtOAc in hexanes) = 0.12. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, 2H, Ar-H, J = 8.8 Hz, *Z*-isomer), 8.17 (d, 2H, Ar-H, J = 8.8 Hz, *E*-isomer), 7.75 (d, 2H, Ar-H, J = 8.3 Hz, *Z*-isomer), 7.74 (d, 2H, Ar-H, J = 8.3 Hz, *E*-isomer), 7.72 (s, 1H, Ar-H, *Z*-isomer), 7.64 (s, 1H, Ar-H, *E*-isomer), 7.33-7.29 (m, 2H, Ar-H, both *E* and *Z*-isomers), 7.25-7.22 (m, 1H, Ar-H, both *E* and *Z*-isomers), 7.21-7.16 (m, 2H, Ar-H, both *E* and *Z*-

isomers), 6.91 (d, 2H, Ar-H, *J* = 8.8 Hz, *Z*-isomer), 6.82 (d, 1H, CHF, $^3J_{FH}$ = 36.6 Hz, *Z*-isomer), 6.55 (d, 1H, CHF, $^3J_{FH}$ = 23.5 Hz, *E*-isomer), 4.42 (t, 2H, *J* = 7.1 Hz, *Z*-isomer), 4.38 (t, 2H, CH_2, *J* = 7.4 Hz, *E*-isomer), 2.71-2.65 (m, 2H, both *E* and *Z*-isomers), 2.34-2.25 (m, 2H, both *E* and *Z*-isomers). ^{19}F NMR (282 MHz, $CDCl_3$): δ –100.64 (d, $^3J_{FH}$ = 21.4 Hz, *E*-isomer), –113.37 (d, $^3J_{FH}$ = 39.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{19}H_{18}FN_4O_2$ $[M + H]^+$ 353.1408, found 353.1411.

4-{1-Fluoro-2-[4-(trifluoromethyl)phenyl]vinyl}-1-(3-phenylpropyl)-1*H*-1,2,3-triazole (51)

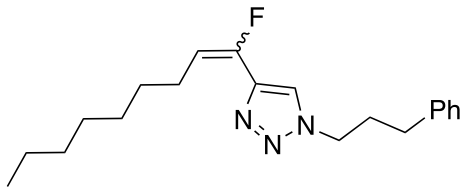


Method A: 4-(Trifluoromethyl)benzaldehyde: 20 mg (0.115 mmol); sulfone **33**: 57.0 mg (0.14 mmol, 1.2 molar equiv); DBU: 70.0 mg (0.46 mmol, 4.0 molar equiv); THF (3.2 mL). Eluting solvent for column chromatography: 50% methylene chloride in hexanes. Yield of *E*/*Z*-**51**: 34.2 mg (80%), as a white solid, *E*/*Z* ratio: 63/37. R_f (10% EtOAc in hexanes) = 0.35.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, 2H, Ar-H, *J* = 8.3 Hz, *Z*-isomer), 7.69 (s, 1H, Ar-H, *Z*-isomer), 7.62 (d, 2H, Ar-H, *J* = 7.4 Hz, both *E* and *Z*-isomers), 7.57 (d, 2H, Ar-H, *J* = 8.3 Hz, *E*-isomer), 7.53 (s, 1H, Ar-H, *E*-isomer), 7.34-7.21 (m, 3H, Ar-H, both *E* and *Z*-isomers), 7.19 (d, 2H, *J* =7.4 Hz, *Z*-isomer), 7.15 (d, 2H, Ar-H, *J* =7.4 Hz, *E*-isomer), 6.78 (d, 1H, CHF, $^3J_{FH}$ = 40.5 Hz, *Z*-isomer), 6.55 (d, 1H, CHF, $^3J_{FH}$ = 23.0 Hz, *E*-isomer), 4.41 (t, 2H, *J* = 7.1 Hz, *Z*-isomer), 4.36 (t, 2H, CH_2, *J* = 7.1 Hz, *E*-isomer), 2.69 (t, 2H, *J* = 7.4 Hz, *Z*-isomer), 2.64 (t, 2H, CH_2, *J* = 7.4 Hz, *E*-isomer), 2.30 (quint, 2H, *J* = 7.4 Hz, *Z*-isomer), 2.25 (quint, 2H, CH_2, *J* = 7.4 Hz, *E*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$): δ –63.14 (s), –102.93 (d, $^3J_{FH}$ = 21.4 Hz, *E*-

isomer), –115.81 (d, $^3J_{FH}$ = 39.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{20}H_{18}F_4N_3$ $[M + H]^+$ 376.1431, found 376.1427.

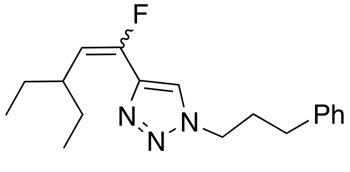
4-(1-Fluoronon-1-en-1-yl)-1-(3-phenylpropyl)-1*H*-1,2,3-triazole (52)



Method B: Octanal: 20.0 mg (0.160 mmol); sulfone **33**: 79.1 mg (0.19 mmol, 1.2 molar equiv); LHMDS: 0.380 mL (1 M, 0.380 mmol, 2.4 molar equiv); DMF (1.1 mL), DMPU (1.1 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**52**: 32.9 mg (63%), as a pale yellow solid, *E*/*Z* ratio: 36/64. R_f (20% EtOAc in hexanes) = 0.2.

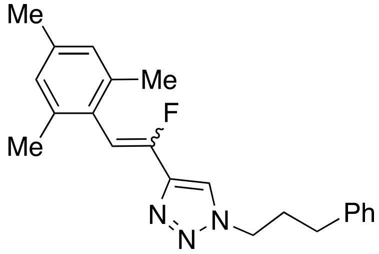
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H, Ar-H, *E*-isomer), 7.48 (s, 1H, Ar-H, *Z*-isomer), 7.31 (t, 2H, Ar-H, *J* = 7.4 Hz, both *E* and *Z*-isomers), 7.22 (t, 1H, Ar-H, *J* = 7.1 Hz, both *E* and *Z*-isomers), 7.19-7.17 (m, 2H, Ar-H, both *E* and *Z*-isomers), 5.77 (dt, 1H, CHF, $^3J_{FH}$ = 39.1 Hz, $^3J_{HH}$ = 7.8 Hz, *Z*-isomer), 5.48 (dt, 1H, CHF, $^3J_{FH}$ = 22.6 Hz, $^3J_{HH}$ = 8.1 Hz, *E*-isomer), 4.38-4.34 (m, 2H, both *E*- and *Z*-isomers), 2.67 (q, 2H, *J* = 7.1 Hz, both *E*- and *Z*-isomers), 2.60 (q, 4H, *J* = 7.7 Hz, *Z*-isomer), 2.30-2.23 (m, 4H, *E*-isomer), 1.49-143 (m, 2H, both *E*- and *Z*-isomers), 1.37-1.23 (m, 8 H, both *E*- and *Z*-isomers), 0.90-0.86 (m, 3H, CH_3, both *E*- and *Z*-isomers). ^{19}F NMR (282 MHz, $CDCl_3$): δ –115.34 (d, $^3J_{FH}$ = 24.4 Hz, *E* isomer), –124.51 (d, $^3J_{FH}$ = 39.7 Hz, *Z* isomer). HRMS (ESI) calcd. for $C_{20}H_{28}FN_3Na$ $[M+Na]^+$ 352.2159, found 352.2161.

4-(3-Ethyl-1-fluoropent-1-en-1-yl)-1-(3-phenylpropyl)-1*H*-1,2,3-triazole (53)



Method B: 2-Ethylbutanal: 20.0 mg (0.20 mmol); sulfone **33**: 100.0 mg (0.24 mmol, 1.2 molar equiv); LHMDS: 0.480 mL (1 M, 0.480 mmol, 2.4 molar equiv); DMF (1.5 mL), DMPU (1.5 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**53**: 34.5 mg (57%), as a white solid, *E*/*Z* ratio: 19/81. R_f (20% EtOAc in hexanes) = 0.21. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H, Ar-H, *E*-isomer), 7.49 (s, 1H, Ar-H, *Z*-isomer), 7.31 (t, 2H, Ar-H, J =7.4 Hz, both *E* and *Z*-isomers), 7.22 (t, 1H, Ar-H, J =7.4 Hz, both *E* and *Z*-isomers), 7.18 (d, 2H, Ar-H, J =7.4 Hz, both *E* and *Z*-isomers), 5.53 (dd, 1H, CHF, $^3J_{FH}$ = 39.6 Hz, $^3J_{HH}$ = 10.1 Hz, *Z*-isomer), 5.21 (dd, 1H, CHF, $^3J_{FH}$ = 23.7 Hz, $^3J_{HH}$ = 11.3 Hz, *E*-isomer), 4.36 (t, 2H, CH_2, J = 7.1 Hz, both *E* and *Z*-isomers), 3.22-3.14 (m, 1H, CH, *E*-isomer), 2.67 (t, 2H, CH_2, J = 7.4 Hz, both *E* and *Z*-isomers), 2.54-2.46 (m, 1H, CH, *Z*-isomer), 2.31-2.23 (m, 2H, CH_2, both *E* and *Z*-isomers), 1.57-1.50 (m, 2H, CH_2, both *E* and *Z*-isomers), 1.37-1.26 (m, 2H, CH_2, both *E* and *Z*-isomers), 0.93-0.88 (m, 6H, $2CH_3$, both *E* and *Z*-isomers). ^{19}F NMR (282 MHz, $CDCl_3$): δ –113.99 (d, $^3J_{FH}$ = 24.4 Hz, *E* isomer), –124.55 (d, $^3J_{FH}$ = 39.7 Hz, *Z* isomer). HRMS (ESI) calcd. for $C_{18}H_{25}FN_3$ $[M + H]^+$ 302.2027, found 302.2031.

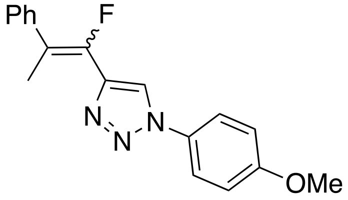
4-(1-Fluoro-2-mesitylvinyl)-1-(3-phenylpropyl)-1*H*-1,2,3-triazole (54)



Method B: 2,4,6-Trimethylbenzaldehyde: 15.0 mg (0.10 mmol); sulfone **33**: 50.4 mg (0.12 mmol, 1.2 molar equiv); LHMDS: 0.240 mL (1 M, 0.242 mmol, 2.4 molar equiv); DMF (0.760 mL), DMPU (0.760 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**54**: 16.7 mg (47%), as a white solid, *E*/*Z* ratio: 26/74. R_f (20% EtOAc in hexanes) =

0.45. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.61 (s, 1H, Ar-H, *Z*-isomer), 7.33-7.19 (m, Ar-H, 3H *E*-isomer and 5H *Z*-isomer), 7.07 (d, 2H, Ar-H, J = 7.3 Hz, *E*-isomer), 6.92 (s, 2H, Ar-H, both *E* and *Z*-isomers), 6.76 (d, 1H, CHF, $^3J_{FH}$ = 41.5 Hz, *Z*-isomer), 6.59 (s, 1H, Ar-H, *E*-isomer), 6.36 (d, 1H, CHF, $^3J_{FH}$ = 18.5 Hz, *E*-isomer), 4.40 (t, 2H, CH$_2$, J = 7.1 Hz, *Z*-isomer), 4.17 (t, 2H, CH$_2$, J = 6.8 Hz, *E*-isomer), 2.71 (t, 2H, CH$_2$, J = 7.3 Hz, *Z*-isomer), 2.49 (t, 2H, CH$_2$, J = 7.3 Hz, *E*-isomer), 2.33-2.27 (m, 3H *E*-isomer and 11H *Z*-isomers), 2.15 (s, 6H, *E*-isomer , 2CH$_3$), 2.10 (quint, 2H, *E*-isomer, J = 7.2 Hz). ^{19}F NMR (282 MHz, CDCl$_3$): δ –114.33 (d, $^3J_{FH}$ = 21.4 Hz, *E*-isomer), –115.50 (d, $^3J_{FH}$ = 42.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{22}H_{25}FN_3$ [M + H]$^+$ 350.2038, found 350.2027.

4-(1-fluoro-2-phenylprop-1-en-1-yl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (55)



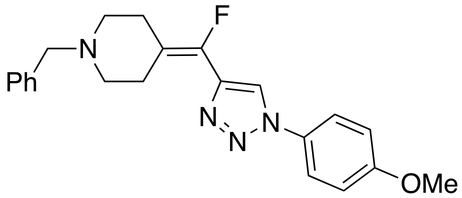
Method C: Acetophenone: 20.0 mg (0.17 mmol); sulfone **27**: 80.9 mg (0.20 mmol, 1.2 molar equiv); LHMDS: 0.410 mL (1 M, 0.410 mmol, 2.4 molar equiv); THF (2.0 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**55**: 33.0 mg (64%), as a white solid. Isomer ratio major/minor : 72:28

^{1}H NMR (500 MHz, CDCl$_3$), **Major Isomer**: δ 8.04 (s, 1H, Ar-H), 7.67 (d, 2H, Ar-H, J = 8.8 Hz), 7.50 (d, 2H, Ar-H, J = 7.8 Hz), 7.41 (t, 2H, Ar-H, J = 7.6 Hz), 7.31 (t, 1H, Ar-H, J = 7.4 Hz), 7.04 (d, 2H, Ar-H, J = 9.2 Hz), 3.87 (s, 3H, CH$_3$), 2.57 (d, 3H, CH$_3$, J = 3.7 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): δ 160.2, four resonances at 145.8, 143.9, 143.7, 143.4 (two doublets for 2C), 138.6, 130.3, 128.5 (d, 2C, J_{CF} = 4.1 Hz), 128.4 (2C), 127.5, 122.4 (2C), 120.5, 118.0 (d, J_{CF} =

12.4 Hz), 115.1 (2C), 55.9, 17.5 (d, J_{CF} = 3.7 Hz). ^{19}F NMR (282 MHz, CDCl$_3$): δ -116.57 (s). R_f (20% EtOAc in hexanes) = 0.27.

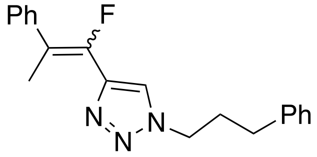
Minor Isomer: δ 7.40-7.32 (m, 5H, Ar-H), 7.27-7.25 (m, 2H, Ar-H), 6.95-6.91 (m, 3H, Ar-H), 3.83 (s, 3H, CH$_3$), 2.21 (d, 3H, CH$_3$, J = 3.7 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): δ 160.1, 145.9 (d, J_{CF} = 240.8 Hz), 139.4 (d, J_{CF} = 7.3 Hz), 130.2, 129.2 (2C), 128.8 (d, 2C, J_{CF} = 2.7 Hz), 128.1, 122.3 (2C), 120.6 (d, J_{CF} = 5.1 Hz), 119.7 (d, J_{CF} = 19.2 Hz), 114.9 (2C), 55.8, 17.8 (d, J_{CF} = 6.0 Hz). ^{19}F NMR (282 MHz, CDCl$_3$): δ -116.46 (s). R_f (20% EtOAc in hexanes) = 0.22.

1-Benzyl-4-{fluoro[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methylene}piperidine (56)



Method C: 1-Benzylpiperidin-4-one: 20.0 mg (0.11 mmol); sulfone **27**: 56.6 mg (0.14 mmol, 1.3 molar equiv); LHMDS: 0.260 mL (1 M, 0.262 mmol, 2.4 molar equiv); THF (1.3 mL). Eluting solvent for column chromatography: 40% EtOAc in hexanes. Yield of *E*/*Z*-**58**: 36.2 mg (87%), as a semi solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.92 (s, 1H, Ar-H), 7.63 (d, 2H, Ar-H, J =9.3 Hz), 7.36-7.32 (m, 4H, Ar-H), 7.28-7.25 (m, 1H, Ar-H), 7.02 (d, 2H, Ar-H, J = 8.3 Hz), 3.87 (s, 3H, CH$_3$), 3.57 (s, 2H, CH$_2$), 3.00 (t, 2H, CH$_2$, J = 4.9 Hz), 2.59-2.54 (m, 6H, 3CH$_2$). ^{13}C NMR (125 MHz, CDCl$_3$): δ 160.2, four resonances at 143.4, 143.2, 142.9, 141.6 (two doublets for 2C), 138.4, 130.4, 129.4 (2C), 128.4 (2C), 127.3, 122.4 (2C), 119.9, 118.9 (d, J_{CF} = 15.1 Hz), 115.0 (2C), 63.1, 55.8, 54.3, 53.8, 27.0 (d, J_{CF} = 4.6 Hz), 26.2 (d, J_{CF} = 7.3 Hz). ^{19}F NMR (282 MHz, CDCl$_3$): δ -121.99 (s). HRMS (ESI) calcd. for $C_{22}H_{24}FN_4O$ $[M + H]^+$ 379.1929, found 379.1924.

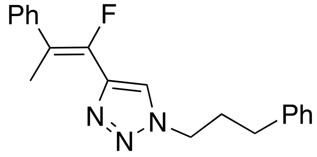
4-(1-Fluoro-2-phenylprop-1-en-1-yl)-1-(3-phenylpropyl)-1*H*-1,2,3-triazole (57)



Method C: Acetophenone: 20.0 mg (0.17 mmol); sulfone **33**: 83.2 mg (0.20 mmol, 1.2 molar equiv); LHMDS: 0.410 mL (1 M, 0.410 mmol, 2.4 molar equiv); THF (2.0 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**57**: 42.2 mg (77%), as a white solid. Isomer ratio major/minor: 80:20

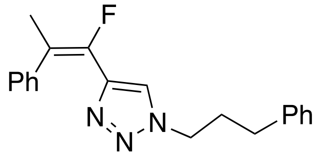
The diastereomers were separated by column chromatography. Stereochemistry of the major isomer was determined by the X-ray structure confirming the *Z*-stereochemistry of the olefin.

Major (*Z*-) isomer:



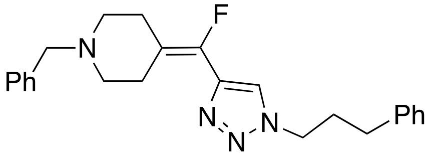
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.65 (s, 1H, Ar-H), 7.48 (d, 2H, Ar-H, J = 7.4 Hz), 7.39 (t, 2H, Ar-H, J = 7.6 Hz), 7.33-7.28 (m, 3H, Ar-H), 7.24-7.19 (m, 3H, Ar-H), 4.40 (t, 2H, CH$_2$, J = 7.1 Hz), 2.69 (t, 2H, CH$_2$, J = 7.4 Hz), 2.52 (d, 3H, CH$_3$, J = 3.2 Hz), 2.30 (quint, 2H, CH$_2$, J = 7.2 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): δ 145.1 (d, J_{CF} = 233.9 Hz), 143.0 (d, J_{CF} = 39.4 Hz), 140.2, 138.6, 128.9 (2C), 128.6 (2C), 128.4 (d, 2C, J_{CF} = 4.1 Hz), 128.3 (2C), 127.5, 126.6, 122.3 (d, J_{CF} = 2.3 Hz), 117.4 (d, J_{CF} = 13.3 Hz), 49.7, 32.6, 31.8, 17.4 (d, J_{CF} = 4.1 Hz). ^{19}F NMR (282 MHz, CDCl$_3$): δ -116.33 (s). R_f (20% EtOAc in hexanes) = 0.20.

Minor (*E*-) isomer:



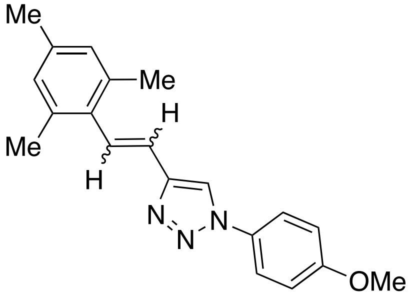
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.36-7.31 (m, 3H, Ar-H), 7.28 (t, 2H, Ar-H, J = 7.4 Hz), 7.22-7.19 (m, 3H, Ar-H), 7.06 (d, 2H, Ar-H, J = 7.4 Hz), 6.54 (s, 1H, Ar-H), 4.15 (t, 2H, CH$_2$, J = 6.7 Hz), 2.48 (t, 2H, CH$_2$, J = 7.4 Hz), 2.18 (d, 3H, CH$_3$, J = 4.1 Hz), 2.07 (quint, 2H, CH$_2$, J = 7.2 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): δ 146.1 (d, J_{CF} = 241.2 Hz), 141.0 (d, J_{CF} = 33.4 Hz), 140.2, 139.6 (d, J_{CF} = 7.3 Hz) 129.1 (2C), 128.82 (2C), 128.77 (d, 2C, J_{CF} = 2.7 Hz), 128.6 (2C), 127.9, 126.6, 122.6 (d, J_{CF} = 5.5 Hz), 119.3 (d, J_{CF} = 19.7 Hz), 49.4, 32.4, 31.6, 17.7 (d, J_{CF} = 6.0 Hz). ^{19}F NMR (282 MHz, CDCl$_3$): δ -115.6 (s). HRMS (ESI) calcd. for $C_{20}H_{20}FN_3Na$ [M + Na]$^+$ 344.1533, found 344.1536. R_f (20% EtOAc in hexanes) = 0.10.

1-Benzyl-4-[fluoro(1-(3-phenylpropyl)-1*H*-1,2,3-triazol-4-yl]methylene)piperidine (58)



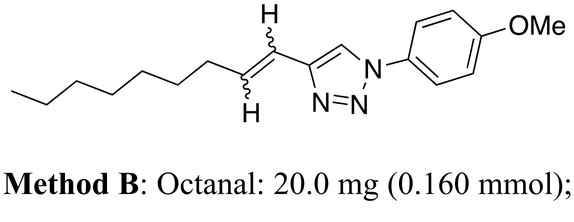
Method C: 1-Benzylpiperidin-4-one: 20.0 mg (0.11 mmol); sulfone **33**: 52.8 mg (0.13 mmol, 1.2 molar equiv); LHMDS: 0.260 mL (1 M, 0.262 mmol, 2.4 molar equiv); THF (1.3 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**58**: 25.0 mg (58%), as a semi solid. R_f (20% EtOAc in hexanes) = 0.23. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.53 (s, 1H, Ar-H), 7.36-7.25 (m, 7H, Ar-H), 7.22 (t, 1H, Ar-H, J = 7.4 Hz), 7.18 (d, 2H, Ar-H, J = 7.8 Hz), 4.36 (t, 2H, CH$_2$, J = 6.9 Hz), 3.55 (s, 2H, CH$_2$), 2.94 (t, 2H, CH$_2$, J = 4.8 Hz), 2.66 (t, 2H, CH$_2$, J = 7.6 Hz), 2.56-2.52 (m, 6H), 2.26 (quint, 2H, CH$_2$, J = 7.2 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): δ 142.8 (d, J_{CF} = 227.9 Hz), 142.7 (d, J_{CF} = 40.3 Hz), 140.3 138.8, 129.4 (2C), 128.9 (2C), 128.7 (2C), 128.4 (2C), 127.2, 126.7, 121.6, 118.5 (d, J_{CF} = 14.8 Hz), 63.2, 54.4, 53.9, 49.7, 32.8, 31.7, 27.2 (d, J_{CF} = 4.6 Hz), 26.3 (d, J_{CF} = 7.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ -121.52 (s). HRMS (ESI) calcd. for $C_{24}H_{28}FN_4$ $[M + H]^+$ 391.2293, found 391.2298.

1-(4-Methoxyphenyl)-4-(2,4,6-trimethylstyryl)-1*H*-1,2,3-triazole (59)



Method B: 2,4,6-Trimethylbenzaldehyde: 20.0 mg (0.14 mmol); sulfone **37**: 65.7 mg (0.17 mmol, 1.2 molar equiv); LHMDS: 0.340 mL (1 M, 0.340 mmol, 2.4 molar equiv); DMF (1.0 mL), DMPU (1.0 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**59**: 32.7 mg (73%), as a white solid, *E*/*Z* ratio: 33/67. R_f (40% EtOAc in hexanes) = 0.71. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H, Ar-H, *E*-isomer), 7.66 (d, 2H, Ar-H, J = 8.8 Hz, *E*-isomer), 7.42 (d, 1H, =CH, J = 16.6 Hz, *E*-isomer), 7.37 (d, 2H, Ar-H, J = 9.2 Hz, *Z*-isomer), 7.04 (d, 2H, Ar-H, J = 9.2 Hz, *E*-isomer), 6.96-6.91 (m, 2H *E*-isomer, 5H *Z*-isomer), 6.68-6.65 (m, 1H *E*-isomer, 2H *Z*-isomer), 3.88 (s, 3H, OCH_3, *E*-isomer), 3.83 (s, 3H, OCH_3, *Z*-isomer), 2.38 (s, 3H, CH_3, *Z*-isomer), 2.33 (s, 6H, $2CH_3$, *E*-isomer), 2.30 (s, 3H, CH_3, *E*-isomer), 21.4 (s, 6H, $2CH_3$, *Z*-isomer). HRMS (ESI) calcd. for $C_{20}H_{22}N_3O$ $[M+H]^+$ 320.1757, found 320.176.

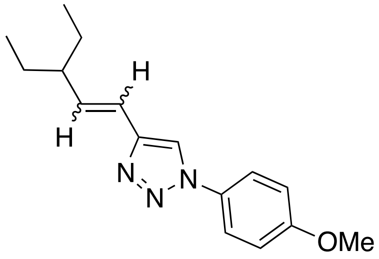
1-(4-Methoxyphenyl)-4-(non-1-en-1-yl)-1*H*-1,2,3-triazole (60)



Method B: Octanal: 20.0 mg (0.160 mmol); sulfone **37**: 73.4 mg (0.190 mmol, 1.2 molar equiv);

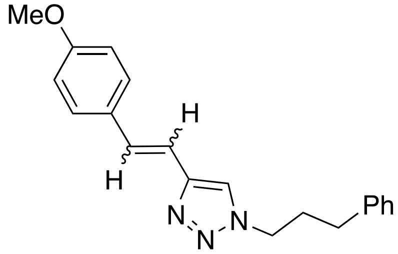
LHMDS: 0.380 mL (1 M, 0.384 mmol, 2.4 molar equiv); DMF (1.2 mL), DMPU (1.2 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**60**: 33.8 mg (71%), as a colorless semi solid, *E*/*Z* ratio: 72/28. R_f (20% EtOAc in hexanes) = 0.31. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H, Ar-H, *Z*-isomer), 7.76 (s, 1H, Ar-H, *E*-isomer), 7.64 (d, 2H, Ar-H, *J* = 9.2 Hz, *Z*-isomer), 7.61 (d, 2H, Ar-H, *J* = 9.2 Hz, *E*-isomer), 7.03-7.00 (m, 2H, Ar-H, both *E* and *Z*-isomers), 6.52-6.46 (m, 1H, =CH, both *E* and *Z*-isomers), 6.43 (d, 1H, =CH, *J* = 16.2 Hz, *E*-isomer), 5.82 (dt, 1H, =CH, *J* = 11.6, 7.0 Hz, *Z*-isomer), 3.87 (s, 3H, OCH_3, *Z*-isomer) 3.86 (s, 3H, OCH_3, *E*-isomer), 2.45 (dq, 2H, CH_2, *J* = 7.3, 1.4 Hz, *Z*- isomer), 2.23 (q, 2H, CH_2, *J* = 6.9 Hz, *E*- isomer), 1.53-1.45 (m, 2H, CH_2, both *E* and *Z*- isomers), 1.39-1.23 (m, 8H, $4CH_2$, both *E* and *Z*- isomers), 0.90-0.86 (m, 3H, CH_3, both *E* and *Z*- isomers). HRMS (ESI) calcd. for $C_{18}H_{26}N_3O$ $[M+H]^+$ 300.2070, found 300.2071.

4-(3-Ethylpent-1-en-1-yl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (61)



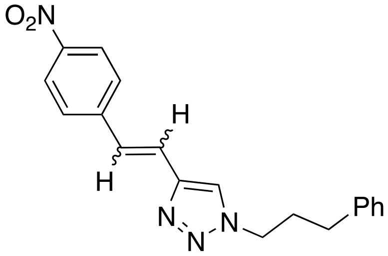
Method B: 2-Ethylbutnanal: 20.0 mg (0.20 mmol); sulfone **37**: 92.4 mg (0.24 mmol, 1.2 molar equiv); LHMDS: 0.480 mL (1.0 M, 0.480 mmol, 2.4 molar equiv); DMF (1.5 mL), DMPU (1.5 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**61**: 36.3 mg (67%), as a colorless semi solid, *E*/*Z* ratio: 86/14. R_f (20% EtOAc in hexanes) = 0.30. ^{1}H NMR (500 MHz, $CDCl_6$) δ 7.80 (s, 1H, Ar-H, *Z*-isomer), 7.77 (s, 1H, Ar-H, *E*-isomer), 7.64-7.60 (m, Ar-H, 2H both *E* and *Z*-isomers), 7.00 (d, 2H, Ar-H, *J* = 8.8 Hz, both *E* and *Z*-isomers), 6.51 (d, 1H, =CH, *J* = 11.9 Hz, *Z*-isomer), 6.41 (d, 1H, =CH, *J* = 16.2 Hz, *E*-isomer), 6.23 (dd, 1H, =CH, *J* = 16.2, 8.9 Hz, *E*-isomer), 5.52 (t, 1H, =CH, *J* = 11.0 Hz, *Z*-isomer), 3.86 (s, 3H, OCH_3, both *E* and *Z*-isomers), 2.00-1.93 (m, 1H, CH, both *E* and *Z*- isomers), 1.56-1.48 (m, 2H, CH_2, both *E* and *Z*- isomers), 1.41-1.32 (m, 2H, CH_2, both *E* and *Z*- isomers), 0.90 (t, 6H, $2CH_3$, *J* = 7.5 Hz, both *E* and *Z*- isomers). HRMS (ESI) calcd. for $C_{16}H_{22}N_3O$ $[M+H]^+$ 272.1757, found 272.1757.

4-(4-Methoxystyryl)-1-(3-phenylpropyl)-1*H*-1,2,3-triazole (62)



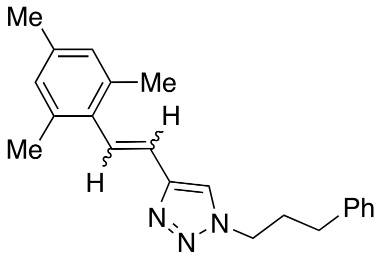
Method B: 4-Methoxybenzaldehyde: 20 mg (0.15 mmol); sulfone **33**: 71.7 mg (0.18 mmol, 1.2 molar equiv); LHMDS: 0.460 mL (1.0 M, 0.460 mmol, 2.4 molar equiv); DMF (1.1 mL), DMPU (1.1 mL). Eluting solvent for column chromatography: 40% EtOAc in hexanes. Yield of *E*/*Z*-**62**: 31.2 mg (65%), as a white solid, *E*/*Z* ratio: 72/28. R_f (40% EtOAc in hexanes) = 0.52. ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1H, Ar-H, *E*-isomer), 7.44 (d, 2H, Ar-H, *J* = 8.8 Hz, *E*-isomer), 7.33-7.26 (m, 3H *E* and *Z*-isomers), 7.23 (d, 1H, Ar-H, *J* = 6.0 Hz, both *E*-isomer and *Z*-isomers), 7.21-7.18 (m, 2H *E*-isomer, 1H *Z*-isomer), 7.13-7.10 (m, 3H, *Z*-isomer), 6.96 (d, 1H, =CH, *J* = 16.6 Hz, *E*-isomer), 6.91-6.87 (m, 2H both *E* and *Z*-isomers), 6.65 (AB q, 2H, =CH, *J* = 11.9 Hz, *Z*-isomer), 4.36 (t, 2H, CH_2, *J* = 7.1 Hz, *E*-isomer), 4.22 (t, 2H, CH_2, *J* = 6.9 Hz, *Z*-isomer), 3.83 (s, 3H, OCH_3, *E*-isomer), 3.82 (s, 3H, OCH_3, *Z*-isomer), 2.68 (t, 2H, CH_2, *J* = 7.6 Hz, *E*-isomer), 2.58 (t, 2H, CH_2, *J* = 7.4 Hz, *Z*-isomer), 2.28 (quint, 2H, CH_2, *J* = 7.4 Hz, *E*-isomer), 2.16 (quint, 2H, CH_2, *J* = 7.4 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{20}H_{21}FN_3O$ $[M+H]^+$ 338.1663, found 338.1667.

4-(4-Nitrostyryl)-1-(3-phenylpropyl)-1*H*-1,2,3-triazole (63)



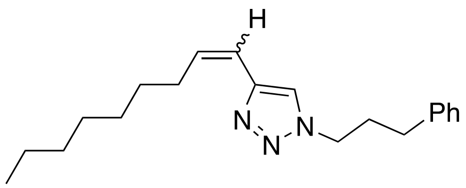
Method B: 4-Nitrobenzaldehyde: 20.0 mg (0.132 mmol); sulfone **38**: 63.3 mg (0.159 mmol, 1.2 molar equiv); LHMDS: 0.320 mL (1.0 M, 0.320 mmol, 2.4 molar equiv); DMF (1.1 mL), DMPU (1.1 mL). Eluting solvent for column chromatography: 40% EtOAc in hexanes. Yield of *E*/*Z*-**63**: 19.5 mg (44%), as a yellow solid, *E*/*Z* ratio: 83/17. R_f (20% EtOAc in hexanes) = 0.31. ^{1}H NMR (500 MHz, C_6D_6) δ 7.85 (d, 2H, Ar-H, J = 8.8 Hz, *E*-isomer), 7.83 (d, 2H, Ar-H, J = 9.1 Hz, *Z*-isomer), 7.29 (d, 1H, =CH, J = 16.6 Hz, *E*-isomer), 7.16-7.04 (m, 3H both *E* and *Z*-isomers), 7.96 (d, 1H, =CH, J = 16.6 Hz, *E*-isomer), 6.93-6.89 (m, 4H *E*-isomer, 2H *Z*-isomer), 6.83 (d, 2H, Ar-H, J = 7.0 Hz, *Z*-isomer), 6.68 (d, 1H, =CH, J = 12.5 Hz, *Z*-isomer), 6.54 (s, 1H, Ar-H, *E*-isomer), 6.44 (s, 1H, Ar-H, *Z*-isomer), 6.16 (d, 1H, =CH, J = 12.5 Hz, *Z*-isomer), 3.63 (t, 2H, CH_2, J = 7.0 Hz, *E*-isomer), 3.48 (t, 2H, CH_2, J = 6.9 Hz, *Z*-isomer), 2.22 (t, 2H, CH_2, J = 7.5 Hz, *E*-isomer), 2.11 (t, 2H, CH_2, J = 7.5 Hz, *Z*-isomer), 1.71 (quint, 2H, CH_2, J = 7.3 Hz, *E*-isomer), 1.59 (quint, 2H, CH_2, J = 7.2 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{20}H_{21}FN_3O$ $[M+H]^+$ 338.1663, found 338.1667. HRMS (ESI) calcd. for $C_{19}H_{18}FN_4O_2$ $[M+H]^+$ 353.1408, found 353.1411.

1-(3-Phenylpropyl)-4-(2,4,6-trimethylstyryl)-1*H*-1,2,3-triazole (64)



Method B: 2,4,6-Trimethylbenzaldehyde: 20.0 mg (0.14 mmol); sulfone **38**: 67.8 mg (0.17 mmol, 1.2 molar equiv); LHMDS: 0.340 mL (1.0 M, 0.340 mmol, 2.4 molar equiv); DMF (1.0 mL), DMPU (1.0 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**64**: 39.3 mg (85%), as a white solid, *E*/*Z* ratio: 15/85. R_f (20% EtOAc in hexanes) = 0.31. ^{1}H NMR (500 MHz, acetone-d_6) δ 8.10 (s, 1H, Ar-H, *E*-isomer), 7.36 (d, 1H, =CH, *J* = 16.6 Hz, *E*-isomer), 7.32-7.25 (m, 4H *E*-isomer, 2H *Z*-isomer), 7.21-7.18 (m, 1H, both *E*-isomer and *Z*-isomers), 7.13 (d, 2H, Ar-H, *J* = 7.9 Hz, *Z*-isomer), 6.93 (s, 2H, Ar-H, *Z*-isomer), 6.88 (s, 2H, *E*-isomer), 6.84 (d, 1H, =CH, *J* = 12.0 Hz, *Z*-isomer), 6.64 (d, 1H, =CH, *J* = 17.0 Hz, *E*-isomer), 6.61 (s, 1H, Ar-H, *Z*-isomer), 6.59 (d, 1H, =CH, *J* = 12.0 Hz, *Z*-isomer), 4.45 (t, 2H, CH_2, *J* = 7.1 Hz, *E*-isomer), 4.20 (t, 2H, CH_2, *J* = 6.7 Hz, *Z*-isomer), 2.70 (t, 2H, CH_2, *J* = 7.6 Hz, *E*-isomer), 2.47 (t, 2H, CH_2, *J* = 7.6 Hz, *Z*-isomer), 2.32 (s, 6H, $2CH_3$, *E*-isomer), 2.27 (s, 3H, CH_3, *Z*-isomer), 2.24 (s, 3H, CH_3, *E*-isomer), 21.4 (s, 6H, $2CH_3$, *Z*-isomer), 2.06-2.00 (m, 2H, CH_2, both *E* and *Z*-isomers). HRMS (ESI) calcd. for $C_{22}H_{26}N_3$ $[M+H]^+$ 332.2121, found 332.2126.

4-(Non-1-en-1-yl)-1-(3-phenylpropyl)-1*H*-1,2,3-triazole (65)

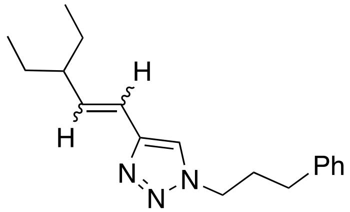


Method B: Octanal: 20.0 mg (0.16 mmol); sulfone **38**: 73.4 mg (0.19 mmol, 1.2 molar equiv);

LHMDS: 0.380 mL (1 M, 0.38 mmol, 2.4 molar equiv); DMF (1.2 mL), DMPU (1.2 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**65**: 15.5 mg (31%), as a colorless semi solid, *E*/*Z* ratio: 7/93. R_f (20% EtOAc in hexanes) = 0.31.

^{1}H NMR (500 MHz, C_6D_6) δ 7.14-7.11 (m, 2H *Z*-isomer, 3H, *E*-isomer), 7.06 (t, 1H, Ar-H, *J* = 7.3 Hz, both *E* and *Z*-isomers), 6.89 (d, 2H, Ar-H, *J* = 7.3 Hz, both *E* and *Z*-isomers), 6.71 (s, 1H, Ar-H, *E*-isomer), 6.69 (s, 1H, Ar-H, *Z*-isomer), 6.60 (d, 1H, =CH, *J* = 11.6 Hz, *Z*-isomer), 6.56 (d, 1H, =CH, *J* = 16.2 Hz, *E*-isomer), 5.74 (dt, 1H, =CH, *J* = 11.3, 7.3 Hz, *Z*-isomer), 3.64-3.60 (m, 2H, CH_2, both *E* and *Z*-isomers), 2.66 (app q, 2H, J_{app} = 7.3 Hz, both *E* and *Z*- isomers), 2.19 (t, 2H, CH_2, *J* = 7.5 Hz, both *E* and *Z*- isomers), 1.68 (quint, 2H, CH_2, *J* = 7.3 Hz, both *E* and *Z*- isomers), 1.51 (quint, 2H, CH_2, *J* = 7.4 Hz, both *E* and *Z*- isomers), 1.37 (quint, 2H, CH_2, *J* = 7.2 Hz, both *E* and *Z*- isomers), 1.32-1.19 (m, 6H, $3CH_2$, both *E* and *Z*- isomers), 0.86 (t, 3H, CH_3, *J* = 7.0 Hz, both *E* and *Z*- isomers). HRMS (ESI) calcd. for $C_{20}H_{30}N_3[M+H]^+$ 312.2434, found 312.2437.

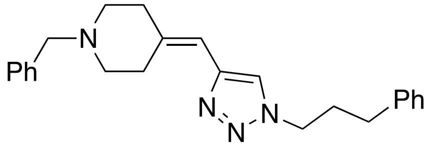
4-(3-Ethylpent-1-en-1-yl)-1-(3-phenylpropyl)-1*H*-1,2,3-triazole (66)



Method B: 2-Ethylbutnanal: 20.0 mg (0.20 mmol); sulfone **38**: 95.6 mg (0.24 mmol, 1.2 molar equiv); LHMDS: 0.480 mL (1.0 M, 0.480 mmol, 2.4 molar equiv); DMF (1.5 mL), DMPU (1.5 mL). Eluting solvent for column chromatography: 20% EtOAc in hexanes. Yield of *E*/*Z*-**66**: 23.6 mg (41%), as a colorless semi solid, *E*/*Z* ratio: 77/23. R_f (20% EtOAc in hexanes) = 0.30. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H, Ar-H, *Z*-isomer), 7.38 (s, 1H, Ar-H, *E*-isomer), 7.30 (t, 2H, Ar-H, *J* = 7.4 Hz, both *E* and *Z*-isomers), 7.21 (t, 1H, Ar-H, *J* = 7.0 Hz, both *E* and *Z*-

isomers), 7.18 (d, 2H, Ar-H, *J* = 7.4 Hz, both *E* and *Z*-isomers), 6.48 (d, 1H, =CH, *J* = 11.5 Hz, *Z*-isomer), 6.35 (d, 1H, =CH, *J* = 16.1 Hz, *E*-isomer), 6.14 (dd, 1H, =CH, *J* = 16.1, 9.2 Hz, *E*-isomer), 5.46 (t, 1H, =CH, *J* = 11.0 Hz, *Z*-isomer), 4.35-4.31(m, 2H, CH_2, both *E* and *Z*-isomers), 2.66 (t, 2H, CH_2, *J* =7.4 Hz, both *E* and *Z*- isomers), 2.30-1.19 (m, 2H, CH_2, both *E* and *Z*- isomers), 1.98-1.90 (m, 1H, CH, both *E* and *Z*- isomers), 1.56-1.46 (m, 2H, CH_2, both *E* and *Z*- isomers), 1.39-1.29 (m, 2H, CH_2, both *E* and *Z*- isomers), 0.88 (t, 6H, $2CH_3$, *J* = 7.4 Hz, both *E* and *Z*- isomers). HRMS (ESI) calcd. for $C_{18}H_{26}N_3$ $[M+H]^+$ 284.2121, found 284.2124.

1-Benzyl-4-((1-(3-phenylpropyl)-1*H*-1,2,3-triazol-4-yl)methylene)piperidine (67)



Method C: 1-Benzylpiperidin-4-one: 20.0 mg (0.11 mmol); sulfone **38**: 52.8 mg (0.13 mmol, 1.2 molar equiv); LHMDS: 0.260 mL (1.0 M, 0.262 mmol, 2.4 molar equiv); THF (1.3 mL). Eluting solvent for column chromatography: 40% EtOAc in hexanes. Yield of *E*/*Z*-**67**: 23.1 mg (59%), as a semi solid. R_f (40% EtOAc in hexanes) = 0.57. ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.24 (m, 8H, Ar-H), 7.21 (t, 1H, Ar-H, *J* = 7.4 Hz), 7.17 (d, 2H, Ar-H, *J* = 6.9 Hz), 6.18 (s, 1H, =CH), 4.33 (t, 2H, CH_2, *J* = 7.2 Hz), 3.54 (s, 2H, CH_2), 2.74 (t, 2H, CH_2, *J* = 5.7 Hz), 2.66 (t, 2H, CH_2, *J* = 7.5 Hz), 2.52 (quint, 4H, CH_2, *J* = 5.5 Hz), 2.41 (t, 2H, CH_2, *J* = 5.5 Hz), 2.24 (quint, 2H, CH_2, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.3, 142.1, 140.4 138.5, 129.4 (2C), 128.8 (2C), 128.6 (2C), 128.4 (2C), 127.2, 126.5, 121.3, 111.7, 63.1, 55.0, 54.2, 49.5, 36.5, 32.7, 31.9, 30.1. HRMS (ESI) calcd. for $C_{24}H_{29}N_4$ $[M+H]^+$ 373.2387, found 373.2394.

NOTE: Comparison of the NMR spectra of isomers of **55** to **57** for which structure was determined by X-ray analysis, shows distinctive difference in the NMR shift of the triazolyl proton. This suggests the major isomer of **55** as *Z*- and the minor as *E*-isomer.

REFERENCES

1. Fan, W.-Q.; Katritzky, A. R.: In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science: New York, 1996.

2. Angell, Y. L.; Burgess, K.: Peptidomimetics via Copper-Catalyzed Azide–Alkyne Cycloadditions, *Chem. Soc. Rev.* **2007**, *36*, 1674–1689.

3. Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H.: CuI-Catalyzed Alkyne–Azide “Click” Cycloadditions from a Mechanistic and Synthetic Perspective, *Eur. J. Org. Chem.* **2006**, 51–68.

4. Appendino, G.; Bacchiega, S.; Minassi, A.; Cascio, M. G.; Petrocellis, L. D.; Marzo, V. D.: The 1,2,3-Triazole Ring as a Peptido- and Olefinomimetic Element: Discovery of Click Vanilloids and Cannabinoids, *Angew. Chem., Int. Ed.* **2007**, *46*, 9312 –9315.

5. Agalave, S. G.; Maujan, S. R.; Pore, V. S.: Click Chemistry: 1,2,3-Triazoles as Pharmacophores, *Chem. Asian J.* **2011**, *6,* 2696 – 2718.

6. Moses, J. E.; Moorhouse, A. D.: The Growing Applications of Click Chemistry, *Chem. Soc. Rev*. **2007**, *36*, 1249–1262.

7. Aragão-Leoneti, V.; Campo, V. L.; Gomes, A. S.; Field, R. A.; Carvalho, I.: Application of Copper(I)-Catalysed Azide/Alkyne Cycloaddition (CuAAC) ‘Click Chemistry’ in Carbohydrate Drug and Neoglycopolymer Synthesis, *Tetrahedron* **2010**, *66*, 9475-9492.

8. Kolb, H. C.; Sharpless, K. B.: The Growing Impact of Click Chemistry on Drug Discovery, *Drug Discovery Today* **2003**, *8*, 1128-1137.

9. Binder, W. H.; Sachsenhofer, R.: **‘**Click’ Chemistry in Polymer and Materials Science, *Macromol. Rapid Commun*. **2007**, *28*, 15–54.

10. Lutz, J. F.: 1,3-Dipolar Cycloadditions of Azides and Alkynes: A Universal Ligation Tool in Polymer and Materials Science, *Angew. Chem., Int. Ed.* **2007,** *46,* 1018-1025.

11. Huisgen, R.: 1,3-Dipolar Cycloadditions Past and Future, *Angew. Chem., Int. Ed Engl.* **1963**, *2*, 565-632

12. Tornøe, C. W.; Christensen, C.; Meldal, M.: Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides, *J. Org. Chem.* **2002,** *67,* 3057-3064.

13. Rostovtsev, V.; Green, L.; Fokin, V.; Sharpless, B.: A Stepwise Huisgen Cycloaddition Process: Copper(i)-Catalyzed Regioselective " Ligation " of Azides and Terminal Alkynes, *Angew. Chem Int. Ed.* **2002,** *41,* 2596-2599.

14. Gil, M. V.; Arévalo, M. J.; López, Ó.: Click Chemistry – What's in a Name? Triazole Synthesis and Beyond, *Synthesis,* **2007**, 1589–1620.

15. Tornøe, C. W.; Meldal, M.: Cu-Catalyzed Azide-Alkyne Cycloaddition, *Chem. Rev.* **2008**, *108*, 2952–3015.

16. Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Fokin, V. V.; Noodleman, L.; Sharpless, K. B.: Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates, *J. Am. Chem. Soc.* **2005**, *127*, 210 – 216.

17. Rodionov, V. O.; Fokin, V. V.; Finn, M. G.: Mechanism of the Ligand-Free CuI-Catalyzed Azide–Alkyne Cycloaddition Reaction, *Angew. Chem. Int. Ed.* **2005**, *44*, 2210 –2215.

18. Ahlquist, M.; Fokin, V. V.: Enhanced Reactivity of Dinuclear Copper(I) Acetylides in Dipolar Cycloadditions, *Organometallics* **2007**, *26,* 4389-4391.

19. *Current Fluoroorganic Chemistry: New Synthetic Directions, Technologies, Materials, and Biological Applications;* Soloshonok, V. A.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J. F., Eds.; American Chemical Society: Washington DC, **2007.**

20. Smart, B. E.: Fluorine Substituent Effect (On Bioactivity), *J. Fluorine Chem.* **2001**, *109*, 3-11.

21. O'Hagan, D.: Understanding Organofluorine Chemistry. An Introduction to the C–F Bond, *Chem. Soc. Rev.* **2008**, *37,* 308–319.

22. Berger, R.; Resnati, G.; Metrangolo, P.; Weberd, E.; Hulliger, J.: Organic Fluorine Compounds: A Great Opportunity for Enhanced Materials Properties, *Chem. Soc. Rev.* **2011**, *40*, 3496–3508.

23. Whiting, M.; Tripp, J. C.; Lin, Y.-C.; Lindstrom, W.; Olson, A. J.; Elder, J. H.; K. Sharpless, B.; Fokin, V. V.: Rapid Discovery and Structure-Activity Profiling of Novel Inhibitors of Human Immunodeficiency Virus Type 1 Protease Enabled by the Copper(I)-Catalyzed Synthesis of 1,2,3-Triazoles and Their Further Functionalization, *J. Med. Chem.* **2006**, *49,* 7697-7710.

24. Llano-Sotelo, B.; Dunkle, J.; Klepacki, D.; Zhang, W.; Fernandes, P.; Cate, J. H. D.; Mankin, A. S.: Binding and Action of CEM-101, A New Fluoroketolide Antibiotic That Inhibits Protein Synthesis, *Antimicrob. Agents Chemother* **2010**, *54*, 4961-4970.

25. Gill, C.; Jadhav, G.; Shaikh, M.; Kale, R.; Ghawalkar, A.; Nagargoje, D.; Shiradkar, M.: Clubbed [1,2,3] Triazoles by Fluorine Benzimidazole: A Novel Approach to

H37Rv Inhibitors as a Potential Treatment for Tuberculosis, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6244–6247.

26. Hausner, S. H.; Marik, J.; Gagnon, M. K. J.; Sutcliffe, J. L.: In Vivo Positron Emission Tomography (PET) Imaging with an $\alpha_v\beta_6$ Specific Peptide Radiolabeled using ^{18}F-" Click " Chemistry: Evaluation and Comparison with the Corresponding 4-[^{18}F]Fluorobenzoyl- and 2-[^{18}F]Fluoropropionyl-Peptides, *J. Med. Chem.* **2008**, *51,* 5901–5904.

27. Pisaneschi, F.; Nguyen, Q.-D.; Shamsaei, E.; Glaser, M.; Robins, E.; Kaliszczak, M.; Smith, G.; Spivey, A. C.; Aboagye, E. O: Development of a New Epidermal Growth Factor Receptor Positron Emission Tomography Imaging Agent Based on the 3-Cyanoquinoline Core: Synthesis and Biological Evaluation, *Bioorg. Med. Chem.* **2010**, *18*, 6634–6645.

28. Michel, K.; Büther, K.; Law, M. P.; Wagner, S.; Schober, O.; Hermann, S.; Schäfers, M.; Riemann, B.; Höltke, C.; Kopka, K.: Development and Evaluation of Endothelin-A Receptor (Radio) Ligands for Positron Emission Tomography, *J. Med. Chem.* **2011**, *54*, 939–948.

29. Fujinaga, M.; Maeda, J.; Yui, J.; Hatori, A.; Yamasaki, T.; Kawamura, K.; Kumata, K.; Yoshida, Y.; Nagai, Y.; Higuchi, M.; Suhara, T.; Fukumura, T.; Zhang, M.-R.: Characterization of 1-(2-[^{18}F]Fluoro-3-pyridyl)-4-(2-isopropyl-1-oxo-isoindoline-5-yl)-5-methyl-1*H*-1,2,3-triazole, a PET Ligand for Imaging the Metabotropic Glutamate Receptor Type 1 in Rat and Monkey Brains, *J. Neurochem.* **2012**, *121*, 115–124.

30. Dutheuil, G.; Couve-Bonnaire, S.; Pannecoucke, X.: Diastereomeric Fluoroolefins as Peptide Bond Mimics Prepared by Asymmetric Reductive Amination of α-Fluoroenones, *Angew. Chem. Int. Ed.* **2007**, *46*, 1290-1292.

31. Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X.: Chiral Dipeptide Mimics Possessing a Fluoroolefin Moiety: A Relevant Tool for Conformational and Medicinal Studies, *Org. Biomol. Chem.* **2007**, 5, 1151-1157.

32. Veken, P. V.; Senten, K.; Kertesz, I.; De Meester, I.; Lambeir, A. M.; Maes, M. B.; Scharpe, S.; Haemers, A.; Augustyns, K.: Fluoroolefins as Peptidomimetic Inhibitors of Dipeptidyl Peptidases, *J. Med. Chem.*, **2005**, *48*, 1768-1780.

33. Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F.: Synthetic Approaches to Monofluoroalkenes, *Chem. Soc. Rev.* **2011**, *40*, 2867–2908.

34. Zajc, B.; Kumar, R.: Synthesis of Fluoroolefins via Julia–Kocienski Olefination, *Synthesis*, **2010**, 1822-1836.

35. Tao, C.-Z.; Cui, X.; Li, J.; Liu, A.-X.; Liu, L.; Guo, Q.-X.: Copper-Catalyzed Synthesis of Aryl Azides And 1-Aryl-1,2,3-Triazoles from Boronic Acids,

Tetrahedron Lett. **2007**, *48,* 3525-3529.

36. Grimes, K. D.; Gupte, A.; Aldrich, C. C.: Copper(II)-Catalyzed Conversion of Aryl/Heteroaryl Boronic Acids, Boronates, and Trifluoroborates into the Corresponding Azides: Substrate Scope and Limitations, *Synthesis* **2010**, 1441–1448.

37. Ngai, M. H.; Yang, P.-Y.; Liu, K.; Shen, Y.; Wenk, M. R.; Yao, S. Q.; Lear, M, J.: Click-Based Synthesis and Proteomic Profiling of Lipstatin Analogues, *Chem. Commun.* **2010**, *46*, 8335–8337.

38. Aucagne, V.; Leigh, D. A.: Chemoselective Formation of Successive Triazole Linkages in One Pot: “Click−Click” Chemistry, *Org. Lett.* **2006**, *8*, 4505-4507.

39. Lakshman, M. K.; Singh, M. K.; Parrish, D.; Balachandran, R.; Day, B. W.: Azide-Tetrazole Equilibrium of C-6 Azidopurine Nucleosides and Their Ligation Reactions with Alkynes*, J. Org. Chem*. **2010**, *75*, 2461–2473.

40. Agard, N. J.; Prescher, J. A.; Bertozzi, C. R.: A Strain-Promoted [3 + 2] Azide-Alkyne Cycloaddition for Covalent Modification of Biomolecules in Living Systems, *J. Am. Chem. Soc*. **2004**, *126*, 15046-15047.

41. Baskin, J. M.; Preschner, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R.: Copper-Free Click Chemistry for Dynamic in Vivo Imaging, *Proc. Nat. Acad. Sci. U.S.A.* **2007,** *104,* 16793-16797.

42. Sletten, E. M.; Bertozzi, C. R.: Bioorthogonal Chemistry: Fishing for Selectivity in a Sea of Functionality, Angew. Chem., Int. Ed., 2009, 48, 6974-6998.

43. Chenoweth, K.; Chenoweth, D.; Goddard III, and W. A.: Cyclooctyne-Based Reagents for Uncatalyzed Click Chemistry: A Computational Survey, *Org. Biomol. Chem*. **2009**, *7*, 5255-5258.

44. Schoenebeck, F.; Ess, D. H.; Jones, G. O.; Houk, K. N.: Reactivity and Regioselectivity in 1,3-Dipolar Cycloadditions of Azides to Strained Alkynes and Alkenes: A Computational Study, *J. Am. Chem. Soc*. **2009**, 131, 8121-8133.

45. Lam, Y.-h.; Stanway, S. J.; Gouverneur, V.: Recent Progress in the Use of Fluoroorganic Compounds in Pericyclic Reactions, *Tetrahedron* **2009**, *65*, 9905-9933.

46. Grée, D.; Grée, R.: Effect of Fluorine or Oxygen Atom(s) in Propargylic Position in the Reactivity in Click Chemistry, *Tetrahedron Lett*. **2010**, *51*, 2218.

47. Blakemore, P. R.: The Modified Julia Olefination: Alkene Synthesis *via* the Condensation of Metallated Heteroarylalkylsulfones with Carbonyl Compounds, *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2563-2585.

48. Plesniak, K.; Zarecki, A.; Wicha, J.: The Smiles Rearrangement and the Julia–Kocienski Olefination Reaction, *Top. Curr. Chem.* **2007**, *275*, 163-250.

49. Aïssa, C.: Mechanistic Manifold and New Developments of the Julia–Kocienski Reaction, *Eur. J. Org. Chem.* **2009**, 1831–1844.

50. Zajc, B.; Kake, S.: Exceptionally Mild, High-Yield Synthesis of α-Fluoro Acrylates, *Org. Lett.* **2006**, *8*, 4457-4460.

51. He, M.; Ghosh, A. K.; Zajc, B., Julia Olefination as a General Route to Phenyl (α-Fluoro)vinyl Sulfones, *Synlett* **2008**, 999-1004.

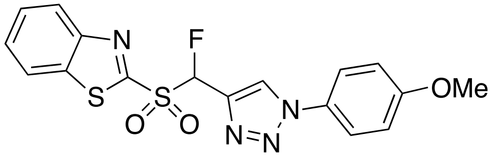
```
1222-RK-04-246-pure-1H

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

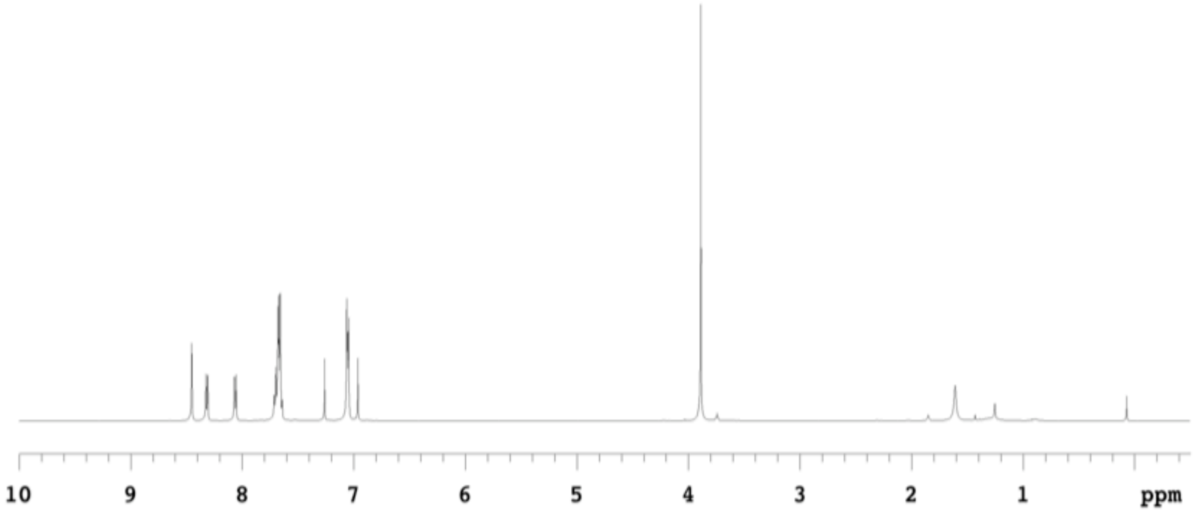
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-246-pure-1H
INOVA-500  "riga"

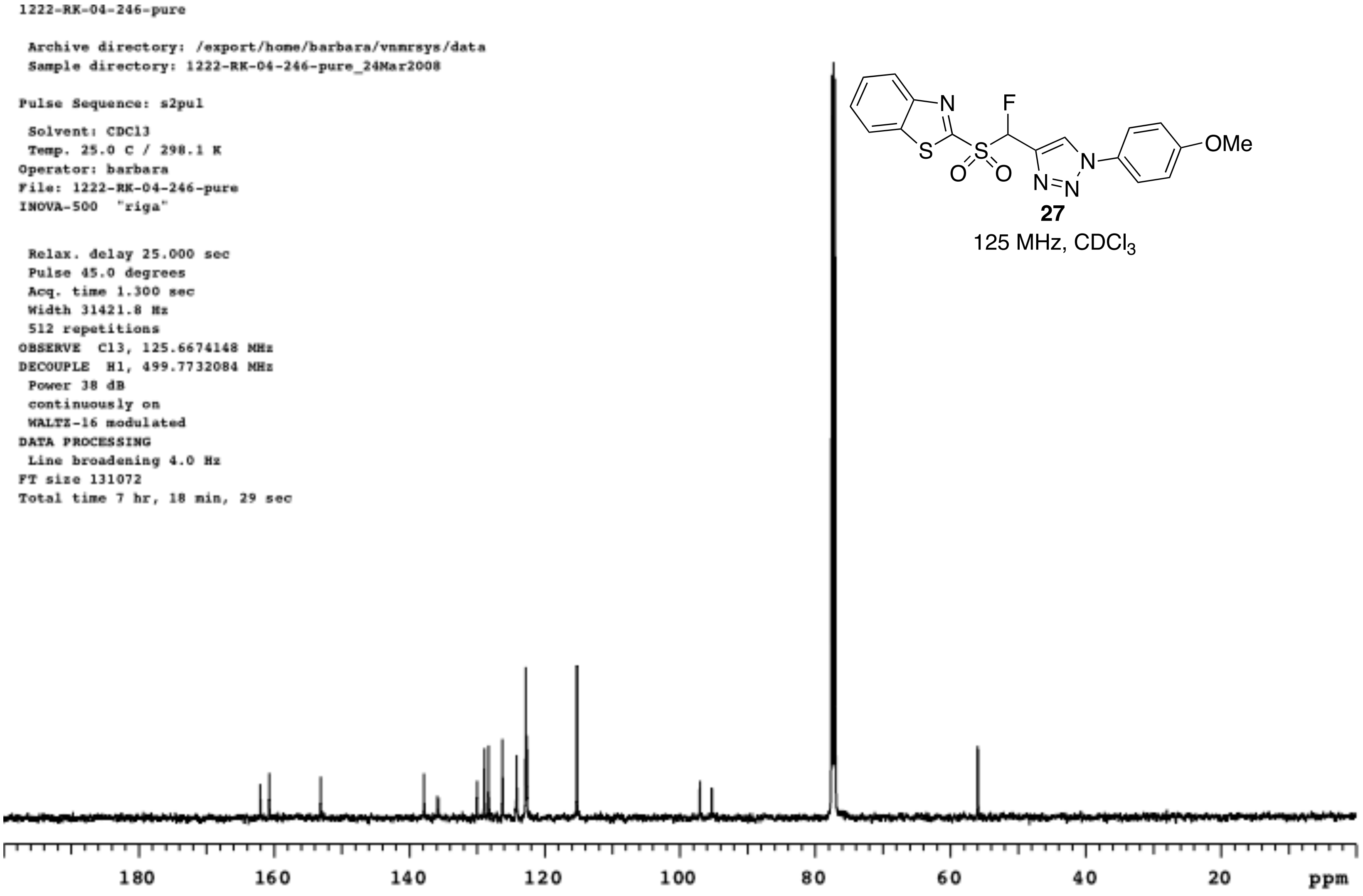
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 52 repetitions
OBSERVE   H1, 499.7707216 MHz
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 32768
Total time 9 min, 40 sec
```



27

500 MHz, $CDCl_3$





```
1222-RK-04-246-pure

 Archive directory: /export/home/barbara/vnmrsys/data
 Sample directory: 1222-RK-04-246-pure_24Mar2008

Pulse Sequence: s2pul

 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-246-pure
INOVA-500  "riga"


 Relax. delay 25.000 sec
 Pulse 45.0 degrees
 Acq. time 1.300 sec
 Width 31421.8 Hz
 512 repetitions
OBSERVE  C13, 125.6674148 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 38 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 4.0 Hz
FT size 131072
Total time 7 hr, 18 min, 29 sec
```

27

125 MHz, $CDCl_3$

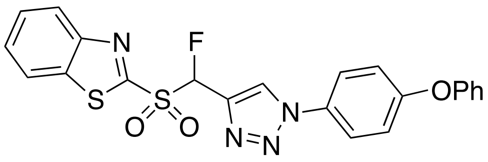
```
1222-RK-04-242-2ndfraction

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

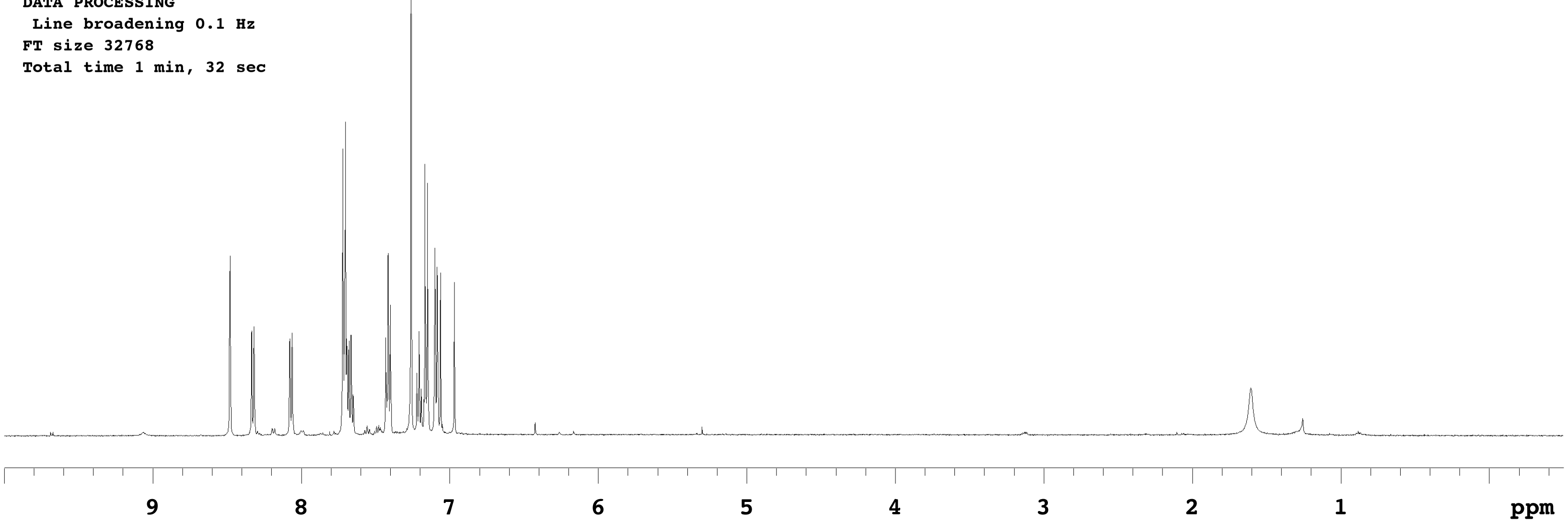
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-242-2ndfraction
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 24 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 32 sec
```



28

500 MHz, $CDCl_3$

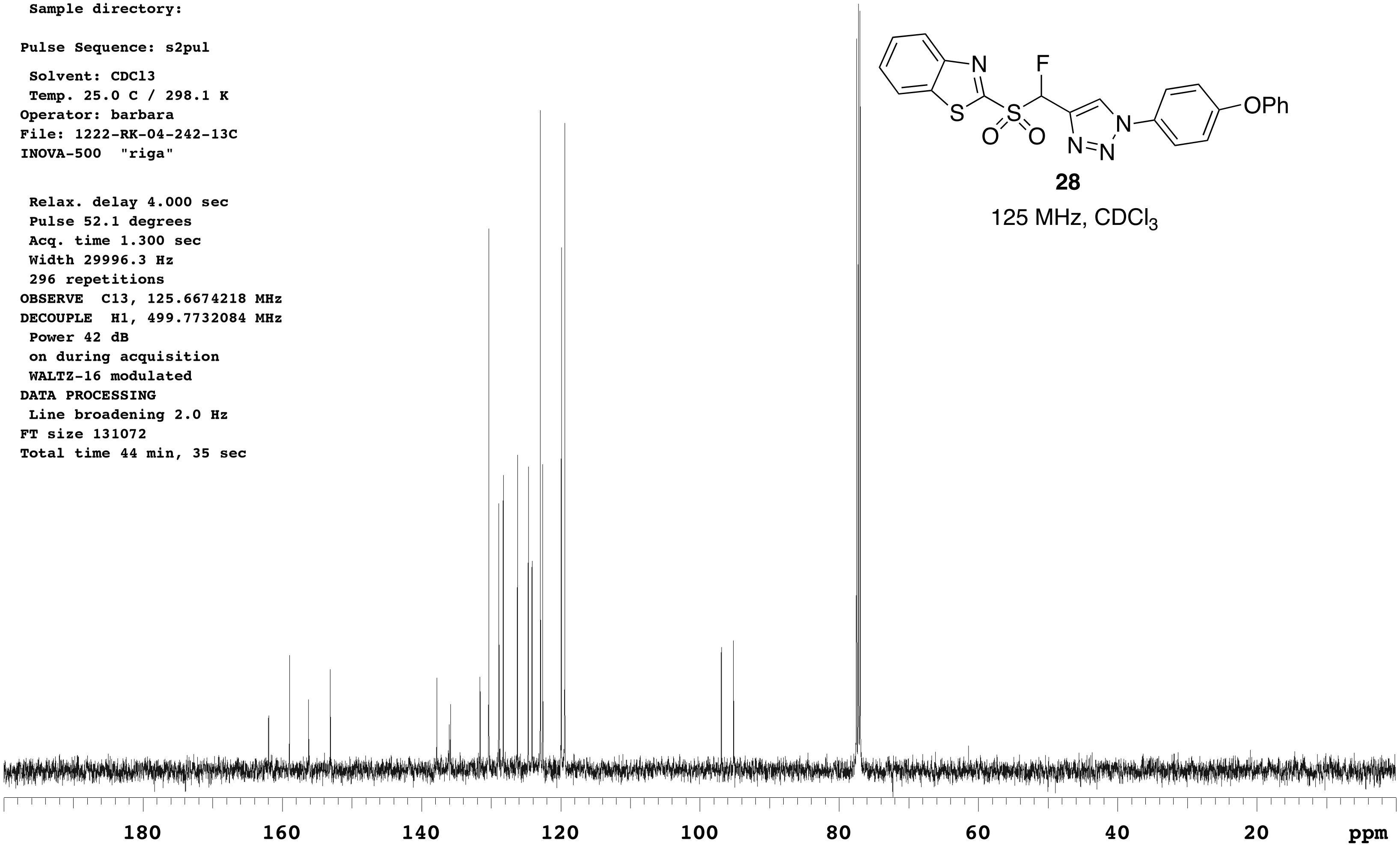


```
1222-RK-04-442-13C

 Archive directory: /export/home/barbara/vnmrsys/data
 Sample directory:

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-242-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 296 repetitions
OBSERVE  C13, 125.6674218 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 131072
Total time 44 min, 35 sec
```



28

125 MHz, $CDCl_3$

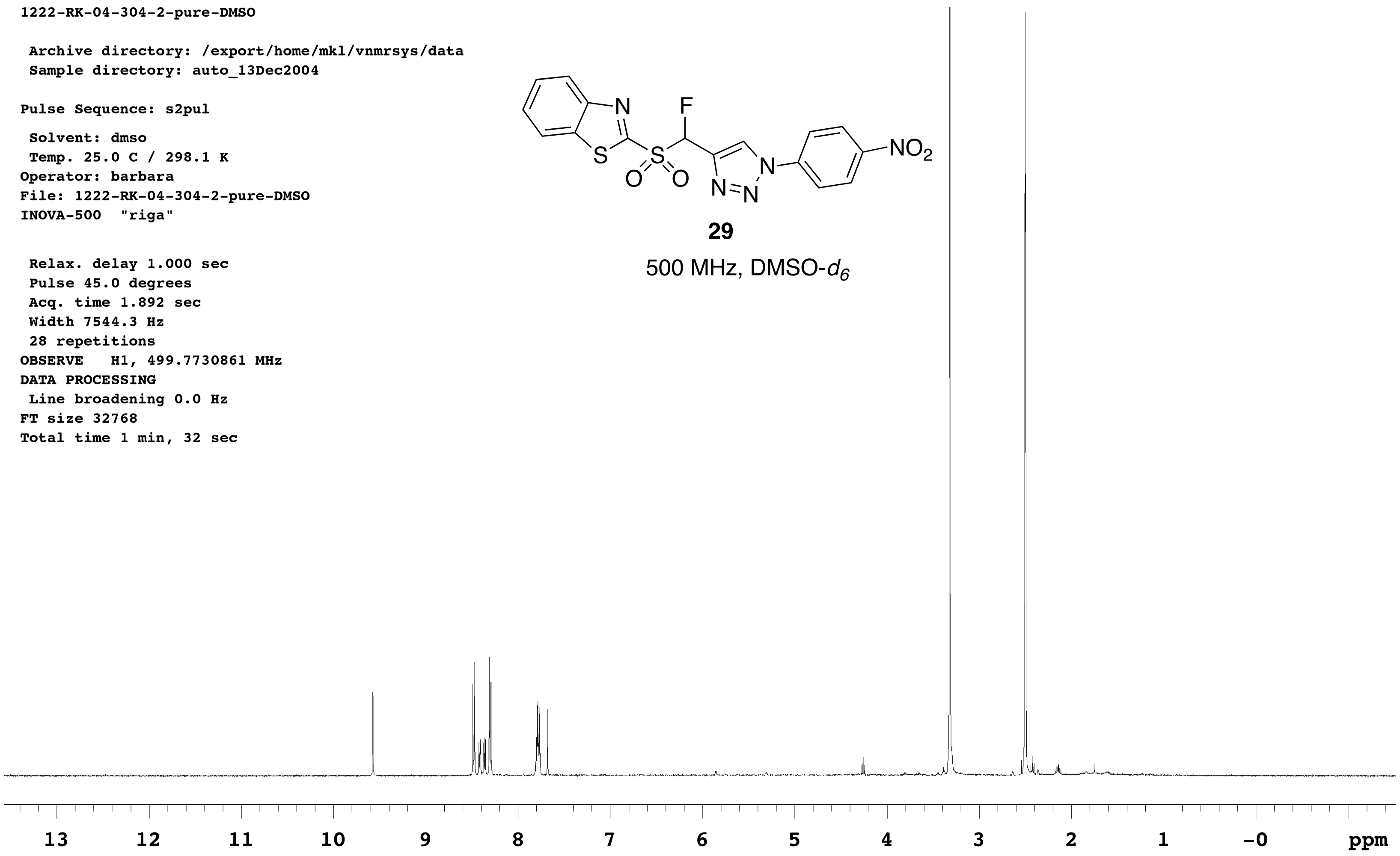
```
1222-RK-04-304-2-pure-DMSO

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: dmso
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-304-2-pure-DMSO
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 28 repetitions
OBSERVE   H1, 499.7730861 MHz
DATA PROCESSING
 Line broadening 0.0 Hz
FT size 32768
Total time 1 min, 32 sec
```



29

500 MHz, DMSO-d_6

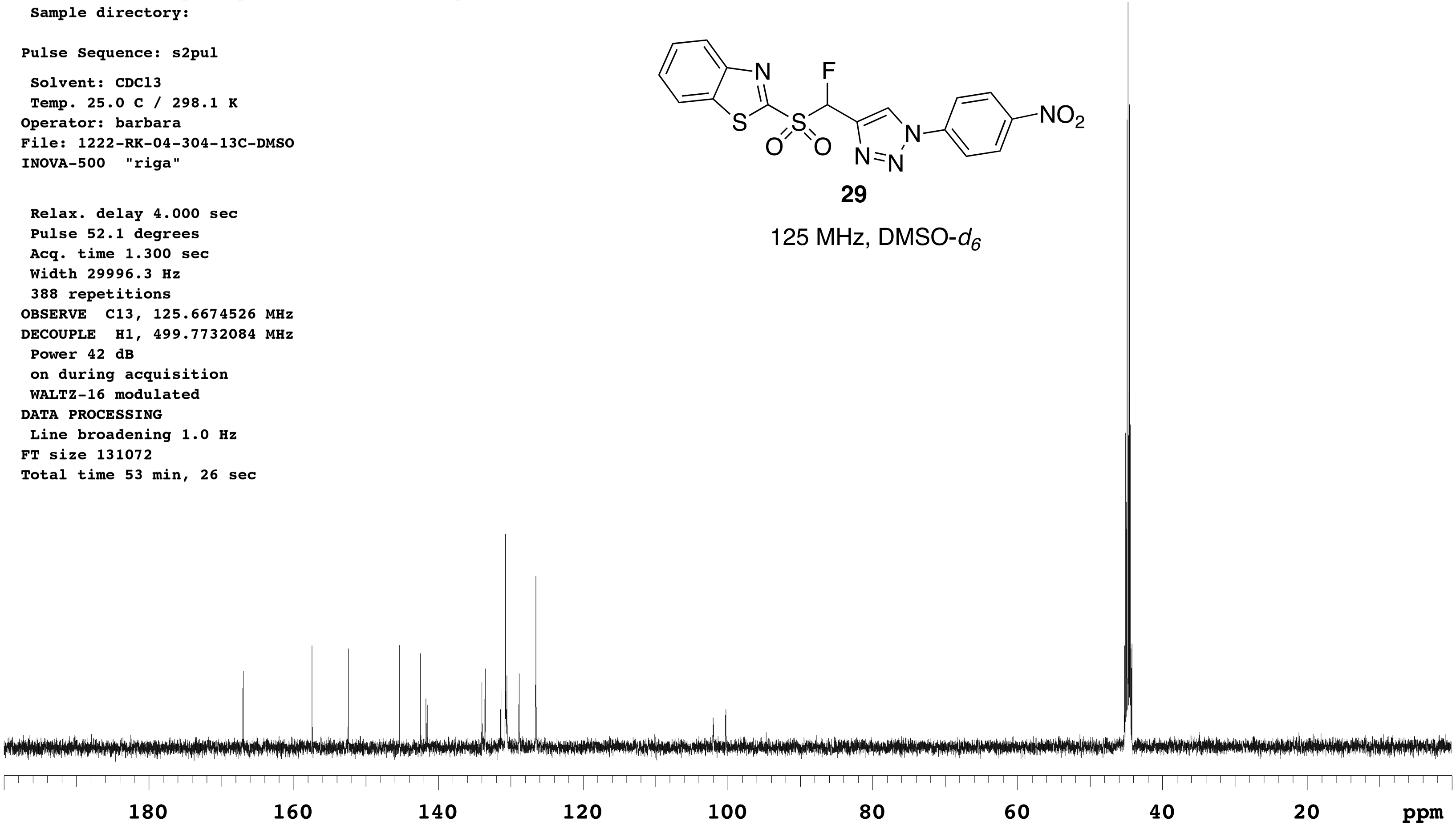
```
1222-RK-04-304-13C-DMSO

 Archive directory: /export/home/barbara/vnmrsys/data
 Sample directory:

Pulse Sequence: s2pul

 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-304-13C-DMSO
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 388 repetitions
OBSERVE  C13, 125.6674526 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 53 min, 26 sec
```



29

125 MHz, DMSO-d_6

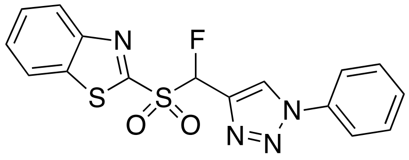
```
1222-RK-04-259-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

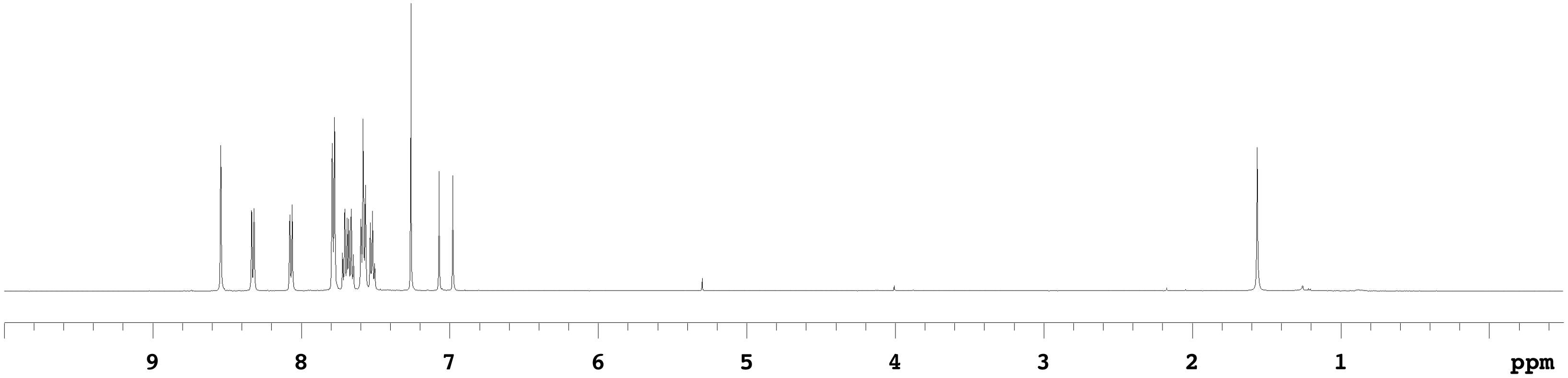
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-259-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 20 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 32 sec
```



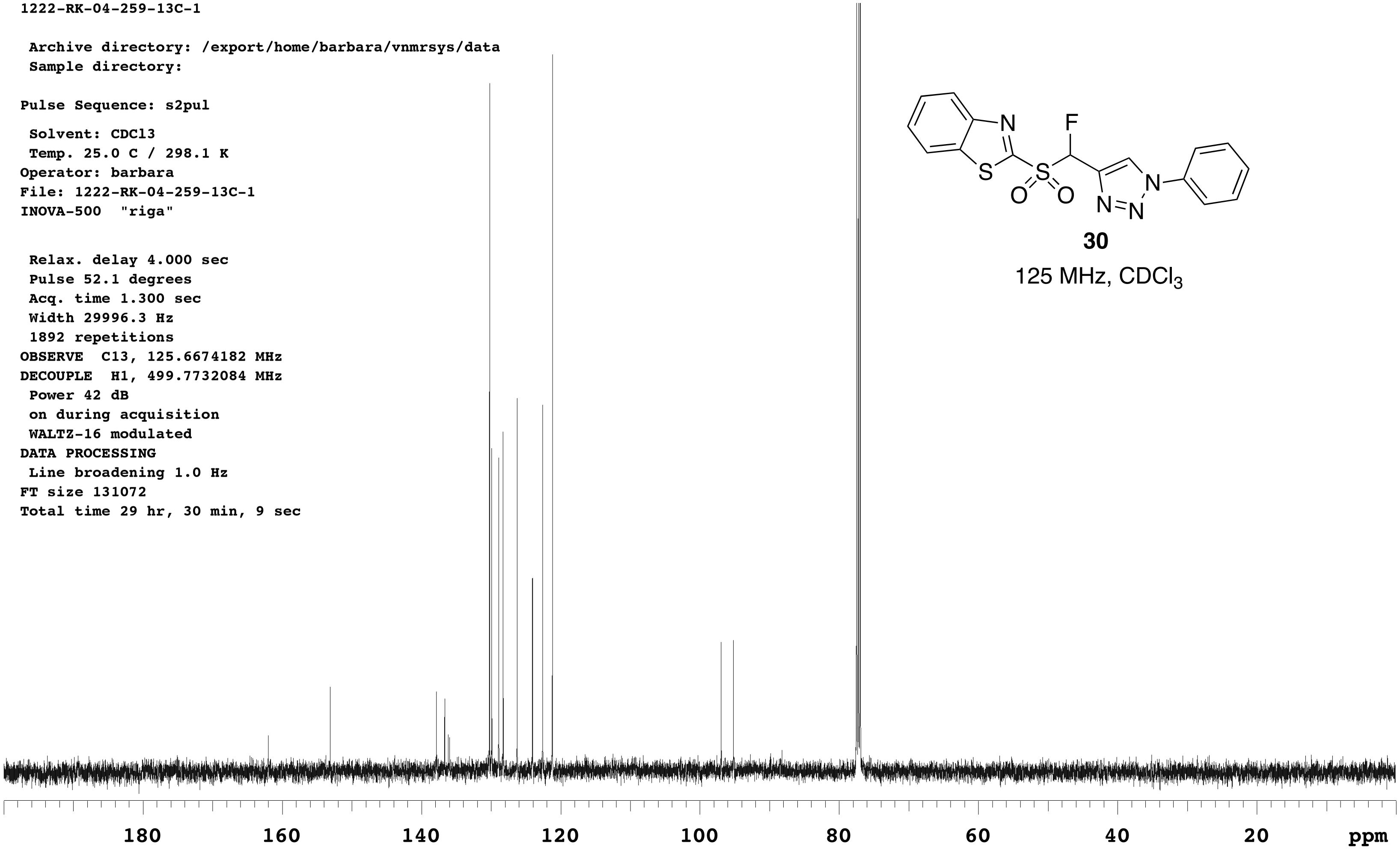
30

500 MHz, $CDCl_3$



30

125 MHz, $CDCl_3$



```
1222-RK-04-259-13C-1

 Archive directory: /export/home/barbara/vnmrsys/data
 Sample directory:

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-259-13C-1
INOVA-500  "riga"

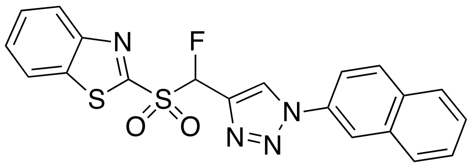

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 1892 repetitions
OBSERVE  C13, 125.6674182 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 29 hr, 30 min, 9 sec
```

```
1222-RK-04-257-PURE

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

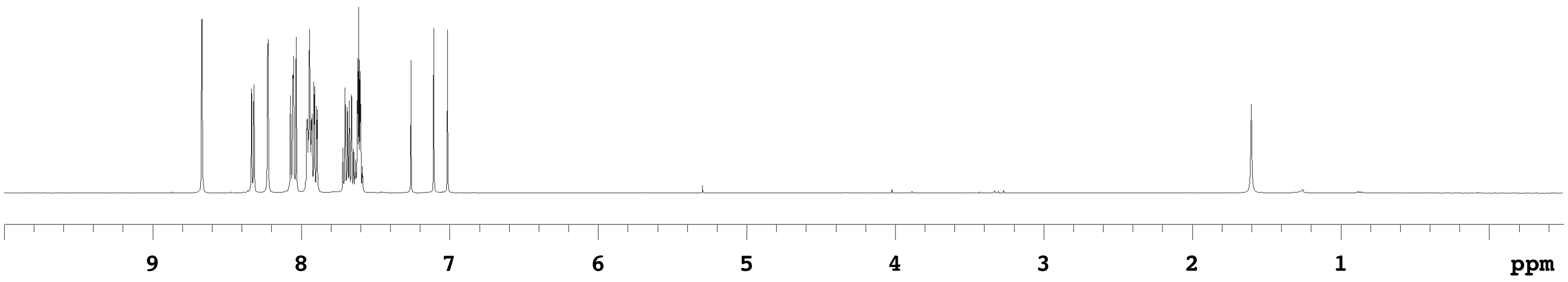
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-257-PURE
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 16 repetitions
OBSERVE   H1, 499.7707207 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 32 sec
```



31

500 MHz, $CDCl_3$



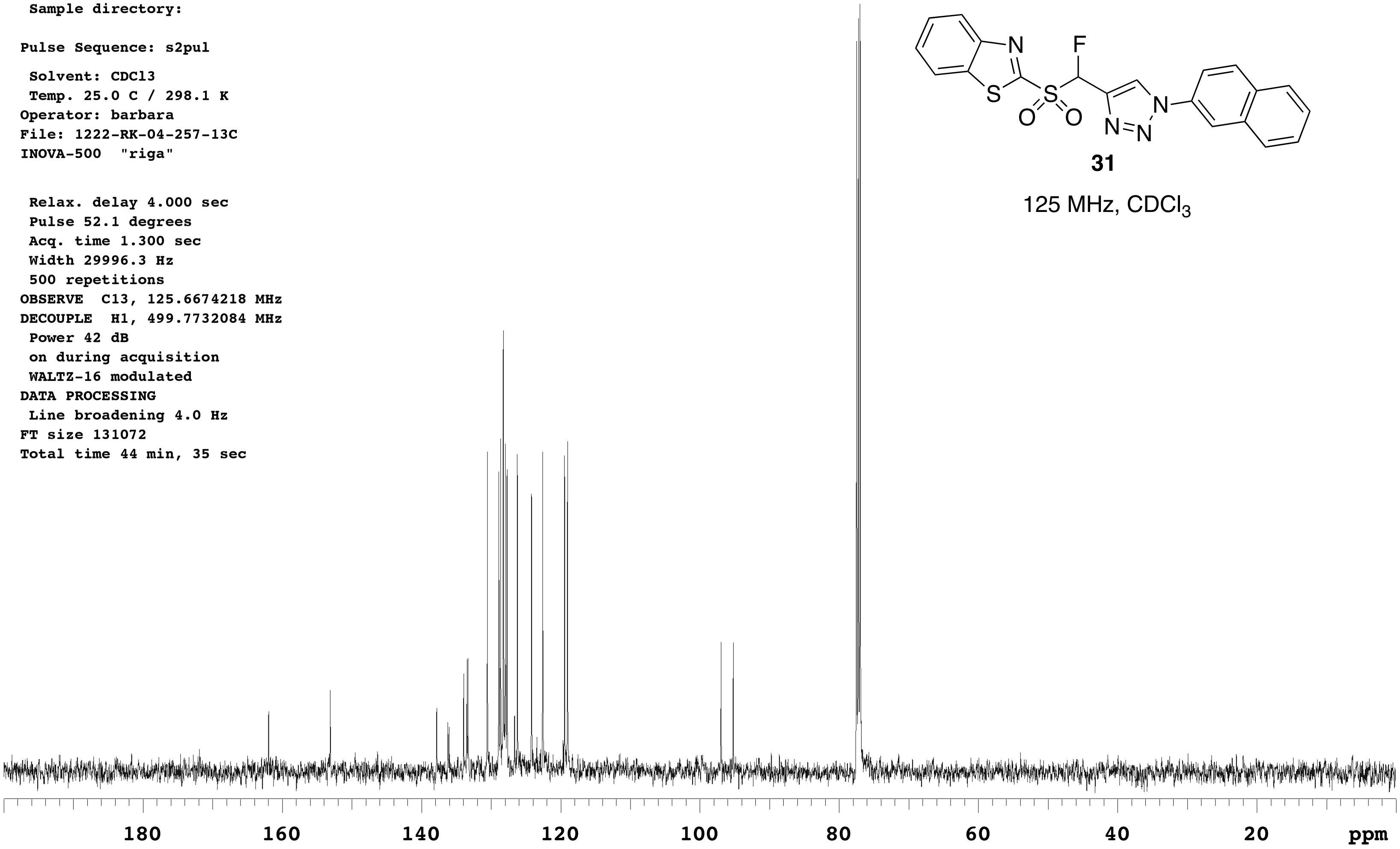
```
1222-RK-04-258-13C

 Archive directory: /export/home/barbara/vnmrsys/data
 Sample directory:

Pulse Sequence: s2pul

 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-257-13C
INOVA-500  "riga"


 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 500 repetitions
OBSERVE  C13, 125.6674218 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 4.0 Hz
FT size 131072
Total time 44 min, 35 sec
```



31

125 MHz, $CDCl_3$

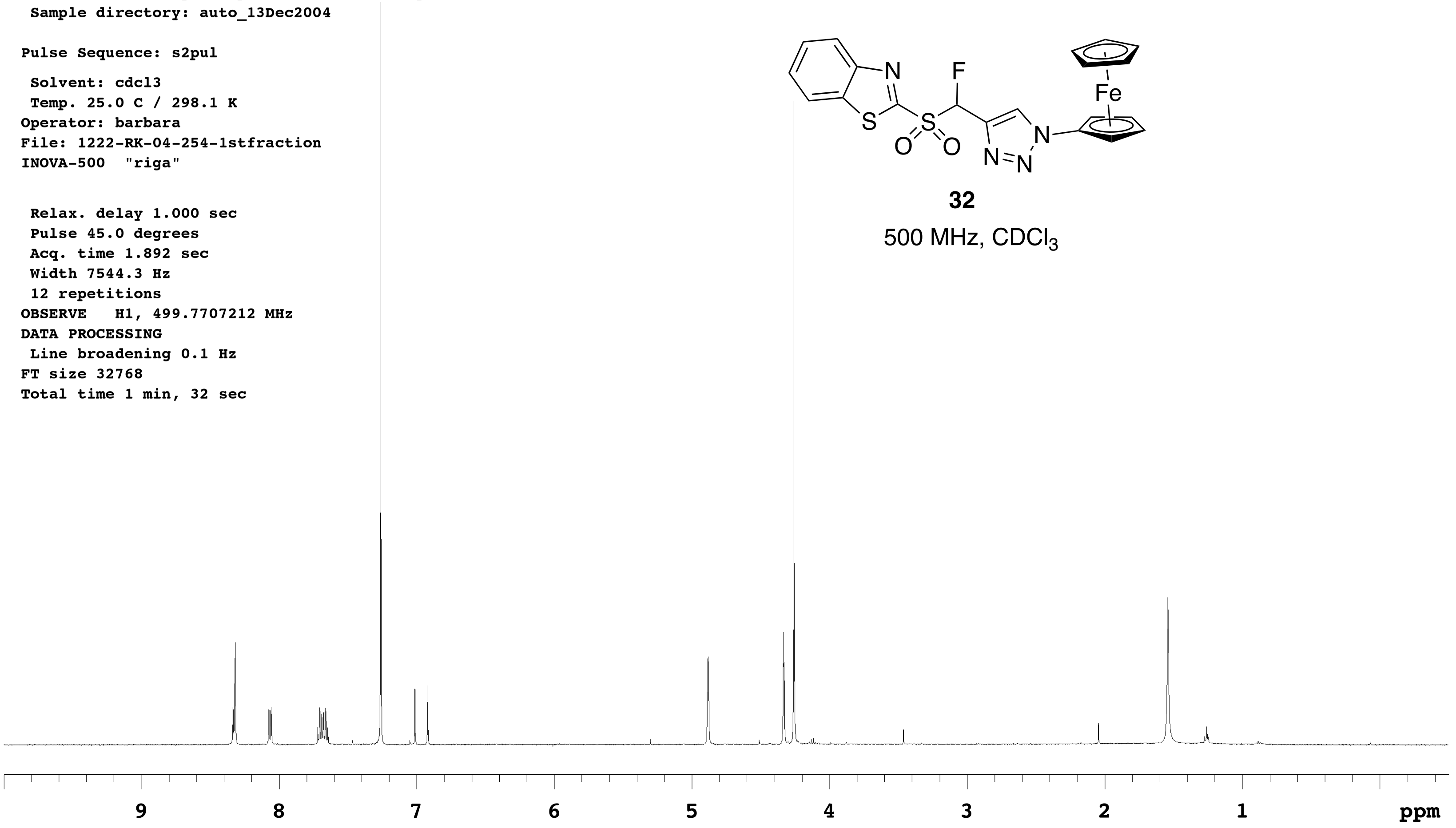
```
1222-RK-04-254-1stfraction

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-254-1stfraction
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 12 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 32 sec
```



32

500 MHz, $CDCl_3$

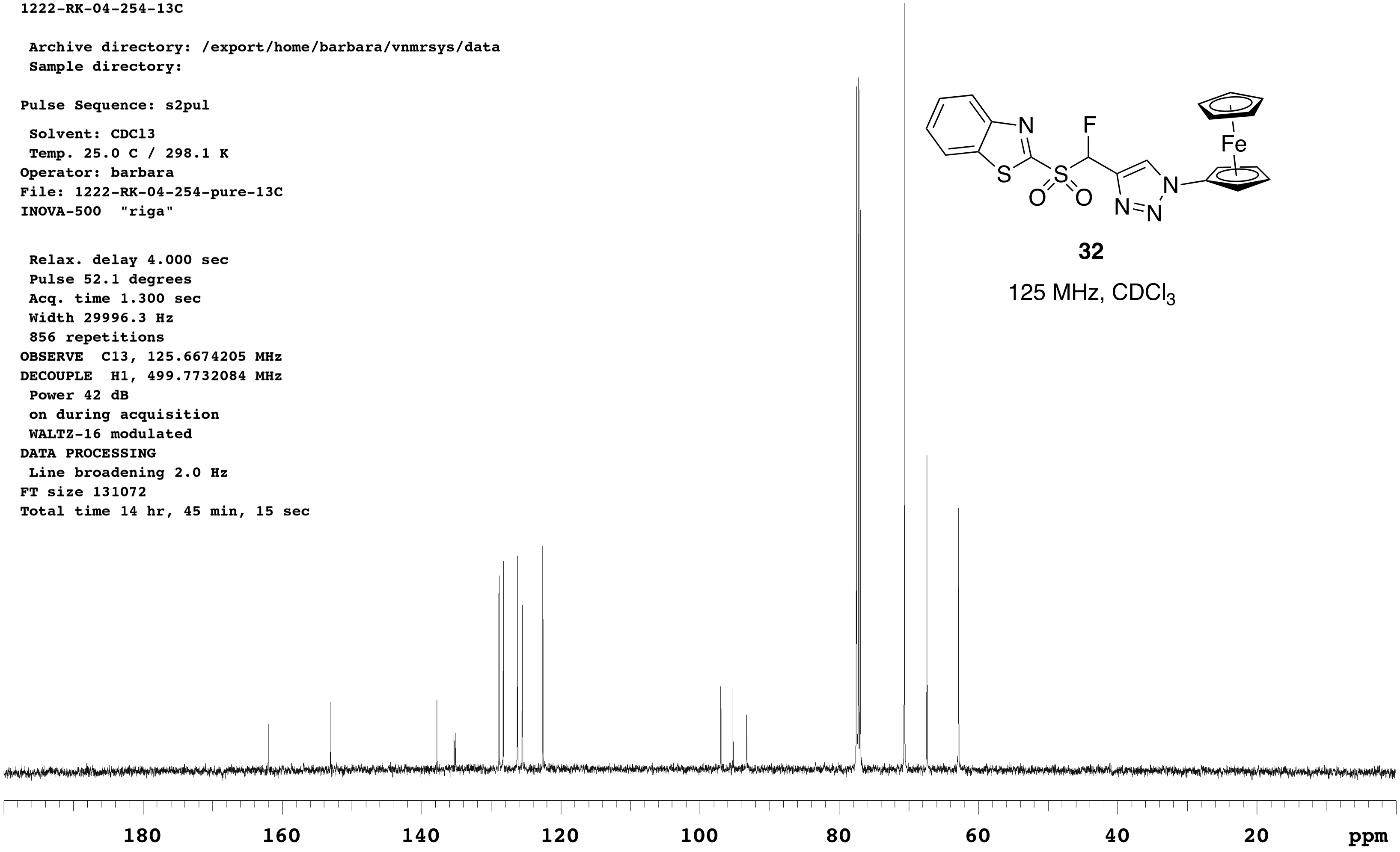
```
1222-RK-04-254-13C

 Archive directory: /export/home/barbara/vnmrsys/data
 Sample directory:

Pulse Sequence: s2pul

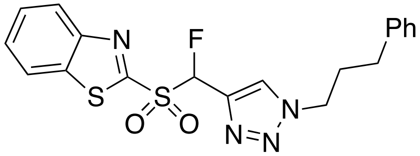
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-254-pure-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 856 repetitions
OBSERVE  C13, 125.6674205 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 131072
Total time 14 hr, 45 min, 15 sec
```



32

125 MHz, $CDCl_3$



33

500 MHz, $CDCl_3$

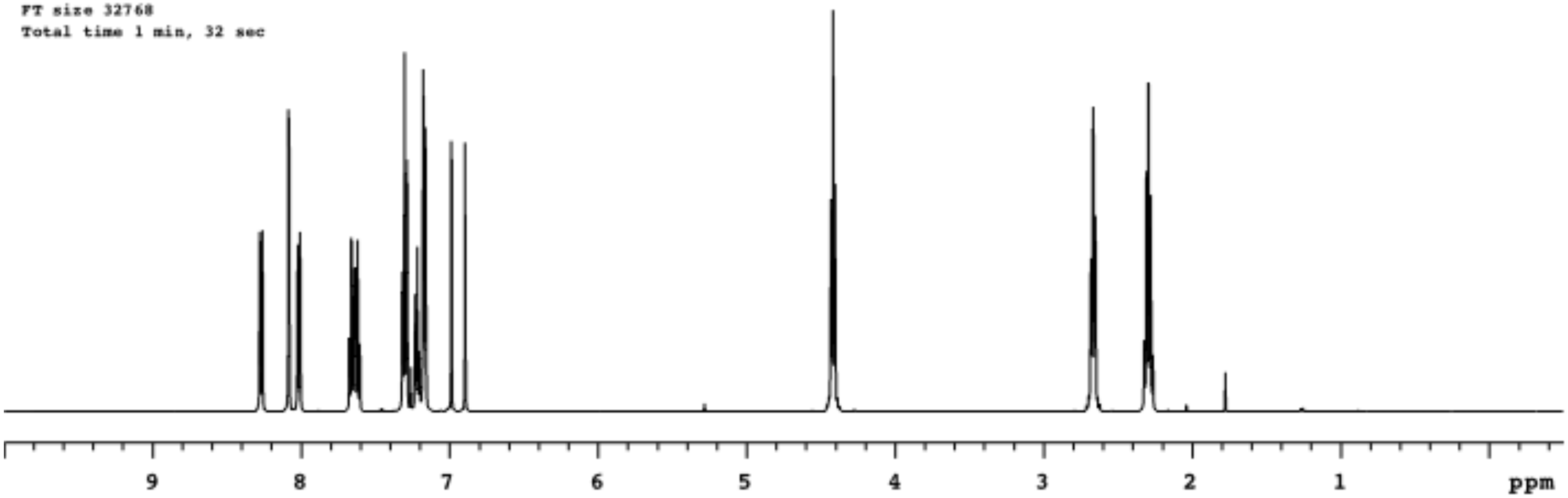
```
1222-RK-04-258-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-258-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 32 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 32 sec
```

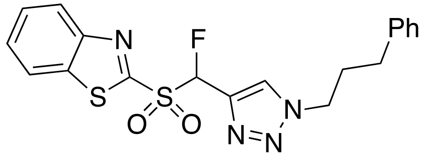


```
1222-RK-04-258-pure-13C

Pulse Sequence: s2pul

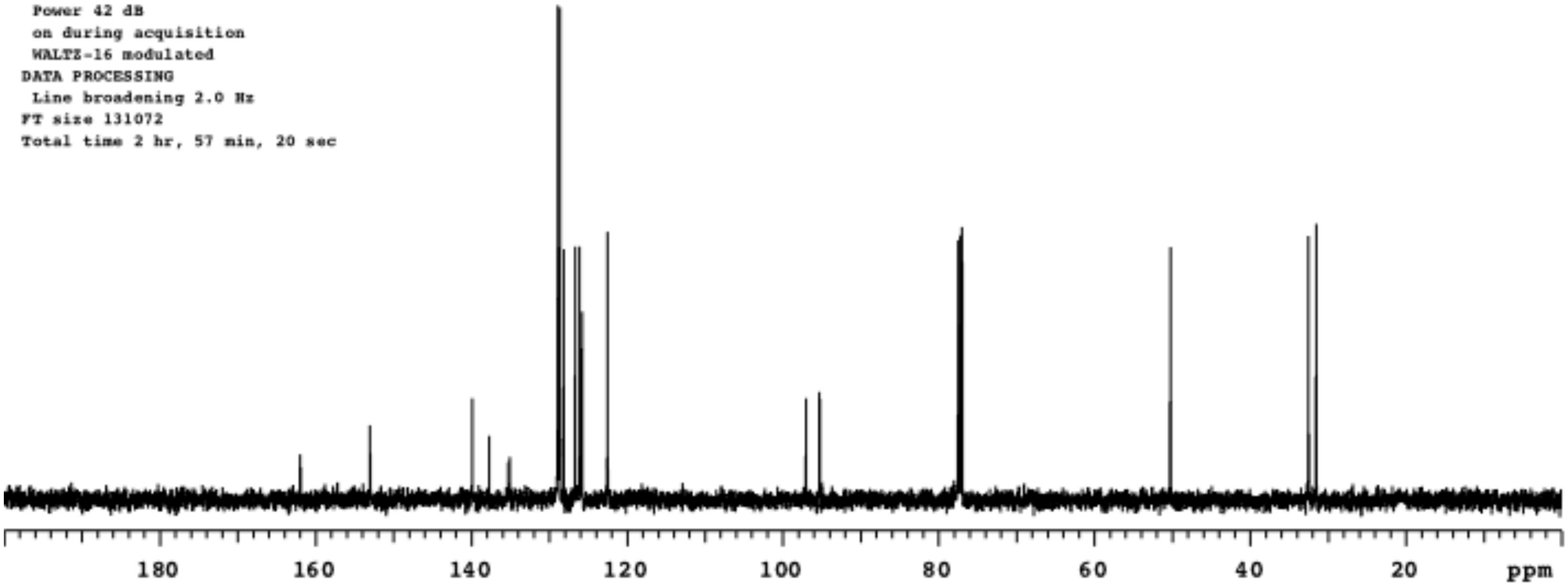
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-258-pure-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 52 repetitions
OBSERVE  C13, 125.6674273 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec
```



33

125 MHz, $CDCl_3$



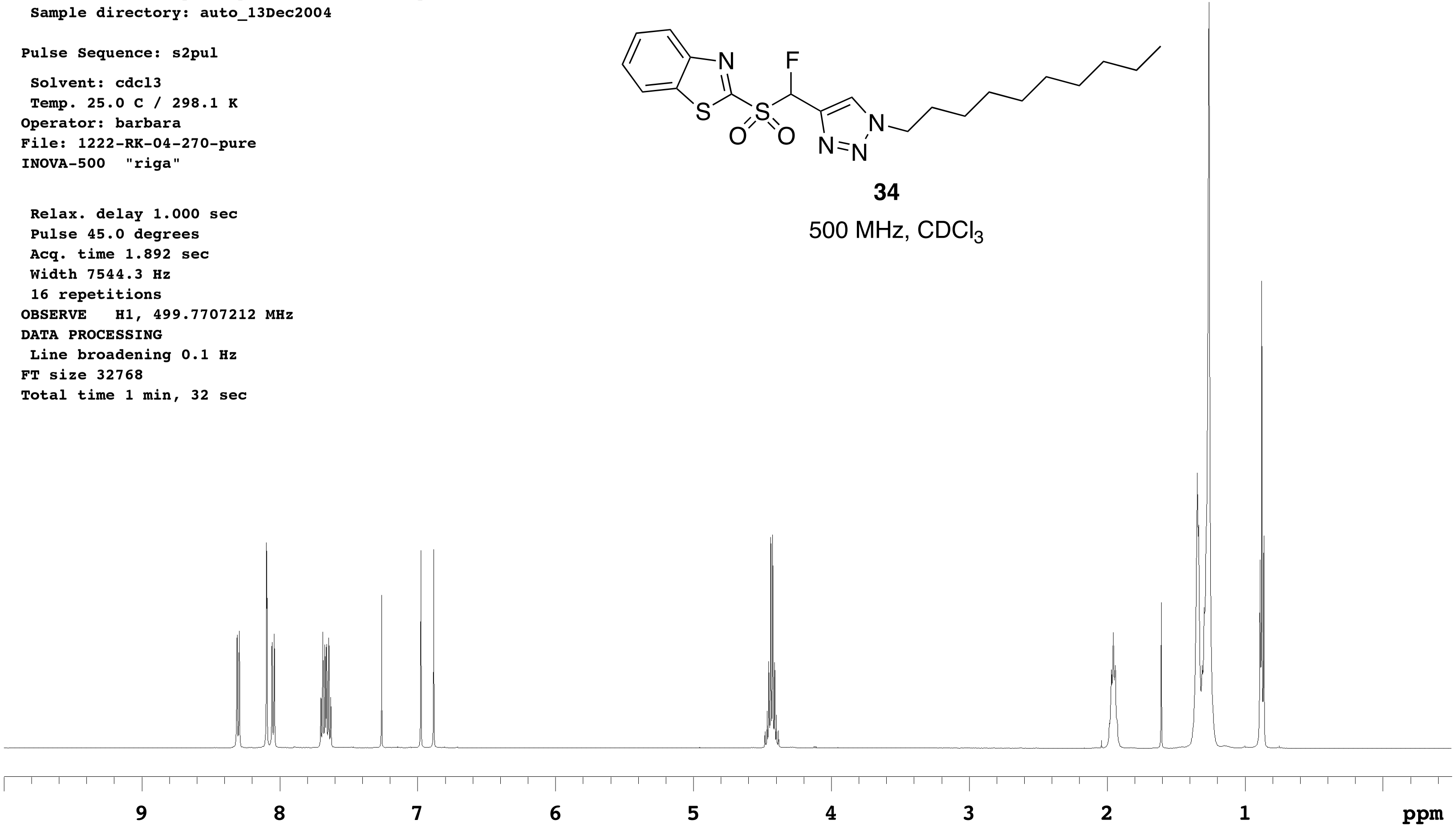
```
1222-RK-04-270-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-270-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 16 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 32 sec
```



34

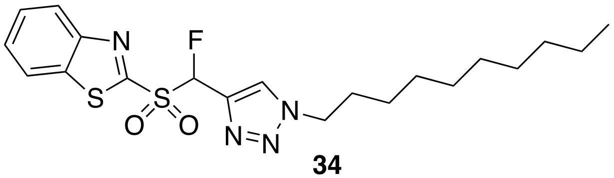
500 MHz, $CDCl_3$

```
1222-RK-04-270-13C

Pulse Sequence: s2pul

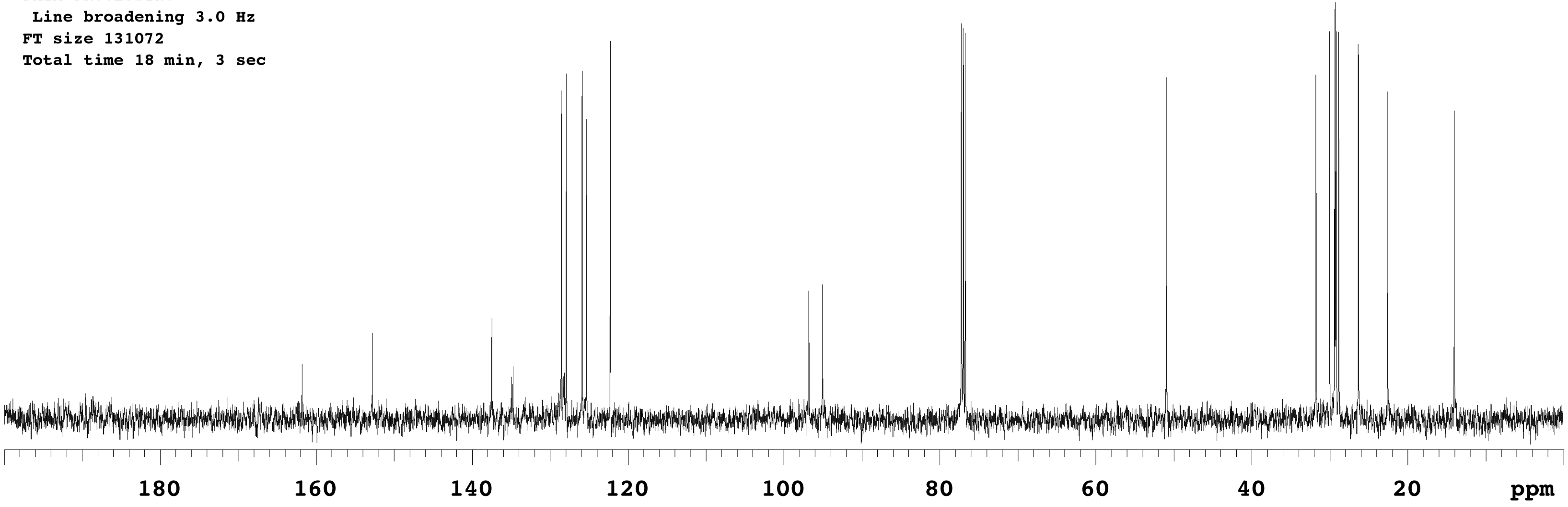
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-270-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 64 repetitions
OBSERVE  C13, 125.6674571 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 3.0 Hz
FT size 131072
Total time 18 min, 3 sec
```



34

125 MHz, $CDCl_3$



```
1222-RK-04-247-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

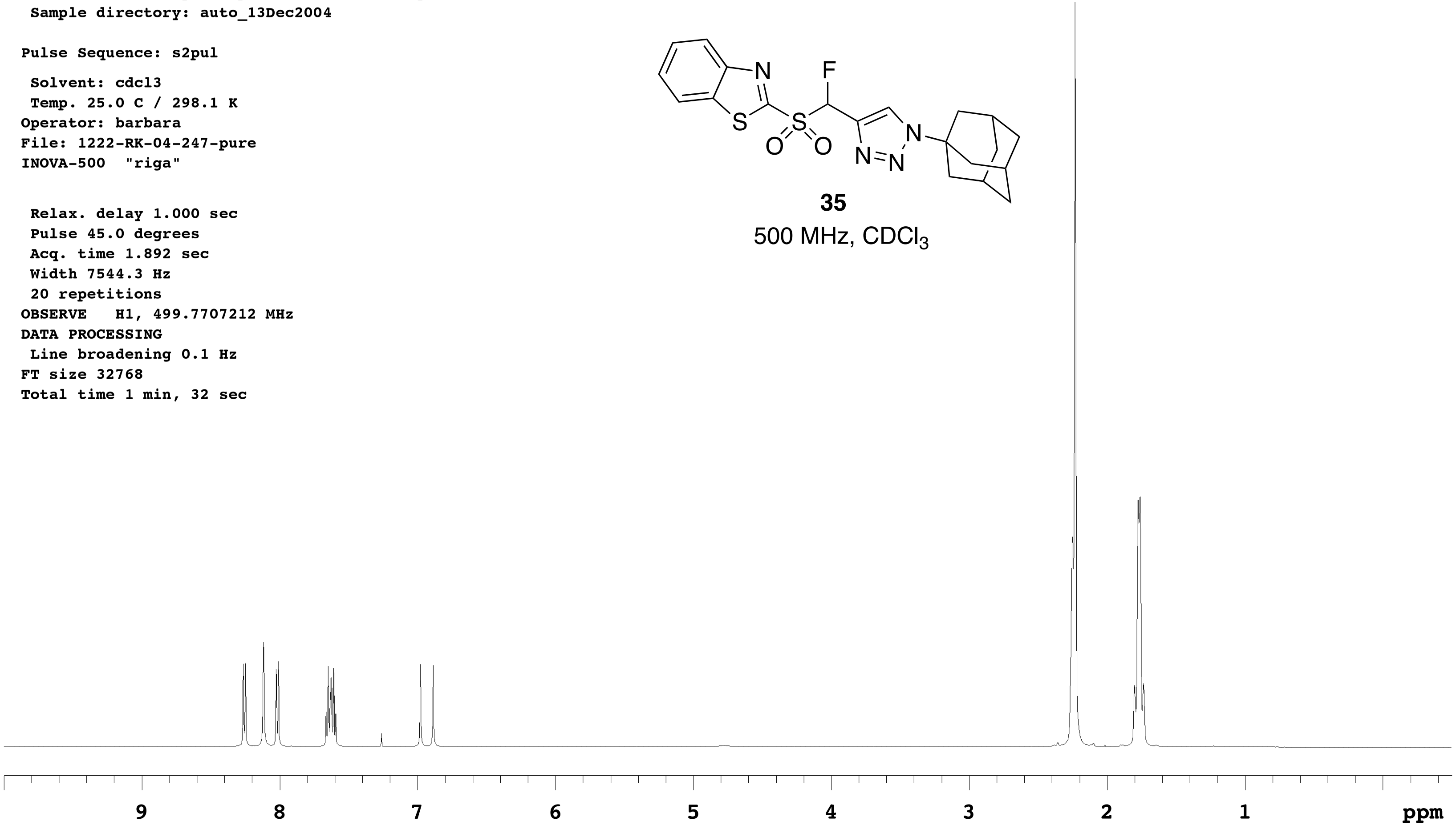
Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-247-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 20 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 32 sec
```

35

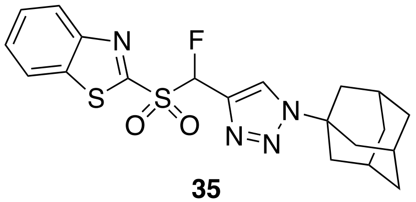
500 MHz, $CDCl_3$



```
1222-RK-04-247-13C

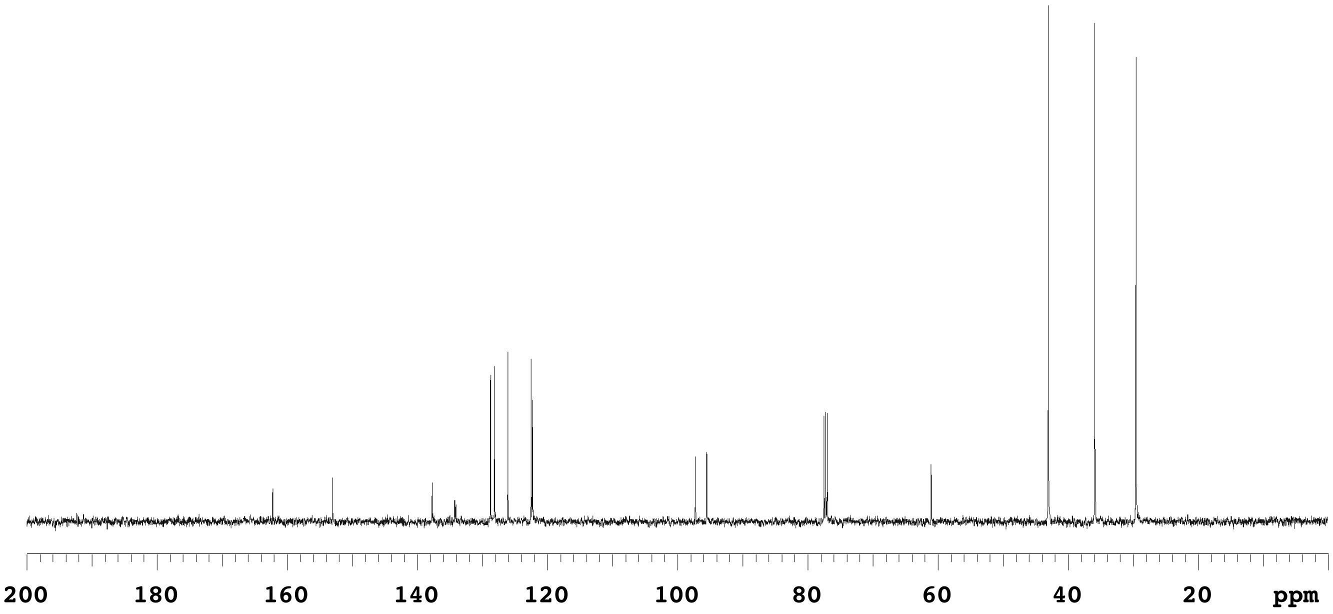
Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-247-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 84 repetitions
OBSERVE  C13, 125.6674273 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 3.0 Hz
FT size 131072
Total time 18 min, 3 sec
```



35

125 MHz, $CDCl_3$

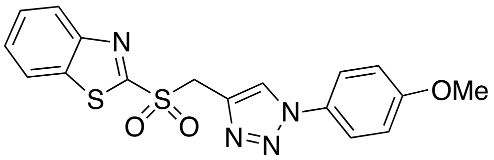


```
1222-RK-06-424-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

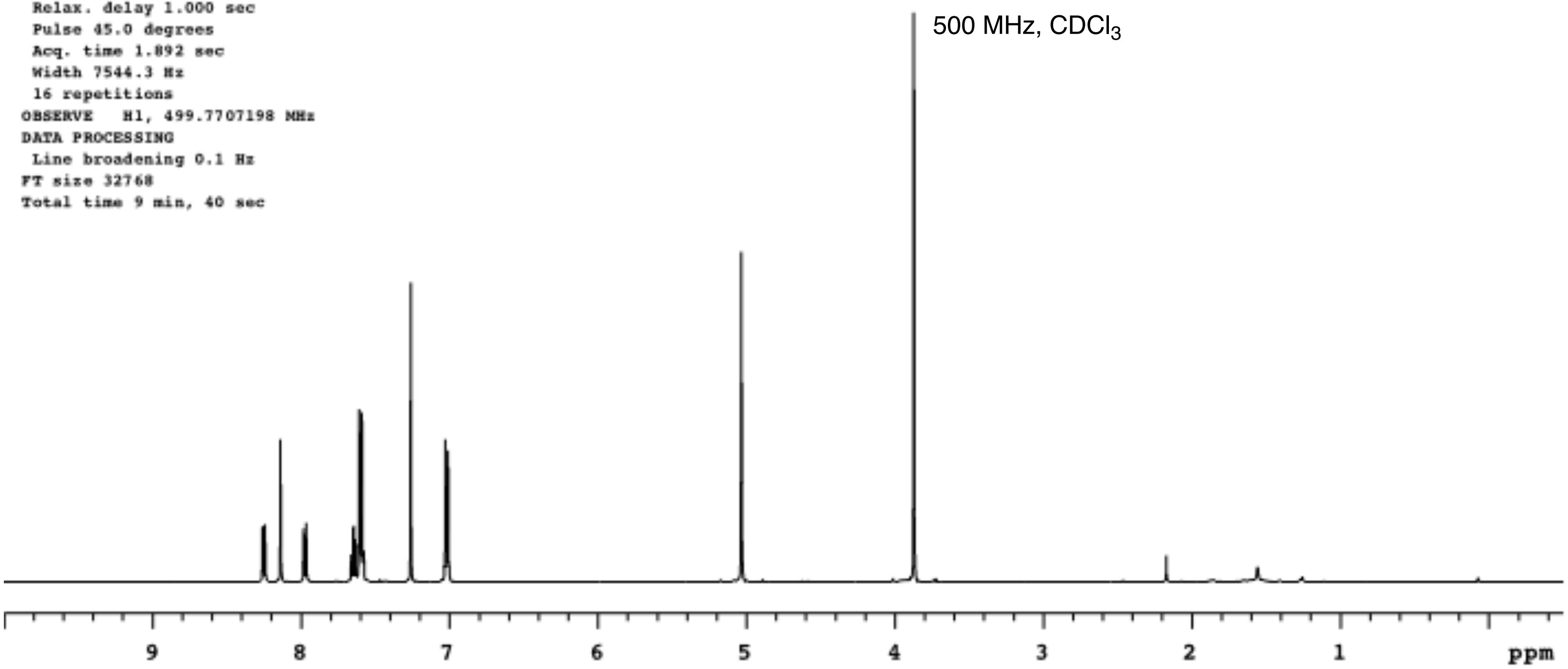
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-06-424-pure
INOVA-500  "riga"

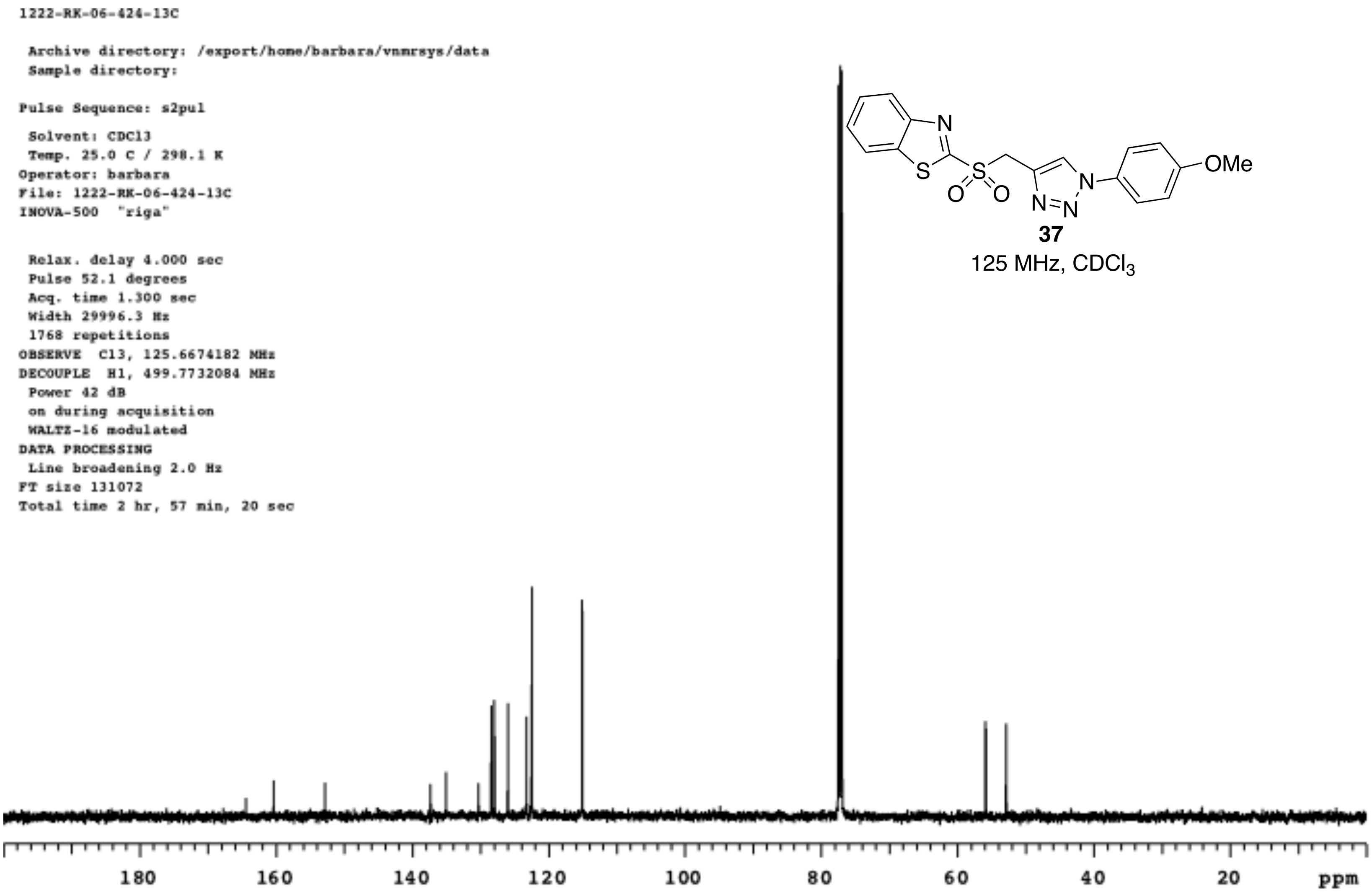
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 16 repetitions
OBSERVE   H1, 499.7707198 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



37

500 MHz, CDCl$_3$





```
1222-RK-06-424-13C

 Archive directory: /export/home/barbara/vnmrsys/data
 Sample directory:

Pulse Sequence: s2pul

 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-06-424-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 1768 repetitions
OBSERVE  C13, 125.6674182 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec
```

37

125 MHz, $CDCl_3$

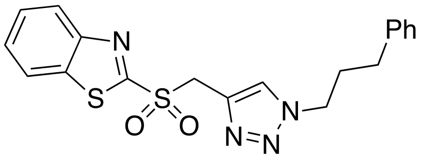
```
1222-RK-06-423-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

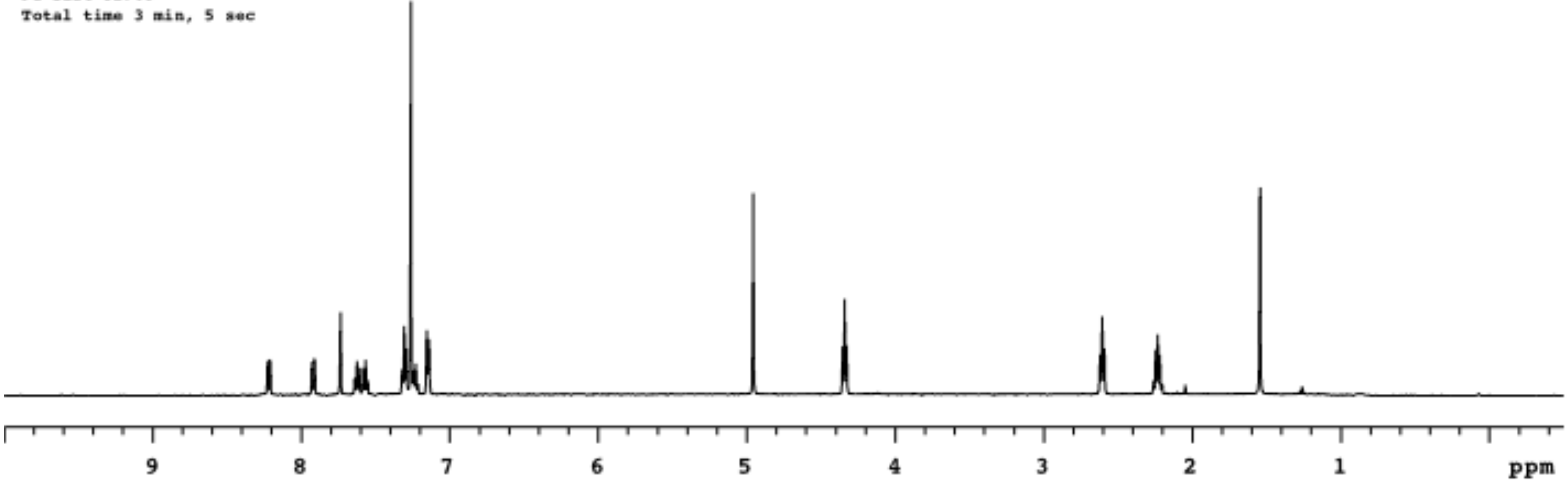
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-06-423-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 20 repetitions
OBSERVE   H1, 499.7707184 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 3 min, 5 sec
```



38

500 MHz, CDCl$_3$

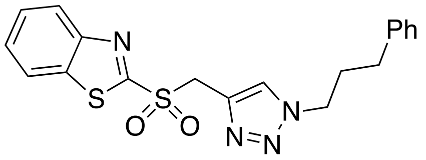


```
1222-RK-06-423-pure-13C

 Archive directory: /export/home/barbara/vnmrsys/data
 Sample directory:

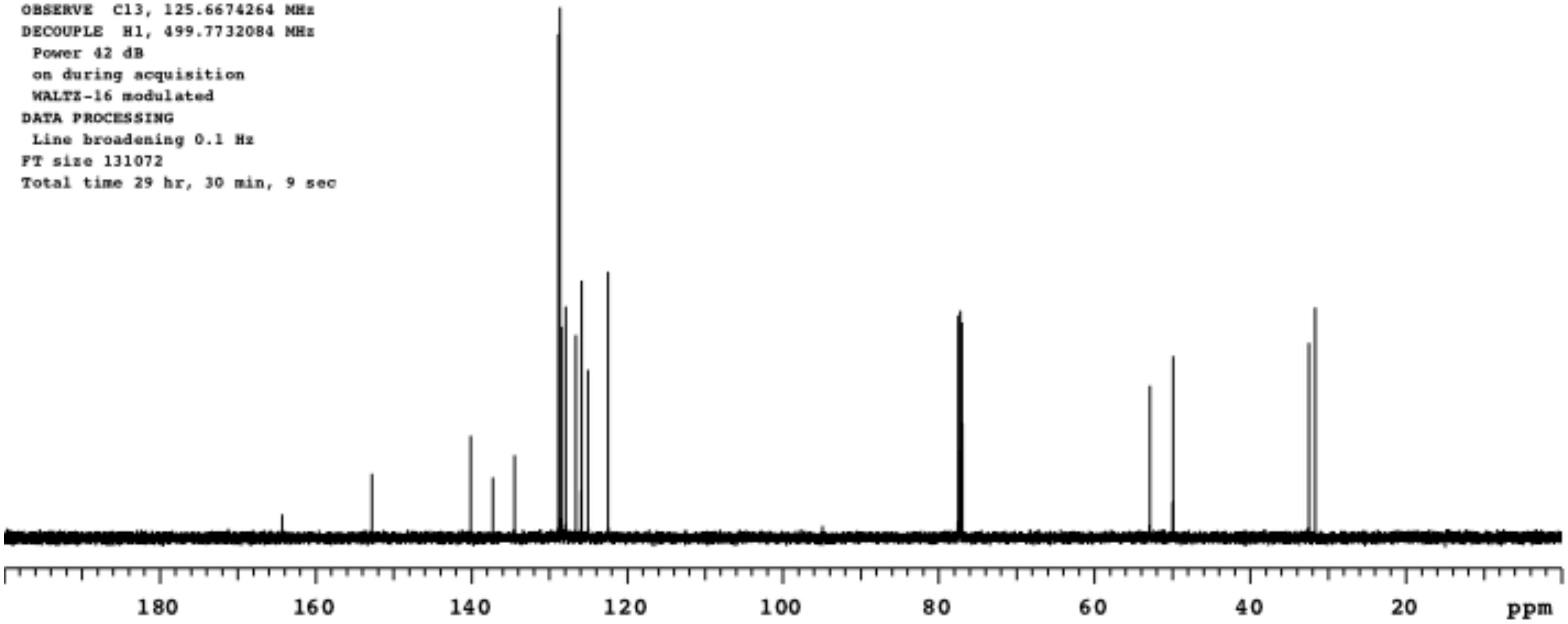
Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-06-423-pure-13C
INOVA-500  "riga"

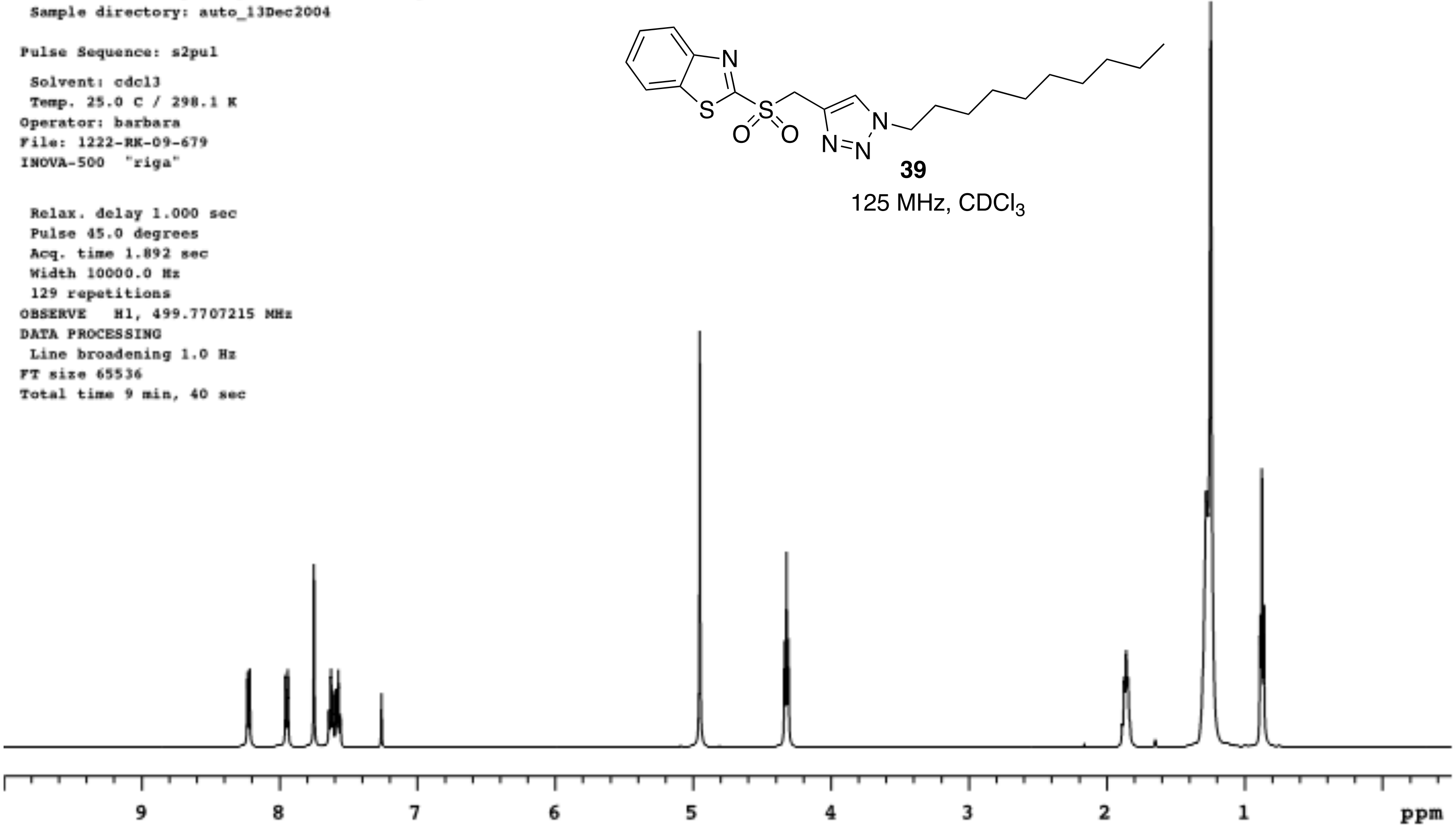
 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 284 repetitions
OBSERVE  C13, 125.6674264 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 131072
Total time 29 hr, 30 min, 9 sec
```



38

125 MHz, $CDCl_3$





```
1222-RK-09-679

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-09-679
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 129 repetitions
OBSERVE   H1, 499.7707215 MHz
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 9 min, 40 sec
```

39

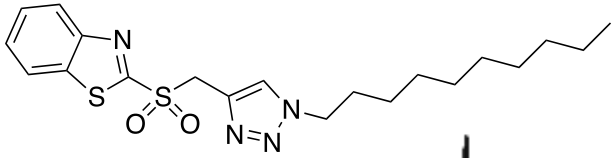
125 MHz, $CDCl_3$

1222-RK-09-679-13C

Pulse Sequence: s2pul

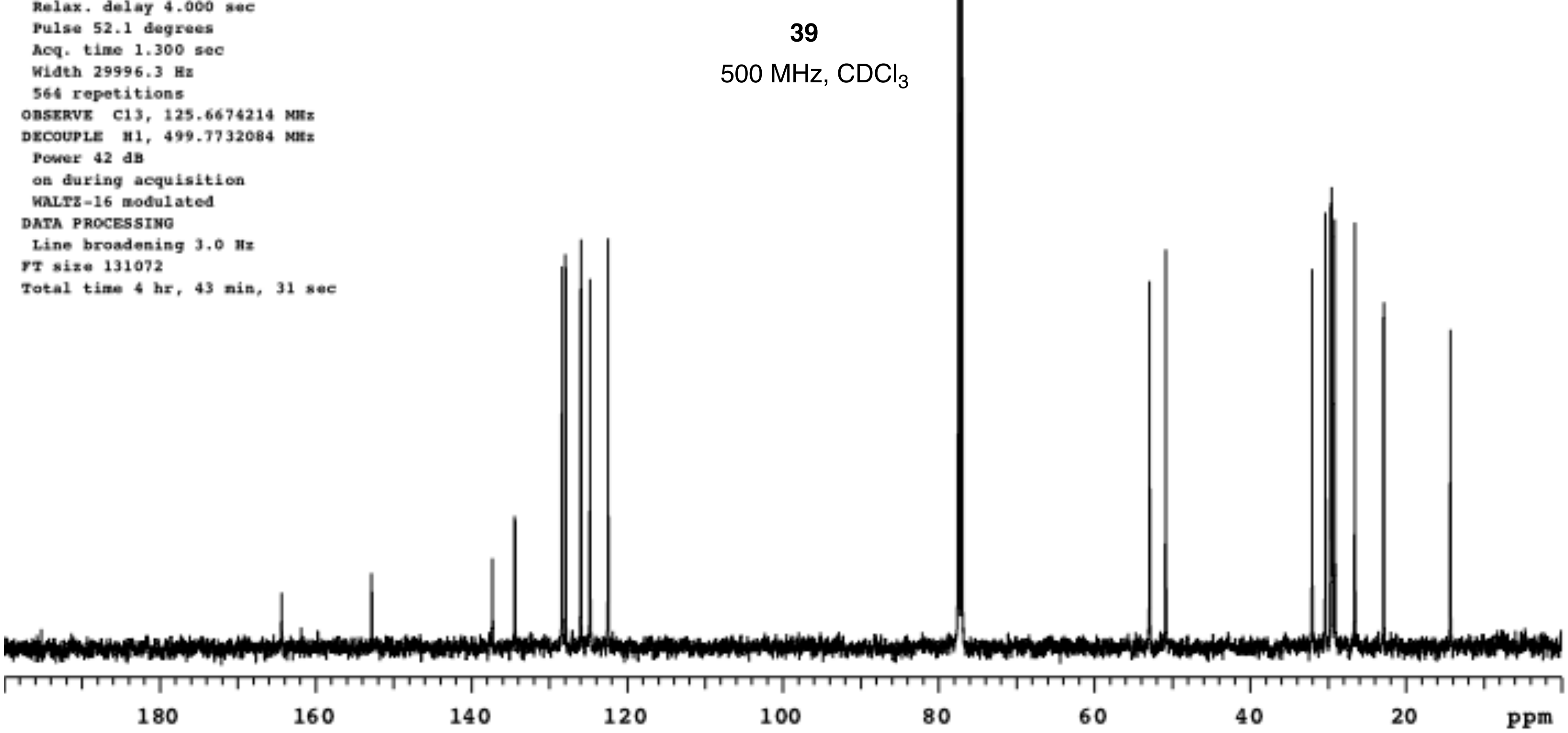
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-09-679-13C
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
564 repetitions
OBSERVE C13, 125.6674214 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 131072
Total time 4 hr, 43 min, 31 sec



39

500 MHz, $CDCl_3$



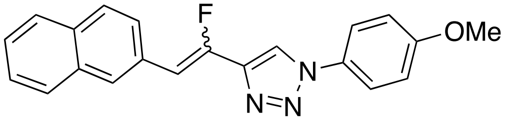
```
1222-RK-04-288

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

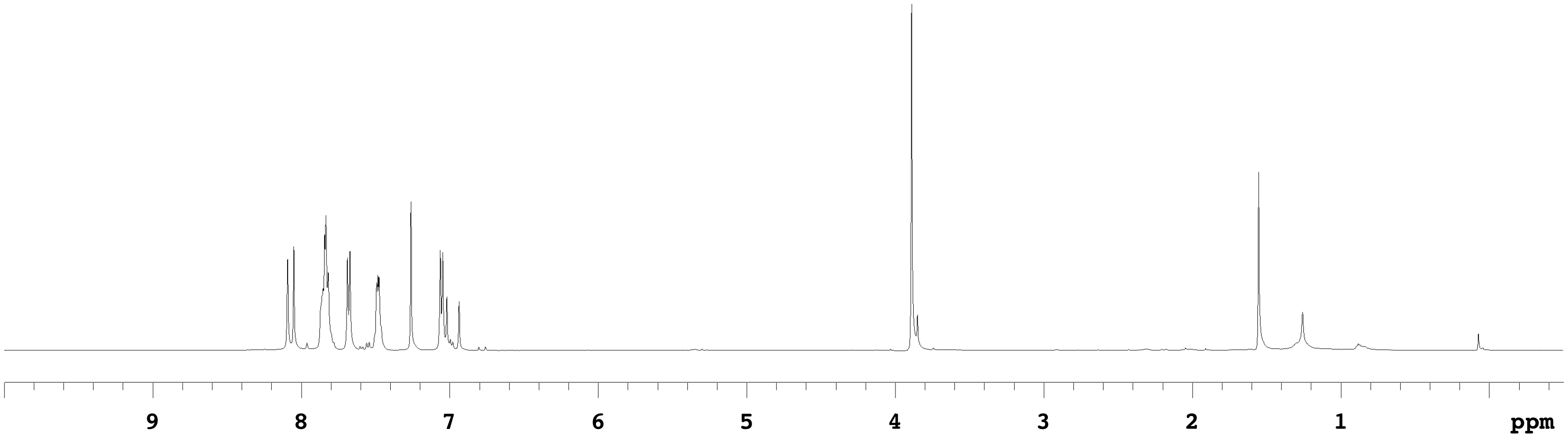
Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-288
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 32 repetitions
OBSERVE   H1, 499.7707209 MHz
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 1 min, 32 sec
```



40: *E/Z* 7/93
500 MHz, $CDCl_3$



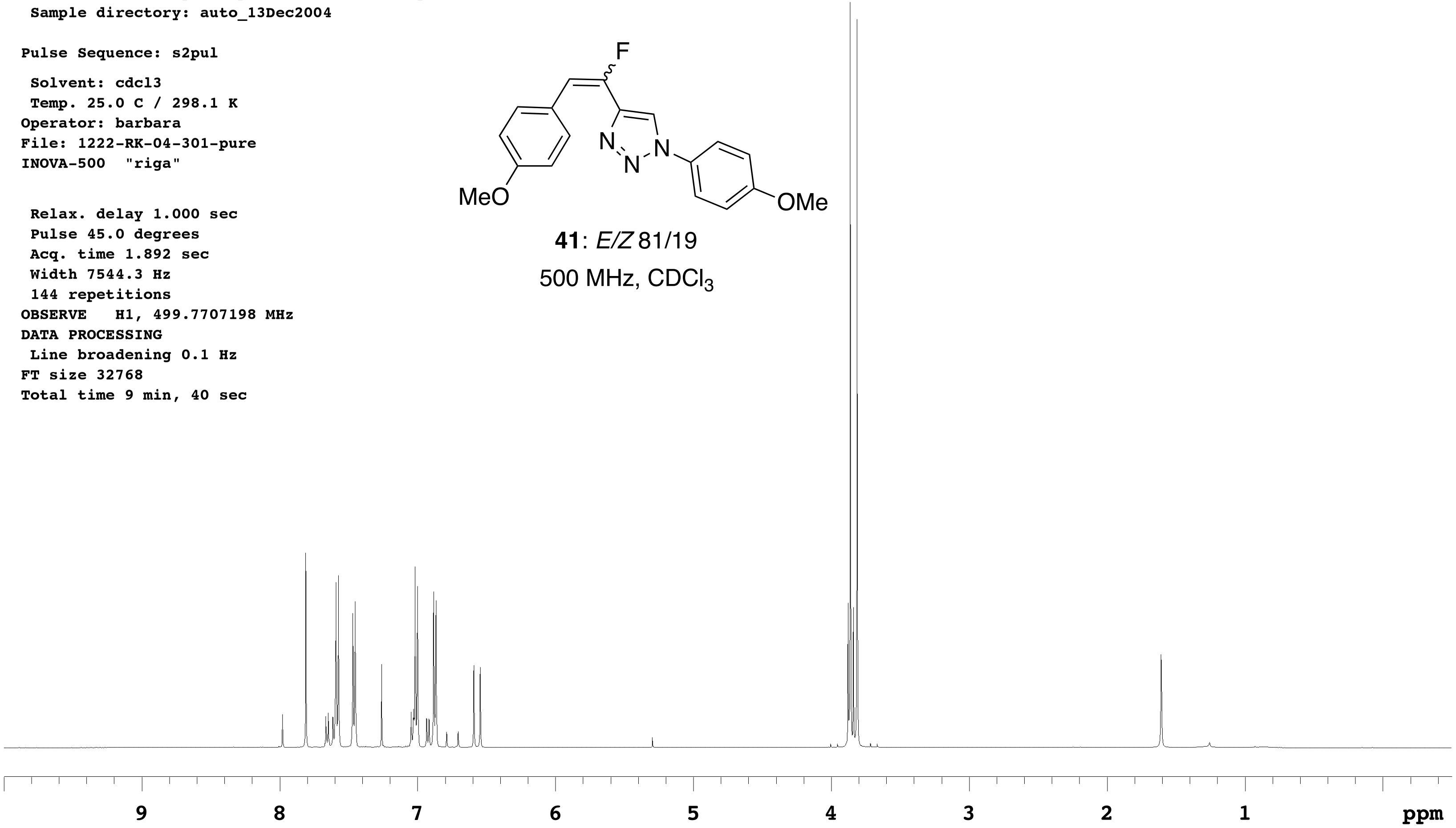
```
1222-RK-04-301-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-301-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 144 repetitions
OBSERVE   H1, 499.7707198 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



41: *E/Z* 81/19

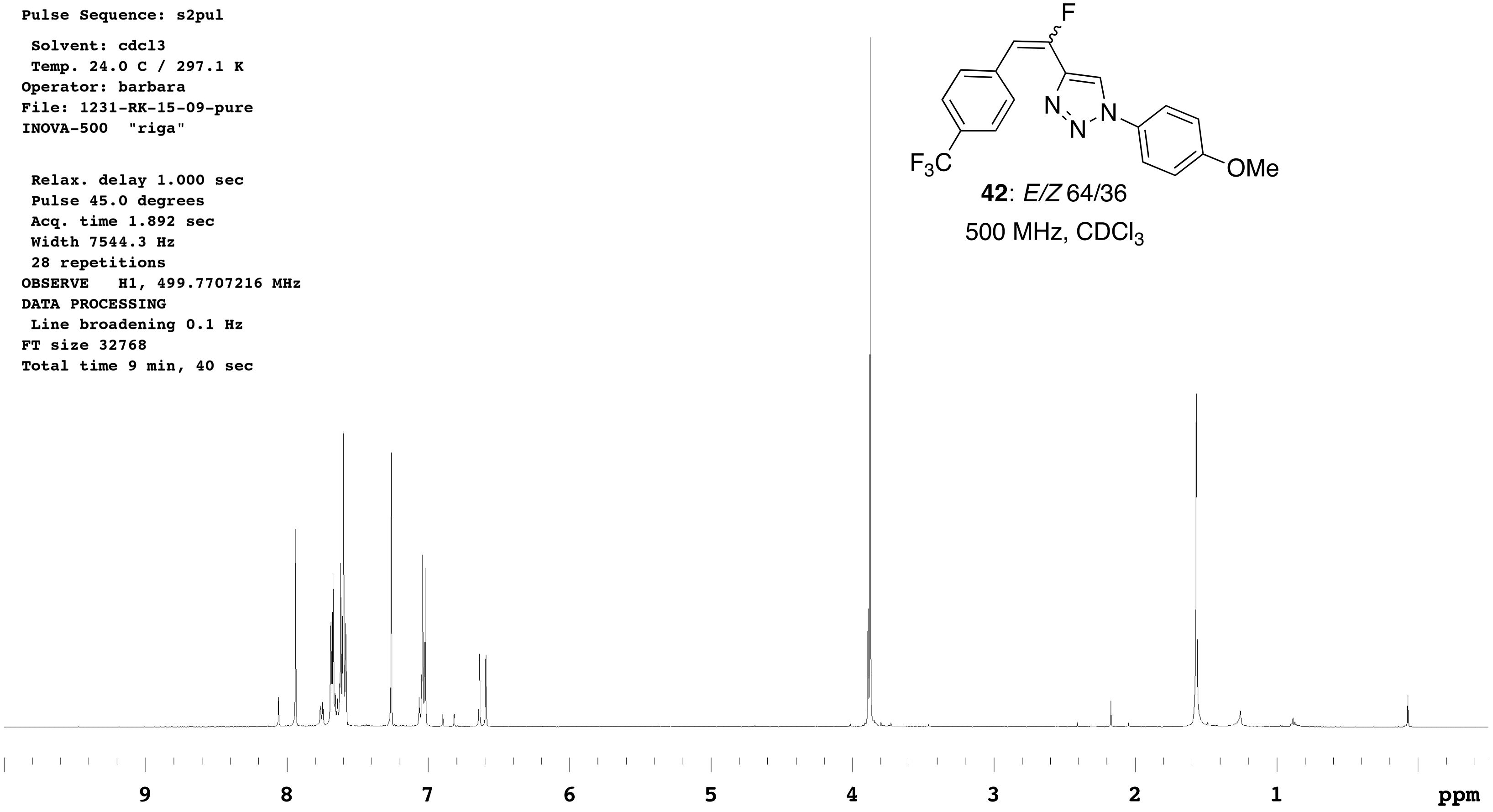
500 MHz, $CDCl_3$

```
1231-RK-15-09-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 24.0 C / 297.1 K
Operator: barbara
File: 1231-RK-15-09-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 28 repetitions
OBSERVE   H1, 499.7707216 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



42: *E/Z* 64/36

500 MHz, $CDCl_3$

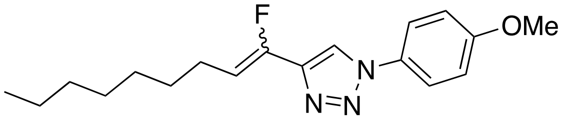
```
1222-RK-04-328-1stfraction

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

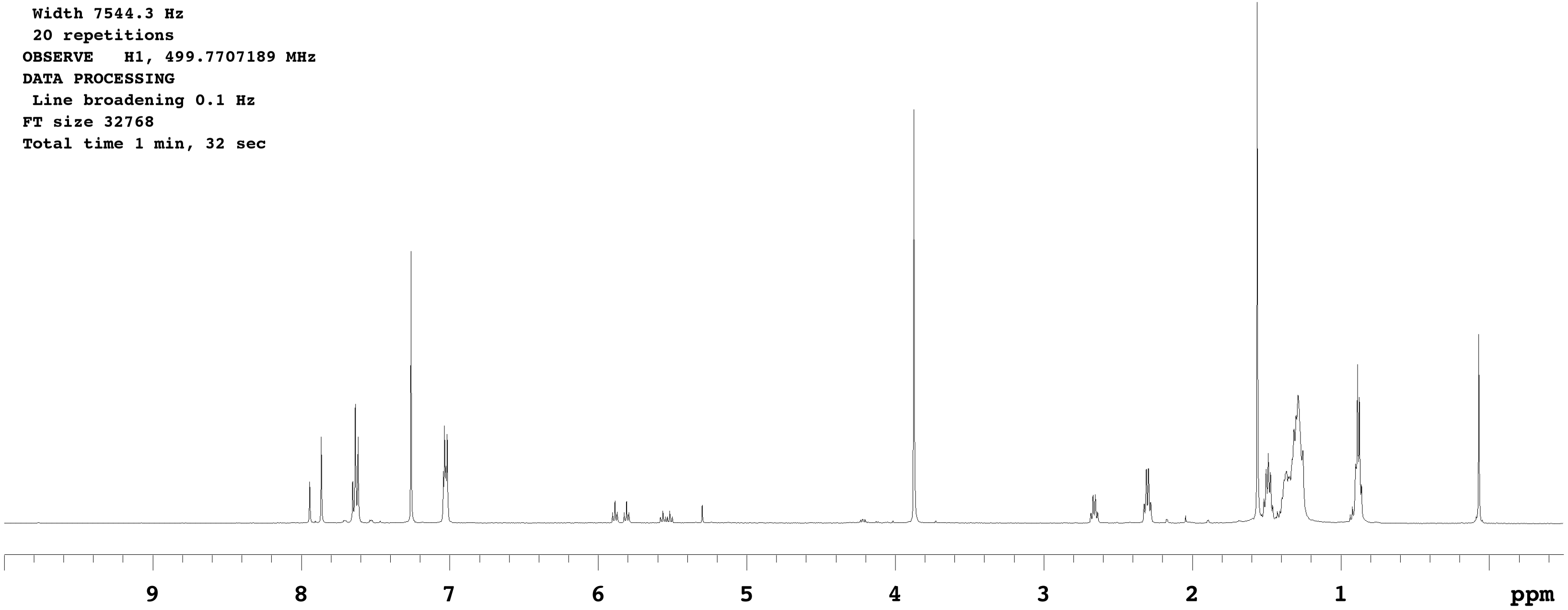
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-328-1stfraction
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 20 repetitions
OBSERVE   H1, 499.7707189 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 32 sec
```



43: *E*/*Z* 34/66

500 MHz, $CDCl_3$



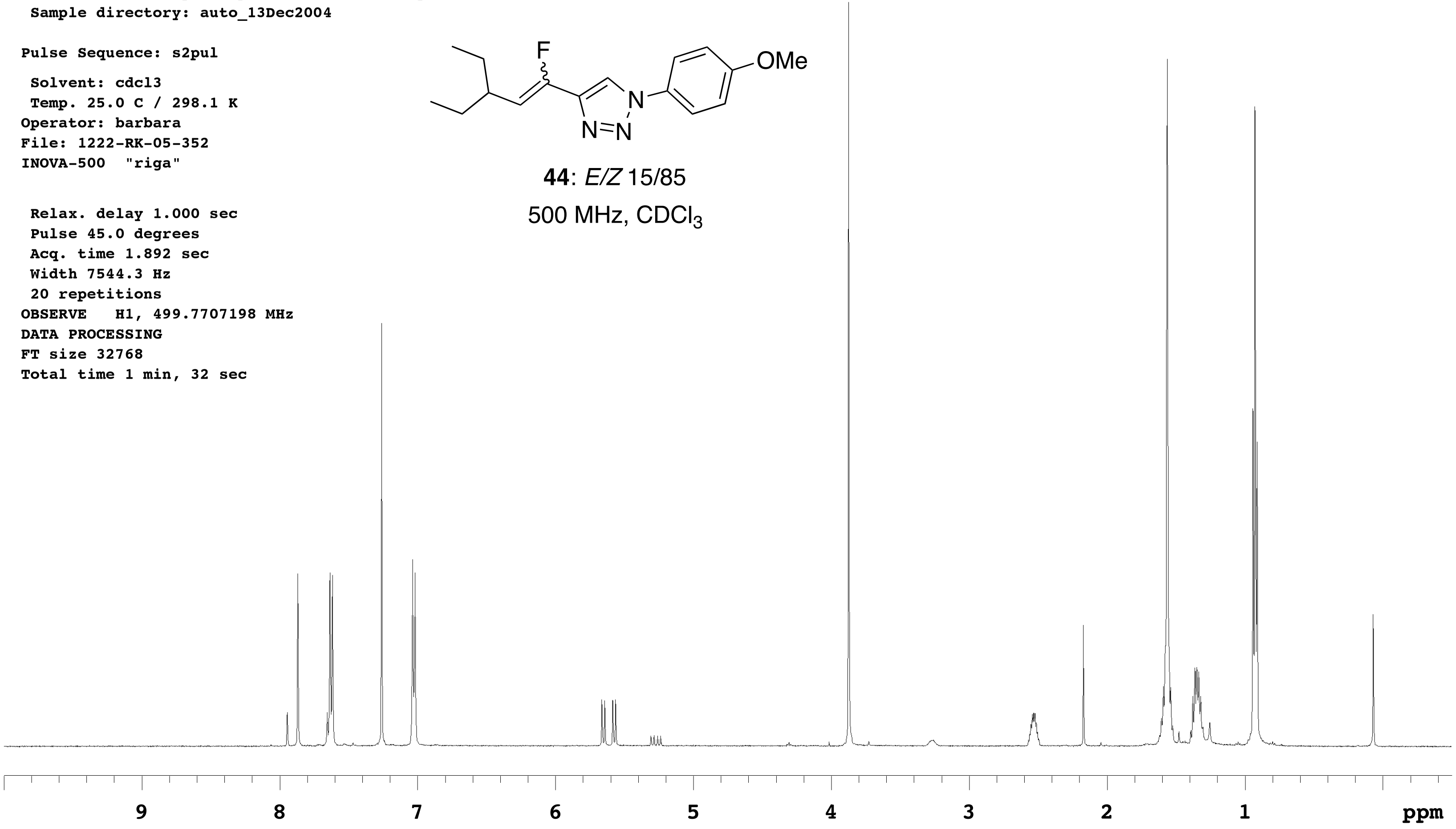
```
1222-RK-05-352

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

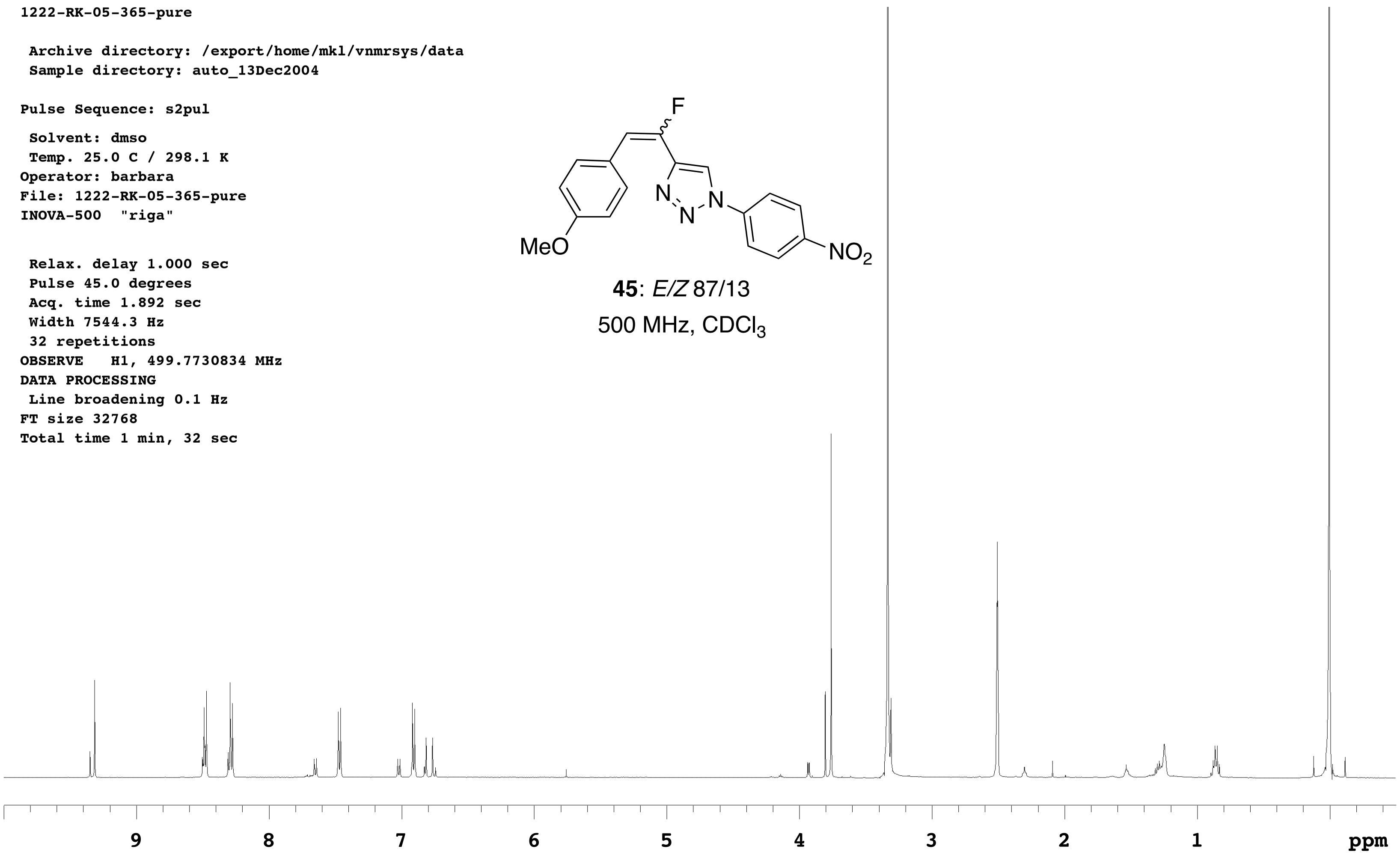
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-05-352
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 20 repetitions
OBSERVE   H1, 499.7707198 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 32 sec
```



44: *E/Z* 15/85

500 MHz, $CDCl_3$



```
1222-RK-05-365-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: dmso
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-05-365-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 32 repetitions
OBSERVE   H1, 499.7730834 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 32 sec
```

45: *E/Z* 87/13

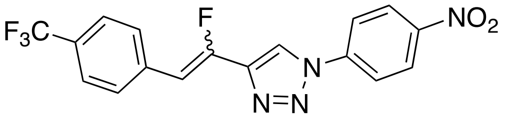
500 MHz, $CDCl_3$

```
1231-RK-14-85-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

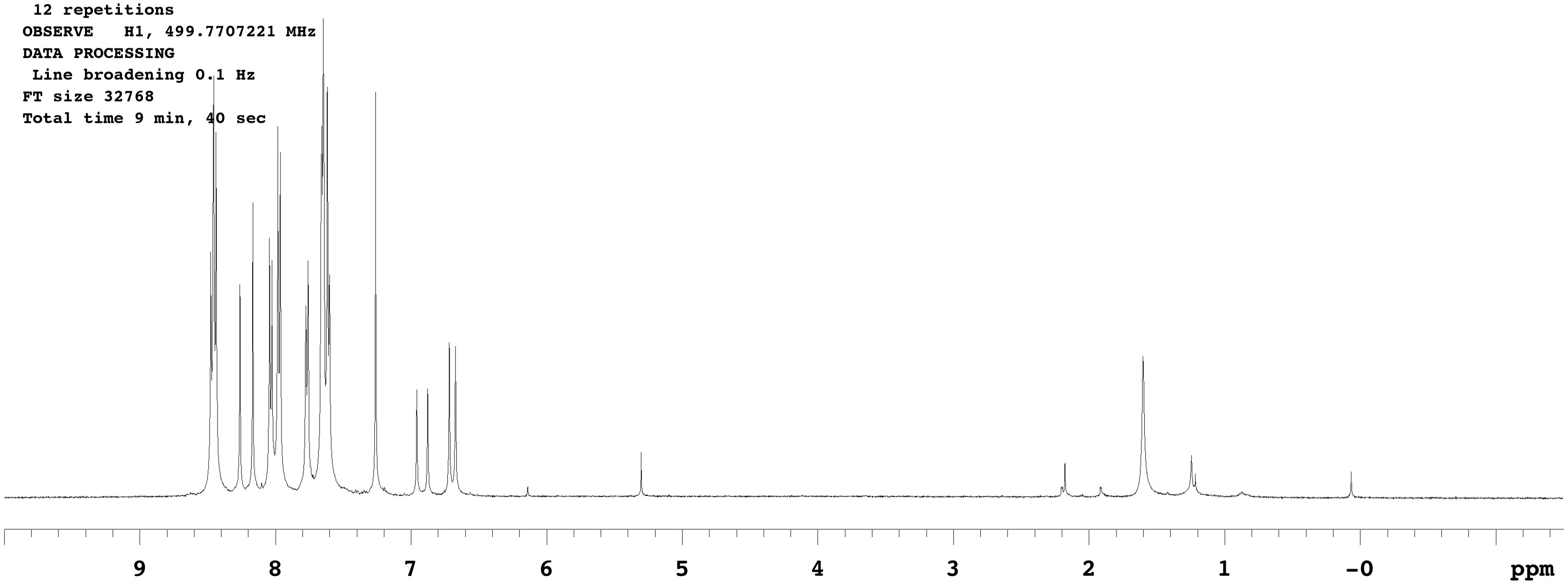
Pulse Sequence: s2pul
 Solvent: cdcl3
 Ambient temperature
Operator: barbara
File: 1231-RK-14-85-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 12 repetitions
OBSERVE   H1, 499.7707221 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



46: *E/Z* 15/85

500 MHz, $CDCl_3$

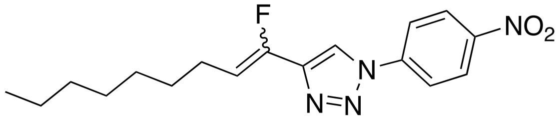


```
1222-RK-05-346-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

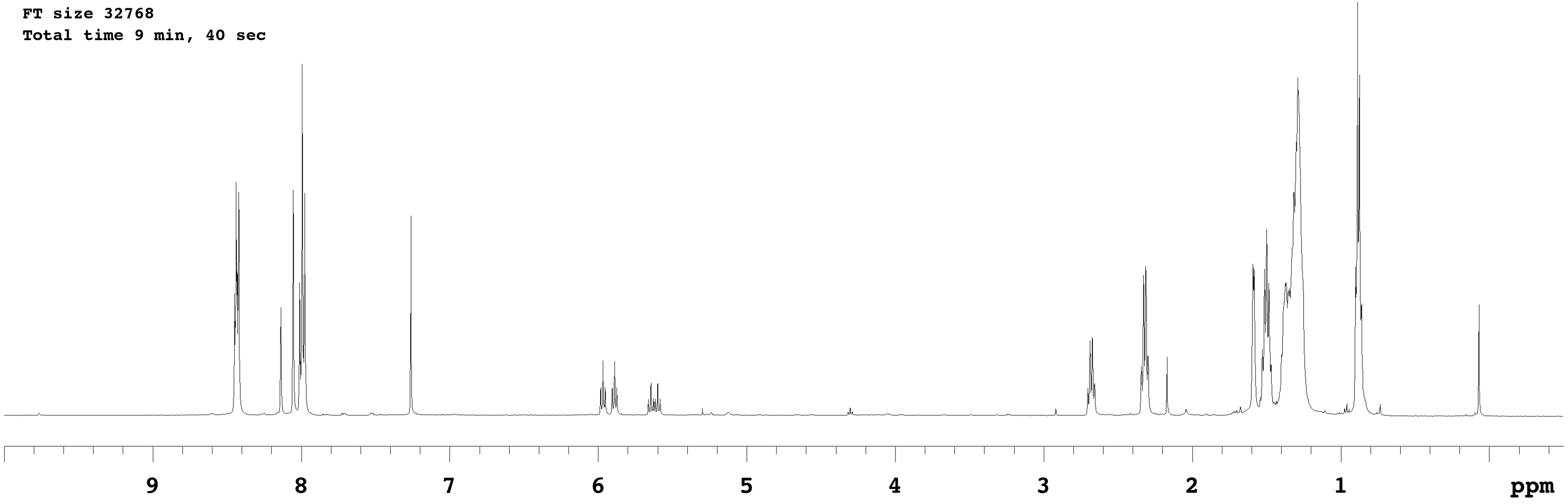
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-05-346-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 12 repetitions
OBSERVE   H1, 499.7707207 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



47: *E/Z* 32/68

500 MHz, $CDCl_3$

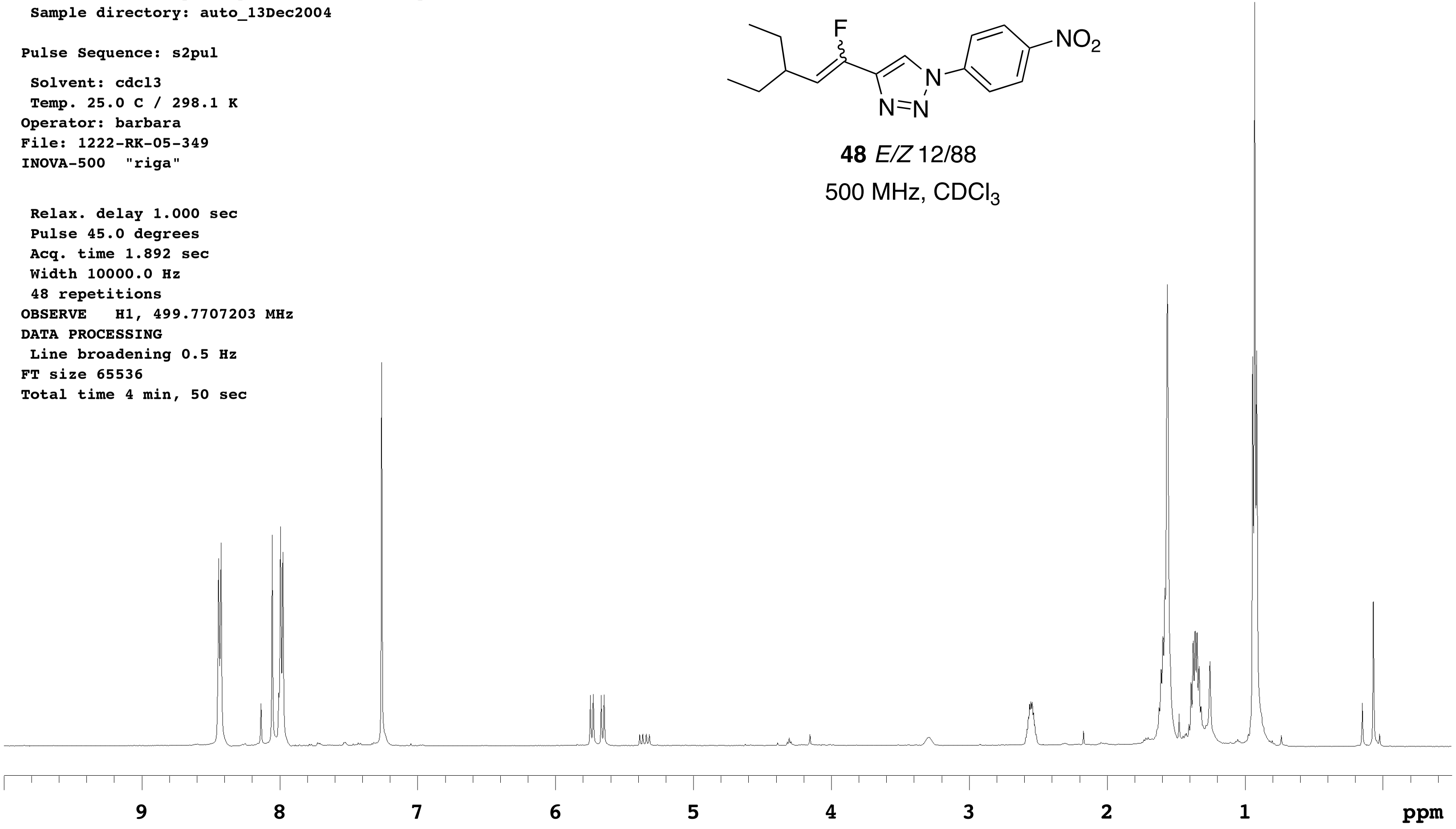


```
1222-RK-05-349

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

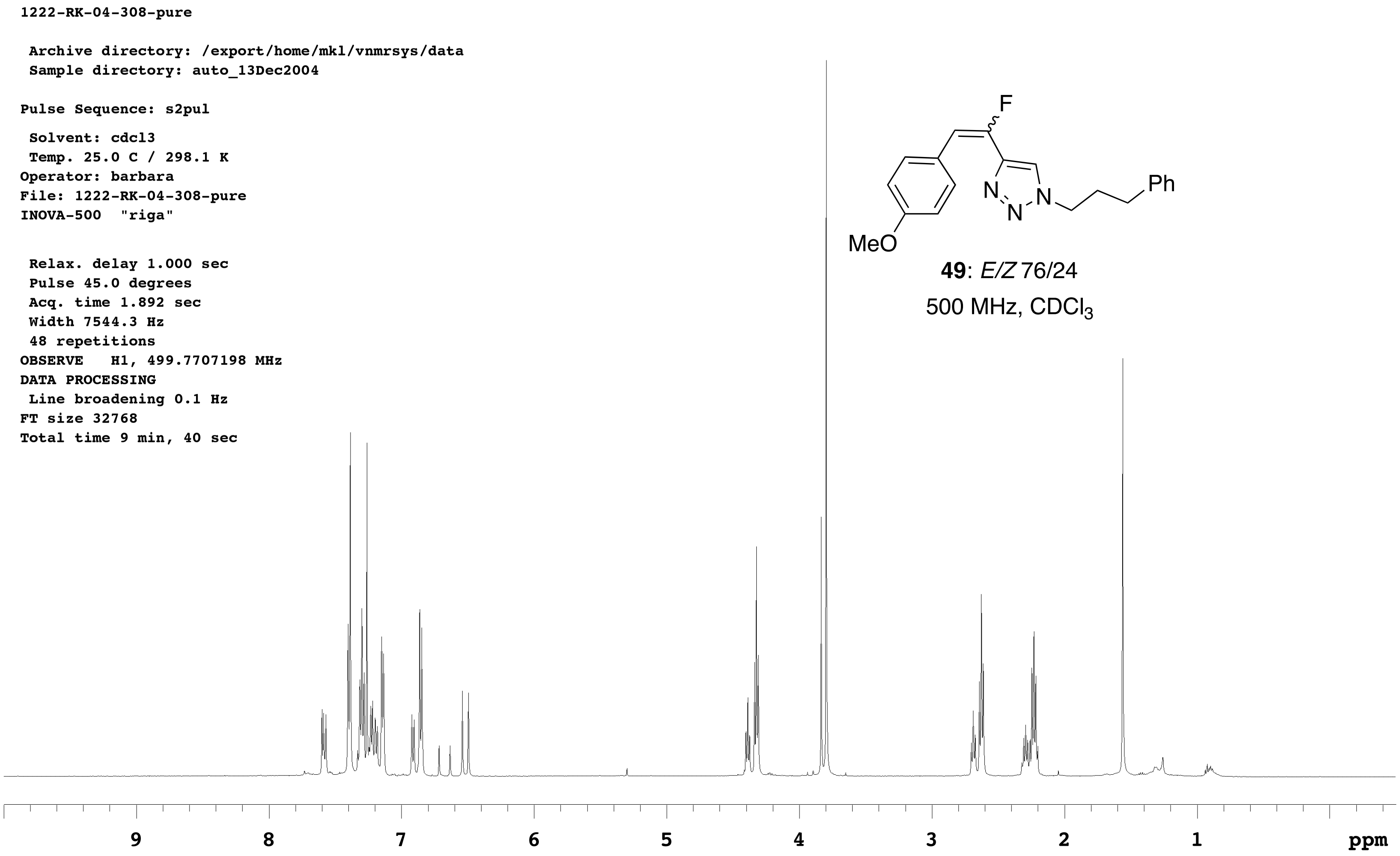
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-05-349
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 48 repetitions
OBSERVE   H1, 499.7707203 MHz
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 4 min, 50 sec
```



48 *E/Z* 12/88

500 MHz, $CDCl_3$



```
1222-RK-04-308-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-308-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 48 repetitions
OBSERVE   H1, 499.7707198 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```

49: *E/Z* 76/24

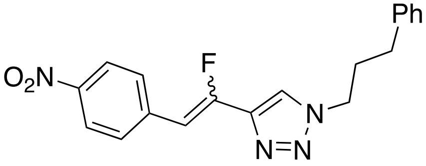
500 MHz, $CDCl_3$

```
1222-RK-04-314-pure

 Archive directory: /export/home/barbara/vnmrsys/data
 Sample directory:

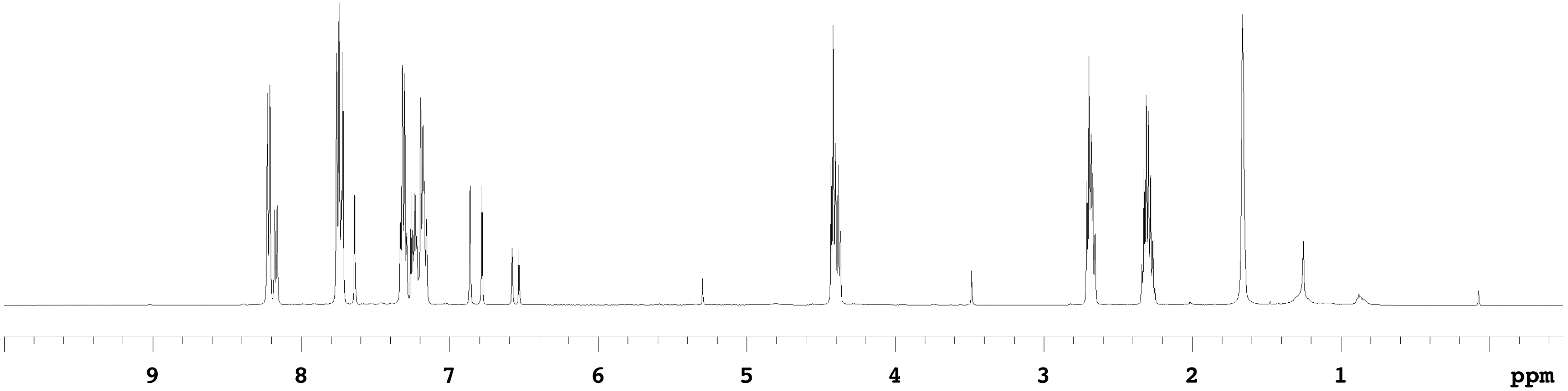
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-314-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 64 repetitions
OBSERVE   H1, 499.7707189 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



50: *E/Z* 38/62

500 MHz, $CDCl_3$



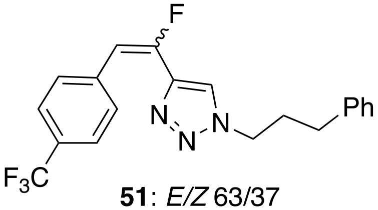
```
1231-RK-14-86-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

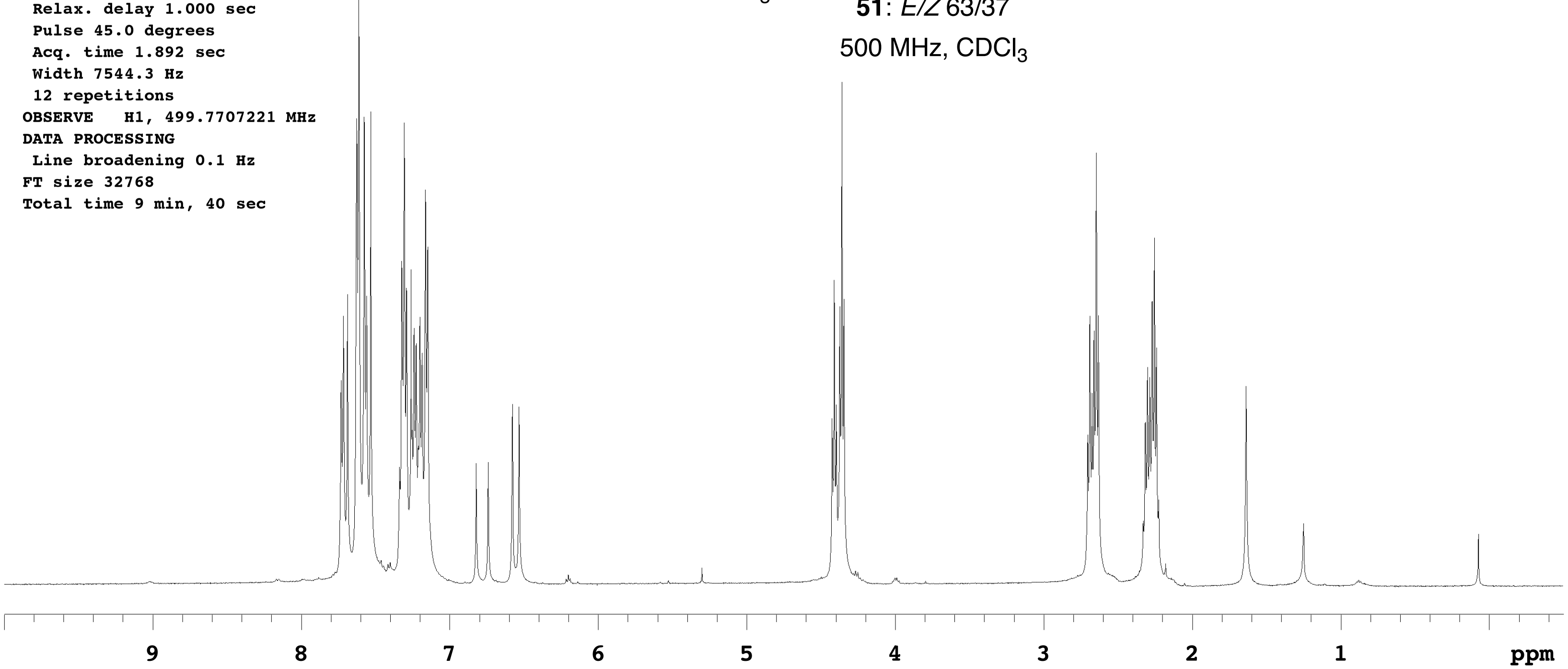
 Solvent: cdcl3
 Ambient temperature
Operator: barbara
File: 1231-RK-14-86-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 12 repetitions
OBSERVE   H1, 499.7707221 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



51: *E/Z* 63/37

500 MHz, $CDCl_3$

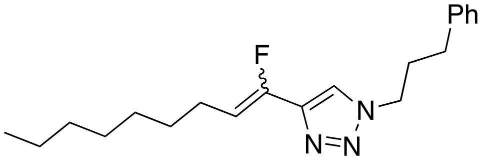


```
1222-RK-04-312-pure-2

 Archive directory: /export/home/barbara/vnmrsys/data
 Sample directory:

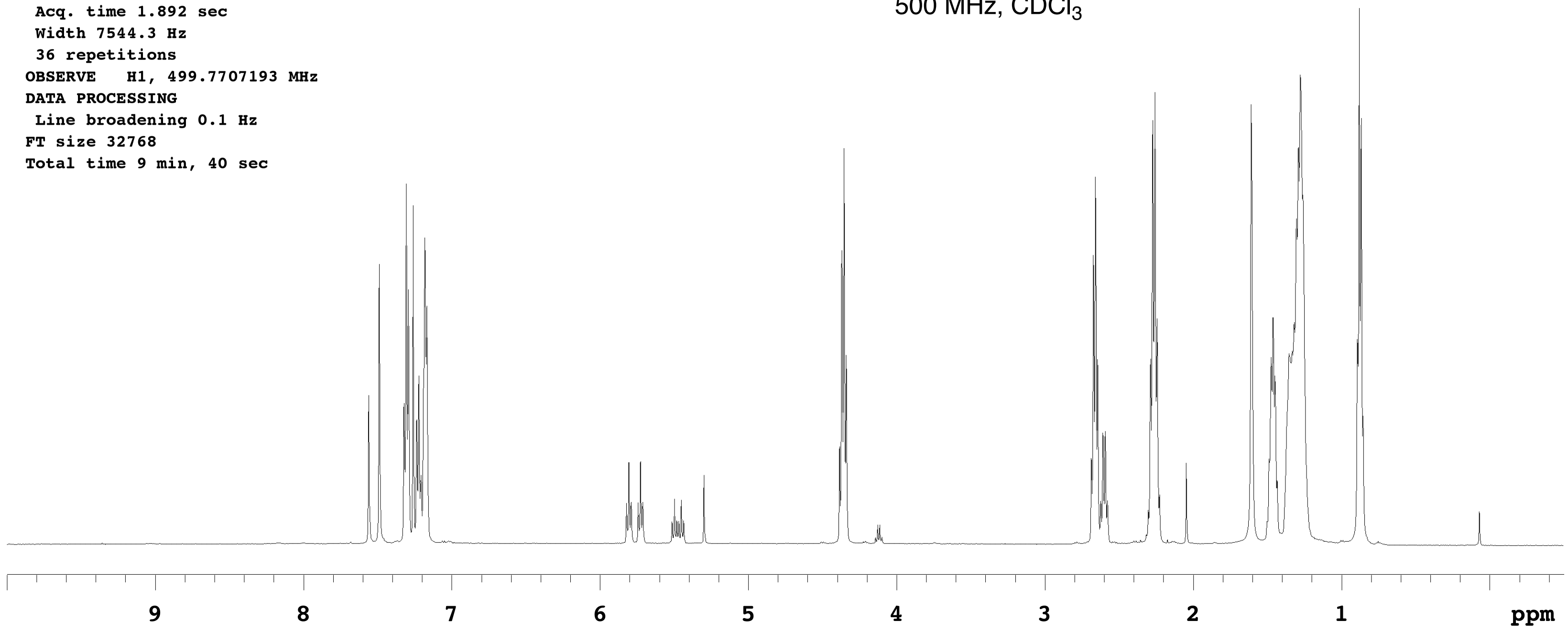
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-04-312-pure-2
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 36 repetitions
OBSERVE   H1, 499.7707193 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



52: *E/Z* 36/64

500 MHz, $CDCl_3$



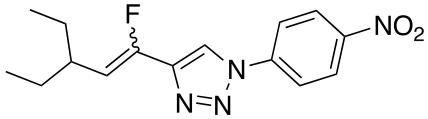
```
1222-RK-05-336

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004
 File: 1222-RK-05-336

Pulse Sequence: s2pul

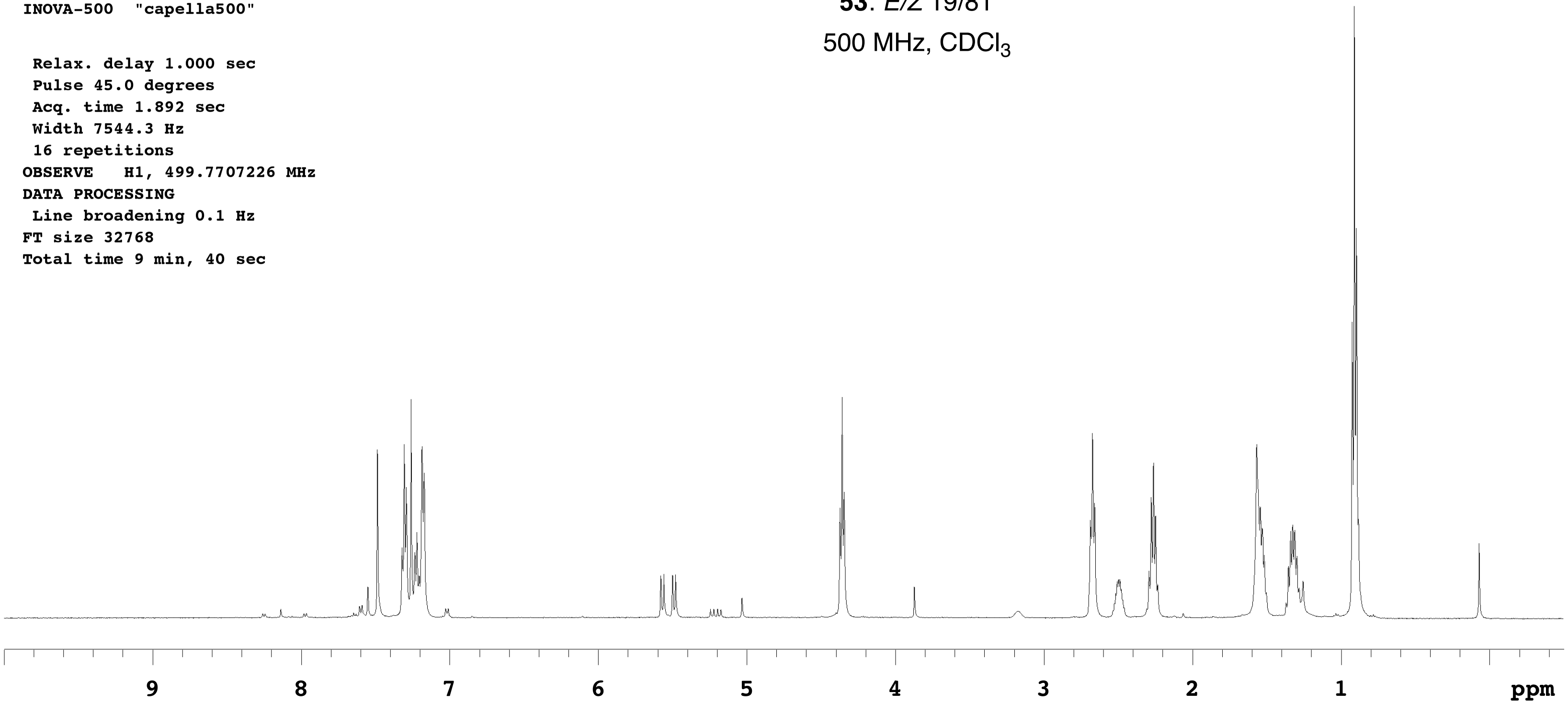
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-05-336
INOVA-500  "capella500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 16 repetitions
OBSERVE   H1, 499.7707226 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



53: *E/Z* 19/81

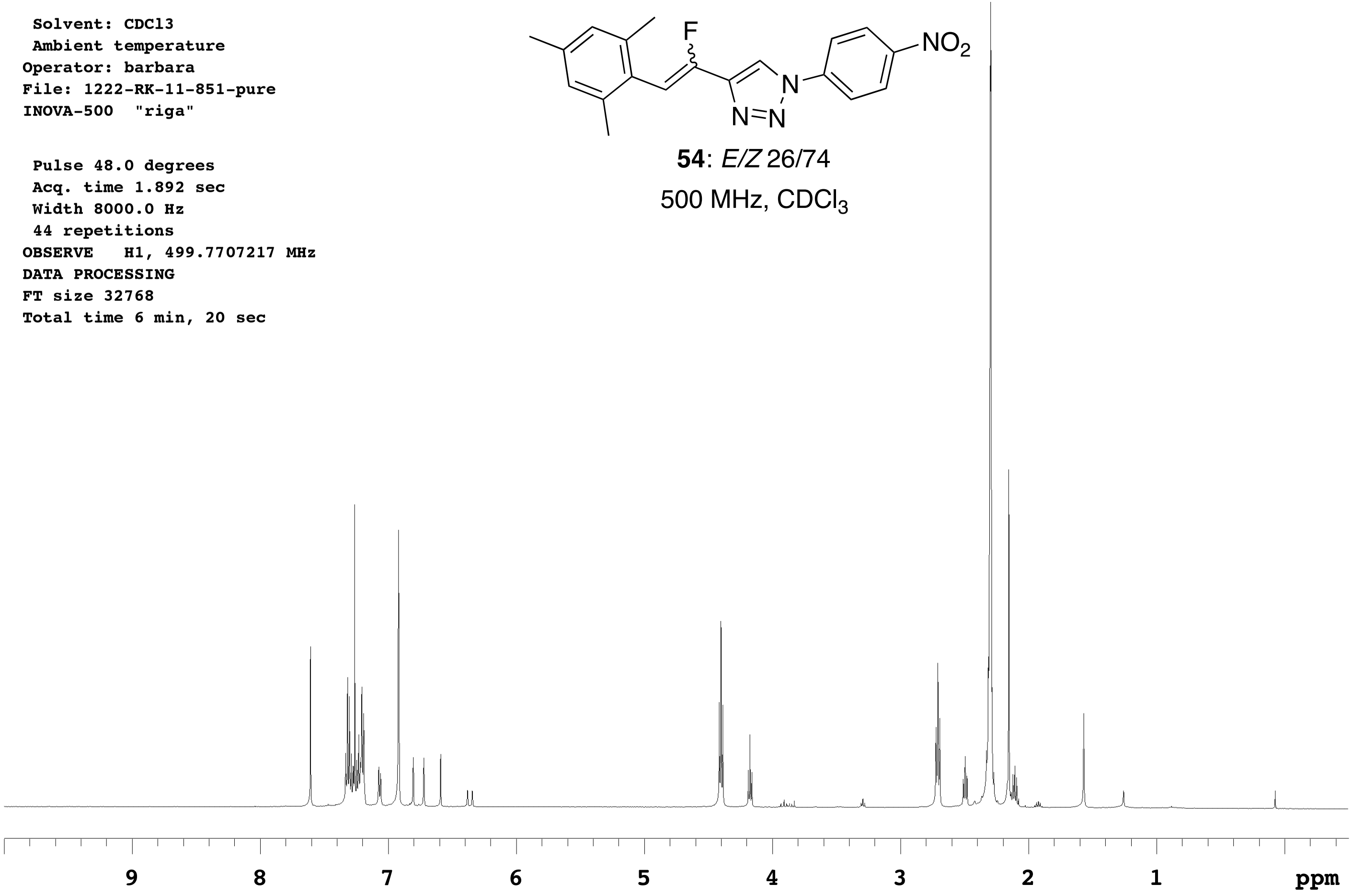
500 MHz, $CDCl_3$



```
1222-RK-11-851-pure

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: barbara
File: 1222-RK-11-851-pure
INOVA-500  "riga"

 Pulse 48.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
OBSERVE   H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 20 sec
```



54: *E/Z* 26/74

500 MHz, $CDCl_3$

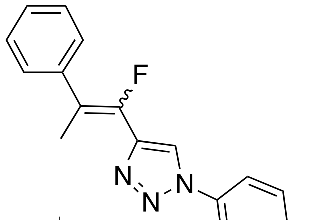
```
1222-RK-05-381-1

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

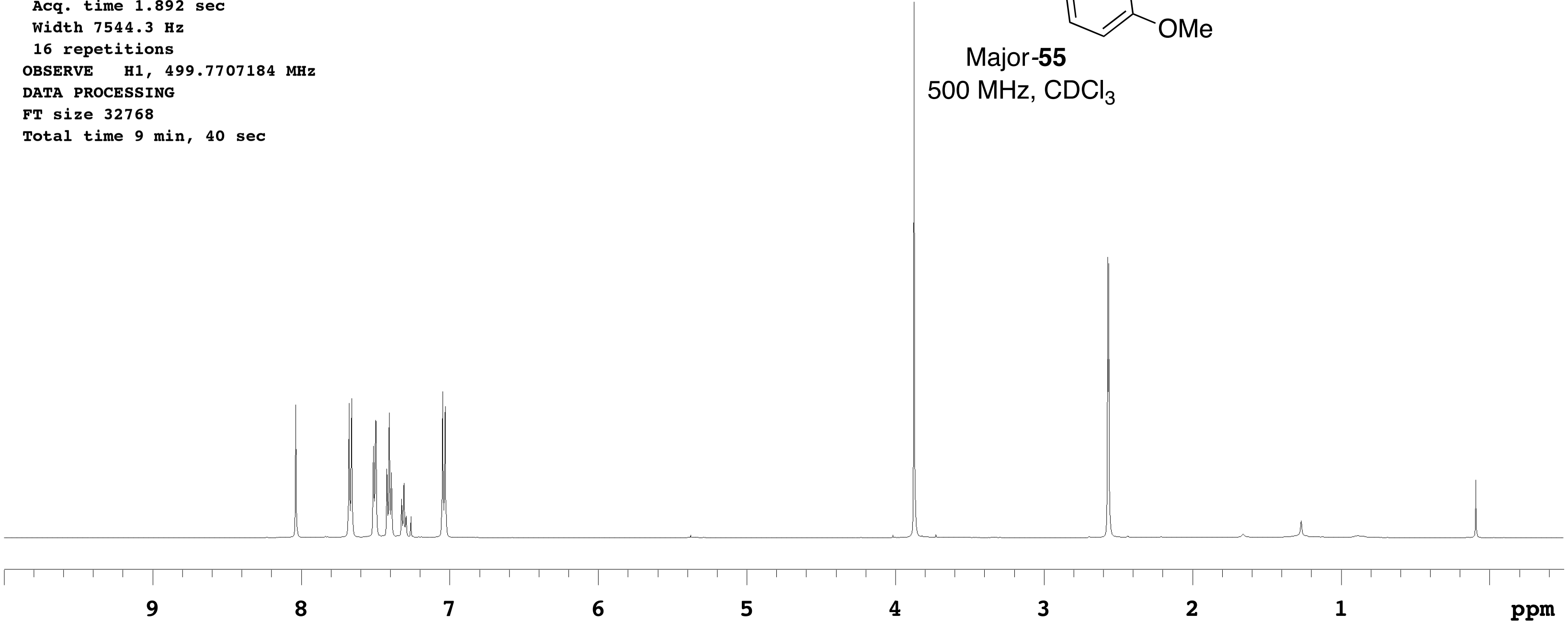
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-05-381-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 16 repetitions
OBSERVE   H1, 499.7707184 MHz
DATA PROCESSING
FT size 32768
Total time 9 min, 40 sec
```



Major-**55**

500 MHz, $CDCl_3$

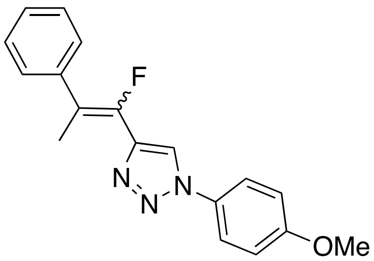


```
1222-RK-05-381-13C

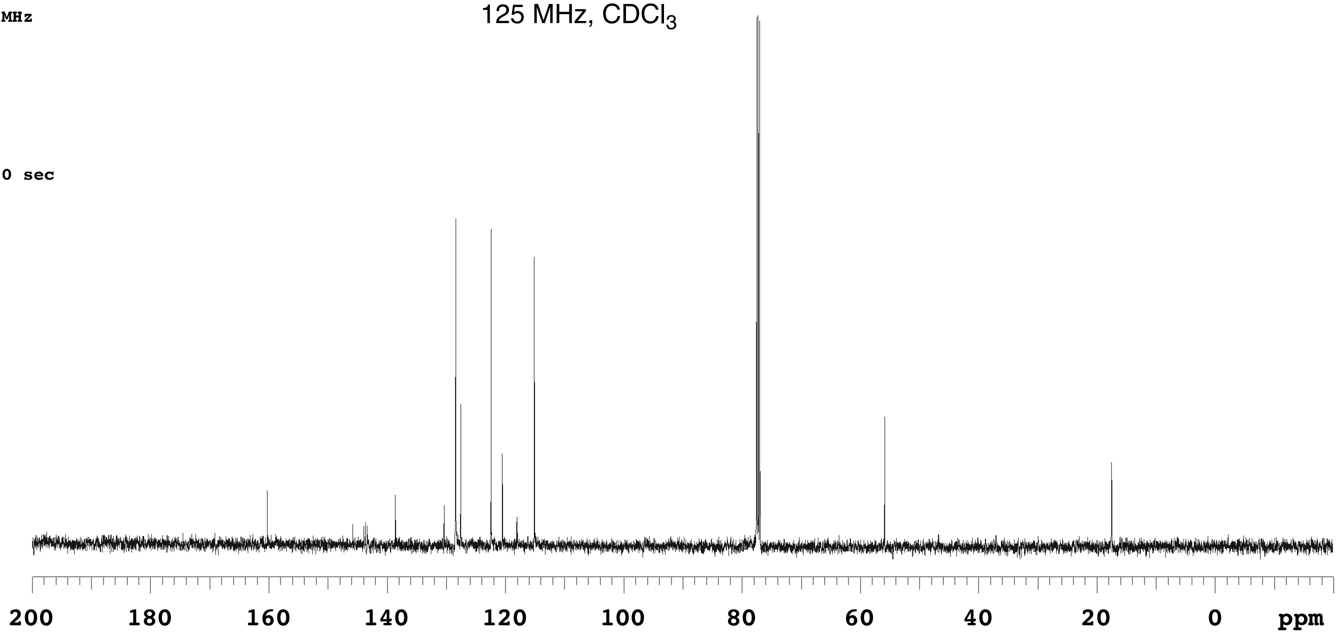
 Archive directory: /export/home/barbara/vnmrsys/data
 Sample directory:

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-05-381-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 176 repetitions
OBSERVE  C13, 125.6674214 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec
```



Major-**55**
125 MHz, $CDCl_3$



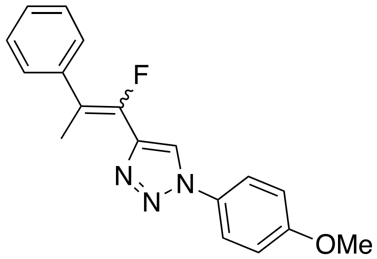
```
1222-RK-05-fraction2

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

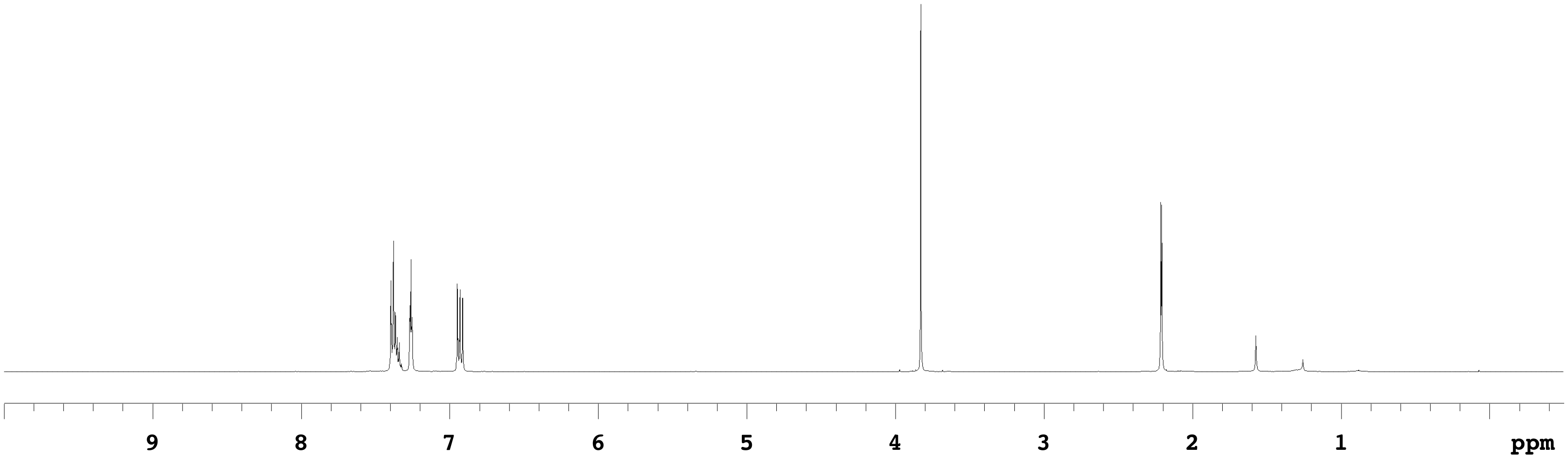
Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-05-381-fraction2
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 20 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
```



Minor-**55**
500 MHz, $CDCl_3$

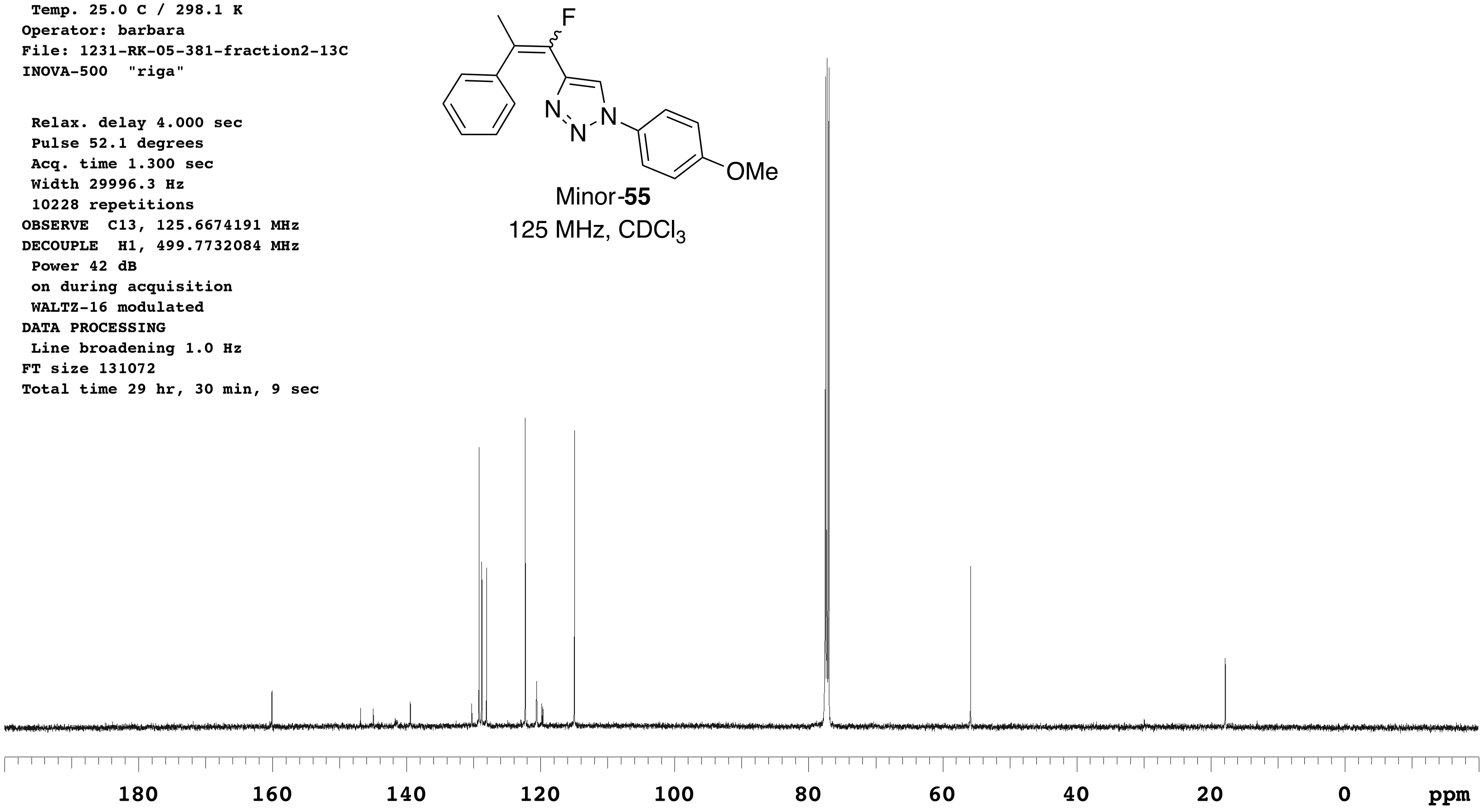


1231-RK-05-381-fraction2-13C

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-05-381-fraction2-13C
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
10228 repetitions
OBSERVE C13, 125.6674191 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 29 hr, 30 min, 9 sec



Minor-**55**
125 MHz, $CDCl_3$

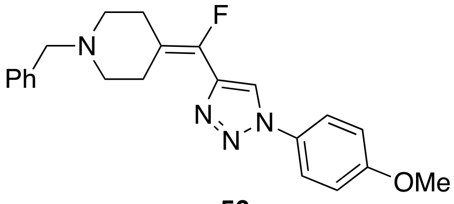
```
1222-RK-05-392-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

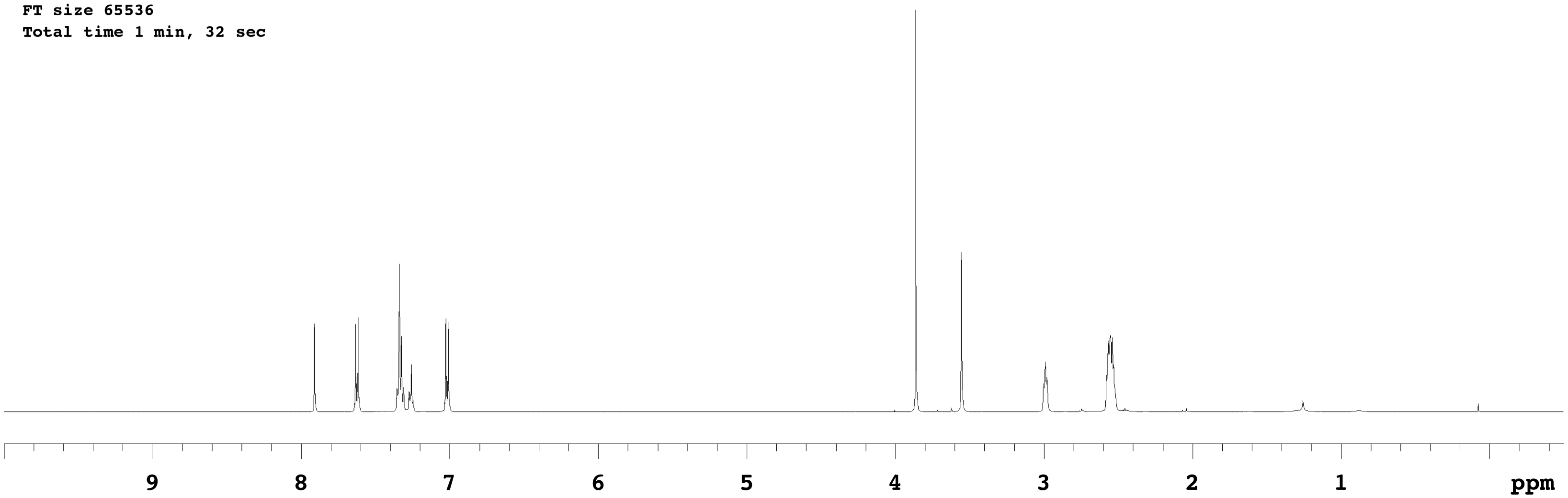
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-05-392-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 16 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 1 min, 32 sec
```



56

500 MHz, $CDCl_3$



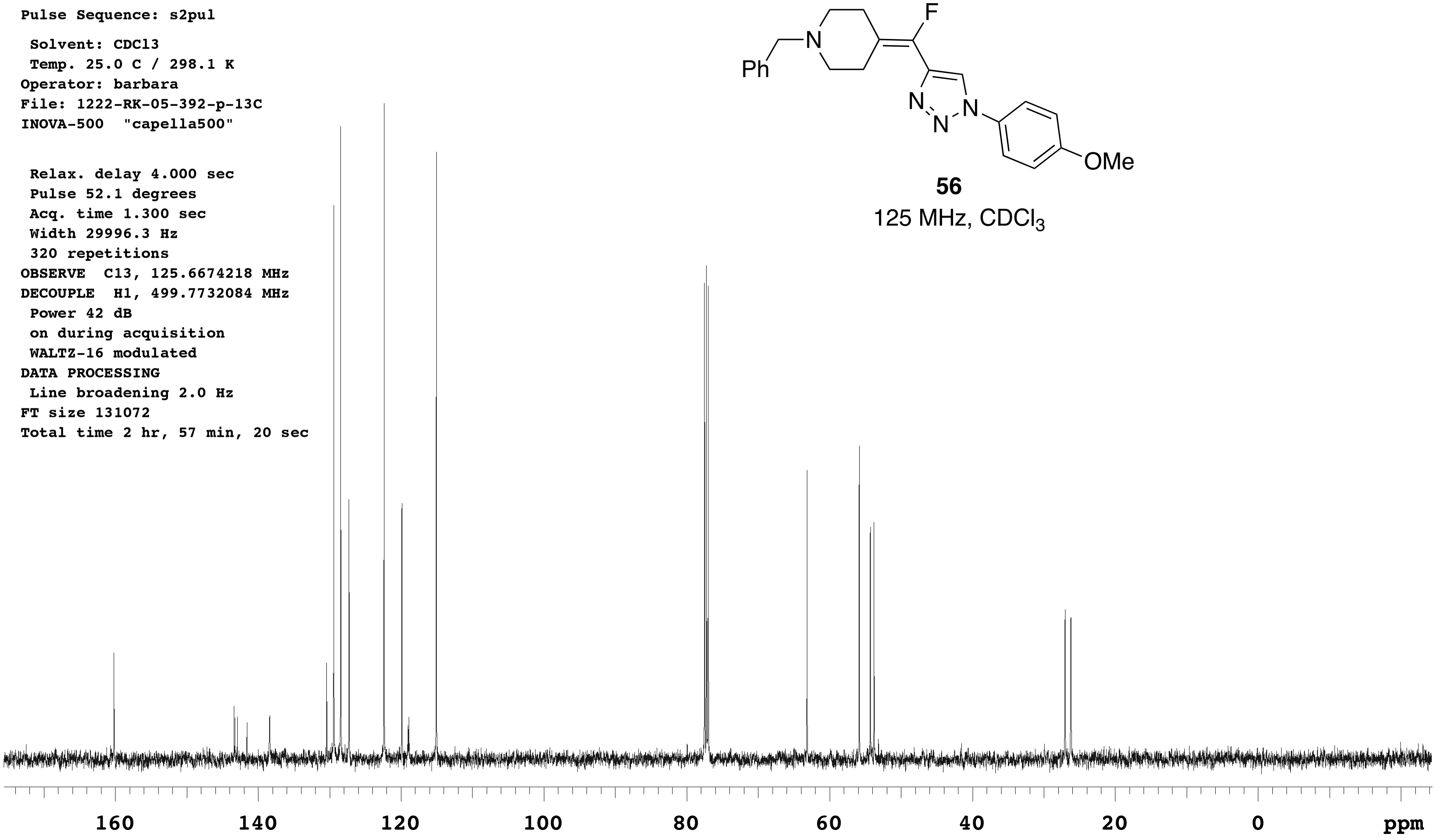
1222-RK-05-392-p-13C

Archive directory: /export/home/barbara/vnmrsys/data
File: 1222-RK-05-392-p-13C

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-05-392-p-13C
INOVA-500 "capella500"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
320 repetitions
OBSERVE C13, 125.6674218 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec



56

125 MHz, $CDCl_3$

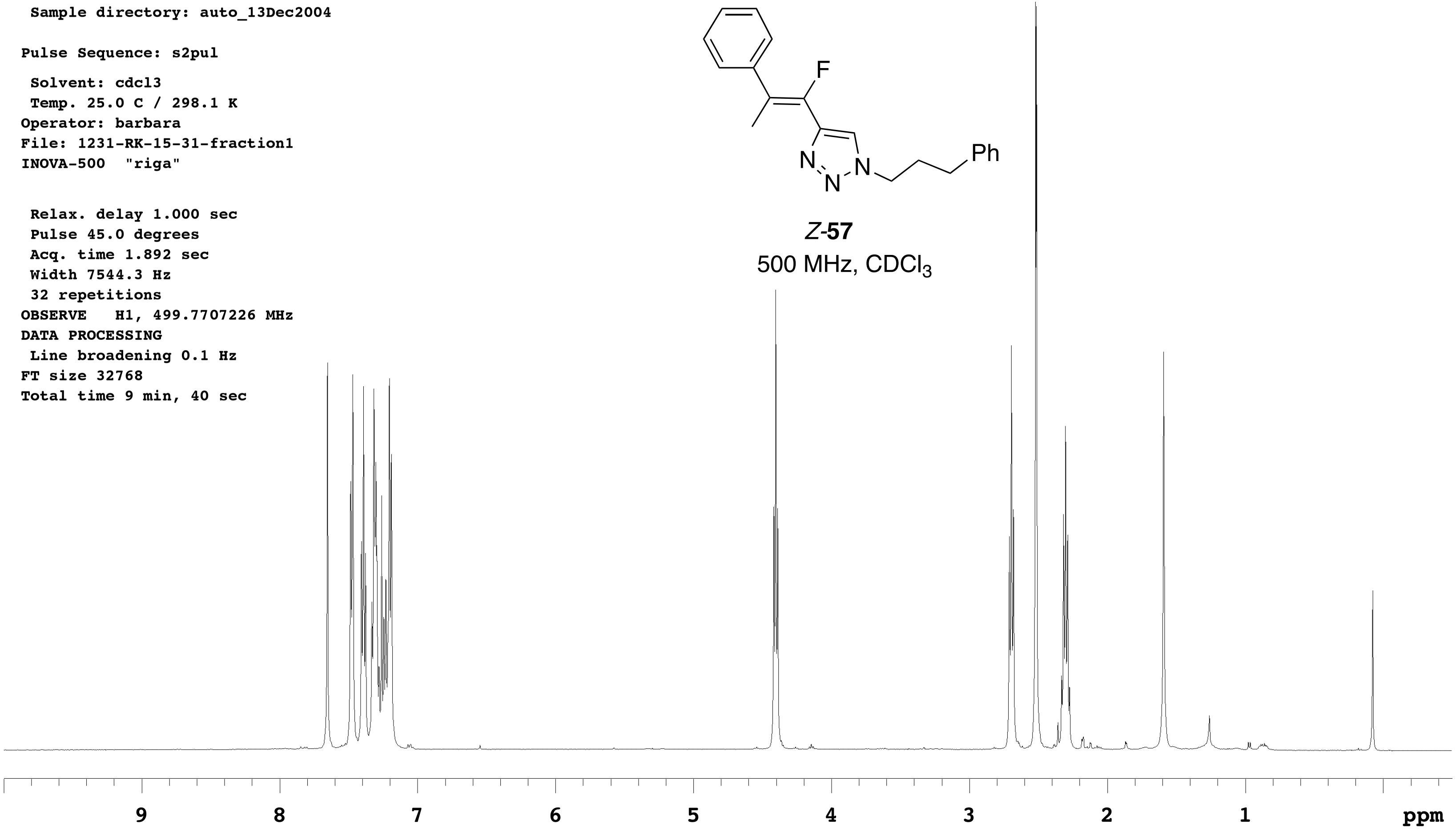
```
1231-RK-15-31-fraction1

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-31-fraction1
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 32 repetitions
OBSERVE   H1, 499.7707226 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



Z-**57**

500 MHz, $CDCl_3$

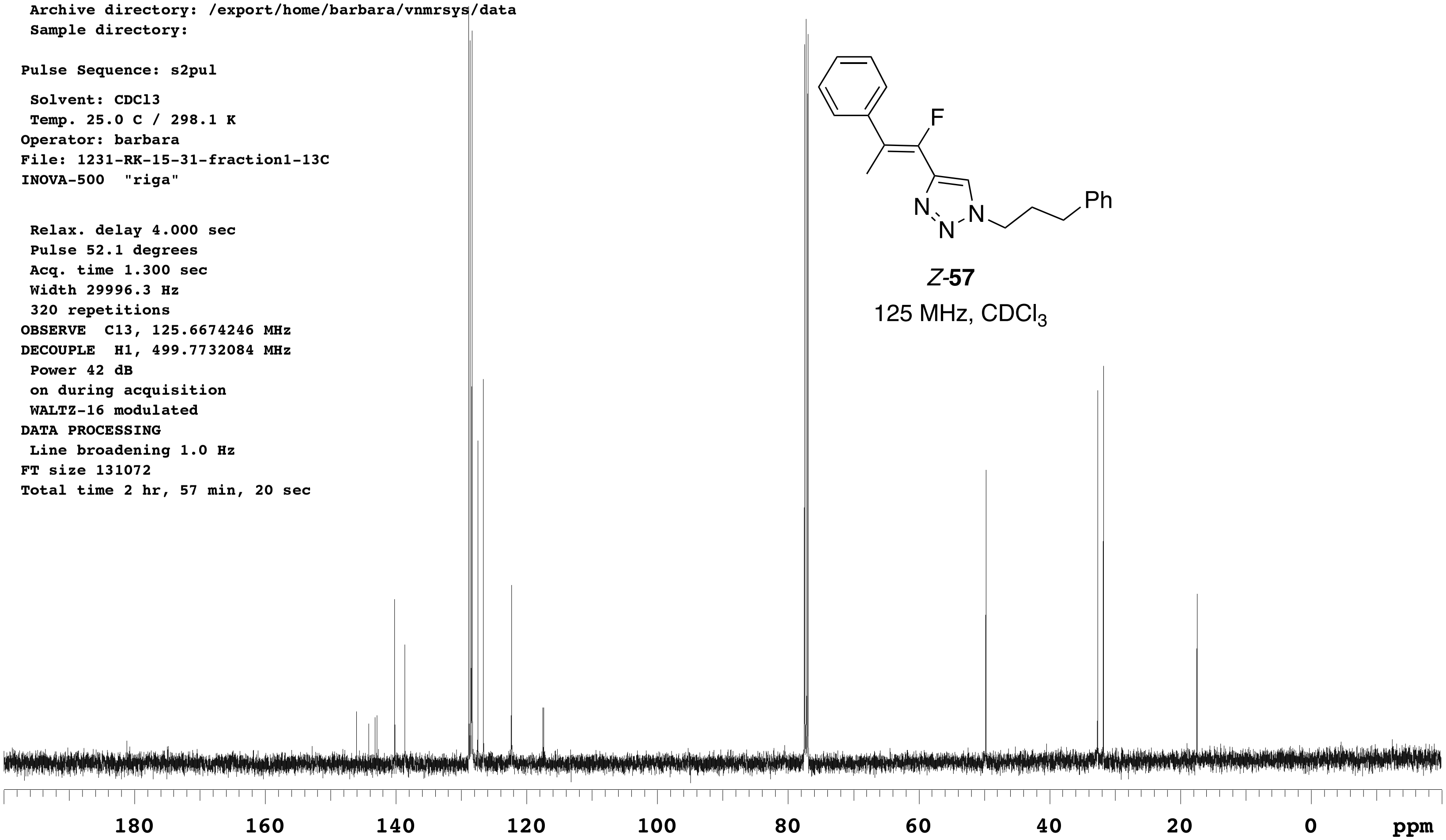
```
1231-RK-15-31-fraction1-13C

 Archive directory: /export/home/barbara/vnmrsys/data
 Sample directory:

Pulse Sequence: s2pul

 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-31-fraction1-13C
INOVA-500  "riga"


 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 320 repetitions
OBSERVE  C13, 125.6674246 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec
```



Z-**57**

125 MHz, $CDCl_3$

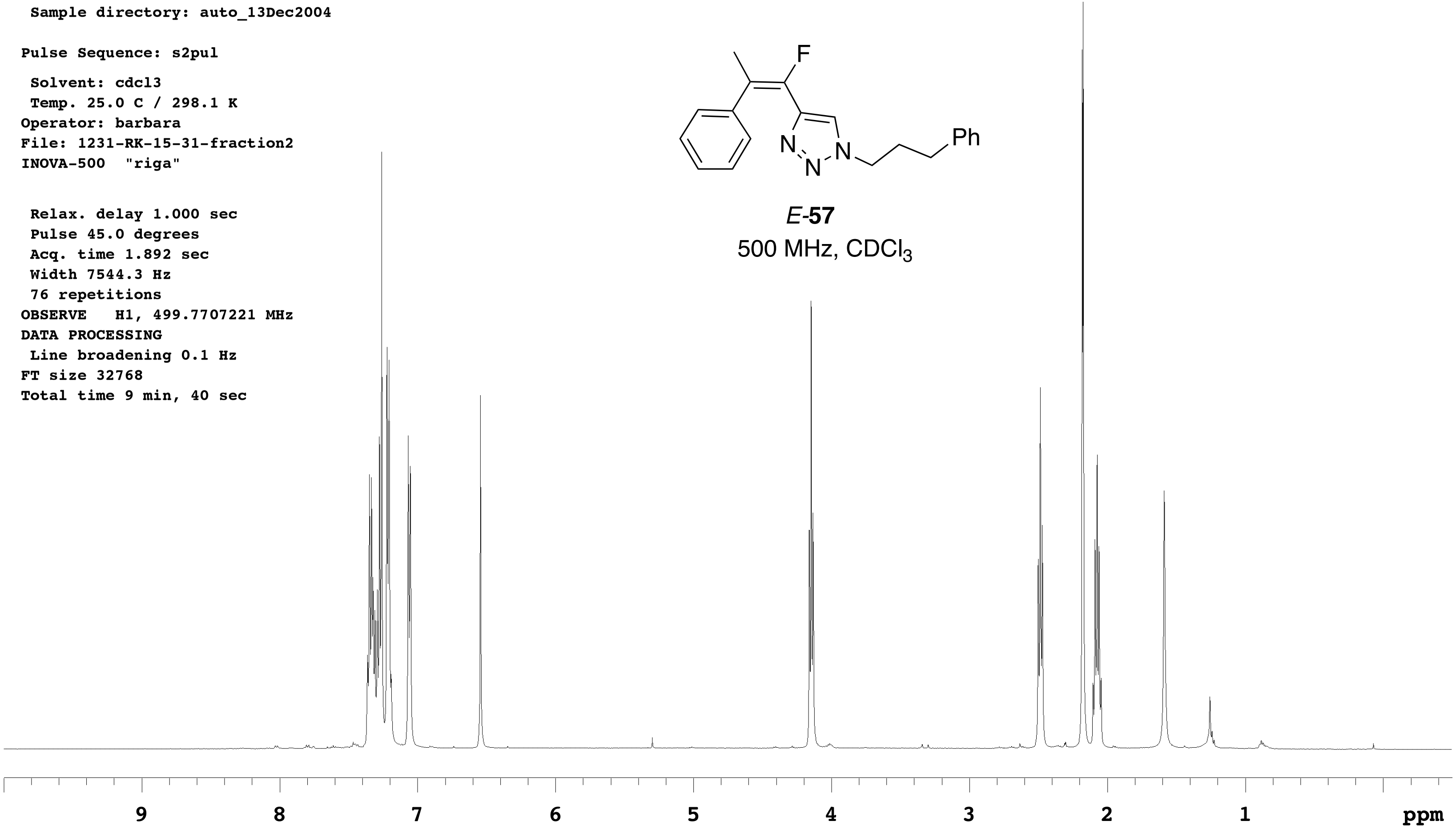
1231-RK-15-31-fraction2

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-31-fraction2
INOVA-500 "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 76 repetitions
OBSERVE   H1, 499.7707221 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec



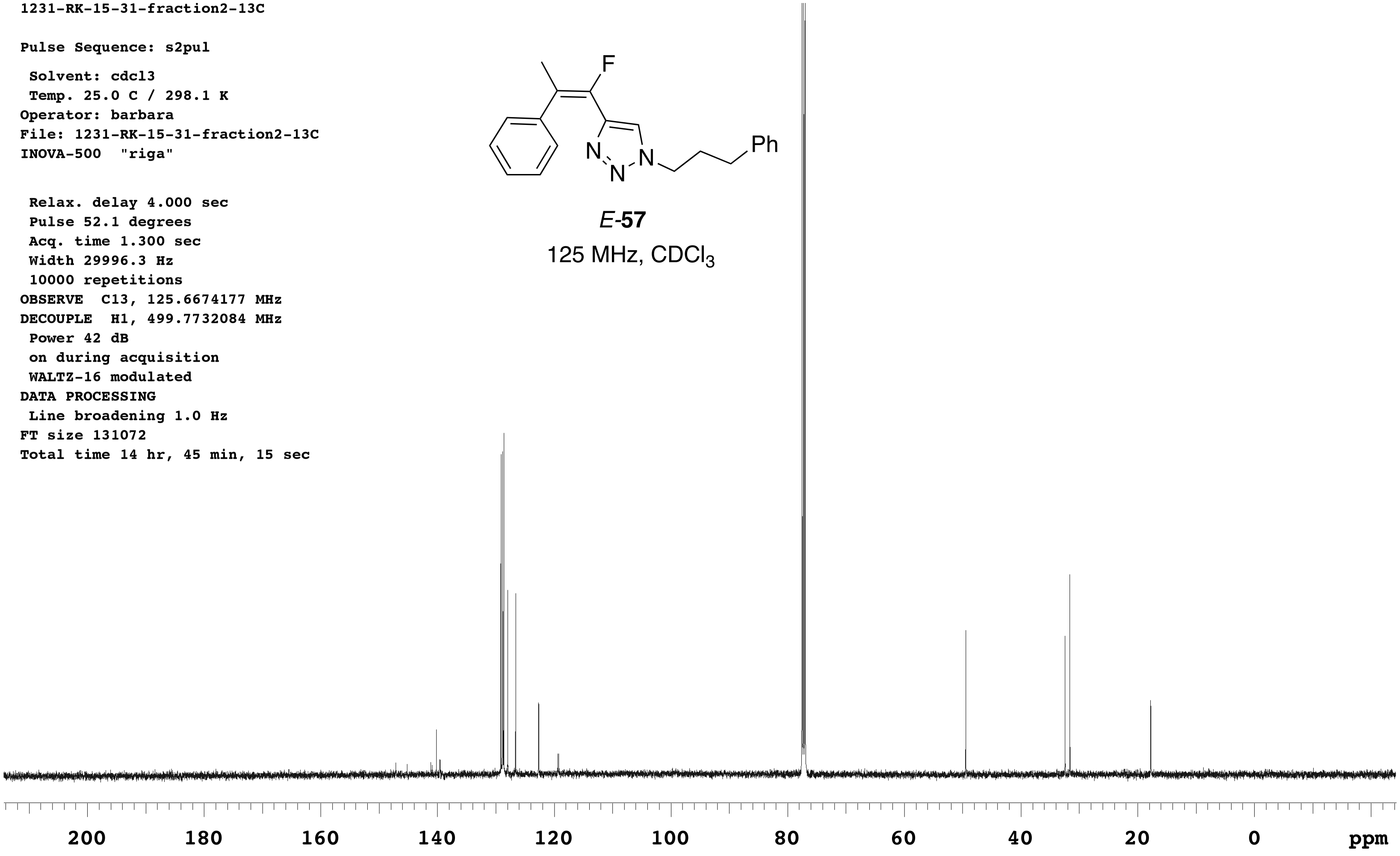
E-**57**
500 MHz, $CDCl_3$

1231-RK-15-31-fraction2-13C

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-31-fraction2-13C
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
10000 repetitions
OBSERVE C13, 125.6674177 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 14 hr, 45 min, 15 sec



E-**57**

125 MHz, $CDCl_3$

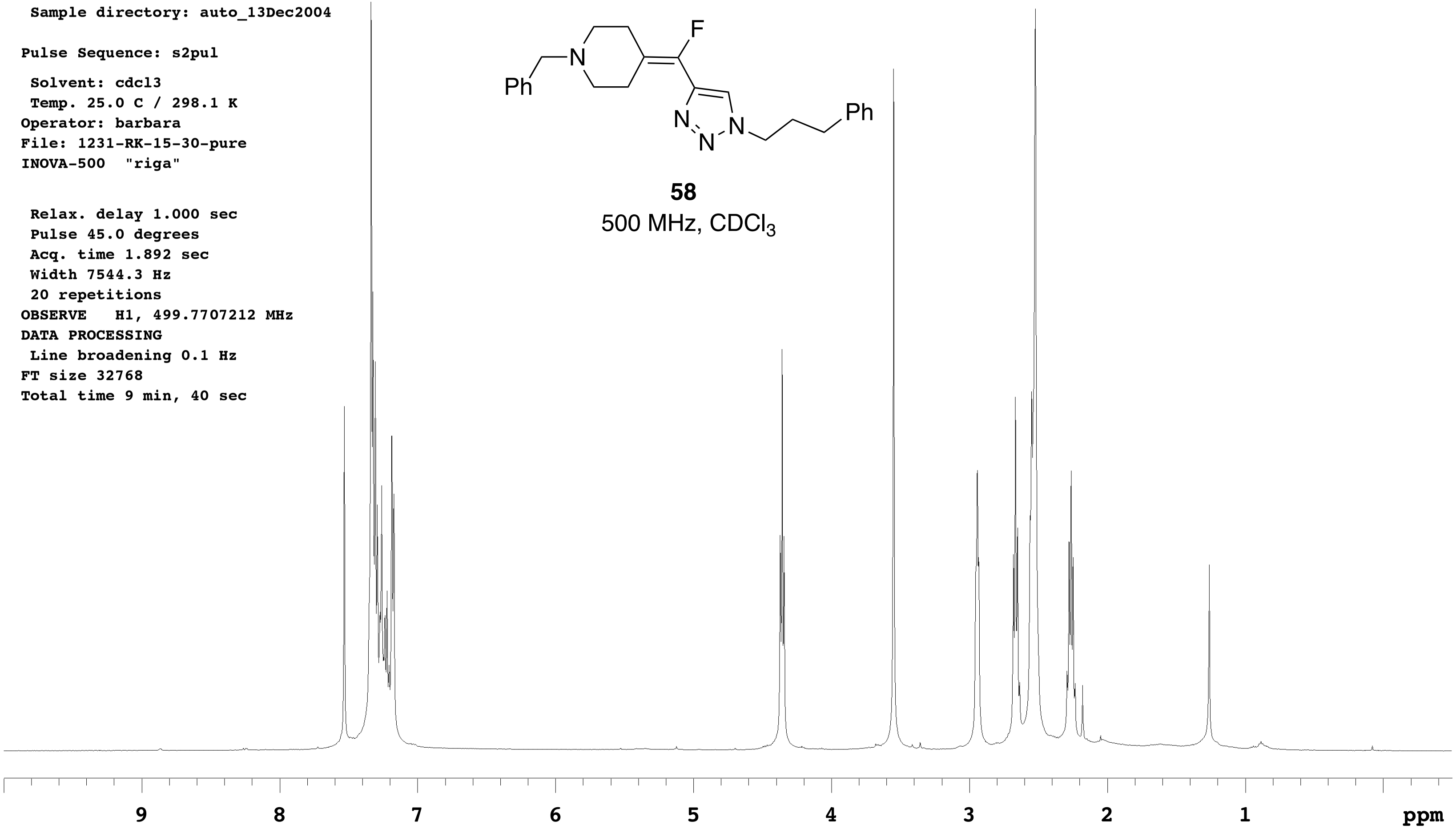
```
1231-RK-15-30-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-30-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 20 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



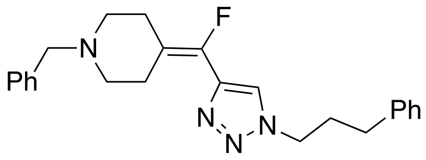
58

500 MHz, $CDCl_3$

```
1231-Rk-15-30-13C

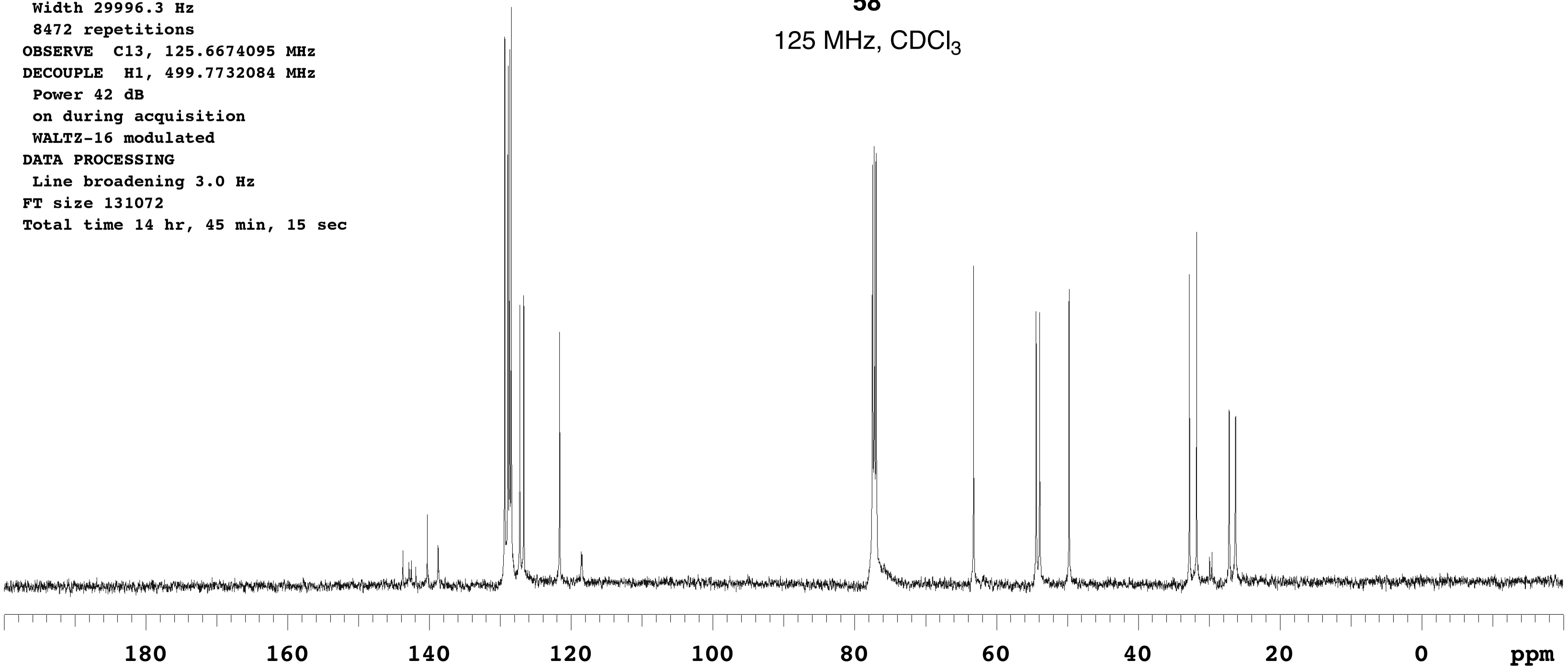
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-Rk-15-30-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 8472 repetitions
OBSERVE  C13, 125.6674095 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 3.0 Hz
FT size 131072
Total time 14 hr, 45 min, 15 sec
```



58

125 MHz, $CDCl_3$

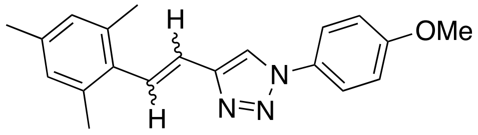


```
1222-RK-06-480-cdcl3

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

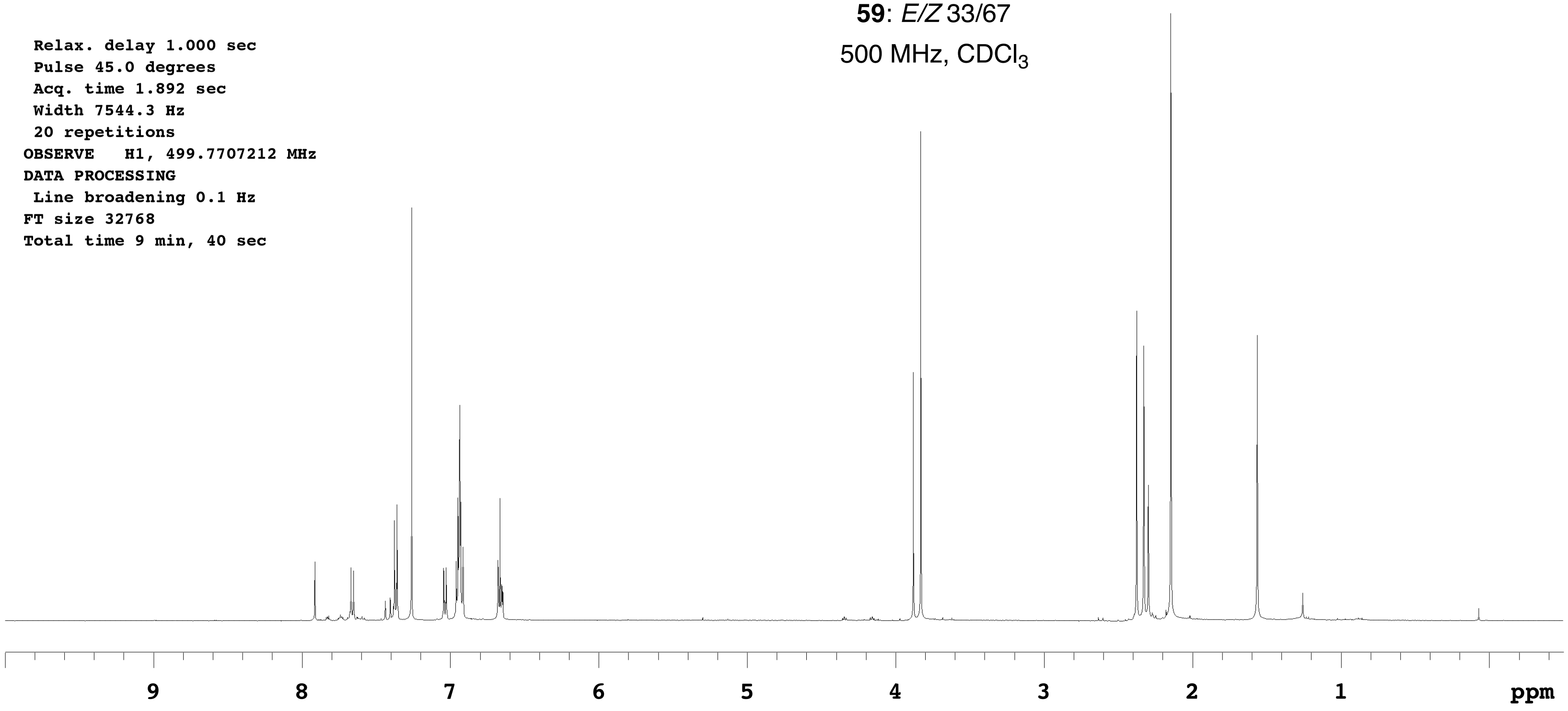
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-06-480-cdcl3
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 20 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



59: *E*/*Z* 33/67

500 MHz, $CDCl_3$



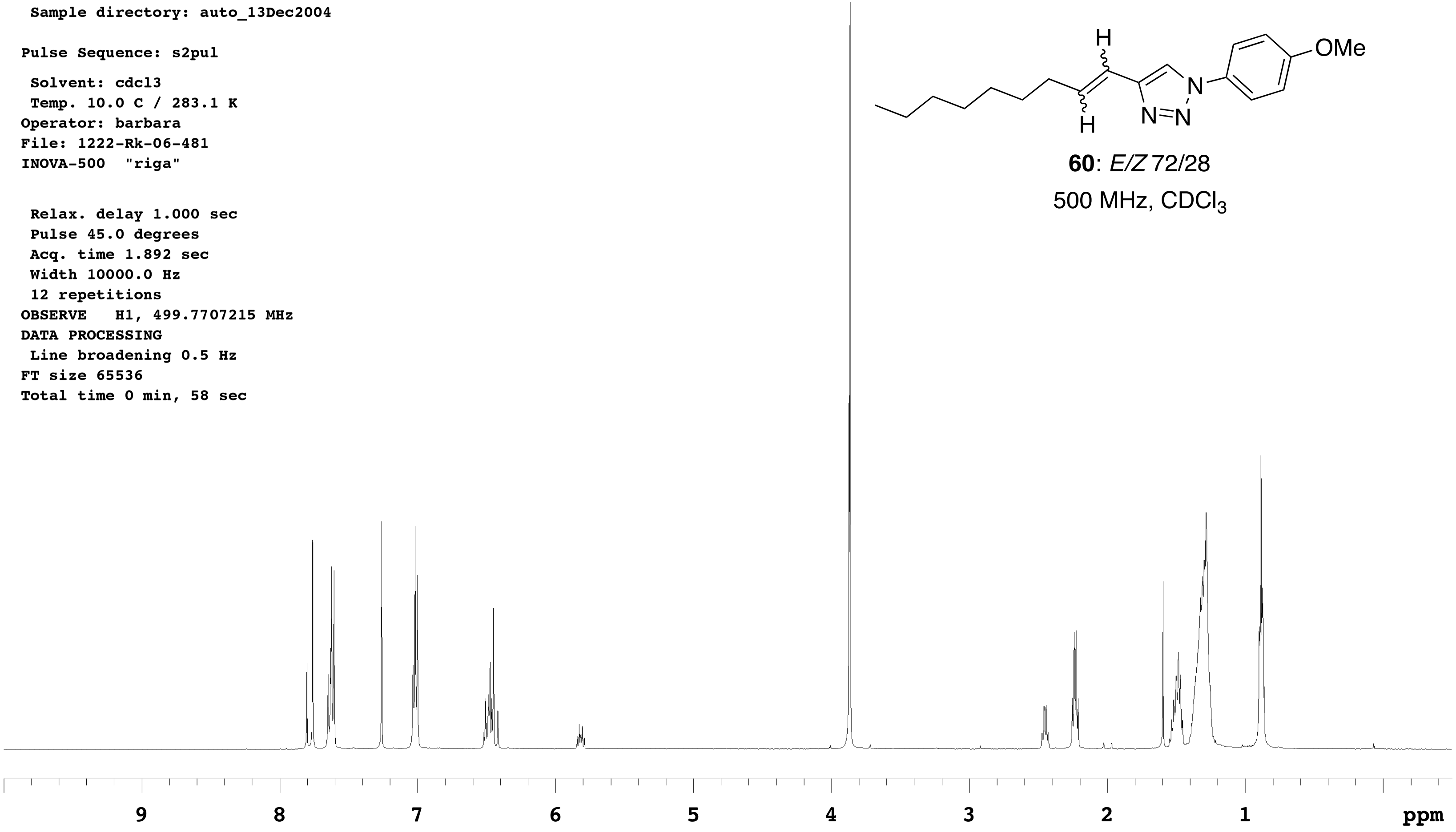
```
1222-Rk-06-481

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 10.0 C / 283.1 K
Operator: barbara
File: 1222-Rk-06-481
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 12 repetitions
OBSERVE   H1, 499.7707215 MHz
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 0 min, 58 sec
```



60: *E/Z* 72/28

500 MHz, $CDCl_3$

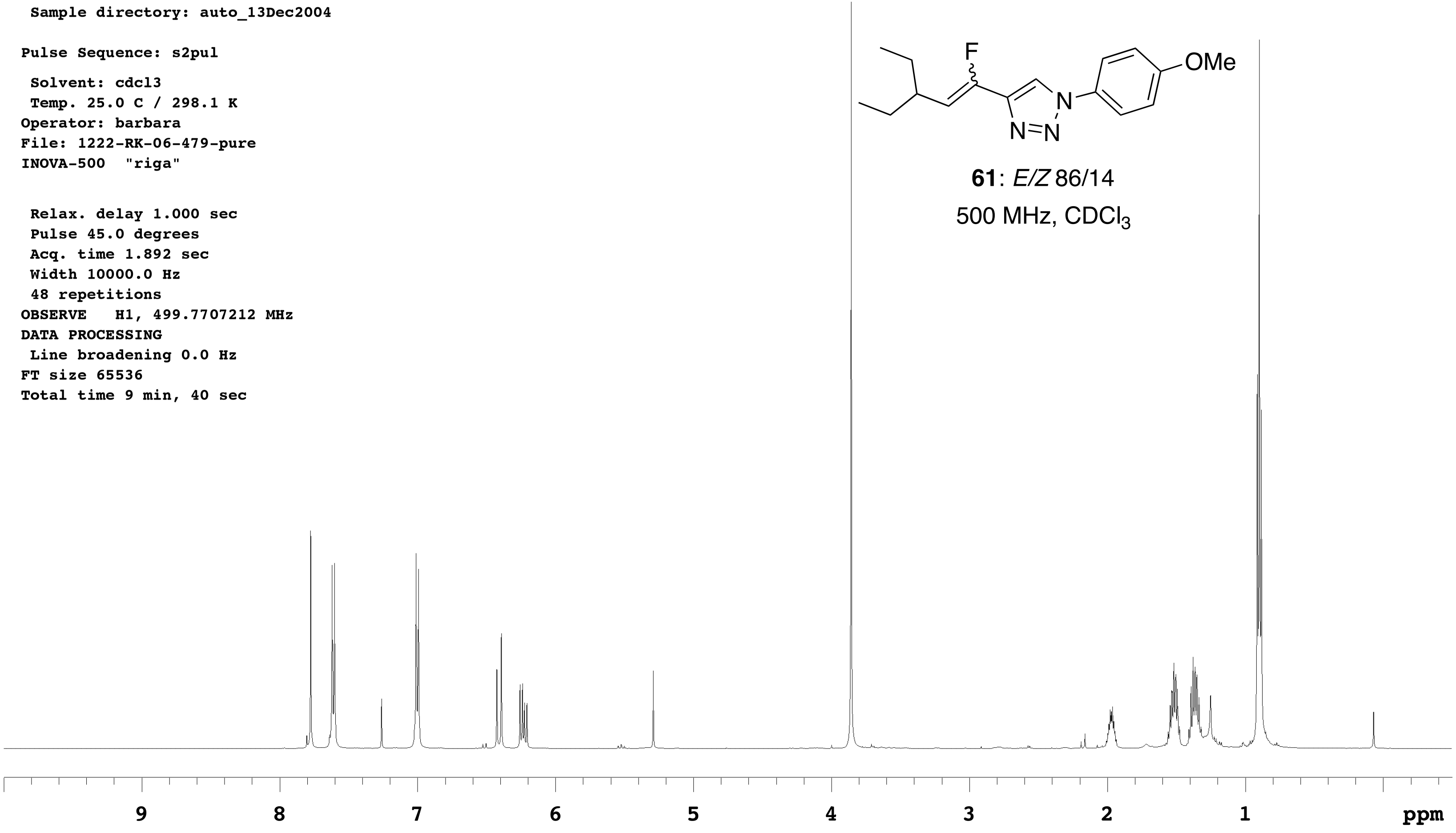
```
1222-RK-06-479-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-06-479-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 48 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.0 Hz
FT size 65536
Total time 9 min, 40 sec
```



61: *E/Z* 86/14

500 MHz, $CDCl_3$

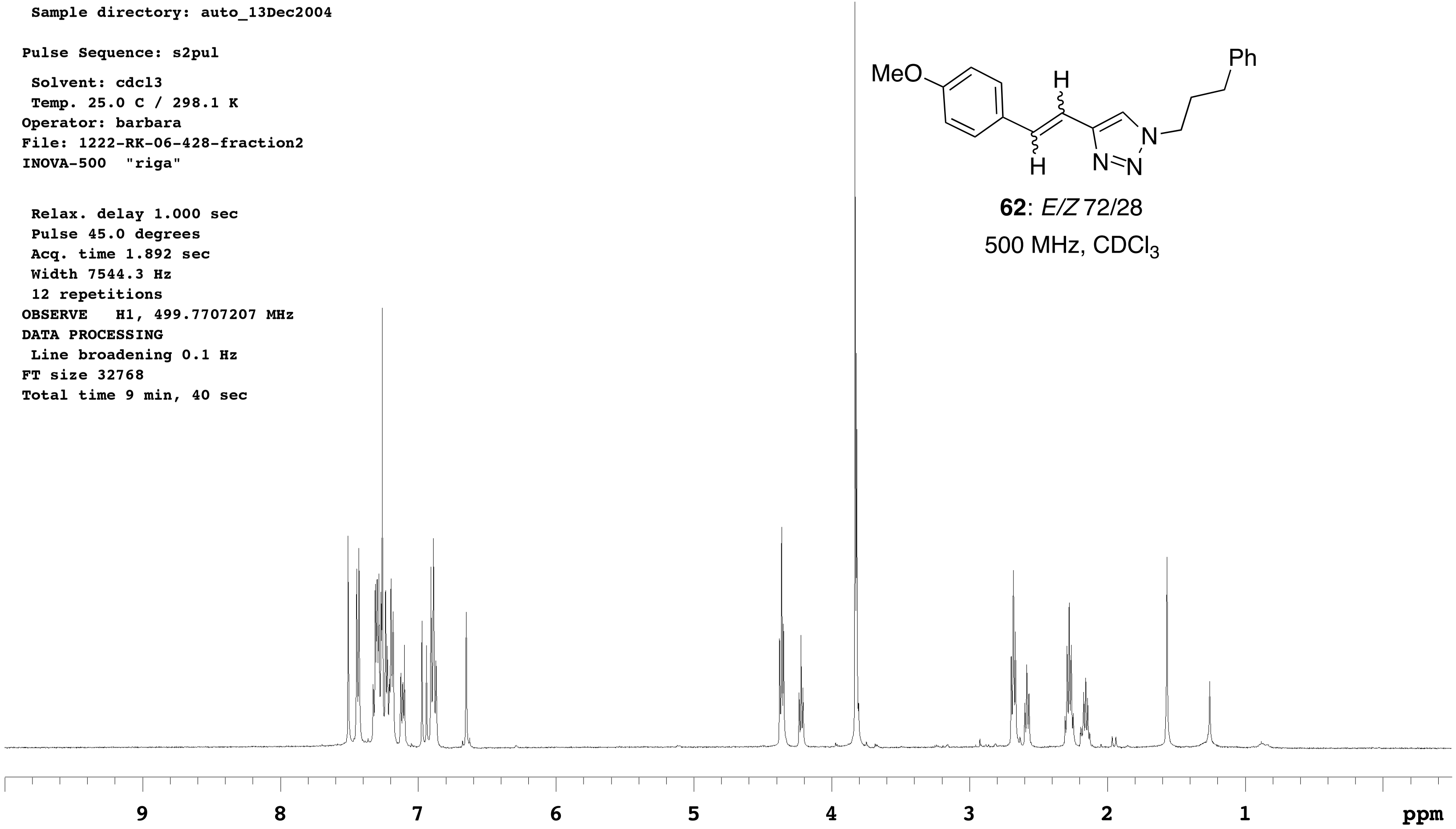
```
1222-RK-06-428-fraction2

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

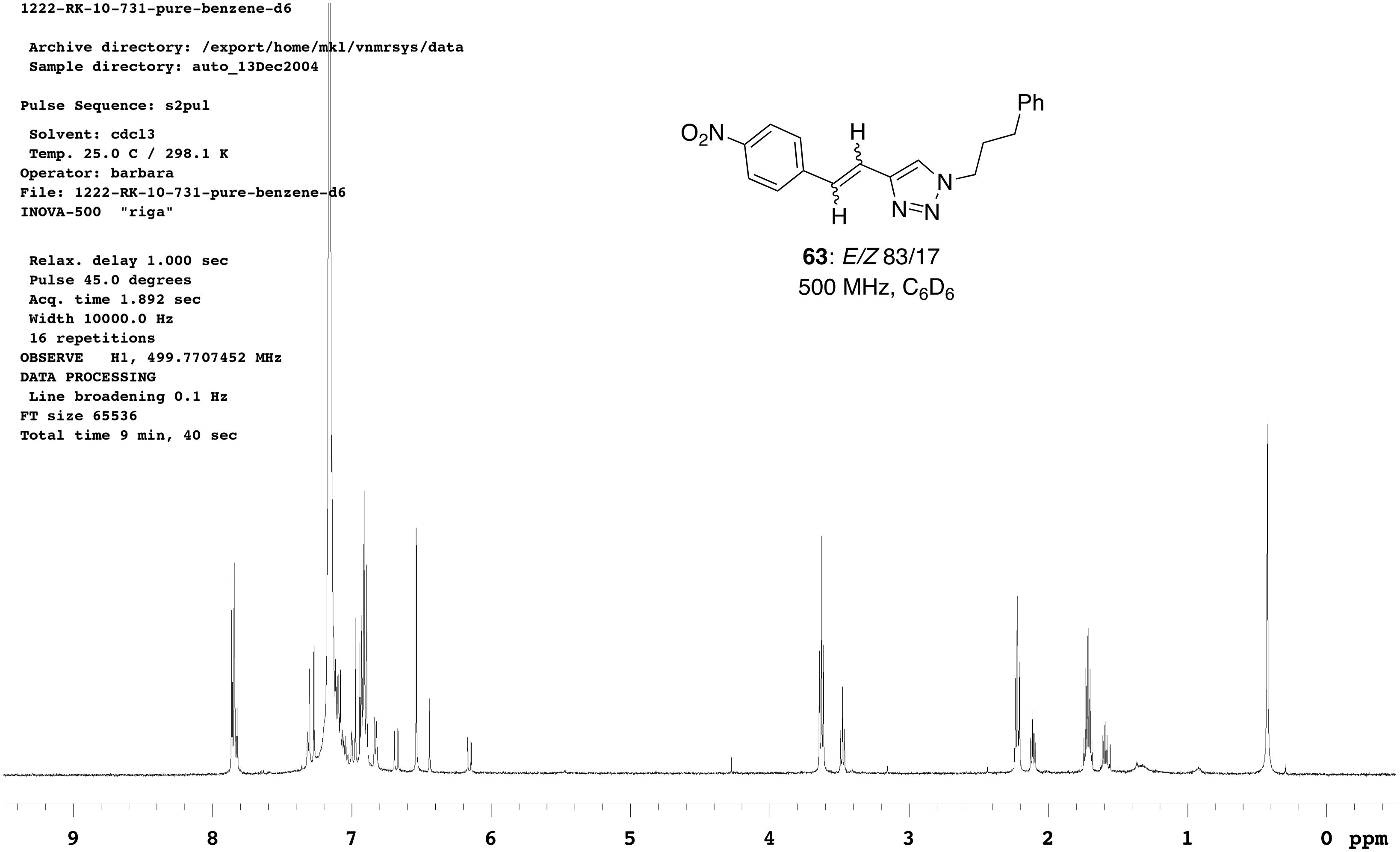
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-06-428-fraction2
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 12 repetitions
OBSERVE   H1, 499.7707207 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



62: *E/Z* 72/28

500 MHz, $CDCl_3$



```
1222-RK-10-731-pure-benzene-d6

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-10-731-pure-benzene-d6
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 16 repetitions
OBSERVE   H1, 499.7707452 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
```

63: *E/Z* 83/17
500 MHz, C_6D_6

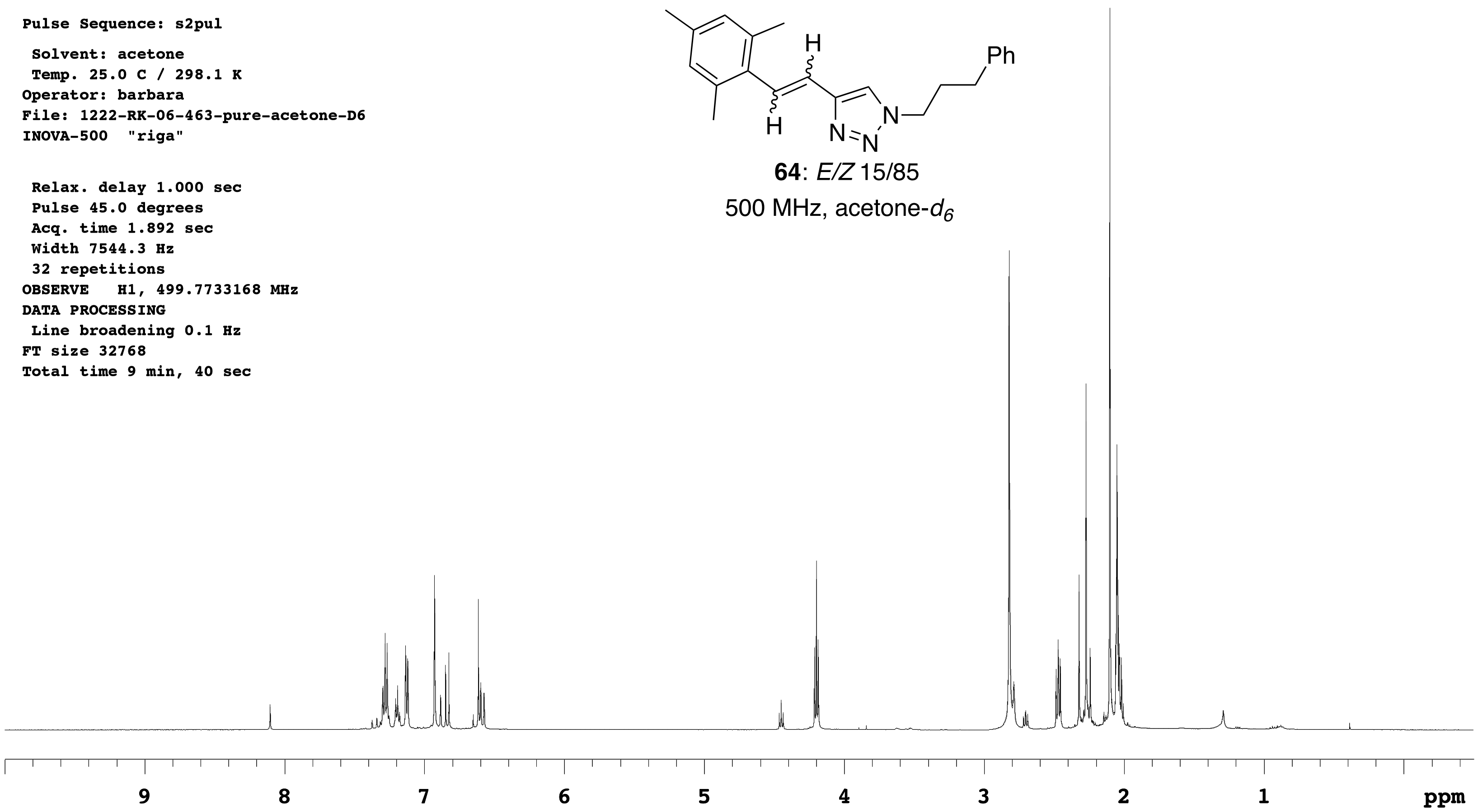
```
1222-RK-06-463-pure-1cetone-D6

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: acetone
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-06-463-pure-acetone-D6
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 32 repetitions
OBSERVE   H1, 499.7733168 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



64: *E/Z* 15/85

500 MHz, acetone-d_6

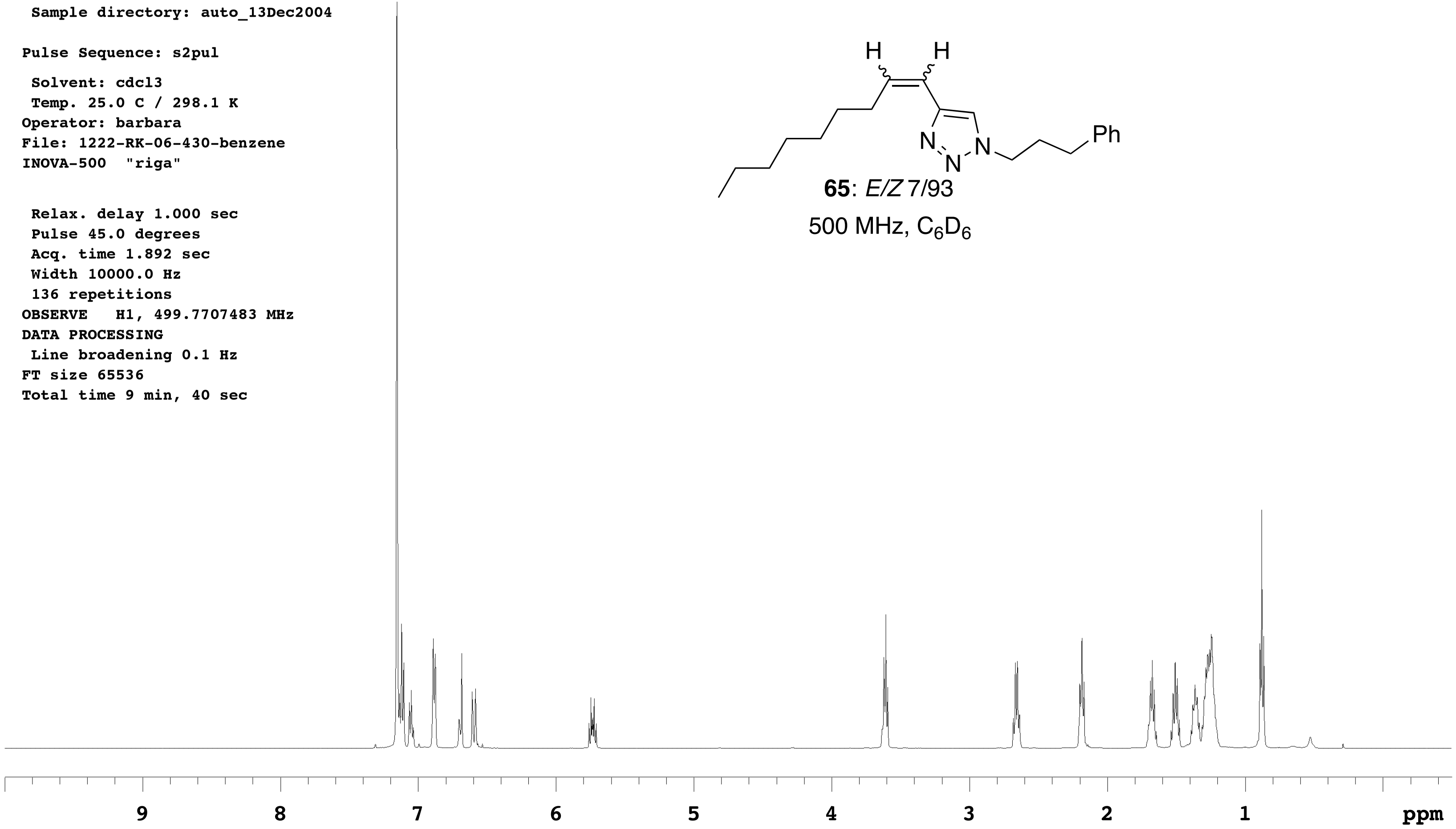
```
1222-RK-06-430-benzene

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-06-430-benzene
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 136 repetitions
OBSERVE   H1, 499.7707483 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
```



65: *E/Z* 7/93

500 MHz, C_6D_6

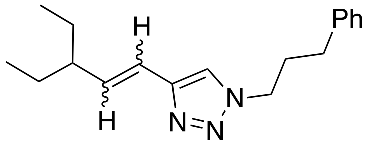
```
1222-RK-06-433-1stfraction

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

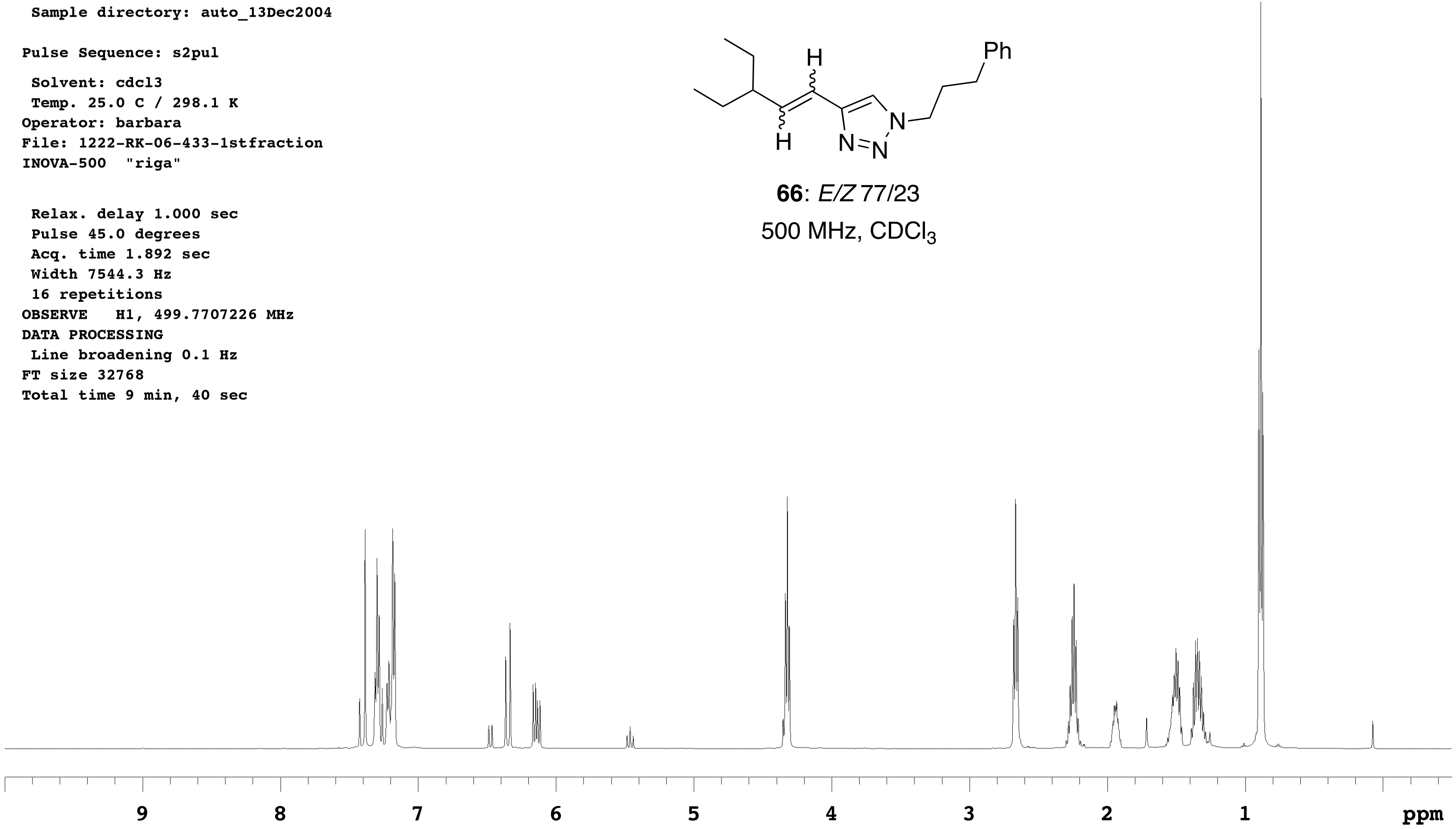
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-06-433-1stfraction
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 16 repetitions
OBSERVE   H1, 499.7707226 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



66: *E/Z* 77/23

500 MHz, $CDCl_3$



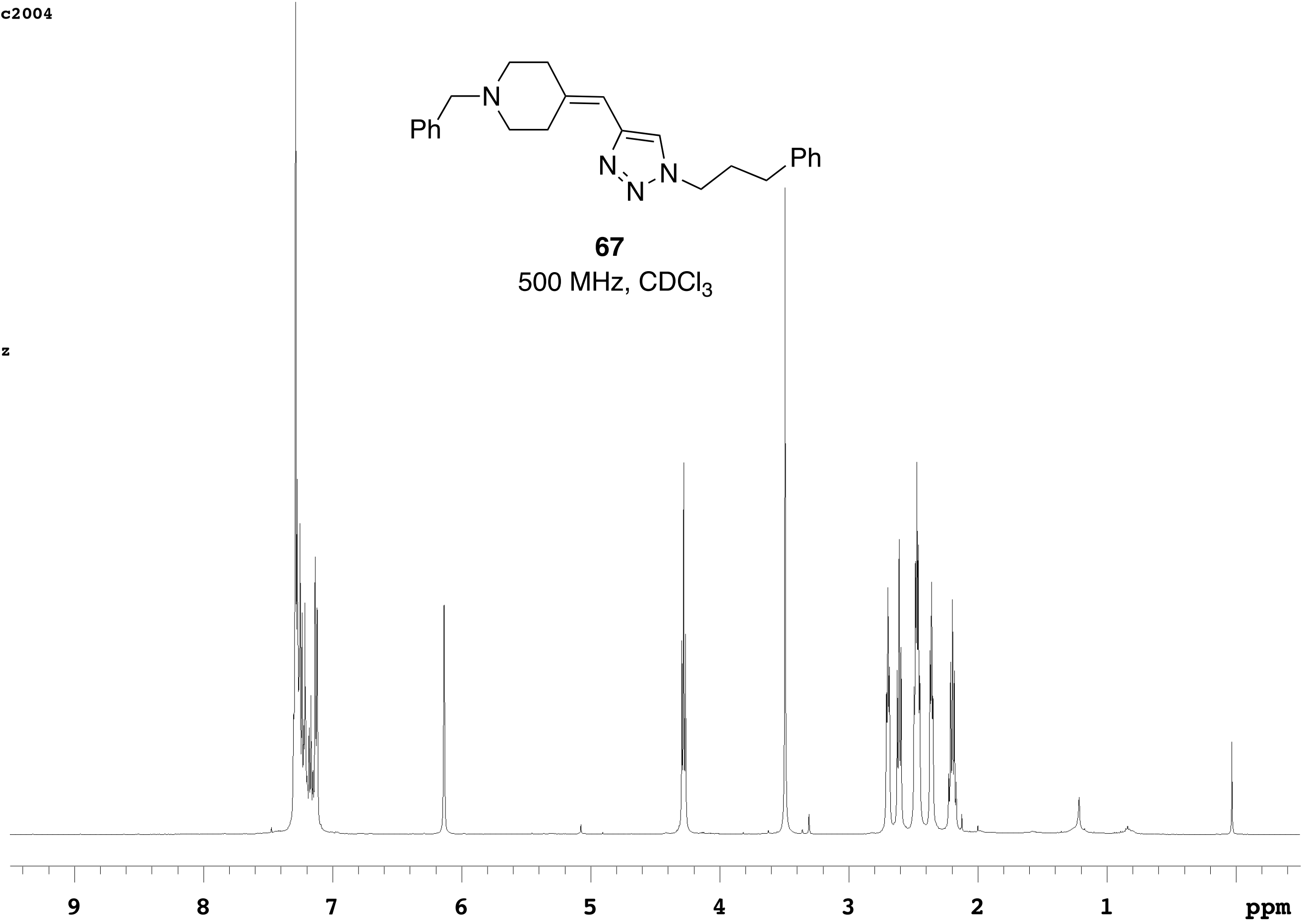
```
1222-RK-10-734-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-10-734-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 20 repetitions
OBSERVE   H1, 499.7707452 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
```



67

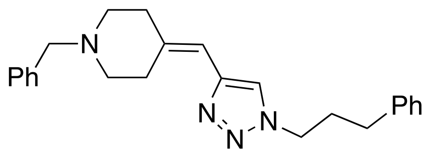
500 MHz, $CDCl_3$

1222-RK-10-734-13C

Pulse Sequence: s2pul

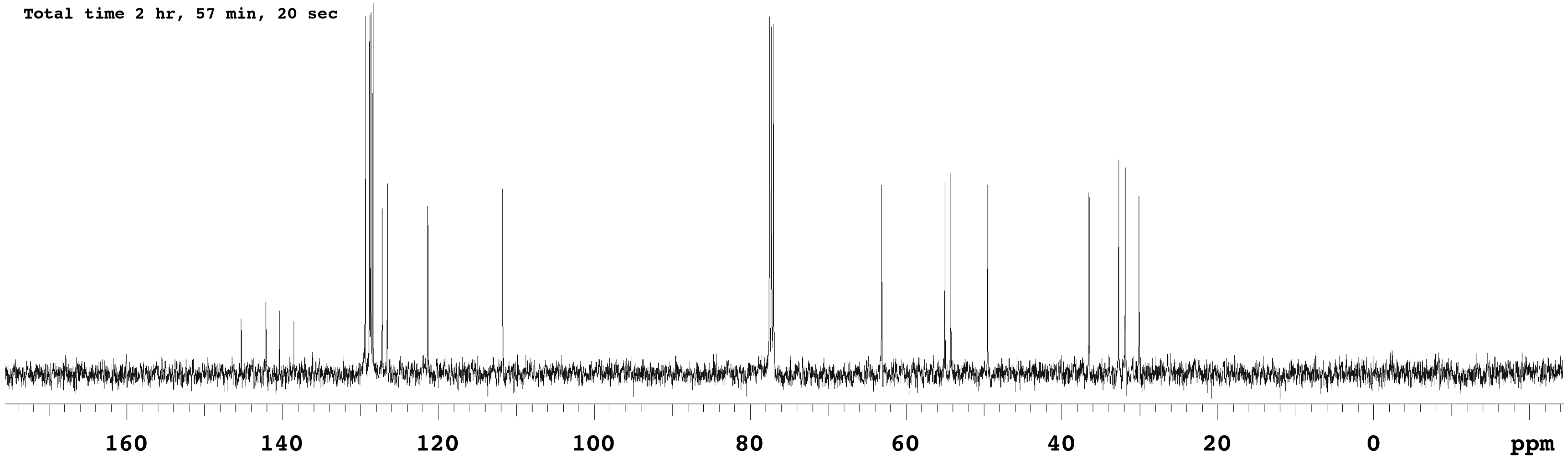
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-10-734-13C
INOVA-500 "capella500"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
120 repetitions
OBSERVE C13, 125.6674232 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec



67

125 MHz, $CDCl_3$

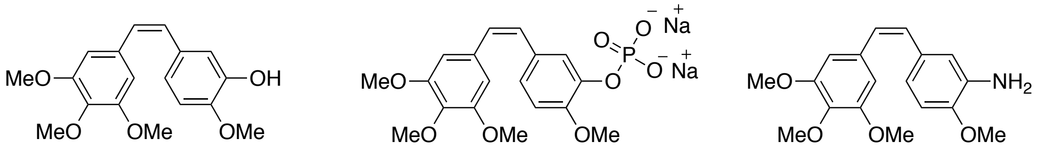


PART 3

SYNTHESIS OF TRIAZOLE-BASED COMBRETASTATIN ANALOGS AND EVALUATION OF THEIR BIOLOGICAL ACTIVITY

3.1 INTRODUCTION

Combretastatins are a class of stilbene like compounds that have potent antitumor activity.[1-4] Among the various members of this family, combretastatin A-4 (**1**, shown in Figure 1) is the structurally simplest and the most potent antitumor agent that has cytotoxicity against various cancer cell lines, including multi-drug resistant cancer cell lines, and has an ability to inhibit tubulin polymerization.[1-4]



Combretastatin A-4
1

Dipotassium salt of combretastatin A-4
2

Amino-derivative of combretastatin A-4
3

Figure 1. Combretastatin A-4 and its prodrug analogs.

Combretastatin A-4 (CA-4) **1**, was originally isolated from the South African tree *Combretum caffrum* by Pettit et al.[5] Although this compound is the most potent among the combretastatin family, one of the major problems associated with using it as a drug is its poor water solubility. To overcome this problem, various combretastatin analogs have been synthesized[1-5] and the disodium salt[6] of CA-4 (**2**) shown in Figure 1, is in the clinical trials as prodrug.[8] Amino derivative **3**[7] (shown in Figure 1), another potent anti-tumor analog that has higher water solubility than CA-4 (1),[1] is also in the clinical trials.[8]

Molecular structures of this class of compounds can be viewed as comprised of three parts, i.e. two substituted aromatic rings (**A** and **B)**, and a bridge connecting the two rings as shown in Figure 2. The activity of combretastatins depends upon various factors, such as types of the aromatic of the rings and the nature of their substituents, shape and stereochemistry of the bridge connecting the rings, etc. Structure-activity relationship studies have shown that the compounds with the *cis* arrangement of the two aryl rings are more active than the *trans* ones (Figure 2).[1,8,9]

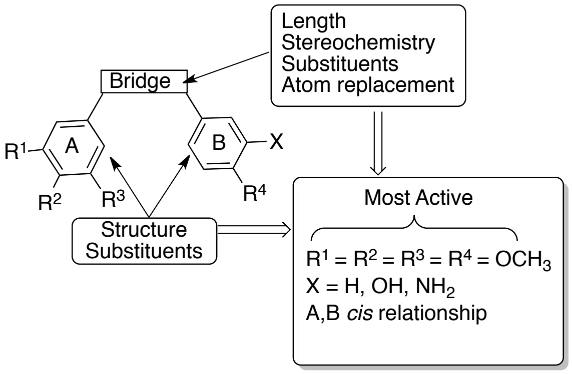


Figure 2. SAR studies of various combretastatin analogs.

Three methoxy substituents in ring **A** are suggested to be important for the cytotoxicity of these compounds.[1,8,9] However, 3-halo- substituted analogs **4a-c** (shown in Figure 3) showed cytotoxicity that was comparable to that of CA-4 (**1**).[10] The presence of *p*-methoxy substituent in ring **B** was found to be critical for the activity. Some other analogs heteroatom-containing substituent in *para* posision, or with heteroatom as part of ring structure, were also highly active (**12c**,**d and 14**, Figure 3). The nature of *meta* substituents in ring **B** is shown to be less critical for biological activity.[1,8-10]

A library of this class of compounds has been prepared by changing different parts of the CA-4 (as shown in Figure 3), and tested for biological activity against various cancer cell lines.[1-10]

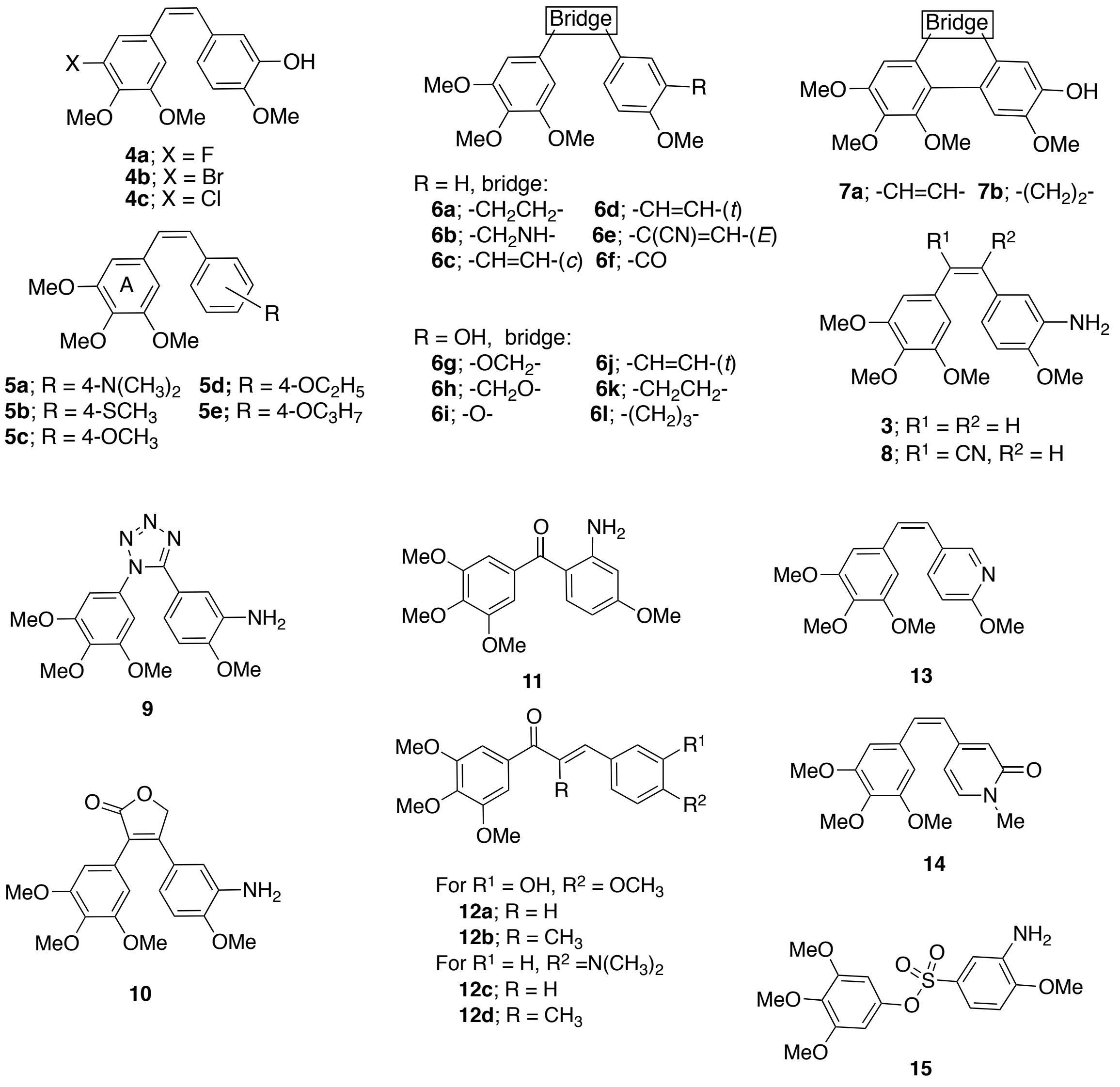


Figure 3. Examples of combretastatin analogs.

3.1.1 Fluorinated Combretastatin Analogs

Fluorine is a known modulator of the biological and physiochemical properties of organic compounds.[10-13] Due to their unique properties, fluoroorganic compounds constitute an integral part of the pharmaceutical industry.[14-17] In recent years, various fluorinated combretastatin analogs have been prepared and tested for their activities against various cancer cell lines.[1,10,18-20] Examples of such fluoro-combretastatins are shown in Figure 4. Interestingly, introduction of fluorine in some cases has enhanced the activity of combretastatin analogs. For instances, **21b** is more active than CA-4 (**1**) against BMEC and H-460 cell lines; **21c**, **21f** and **21h** are more active than CA-4 (**1**) against HT29 cell lines.[19] Similarly, **21i** and **21j** are comparable to CA-4 against BMEC and more active against HT29 cell lines.[19] Also, **17b** showed an activity against K562 human myelogenous leukaemia cell lines that was comparable to that of CA-4 (**1**).[20]

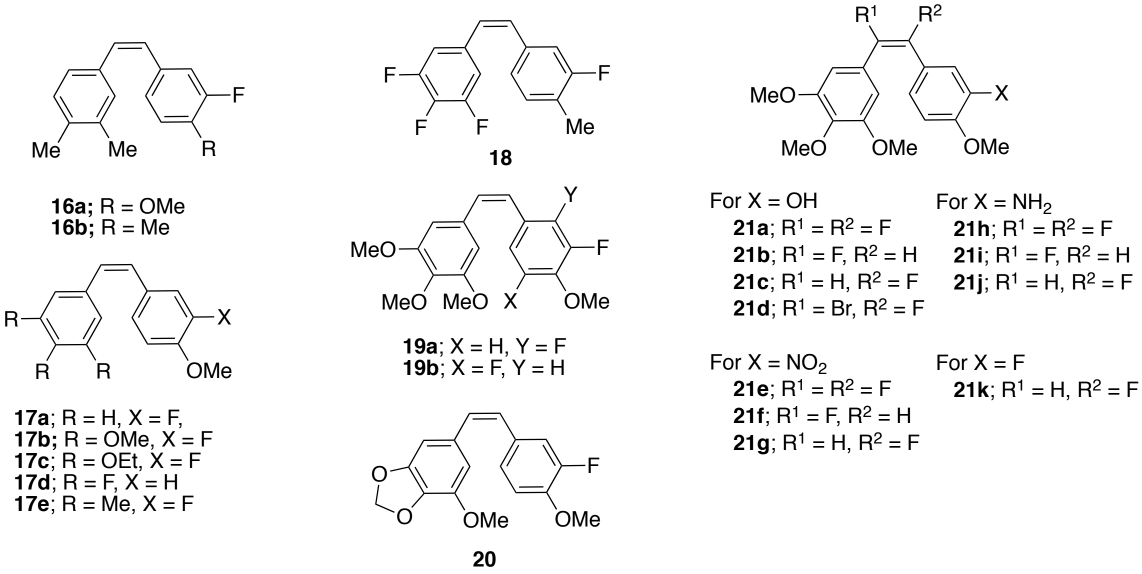


Figure 4. Examples of fluorinated combretastatin analogs.

3.1.2 Triazole-Derived Combretastatins

Several 1,2,3-triazoles are of biological relevance and some examples of such compounds are shown in Part 2.[21-25] Various 1,4- and 1,5-disubstituted triazole-derived combretastatin analogs, where triazole ring is replacing the bridge connecting the two aryl rings, have also been synthesized and tested for their biological activities.[26-29] Examples of such compounds are shown in Figure 5. Amino derivative of 1,5-

disubstituted triazole **23e** has been found to show cytotoxicity against K562 cell lines, which is comparable to that of CA-4 (**1**).[26,27] Recently, Dauzonne et al. also reported the synthesis of 4,5-disubstituted 1,2,3-triazolyl analogs of combretastatin.[29] Biological activity of these compounds against endothelial cells was observed to be much lower than that of CA-4 (**1**).[29]

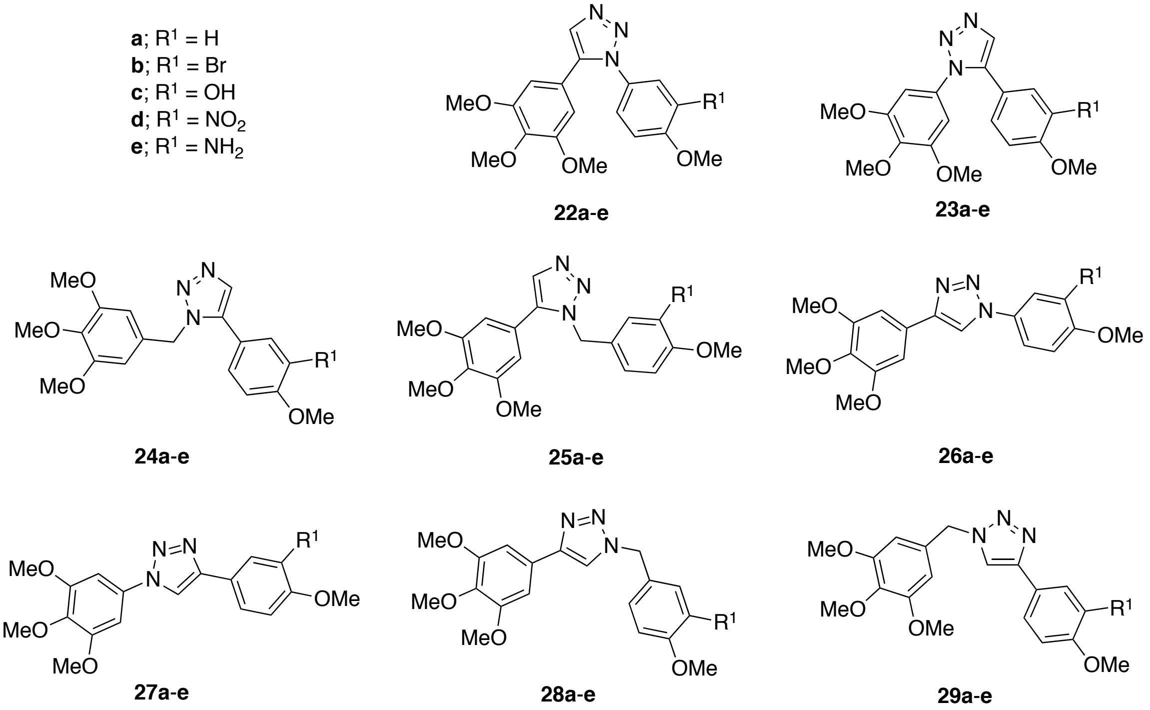
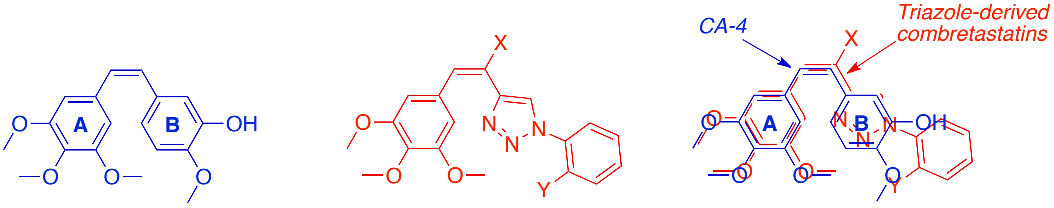


Figure 5. Examples of triazole-derived combretastatin analogs.

An efficient approach for the synthesis of vinyl and fluorovinyl triazoles, via 'click reaction-Julia olefination' was developed and presented in Part 2. DBU-mediated condensation reactions of triazole-derived Julia-Kocienski reagents with aryl aldehydes provided the fluorovinyl triazoles with predominant *cis* arrangement (*E*-selectivity) of the two aromatic rings. Such fluorovinyl triazoles obtained by condensations with 3,4,5-trimethoxybenzaldehyde can be good candidates as combretastatin analogs. Figure 6 shows the superimposed structure of the triazole derived combretastatin analogs and CA-

4 (**1**). If the aryl substituent of the triazole unit contains any *ortho* substituent Y, this can mimic the oxygen atom of the OCH_3 substituent at the *para* position of ring **B** of CA-4 (**1**). This prompted our interest towards synthesis of such triazole-derived combretastatin analogs. This chapter describes the synthesis of such combretastatin analogs and their biological evaluation as antitumor agents.



Combretastatin A-4 (*CA-4*)

1

Triazole-derived combretastatins

X = H, F

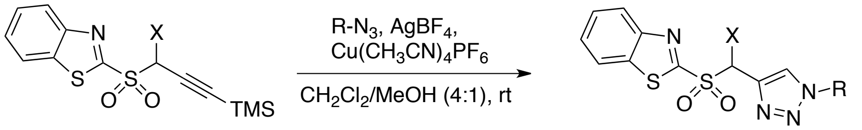
Superimposed structure

Figure 6. CA-4, triazole-derived combretastatin analogs and superimposed structures.

3.2 RESULTS AND DISCUSSION

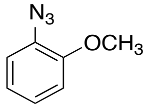
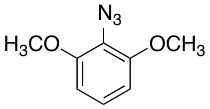
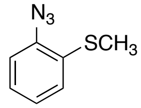
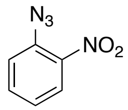
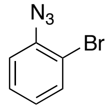
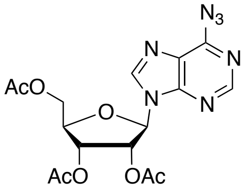
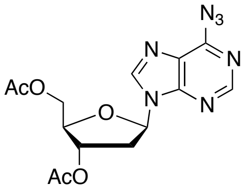
The TMS-protected propargyl benzothiazolyl sulfone **30** and the fluoro analog **31** (for synthesis see Part 1) were reacted with *ortho* substituted aryl azides under $Cu(CH_3CN)_4PF_6$–$AgBF_4$ conditions (Table 1).[30] The triazole-derived Julia-Kocienski reagents **32-37** were obtained in yields ranging from 28% to 85% (Table 1). A Reaction of **31** with 2-nitrophenyl azide gave a low 28% yield of **36** (entry 5) and moderate yields with 2,6-dimethoxyphenyl azide and of **35** with 2-(methylthio)phenyl azide (50% and 57%, respectively, entries 3 and 4). 2-Methoxyphenyl azide reacted efficiently with both protio (**30)** and fluoro (**31)** reagents and gave high yields of products (83% and 85% respectively, entries 1 and 2). Reaction of 2-bromophenyl azide was also high yielding (81%, entry 6). Recently, Lakshman et al. reported the synthesis of C-6 azido purine nucleosides and their ligation reactions with various alkynes.[31]

Table 1. Synthesis of Triazole-Derived Julia-Kocienski Reagents



30; X = H
31; X = F

32; X = H, R = 2-OMePh
33-39; X = F

Entry	R-N$_3$	X =	Product	%Yield[a]
1		H	**32**	83
2		F	**33**	85
3		F	**34**	50
4		F	**35**	57
5		F	**36**	28
6		F	**37**	81
7		F	**38**	86
8		F	**39**	53

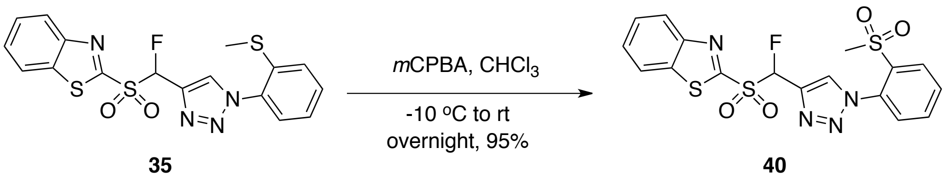
[a] Yields of purified products.

We were interested in the triazole-combretastatin anaolgs of these nucleoside azides for the following reasons: (i) N^7 nitrogen could act like an *ortho* substituent to aryl group; (ii) the presence of free hydroxyl groups in the sugar moiety increases the water solubility of nucleoside derivatives. This would be of great advantage, since poor water solubility limits the use of combretastatin analogs as drugs. (iii) Additionally, nucleosides represent an important, ubiquitous, prevalent biological scaffold.

Two nucleoside azides i.e. 6-azidopurine ribo- and 2'-deoxyribo derivatives (entries 7 and 8) were also reacted with compound **30** to obtain the corresponding triazole-derived fluoro-Julia reagents **38** and **39**, respectively (entries 7 and 8).

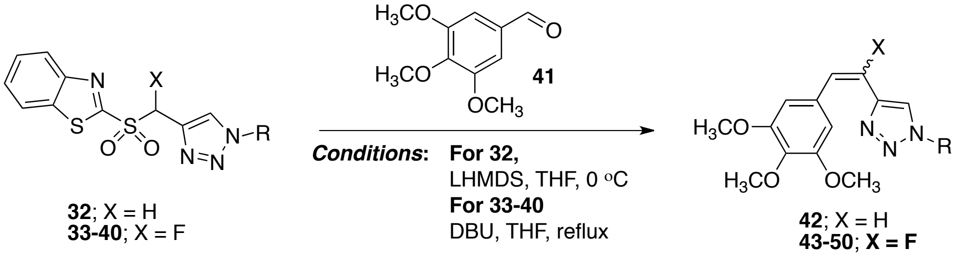
The *N*-[2-(methylthio)]phenyl derivative **35** was also converted to the corresponding sulfone derivative **40** in yield 95% by *m*CPBA oxidation (Scheme 1).

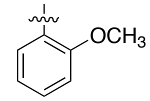
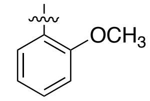
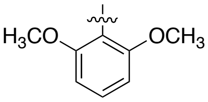
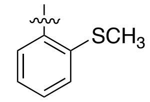
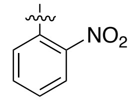
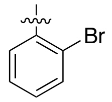
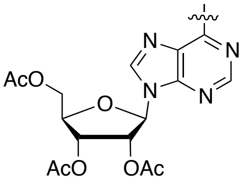
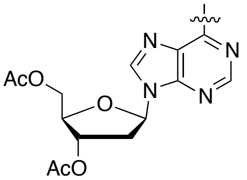
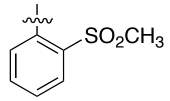
Scheme 1. Synthesis of Bis-Sulfone Derivative **40** by *m*CPBA Oxidation of **35**



Compounds **33** to **40** were reacted with 3,4,5-trimethoxybenzaldehyde **41** using DBU in refluxing THF. The results of olefination reactions are as shown in Table 2. Reactions of fluorinated triazole-derived Julia reagents under DBU conditions gave *cis* olefin (*cis* arrangement of the aryl and the triazole ring at the double bond, *E*-isomer) as the major product. We have previously observed that the DBU mediated olefinations of unfluorinated triazole-derived Julia-Kocienski reagents were very sluggish. Therefore the unfluorinated reagent **32** was reacted with trimethoxybenzaldehyde using LHMDS in THF at 0 °C and *trans* olefin (*E*-isomer) was obtained as the major product. Interestingly, unlike the fluorovinyl triazoles **43-47**, the diastereomers of vinyl triazole **42** were well separable on TLC and could be isolated separately by silica gel column chromatography.

Table 2. Condensation Reactions of Triazole-Derived Julia Reagents

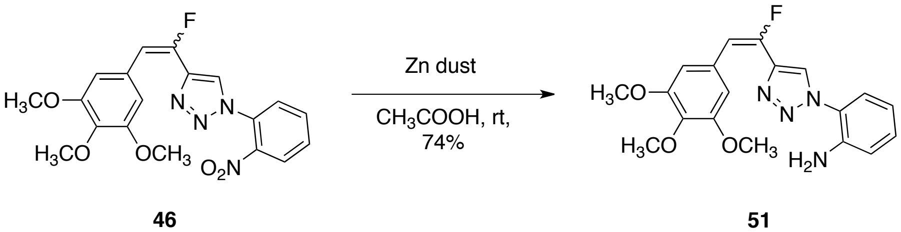


Entry	X =	R =	Sulfone	Product; %Yield^a; *E/Z* ratio^b
1	H		**32**	**42**; 68; 79/21^c
2	F		**33**	**43**; 52; 75/25
3	F		**34**	**44**; 72; 65/35
4	F		**35**	**45**; 73; 71/29
5	F		**36**	**46**; 55; 80/20
6	F		**37**	**47**; 73; 88/12
7	F		**38**	**48**; 66; 66/34
8	F		**39**	**49**; 54; 72/28
9	F		**40**	**50**; 65; 73/27

^{a}Yield of the purified product. ^{b}*E/Z* ratio of products in the crude mixture was determined by ^{19}F NMR. $^{c\,b}$*E/Z* ratio of products in the crude mixture was determined by ^{1H} NMR; diastereomers were separated by column chromatography.

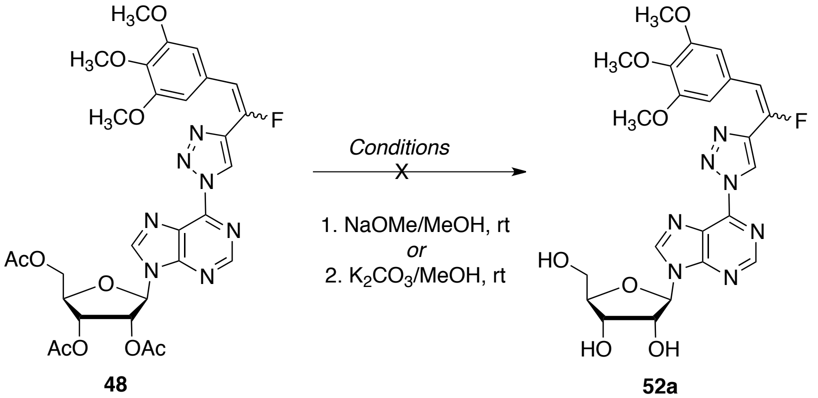
The NO_2 group of fluorovinyl triazole **46** was reduced using zinc dust in acetic acid and the amino derivative **51** was obtained in 74 % yield (Scheme 2).

Scheme 2. Synthesis of *N*-(2-Amino)phenyl Derivative **51**



Further, to obtain the nucleoside derivatives with free hydroxyls, the removal of acetate groups from compound **48** was attempted using two conditions, i.e. NaOMe/MeOH and K_2CO_3/MeOH (Scheme 3). However, the desired deprotected nucleoside derivative of fluorovinyl triazole **48** could not be obtained under either of the two reaction conditions tested. An S_NAr reaction, where the triazole moiety was displaced by MeO^- ion, was observed, leading to the C-6 methoxy derived product.

Scheme 3. Attempts at Deprotection of Hydroxyls in Nucleoside Derivatives

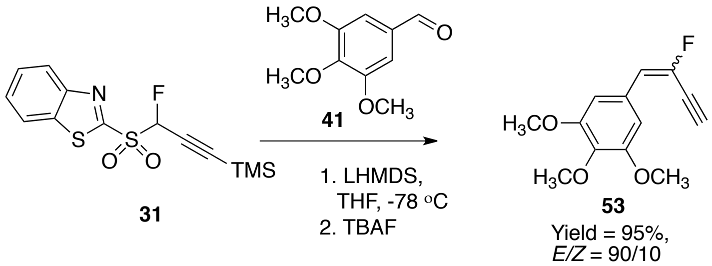


No further conditions were tested for removal of the acetate groups and an alternative approach for the synthesis of nucleoside derivatives was undertaken. Since the click reactions with TMS protected fluoropropargyl BT sulfone **31** involved the use of fluoride ion, the silyl protected nucleoside azides would not be suitable candidates under these conditions.

We have developed a method for *E*-selective synthesis of fluoroenynes, by condensation reactions of **31** with aldehydes (please see Part 1 of Chapter 1. The silyl-free fluoroenynes were obtained in high yields and with high *E*-selectivity using LHMDS/THF/-78 ºC conditions. Since click reactions of terminal alkynes do not require the use of fluoride ion, the TBDMS-protected nucleoside azides could be reacted successfully without the removal of TBDMS group in the reaction. We therefore decided to reverse the sequence of reactions by synthesizing the fluoroenyne first and then subjecting it to azide-akyne cycloaddition reaction.

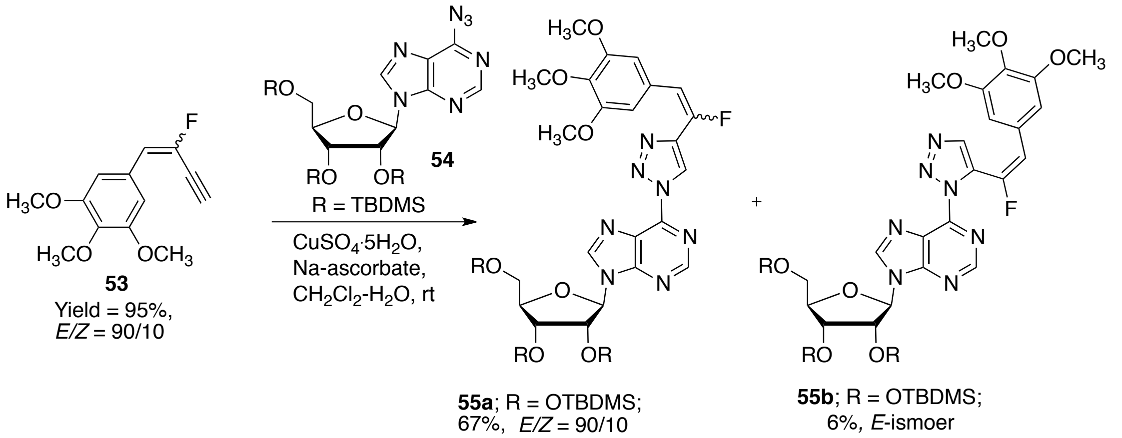
To obtain the requisite fluoroenyne derivative **53**, TMS protected fluoropropargyl BT sulfone **31** was reacted with 3,4,5-trimetoxybenzaldehyde using LHMDS in THF at -78 ºC (Scheme 4). Removal of the TMS group was performed *in situ* by the use of tetrabutyl ammonium fluoride, after all the aldehyde was consumed. The fluoroenyne derivative **53** was obtained in 95% yield, and 90/10 *E/Z* ratio.

Scheme 4. Synthesis of Fluoroenyne **53**



The *E/Z*-mixture of fluoroenyne **53** was reacted with TBDMS protected C-6 azidopurine derivative **54** under classical click conditions, using $CuSO_4$-sodium ascorbate catalyst system in CH_2Cl_2-H_2O.[31] The fluorovinyl triazole **55a** was obtained in 67 % yield and 90/10 *E/Z* ratio (Scheme 5). In addition to the major 1,4-disubstituted product **55a**, a minor 1,5-disubstituted triazole product **55b** was also obtained in 6% yield (Scheme 5). The formation of minor 1,5-disubstituted triazole has also been reported by Lakshman et al.[31]

Scheme 5. Synthesis of Nucleoside Derivative by Olefination-Click Reaction

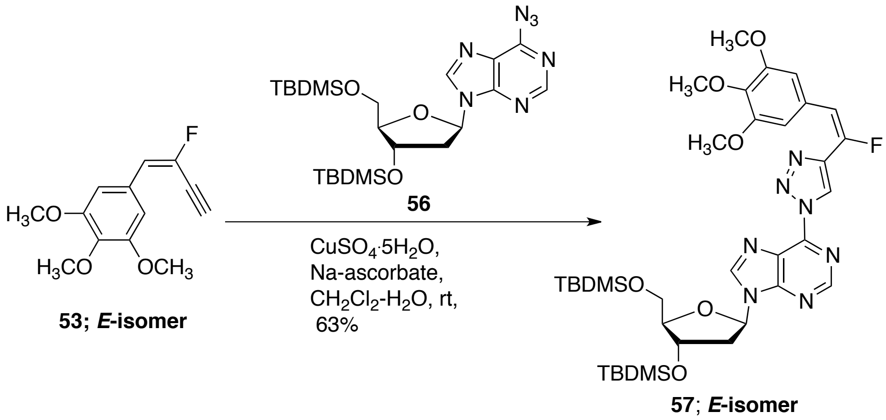


Alternatively, a fraction of the *E*-isomer of fluoroenyne **53** was separated by column chromatography and upon reaction with azide **56**, *E*-isomer of 2'-deoxyribo purine derivative **57** was obtained in 63% yield (Scheme 6).

Since the separation of diastereomers of the vinyl triazole **42** bearing of *N*-(2-methoxyphenyl) substituent, provided access to its pure *cis* isomer, we were also interested in the synthesis of pure *cis* isomer of the fluoro analog **43** for comparison reasons. The comparison of the biological activity of the two pure *cis* olefins would allow us to assess the influence of fluorine substitution on the bioactivity of these compounds. Reaction of 2-methoxyphenyl azide with *E*-fluoroenyne **53**, using the conditions shown in Scheme 6, provided fluorovinyl triazole **43** in 80% yield. However, NMR analysis of the products showed that the batch of fluoroenyne **53** used contained 2-

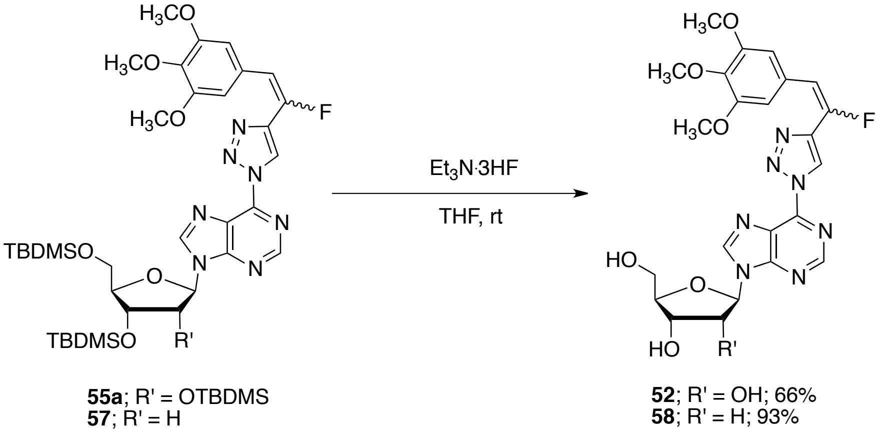
3% of the other isomer, and therefore the *E/Z* ratio of fluorovinyl triazole **43** obtained was 97/3.

Scheme 6. Synthesis of *E*-isomer of 2'-Deoxyribo Nucleoside Analog **57**



Deprotection of hydroxyl groups of nucleoside analogs **55a** and **57** was undertaken next. Deprotection of hydroxyls was carried out using $Et_3N \cdot 3HF$ in THF, without any side reactions. Deprotected nucleoside analog **52** and **58** were obtained in 66% and 93% yield, respectively (Scheme 7).

Scheme 7. Deprotection of Hydroxyl Groups of Nucleoside Analogs **55a** and **57**



Testing of biological activity of combretastatin analogs was performed in collaboration.[32] Combretastatin analogs with were tested for their biological activity against the HeLa cancer cell lines.[32] The results of biological activity were compared with CA-4 (**1**) and colchicine, which is another potent tubulin polymerization inhibitor. The results of the biological activity are shown in Table 3.

Table 3. Activity of Triazole-Derived Combretastatin Analogs Against HeLa Cancer Cell Lines[32]

Entry	Compound	*Cis/trans* ratio of the tested sample	Cell density (EC_{50})
1	**Colchicine**	na	25.4 ± 6.5 nM
2	**C A-4 (1)**	na	1.4 ± 0.1 nM
3	**42**	100/0	19.5 ± 1.7 µM
4	**43**	97/3	> 50 µM
5	**44**	70/30	> 50 µM
6	**45**	72/28	> 50 µM
7	**46**	80/20	> 50 µM
8	**47**	88/12	> 50 µM
9	**50**	77/23	> 50 µM
10	**51**	85/15	14.3 + 1.6 µM
11	**52**	83/17	> 50 µM
12	**58**	100/0	>50 µM

[a] *Cis* and *trans* refers to the relative position of the trimethoxyphenyl and triazolyl moieties at the double bond.

Only two compounds. i.e. **32** (EC_{50} = 19.5 ± 1.7µM) and **52** (EC_{50} = 14.3 + 1.6 µM), showed a moderate activity that was three orders of magnitude less than that of CA-4 (**1**) (EC_{50} = 1.4 ± 0.1 nM). Other compounds were found to be inactive with EC_{50} values higher than 50 µM. The tubulin polymerization inhibition ability of the two triazole-combretastatin analogs was also lower than that of CA-4 (**1**) and colchicine. Interestingly, the protio analog **42** (only *cis* isomer) showed a moderate activity, whereas the fluoro analog **43** that contained 3% of the *trans* isomer was found to be inactive. The lower activity of **43** compared to **42** could either be due to the presence of small amount of *trans* olefin or to the presence of fluorine substituent at the olefinic bond, or both.

3.3 CONCLUSION

The vinyl and fluorovinyl triazole analogs of combretstatin A-4 were synthesized in a two-step reaction sequence from TMS-protected propargyl and fluoroproargyl BT sulfones. The analogs had unchanged trimethoxyphenyl ring **A** and *N*-substituted triazole ring instead of ring **B**. The click reaction–Julia olefinations sequence provided *cis* olefins as the major isomers in the case of fluoro analogs, however higher *cis/trans* ratio could be obtained by the reversal of the reaction sequence. The acetate-protected nucleoside analogs were also synthesized via click reaction-Julia olefination route, but removal of acetates to obtain the free hydroxyls could not be achieved. Therefore, TBDMS-protected nucleoside analogs bearing fluorovinyl triazole substituent were synthesized by olefination-click reaction sequence. Comndensation of fluoroproprgyl BT sulfone with 3,4,5-trimethoxybenzaldehyde gave fluoroenyne that was subjected to fluoride-free click reaction. The desired ribo and 2’-deoxyribo nucleoside analogs were obtained via fluoride mediated silyl-deprotection. The biological evaluation of these compounds against HeLa cancer cell lines revealed only moderate activity of the two analogs, whereas the others were inactive.

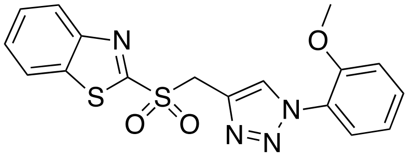
EXPERIMENTAL SECTION

THF was distilled over $LiAlH_4$, and then over sodium. LHMDS (1.0 M in THF) was also obtained from commercial sources. For reactions, which were performed under a nitrogen atmosphere, glassware was dried with hot gun under vacuum. Thin layer chromatography was performed on 250 μm silica plates and column chromatographic purifications were performed on silica gel. The mesh size of silica gel and the eluting solvents are reported for each compound separately. Aryl azides were synthesized from the corresponding boronic acid derivatives using literature procedure[33] and as described in Part 2 of this chapter. Nucleoside azides were obtained from Prof. Mahesh K. Lakshman's laboratory at the City College of New York and their synthesis is reported.[31] All other reagents were obtained from commercial sources and used without further purification. ^1H NMR spectra were recorded at 500 MHz in $CDCl_3$, acetone-d_6 and CD_3OD. ^{13}C specta were recorded at 125 MHz using $CDCl_3$, acetone-d_6 and CD_3OD. ^{19}F NMR spectra were recorded at 282 MHz using $CFCl_3$ as internal standard. Chemical shifts (δ) are reported in parts per million and coupling constants (J) are in hertz.

Click reactions of sulfones 30 and 31 with aryl azides:

General Procedure. To a stirring solution of azide (1.0 molar equiv) in 4:1 (v/v) CH_2Cl_2/MeOH (28.0 mL per mmol of azide) in a dry flask, sulfone **30** or **31** (1.2 molar equiv), $Cu(CH_3CN)_4PF_6$ (0.20 molar equiv) and $AgBF_4$ (0.20 molar equiv) were added sequentially. The stirring was continued at room temperature until TLC showed disappearance of the azide. The solvents were evaporated under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel. Silica gel mesh size and the eluting solvents for chromatography are indicated under the specific compound headings.

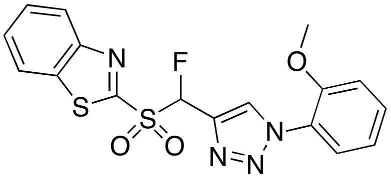
2-{[(1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methyl}sulfonyl)benzo[*d*]thiazole (32)



2-Methoxyphenyl azide: 160 mg (1.07 mmol); sulfone **30**: 399 mg (1.29 mmol). Column chromatography: silica gel mesh 100-200, eluting solvent 40% EtOAc in hexanes. Yield of **32**: 341.2 mg (83%) of off white solid. *R*f (40% EtOAc in hexanes) = 0.17.

^{1}H NMR (500 MHz, CDCl$_3$): δ 8.32 (s, 1H, Ar-H), 8.25 (d, 1H, Ar-H, *J* = 8.3 Hz), 7.96 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.75 (dd, 1H, Ar-H, *J* = 8.1, 1.7 Hz), 7.64 (td, 1H, Ar-H, 8.1, 1.2), 7.58 (td, 1H, Ar-H, *J* = 7.7, 1.2 Hz), 7.42 (td, 1H, Ar-H, *J* = 8.1, 1.0 Hz), 7.10-7.05 (m, 2H, Ar-H), 5.05 (s, 2H, CH$_2$), 3.81 (s, 3H, CH$_3$). ^{13}C NMR (125 MHz, CDCl$_3$): δ 152.8, 151.1, 137.3, 133.9, 130.6, 128.38, 127.9, 127.2, 126.0, 125.9, 125.4, 122.5, 121.5, 112.5, 56.1, 52.8. HRMS (ESI) calcd. for $C_{17}H_{15}N_4O_3S_2$ [M+H]$^+$, 387.0580, found 387.0597.

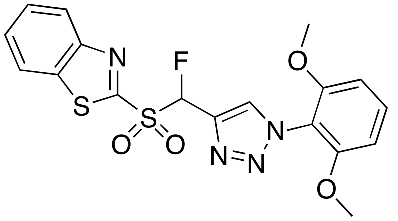
2-{Fluoro[1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methylsulfonyl}benzo[*d*]-thiazole (33)



2-Methoxyphenyl azide: 224 mg (1.50 mmol); sulfone **31**: 588.6 mg (1.80 mmol). Column chromatography: silica gel mesh 200-300, eluting solvent 40% EtOAc in hexanes. Yield of **33**: 514.7 mg (85%) of off white solid. *R*f (20% EtOAc in hexanes) =

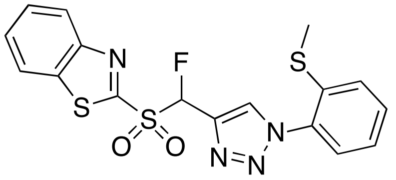
0.10. ^{1}H NMR (500 MHz, $CDCl_3$): 8.70 (d, 1H, Ar-H, J = 2.3 Hz), 8.32 (d, 1H, Ar-H, J = 8.3 Hz), 8.06 (d, 1H, Ar-H, J = 8.3 Hz), 7.85 (d, 1H, Ar-H, J = 8.8 Hz), 7.71-7.64 (m, 2H, Ar-H), 7.47 (t, 1H, Ar-H, J = 8.5 Hz), 7.16-7.11 (m, 2H, Ar-H), 7.02 (d, 1H, CHF, $^2J_{FH}$ = 46.5 Hz), 3.91 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.2, 153.1, 151.1, 137.8, 134.7 (d, $^2J_{CF}$ = 23.8 Hz), 131.0, 128.8, 128.2, 128.0, 126.2, 125.8, 125.5, 122.5, 121.5, 112.6, 96.3 (d, $^1J_{CF}$ = 219.7 Hz), 56.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ -165.5 (d, $^2J_{FH}$ = 45.8). HRMS (ESI) calcd. for $C_{17}H_{14}FN_4O_3S_2$ $[M+H]^+$, 405.0486, found 405.0506.

2-{[1-(2,6-Dimethoxyphenyl)-1H-1,2,3-triazol-4-yl]fluoromethylsulfonyl}benzo[*d*]-thiazole (34)



2, 6-Dimethoxyphenyl azide: 70.0 mg (0.39 mmol); sulfone **31**: 153.7 mg (0.47 mmol). Column chromatography: silica gel mesh 200-300, eluting solvent 40% EtOAc in hexanes. Yield of **34**: 84.0 mg (50%) of off white solid. R_f (40% EtOAc in hexanes) = 0.24. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (d, 1H, Ar-H, J = 8.3 Hz), 8.20 (d, 1H, Ar-H, J = 2.3 Hz), 8.05 (d, 1H, Ar-H, J = 8.3 Hz), 7.70-7.63 (m, 2H, Ar-H), 7.44(t, 1H, Ar-H, J = 8.5 Hz), 7.01(d, 1H, CHF, $^2J_{FH}$ = 46.5 Hz), 6.69(d, 2H, Ar-H, J = 8.8 Hz), 3.78 (s, 6H, $2CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 155.8,153.1, 137.8, 134.2 (d, $^2J_{CF}$ = 23.8 Hz), 132.1, 129.5, 128.7, 128.1, 126.2, 122.5, 114.7, 104.8, 96.4 (d, $^1J_{CF}$ = 219.7Hz), 56.4. ^{19}F NMR (282 MHz, $CDCl_3$) : δ -164.8 (d, $^2J_{FH}$ = 45.8). HRMS (ESI) calcd. for $C_{18}H_{15}FN_4NaO_4S_2$ $[M+Na]^+$, 457.0411, found 457.0402.

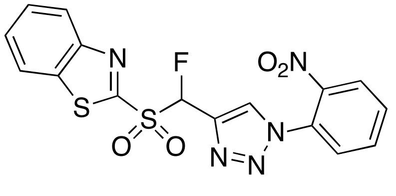
2-{Fluoro{1-(2-(methylthio)phenyl)-1H-1,2,3-triazol-4-yl}methylsulfonyl]benzo[*d*]-thiazole (35)



(2-Azidophenyl)(methyl)sulfane: 100 mg (0.61 mmol); sulfone **31**: 238.7 mg (0.73 mmol). Column chromatography: silica gel mesh 200-300, eluting solvent 40% EtOAc in hexanes. Yield of **35**: 145.5 mg (57%) of white solid. R_f (20% EtOAc in hexanes) = 0.13. ^{1}H NMR (500 MHz, $CDCl_3$) : δ 8.48 (d, 1H, Ar-H, J = 1.4 Hz), 8.31 (d, 1H, Ar-H, J = 8.3 Hz), 8.05 (d, 1H, Ar-H, J = 7.8 Hz), 7.70-7.63 (m, 2H, Ar-H), 7.51 (t, 1H, Ar-H, J = 7.6 Hz), 7.48 (d, 1H, Ar-H, J = 7.8 Hz), 7.44 (d, 1H, Ar-H, J = 7.8 Hz), 7.34 (t, 1H, Ar-H, J = 7.6 Hz), 7.02 (d, 1H, CHF, $^2J_{FH}$ = 46.1 Hz), 2.37(s, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0, 153.1,137.8, 135.4, 135.3, 135.0 (d, $^2J_{CF}$ = 17.9 Hz), 131.0, 128.8, 128.2, 128.0, 127.9, 127.0, 126.3, 126.2, 122.5, 96.2 (d, $^1J_{CF}$ = 220.2 Hz), 16.2. ^{19}F NMR (282 MHz, $CDCl_3$) : δ -166.1 (d, $^2J_{FH}$ = 45.8). HRMS (ESI) calcd. for $C_{17}H_{14}FN_4O_2S_3$ $[M+H]^+$, 421.0257, found 421.0267.

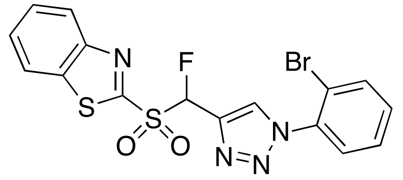
2-{Fluoro[1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl]methylsulfonyl}benzo[*d*]thiazole (36)



2-Nitrophenyl azide: 100 mg (0.61 mmol); sulfone **31**: 239 mg (0.73 mmol). Column chromatography: silica gel mesh 200-300, eluting solvent 40% EtOAc in hexanes. Yield of **36**: 71.0 mg (28%) of light yellow solid. R_f (40% acetone in hexanes) = 0.17.

^{1}H NMR (500 MHz, $CDCl_3$) : δ 8.44 (d, 1H, Ar-H, J = 1.4 Hz), 8.33 (d, 1H, Ar-H, J = 7.8 Hz), 8.18 (d, 1H, Ar-H, J = 8.3 Hz), 8.07 (d, 1H, Ar-H, J = 7.8 Hz), 7.87 (t, 1H, Ar-H, J = 7.6 Hz), 7.79 (t, 1H, Ar-H, J = 7.8 Hz), 7.72-7.65 (m, 3H, Ar-H), 7.02 (d, 1H, CHF, $^2J_{FH}$ = 46.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.7, 153.1, 144.6, 137.9, 136.2 (d, $^2J_{CF}$ = 24.8 Hz), 134.4, 131.9, 129.8, 128.9, 128.6, 128.3, 127.7, 126.3, 126.2, 122.6, 95.9 (d, $^1J_{CF}$ = 221.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) : δ -167.3 (d, $^2J_{FH}$ = 45.8). HRMS (ESI) calcd. for $C_{16}H_{10}FN_5NaO_4S_2$ $[M+Na]^+$, 422.0050, found 422.0098.

2-{[1-(2-Bromophenyl)-1H-1,2,3-triazol-4-yl]fluoromethylsulfonyl}benzo[*d*]thiazole (37)

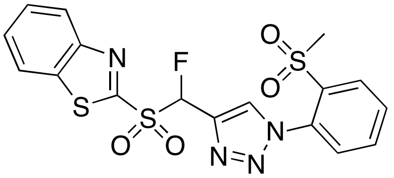


2-Bromophenyl azide: 99 mg (0.50 mmol); sulfone **31**: 196.2 mg (0.60 mmol). Column chromatography: silica gel mesh 200-300, eluting solvent 40% acetone in hexanes. Yield of **37**: 184 mg (81%) of light yellow solid. R_f (40% acetone in hexanes) = 0.46

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (d, 1H, Ar-H, J = 1.5 Hz), 8.27 (d, 1H, Ar-H, J = 8.2 Hz), 8.03 (d, 1H, Ar-H, J = 7.9 Hz), 7.74 (d, 1H, Ar-H, J = 7.9 Hz), 7.67-7.60 (m, 2H, Ar-H), 7.56 (d, 1H, Ar-H, J = 7.9 Hz), 7.50 (t, 1H, Ar-H, J = 7.6 Hz), 7.41 (t, 1H, Ar-H, J = 7.6 Hz), 7.03 (d, 1H, CHF, $^2J_{FH}$ = 46.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.8, 152.9, 137.7, 135.8, 135.2 (d, $^2J_{CF}$ = 24.7 Hz), 134.1, 132.0, 128.81, 128.80, 128.2, 128.1, 128.98, 127.97, 126.0, 122.5, 118.6, 96.1 (d, $^1J_{CF}$ = 221.1 Hz). ^{19}F NMR (282 MHz,

$CDCl_3$) : δ -166.5 (d, $^2J_{FH}$ = 45.8). HRMS (ESI) calcd. for $C_{16}H_{10}BrFN_4NaO_2S_2$ $[M+Na]^+$, 474.9305, found 474.9318.

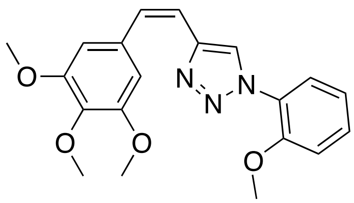
2-{Fluoro[1-(2-(methylsulfonyl)phenyl)-1H-1,2,3-triazol-4-yl]methylsulfonyl}-benzo[*d*]thiazole (40)



To a stirring solution of compound **35** (100 mg, 0.24 mmol, 1 molar equiv) in $CHCl_3$ (0.600 mL) at was –10 ºC (ice-salt cooling) a solution of *m*CPBA (124.3 mg, 0.72 mmol, 3.0 molar equiv) in $CHCl_3$ (1.4 mL) was added dropwise. After complete addition the mixture was allowed to warm to rt and stirred overnight. Saturated aq. solution of $NaHCO_3$ (4.0 mL) was then added and mixture was vigorously stirred for 10 min. Layers were separated, the aqueous layer was extracted with $CHCl_3$ (2 x), and the combined organic layer was washed with sat aq $NaHCO_3$, water and brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel mesh 200-300, eluent: 40% EtOAc in hexanes) to obtain 103 mg (95%) of **40** as a white solid. R_f (40% EtOAc in hexanes) = 0.25. ^{1}H NMR (500 MHz, $CDCl_3$) : δ 8.48 (br s, 1H, Ar-H), 8.29-8.27 (m, 2H, Ar-H), 8.05 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.87-7.80 (m, 2H, Ar-H), 7.69-7.62 (m, 2H, Ar-H), 7.57 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.02 (d, 1H, CHF, $^2J_{FH}$ = 46.1 Hz), 3.09 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.8, 153.0,137.8, 137.1, 135.7 (d, $^2J_{CF}$ = 23.8 Hz), 135.1, 134.5, 131.9, 131.2, 129.6, 129.2, 128.8, 128.2, 126.1, 122.6, 95.9 (d, $^1J_{CF}$ = 221.5 Hz), 45.2. ^{19}F NMR (282 MHz, $CDCl_3$) : *δ* -168.0 (d, $^2J_{FH}$ = 45.8). HRMS

(ESI) calcd. for $C_{17}H_{14}FN_4O_4S_2$ $[M+H]^+$, 453.0156, found 453.0163.

Synthesis of (*Z*)-1-(2-methoxyphenyl)-4-(3,4,5-trimethoxystyryl)-1*H*-1,2,3-triazole (42)



A stirring solution of sulfone **32** (50 mg, 0.129 mmol, 1 molar equiv) and 3,4,5-trimethoxybenzaldehyde (30.5 mg, 0.155 mmol, 1.2 molar equiv) in THF (2.0 mL) was cooled to 0 °C (ice bath) and under nitrogen LHMDS (0.320 mL, 1.2 mmol, 2.4 molar equiv) was added to the reaction mixture. The reaction mixture was stirred at 0 °C for 2 h, saturated aq NH_4Cl was added and the mixture was poured into EtOAc. Organic layer was separated and the aqueous layer was extracted with EtOAc three times. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. *E*/*Z* ratio of the products was determined by ^{1}H NMR of the crude reaction mixture before *E*/*Z* (79/21) product mixture was isolated by column chromatography using silica gel. Column chromatography: silica gel mesh 200-300, eluting solvent 20% acetone in hexanes. Yield of *E*/*Z*-**42**: 32.3 mg (68%)

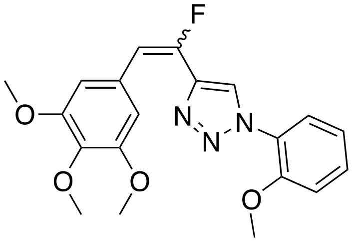
cis (*Z)*-Isomer : 7.2 mg, dirty white solid, R_f (20% acetone in hexanes) = 0.20

trans (*E)*-Isomer : 25.0 mg dirty white solid, R_f (20% acetone in hexanes) = 0.14

^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.78 (dd, 1H, Ar-H, J = 7.9, 1.5 Hz), 7.74 (s, 1H, Ar-H), 7.38 (td, 1H, Ar-H, J = 7.9, 1.5 Hz), 7.07 (td, 1H, Ar-H, J = 7.6, 1.2 Hz), 7.02 (dd, 1H, Ar-H, J = 8.4, 0.8 Hz), 6.76 (d, 1H, =CH, J = 11.9 Hz), 6.70 (d, 1H, =CH, J = 11.9 Hz), 6.68 (s, 2H, Ar-H), 3.87 (s, 3H, CH_3), 3.81 (s, 6H, $2CH_3$), 3.79 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.6, 150.9, 144.0, 133.5, 131.5, 130.2, 126.2, 125.2, 124.2, 121.4, 120.2, 112.4, 105.58, 105.55, 61.2, 56.3, 55.8. HRMS (ESI) calcd. for $C_{20}H_{22}N_3O_4$ $[M+H]^+$ 368.1605, found 368.1609.

General procedure for condensations of fluorinated triazole-derived Julia reagents: To a stirred solution of the triazole-derived Julia reagents (1 molar equiv) and 3,4,5-trimethoxybenzaldehyde **41** (1.2-1.3 molar equiv) in dry THF (21 mL per mmol of sulfone) at a solution of DBU (4.0 molar equiv) in dry THF (9.2 mL per mmol of sulfone) at room temperaure. The reaction mixture was then stirred at reflux until complete consumption of aldehyde was observed by TLC. The solvent was evaporated under reduced pressure and the *E*/*Z* ratio was analyzed by ^{19}F NMR. The crude product was purified by column chromatography using silica gel. The mesh size for silica gel and the eluting solvents for reaction of individual sulfone are given below.

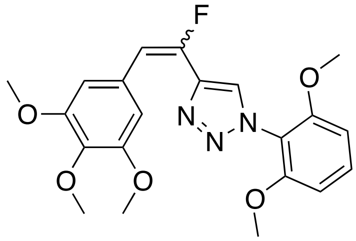
***E/Z*-4-(1-fluoro-2-(3,4,5-trimethoxyphenyl)vinyl)-1-(2-methoxyphenyl)-1*H*-1,2,3-triazole (43)**



Sulfone **33**: 202.2 mg (0.50 mmol); aldehyde **41**: 127.5 mg (0.65 mmol, 1.3 molar equiv); DBU: 305 mg (2.0 mmols, 4.0 molar equiv). Column chromatography: silica gel mesh 200-300, eluting solvent: 20% EtOAc in hexanes. Yield of *E/Z*-**43**: 100.2 mg (52%) of white solid, *E/Z* = 75/25. R_f (40% acetone in hexanes) = 0.69. ^{1}H NMR (500 MHz,

$CDCl_3$) : *δ* 8.22 (s, 1H, Ar-H, *Z*-isomer), 8.04 (s, 1H, Ar-H, *E*-isomer), 7.81 (d, 1H, Ar-H, *J* = 7.8 Hz, *Z*-isomer), 7.78 (d, 1H, Ar-H, *J* = 7.8 Hz, *E*-isomer), 7.47 (t, 1H, Ar-H, *J* = 7.8 Hz, *E*-isomer), 7.47 (t, 1H, Ar-H, *J* = 7.8 Hz, *Z*-isomer), 7.15-7.06 (m, 2H, Ar-H, both *E*- and Z-isomers), 6.92 (s, 2H, ArH, *Z*-isomer), 6.82 (s, 2H, ArH, *E*-isomer), 6.73 (d, 1H, =CH, $^3J_{FH}$ = 40.5 Hz, *Z*-isomer), 6.55 (d, 1H, =CH, $^3J_{FH}$ = 22.5 Hz, *E*-isomer), 3.92 (s, 3H, CH_3, *Z*-isomer), 3.90 (s, 6H, $2CH_3$, *Z*-isomer), 3.88 (s, 3H, CH_3, *Z*-isomer), 3.86(s, 3H, CH_3, *E*-isomer), 3.84 (s, 3H, CH_3, *E*-isomer), 3.82 (s, 6H, $2CH_3$, *E*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$): δ -106.73 (d, $^3J_{FH}$ = 24.4 Hz, *E*-isomer), 119.45 (d, $^3J_{FH}$ = 42.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{20}H_{21}FN_3O_4$ $[M+H]^+$ 386.1511, found 386.1516.

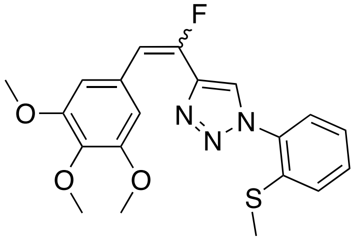
***E/Z*-1-(2,6-Dimethoxyphenyl)-4-(1-fluoro-2-(3,4,5-trimethoxyphenyl)vinyl)-1*H*-1,2,3-triazole (44)**



Sulfone **34**: 30 mg (0.069 mmol); aldehyde **41**: 17.7 mg (0.090 mmol, 1.3 molar equiv); DBU: 42.0 mg (0.276 mmols, 4.0 molar equiv). Column chromatography: silica gel mesh 200-300, eluting solvent: 20% EtOAc in hexanes. Yield of *E/Z*-**44**: 20.7 mg (72%) of yellow solid, *E/Z* = 65/35. R_f (20% acetone in hexanes) = 0.17. ^1H NMR (500 MHz, $CDCl_3$) : δ 7.75 (s, 1H, Ar-H, *Z*-isomer), 7.62 (s, 1H, Ar-H, *E*-isomer), 7.45-7.39 (m, 1H, Ar-H, both *E*- and *Z*- isomers), 6.91 (s, 2H, Ar-H, *Z*-isomer), 6.87 (s, 2H, Ar-H, *E*-isomer), 6.74 (d, 1H, =CH, $^3J_{FH}$ = 40.5 Hz, *Z*-isomer), 6.70 (d, 2H, Ar-H, *J* = 8.8 Hz, *Z*-

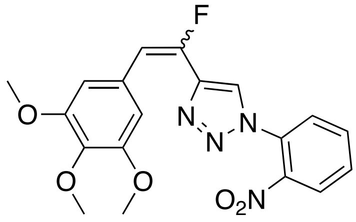
isomer), 6.66 (d, 2H, Ar-H, J = 8.3 Hz, *E*-isomer), 6.54 (d, 1H, =CH, $^3J_{FH}$ = 22.6 Hz, *E*-isomer), 3.90 (s, 3H, CH_3, *E*-isomer), 3.83 (s, 3H, CH_3, *Z*-isomer), 3.84 (s, 6H, 2CH_3, *Z*-isomer), 3.82 (s, 6H, 2CH_3, *E*-isomer), 3.79 (s, 6H, 2CH_3, *Z*-isomer), 3.75 (s, 6H, 2CH_3, *E*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$) : δ -105.19 (d, $^3J_{FH}$ = 24.4 Hz, *E*-isomer), 119.37 (d, $^3J_{FH}$ = 39.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for C21H23FN3O5 $[M+H]^+$ 416.1616, found 416.1624.

_E/Z_-4-[1-Fluoro-2-(3,4,5-trimethoxyphenyl)vinyl]-1-(2-(methylthio)phenyl)-1*H*-1,2,3-triazole (45)



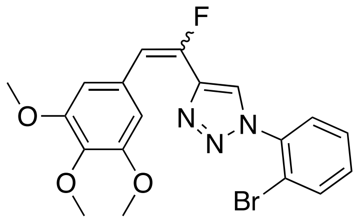
Sulfone **35**: 50 mg (0.12 mmol); aldehyde **41**: 28.3 mg (0.144 mmol, 1.2 molar equiv); DBU: 73.0 (0.48 mmols, 4.0 moalr equiv). Column chromatography: silica gel mesh 200-300, eluting solvent: 20% EtOAc in hexanes. Yield of *E/Z*-**45**: 36.9 mg (77%) of white solid, *E/Z* = 71/29. R_f (20% acetone in hexanes) = 0.27. ^{1}H NMR (500 MHz, $CDCl_3$) : δ 8.02 (s, 1H, Ar-H, *Z*-isomer), 7.83 (s, 1H, Ar-H, *E*-isomer), 7. 35-7.29 (m, 4H, Ar-H, both *E*- and *Z*-isomers), 6.92 (s, 2H, Ar-H, Z-isomer), 6.84 (s, 2H, Ar-H, *E*-isomer), 6.76 (d, 1H, =CH, $^3J_{FH}$ = 40.6 Hz, Z-isomer), 6.58 (d, 1H, =CH, $^3J_{FH}$ = 22.6 Hz, *E*-isomer), 3.90 (s, 6H, 2CH_3, *Z*-isomer), 3.89 (s, 3H, CH_3, *Z*-isomer), 3.85 (s, 3H, CH_3, *E*-isomer), 3.82 (s, 6H, 2CH_3, *E*-isomer), 2.42 (s, 3H, CH_3, *Z*-isomer), 2.39 (s, 3H, CH_3, *E*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$) : δ -107.0 (d, $^3J_{FH}$ = 21.4 Hz, *E*-isomer), 119.66 (d, $^3J_{FH}$ = 39.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{20}H_{21}FN_3O_3S$ $[M+H]^+$ 402.1282, found 402.1286.

_E/Z_-4-[1-Fluoro-2-(3,4,5-trimethoxyphenyl)vinyl]-1-(2-nitrophenyl)-1_H_-1,2,3-triazole (46)



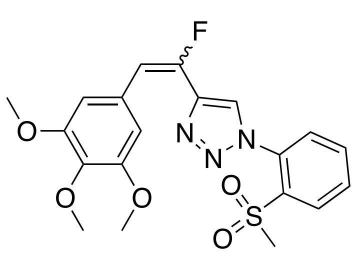
Sulfone **36**: 50 mg (0.12 mmol); aldehyde: 30.4 mg (0.155 mmol, 1.3 molar equiv); DBU: 73.1 (0.48 mmols, 4.0 molar equiv). Column chromatography: silica gel mesh 200-300, eluting solvent: 40% EtOAc in hexanes. Yield of *E/Z*-**46**: 26.2 mg (55%) of yellow solid, *E/Z* = 80/20. R_f (40% EtOAc in hexanes) = 0.33. ^{1}H NMR (500 MHz, $CDCl_3$) : δ 8.13 (d, 1H, Ar-H, J = 8.3 Hz, Z-isomer), 8.11 (d, 1H, Ar-H, J = 7.8 Hz, *E*-isomer), 7.96 (s, 1H, Ar-H, *Z*-isomer), 7.85-7.72 (m, Ar-H, 3H E-isomer and 2H *Z*-isomer), 7.67 (d, 1H, Ar-H, J = 7.8 Hz, *Z*-isomer), 7.58 (d, 1H, Ar-H, J = 7.8 Hz, *E*-isomer), 6.91 (s, 2H, Ar-H, *Z*-isomer), 6.79 (s, 2H, Ar-H, *E*-isomer), 6.77 (d, 1H, =CH, $^3J_{FH}$ = 40.5 Hz, *Z*-isomer), 6.61 (d, 1H, =CH, $^3J_{FH}$ = 22.6 Hz, *E*-isomer), 3.93 (s, 6H, 2CH_3, *Z*-isomer), 3.91 (s, 3H, CH_3, *Z*-isomer), 3.88 (s, 3H, CH_3, *E*-isomer), 3.82 (s, 6H, 2CH_3, *E*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$): δ -107.65 (d, $^3J_{FH}$ = 21.4 Hz, *E*-isomer), 120.10 (d, $^3J_{FH}$ = 39.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{19}H_{18}FN_4O_5$ $[M+H]^+$ 401.1256, found 401.1261.

_E/Z_-1-(2-Bromophenyl)-4-[1-fluoro-2-(3,4,5-trimethoxyphenyl)vinyl]-1_H_-1,2,3-triazole (47)



Sulfone **37**: 100 mg (0.22 mmol); aldehyde: 56.9 mg (0.29 mmol, 1.3 molar equiv); DBU: 134 (0.88 mmols, 4.0 molar equiv). Column chromatography: silica gel mesh 200-300, eluting solvent: 40% acetone in hexanes. Yield of *E/Z*-**47** : 69.9 mg (73%) of white solid, *E/Z* = 88/12. R_f (20% acetone in hexanes) = 0.16. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.06 (s, 1H, Ar-H, *Z*-isomer), 7.86 (s, 1H, Ar-H, *E*-isomer), 7.79 (d, 1H, Ar-H, J = 7.8 Hz, *Z*-isomer), 7.75 (d, 1H, Ar-H, J = 7.8 Hz, *E*-isomer), 7.60 (d, 1H, Ar-H, J = 7.8 Hz, *Z*-isomer), 7.55-7.39 (m, Ar-H, 3H *E*-isomer and 2H *Z*- isomer), 6.92 (s, 2H, Ar-H, *Z*-isomer), 6.83 (s, 2H, Ar-H, *E*-isomer), 6.77 (d, 1H, =CH, $^3J_{FH}$ = 41.0 Hz, *Z*-isomer), 6.61 (d, 1H, =CH, $^3J_{FH}$ = 22.1 Hz, *E*-isomer), 3.91 (s, 6H, 2CH$_3$, *Z*-isomer), 3.89 (s, 3H, CH$_3$, *Z*-isomer), 3.86 (s, 3H, CH$_3$, *E*-isomer), 3.83 (s, 6H, 2CH$_3$, *E*-isomer). ^{19}F NMR (282 MHz, CDCl$_3$) : δ -107.37 (d, $^3J_{FH}$ = 24.4 Hz, *E*-isomer), 119.81 (d, $^3J_{FH}$ = 39.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{19}H_{18}BrFN_3O_3$ $[M+H]^+$ 434.0510, found 434.0512.

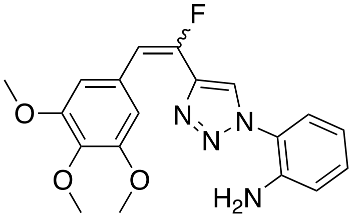
***E/Z*-4-[1-fluoro-2-(3,4,5-trimethoxyphenyl)vinyl]-1-[2-(methylsulfonyl)phenyl]-1*H*-1,2,3-triazole (50)**



Sulfone **40**: 45 mg (0.10 mmol); aldehyde: 25.5 mg (0.13 mmol, 1.2 molar equiv); DBU: 61 mg (0.40 mmols, 4.0 molar equiv). Column chromatography: silica gel mesh 200-

300, eluting solvent: 40% acetone in hexanes. Yield of *E/Z*-**50**: 28.0 mg (65%) of white solid, *E/Z* = 73/27. R_f (40% EtOAc in hexanes) = 0.5. ^{1}H NMR (500 MHz, $CDCl_3$) : δ 8.31 (dd, 1H, Ar-H, *J* = 7.8, 1.5 Hz, *Z*-isomer), 8.27 (dd, 1H, Ar-H, *J* = 7.6, 1.7 Hz, *E*-isomer), 8.05 (s, 1H, Ar-H, *Z*-isomer), 7.88-7.78 (m, Ar-H, 3H *E*-isomer, 2H *Z*-isomer), 7.55 (dd, 1H, Ar-H, *J* = 7.6, 1.2 Hz, *Z*-isomer), 7.44 (dd, 1H, Ar-H, *J* = 7.6, 1.7 Hz, *E*-isomer), 6.91 (s, 2H, Ar-H, *Z*-isomer), 6.78 (s, 2H, Ar-H, *E*-isomer), 6.75 (d, 1H, =CH, $^3J_{FH}$ = 40.0 Hz, *Z*-isomer), 6.60 (d, 1H, =CH, $^3J_{FH}$ = 22.5 Hz, *E*-isomer), 3.90 (s, 3H, CH_3, *E*-isomer), 3.88 (s, 3H, CH_3, *Z*-isomer), 3.84 (s, 6H, $2CH_3$, *Z*-isomer), 3.83 (s, 6H, $2CH_3$, *E*-isomer), 3.18 (s, 3H, CH_3, *E*-isomer), 3.16 (s, 3H, CH_3, *Z*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$): δ -108.16 (d, $^3J_{FH}$ = 21.4 Hz, *E*-isomer), 119.74 (d, $^3J_{FH}$ = 39.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{20}H_{21}FN_3O_5S$ $[M+H]^+$ 434.1186, found 434.1180.

_E/Z_-2-(4-(1-fluoro-2-(3,4,5-trimethoxyphenyl)vinyl)-1_H_-1,2,3-triazol-1-yl)aniline (51)

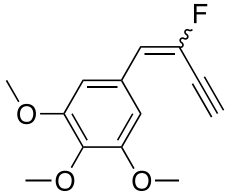


In a small vial, compound *E/Z*-**46** 20 mg (0.050 mmols) was dissolved in 600-microliter glacial acetic acid with vigorous stirring. Zinc dust (170 mg) was added and the vial was sealed with Teflon cap. Suspension was stirred vigorously at rt for 2 hours. TLC showed consumption of **46** at this time. Reaction mixture was diluted with ethyl acetate and filtered through a celite pad using 9-10 mL ethyl acetate. The filtrate was treated with 6 mL sat aqs $NaHCO_3$ solution and layers were separated. Organic layer was washed one time with brine and dried over Na_2SO_4. Solvent evaporation yielded 13.6 mg (74%) of

E/*Z*-**51** as a dirty white solid as the pure product. *E*/*Z* ratio = 76/24. R_f (40% EtOAc in hexanes) = 0.52.

^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.95 (s, 1H, Ar-H, *Z*-isomer), 7.82 (s, 1H, Ar-H, *E*-isomer), 7.29-7.24 (m, Ar-H, 1H *E*-isomer and 2H *Z*- isomer), 7.13 (d, 1H, Ar-H, *J* = 7.8 Hz, *Z*-isomer), 6.92 (s, 2H, Ar-H, *Z*-isomer), 6.91-6.84 (m, Ar-H, 3H *E*-isomer and 2H *Z*-isomer), 6.83 (t, 1H, *E*-isomer, *J* = 7.6 Hz), 6.74 (d, 1H, =CH, $^3J_{FH}$ = 40.5 Hz, *Z*-isomer), 6.59 (d, 1H, =CH, $^3J_{FH}$ = 23.0 Hz, *E*-isomer), 4.54 (br s, 2H, NH2, *Z*-isomer), 4.51 (br s, 2H, NH_2, *E*-isomer), 3.93 (s, 6H, $2CH_3$, *Z*-isomer), 3.91 (s, 3H, CH_3, *Z*-isomer), 3.88 (s, 3H, CH_3, *E*-isomer), 3.82 (s, 6H, $2CH_3$, *E*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$) : δ -107.03 (d, $^3J_{FH}$ = 24.4 Hz, *E*-isomer), 119.78 (d, $^3J_{FH}$ = 39.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{19}H_{20}FN_4O_3$ $[M+H]^+$ 371.1514, found 371.1517.

***E*/*Z*-5-(2-fluorobut-1-en-3-yn-1-yl)-1,2,3-trimethoxybenzene (53)**



A solution of 3,4,5-trimethoxybenzaldehyde **41** (100 mg, 0.51 mmol, 1.0 molar equiv) and sulfone **31** (200 mg, 0.61 mmol, 1.2 molar equiv) in dry THF (13.0 mL) was cooled under nitrogen to –78 °C (dry ice/isoPrOH). LHMDS (1.0 M solution in THF, 1.22 mL, 2.4 molar equiv) was added, the reaction mixture was stirred at –78 °C for 10 min and checked by TLC (20% acetone in hexanes), which showed disappearance of the aldehyde. TBAF (1.0 M solution in THF, 0.61 mL, 1.2 molar equiv) was added and the reaction mixture was allowed to stir for another 5 minutes. Saturated aq NH_4Cl was added and the mixture was poured into EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude reaction mixture was analyzed by ^{19}F NMR and mixture (*E*/*Z* ratio: 90/10) was isolated by column chromatography (20% acetone in hex anes). Yield of *E/Z*-**53**: 115.2 mg (95%, a pale yellow solid). *E/Z* ratio: 90/10.

In another reaction, 200 mg of 3,4,5-trimethoxybenzaldehyde **41** (1.02 mmol, 1.0 molar equiv) was reacted with sulfone **31** (398 mg, 1.22 mmol, 1.2 molar equiv) using the same procedure described above and a portion of pure *E*-isomer was separated by column chromatography purification.

Aldehyde **41**: 200 mg (1.02 mmol, 1.0 molar equiv); Sufone **31**: 398 mg (1.22 mmol, 1.2 molar equiv); LHMDS: 1.22 mL (1.0 M solution in THF, 2.4 molar equiv); THF: 26.0 mL; TBAF: 1.2 mL (1.0 M solution in THF, 1.2 molar equiv). Column chromatography: silica gel mesh 200-300, eluting solvent: 20% acetone in hexanes. Two fractions were collected:

First fraction: 102.3 mg, *E/Z* mixture (light yellow solid). R_f (20% acetone in hexanes) = 0.47. **Second fraction**: 125.6 mg, pure *E*-isomer (light yellow solid). R_f (20% acetone in hexanes) = 0.44. Combined yield of **53**: 227.9 mg (95%), *E*/*Z* ratio: 94/6.

^{1}H, ^{19}F and ^{13}C NMR and HRMS data of pure *E*-isomer :

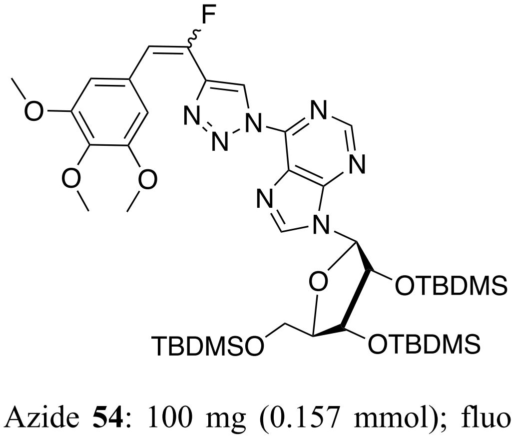
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (s, 1H, Ar-H, 2H), 6.60 (d, 1H, =CH, $^3J_{FH}$ = 17.1 Hz), 3.881 (s, 3H, CH_3), 3.878 (s, 6H, $2CH_3$), 3.69 (d, 1H, ≡CH, $^4J_{FH}$ = 4.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.3, 144.1 (d, $^1J_{CF}$ = 231.6 Hz), 138.6, 126.9 (d, J_{CF} = 9.6 Hz), 119.2 (d, 2C, $^2J_{CF}$ = 32.0 Hz), 105.6 (2C), 86.4 (d, J_{CF} = 7.3 Hz), 76.1 (d, $^2J_{CF}$ = 42.1

Hz), 61.1, 56.3. ^{19}F NMR (282 MHz, $CDCl_3$) : δ -106.82 (d, $^3J_{FH}$ = 18.3). HRMS (ESI) calcd. for $C_{13}H_{14}FO_3$ $[M+H]^+$ 237.0921, found 237.0926.

General procedure for click reactions of fluoroenyne 53 with nucleoside azides (54 and 56) and 2-methoxyphenyl azide

In a dry vial, azide (1.0 molar equiv) and fluoroenyne **53** (1.2 molar equiv) were dissolved in methylene chloride (6.4 mL per mmol) and $CuSO_4{\cdot}5H_2O$ (0.1 molar equiv) was added. Sodium ascobate (0.2 molar equiv) was dissolved in water (16.0 mL per mmol of sodium ascorbate) in separate dry vial. A biphasic mixture was stirred at room temperature until TLC indicated the consumption of azide. The reaction mixture was diluted with methylene chloride or ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by column chromatography using silica gel.

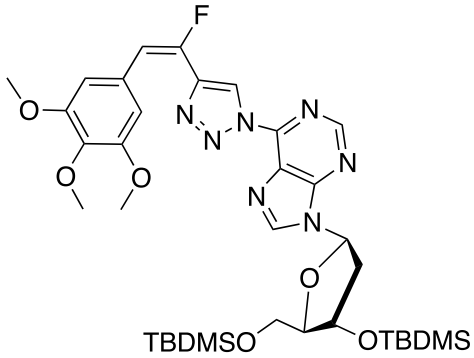
E/Z*-9-{3,4-bis[(tert-butyldimethylsilyl)oxy]-5-[((tert-butyldimethylsilyl)oxy)methyl]-tetrahydrofuran-2-yl}-6-{4-[1-fluoro-2-(3,4,5-trimethoxyphenyl)vinyl]-1*H*-1,2,3-triazol-1-yl}-9*H*-purine (*E/Z*-55a*)



Azide **54**: 100 mg (0.157 mmol); fluoroenyne **53** (*E/Z* 90/10): 44.5 mg (0.188 mmol); $CuSO_4{\cdot}5H_2O$: 4.0 mg (0.016 mmol); Na-ascorbate: 6.1 mg (0.031 mmol); CH_2Cl_2: 1.0

mL, Water: 0.500 mL. Column chromatography: silica gel mesh 200-300, eluting solvent: 20% EtOAc in hexanes. Yield of *E/Z*-**55a**: 91.2 mg (67%) of white foam, *E/Z* = 90/10. R_f (10% EtOAc in hexanes) = 0.25. ^{1}H NMR (500 MHz, CDCl$_3$): δ 9.24 (s, 1H, Ar-H, *Z*-isomer), 9.23 (s, 1H, Ar-H, *E*-isomer), 8.97 (s, 1H, Ar-H, *Z*-isomer), 8.95 (s, 1H, Ar-H, *E*-isomer), 8.66 (s, 1H, Ar-H, *Z*-isomer), 8.63 (s, 1H, Ar-H, *E*-isomer), 6.99 (s, 2H, Ar-H, *E*-isomer), 6.95 (s, 2H, Ar-H, *Z*-isomer), 6.87 (d, 1H, $^3J_{FH}$ = 40.5 Hz, *Z*-isomer), 6.84 (d, 1H, $^3J_{FH}$ = 24.9 Hz, *E*-isomer), 6.23 (d, 1H, H-1′, *Z*-isomer, *J* =5.4), 6.21 (d, 1H, H-1′, *E*-isomer, *J* =4.9), 4.64 (t, 1H, H-2′, *J* = 4.9, both *E*- and *Z*-isomers), 4.34-4.31 (m, 1H, H-3′, both *E*- and *Z*-isomers), 4.20-4.17 (m, 1H, H-4′, both *E*- and *Z*-isomers), 4.06-4.02 (m, 1H, H-5′, both *E*- and *Z*-isomers), 3.91 (s, 6H, 2CH$_3$, *Z*-isomer), 3.89 (s, 3H, CH$_3$, *Z*-isomer), 3.88-3.81 (m, 10H *E*-isomer, 1H *Z*-isomer), two rasonances 0.98 and 0.97 (2s, 9H, *t*-Bu, both *E*- and *Z*-isomers), 0.94 (s, 9H, *t*-Bu, both *E*- and *Z*-isomers), two rasonances 0.80 and 0.79 (2s, 9H, *t*-Bu, both *E*- and *Z*-isomers), three rasonances 0.18, 0.17 and 0.16 (3s, 6H, 2Si-CH$_3$, both *E*- and *Z*-isomers), two rasonances 0.111 and 0.108 (2s, 6H, 2Si-CH$_3$, both *E*- and *Z*-isomers), two rasonances -0.011 and -0.023 (2s, 3H, Si-CH$_3$, both *E*- and *Z*-isomers), two rasonances -0.23 and -0.25 (2s, 3H, Si-CH$_3$, both *E*- and *Z*-isomers). ^{19}F NMR (282 MHz, CDCl$_3$): δ -106.68 (d, $^3J_{FH}$ = 24.4, *E*-isomer), 120.18 (d, $^3J_{FH}$ = 39.7, *Z*-isomer). HRMS (ESI) calcd. for $C_{41}H_{67}FN_7O_7Si_3$ $[M+H]^+$ 872.4388 found 872.4392 .

***E*-9-{4-(tert-butyldimethylsilyloxy)-5-[(tert-butyldimethylsilyloxy)-methyl]tetrahydrofuran-2-yl}-6-{4-[1-fluoro-2-(3,4,5-trimethoxyphenyl)-vinyl]-1H-1,2,3-triazol-1-yl}-9H-purine (*E*-57)**



Azide **56**: 51 mg (0.10 mmol); fluoroenyne **53** (*E*-isomer): 28.3 mg (0.12 mmol); $CuSO_4{\cdot}5H_2O$: 2.5 mg (0.01 mmol); Na-ascorbate: 4.0 mg (0.02 mmol); CH_2Cl_2: 0.640 mL, Water: 0.318 mL. Column chromatography: silica gel mesh 200-300, eluting solvent: 20% EtOAc in hexanes. Yield of *E*-**57**: 47.1mg (63%) of white foam. R_f (20% EtOAc in hexanes) = 0.13. ^1H NMR (500 MHz, $CDCl_3$): δ 9.19 (s, 1H, Ar-H), 8.93 (s, 1H, Ar-H), 8.55 (s, 1H, Ar-H), 6.97 (s, 2H, Ar-H), 6.62 (d, 1H, $^3J_{FH}$ = 24.4 Hz), 6.58 (t, 1H, H-1′ J = 6.6 Hz), 4.65-4.62 (m, 1H, H-3′), 4.06 (app q, 1H, H-4′, $J_{app} \approx 3.2$ Hz), 3.89 (dd, 1H, H-5′, J = 11.3, 4.0, Hz), 3.85 (s, 3H, CH_3), 3.84 (s, 6H, $2CH_3$), 3.79 (dd, 1H, H-5′, J = 11.3, 3.1, Hz), 2.66 (app quint, 1H, H-2′, $J_{app} \approx 6.4$ Hz), 2.52 (ddd, 1H, H-2′, J = 13.1, 6.1, 3.9 Hz), 0.92 and 0.90 (2s, 18H, t-Bu), three rasonances 0.11, 0.09 and 0.08 (3s, 12H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 153.3, 152.3, 148.8 (d, $^1J_{CF}$ = 234.4 Hz), 145.1, 144.4, 141.6 (d, $^2J_{CF}$ = 38.4 Hz), 138.1, 127.5 (d, $^2J_{CF}$ = 11.9 Hz), 124.0, 123.4, 113.4 (d, $^2J_{CF}$ = 30.2 Hz), 106.9, 88.5, 72.1, 62.9, 61.1, 56.4, 41.7, 26.1, 25.9, 18.6, 18.2, -4.5, -4.6, -5.2, -5.3. ^{19}F NMR (282 MHz, $CDCl_3$) : δ -106.82 (d, $^3J_{FH}$ = 24.4). HRMS (ESI) calcd. for $C_{35}H_{53}FN_7O_6Si_2$ [M + H]+ 742.3574, found 742.3571.

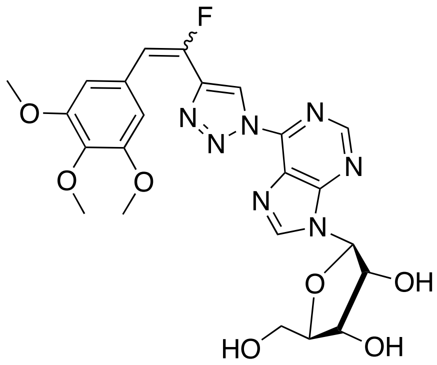
Synthesis of *E/Z*-43 by click reaction of fluoroenyne 53 with 2-methoxyphenyl azide

2-Methoxyphenyl azide: 30 mg (0.20 mmol); fluoroenyne **53** (*E/Z* 97/3): 56.6 mg (0.24 mmol); $CuSO_4{\cdot}5H_2O$: 5.0 mg (0.02 mmol); Na-ascorbate: 7.9 mg (0.04 mmol); CH_2Cl_2: 1.2 mL, Water: 0.600 mL. Column chromatography: silica gel mesh 200-300, eluting solvent: 25% EtOAc in hexanes. Yield of *E/Z*-**43**: 62 mg (63%) of pale yellow solid. *E/Z* ratio: 97/3.

General procedure for desilylation of nucleoside derivatives

In a clean, dry plastic vial nucleoside derivative *E/Z*-**55a** or *E*-**57** (1.0 molar equiv) was dissolved in anhydrous THF (15.6 mL per mmol of substrate). $Et_3N{\cdot}3HF$ (4.0 molar equiv) was added using a syringe. Vial was filled with N_2 and the reaction mixture was stirred at room temperature for 30 h, until TLC indicated complete consumption of the starting material. Solvent was removed under air and the crude reaction mixture was purified by column chromatography using silica gel (200-300 mesh).

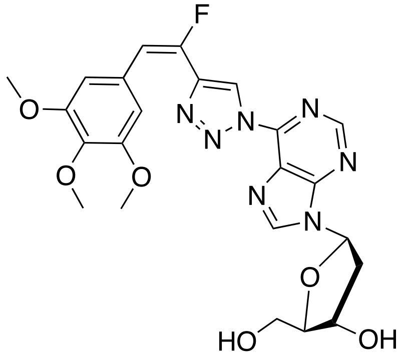
***E/Z*-2-{6-[4-(1-fluoro-2-(3,4,5-trimethoxyphenyl)vinyl)-1*H*-1,2,3-triazol-1-yl]-9*H*-purin-9-yl}-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (52)**



Compound **55** (*E/Z*-85/15): 28.0 mg (0.032 mmol, 1.0 molar equiv); $Et_3N{\cdot}3HF$: 21.0 microliter (0.128 mmols, 4.0 molar equiv); THF: 0.500 mL). Eluting solvent: 40% EtOAc in hecanes followed by 8% MeOH in methylene chloride). Yield of *E/Z*-**52**: 11.2 mg (66%) of white solid. *E/Z* ratio: 85/15. R_f (5% MeOH in methylene chloride) = 0.03.

^{1}H NMR (500 MHz, CD_3OD): δ 9.19 (s, 1H, Ar-H, *Z*-isomer), 9.18 (s, 1H, Ar-H, *E*-isomer), 8.93-8.90 (3s, 2H, Ar-H, both *E*- and *Z*-isomers), 6.91 (s, 2H, Ar-H, *Z*-isomer), 6.89 (s, 2H, Ar-H, *E*-isomer), 6.70 (d, 1H, $^{3}J_{FH}$ = 23.0 Hz, *E*-isomer), 6.698 (d, 1H, $^{3}J_{FH}$ = 40.5 Hz, *Z*-isomer), 6.24-6.21 (m, 1H, H-1′, both *E* and Z-isomers), 4.76 (t, 1H, H-2′, *J* = 4.9, *Z*-isomer), 4.73 (t, 1H, H-2′, *J* = 5.1, *E*-isomer), 4.42 (t, 1H, H-3′, *J* = 4.6, *Z*-isomer), 4.40 (t, 1H, H-3′, *J* = 4.4, *E*-isomer), 4.20-4.17 (m, 1H, H-4′, both *E*- and *Z*-isomers), 3.96-3.90 (m, 1H, H-5′, both *E*- and *Z*-isomers), 3.91 (s, 6H, $2CH_3$, *Z*-isomer), 3.89 (s, 3H, CH_3, *Z*-isomer), 3.88-3.81 (m, 10H *E*-isomer, 1H *Z*-isomer). ^{19}F NMR (282 MHz, acetone-d_6) : δ -105.84 (d, $^{3}J_{FH}$ = 21.4, *E*-isomer), -119.38 (d, $^{3}J_{FH}$ = 40.4, *Z*-isomer).. HRMS (ESI) calcd. for $C_{23}H_{25}FN_7O_7$ $[M+H]^+$ 530.1794, found 530.1795.

5-{6-[4-((*E*)-1-fluoro-2-(3,4,5-trimethoxyphenyl)vinyl)-1H-1,2,3-triazol-1-yl]-9H-purin-9-yl}-2-(hydroxymethyl)tetrahydrofuran-3-ol (58)



Compound *E*-**57**: 28.0 mg (0.051 mmol, 1.0 molar equiv); $Et_3N \cdot 3HF$: 33.0 microliter (0.204 mmols, 4.0 molar equiv); THF: 0.800 mL). Eluting solvent: 5% MeOH in methylene chloride). Yield of *E*-**58**: 11.2 mg (66%) of white solid. *E/Z* ratio: 85/15. R_f (10% MeOH in methylene chloride) = 0.19. 1H NMR (500 MHz, acetone-d_6): δ 9.33 (s, 1H, Ar-H), 8.94 (s, 1H, Ar-H), 8.90 (s, 1H, Ar-H), 6.97 (s, 2H, Ar-H), 6.74 (d, 1H, $^{3}J_{FH}$ =

23.5 Hz), 6.68 (t, 1H, H-1′ J = 6.7 Hz), 4.74-4.72 (m, 2H, H-3′), 4.54 (d, 1H, OH, J = 3.7 Hz), 4.48 (dd, 1H, OH, J = 6.4, 4.6 Hz), 4.12 (app q, 1H, H-4′, $J_{app} \approx 3.1$ Hz), 3.88-3.84 (m, 1H, H-5′), 3.82-3.78 (m, 7H, H-5′ and 2CH_3), 3.74 (s, 3H, CH_3), 2.92 (app quint, 1H, H-2′, Japp ≈ 6.6 Hz), 2.56 (ddd, 1H, H-2′, J = 13.4, 5.9, 3.2Hz). ^{13}C NMR (125 MHz, CD_3OD): δ 155.7, 154.8, 153.1, 150.2 (d, $^{1}J_{CF}$ = 236.6 Hz), 148.0, 145.4, 142.1 (d, $^{2}J_{CF}$ = 37.1 Hz), 129.3 (d, $^{2}J_{CF}$ = 11.9 Hz), 125.4, 125.3, 124.8, 114.4 (d, $^{2}J_{CF}$ = 29.3 Hz), 108.2, 89.9, 86.9, 72.7, 63.3, 61.4, 56.9, 41.7. ^{19}F NMR (282 MHz, acetone-d_6) : δ -106.07 (d, $^{3}J_{FH}$ = 24.4). HRMS (ESI) calcd. for $C_{23}H_{25}FN_7O_6$ $[M+H]^+$ 514.1845, found 514.1849.

REFERENCES

1. Nam, N.-H.: Combretastatin A-4 Analogues as Antimitotic Antitumor Agents, *Curr. Med. Chem.* **2003**, *10,* 1697-1722.

2. Cirla, A.; Mann, J.: Combretastatins: from Natural Products to Drug Discovery, *Nat. Prod. Rep.* **2003**, *20*, 558–564.

3. Marrelli, M.; Conforti, F.; Statti, G. A.; Cachet, X.; Michel, S.; Tillequin, F.; Menichini, F.: Biological Potential and Structure-Activity Relationships of Most Recently Developed Vascular Disrupting Agents: An Overview of New Derivatives of Natural Combretastatin A-4, *Curr. Med. Chem.* **2011**, *18,* 3035-3081.

4. Shan, Y.; Zhang, J.; Liu, Z.; Wang, M.; Dong, Y.: Developments of Combretastatin A-4 Derivatives as Anticancer Agents, *Curr. Med. Chem.* **2011**, *18,* 523-538.

5. Pettit, G. R.; Singh, S. B.; Hamel, E.; Lin, C. M.; Alberts, D. S.; Garcia-Kendall, D.: Isolation and Structure of the Strong Cell Growth and Tubulin Inhibitor Combretastatin A-4, *Experientia* **1989**, *45*, 209-211.

6. Pettit, G. R.; Combretastatin A-4 Prodrug, US Patent No. 5561122.

7. Ohsumi, K.; Nakagawa, R.; Fukuda, Y.; Hatanaka, T.; Morinaga, Y.; Nihei, Y.; Ohishi, K.; Suga, Y.; Akiyama, Y.; Tsuji, T.: Novel Combretastatin Analogues Effective Against Murine Solid Tumors: Design and Structure-Activity Relationships, *J. Med. Chem*. **1998**, *41*, 3022-3032.

8. Tron, G. C.; Pirali, T.; Sorba, G.; Pagliai, F.; Busacca, S.; Genazzani, A. A.: Medicinal Chemistry of Combretastatin A4: Present and Future Directions, *J. Med. Chem.* **2006**, *49*, 3033-3044.

9. Maya, A. B. S.; Pérez-Melero, C.; Mateo, C.; Alonso, D.; Fernández, J. L.; Gajate, C.; Mollinedo,F.; Peláez, R.; Caballero, E.; Medarde, M.: Further Naphthylcombretastatins. An Investigation on the Role of the Naphthalene Moiety, *J. Med. Chem.* **2005**, *48,* 556-568.

10. Pettit, G. R.; Minardi, M. D.; Rosenberg, H. J.; Hamel, E.; Bibby, M. C.; Martin, S. W.; Jung, M. K.; Pettit, R. K.; Cuthbertson, T. J.; Chapuis, J.-C.: Antineoplastic Agents. 509. Synthesis of Fluorcombretastatin Phosphate and Related 3-Halostilbenes, *J. Nat. Prod.* **2005**, *68,* 1450-1458.

11. Kirsch, P. *Modern Fluoroorganic Chemistry. Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, **2004**.

12. *Current Fluoroorganic Chemistry: New Synthetic Directions, Technologies,*

Materials, and Biological Applications; Soloshonok, V. A.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J. F., Eds.; American Chemical Society: Washington DC, **2007**.

13. Smart, B. E.: Fluorine Substituent Effect (On Bioactivity), *J. Fluorine Chem.* **2001**, *109*, 3-11.

14. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V.: Fluorine in Medicinal Chemistry, *Chem. Soc. Rev*. **2008**, *37*, 320-330.

15. Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M.: Fluorine In Medicinal Chemistry, *Chembiochem* **2004**, *5*, 637-643.

16. Ismail, F. M. D.: Important Fluorinated Drugs in Experimental and Clinical Use, *J. Fluorine Chem.* **2002**, *118*, 27-33.

17. Bégué, J.-P.; Bonnet-Delpon, D.: Recent Advances (1995–2005) in Fluorinated Pharmaceuticals Based on Natural Products, *J. Fluorine Chem.* **2006**, *127*, 992-1012.

18. Lawrence, N. J.; Hepworth, L. A.; Rennison, D.; McGown, A. T.; Hadfield, J. A.: Synthesis and Anticancer Activity of Fluorinated Analogues of Combretastatin A-4, *J. Fluorine Chem.* **2003**, *123*, 101-108.

19. Alloatti, D.; Giannini, G.; Cabri, W.; Lustrati, I.; Marzi, M.; Ciacci, A.; Gallo, G.; Tinti, M. O.; Marcellini, M.; Riccioni, T.; Guglielmi, M. B.; Carminati, P.; Pisano, C.: Synthesis and Biological Activity of Fluorinated Combretastatin Analogues, *J. Med. Chem.* **2008**, *51,* 2708-2721.

20. Gaukroger, K.; Hadfield, J. A.; Lawrence, N. J. Nolan*,* S. McGown*,* A. T.: Structural Requirements for the Interaction of Combretastatins with Tubulin: How Important is the Trimethoxy Unit, *Org. Biomol. Chem.* **2003**, *1*, 3033-3037.

21. Angell, Y. L.; Burgess, K.: Peptidomimetics via Copper-Catalyzed Azide–Alkyne Cycloadditions, *Chem. Soc. Rev.* **2007**, *36*, 1674-1689.

22. Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H.: CuI-Catalyzed Alkyne–Azide "Click" Cycloadditions from a Mechanistic and Synthetic Perspective, *Eur. J. Org. Chem.* **2006**, 51–68.

23. Appendino, G.; Bacchiega, S.; Minassi, A.; Cascio, M. G.; Petrocellis, L. D.; Marzo, V. D.: The 1,2,3-Triazole Ring as a Peptido- and Olefinomimetic Element: Discovery of Click Vanilloids and Cannabinoids, *Angew. Chem. Int. Ed*. **2007**, *46*, 9312-9315.

24. Agalave, S. G.; Maujan, S. R.; Pore, V. S.: Click Chemistry: 1,2,3-Triazoles as Pharmacophores, *Chem. Asian J.* **2011**, *6,* 2696 —2718.

25. Kolb, H. C.; Sharpless, K. B.: The Growing Impact of Click Chemistry on Drug Discovery, *Drug Discovery Today* **2003**, *8*, 1128-1137.

26. Odlo, K.; Fournier-Dit-Chabert, J.; Ducki, S.; Gani, O. A. B. S. M.; Sylte, I.; Hansen, T. V.: 1,2,3-Triazole Analogs of Combretastatin A-4 as Potential Microtubule-Binding Agents, *Bioorg. Med. Chem*. **2010**, *18*, 6874-6885.

27. Odlo, K.; Hentzen, J.; Fournier dit Chabert, J.; Ducki, S.; Gani, O. A. B. S. M.; Sylte, I.; Skrede, M.; Flørenes, V. A.; Hansen, T. V.: 1,5-Disubstituted 1,2,3-Triazoles as Cis-Restricted Analogues of Combretastatin A-4: Synthesis, Molecular Modeling and Evaluation as Cytotoxic Agents and Inhibitors of Tubulin, *Bioorg. Med. Chem*. **2008**, *16*, 4829-4838.

28. Cafici, L.; Pirali, T.; Condorelli, F.; Grosso, E. D.; Massarotti, A.; Sorba, G.; Canonico, P. L.; Tron, G. C.; Genazzani, A. A.: Solution-Phase Parallel Synthesis and Biological Evaluation of Combretatriazoles, *J. Comb. Chem.* **2008**, *10,* 732-740.

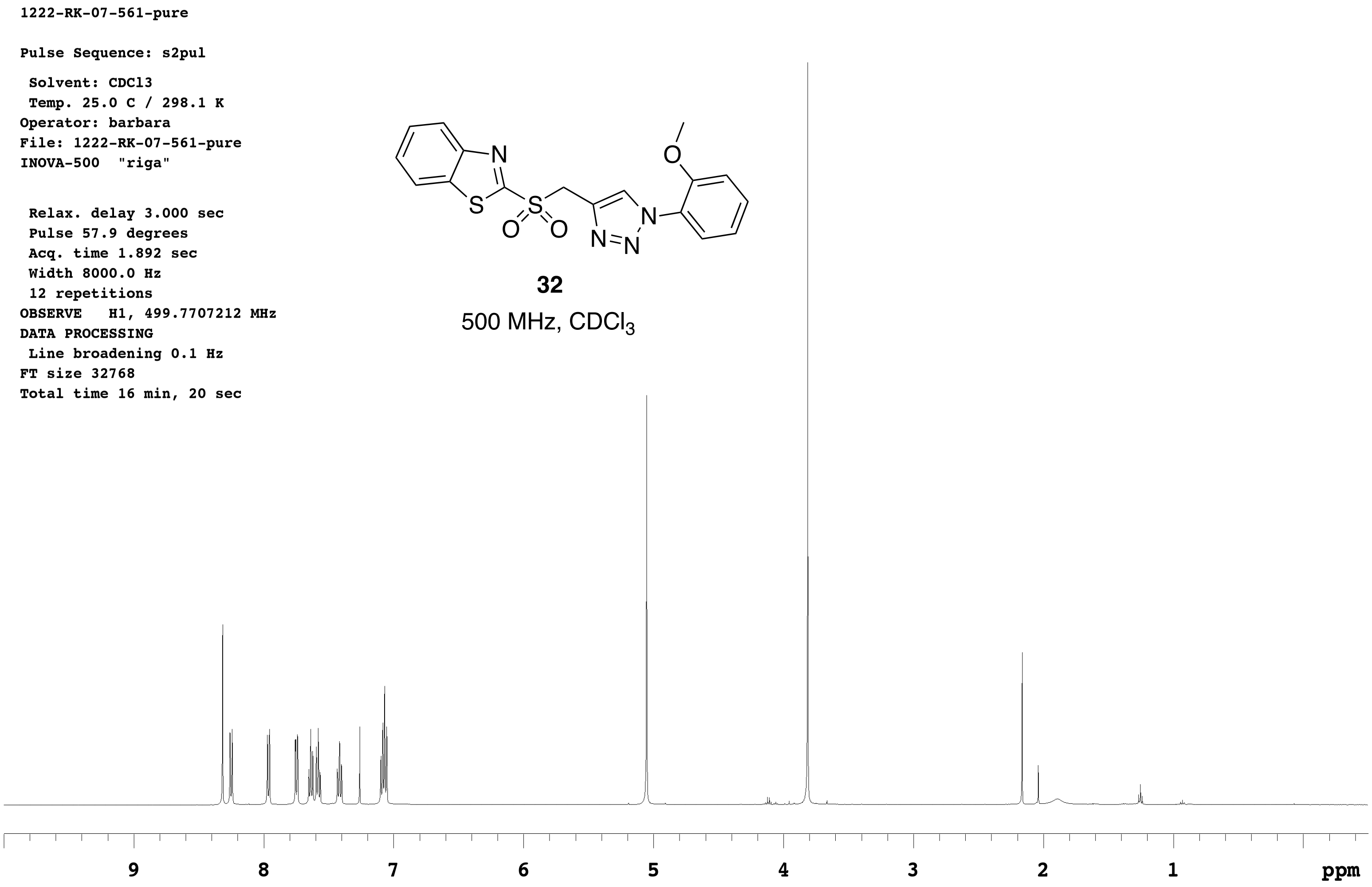
29. Blanch, N. M.; Chabot, G. G.; Quentin, L.; Scherman, D.; Bourg, S.; Dauzonne, D.: In Vitro And In Vivo Biological Evaluation of New 4,5-Disubstituted 1,2,3-Triazoles as Cis-Constrained Analogs of Combretastatin A4, *Eur. J. Org. Chem.* **2012**, *54*, 22-32.

30. Aucagne, V.; Leigh, D. A.: Chemoselective Formation of Successive Triazole Linkages in One Pot: “Click−Click” Chemistry, *Org. Lett*. **2006**, *8*, 4505-4507.

31. Lakshman, M. K.; Singh, M. K.; Parrish, D.; Balachandran, R.; Day, B. W.: Azide-Tetrazole Equilibrium of C-6 Azidopurine Nucleosides and Their Ligation Reactions with Alkynes*, J. Org. Chem*. **2010**, *75*, 2461–2473.

32. Biological studies were performed in collaboration with Drs. Andreas Vogt, Billy Day and Livia Salum at the University of Pittsburgh.

33. Tao, C.-Z.; Cui, X.; Li, J.; Liu, A.-X.; Liu, L.; Guo, Q.-X.: Copper-Catalyzed Synthesis of Aryl Azides And 1-Aryl-1,2,3-Triazoles from Boronic Acids, *Tetrahedron Lett.* **2007**, *48,* 3525-3529.



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Operator: barbara
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INOVA-500  "riga"

 Relax. delay 3.000 sec
 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 12 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 16 min, 20 sec
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32

500 MHz, CDCl$_3$

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Operator: barbara
File: 1222-RK-07-561-13C
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 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
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OBSERVE  C13, 125.6674223 MHz
DECOUPLE  H1, 499.7732084 MHz
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 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
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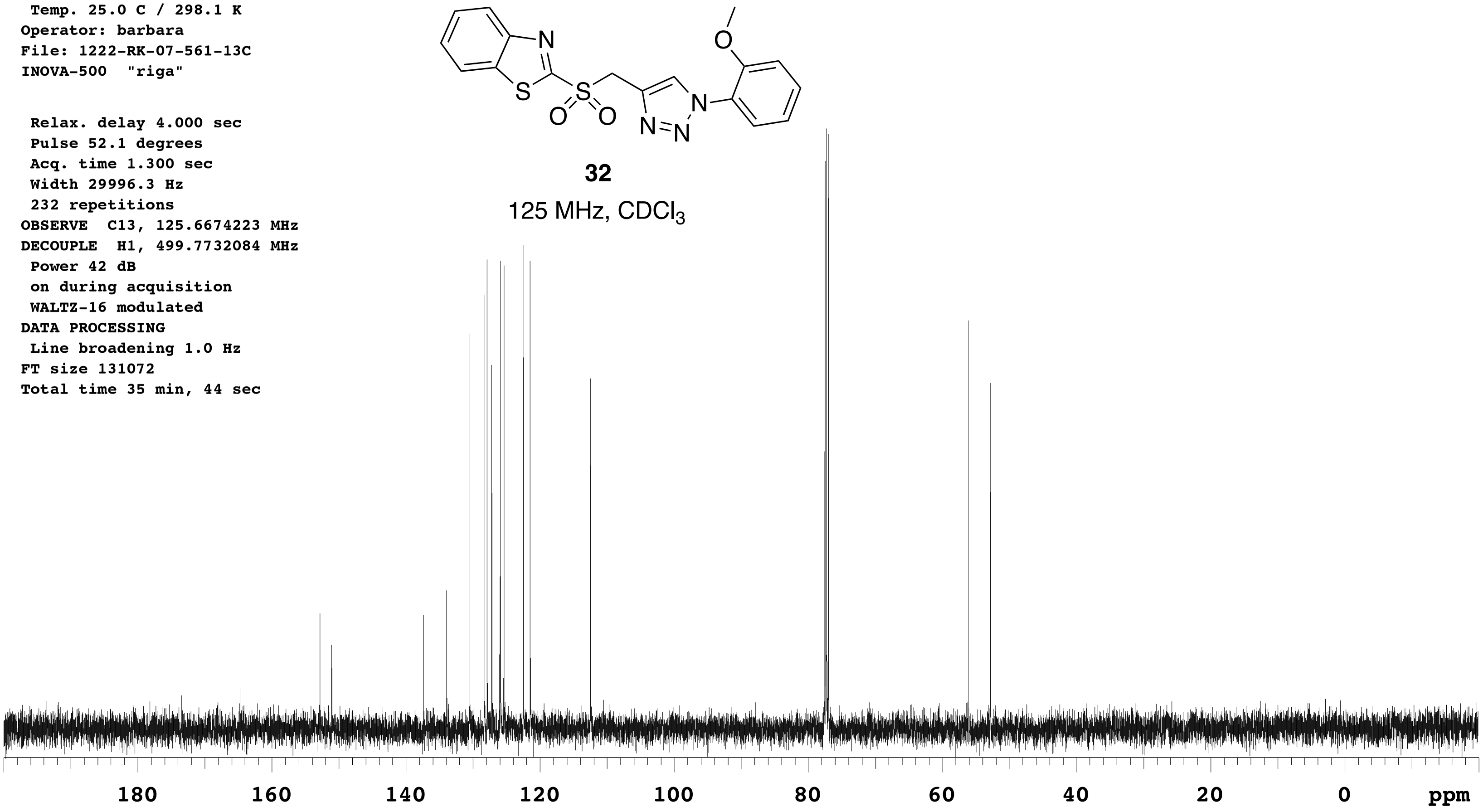

32

125 MHz, $CDCl_3$

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 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-06-413-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
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OBSERVE   H1, 499.7707215 MHz
DATA PROCESSING
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FT size 65536
Total time 9 min, 40 sec
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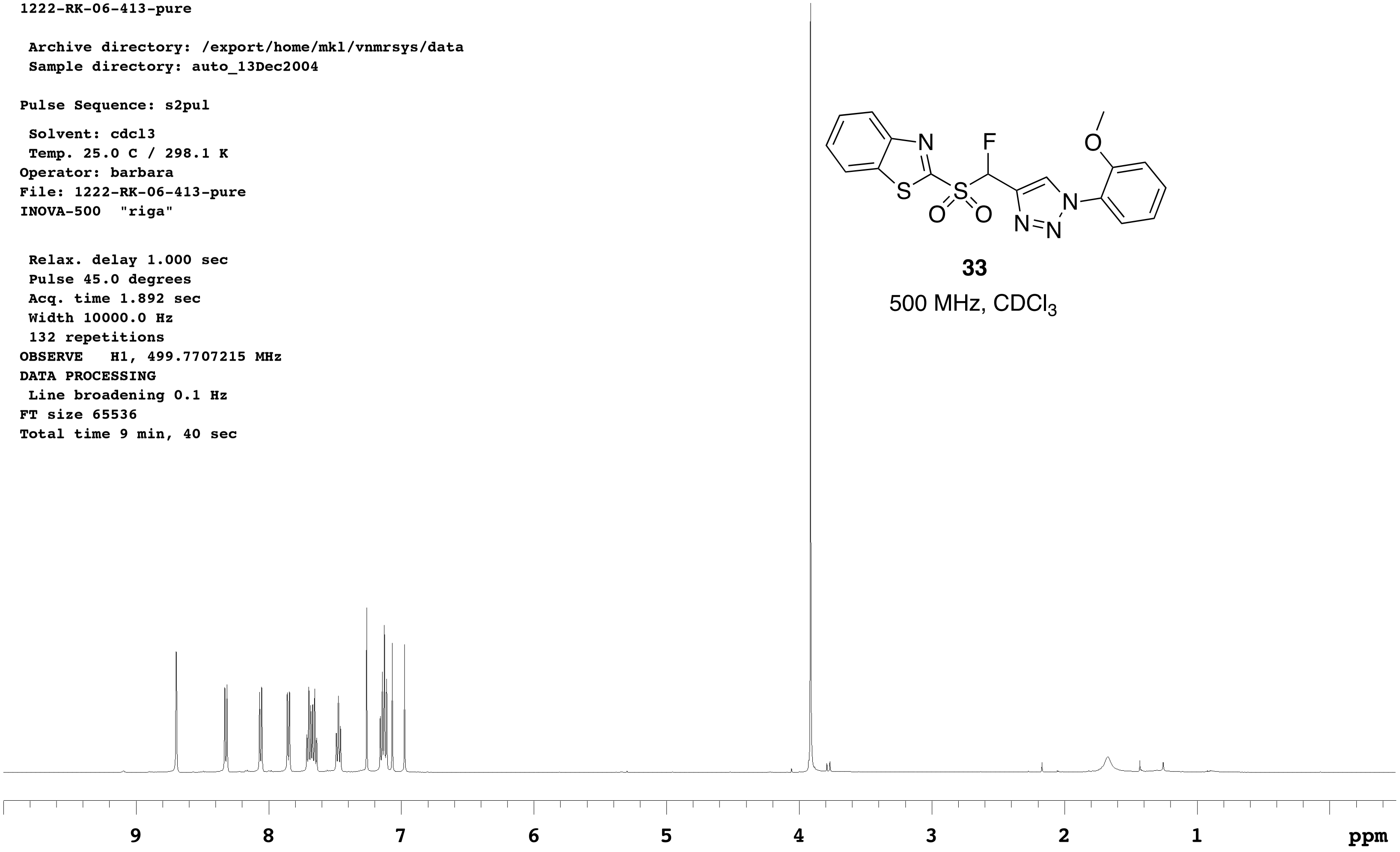

33

500 MHz, $CDCl_3$

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1222-RK-06-413-13C

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 Sample directory:

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 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-06-413-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 352 repetitions
OBSERVE  C13, 125.6674205 MHz
DECOUPLE  H1, 499.7732084 MHz
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 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
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FT size 131072
Total time 2 hr, 57 min, 20 sec
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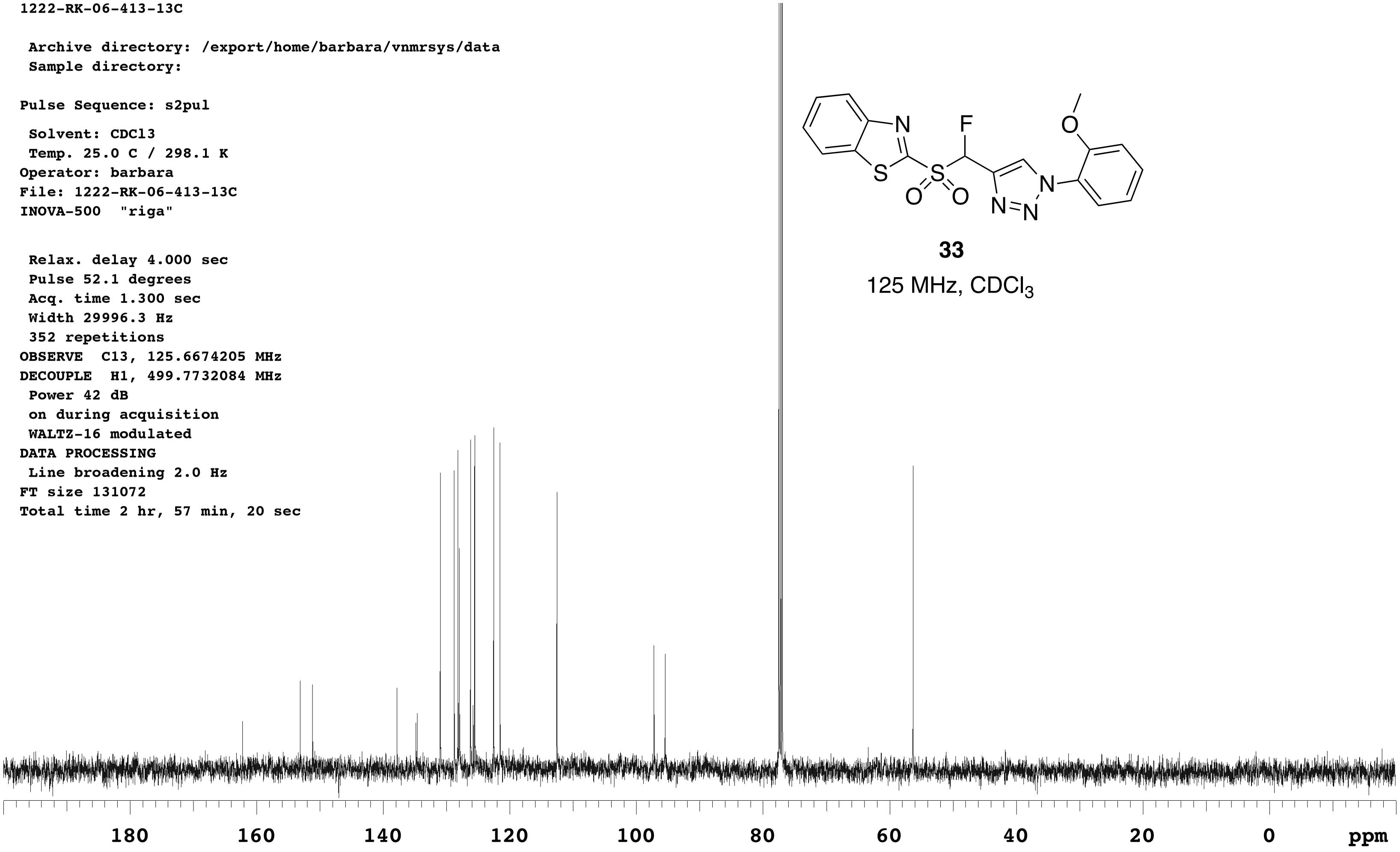

33

125 MHz, $CDCl_3$

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 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-08-564-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
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DATA PROCESSING
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FT size 32768
Total time 9 min, 40 sec
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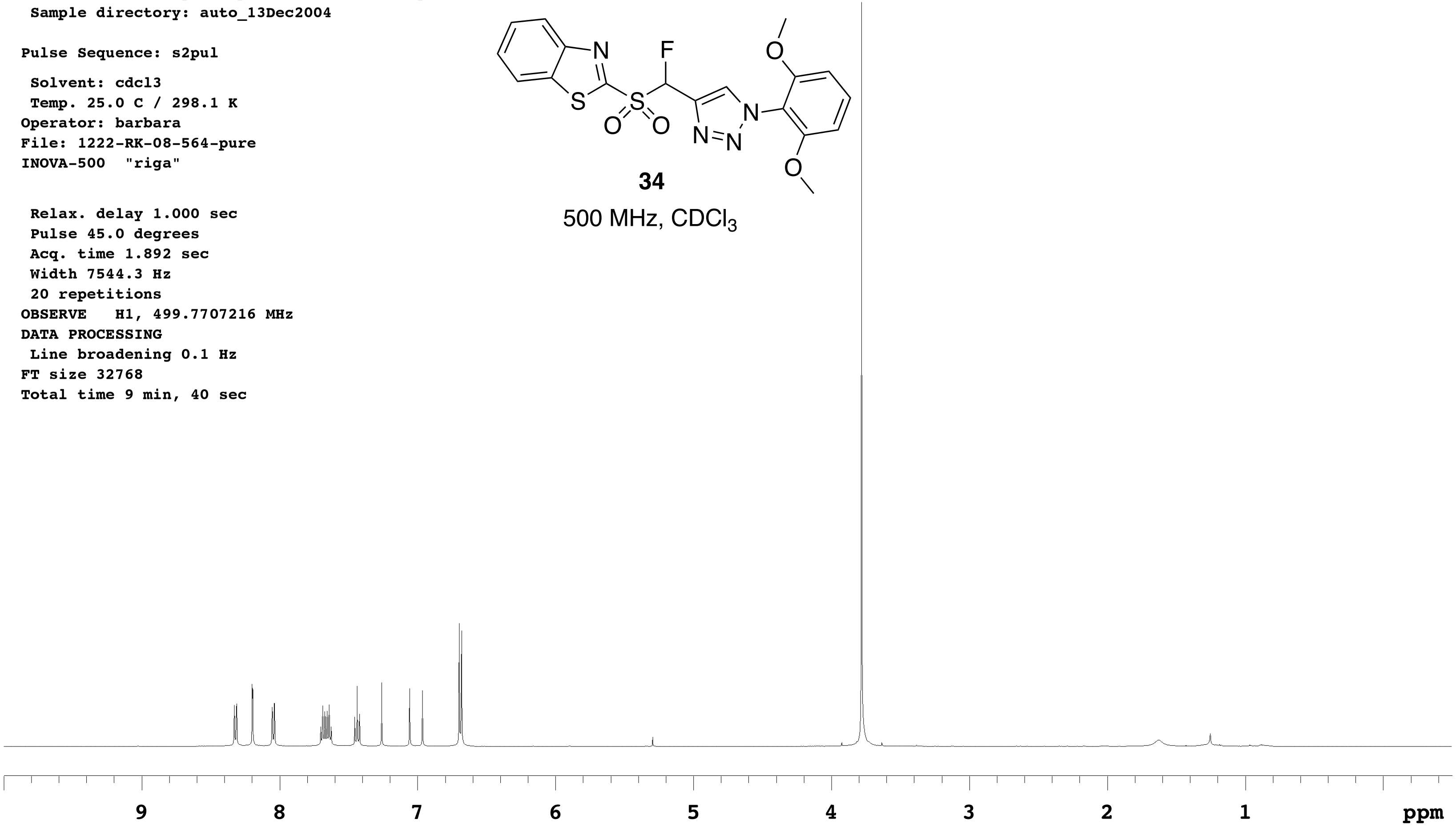

34

500 MHz, $CDCl_3$

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1222-RK-08-564-13C

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 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-08-564-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 664 repetitions
OBSERVE  C13, 125.6674177 MHz
DECOUPLE  H1, 499.7732084 MHz
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 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
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FT size 131072
Total time 2 hr, 57 min, 20 sec
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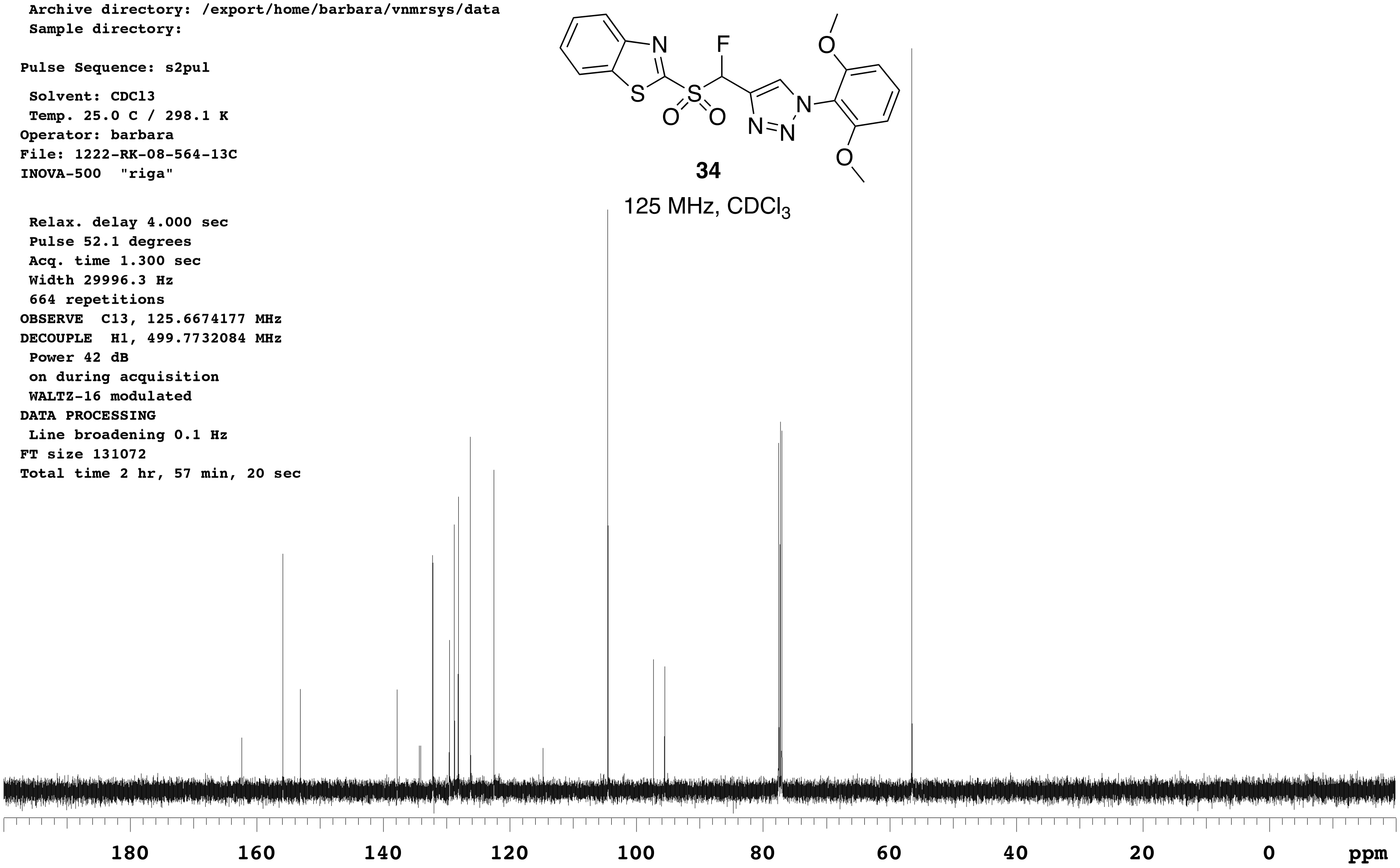

34

125 MHz, $CDCl_3$

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1222-RK-07-577-pure

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 Sample directory: auto_13Dec2004

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 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-08-577-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 64 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
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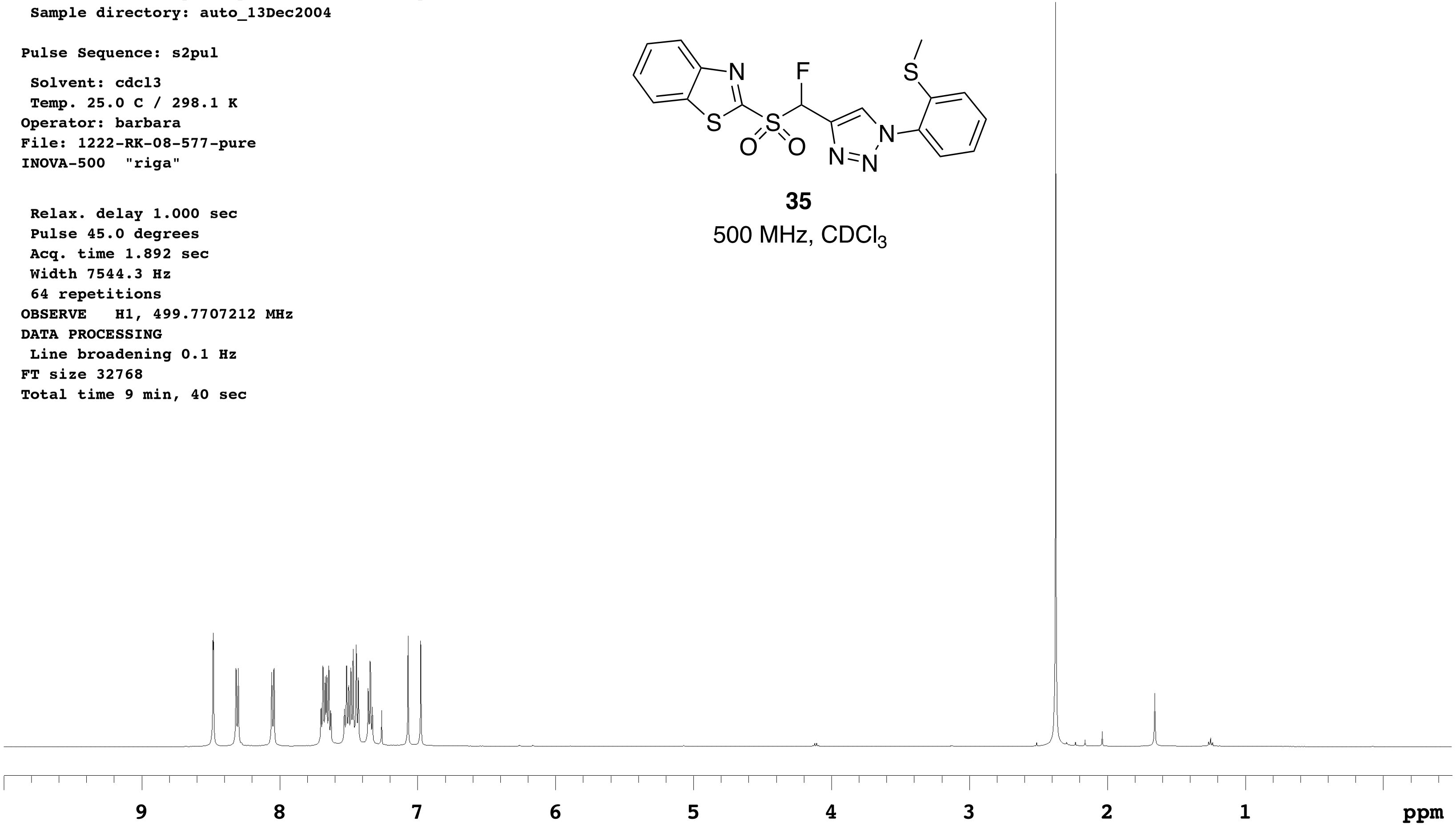

35

500 MHz, $CDCl_3$

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1222-RK-08-577-13C

 Archive directory: /export/home/barbara/vnmrsys/data
 Sample directory:

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-08-577-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 336 repetitions
OBSERVE  C13, 125.6674526 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 4.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec
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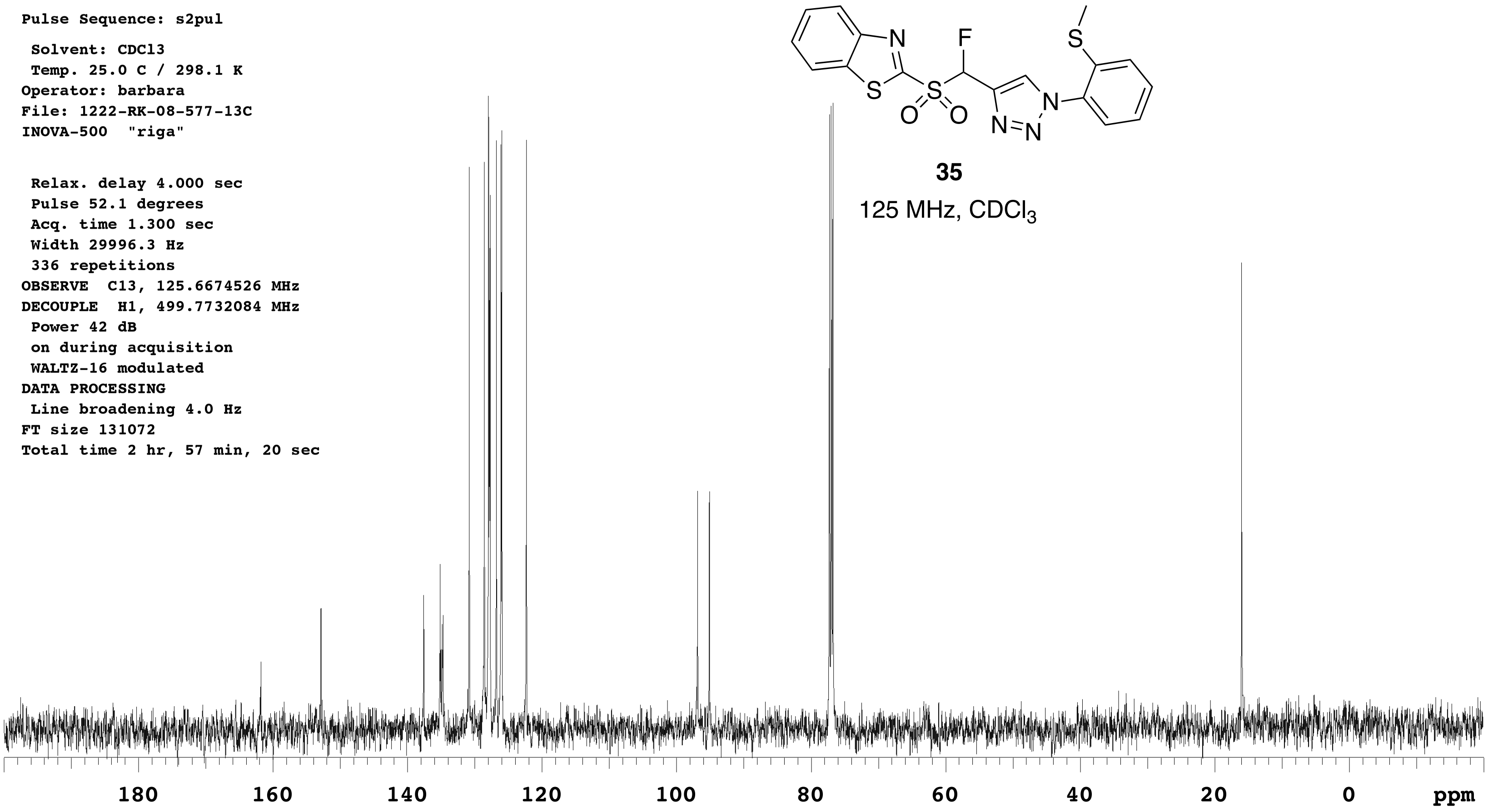

35

125 MHz, $CDCl_3$

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1222-RK-08-578-pure

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 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-08-578-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
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OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
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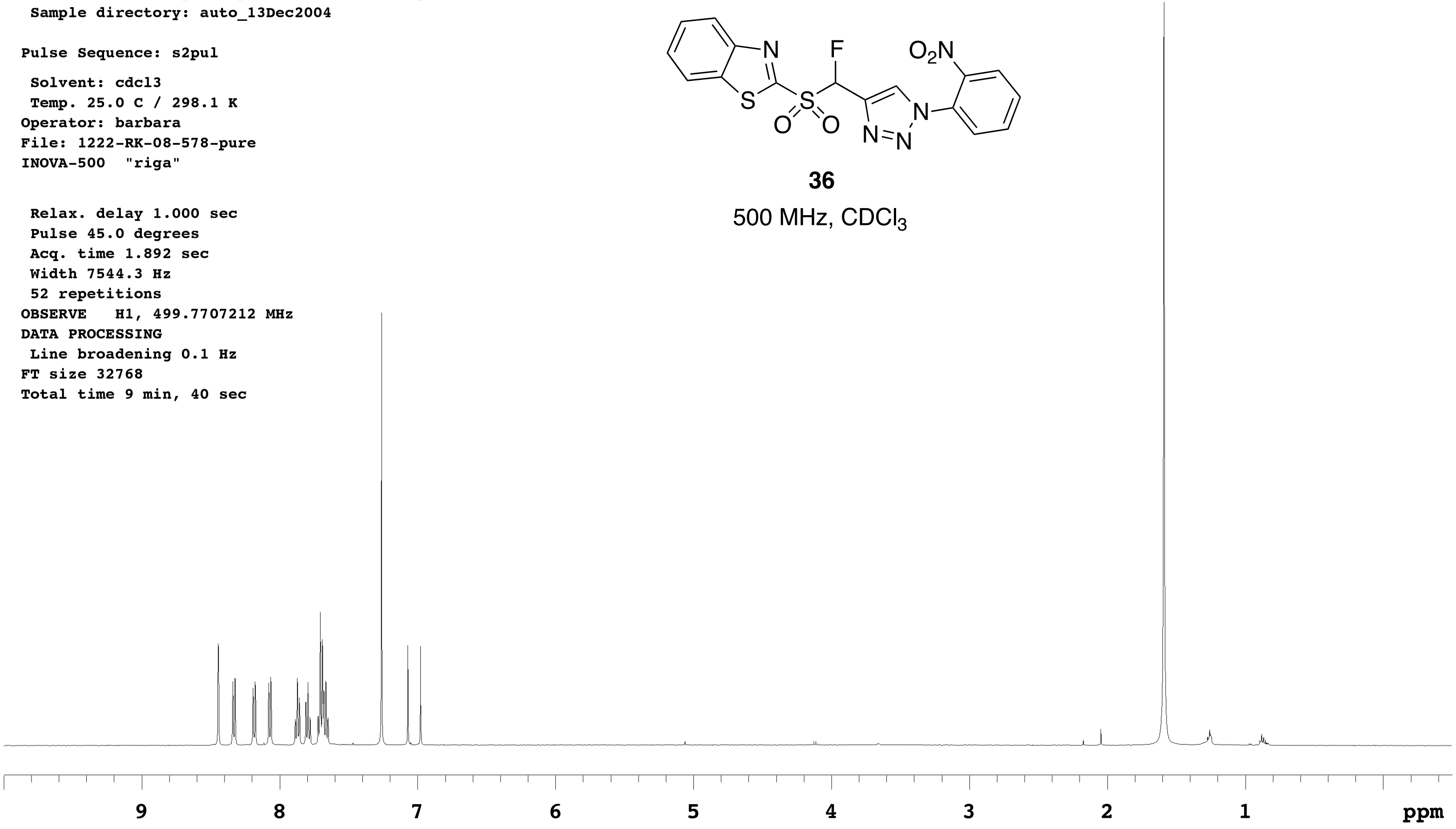
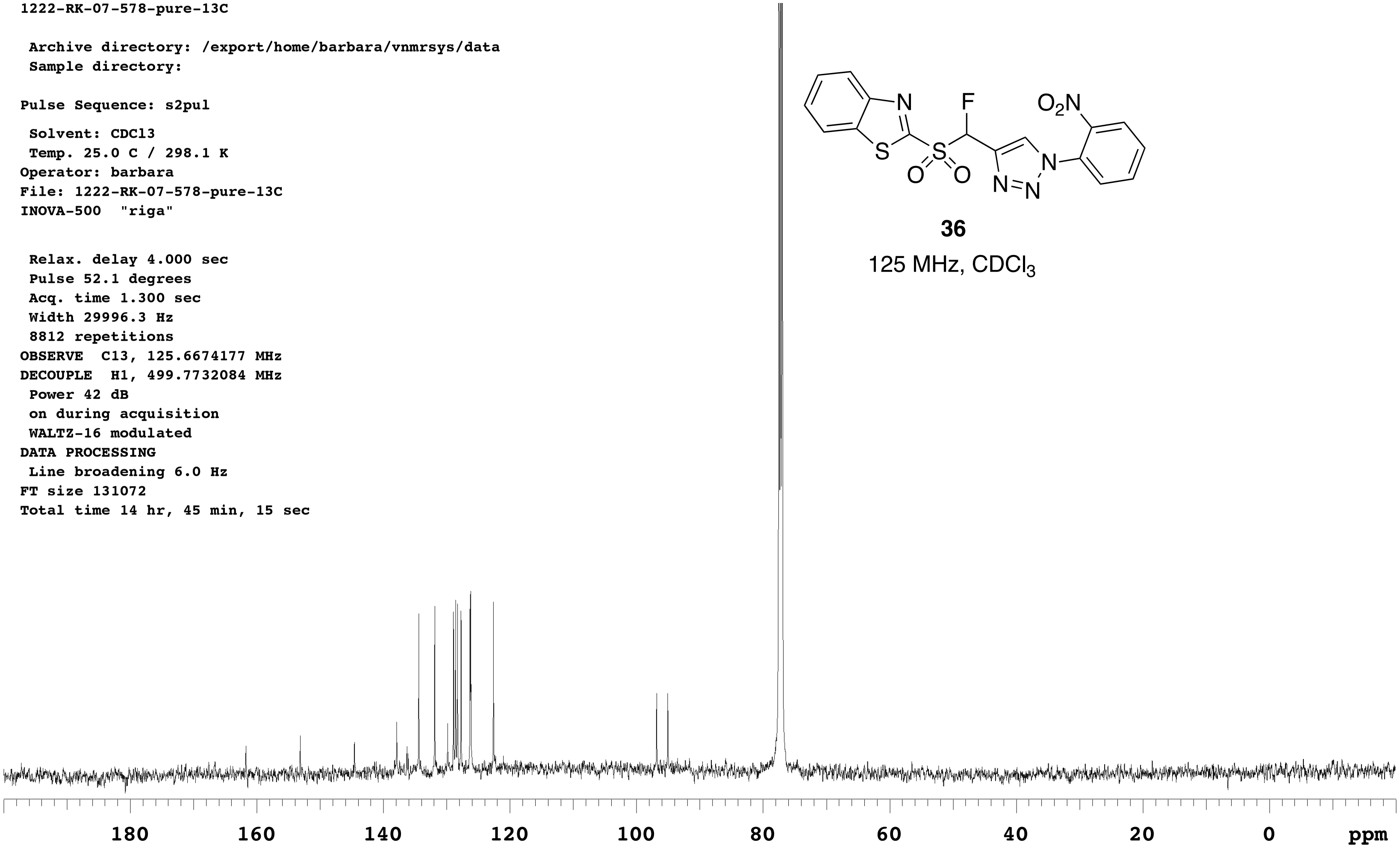


36

500 MHz, $CDCl_3$



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1222-RK-07-578-pure-13C

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 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-07-578-pure-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
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OBSERVE  C13, 125.6674177 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 6.0 Hz
FT size 131072
Total time 14 hr, 45 min, 15 sec
```

36

125 MHz, $CDCl_3$

```
1222-RK-08-600-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-08-600-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 20 repetitions
OBSERVE   H1, 499.7707203 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
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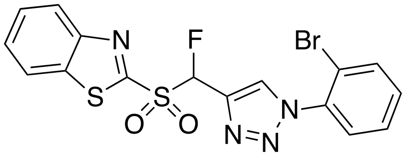
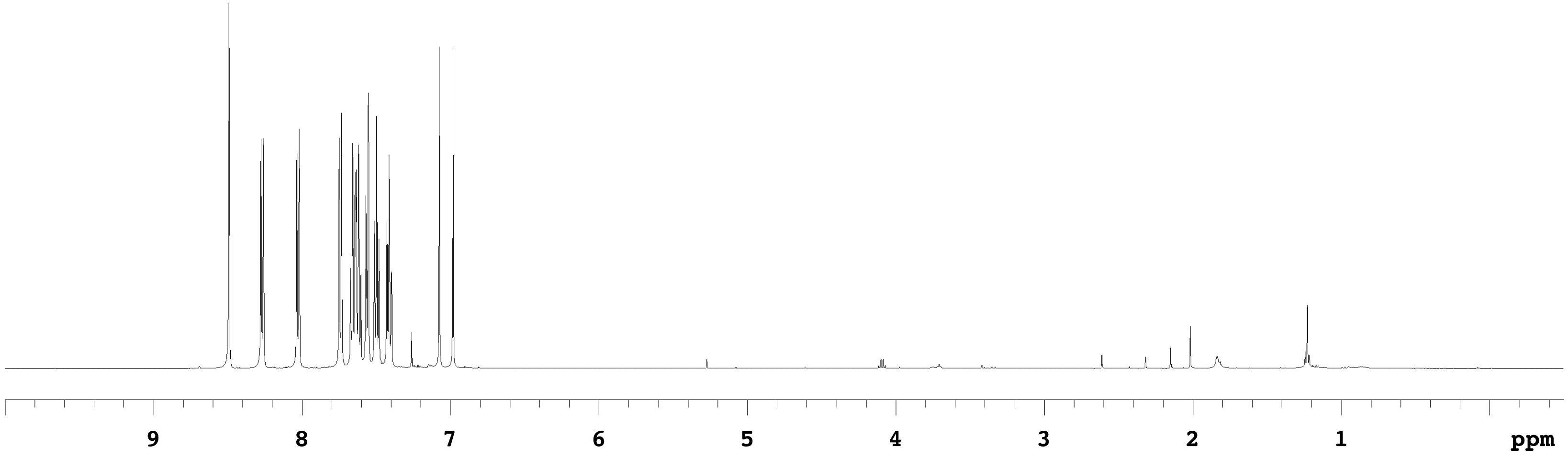


37

500 MHz, $CDCl_3$



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 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-08-600-13C
INOVA-500  "riga"

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 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 200 repetitions
OBSERVE  C13, 125.6674351 MHz
DECOUPLE  H1, 499.7732084 MHz
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 on during acquisition
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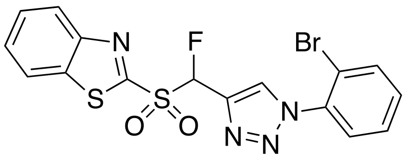
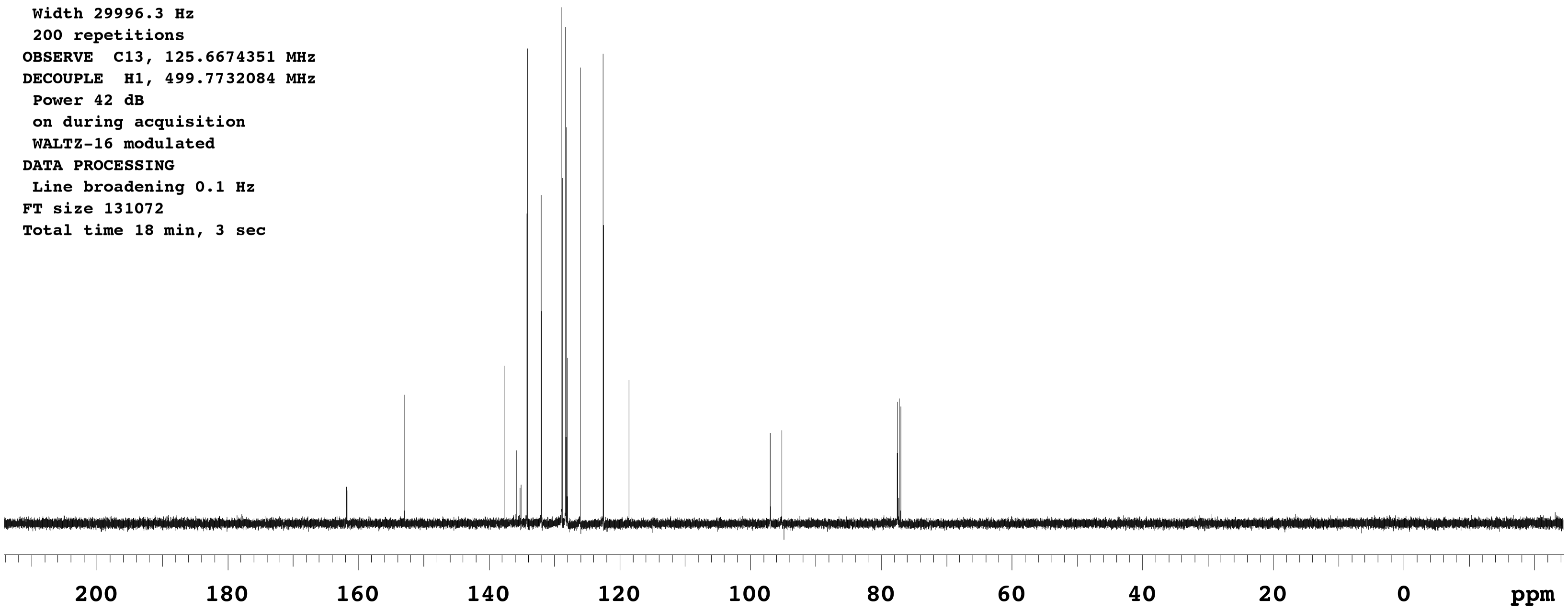


37

125 MHz, $CDCl_3$

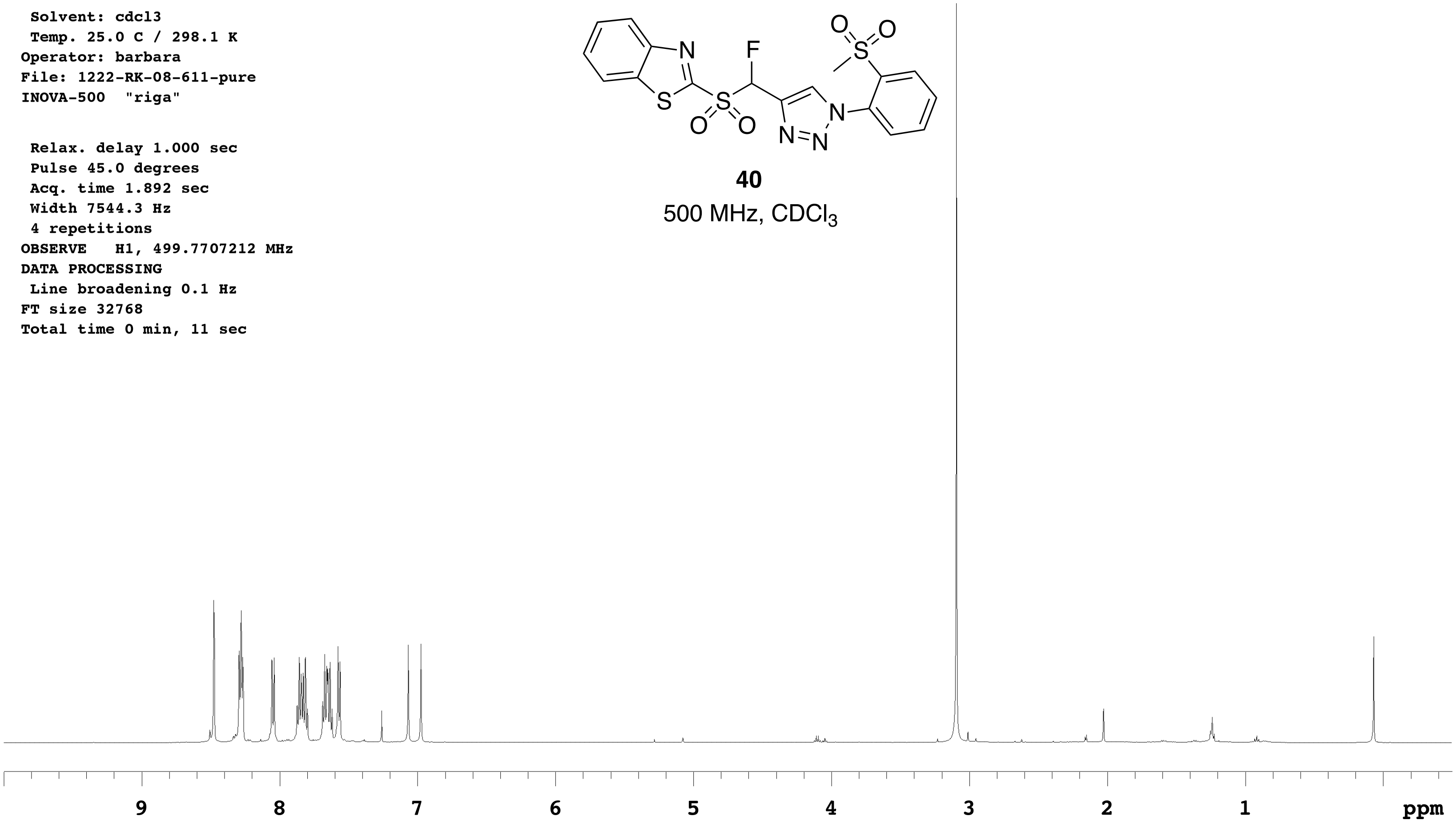


1222-RK-08-611-pure

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-08-611-pure
INOVA-500 "riga"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 7544.3 Hz
4 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 0 min, 11 sec



40

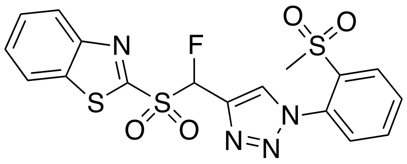
500 MHz, $CDCl_3$

```
1222-RK-08-611-13C

 Archive directory: /export/home/barbara/vnmrsys/data
 Sample directory:

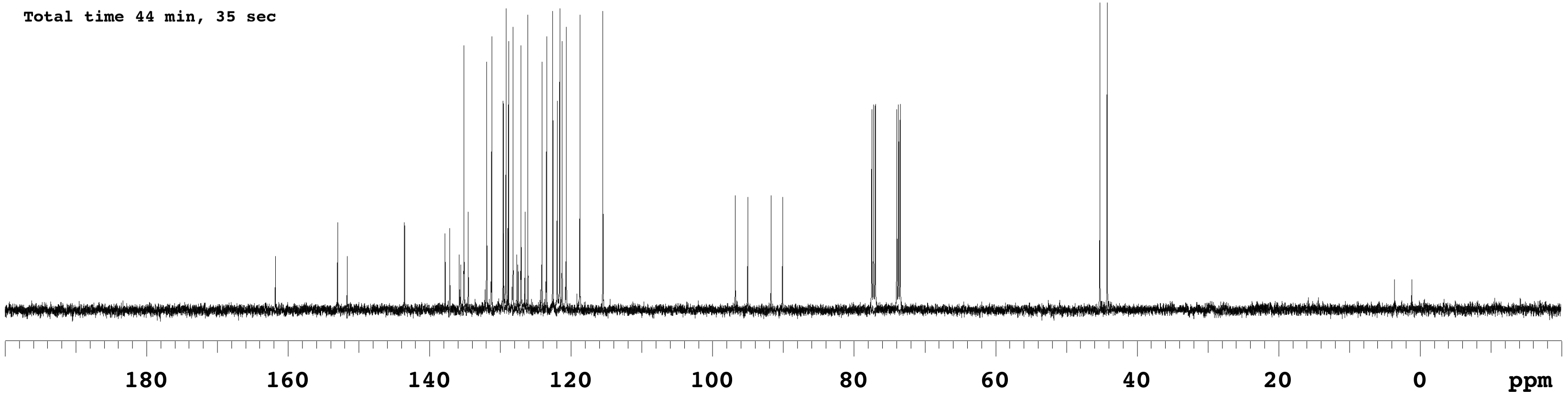
Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-08-611-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 336 repetitions
OBSERVE  C13, 125.6674278 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 131072
Total time 44 min, 35 sec
```



40

125 MHz, $CDCl_3$



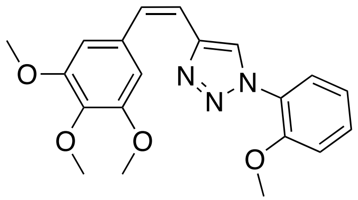
```
1231-RK-12-942-fraction1

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

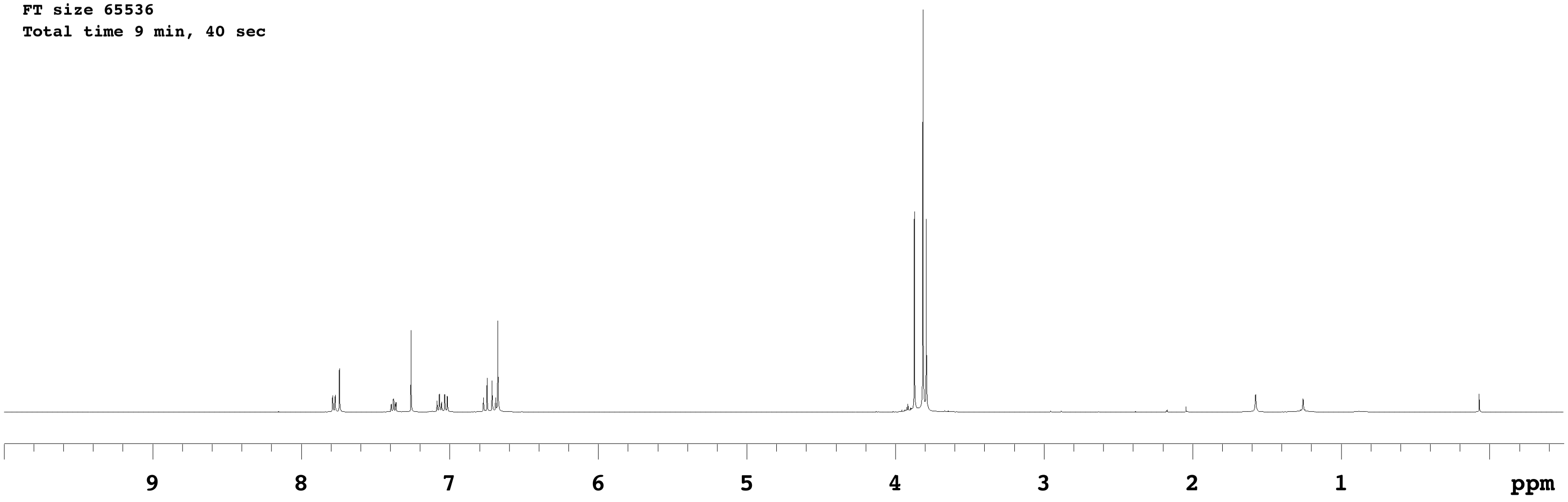
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-12-942-fraction2
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 16 repetitions
OBSERVE   H1, 499.7707218 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
```



Z-**42**

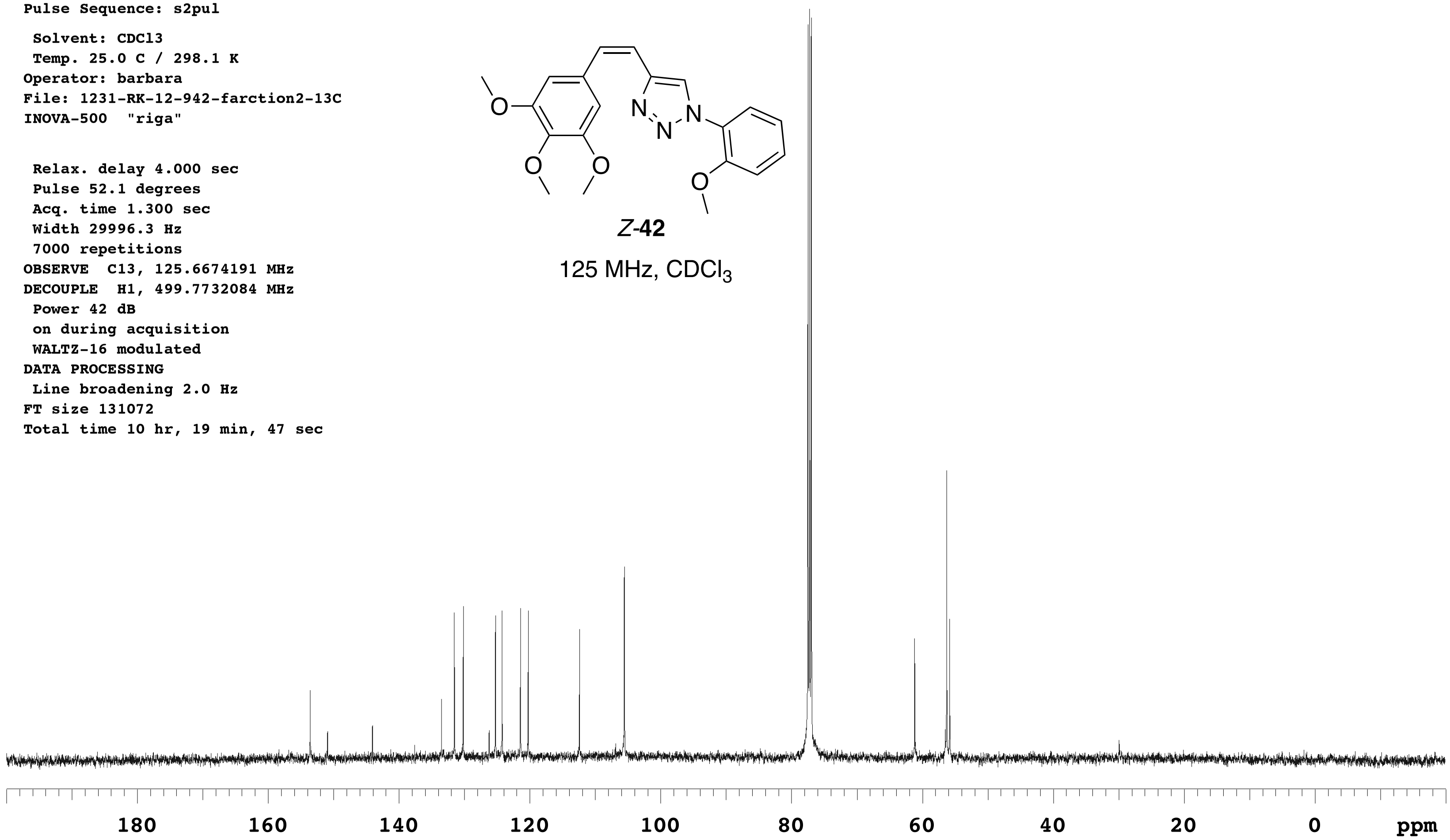
500 MHz, $CDCl_3$



```
1231-RK-12-942-farction2-13C

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-12-942-farction2-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 7000 repetitions
OBSERVE  C13, 125.6674191 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 131072
Total time 10 hr, 19 min, 47 sec
```



Z-**42**

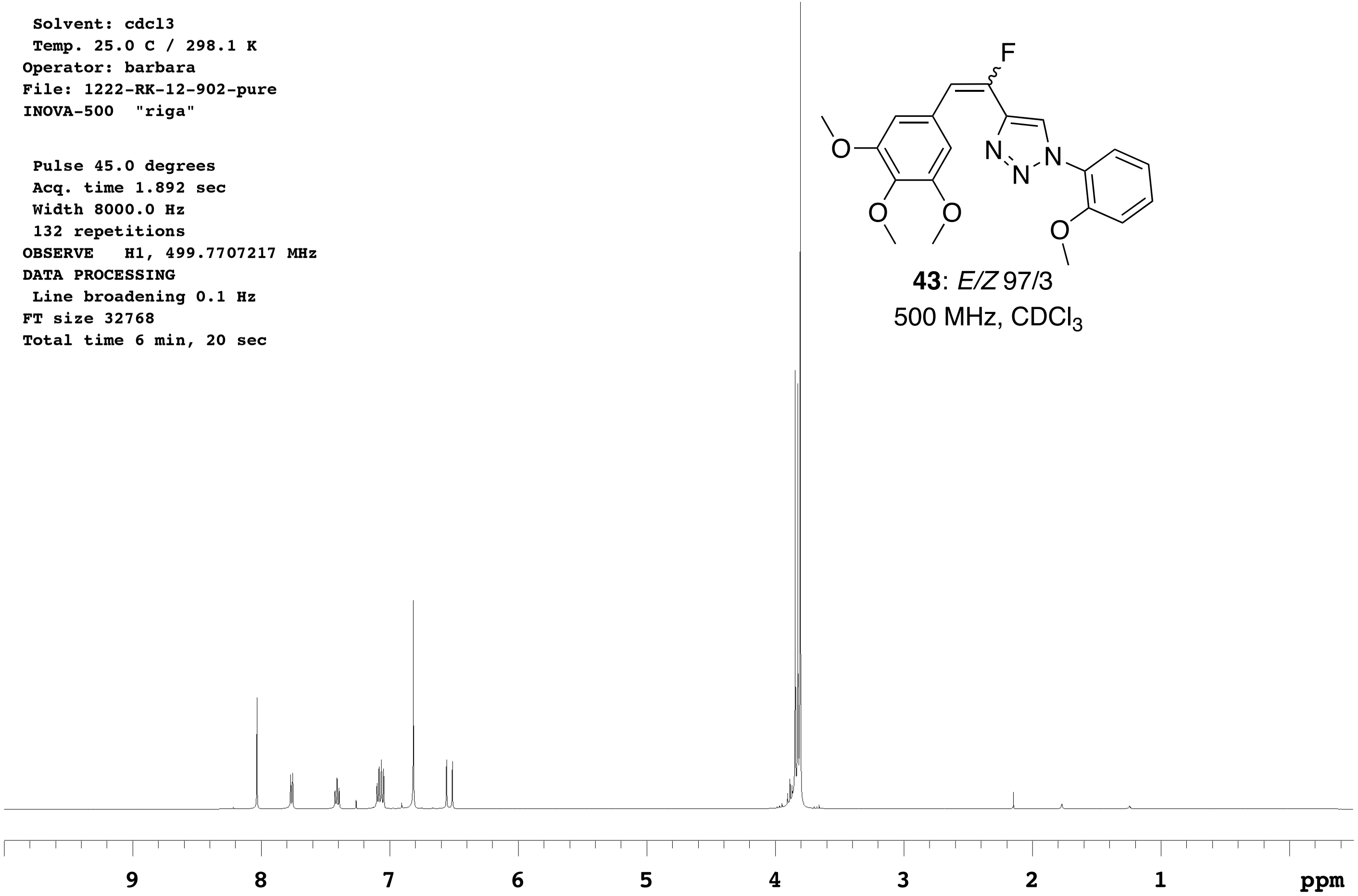
125 MHz, $CDCl_3$

1222-RK-12-902-pure

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-12-902-pure
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
132 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec



43: *E/Z* 97/3
500 MHz, $CDCl_3$

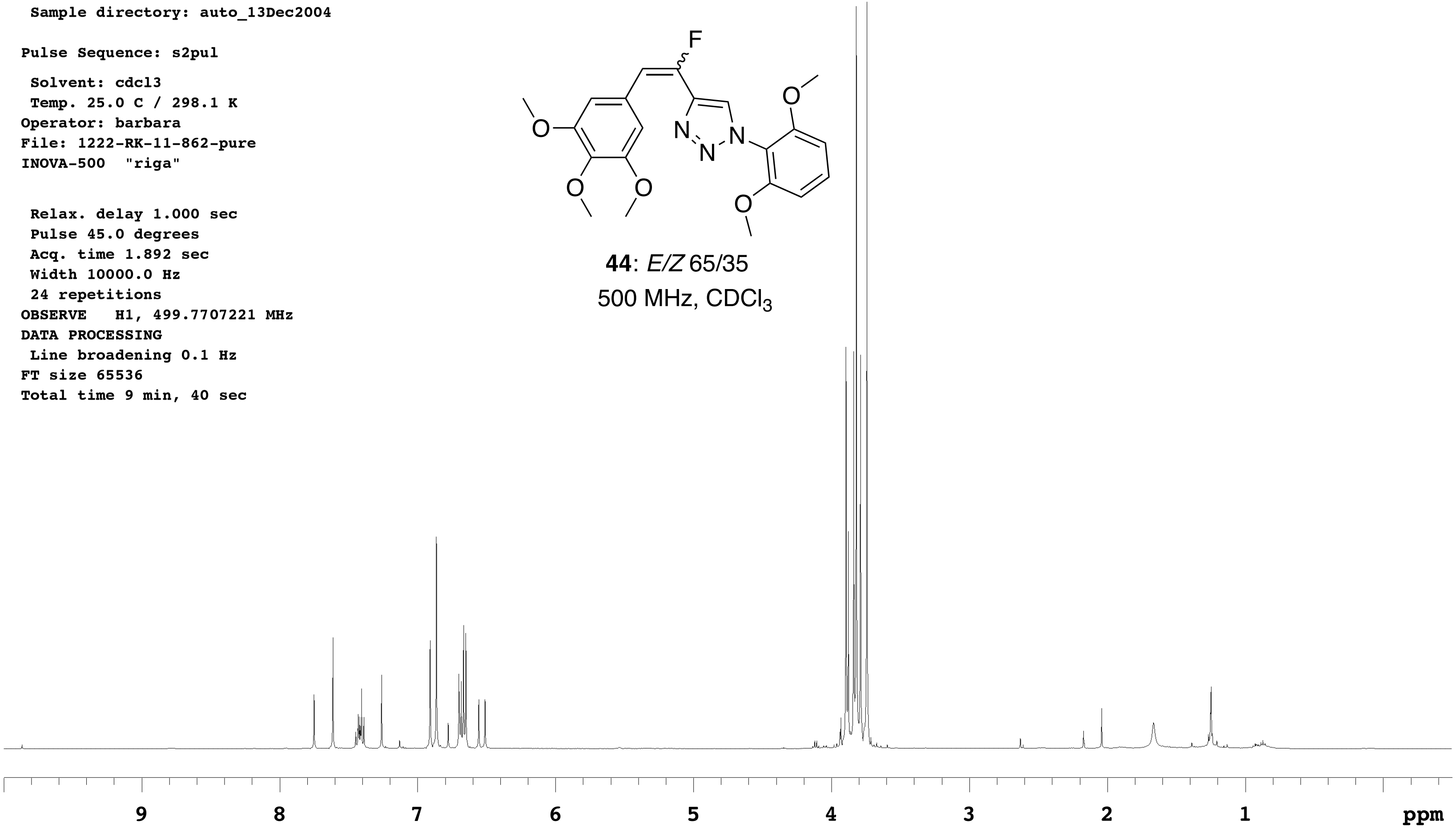
```
1222-RK-11-862-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-11-862-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 24 repetitions
OBSERVE   H1, 499.7707221 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
```



44: *E/Z* 65/35
500 MHz, $CDCl_3$

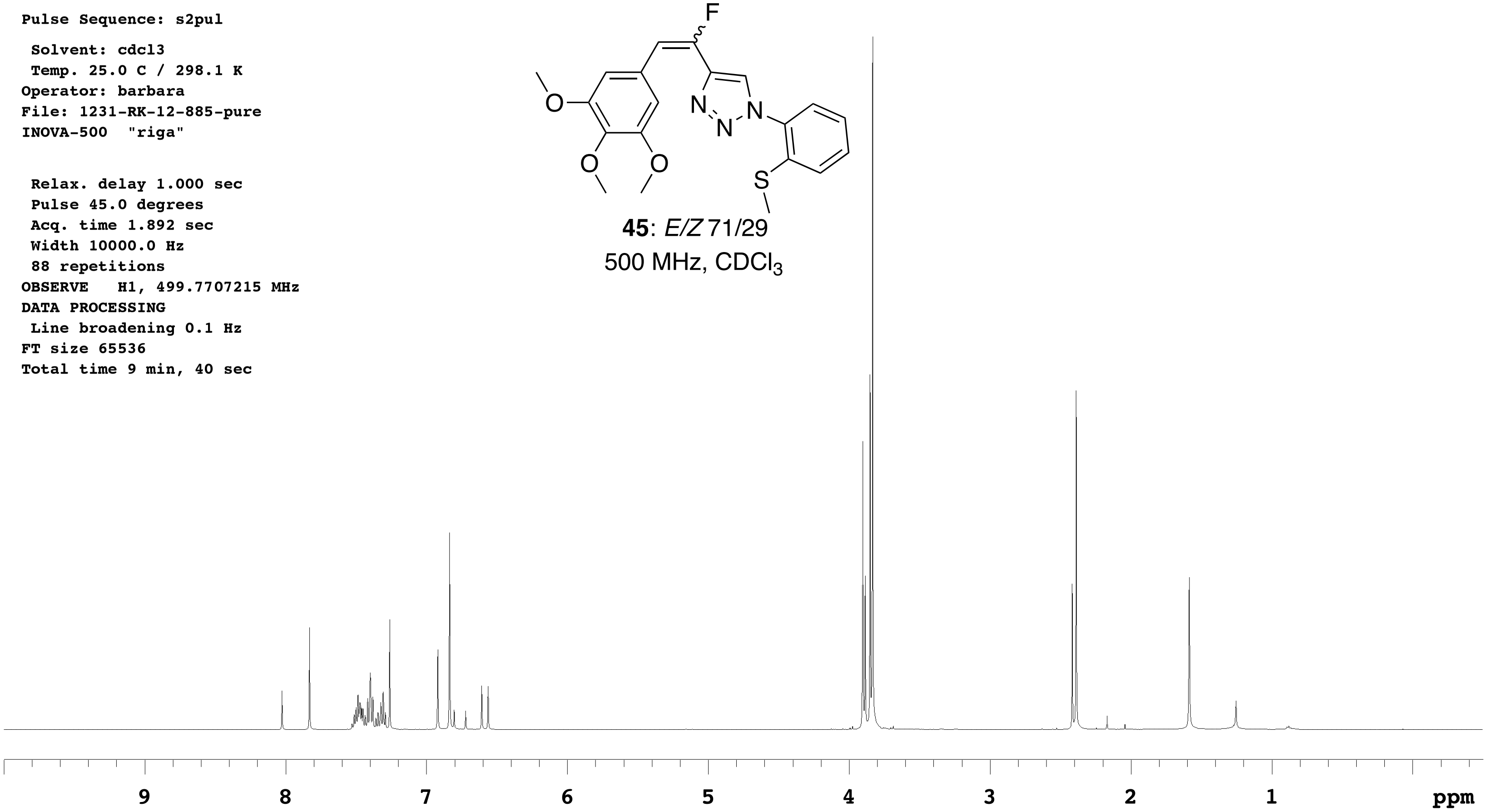
```
1231-RK-12-885-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-12-885-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 88 repetitions
OBSERVE   H1, 499.7707215 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
```



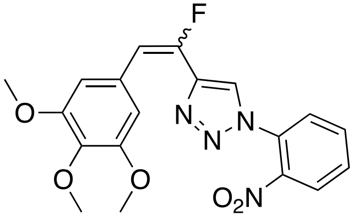
45: *E/Z* 71/29

500 MHz, $CDCl_3$

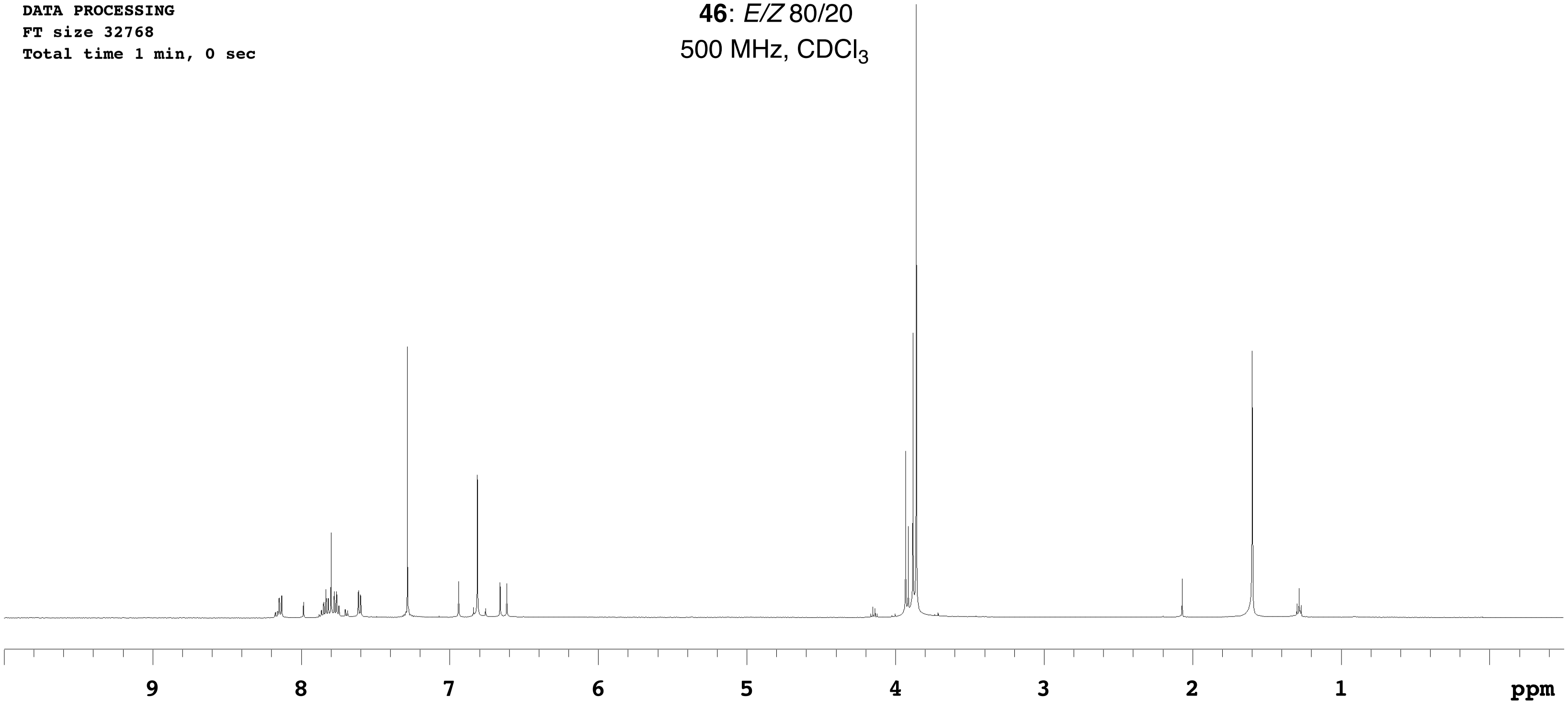
```
1222-RK-08-595-pure-1

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: barbara
File: 1222-RK-08-595-pure-1
INOVA-500  "riga"

 Pulse 48.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 32 repetitions
OBSERVE   H1, 499.7707095 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 0 sec
```



46: *E/Z* 80/20
500 MHz, $CDCl_3$



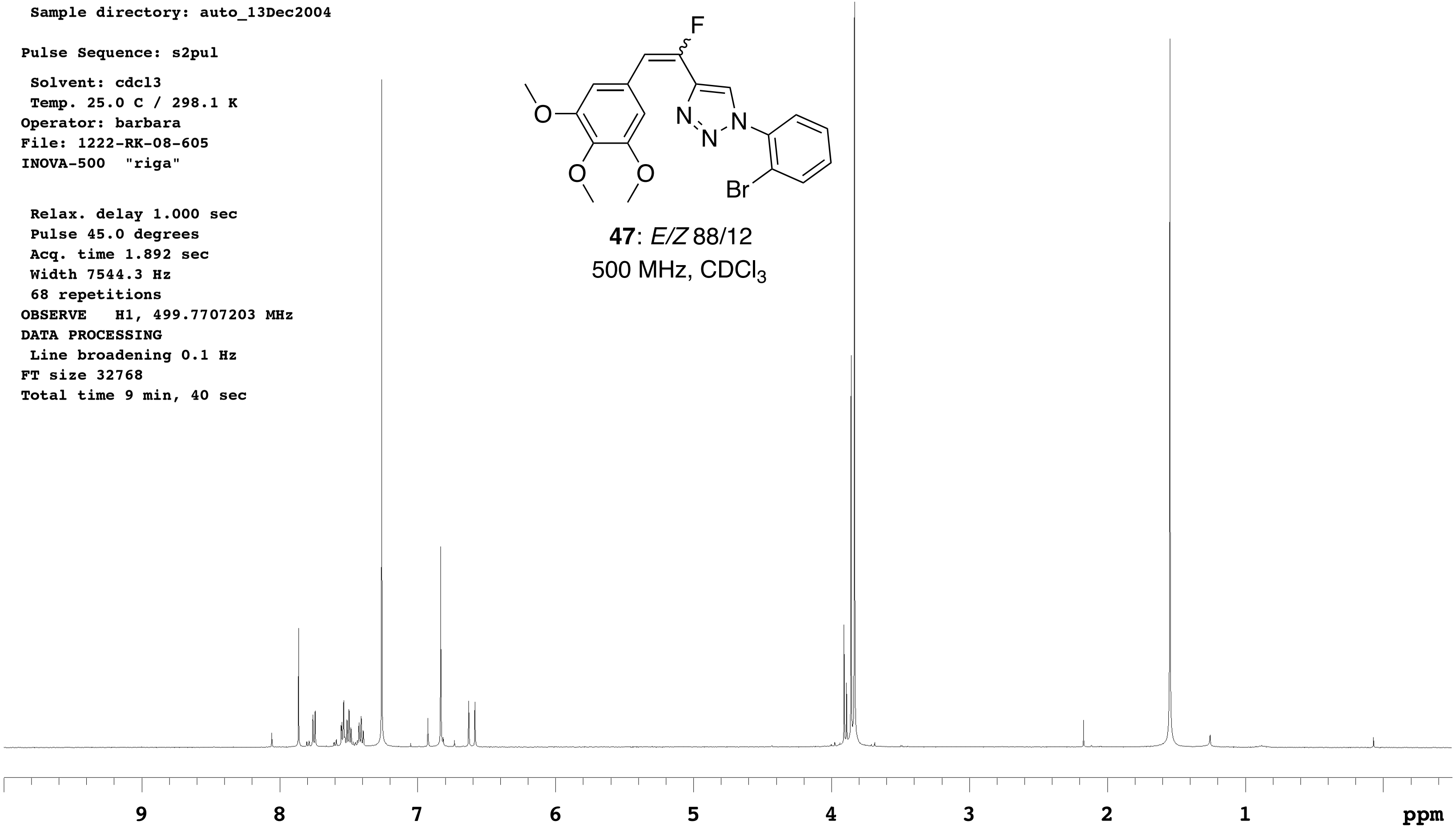
```
1222-RK-08-605

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-08-605
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 68 repetitions
OBSERVE   H1, 499.7707203 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```

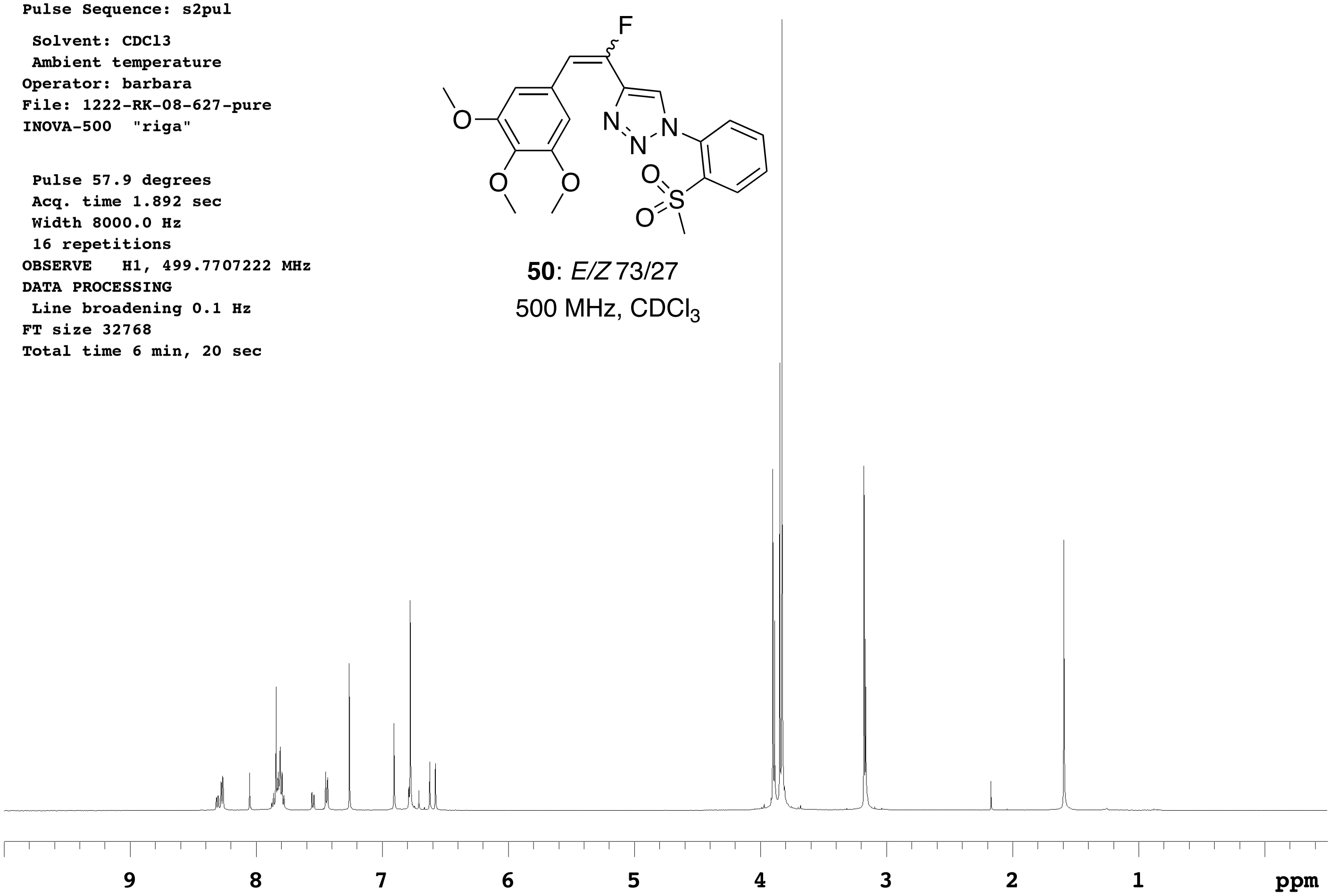


47: *E/Z* 88/12
500 MHz, $CDCl_3$

```
1222-RK-08-627-pure

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: barbara
File: 1222-RK-08-627-pure
INOVA-500  "riga"

 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 16 repetitions
OBSERVE   H1, 499.7707222 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec
```



50: *E/Z* 73/27

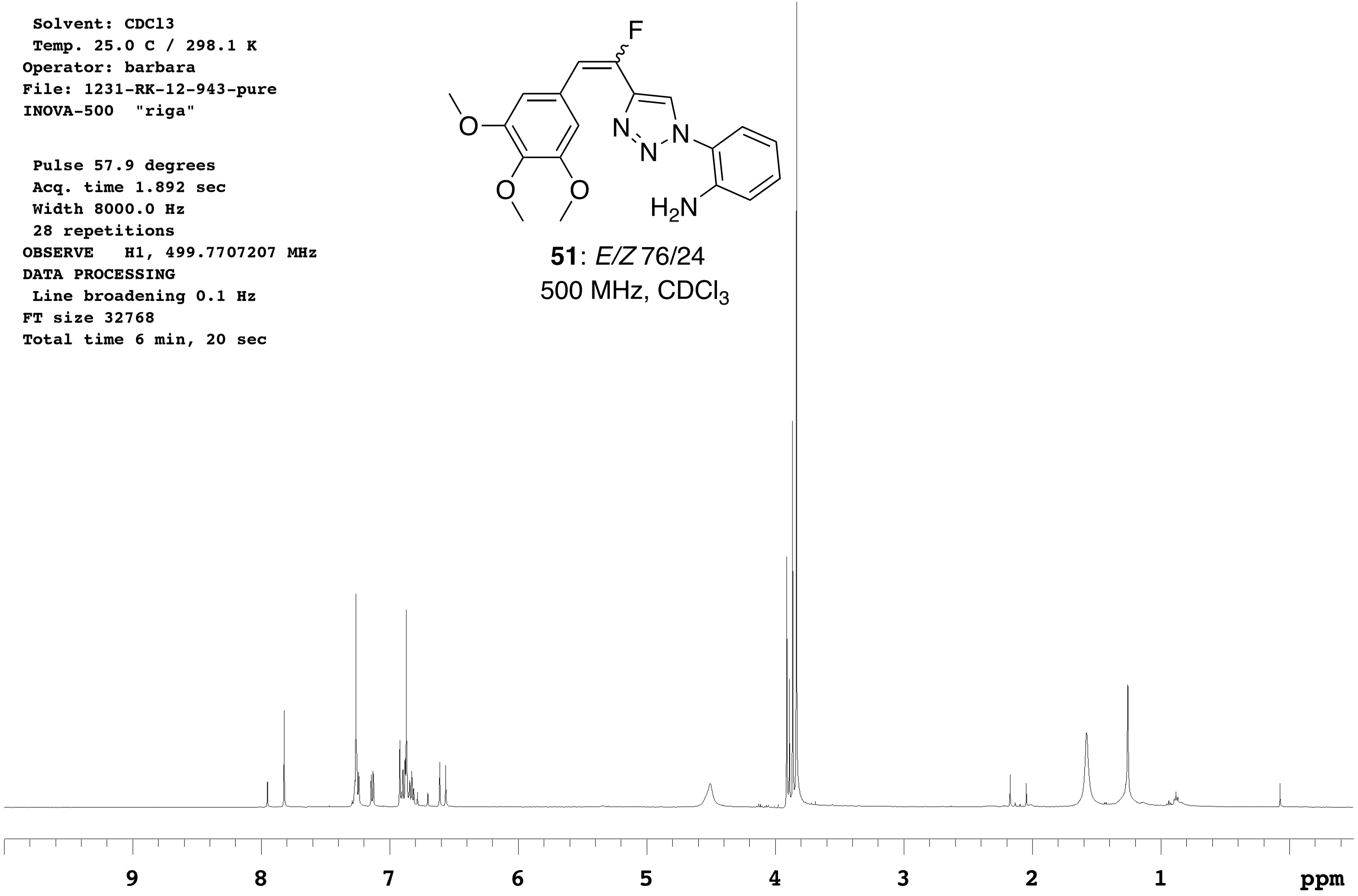
500 MHz, $CDCl_3$

1231-RK-12-943-pure

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-12-943-pure
INOVA-500 "riga"

Pulse 57.9 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
28 repetitions
OBSERVE H1, 499.7707207 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec



51: *E/Z* 76/24
500 MHz, $CDCl_3$

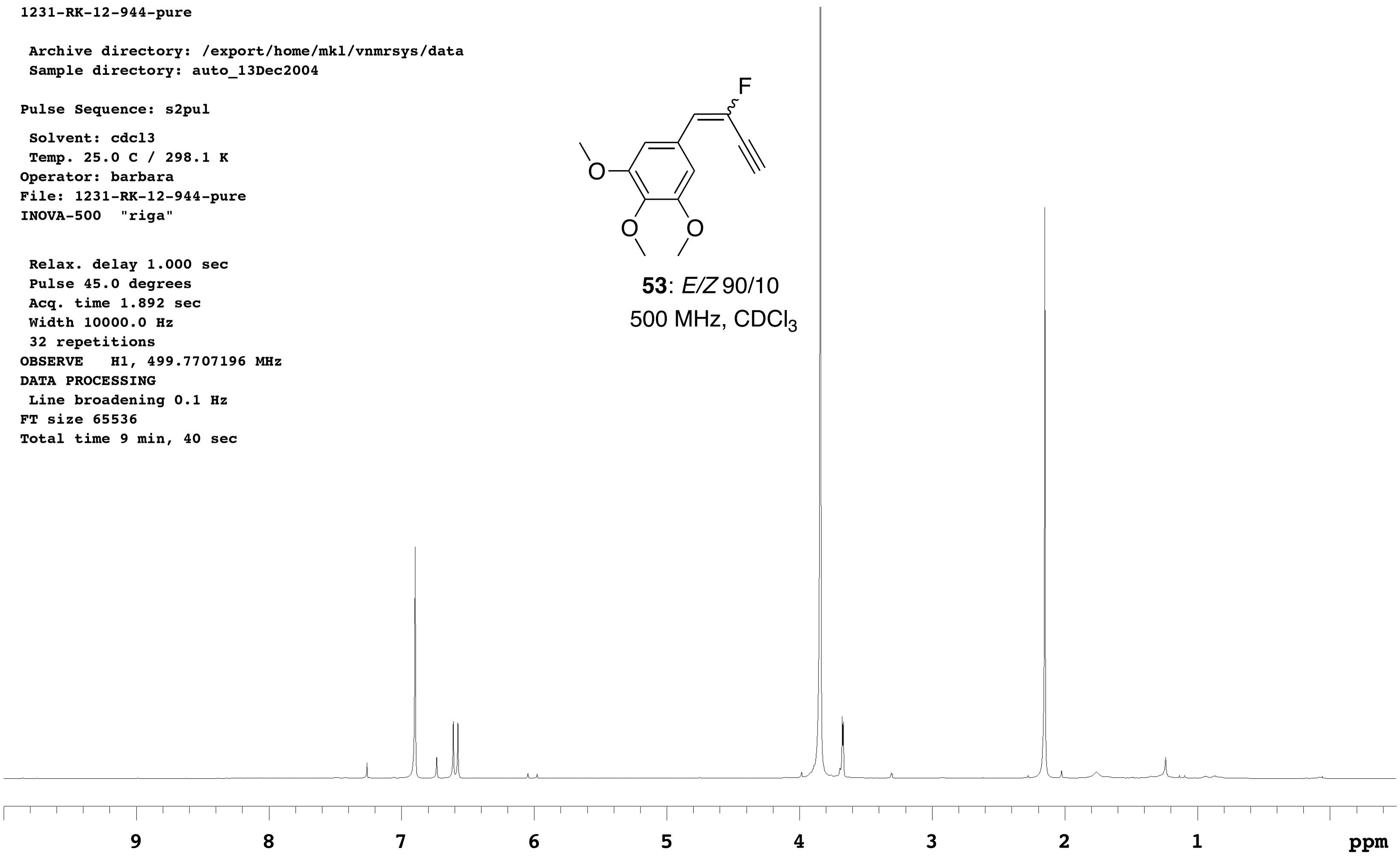
```
1231-RK-12-944-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-12-944-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 32 repetitions
OBSERVE   H1, 499.7707196 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
```



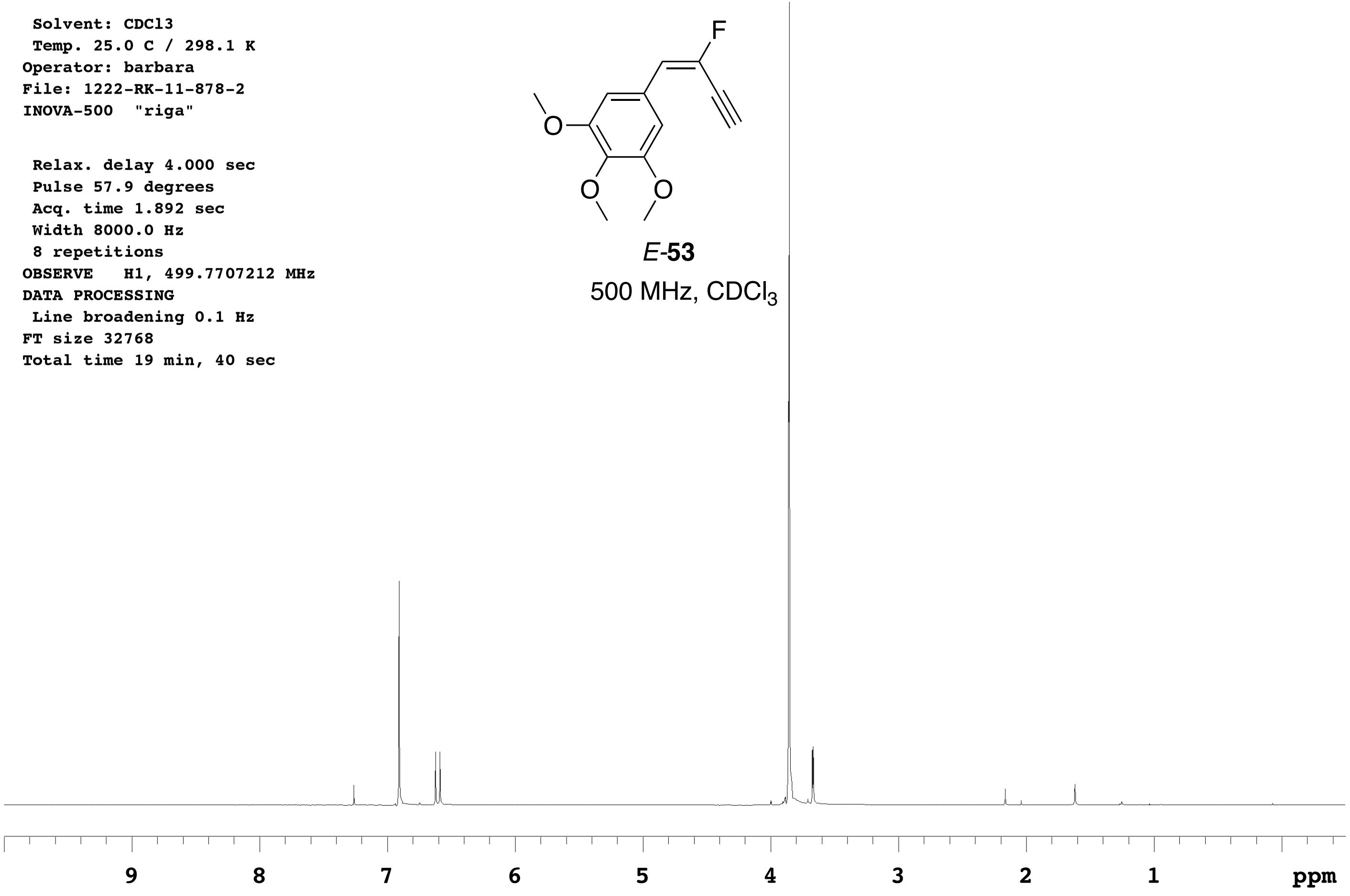
53: *E/Z* 90/10

500 MHz, $CDCl_3$

```
1222-RK-11-878-2

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-11-878-2
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 8 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 19 min, 40 sec
```



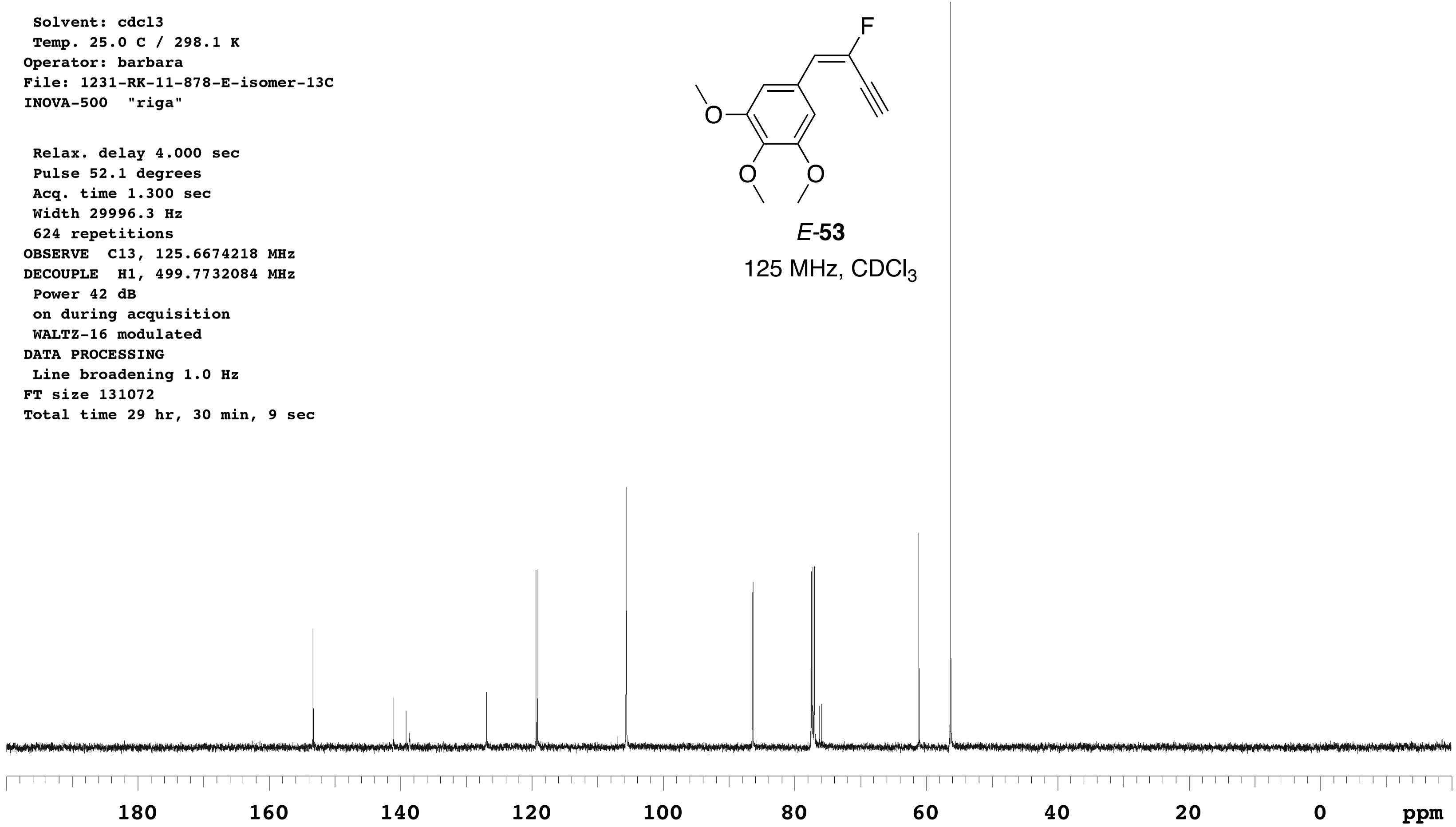
E-**53**

500 MHz, $CDCl_3$

```
1231-RK-11-878-E-isomer-13C

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-11-878-E-isomer-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 624 repetitions
OBSERVE  C13, 125.6674218 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 29 hr, 30 min, 9 sec
```



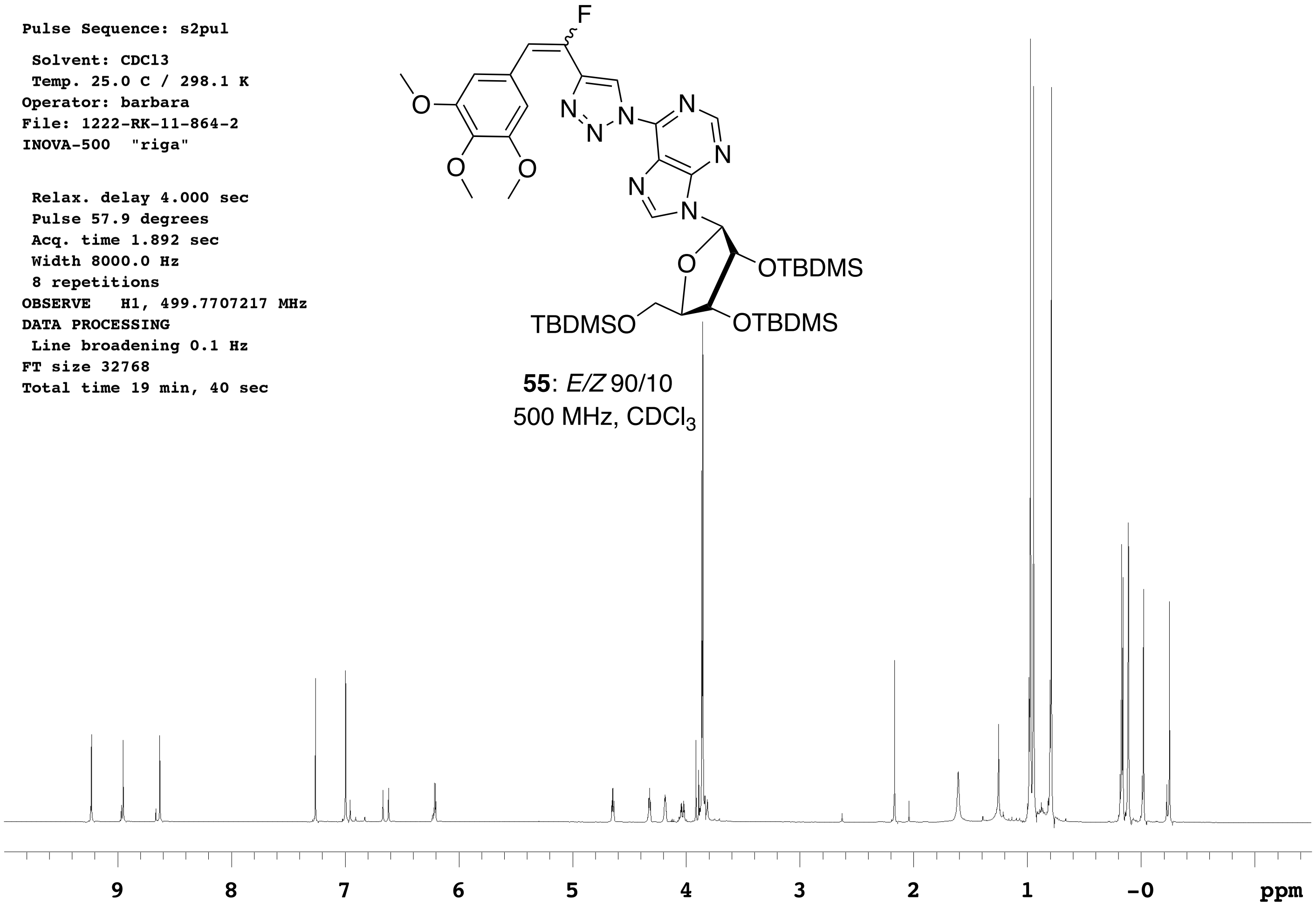
E-**53**

125 MHz, $CDCl_3$

```
1222-RK-11-864-2

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-11-864-2
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 8 repetitions
OBSERVE   H1, 499.7707217 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 19 min, 40 sec
```



55: *E/Z* 90/10
500 MHz, $CDCl_3$

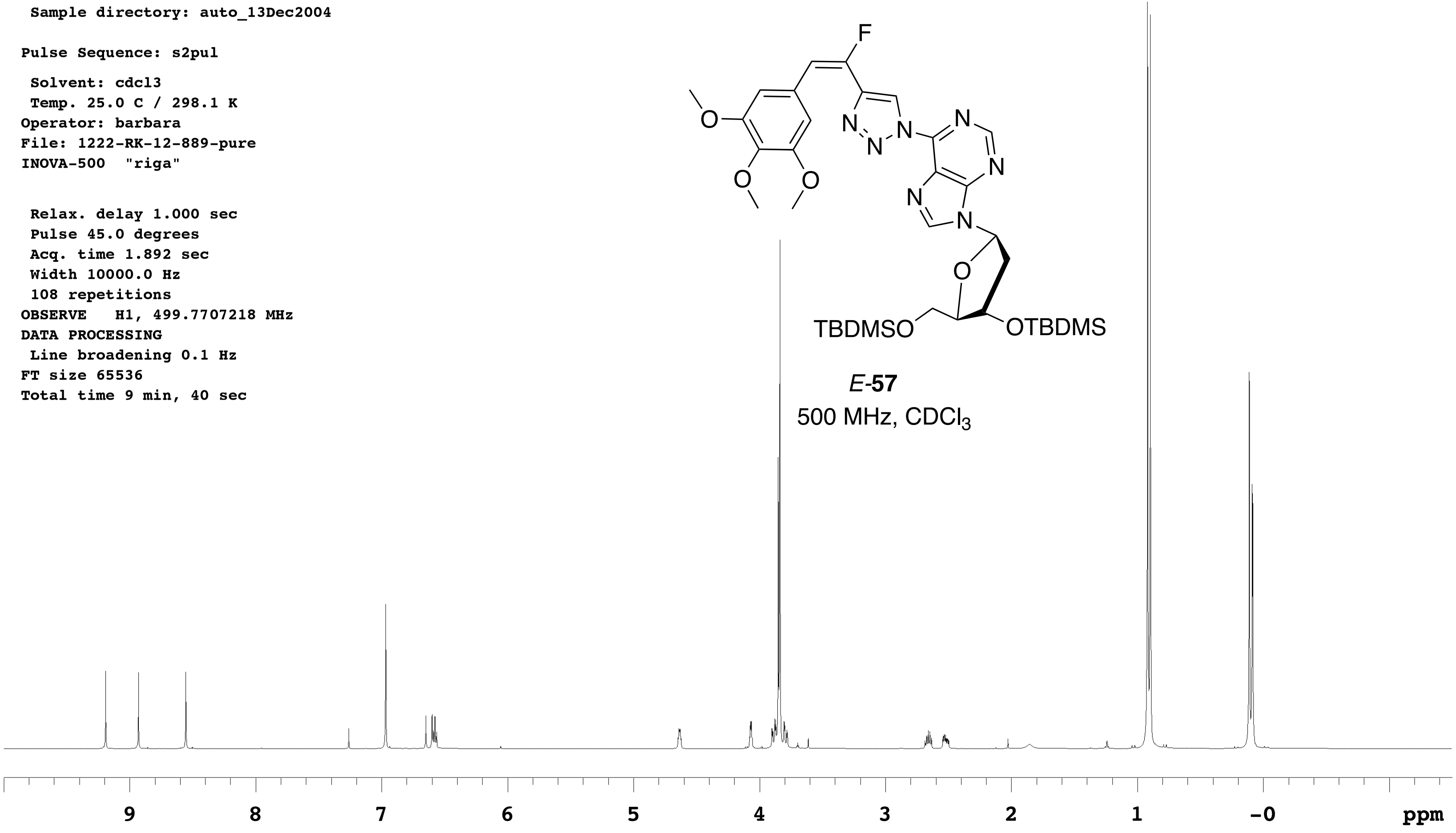
```
1222-RK-12-889-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-12-889-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 108 repetitions
OBSERVE   H1, 499.7707218 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
```



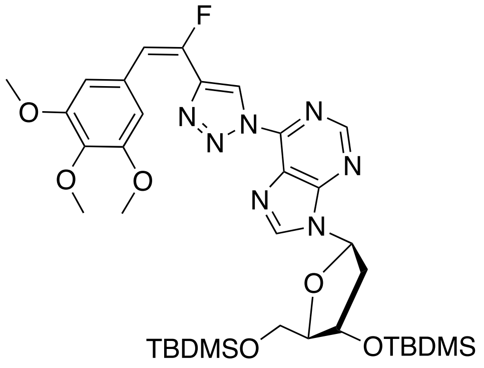
E-**57**

500 MHz, $CDCl_3$

```
1222-RK-12-889-13C

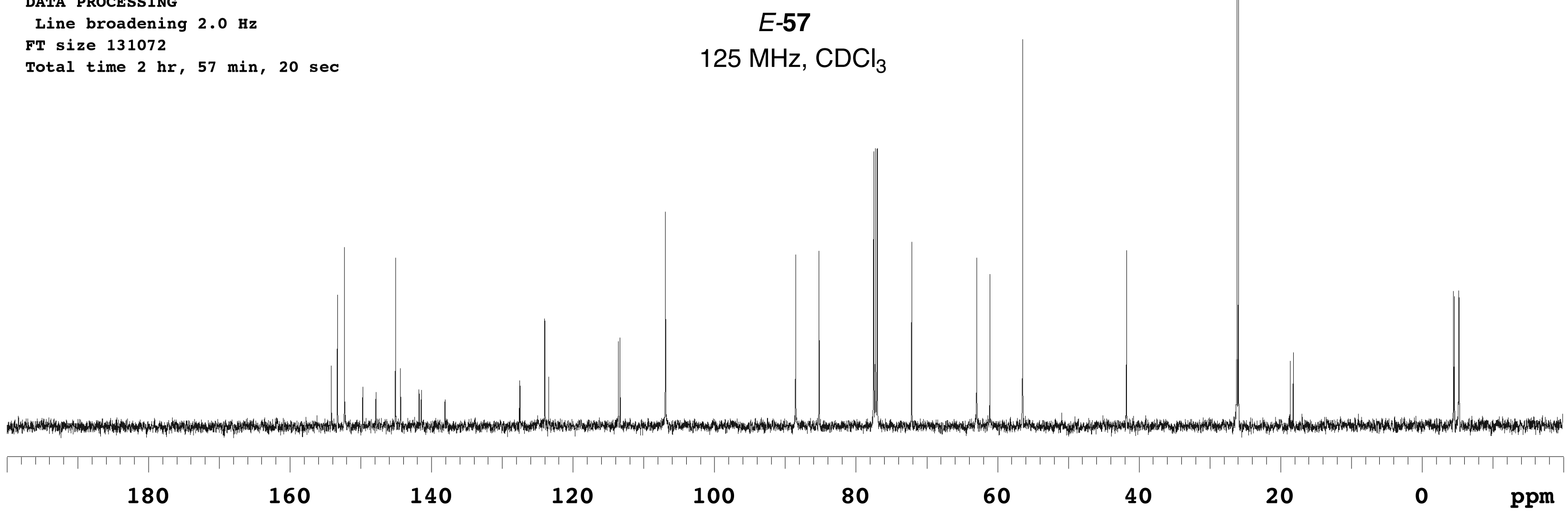
Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-12-889-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 344 repetitions
OBSERVE  C13, 125.6674232 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec
```



E-**57**

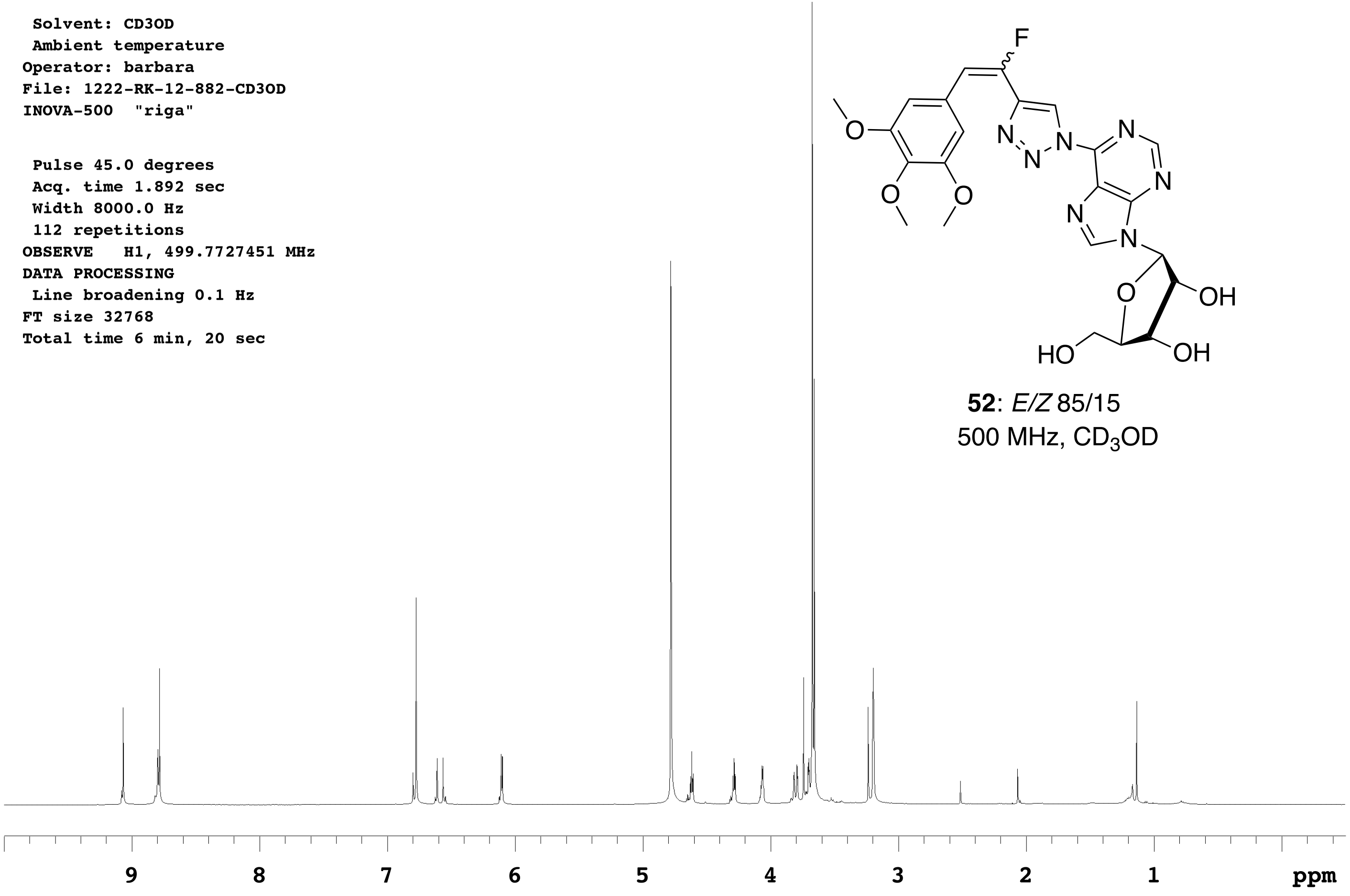
125 MHz, $CDCl_3$



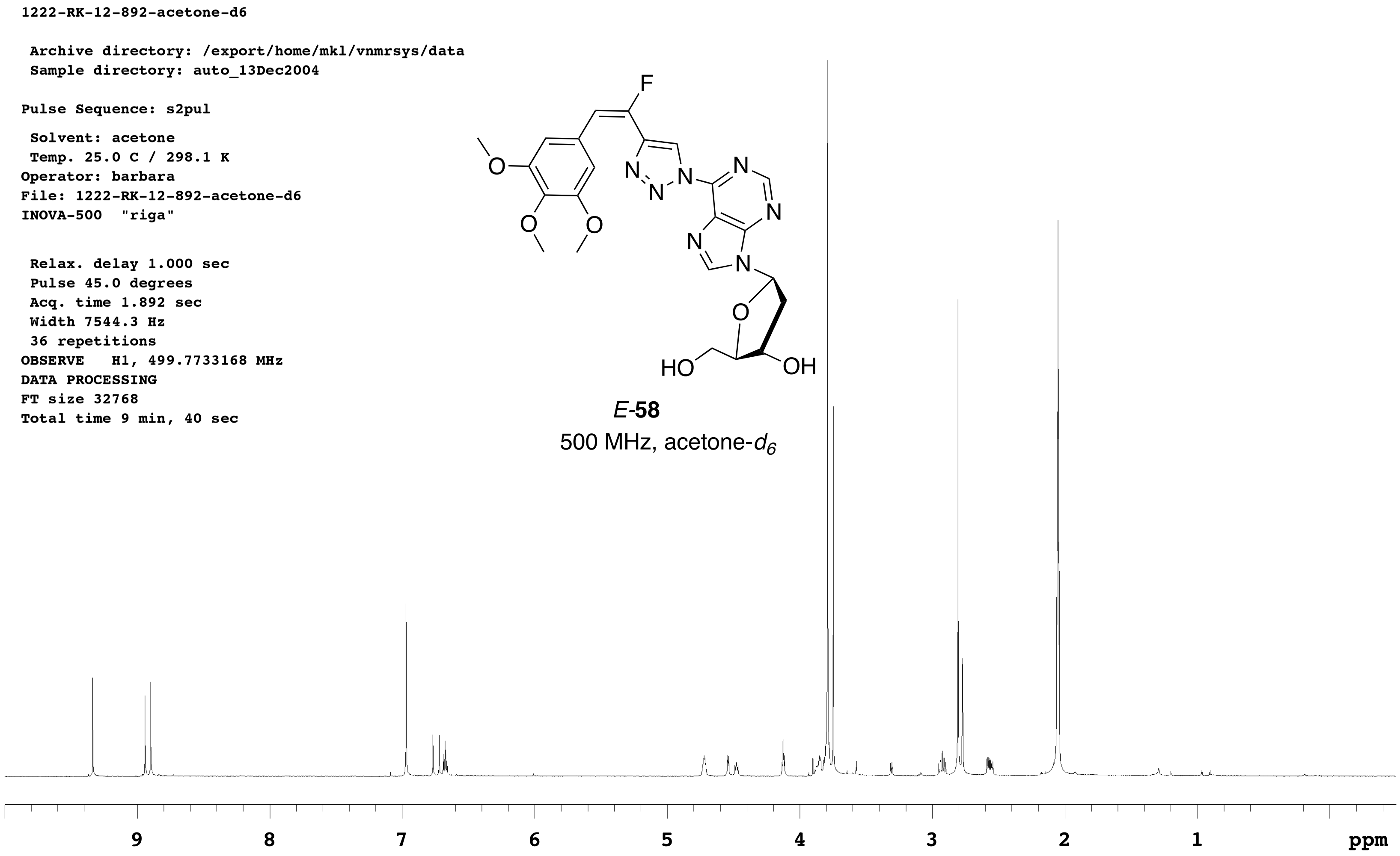
```
1222-RK-12-882-CD3OD

Pulse Sequence: s2pul
 Solvent: CD3OD
 Ambient temperature
Operator: barbara
File: 1222-RK-12-882-CD3OD
INOVA-500  "riga"

 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 112 repetitions
OBSERVE   H1, 499.7727451 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec
```



52: *E/Z* 85/15
500 MHz, CD_3OD



```
1222-RK-12-892-acetone-d6

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: acetone
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-12-892-acetone-d6
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 36 repetitions
OBSERVE   H1, 499.7733168 MHz
DATA PROCESSING
FT size 32768
Total time 9 min, 40 sec
```

E-**58**

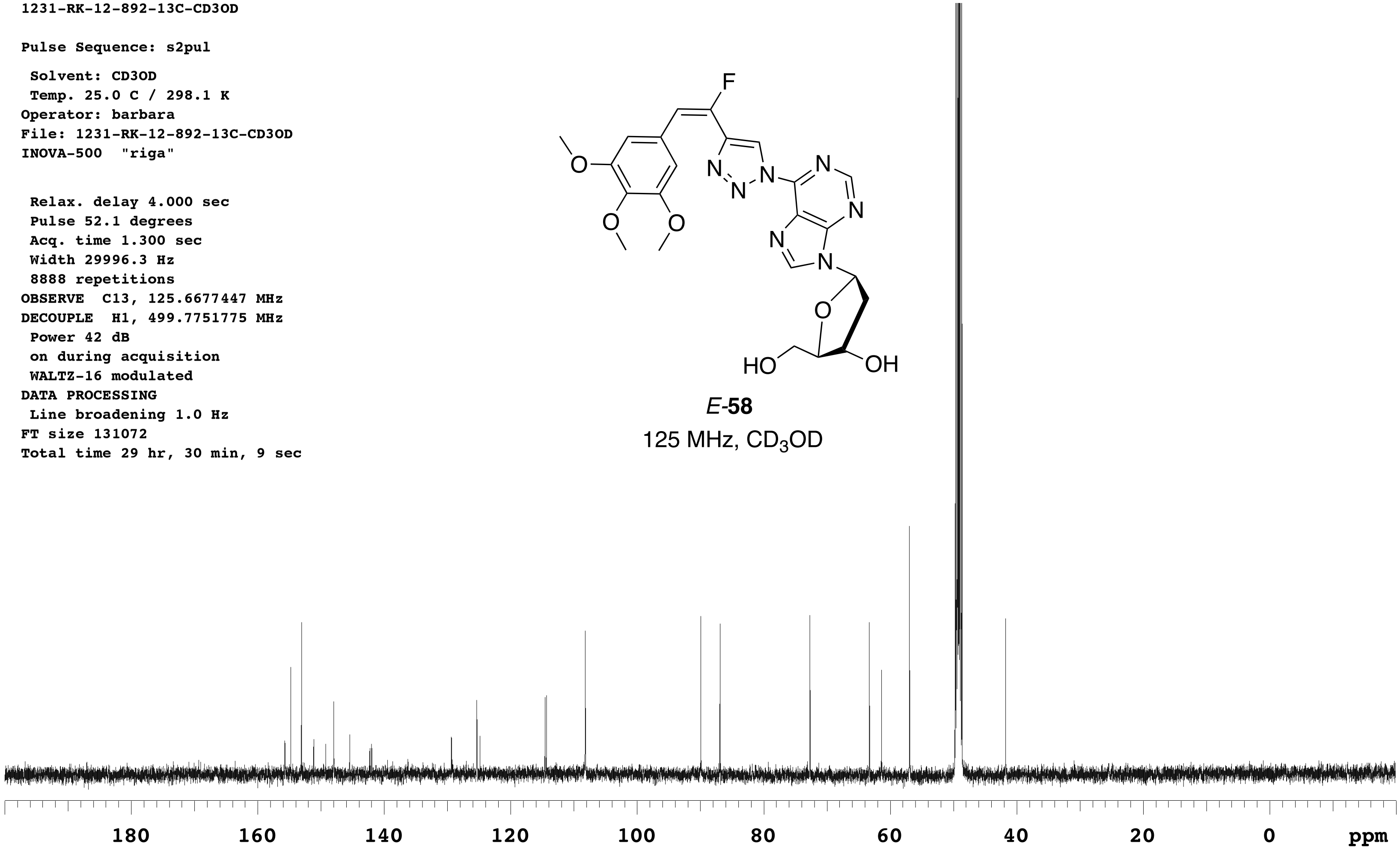
500 MHz, acetone-d_6

1231-RK-12-892-13C-CD3OD

Pulse Sequence: s2pul

Solvent: CD3OD
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-12-892-13C-CD3OD
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
8888 repetitions
OBSERVE C13, 125.6677447 MHz
DECOUPLE H1, 499.7751775 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 29 hr, 30 min, 9 sec



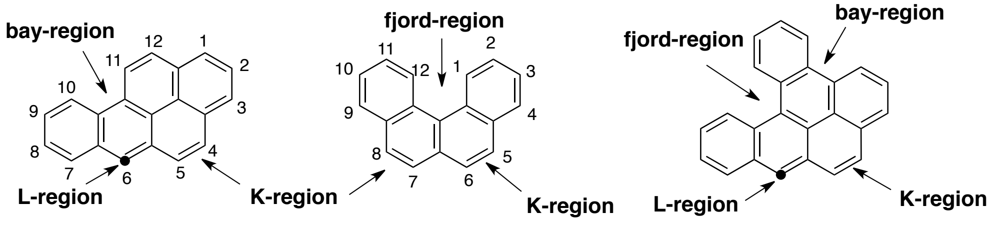
E-**58**
125 MHz, CD_3OD

CHAPTER 2

SYNTHESIS OF METABOLITES AND DEOXYADENOSINE ADDUCT OF 5-FLUOROBENZO[*c*]PHENANTHRENE

GENERAL INTRODUCTION

Polycyclic aromatic hydrocarbons (PAHs) are a class of organic compounds that contain two or more fused aromatic rings. These compounds are pervasive pollutants that pose a great health risk to humans. They can be present in air, water and soil. Some of these compounds are potent mutagens and carcinogens, and unfortunately the sources of their production are our everyday activities and some natural processes.[1-2] The examples of everyday activities that produce these compounds are burning of wood, cigarette smoking, fuel burning from vehicles and industries, and even preparation of food at home, e.g. grilling and roasting of food at high temperature also produces small amounts of these compounds. The natural sources of their production include forest fire and volcano eruptions. Among a large number of PAHs known, those containing a congested bay or fjord-region have been found to be among the most potent. The bay and fjord regions refer to the regions produced by nonlinear condensation of benzo rings (see Figure 1). The metabolites of hydrocarbons that contain bay and fjord regions are very good DNA alkylating agents and are responsible for their biological activity. Parts of PAHs referred to as K-region and L-region are as shown in Figure 1.[1-2]



Benzo[*a*]pyrene **1**

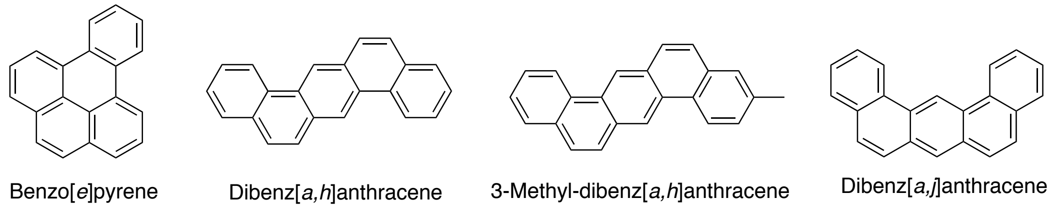
Benzo[*c*]phenanthrene **2**

Dibenzo[*a,l*]pyrene **3**

Figure 1. Examples of some PAHs and different regions in these hydrocarbons.

1.1 History of Chemical Carcinogenesis by Polycyclic Aromatic Hydrocarbons:

The carcinogenesis caused by PAHs came into light in 1775, when Percivall Pott, a surgeon at St. Bartholomew Hospital in London observed the cancer caused by the contamination of skin by soot.[1] This observation was confirmed by Volkmann and Bell describing the skin cancer among the workers in paraffin industry. Further, the experimental production of cancer by Yamagawa and Ichikawa in 1915 and soon after this in 1918 by application of coal tar to laboratory animals' skin strongly supported the observation.[1] After having identified the source of cancer production, interest of the scientists was to identify the chemicals that were responsible for cancer. Synthesis of various PAHs, their isolation from coal tar, and carcinogenic studies revealed that the major and highly carcinogenic component of the coal tar distillate was benzo[*a*]pyrene (B*a*P).[1-8] The minor component benzo[*e*]pyrene (B*e*P) was found to be non-carcinogenic (see Figures 1 and 2 for B*a*P and B*e*P).[8] Scientists Kennaway, Cook, Hewett and Mayneord were awarded with first Anna Fuller Memorial prize for their major contribution in the study of the chemical carcinogenesis produced by polycyclic aromatic hydrocarbons.[1] During this period other PAHs, i.e. dibenz[*a,h*]anthracene (DB[*a,h*]A), dibenz[*a,j*]anthracene (DB[*a,j*]A), 3-methyl-dibenz[*a,h*]anthracene (3-Me-DB[*a,h*]A) (see in Figure 2) were also synthesized and found to possess strong carcinogenic activity.[1]

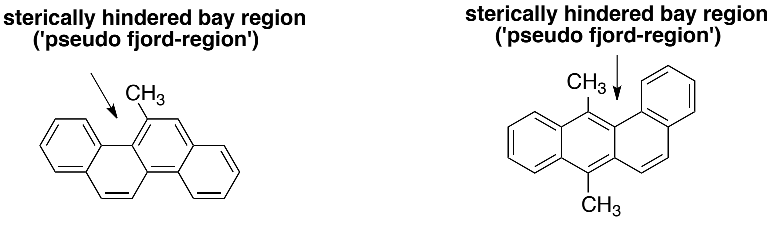


Benzo[*e*]pyrene **4** Dibenz[*a,h*]anthracene **5** 3-Methyl-dibenz[*a,h*]anthracene **6** Dibenz[*a,j*]anthracene **7**

Figure 2. Structures of B[*e*]P, DB[*a,h*]A, 3-Me-DB[*a,h*]A and DB[*a,j*]A.

1.2 Structure-Activity Relation

The fact that only some of the large numbers of PAHs are carcinogenic intrigued the scientists towards the structure-activity relationship studies of these molecules. Biological studies revealed that compounds with four to six benzo rings, often containing sterically crowded bay or fjord-regions, are among the most potent carcinogens. Although there are some exceptions, that is PAHs that contain these regions do not show carcinogenic activity such as benzo[*e*]pyrene (B*e*P) (Figure 2).[8] The basis for the idea was the change in biologically activity of some PAHs, upon regiospecific methyl substitution. The alteration of carcinogenic activity depended on the position of methyl substitution.[2] For example, 5-methylchrysene (5-MeCh) and 7,12-dimethylbenz[*a*]-anthracene (DMBA) were found to be much more potent carcinogens than their parent hydrocarbons. The increase in activity was attributed to formation of sterically hindered bay-region or pseudo fjord-region upon methyl substitution (see Figure 3). DMBA is one of the most carcinogenic hydrocarbons known with tumorigenic activity comparable to B*a*P.[2]



5-Methylchrysene

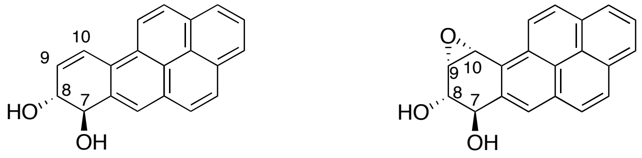
8

7,12-Dimethylbenz[*a*]anthracene

9

Figure 3. PAHs with sterically congested bay region (pseudo fjord region): 5-MeCh (left) and DMBA (right).

In 1950, Boyland proposed the formation of PAH epoxides that could be the potential intermediates for interaction with cellular constituents and hence leading to the hazards.[1-2] In 1955, Pulman and Pulman proposed 'K-region theory' to correlate the carcinogenicity of PAHs with the extent of olefinic character in different parts of the molecule.[1,2] The reactive intermediates were suggested to be the epoxides formed in the K-region, because of the higher electron density and more olefinic character in this region. Synthesis of K-region epoxides and their biological testing indicated either none or weak activity of these intermediates. It was therefore concluded that K-region epoxides were not the potential intermediates for DNA binding and hence the carcinogenic activity.[1,9] Synthesis of regioisomeric dihydrodiols of B*a*P and their biotransformations indicated that 7,8-dihydrodiol binds to DNA to a much greater extent than other dihydrodiols, as well as the parent hydrocarbon.[10] This led to the belief that 7,8-dihydrodiol further oxidizes at the adjacent double bond to form diol epoxides, and this assumption was also supported by various biological studies. These highly electrophilic species were thought to be the reactive intermediates for DNA binding.[11-19] Independent synthesis of 7,8-diol-9,10-epoxide metabolites of B*a*P (shown in Figure 4) provided the ultimate proof of their intermediacy in binding of the hydrocarbon to cellular species.[13,20-21]



(±) -7,8-dihydrodiol of B*a*P

10

(±) -7,8-diol-9,10-epoxide of B*a*P

11

Figure 4. 7, 8-Dihydrodiol and 7,8-diol-9,10- epoxide metabolites of B*a*P.

In 1977, Jerina et al. proposed the 'bay region theory' suggesting that the epoxide adjacent to bay region would have the highest electrophilicity and thus would be the preferred site for interaction with cellular species.[1-2] This theory has been able to explain the tumorigenic activity of various bay and/or fjord regions containing PAHs.

1.3 Metabolic Activation of PAHs

There are many pathways proposed for the metabolism and DNA binding of PAHs.[1-2] The two major mechanisms i. e. diol epoxide pathway and radical cation pathway are described below.

1.3.1 Diol Epoxide Pathway

The mechanism of metabolic activation of PAHs containing bay or fjord-region involves their oxidation by enzyme cytochrome P450 to produce epoxide.[1-2,22] The epoxide is then converted to enantiomeric pair of *trans* dihydrodiols by hydrolysis in the presence of hydrolase epoxidases.

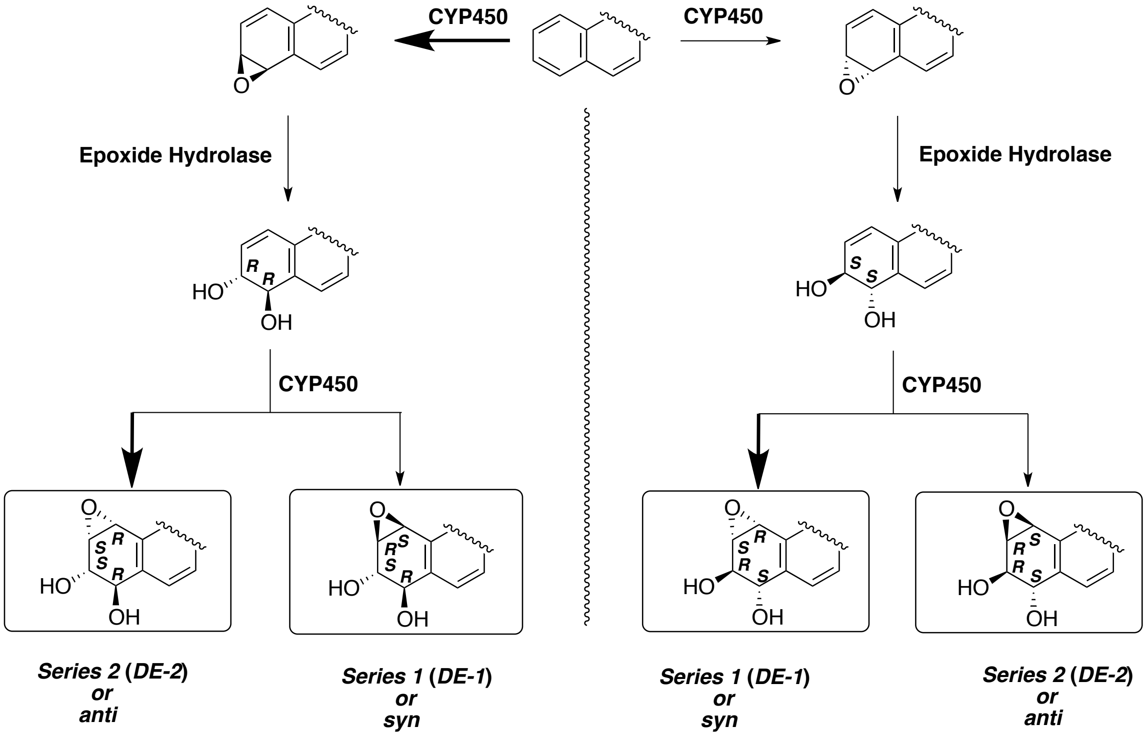


Figure 5. Monooxygenase pathway for metabolism of PAHs.

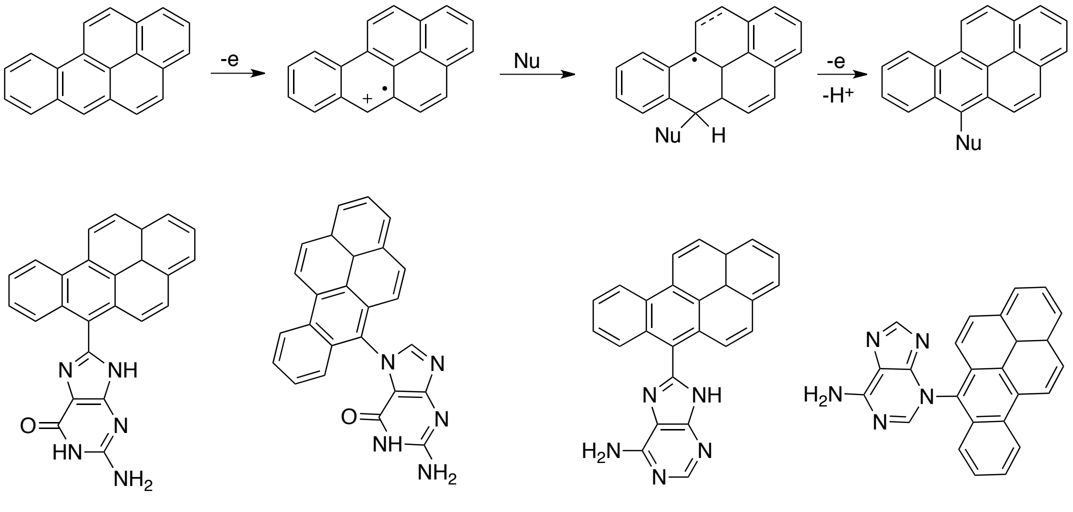
The dihydrodiol undergoes further oxidation by cytochrome P450 to produce two enantiomeric pairs of diastereomeric diol epoxides (see Figure 5). The diol epoxides in which the benzylic hydroxyl and epoxide ring are on the same side are called *syn* or series-1 diol epoxides (DE-1), whereas when these groups are on the opposite side, the diol epoxides are called *anti* or series-2 (DE-2). In absence of any steric or electronic factors two hydroxyl groups in series-1 diol epoxides prefer the quasi-diaxial orientation and quasi-diequatorial in series-2 diol epoxides.[1] The tumorigenic activity of these diol epoxides is generally different and depends upon their stereochemistry. It is important to mention that in case of B*a*P, the first oxidation by cytochrome P450 predominantly produces the epoxide in which benzylic carbon has *R*-absolute configuration. Further the hydrolase epoxidases mediated hydrolysis of the major isomer produces the *trans*-(*R,R*)-dihydrodiol, whereas the minor isomer forms the *trans*-(*S,S*)-dihydrodiol. Interestingly, the second oxidation of the enantiomeric dihydrodiols takes place in such a manner that the *trans*-(*R,R*)-dihydrodiol is metabolized mainly to *anti* diol epoxide, whereas *trans*-(S,S)-dihydrodiol gives *syn* diol epoxide as the major diastereomer. [1-2,22]

1.3.2 Conformational Effects on Carcinogenicity

In most cases the carcinogenic acitivity of PAHs containing bay or fjord regions is carried out by series-2 diol epoxides, whereas series-1 diol epoxides are either inactive or show a weak activity.[22] One exception to this common trend is benzo[*c*]phenanthrene (B*c*Ph) where both series-2 as well as series-1 diol epoxides are active.[23-24] The difference in activity of two series of diol epoxides may not be solely dependent on their relative configuration, but the preferred conformations of hydroxyl groups can also play an important role. As mentioned earlier in the absence of some specific steric and electronic factors, the hydroxyl groups in series-2 diol epoxides prefer the quasi-diequatorial orientation, whereas in series-1 isomers the quasi-diaxial arrangement is preferred. The change in conformation metabolites can alter their activity. Introduction of fluorine at position C-6 of B*a*P changes the conformation of hydroxyl groups in series-2 diol epoxides to quasi-diaxial. It has been shown that 6-fluoro-B*a*P (7*R*,8*S*,9*S*,10*R*)-diol epoxide is non-carcinogenic, in contrast its to highly active protio analog.[25-26] In some cases, the steric interactions between atoms within the fjord region force the PAH ring system out of planarity.[27-29] In B*c*Ph diol epoxides, these steric interactions in fjord region lead to the quasi-diequatorial orientation of the vicinal hydroxyl groups also in series-1 diol epoxides and biological activity of all four isomers of diol epoxide isomers.[23,24]

1.3.3 Radical Cation Pathway

In addition to widely accepted diol epoxide route for the metabolism of PAHs, another important pathway is one-electron oxidation or radical cation pathway.



6-BP-8-Gua
12

6-BP-7-Gua
13

6-BP-8-Ade
14

6-BP-3-Gua
15

Figure 6. Mechanism of radical cation pathway of B*a*P metabolism (top), and major B*a*P

guanine and adenine adducts (bottom).

Cavalieri and Rogan showed that oxidation of B*a*P by $Mn(OAc)_3$ in acetic acid produced the B*a*P radical cation which reacted with nucleophiles (acetates) to yield 6-AcO-B*a*P.[1] Cytochrome P450 peroxidase mediated oxidation of B*a*P and other PAHs furnished the same radical cations that reacted with DNA to produce depurinated DNA adducts of these PAHs.[30-32] The structures of such adenine and guanine adducts of B*a*P are shown in Figure 6. The DNA-hydrocarbon bond via this pathway was formed at the point of highest electron density, e.g. position 6 in B*a*P (See Figure 6). [30-31] PAH-DNA adduct formation by radical cation pathway depends upon the ease of the radical cation formation that is measured by ionization potential and the degree of charge localization. It was suggested that only PAHs with an ionization potential less than 7.35 eV exhibit significant binding to DNA. Although there is correlation between the carcinogenic activity and the ionization potential of PAHs, some important exceptions were observed (e. g. high carcinogenicity of DB[*a,h*]A and 5-MeCh with ionization potentials greater than 7.35 eV).[1]

Diol epoxide pathway is accepted to play an important role in PAH carcinogenesis, but the involvement of other mechanisms cannot be ruled out. Although not shown here, metabolic path involving reactive and redox-active *ortho*-quinones has been recently reported.[1,2,33-35]

1.4 PAH-DNA Interactions

PAHs as such do not react with DNA, however their metabolic activation in the cells converts them to some reactive intermediates. As mentioned earlier, several metabolic pathways have been proposed that contribute to mutagenic and tumorigenic activity of PAHs. The reactive species produced upon metabolism of a PAH can cause covalent alkylation of DNA. In 1973, Borgen *et al.* reported that the 7,8-dihydrodiol metabolite of B*a*P, binds to a 10-fold greater extent to DNA *in vitro* than the parent hydrocarbon.[10]

In the diol epoxide pathway, the diol epoxides are electrophilic species and upon reaction with exocyclic amino groups of 2'-deoxyadenosine (dA) and 2'-deoxyguanosine (dG) produce DNA adducts. Adducts are formed by the C-O bond cleavage and the C-N bond formation in the oxirane part of the diol epoxide. Each diol epoxide isomer can form two adducts with each dA and dG, by c*is* and *trans* ring opening of the epoxide by the exocyclic amino group (see Figure 7). Since four diol epoxide metabolites are produced upon metabolism of a PAH, their alkylation of DNA can lead to sixteen different nucleoside adducts (eight dA and eight dG adducts).[36,37]

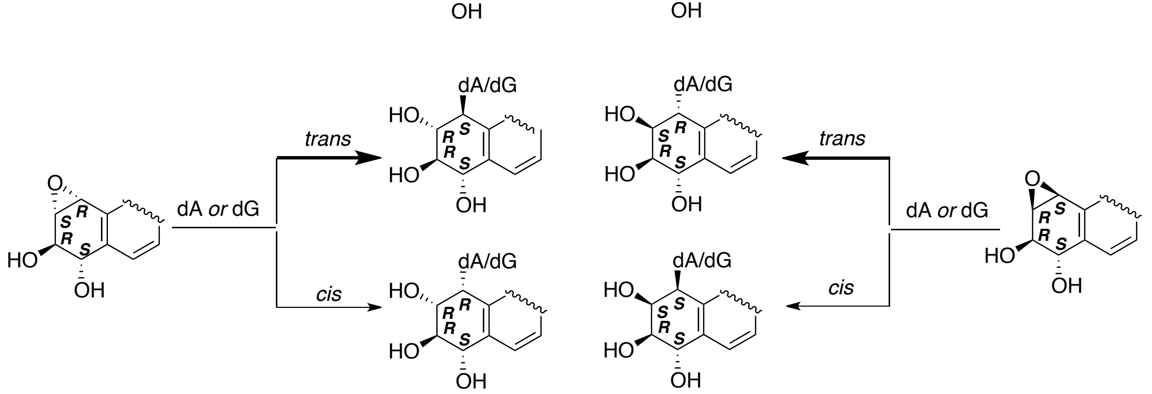


Figure 7. DNA adducts formed upon PAH metabolism to diol epoxides and their binding to dA and dG.

These DNA adducts, if not repaired, can cause translesional DNA synthesis that can result in mutation by change in the DNA sequence.[38]

All four diol epoxide isomers of a PAH react with DNA to a different extent and have different binding preference for dA and dG. Studies show that diol epoxides derived from planar hydrocarbons, e.g. B*a*P, 5-MeCh, 7-methylbenz[*a*]anthracene (7-MBA), dibenz[*a,j*]anthracene (DB[*a,j*]A), and benz[*a*]anthracene (B[*a*]A) predominantly form adducts with dG, whereas non-planar hydrocarbons, e.g. 7,12-DMBA, 5,6-dimethylchrysene, B*c*Ph and benzo[*g*]chrysene (B*g*Ch) form adducts predominantly with dA.[39,40]

1.4.1 Mechanism of DNA Binding of PAHs:

The mechanism of reaction between DNA and diol epoxides is not though fully understood but studies show that the first step is the intercalation of the PAH diol epoxide into DNA to form a non-covalent complex (Figure 8), that is followed by the covalent bonding via an acid catalyzed epoxide ring opening by N^6 of dA of N^2 of dG.[37,39-42] Towards this study, the hydrolysis of diol epoxides of B*a*P is suggested to proceed through the intermediacy of benzylic carbocation.[43] Such a reactive intermediate can be trapped by different nucleophiles. This carbocation is assumed to be trapped by exocyclic amino groups of deoxyadenosine (dA) and deoxyguanosine (dG) to produce DNA adducts. In the aqueous DNA environment, this carbocation intermediate can also be trapped by water to form tetraol derivatives (Figure 8).[43]

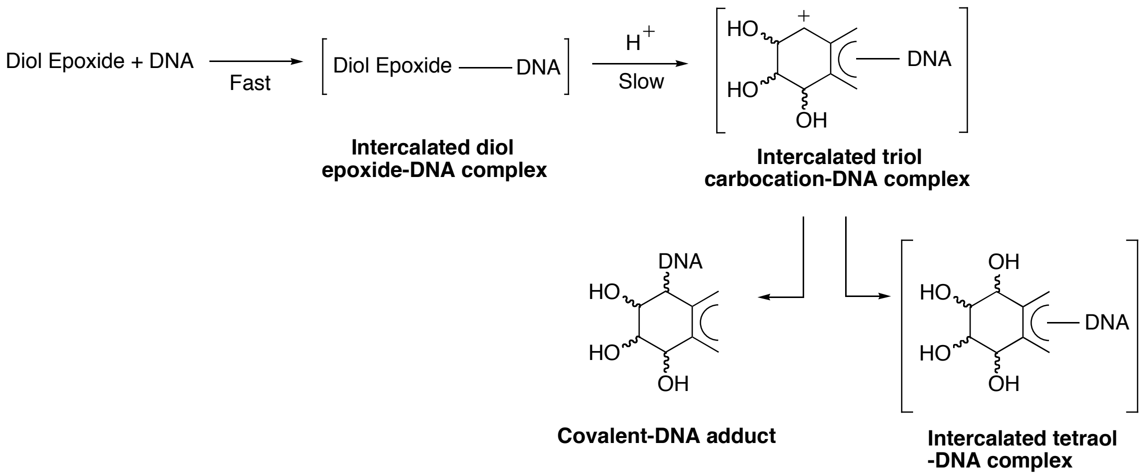


Figure 8. Mechanism of DNA binding and hydrolysis of diol epoxides.

The reactivity of diol epoxides towards water and DNA depends upon many factors. Number of aromatic rings in the hydrocarbon and the shape of molecule play an important role in the reactions of these metabolites with DNA.[39] It is known that in both planar as well as non-planar hydrocarbons, the diol epoxides of four membered PAHs (e.g., B*c*Ph, 5-MeCh) are trapped by DNA to a greater extent than those derived from five aromatic rings (e. g., DB[*a,j*]A, B*a*P, and B*g*Ch).[39] Also, in most cases studied, it is observed that among all the isomers of diol epoxides, the *R,S,S,R*- configurational isomer binds to DNA more extensively than other isomers. In vitro DNA binding studies of the diol epoxides of 30 different PAHs in aqueous medium reveal that fjord-region diol-epoxides of non-planar and tetracyclic PAHs form DNA adducts more efficiently compared to the bay-region diol-epoxides of planar and pentacyclic PAHs.[39] As discussed above, in the aqueous medium, alternative reaction could be hydrolysis of diol epoxides to tetraols.[43] In the reactions of DNA with diol epoxides, the ionization of diol epoxide in the intercalated complex, is considered to be a major key step that decides the extent of hydrolysis and formation of DNA adducts.[39,43] A larger number of aromatic rings and a planar aromatic system should favor this ionization step in these molecules.

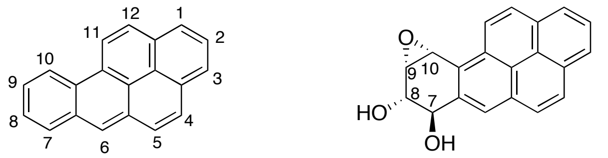
As water is less nucleophilic than DNA, the increased ionization should produce more hydrolysis products. In the case of diol epoxides of planar PAHs, ionization is favored due to charge delocalization over the aromatic system. So the reaction of diol epoxides with DNA may proceed through fully ionized intermediate. However, in the case of diol epoxides of non-planar PAHs, this charge delocalization is hindered due to non-planarity of the molecule, so the reaction of diol epoxide might proceed through partially ionized intermediate. Similarly, the amount of charge delocalization is higher in the case of pentacyclic PAHs compared to tetracyclic PAHs. This could be the cause for the more hydrolysis products and lesser amount of adducts formation from the pentacyclic PAHs, compared to tetracyclic PAHs. Also, it is known that the (*R,S,S,R*)-diol epoxide of the four-membered, non-planar B*c*Ph is hydrolyzed 10-fold more slowly than the five-membered, planar B*a*P.[22] Slower reaction of diol epoxides of B*c*Ph with water probably allows the competing reaction of more nucleophilic DNA to form higher percentage of adducts.

The preference of adducts formation of the diol epoxides of a PAH with either deoxyguanosine or deoxyadenosine differs from one hydrocarbon to another and depends mainly upon the structure of the hydrocarbon. B*a*P diol epoxides form preferentially DNA adducts with deoxyguanosine, whereas in the scase of B*c*Ph, deoxyadenosine adducts are the major ones formed.[39] In general, the ratio of deoxyadenosine/ deoxyguanosine adducts is greater for the non-planar hydrocarbons than for the planar ones.

1.5 Fluorinated Polycyclic Aromatic Hydrocarbons As Probes for Carcinogenesis Studies

Fluorine is a very well known modulator of the physical, chemical and biological properties of the molecules.[44,44] The change in the biological properties generally depends upon the position of fluorine in the molecule. The fluorine substitution in one position may increase the activity dramatically, whereas it may decrease to great extent in the other position. This effect has also been observed in polycyclic aromatic hydrocarbons and their metabolites. The changes in the tumorigenic activity of these compounds depends upon the site of fluorine substitution.[24] To study the effect of fluorine substitution on the biological activity, regiospecifically fluorinated derivatives of various PAHs and their metabolites have been synthesized, and in some cases these compounds have been used as probes for understanding the mechanism of their metabolism in the cellular system.

Various fluoro derivatives of B*a*P and their metabolites have been synthesized and tested for tumorigenic activity.[46-49] Fluorine substitution at C-7, C-8, C-9 and C-10 positions of B*a*P has been found to reduce the tumor initiating activity and carcinogenicity in the mouse models compared to B*a*P.[49] The metabolism studies revealed no formation of the dihydrodiol metabolites at 7,8- positions in the case of 7-F- and 8-F- derivatives. These dihydrodiol metabolites were observed for 9-F and 10-F- analogs, but fluorine at the double bond at either 9 or 10 position can block further oxidation to diol epoxide. Thus, the lower or no activity clearly indicates that the bay region diol epoxide (7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydroB*a*P, **11** in Figure 9) is important metabolite responsible for the tumorigenic activity of B*a*P.[49]



Benzo[*a*]pyrene

1

(±)-7,8-diol-9,10-epoxide of B*a*P

11

Figure 9. B*a*P and its bay region diol epoxide.

A significant drop in the tumorigenic activity of B*a*P and its metabolites was observed upon fluorine substitution at position C-6.[50] The parent 6-FB*a*P hydrocarbons is active, but has lower activity than B*a*P. On the other hand, the *R,S,S,R* diol epoxide isomer of 6-FB*a*P has no tumorigenic activity, in contrast to its highly active unfluorinated analog.[26,50,51] Introduction of fluorine to *peri* position to benzylic hydroxyl alters the orientation of the hydroxyl groups in 7*R*,8*S*-dihydrodiol as well as in the diol epoxide metabolites. As a consequence, the vicinal hydroxyl groups in 7*R*,8*S*-dihydrodiol as well as in series-2 diol epoxide adopt a quasi-diaxial orientation (Figure 10).[25, 51]

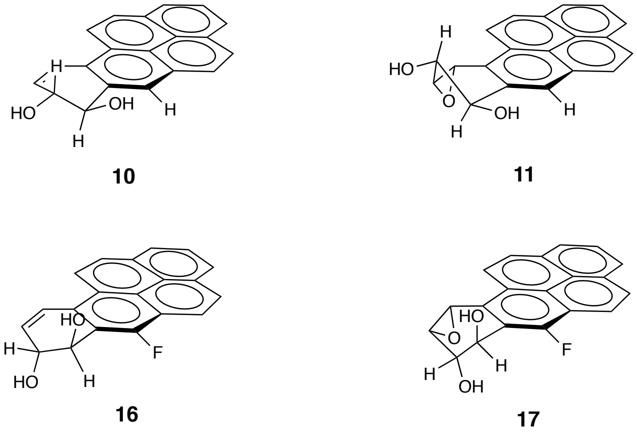
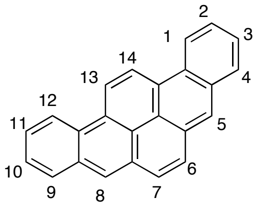


Figure 10. Conformations of hydroxyl groups in dihydrodiol and series-2 diol epoxide of B*a*P (top) and 6-F-B*a*P (bottom).

Hecht et al. reported the synthesis and tumor initiating activity of various fluoro derivatives of 5-methylchrysene (see Figure 3 for 5-MeC).[52,53] It was observed that fluorine substitution in the hydrocarbon decreases the activity from marginally to significantly.[53] Among the fluoro drivarives, 6-F-, 7-F-, 9-F- and 11-F-5-methylchrysenes were found to show a higher activity that was closer to unfluorinated analog 5-MeCh. 1-F-, 3-F- and 12-F- derivatives had lower activity than 5-MeCh.[53] These results suggest the formation of diol epoxide in the C-1–C-4 ring as the important metabolic pathway leading to tumor initiation by 5-MeCh.[53]

The mutagenicity and tumor-initiating activity of four fluorinated derivatives of 7,12-dimethylbenz[*a*]anthracene (see Figure 3 for DMBA) were also studied and compared with the parent non-fluorinated hydrocarbon. It was observed that fluorine substitution in pseudo fjord region[54] (i. e. positions C-1 and C-2), as well as K-region[54] (i.e. C-5) reduces the mutagenicity and tumor initiating activity. Similarly, C-4 fluorinated hydrocarbon showed substantially attenuated activity.[55] Introduction of fluorine to positions C-8,[55] C-9[56] and C-11,[54] does not alter the activity of the parent hydrocarbon. However fluorine at C-10[56] position dramatically increased the tumor initiating activity of DMBA.[56] These results also suggest that formation of pseudo-fjord region diol epoxides is the major pathway responsible for the tumorigenic activity of DMBA.

In the case of dibenzo[*a,i*]pyrene, fluorine substitution in the angular rings was reported to reduce the tumorigenicity of the molecule (see Figure 11 for dibenzo[*a,i*]pyrene). The tumor initiating activity of 2-F-, 3-F- and 2,10-diF- derivatives was studied on the mouse skin.[57] The formation of dihydrodiol metabolites was inhibited in the metabolism of these fluorinated derivatives.[57] This indicates that angular ring diol epoxides that are formed by the oxidation of dihydrodiol, are responsible for the carcinogenicity of dibenzo[*a,i*]pyrene.



Dibenzo[a,i]pyrene

18

Figure 11. Structure of dibenzo[*a,i*]pyrene.

In addition to these examples, there are many reports on the synthesis of fluorinated PAHs and their metablotes, evaluation of their biological activity, their use as probes for structure activity relationship. Fluorinated benzo[*c*]phenanthrene derivatives have also been used as important tools for the metabolism and DNA binding studies of B*c*Ph. The details of these studies are described in the Parts 1 and 2 of this chapter.

REFERENCES

1. Luch, A.; Baird, W. M. *The Carcinogenic Effects of Polycyclic Aromatic Hydrocarbons*, Luch, A., Ed.; Imperial College Press: London, 2005; pp 1-96.

2. Harvey, R. G. Structure-activity relationships. In: *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*, Cambridge University Press: Cambridge, 1991; pp 26-49.

3. Kennaway, E. L.: Experiments on Cancer-Producing Substances, *Br. Med. J.* **1925**, *2*, 1-4.

4. Hieger, I.: The Spectra of Cancer-Producing Tars and Oils and of Related Substances, *Biochem. J.* **1930**, *24*, 505-511.

5. Kennaway, E. L.; Hieger, I.: Carcinogenic Substances and Their Fluorescence Spectra. *Br. Med. J.* **1930**, *1*, 1044-1046.

6. Kennaway, E.: Further Experiments on Cancer-Producing Substances, *Biochem. J.* **1930**, *24*, 497-504.

7. Cook, J. W.; Haslewood, G. A. D.; Hewett, C. L.; Hieger, I.; Kennaway, E. L.; Mayneord, W.V.: Chemical Compounds as Carcinogenic Agents, *Am. J. Cancer* **1937**, 29, 219-259.

8. Kennaway, E. L.: The Identification of a Carcinogenic Compound in Coal Tar, *Br. Med. J.* **1955**, *2*, 749-752.

9. Baird,.; Harvey, R. G.; Brookes, P.: Comparison of the Cellular DNA-Bound Products of benzo[*a*]pyrene with the Products Formed by Reaction of Benzo[a]pyrene-4,5-oxide with DNA, *Cancer Res.* **1975**, *35*, 54-57.

10. Borgen, A.; Darvey, H.; Castagnoli, N.; Crocker, T. T.; Rasmussen, R. E.; Wang, I. Y.: Metabolic Conversion of Benzo(a)pyrene by Syrian Hamster Liver Microsomes and Binding of Metabolites to Deoxyribo-nucleic Acid, *J. Med. Chem.* **1973**, *16*, 502–506.

11. Sims, P.; Grover, P. L.; Swaisland, A.; Pal, K.; Hewer, A.: Metabolic Activation of Benzo[*a*]pyrene Proceeds by a Diol-Epoxide, *Nature* **1974**, *252*, 326-328.

12. Daudel, P.; Duquesne, M.; Vigny, P.; Grover, P. L.; Sims, P.: Fluorescence Spectral Evidence that Benzo[a]pyrene-DNA Products in Mouse Skin Arise from Diol-Epoxides, *FEBS Lett.* **1975**, 57, 250-253.

13. King, H. W. S.; Osborne, M. R.; Beland, F. A.; Harvey, R. G.; Brookes, P.: (±)-7α,8β-Dihydroxy-9β,10β-Epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene is an

Intermediate in the Metabolism and Binding to DNA of Benzo[a]pyrene, *Proc. Natl. Acad. Sci. USA* **1976**, *73*, 2679-2681.

14. Newbold, R. F.; Brookes, P.: Exceptional Mutagenicity of a Benzo[*a*]pyrene Diol Epoxide in Cultured Mammalian Cells, *Nature* **1976**, *261*, 52-54.

15. Huberman, E.; Sachs, L.; Yang, S. K.; Gelboin, H. V.: Identification of Mutagenic Metabolites of Benzo[*a*]pyrene in Mammalian Cells, *Proc. Natl. Acad. Sci. USA* **1976**, *73*, 607-611.

16. Jeffrey, A. M.; Weinstein, I. B.; Jennette, K. W.; Grzeskowiak, K.; Nakanishi, K.: Structures of Benzo[*a*]pyrene Nucleic Acid Adducts Formed in Human and Bovine Bronchial Explants, *Nature* **1977**, *269*, 348-350.

17. Chouroulinkov, I.; Gentil, A.; Grover, P. L.; Sims, P.: Tumour Initiating Activities on Mouse Skin of Dihydrodiols Derived from Benzo[*a*]pyrene, *Br. Med. J.* **1976**, *34*, 523-532.

18. Levin, W.; Wood, A. W.; Yagi, H.; Jerina, D. M.; Conney, A. H.: *(±)-trans*-7,8-Dihydroxy-7,8-Dihydrobenzo[*a*]pyrene: A Potent Skin Carcinogen When Applied Topically to Mice, *Proc. Natl. Acad. Sci. USA* **1976**, *73*, 3867-3871.

19. Kapitulnik, J.; Levin, W.; Conney, A. H.; Yagi, H.; Jerina, D. M.: Benzo[*a*]-pyrene 7,8-Dihydrodiol is More Carcinogenic than Benzo[*a*]pyrene in Newborn Mice, *Nature* **1977**, *266*, 378-380.

20. Yagi, H.; Hemandez, O.; Jerina, D. M.: Synthesis of (±)-(±)-7α,8β-Dihydroxy-9β,10β-Epoxy-7,8,9,10-Tetrahydrobenzo[*a*]pyrene a Potential Metabolite of the Carcinogen Benzo[*a*]pyrene with Stereochemistry Related to the Antileukemic Tripolides *J. Am. Chem. Soc*. **1975**, *97*, 6881-6883.

21. Yagi, H.; Thakker, D. R.; Hemandez, O.; Koreeda, M.; Jerina, D. M.: Synthesis and Reactions of the Highly Mutagenic 7,8-Diol 9,10-Epoxides of the Carcinogen Benzo[*a*]pyrene, *J. Am. Chem. Soc*. **1977**, *99*, 1604-1611.

22. Jerina, D. M.; Sayer, J. M.; Agarwal, S. K.; Yagi, H.; Levin, W.; Wood, A. W.; Conney, A. H.; Pruess-Schwartz, D.; Baird, W. M.; Pigott, M. A.; Dipple, A.: Reactivity and Tumorigenic Activity of Bay-Region Diol Epoxides Derived from Polycyclic Aromatic Hydrocarbons, *Biological Reactive Intermediates III*; Kocsis, J. J.; Jollow, D. J., Witmer, C. M., Nelson, J. O., Snyder, R., Eds.; Plenum Press: New York, 1986; pp 11-30.

23. Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Jerina, D. M.: Novel Bay Region Diol Epoxides from Benzo[*c*]phenanthrene. *J. Am. Chem. Soc.* **1981**, *103*, 4970-4972.

24. Jerina, D. M.; Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Ittah, Y.; Thakker, D. R; Wood, A. W.; Chang, R. L.; Levin, W.; Conney, A. H.: Highly Tumorigenic Bay-Region Diol Epoxides from the Weak Carcinogen Benzo[*c*]phenanthrene, *Biological Reactive Intermediates II Part A*; Snyder, R., Parke, D., Kocsis, J. J., Jollow, D. J., Gibson, G., Witmer, C. M.; Eds.; Plenum Press: New York, 1986; pp 501-523.

25. Chang, R. L.; Wood, A. W.; Conney, A. H.; Yagi, H.; Sayer, J. M.; Thakker, D. R.; Jerina, D. M.; Levin, W. Role of Diaxial versus Diequatorial Hydroxyl Groups in the Tumorigenic Activity of a Benzo[*a*]pyrene bay-region diol epoxide, *Proc. Natl. Acad. Sci. USA*, **1987**, *84*, 8633-8636.

26. Thakker, D. R.; Yagi, H.; Sayer, J. M.; Kapur, U.; Levin, W.; Chang, R. L.; Wood, A. W.; Conney, A. H.; Jerina, D. M.: Effects of a 6-Fluoro Substituent on the Metabolism of Benzo[*a*]pyrene 7,8-Dihydrodiol to Bay-Region Diol Epoxides by Rat Liver Enzymes*, J. Biol. Chem*. **1984**, *259*, 11249-11256.

27. Katz, A. K.; Carrell, H. L.; Glusker, J. P.: Dibenzo[*a*,*l*]pyrene (Dibenzo[*def*,*p*]-chrysene): Fjord-Region Distortions, *Carcinogenesis* **1998**, *19*, 1641–1648..

28. Bae, S.; Mah, H.; Chaturvedi, S.; Jeknic, T. M.; Baird, W. M.; Katz, A. M.; Carrell, H. L.; Glusker, J. P.; Okazaki, T.; Laali, K. K.; Zajc, B.; Lakshman, M. K.: Synthetic, Crystallographic, Computational, and Biological Studies of 1,4-Difluorobenzo[*c*]phenanthrene and Its Metabolites, *J. Org. Chem.* **2007**, *72*, 7625-7633.

29. Lakshman, M. K.; Kole, P.; Chaturvedi, S.; Saugier, J. H.; Yeh, H. J. C.; Glusker, J. P.; Carrell, H. L.; Katz, A. K.; Afshar, C. E.; Dashwood, W.-M.; Kenniston, G.; Baird, W. M.: Methyl Group-Induced Helicity in 1,4-Dimethylbenzo[*c*]-phenanthrene and Its Metabolites: Synthesis, Physical, and Biological Properties, *J. Am. Chem. Soc.* **2000**, *122*, 12629-12636.

30. RamaKrishna, N. V. S.; Gao, F.; Padmavathi, N. S.; Cavalieri, E. L.; Rogan, E. G.; Cerny, R. L.; Gross, M. L.: Model Adducts of Benzo[*a* Ipyrene and Nucleosides Formed from Its Radical Cation and Diol Epoxide, *Chem. Res. Toxicol.* **1992**, *5*, 293-302.

31. Rogan, E. G.; Cavalieri, E. L.; Tibbels, S. R.; Cremonesi, P.; Warner, C. D.; Nagel, D. L.; Tomer, K. B.; Cerny, R. L.; Gross, M. L.: Synthesis and Identification of Benzo[*a*]pyrene Guanine Nucleoside Adducts Formed by Electrochemical Oxidation by Horseradish Peroxidase Catalyzed Reaction of Benzo[*a*lpyrene with DNA, *J. Am. Chem. Soc.* **1988**, *110*, 4023-4029.

32. Cavalieri, E. L.; Rogan, E. G.; Li, K.-M.; Todorovic, R.; Ariese, F.; Jankowiak, R.; Grubor, N.; Small, G. J.: Identification and Quantification of the Depurinating DNA Adducts Formed in Mouse Skin Treated with Dibenzo[*a*,*l*]pyrene

(DB[*a,l*]P) or Its Metabolites and in Rat Mammary Gland Treated with DB[*a,l*]P, *Chem. Res. Toxicol.* **2005**, *18*, 976-983.

33. Bolton, J. L.; Trush, M. A.; Penning, T. M.; Dryurst, G.; Monks, T. J.: Role of Quinones in Toxicology, *Chem. Res. Toxicol.* **2000**, *13*, 135-160.

34. Penning, T. M.; Burczynski, M. E.; Hung, C.-F.; McCoull, K. D.; Palackal, N. T.; Tsuruda, L. S.: Dihydrodiol Dehydrogenases and Polycyclic Aromatic Hydrocarbon Activation: Generation of Reactive and Redox Active *o*-Quinones, *Chem. Res. Toxicol.* **1999**, *12*, 1-18.
35. Palackal, N. T.; Burczynski, M. E.; Harvey, R. G.; Penning, T. M.: The Ubiquitous Aldehyde Reductase (AKR1A1) Oxidizes Proximate Carcinogen *trans*-Dihydrodiols to *o*-Quinones*:* Potential Role in Polycyclic Aromatic Hydrocarbon Activation, *Biochemistry* **2001**, *40*, 10901-10910.

36. Champeil, E.; Pradhan, P.; Lakshman, M. K.: Palladium-Catalyzed Synthesis of Nucleoside Adducts from Bay and Fjord-Region Diol Epoxides, *J. Org. Chem.* **2007**, *72*, 5035-5045.

37. Jerina, D. M.; Chadha, A.; Cheh, A. M.; Schurdak, M. E.; Wood, A. W.; Sayer, J. M. In *Biological Reactive Intermediates IV*; Witmer, C. M., Snyder, R., Jollow, D. J., Kalf, G. F., Kocsis, J. J., Sipes, I. G., Eds.; Plenum Press: New York, 1991; pp 533-553.

38. Frank, E. G.; Sayer, J. M.; Kroth, H.; Ohashi, E.; Ohmori, H.; Jerina, D. M.; Woodgate, R.: Translesion Replication of Benzo[*a*]pyrene and Benzo[*c*]phen-anthrene Diol Epoxide Adducts of Deoxyadenosine and Deoxyguanosine by Human DNA Polymerase ι, *Nucleic Acids Res.* **2002**, *30*, 5284-5292.

39. Szeliga, J.; Dipple, A.: DNA Adduct Formation by Polycyclic Aromatic Hydrocarbon Dihydrodiol Epoxides, *Chem. Res. Toxicol.* **1998**, *11*, 1-11.

40. Harvey, R. G.; Geacintov, N. E.: Intercalation and Binding of Carcinogenic Hydrocarbon Metabolites to Nucleic Acids, *Acc. Chem. Res.* **1988**, *21*, 66-73.

41. Lin, J.; LeBreton, P. R.; Shipman, L. L.: Reaction of the 7,8-DioI 9,l0-Epoxide of Benzo[a]pyrene with Guanine In DNA. Ab Initio Calculations and Proposed Reaction Mechanism *J. Phys. Chem*. **1980**, *84*, 642-649.

42. Meehan, T.; Gamper, H.; Becker, J. F.: Characterization of reversible, physical binding of benzo[a]pyrene derivatives to DNA, *J. Biol. Chem.***,** **1982**, *257*, 10479-10485.

43. Islam, N. B.; Gupta, S. C.; Yagi, H.; Jerina, D. M.; Whalen, D. L.: Trapping of a Carbocationic Intermediate in the Spontaneous Hydrolysis Reaction of 7β, 8α-

Dihydroxy-9β, 10β-epoxy-7,8,9,l0-tetrahydrobenzao[*a*]pyrene: Mechanism of the Spontaneous and General Acid Catalyzed Hydrolysis Reactions of Bay-Region Benzo[*a*]pyrene 7,8-Diol 9,l0-Epoxides, *J. Am. Chem. Soc.* **1990**, *112*, 6363-6369.

44. Smart, B. E.: Fluorine Substituent Effects (on Bioactivity), *J. Fluorine Chem.* **2001**, *109*, 3-11.

45. Lemal, D. M.: Perspective on Fluorocarbon Chemistry, *J. Org. Chem.* **2004**, *69*, 1-11.

46. Newman, M. S.; Khanna, V. K.; Kanakarajan, K.: A Novel Synthesis of 7-Fluorobenzo[*a*]pyrene Involving Two New Molecular Rearrangements, *J. Am.Chem. Soc.* **1979**, *101*, 6788-6789.

47. Newman, M. S.; Kannan, R.: Syntheses of 8- and 9-Fluorobenzo[*a*]pyrenes and 9-Fluoro- and 10-Fluoro-7,12-dimethylbenz[*a*]anthracenes, *J. Org. Chem.* **1979**, *44,* 3388-3390.

48. Newman, M. S.; Khanna, V. K.: The Synthesis of 10-Fluorobenzo[*a*]pyrene, *Bull. Soc. Chim. Belg.* **1979**, *88*, 871-873.

49. Buhler, D. R.; Unlu, F.; Thakker, D. R.; Slaga, T. J.; Newman, M. S.; Levin, W.; Conney, A. H.; Jerina, D. M.: Metabolism and Tumorigenicity of 7-, 8-, 9-, and 10-Fluorobenzo[*a*]pyrenes, *Cancer Res.* **1982**, *42*, 4779-4783.

50. Buhler, D. R.; Unlu, F.; Thakker, D. R.; Slaga, T. J.; Conney, A. H.; Wood, A. W.; Chang, R. L.; Levin, W.; Jerina, D. M.: Effect of 6-Fluoro Substituent on the Metabolism and Biological Activity of Benzo[*a*]pyrenes, *Cancer Res.* **1983**, *43*, 1541-1549.

51. Zajc, B.: Synthesis of (±)-*trans*-7,8-Dihydrodiol of 6-Fluoro-benzo[*a*]pyrene via Hydroxyl-Directed Regioselective Functionalization of Substituted Pyrene, *J. Org. Chem.* **1999,** *64,* 1902-1907.

52. Hecht, S. S.; Loy, M.; Mazzarese, R.; Hoffmann, D.: Synthesis and Mutagenicity of Modified Chrysenes Related to the Carcinogen, 5-Methylchrysene, *J. Med. Chem.* **1978**, *21*: 38-44.

53. Hecht, S. S.; Hirota, N.; Loy, M.; Hoffmann, D.: Tumor-initiating Activity of Fluorinated 5-Methylchrysenes, *Cancer Res.* **1978**, *38*, 1694-1698.

54. Huberman, E.; Slaga, T. J.: Mutagenicity and Tumor-initiating Activity of Fluorinated Derivatives of 7,12-Dimethylbenz[*a*]anthracene, *Cancer Res.* **1979**, *39*, 411-414.

55. Harvey, R. G., and Dunne, F. A.: Multiple Regions of Metabolic Activation of Carcinogenic Hydrocarbons, *Nature* 1978, *273*, 566-567.

56. DiGiovanni, J.; Decina, P. C.; Diamond, L.: Tumor Initiating Activity of 9- and 10-Fluoro-7,12-dimethylbenz[*a*]anthracene (DMBA) and the Effect of 2,3,7,8-Tetrachlorodibenzo-pdioxin on Tumor Initiation by Monofluoro Derivatives of DMBA in SENCAR Mice, *Carcinogenesis* **1983**, *4*,1045-1049.

57. Hecht, S. S.; LaVoie, E. J.; Bedenko, V.; Pingaro, L.; Katayama, S.; Hoffmann, D.; Sardella, D. J.; Boger, E.; Lehr, R. E.: Reduction of Tumorigenicity and of Dihydrodiol Formation by Fluorine Substitution in the Angular Rings of Dibenzo[*a,i*]pyrene, *Cancer Res.* **1981**, *41*, 4341-4345.

PART 1

SYNTHESIS OF METABOLITES OF 5-FLUOROBENZO[*c*]PHENANTHRENE

1.1 INTRODUCTION

1.1.1 Benzo[*c*]phenanthrene and Its Metabolism

Benzo[*c*]phenanthrene (B*c*Ph) is a unique polycyclic aromatic hydrocarbon. It has four fused rings and contains the congested fjord region. The crowding in fjord region causes H-H repulsion that leads to non-planarity in the molecule (see Figure 1**)**. B*c*Ph is distorted from planarity by about 27°.[1] The substitution in the fjord region of B*c*Ph has been reported to increase this distortion.[1,2]

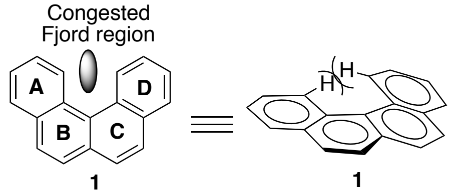


Figure 1. Sterically congested fjord region and non-planarity in benzo[*c*]phenanthrene.

B*c*Ph itself has lower tumorigenic activity compared to many bay region containing planar hydrocarbons like B*a*P, but its metabolites have been found to be very good DNA alkylating agents and highly potent carcinogens.[3,4] Upon motabolism in the fjord region B*c*Ph forms four diol epoxides i. e. *syn* (series-1) and *anti* (series-2) that are two enantiomeric sets of diastereomers, as shown in Figure 2.

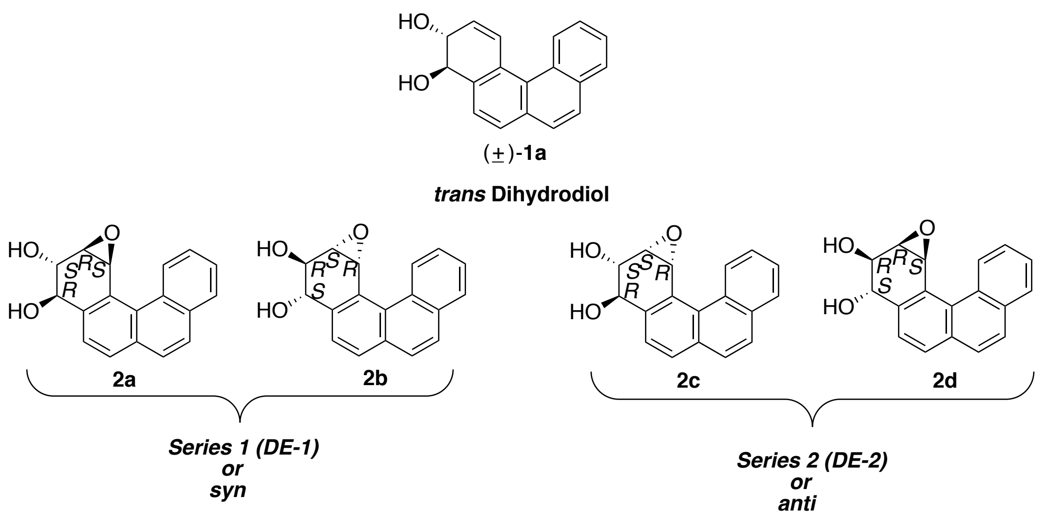


Figure 2. *trans* Dihydrodiol and isomeric diol epoxides of B*c*Ph.

It is important to mention that unlike other hydrocarbons, where most of the tumorigenic activity is due to series-2 diol epoxides, in B*c*Ph, both seies-1 as well as series-2 diol epoxides, are highly active.[3,5] This exceptional activity of series-1 diol epoxides is attributed to the change in conformation of hydroxyl groups, because of the steric repulsions in the hindered fjord region. Due to these repulsions, series-1 diol epoxides also adopt the quasi-diequatorial orientation of hydroxyl groups, unlike the bay region series-1 diol epoxides.[3,6]

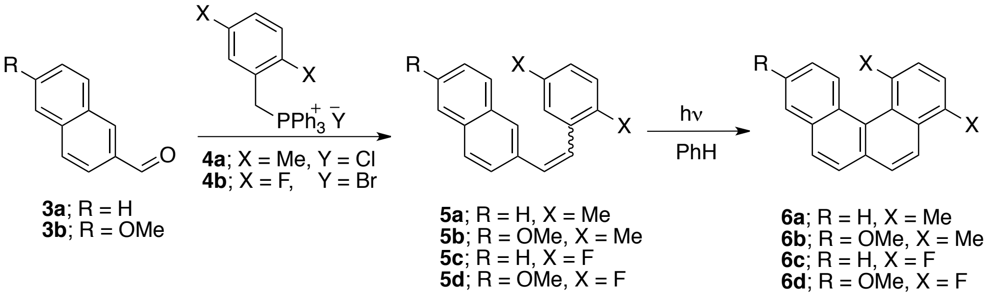
Fluorine substitution has been found to affect the metabolism of B*c*Ph. Importantly, it can potentially be used as a probe in structure activity relation studies of this hydrocarbon.

1.1.2 Previous Reports on the Synthesis of Derivatives of Fluorinated Benzo[*c*]phenanthrene and Their Metabolites

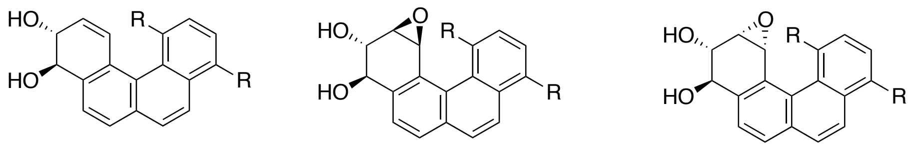
Lakshman et al. have reported the effect of fluoro and methyl substitution in the fjord region on the planarity of the molecule, its metabolism and the DNA alkylation.[1,2] The synthesis of the parent hydrocarbons, i.e. 1,4-dimethylbenzo[*c*]phenanthrene (1,4-

DMB*c*Ph **6a**, Scheme 1)[2] and 1,4-difluorobenzo[c]phenanthrene (1,4-DFB*c*Ph, **6c**, Scheme 1)[1] and their methoxy derivatives **6b** and **6d**, respectively involved Wittig reaction-photocyclization approach (Scheme 1).[1,2] The methoxy derivatives **6b** and **6d** were further converted to corresponding fjord region metabolites i.e. dihydrodiols and diol epoxides.[1,2] The dihydrodiols and diol epoxides of 1,4-DMB*c*Ph and 1,4-DFB*c*Ph are shown in Figure 3.

Scheme 1. Synthesis of 1,4-DMB*c*Ph, 1,4-DFB*c*Ph and Methoxy Derivatives



It was found that methyl and fluoro substituents in the fjord region influence the planarity of the molecule and that leads to altered metabolic activation and DNA binding. Also, X-ray crystallographic studies showed that 1,4-DMB*c*Ph[1] and 1,4-DFB*c*Ph[2] are distorted from planarity by 36.6° and 33.5°, respectively as compared to B*c*Ph (27°). 1,4-DMB*c*Ph showed 3-fold lower metabolic activation than B*c*Ph. Compared to B*c*Ph dihydrodiols **1a**, the metabolic activation of dihydrodiol metabolites of 1,4-DMB*c*Ph **(±)-7a** and 1,4-DFB*c*Ph **(±)-7b** to DNA alkylating agents was found to be 11-fold and 4-fold lower, respectively.[1,2] Interestingly, in the case of 1,4-DFB*c*Ph, the hydroxyl groups in series-1 diol epoxide **(±)-8b** exist in quasi-diaxial conformation, which is not the case for B*c*Ph series-1 diol epoxides **2a** and **2b**.[2]



Dihydrodiols

(±)-**7a**; R = Me
(±)-**7b**; R = F

Series 1
diol epoxides

(±)-**8a**; R = Me
(±)-**8b**; R = F

Series 2
diol epoxides

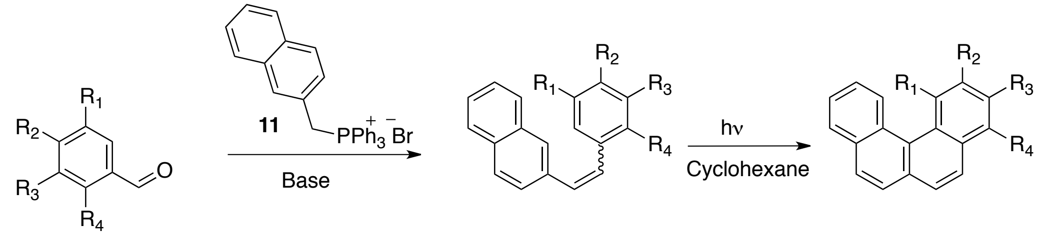
(±)-**9a**; R = Me
(±)-**9b**; R = F

Figure 3. Dihydrodiol and diol epoxides metabolites of 1,4-DMB*c*Ph and 1,4-DFB*c*Ph.

Another interesting observation for series-1 diol epoxide of 1,4-DFB*c*Ph (±)-**8b** was the intramolecular hydrogen bonding between the hydrogen of benzylic hydroxyl group and the epoxide oxygen. The molecular distortion due to the presence of fluorine in fjord region, and intramolecular hydrogen bonding were suggested to be responsible for the conformational change of series-1 diol epoxide of 1,4-DFB*c*Ph (±)-**8b**.[2]

Ittah et al. have reported synthesis and tumorigenic activity of 1-F-, 2-F-, 3-F-, 4-F- and 6-FB*c*Ph derivatives.[3,7] Synthesis involved photocyclization of suitable fluorostilbenes in cyclohexane. The requisite fluorostilbene precursors for these synthesis of 1-F-, 2-F-, 3-F- and 4-FB*c*Ph derivatives were obtained by the Wittig reaction of triphenylphosphonium salt of 2-bromomethylnaphthalene with isomeric fluorobenzaldehydes (Scheme 2).[7]

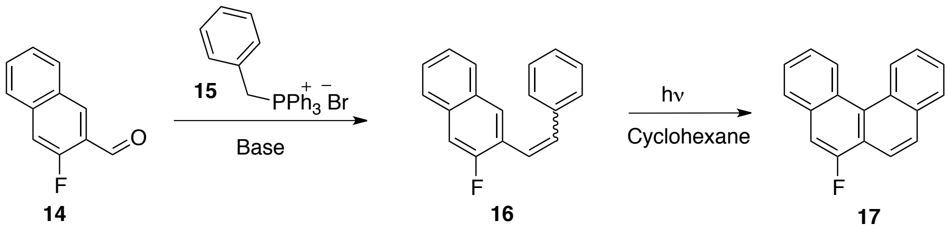
Scheme 2. Synthesis of Substituted Monofluoro-B*c*Ph Derivatives



10a; R_1, R_2, R_3 = H, R_4 = F
10b; R_1, R_2, R_4 = H, R_3 = F
10c; R_1, R_3, R_4 = H, R_2 = F
10d; R_2, R_3, R_4 = H, R_1 = F

12a; R_1, R_2, R_3 = H, R_4 = F
12b; R_1, R_2, R_4 = H, R_3 = F
12c; R_1, R_3, R_4 = H, R_2 = F
12d; R_2, R_3, R_4 = H, R_1 = F

13a; R_1, R_2, R_3 = H, R_4 = F
13b; R_1, R_2, R_4 = H, R_3 = F
13c; R_1, R_3, R_4 = H, R_2 = F
13d; R_2, R_3, R_4 = H, R_1 = F

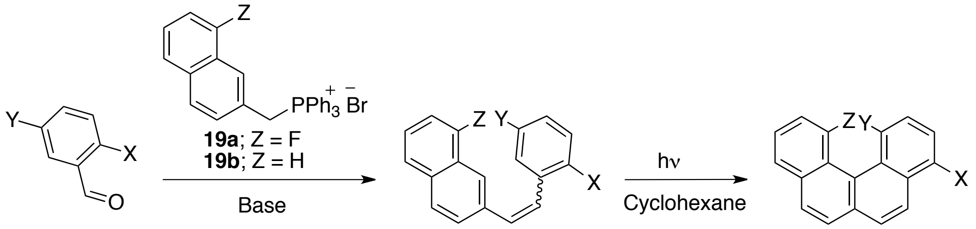


Similarly, Wittig reaction of 3-fluoro-2-naphthaldehyde with benzyltriphenylphosphonium bromide produced the fluoroolefin precursor for 6-FB*c*Ph synthesis (Scheme 2).

The tumorigenic study of these compounds on the mouse skin indicated that all compounds were more active than B*c*Ph, except for 2-FB*c*Ph, where the activity dropped marginally. The activity of 3-F- and 6-F- derivatives was exceptionally high.[7] For 6-FB*c*Ph, the activity was found to be 4.5-5 folds higher than in the case of B*c*Ph. It was suggested that fluorine substitution in the K-region suppresses the metabolism of the hydrocarbon in this region, thus leading to increased metabolism in the bay region and consequently higher tumorigenic activity. The reason for the significantly higher tumorigenic activity of 3-FB*c*Ph is not yet understood.

Mallory et al. reported synthesis of 1-F- and 1,12-DFB*c*Ph.[8] The synthetic approach was similar to that reported by Ittah et al.[7] described above. Variously substituted 1-F- as well as 1,12-DFB*c*Ph derivatives were synthesized by Wittig reaction-photocyclization sequence (Scheme 3).[8]

Scheme 3. Synthesis of Substituted Monofluoro and Difluoro-B*c*Ph Derivatives



18a; X = Me, Y= F
18b; X = OMe, Y= F
18c; X = Br, Y= F
18d; X = CN, Y= F
18e; X = H, Y= H
18f; X = OMe, Y= H
18g; X = Br, Y= H
18h; X = CN, Y=H

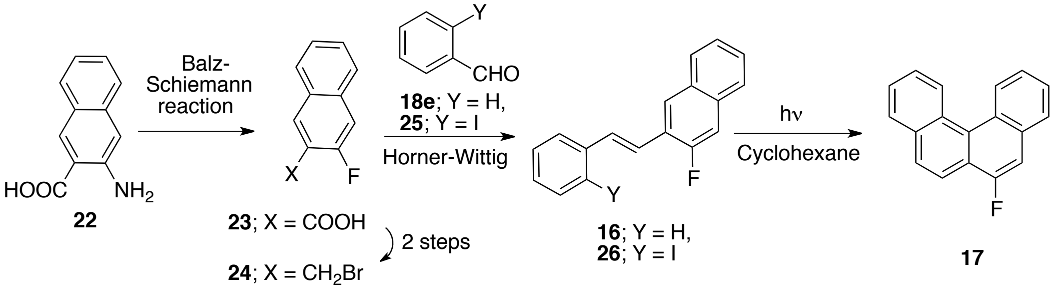
For Z = F, **20a**; X = Me, Y = F
20b; X = OMe, Y = F
20c; X = Br, Y = F
20d; X = CN, Y = F
20e; X = H, Y = H
20f; X = OMe, Y = H
20g; X = Br, Y = H
20h; X = CN, Y = H
For Z = H, **20i**; X = OMe, Y = F
20j; X = Br, Y= F
20k; X = CN, Y= F

For Z = F, **21a**; X = Me, Y = F
21b; X = OMe, Y = F
21c; X = Br, Y = F
21d; X = CN, Y = F
21e; X = H, Y = H
21f; X = OMe, Y = H
21g; X = Br, Y = H
21h; X = CN, Y = H
For Z = H, **21i**; X = OMe, Y = F
21j; X = Br, Y= F
21k; X = CN, Y= F

The 'through space' H-F and F-F coupling in the fjord region in these compounds was studied and was found to be independent of the nature of the substituents on the hydrocarbon. Other substituted monofluoro- and difluoroB*c*Ph derivatives were also synthesized by using the same method (Scheme 3).[8]

Marx et al. reported the synthesis of K-region monofluoro B*c*Ph derivatives.[9] Synthesis of 6-FB*c*Ph involved straightforward conversions starting from 2-aminonaphthalene-3-carboxylic acid. Balz-Schiemann reaction provided 2-fluoronaphthalene-3-carboxylic acid that was converted to Horner-Wittig precursor in three steps.[9]

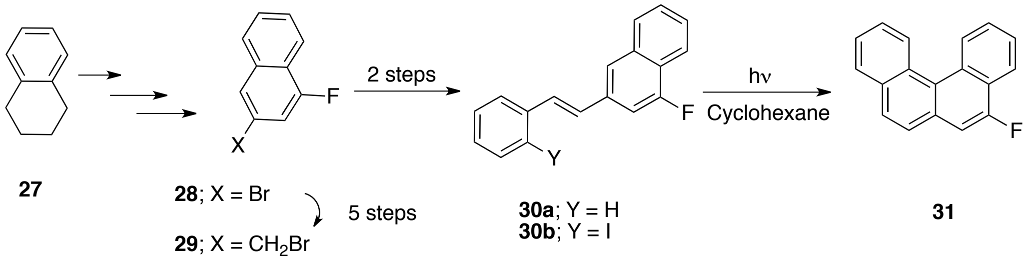
Scheme 4. Synthesis of 6-FB*c*Ph



Olefinations with benzaldehyde and *o*-iodobenzaldehyde provided the fluoroolefins that could successfully be photocyclized 6-FB*c*Ph (Scheme 4).[9]

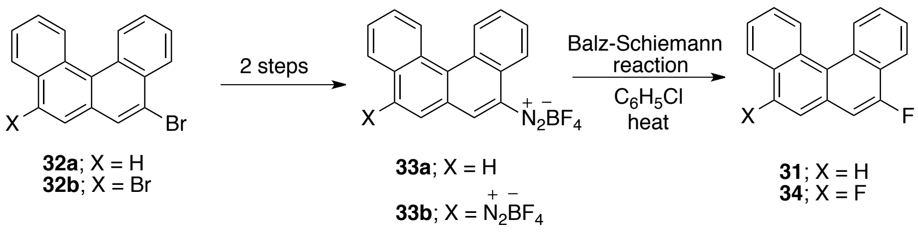
Synthesis of 5-FB*c*Ph needed a multistep approach.[9] The key precursor 1-fluoro-3-bromonaphthalene was synthesized in more than 10 steps with overall yield <1%. Further, the Horner-Wittig olefination reaction was not successful, so the olefin precursors were obtained by Michaelis-Arbuzov reaction. The photocyclization of the olefins provided 5-FB*c*Ph (Scheme 5).[9]

Scheme 5. Multistep Synthesis of 5-FB*c*Ph



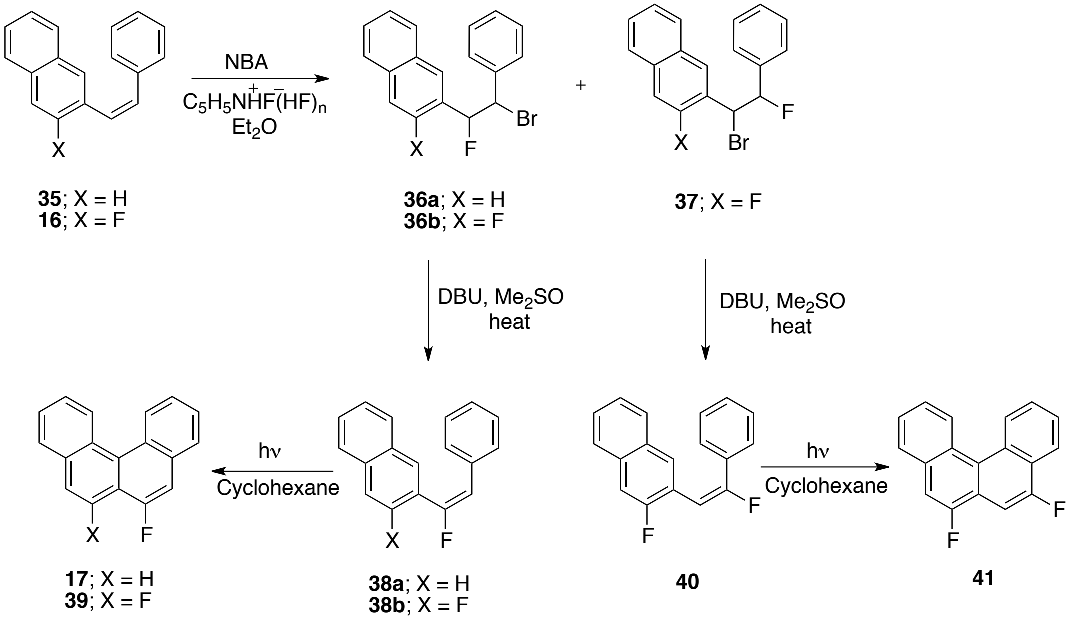
Mirsadhegi et al. reported the synthesis of various K-region monofluoro- and difluoro B*c*Ph derivatives.[10] 5-FB*c*Ph and 5,8-DFB*c*Ph derivatives were synthesized by Balz-Schiemann reaction (Scheme 6). The required diazonium tetrafluoroborate precursors **33a** and **33b** were obtained in two steps from the corresponding bromo-derivatives **32a** and **32b** (Scheme 6).[10]

Scheme 6. Synthesis of 5-FB*c*Ph and 5,8-DFB*c*Ph



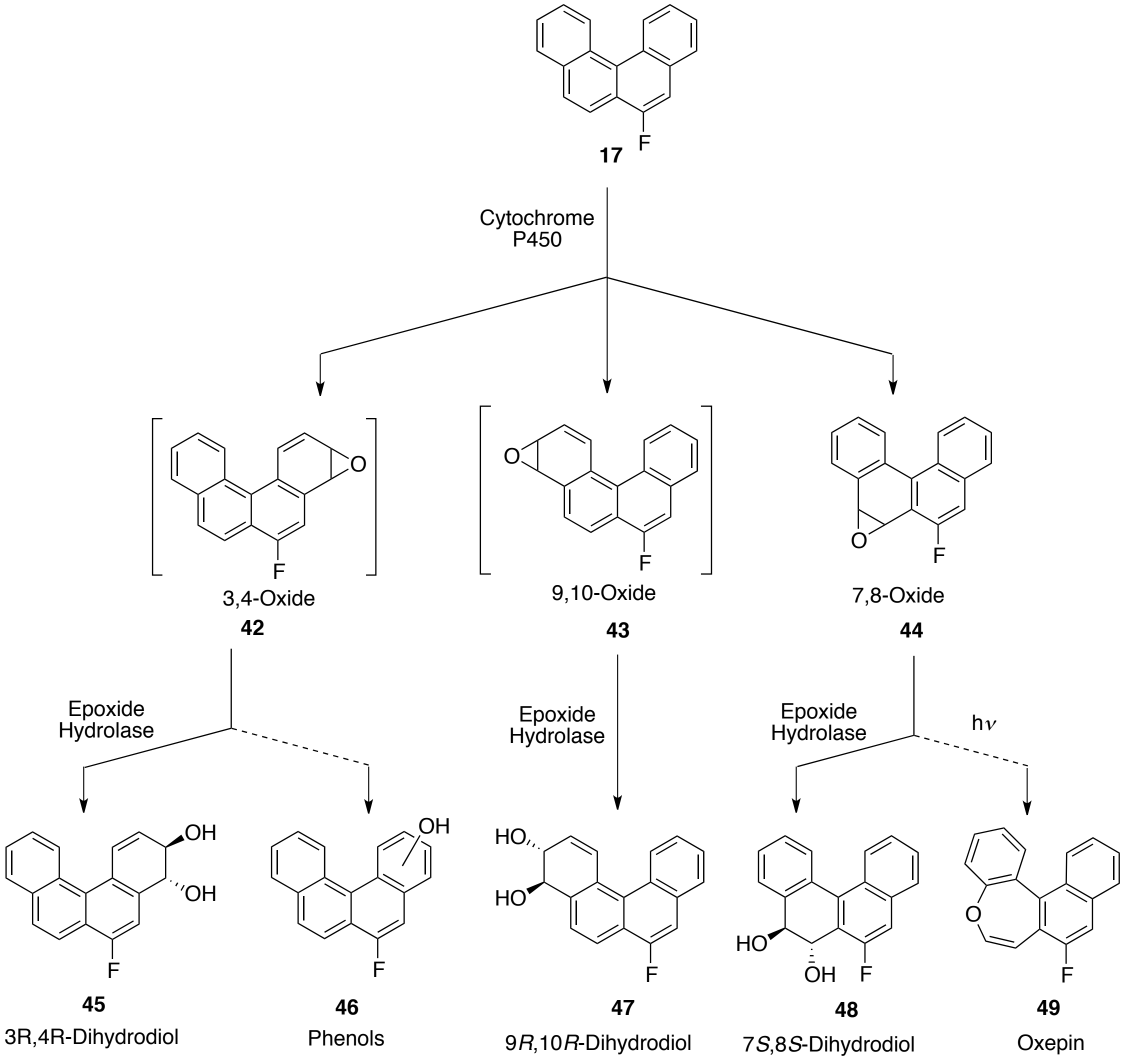
6-FB*c*Ph, 5,7-DFB*c*Ph and 6,7-DFB*c*Ph were obtained by photocyclization of fluoroolefins. The requisite fluoroolefin derivatives were obtained from the unfluorinated olefins via bromofluorination, followed by dehydrobromination.[10]

Scheme 7. Synthesis of K-Region Fluoro B*c*Ph Derivatives



Prasad et al. studied metabolism of 6-FB*c*Ph by rat liver microsomes.[11] Fluorine at this position was observed to block the oxidation at the 5,6-double bond. Interestingly, whereas the major metabolite of B*c*Ph is 5,6-dihydrodiol, 7,8-epoxide was found to be the major metabolite of 6-FB*c*Ph, and only small amount of 7,8-dihydrodiol was observed (Scheme 8). Also, dihydrodiol metabolites of both angular rings of 6-FB*c*Ph with double bond in fjord region, i.e. 3,4-dihydodiol as well as 9,10-dihydrodiol were formed. The amount of these dihydrodiol metabolites was 2.5 times higher than in the case of B*c*Ph. An unusual oxepin compound was also obtained from 7,8-epoxide (Scheme 8).[11]

Scheme 8. Various Products from Metabolism of 6-FB*c*Ph



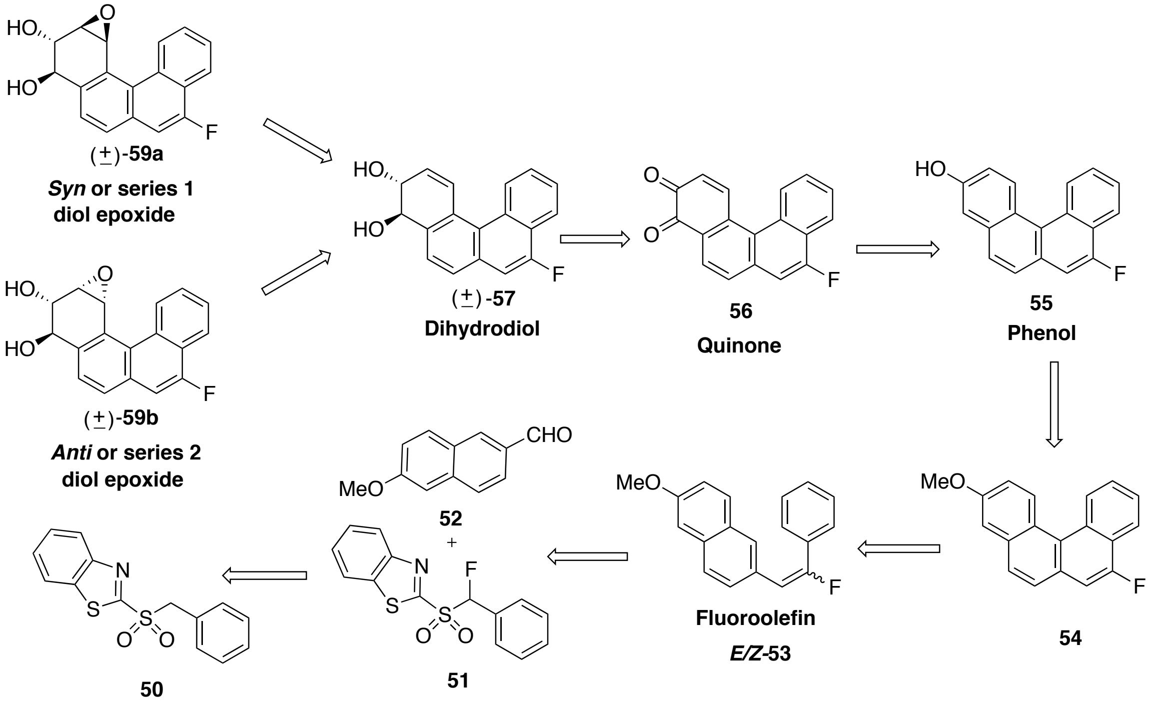
Since, fluorine can substantially alter biological activity of PAHs and metabolites, fluorinated PAHs can serve as useful probes for the better understanding of the structure-activity relationship on molecular level. In this context, various K-region fluoro B*c*Ph derivatives have been prepared; however there are only limited studies about their metabolism and interactions with DNA. In order to get a better understanding of metabolism, DNA binding and tumorigenic activity, it is critical to synthesize the metabolites and DNA adducts of these derivatives. Towards this goal, we wanted to develop a modular approach for the synthesis of fjord region metabolites i.e. dihydrodiol and diol epoxides, and the nucleoside adducts of 5-Fluoro B*c*Ph (5-FB*c*Ph). Introduction of fluorine into B*c*Ph desymmetrises the molecule (see Figure 1 for B*c*Ph). 5-FB*c*Ph, therefore can undergo metabolism in either of the two angular rings **A** and **D** (shown in Figure 1) that are part of the fjord region. Metabolism of ring **D** would result in dihydrodiol and diol epoxide metabolites with *peri* fluorine substitution, whereas ring **A** metabolism would result in metabolites with remote fluorine substitution.

Part of my research involves development of the modular approach for the synthesis of putative metabolites of 5-FB*c*Ph. Specifically, the focus of my work is synthesis of dihydrodiol and diol epoxide metabolites of ring **A**, that is remote to the site of fluorine substitution. We wish to assess the effect of fluorine on the conformational properties of B*c*Ph dihydrodiol and diol epxide metabolites, by comparison to those of B*c*Ph. In the long term goal, DNA modified by fluorinated B*c*Ph diol epoxide adduct can be used as a probe of DNA conformation. DNA-PAH adduct can adopt multiple conformations and solution structures of minor conformations are often difficult to assess. Modification of a PAH by fluorine remote from the site of attachment to DNA, provides an additional tool for structure elucidation by ^{19}F NMR. However, for such studies, it is critical that fluorine does not alter the conformation of DNA.

1.2 RESULTS AND DISCUSSION

Retrosynthetic plan for the synthesis of diol epoxides is outlined in Scheme 9. Both series-1 (±)-**59a** and series-2 (±)-**59b** diol epoxides can be obtained from the common precursor dihydrodiol (±)-**57**. Reduction of *ortho*-quinone **56** will provide access to compound **57**. The *ortho*-quinone **56** in turn can be obtained by oxidation of phenol derivative **55**. Photocyclization of methoxy aryl substituted fluoroolefin **53**, followed by removal of the methyl group will provide phenol **55**. The modular approach of metalation-electrophilic fluorination and fluoro-Julia olefination for such fluoroolefin precursors has been developed in our group and is now well established.[12]

Scheme 9. Retrosynthetic Plan for Metabolites of 5-FB*c*Ph

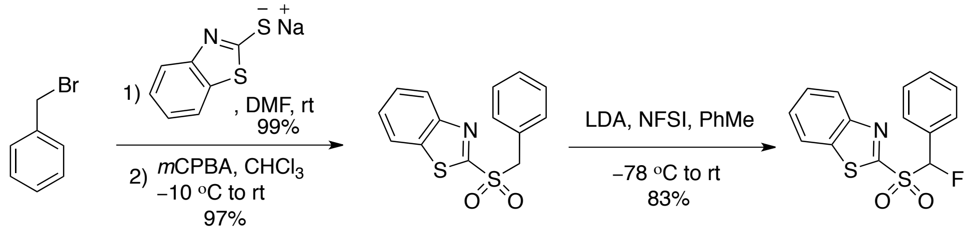


1.2.1 Synthesis of α-Fluorobenzyl 1,3-Benzothiazolyl Sulfone (51)

α-Fluorobenzyl-1,3-benzothiazol-2-yl sulfone (α-fluorobenzyl BT sulfone) **51**, the required precursor for fluoro-Julia olefination was synthesized in three steps by the known method reported by Ghosh et al.[13] Reaction of commercially available benzyl bromide with sodium salt of 2-mercapto-1,3-benzothiazole in DMF provided the corresponding sulfide in 99% yield (Scheme 10). Oxidation with *m*CPBA of the sulfide in $CHCl_3$ yielded sulfone **50** in 97% yield. Sulfone **50** as well as its sulfide precursor were of sufficient purity after the work-up and no further purification was required.

Fluorination of sulfone **50** was performed by metalation by LDA, followed by electrophilic fluorination using *N*-fluorobenzenesulfonimide (NFSI). The selection of solvent and addition of fluorinating reagent are critical for these reactions due to the competing single-electron transfer (SET) process that results in the recovery of the starting materials.[14,15] In this case the reaction was carried out in toluene, and solid NFSI was added to the metalated sulfone **50**. The desired α-fluorobenzyl BT sulfone **51** was obtained in 83% yield.

Scheme 10. Synthesis of α-Fluorobenzyl BT Sulfone **51**

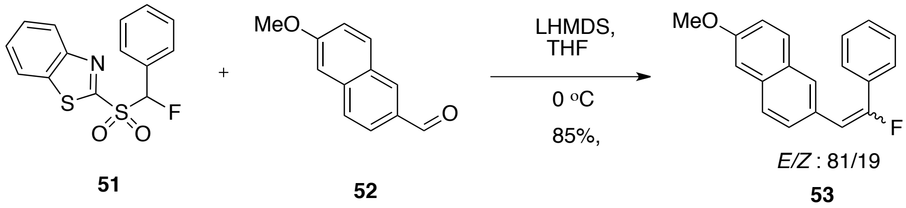


50 **51**

1.2.2 Synthesis of Fluorostilbene Derivative 53

The fluoro-Julia olefination reaction for synthesis of fluoroolefins has been well studied by Zajc et al.[12] In this context, synthesis of fluorostilbene-like molecules was developed by Ghosh et al.[13] Reactions of fluorobenzyl of (fluoromethyl) aryl BT sulfones with aryl aldehydes using LHMDS in THF resulted in stilbene-like products in high yields.[13] Following this methodology, Allendörfer et al. subsequently, reported synthesis of some substituted or heretoaryl-derived fluorostilbene-like molecules.[16] This very efficient approach for synthesis of diverse fluoroolefins has not yet been used in the synthesis of fluorinated polycyclic aromatic hydrocarbons. Condensation of fluoro Julia reagent **51** with 6-methoxy-2-naphthaldehyde **52** using LHMDS base in THF at 0 °C, yielded the requisite fluoroolefin **53** in 85% yield, with *E/Z* ratio of 81/19 (Scheme 11).

Scheme 11. Synthesis of 1,2-Diaryl Fluoroolefin Precursor via Julia-Kocienski Olefination



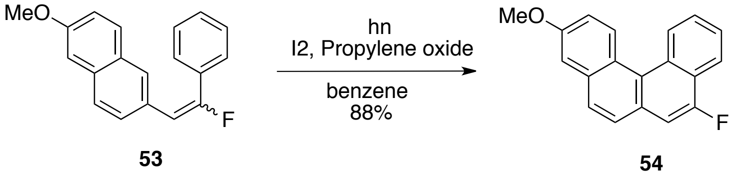
1.2.3 Synthesis of Substituted 5-Fluorobenzo[*c*]phenanthrene *via* Photocyclization of Fluoroolefin 53

Photocyclization of stilbenes is a well-established, in many cases an efficient approach for the synthesis of various polycyclic aromatic hydrocarbons.[17-21] Original method of photocyclization of stilbenes, developed by Mallory et al.,[17] involved the ultraviolet irradiation of stilbenes-like derivatives in solution, using catalytic iodine and oxygen as oxidants. The utility of this approach was demonstrated for the synthesis of variously functionalized phenanthrenes,[18] benzo[*c*]phenanthrenes,[19] chrysenes,[19,20] and benzo[*g*]chrysenes.[21]

Liu et al. reported an improved photocyclization method by using stoichiometric iodine and propylene oxide in the absence of air.[22] A significant improvement in the yields as well as the purity of the products was noticed. This approach is now widely used in the photocyclization reaction of diaryl olefins and has also been reported for the synthesis of fluorinated polycyclic aromatic hydrocarbons.[2,7-10]

The *E/Z* mixture of olefin **53** was subjected to photochemical cyclization ring closure using the improved cyclization method.[22] It should be noted that the fact that fluoroolefin **53** is a mixture of *E/Z* isomers, is not important since, under photolytic conditions, *E/Z* isomerization of 1,2-diaryl olefins occurs with the requisite *Z*-isomer cyclizing to the aromatic system. Photo irradiation of **53** in benzene, using 450 W medium-pressure Hg lamp, in the presence of 1.1 molar equivalent I_2, and an excess of propylene oxide, produced after 10-12 hours the methoxy substituted 5-fluoro B*c*Ph derivative **54**, and the yields were in the range of 86-90% upon repetitive experiments (Scheme 12). The reactions were very clean and no other side products were observed. It is important to mention that the previously reported photocyclization method for synthesis of unsubstituted 5-FB*c*Ph needed high dilution.[9] In our case, the concentration did not have much effect on the reaction time as well as the yield and the purity of the product.

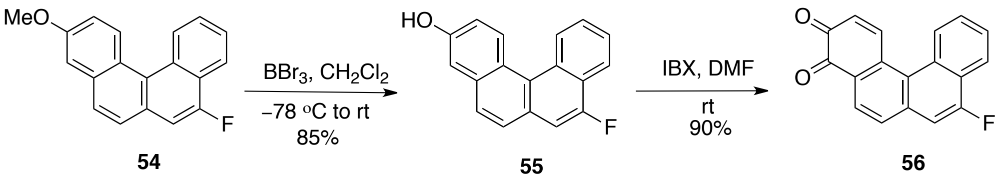
Scheme 12. Photocyclization of **53** to 5-FB*c*Ph Derivative



1.2.4 Synthesis of *trans*-Dihydrodiol (±)-57

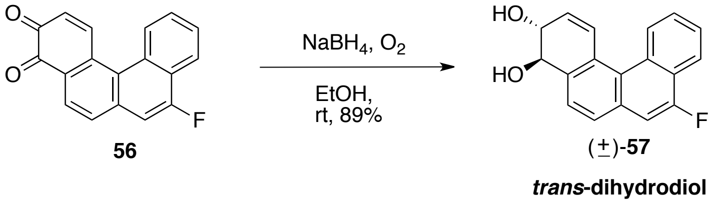
Compound **54**, the key intermediate for dihydrodiol synthesis, was converted to the phenol derivative **55** by the removal of methyl group, using BBr_3 in methylene chloride (Scheme 13).[1,2] The product was obtained in 85% yield and subjected to IBX oxidation in DMF. The *o*-quinone **56** was isolated in 90% yield, as a deep red solid (Scheme 13).

Scheme 13. Synthesis of *o*-Quinone Derivative of 5-FB*c*Ph



Quinone **56** was subjected to $NaBH_4$ reduction in ethanol and in the presence of O_2, to obtain the racemic *trans* dihydrodiol (±)-**57** in 89 % yield (Scheme 14).[1,2]

Scheme 14. Synthesis of *trans* Dihydrodiol Metabolite of 5-FBcPh



The ^1H NMR spectrum of (±)-**57** is shown in Figure 4. The conformational preference of the hydroxyl groups in (±)-**57** was assessed by comparing the coupling constants of H_9-H_{10} (C**H**OH-C**H**OH) protons to those of H_3-H_4 in unsubstituted B*c*Ph dihydrodiol (Table 1). The coupling constant $J_{9\text{-}10} = 11.5$ Hz (acetone-d_6) in compound (±)-**70** is comparable to $J_{3\text{-}4} = 11.0$ Hz (acetone-d_6)[11] of B*c*Ph dihydrodiol (also 10.3 in methanol-d_4).[23] This indicates the quasi-diaxial orientation of hydrogens (H_9 and H_{10}) and hence the quasi-diequatorial orientation of the hydroxyl groups. The $J_{9\text{-}10}$ value in (±)-**57** was also compared with that in dihydrodiols of 6-FB*c*Ph[11] and 1,4-DFB*c*Ph,[2] respectively and comparable values of 11.7 Hz and 11.0 Hz, respectively (see Table 1).

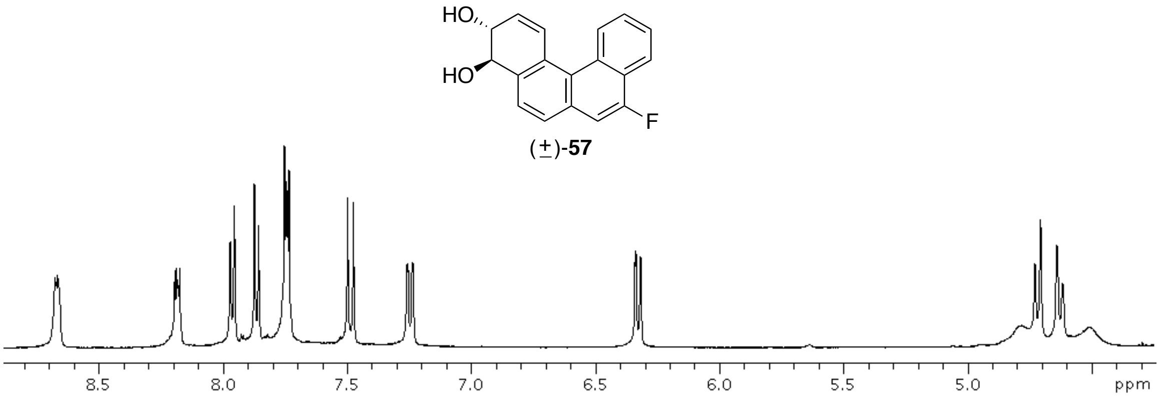


Figure 4. ^1H NMR spectrum of dihydrodiol of 5-FB*c*Ph in acetone-d_6.

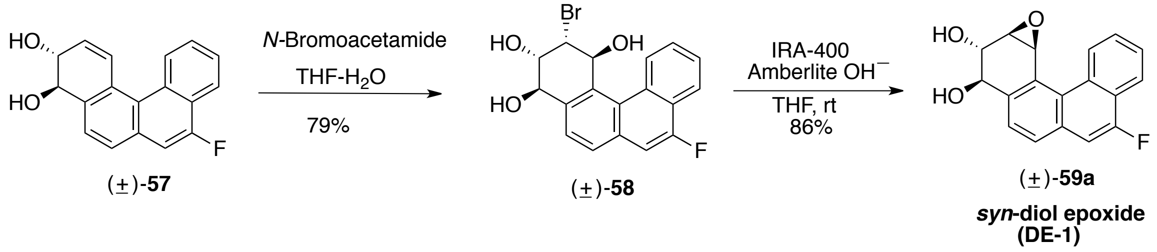
1.2.5 Synthesis of Diol Epoxides

trans-Dihydrodiol derivative can be used as a common precursor for synthesis of both, series-1 (*syn*) and series-2 (*anti*) diol epoxides.[1,2,23-25]

Series-1 (*Syn*) Diol Epoxide

Synthesis of series-1 diol epoxide from dihydrodiol precursor can be achieved in two steps.[1,2,25] The first step involves the bromohydrin formation, followed by cyclization to epoxide. Dihydrodiol derivative (±)-**57** was reacted with *N*-bromoacetamide in THF-water to get the bromotriol derivative (±)-**58** in 79% yield (Scheme 15).

Scheme 15. Synthesis of Series-1 Diol Epoxide of 5-FB*c*Ph



Cyclization using Amberlite IRA-400 in dry THF provided (±)-*syn* diol epoxide (±)-**59a** in 86% yield (Scheme 15). The coupling constant for H_9-H_{10} coupling in compound (±)-**59a** was compared with series-1 diol epoxides of B*c*Ph[25] and 1,4-DFB*c*Ph[2] respectively (see Table 1). The coupling constant $J_{9\text{-}10} = 9.2$ Hz (both in $dmso\text{-}d_6$ and $acetone\text{-}d_6$) in compound (±)-**59a** is comparable with $J_{3\text{-}4} = 9.0$ Hz ($dmso\text{-}d_6$) in DE-1 of B*c*Ph.[25] But the value differs from $J_{9\text{-}10} = 2.1$ Hz ($acetone\text{-}d_6$) in the DE-1 of 1,4-DFB*c*Ph, where the quasi-diaxial orientation of hydroxyls has been reported in DE-1.[2] This indicates that hydroxyl groups in (±)-**59a** are in quasi-diequatorial orientation and that fluorine substitution at position 5 does not alter the conformation upon conversion to of the remote angular ring to diol epoxide. The ^{1}H NMR spectrum of compound (±)-**59** is shown in Figure 5.

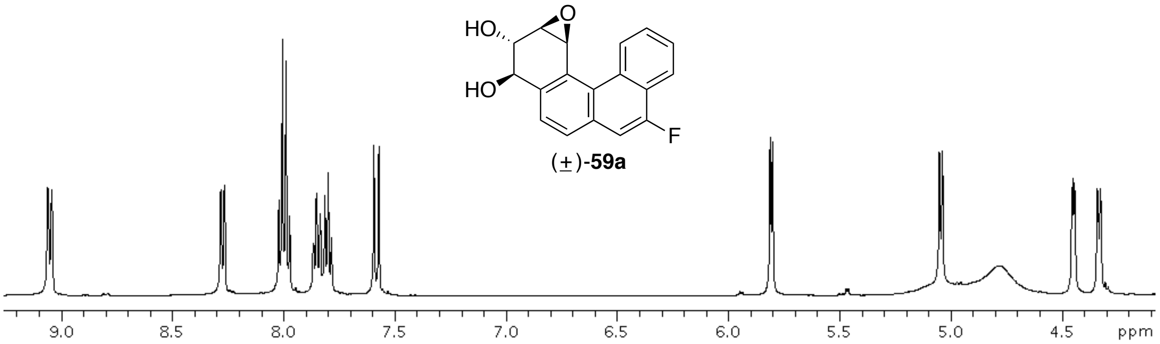


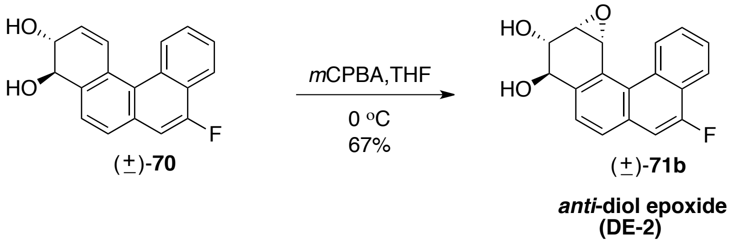
Figure 5. ^{1}H NMR spectrum of 5-FB*c*PhDE-1 in acetone-d_6.

Series-2 (*Anti*) Diol Epoxide

Peroxyacid mediated epoxidation of olefinic bond in dihydrodiols, where the hydroxyl groups are not part of the bay or fjord region, proceeds from the face opposite to that of the benzylic hydroxy group, leading to series-2 or *anti* diol epoxides. Reaction conditions require dry THF as solvent.[1,2,23] Reactions with *m*CPBA in $CHCl_3$ were reported to produce the *m*-chlorobenzoate adducts of diol epoxide as side products.[23,26] This further decomposition of the diol epoxide to undesired adducts was not observed in reactions in dry THF.

Following the literature procedures, *m*CPBA oxidation of compound (±)-**57** in anhydrous THF at 0 °C furnished (±)-*anti* diol epoxides (±)-**59b** in 67% yield (Scheme 16).

Scheme 16. Synthesis of Series-2 Diol Epoxide of 5-FB*c*Ph



The ^{1}H NMR spectrum of compound (±)-**59b** is shown in Figure 6. The coupling constant $J_{9\text{-}10}$ = 8.3 Hz (*dmso-d_6*) in (±)-**59b** is comparable with DE-2 of both B*c*Ph ($J_{3\text{-}4}$ = 8.0 Hz, dmso-d_6)[25] and 1,4-DFB*c*Ph ($J_{9\text{-}10}$ = 8.5 Hz, dmso-d_6)[2] respectively (see Table 1). Thus the quasi-diequatorial arrangement of hydroxyl groups in series-2 diol epoxides (±)-**59b** is consistent with that observed in B*c*Ph[25] and 1,4-DFB*c*Ph.[2]

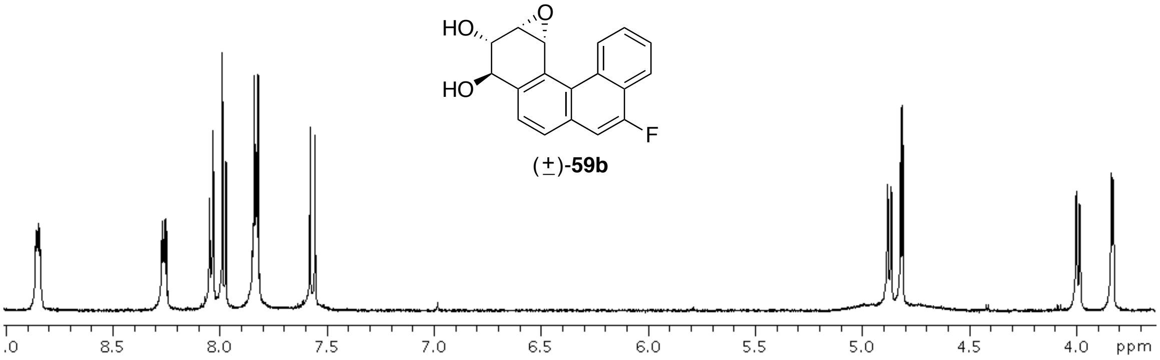
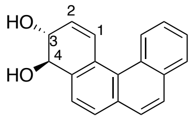
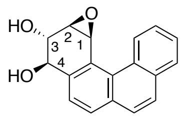
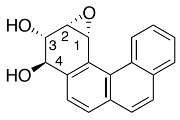
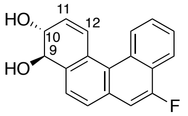
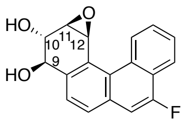
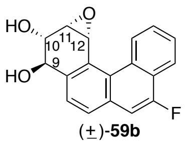
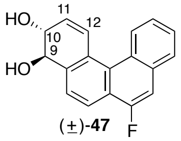
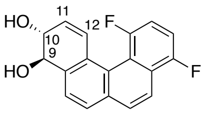
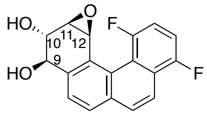
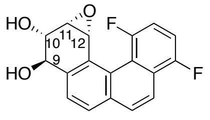


Figure 6. ^{1}H NMR spectrum of 5-FB*c*PhDE-2 in acetone-d_6.

Table 1. $^{3}J_{\text{H-H}}$ Values for C**H**-OH– C**H**-OH Coupling

Dihydrodiol	***J* (Hz) (NMR Solvent)**	**Diol Epoxide-1**	***J* (Hz) (NMR Solvent)**	**Diol Epoxide-2**	***J* (Hz), (NMR Solvent)**
 (±)-**1a** B*c*Ph	H_3-H_4 = 11.0 (acetone-d_6)[11]	 (±)-**2** B*c*PhDE-1	H_3-H_4 = 9.0 (dmso-d_6)[25]	 (±)-**2** B*c*PhDE-2	H_3-H_4 = 8.0 (dmso-d_6)[25]
 (±)-**57** 5-FB*c*Ph	H_9-H_{10} = 11.5 (acetone-d_6) H_9-H_{10} = 11.1 (dmso-d_6)	 (±)-**59a** 5-FB*c*PhDE-1	H_9-H_{10} = 9.2 (acetone-d_6) H_9-H_{10} = 9.2 (dmso-d_6)	 (±)-**59b** 5-FB*c*PhDE-2	H_9-H_{10} = 8.5 (acetone-d_6) H_9-H_{10} = 8.3 (dmso-d_6)
 (±)-**47** 6-FB*c*Ph	H_9-H_{10} = 11.7 (acetone-d_6)[11]	---	---	---	---
 (±)-**7b** 1,4-DFB*c*Ph	H_9-H_{10} = 11.0 (acetone-d_6)[2]	 (±)-**8b** 1,4-DFB*c*PhDE-1	H_9-H_{10} = 2.1 (acetone-d_6)[2]	 (±)-**9b** 1,4-DFB*c*PhDE-2	H_9-H_{10} = 8.5 (dmso-d_6)[2]

1.3 CONCLUSION

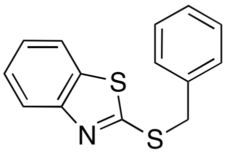
K-region fluorinated benzo[*c*]phenanthrene derivatives were synthesized by a modular approach, using fluoro-Julia-Kocienski olefination and subsequent photocyclization. This is the first example of the use of fluoro-Julia-Kocienski olefination in the synthesis of polycyclic aromatic hydrocarbons. The presence of fluorine at the olefinic bond did affect the photocyclization reaction that required longer reaction time. Photocyclization could also be performed at high olefin concentration, and the product was obtained in high yield as well as high purity. The methoxy-derivative of 5-FB*c*Ph obtained from photocyclization was successfully converted to its putative fjord region metabolites i.e. 3,4-dihydrodiol as well as *syn* and *anti* diol epoxides. The coupling constants between carbinol protons in these metabolites were compared with metabolites of B*c*Ph as well as to those of 6-FB*c*Ph (dihydrodiol) and 1,4-DFB*c*Ph. These values revealed the quasi-diequatorial orientation of the hydroxyl groups in dihydrodiol as well as the series-1 and series-2 diol epoxides of 5-FB*c*Ph. These data indicate that fluorine at a remote position to the oxidized ring does not alter the conformation of the dihydrodiol and diol epoxides, in comparison to unsubstituted B*c*Ph.

EXPERIMENTAL SECTION

THF was distilled over $LiAlH_4$, and then over sodium. For reactions, which were performed under a nitrogen atmosphere, glassware was dried with hot gun under vacuum. Toluene was distilled over sodium. All other reagents were obtained from commercial sources and used without further purification. Thin layer chromatography was performed on 250 μm silica plates and column chromatographic purifications were performed on silica gel. The mesh size of silica gel and the eluting solvents are reported for each compound separately. ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$, acetone-*d*$_6$ dmso- *d*$_6$. ^{13}C specta were recorded at 125 MHz using $CDCl_3$, acetone-*d*$_6$ and dmso-*d*$_6$. ^{19}F NMR spectra were recorded at 282 MHz using $CFCl_3$ as internal standard. Chemical shifts (δ) are reported in parts per million and coupling constants (J) are in hertz.

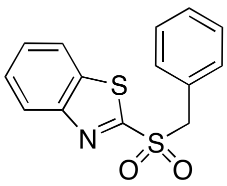
Synthesis of 2-(benzylsulfonyl)benzo[*d*]thiazole (50)

Step 1. Synthesis of 2-(Benzylthio)benzo[d]thiazole



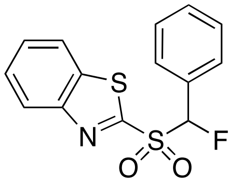
To a solution of benzyl bromide (2.00 g, 1 molar equiv) in 20 mL DMF, the sodium salt of 2-mercapto-1,3-benzothiazole (2.65 g, 1.2 molar equiv) was added and the reaction mixture was stirred for 3 h. 10 mL water was added and the reaction mixture was poured to a separatory funnel with EtOAc. Layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layer was thoroughly washed with water and finally with brine, dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product that was pale yellow solid was used for the further step without purification. Yield: 2.98 g (99%). *R*f (10% EtOAc in hexanes) = 0.46. ^{1}H NMR (500 MHz, CDCl$_3$): *δ* 7.95 (d, 1H, Ar-H, *J* = 7.9 Hz), 7.75 (d, 1H, Ar-H, *J* = 7.9 Hz), 7.49 (d, 2H, Ar-H, *J* = 7.6 Hz), 7.45 (t, 1H, Ar-H, *J* = 7.8 Hz), 7.37–7.29 (m, 4H, Ar-H), 4.63 (s, 2H, CH$_2$). ^{13}C NMR (125 MHz, CDCl$_3$): *δ* 166.5, 153.3, 136.3, 135.4, 129.2, 128.8, 127.9, 126.2, 124.4, 121.7, 121.1, 37.8.

Step 2: *Oxidation of 2-(Benzylthio)benzo[d]thiazole*



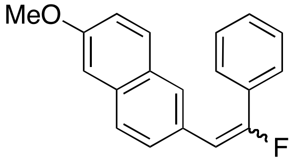
To a stirring solution of benzylthio)benzo[*d*]thiazole (2.00 g, 7.78 mmol) in CHCl$_3$ (24.0 mL) at –10 °C (ice-salt) a solution of *m*-CPBA (4.03 g, 23.4 mmol, 3 molar equiv) in CHCl$_3$ (56.0 mL) was added dropwise. After complete addition, the mixture was stirred for an additional 10 min at –10 °C, allowed to warm to room temperature and stirred for 15 h. The reaction was quenched with 30 mL of saturated aqueous NaHCO$_3$ solution, the organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layer was thoroughly washed with water and finally with brine and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under reduced pressure to yield 2.19 g (97%) of **50** as a pale yellow solid that was subjected to fluorination without further purification. *R*f (20% EtOAc in hexanes) = 0.29. ^{1}H NMR (500 MHz, CDCl$_3$): *δ* 8.27 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.95 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.65 (td, 1H, Ar-H, *J* = 8.3; 0.9 Hz), 7.58 (td, 1H, Ar-H, *J* = 7.8; 0.9 Hz), 7.34–7.27 (m, 5H, Ar-H), 4.76 (s, 2H, CH2). ^{13}C NMR (125 MHz, CDCl$_3$): *δ* 165.4, 152.7, 137.2, 131.3, 129.4, 129.1, 128.2, 127.8, 126.5, 125.6, 122.5, 61.2.

Synthesis of 2-[fluoro(phenyl)methylsulfonyl]benzo[*d*]thiazole (51)



A stirring solution of sulfone **50** (1.00 g, 3.46 mmol, 1 molar equiv) in dry toluene (30.0 mL) was cooled to –78 ˚C (dry ice/*iso*PrOH) under nitrogen. LDA (1.90 mL, 3.80 mmol, 1.1 molar equiv) was added and after 15 min, solid NFSI (1.31 g, 4.15 mmol, 1.2 molar equiv) was added. The reaction mixture was allowed to stir at –78 ˚C for 50 min, then warmed to room temperature and the stirring was continued for an additional 50 min. Saturated aq NH_4Cl (10 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted three times with EtOAc and the combined organic layer was washed with saturated aq $NaHCO_3$, water, and brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel mesh 200-300, eluent: 50% methylene chloride in hexanes) to yield 0.882 g (83%) of **51** as a pale yellow solid. R_f (20% EtOAc in hexanes) = 0.36. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (d, 1H, Ar-H, J = 8.2 Hz), 8.01 (d, 1H, Ar-H, J = 7.6 Hz), 7.67–7.59 (m, 4H, Ar-H), 7.53 (t, 1H, Ar-H, J = 7.3 Hz), 7.47 (t, 2H, Ar-H, J = 7.6 Hz), 6.65 (d, 1H, CHF, $^2J_{FH}$ = 46.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.9, 152.9, 137.7, 131.7, 129.0, 128.55, 128.49, 128.0, 126.5 (d, $^2J_{CF}$ = 19.2 Hz), 125.9, 122.5, 102.1 (d, $^1J_{CF}$ = 222.9 Hz). ^{19}F NMR (282 MHz): δ −173.08 (d, $^2J_{FH}$ = 45.8 Hz).

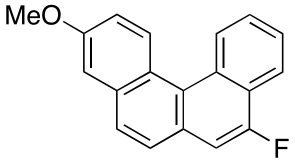
Synthesis of 2-(2-fluoro-2-phenylvinyl)-6-methoxynaphthalene (53)



A solution of fluoro sulfone **51** (0.500 g, 1.63 mmol, 1.0 molar equiv) and 6-methoxy-2-naphthaldehyde **52** (0.364 g, 1.95 mmol, 1.2 molar equiv) in dry THF (60.0 mL) was cooled under nitrogen to 0 °C (ice bath). LHMDS (1.0 M solution in THF, 3.9 mL, 2.4 molar equiv) was added. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq NH_4Cl was added and the mixture was poured into EtOAc. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude reaction mixture was analyzed by ^{19}F NMR, and the combined *E*/*Z* product mixture was isolated by column chromatography (silica gel mesh 200-300, eluent: 20% EtOAc in hexanes). Yield of fluoroolefin **53**: 0.385 g (85%) of pale yellow solid, *E*/*Z* ratio 81/19. R_f (20% EtOAc in hexanes) = 0.64. ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H, Ar-H, *Z*-isomer), 7.78 (d, 1H, J = 8.6 Hz, Ar-H, *Z*-isomer), 7.74 (t, 2H, Ar-H, J = 8.1 Hz, *Z*-isomer), 6.79 (d, 1H, Ar-H, J = 7.3 Hz, *Z*-isomer), 7.60 (d, 2H, Ar-H, J = 8.2 Hz, *E*-isomer), 7.55 (d, 1H, Ar-H, J = 8.5 Hz, *E*-isomer), 7.47 (d, 2H, Ar-H, J = 7.3 Hz, *E*-isomer), 7.43 (t, 1H, Ar-H, J = 7.9 Hz, *Z*-isomer), 7.38-7.36 (m, 1H, Ar-H, *Z*-isomer), 7.34 (d, 1H, Ar-H, J = 7.0 Hz, *E*-isomer), 7.31-7.28 (m, Ar-H, 2H *E*-isomer, 1H *Z*-isomer), 7.20 (dd, 1H, Ar-H, J = 8.5,1.5 Hz, *E*-isomer), 7.15 (dd, 1H, Ar-H, J = 8.9, 2.4 Hz, *Z*-isomer), 7.13-7.10 (m, 1H, Ar-H, both *E* and *Z*-isomers), 7.07 (d, 1H, Ar-H, J = 2.1 Hz, *E*-isomer) 6.59 (d, 1H, CHF, $^3J_{FH}$ = 21.7 Hz, *Z*-isomer), 6.45 (d, 1H, CHF, $^3J_{FH}$ = 39.7 Hz, *E*-isomer), 3.94 (s, 3H, CH_3, *Z*-

isomer), 3.91 (s, 3H, CH_3, *E*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$): δ –97.37 (d, $^3J_{FH}$ = 21.4 Hz, *E*-isomer), –115.49 (d, $^3J_{FH}$ = 39.7 Hz, *Z*-isomer). HRMS (ESI) calcd. for $C_{19}H_{15}FNaO$ $[M+H]^+$ 301.0999, found 301.1013.

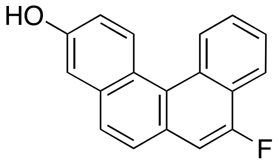
Synthesis of 8-fluoro-3-methoxybenzo[*c*]phenanthrene (54)



Fluoroolefin **53** (0.600 g, 2.16 mmol) was dissolved in benzene (320 mL) in a photoreactor and I_2 (605 mg, 2.38 mmol, 1.1 molar equiv) was added. The solution was purged with a slow stream of N_2 for 10 minutes and then propylene oxide (25 mL) was added. The reaction mixture was irradiated with UV light using 450 W medium-pressure Hg lamp for 10 h. Solvent was removed under reduced pressure and the crude reaction mixture was purified by silica gel column chromatography (silica gel mesh 200-300, eluent: 10 % EtOAc in hexanes) to yield 0.525 g (88%) of compound **54** as a light yellow solid. R_f (10% EtOAc in hexanes) = 0.46. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.08 (d, 1H, Ar-H, J = 8.5 Hz), 8.96 (d, 1H, Ar-H, J = 9.2 Hz), 8.31 (d, 1H, Ar-H, J = 7.6 Hz), 7.83 (d, 1H, Ar-H, J = 8.6 Hz), 7.75–7.68 (m, 3H, Ar-H), 7.46 (d, 1H, Ar-H, J = 10.7 Hz), 7.37 (d, 1H, Ar-H, J = 2.8 Hz), 7.34 (dd, 1H, Ar-H, J = 9.2, 2.8 Hz), 4.01 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.5, 156.7 (d, J_{CF} = 251.3 Hz), 134.7, 131.6 (d, J_{CF} = 9.6 Hz), 129.6 (d, J_{CF} = 9.6 Hz), 129.1, 128.0 (d, J_{CF} = 2.7 Hz), 127.6, 127.1, 127.0 (d, J_{CF} = 3.7 Hz), 126.3 (d, J_{CF} = 1.4 Hz), 125.1, 124.9 (d, J_{CF} = 15.6 Hz), 124.8, 121.2 (d,

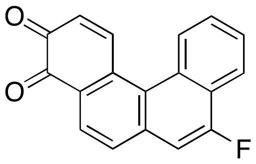
J_{CF} = 6.4 Hz), 117.6, 108.8 (d, J_{CF} = 19. 7 Hz), 108.2, 55.5. ^{19}F NMR (282 MHz, $CDCl_3$): δ −126.86 (d, $^2J_{FH}$ = 9.2 Hz). HRMS (ESI) calcd. for $C_{19}H_{13}FO$ $[M]^+$, 276.0945, found 276.0946.

Synthesis of 8-fluorobenzo[*c*]phenanthren-3-ol (55)



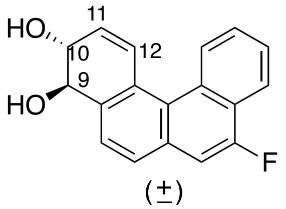
A solution of solution of 5-FB*c*Ph derivative **54** (1.0 g, 3.62 mmol) in CH_2Cl_2 (60.0 mL) was cooled to at –78 °C (dry ice/*iso*PrOH) under nitrogen and BBr_3 (1 molar solution in pentane, 10.9 mL, 10.9 mmol, 3.0 molar equiv) was added slowly using a syringe. The resulting light brown solution was stirred at allowed to warm to rt over 1 h and stirred at rt for 4 h. Reaction mixture was again cooled to 0 °C (ice bath) and a sat $NaHCO_3$ solution (30 mL) was added slowly. Organic layer was separated and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layer was thoroughly washed with water and finally with brine, dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. Crude reaction mixture was purified by column chromatography using silica gel column (mesh 200-300, eluent: 20% EtOAc in hexanes). Yield of phenol derivative **55**: 0.807 g (85%) of off white solid. R_f (10% EtOAc in hexanes) = 0.19. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.07 (d, 1H, Ar-H, J = 8.2 Hz), 8.96 (d, 1H, Ar-H, J = 9.2 Hz), 8.31 (d, 1H, Ar-H, J = 7.6 Hz), 7.78–7.68 (m, 4H, Ar-H), 7.46 (d, 1H, Ar-H, J = 11.0 Hz), 7.36 (d, 1H, Ar-H, J = 2.7 Hz), 7.27 (dd, 1H, Ar-H, J = 9.4, 2.8 Hz), 5.08 (s, 1H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.8 (d, J_{CF} = 251.3 Hz), 153.4, 134.8 (d, J_{CF} = 0.9 Hz), 131.6 (d, J_{CF} = 5.0 Hz), 129.7 (d, J_{CF} = 9.6 Hz), 129.6, 128.1 (d, J_{CF} = 3.2 Hz), 127.33, 127.31, 127.2, 126.4 (d, J_{CF} = 1.8 Hz), 125.3, four resonances for two C, a doublet each: 125.0, 124.91, 124.89, 124.87 (C-F coupling), 121.3 (d, J_{CF} = 6.9 Hz), 117.1, 111.6, 108.9 (d, J_{CF} = 20.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −126.72 (d, $^2J_{FH}$ = 9.2 Hz). HRMS (ESI) calcd. for $C_{18}H_{10}FO$ $[M-H]^-$, 261.0721, found 261.0724.

Synthesis of 8-fluorobenzo[*c*]phenanthrene-3,4-dione (56)



A solution of phenol **55** (0.360 g, 1.37 mmol, 1.0 molar equiv) and IBX (1.15 g, 4.12 mmols, 3 molar equiv) in DMF (20 mL) was stirred at rt for 3 h. A sat aqs solution of $NaHCO_3$ (10 mL) was added and stirring was continued for next 5 min. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Deep red solid was obtained that was used for further reaction without purification. Yield of *o*-quinone **56**: 0.340 g (90%). R_f (methylene chloride) = 0.83. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (d, 1H, Ar-H, J = 10.7 Hz), 8.32 (d, 1H, Ar-H, J = 7.6 Hz), 8.28-8.25 (m, 2H, Ar-H), 7.85 (d, 1H, Ar-H, J = 8.2 Hz), 7.81–7.76 (m, 2H, Ar-H), 7.32 (d, 1H, =CH, J = 10.7 Hz), 6.55 (d, 1H, =CH, J = 10.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.3, 179.5, 159.6 (d, J_{CF} = 259.5 Hz), 144.6, 138.5 (d, J_{CF} = 11.0 Hz), 132.6, 130.9 (d, J_{CF} = 5.6 Hz), 130.6, 130.1 (d, J_{CF} = 6.0 Hz), 129.5 (d, J_{CF} = 2.8 Hz), 128.6, 127.9, 127.8, 127.1, 126.5, 126.3 (d, J_{CF} = 18.8 Hz), 122.3 (d, J_{CF} = 6.9 Hz), 108.2 (d, J_{CF} = 20.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −118.75 (d, $^2J_{FH}$ = 9.2 Hz). HRMS (ESI) calcd. for $C_{18}H_{10}FO_2$ $[M+H]^+$, 277.0659, found 261.0661.

Synthesis of *trans*-(±)-8-fluoro-3,4-dihydrobenzo[*c*]phenanthrene-3,4-diol (57)

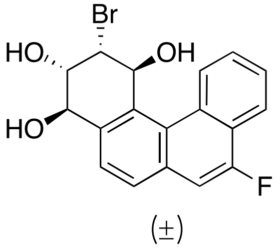


A red suspension of quinone **56** (0.300 g, 1.09 mmol) in EtOH (150 mL) was purged with O_2 for 5 minutes and $NaBH_4$ (1.03 g, 27.2 mmol) was added. Red suspension was turned to a light yellow solution that was stirred for 72 h under O_2 balloon. At this time H_2O (50 mL) was added and the solvent were removed under reduced pressure. Crude reaction mixture was diluted with 150 mL EtOAc and washed with water and brine. Organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. A light yellowish soild was obtained as crude reaction mixture. NMR analysis of this mixture showed signals only for the dihydrodiol (±)-**57**, therefore no further purification was performed. Yield of (±)-**57**: 0.272 g (89%). R_f (5% MeOH in methylene chloride) = 0.20. ^{1}H NMR (500 MHz, acetone-d_6): δ 8.69-8.65 (m, 1H, Ar-H), 8.20-8.17 (m, 1H, Ar-H), 7.96 (d, 1H, Ar-H, J = 7.8 Hz), 7.86 (d, 1H, Ar-H, J = 7.8 Hz), 7.76–7.73 (m, 2H, Ar-H), 7.49 (d, 1H, Ar-H, J = 11.5 Hz), 7.25 (dd, 1H, =CH, J = 10.1, 1.9 Hz), 6.33 (dd, 1H, =CH, J = 10.1, 1.8 Hz), 4.78 (br s, 1H, OH), 4.72 (d, 1H, H-9, J = 11.5 Hz), 4.63 (dt, 1H, H-10, J = 11.5, 2.3 Hz), 4.50 (br s, 1H, OH).

(500 MHz, dmso-d_6): δ 8.61-8.57 (m, 1H, Ar-H), 8.17-8.13 (m, 1H, Ar-H), 7.87 (AB quartet, 2H, Ar-H, J = 8.5 Hz), 7.78–7.74 (m, 2H, Ar-H), 7.61 (d, 1H, Ar-H, J = 12.0 Hz), 7.17 (dd, 1H, =CH, J = 10.1, 2.3 Hz), 6.26 (dd, 1H, =CH, J = 10.1, 1.8 Hz), 5.71 (br s, 1H, OH), 5.39 (br s, 1H, OH), 4.55 (d, 1H, H-9, J = 11.1 Hz), 4.47 (dt, 1H, H-10, J = 11.1, 2.3 Hz).

^{13}C NMR (125 MHz, dmso-d_6): δ 155.5 (d, J_{CF} = 249.5 Hz), 137.6, 133.0, 131.2 (d, J_{CF} = 10.1 Hz), 130.9 (d, J_{CF} = 4.6 Hz), 128.8, 128.1 (d, J_{CF} = 2.8 Hz), 127.1(d, J_{CF} = 5.5 Hz), 126.8, 126.7, 125.8, 124.9, 124.4 (d, J_{CF} = 18.3 Hz), 123.9, 120.2 (d, J_{CF} = 6.4 Hz), 107.9 (d, J_{CF} = 19.7 Hz), 74.1, 70.6. ^{19}F NMR (282 MHz, acetone-d_6): δ −126.92 (d, $^2J_{FH}$ = 12.2 Hz). HRMS (ESI) calcd. for $C_{18}H_{12}FO_2$ [M-H]$^-$, 279.0827, found 279.0834.

Synthesis of (±)2-Bromo-8-fluoro-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene-1,3,4-triol (58)



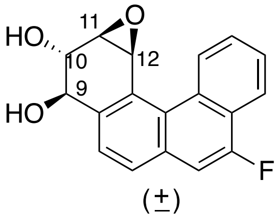
To a solution of dihydrodiol (±)-**57** (0.100 g, 0.357 mmol) in THF (10 mL) and H_2O (5 mL) was added *N*-bromoacetamide (0.49 mg, 0.357 mmol). The mixture was protected from light and allowed to stir at room temperature for 24 h. The mixture was diluted with 50 mL EtOAc and the organic layer was washed y with water and brine. The organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. The resulting brownish white solid was washed with cold Et_2O (5 mL X 2) to obtain the pure bromo triol (±)-**58** as a white solid (Yield: 0.106 g, 79%). R_f (silica, 5% MeOH in methylene chloride) = 0.07. ^{1}H NMR (500 MHz, acetone-d_6): δ 9.63-9.60 (m, 1H, Ar-H), 8.25-8.24 (m, 1H, Ar-H), 8.02 (d, 1H, Ar-H, J = 8.3 Hz), 7.98 (d, 1H, Ar-H, J = 8.3 Hz), 7.82–7.78 (m, 2H, Ar-H), 7.57 (d, 1H, Ar-H, J = 11.5 Hz), 5.83-5.80 (m, 2H), 4.92-4.84 (m, 3H), 4.67-4.65 (m, 2H). ^{13}C NMR (125 MHz, acetone-d_6): δ 157.5 (d, J_{CF} = 249.9

Hz), 139.5 133.7 (d, J_{CF} = 9.9 Hz), 132.8 (d, J_{CF} = 4.4 Hz), 131.1, 130.3 (d, J_{CF} = 5.0 Hz), 130.0 (d, J_{CF} = 2.8 Hz), 129.0, 128.4, 127.8 (d, J_{CF} = 1.8 Hz), 126.2 (d, J_{CF} = 16.8 Hz), 121.4 (d, J_{CF} = 7.8 Hz), 109.5 (d, J_{CF} = 20.1 Hz), 74.4, 72.5, 69.7, 60.7.

^{19}F NMR (282 MHz, acetone-d_6): δ −126.55 (d, $^2J_{FH}$ = 9.2 Hz). HRMS (ESI) calcd. for $C_{18}H_{14}BrFNaO_3$ [M+Na]$^+$, 399.0003, found 399.0001.

One quaternary carbon not observed, buried under other resonances.

Synthesis of (±)-7-fluoro-1a,2,3,11d-tetrahydrobenzo[5,6]phenanthro[3,4-*b*]oxirene-2,3-diol (59a)



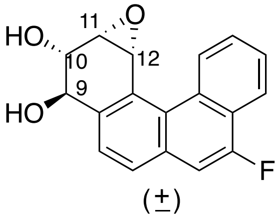
Bromotriol (±)-**58** (0.040 g, 0.106 mmol) was dissolved in anhydrous THF (4.2 mL) under N_2 and dry IRA-400 Amberite HO$^-$ (0.642 g) was added. The reaction mixture was stirred at room temperature for 4 h and the Amberlite was filtered off. Solvent removal gave a white solid that was washed with 2-3 mL cold ether to obtain the diol epoxide (±)-**59** as a white powder. Yield of (±)-**59**: 0.027 g (86%). R_f (silica, 5% MeOH in methylene chloride) = 0.33. ^{1}H NMR (500 MHz, acetone-d_6): δ 9.26-9.22 (m, 1H, Ar-H), 8.27-8.24 (m, 1H, Ar-H), 8.04 (d, 1H, Ar-H, J = 8.3 Hz), 8.00 (d, 1H, Ar-H, J = 8.3 Hz), 7.85–7.80 (m, 2H, Ar-H), 7.59 (d, 1H, Ar-H, J = 11.5 Hz), 4.95 (br s, 2H, 2OH), 4.85 (d, 1H, H-9, J = 9.2 Hz), 4.38 (d, 1H, H-12, J = 4.1), 3.97 (dd, 1H, H-11, J = 4.4, 2.1 Hz), 3.81 (dd, 1H, H-10, J = 9.2, 1.8 Hz).

(500 MHz, dmso-d_6): δ 9.17-9.14 (br d, 1H, Ar-H, J = 7.4 Hz), 8.25-8.22 (m, 1H, Ar-H),

8.07 (d, 1H, Ar-H, J = 8.3 Hz), 7.93 (d, 1H, Ar-H, J = 8.3 Hz), 7.87–7.82 (m, 2H, Ar-H), 7.73 (d, 1H, Ar-H, J = 11.5 Hz), 5.89 (d, 1H, OH, J = 6.5 Hz), 5.88 (d, 1H, OH, J = 5.1 Hz), 4.67 (dd, 1H, H-9, J = 9.2, 6.0 Hz), 4.35 (d, 1H, H-12, J = 4.2 Hz), 3.89 (dd, 1H, H-11, J = 4.4, 2.1 Hz), 3.59 (dd, 1H, H-10, J = 9.2, 3.9, 1.8 Hz).

^{13}C NMR (125 MHz, acetone-d_6): δ 157.5 (d, J_{CF} = 249.9 Hz), 141.2, 133.0 (d, J_{CF} = 10.1 Hz), 132.6 (d, J_{CF} = 4.9 Hz), 130.5 (d, J_{CF} = 5.5 Hz), 129.3, 128.7 (d, J_{CF} = 3.2 Hz), 128.6, 128.5, 128.2, 126.3, 126.1 (d, J_{CF} = 18.3 Hz), 121.7 (d, J_{CF} = 7.3 Hz), 109.2 (d, J_{CF} = 19.7 Hz), 73.6, 72.9, 63.6, 51.6. ^{19}F NMR (282 MHz, acetone-d_6): δ −126.61 (d, $^2J_{FH}$ = 9.2 Hz). HRMS (ESI) calcd. for $C_{18}H_{13}FNaO_3$ [M+Na]$^+$, 319.0741, found 319.0757.

Synthesis of (±)7-fluoro-1a,2,3,11d-tetrahydrobenzo[5,6]phenanthro[3,4-*b*]oxirene-2,3-diol (59b)



A solution of solution of dihydrodiol (±)-**57** (0.100 g, 0.36 mmol) in anhydrous THF (16.0 mL) was cooled to at 0 °C (ice bath) under nitrogen *m*CPBA (0.554 g, 3.21 mmol, 9.0 molar equiv) was added with stirring. The reaction mixture was allowed to warm to rt and stirred at rt for 2 h. Reaction mixture was diluted with EtOAc and washed with 1N solution of NaOH solution (15 mL X 3) and then with water and brine. Organic layer was separated dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. Crude reaction mixture was washed with cold ether (5 mL X 2) to obtain 71.2 mg (67%) of white powder. R_f (40% acetone in hexanes) = 0.31.

^{1}H NMR (500 MHz, acetone-d_6): δ 8.84-8.80 (m, 1H, Ar-H), 8.26-8.22 (m, 1H, Ar-H), 8.01 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.95 (d, 1H, Ar-H, *J* = 8.3 Hz), 7.82–7.78 (m, 2H, Ar-H), 7.54 (d, 1H, Ar-H, *J* = 11.5 Hz), 4.84 (d, 1H, H-12, *J* = 8.3 Hz), 4.79 (d, 1H, H-9, *J* = 4.6 Hz), 3.96 (dd, 1H, H-10, *J* = 8.7, 1.8 Hz), 3.80 (dd, 1H, H-11, *J* = 4.6, 1.8 Hz).

(500 MHz, dmso-d_6): δ 8.70 (app br d, 1H, Ar-H, *J* = 7.4 Hz), 8.20-8.18 (m, 1H, Ar-H), 7.97 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.91 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.83–7.79 (m, 2H, Ar-H), 7.66 (d, 1H, Ar-H, *J* = 11.5 Hz), 5.88 (br s, 1H, OH), 5.69 (br s, 1H, OH), 4.70 (d, 1H, H-12, *J* = 4.1 Hz), 4.60 (br d, 1H, H-9, *J* = 6.9 Hz), 3.80 (br d, 1H, H-10, *J* = 8.3 Hz), 3.71 (d, 1H, H-11, *J* = 3.2 Hz).

^{13}C NMR (125 MHz, dmso-d_6): δ 155.5 (d, J_{CF} = 250.4 Hz), 140.4, 130.8 (d, J_{CF} = 10.1 Hz), 130.0 (d, J_{CF} = 5.0 Hz), 127.8 (d, J_{CF} = 5.6 Hz), 127.6 (d, J_{CF} = 2.7 Hz), 127.2, 126.9, 126.6, 124.4 (d, J_{CF} = 18.8 Hz), 124.1, 120.5 (d, J_{CF} = 6.4 Hz), 107.8 (d, J_{CF} = 19.7 Hz), 70.8, 69.7, 57.1, 54.1. ^{19}F NMR (282 MHz, acetone-d_6): δ −126.61 (d, $^2J_{FH}$ = 12.2 Hz). HRMS (ESI) calcd. for $C_{18}H_{13}FNaO_3$ $[M+Na]^+$, 319.0741, found 319.0730.

REFERENCES

1. Lakshman, M. K.; Kole, P.; Chaturvedi, S.; Saugier, J. H.; Yeh, H. J. C.; Glusker, J. P.; Carrell, H. L.; Katz, A. K.; Afshar, C. E.; Dashwood, W.-M.; Kenniston, G.; Baird, W. M.: Methyl Group-Induced Helicity in 1,4-Dimethylbenzo[*c*]-phenanthrene and Its Metabolites: Synthesis, Physical, and Biological Properties, *J. Am. Chem. Soc.* **2000**, *122*, 12629-12636.

2. Bae, S.; Mah, H.; Chaturvedi, S.; Jeknic, T. M.; Baird, W. M.; Katz, A. M.; Carrell, H. L.; Glusker, J. P.; Okazaki, T.; Laali, K. K.; Zajc, B.; Lakshman, M. K.: Synthetic, Crystallographic, Computational, and Biological Studies of 1,4-Difluorobenzo[*c*]phenanthrene and Its Metabolites, *J. Org. Chem.* **2007**, *72*, 7625-7633.

3. Jerina, D. M.; Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Ittah, Y.; Thakker, D. R; Wood, A. W.; Chang, R. L.; Levin, W.; Conney, A. H.: Highly Tumorigenic Bay-Region Diol Epoxides from the Weak Carcinogen Benzo[*c*]phenanthrene, *Biological Reactive Intermediates II Part A*; Snyder, R., Parke, D., Kocsis, J. J., Jollow, D. J., Gibson, G., Witmer, C. M.; Eds.; Plenum Press: New York, 1986; pp 501-523.

4. Szeliga, J.; Dipple, A.: DNA Adduct Formation by Polycyclic Aromatic Hydrocarbon Dihydrodiol Epoxides, *Chem. Res. Toxicol.* **1998**, *11*, 1-11.

5. Levin, W.; Wood, A. W.; Chang, R. L.; Ittah, Y.; Croisy-Delcey, M.; Yagi, H.; Jerina, D. M; Conney, A. H.: Exceptionally High Tumor-initiating Activity of Benzo[*c*]phenanthrene Bay-Region Diol-Epoxides on Mouse Skin, *Cancer Res.* **1980**, *40*, 3910-3914.

6. Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Jerina, D. M.: Novel Bay Region Diol Epoxides from Benzo[*c*]phenanthrene. *J. Am. Chem. Soc.* **1981**, *103*, 4970-4972.

7. Ittah, Y.; Jerina, D. M.: Synthesis of Monofluorobenzo[*c*]phenanthrenes, *Flouorine Chem.* **1980**, *16*, 137-144.

8. Mallory, F. B.; Mallory, C. W.; Ricker, W. M.: Nuclear Spin-Spin Coupling via Nonbonded Interactions. 4. F-F and H-F Coupling in Substituted Benzo[*c*]-phenanthrenes, *J. Org. Chem.* **1985**, *50*, 457-461.

9. Marx, G. S.; Bergmann, E. D.: Synthesis of 5-and 6-Fluorobenzo[*c*]phenanthrene by Photocyclization, *J. Org. Chem.* **1972**, *37,* 1807-1810.

10. Mirsadeghi, S.; Prasad, G. K. B; Whittaker, N.; Thakker, D. R.: Synthesis of the K-Region Monofluoro- and Difluorobenzo[*c*]phenanthrenes, *J. Org. Chem.* **1989**, *54,* 3091-3096.

11. Prasad, G. K. B; Mirsadeghi, S.; Boehlert, C.; Byrd, A; Thakker, D. R.: Oxidative Metabolism of the Carcinogen 6-Fluorobenzo[*c*]phenanthrene *J. Biol. Chem*. **1988**, *263*, 3676-3683.

12. Zajc, B.; Kumar, R.: Synthesis of Fluoroolefins via Julia–Kocienski Olefination, *Synthesis* **2010**, 1822-1836.

13. Ghosh, A. K.; Zajc, B.: High-Yield Synthesis of Fluorinated Benzothiazolyl Sulfones: General Synthons for Fluoro-Julia Olefinations, *Org. Lett.* **2006**, *8*, 1553–1556.

14. Differding, E.; Rüegg, G. M.: Nucleophilic Substitution Versus Electron Transfer: 1. On the Mechanism of Electrophilic Fluorinations, *Tetrahedron Lett.* **1991**, *32*, 3815-3818.

15. Differding, E.; Wehrli, M.: Nucleophilic Substitution Versus Electron Transfer: 2. S_N2 at Flouride and Electron Transfer are Competing and Different Pathways in Electrophilic Flourinations, *Tetrahedron Lett.* **1991**, *32*, 3819-3822.

16. Allendörfer, N.; Es-Sayed, M.; Nieger, M.; Bräse, S.: Novel Aromatic Fluoroolefins via Fluoro-Julia-Kocienski Olefination, *Synthesis* **2010**, 3439–3448.

17. Mallory, F. B.; Wood, C. S.; Gordon, J. T.; Lindquist, L. C.; Savitz, M. L.: Photochemistry of Stilbenes, *J. Am. Chem. Soc.* **1962**, *84*, 4361-4362.

18. Wood, C. S.; Mallory, F. B.: Photochemistry of Stilbenes. IV. The Preparation of Substituted Phenanthrenes, *J. Org. Chem*. **1964**, *29*, 3373-3377.

19. Nagel, D. L.; Kupper, R.; Antonson, K.; Wallcave, L.: Synthesis of Alkyl-Substituted Benzo[*c*]phenanthrenes and Chrysenes by Photocyclization, *J. Org. Chem.* **1977**, *42*, 3626-3628.

20. Amin, S.; Camanzo, J.; Huie, K.; Hecht, S. S.: Improved Photochemical Synthesis of 5-Methylchrysene Derivatives and Its Application to the Preparation of 7,8-Dihydro-7,8-dihydroxy-5-methylchryse, *J. Org. Chem.* **1984**, *49*, 381-384.

21. Utermoehlen, C. M.; Singh, M.; Lehr, R. E.: Fjord Region 3,4-Diol 1,2-Epoxides and Other Derivatives in the 1,2,3,4- and 5,6,7,8-Benzo Rings of the Carcinogen Benzo[*g*]chrysene, *J. Org. Chem*. **1987**, *52*, 5574-5582.

22. Liu, L.; Yang, B.; Katz, T. J.; Poindexter, M. K.: Improved Methodology for Photocyclization Reactions, *J. Org. Chem.* **1991**, *56*, 3569-3575.

23. Yagi, H.; Thakker, D. R.; Hemandez, O.; Koreeda, M.; Jerina, D. M.: Synthesis and Reactions of the Highly Mutagenic 7,8-Diol 9,10-Epoxides of the

Carcinogen Benzo[*a*]pyrene. *J. Am. Chem. Soc*. **1977**, *99*, 1604-1611.

24. Jerina, D. M.; Sayer, J. M.; Agarwal, S. K.; Yagi, H.; Levin, W.; Wood, A. W.; Conney, A. H.; Pruess-Schwartz, D.; Baird, W. M.; Pigott, M. A.; Dipple, A.: Reactivity and Tumorigenic Activity of Bay-Region Diol Epoxides Derived from Polycyclic Aromatic Hydrocarbons, *Biological Reactive Intermediates III*; Kocsis, J. J.; Jollow, D. J., Witmer, C. M., Nelson, J. O., Snyder, R., Eds.; Plenum Press: New York, 1986; pp 11-30.

25. Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Jerina, D. M.: Novel Bay Region Diol Epoxides from Benzo[*c*]phenanthrene. *J. Am. Chem. Soc.* **1981**, *103*, 4970-4972.

26. Yagi, H.; Hemandez, O.; Jerina, D. M.: Synthesis of (±)-7α,8β-Dihydroxy-9β,10β-Epoxy-7,8,9,10-Tetrahydrobenzo[*a*]pyrene a Potential Metabolite of the Carcinogen Benzo[*a*]pyrene with Stereochemistry Related to the Antileukemic Tripolides *J. Am. Chem. Soc*. **1975**, *97*, 6881-6883.

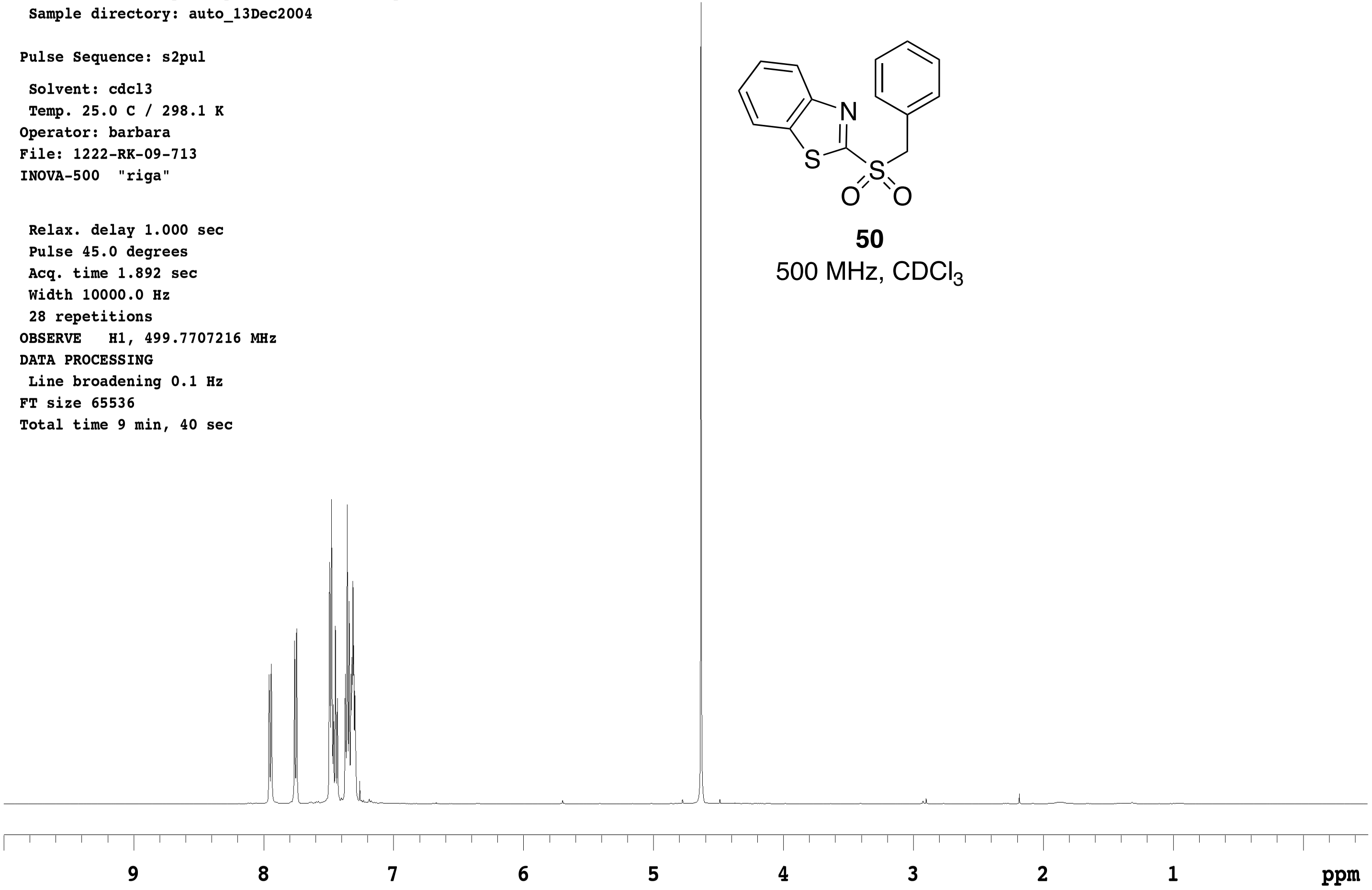
1222-RK-09-713

Archive directory: /export/home/mkl/vnmrsys/data
Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-09-713
INOVA-500 "riga"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 10000.0 Hz
28 repetitions
OBSERVE H1, 499.7707216 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec



50

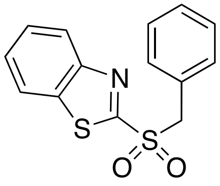
500 MHz, $CDCl_3$

1222-RK-09-714-13C-CDCL3

Pulse Sequence: s2pul

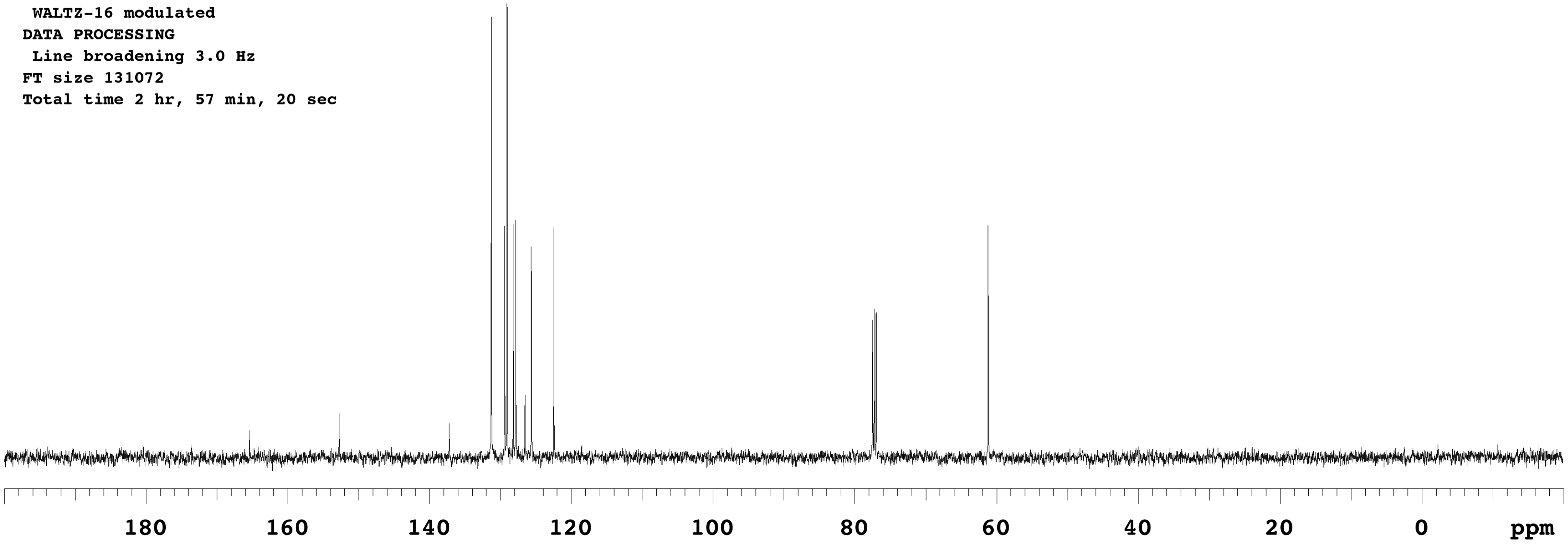
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-09-714-13C-CDCL3
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
56 repetitions
OBSERVE C13, 125.6674287 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec



50

125 MHz, $CDCl_3$



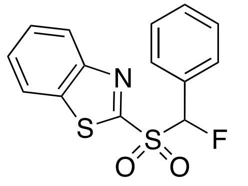
```
1222-RK-09-717-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

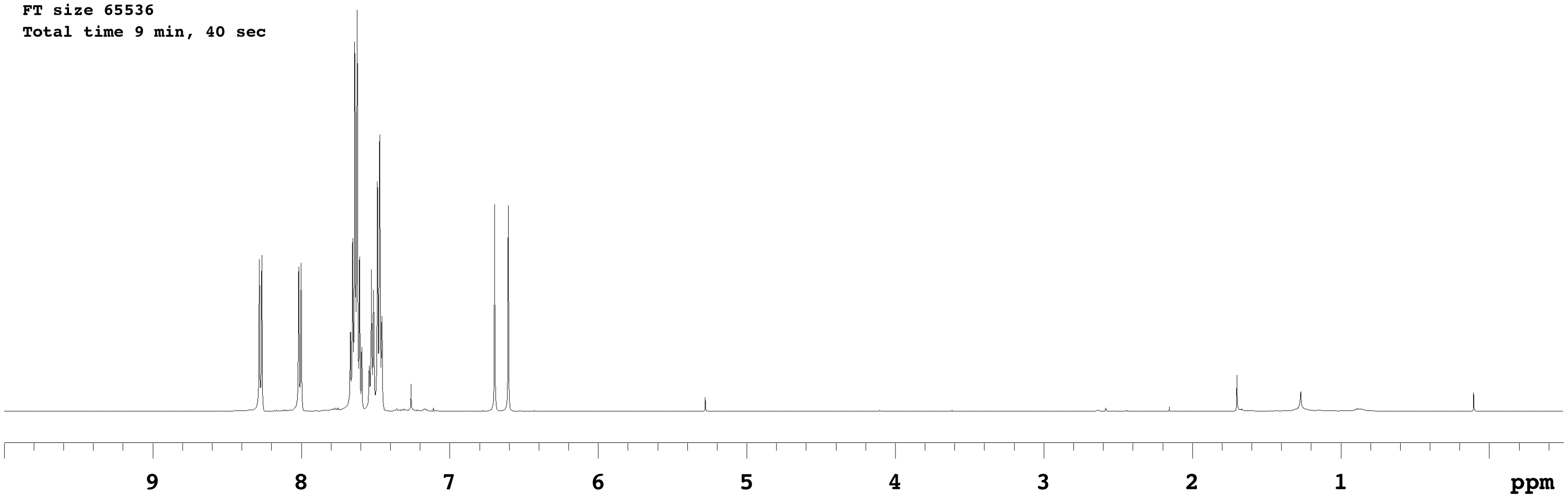
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-09-717-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 36 repetitions
OBSERVE   H1, 499.7707215 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
```



51

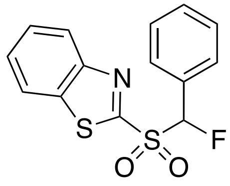
500 MHz, $CDCl_3$



```
1222-RK-09-717-13C

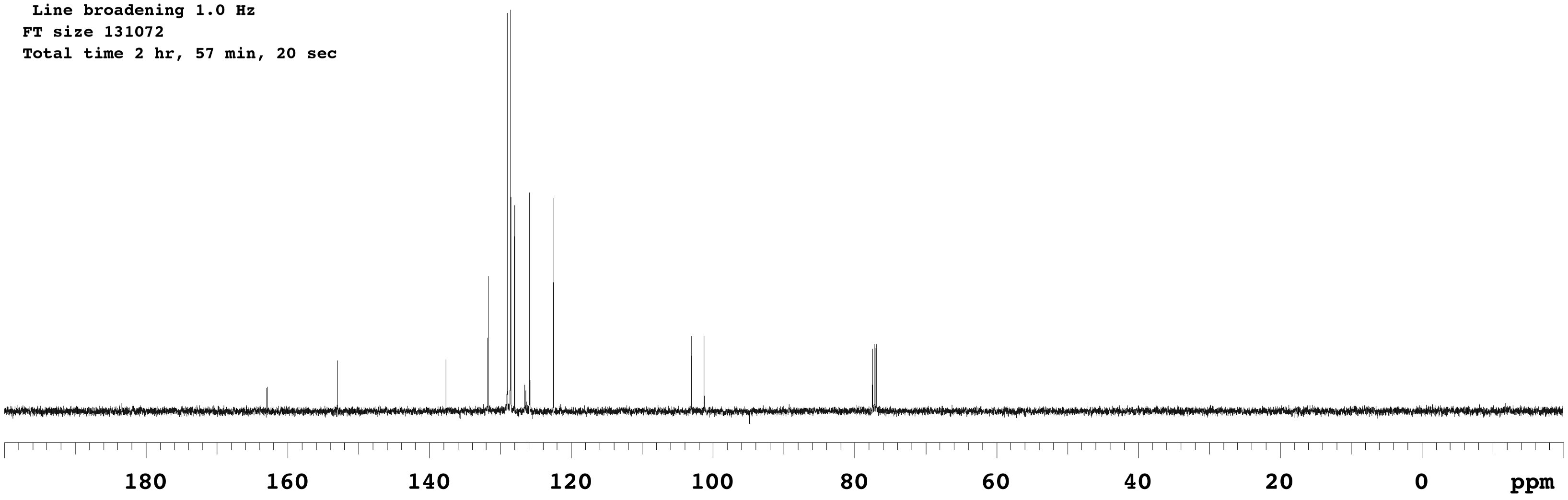
Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-09-717-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 32 repetitions
OBSERVE  C13, 125.6674319 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec
```



51

125 MHz, $CDCl_3$



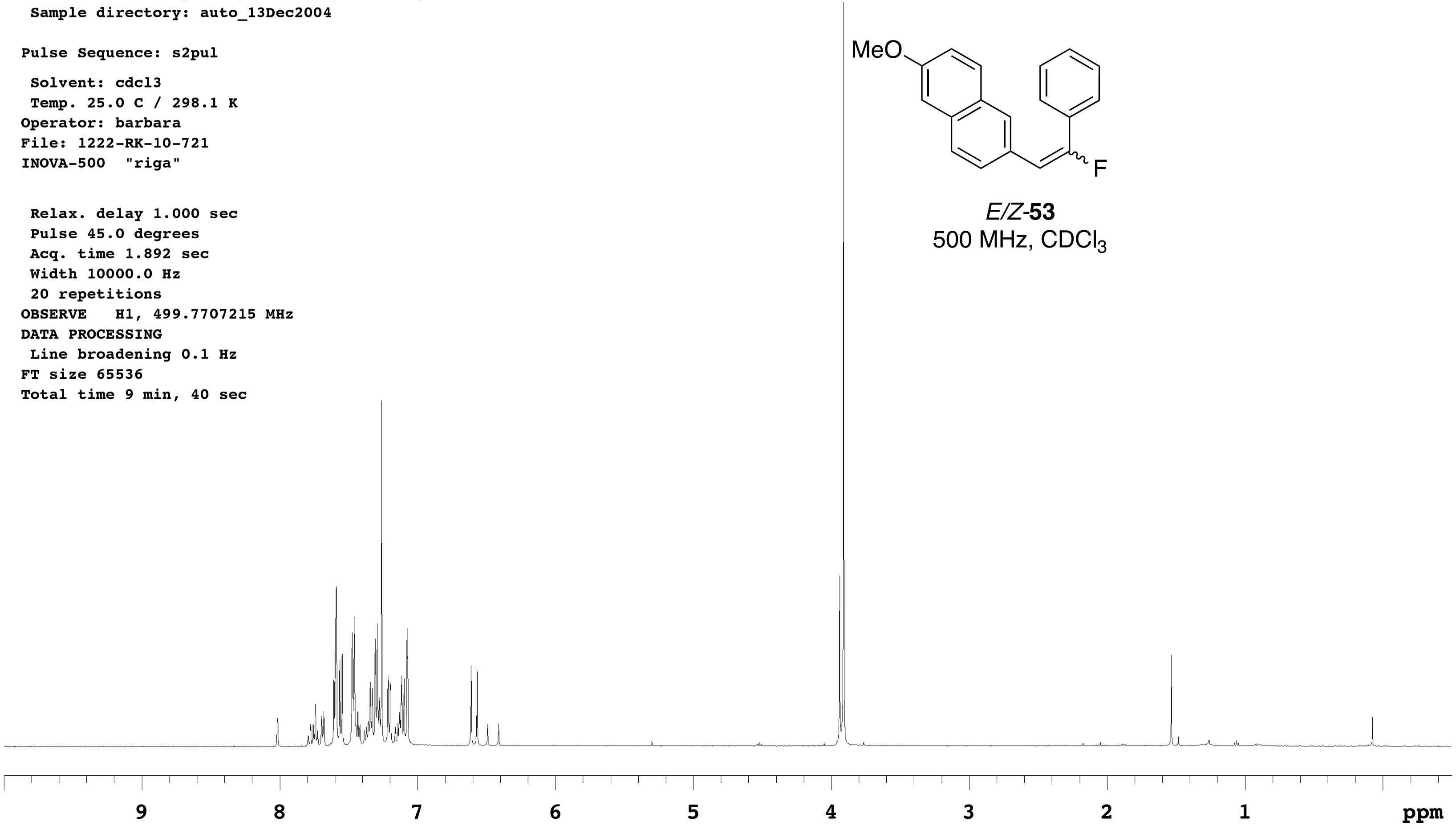
```
1222-RK-10-721

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-10-721
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 20 repetitions
OBSERVE   H1, 499.7707215 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
```



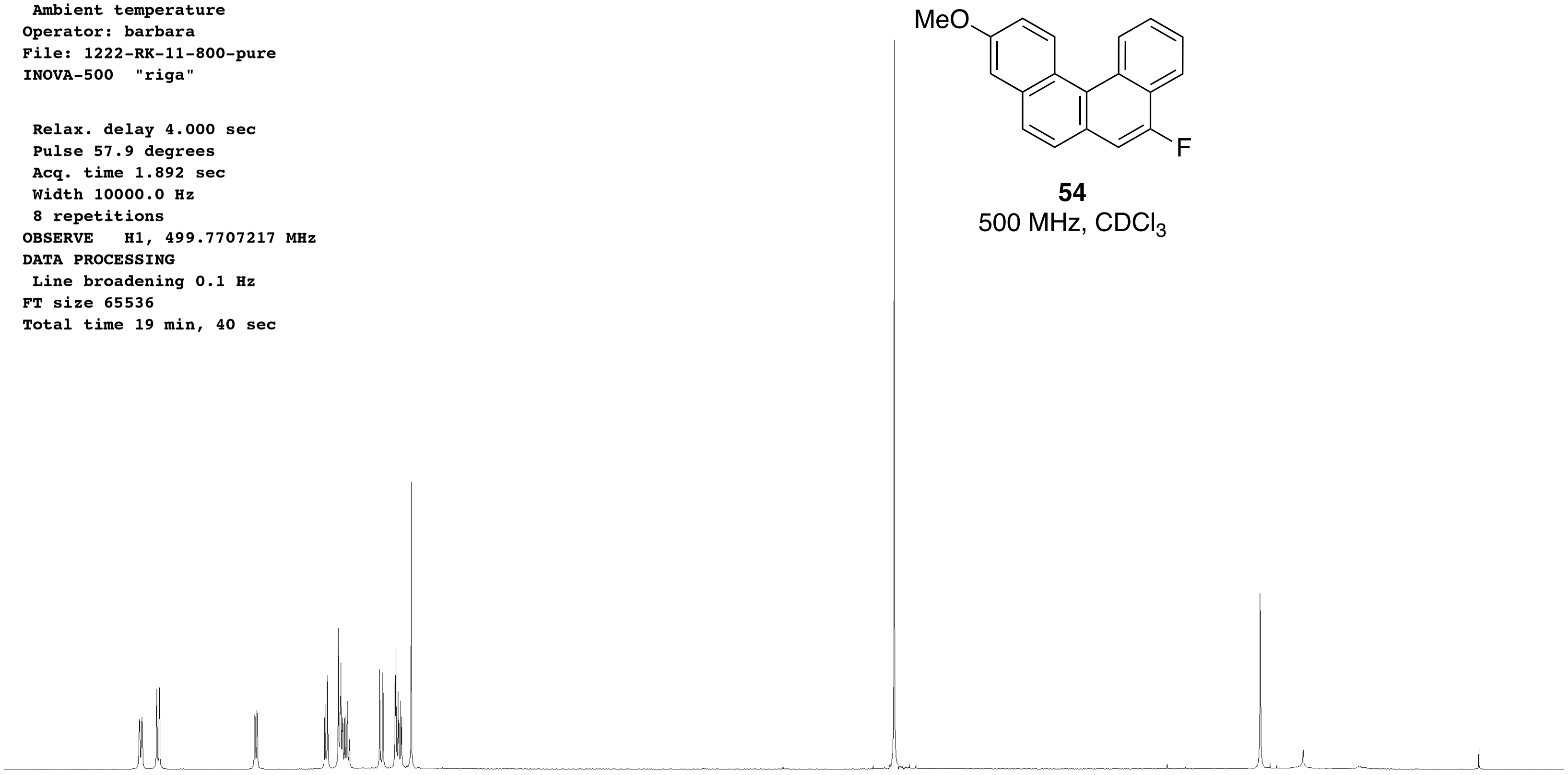
E/Z-**53**
500 MHz, $CDCl_3$

1222-RK-11-800-pure

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
Operator: barbara
File: 1222-RK-11-800-pure
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 57.9 degrees
Acq. time 1.892 sec
Width 10000.0 Hz
8 repetitions
OBSERVE   H1, 499.7707217 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 19 min, 40 sec



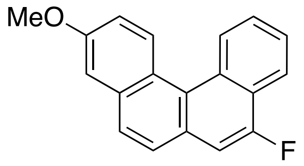
54
500 MHz, $CDCl_3$

1222-RK-10-739-13C

Pulse Sequence: s2pul

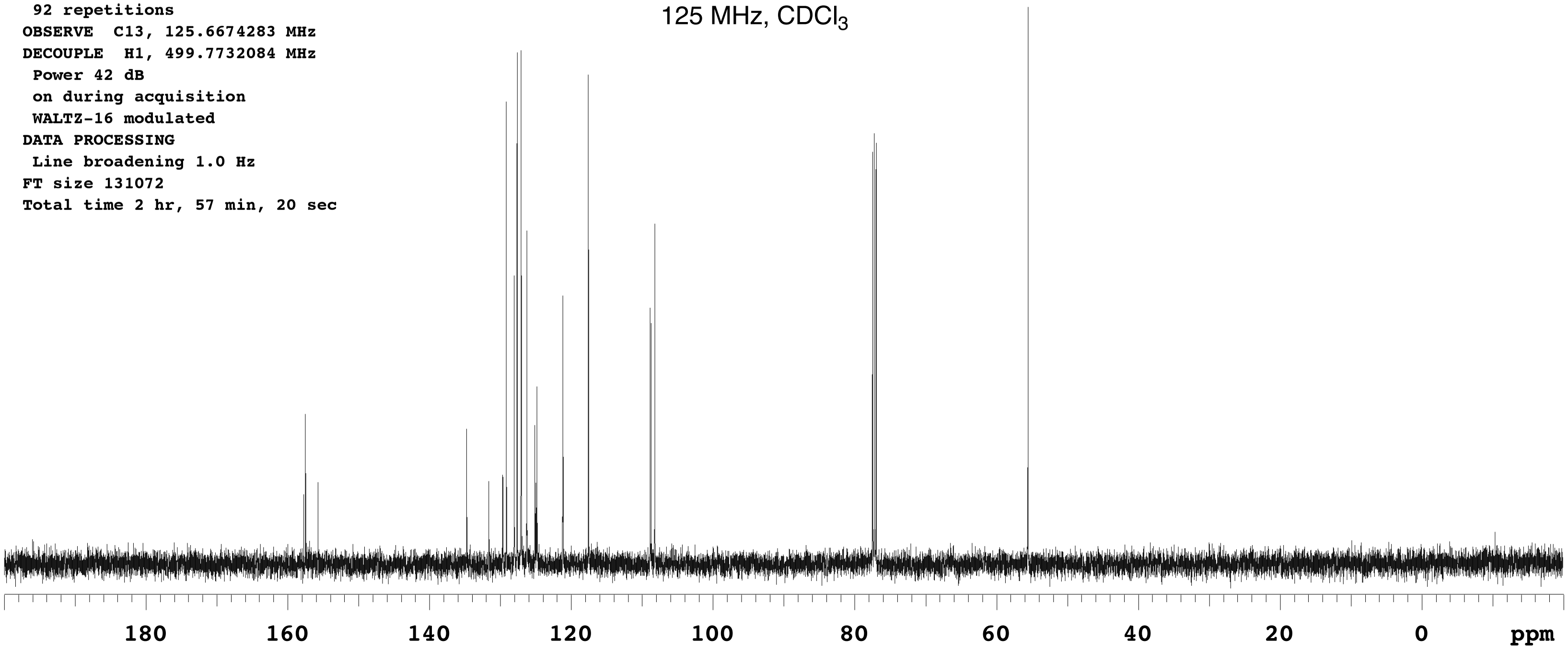
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-10-739-13C
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
92 repetitions
OBSERVE C13, 125.6674283 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec



54

125 MHz, $CDCl_3$



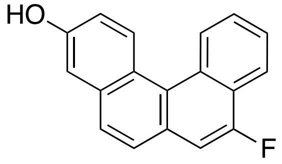
1222-RK-11-876-pure

Archive directory: /export/home/mkl/vnmrsys/data
Sample directory: auto_13Dec2004
File: 1222-RK-11-876-pure

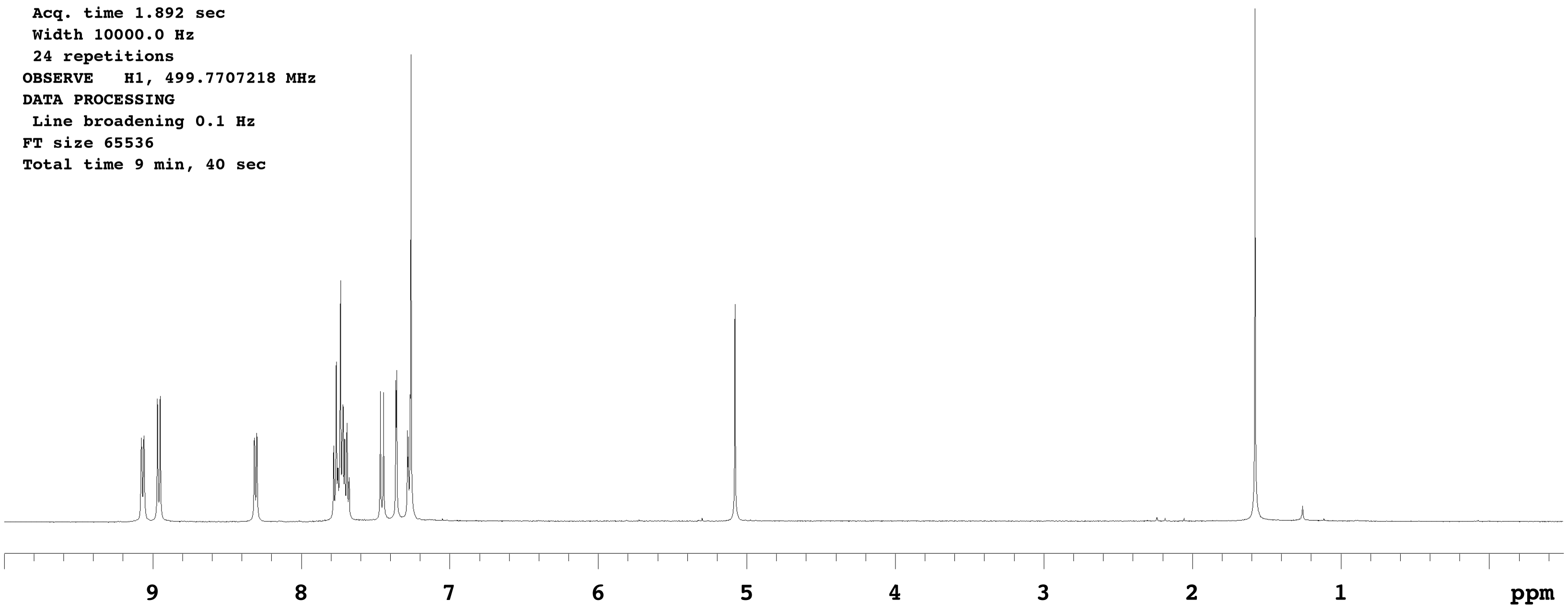
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-11-876-pure
INOVA-500 "capella500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 10000.0 Hz
24 repetitions
OBSERVE H1, 499.7707218 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec



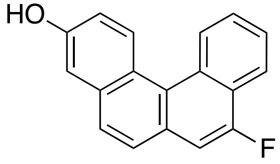
55
500 MHz, $CDCl_3$



```
1222-RK-11-808-13C.ps

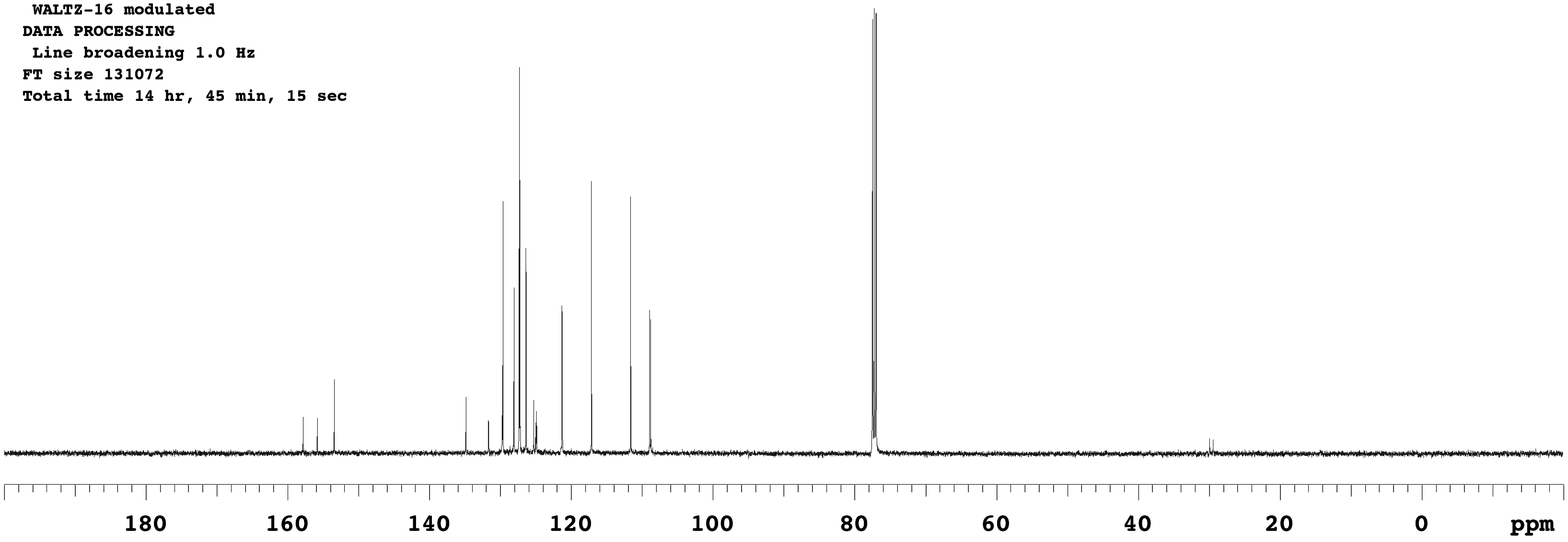
Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-11-808-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 8592 repetitions
OBSERVE  C13, 125.6674205 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 14 hr, 45 min, 15 sec
```



55

125 MHz, $CDCl_3$



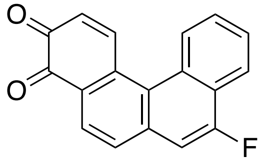
```
1222-RK-12-884-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004
 File: 1222-RK-12-884-pure

Pulse Sequence: s2pul

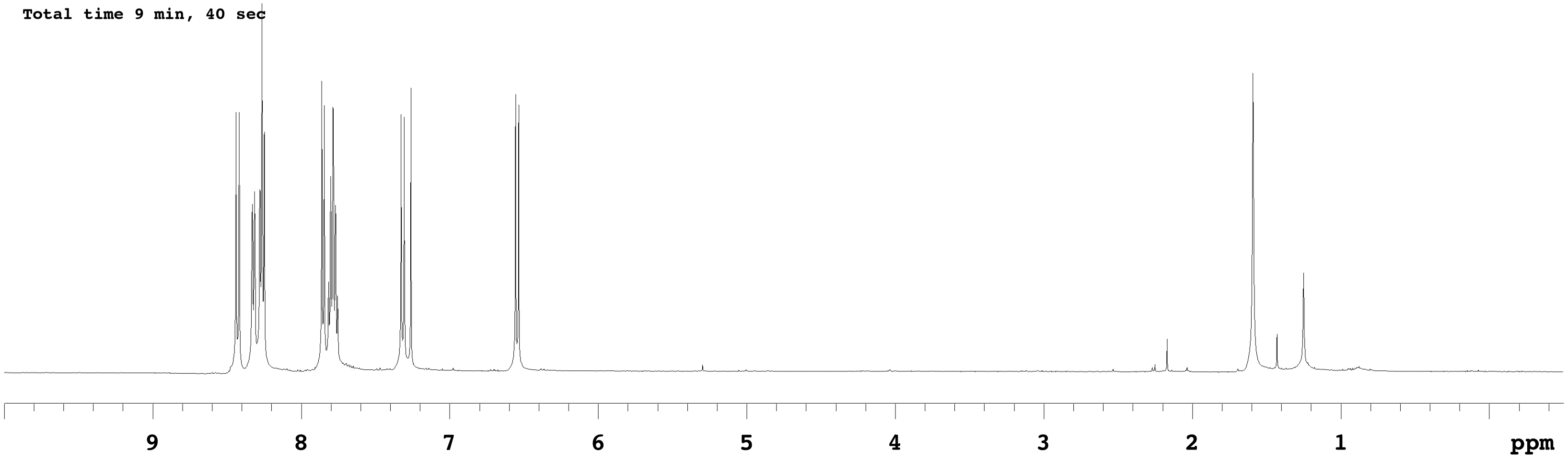
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-12-884-pure
INOVA-500  "capella500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 24 repetitions
OBSERVE   H1, 499.7707215 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
```



56

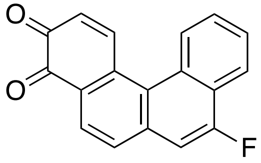
500 MHz, $CDCl_3$



```
1222-RK-11-814-13C

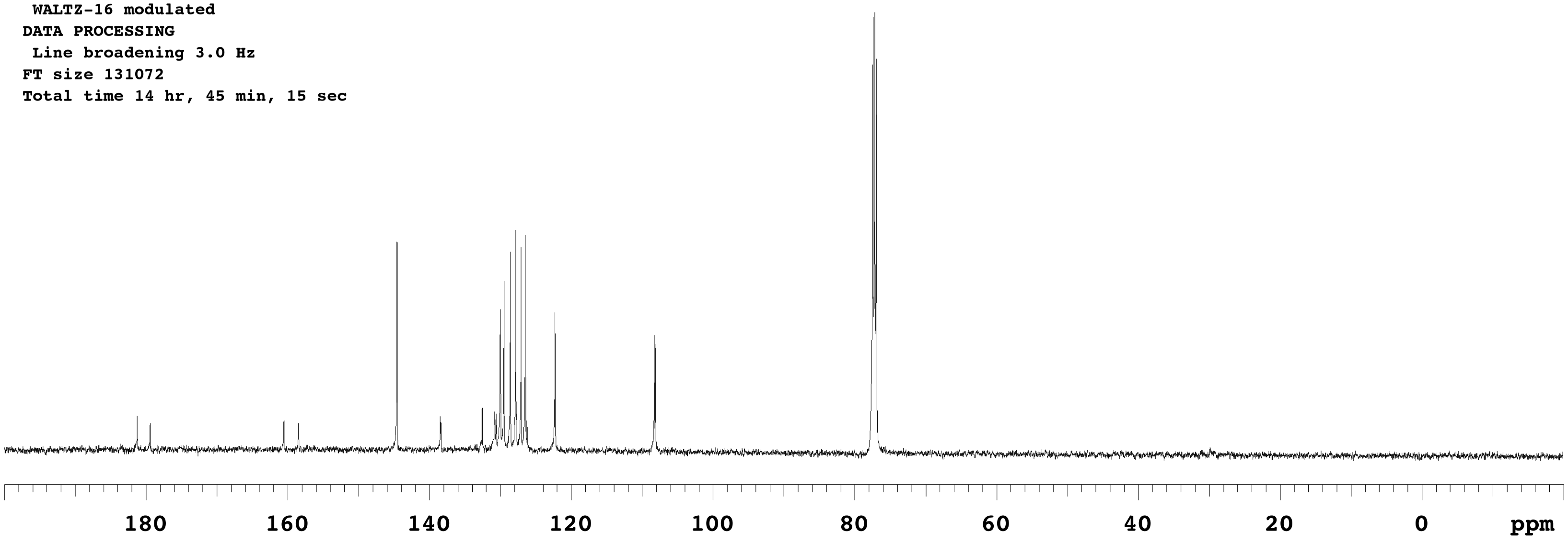
Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-11-814-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 8388 repetitions
OBSERVE  C13, 125.6674287 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 3.0 Hz
FT size 131072
Total time 14 hr, 45 min, 15 sec
```



56

125 MHz, $CDCl_3$



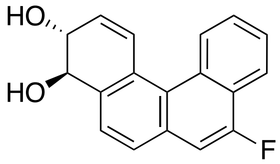
```
1222-RK-12-937-pure-acetone-d6

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004
 File: 1222-RK-12-937-pure-acetone-d6

Pulse Sequence: s2pul

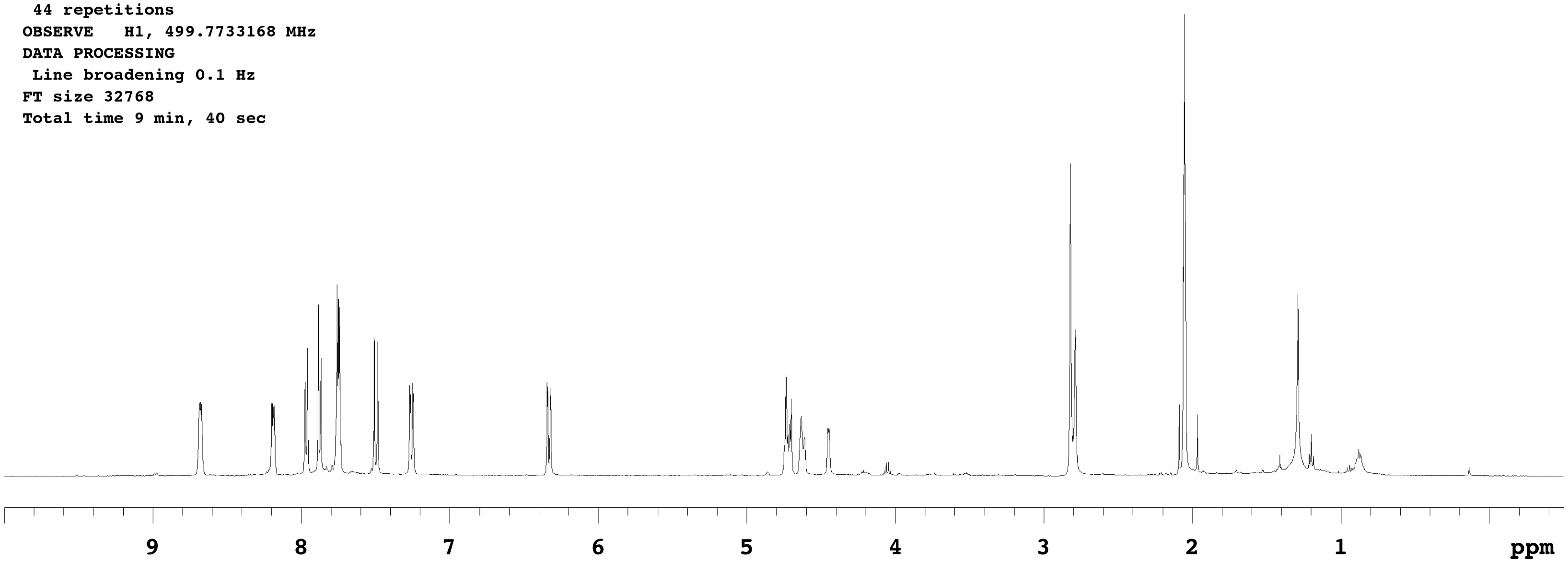
 Solvent: acetone
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-12-937-pure-acetone-d6
INOVA-500  "capella500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 44 repetitions
OBSERVE   H1, 499.7733168 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



(±)-**57**

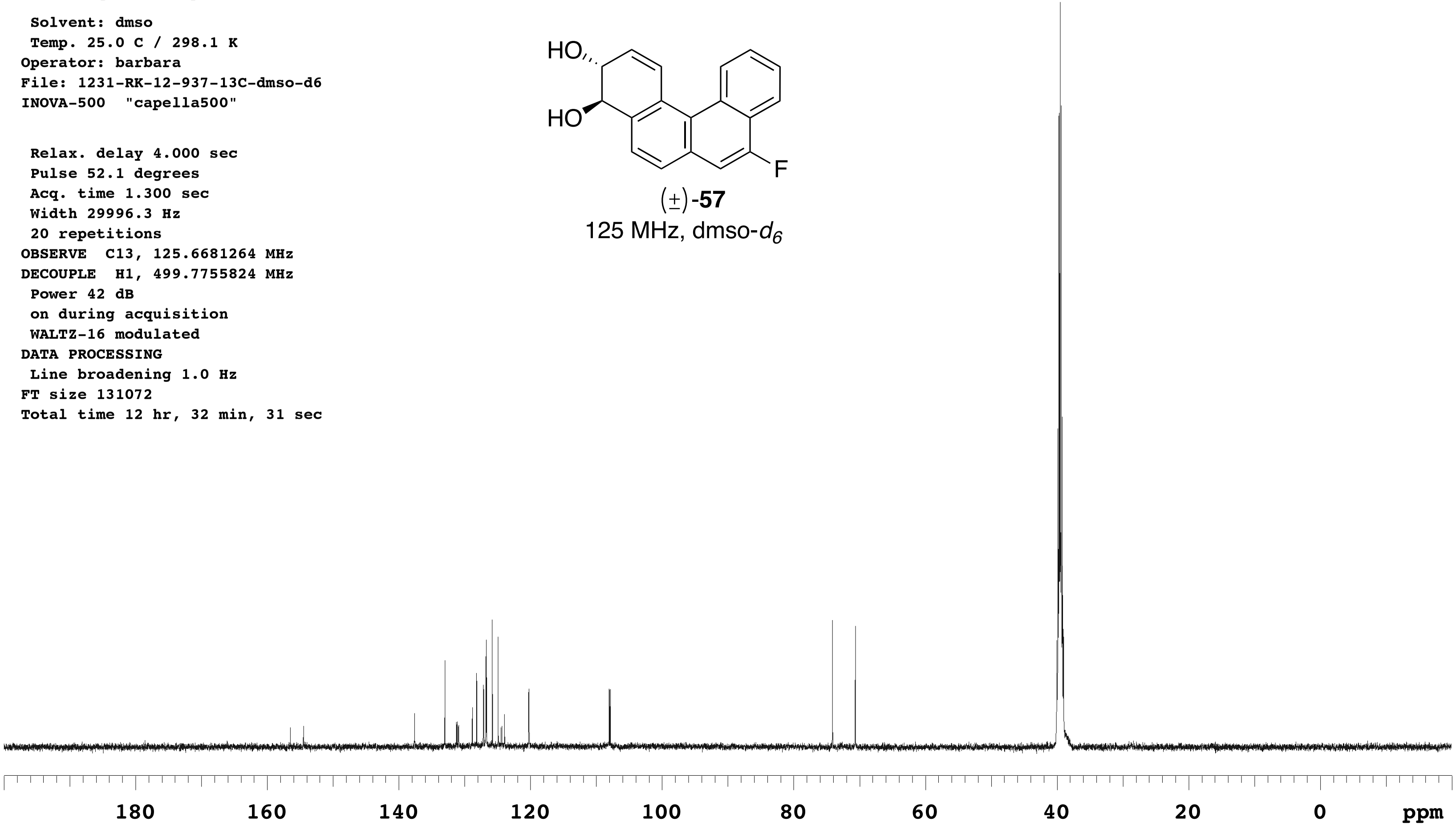
500 MHz, acetone-d_6



```
1231-RK-12-937-13C-dmso-d6

Pulse Sequence: s2pul
 Solvent: dmso
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-12-937-13C-dmso-d6
INOVA-500  "capella500"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 20 repetitions
OBSERVE  C13, 125.6681264 MHz
DECOUPLE  H1, 499.7755824 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 12 hr, 32 min, 31 sec
```



(±)-**57**
125 MHz, dmso-d_6

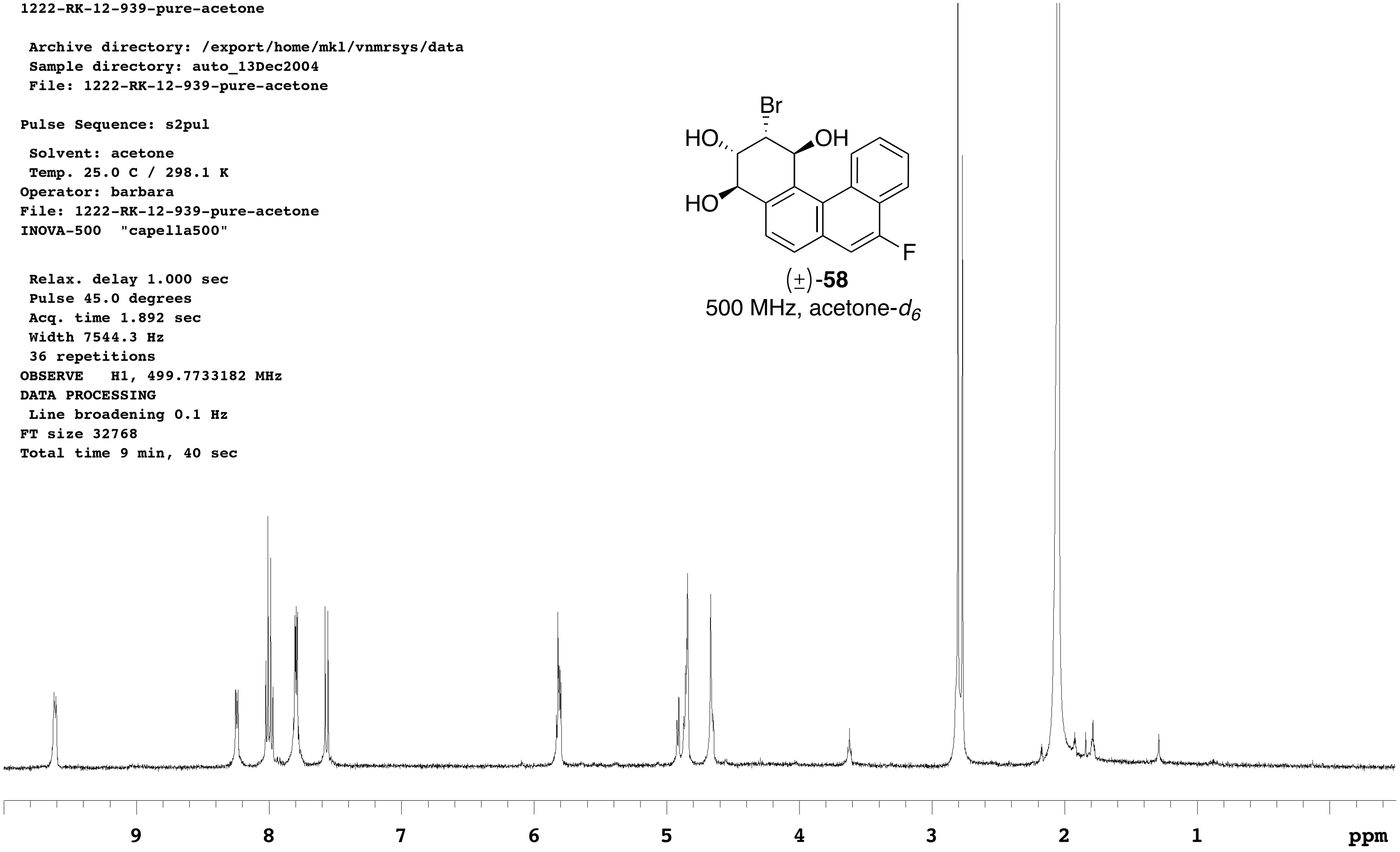
```
1222-RK-12-939-pure-acetone

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004
 File: 1222-RK-12-939-pure-acetone

Pulse Sequence: s2pul

 Solvent: acetone
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1222-RK-12-939-pure-acetone
INOVA-500  "capella500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 36 repetitions
OBSERVE   H1, 499.7733182 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```

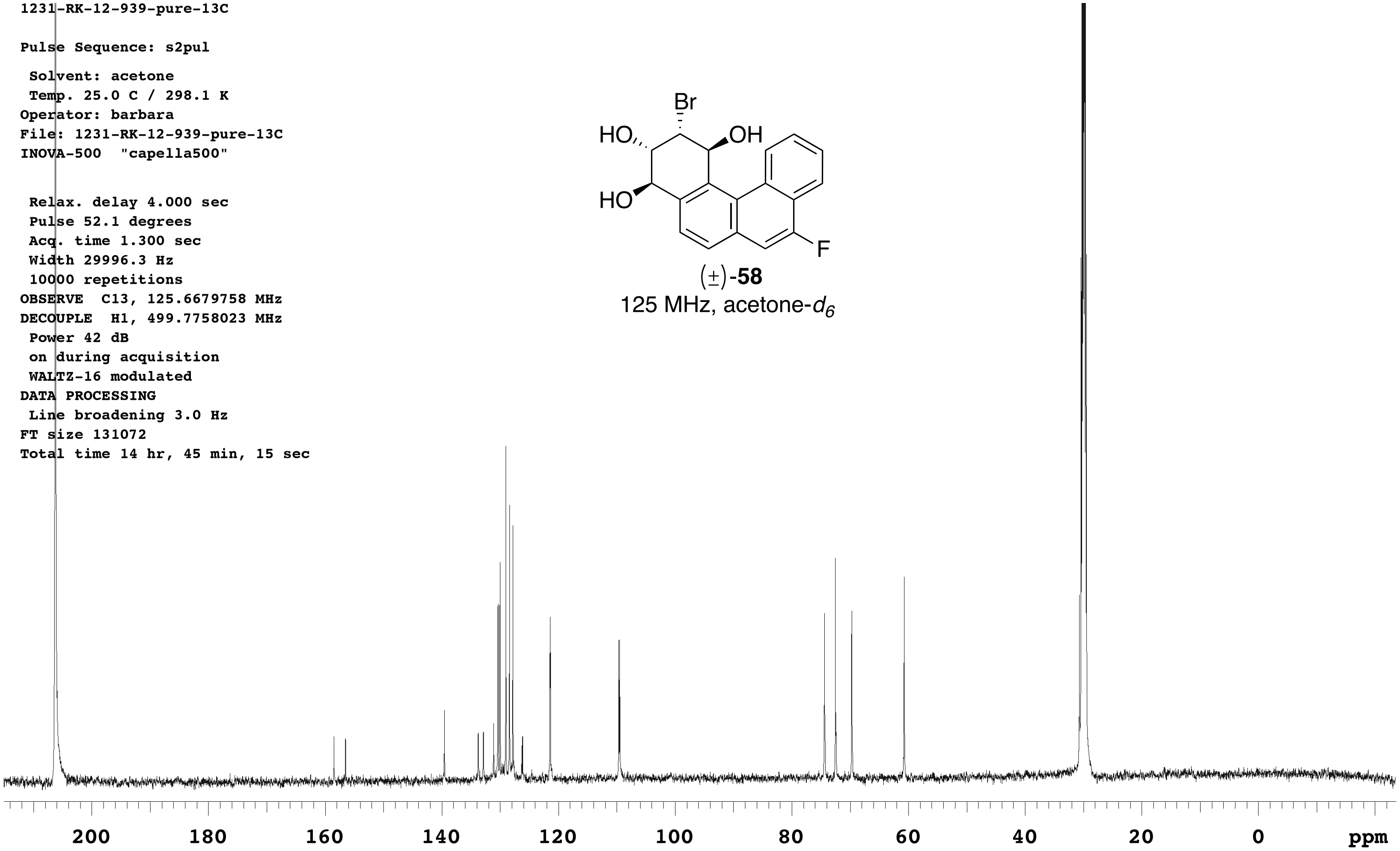


(±)-**58**
500 MHz, acetone-d_6

```
1231-RK-12-939-pure-13C

Pulse Sequence: s2pul
 Solvent: acetone
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-12-939-pure-13C
INOVA-500  "capella500"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 10000 repetitions
OBSERVE  C13, 125.6679758 MHz
DECOUPLE  H1, 499.7758023 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 3.0 Hz
FT size 131072
Total time 14 hr, 45 min, 15 sec
```



(±)-**58**

125 MHz, acetone-d_6

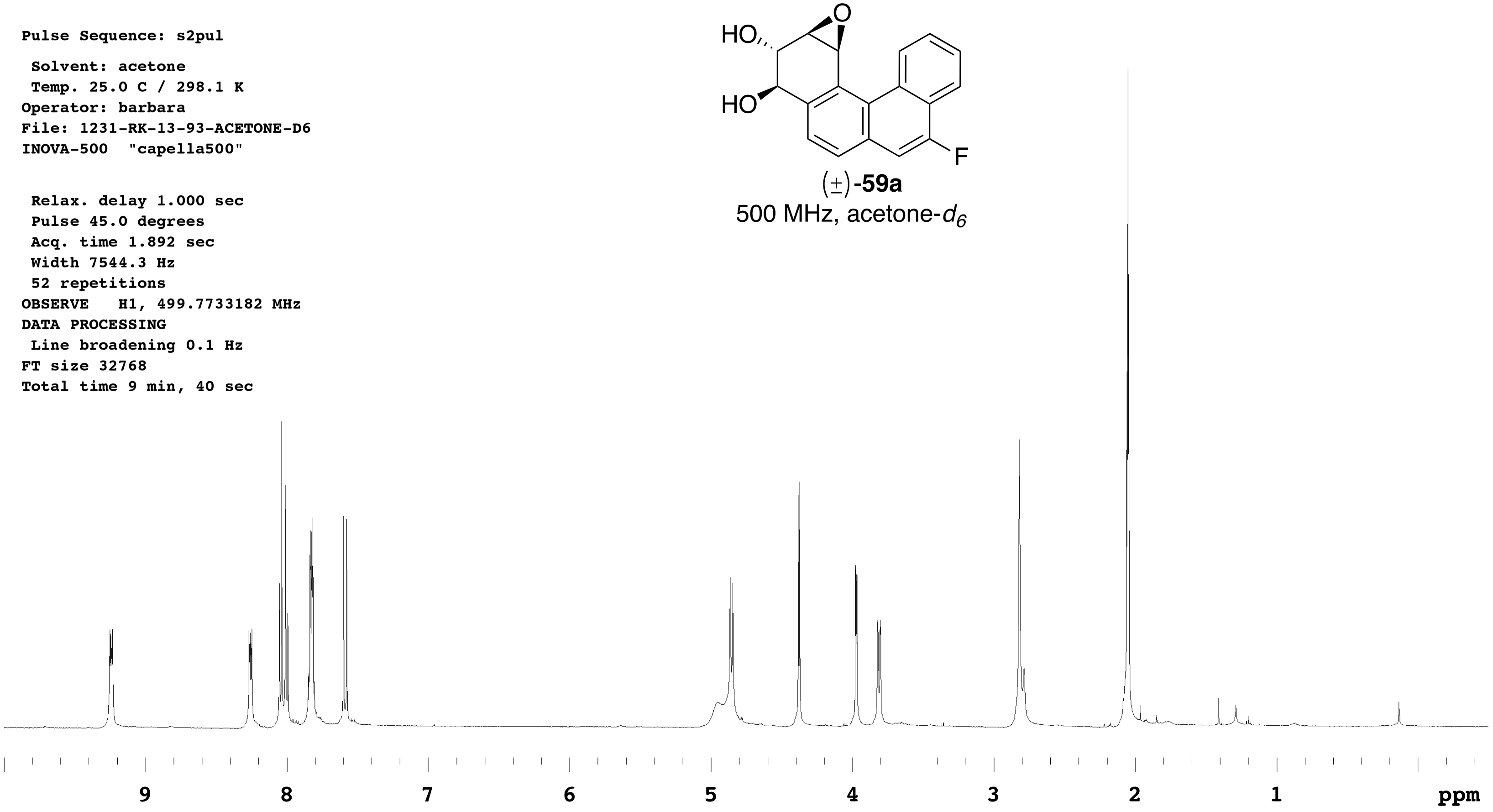
```
1231-RK-13-93-ACETONE-D6

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004
 File: 1231-RK-13-93-ACETONE-D6

Pulse Sequence: s2pul

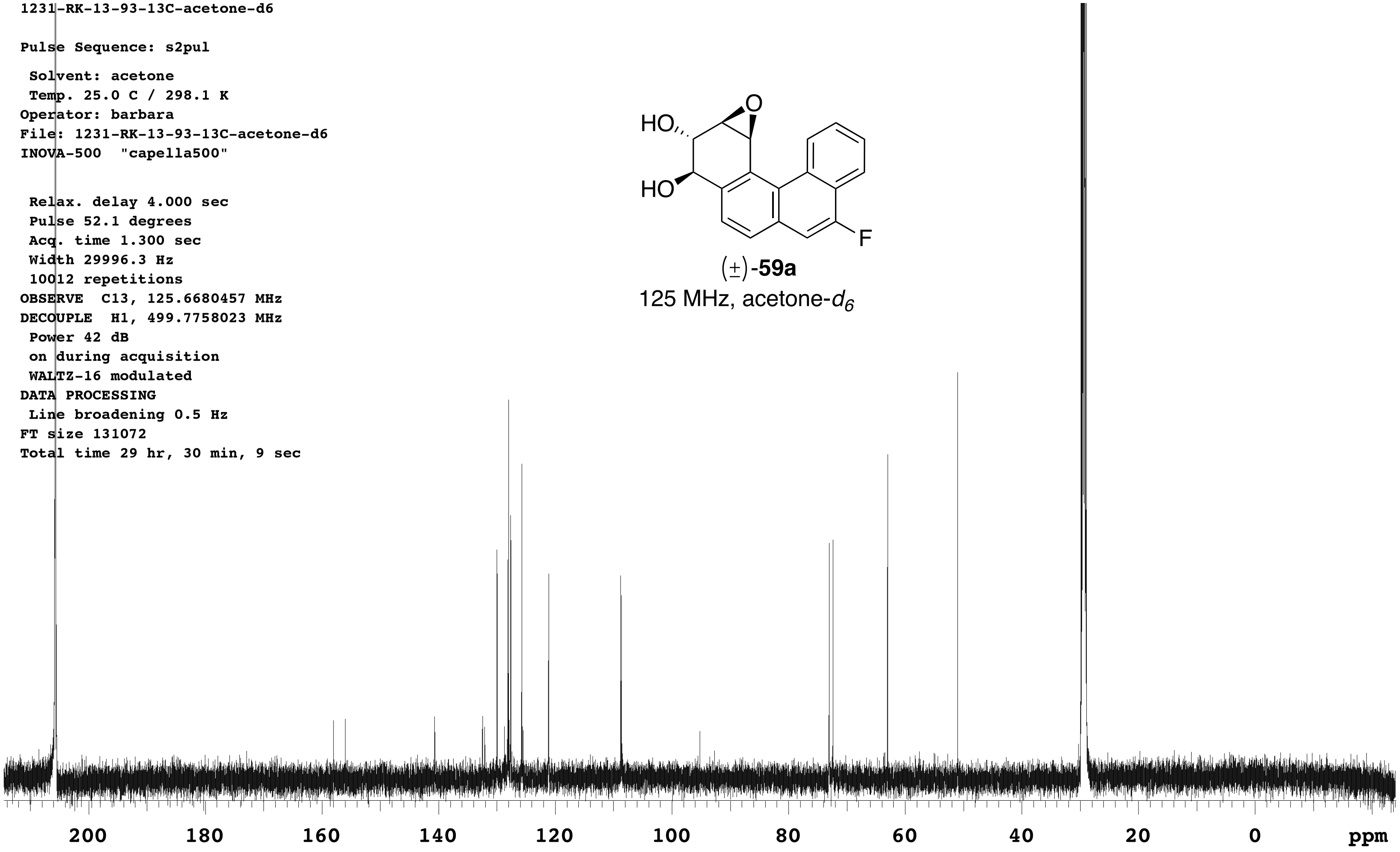
 Solvent: acetone
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-13-93-ACETONE-D6
INOVA-500  "capella500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 52 repetitions
OBSERVE   H1, 499.7733182 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



(±)-**59a**

500 MHz, acetone-d_6



1231-RK-13-93-13C-acetone-d6

Pulse Sequence: s2pul

Solvent: acetone
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-13-93-13C-acetone-d6
INOVA-500 "capella500"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
10012 repetitions
OBSERVE C13, 125.6680457 MHz
DECOUPLE H1, 499.7758023 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 29 hr, 30 min, 9 sec

(±)-**59a**
125 MHz, acetone-d_6

```
1231-RK-13-16-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004
 File: 1231-RK-13-16-pure

Pulse Sequence: s2pul

 Solvent: acetone
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-13-16-pure
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 Pulse 45.0 degrees
 Acq. time 1.892 sec
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 88 repetitions
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DATA PROCESSING
 Line broadening 0.1 Hz
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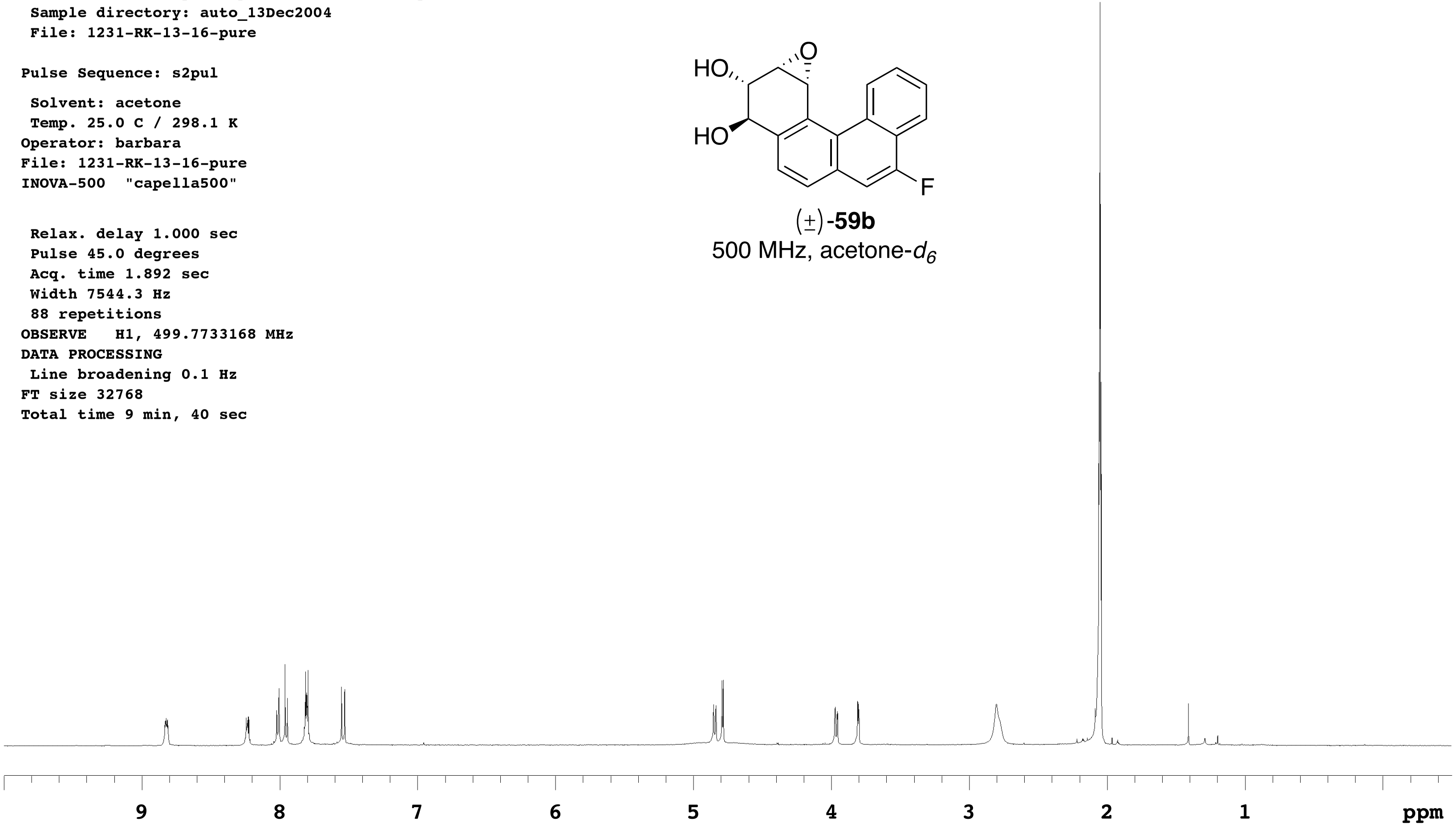

(±)-**59b**
500 MHz, acetone-d_6

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1231-RK-13-16-13C-dmso-d6

Pulse Sequence: s2pul
 Solvent: dmso
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-13-16-13C-dmso-d6
INOVA-500  "capella500"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 10000 repetitions
OBSERVE  C13, 125.6681251 MHz
DECOUPLE  H1, 499.7755824 MHz
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 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
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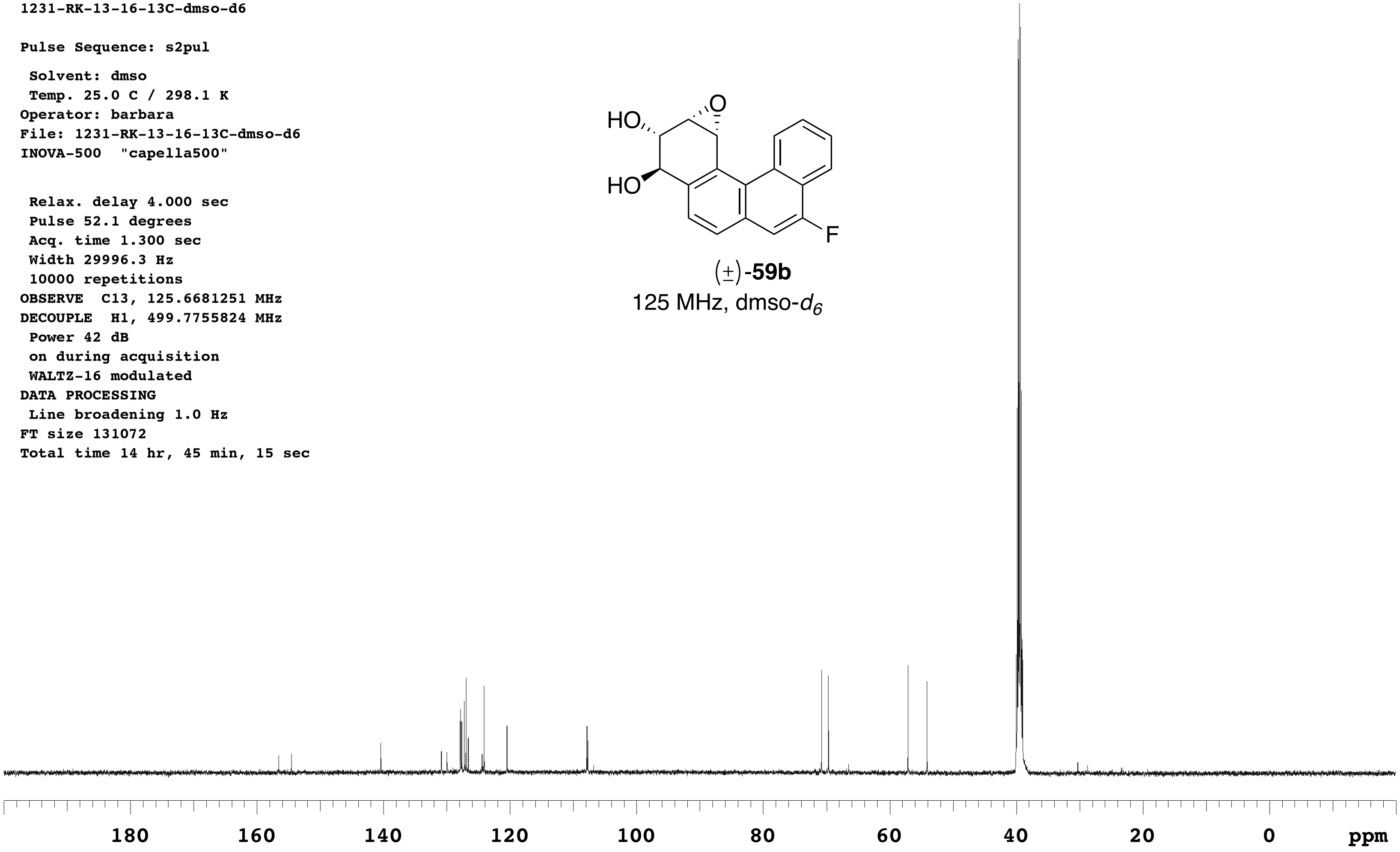


(±)-**59b**

125 MHz, dmso-d_6

PART 2

SYNTHESIS OF DEOXYADENOSINE ADDUCTS OF 5-FLUOROBENZO[*c*]PHENANTHRENE

2.1 INTRODUCTION

Polycyclic aromatic hydrocarbons are widespread environmental pollutants that are produced by incomplete combustion of organic materials.[1-2] Exposure to these compounds can result in harmful health effects via genetic mutations, potentially leading to tumors or cancer.[1-2] Among many PAHs known, those containing bay- or fjord- region are important because these, upon metabolism and DNA alkylation, can result in DNA damage leading to mutations and cancer.

Although metabolism of PAHs can occur through various pathways,[1-6] the diol-epoxide pathway is considered to play a major role in the carcinogenic activity of bay- and fjord-region containing PAHs.[1-3,6] Metabolism of a bay- or fjord- region containing PAH can result in four isomeric diol epoxides.[1-3,6] Each of these diol epoxides can form four adducts by *cis* or *tran*s ring opening of epoxide with the exocyclic amino groups of 2′-deoxyadenosine (dA) and 2′-deoxyguanosine (dG) acting as nucleophiles.[6-10] Therefore, any PAH upon metabolism and DNA alkylation, can produce a total of sixteen nucleoside adducts.[6-8] Figure 1 shows dA and dG adducts of benzo[*c*]phenanthrene (B*c*Ph) diol epoxides.[7-10] These PAH-DNA adducts can undergo either be repaired by the repair enzymes or undergo a error free bypass during replication. On the other hand, error prone replication can lead to change in the DNA sequence that can lead to introduction of mutations, tumors or cancer.[1,2,11]

As described in General Introduction, diol epoxides react with DNA via the initial intercalation followed by formation of covalent bond between the benzylic carbon of the epoxide and N^2 and N^6 amino groups of dG and dA, respectively.[7,12] Hydrolysis of epoxides is a competing process that leads to formation of tetraols.[7,12,13]

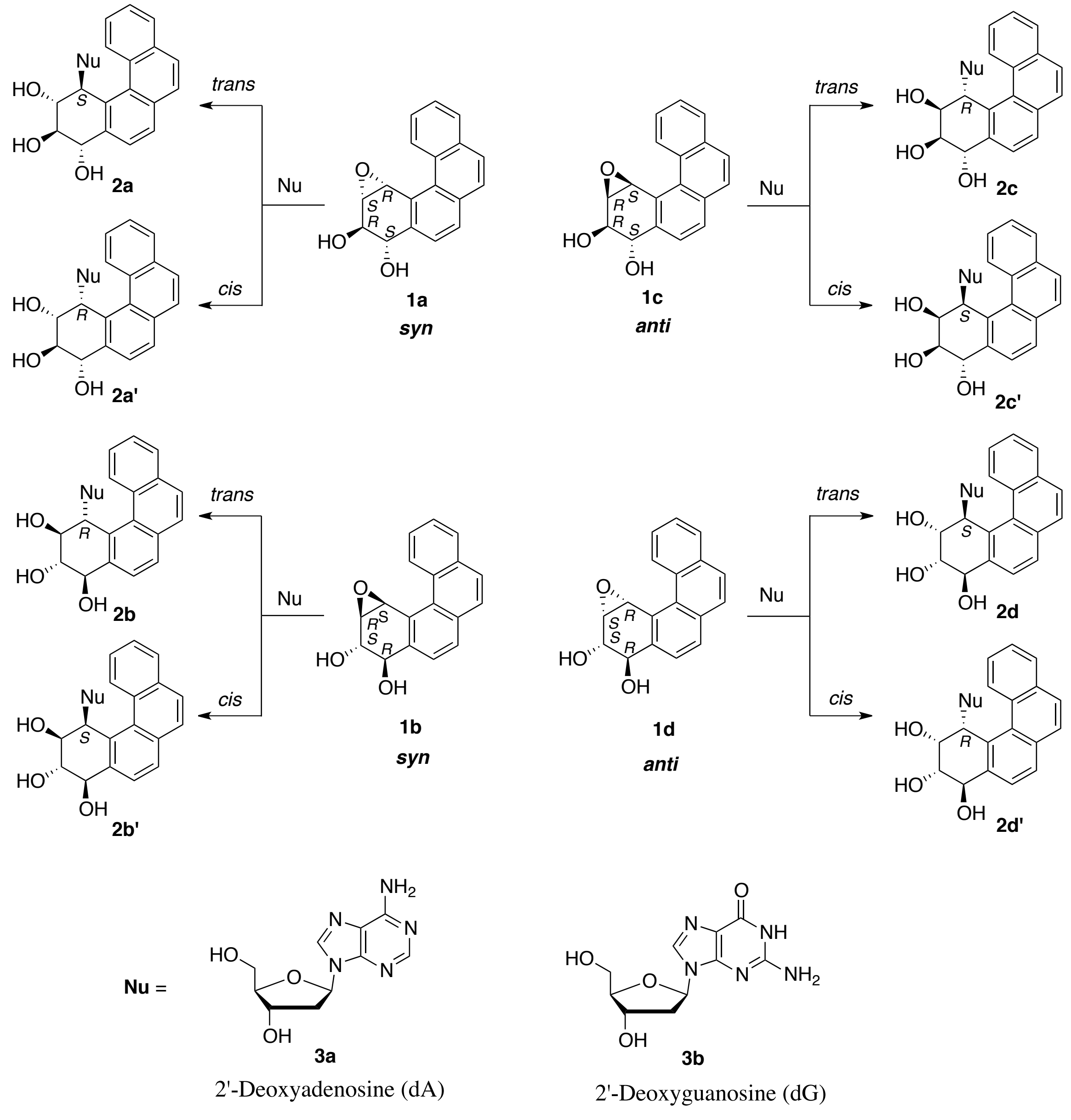


Figure 1. 2′-Deoxyguanosine and 2′-deoxyadenosine adducts obtained from four configurational isomers of benzo[*c*]phenanthrene diol epoxides.

The formation of DNA adducts varies from for different PAHs, that can vary in shape (planarity and non-planarity) and number of aromatic rings in the hydrocarbon.[7,8] Reactions of various PAH diol epoxides with calf thymus DNA revealed interesting results.[7,8] Diol epoxides of benzo[*a*]pyrene (B*a*P), which is a planar five-ring hydrocarbon, form only <10% DNA adducts, along with large quantities of tetraols by hydrolysis, whereas diol epoxides of non-planar and four-ring B*c*Ph form 60-75% of DNA adducts and only 25-40% of tetraols.[7,8] In an individual PAH, reactivity of the four diol epoxide configurational isomers towards purine bases is also not always the same and they alkylate the DNA to different extent. [7,8] Studies have shown that in general in most of the PAHs, *R,S,S,R* diol epoxide binds to DNA to larger extent than the other isomers, except in the case of diol epoxides of B*c*Ph, where all four diol epoxide isomers react efficiently with DNA. [7-10]

Table 1. Stereoselectivities of Reactions of the Four Diol Epoxide Isomers of Various PAHs[a] with DNA[8]

Isomer	**Adduct**	**Preferential epoxide opening by DNA**	**Exceptions**
R,S,S,R	dG	*trans*	
	dA	*trans*	
S,R,S,R	dG	*cis*	*trans* for B*g*C; *trans* = *cis* for B*c*Ph
	dA	*trans*	*cis* for B*a*P
S,R,R,S	dG	*trans*	
	dA	*trans*	*cis* for DMBA
R,S,R,S	dG	*cis*	*cis* = *trans* for DBA; *trans* for B*c*Ph and B*g*C
	dA	*cis*	*trans* for B*g*C

[a]PAHs that were compared: B*a*P; B*c*Ph; 5,6-dimethylchrysene (DMCh); 5-methylchrysene (5-MeCh); benzo[*a*]anthracene (BA); dibenz[*a,j*]anthracene (DBA); benzo[*g*]chrysene (BgCh); 7,12-dimethyl benzo[*a*]anthracene (DMBA); 7-methyl benzo[*a*]anthracene (MBA).

Furthermore, diol epoxides of different PAHs have different preferences for two purine bases.[7,8] For examples, in the case of non-planar B*c*Ph, diol epoxides prefer to form adducts by alkylation of N^6-amino groups of dA in the major groove of DNA, whereas in the case of planar B*a*P, there is high preference for alkylation of N^2-amino groups of dG and in the minor grove of DNA.[7-10] Table 1 shows the preference for *trans* or *cis* ring opening of diol epoxide isomers by dA or dG, for various bay- and fjord region PAHs.[8]

The following scenario emerges on the reactivity of diol epoxides of various PAHs with DNA and stereoselectivity of adduct formation: (i) Diol epoxides of various PAHs have different reactivity with DNA depending upon the their structure. The diol epoxides derived from PAHs with five rings bind to DNA to lesser extent than those derived from four membered PAHs.[7] (ii) For different PAHs, individual configurational isomers of diol epoxides react differently with DNA.[7] Among the four configurational isomers, *R,S,S,R* binds more to DNA than the others. (iii) Diol epoxides of different PAHs have different preferences for binding to dA and dG. The diol epoxides derived from planar PAHs prefer to bind to dG, whereas those derived from non-planar PAHs bind preferentially to dA.[7] (iv) The major adducts formed in all PAHs studied arise from the *trans* ring opening of epoxide.[7]

These points correlate the nature of PAHs, their metabolites and their reactions with DNA, however there is no general correlation between the DNA alkylation and tumorigenicity of diol epoxides and their parent hydrocarbons. For example: (i) The highly tumorigenic diol epoxides of B*a*P form DNA adducts as efficiently as those of dibenz[*a,j*]anthracene (DBA), that are weakly tumorigenic. (ii) In both B*a*P and B*c*Ph, the *R,S,S,R* diol epoxide is the most tumorigenic isomer, irrespective of the fact that in B*c*Ph, this isomer reacts very effectively with DNA, whereas in the case of B*a*P, it reacts with DNA only to a small extent. (iii) Among B*c*Ph diol epoxides, *R,S,R,S* isomer alkylates DNA efficiently but is inactive as carcinogen. (iv) Also, both *R,S,R,S* (DE-1) and *R,S,S,R* (DE-2) isomers of B*c*Ph, bind preferably to dA and to a similar extent, however the former shows no tumorigenic activity.[7,8]

To get an insight into chemical reactivity of an individual diol epoxide with DNA, and biological properties of the modified DNA, the site specific modification of DNA by incorporation of stereochemically defined diol epoxide adduct is critical. In this direction, various studies have been performed on different PAHs and a significant amount of information has been obtained about the structure activity relations of different PAHs.[7,14-18]

Three approaches were used for the site-specific modification of DNA:

1. Direct reaction of diol epoxides with DNA: This involves direct reaction of a short oligonucleotide with individual diol epoxides.[19,20] The limitations of this method is formation of tetraols by competing hydrolysis that is a significant competing process.[7,19] Poor nucleophilicity of exocyclic amino groups of nucleobases is another limitation for formation of adducts. Finally, reactions of diol epoxides with multiple reactive sites in DNA are possible.

2. Post-oligomerization modification approach: This method was developed by Harris et al.[21-22], where stereochemically defined PAH amino triol derivatives were reacted with a matrix-bound oligonucleotide containing a nucleoside bearing halide or triflate leaving groups. The major limitations of this approach include the low yields and dependence of adducts formation on DNA sequence.[22,23]

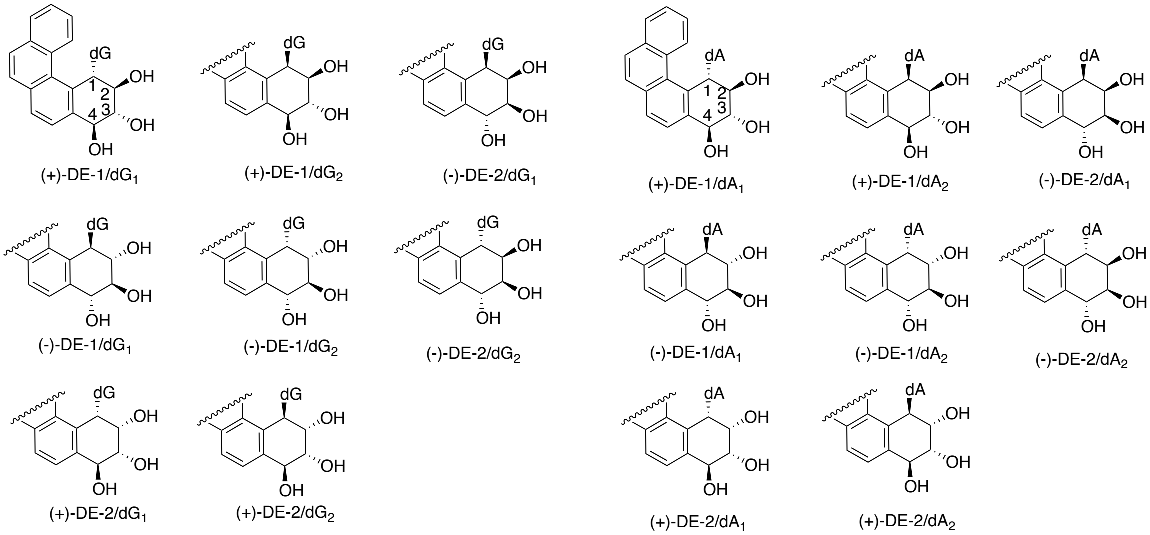
3. Total synthesis approach: This approach involves synthesis of mononucleoside adducts of stereochemically defined diol epoxides. For this, amino triol derivatives of PAHs are reacted with nucleosides halides[14-17,24-29] or triflates.[30] Incorporation of these mononucleoside adducts into oligonucleotides using solid-phase synthesis provides access to DNA modified by stereochemically defined diol epoxide adducts.[17,25,27,30] This approach overcomes many of the limitations of the above two methods, such as formation of tetraols by hydrolysis, reactions of diol epoxides at multiple sites in DNA, *cis* and *trans* ring opening of the epoxides by nucleobases in DNA, and the low yield of DNA adducts. Other advantages of this approach include access to all possible streochemically defined PAH-nulceoside adducts, large-scale synthesis of these adducts, and more importantly, access to minor adduct isomers that may not be achieved by other methods.[29]

2.1.1 Synthesis of B*c*PhDE-DNA Adducts:

Benzo[*c*]phenanthrene is a unique member of the PAH family. The hydrocarbon has a low tumorigenic activity but its diol epoxides, as discussed above and in Part 1, are very good DNA alkylating agents and highly tumorigenic.[8,31] Although all the four diol epoxides (shown in Figure 1) alkylate DNA nearly equally efficiently, their tumorigenic activity differs significantly. [8,31] To get an insight into the structure activity relationship, reactivity of stereochemically defined diol epoxides of B*c*Ph with DNA was studied.[9] Further synthesis[10,26,29,30] and studies of B*c*PhDE mononucleoside adducts as well as of DNA, site specifically modified by B*c*PhDE adducts were reported as well.[30]

Jerina et al studied direct reaction of all four B*c*Ph diol epoxide isomers of B*c*Ph with calf thymus DNA *in vitro*.[9] All four isomers showed preference for covalent binding to DNA over hydrolysis to tetraol.[9] All sixteen dA and dG adducts were isolated, with higher yields of dA adducts as compared to dG adducts.[9] Interestingly, dA adducts of (+)-DE-1and (-)-DE-2 that are the most tumorigenic diol epoxide isomers on mouse skin, were produced in high yields.[9] For analysis and characterization of these adducts, obtained by the direct reaction of DNA with diol epoxide isomers, chemical synthesis was performed by reaction of racemic diol epoxides with nucleosides.[10] Both series 1 as well as series 2 diol epoxides of B*c*Ph were reacted with dA and dG and the *cis* and *trans* ring opened adducts were separated by HPLC and characterized by NMR and circular dichroism (CD) spectroscopy.[10] The chemical shifts of protons in the tetrahydro ring, and their coupling constants are listed in Table 2. For DE-1, dA_1, and dG_1 represent the *trans* ring opened, and dA_2 and dG_2 represent the *cis* ring opened products, respectively (Scheme above Table 2). In DE-2, the order is reverse; dA1, and dG1 represent the *cis* ring-opened, and dA_2 and dG_2 represent the *trans* ring opened products respectively. In the case of DE-1, the *cis* and *trans* ring opened adducts could be distinguished on the basis of the coupling constants of protons in the tetrahydro ring. In both cases, the purine substituent at C-1 position was pseudoaxial but the coupling constant $J_{2,3}$ for *cis* adducts (DE-1/dA_2 and DE1/dG_2) was 9-10 Hz, whereas this value is only 2-3 Hz for *trans* adducts (DE-1/dA_1 and DE-1/dG_1).[10] In the case of adducts that were derived from DE-2, the *cis* and *trans* adducts were distinguished by empirical methods, via comparison of the change in C_1-H proton chemical shift in two adducts.

Table 2. Chemical Shifts and Coupling Constants of the Methine Protons in Tetrahydro Ring of Acetate Derivatives of dA and dG Adducts of DE-1 and DE-2 of B*c*Ph and Tetraol Derivatives (Solvent: Acetone-d_6) [10]



(+)-DE-1/dG$_1$ (+)-DE-1/dG$_2$ (-)-DE-2/dG$_1$ (+)-DE-1/dA$_1$ (+)-DE-1/dA$_2$ (-)-DE-2/dA$_1$

(-)-DE-1/dG$_1$ (-)-DE-1/dG$_2$ (-)-DE-2/dG$_2$ (-)-DE-1/dA$_1$ (-)-DE-1/dA$_2$ (-)-DE-2/dA$_2$

(+)-DE-2/dG$_1$ (+)-DE-2/dG$_2$ (+)-DE-2/dA$_1$ (+)-DE-2/dA$_2$

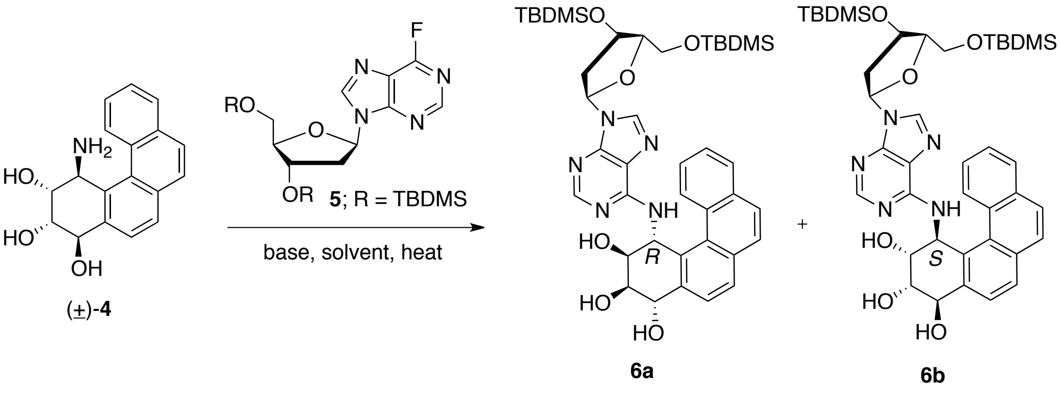
Compound	**C$_1$-H**		**C$_2$-H**		**C$_3$-H**		**C$_4$-H**
	***δ* (ppm)**	***J*$_{1,2}$ (Hz)**	***δ* (ppm)**	***J*$_{2,3}$ (Hz)**	***δ* (ppm)**	***J*$_{3,4}$ (Hz)**	***δ* (ppm)**
cis-1 tetraol	7.33	2.4	5.06	10.5	5.91	5.4	6.43
(-)DE-1/dG$_2$	7.00	3.5	5.07	10.2	5.97	4.6	6.32
(+)DE-1/dG$_2$	6.93	3.4	5.01	10.1	5.96	4.3	6.31
(-)DE-1/dA$_2$	7.12	3.4	4.85	8.7	5.85	2.2	6.20
(+)DE-1/dA$_2$	7.13	3.2	4.85	8.5	5.85	2.0	6.20
trans-1 tetraol	6.99	3.8	5.45	3.2	5.16	8.1	6.66
(-)DE-1/dG$_1$	6.23	3.2	5.93	2.8	5.17	8.0	6.68
(+)DE-1/dG$_1$	6.22	3.5	5.93	3.2	5.17	8.2	6.68
(-)DE-1/dA$_1$	6.66	~2.5	5.79	3.4	5.25	7.8	6.87
(+)DE-1/dA$_1$	6.66	~2.8	5.79	3.5	5.25	7.8	6.87
cis-2 tetraol	7.55	3.9	5.97	2.3	5.73	8.6	6.69
(-)DE-2/dG$_1$	7.00	4.3	6.30	2.0	5.71	8.6	6.72
(+)DE-2/dG$_1$	7.30	4.7	6.14	1.9	5.72	9.3	6.70
(-)DE-2/dA$_1$	7.40	4.0	6.10	1.8	5.76	7.7	6.71
(+)DE-2/dA$_1$	7.40	3.9	6.11	~1.9	5.76	7.8	6.72
trans-2 tetraol	6.75	4.9	5.97	2.5	5.69	8.3	6.53
(-)DE-2/dG$_2$	6.26	4.1	6.34	2.6	5.91	8.4	6.49
(+)DE-2/dG$_2$	6.25	4.5	6.36	1.6	5.88	8.5	6.49
(-)DE-2/dA$_2$	6.61	<4	6.25	2.7	5.99	8.3	6.43
(+)DE-2/dA$_2$	6.62	<4	6.26	2.6	5.99	8.3	6.43

A similar trend in the change of C_1-H proton chemical shift was observed in the corresponding tetraols and adducts of bay region DE-2 diol epoxides, which was helpful in assigning the stereochemistry of addition.[10]

In the CD spectroscopy analysis, the adducts with 1*R*-absolute configuration showed a negative CD band between 250-260 nm whereas those with 1*S*-absolute configuration showed a positive band between 250-260.[10] An empirical correlation was observed in the CD bands of the adducts of B*c*Ph diol epoxides and those of B*a*P diol epoxides with *R* configuration at the point of attachment of purine to tetrahydro ring.[10]

Synthesis of dA adducts of B*c*PhDE-2 by the total synthesis approach was reported by Lakshman et al.[26] In this approach, the amino triaol (±)-**4** was reacted with 6-fluoro-9-(2′-deoxy-β-D-*erythro*-pentofuranosyl)purine (6-FP) **5** in a S_NAr reaction (Scheme 1). The requisite amino triol (±)-**4** was obtained by aminolysis of racemic DE-2 metabolite of B*c*Ph.[26]

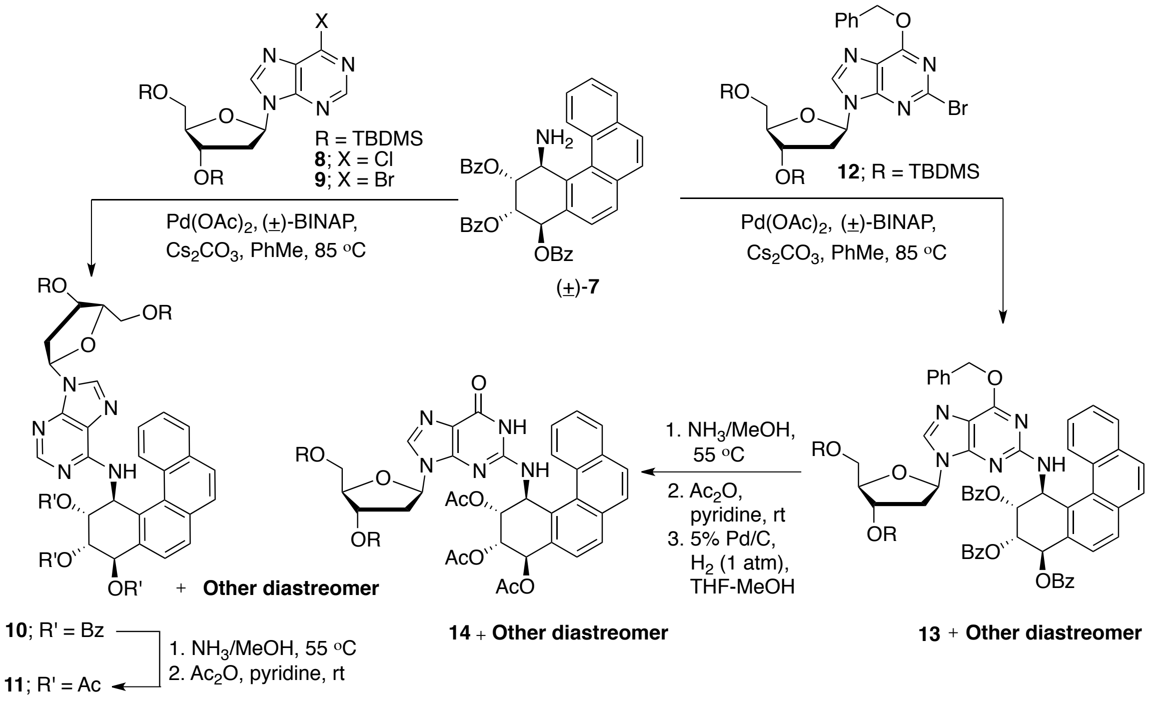
Scheme 1. Synthesis of dA Adducts of B*c*PhDE-2 by S_NAr Reaction



An interesting observation made in this report was that although the major product of the aminolysis reaction resulted from the addition of amine to the benzylic carbon, i.e. compound (±)-**4**, a minor product was also obtained by addition of the amine to the non-benzylic position. This minor non-benzylic ring opening of the epoxide was also observed in the reactions of diol epoxide with the azide ion (NaN_3) in DMF at 60 °C. Interestingly, when the azidation reaction was performed in 1:1 THF-water, azido triol with azide group at the benzylic position was obtained as the sole product.[26] The chemical shifts of the protons in the tetrahydro ring of adducts **6a** and **6b** were comparable to those obtained by *trans* ring opening of B*c*PhDE-2 by *N*^{6}-amino group of deoxyadenosine described above, (+)DE-2/dA2 and (-)DE-2/dA2, respectively (see Scheme above Table 2).[10]

Synthesis of dA (**11**) and dG (**14**) adducts of series 2 diol epoxide of B*c*Ph by palladium catalyzed C-N bond forming reactions was reported by Lakshman et al.[29] In this report, chloro- and bromonucleoside derivatives were successfully reacted with amino tribenzoate derivative (±)-**7**, to obtain triacetate derivatives of dA and dG adducts **11** and **14**, respectively (Scheme 2). The amino triol derivative was obtained by epoxide ring opening by the azide, followed by the benzoylation of hydroxyls and reduction of the azide. For the synthesis of *N*^{6}-dA adducts **11**, both C-6 chloro- (**8)** as well C-6 bromopurine-2'-deoxyriboside (**9**) derivatives were suitable candidates, however the bromo derivatives (**9**) gave higher yields of products. For the synthesis of dG adduct, 2-bromo-2'-deoxyinosine (**12**) was found be the best coupling partner for the amine (±)-**7** and the yields of product obtained was higher those obtained in case of dA adduct.[29] This methodology was also efficient in synthesis of dA as well as dG adducts of series 1 B*a*P diol epoxide. [29] The diastereomers of peracetate derivatives **11** and **14** were separated and characterized by NMR and CD spectroscopy techniques. [29]

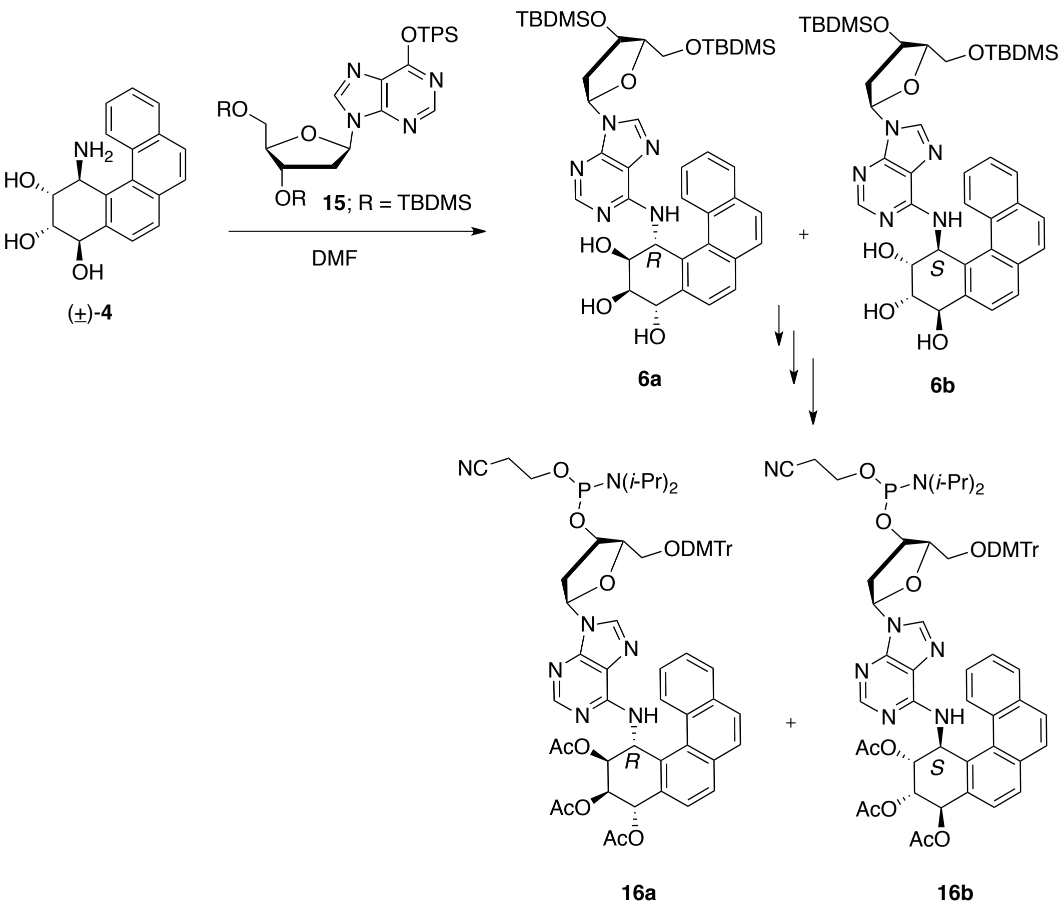
Scheme 2. Synthesis of B*c*PhDE-2-dA Adducts by Palladium-Catalyzed C-N Coupling Approach



In the CD studies, in the case of dA adducts **11**, the isomer that showed a positive band at 248 nm was assigned 1*S* absolute configuration at the point of attachment of the nucleobase, whereas the isomer showed a negative band at the same wavelength was assigned 1*R* configuration. Similar trend in the signs of CD bands was observed for dG adducts **14**, i.e. a positive band at 257 nm for 1*S* and a negative band for 257 nm for 1*R* configuration at the point of attachment of the nucleobase.[29]

Synthesis of dA adducts of series 2 diol epoxide of B*c*Ph was also reported by Seidel et al.[30] *trans*-Ring opened amino triol derivative (±)-**5** was obtained by the treatment of B*c*PhDE-2 with concentrated NH_3/MeOH solution.[30] Reaction of (±)-**5** with C-6 sulfonate derivative of purine-2′-deoxyriboside **15** in DMF at 80 °C produced the desired diastereomeric mixture of dA adducts (Scheme 3).

Scheme 3. Synthesis of dA Adducts of B*c*PhDE-2 and Phosphoramidite Derivatives



The diastereomers **6a** and **6b** were separated by HPLC and converted to phosphoramidite derivatives **16a** and **16b**, respectively, by protection and deprotection chemistry.[30] These phosphoramidite derivatives were further used in the synthesis of two 21-mers with the partial sequence of the human Ha-ras proto-oncogene surrounding codon 61, dACCGCCGGCCA^{1*}GGAGGAGTAC and dACCGCCGGCCA^{2*}-GGAGGAGTAC (A^{1*} and A^{2*} represent the adducted deoxyadenosine).[30]

2.1.2 NMR Solution Structure Studies of B*c*Ph-DNA Adducts

Solution structures of B*c*Ph diol epoxide adducted DNA duplexes have been studied by NMR and results of these studies are summarized in Table 3.

Table 3. NMR Solution Structure Studies of B*c*PhDE Adducted DNA Duplexes

Entry	DNA sequence	Adduct configuration, diol epoxide configuration	Ring opened	Properties
Deoxyadenosine Adducts of B*c*PhDE				
1[32]	5′-CTCTC**A**CTTCC-3′ 3′-GAGAGTGAAGG-5′	1*S* adduct, DE-2 (1*R*,2*S*,3*S*,4*R*)	*trans*	PAH is intercalated and towards the 3′-end, normal Watson and Crick base-pairing is maintained at the adduct. One or more minor conformers. H-3 and H-4 of the PAH pseudo diaxial whereas H-1 and H-2 of the PAH pseudo diequatorial.
2[33]	5′-CTCTC**A**CTTCC-3′ 3′-GAGAGTGAAGG-5′	1*R* adduct DE-2 (1*S*,2*R*,3*R*,4*S*) *trans*	*trans*	PAH is intercalated and towards the 5′-end, normal Watson and Crick base-pairing is maintained at the adduct, apparently single conformer. H-1 and H-2 of the PAH pseudo diaxial whereas H-3 and H-4 of the PAH pseudo diequatorial.
Deoxyguanosine Adducts of B*c*PhDE				
3[34]	5′-CCATC**G**CTACC-3′ 3′-GGTAGCGATGG-5′	1*S* adduct DE-2 (1*R*,2*S*,3*S*,4*R*)	*trans*	PAH intercalation occurs from the minor groove and is oriented towards the 5′-end of the modified strand.
4[34]	5′-CCATC**G**CTACC-3′ 3′-GGTAGCGATGG-5′	1*R* adduct DE-2 (1*S*,2*R*,3*R*,4*S*)	*trans*	PAH intercalation occurs from the minor groove and is oriented towards the 3′-end of the modified strand.
5[35]	5′-ATCGC**G**CGGCATG-3′ 3′-TAGCGCGCCGTAC-5′	1*R* adduct DE-2 (1*S*,2*R*,3*R*,4*S*)	*trans*	PAH intercalated from 3′-end of the modified strand with terminal ring faced into the major groove.

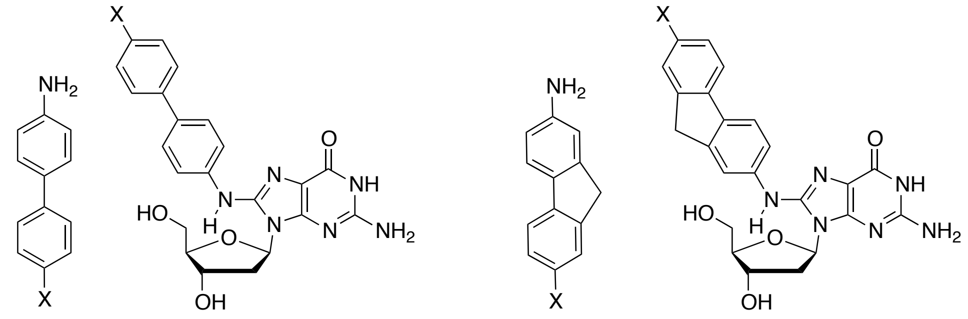
2.1.3 Fluorinated Adducts as Probes for Conformational Heterogeneity

Fluorine is known to change physical, chemical and biological properties of molecules and the change depends upon the position of fluorine in the molecules.[36] Change in the biological activity of PAHs upon regiospecific introduction of fluorine has been demonstrated in literature[31,37-44] and described in details in Part 1 of Chapter 2. Fluorinated PAHs have been used as probes for study of structure activity relations of these compounds.[37-44] Since, ^{19}F NMR spectroscopy is an additional tool in structure determination, fluorinated PAHs offer useful probes in structure elucidation of PAH-DNA adducts.[47]

PAH modified DNA can adopt one or multiple confirmations depending upon structure of the hydrocarbon (shape and stereochemistry), and the base sequence surrounding the adduct. In some cases, it is difficult to analyze the minor confirmations using ^{1}H NMR and other techniques. ^{19}F spectroscopy can also serve as a useful tool for analysis of such minor conformers of DNA. The adducts derived from fluorine-containing aryl amines that are another class of carcinogenic compounds, have been used as models for probing conformational heterogeneity induced by these compounds by the use of ^{19}F spectroscopy.[45,46] Also, this approach has been used recently for probing conformational heterogeneity induced by PAH-DNA adducts.[47]

Cho et al. have shown that ^{19}F NMR spectroscopy can be used to probe the conformational heterogeneity of DNA duplexes that are modified by two arylamine compounds **18** and **22** shown in Figure 2.[45] The DNA sequences d[CTTCTTG*ACCTC]-·d[GAGGTCAAGAAG], where G* is either *N*-(deoxyguanosin-8-yl)-4′-fluoro-4-aminobiphenyl (dG-C8-FABP) (**20**) or *N*-(deoxyguanosin-8-yl)-7-

fluoro-2-aminofluorene (dG-C8-FAF) (**24**), were studied by ^{19}F NMR. Results were compared to those obtained by the use of ^{1}H NMR for duplex containing unfluorinated aryl amine **17**.[45]



17; X = H
18; X = F

19; X = H
20; X = F

21; X = H
22; X= F

23; X = H
24; X = F

Figure 2. Aryl amines and their dG adducts used for study of DNA conformational heterogeneity.

The ^{19}F NMR spectrum of DNA containing modified nucleoside **20** showed a single signal, but two signals in 55:45 ratio were in ^{19}F NMR of duplex containing modified nucleoside **24**. The authors concluded that DNA modified by **22** exists in two conformations, whereas that modified by **18** exists only in one conformation. These observations were consistent to those obtained by ^{1}H NMR studies of DNA adducted with the protio analogs **17**[48] and **21**,[49] respectively. The two conformations of DNA modified by **22** are shown in Figure 3. In "B-type" (PAH resides in the major groove of the undistorted DNA, Figure 3), and in "stacked" or "S-type", PAH resides in the helix at the adduct site. [45]

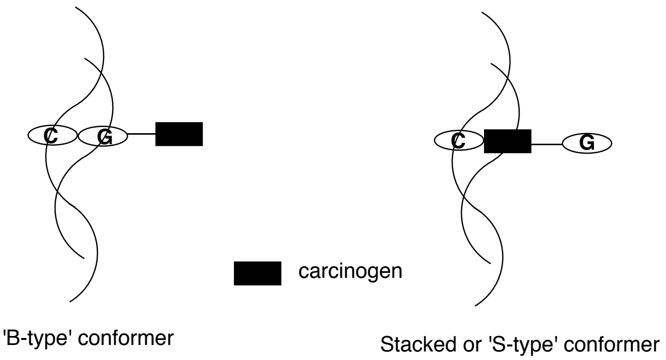


Figure 3. Two conformations of DNA modified by dG adducts of aminofluorene.

Cho et al. also studied the oligonucleotide sequence effects on aminofluorene-induced conformational heterogeneity using 7-fluoro-2-aminofluorene as a probe.[46] Eight 12-mer DNA duplexes, each containing a 7-fluoro-2-aminofluorene adducted dG **24** were prepared. The sequences of oligomers were d[CTTCT**AG*_N_**CCTC]: and d[CTTCT**CG*_N_**CCTC], where *N* = G, A, C, T and G* = **24**. The heterogeneity studies were performed using UV, CD and dynamic ^{19}F NMR spectroscopy. Studies showed that in all DNA duplexes S- and B-type conformations were in dynamic equilibrium that was sequence dependent. The correlation of S/B equilibrium with efficiency of *Escherichia coli* UvrABC-based nucleotide excision repair indicated that the S conformer is more susceptible to repair than the B conformer.[46]

Recently, Cho et al. also studied the potential utility of 2-fluoro B*a*P diol epoxides-dG adducts as models for conformational analysis of B*a*P-adducted DNA.[47] For this, series 2 2-fluorobenzo[*a*]pyrene-7,8-dihydrodiol-9,10-epoxides (FBPDEs) **26a** (*R,S,S,R*) and **26b** (*S,R,R,S*) (Figure 4) were synthesized using a multistep synthetic approach.[47] The analysis of these diol epoxides of FB*a*P (**26a** and **26b**) and the protio anaolgs (**25a** and **25b**) indicated the pseudo-diequatorial orientation of the hydroxyl groups in both cases. The major *trans*-*anti*-N^2-dG-FBPDEs adducts were obtained by reaction of **26a** and **26b** with deoxyguanosine 5′-monophosphate. These were incorporated into 11-mer oligonucleotide with a sequence 5′-CCAT**X**G*CTACC-3′, (where X = dT and dC, and G* = FBPBE-N^2-dG adduct).[47]

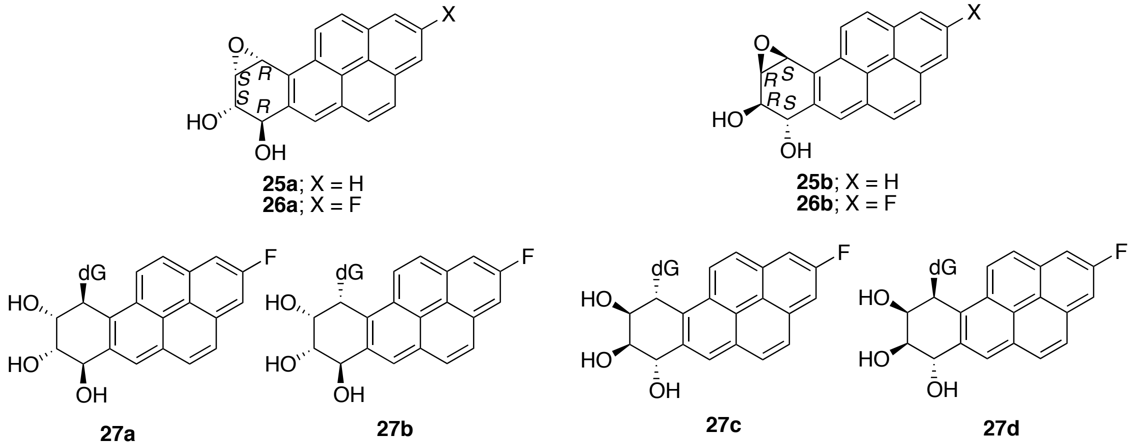


Figure 4. Series 2 diol epoxides of 2-FB*a*P and their dG adducts.

DNA duplexes [(5′-CCAT**T**G*CTACC-3′): (5′-GGTAGC**A**ATGG-3′)] and [(5′-CCAT**C**G*CTACC-3′): (5′-GGTAGC**G**ATGG-3′)] were also obtained by pairing with the complementary strands. The study showed that fluorine at 2-position of B*a*P does not alter the conformations of series 2 diol epoxides, their adducts or DNA-duplex thus making it a useful model for conformational heterogeneity studies of B*a*P-adducted DNA.

Thus DNA adducts of stereochemically defined PAHs-containing a remote fluorine substituent can be useful probes for conformational analysis of the adducted DNA, as fluorine in the remote position does not alter the conformation of the hydrocarbon and its metabolites. This chapter will describes the synthesis of 2′-deoxyadenosine adducts of fluoro-substituted benzo[*c*]phenanthrene diol epoxides. Specifically, synthesis of dA adducts of series 2 diol epoxides of 5-

fluorobenzo[*c*]phenanthrene is described. Assignment of the absolute configuration in dihydrodiol and diol epoxide derivative, as well as in dA adducts using CD spectroscopy is shown.

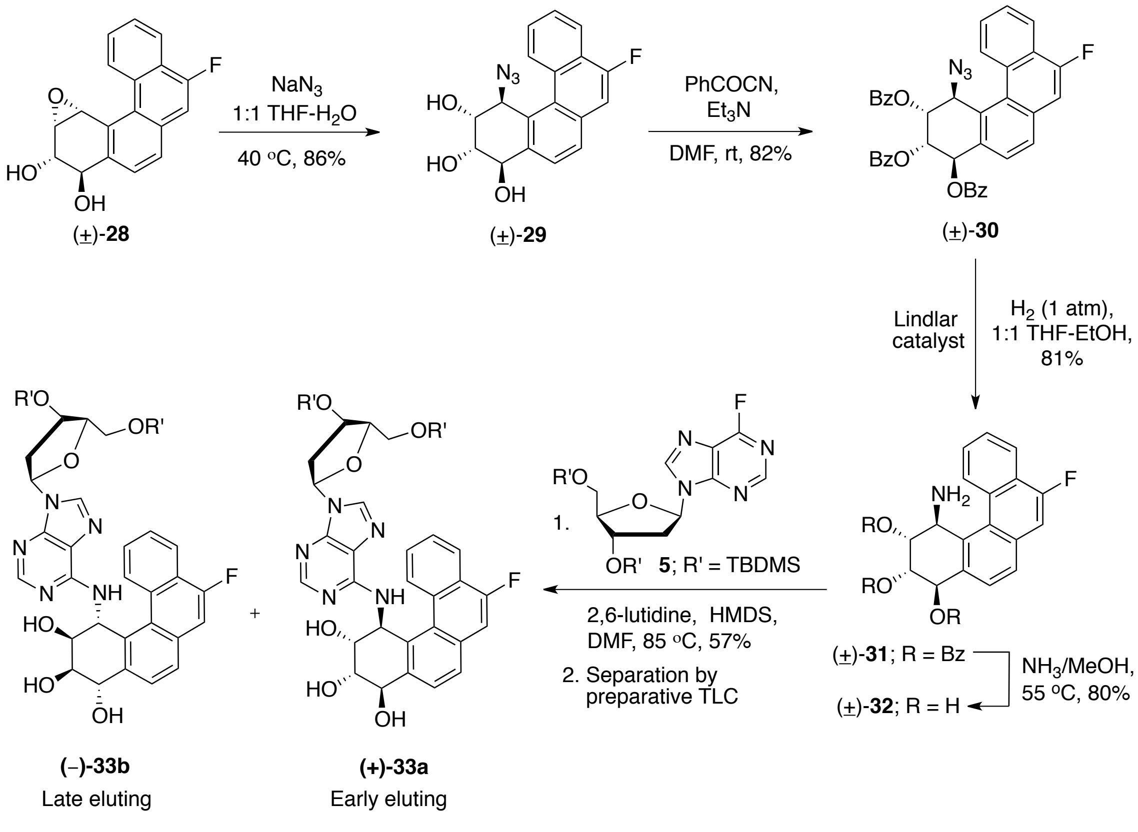
2.2 RESULTS AND DISCUSSION

2.2.1 Synthesis of dA Adducts of 5-Fluorobenzo[*c*]phenanthrene

Towards the total synthesis of B*c*PhDE-2-dA adducts, an efficient method for regioselective and stereoselective synthesis of amino triol derivative of B*c*Ph was developed by Lakshman et al.[26] The epoxide ring opening of the diol epoxide of B*c*Ph by azide ion in THF-water mixed solvent was observed to be regioselective, and only the benzylic C-1 derived azide (azido-precursor of (±)-**4**, shown in Scheme 1), with *trans* ring opening of epoxide was obtained.[26] In the present work, the requisite series-2 diol epoxide (±)-**28** was synthesized as reported in Part 1 of Chapter 2.

Diol epoxide-2 (±)-**28** was reacted with NaN_3 in 1:1 THF-water at 40 ^{o}C to give azido triol derivative (±)-**29** (86% yield) that was further subjected to benzoylation using benzoyl cyanide and Et_3N in DMF (Scheme 4). The azido tribenzoate derivative (±)-**30** was obtained in 82% yield. Reduction of azide by hydrogenation using Lindlar catalyst and H_2 (1 atm) in 1:1 THF-ethanol yielded 81% of the amino tribenzoate derivative (±)-**31** (Scheme 4). Interestingly, when reduction of the azide was attempted on azido triol derivative (±)-**29** using either hydrogenation with Lindlar catalyst in THF-ethanol, or 10% Pd/C in ethanol, the crude reaction mixture showed a signal at -73 ppm as the major signal in ^{19}F NMR, which does not correspond to the fluorine bonded to aromatic ring. In addition, a small doublet at -123 ppm was also observed that might correspond to the desired reduced amino triol derivative (±)-**32**. Also, the ^{1}H NMR of the crude reaction mixture showed the presence of more than one product. When the crude mixture obtained in the hydrogenation of (±)-**29** using 10% Pd/C was subjected to peracetylation, the signal at -73 ppm was no more observed in the ^{19}F NMR, and the amino tetraacetate derivative was obtained in 21% yield over two steps. Removal of benzoates from compound (±)-**31** using saturated solution of ammonia in methanol at 55 °C provided the amino triol derivative (±)-**32** in 80% yield (Scheme 4). Further, (±)-**32** was reacted with 6-fluoro-9-(2′-deoxy-β-D-*erythro*-pento-furanosyl) purine **15** (Scheme 4), as reported [26]

Scheme 4. Synthesis of dA Adducts of Racemaic Series-2 Diol Epoxide of 5-FB*c*Ph



Reaction conditions, i.e. base and solvent, were critical for the success of this reaction. When reaction was performed using diisopropylethyl amine (DIPEA) in DMSO, the conditions that were used for synthesis of adducts of B*a*P diol epoxides,[50] only 15% yield of the slightly impure products **33** was obtained. On the other hand, the use of 2,6-lutidine and DMF[26] as a solvent improved the yield significantly to 57%. The diastereomers (+)-**33a** and (–)-**33b** were separated by preparative TLC using 1000 micron silica gel plate and 7% MeOH, 43% EtOAc, 50% hexanes as mobile phase.[26] The early and late eluting isomers were characterized by NMR and CD spectroscopy techniques. The ^{1}H NMR resonances and the coupling constants of the protons in the tetrahydro ring of B*c*Ph residue are listed in Table 4.

Table 4. ^{1}H NMR Chemical Shifts and Coupling Constants of Methine Protons in B*c*Ph Tetrahydro Ring of dA Adducts Measured in Acetone-d_6

Adduct	**H-12**		**H-11**		**H-10**		**H-9**	
	δ (ppm)	J (Hz)	δ (ppm	J (Hz)	δ (ppm)	J (Hz)	δ (ppm)	J (Hz)
Early eluting (–)-**33a**	6.59 (br s)	na	4.65 (br s)	na	4.41 (dd)	$J_{9,10} = 6.9$ $J_{10,11} = 2.8$	4.95 (d)	$J_{9,10} = 6.7$
Late eluting (+)-**33b**	6.59 (br s)	na	4.66 (br s)	na	4.41 (dd)	$J_{9,10} = 6.7$ $J_{10,11} = 2.6$	4.96 (d)	$J_{9,10} = 6.7$

CD spectrum (Figure 5) of the early eluting isomer (+)-**33a** showed a positive band at 245 nm indicating the *S*-absolute configuration at C-12, which is bonded to the amine of dA. Late eluting isomer (–)-**33b** showed a negative band at 245 nm which was nearly a mirror image of that obtained from (+)-**33a**, indicating the *R*-absolute configuration at C-12.

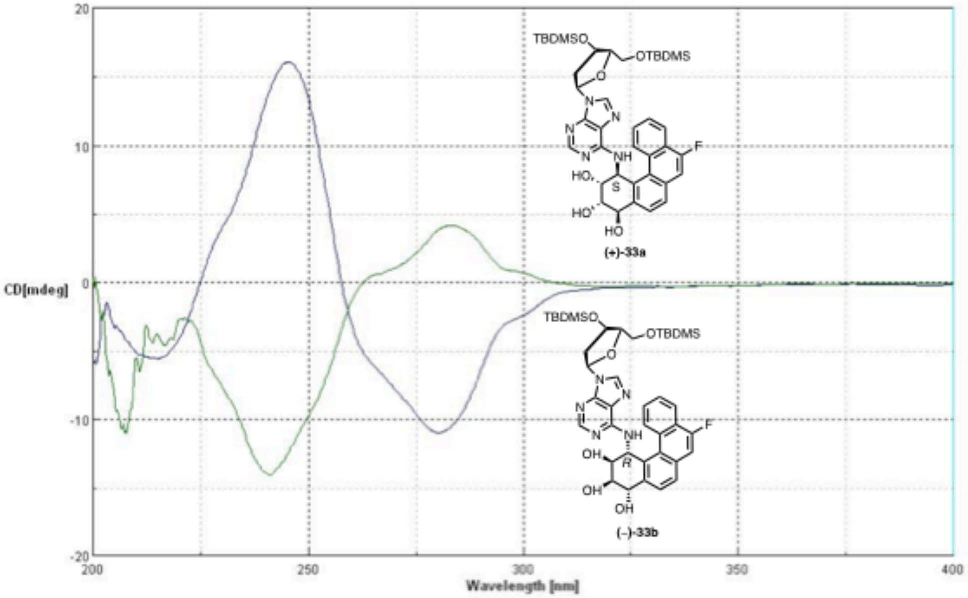


Figure 5. CD spectra of early eluting (+)-**33a** and late eluting (–)-**33b** adducts.

2.2.2 Assignment of Absolute Configuration

Although Figure 5 shows CD spectra and chirality assignments to the adducts at the point of attachment of the hydrocarbon to the nucleoside, it should be noted that this is based on comparison to CD spectra of mononucleoside adducts of unsubstituted B*c*Ph. Although in our case fluorine is remote to attachment of 5-FB*c*Ph diol epoxide to dA, we had to unequivocally assign the chirality of individual dA adducts of series 2 diol epoxides of 5-FB*c*Ph. For this, synthesis of enantiomerically pure series 2 diol epoxides of 5-FB*c*Ph was undertaken. Since diol epoxides are synthesized from a *trans*-dihydrodiol, using highly stereoselective reactions, assignment of absolute configuration to the dihydrodiol enantiomer is will be critical for assigning the absolute configuration to diol epoxides and subsequently the adducts that are be obtained from these diol epoxides.

Circular Dichroism spectroscopy is a useful technique for assignment of chirality and has been used in the stereochemistry determination in the study of PAH metabolites using Exciton Chirality Method.[51-54]

Jerina et al. reported the resolution of B*c*Ph dihydrodiol enantiomers by reacting the racemic mixture with bis(–)-menthoxyacetyl chloride, and separating the diastereomers by HPLC.[54] The early eluting isomer was converted to tetrahydrodiol by reduction of the double bond and removal of the ester. For the assignment of absolute configuration, exciton chirality method developed by Nakanishi et al.,[51] was used. Tetrahydrodiol derivative was further converted to bis *p*-(*N,N*-dimethylamino)benzoate ester derivative **34** (shown in Figure 6). CD spectrum of this compound showed a strong negative band at 323 nm, was zero at 309 nm and had a positive band at 298 nm that indicated the *RR* configuration for the bis-ester and hence for the dihydrodiol precursor.[54]

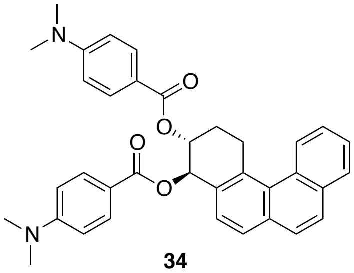


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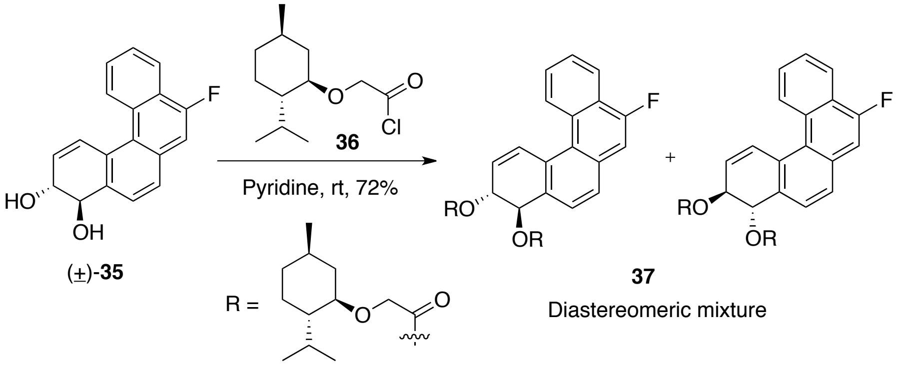
Figure 6. Bis (*p*-*N,N*-dimethylamino)benzoate ester of 3,4-dihydroxy-1,2,3,4-tetrahydro BcPh used by Jerina et al for assignment of chirality to B*c*Ph dihydrodiol.

Lakshman et al. also reported the resolution of B*c*Ph dihydrodiol enantiomers by converting them to (–)-menthoxymethyl ether diastereomers.[55] The method was equally efficient in separation of the diasteromers.[55]

Following the approach used by Jerina et al.,[54] the racemic mixture of the 5-fluorobenzo[*c*]phenanthrene dihydrodiol (±)-**35** (synthesis shown in Part 1 of Chapter 2), was reacted with (–)-menthoxyacetyl chloride **36** (Scheme 5).

Scheme 5. Synthesis of Dihydro Bis(–)-Menthoxy Acetic Esters of 5-FluoroB*c*Ph



The diastereomeric mixture of bis(–)-menthoxyacetic esters (bis-MMA esters) derivatives **37** was obtained in 72% yield (Scheme 5) and was subjected to silica gel column chromatography using 230-400 mesh. Elution with 8% diethyl ether in cyclohexane gave separation of only a portion of the early eluting isomer (–)-**37a** ($[\alpha]_D$ = –230.0 at C = 0.18) (see Figure 7). Late eluting isomer **37b** could not be separated and was collected as a mixture with (–)-**37a**.

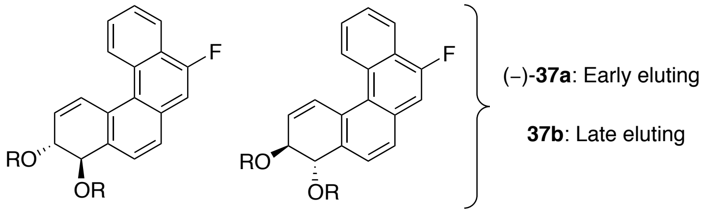


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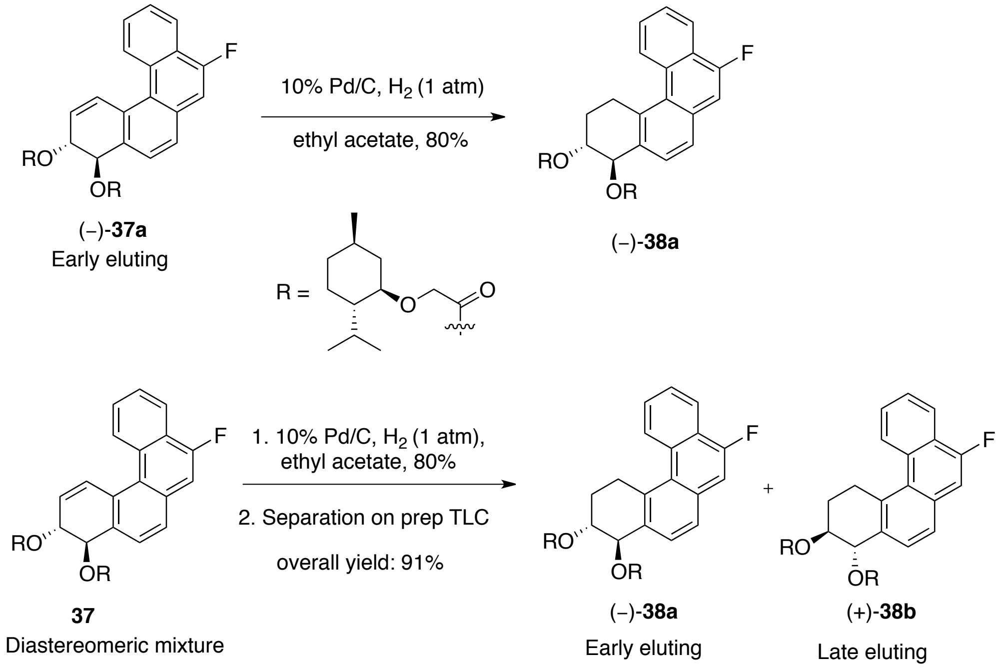
Figure 7. Early and late eluting isomers of bis(-)-menthoxyacetic esters derivatives **37**.

Early eluting isomer (–)-**37a** was subjected to reduction using 5% Pd/C and H_2 (1 atm) to obtain the tetrahydro bis-MMA ester derivative (–)-**38a** in 80% yield (Scheme 6, upper part).

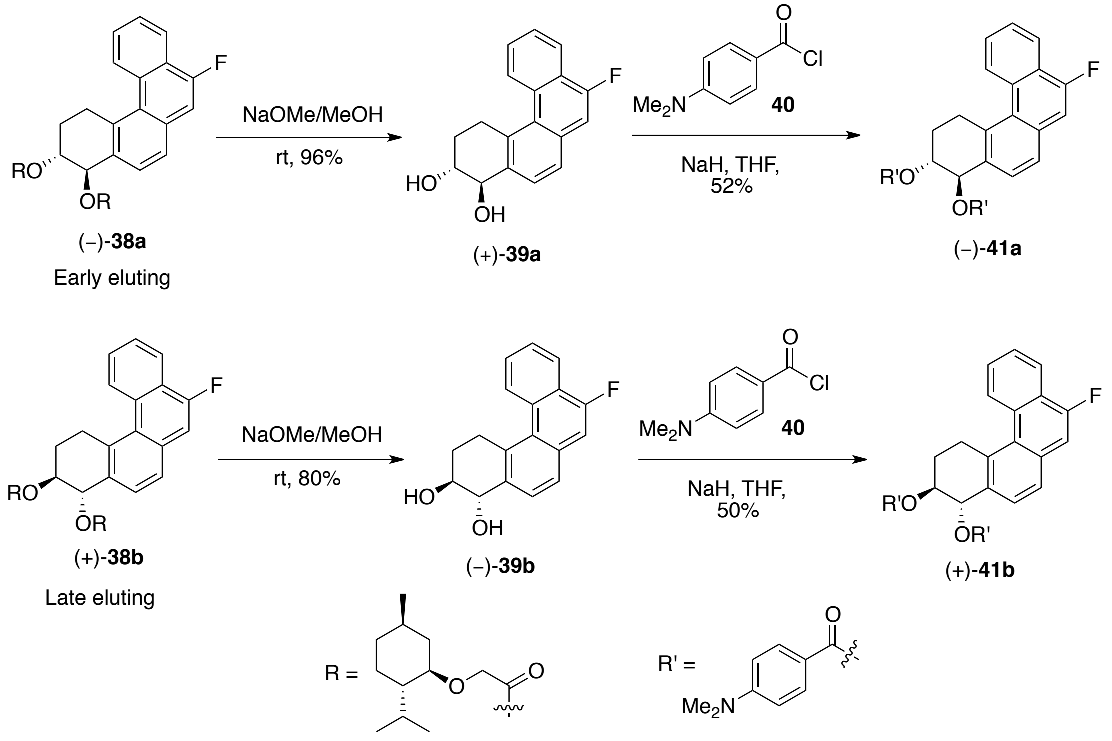
Scheme 6. Synthesis of Tetrahydro Bis(–)-Menthoxy Acetic Esters



When the diasteromeric mixture of dihydro bis-MMA ester **37** was reduced using the same condition (Scheme 6, lower part), the tetrahydro bis-MMA ester diasteromers (–)-**38a** and (+)-**38b** showed a better separation on TLC and could be separated on a preparative TLC plate using 1000 micron silica gel plate and 5% EtOAc in hexanes as eluent. The overall combined yield of the reaction was 91%. The early eluting isomer (–)-**38a** ($[\alpha]_D = -138.8$ at C = 0.47) was obtained as a colorless sticky liquid, where as the late eluting isomer (+)-**38b** ($[\alpha]_D = +15.9°$ at C = 0.27) was a white solid. To be insure that the elution order of the isomers of diastereomeric mixture of dihydro bis-MMA esters **37** does not change upon reduction, the sign of rotation of the early eluting reduced isomer (–)-**38a** was compared with the reduced product of the optically pure dihydro bis-MMA ester (–)-**37a**. The same sign of rotation (negative value) of the two confirmed that the elution order of diastereomers did not change upon reduction.

Removal of esters in the early eluting isomer of tetrahydro bis-MMA ester (–)-**38a** using a catalytic amount of NaOMe in MeOH provided the free tetrahydrodiol derivative (+)-**39a** ($[\alpha]_D$= +13.3° at C = 0.4) in 96% yield (Scheme 7).[54] The sign of optical rotation was changed upon removal of the esters and that was consistent with tetrahydrodiol of unsubstituted B*c*Ph as reported by Jerina et al.[54]

Scheme 7. Synthesis of Bis(*p*-*N,N*-dimethylamino)benzoate Derivatives



Thus, the absolute configuration of the early eluting dihydro bis-MMA ester derivative

Similarly, removal of the ester groups of the late eluting isomer (+)-**38b** using the same conditions provided the corresponding tetrahydrodiol derivative (–)-**39b** ($[\alpha]_D$= −11.5° at C = 0.4) in 80% yield (Scheme 7). Compounds (+)-**39a** and (–)-**39b** were converted to bis(*p*-*N,N*-dimethylamino)benzoate derivatives (–)-**41a** and (+)-**41b** respectively by their reactions with *p*-(*N,N*-dimethylamino)benzoyl chloride **40** using NaH in THF (Scheme 7). The products were obtained in yields 52% and 56% respectively. CD spectrum of isomer (–)-**41a** that was derived from the early eluting diastereomer (–)-**37a** of dihydro bis-MMA esters, showed a negative band at 323 nm was zero at 309 nm and showed a strong positive band at 298 nm. This indicates the (*R,R*)-absolute configuration for the bis ester derivative (–)-**41a** and the eluting diastereomer (–)-**37a** of dihydro bis-MMA esters.

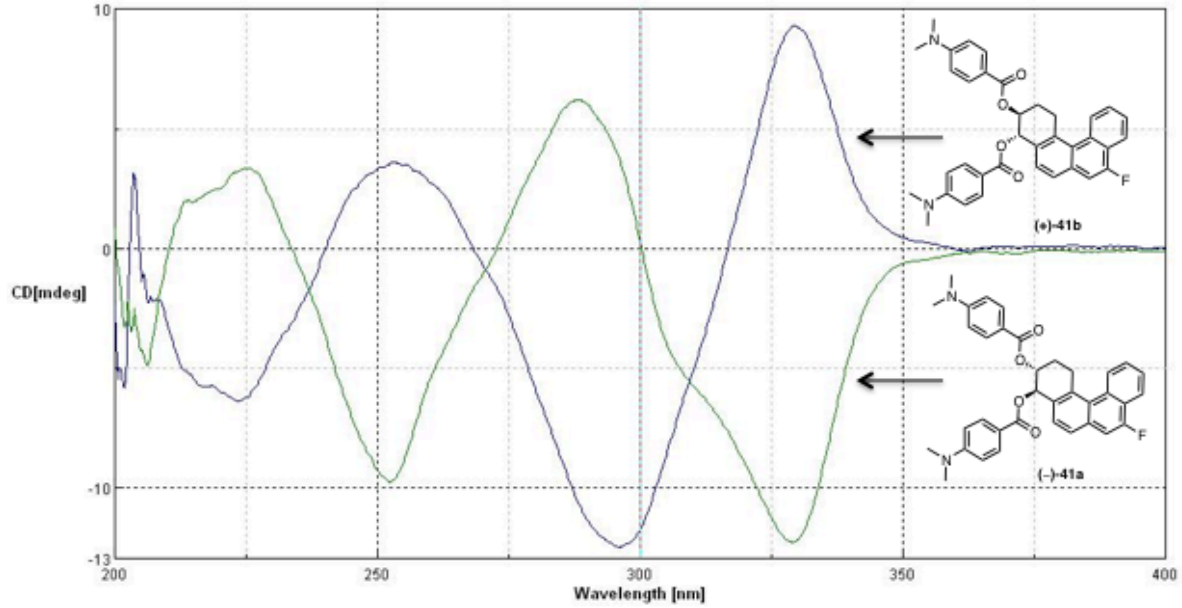


Figure 8. CD spectra of Bis (*p-N,N*-dimethylamino)benzoate ester of 3,4-dihydroxy-1,2,3,4-tetrahydro 5-FBcPh [(–)-**41a** and (+)-**41b**].

CD spectrum of compound (+)-**41b** showed a strong positive band at 323 nm was zero at 309 nm and a strong negative band at 298 nm. This indicates the (*S,S*)-absolute configuration for the bis ester derivative (+)-**41b**. The CD spectra of (–)-**41a** and (+)-**41b** are shown in Figure 8. The conformational analysis of compound (–)-**41a** was performed on the basis of coupling constants of H9, H10 and H11 protons. The choice of 141° dihedral angle between H9 and H10 originates from analysis of the H-10 resonance. The observed pattern of H-10 is ddd, with *J* = 3.2, 5.5, and 8.3 Hz. The 5.5 Hz corresponds to H9-H10 coupling. Therefore, 3.2 Hz and 8.3 Hz couplings must be due to

H10-H11$_{eq}$ and H10-H11$_{ax}$ coupling, respectively. This would result in a nearly 20° dihedral angle between H10 and H11$_{ax}$. In the alternative conformation resulting from the same 5.5 Hz value for H9-H10 coupling, where the dihedral angle is 34° between H9 and H10, H10 would show no large *J* value, since H9, H10, H11$_{ax}$ and H11$_{eq}$ are all staggered (Figure 8, bottom). Therefore, the conformer with the larger, 141° H9-H10 dihedral angle, was selected (Figure 8, top). In this conformation the substituents are not predominantly diequatorial, but are *clearly not* diaxial.

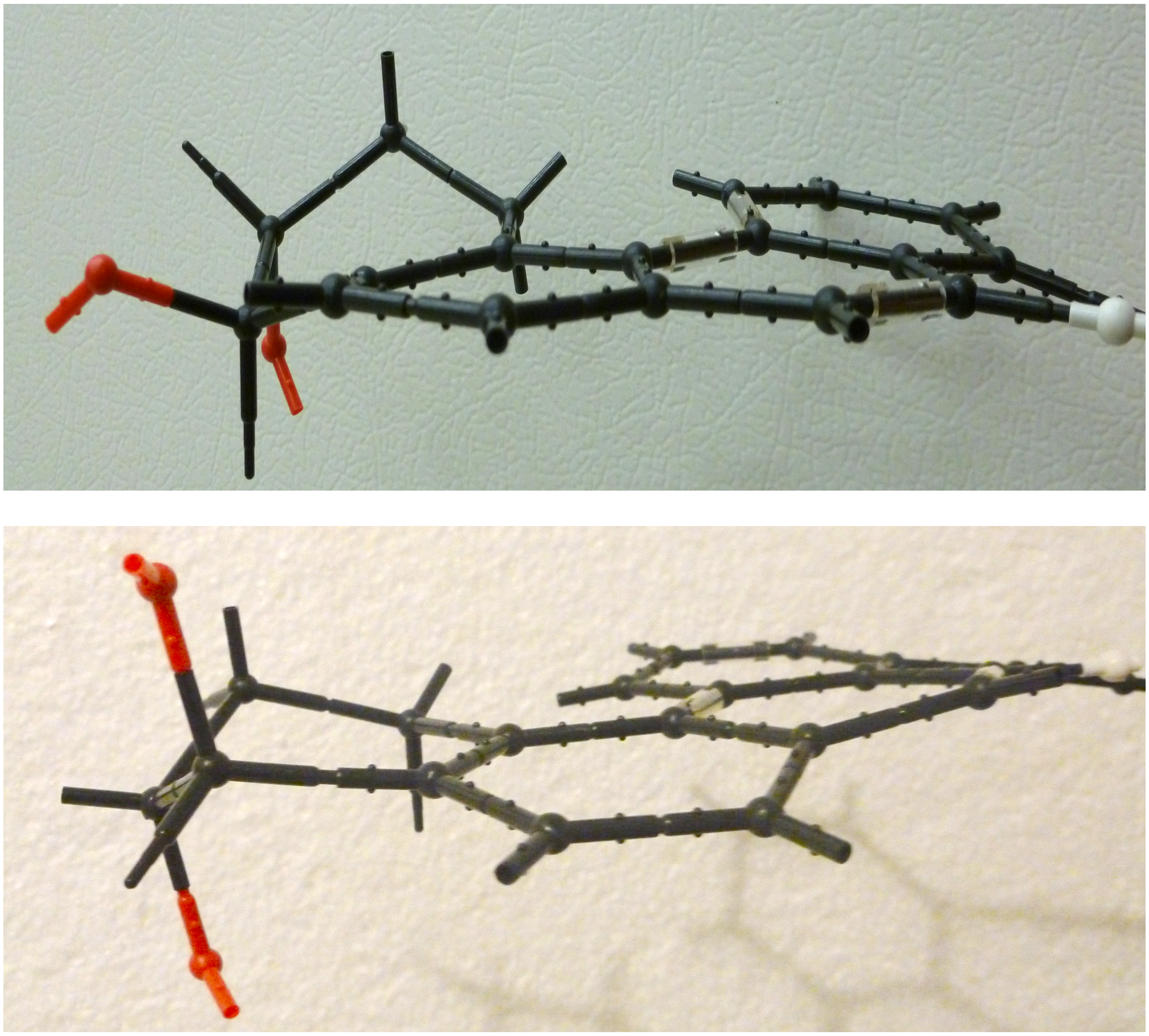


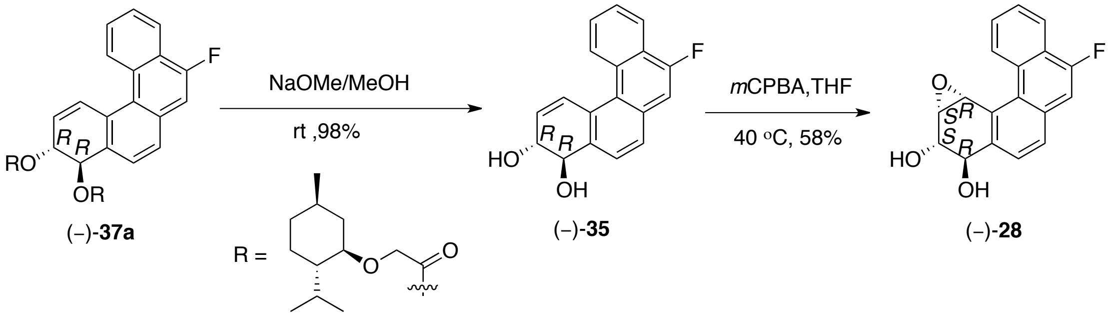
Figure 9. Possible conformations of *p*-(*N,N*-dimethylamino)benzoates in (–)-**41a**.

(–)-**37a** was 9*R,*10*R* and the removal of esters from (–)-**37a** can provide an access to enantiomerically pure 9*R,*10*R* isomer of dihydrodiol **35** that can be converted to enantiopure diol epoxide derivatives.

2.2.3 Synthesis of Optically Pure Series 2 Diol-Epoxide and its dA-Adduct

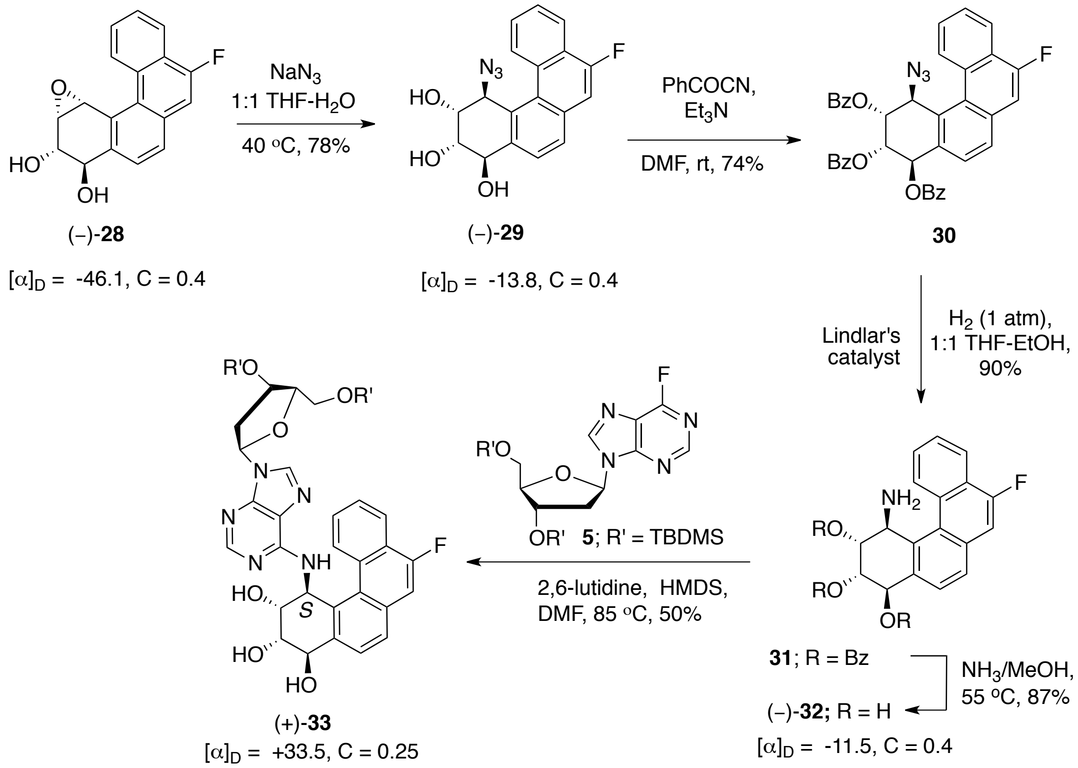
The early eluting isomer (–)-**37a** was converted to optically pure *trans* dihydrodiol derivative (–)-**35** ($[\alpha]_D$ = –41.1° at C = 0.6) by removal of esters using catalytic amount of NaOMe in methanol, in 98% yield (Scheme 8).[54] *m*CPBA oxidation in THF resulted in optically pure 9*R,*10*S*,11*S*,12*R* diol epoxide (–)-**28** ($[\alpha]_D$ = –46.1° at C = 0.4) in 58% yield (Scheme 8).

Scheme 8. Synthesis of Optically Pure *R,R*-Dihydrodiol and *R,S,S,R*-Diol Epoxide



This Diol epoxide isomer (–)-**28** was converted to the dA adduct of 5-fluoro-B*c*Ph **33** as shown in Scheme 9, using the same reaction sequence as was used for conversion of racemic diol epoxide **28** (Scheme 4).

Scheme 9. Synthesis of dA Adduct of Optically Pure Diol Epoxide



CD spectrum of (+)-**33** showed a positive band at 244 nm which matched the CD spectrum of the early eluting **33a** obtained from the racemic diol epoxide (±)-**28**. Since (+)-**33** was obtained from optically pure *R,S,S,R* diol epoxide, using highly stereoselective azide *trans* ring opening and following the synthetic sequence where no scrambling of stereochemistry has been observed, the absolute configuration of the adduct **33** and **33a** should be 9*R*,10*S*,11*R*,12*S*.

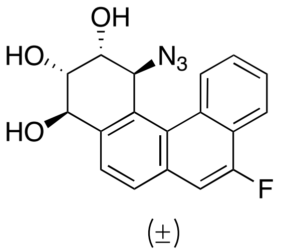
2.3 CONCLUSION

A 2′-deoxyadenosine adduct of series 2 diol epoxide of 5-fluorobenzo[*c*]phenanthrene was synthesized by a total synthesis approach. The requisite aminotriol derivative was obtained by *trans* ring opening of epoxide by the azide followed by reduction of the azide of azido triol derivative to amine. Protection of alcohols as benzoates was critical for the reduction. Removal of benzoates provides the amino triaol derivative that upon S_NAr reaction with TBDMS protected 6-fluoropurine-2'-deoxyriboside gave diastereomeric mixture of dA adducts of 5FB*c*Ph. Separation of distereomers by preparative TLC provide access to the pure diastereomers. CD spectra of the two isomers indicated *S* absolute configuration for early eluting and *R* absolute configuration for late eluting isomer at the carbon atom of B*c*Ph that is bonded to nucleoside. Racemic dihydrodiol derivative was resolved by converting to bis(–)-menthoxyacetic esters derivative and the absolute configuration to the dihydrodiol was assigned by CD spectroscopy. The resolved dihydrodiol isomer with *R,R* absolute configuration at the carbons bearing hydroxyl groups, was converted to stereochemically defined *R,S,S,R* diol epoxide isomer. Stereoselective *trans* ring opening of this diol epoxide isomer followed by steps, provided an access to a single isomer of dA adduct of 5-F-B*c*PhDE-2 with *S*-configuration at the site of attachment to dA. Comparison of CD spectra of this single isomer with the separated adduct diastereomers obtained from the racemic dihydrodiol, indicated that the first eluting diasteromer was derived from *R,R* dihydrodiol and *R,S,S,R* diol epoxide isomers.

EXPERIMENTAL SECTION

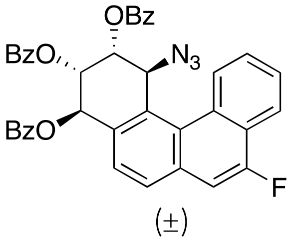
For reactions, which were performed under a nitrogen atmosphere, glassware was dried with hot gun under vacuum. THF was distilled over $LiAlH_4$, and then over sodium. All other reagents were obtained from commercial sources and used without further purification. Thin layer chromatography was performed on 250 µm silica plates and column chromatographic purifications were performed on silica gel. The mesh size of silica gel and the eluting solvents are reported for each compound separately. ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$, acetone-d_6 dmso- d_6. ^{13}C specta were recorded at 125 MHz using $CDCl_3$, acetone-d_6 and dmso- d_6. ^{19}F NMR spectra were recorded at 282 MHz using $CFCl_3$ as internal standard. Chemical shifts (δ) are reported in parts per million and coupling constants (J) are in hertz.

1-Azido-8-fluoro-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene-2,3,4-triol [(±)-29]



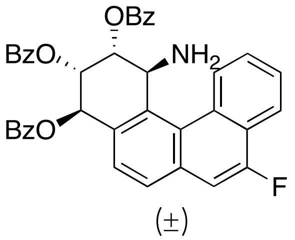
Diol epoxide (±)-**28** (0.085 g, 0.286 mmol) was dissolved in THF (19.5 mL) and then (19.5 mL) water was added followed by addition of sodium azide (0.283 g, 4.3 mmol). Reaction mixtures was stirred at 40 °C for 90 h. All diol epoxide was consumed at this time. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. Combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. White solid obtained as a crude mixture was washed with cold ether (2 mL X 2) to obtain the 0.084 g (86%) yield of pure azido triol (±)-**29** as white powder. R_f (silica, 5% MeOH in methylene chloride) = 0.13. ^{1}H NMR (500 MHz, acetone-d_6): δ 9.02 (d, 1H, Ar-H, J = 8.8 Hz), 8.26 (d, 1H, Ar-H, J = 8.3 Hz), 8.01 (d, 1H, Ar-H, J = 8.3 Hz), 7.95 (d, 1H, Ar-H, J = 8.3 Hz), 7.86 (td, 1H, Ar-H, J = 8.3, 1.5 Hz), 7.80 (t, 1H, Ar-H, J = 7.6 Hz), 7.59 (d, 1H, Ar-H, J = 11.1 Hz), 5.75 (d, 1H, J = 5.5 Hz), 4.96-4.95 (m, 2H), 4.62 (br s, 1H, OH), 4.50 (br s, 1H, OH), 4.36 (dd, 1H, J = 6.0, 2.3 Hz), 4.24 (dd, 1H, J = 6.0, 2.3 Hz). ^{13}C NMR (125 MHz, acetone-d_6): δ 157.4 (d, J_{CF} = 250.4 Hz), 140.2, 134.0 (d, J_{CF} = 10.1 Hz), 132.8 (d, J_{CF} = 4.1 Hz), 130.6 (d, J_{CF} = 5.0 Hz), 129.4, 128.6 (d, J_{CF} = 2.8 Hz), 128.3, 128.2, 127.8, 126.1 (d, J_{CF} = 17.4 Hz), 121.7 (d, J_{CF} = 7.8 Hz), 109.6 (d, J_{CF} = 20.1 Hz), 74.1, 73.2, 73.0, 64.9. ^{19}F NMR (282 MHz, acetone-d_6): −126.15 (d, $^2J_{FH}$ = 12.2 Hz). HRMS (ESI) calcd. for $C_{18}H_{14}FN_3NaO_3$ $[M+Na]^+$, 362.0911, found 362.0910.

1-Azido-8-fluoro-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene-2,3,4-triyl tribenzoate [(±)-30]



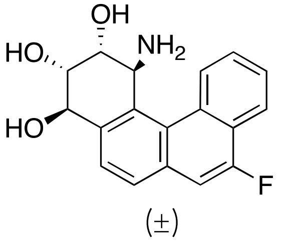
Azido triol (±)-**29** (0.080 g, 0.236 mmol, 1.0 molar equiv) was dissolved in DMF (14.6 mL) in a 50 mL dry rb flask equipped with magnetic stirrer and dry Et_3N (0.330 mL, 2.36 mmol, 10.0 molar equiv) and benzoyl cyanide (0.309 g, 2.36 mmol, 10.0 molar equiv) were added in the order and the reaction mixture (a light green solution) was stirred at room temperature for 2 h. TLC showed disappearance of azido trioal at this time. 10 mL sat solution of $NaHCO_3$ was added followed by addition of EtOAc (15-20 mL). The organic layer was separated and the aqueous layer was extracted three times with EtOAc. Combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography (silica gel mesh 200-300, eluent: 20% ethyl acetate in hexanes). Yield of (±)-**30**: 0.127 g (82%, a pale yellow solid). R_f (20% EtOAc in hexanes) = 0.44. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.02 (d, 1H, Ar-H, J = 8.3 Hz), 8.31 (d, 1H, Ar-H, J = 7.8 Hz), 8.14 (d, 2H, Ar-H, J = 7.8 Hz), 7.97 (d, 1H, Ar-H, J = 7.8 Hz), 7.94 (d, 1H, Ar-H, J = 8.3 Hz), 7.86 (t, 1H, Ar-H, J = 7.8 Hz), 7.80-7.72 (m, 4H, Ar-H), 7.58 (t, 1H, Ar-H, J = 7.3 Hz), 7.53-7.47 (m, 2H, Ar-H), 7.46 (t, 2H, Ar-H, J = 7.3 Hz), 7.41 (d, 1H, Ar-H, J = 10.8 Hz), 7.37 (t, 2H, Ar-H, J = 7.3 Hz), 7.32 (t, 2H, Ar-H, J = 7.8 Hz), 7.13 (d, 1H, J = 7.3 Hz), 6.34 (dd, 1H, J = 7.3, 2.4 Hz), 6.17 (dd, 1H, J = 4.4, 2.9 Hz), 5.92 (d, 1H, J = 4.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): Please note: in the region 134.3-126.4 only listing of resonances is provides, due to overlapping signals and no attempts were made to determine coupling with F. δ 166.7, 165.8, 165.6, 157.7 (d, J_{CF} = 254.5 Hz), 134.3, 134.2, 134.1, 133.8, 133.7, 133.6, 131.5, 131.5, 131.19, 131.26, 130.3, 130.1, 129.9, 129.5, 129.4, 129.1, 128.8, 128.7, 128.5, 128.0, 127.5, 127.1, 126,4, 126.0 (d, J_{CF} = 17.4 Hz), 121.9 (d, J_{CF} = 7.8 Hz), 108.8 (d, J_{CF} = 19.2 Hz), 72.9, 71.8, 70.6, 60.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ −123.76 (d, $^2J_{FH}$ = 12.2 Hz). HRMS (ESI) calcd. for $C_{39}H_{26}FN_3NaO_6$ $[M+Na]^+$, 674.1698, found 674.1722.

1-Amino-8-fluoro-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene-2,3,4-triyl tribenzoate [(±)-31]



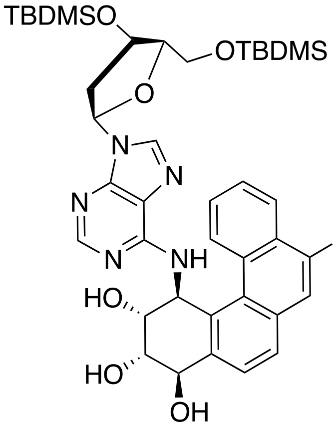
Azido tribenzoate (±)-**30** (0.078 g, 0.120 mmol) was dissolved in 1:1 ethanol/THF (32 mL) in a two-neck flask. Lindlar catalyst (310 mg) was added and the reaction mixture was degassed and filled with hydrogen gas. This was repeated three times. Mixture was stirred for 5 hours under hydrogen gas. Mixture was filtered through celite with the aid of 15-20 ml ethyl acetate. The filterate was concentrated and the crude mixture was purified by column chromatography (silica gel mesh 200-300, eluent : 20% ethyl acetate in hexanes). Yield of (±)-**31**: 0.061 g (81%, a light yellow foam). R_f(20% EtOAc in hexanes) = 0.29. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.66 (d, 1H, Ar-H, J = 8.5 Hz), 8.27 (d, 1H, Ar-H, J = 7.9 Hz), 8.15 (d, 2H, Ar-H, J = 7.6 Hz), 7.99 (d, 2H, Ar-H, J = 7.6 Hz), 7.86 (d, 1H, Ar-H, J = 8.6 Hz), 7.81 (t, 1H, Ar-H, J = 7.8 Hz), 7.76-7.69 (m, 4H, Ar-H), 7.57 (t, 1H, Ar-H, J = 7.3 Hz), 7.51 (t, 1H, Ar-H, J = 7.3 Hz), 7.48-7.44 (m, 3H, Ar-H), 7.38-7.35 (m, 3H, Ar-H), 7.30 (t, 2H, Ar-H, J = 7.6 Hz), 7.06 (d, 1H, J = 7.6 Hz), 6.70 (dd, 1H, J = 7.5, 2.6 Hz), 6.08 (dd, 1H, J = 4.2, 2.5 Hz), 5.49 (d, 1H, J = 4.3 Hz), 2.30 (br s, 2H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$): Please note: in the region 134.3-127.1 only listing of resonances is provides, due to overlapping signals and no attempts were made to determine coupling with F. δ 166.8, 166.2, 166.0, 157.5 (d, J_{CF} = 254.5 Hz), 134.3, 134.2, 133.8, 133.6, 133.41, 133.39, 132.89, 132.86, 132.13, 131.09, 130.2, 130.1, 131.0, 129.9, 129.8, 129.70, 129.66, 129.5, 129.4, 129.1, 128.8, 128.7, 128.6, 128.1, 128.0, 127.2, 127.1, 126.4 (d, J_{CF} = 16.9 Hz), 121.4 (d, J_{CF} = 7.8 Hz), 108.9 (d, J_{CF} = 20.1 Hz), 75.8, 73.3, 70.8, 52.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ −124.9 (d, $^{2}J_{FH}$ = 12.2 Hz). HRMS (ESI) calcd. for $C_{39}H_{29}FNO_6$ $[M+H]^+$, 626.1973, found 626.1973.

1-Amino-8-fluoro-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene-2,3,4-triol [(±)-32]



In a 25 mL rb flask, a solution of amino tribenzoate (±)-**31** (0.054g, 0.086 mmol) in methanol saturated with ammonia was stirred at 55 °C for 12 h. TLC showed the disappearance of starting material. Solvent was removed under reduced pressure and the crude mixture was washed with diethyl ether (2 mL X 3) to obtain 20.4 mg (80%) of pure amino triol (±)-**32** as a dirty yellowish powder. R_f(10% methanol in methylene chloride) = 0.14. ^{1}H NMR (500 MHz, dmso-d_6): δ 9.99-9.97 (m, 1H, Ar-H), 8.16-8.14 (m, 1H, Ar-H), 7.89 (d, 1H, Ar-H, J = 8.3 Hz), 7.80 (d, 1H, Ar-H, J = 8.3 Hz), 7.77-7.74 (m, 2H, Ar-H), 7.63 (d, 1H, Ar-H, J = 11.2 Hz), 5.39 (br s, 1H, OH), 4.82 (d, 1H, J = 5.9 Hz), 4.69 (d, 1H, J = 2.9 Hz), 4.65 (d, 1H, J = 3.9 Hz), 4.56 (d, 1H, J = 6.8 Hz), 4.35-4.32 (m, 1H), 4.01 (app q, 1H, $J_{app} \approx 3.4$ Hz), 2.32 (br s, 2H, NH_2). ^{13}C NMR (125 MHz, dmso-d_6): δ 155.5 (d, J_{CF} = 248.5 Hz), 139.4, 134.3, three rasonances at 131.95, 131.92, 131.84 for two C, 130.3, 128.3, 127.62, 127.59, 127.0, 126.5, 124.3 (d, J_{CF} = 16.9 Hz), 119.8 (d, J_{CF} = 7.3 Hz), 108.7 (d, J_{CF} = 18.8 Hz), 75.7, 72.7, 70.4, 54.7. ^{19}F NMR (282 MHz, dmso-d_6): δ −127.03 (d, $^{2}J_{FH}$ = 9.2 Hz). HRMS (ESI) calcd. for $C_{18}H_{17}FNO_3$ $[M+H]^+$, 314.1187, found 314.1212.

Synthesis of 5-FB*c*PhDE-dA adducts 33 from (±)-32



In a small size dry vial, amino triol (±)-**32** (12.5 mg, 0.40 mmol, 1.0 molar equiv) and fluoronucleoside **5** (38.6 mg, 0.080 mmol, 2.0 molar equiv) were dissolved in DMF (0.800 mL) under N_2 atmosphere. 2,6-Lutidine (20 microliter) and hexamethyl disiloxane (HMDS) (0.500 mL) were added sequentially. Vial was filled with N_2 and the reaction mixture was stirred vigrously at 85 °C. Reaction was monitored by TLC and after 15 h, when some amino triaol was left unreacted, more of fluoronucleoside (19.0 mg, 0.040 mmol, 1 molar equiv) was added and stirring was continued at this temperature for next 7 h. Amino triol was still observed in the reaction mixture on the TLC. Reaction mixture was diluted with 15 mL ethyl acetate and 5 mL water was added. Organic layer was separated. Aqueous layer was extracted one more time with ethyl acetate. Combined organic layer was wahsed with water and brine and then dried over Na_2SO_4. Solvent was removed under reduced pressure. The crude reaction mixture (89.0 mg) was loaded on preparative TLC (silica gel, 1000 micron) and developed in mixture solvent containing 7% MeOH, 43% EtOAc, 50% hexanes. Three fractions were collected as follows: pure early eluting isomer (6.0 mg, white solid), late eluting isomer (2.8 mg, white solid) and a mixture of early and late eluting isomers (8.8 mg, white solid).

Combined yield of **33**: 17.6 mg (57%). HRMS (ESI) calcd. for $C_{40}H_{55}FN_5O_6Si_2$ $[M+H]^+$, 776.3669, found 776.3669.

Early eluting diastereomer of 5-FB*c*Ph-dA adduct (+)-33a

R_f(10% methanol in methylene chloride) = 0.33. Specific rotation $[\alpha]_D$ = +29.3 at conc. 0.40 g/100 mL (solvent: THF).

^{1}H NMR assignments are based upon the 2D-NMR (NOESY and COSY) analysis.

^{1}H NMR (600 MHz, acetone-*d*$_6$): δ 8.83 (d, 1H, Ar-H, H-1, *J* = 8.4 Hz), 8.55 (s, 1H, Ar-H, H-2″), 8.18-8.15 (m, 2H, Ar-H, H-8″ and H-4), 7.89 (s, 2H, Ar-H, H-8 and H-7), 7.61 (t, 1H, Ar-H, H-3, *J* = 7.5 Hz), 7.52 (d, 1H, Ar-H, H-6, *J* = 11.4 Hz), 7.34-731 (m, 2H, H-2 and NH), 6.59 (br s, H-12), 6.49 (t, 1H, H-1′, *J* = 6.3), 5.01 (br s, 1H, OH), 4.96 (d, 1H, H-9, *J* = 6.7), 4.81-4.78 (m, 1H, H-3′), 4.65 (br s, 1H, H-11), 4.41 (dd, 1H, H-10, *J* = 6.7, 2.6 Hz), 4.38 (br s, 1H, OH), 4.29 (br s, 1H, OH), 4.01-3.98 (m, 1H, H-4′), 3.93 (dd, 1H, H-5′, *J* = 11.3, 5.7 Hz), 3.80 (dd, 1H, H-5′, *J* = 10.8, 3.5 Hz), 3.02 (app quint, 1H, H-2′, J_{app} =6.4 Hz), 2.47 (ddd, 1H, H-5′, *J* = 13.0, 6.0, 4.0 Hz), 0.97 (s, 9H, *t*-Bu), 0.90 (s, 9H, *t*-Bu), 0.18 (s, 6H, 2Si-CH_3), 0.08 (s, 3H, Si-CH_3), 0.06 (s, 3H, Si-CH_3).

^{19}F NMR (282 MHz, dmso-*d*$_6$): δ −127.03 (d, $^2J_{\text{FH}}$ = 9.2).

Late eluting diastereomer of 5-FB*c*Ph-dA adduct (−)-33b

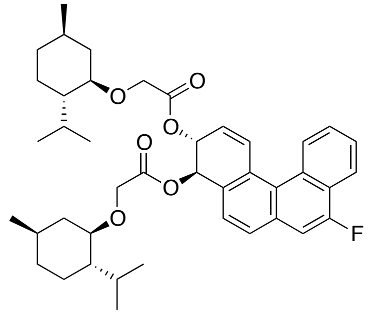
R_f(10% methanol in methylene chloride) = 0.33. Specific rotation $[\alpha]_D$ = −61.1 at conc. 0.40 g/100 mL (solvent: THF).

^{1}H NMR assignments are based upon the 2D-NMR (NOESY and COSY) analysis.

^{1}H NMR (600 MHz, acetone-*d*$_6$): δ 8.85 (d, 1H, Ar-H, H-1, *J* = 8.2 Hz), 8.55 (s, 1H, Ar-H, H-2″), 8.17 (d, 1H, Ar-H, H-4, *J* = 7.9 Hz), 8.11 (s, 1H, Ar-H, H-8″), 7.94 (AB q, 2H, Ar-H, H-8 and H-7, *J* =8.2 Hz), 7.62 (t, 1H, Ar-H, H-3, *J* = 7.3 Hz), 7.55 (d, 1H, Ar-H, H-6, *J* = 11.1 Hz), 7.33 (t, 1H, Ar-H, H-2, *J* = 7.0 Hz), 7.27 (d, 1H, Ar-H, NH, *J* = 7.0 Hz), 6.61 (br s, H-12), 6.48 (t, 1H, H-1′, *J* = 6.3), 5.00 (d, 1H, H-9, *J* = 6.7), 4.86 (br s, 1H, OH), 4.80-4.78 (m, 1H, H-3′), 4.66 (br s, 1H, H-11), 4.41 (dd, 1H, H-10, *J* = 6.9, 2.8 Hz), 4.37 (br s, 1H, OH), 4.24 (br s, 1H, OH), 4.01-3.99 (m, 1H, H-4′), 3.93 (dd, 1H, H-5′, *J* = 11.1, 5.3 Hz), 3.83 (dd, 1H, H-5′, *J* = 11.0, 4.0 Hz), 2.99 (app quint, 1H, H-2′, J_{app} =6.4 Hz), 2.46 (ddd, 1H, H-5′, *J* = 13.0, 6.0, 4.0 Hz), 0.97 (s, 9H, *t*-Bu), 0.89 (s, 9H, *t*-Bu), 0.19 (s, 6H, 2Si-CH_3), 0.08 (s, 3H, Si-CH_3), 0.05(s, 3H, Si-CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ −126.82 (d, $^2J_{FH}$ = 12.2).

8-Fluoro-3,4-dihydrobenzo[*c*]phenanthrene-3,4-diyl bis{2-[((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy]acetate} (37)



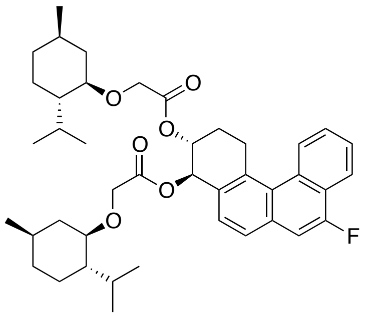
In a 10 mL dry flask, dihydrodiol (±)-**32** (25 mg, 0.089 mmol) and (−)-menthoxyacetyl chloride **36** (82.9 mg, 0.356 mmol, 4.0 molar equiv) were dissolved in anhydrous pyridine (2 mL) at 5 °C under N_2 and the reaction mixture was stirred at this temperature for 15 h. Reaction mixture was then diluted with ethyl acetate (15 mL) and water (3-4 mL) was added. Organic layer was separated and aqueous layer was extracted three times with ethyl acetate. Combined organic layer was wahsed with water and brine and then dried over Na_2SO_4. Solvent was removal under reduced pressure gave a yellow oil that was subjected to column chromatography (silica gel mesh 200-300, eluent: 5-10% EtOAc in hexanes). Compound **37** was obtained as the mixture of disatereomers in 43.1 mg (72%) yield as white solid.

Some portion of the early eluting diastereomer was separated by column chromatography using silica gel mesh size 230-400 and eluting with 8% ethyl ether in cyclohexane. R_f (5% EtOAc in hexanes) = 0.36. Specific rotation $[\alpha]_D = -230$ at conc. 0.18 g/100 mL (solvent: THF). HRMS (ESI) calcd. for $C_{40}H_{53}FNaO_6$ $[M+Na]^+$, 695.3718, found 695.3748.

^{1}H and ^{19}F NMR data of the early eluting isomer is given below:

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (d, 1H, Ar-H, J = 7.3 Hz), 8.22 (dd, 1H, Ar-H, J = 8.3, 2.0 Hz), 7.72 (d, 1H, Ar-H, J = 8.3 Hz), 7.72-7.66 (m, 2H, Ar-H), 7.57-7.54 (m, 2H, Ar-H), 7.30 (d, 1H, Ar-H, J = 10.7 Hz), 6.38 (d, 1H, Ar-H, J = 5.9 Hz), 6.32 (dd, 1H, J = 10.3, 4.4 Hz), 5.71 (t, 1H, J = 5.1 Hz), 4.21-4.07 (m, 4H), 3.19-3.13 (m, 2H), 2.32-2.22 (m, 2H), 2.03 (d, 2H, J = 12.2 Hz), 1.67-1.57 (m, 4H), 1.37-1.24 (m, 4H), 0.98-0.79 (m, 18H), 0.77 (d, 3H, J =6.8 Hz), 0.73 (d, 3H, J = 6.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170.5, 157.5 (d, J_{CF} = 253.6 Hz), 133.6 (d, J_{CF} = 10.1 Hz), 131.5, 131.4 (d, J_{CF} = 5.0 Hz), 130.1, 129.8, 128.9, 128.4 (d, J_{CF} = 5.0 Hz), 127.2, 127.0 (d, 2C, J_{CF} = 13.7 Hz), 126.1, 125.8 (d, J_{CF} = 18.3 Hz), 123.2, 121.4 (d, J_{CF} = 6.4 Hz), 108.1(d, J_{CF} = 20.1 Hz), 80.7, 80.5, 71.5, 68.9, 66.2, 66.0, 48.3, 40.2, 40.2, 40.1, 34.5 (2C), 31.7, 31.6, 29.9, 25.7, 23.5, 22.5, 21.2, 21.1, 16.5, 16.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ −124.89 (d, $^2J_{FH}$ = 12.2).

8-Fluoro-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene-3,4-diyl bis(2-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}acetate) (38)



In a two-neck flask compound **37** (80 mg, 0.120 mmol) was dissolved in ethyl acetate (2.0 mL) and 5% Pd/C (16.0 mg) was added. Reaction mixture was degassed and filled with hydrogen gas. This procedure was repeated three times and then the suspension was stirred for 3 h under hydrogen gas. Mixture was filtered through Celite with the aid of 8-10 ml ethyl acetate. The removal of solvent under reduced pressure provided **38** as the mixture of diastereomers (yield: 73.3 mg, 91%) as a colorless sticky solid that was subjected to preparative TLC. Diastereomeric mixture was loaded on two silica gel preparative TLC plates (1000 micron) that were developed 5 times in 5% EtOAc in hexanes mobile phase. The early eluting isomer (−)**-38a** was obtained 27 mg (a white solid), and late eluting isomer (+)**-38b** was obtained 32 mg (a white solid). ^{1}H, ^{19}F and ^{13}C data for the two isomers is give below:

Early eluting isomer (−)-38a:

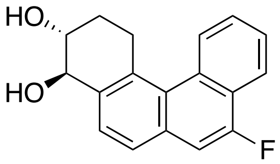
R

R_f (5% EtOAc in hexanes) = 0.30. Specific rotation: $[\alpha]_D = -138.8$ at conc. 0.47 g/100 mL (solvent: THF). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.77-8.73 (m, 1H, Ar-H), 8.28-8.24 (m, 1H, Ar-H), 7.72-7.68 (m, 3H, Ar-H), 7.48 (d, 1H, Ar-H, J =7.8 Hz), 7.33 (d, 1H, Ar-H, J = 10.7 Hz), 6.43 (d, 1H, J = 4.9 Hz), 5.42 (ddd, 1H, J = 8.6, 5.1, 3.6 Hz), 4.22-4.11 (m, 4H), 3.73-3.63 (m, 2H), 3.21-3.16 (m, 2H), 2.34-2.25 (m, 3H), 2.06 (d, 3H, J = 12.7 Hz), 1.67-1.60 (m, 4H), 1.39-1.25 (m, 4H), 1.01-0.82 (m, 18H), 0.79 (d, 3H, J =6.8 Hz), 0.76 (d, 3H, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 170.6, 157.3 (d, J_{CF} = 252.7 Hz), 135.9, 133.2 (d, J_{CF} = 10.1 Hz), 132.5 (d, J_{CF} = 5.0 Hz), 131.5, 128.4, 128.3, three rasonances at 127.59, 127.58 and 127.54 (2C), 126.8, 126.7, 125.9 (d, J_{CF} = 17.9 Hz), 121.4 (d, J_{CF} = 7.8 Hz), 108.7 (d, J_{CF} = 20.1 Hz). 80.7, 80.6, 73.0, 72.2, 66.3, 66.2, 48.4, 48.3, 40.3, 40.2, 34.6 (2C), 31.71, 31.69, 29.6, 27.0, 25.8, 25.7, 23.5, 22.51, 22.47, 21.18, 21.17, 16.54, 16.49. ^{19}F NMR (282 MHz, $CDCl_3$): δ −125.36 (d, $^2J_{FH}$ = 9.2). HRMS (ESI) calcd. for $C_{42}H_{56}FO_6$ $[M+H]^+$, 675.4055, found 675.4055.

Late eluting isomer (+)-38b:

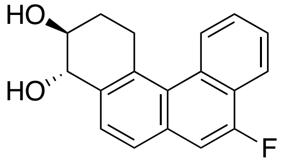
R_f (5% EtOAc in hexanes) = 0.27. Specific rotation $[\alpha]_D$ = +15.9° at conc. 0.27 g/100 mL (solvent: THF). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.76-8.73 (m, 1H, Ar-H), 8.28-8.24 (m, 1H, Ar-H), 7.72-7.68 (m, 3H, Ar-H), 7.48 (d, 1H, Ar-H, J =7.8 Hz), 7.33 (d, 1H, Ar-H, J = 10.7 Hz), 6.43 (d, 1H, J = 5.9 Hz), 5.44 (ddd, 1H, J = 8.7, 5.2, 3.5 Hz), 4.22-4.10 (m, 4H), 3.75-3.64 (m, 2H), 3.21-3.15 (m, 2H), 2.32-2.23 (m, 3H), 2.10-2.01 (m, 3H), 1.65-1.59 (m, 4H), 1.38-1.26 (m, 4H), 1.02-0.80 (m, 18H), 0.77(t, 6H, J =6.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 170.6, 157.3 (d, J_{CF} = 253.1 Hz), 135.9, 133.2 (d, J_{CF} = 10.1), 132.5 (d, J_{CF} = 5.0 Hz), 131.6, 128.3, 128.2, three rasonances at 127.58, 127.56 and 127.51 (2C), 126.8, 126.7, 125.9 (d, J_{CF} = 17.9 Hz), 121.4 (d, J_{CF} = 7.8 Hz), 108.7 (d, J_{CF} = 19.7 Hz), 80.9, 80.8, 73.2, 72.3, 66.5, 66.4, 53.6, 48.4 (2C), 40.4, 40.3, 34.62, 34.60, 31.73, 31.72, 29.8, 27.3, 25.75, 25.71, 23.5, 22.5, 22.48, 21.17, 21.12, 16.5. ^{19}F NMR (282 MHz, $CDCl_3$): δ −125.39 (d, $^2J_{FH}$ = 12.2 Hz). HRMS (ESI) calcd. for $C_{42}H_{55}FNaO_6$ $[M+Na]^+$, 695.3875, found 695.3884.

(+)-8-Fluoro-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene-3,4-diol (+)-39a



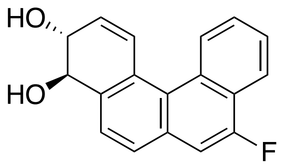
In a small vial, the early eluting **(−)-38a** (25.0 mg, 0.037 mmol) was dissolved in 1:1 methanol/THF solution (2mL) and a catalytic amount of NaOMe was added. Reaction mixture was stirred for at room temperature for 2 h. Starting material was consumed at this time. Reaction mixture was poured into 10 mL ethyl acetate in a separatory funnel water and 10 mL water was added. Layers were separated and aqs layer extracted three times with EtOAc. Combined organic layer was washed with water and brine and then dried over Na_2SO_4. Solvent removal under reduced pressure gave a slightly impure crude mixture that was purified by column chromatography (silica gel mesh 200-300, eluent: 20% EtOAc/ hexanes followed by 60% EtOAc/ hexanes). Yield of (+)-**39a**: 10 mg (96%, a light yellow solid). R_f (50% acetone in hexanes) = 0.34. Specific rotation: $[\alpha]_D = +13.3$ at conc. 0.4g/100 mL (solvent: THF). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.96-8.93 (m, 1H, Ar-H), 8.22 (dd, 1H, Ar-H, J = 7.4, 2.0 Hz), 7.86 (d, 1H, Ar-H, J =8.3 Hz), 7.83 (d, 1H, Ar-H, J = 8.3 Hz), 7.78-7.72 (m, 2H, Ar-H), 7.51 (d, 1H, J = 11.2 Hz), 4.70 (d, 1H, J = 5.9 Hz), 4.56 (br s, 1H, OH), 4.17 (br s, 1H, OH), 4.07-4.02 (m, 1H), 3.71-3.60 (m, 2H), 2.22-2.16 (m, 1H), 1.86-1.79 (m, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ 158.0 (d, J_{CF} = 250.4 Hz), 138.3, 136.2, 134.1 (d, J_{CF} = 4.6 Hz), 133.8 (d, J_{CF} = 10.1 Hz), three rasonances at 129.8, 129.69 and 129.67 (2C), 128.5, 128.1 (d, J_{CF} = 5.0 Hz), 127.6, 127.4, 126.8 (d, J_{CF} = 17.4 Hz), 121.8 (d, J_{CF} = 7.3 Hz), 109.6 (d, J_{CF} = 19.7 Hz), 76.2, 73.4, 31.9, 30.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ −125.39 (d, $^2J_{FH}$ = 12.2 Hz). HRMS (ESI) calcd. for $C_{18}H_{16}FO_2$ $[M+H]^+$, 283.1129, found 283.1129.

(−)-8-Fluoro-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene-3,4-diol (−)-39b



21.0 mg of late eluting bis ester (+)-**38b** was treated with NaOMe using the same procedure that was used for the early eluting isomer (−)-**38a**. Yield of (−)-**39b**: 7.0 mg (80%, white solid). R_f (50% acetone in hexanes) = 0.32. Specific rotation: $[\alpha]_D = -11.5$ at conc. = 0.4g/100 mL (solvent: THF). ^{1}H NMR (500 MHz, CD_3OD): δ 8.87 (d, 1H, Ar-H, J =7.8 Hz), 8.20 (dd, 1H, Ar-H, J = 7.4, 2.0 Hz), 7.78 (s, 2H, Ar-H), 7.72-7.67 (m, 2H, Ar-H), 7.40 (d, 1H, J = 11.2 Hz), 4.70 (d, 1H, J = 6.4 Hz), 4.05 (ddd, 1H, J = 9.6, 6.2, 3.3 Hz), 3.70-3.59 (m, 2H), 2.22-2.16 (m, 1H), 1.86-1.78 (m, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ 158.0 (d, J_{CF} = 249.9 Hz), 138.3, 136.2, 134.1 (d, J_{CF} = 4.6 Hz), 133.8 (d, J_{CF} = 10.1 Hz), three rasonances at 129.8, 129.69 and 129.67 (2C), 128.5, 128.1 (d, J_{CF} = 5.0 Hz), 127.6, 127.4, 126.8 (d, J_{CF} = 17.4 Hz), 121.8 (d, J_{CF} = 7.3 Hz), 109.6 (d, J_{CF} = 19.7 Hz), 76.2, 73.4, 31.9, 30.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ −125.39 (d, $^2J_{FH}$ = 12.2 Hz). HRMS (ESI) calcd. for $C_{18}H_{15}FNaO_2$ $[M+Na]^+$, 305.0948, found 305.0965.

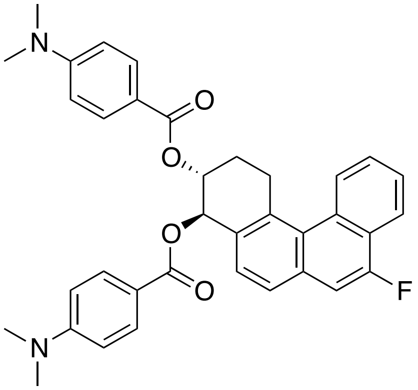
Synthesis of (−)-(3*R*,4*R*)-8-fluoro-3,4-dihydrobenzo[*c*]phenanthrene-3,4-diol (−)-35 form (−)-37



In a small vial, the early eluting **(−)-37a** (61.0 mg, 0.091 mmol) was dissolved in 1:1 methanol/THF solution (5mL) and a catalytic amount of NaOMe was added. Reaction mixture was stirred at room temperature for 2 h. Starting material was consumed at this time. Reaction mixture was poured into 10 mL ethyl acetate in a separatory funnel water and 10 mL water was added. Layers were separated and aqs layer extracted three times with EtOAc. Combined organic layer was washed with water and brine and then dried over Na_2SO_4. Solvent removal under reduced pressure gave a slightly impure crude mixture that was purified by column chromatography (silica gel mesh 200-300, eluent: 20% EtOAc/ hexanes followed by 60% EtOAc/ hexanes). Yield of (−)-**35**: 25.0 mg (98%, a light yellow solid). Specific rotation: $[\alpha]_D = -41.1$ at conc. 0.6g/100 mL (solvent: THF).

NMR data and HRMS data of the racemic mixture of *trans* dihydrodiol are shown in Part 1 of this chapter.

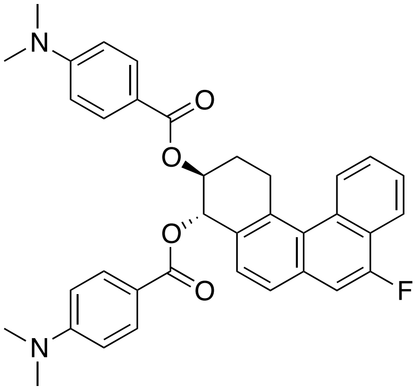
(−)-(3*R*,4*R*)-8-fluoro-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene-3,4-diyl bis[4-(dimethylamino)benzoate] (−)-41a



To a suspension of NaH (15.0 mg) in anhydrous THF (1.2 mL) in a dry small vial, under N_2 was added (+)-**39a** (4.0 mg, 0.14 mmol, 1.0 molar equiv). The light greenish suspension was stirred at room temperature for 30 minute and then *p*-(*N,N*-dimethylamino)benzoyl chloride (**40**) (21.0 mg, 0.112 mmol, 8.0 molar equiv) was added solid and stirring was continued for 24 hours under N_2. All the starting material was consumed at this time. 1 mL NH_4Cl saturated solution was added followed by addition of

10 mL ethyl acetate. Layers were separated and the organic layer was washed once with water and then brine and then dried over Na_2SO_4. Solvent removal gave a white solid that was loaded on preparative silica plate (500 micron) and eluted with 20% ethyl acetate/hexanes to yield 4.2 mg (52%, white solid) of bisester (−)-**41a**. R_f (50% acetone in hexanes) = 0.38. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.86-8.82 (m, 1H, Ar-H), 8.27-8.24 (m, 1H, Ar-H), 7.94 (d, 2H, Ar-H, J = 9.2 Hz), 7.91 (d, 2H, Ar-H, J = 8.8 Hz), 7.72-7.67 (m, 3H, Ar-H), 7.62 (d, 1H, J = 7.8 Hz), 7.34 (d, 1H, J = 11.1 Hz), 6.72 (d, 1H, J = 5.5 Hz), 6.61 (d, 4H, J = 8.8 Hz), 5.64-5.61 (m, 1H), 3.86-3.73 (m, 2H), 3.014 (s, 6H), 3.010 (s, 6H), 2.47-2.41 (m, 1H), 1.26-1.19 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −126.08 (d, $^2J_{FH}$ = 12.2 Hz). HRMS (ESI) calcd. for $C_{36}H_{33}FN_2NaO_4$ $[M+Na]^+$, 599.2317, found 599.2301.

(+)-(3*S*,4*S*)-8-fluoro-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene-3,4-diyl bis(4-[dimethylaminobenzoate] (+)-41b



Tetrahydrodiol (−)-**39b** was reacted with reacted with *p*-(*N,N*-dimethylamino)benzoyl chloride **(40)** using the procedure used for reaction of (+)-**39a** .

(−)-**39b**: 4.0 mg (0.14 mmol, 1.0 molar equiv); *p*-(*N,N*-dimethylamino)benzoyl chloride (**40)** (21.0 mg, 0.112 mmol, 8.0 molar equiv); NaH (15 mg); THF (1.2 mL).

Yield of (+)-**41b**: 3.7 mg (50%) of white solid. R_f (50% acetone in hexanes) = 0.38. ^{1}H NMR (500 MHz, CD$_3$OD): δ 8.86-8.82 (m, 1H, Ar-H), 8.28-8.24 (m, 1H, Ar-H), 7.94 (d, 2H, Ar-H, J = 9.2 Hz), 7.92 (d, 2H, Ar-H, J = 9.2 Hz), 7.72-7.67 (m, 3H, Ar-H), 7.62 (d, 1H, J = 8.3 Hz), 7.34 (d, 1H, J = 10.6 Hz), 6.72 (d, 1H, J = 5.5 Hz), 6.61 (d, 4H, J = 8.8 Hz), 5.63 (ddd, 1H, J = 8.4, 5.4, 3.1 Hz), 3.86-3.73 (m, 2H), 3.013 (s, 6H), 3.009 (s, 6H), 2.47-2.41 (m, 1H), 1.26-1.19 (m, 1H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 166.8, 166.6, 157.1 (d, J_{CF} = 251.3 Hz), 153.7, 153.6, 135.9, five rasonances at 133.09, 133.01, 132.98, 132.75, 132.71 (4C), 131.9 (2C), 131.7 (2C), 128.6, 128.5, 127.6, 127.3 (d, J_{CF} = 4.6 Hz), 126.7, 126.5, 125.9 (d, J_{CF} = 18.1 Hz), 121.3 (d, J_{CF} = 7.8 Hz), 117.0 (d, J_{CF} = 27.9 Hz), 110.94 (2C), 110.92 (2C), 108.8 (d, J_{CF} = 19.7 Hz), 72.3, 71.8, 40.27 (2C), 40.25 (2C), 30.0, 29.9. ^{19}F NMR (282 MHz, CDCl$_3$): δ −126.08 (d, $^2J_{FH}$ = 12.2 Hz). HRMS (ESI) calcd. for $C_{36}H_{33}FN_2NaO_4$ [M+Na]$^+$, 599.2317, found 599.2334.

REFERENCES

1. Luch, A.; Baird, W. M. *The Carcinogenic Effects of Polycyclic Aromatic Hydrocarbons*, Luch, A., Ed.; Imperial College Press: London, 2005.

2. Harvey, R. G. Structure-Activity Relationships. In: *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*, Cambridge University Press: Cambridge, 1991.

3. Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*; Cambridge University Press: Cambridge, 1991.

4. Cavalieri, E. L.; Rogan, E. G.: Central Role of Radical Cations in Metabolic Activation of Polycyclic Aromatic Hydrocarbons, *Xenobiotica* **1995**, *25*, 677-688.

5. Bolton, J. L.; Trash M. A.; Penning, T. M.; Dryhurst, G.; Monks, T. J.: Role of Quinones in Toxicology, *Chem. Res. Toxicol.* **2000**, *13*, 135-160.

6. Jerina, D. M.; Sayer, J. M.; Agarwal, S. K.; Yagi, H.; Levin, W.; Wood, A. W.; Conney, A. H.; Pruess-Schwartz, D.; Baird, W. M.; Pigott, M. A.; Dipple, A.: Reactivity and Tumorigenic Activity of Bay-Region Diol Epoxides Derived from Polycyclic Aromatic Hydrocarbons, *Biological Reactive Intermediates III*; Kocsis, J. J.; Jollow, D. J., Witmer, C. M., Nelson, J. O., Snyder, R., Eds.; Plenum Press: New York, **1986**; pp 11-30.

7. Jerina, D. M.; Chadha, A.; Cheh, A. M.; Schurdak, M. E.; Wood, A. W.; Sayer, J. M.: In *Biological Reactive Intermediates IV*; Witmer, C. M., Snyder, R., Jollow, D. J., Kalf, G. F., Kocsis, J. J., Sipes, I. G., Eds.; Plenum Press: New York, 1991; pp 533-553.

8. Szeliga, J.; Dipple, A.: DNA Adduct Formation by Polycyclic Aromatic Hydrocarbon Dihydrodiol Epoxides, *Chem. Res. Toxicol.* **1998**, *11*, 1-11.

9. Dipple A.; Pigott, M. A.; Agarwal, S. K.; Yagi, H.; Sayer, J. M.; Jerina, D. M.: Optically Active Benzo[*c*]phenanthrene Diol Epoxides Bind Extensively to Adenine in DNA, *Nature* **1987**, *327*, 535–536.

10. Agarwal, S. K., Sayer, J. M., Yeh, H. J. C., Pannell, L. K., Hilton, B. D., Pigott, M. A., Dipple, A., Yagi, H., Jerina, D. M.: Chemical Characterization of DNA Adducts Derived from the Configurationally Isomeric Benzo[*c*]phenanthrene-3,4-Diol 1,2-Epoxide, *J. Am. Chem. Soc*. **1987**, *109*, 2497-2504.

11. Frank, E. G.; Sayer, J. M.; Kroth, H.; Ohashi, E.; Ohmori, H.; Jerina, D. M.; Woodgate, R.: Translesion Replication of Benzo[*a*]pyrene and Benzo[*c*]phenanthrene Diol Epoxide Adducts of Deoxyadenosine and Deoxyguanosine by Human DNA Polymerase ι, *Nucleic Acids Res.* **2002**, *30*, 5284-5292.

12. Harvey, R. G.; Geacintov, N. E.: Intercalation and Binding of Carcinogenic Hydrocarbon Metabolites to Nucleic Acids, *Acc. Chem. Res.* **1988**, *21*, 66-73.

13. Islam, N. B.; Gupta, S. C.; Yagi, H.; Jerina, D. M.; Whalen, D. L.: Trapping of a Carbocationic Intermediate in the Spontaneous Hydrolysis Reaction of 7β, 8α-Dihydroxy-9β, 10β-epoxy-7,8,9,10-tetrahydrobenzao[*a*]pyrene: Mechanism of the Spontaneous and General Acid Catalyzed Hydrolysis Reactions of Bay-Region Benzo[*a*]pyrene 7,8-Diol 9,10-Epoxides, *J. Am. Chem. Soc.* **1990**, *112*, 6363-6369.

14. Lakshman, M. K.; Sayer, J. M.; Jerina, D. M.: Chemical Synthesis of a Bay-Region Polycyclic Aromatic Hydrocarbon Tetrahydroepoxide-Deoxyadenosine Adduct and Its Site-Specific Incorporation into a DNA Oligomer, *J. Am. Chem. Soc.* **1991**, *113*, 6589-6594.

15. Lakshman, M. K.; Sayer, J. M.; Jerina, D. M.: Synthesis and Site-Specific Incorporation of a Bay-Region Cis Ring-Opened Tetrahydro Epoxide-Deoxyadenosine Adduct into a DNA Oligomer *J. Org. Chem.* **1992**, *57*, 3438-3443.

16. Lakshman, M. K.; Sayer, J. M.;Yagi, H.; Jerina, D. M.: Synthesis and Duplex-Forming Properties of a Nonanucleotide Containing an N^6-Deoxyadenosine Adduct of a Bay-Region Diol Epoxide, *J. Org. Chem.* **1992**, *57*, 4585-4590.

17. Chaturvedi, S.; Lakshman, M. K.: Site-Specific Modification of the Human *N-ras* Proto-Oncogene with Each Diol Epoxide Metabolite of Benzo[*a*]pyrene and Thermal Denaturation Studies of the Adducted Duplexes, *Carcinogenesis* **1996**, *17*, 2747-2752.

18. Pilcher, A. S.; Yagi, H.; Jerina, D. M.: A Novel Synthetic Method for Cis-Opened Benzo[*a*]pyrene 7,8-Diol 9,10-Epoxide Adducts at the Exocyclic N^6-Amino Group of Deoxyadenosine *J. Am. Chem. Soc.* **1998**, *120*, 3520-3521.

19. Dipple, A.; Piggot, M. A.; Aggarwal, S. K.; Yagi, H.; Sayer, J. M.; Jerina, D. M.: Optically Active Benzo[*c*]phenanthrene Diol Epoxides Bind Extensively to Adenine in DNA, *Nature* **1987**, *327*, 535-536.

20. Benasutti, M.; Ezzedine, Z. D.; Loechler, E. L.: Construction of an *Escherichia coli* Vector Containing the Major DNA Adduct of Activated Benzo[*a*]pyrene at a Defined Site, *Chem. Res. Toxicol.* **1988**, *1*, 160-168

21. Harris, C. M.; Zhou, L.; Strand, E. A.; Harris, T. M.: New Strategy for the Synthesis of Oligodeoxynucleotides Bearing Adducts at Exocyclic Amino Sites of Purine Nucleosides, *J. Am. Chem. Soc.* **1991**, *113*, 4328-4329

22. Cooper, M. D.; Hodge, R. P.; Tamura, P. J.; Wilkinson, A. S.; Harris, C. M.; Harris, T. M.: Synthesis of Oligonucleotides Containing Bulky Adducts at Guanine N^2 Via

the Phosphoramidite of *O^2-Triflate-O^6-NPE* 2′ -Deoxyxanthosine, *Tetrahedron Lett.* **2000**, *41*, 3555-3558.

23. Lakshman, M. K. Unpublished results.

24. Zajc, B.; Lakshman, M. K.; Sayer, J. M.; Jerina, D. M.: Epoxide and Diol Epoxide Adducts of Polycyclic Aromatic Hydrocarbons at the Exocyclic Amino Group of Deoxyguanosine, *Tetrahedron Lett.* **1992**, *33*, 3409-3412.

25. Custer, L.; Zajc, B.; Sayer, J. M.; Cullinane, C.; Phillips, D. R.; Cheh, A. M.; Jerina, D. M.; Bohr, V. A.; Mazur, S. J.: Stereospecific Differences in Repair by Human Cell Extracts of Synthesized Oligonucleotides Containing trans-Opened 7,8,9,10-Tetrahydrobenzo[*a*]pyrene 7,8-Diol 9,10-Epoxide *N^2-dG* Adduct Stereoisomers Located within the Human K-ras Codon 12 Sequence, *Biochemistry* **1999**, *38*, 569-581.

26. Lakshman, M. K.; Yeh, H. J. C.; Yagi, H. Jerina, D. M.: Synthesis of Deoxyadenosine Adducts from the Highly Carcinogenic Fjord Region Diol Epoxide of Benzo[*c*]phenanthrene, *Tetrahedron Lett.* **1992**, *33*, 7121-7124.

27. Johnson, F.; Bonala, R.; Tawde, D.; Torres, M. C.; Iden, C. R.; Efficient Synthesis of the Benzo[*a*]pyrene Metabolic Adducts of 2′-Deoxyguanosine and 2′-Deoxyadenosine and Their Direct Incorporation into DNA, *Chem. Res. Toxicol.* **2002**, *12*, 1489-1494.

28. Lakshman, M. K.; Gunda, P.: Palladium-Catalyzed Synthesis of Carcinogenic Polycyclic Aromatic Hydrocarbon Epoxide-NucleosideAdducts: The First Amination of a Chloro Nucleoside, *Org. Lett.* **2003**, *5*, 39-42.

29. Champeil, E.; Pradhan, P.; Lakshman, M. K.: Palladium-Catalyzed Synthesis of Nucleoside Adducts from Bay and Fjord-Region Diol Epoxides, *J. Org. Chem*. **2007**, *72*, 5035-5045

30. Steinbrecher, T.; Becker, A.; Stezowski, J. J.; Oesch, F.; Seidel, A. Synthesis of Otigodeoxynucleotides Containing Diastereomeric Dihydrodiol Epoxide-*N^6*-Deoxy-adenosine Adducts of Polycyclic Aromatic Hydrocarbons, *Tetrahedron Lett.* **1993**, *34*, 1773-1774.

31. Jerina, D. M.; Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Ittah, Y.; Thakker, D. R; Wood, A. W.; Chang, R. L.; Levin, W.; Conney, A. H.: Highly Tumorigenic Bay-Region Diol Epoxides from the Weak Carcinogen Benzo[*c*]phenanthrene, *Biological Reactive Intermediates II Part A*; Snyder, R., Parke, D., Kocsis, J. J., Jollow, D. J., Gibson, G., Witmer, C. M.; Eds.; Plenum Press: New York, 1986; pp 501-523.

32. Cosman, M.; Laryea, A.; Fiala, R.; Hingerty, B. E.; Amin, S.; Geacintov, N. E.; Broyde, S.; Patel, D. J.: Solution Conformation of the (−)-*trans*-*anti*-Benzo[*c*]phenanthrene-dA ([BPh]dA) Adduct Opposite dT in a DNA Duplex: Intercalation of the Covalently Attached Benzo[*c*]phenanthrenyl Ring to the 3′-Side of the Adduct Site and Comparison with the (+)-*trans*-*anti*-[BPh]dA Opposite dT Stereoisomer, *Biochemistry* **1995**, *34*, 1295–1307.

33. Cosman, M.; Fiala, R.; Hingerty, B. E.; Laryea, A.; Lee, H.; Harvey, R. G.; Amin, S.; Geacintov, N. E.; Broyde, S.; Patel, D.: Solution Conformation of the (+)-trans-anti-[BPhIdA Adduct opposite dT in a DNA Duplex: Intercalation of the Covalently Attached Benzo[c]phenanthrene to the 5'-Side of the Adduct Site without Disruption of the Modified Base Pair, *Biochemistry* **1993**, *32,* 12488-12497.

34. Lin, C. H.; Huang, X.; Kolbanovskii, A.; Hingerty, B. E.; Amin, S.; Broyde, S.; Geacintov, N. E.; Patel, D. J.: Molecular Topology of Polycyclic Aromatic Carcinogens Determines DNA Adduct Conformation: A Link to Tumorigenic Activity, *J. Mol. Biol.* **2001**, *306*, 1059-1080.

35. Wang, Y.; Schnetz-Boutaud, N. C.; Kroth, H.; Yagi, H.; Sayer, J. M.; Kumar, R.; Jerina, D. M; Stone, M. P: 3′-Intercalation of a *N*2-dG 1*R*-*trans*-*anti*-Benzo[*c*]phenanthrene DNA Adduct in an Iterated (CG)3 Repeat, *Chem. Res. Toxicol.* **2008**, *21*, 1348–1358.

36. Smart, B. E.: Fluorine Substituent Effects (on Bioactivity), *J. Fluorine Chem.* **2001**, *109*, 3-11.

37. Buhler, D. R.; Unlu, F.; Thakker, D. R.; Slaga, T. J.; Newman, M. S.; Levin, W.; Conney, A. H.; Jerina, D. M.: Metabolism and Tumorigenicity of 7-, 8-, 9-, and 10-Fluorobenzo[*a*]pyrenes, *Cancer Res.* **1982**, *42*, 4779-4783.

38. Buhler, D. R.; Unlu, F.; Thakker, D. R.; Slaga, T. J.; Conney, A. H.; Wood, A. W.; Chang, R. L.; Levin, W.; Jerina, D. M.: Effect of 6-Fluoro Substituent on the Metabolism and Biological Activity of Benzo[*a*]pyrenes, *Cancer Res.* **1983**, *43*, 1541-1549.

39. Hecht, S. S.; Loy, M.; Mazzarese, R.; Hoffmann, D.: Synthesis and Mutagenicity of Modified Chrysenes Related to the Carcinogen, 5-Methylchrysene, *J. Med. Chem.* **1978**, *21*, 38-44.

40. Hecht, S. S.; Hirota, N.; Loy, M.; Hoffmann, D.: Tumor-initiating Activity of Fluorinated 5-Methylchrysenes, *Cancer Res.* **1978**, *38*, 1694-1698.

41. Huberman, E.; Slaga, T. J.: Mutagenicity and Tumor-initiating Activity of Fluorinated Derivatives of 7,12-Dimethylbenz[*a*]anthracene, *Cancer Res.* **1979**, *39*, 411-414.

42. Hecht, S. S.; LaVoie, E. J.; Bedenko, V.; Pingaro, L.; Katayama, S.; Hoffmann, D.; Sardella, D. J.; Boger, E.; Lehr, R. E.: Reduction of Tumorigenicity and of Dihydrodiol Formation by Fluorine Substitution in the Angular Rings of Dibenzo[*a,i*]pyrene, *Cancer Res.* **1981**, *41*, 4341-4345.

43. Bae, S.; Mah, H.; Chaturvedi, S.; Jeknic, T. M.; Baird, W. M.; Katz, A. M.; Carrell, H. L.; Glusker, J. P.; Okazaki, T.; Laali, K. K.; Zajc, B.; Lakshman, M. K.: Synthetic, Crystallographic, Computational, and Biological Studies of 1,4-Difluorobenzo[*c*]phenanthrene and Its Metabolites, *J. Org. Chem.* **2007**, *72*, 7625-7633.

44. Thakker, D. R.; Yagi, H.; Sayer, J. M.; Kapur, U.; Levin, W.; Chang, R. L.; Wood, A. W.; Conney, A. H.; Jerina, D. M.: Effects of a 6-Fluoro Substituent on the Metabolism of Benzo[*a*]pyrene 7,8-Dihydrodiol to Bay-Region Diol Epoxides by Rat Liver Enzymes*, J. Biol. Chem*. **1984**, *259*, 11249-11256.

45. Zhou, L.; Rajabzadeh, G.; Traficante, D. D.; Cho, B. P.: Conformational Heterogeneity of Arylamine-Modified DNA: ^{19}F NMR Evidence, *J. Am. Chem. Soc.* **1997**, *119*, 5384-5389.

46. Meneni, S. R.; Shell, S. M.; Gao, L.; Jurecka, P.; Lee, W.; Sponer, J.; Zou, Y.; Chiarelli, M. P.; Cho, B. P.: Spectroscopic and Theoretical Insights into Sequence Effects of Aminofluorene-Induced Conformational Heterogeneity and Nucleotide Excision Repair, *Biochemistry* **2007**, *46*, 11263–11278.

47. Yang, T.; Huang, Y.; Cho, Cho, B. P.: Synthesis and Characterization of Enantiomeric *anti*-2-Fluorobenzo[*a*]pyrene-7,8-dihydrodiol-9,10-epoxides and Their 2'-Deoxy-guanosine and Oligodeoxynucleotide Adducts, *Chem. Res. Toxicol.* **2006**, *19,* 242-254.

48. Cho, B. P.; Beland, F. A.; Marques, M. M.: NMR Structural Studies of a 15-mer DNA Sequence from a *ras* Protooncogene, Modified at the First Base of Codon 61 with the Carcinogen 4-Aminobiphenyl, *Biochemistry* **1992**, *31*, 9587-9602.

49. Cho, B. P.; Beland, F. A.; Marques, M. M.: NMR Structural Studies of a 15-mer DNA Duplex from a *ras* Protooncogene Modified with the Carcinogen 2-Aminofluorene: Conformational Heterogeneity, *Biochemistry* **1994**, *33*, 1373-1384.

50. Lakshman, M. K.; Keeler, J. C.; Ngassa, F. N; Hilmer, J. H.; Pradhan, P.; Zajc, B.; Thomasson, K. A.: Highly Diastereoselective Synthesis of Nucleoside Adducts from the Carcinogenic Benzo[*a*]pyrene Diol Epoxide and a Computational Analysis, *J. Am. Chem. Soc*. **2007**, *129*, 68-76.

51. Harada, N.; Chen, S.-m. L.; Nakanishi, K.: Quantitative Definition of Exciton Chirality and the Distant Effect in the Exciton Chirality Method, *J. Am. Chem. Soc*. **1975**, *97*, 5345-5352.

52. Yagi, H.; Akagi, H.; Thakker, D. R.; Mah, H. D.; Koreeda, M.; Jerina, D. M.: Absolute Stereochemistry of the Highly Mutagenic 7,8-Diol 9,l0-Epoxides Derived from the Potent Carcinogen *trans*-7,8-Dihydroxy-7,8-dihydro-benzo[*a*]pyrene, *J. Am. Chem. Soc*. **1977**, *99*, 2558-2559.

53. Yagi, H.; Jerina, D. M: Absolute Configuration of the *trans* -9,l0-Dihydrodiol Metabolite of the Carcinogen Benzo[*a*]pyrene, *J.* Am. Chem. Soc. **1982,** *104,* 4026-4027.

54. Yagi, H.; Thakker, D. R.; Ittah, Y.; Croisy-Decley, M.; Jerina, D. M.: Synthesis and Assignment of Absolute Configuration to the *trans* 3,4-Dihydrodiols and 3,4-Diol-1,2-Epoxides of Benzo[*c*]phenanthrene, *Tetrahedron Lett.* **1983**, *24,* 1349-1352.

55. Lakshman, M. K.; Chaturvedi, S.; Kole, P. L.; Windels, J. H.; Myers, M. B.; Brown, M. A.: Resolution of Polycyclic Aromatic Hydrocarbon Dihydrodiols Via Diastereomeric Formaldehyde Acetals, *Tetrahedron: Asymmetry* **1997**, *8*, 3375-3378.

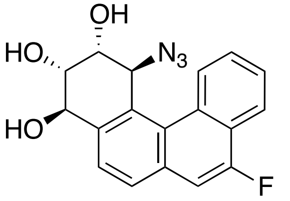
```
1231-RK-13-99-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004
 File: 1231-RK-13-99-pure

Pulse Sequence: s2pul

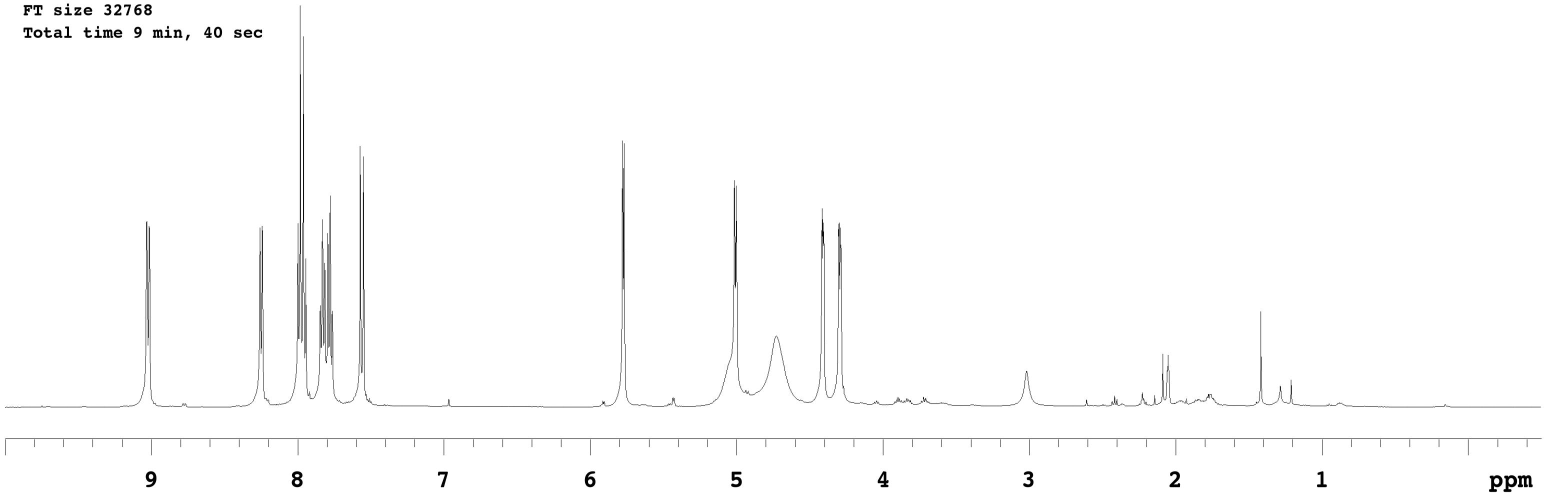
 Solvent: acetone
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-13-99-pure
INOVA-500  "capella500"

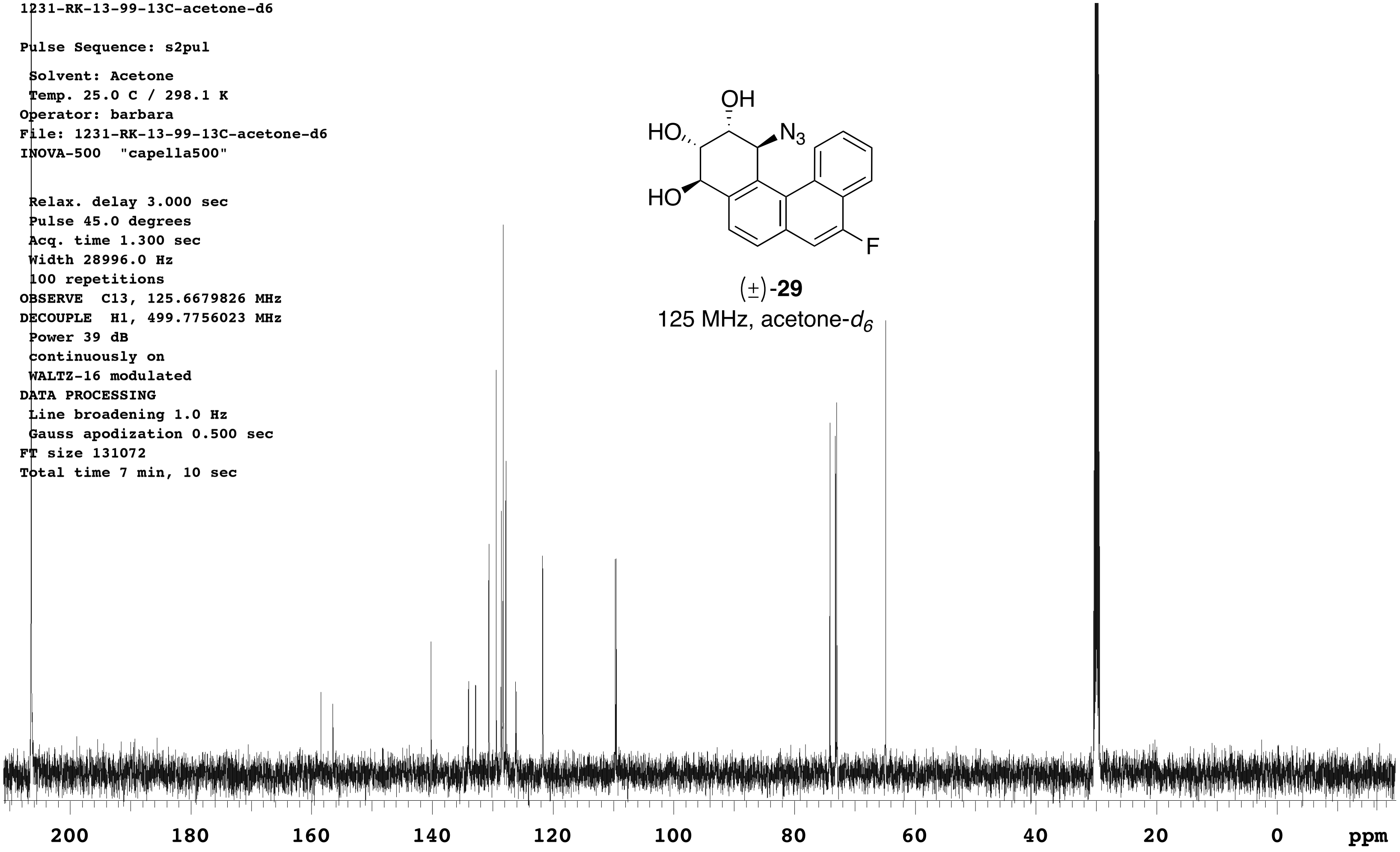
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 44 repetitions
OBSERVE   H1, 499.7733163 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```



(±)-**29**

500 MHz, acetone-d_6





```
1231-RK-13-99-13C-acetone-d6

Pulse Sequence: s2pul
 Solvent: Acetone
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-13-99-13C-acetone-d6
INOVA-500  "capella500"

 Relax. delay 3.000 sec
 Pulse 45.0 degrees
 Acq. time 1.300 sec
 Width 28996.0 Hz
 100 repetitions
OBSERVE  C13, 125.6679826 MHz
DECOUPLE  H1, 499.7756023 MHz
 Power 39 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
 Gauss apodization 0.500 sec
FT size 131072
Total time 7 min, 10 sec
```

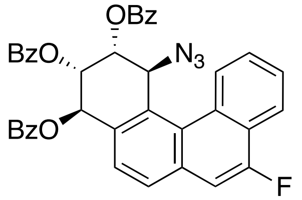
(±)-**29**

125 MHz, acetone-d_6

```
1231-RK-14-44-pure-CDCl3

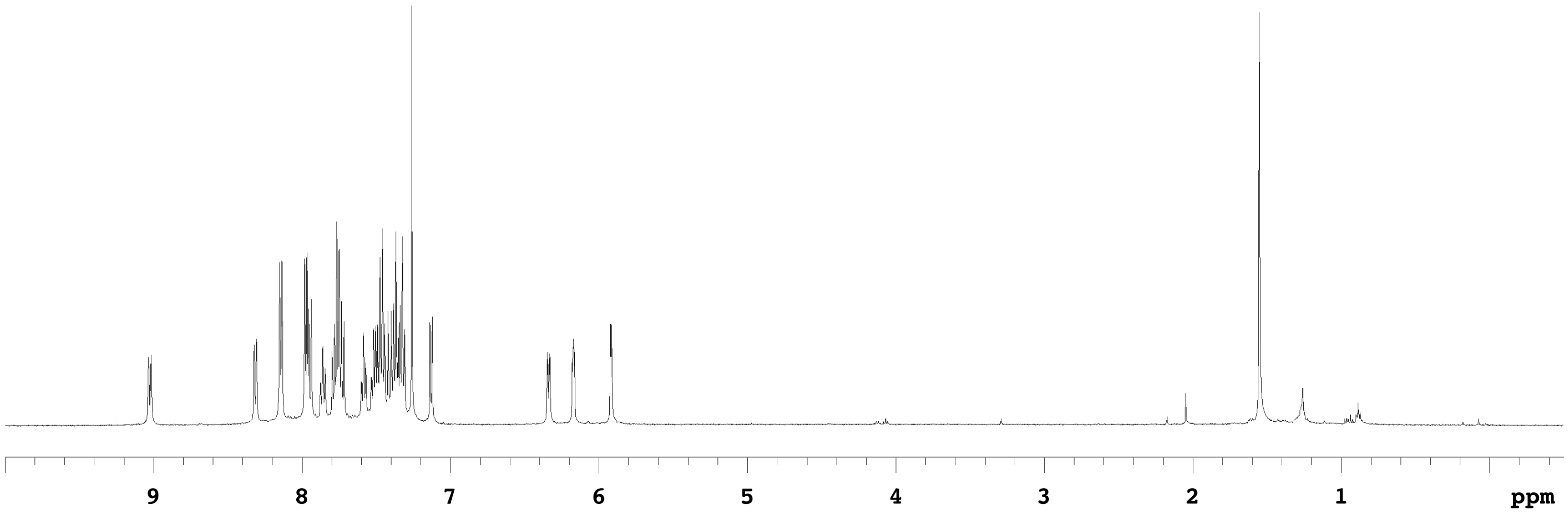
Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-14-44-pure-CDCl3
INOVA-500  "capella500"

 Relax. delay 3.000 sec
 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 12 repetitions
OBSERVE   H1, 499.7707226 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 16 min, 20 sec
```



(±)-**30**

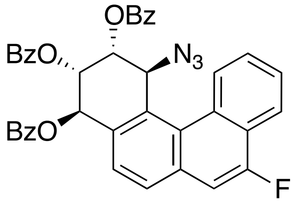
500 MHz, $CDCl_3$



```
1231-RK-15-48-13C

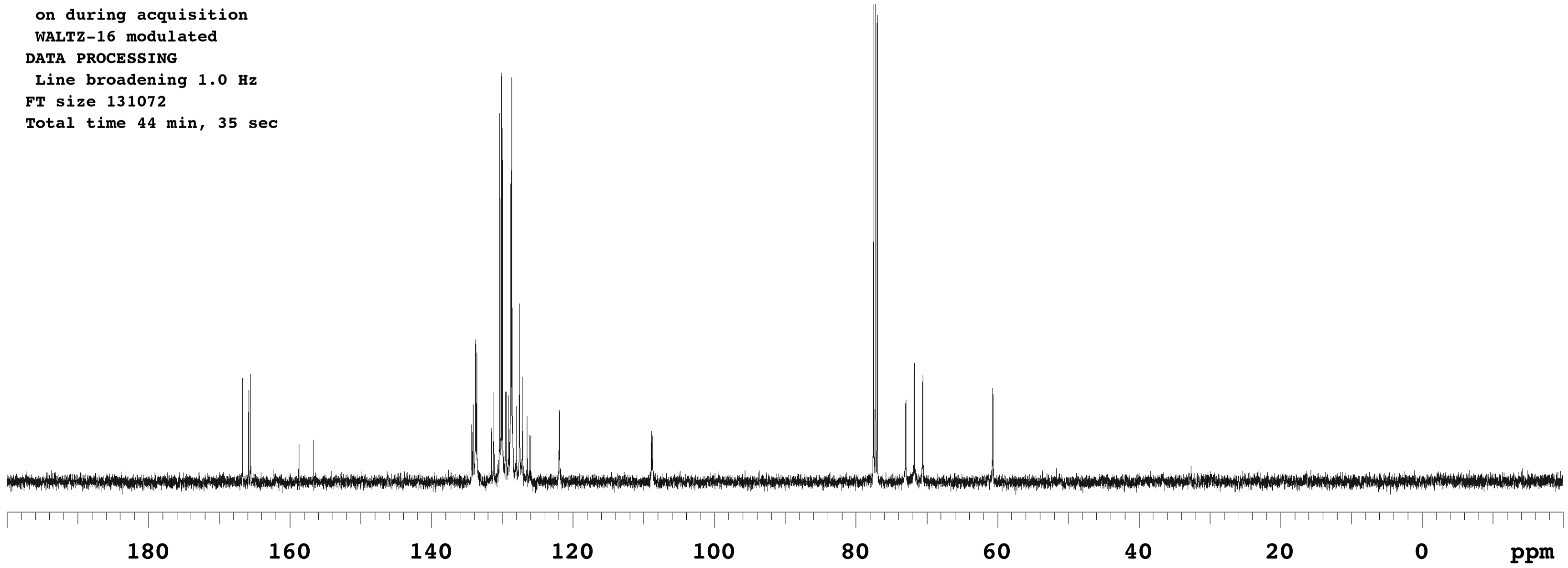
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-48-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 464 repetitions
OBSERVE  C13, 125.6674237 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 44 min, 35 sec
```



(±)-**30**

125 MHz, $CDCl_3$



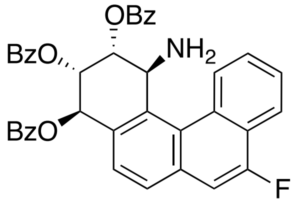
```
1231-RK-14-70-pure-1H

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004
 File: 1231-RK-14-70-pure-1H

Pulse Sequence: s2pul

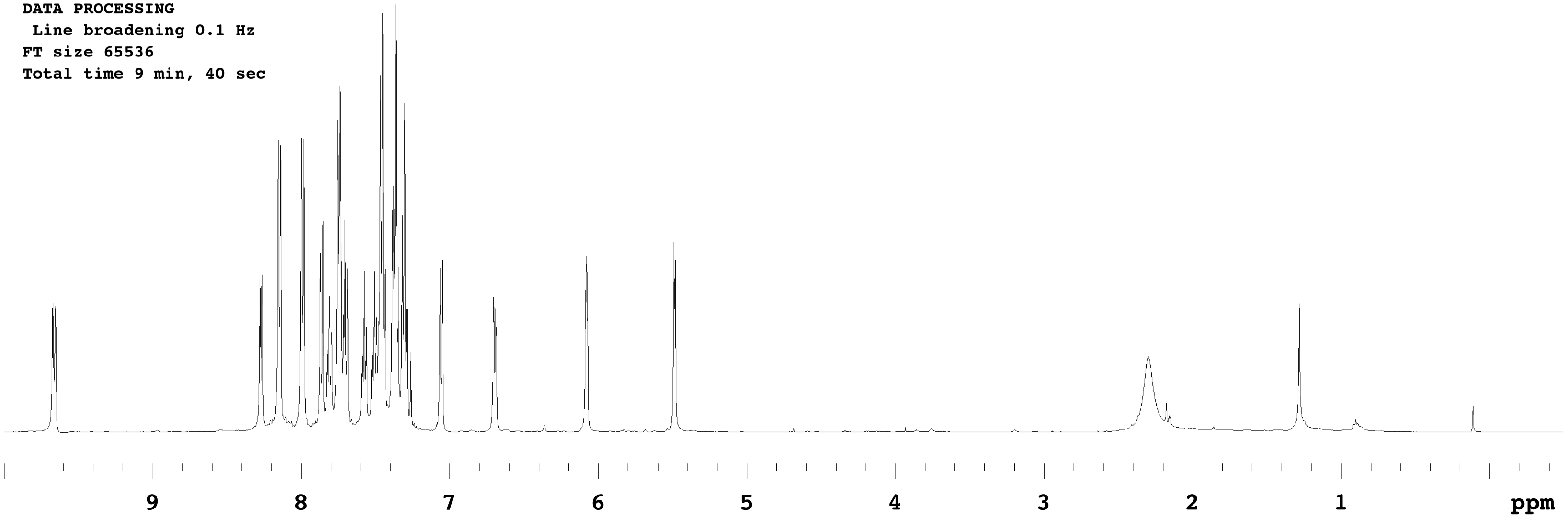
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-14-70-pure-1H
INOVA-500  "capella500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 88 repetitions
OBSERVE   H1, 499.7707227 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 9 min, 40 sec
```



(±)-**31**

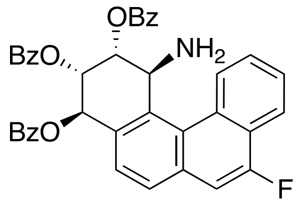
500 MHz, $CDCl_3$



```
1231-RK-14-70-13C-CDCl3

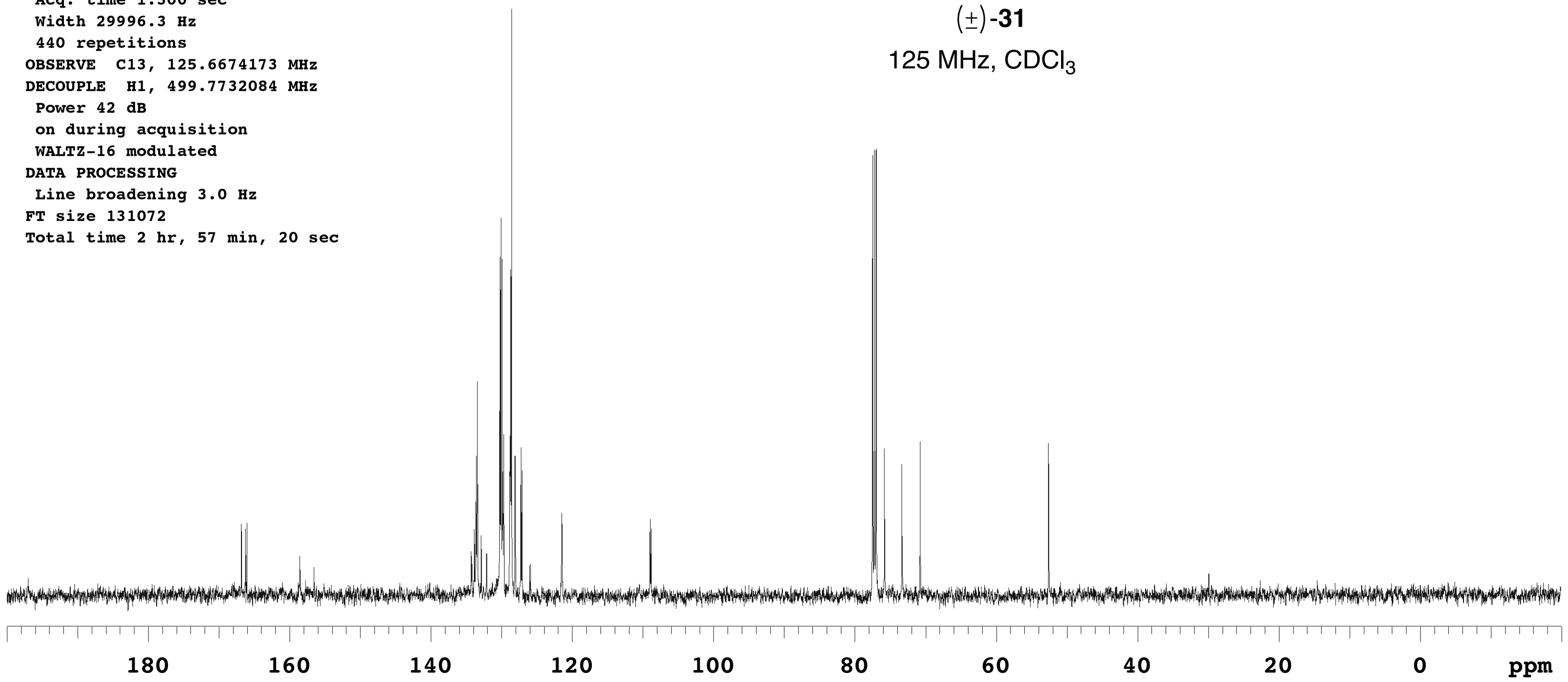
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-14-70-13C-CDCl3
INOVA-500  "capella500"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 440 repetitions
OBSERVE  C13, 125.6674173 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 3.0 Hz
FT size 131072
Total time 2 hr, 57 min, 20 sec
```



(±)-**31**

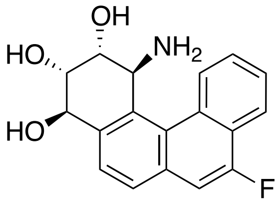
125 MHz, CDCl$_3$



```
1231-RK-15-54-dmso-d6

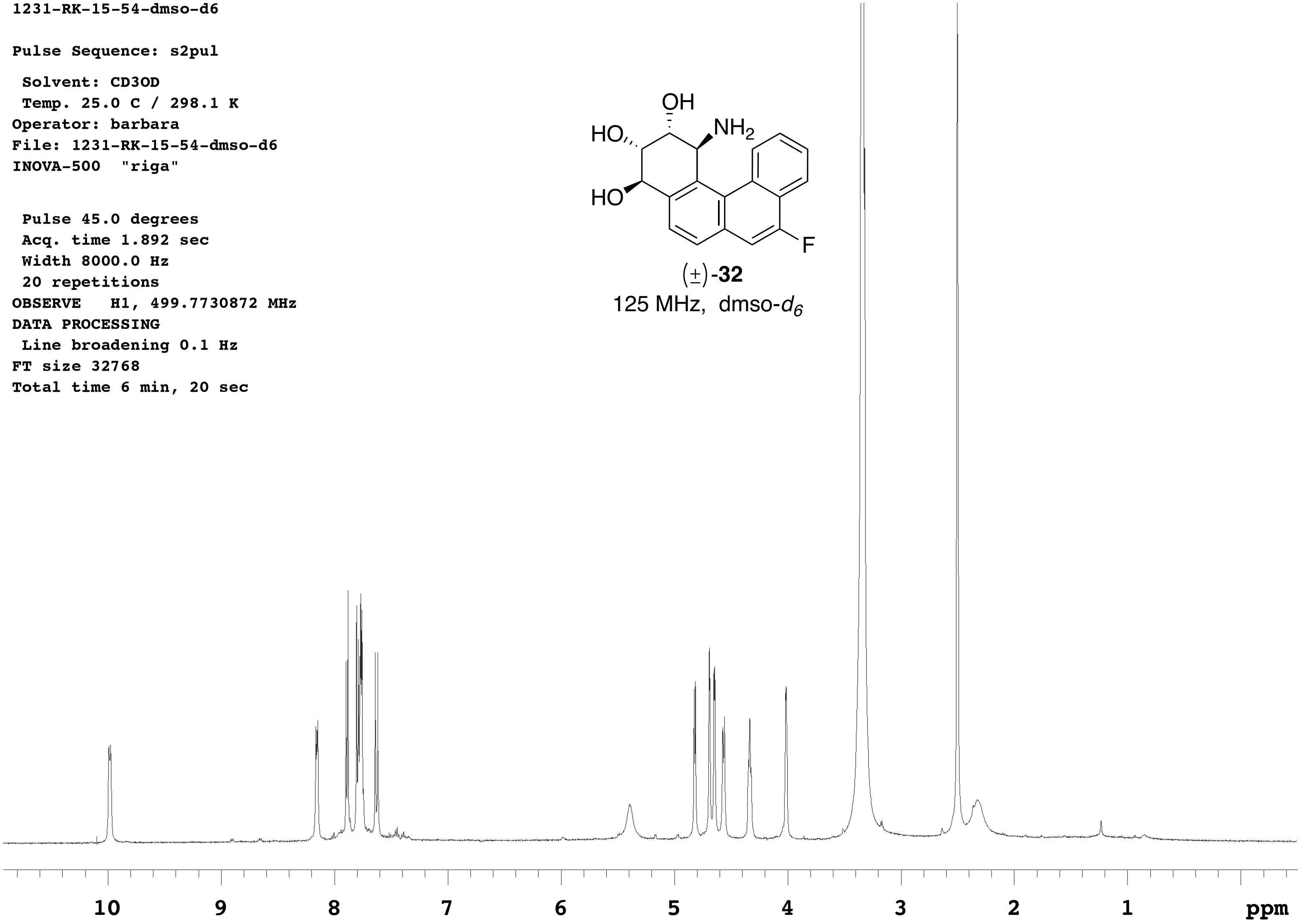
Pulse Sequence: s2pul
 Solvent: CD3OD
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-54-dmso-d6
INOVA-500  "riga"

 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 20 repetitions
OBSERVE   H1, 499.7730872 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec
```



(±)-**32**

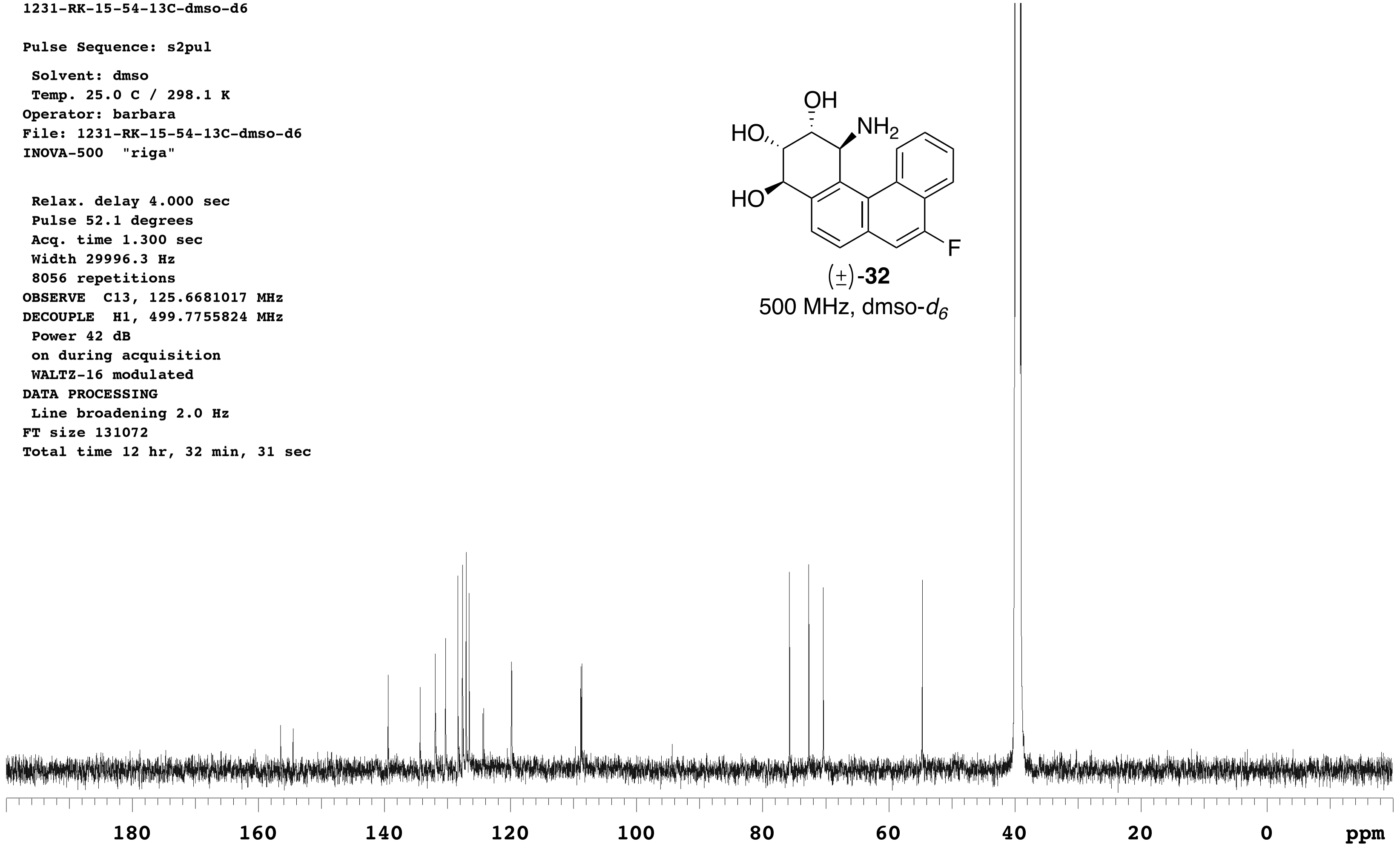
125 MHz, dmso-*d*$_6$



```
1231-RK-15-54-13C-dmso-d6

Pulse Sequence: s2pul
 Solvent: dmso
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-54-13C-dmso-d6
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 8056 repetitions
OBSERVE  C13, 125.6681017 MHz
DECOUPLE  H1, 499.7755824 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 131072
Total time 12 hr, 32 min, 31 sec
```



(±)-**32**

500 MHz, dmso-d_6

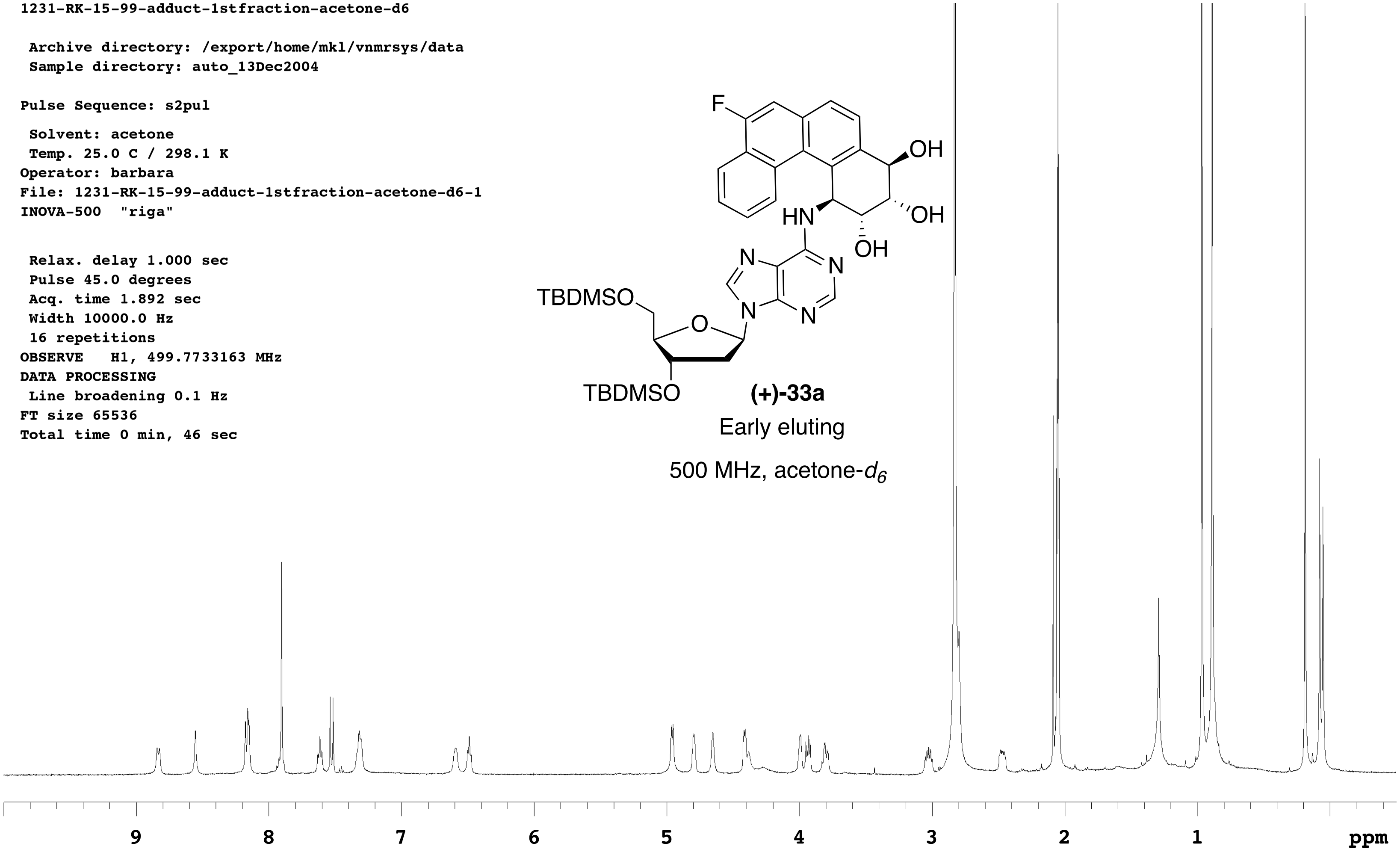
```
1231-RK-15-99-adduct-1stfraction-acetone-d6

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: acetone
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-99-adduct-1stfraction-acetone-d6-1
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 16 repetitions
OBSERVE   H1, 499.7733163 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 0 min, 46 sec
```



(+)-33a

Early eluting

500 MHz, acetone-d_6

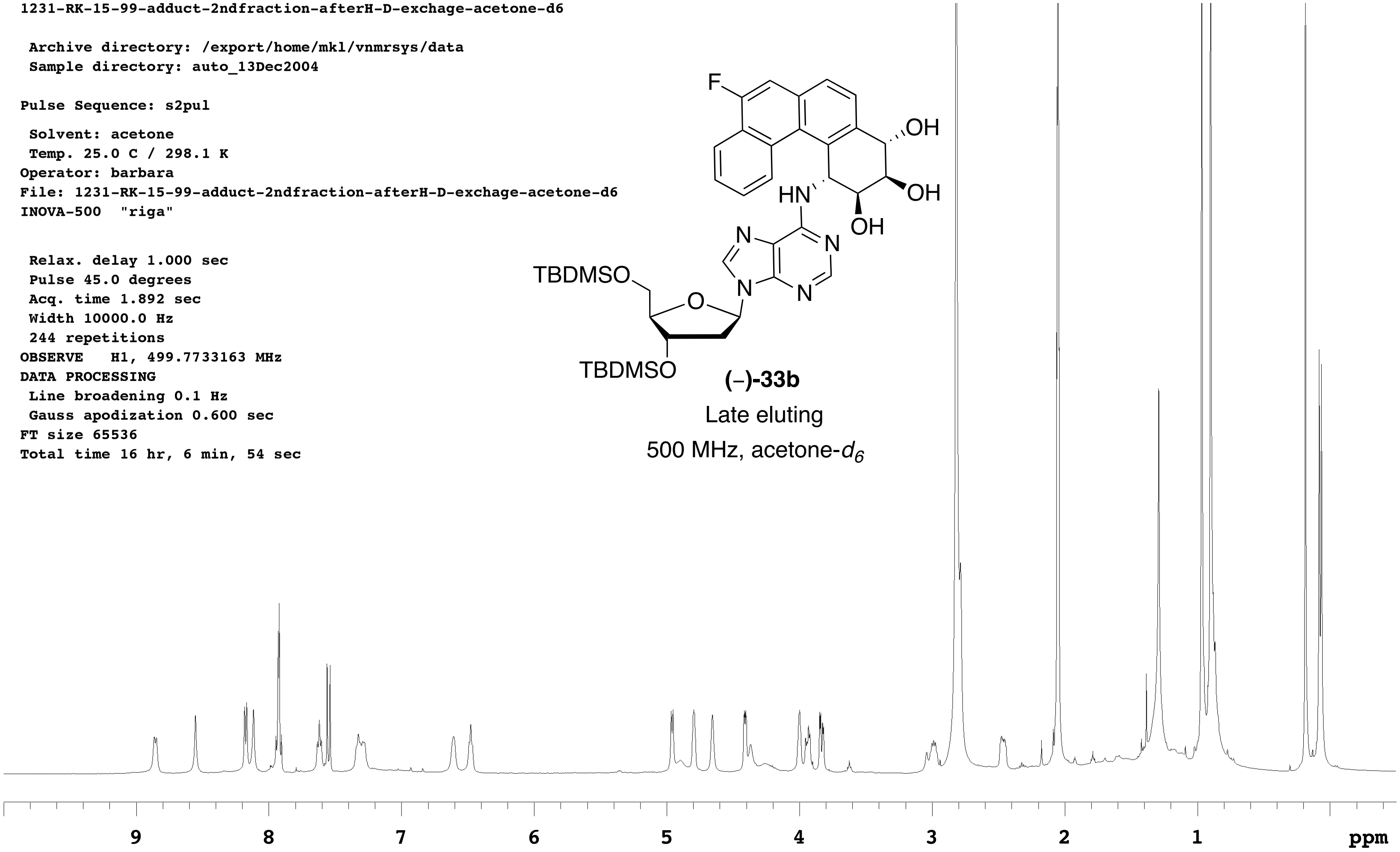
```
1231-RK-15-99-adduct-2ndfraction-afterH-D-exchage-acetone-d6

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul

 Solvent: acetone
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-99-adduct-2ndfraction-afterH-D-exchage-acetone-d6
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10000.0 Hz
 244 repetitions
OBSERVE   H1, 499.7733163 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
 Gauss apodization 0.600 sec
FT size 65536
Total time 16 hr, 6 min, 54 sec
```



(–)-33b

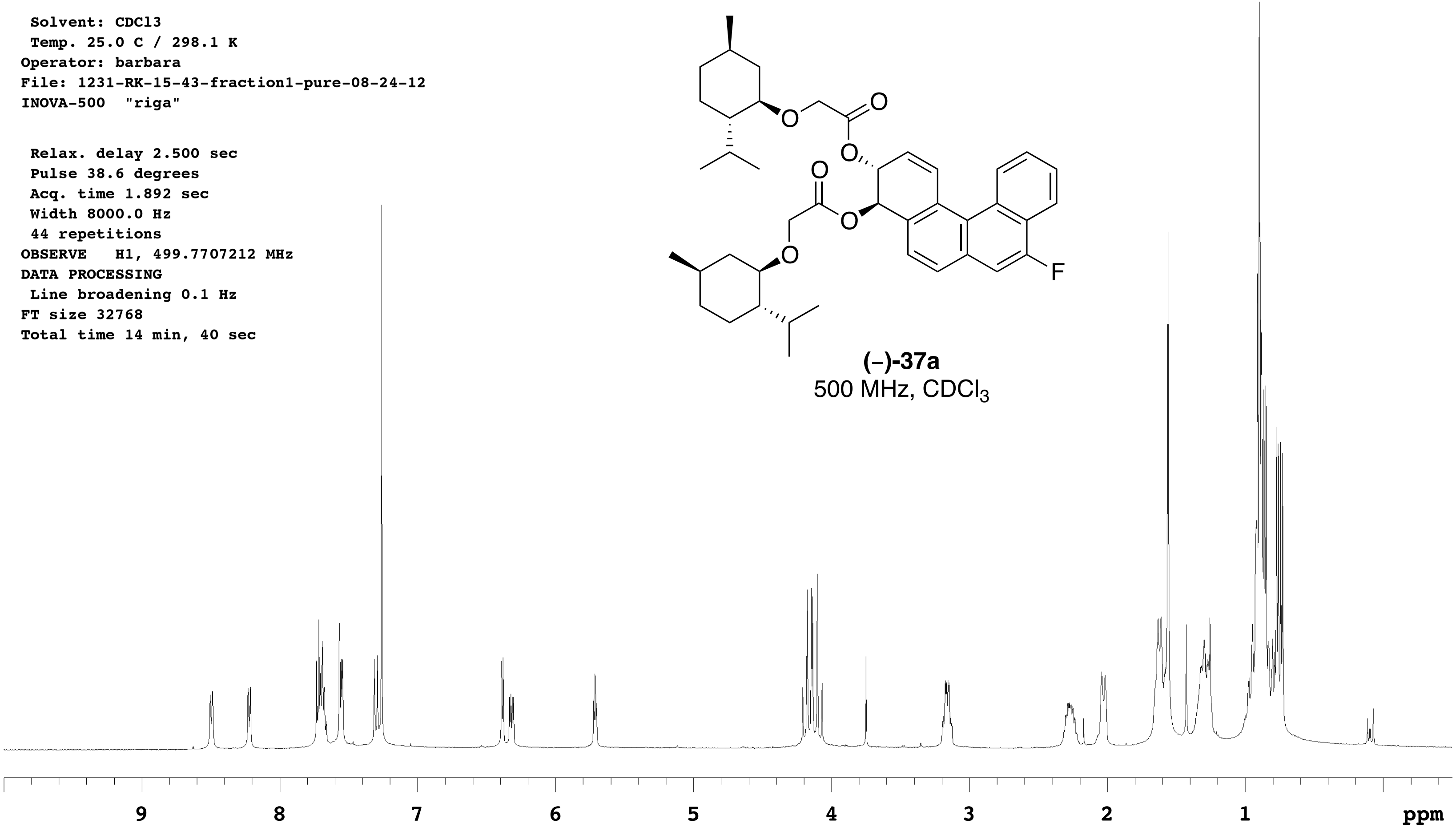
Late eluting

500 MHz, acetone-d_6

```
1231-RK-15-43-fraction1-pure-08-24-12

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-43-fraction1-pure-08-24-12
INOVA-500  "riga"

 Relax. delay 2.500 sec
 Pulse 38.6 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 14 min, 40 sec
```



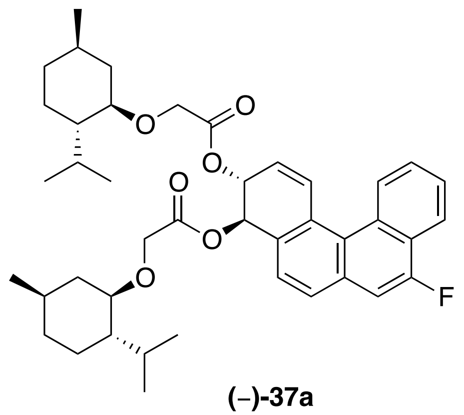
(−)-37a

500 MHz, $CDCl_3$

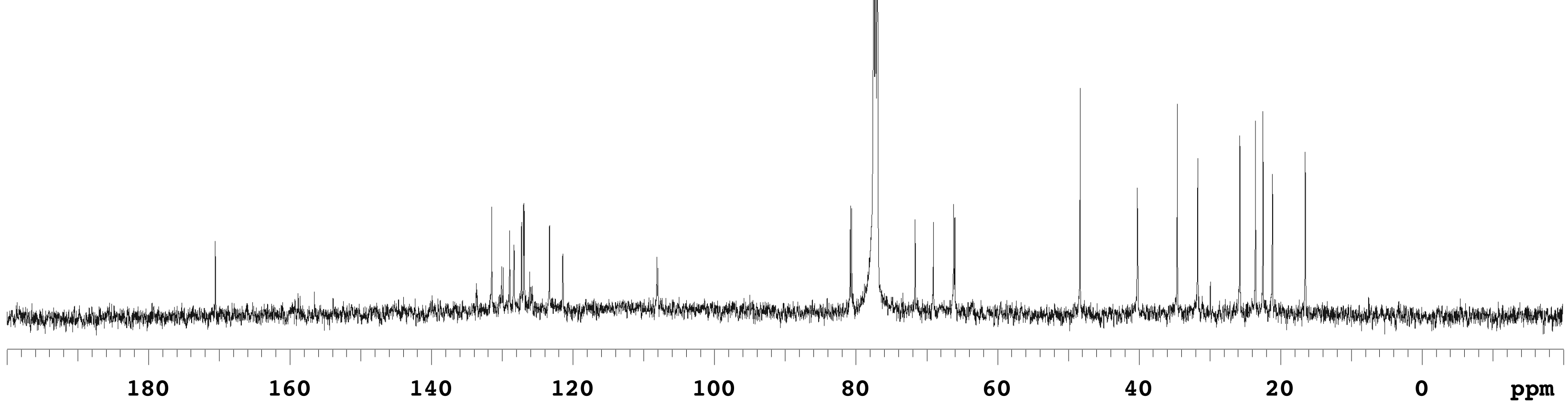
```
1231-RK-15-43-fraction1-13C-CDCl3-08-24-12

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-43-fraction1-13C-CDCl3-08-24-12
INOVA-500  "capella500"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 13000 repetitions
OBSERVE  C13, 125.6674214 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 3.0 Hz
FT size 131072
Total time 19 hr, 10 min, 43 sec
```



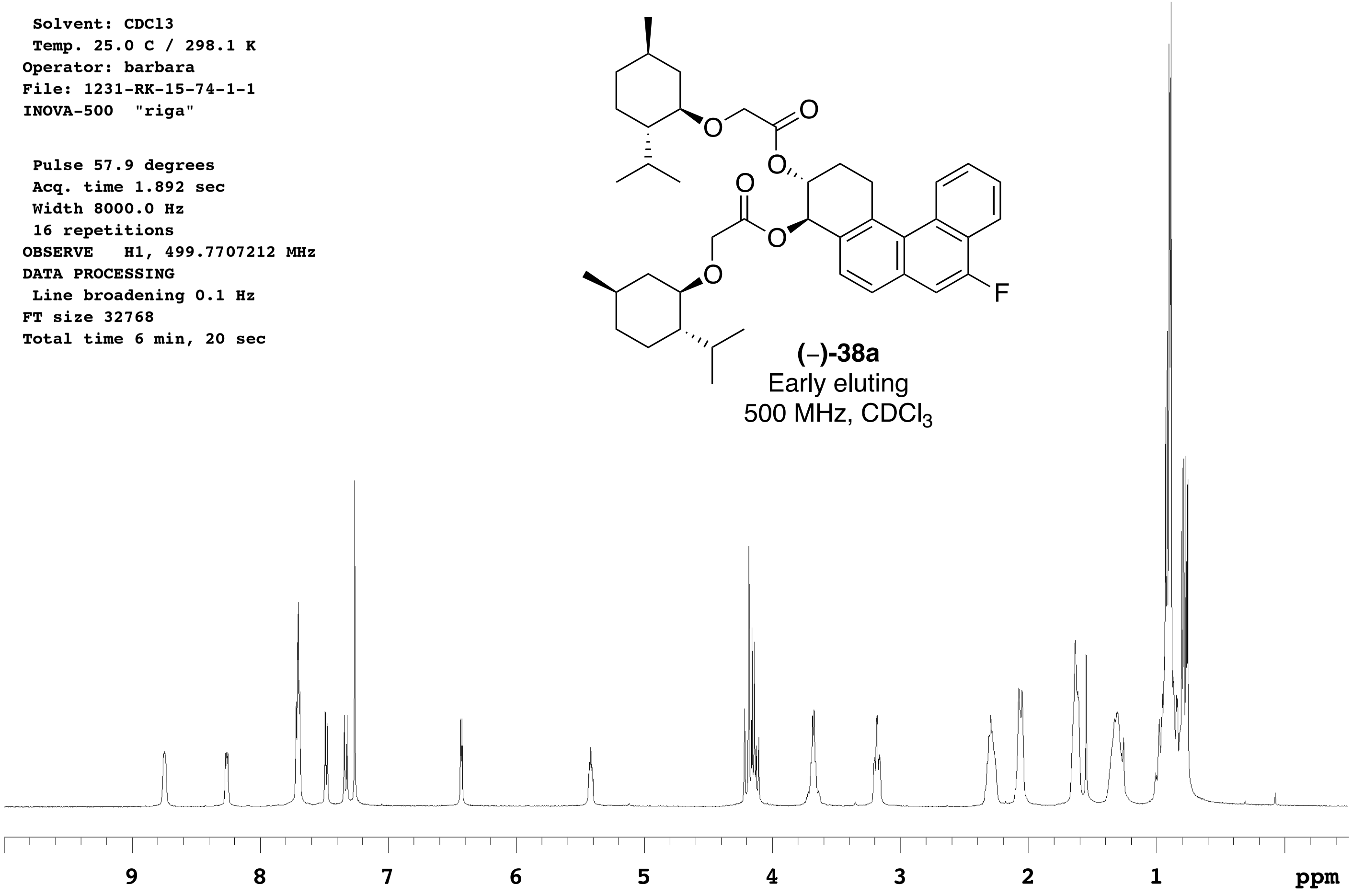
(–)-37a
125 MHz, $CDCl_3$



```
1231-RK-15-74-1-1

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-74-1-1
INOVA-500  "riga"

 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 16 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec
```

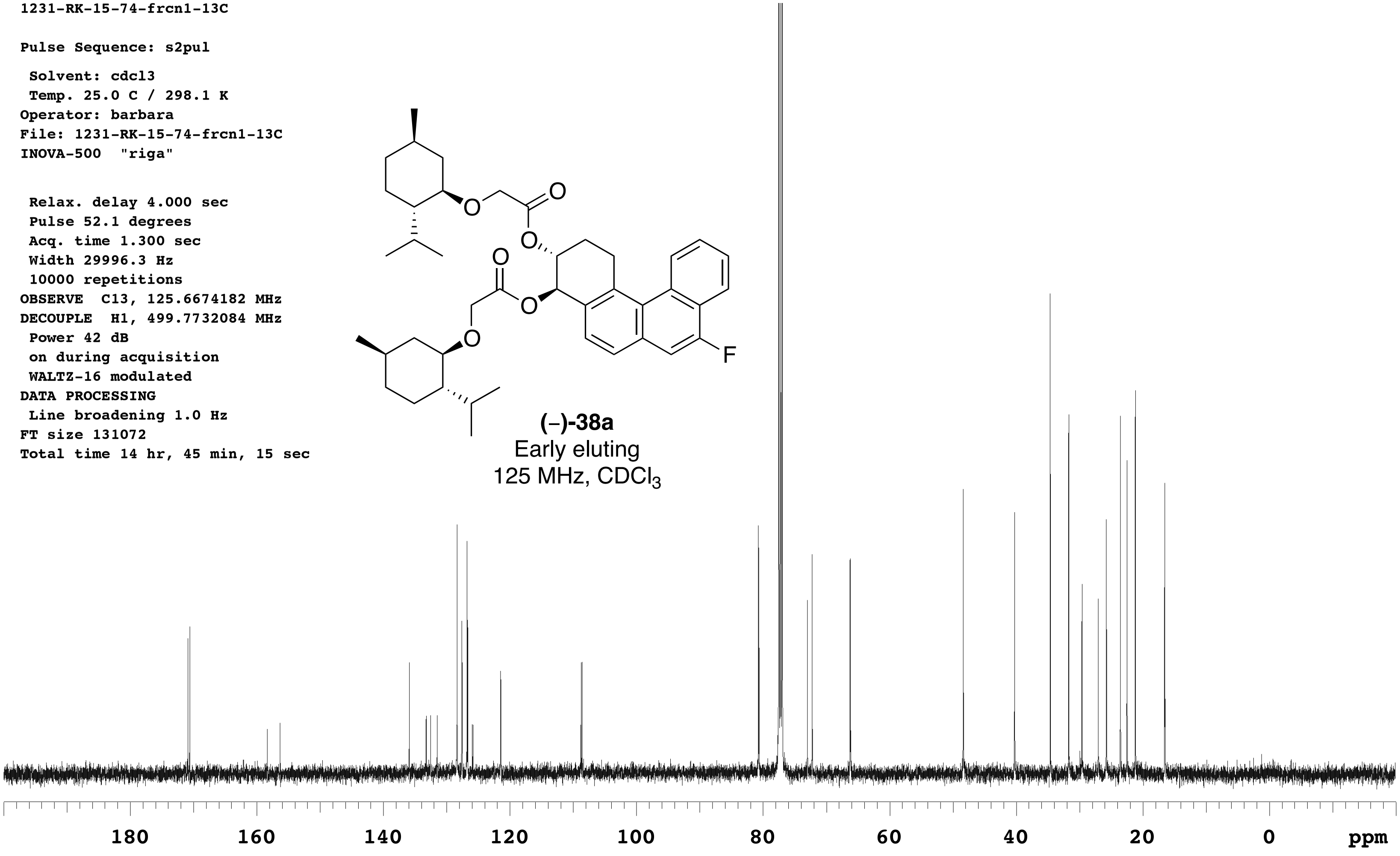


(–)-38a
Early eluting
500 MHz, $CDCl_3$

```
1231-RK-15-74-frcn1-13C

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-74-frcn1-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 10000 repetitions
OBSERVE  C13, 125.6674182 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 14 hr, 45 min, 15 sec
```

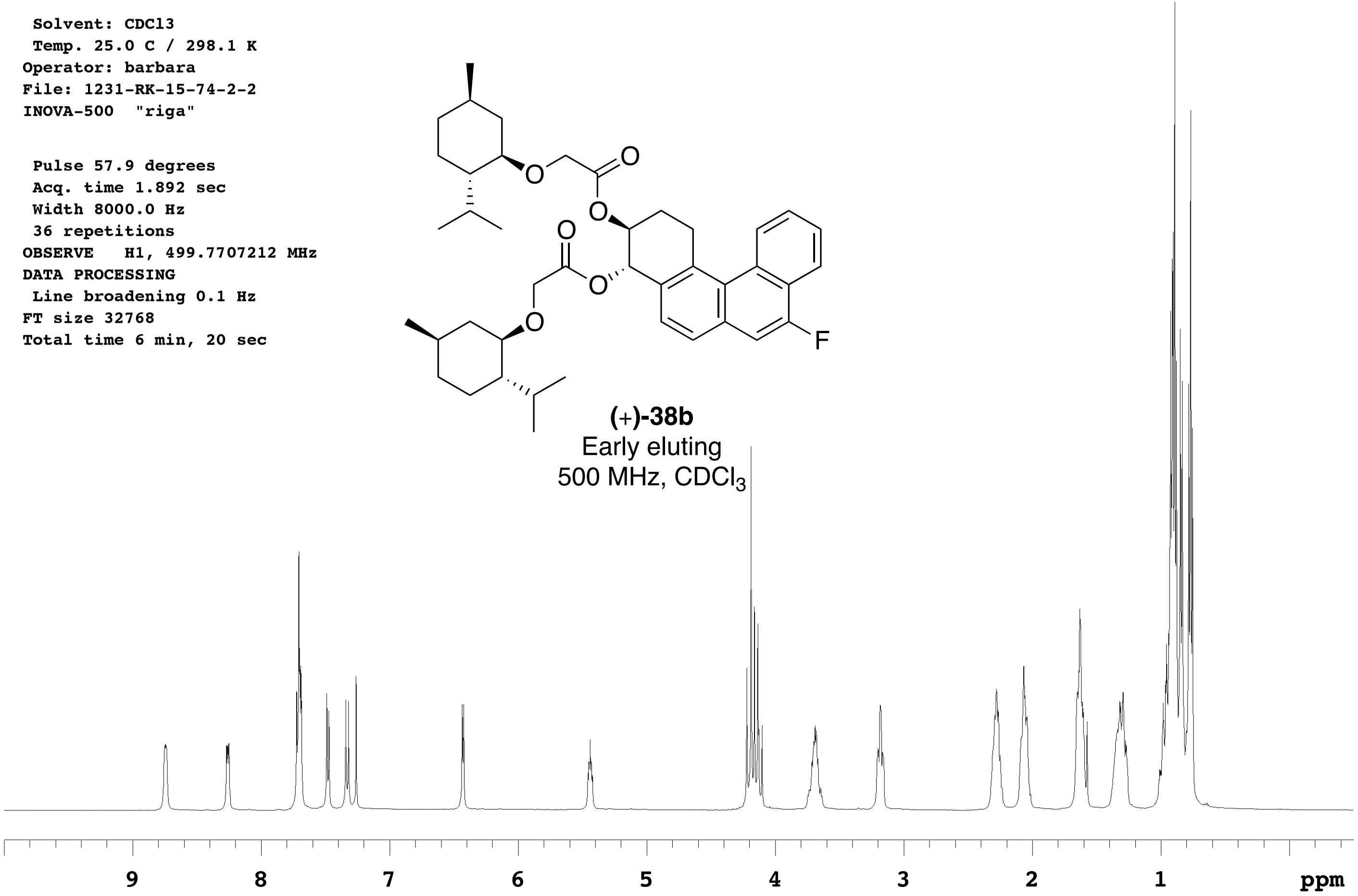


(−)-38a
Early eluting
125 MHz, $CDCl_3$

```
1231-RK-15-74-2-2

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-74-2-2
INOVA-500  "riga"

 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 36 repetitions
OBSERVE   H1, 499.7707212 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec
```



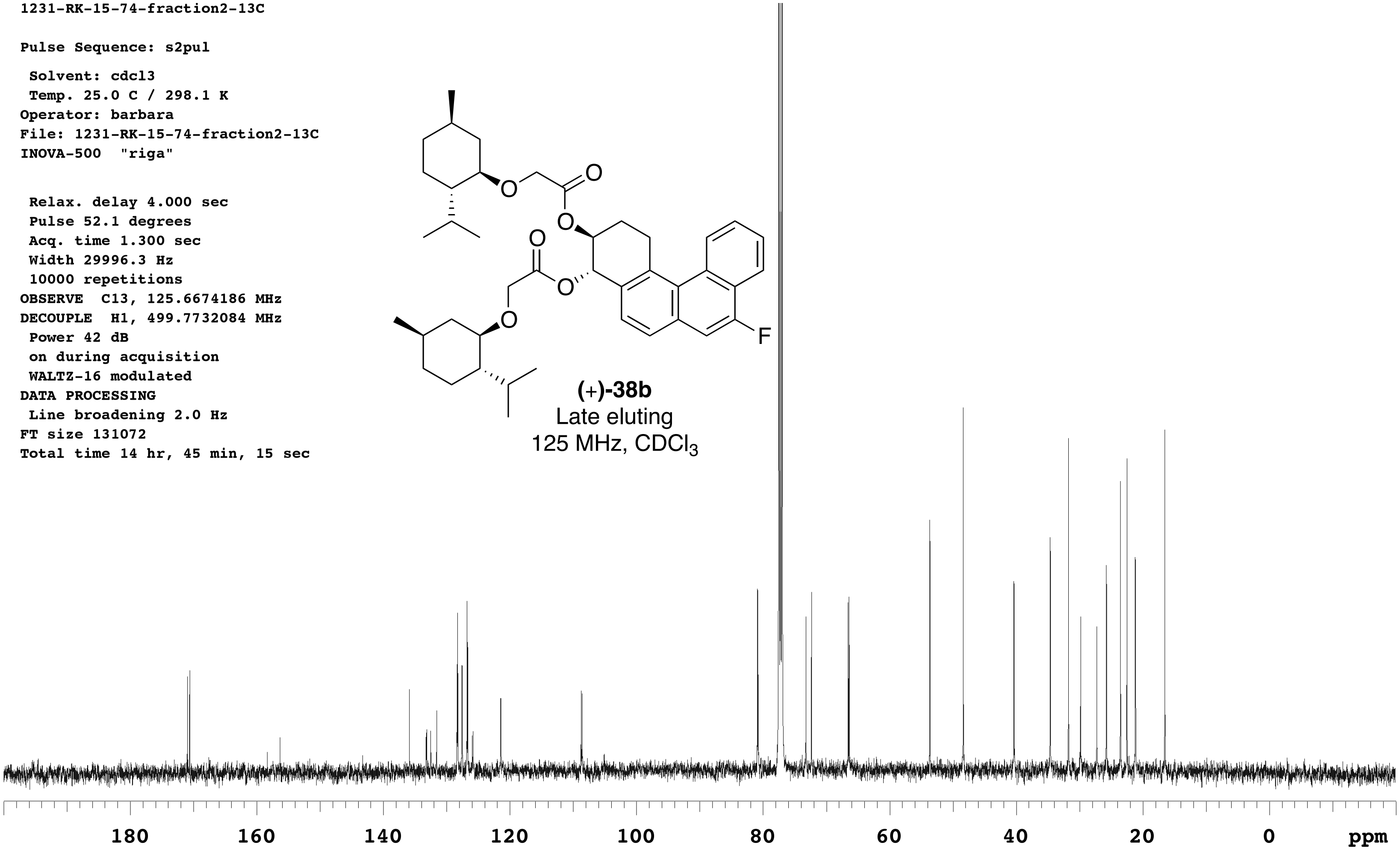
(+)-38b
Early eluting
500 MHz, $CDCl_3$

```
1231-RK-15-74-fraction2-13C

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-74-fraction2-13C
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 10000 repetitions
OBSERVE  C13, 125.6674186 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 131072
Total time 14 hr, 45 min, 15 sec
```

(+)-38b
Late eluting
125 MHz, $CDCl_3$

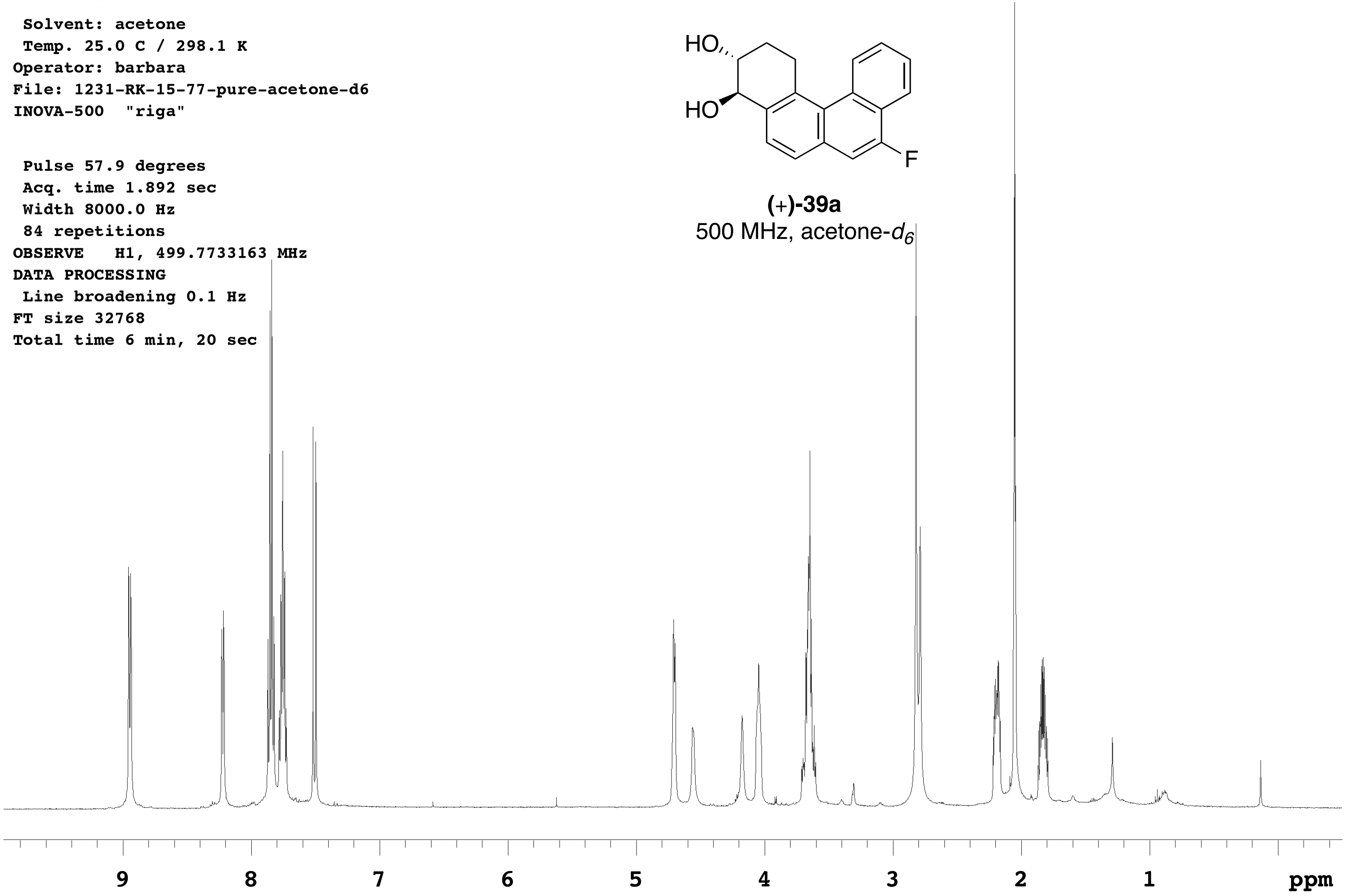


```
1231-RK-15-77-pure-acetone-d6

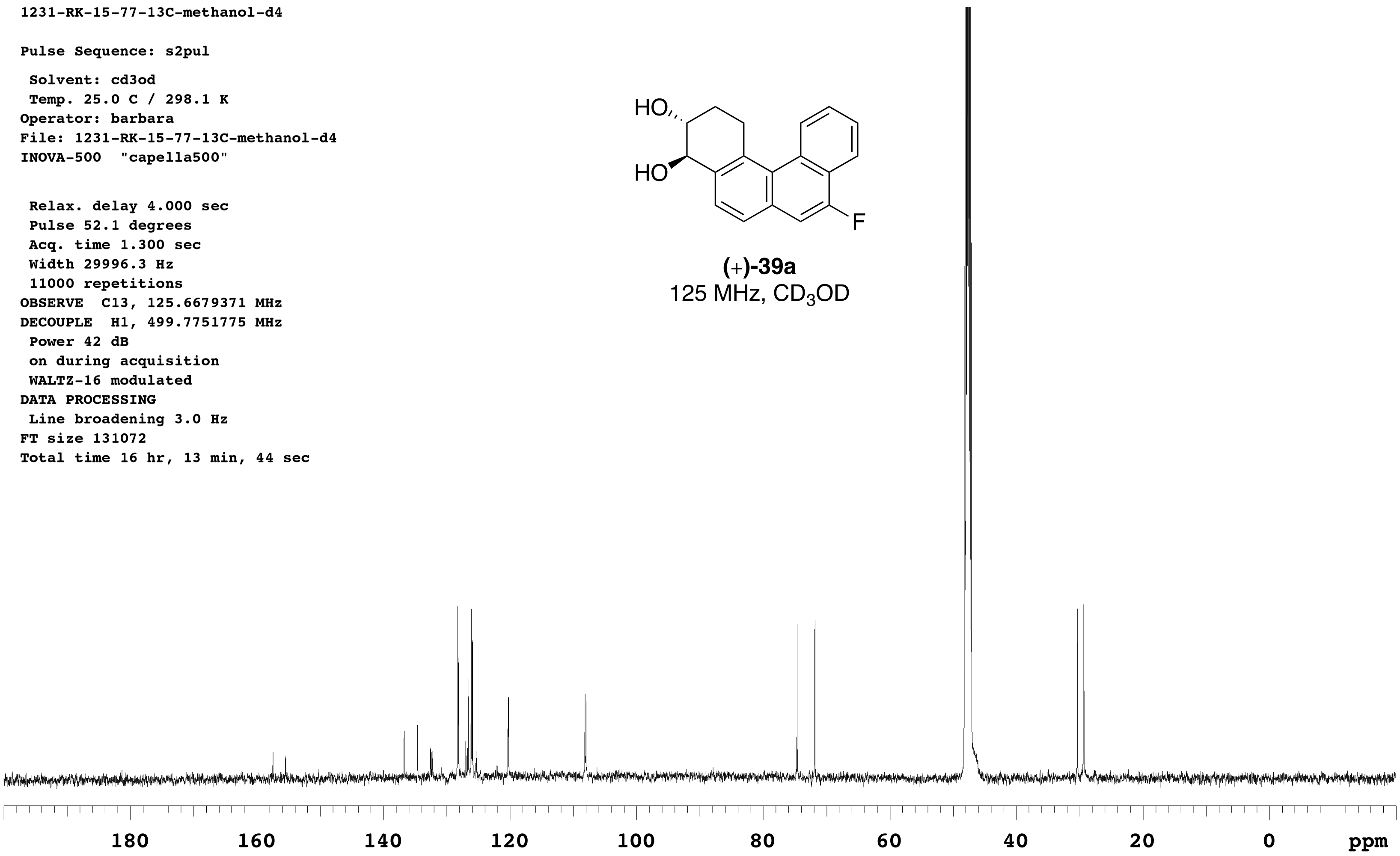
Pulse Sequence: s2pul

 Solvent: acetone
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-77-pure-acetone-d6
INOVA-500  "riga"

 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 84 repetitions
OBSERVE   H1, 499.7733163 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec
```



(+)-39a
500 MHz, acetone-d_6



1231-RK-15-77-13C-methanol-d4

Pulse Sequence: s2pul

Solvent: cd3od
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-77-13C-methanol-d4
INOVA-500 "capella500"

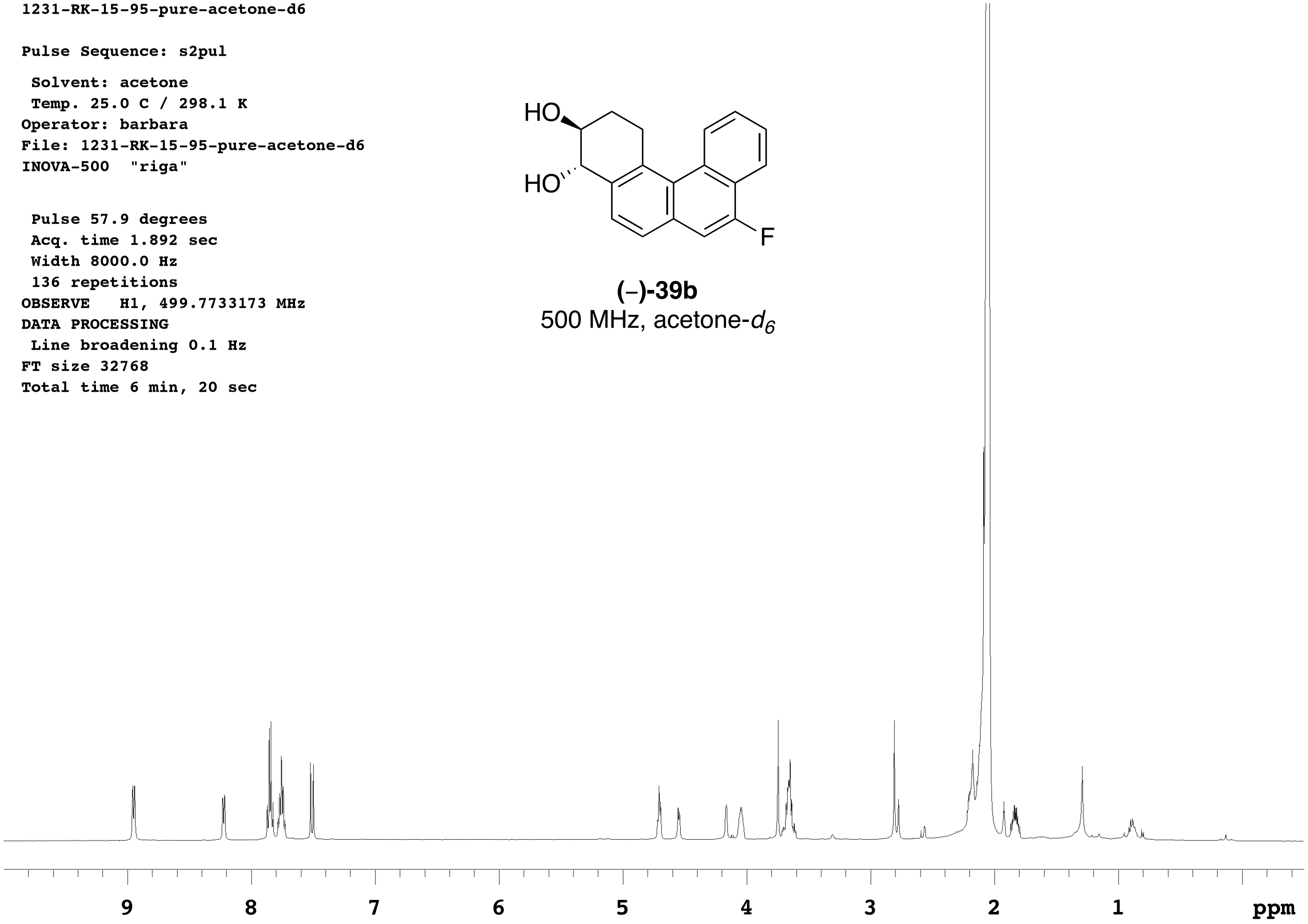
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
11000 repetitions
OBSERVE C13, 125.6679371 MHz
DECOUPLE H1, 499.7751775 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 131072
Total time 16 hr, 13 min, 44 sec

(+)-39a
125 MHz, CD_3OD

```
1231-RK-15-95-pure-acetone-d6

Pulse Sequence: s2pul
 Solvent: acetone
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-95-pure-acetone-d6
INOVA-500  "riga"

 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 136 repetitions
OBSERVE   H1, 499.7733173 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec
```



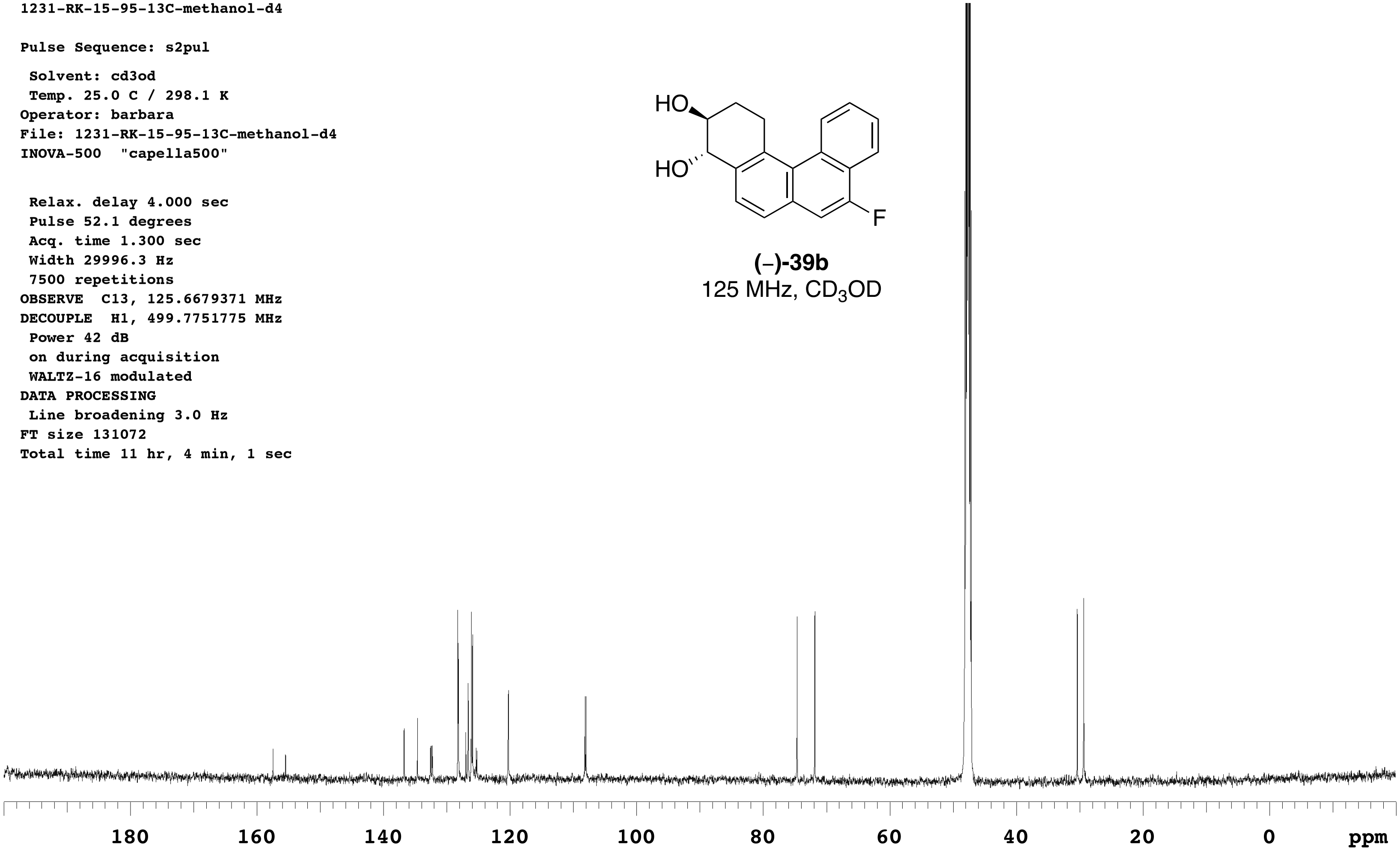
(−)-39b
500 MHz, acetone-d_6

1231-RK-15-95-13C-methanol-d4

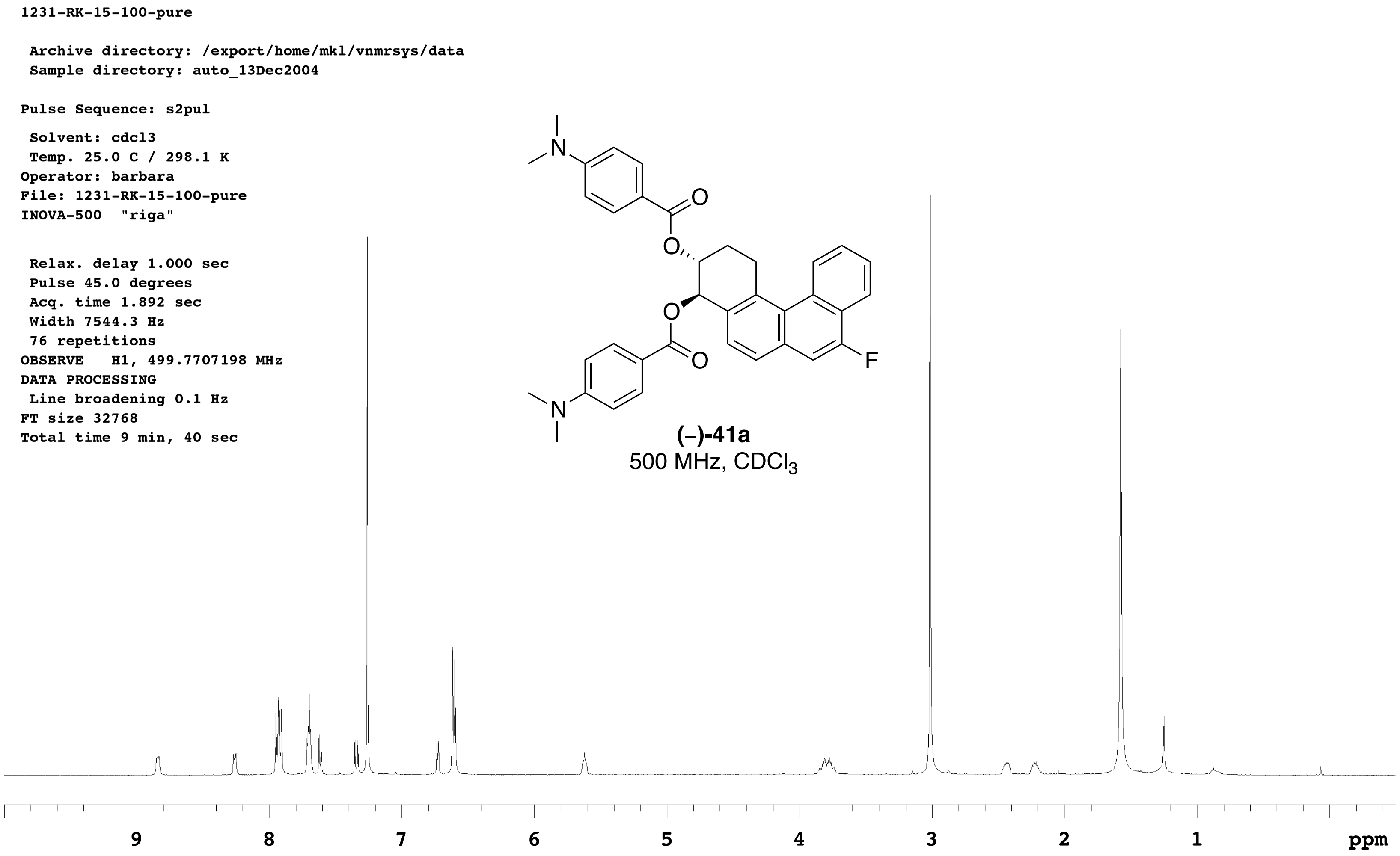
Pulse Sequence: s2pul

Solvent: cd3od
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-95-13C-methanol-d4
INOVA-500 "capella500"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
7500 repetitions
OBSERVE C13, 125.6679371 MHz
DECOUPLE H1, 499.7751775 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 131072
Total time 11 hr, 4 min, 1 sec



(–)-39b
125 MHz, CD_3OD



```
1231-RK-15-100-pure

 Archive directory: /export/home/mkl/vnmrsys/data
 Sample directory: auto_13Dec2004

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-100-pure
INOVA-500  "riga"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 7544.3 Hz
 76 repetitions
OBSERVE   H1, 499.7707198 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 9 min, 40 sec
```

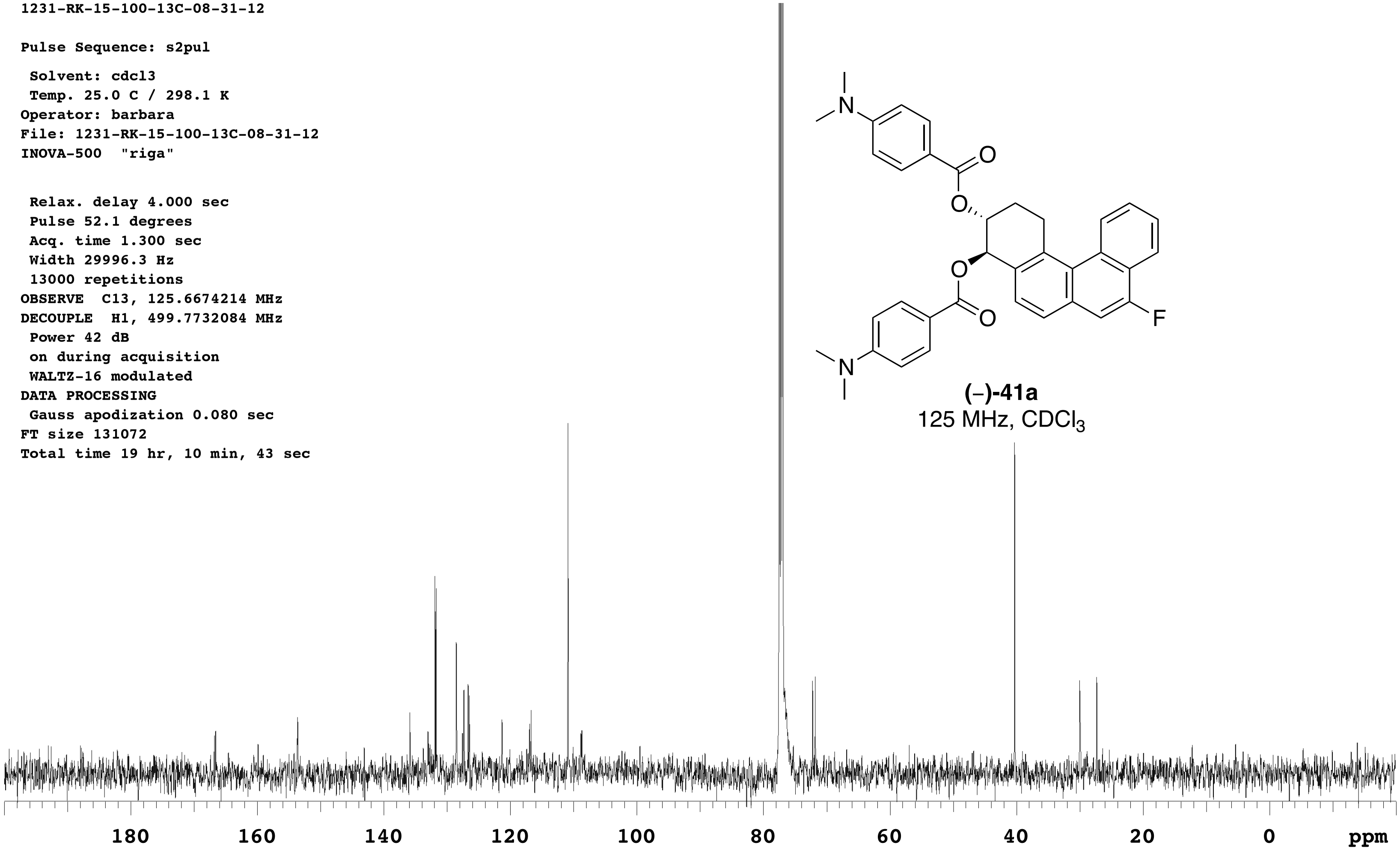
(–)-41a
500 MHz, $CDCl_3$

1231-RK-15-100-13C-08-31-12

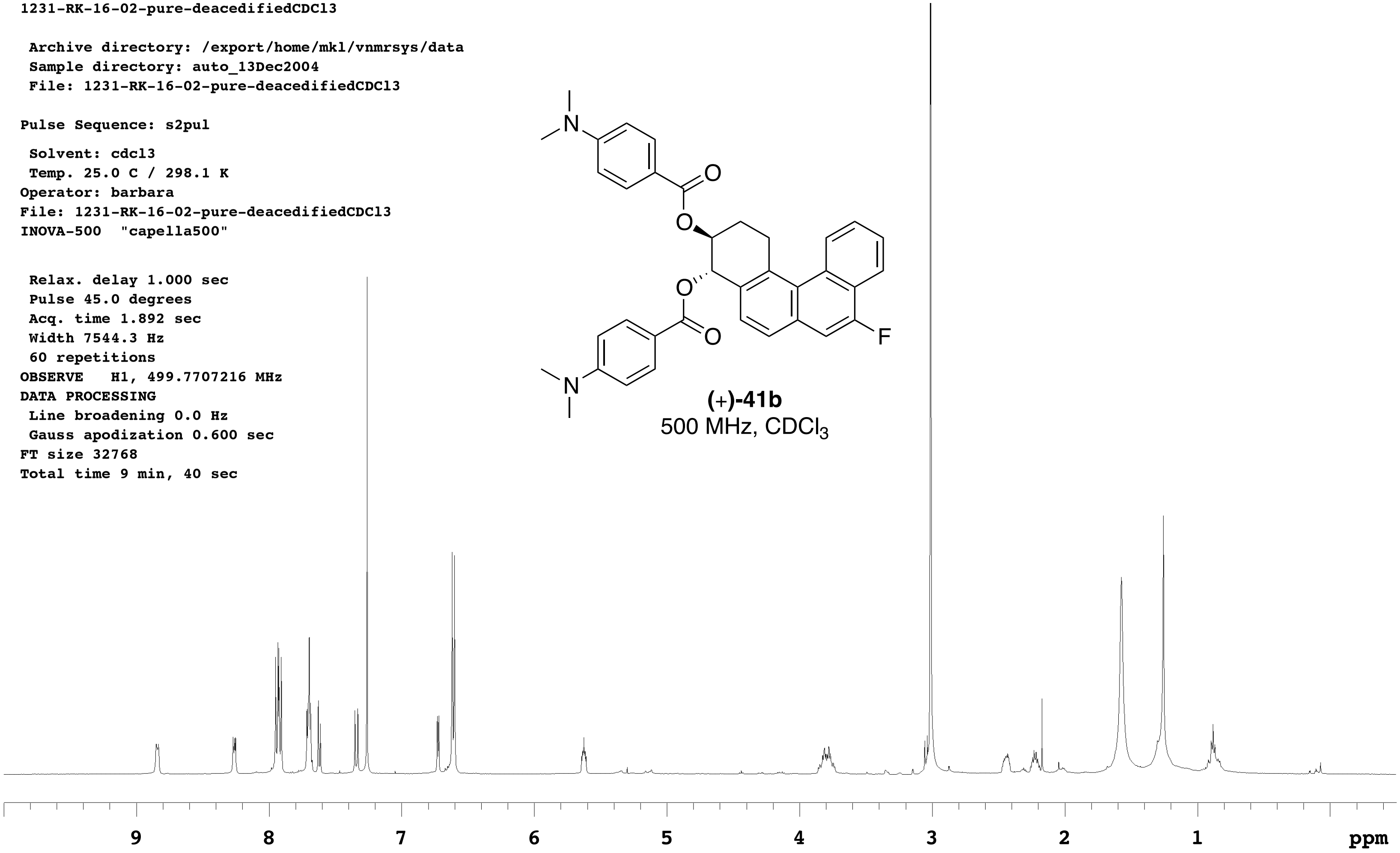
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-15-100-13C-08-31-12
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
13000 repetitions
OBSERVE C13, 125.6674214 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Gauss apodization 0.080 sec
FT size 131072
Total time 19 hr, 10 min, 43 sec



(–)-41a
125 MHz, $CDCl_3$



1231-RK-16-02-pure-deacedifiedCDCl3

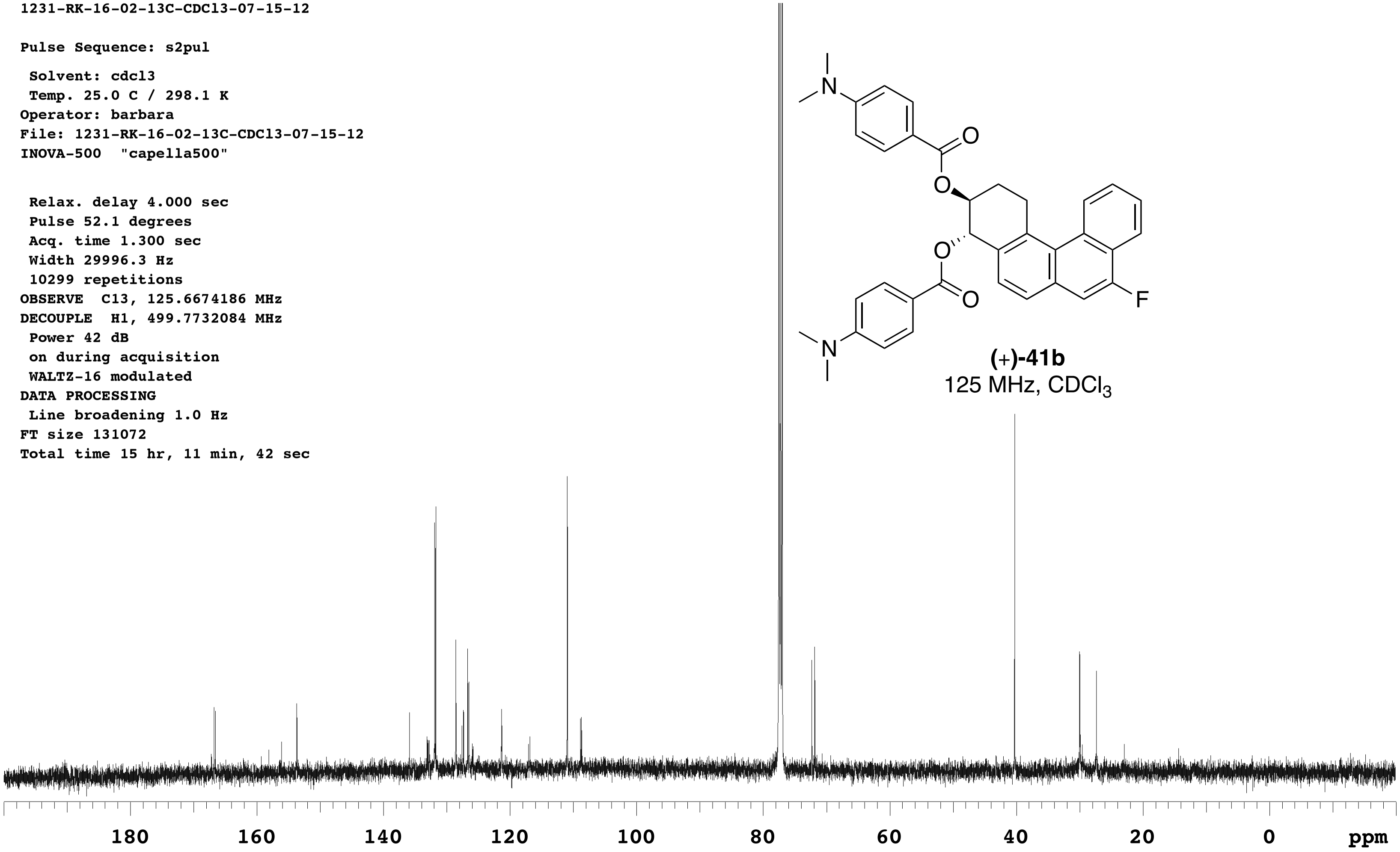
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory: auto_13Dec2004
File: 1231-RK-16-02-pure-deacedifiedCDCl3

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-16-02-pure-deacedifiedCDCl3
INOVA-500 "capella500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 7544.3 Hz
60 repetitions
OBSERVE H1, 499.7707216 MHz
DATA PROCESSING
Line broadening 0.0 Hz
Gauss apodization 0.600 sec
FT size 32768
Total time 9 min, 40 sec

(+)-41b
500 MHz, $CDCl_3$



```
1231-RK-16-02-13C-CDCl3-07-15-12

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-RK-16-02-13C-CDCl3-07-15-12
INOVA-500  "capella500"

 Relax. delay 4.000 sec
 Pulse 52.1 degrees
 Acq. time 1.300 sec
 Width 29996.3 Hz
 10299 repetitions
OBSERVE  C13, 125.6674186 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 42 dB
 on during acquisition
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 15 hr, 11 min, 42 sec
```

(+)-41b
125 MHz, $CDCl_3$

BIBLIOGRAPHY

CHAPTER 1

General Introdcution

1. Kirsch, P. *Modern Fluoroorganic Chemistry. Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004.

2. *Current Fluoroorganic Chemistry: New Synthetic Directions, Technologies, Materials, and Biological Applications;* Soloshonok, V. A.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J. F., Eds.; American Chemical Society: Washington DC, 2007.

3. Smart, B. E.: Fluorine Substituent Effect (On Bioactivity), *J. Fluorine Chem.* **2001**, *109*, 3-11.

4. O'Hagan, D.: Understanding Organofluorine Chemistry. An Introduction to the C–F Bond, *Chem. Soc. Rev.* **2008**, *37,* 308–319.

5. Berger, R.; Resnati, G.; Metrangolo, P.; Weberd, E.; Hulliger, J.: Organic Fluorine Compounds: A Great Opportunity for Enhanced Materials Properties, *Chem. Soc. Rev.* **2011**, *40*, 3496–3508.

6. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V.: Fluorine in Medicinal Chemistry, *Chem. Soc. Rev.* **2008**, *37*, 320-330.

7. Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M.: Fluorine In Medicinal Chemistry, *Chembiochem* **2004**, *5*, 637-643.

8. Ismail, F. M. D.: Important Fluorinated Drugs in Experimental and Clinical Use, *J. Fluorine Chem.* **2002**, *118*, 27-33.

9. Bégué, J.-P.; Bonnet-Delpon, D.: Recent Advances (1995–2005) in Fluorinated Pharmaceuticals Based on Natural Products, *J. Fluorine Chem.* **2006**, *127*, 992-1012.

10. Kirk, L. K.: Fluorine in Medicinal Chemistry: Recent Therapeutic Applications of Fluorinated Small Molecules, *J. Fluorine Chem.* **2006**, *127*, 1013-1029.

11. Jeschke, P.: The Unique Role of Fluorine in the Design of Active Ingredients for Modern Crop Protection, *ChemBioChem* **2004**, *5*, 570-589.

12. Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R.: Fluorinated Organic Materials for Electronic and Optoelectronic Applications: The Role of the Fluorine Atom, *Chem. Commun.* **2007**, 1003-1022.

13. Ding, Y.-S.: ^{18}F-Labeled Biomolecules for PET Studies in the Neurosciences, *J. Fluorine Chem.* **2000**, *101*, 291-295.

14. Moadel, R. M.; Nguyen, A. V.; Lin, E. Y.; Lu, P.; Mani, J.; Blaufox, M. D.; Pollard, J. W.; Dadachova, E.: Positron Emission Tomography Agent 2-Deoxy-2-[^{18}F]fluoro-D-glucose has a Therapeutic Potential in Breast Cancer, *Breast Cancer Research* **2003**, *5*, R199-R205.

15. Hausner, S. H.; Marik, J.; Gagnon, M. K. J.; Sutcliffe, J. L.: In Vivo Positron Emission Tomography (PET) Imaging with an $\alpha_v\beta_6$ Specific Peptide Radiolabeled using ^{18}F-"Click " Chemistry: Evaluation and Comparison with the Corresponding 4-[^{18}F]Fluorobenzoyl- and 2-[^{18}F]Fluoropropionyl-Peptides, *J. Med. Chem.* **2008**, *51,* 5901–5904.

16. Pisaneschi, F.; Nguyen, Q.-D.; Shamsaei, E.; Glaser, M.; Robins, E.; Kaliszczak, M.; Smith, G.; Spivey, A. C.; Aboagye, E. O: Development of a New Epidermal Growth Factor Receptor Positron Emission Tomography Imaging Agent Based on the 3-Cyanoquinoline Core: Synthesis and Biological Evaluation, *Bioorg. Med. Chem.* **2010**, *18*, 6634–6645.

17. Michel, K.; Büther, K.; Law, M. P.; Wagner, S.; Schober, O.; Hermann, S.; Schäfers, M.; Riemann, B.; Höltke, C.; Kopka, K.: Development and Evaluation of Endothelin-A Receptor (Radio) Ligands for Positron Emission Tomography, *J. Med. Chem.* **2011**, *54*, 939–948.

18. Fujinaga, M.; Maeda' J.; Yui, J.; Hatori, A.; Yamasaki, T.; Kawamura, K.; Kumata, K.; Yoshida, Y.; Nagai, Y.; Higuchi, M.; Suhara, T.; Fukumura, T.; Zhang, M.-R.: Characterization of 1-(2-[^{18}F]Fluoro-3-pyridyl)-4-(2-isopropyl-1-oxo- isoindoline-5-yl)-5-methyl-1*H*-1,2,3-triazole, a PET Ligand for Imaging the Metabotropic Glutamate Receptor Type 1 in Rat and Monkey Brains, *J. Neurochem.* **2012**, *121*, 115–124.

19. DINOIU, V.: Chemical Fluorination of Organic Compounds, *Revue Roumaine de Chimie* **2007**, *52*, 219–234.

20. *Modern Organofluorine Chemistry – Synthetic Aspects*, ed. K. K. Laali, Bentham Science Publishers, Hilversum, The Netherlands, 2006, vol. 2.

21. *Fluorine-Containing Synthons*, ed. V. A. Soloshonok, American Chemical Society, Washington, DC, 2005.

22. Lal, G. S.; Pez, G. P.; Syvret, R. G.: Electrophilic NF Fluorinating Agents, *Chem. Rev.* **1996**, 96, 1737−1755.

23. Dutheuil, G.; Couve-Bonnaire, S.; Pannecoucke, X.: Diastereomeric Fluoroolefins as Peptide Bond Mimics Prepared by Asymmetric Reductive Amination of α-Fluoroenones, *Angew. Chem. Int. Ed.* **2007**, *46*, 1290-1292.

24. Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X.: Chiral Dipeptide Mimics Possessing a Fluoroolefin Moiety: A Relevant Tool for Conformational and Medicinal Studies, *Org. Biomol. Chem*. **2007**, *5*, 1151-1157.

25. Veken, P. V.; Senten, K.; Kertesz, I.; De Meester, I.; Lambeir, A. M.; Maes, M. B.; Scharpe, S.; Haemers, A.; Augustyns, K.: Fluoroolefins as Peptidomimetic Inhibitors of Dipeptidyl Peptidases, *J. Med. Chem*. **2005**, *48*, 1768-1780.

26. Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F.: Synthetic Approaches to Monofluoroalkenes, *Chem. Soc. Rev*. **2011**, *40*, 2867–2908.

27. Yanai, H.; Taguchi, T.: Synthetic Methods for Fluorinated Olefins, *Eur. J. Org. Chem.* **2011**, 5939–5954.

28. Zajc, B.; Kumar, R.: Synthesis of Fluoroolefins via Julia–Kocienski Olefination, *Synthesis*, **2010**, 1822-1836.

29. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O.: A Direct Synthesis of Olefins by Reaction of Carbonyl Compounds with Lithio Derivatives of 2-[Alkyl- or (2′-Alkenyl)- or Benzyl-Sulfonyl]-Benzothiazoles, *Tetrahedron Lett*. **1991**, *32*, 1175–1178.

30. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O.: Stereochemistry of the Olefin Formation From *Anti* And *Syn* Heterocyclic β-Hydroxy Sulfones, *Bull. Soc. Chim. Fr.* **1993**, *130*, 336-357.

31. Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O.: Stereochemistry of Direct Olefin Formation From Carbonyl Compounds and Lithiated Heterocyclic Sulfones, *Bull. Soc. Chim. Fr.* **1993**, *130*, 856-878.

32. Blakemore, P. R.: The Modified Julia Olefination: Alkene Synthesis *via* the Condensation of Metallated Heteroarylalkylsulfones with Carbonyl Compounds, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.

33. Plesniak, K.; Zarecki, A.; Wicha, J.: The Smiles Rearrangement and the Julia–Kocienski Olefination Reaction, *Top. Curr. Chem*. **2007**, *275*, 163–250.

34. Aissa, C.: Mechanistic Manifold and New Developments of the Julia–Kocienski Reaction, *Eur. J. Org. Chem*. **2009**, 1831–1844.

35. Chevrie, D.; Lequeux, T.; Demoute, J. P.; Pazenok, S.: A Convenient One-Step Synthesis of Fluoroethylidene Derivatives, *Tetrahedron Lett.* **2003**, *44*, 8127-8130.

36. Ghosh, A. K.; Zajc, B.: High-Yield Synthesis of Fluorinated Benzothiazolyl Sulfones: General Synthons for Fluoro-Julia Olefinations, *Org. Lett*. **2006**, *8*, 1553-1556.

37. Differding, E.; Rüegg, G. M.: Nucleophilic Substitution Versus Electron Transfer: 1. On the Mechanism of Electrophilic Fluorinations, *Tetrahedron Lett.* **1991**, *32*, 3815-3818.

38. Differding, E.; Wehrli, M.: Nucleophilic Substitution Versus Electron Transfer: 2. SN^2 at Flouride and Electron Transfer are Competing and Different Pathways in Electrophilic Flourinations, *Tetrahedron Lett.* **1991**, *32*, 3819-3822.

39. Ghosh, A. K.; Zajc, B.: Fluorinated 1-Phenyl-1*H*-tetrazol-5-yl Sulfone Derivatives as General Reagents for Fluoroalkylidene Synthesis, *J. Org. Chem***.** **2009**, *74,* 8531–8540.

40. Calata, C.; Catel, J.-M.; Pfund, E.; Lequeux, T.: Scope and Limitations of the Julia–Kocienski, Reaction with Fluorinated Sulfonylesters, *Tetrahedron* **2009**, *65*, 3967-3973.

41. Calata, C.; Pfund, E.; Lequeux, T.: Toward the Synthesis of Benzothiazolyl Fluoroaminosulfones, *J. Org. Chem.* **2009**, *74*, 9399-9405.

42. Allendörfer, N.; Es-Sayed, M.; Nieger, M.; Bräse, S.: Novel Aromatic Fluoroolefins via Fluoro-Julia–Kocienski Olefination, *Synthesis* **2010**, 3439-3448.

43. Kake, S.; Zajc, B.: Exceptionally Mild, High-Yield Synthesis of α-Fluoro Acrylates, *Org. Lett*. **2006**, *8*, 4457-4460.

44. Pfund, E.; Lebargy, C.; Rouden, J.; Lequeux, T.: Modified Julia Fluoroolefination: Selective Preparation of Fluoroalkenoates, *J. Org. Chem*. **2007**, *72*, 7871-7877.

45. Alonso, D. A.; Fuensanta, M.; Gómez-Bengoa, E.; Nájera, C. Highly Efficient and Stereoselective Julia–Kocienski Protocol for the Synthesis of α-Fluoro-α,β-unsaturated Esters and Weinreb Amides Employing 3,5-Bis(trifluoromethyl)phenyl (BTFP) Sulfones, *Adv. Synth. Catal.* **2008**, *350*, 1823-1829.

46. del Solar, M.; Ghosh, A. K.; Zajc, B.: Fluoro-Julia Olefination as a Mild, High-Yielding Route to α-Fluoro Acrylonitriles, *J. Org. Chem.* **2008**, *73*, 8206-8211.

47. He, M.; Ghosh, A. K.; Zajc, B.: Julia Olefination as a General Route to Phenyl (α-Fluoro)vinyl Sulfones, *Synlett* **2008**, 999-1004.

48. Ghosh, A. K.; Banerjee, S.; Sinha, S.; Kang, S. B.; Zajc, B.: α-Fluorovinyl Weinreb Amides and α-Fluoroenones From a Common Fluorinated Building Block, *J. Org. Chem.* **2009**, *74*, 3689-3697.

49. Calata, C.; Pfund, E.; Lequeux, T.: Convergent Synthesis of Functionalized

Fluoroallylamines by the Julia-Kocienski Reaction, *Tetrahedron* **2011**, *67*, 1398-1405.

50. Mandal, S. K.; Ghosh, A. K.; Kumar, R.; Zajc, B.: Expedient Synthesis of α-Substituted Fluoroethenes, *Org. Biomol. Chem.* **2012**, *10*, 3164-3167.

51. Prakash, G. K. S.; Shakhmin, A.; Zibinsky, M.; Ledneczki, I.; Chacko, S.; Olah, G. A.: Synthesis of Monofluoroalkenes via Julia–Kocienski Reaction, *J. Fluorine Chem.* **2010**, *131*, 1192-1197.

52. Zhao, Y.; Huang, W.; Zhu, L.; Hu, J.; Difluoromethyl 2-Pyridyl Sulfone: A New *gem*-Difluoroolefination Reagent for Aldehydes and Ketones, *Org. Lett.* **2010**, *12*, 1444-1447.

PART 1

1. Thirsk, C.; Whiting, A.: Polyene Natural Products, *J. Chem. Soc., Perkin Trans 1* **2002**, 999-1023.

2. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D.: Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489.

3. Shi Shun, A. L. K.; Tykwinski, R. R.: Synthesis of Naturally Occurring Polyynes, *Angew. Chem. Int. Ed.* **2006**, *45*, 1034-1057.

4. Meinwald, J.; Meinwald, Y. C.; Chalmers, A. M.; Eisner, T.: Dihydromatricaria Acid: Acetylenic Acid Secreted by Soldier Beetle, *Science* **1968**, *160*, 890-892.

5. Eisner, T.; Hill, D.; Goetz, M.; Jain, S.; Alsop, D.; Camazine, S.; Meinwald, J.: Antifeedant Action of *Z*-Dihydromatricaria Acid From Soldier Beetles, *J. Chem. Ecol.* **1981**, *7*, 1149-1158.

6. Guerrero, A.; Camps, F.; Coll, J.; Riba, M.; Einhorn, J.; Descoins, Ch.; Lallemand, J. Y.: Identification of a Potential Sex Pheromone of the Processionary Moth, Thaumetopoea Pityocampa (Lepidoptera, Notodontidae), *Tetrahedron Lett.* **1981**, *22*, 2013-2016.

7. Quero, C.; Malo, E. A.; Fabriàs, G.; Camps, F.; Lucas, P.; Renou, M.; Guerrero, A.: Reinvestigation of Female Sex Pheromone of Processionary Moth *(Thaumetopoea Pityocampa):* No Evidence for Minor Components, *J. Chem. Ecol.* **1997**, *23*, 713-726.

8. Kinnel, R. B.; Dieter, R. K.; Meinwald, J.; Van Engen, D.; Clardy, J.; Eisner, T.; Stallard, M. O.; Fenical, W.: Brasilenyne and Cis-Dihydrorhodophytin: Antifeedant Medium-Ring Haloethers From a Sea Hare (*Aplysia Brasiliana*), *Proc. Natl. Acad. Sci. USA* **1979**, *76*, 3576-3579.

9. Estevez-Braun, A.; Estevez-Reyes, R.; Moujir, L. M.; Ravelo, A. G.; Gonzalez, A. G.: Antibiotic Activity and Absolute Configuration of 8*S*-Heptadeca-2(*Z*),9(*Z*)-diene-4,6-diyne-1,8-diol From *Bupleurum Salicifolium*, *J. Nat. Prod.* **1994**, *57*, 1178-1182.

10. Ashour, M. L.; Wink, M.: Genus *Bupleurum*: a Review of its Phytochemistry, Pharmacology and Modes of Action, *J. Pharm. Pharmacol.* **2011**, *63*, 305-321.

11. Gupta, A. K.; Shear, N. H.: Terbinafine: An Update, *J. Am. Acad. Dermatol.* **1997**, *37*, 979-988.

12. Abdel-Rahman, S. M.; Nahata, M. C.: Oral Terbinafine: a New Antifungal Agent, *Ann. Pharmacother.* **1997**, *31*, 445-456.

13. Iverson, S. L.; Uetrecht, J. P.: Identification of a Reactive Metabolite of Terbinafine: Insights into Terbinafine-Induced Hepatotoxicity, *Chem. Res. Toxicol.* **2001**, *14*, 175-181.

14. Kirsch, P. *Modern Fluoroorganic Chemistry. Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004.

15. *Current Fluoroorganic Chemistry: New Synthetic Directions, Technologies, Materials, and Biological Applications;* Soloshonok, V. A.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J. F., Eds.; American Chemical Society: Washington DC, 2007.

16. Berger, R.; Resnati, G.; Metrangolo, P.; Weberd, E.; Hulliger, J.: Organic Fluorine Compounds: A Great Opportunity for Enhanced Materials Properties, *Chem. Soc. Rev.* **2011**, *40*, 3496–3508.

17. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V.: Fluorine in Medicinal Chemistry, *Chem. Soc. Rev.* **2008**, *37*, 320-330.

18. Fluorine-Containing Synthons, ed. V. A. Soloshonok, American Chemical Society, Washington, DC, 2005.

19. Negishi, E.-i.; Anastasia, L.: Palladium-Catalyzed Alkynylation, *Chem. Rev.* **2003**, *103*, 1979-2017.

20. Doucet, H.; Hierso, J.-C.: Palladium-Based Catalytic Systems for the Synthesis of Conjugated Enynes by Sonogashira Reactions and Related Alkynylations, *Angew. Chem. Int. Ed.* **2007**, *46*, 834-871.

21. Chinchilla, R.; Nájera, C.: The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry, *Chem. Rev.* **2007**, *107*, 874-922.

22. Weibel, J.-M.; Blanc, A.; Pale, P.: Ag-Mediated Reactions: Coupling and Heterocyclization Reactions, *Chem. Rev.* **2008**, *108*, 3149-3173.

23. Yamamoto, Y.: Silver-Catalyzed C_{sp}-H and C_{sp}-Si Bond Transformations and Related Processes, *Chem. Rev.* **2008**, *108*, 3199-3222.

24. Satoh, T.; Tsurugi, H.; Miura, M.: Catalytic Synthesis of Oligoene and Enyne Derivatives Through Carbometalation of Internal Alkynes, *The Chemical Record* **2008**, *8*, 326-336.

25. Tellier, F.; Sauvêtre, R.; Normant, J.-F.: Preparation Et Reactivite De Quelques Enynes Fluores, *Tetrahedron Lett.* **1986**, *27*, 3147-3148.

26. Yoshida, M.; Yoshikawa, S.; Fukuhara, T.; Yoneda, N.; Hara, S.: Stereoselective Synthesis of (*E*)-1-Fluoro-1,3-enynes, *Tetrahedron* **2001**, *57*, 7143-7148.

27. Eddarir, S.; Francesch, C.; Mestdagh, H.; Rolando, C.: Synthesis of Fluorinated Enynes via 1-Bromo 1-Fluoro Alkenes, *Tetrahedron Lett*. **1990**, *31*, 4449-4452.

28. Percy, J. M.; Wilkes, R. D.: A Rapid and Convenient Approach to Functionally Diverse Monofluorinated Vinylic Compounds, *Tetrahedron* **1997**, *53*, 14749-14762.

29. Zhang, X.; Burton, D. J.: A Kinetic Separation Method for the Stereoselective Preparation of (*Z*)- and (*E*)-Monofluoroenynes From *E*/*Z* Mixtures of 1-Bromo-1-fluoroolefins, *J. Fluorine Chem*. **2001**, *112*, 317-324.

30. Xu, J.; Wang, Y.; Burton, D. J.: Site-Specific Preparation of 3-Fluoro-1-substituted-naphthalenes via a Novel Base-Catalyzed Cyclization Reaction from (*E*)-Monofluoroenynes, *Org. Lett*. **2006**, *8*, 2555-2558.

31. Wang, Y.; Xu, J.; Burton, D. J.: A Simple, Two-Step, Site-Specific Preparation of Fluorinated Naphthalene and Phenanthrene Derivatives From Fluorobromo-Substituted Alkenes, *J. Org. Chem*. **2006**, *71*, 7780-7784.

32. Yang, Z.-Y.; Burton, D. J.: A Facile, General Method for the Preparation of Fluorinated Enynes, *Tetrahedron Lett*. **1990**, *31*, 1369-1372.

33. Yang, Z.-Y.; Burton, D. J.: Palladium-Catalyzed Reaction of Fluorinated Vinyl Iodides With Terminal Alkynes: A New and General Route To Fluorinated Enynes, *J. Fluorine Chem*. **1991**, *53*, 307-326.

34. Ichikawa, J.; Ikeura, C.; Minami, T.: A One-Pot Synthesis of Conjugated Fluoroenynes via 2,2-Difluorovinylcopper Intermediates, *J. Fluorine Chem*. **1993**, *63*, 281-285.

35. Sanders, T. C.; Golen, J. A.; Williard, P. G.; Hammond, G. B.: The Crystal Structure of 2-Fluoro-1-(*p*-methoxyphenyl)-1-penten-3-yne, A Fluorinated Vinylacetylene Prepared via Horner-Wadsworth-Emmon Condensation, *J. Fluorine Chem.* **1997**, *85*, 173-175.

36. Benayoud, F.; Chen, L.; Moniz, G. A.; Zapata, A. J.; Hammond, G. B.: Synthesis of α-Fluoro-β,γ-alkenylphosphonates and Conjugated Fluoroenynes From a Common Intermediate (α-Fluoropropargyl)phosphonate, *Tetrahedron* **1998**, *54*, 15541-15554.

37. Zapata, A. J.; Gu, Y.; Hammond, G. B.: The First α-Fluoroallenylphosphonate, the Synthesis of Conjugated Fluoroenynes, and the Stereoselective Synthesis of

Vinylfluorophosphonates Using a New Multifunctional Fluorine-Containing Building Block, *J. Org. Chem.* **2000**, *65*, 227-234.

38. Camps, F.; Coll, J.; Fabriàs, G.; Guerrero, A.; Riba, M.: Fluorinated Analogs of Insect Sex Pheromones, *Experientia* **1984,** *40*, 933-934.

39. Camps, F.; Fabriàs, G.; Guerrero, A.: Synthesis of a Fluorinated Analog of the Sex Pheromone of the Processionary Moth *Thaumetopoea Pityocampa*, *Tetrahedron*, **1986**, *42*, 3623-3629.

40. Camps, F.; Fabriàs, G.; Gasol, V.; Guerrero, A.; Hernández, R.; Montoya, R.: Analogs of Sex Pheromone of the Processionary Moth, *Thaumetopoea Pityocampa*: Synthesis and Biological Activity, *J. Chem. Ecol.* **1988**, *14*, 1331-1346.

41. Blakemore, P. R.: The Modified Julia Olefination: Alkene Synthesis *via* the Condensation of Metallated Heteroarylalkylsulfones with Carbonyl Compounds, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.

42. Plesniak, K.; Zarecki, A.; Wicha, J.: The Smiles Rearrangement and the Julia–Kocienski Olefination Reaction, *Top. Curr. Chem*. **2007**, *275*, 163–250.

43. Aissa, C.: Mechanistic Manifold and New Developments of the Julia–Kocienski Reaction, *Eur. J. Org. Chem*. **2009**, 1831–1844.

44. Zajc, B.; Kumar, R.: Synthesis of Fluoroolefins via Julia–Kocienski Olefination, *Synthesis*, **2010**, 1822-1836.

45. Ghosh, A. K.; Zajc, B.: High-Yield Synthesis of Fluorinated Benzothiazolyl Sulfones: General Synthons for Fluoro-Julia Olefinations, *Org. Lett*. **2006**, *8*, 1553-1556.

46. Ghosh, A. K.; Zajc, B.: Fluorinated 1-Phenyl-1*H*-tetrazol-5-yl Sulfone Derivatives as General Reagents for Fluoroalkylidene Synthesis, *J. Org. Chem***.** **2009**, *74,* 8531–8540.

47. Kake, S.; Zajc, B.: Exceptionally Mild, High-Yield Synthesis of α-Fluoro Acrylates, *Org. Lett*. **2006**, *8*, 4457-4460.

48. del Solar, M.; Ghosh, A. K.; Zajc, B.: Fluoro-Julia Olefination as a Mild, High-Yielding Route to α-Fluoro Acrylonitriles, *J. Org. Chem.* **2008**, *73*, 8206-8211.

49. He, M.; Ghosh, A. K.; Zajc, B.: Julia Olefination as a General Route to Phenyl (α-Fluoro)vinyl Sulfones, *Synlett* **2008**, 999-1004.

50. Ghosh, A. K.; Banerjee, S.; Sinha, S.; Kang, S. B.; Zajc, B.: α-Fluorovinyl Weinreb Amides and α-Fluoroenones From a Common Fluorinated Building

Block, *J. Org. Chem.* **2009**, *74*, 3689-3697.

51. Mandal, S. K.; Ghosh, A. K.; Kumar, R.; Zajc, B.: Expedient Synthesis of α-Substituted Fluoroethenes, *Org. Biomol. Chem.* **2012**, *10*, 3164-3167.

52. Bonini, C.; Chiummiento, L.; Videtta, V.: Direct Preparation of *Z*-1,3-Enyne Systems with a TMS-Propargylic Sulfone: Application of a One-Pot Julia Olefination, *Synlett* **2006**, 2079-2082.

53. Bonini, C.; Chiummiento, L.; Videtta, V.: One-Pot Practical Preparation of Novel Propargylic Aryl and Heteroaryl Sulfides and Sulfones, *Synlett* **2005**, 3067-3070.

54. Hoogboom, J.; Swager, T. M.: Increased Alignment of Electronic Polymers in Liquid Crystals via Hydrogen Bonding Extension, *J. Am. Chem. Soc.* **2006**, *128*, 15058-15059.

55. Neuvonen, H.; Neuvonen, K.; Koch, A.; Kleinpeter, E.; Pasanen, P.: Electron-Withdrawing Substituents Decrease the Electrophilicity of the Carbonyl Carbon. An Investigation with the Aid of ^{13}C NMR Chemical Shifts, ν(C=O) Frequency Values, Charge Densities, and Isodesmic Reactions To Interprete Substituent Effects on Reactivity, *J. Org. Chem.* **2002**, *67*, 6995-7003.

56. Ziegler, C. B., Jr.; Heck, R. F.: Palladium-Catalyzed Vinylic Substitution with Highly Activated Aryl Halides, *J. Org. Chem.* **1978**, *43*, 2941-2946.

57. Beletskaya, I. P.; Cheprakov, A. V.: The Heck Reaction as a Sharpening Stone of Palladium Catalysis, *Chem. Rev.* **2000**, *100*, 3009-3066.

58. Lagisetty, P.; Zhang, L.; Lakshman, M. K.: Simple Methodology for Heck Arylation at C- 8 of Adenine Nucleosides, *Adv. Synth. Catal.* **2008**, *350*, 602-608.

PART 2

1. Fan, W.-Q.; Katritzky, A. R.: In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science: New York, 1996.

2. Angell, Y. L.; Burgess, K.: Peptidomimetics via Copper-Catalyzed Azide–Alkyne Cycloadditions, *Chem. Soc. Rev.* **2007**, *36*, 1674–1689.

3. Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H.: CuI-Catalyzed Alkyne–Azide “Click” Cycloadditions from a Mechanistic and Synthetic Perspective, *Eur. J. Org. Chem.* **2006**, 51–68.

4. Appendino, G.; Bacchiega, S.; Minassi, A.; Cascio, M. G.; Petrocellis, L. D.; Marzo, V. D.: The 1,2,3-Triazole Ring as a Peptido- and Olefinomimetic Element: Discovery of Click Vanilloids and Cannabinoids, *Angew. Chem., Int. Ed*. **2007**, *46*, 9312 –9315.

5. Agalave, S. G.; Maujan, S. R.; Pore, V. S.: Click Chemistry: 1,2,3-Triazoles as Pharmacophores, *Chem. Asian J.* **2011**, *6,* 2696 – 2718.

6. Moses, J. E.; Moorhouse, A. D.: The Growing Applications of Click Chemistry, *Chem. Soc. Rev*. **2007**, *36*, 1249–1262.

7. Aragão-Leoneti, V.; Campo, V. L.; Gomes, A. S.; Field, R. A.; Carvalho, I.: Application of Copper(I)-Catalysed Azide/Alkyne Cycloaddition (CuAAC) ‘Click Chemistry’ in Carbohydrate Drug and Neoglycopolymer Synthesis, *Tetrahedron* **2010**, *66*, 9475-9492.

8. Kolb, H. C.; Sharpless, K. B.: The Growing Impact of Click Chemistry on Drug Discovery, *Drug Discovery Today* **2003**, *8*, 1128-1137.

9. Binder, W. H.; Sachsenhofer, R.: **‘**Click’ Chemistry in Polymer and Materials Science, *Macromol. Rapid Commun*. **2007**, *28*, 15–54.

10. Lutz, J. F.: 1,3-Dipolar Cycloadditions of Azides and Alkynes: A Universal Ligation Tool in Polymer and Materials Science, *Angew. Chem., Int. Ed.* **2007,** *46,* 1018-1025.

11. Huisgen, R.: 1,3-Dipolar Cycloadditions Past and Future, *Angew. Chem., Int. Ed Engl*. **1963**, *2*, 565-632

12. Tornøe, C. W.; Christensen, C.; Meldal, M.: Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides, *J. Org. Chem.* **2002,** *67,* 3057-3064.

13. Rostovtsev, V.; Green, L.; Fokin, V.; Sharpless, B.: A Stepwise Huisgen Cycloaddition Process: Copper(i)-Catalyzed Regioselective " Ligation " of Azides and Terminal Alkynes, *Angew. Chem Int. Ed.* **2002,** *41,* 2596-2599.

14. Gil, M. V.; Arévalo, M. J.; López, Ó.: Click Chemistry – What's in a Name? Triazole Synthesis and Beyond, *Synthesis,* **2007**, 1589–1620.

15. Tornøe, C. W.; Meldal, M.: Cu-Catalyzed Azide-Alkyne Cycloaddition, *Chem. Rev.* **2008**, *108*, 2952–3015.

16. Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Fokin, V. V.; Noodleman, L.; Sharpless, K. B.: Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates, *J. Am. Chem. Soc.* **2005**, *127*, 210 – 216.

17. Rodionov, V. O.; Fokin, V. V.; Finn, M. G.: Mechanism of the Ligand-Free CuI-Catalyzed Azide–Alkyne Cycloaddition Reaction, *Angew. Chem. Int. Ed.* **2005**, *44*, 2210 –2215.

18. Ahlquist, M.; Fokin, V. V.: Enhanced Reactivity of Dinuclear Copper(I) Acetylides in Dipolar Cycloadditions, *Organometallics* **2007**, *26,* 4389-4391.

19. *Current Fluoroorganic Chemistry: New Synthetic Directions, Technologies, Materials, and Biological Applications;* Soloshonok, V. A.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J. F., Eds.; American Chemical Society: Washington DC, **2007.**

20. Smart, B. E.: Fluorine Substituent Effect (On Bioactivity), *J. Fluorine Chem.* **2001**, *109*, 3-11.

21. O'Hagan, D.: Understanding Organofluorine Chemistry. An Introduction to the C–F Bond, *Chem. Soc. Rev.* **2008**, *37,* 308–319.

22. Berger, R.; Resnati, G.; Metrangolo, P.; Weberd, E.; Hulliger, J.: Organic Fluorine Compounds: A Great Opportunity for Enhanced Materials Properties, *Chem. Soc. Rev.* **2011**, *40*, 3496–3508.

23. Whiting, M.; Tripp, J. C.; Lin, Y.-C.; Lindstrom, W.; Olson, A. J.; Elder, J. H.; K. Sharpless, B.; Fokin, V. V.: Rapid Discovery and Structure-Activity Profiling of Novel Inhibitors of Human Immunodeficiency Virus Type 1 Protease Enabled by the Copper(I)-Catalyzed Synthesis of 1,2,3-Triazoles and Their Further Functionalization, *J. Med. Chem.* **2006**, *49,* 7697-7710.

24. Llano-Sotelo, B.; Dunkle, J.; Klepacki, D.; Zhang, W.; Fernandes, P.; Cate, J.

H. D.; Mankin, A. S.: Binding and Action of CEM-101, A New Fluoroketolide Antibiotic That Inhibits Protein Synthesis, *Antimicrob. Agents Chemother* **2010**, *54*, 4961-4970.

25. Gill, C.; Jadhav, G.; Shaikh, M.; Kale, R.; Ghawalkar, A.; Nagargoje, D.; Shiradkar, M.: Clubbed [1,2,3] Triazoles by Fluorine Benzimidazole: A Novel Approach to H37Rv Inhibitors as a Potential Treatment for Tuberculosis, *Bioorg. Med. Chem. Lett*. **2008**, *18*, 6244–6247.

26. Hausner, S. H.; Marik, J.; Gagnon, M. K. J.; Sutcliffe, J. L.: In Vivo Positron Emission Tomography (PET) Imaging with an $\alpha_v\beta_6$ Specific Peptide Radiolabeled using ^{18}F-" Click " Chemistry: Evaluation and Comparison with the Corresponding 4-[^{18}F]Fluorobenzoyl- and 2-[^{18}F]Fluoropropionyl-Peptides, *J. Med. Chem.* **2008**, *51,* 5901–5904.

27. Pisaneschi, F.; Nguyen, Q.-D.; Shamsaei, E.; Glaser, M.; Robins, E.; Kaliszczak, M.; Smith, G.; Spivey, A. C.; Aboagye, E. O: Development of a New Epidermal Growth Factor Receptor Positron Emission Tomography Imaging Agent Based on the 3-Cyanoquinoline Core: Synthesis and Biological Evaluation, *Bioorg. Med. Chem*. **2010**, *18*, 6634–6645.

28. Michel, K.; Büther, K.; Law, M. P.; Wagner, S.; Schober, O.; Hermann, S.; Schäfers, M.; Riemann, B.; Höltke, C.; Kopka, K.: Development and Evaluation of Endothelin-A Receptor (Radio) Ligands for Positron Emission Tomography, *J. Med. Chem*. **2011**, *54*, 939–948.

29. Fujinaga, M.; Maeda' J.; Yui, J.; Hatori, A.; Yamasaki, T.; Kawamura, K.; Kumata, K.; Yoshida, Y.; Nagai, Y.; Higuchi, M.; Suhara, T.; Fukumura, T.; Zhang, M.-R.: Characterization of 1-(2-[^{18}F]Fluoro-3-pyridyl)-4-(2-isopropyl-1-oxo-isoindoline-5-yl)-5-methyl-1*H*-1,2,3-triazole, a PET Ligand for Imaging the Metabotropic Glutamate Receptor Type 1 in Rat and Monkey Brains, *J. Neurochem*. **2012**, *121*, 115–124.

30. Dutheuil, G.; Couve-Bonnaire, S.; Pannecoucke, X.: Diastereomeric Fluoroolefins as Peptide Bond Mimics Prepared by Asymmetric Reductive Amination of α-Fluoroenones, *Angew. Chem. Int. Ed*. **2007**, *46*, 1290-1292.

31. Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X.: Chiral Dipeptide Mimics Possessing a Fluoroolefin Moiety: A Relevant Tool for Conformational and Medicinal Studies, *Org. Biomol. Chem*. **2007**, 5, 1151-1157.

32. Veken, P. V.; Senten, K.; Kertesz, I.; De Meester, I.; Lambeir, A. M.; Maes, M. B.; Scharpe, S.; Haemers, A.; Augustyns, K.: Fluoroolefins as Peptidomimetic Inhibitors of Dipeptidyl Peptidases, *J. Med. Chem*., **2005**, *48*, 1768-1780.

33. Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F.: Synthetic Approaches to Monofluoroalkenes, *Chem. Soc. Rev*. **2011**, *40*, 2867–2908.

34. Zajc, B.; Kumar, R.: Synthesis of Fluoroolefins via Julia–Kocienski Olefination, *Synthesis*, **2010**, 1822-1836.

35. Tao, C.-Z.; Cui, X.; Li, J.; Liu, A.-X.; Liu, L.; Guo, Q.-X.: Copper-Catalyzed Synthesis of Aryl Azides And 1-Aryl-1,2,3-Triazoles from Boronic Acids, *Tetrahedron Lett.* **2007**, *48,* 3525-3529.

36. Grimes, K. D.; Gupte, A.; Aldrich, C. C.: Copper(II)-Catalyzed Conversion of Aryl/Heteroaryl Boronic Acids, Boronates, and Trifluoroborates into the Corresponding Azides: Substrate Scope and Limitations, *Synthesis* **2010**, 1441–1448.

37. Ngai, M. H.; Yang, P.-Y.; Liu, K.; Shen, Y.; Wenk, M. R.; Yao, S. Q.; Lear, M, J.: Click-Based Synthesis and Proteomic Profiling of Lipstatin Analogues, *Chem. Commun.* **2010**, *46*, 8335–8337.

38. Aucagne, V.; Leigh, D. A.: Chemoselective Formation of Successive Triazole Linkages in One Pot: "Click−Click" Chemistry, *Org. Lett*. **2006**, *8*, 4505-4507.

39. Lakshman, M. K.; Singh, M. K.; Parrish, D.; Balachandran, R.; Day, B. W.: Azide-Tetrazole Equilibrium of C-6 Azidopurine Nucleosides and Their Ligation Reactions with Alkynes*, J. Org. Chem*. **2010**, *75*, 2461–2473.

40. Agard, N. J.; Prescher, J. A.; Bertozzi, C. R.: A Strain-Promoted [3 + 2] Azide-Alkyne Cycloaddition for Covalent Modification of Biomolecules in Living Systems, *J. Am. Chem. Soc*. **2004**, *126*, 15046-15047.

41. Baskin, J. M.; Preschner, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R.: Copper-Free Click Chemistry for Dynamic in Vivo Imaging, *Proc. Nat. Acad. Sci. U.S.A.* **2007,** *104,* 16793-16797.

42. Sletten, E. M.; Bertozzi, C. R.: Bioorthogonal Chemistry: Fishing for Selectivity in a Sea of Functionality, Angew. Chem., Int. Ed., 2009, 48, 6974-6998.

43. Chenoweth, K.; Chenoweth, D.; Goddard III, and W. A.: Cyclooctyne-Based Reagents for Uncatalyzed Click Chemistry: A Computational Survey, *Org. Biomol. Chem*. **2009**, *7*, 5255-5258.

44. Schoenebeck, F.; Ess, D. H.; Jones, G. O.; Houk, K. N.: Reactivity and Regioselectivity in 1,3-Dipolar Cycloadditions of Azides to Strained Alkynes and Alkenes: A Computational Study, *J. Am. Chem. Soc*. **2009**, 131, 8121-8133.

45. Lam, Y.-h.; Stanway, S. J.; Gouverneur, V.: Recent Progress in the Use of Fluoroorganic Compounds in Pericyclic Reactions, *Tetrahedron* **2009**, *65*, 9905-9933.

46. Grée, D.; Grée, R.: Effect of Fluorine or Oxygen Atom(s) in Propargylic Position in the Reactivity in Click Chemistry, *Tetrahedron Lett.* **2010**, *51*, 2218.

47. Blakemore, P. R.: The Modified Julia Olefination: Alkene Synthesis *via* the Condensation of Metallated Heteroarylalkylsulfones with Carbonyl Compounds, *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2563-2585.

48. Plesniak, K.; Zarecki, A.; Wicha, J.: The Smiles Rearrangement and the Julia–Kocienski Olefination Reaction, *Top. Curr. Chem.* **2007**, *275*, 163-250.

49. Aïssa, C.: Mechanistic Manifold and New Developments of the Julia–Kocienski Reaction, *Eur. J. Org. Chem.* **2009**, 1831–1844.

50. Zajc, B.; Kake, S.: Exceptionally Mild, High-Yield Synthesis of α-Fluoro Acrylates, *Org. Lett.* **2006**, *8*, 4457-4460.

51. He, M.; Ghosh, A. K.; Zajc, B., Julia Olefination as a General Route to Phenyl (α-Fluoro)vinyl Sulfones, *Synlett* **2008**, 999-1004.

PART 3

1. Nam, N.-H.: Combretastatin A-4 Analogues as Antimitotic Antitumor Agents, *Curr. Med. Chem.* **2003**, *10,* 1697-1722.

2. Cirla, A.; Mann, J.: Combretastatins: from Natural Products to Drug Discovery, *Nat. Prod. Rep.* **2003**, *20*, 558–564.

3. Marrelli, M.; Conforti, F.; Statti, G. A.; Cachet, X.; Michel, S.; Tillequin, F.; Menichini, F.: Biological Potential and Structure-Activity Relationships of Most Recently Developed Vascular Disrupting Agents: An Overview of New Derivatives of Natural Combretastatin A-4, *Curr. Med. Chem.* **2011**, *18,* 3035-3081.

4. Shan, Y.; Zhang, J.; Liu, Z.; Wang, M.; Dong, Y.: Developments of Combretastatin A-4 Derivatives as Anticancer Agents, *Curr. Med. Chem.* **2011**, *18,* 523-538.

5. Pettit, G. R.; Singh, S. B.; Hamel, E.; Lin, C. M.; Alberts, D. S.; Garcia-Kendall, D.: Isolation and Structure of the Strong Cell Growth and Tubulin Inhibitor Combretastatin A-4, *Experientia* **1989**, *45*, 209-211.

6. Pettit, G. R.; Combretastatin A-4 Prodrug, US Patent No. 5561122.

7. Ohsumi, K.; Nakagawa, R.; Fukuda, Y.; Hatanaka, T.; Morinaga, Y.; Nihei, Y.; Ohishi, K.; Suga, Y.; Akiyama, Y.; Tsuji, T.: Novel Combretastatin Analogues Effective Against Murine Solid Tumors: Design and Structure-Activity Relationships, *J. Med. Chem*. **1998**, *41*, 3022-3032.

8. Tron, G. C.; Pirali, T.; Sorba, G.; Pagliai, F.; Busacca, S.; Genazzani, A. A.: Medicinal Chemistry of Combretastatin A4: Present and Future Directions, *J. Med. Chem.* **2006**, *49*, 3033-3044.

9. Maya, A. B. S.; Pérez-Melero, C.; Mateo, C.; Alonso, D.; Fernández, J. L.; Gajate, C.; Mollinedo,F.; Peláez, R.; Caballero, E.; Medarde, M.: Further Naphthylcombretastatins. An Investigation on the Role of the Naphthalene Moiety, *J. Med. Chem.* **2005**, *48,* 556-568.

10. Pettit, G. R.; Minardi, M. D.; Rosenberg, H. J.; Hamel, E.; Bibby, M. C.; Martin, S. W.; Jung, M. K.; Pettit, R. K.; Cuthbertson, T. J.; Chapuis, J.-C.: Antineoplastic Agents. 509. Synthesis of Fluorcombretastatin Phosphate and Related 3-Halostilbenes, *J. Nat. Prod.* **2005**, *68,* 1450-1458.

11. Kirsch, P. *Modern Fluoroorganic Chemistry. Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, **2004**.

12. *Current Fluoroorganic Chemistry: New Synthetic Directions, Technologies, Materials, and Biological Applications;* Soloshonok, V. A.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J. F., Eds.; American Chemical Society: Washington DC, **2007**.

13. Smart, B. E.: Fluorine Substituent Effect (On Bioactivity), *J. Fluorine Chem*. **2001**, *109*, 3-11.

14. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V.: Fluorine in Medicinal Chemistry, *Chem. Soc. Rev*. **2008**, *37*, 320-330.

15. Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M.: Fluorine In Medicinal Chemistry, *Chembiochem* **2004**, *5*, 637-643.

16. Ismail, F. M. D.: Important Fluorinated Drugs in Experimental and Clinical Use, *J. Fluorine Chem.* **2002**, *118*, 27-33.

17. Bégué, J.-P.; Bonnet-Delpon, D.: Recent Advances (1995–2005) in Fluorinated Pharmaceuticals Based on Natural Products, *J. Fluorine Chem.* **2006**, *127*, 992-1012.

18. Lawrence, N. J.; Hepworth, L. A.; Rennison, D.; McGown, A. T.; Hadfield, J. A.: Synthesis and Anticancer Activity of Fluorinated Analogues of Combretastatin A-4, *J. Fluorine Chem.* **2003**, *123*, 101-108.

19. Alloatti, D.; Giannini, G.; Cabri, W.; Lustrati, I.; Marzi, M.; Ciacci, A.; Gallo, G.; Tinti, M. O.; Marcellini, M.; Riccioni, T.; Guglielmi, M. B.; Carminati, P.; Pisano, C.: Synthesis and Biological Activity of Fluorinated Combretastatin Analogues, *J. Med. Chem.* **2008**, *51,* 2708-2721.

20. Gaukroger, K.; Hadfield, J. A.; Lawrence, N. J. Nolan*,* S. McGown*,* A. T.: Structural Requirements for the Interaction of Combretastatins with Tubulin: How Important is the Trimethoxy Unit, *Org. Biomol. Chem.* **2003**, *1*, 3033-3037.

21. Angell, Y. L.; Burgess, K.: Peptidomimetics via Copper-Catalyzed Azide–Alkyne Cycloadditions, *Chem. Soc. Rev.* **2007**, *36*, 1674-1689.

22. Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H.: CuI-Catalyzed Alkyne–Azide "Click" Cycloadditions from a Mechanistic and Synthetic Perspective, *Eur. J. Org. Chem.* **2006**, 51–68.

23. Appendino, G.; Bacchiega, S.; Minassi, A.; Cascio, M. G.; Petrocellis, L. D.; Marzo, V. D.: The 1,2,3-Triazole Ring as a Peptido- and Olefinomimetic Element: Discovery of Click Vanilloids and Cannabinoids, *Angew. Chem. Int. Ed*. **2007**, *46*, 9312-9315.

24. Agalave, S. G.; Maujan, S. R.; Pore, V. S.: Click Chemistry: 1,2,3-Triazoles as Pharmacophores, *Chem. Asian J.* **2011**, *6,* 2696 –-2718.

25. Kolb, H. C.; Sharpless, K. B.: The Growing Impact of Click Chemistry on Drug Discovery, *Drug Discovery Today* **2003**, *8*, 1128-1137.

26. Odlo, K.; Fournier-Dit-Chabert, J.; Ducki, S.; Gani, O. A. B. S. M.; Sylte, I.; Hansen, T. V.: 1,2,3-Triazole Analogs of Combretastatin A-4 as Potential Microtubule-Binding Agents, *Bioorg. Med. Chem*. **2010**, *18*, 6874-6885.

27. Odlo, K.; Hentzen, J.; Fournier dit Chabert, J.; Ducki, S.; Gani, O. A. B. S. M.; Sylte, I.; Skrede, M.; Flørenes, V. A.; Hansen, T. V.: 1,5-Disubstituted 1,2,3-Triazoles as Cis-Restricted Analogues of Combretastatin A-4: Synthesis, Molecular Modeling and Evaluation as Cytotoxic Agents and Inhibitors of Tubulin, *Bioorg. Med. Chem*. **2008**, *16*, 4829-4838.

28. Cafici, L.; Pirali, T.; Condorelli, F.; Grosso, E. D.; Massarotti, A.; Sorba, G.; Canonico, P. L.; Tron, G. C.; Genazzani, A. A.: Solution-Phase Parallel Synthesis and Biological Evaluation of Combretatriazoles, *J. Comb. Chem.* **2008**, *10,* 732-740.

29. Blanch, N. M.; Chabot, G. G.; Quentin, L.; Scherman, D.; Bourg, S.; Dauzonne, D.: In Vitro And In Vivo Biological Evaluation of New 4,5-Disubstituted 1,2,3-Triazoles as Cis-Constrained Analogs of Combretastatin A4, *Eur. J. Org. Chem.* **2012**, *54*, 22-32.

30. Aucagne, V.; Leigh, D. A.: Chemoselective Formation of Successive Triazole Linkages in One Pot: "Click−Click" Chemistry, *Org. Lett*. **2006**, *8*, 4505-4507.

31. Lakshman, M. K.; Singh, M. K.; Parrish, D.; Balachandran, R.; Day, B. W.: Azide-Tetrazole Equilibrium of C-6 Azidopurine Nucleosides and Their Ligation Reactions with Alkynes*, J. Org. Chem*. **2010**, *75*, 2461–2473.

32. Biological studies were performed in collaboration with Drs. Andreas Vogt, Billy Day and Livia Salum at the University of Pittsburgh.

33. Tao, C.-Z.; Cui, X.; Li, J.; Liu, A.-X.; Liu, L.; Guo, Q.-X.: Copper-Catalyzed Synthesis of Aryl Azides And 1-Aryl-1,2,3-Triazoles from Boronic Acids, *Tetrahedron Lett.* **2007**, *48,* 3525-3529.

CHAPTER 2

GENERAL INTRODUCTION

1. Luch, A.; Baird, W. M. *The Carcinogenic Effects of Polycyclic Aromatic Hydrocarbons*, Luch, A., Ed.; Imperial College Press: London, 2005; pp 1-96.

2. Harvey, R. G. Structure-activity relationships. In: *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*, Cambridge University Press: Cambridge, 1991; pp 26-49.

3. Kennaway, E. L.: Experiments on Cancer-Producing Substances, *Br. Med. J.* **1925**, *2*, 1-4.

4. Hieger, I.: The Spectra of Cancer-Producing Tars and Oils and of Related Substances, *Biochem. J.* **1930**, *24*, 505-511.

5. Kennaway, E. L.; Hieger, I.: Carcinogenic Substances and Their Fluorescence Spectra. *Br. Med. J.* **1930**, *1*, 1044-1046.

6. Kennaway, E.: Further Experiments on Cancer-Producing Substances, *Biochem. J.* **1930**, *24*, 497-504.

7. Cook, J. W.; Haslewood, G. A. D.; Hewett, C. L.; Hieger, I.; Kennaway, E. L.; Mayneord, W.V.: Chemical Compounds as Carcinogenic Agents, *Am. J. Cancer* **1937**, 29, 219-259.

8. Kennaway, E. L.: The Identification of a Carcinogenic Compound in Coal Tar, *Br. Med. J.* **1955**, *2*, 749-752.

9. Baird,.; Harvey, R. G.; Brookes, P.: Comparison of the Cellular DNA-Bound Products of benzo[*a*]pyrene with the Products Formed by Reaction of Benzo[a]pyrene-4,5-oxide with DNA, *Cancer Res.* **1975**, *35*, 54-57.

10. Borgen, A.; Darvey, H.; Castagnoli, N.; Crocker, T. T.; Rasmussen, R. E.; Wang, I. Y.: Metabolic Conversion of Benzo(a)pyrene by Syrian Hamster Liver Microsomes and Binding of Metabolites to Deoxyribo-nucleic Acid, *J. Med. Chem.* **1973**, *16*, 502–506.

11. Sims, P.; Grover, P. L.; Swaisland, A.; Pal, K.; Hewer, A.: Metabolic Activation of Benzo[*a*]pyrene Proceeds by a Diol-Epoxide, *Nature* **1974**, *252*, 326-328.

12. Daudel, P.; Duquesne, M.; Vigny, P.; Grover, P. L.; Sims, P.: Fluorescence Spectral Evidence that Benzo[a]pyrene-DNA Products in Mouse Skin Arise from Diol-Epoxides, *FEBS Lett.* **1975**, 57, 250-253.

13. King, H. W. S.; Osborne, M. R.; Beland, F. A.; Harvey, R. G.; Brookes, P.: (±)-7α,8β-Dihydroxy-9β,10β-Epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene is an Intermediate in the Metabolism and Binding to DNA of Benzo[a]pyrene, *Proc. Natl. Acad. Sci. USA* **1976**, *73*, 2679-2681.

14. Newbold, R. F.; Brookes, P.: Exceptional Mutagenicity of a Benzo[*a*]pyrene Diol Epoxide in Cultured Mammalian Cells, *Nature* **1976**, *261*, 52-54.

15. Huberman, E.; Sachs, L.; Yang, S. K.; Gelboin, H. V.: Identification of Mutagenic Metabolites of Benzo[*a*]pyrene in Mammalian Cells, *Proc. Natl. Acad. Sci. USA* **1976**, *73*, 607-611.

16. Jeffrey, A. M.; Weinstein, I. B.; Jennette, K. W.; Grzeskowiak, K.; Nakanishi, K.: Structures of Benzo[*a*]pyrene Nucleic Acid Adducts Formed in Human and Bovine Bronchial Explants, *Nature* **1977**, *269*, 348-350.

17. Chouroulinkov, I.; Gentil, A.; Grover, P. L.; Sims, P.: Tumour Initiating Activities on Mouse Skin of Dihydrodiols Derived from Benzo[*a*]pyrene, *Br. Med. J.* **1976**, *34*, 523-532.

18. Levin, W.; Wood, A. W.; Yagi, H.; Jerina, D. M.; Conney, A. H.: *(±)-trans*-7,8-Dihydroxy-7,8-Dihydrobenzo[*a*]pyrene: A Potent Skin Carcinogen When Applied Topically to Mice, *Proc. Natl. Acad. Sci. USA* **1976**, *73*, 3867-3871.

19. Kapitulnik, J.; Levin, W.; Conney, A. H.; Yagi, H.; Jerina, D. M.: Benzo[*a*]-pyrene 7,8-Dihydrodiol is More Carcinogenic than Benzo[*a*]pyrene in Newborn Mice, *Nature* **1977**, *266*, 378-380.

20. Yagi, H.; Hemandez, O.; Jerina, D. M.: Synthesis of (±)-(±)-7α,8β-Dihydroxy-9β,10β-Epoxy-7,8,9,10-Tetrahydrobenzo[*a*]pyrene a Potential Metabolite of the Carcinogen Benzo[*a*]pyrene with Stereochemistry Related to the Antileukemic Tripolides *J. Am. Chem. Soc*. **1975**, *97*, 6881-6883.

21. Yagi, H.; Thakker, D. R.; Hemandez, O.; Koreeda, M.; Jerina, D. M.: Synthesis and Reactions of the Highly Mutagenic 7,8-Diol 9,10-Epoxides of the Carcinogen Benzo[*a*]pyrene, *J. Am. Chem. Soc*. **1977**, *99*, 1604-1611.

22. Jerina, D. M.; Sayer, J. M.; Agarwal, S. K.; Yagi, H.; Levin, W.; Wood, A. W.; Conney, A. H.; Pruess-Schwartz, D.; Baird, W. M.; Pigott, M. A.; Dipple, A.: Reactivity and Tumorigenic Activity of Bay-Region Diol Epoxides Derived from Polycyclic Aromatic Hydrocarbons, *Biological Reactive Intermediates III*; Kocsis, J. J.; Jollow, D. J., Witmer, C. M., Nelson, J. O., Snyder, R., Eds.; Plenum Press: New York, 1986; pp 11-30.

23. Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Jerina, D. M.: Novel Bay Region Diol Epoxides from Benzo[*c*]phenanthrene. *J. Am. Chem. Soc.* **1981**, *103*, 4970-4972.

24. Jerina, D. M.; Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Ittah, Y.; Thakker, D. R; Wood, A. W.; Chang, R. L.; Levin, W.; Conney, A. H.: Highly Tumorigenic Bay-Region Diol Epoxides from the Weak Carcinogen Benzo[*c*]phenanthrene, *Biological Reactive Intermediates II Part A*; Snyder, R., Parke, D., Kocsis, J. J., Jollow, D. J., Gibson, G., Witmer, C. M.; Eds.; Plenum Press: New York, 1986; pp 501-523.

25. Chang, R. L.; Wood, A. W.; Conney, A. H.; Yagi, H.; Sayer, J. M.; Thakker, D. R.; Jerina, D. M.; Levin, W. Role of Diaxial versus Diequatorial Hydroxyl Groups in the Tumorigenic Activity of a Benzo[*a*]pyrene bay-region diol epoxide, *Proc. Natl. Acad. Sci. USA*, **1987**, *84*, 8633-8636.

26. Thakker, D. R.; Yagi, H.; Sayer, J. M.; Kapur, U.; Levin, W.; Chang, R. L.; Wood, A. W.; Conney, A. H.; Jerina, D. M.: Effects of a 6-Fluoro Substituent on the Metabolism of Benzo[*a*]pyrene 7,8-Dihydrodiol to Bay-Region Diol Epoxides by Rat Liver Enzymes*, J. Biol. Chem*. **1984**, *259*, 11249-11256.

27. Katz, A. K.; Carrell, H. L.; Glusker, J. P.: Dibenzo[*a*,*l*]pyrene (Dibenzo[*def*,*p*]-chrysene): Fjord-Region Distortions, *Carcinogenesis* **1998**, *19*, 1641–1648..

28. Bae, S.; Mah, H.; Chaturvedi, S.; Jeknic, T. M.; Baird, W. M.; Katz, A. M.; Carrell, H. L.; Glusker, J. P.; Okazaki, T.; Laali, K. K.; Zajc, B.; Lakshman, M. K.: Synthetic, Crystallographic, Computational, and Biological Studies of 1,4-Difluorobenzo[*c*]phenanthrene and Its Metabolites, *J. Org. Chem.* **2007**, *72*, 7625-7633.

29. Lakshman, M. K.; Kole, P.; Chaturvedi, S.; Saugier, J. H.; Yeh, H. J. C.; Glusker, J. P.; Carrell, H. L.; Katz, A. K.; Afshar, C. E.; Dashwood, W.-M.; Kenniston, G.; Baird, W. M.: Methyl Group-Induced Helicity in 1,4-Dimethylbenzo[*c*]-phenanthrene and Its Metabolites: Synthesis, Physical, and Biological Properties, *J. Am. Chem. Soc.* **2000**, *122*, 12629-12636.

30. RamaKrishna, N. V. S.; Gao, F.; Padmavathi, N. S.; Cavalieri, E. L.; Rogan, E. G.; Cerny, R. L.; Gross, M. L.: Model Adducts of Benzo[*a* Ipyrene and Nucleosides Formed from Its Radical Cation and Diol Epoxide, *Chem. Res. Toxicol.* **1992**, *5*, 293-302.

31. Rogan, E. G.; Cavalieri, E. L.; Tibbels, S. R.; Cremonesi, P.; Warner, C. D.; Nagel, D. L.; Tomer, K. B.; Cerny, R. L.; Gross, M. L.: Synthesis and Identification of Benzo[*a*]pyrene Guanine Nucleoside Adducts Formed by Electrochemical Oxidation by Horseradish Peroxidase Catalyzed Reaction of Benzo[*a*lpyrene with DNA, *J. Am. Chem. Soc.* **1988**, *110*, 4023-4029.

32. Cavalieri, E. L.; Rogan, E. G.; Li, K.-M.; Todorovic, R.; Ariese, F.; Jankowiak, R.; Grubor, N.; Small, G. J.: Identification and Quantification of the Depurinating DNA Adducts Formed in Mouse Skin Treated with Dibenzo[*a*,*l*]pyrene (DB[*a*,*l*]P) or Its Metabolites and in Rat Mammary Gland Treated with DB[*a,l*]P, *Chem. Res. Toxicol.* **2005**, *18*, 976-983.

33. Bolton, J. L.; Trush, M. A.; Penning, T. M.; Dryurst, G.; Monks, T. J.: Role of Quinones in Toxicology, *Chem. Res. Toxicol.* **2000**, *13*, 135-160.

34. Penning, T. M.; Burczynski, M. E.; Hung, C.-F.; McCoull, K. D.; Palackal, N. T.; Tsuruda, L. S.: Dihydrodiol Dehydrogenases and Polycyclic Aromatic Hydrocarbon Activation: Generation of Reactive and Redox Active *o*-Quinones, *Chem. Res. Toxicol.* **1999**, *12*, 1-18.
35. Palackal, N. T.; Burczynski, M. E.; Harvey, R. G.; Penning, T. M.: The Ubiquitous Aldehyde Reductase (AKR1A1) Oxidizes Proximate Carcinogen *trans*-Dihydrodiols to *o*-Quinones*:* Potential Role in Polycyclic Aromatic Hydrocarbon Activation, *Biochemistry* **2001**, *40*, 10901-10910.

36. Champeil, E.; Pradhan, P.; Lakshman, M. K.: Palladium-Catalyzed Synthesis of Nucleoside Adducts from Bay and Fjord-Region Diol Epoxides, *J. Org. Chem.* **2007**, *72*, 5035-5045.

37. Jerina, D. M.; Chadha, A.; Cheh, A. M.; Schurdak, M. E.; Wood, A. W.; Sayer, J. M. In *Biological Reactive Intermediates IV*; Witmer, C. M., Snyder, R., Jollow, D. J., Kalf, G. F., Kocsis, J. J., Sipes, I. G., Eds.; Plenum Press: New York, 1991; pp 533-553.

38. Frank, E. G.; Sayer, J. M.; Kroth, H.; Ohashi, E.; Ohmori, H.; Jerina, D. M.; Woodgate, R.: Translesion Replication of Benzo[*a*]pyrene and Benzo[*c*]phenanthrene Diol Epoxide Adducts of Deoxyadenosine and Deoxyguanosine by Human DNA Polymerase ι, *Nucleic Acids Res.* **2002**, *30*, 5284-5292.

39. Szeliga, J.; Dipple, A.: DNA Adduct Formation by Polycyclic Aromatic Hydrocarbon Dihydrodiol Epoxides, *Chem. Res. Toxicol.* **1998**, *11*, 1-11.

40. Harvey, R. G.; Geacintov, N. E.: Intercalation and Binding of Carcinogenic Hydrocarbon Metabolites to Nucleic Acids, *Acc. Chem. Res.* **1988**, *21*, 66-73.

41. Lin, J.; LeBreton, P. R.; Shipman, L. L.: Reaction of the 7,8-DioI 9,l0-Epoxide of Benzo[a]pyrene with Guanine In DNA. Ab Initio Calculations and Proposed Reaction Mechanism *J. Phys. Chem*. **1980**, *84*, 642-649.

42. Meehan, T.; Gamper, H.; Becker, J. F.: Characterization of reversible, physical binding of benzo[a]pyrene derivatives to DNA, *J. Biol. Chem.***,** **1982**, *257*, 10479-10485.

43. Islam, N. B.; Gupta, S. C.; Yagi, H.; Jerina, D. M.; Whalen, D. L.: Trapping of a

Carbocationic Intermediate in the Spontaneous Hydrolysis Reaction of 7β, 8α-Dihydroxy-9β, 10β-epoxy-7,8,9,l0-tetrahydrobenzao[*a*]pyrene: Mechanism of the Spontaneous and General Acid Catalyzed Hydrolysis Reactions of Bay-Region Benzo[*a*]pyrene 7,8-Diol 9,l0-Epoxides, *J. Am. Chem. Soc.* **1990**, *112*, 6363-6369.

44. Smart, B. E.: Fluorine Substituent Effects (on Bioactivity), *J. Fluorine Chem.* **2001**, *109*, 3-11.

45. Lemal, D. M.: Perspective on Fluorocarbon Chemistry, *J. Org. Chem.* **2004**, *69*, 1-11.

46. Newman, M. S.; Khanna, V. K.; Kanakarajan, K.: A Novel Synthesis of 7-Fluoro-benzo[*a*]pyrene Involving Two New Molecular Rearrangements, *J. Am.Chem. Soc.* **1979**, *101*, 6788-6789.

47. Newman, M. S.; Kannan, R.: Syntheses of 8- and 9-Fluorobenzo[*a*]pyrenes and 9-Fluoro- and 10-Fluoro-7,12-dimethylbenz[*a*]anthracenes, *J. Org. Chem.* **1979**, *44,* 3388-3390.

48. Newman, M. S.; Khanna, V. K.: The Synthesis of 10-Fluorobenzo[*a*]pyrene, *Bull. Soc. Chim. Belg*. **1979**, *88*, 871-873.

49. Buhler, D. R.; Unlu, F.; Thakker, D. R.; Slaga, T. J.; Newman, M. S.; Levin, W.; Conney, A. H.; Jerina, D. M.: Metabolism and Tumorigenicity of 7-, 8-, 9-, and 10-Fluorobenzo[*a*]pyrenes, *Cancer Res.* **1982**, *42*, 4779-4783.

50. Buhler, D. R.; Unlu, F.; Thakker, D. R.; Slaga, T. J.; Conney, A. H.; Wood, A. W.; Chang, R. L.; Levin, W.; Jerina, D. M.: Effect of 6-Fluoro Substituent on the Metabolism and Biological Activity of Benzo[*a*]pyrenes, *Cancer Res.* **1983**, *43*, 1541-1549.

51. Zajc, B.: Synthesis of (±)-*trans*-7,8-Dihydrodiol of 6-Fluoro-benzo[*a*]pyrene via Hydroxyl-Directed Regioselective Functionalization of Substituted Pyrene, *J. Org. Chem.* **1999,** *64,* 1902-1907.

52. Hecht, S. S.; Loy, M.; Mazzarese, R.; Hoffmann, D.: Synthesis and Mutagenicity of Modified Chrysenes Related to the Carcinogen, 5-Methylchrysene, *J. Med. Chem.* **1978**, *21*: 38-44.

53. Hecht, S. S.; Hirota, N.; Loy, M.; Hoffmann, D.: Tumor-initiating Activity of Fluorinated 5-Methylchrysenes, *Cancer Res.* **1978**, *38*, 1694-1698.

54. Huberman, E.; Slaga, T. J.: Mutagenicity and Tumor-initiating Activity of Fluorinated Derivatives of 7,12-Dimethylbenz[*a*]anthracene, *Cancer Res.* **1979**, *39*, 411-414.

55. Harvey, R. G., and Dunne, F. A.: Multiple Regions of Metabolic Activation of Carcinogenic Hydrocarbons, *Nature* 1978, *273*, 566-567.

56. DiGiovanni, J.; Decina, P. C.; Diamond, L.: Tumor Initiating Activity of 9- and 10-Fluoro-7,12-dimethylbenz[*a*]anthracene (DMBA) and the Effect of 2,3,7,8-Tetrachlorodibenzo-pdioxin on Tumor Initiation by Monofluoro Derivatives of DMBA in SENCAR Mice, *Carcinogenesis* **1983**, *4*,1045-1049.

57. Hecht, S. S.; LaVoie, E. J.; Bedenko, V.; Pingaro, L.; Katayama, S.; Hoffmann, D.; Sardella, D. J.; Boger, E.; Lehr, R. E.: Reduction of Tumorigenicity and of Dihydrodiol Formation by Fluorine Substitution in the Angular Rings of Dibenzo[*a,i*]pyrene, *Cancer Res.* **1981**, *41*, 4341-4345.

PART 1

1. Lakshman, M. K.; Kole, P.; Chaturvedi, S.; Saugier, J. H.; Yeh, H. J. C.; Glusker, J. P.; Carrell, H. L.; Katz, A. K.; Afshar, C. E.; Dashwood, W.-M.; Kenniston, G.; Baird, W. M.: Methyl Group-Induced Helicity in 1,4-Dimethylbenzo[*c*]-phenanthrene and Its Metabolites: Synthesis, Physical, and Biological Properties, *J. Am. Chem. Soc.* **2000**, *122*, 12629-12636.

2. Bae, S.; Mah, H.; Chaturvedi, S.; Jeknic, T. M.; Baird, W. M.; Katz, A. M.; Carrell, H. L.; Glusker, J. P.; Okazaki, T.; Laali, K. K.; Zajc, B.; Lakshman, M. K.: Synthetic, Crystallographic, Computational, and Biological Studies of 1,4-Difluorobenzo[*c*]phenanthrene and Its Metabolites, *J. Org. Chem.* **2007**, *72*, 7625-7633.

3. Jerina, D. M.; Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Ittah, Y.; Thakker, D. R; Wood, A. W.; Chang, R. L.; Levin, W.; Conney, A. H.: Highly Tumorigenic Bay-Region Diol Epoxides from the Weak Carcinogen Benzo[*c*]phenanthrene, *Biological Reactive Intermediates II Part A*; Snyder, R., Parke, D., Kocsis, J. J., Jollow, D. J., Gibson, G., Witmer, C. M.; Eds.; Plenum Press: New York, 1986; pp 501-523.

4. Szeliga, J.; Dipple, A.: DNA Adduct Formation by Polycyclic Aromatic Hydrocarbon Dihydrodiol Epoxides, *Chem. Res. Toxicol.* **1998**, *11*, 1-11.

5. Levin, W.; Wood, A. W.; Chang, R. L.; Ittah, Y.; Croisy-Delcey, M.; Yagi, H.; Jerina, D. M; Conney, A. H.: Exceptionally High Tumor-initiating Activity of Benzo[*c*]phenanthrene Bay-Region Diol-Epoxides on Mouse Skin, *Cancer Res.* **1980**, *40*, 3910-3914.

6. Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Jerina, D. M.: Novel Bay Region Diol Epoxides from Benzo[*c*]phenanthrene. *J. Am. Chem. Soc.* **1981**, *103*, 4970-4972.

7. Ittah, Y.; Jerina, D. M.: Synthesis of Monofluorobenzo[*c*]phenanthrenes, *Flouorine Chem.* **1980**, *16*, 137-144.

8. Mallory, F. B.; Mallory, C. W.; Ricker, W. M.: Nuclear Spin-Spin Coupling via Nonbonded Interactions. 4. F-F and H-F Coupling in Substituted Benzo[*c*]-phenanthrenes, *J. Org. Chem.* **1985**, *50*, 457-461.

9. Marx, G. S.; Bergmann, E. D.: Synthesis of 5-and 6-Fluorobenzo[*c*]phenanthrene by Photocyclization, *J. Org. Chem.* **1972**, *37,* 1807-1810.

10. Mirsadeghi, S.; Prasad, G. K. B; Whittaker, N.; Thakker, D. R.: Synthesis of the K-Region Monofluoro- and Difluorobenzo[*c*]phenanthrenes, *J. Org. Chem.* **1989**,

54, 3091-3096.

11. Prasad, G. K. B; Mirsadeghi, S.; Boehlert, C.; Byrd, A; Thakker, D. R.: Oxidative Metabolism of the Carcinogen 6-Fluorobenzo[*c*]phenanthrene *J. Biol. Chem*. **1988**, *263*, 3676-3683.

12. Zajc, B.; Kumar, R.: Synthesis of Fluoroolefins via Julia–Kocienski Olefination, *Synthesis* **2010**, 1822-1836.

13. Ghosh, A. K.; Zajc, B.: High-Yield Synthesis of Fluorinated Benzothiazolyl Sulfones: General Synthons for Fluoro-Julia Olefinations, *Org. Lett.* **2006**, *8*, 1553–1556.

14. Differding, E.; Rüegg, G. M.: Nucleophilic Substitution Versus Electron Transfer: 1. On the Mechanism of Electrophilic Fluorinations, *Tetrahedron Lett.* **1991**, *32*, 3815-3818.

15. Differding, E.; Wehrli, M.: Nucleophilic Substitution Versus Electron Transfer: 2. S_N2 at Flouride and Electron Transfer are Competing and Different Pathways in Electrophilic Flourinations, *Tetrahedron Lett.* **1991**, *32*, 3819-3822.

16. Allendörfer, N.; Es-Sayed, M.; Nieger, M.; Bräse, S.: Novel Aromatic Fluoroolefins via Fluoro-Julia-Kocienski Olefination, *Synthesis* **2010**, 3439–3448.

17. Mallory, F. B.; Wood, C. S.; Gordon, J. T.; Lindquist, L. C.; Savitz, M. L.: Photochemistry of Stilbenes, *J. Am. Chem. Soc.* **1962**, *84*, 4361-4362.

18. Wood, C. S.; Mallory, F. B.: Photochemistry of Stilbenes. IV. The Preparation of Substituted Phenanthrenes, *J. Org. Chem*. **1964**, *29*, 3373-3377.

19. Nagel, D. L.; Kupper, R.; Antonson, K.; Wallcave, L.: Synthesis of Alkyl-Substituted Benzo[*c*]phenanthrenes and Chrysenes by Photocyclization, *J. Org. Chem.* **1977**, *42*, 3626-3628.

20. Amin, S.; Camanzo, J.; Huie, K.; Hecht, S. S.: Improved Photochemical Synthesis of 5-Methylchrysene Derivatives and Its Application to the Preparation of 7,8-Dihydro-7,8-dihydroxy-5-methylchryse, *J. Org. Chem.* **1984**, *49*, 381-384.

21. Utermoehlen, C. M.; Singh, M.; Lehr, R. E.: Fjord Region 3,4-Diol 1,2-Epoxides and Other Derivatives in the 1,2,3,4- and 5,6,7,8-Benzo Rings of the Carcinogen Benzo[*g*]chrysene, *J. Org. Chem*. **1987**, *52*, 5574-5582.

22. Liu, L.; Yang, B.; Katz, T. J.; Poindexter, M. K.: Improved Methodology for Photocyclization Reactions, *J. Org. Chem.* **1991**, *56*, 3569-3575.

23. Yagi, H.; Thakker, D. R.; Hemandez, O.; Koreeda, M.; Jerina, D. M.: Synthesis and Reactions of the Highly Mutagenic 7,8-Diol 9,10-Epoxides of the Carcinogen Benzo[*a*]pyrene. *J. Am. Chem. Soc*. **1977**, *99*, 1604-1611.

24. Jerina, D. M.; Sayer, J. M.; Agarwal, S. K.; Yagi, H.; Levin, W.; Wood, A. W.; Conney, A. H.; Pruess-Schwartz, D.; Baird, W. M.; Pigott, M. A.; Dipple, A.: Reactivity and Tumorigenic Activity of Bay-Region Diol Epoxides Derived from Polycyclic Aromatic Hydrocarbons, *Biological Reactive Intermediates III*; Kocsis, J. J.; Jollow, D. J., Witmer, C. M., Nelson, J. O., Snyder, R., Eds.; Plenum Press: New York, 1986; pp 11-30.

25. Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Jerina, D. M.: Novel Bay Region Diol Epoxides from Benzo[*c*]phenanthrene. *J. Am. Chem. Soc.* **1981**, *103*, 4970-4972.

26. Yagi, H.; Hemandez, O.; Jerina, D. M.: Synthesis of (±)-7α,8β-Dihydroxy-9β,10β-Epoxy-7,8,9,10-Tetrahydrobenzo[*a*]pyrene a Potential Metabolite of the Carcinogen Benzo[*a*]pyrene with Stereochemistry Related to the Antileukemic Tripolides *J. Am. Chem. Soc*. **1975**, *97*, 6881-6883.

PART 2

1. Luch, A.; Baird, W. M. *The Carcinogenic Effects of Polycyclic Aromatic Hydrocarbons*, Luch, A., Ed.; Imperial College Press: London, 2005.

2. Harvey, R. G. Structure-Activity Relationships. In: *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*, Cambridge University Press: Cambridge, 1991.

3. Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*; Cambridge University Press: Cambridge, 1991.

4. Cavalieri, E. L.; Rogan, E. G.: Central Role of Radical Cations in Metabolic Activation of Polycyclic Aromatic Hydrocarbons, *Xenobiotica* **1995**, *25*, 677-688.

5. Bolton, J. L.; Trash M. A.; Penning, T. M.; Dryhurst, G.; Monks, T. J.: Role of Quinones in Toxicology, *Chem. Res. Toxicol.* **2000**, *13*, 135-160.

6. Jerina, D. M.; Sayer, J. M.; Agarwal, S. K.; Yagi, H.; Levin, W.; Wood, A. W.; Conney, A. H.; Pruess-Schwartz, D.; Baird, W. M.; Pigott, M. A.; Dipple, A.: Reactivity and Tumorigenic Activity of Bay-Region Diol Epoxides Derived from Polycyclic Aromatic Hydrocarbons, *Biological Reactive Intermediates III*; Kocsis, J. J.; Jollow, D. J., Witmer, C. M., Nelson, J. O., Snyder, R., Eds.; Plenum Press: New York, **1986**; pp 11-30.

7. Jerina, D. M.; Chadha, A.; Cheh, A. M.; Schurdak, M. E.; Wood, A. W.; Sayer, J. M.: In *Biological Reactive Intermediates IV*; Witmer, C. M., Snyder, R., Jollow, D. J., Kalf, G. F., Kocsis, J. J., Sipes, I. G., Eds.; Plenum Press: New York, 1991; pp 533-553.

8. Szeliga, J.; Dipple, A.: DNA Adduct Formation by Polycyclic Aromatic Hydrocarbon Dihydrodiol Epoxides, *Chem. Res. Toxicol.* **1998**, *11*, 1-11.

9. Dipple A.; Pigott, M. A.; Agarwal, S. K.; Yagi, H.; Sayer, J. M.; Jerina, D. M.: Optically Active Benzo[*c*]phenanthrene Diol Epoxides Bind Extensively to Adenine in DNA, *Nature* **1987**, *327*, 535–536.

10. Agarwal, S. K., Sayer, J. M., Yeh, H. J. C., Pannell, L. K., Hilton, B. D., Pigott, M. A., Dipple, A., Yagi, H., Jerina, D. M.: Chemical Characterization of DNA Adducts Derived from the Configurationally Isomeric Benzo[*c*]phenanthrene-3,4-Diol 1,2-Epoxide, *J. Am. Chem. Soc.* **1987**, *109*, 2497-2504.

11. Frank, E. G.; Sayer, J. M.; Kroth, H.; Ohashi, E.; Ohmori, H.; Jerina, D. M.; Woodgate, R.: Translesion Replication of Benzo[*a*]pyrene and Benzo[*c*]phenanthrene Diol Epoxide Adducts of Deoxyadenosine and Deoxyguanosine by Human

DNA Polymerase ι, *Nucleic Acids Res.* **2002**, *30*, 5284-5292.

12. Harvey, R. G.; Geacintov, N. E.: Intercalation and Binding of Carcinogenic Hydrocarbon Metabolites to Nucleic Acids, *Acc. Chem. Res.* **1988**, *21*, 66-73.

13. Islam, N. B.; Gupta, S. C.; Yagi, H.; Jerina, D. M.; Whalen, D. L.: Trapping of a Carbocationic Intermediate in the Spontaneous Hydrolysis Reaction of 7β, 8α-Dihydroxy-9β, 10β-epoxy-7,8,9,l0-tetrahydrobenzao[*a*]pyrene: Mechanism of the Spontaneous and General Acid Catalyzed Hydrolysis Reactions of Bay-Region Benzo[*a*]pyrene 7,8-Diol 9,l0-Epoxides, *J. Am. Chem. Soc.* **1990**, *112*, 6363-6369.

14. Lakshman, M. K.; Sayer, J. M.; Jerina, D. M.: Chemical Synthesis of a Bay-Region Polycyclic Aromatic Hydrocarbon Tetrahydroepoxide-Deoxyadenosine Adduct and Its Site-Specific Incorporation into a DNA Oligomer, *J. Am. Chem. Soc.* **1991**, *113*, 6589-6594.

15. Lakshman, M. K.; Sayer, J. M.; Jerina, D. M.: Synthesis and Site-Specific Incorporation of a Bay-Region Cis Ring-Opened Tetrahydro Epoxide-Deoxyadenosine Adduct into a DNA Oligomer *J. Org. Chem.* **1992**, *57*, 3438-3443.

16. Lakshman, M. K.; Sayer, J. M.;Yagi, H.; Jerina, D. M.: Synthesis and Duplex-Forming Properties of a Nonanucleotide Containing an N^6-Deoxyadenosine Adduct of a Bay-Region Diol Epoxide, *J. Org. Chem.* **1992**, *57*, 4585-4590.

17. Chaturvedi, S.; Lakshman, M. K.: Site-Specific Modification of the Human *N-ras* Proto-Oncogene with Each Diol Epoxide Metabolite of Benzo[*a*]pyrene and Thermal Denaturation Studies of the Adducted Duplexes, *Carcinogenesis* **1996**, *17*, 2747-2752.

18. Pilcher, A. S.; Yagi, H.; Jerina, D. M.: A Novel Synthetic Method for Cis-Opened Benzo[*a*]pyrene 7,8-Diol 9,10-Epoxide Adducts at the Exocyclic N^6-Amino Group of Deoxyadenosine *J. Am. Chem. Soc*. **1998**, *120*, 3520-3521.

19. Dipple, A.; Piggot, M. A.; Aggarwal, S. K.; Yagi, H.; Sayer, J. M.; Jerina, D. M.: Optically Active Benzo[*c*]phenanthrene Diol Epoxides Bind Extensively to Adenine in DNA, *Nature* **1987**, *327*, 535-536.

20. Benasutti, M.; Ezzedine, Z. D.; Loechler, E. L.: Construction of an *Escherichia coli* Vector Containing the Major DNA Adduct of Activated Benzo[*a*]pyrene at a Defined Site, *Chem. Res. Toxicol.* **1988**, *1*, 160-168

21. Harris, C. M.; Zhou, L.; Strand, E. A.; Harris, T. M.: New Strategy for the Synthesis of Oligodeoxynucleotides Bearing Adducts at Exocyclic Amino Sites of Purine Nucleosides, *J. Am. Chem. Soc.* **1991**, *113*, 4328-4329

22. Cooper, M. D.; Hodge, R. P.; Tamura, P. J.; Wilkinson, A. S.; Harris, C. M.; Harris,

T. M.: Synthesis of Oligonucleotides Containing Bulky Adducts at Guanine *N^2* Via the Phosphoramidite of *O^2-Triflate-O^6-NPE* 2′ -Deoxyxanthosine, *Tetrahedron Lett.* **2000**, *41*, 3555-3558.

23. Lakshman, M. K. Unpublished results.

24. Zajc, B.; Lakshman, M. K.; Sayer, J. M.; Jerina, D. M.: Epoxide and Diol Epoxide Adducts of Polycyclic Aromatic Hydrocarbons at the Exocyclic Amino Group of Deoxyguanosine, *Tetrahedron Lett.* **1992**, *33*, 3409-3412.

25. Custer, L.; Zajc, B.; Sayer, J. M.; Cullinane, C.; Phillips, D. R.; Cheh, A. M.; Jerina, D. M.; Bohr, V. A.; Mazur, S. J.: Stereospecific Differences in Repair by Human Cell Extracts of Synthesized Oligonucleotides Containing trans-Opened 7,8,9,10-Tetrahydrobenzo[*a*]pyrene 7,8-Diol 9,10-Epoxide *N^2-dG* Adduct Stereoisomers Located within the Human K-ras Codon 12 Sequence, *Biochemistry* **1999**, *38*, 569-581.

26. Lakshman, M. K.; Yeh, H. J. C.; Yagi, H. Jerina, D. M.: Synthesis of Deoxyadenosine Adducts from the Highly Carcinogenic Fjord Region Diol Epoxide of Benzo[*c*]phenanthrene, *Tetrahedron Lett.* **1992**, *33*, 7121-7124.

27. Johnson, F.; Bonala, R.; Tawde, D.; Torres, M. C.; Iden, C. R.; Efficient Synthesis of the Benzo[*a*]pyrene Metabolic Adducts of 2′-Deoxyguanosine and 2′-Deoxyadenosine and Their Direct Incorporation into DNA, *Chem. Res. Toxicol.* **2002**, *12*, 1489-1494.

28. Lakshman, M. K.; Gunda, P.: Palladium-Catalyzed Synthesis of Carcinogenic Polycyclic Aromatic Hydrocarbon Epoxide-NucleosideAdducts: The First Amination of a Chloro Nucleoside, *Org. Lett.* **2003**, *5*, 39-42.

29. Champeil, E.; Pradhan, P.; Lakshman, M. K.: Palladium-Catalyzed Synthesis of Nucleoside Adducts from Bay and Fjord-Region Diol Epoxides, *J. Org. Chem*. **2007**, *72*, 5035-5045

30. Steinbrecher, T.; Becker, A.; Stezowski, J. J.; Oesch, F.; Seidel, A. Synthesis of Otigodeoxynucleotides Containing Diastereomeric Dihydrodiol Epoxide-*N^6*-Deoxyadenosine Adducts of Polycyclic Aromatic Hydrocarbons, *Tetrahedron Lett.* **1993**, *34*, 1773-1774.

31. Jerina, D. M.; Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Ittah, Y.; Thakker, D. R; Wood, A. W.; Chang, R. L.; Levin, W.; Conney, A. H.: Highly Tumorigenic Bay-Region Diol Epoxides from the Weak Carcinogen Benzo[*c*]phenanthrene, *Biological Reactive Intermediates II Part A*; Snyder, R., Parke, D., Kocsis, J. J., Jollow, D. J., Gibson, G., Witmer, C. M.; Eds.; Plenum Press: New York, 1986; pp 501-523.

32. Cosman, M.; Laryea, A.; Fiala, R.; Hingerty, B. E.; Amin, S.; Geacintov, N. E.; Broyde, S.; Patel, D. J.: Solution Conformation of the (−)-*trans*-*anti*-Benzo[*c*]phenanthrene-dA ([BPh]dA) Adduct Opposite dT in a DNA Duplex: Intercalation of the Covalently Attached Benzo[*c*]phenanthrenyl Ring to the 3′-Side of the Adduct Site and Comparison with the (+)-*trans*-*anti*-[BPh]dA Opposite dT Stereoisomer, *Biochemistry* **1995**, *34*, 1295–1307.

33. Cosman, M.; Fiala, R.; Hingerty, B. E.; Laryea, A.; Lee, H.; Harvey, R. G.; Amin, S.; Geacintov, N. E.; Broyde, S.; Patel, D.: Solution Conformation of the (+)-trans-anti-[BPhIdA Adduct opposite dT in a DNA Duplex: Intercalation of the Covalently Attached Benzo[c]phenanthrene to the 5'-Side of the Adduct Site without Disruption of the Modified Base Pair, *Biochemistry* **1993**, *32,* 12488-12497.

34. Lin, C. H.; Huang, X.; Kolbanovskii, A.; Hingerty, B. E.; Amin, S.; Broyde, S.; Geacintov, N. E.; Patel, D. J.: Molecular Topology of Polycyclic Aromatic Carcinogens Determines DNA Adduct Conformation: A Link to Tumorigenic Activity, *J. Mol. Biol.* **2001**, *306*, 1059-1080.

35. Wang, Y.; Schnetz-Boutaud, N. C.; Kroth, H.; Yagi, H.; Sayer, J. M.; Kumar, R.; Jerina, D. M; Stone, M. P: 3′-Intercalation of a *N*2-dG 1*R*-*trans*-*anti*-Benzo[*c*]phenanthrene DNA Adduct in an Iterated (CG)3 Repeat, *Chem. Res. Toxicol.* **2008**, *21*, 1348–1358.

36. Smart, B. E.: Fluorine Substituent Effects (on Bioactivity), *J. Fluorine Chem.* **2001**, *109*, 3-11.

37. Buhler, D. R.; Unlu, F.; Thakker, D. R.; Slaga, T. J.; Newman, M. S.; Levin, W.; Conney, A. H.; Jerina, D. M.: Metabolism and Tumorigenicity of 7-, 8-, 9-, and 10-Fluorobenzo[*a*]pyrenes, *Cancer Res.* **1982**, *42*, 4779-4783.

38. Buhler, D. R.; Unlu, F.; Thakker, D. R.; Slaga, T. J.; Conney, A. H.; Wood, A. W.; Chang, R. L.; Levin, W.; Jerina, D. M.: Effect of 6-Fluoro Substituent on the Metabolism and Biological Activity of Benzo[*a*]pyrenes, *Cancer Res.* **1983**, *43*, 1541-1549.

39. Hecht, S. S.; Loy, M.; Mazzarese, R.; Hoffmann, D.: Synthesis and Mutagenicity of Modified Chrysenes Related to the Carcinogen, 5-Methylchrysene, *J. Med. Chem.* **1978**, *21*, 38-44.

40. Hecht, S. S.; Hirota, N.; Loy, M.; Hoffmann, D.: Tumor-initiating Activity of Fluorinated 5-Methylchrysenes, *Cancer Res.* **1978**, *38*, 1694-1698.

41. Huberman, E.; Slaga, T. J.: Mutagenicity and Tumor-initiating Activity of Fluorinated Derivatives of 7,12-Dimethylbenz[*a*]anthracene, *Cancer Res.* **1979**, *39*, 411-414.

42. Hecht, S. S.; LaVoie, E. J.; Bedenko, V.; Pingaro, L.; Katayama, S.; Hoffmann, D.; Sardella, D. J.; Boger, E.; Lehr, R. E.: Reduction of Tumorigenicity and of Dihydrodiol Formation by Fluorine Substitution in the Angular Rings of Dibenzo[*a,i*]pyrene, *Cancer Res.* **1981**, *41*, 4341-4345.

43. Bae, S.; Mah, H.; Chaturvedi, S.; Jeknic, T. M.; Baird, W. M.; Katz, A. M.; Carrell, H. L.; Glusker, J. P.; Okazaki, T.; Laali, K. K.; Zajc, B.; Lakshman, M. K.: Synthetic, Crystallographic, Computational, and Biological Studies of 1,4-Difluorobenzo[*c*]phenanthrene and Its Metabolites, *J. Org. Chem.* **2007**, *72*, 7625-7633.

44. Thakker, D. R.; Yagi, H.; Sayer, J. M.; Kapur, U.; Levin, W.; Chang, R. L.; Wood, A. W.; Conney, A. H.; Jerina, D. M.: Effects of a 6-Fluoro Substituent on the Metabolism of Benzo[*a*]pyrene 7,8-Dihydrodiol to Bay-Region Diol Epoxides by Rat Liver Enzymes*, J. Biol. Chem*. **1984**, *259*, 11249-11256.

45. Zhou, L.; Rajabzadeh, G.; Traficante, D. D.; Cho, B. P.: Conformational Heterogeneity of Arylamine-Modified DNA: ^{19}F NMR Evidence, *J. Am. Chem. Soc.* **1997**, *119*, 5384-5389.

46. Meneni, S. R.; Shell, S. M.; Gao, L.; Jurecka, P.; Lee, W.; Sponer, J.; Zou, Y.; Chiarelli, M. P.; Cho, B. P.: Spectroscopic and Theoretical Insights into Sequence Effects of Aminofluorene-Induced Conformational Heterogeneity and Nucleotide Excision Repair, *Biochemistry* **2007**, *46*, 11263–11278.

47. Yang, T.; Huang, Y.; Cho, Cho, B. P.: Synthesis and Characterization of Enantiomeric *anti*-2-Fluorobenzo[*a*]pyrene-7,8-dihydrodiol-9,10-epoxides and Their 2'-Deoxy-guanosine and Oligodeoxynucleotide Adducts, *Chem. Res. Toxicol***. 2006**, *19,* 242-254.

48. Cho, B. P.; Beland, F. A.; Marques, M. M.: NMR Structural Studies of a 15-mer DNA Sequence from a *ras* Protooncogene, Modified at the First Base of Codon 61 with the Carcinogen 4-Aminobiphenyl, *Biochemistry* **1992**, *31*, 9587-9602.

49. Cho, B. P.; Beland, F. A.; Marques, M. M.: NMR Structural Studies of a 15-mer DNA Duplex from a *ras* Protooncogene Modified with the Carcinogen 2-Aminofluorene: Conformational Heterogeneity, *Biochemistry* **1994**, *33*, 1373-1384.

50. Lakshman, M. K.; Keeler, J. C.; Ngassa, F. N; Hilmer, J. H.; Pradhan, P.; Zajc, B.; Thomasson, K. A.: Highly Diastereoselective Synthesis of Nucleoside Adducts from the Carcinogenic Benzo[*a*]pyrene Diol Epoxide and a Computational Analysis, *J. Am. Chem. Soc*. **2007**, *129*, 68-76.

51. Harada, N.; Chen, S.-m. L.; Nakanishi, K.: Quantitative Definition of Exciton Chirality and the Distant Effect in the Exciton Chirality Method, *J. Am. Chem. Soc*. **1975**, *97*, 5345-5352.

52. Yagi, H.; Akagi, H.; Thakker, D. R.; Mah, H. D.; Koreeda, M.; Jerina, D. M.: Absolute Stereochemistry of the Highly Mutagenic 7,8-Diol 9,l0-Epoxides Derived from the Potent Carcinogen *trans*-7,8-Dihydroxy-7,8-dihydro-benzo[*a*]pyrene, *J. Am. Chem. Soc*. **1977**, *99*, 2558-2559.

53. Yagi, H.; Jerina, D. M: Absolute Configuration of the *trans* -9,l0-Dihydrodiol Metabolite of the Carcinogen Benzo[*a*]pyrene, *J.* Am. Chem. Soc. **1982,** *104,* 4026-4027.

54. Yagi, H.; Thakker, D. R.; Ittah, Y.; Croisy-Decley, M.; Jerina, D. M.: Synthesis and Assignment of Absolute Configuration to the *trans* 3,4-Dihydrodiols and 3,4-Diol-1,2-Epoxides of Benzo[*c*]phenanthrene, *Tetrahedron Lett.* **1983**, *24,* 1349-1352.

55. Lakshman, M. K.; Chaturvedi, S.; Kole, P. L.; Windels, J. H.; Myers, M. B.; Brown, M. A.: Resolution of Polycyclic Aromatic Hydrocarbon Dihydrodiols Via Diastereomeric Formaldehyde Acetals, *Tetrahedron: Asymmetry* **1997**, *8*, 3375-3378.

LIST OF PUBLICATIONS

1. Barbara Zajc and **Rakesh Kumar**: *Synthesis of fluoroolefins via Julia–Kocienski olefination*, *Synthesis* **2010**, 1822-1836.

2. **Rakesh Kumar**, Barbara Zajc and Padmanava Pradhan: *Facile synthesis of 4-vinyl-and 4-fluorovinyl-1,2,3-triazoles via bifunctional 'click- olefination' reagents*, *Chem. Commun.* **2011**, *47*, 3891–3893.

3. Samir Kumar Mandal, Arun K. Ghosh, **Rakesh Kumar** and Barbara Zajc*:* *Expedient synthesis of α-substituted fluoroethenes*, *Org. Biomol. Chem*., **2012**, *10*, 3164–3167.

4. Rakesh Kumar and Barbara Zajc: *Stereoselective Synthesis of Conjugated 2-Fluoroenynes*, *J. Org. Chem.*, manuscript accepted.

POSTERS PRESENTED IN SYMPOSIA

1. **Rakesh Kumar** and Barbara Zajc: *Synthesis of regiospecifically fluorinated vinyl triazoles,* Abstracts of papers, 240th National Meeting of the American Chemical Society, Boston, Massachusetts, August 2010.

2. Rakesh Kumar and Barbara Zajc: *High Yield, stereoselective Synthesis of Fluoroenynes*, 236th National Meeting of the American Chemical Society, Philadelphia, Pennsylvania, August 2008