NEW DIRECTIONS WITH TRIAZOLE AND BENZOTRIAZOLE CHEMISTRY: FROM NUCLEOSIDE MODIFICATION TO C–H BOND-ACTIVATION

by

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Abstract

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Manish K. Singh

Advisor: Professor Mahesh K. Lakshman

Engineered peptide molecules are commonly synthesized by utilizing various peptide coupling reagents such as 1*H*-benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), 1*H*-benzotriazol-1-yl-4-methylbenzenesulfonate (Bt–OTs), 1-hydroxybenzotriazole (HOBt), etc. Their ready commercial availability, limited synthetic chemistry applications, and relatively high oxophilicity, prompted us to explore their applicability in new areas of organic synthesis. We have shown, for the first time, the application of BOP for the facile synthesis of C-6 azidopurine ribonucleosides and 2'-deoxyribonucleosides via the O^6-(benzotriazol-1-yl) nucleoside derivatives. In organic solvents these azido nucleosides exhibit azide•tetrazole equilibrium. The extent of azide and tetrazole tautomers in various organic solvents was studied, and relative amount of each tautomer in that solvent was determined. Subsequently, a detailed analysis of Cu-mediated azide-alkyne cycloaddition (CuAAC) leading to C-6 purine triazolyl nucleoside analogues was undertaken. Some of these nucleoside triazole derivatives showed moderate cytotoxic activity in human

colon and ovarian cancer cell lines. In an attempt to alter the biological activity of these nucleoside triazole analogues, purine *N*-directed ruthenium-catalyzed C–H bond functionalization was evaluated. Here a serendipitous discovery of C(sp^3)–H bond functionalization of *N*-methyl-2-pyrrolidone (NMP) was made. This result was developed into a C–H bond functionalization of NMP, and two cyclic, and a silyl ether using two 1,2,3-1*H*-benzotriazoles. Further, BOP and Bt–OTs reagents were applied to develop a new method for the dehydration of aldoximes to nitriles. This aldoxime dehydration method was utilized to develop one of the shortest and simplest routes towards the synthesis of an antiviral agent, 4'-cyano adenosine. Spurred by these findings, we investigated the reactivity of Bt–OTs towards various alcohols and probed the mechanism of reaction. These studies lead to the development of a new method for synthesis of benzotriazolylethers of alcohols. Also, for the first time we showed that $^{-}$OBt anion could act as a leaving group from a benzylic sp^3 hybridized carbon atom. This very important finding led to the utility of benzotriazolyl ethers of benzylic alcohols in a palladium-catalyzed C–C cross-coupling reactions.

To

My Parents,
Shri Shyama Singh & Smt. Usha Singh

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LIST OF ABBREVIATIONS

Abbreviation	Chemical Name
ATP	Adenosine Triphosphate
Ac	Acetyl
BDMS	Bromodimethylsulfonium Bromide
BOP	1*H*-Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium Hexafluorophosphate
BtH	1*H*-Benzotriazole
Bt–OTs	1*H*-Benzotriazol-1-yl-4-methylbenzenesulfonate
br	Broad
cAMP	Cyclic Adenosine Monophosphate
cGMP	Cyclic Guanosine Monophosphate
Cy-JohnPhos	2-(Dicyclohexylphosphino)biphenyl
CuAAC	Copper(I)-Catalyzed Azide-Alkyne Cycloaddition
Cy	Cyclohexyl
DNA	Deoxyribonucleic Acid
DMSO	Dimethyl Sulfoxide
DMF	*N*,*N*-Dimethylformamide
DPPA	Diphenylphosphoryl Azide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIPEA	*N*,*N*-Diisopropylethylamine
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DavePhos	2-Dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl
DPEphos	Bis[(2-diphenylphosphino)phenyl] Ether
DEPT	Distortionless Enhancement by Polarization Transfer

Abbreviation	Chemical Name
DCE	1,2-Dichloroethane
d	Doublet
EtOH	Ethanol
ESI	Electrospray Ionization
EtOAc	Ethyl Acetate
Et_2O	Diethyl Ether
FAD	Flavin Adenine Dinucleotide
HMPA	Hexamethylphosphoramide
HCMV	Human Cytomegalovirus
HOBt	1-Hydroxybenzotriazole
HOAt	1-Hydroxy-7-azabenzotriazole
Hz	Hertz
HMQC	Heteronuclear Multiple Quantum Correlation
J	Coupling Constant
JohnPhos	2-(Di-*tert*-butylphosphino)biphenyl
MeOH	Methanol
m	Multiplet
NMR	Nuclear Magnetic Resonance
NAD^+	Nicotinamide Adenine Dinucleotide
NOESY	Nuclear Overhauser Effect Spectroscopy
n*O*e	Nuclear Overhauser Effect
NMP	*N*-Methylpyrrolidone
PyBOP	(Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

Abbreviation	Chemical Name
quint	Quintet
q	Quartet
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
R_f	Retention Factor
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
s	Singlet
TBDMS	*tertiary*-Butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
THP	Tetrahydropyran
Ts	Tosyl
t-Bu	*tertiary*-Butyl
t	Triplet
VSV	Vesicular Stomatitis Virus
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

CHAPTER 1

SYNTHESIS OF 6-AZIDOPURINE NUCLEOSIDE DERIVATIVES: NMR STUDIES, AND LIGATION REACTIONS WITH TERMINAL ALKYNES

CHAPTER 1

SYNTHESIS OF 6-AZIDOPURINE NUCLEOSIDE DERIVATIVES: NMR STUDIES, AND LIGATION REACTIONS WITH TERMINAL ALKYNES

[1.1] INTRODUCTION

Nucleosides are some of the most ubiquitous compounds found in nature. They are the basic building blocks of DNA and RNA, the genetic code keepers. In addition, nucleosides store energy in the form of ATP, they are components of many enzyme co-factors (NAD^+, FAD), they play an important role in cellular communication (cAMP, cGMP) and are involved in the regulation of metabolic systems etc[1] Considering the pervasiveness and the numerous ways in which nature puts nucleosides to use, it is reasonable to expect that nucleoside analogues will exhibit certain important biological activities. Not only as chemotherapeutic (antiviral, antibacterial, anticancer) agents, nucleoside analogues have found applications in mechanistic studies on enzymatic metabolism of nucleoside and nucleic acid modification.[2,3] Thus development of new, simple and efficient methods to synthesize nucleoside analogues continues to be an active field of research.[4-11] A variety of modified nucleoside analogues have proved to be useful for the treatment of many life-threatening maladies (Figure 1). As shown in Figure 1, modification at any position of a nucleoside can potentially yield a new bioactive molecule.[9,12-15]

Similarly, numerous nucleoside analogues can be prepared by introducing various functional groups at the C-6 position of a nucleoside. Modification at the C-6 position of the purine moiety of a nucleoside has received considerable attention, partly due to the structural similarity

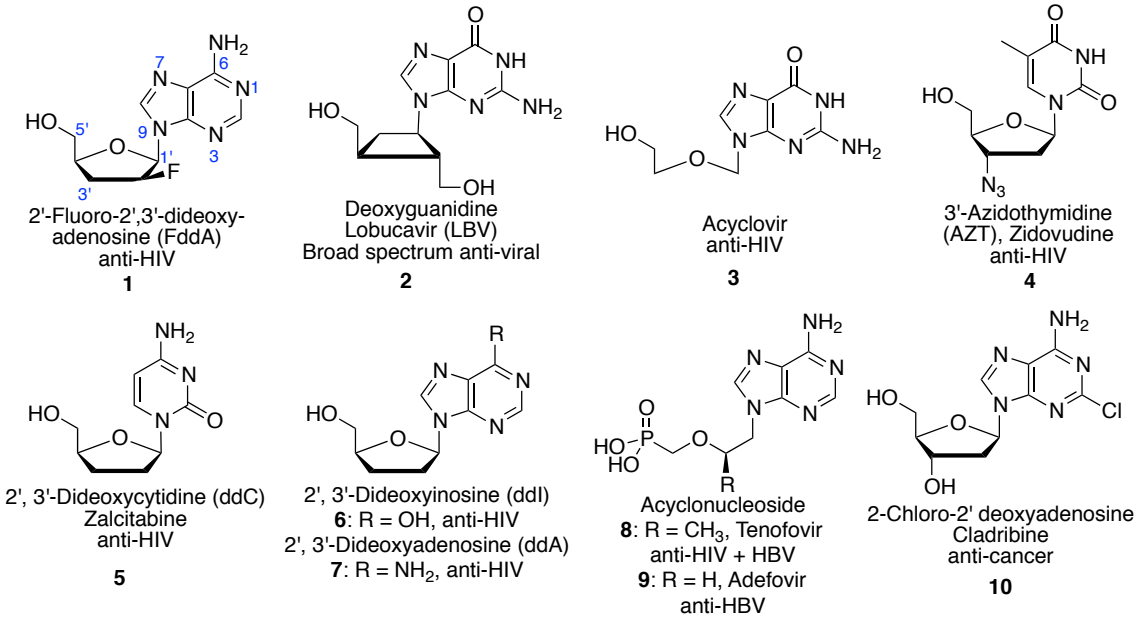


Figure 1. *Some Structurally Diverse Nucleoside Analogues used for the Treatment of Various Life-Threatening Diseases*

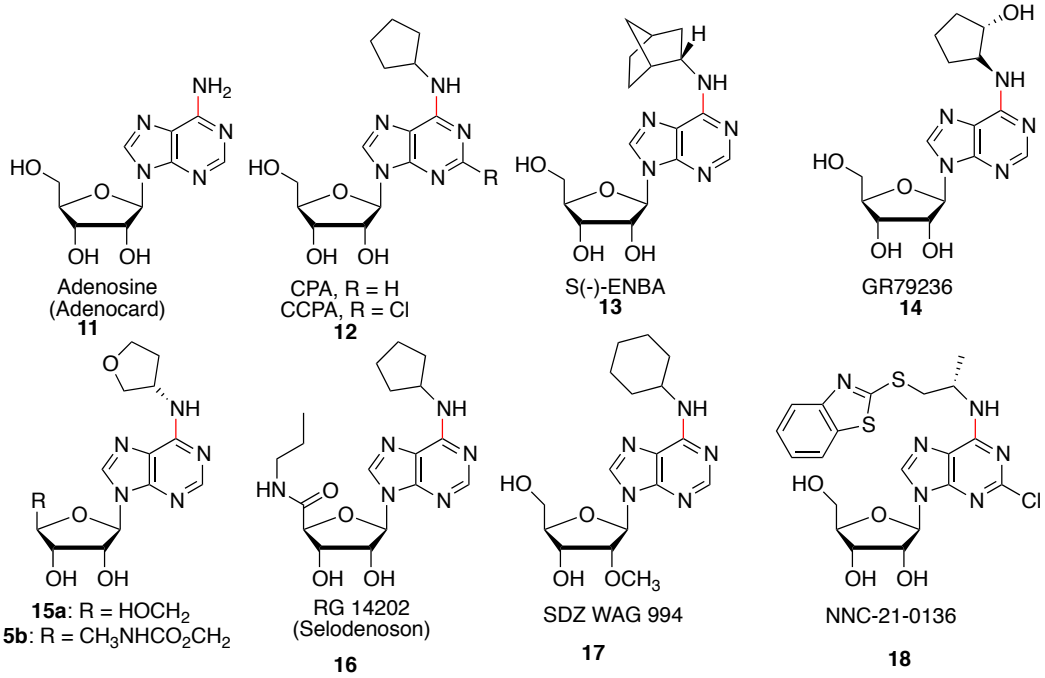
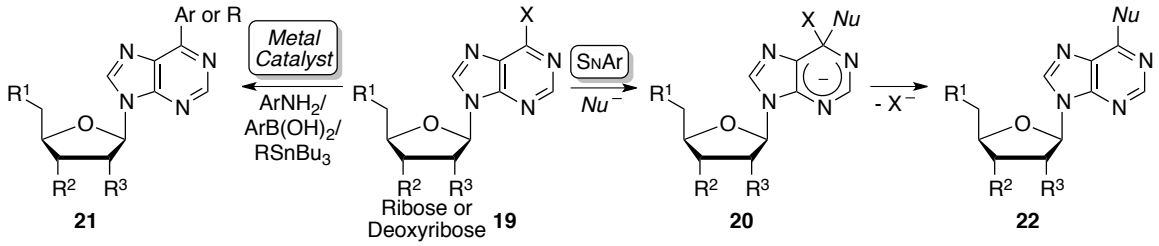


Figure 2. *Adenosine Receptor (AR) Agonists Acting at A_1 Type Adenosine Receptor*

of the N-6 modified nucleosides in 2'-deoxyadenosine with the DNA damage products.[16] Also, N-6 modified nucleosides can potentially lead to new adenosine receptor agonists (Figure 2) which are involved in cardioprotection, cardiac and cerebral ischemia, neuroprotection etc.[17]

S_NAr displacement and metal mediated reactions[18] are the two most widely used methods for the modifications at the C-6 position of a nucleoside (Scheme 1).

Scheme 1. *Synthesis of C-6 Modified Nucleoside via Nucleophilic Displacement and Metal Catalysis*

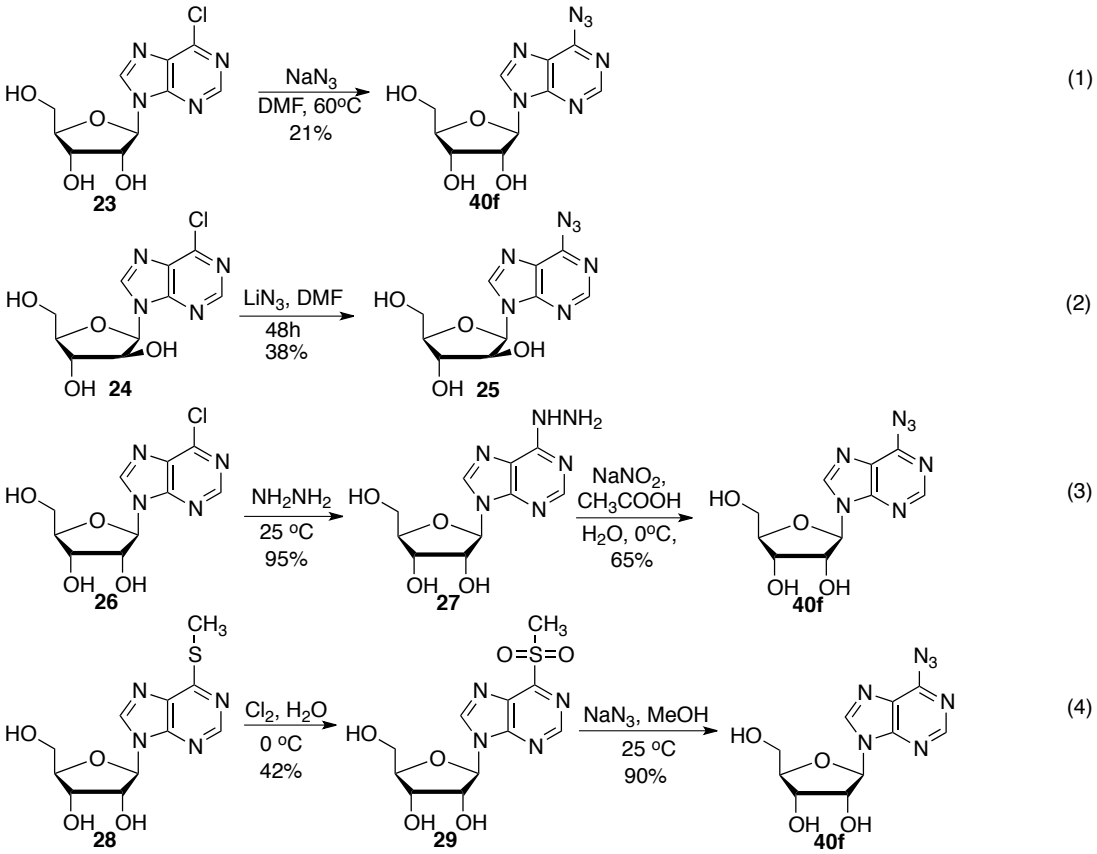


Generally, the electrophilic nucleoside precursor used for the modification at the C-6 position of purine nucleosides via S_NAr displacement are O^6-phosphonium ions,[19-22] halo,[23-29] phenoxy,[30] aryl and alkyl sulfonyl,[31,32] pyridyl,[33] sulfone[34] and imidazolyl[34,35] derivatives. Reactions of less reactive nucleoside substrates (C-6 chloro nucleoside) or less reactive nucleophilic partners (aryl amines) can be realized via metal-catalyzed reactions. For example, Suzuki cross-coupling and arylaminations using palladium catalysts,[36-42] Stille cross-coupling[43,44], Negishi coupling[45] etc. have all been used. Recently, Lakshman et al. reported synthesis of a new class of easily synthesized, convertible nucleosides.[21] These O^6-(benzotriazol-1-yl)inosine as well as the corresponding 2'-deoxy derivatives can undergo S_NAr substitution reactions in a facile manner when allowed to react with nucleophiles, under mild reaction conditions. This lead us to consider whether these new, benzotriazolyl nucleoside derivatives could be used for the synthesis of C-6 azido nucleosides via S_NAr chemistry. In this context, it is notable that a general method that can be invariably applied to the protected and unprotected, ribo and deoxyribo nucleosides for synthesis of corresponding C-6 azido purine derivatives has not been developed.

The most intuitively common method used to synthesize C-6 azido purine nucleoside involves S_NAr displacement of chloride from C-6 position.[46,47] One of the oldest methods to

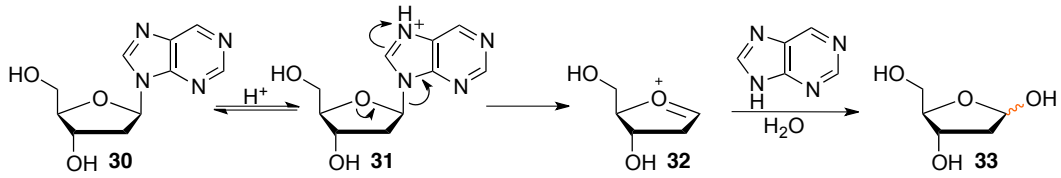
synthesize 6-azido-9-*β*-D-ribofuranosylpurine involves conversion of 6-chloro-9-*β*-D-ribofuranosylpurine to an unstable 6-hydrazino derivative, followed by treatment with nitrous acid (Scheme 2, eq 3).[48]

Scheme 2. *Some Previously Reported Synthesis of C-6 Azidopurine Nucleosides*



The acidic conditions are not compatible with 2'-deoxyribonucleosides, a deoxyribonucleoside can easily undergo deglycosylation via protonation at the N7 nitrogen (Scheme 3). The oxonium ion intermediate **32** (Scheme 3) is not favored in case of ribo nucleosides due to electron-withdrawing hydroxyl group at the C2' position. Thus, ribo nucleosides are comparatively more stable in acidic solution.

Scheme 3. *Acid Catalyzed Deglycosylation of Deoxyribo Nucleosides*



The second method uses 6-methylsulfonyl-9-*β*-D-ribofuranosylpurine to synthesize the azidopurine nucleoside via S_NAr displacement of sulfonyl group (Scheme 2, eq 4).[49] This is a two step process and the oxidation of sulfide to sulfoxide is low yielding. It has been reported in these articles that displacement of chloride from 6-chloro-9-*β*-D ribofuranosyl-purine by azide ion results in decomposition.[48,49] In line with these observations, recently reported syntheses of 6-azido-9-*β*-D-ribofuranosylpurine (Scheme 2, eq 1)[46] and 6-azido-9-*β*-D-arabinofuranosylpurine (Scheme 2, eq 2)[47] by nucleophilic displacement of chloride with azide resulted in low 21% and 38% yields of the respective 6-azidopurine nucleoside analogues.

Clearly, prior methods for the synthesis of C-6 azidopurine nucleosides are not efficient. They either use expensive commercially available materials, such as C-6 chloro deoxyribo or ribonucleoside or harsh acidic conditions (Scheme 2, eq 1), or the precursors are unavailable and require synthesis. These reports further encouraged us to develop a new, efficient, and facile synthesis of C-6 azidopurine nucleosides, using relatively low-cost, commercially available reagents. Further, we proposed to study the copper-catalyzed azide-alkyne (CuAAC) ligation reactions of the 6-azidopurine nucleosides.

The facile and efficient nature of the recently discovered Cu^I-catalyzed azide-alkyne ligation reaction[50,51] has triggered renewed interest in the Huisgen azide-alkyne cycloaddition reactions, one of the most atom economic transformations known.[52] This reaction has found applications in various research areas ranging from medicine to material science. Recently, copper-catalyzed

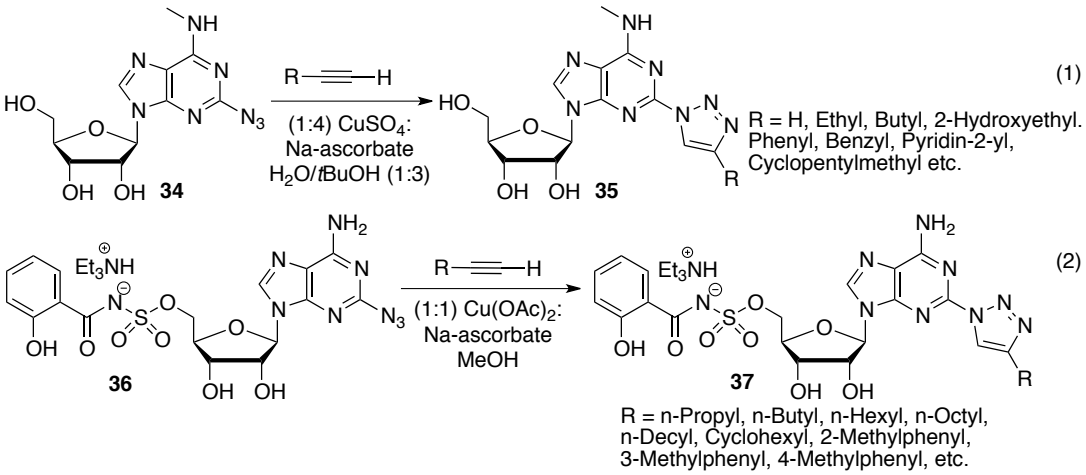
click reaction has been applied to synthesize a variety of new nucleoside derivatives.[15,53-68] A recent review delineates the importance of click reaction in the synthesis of nucleoside analogues.[12]

However, the application of the click reaction towards modification of purine nucleosides, where the nucleoside is the azide donor, has been limited. Partly, this is because of expensive commercially available starting materials needed to synthesize azidopurine nucleosides and the unavailability of a general method to synthesize azidopurine nucleosides from cheaper starting materials or unavailability of suitable precursors. To our knowledge, there have been only two reports describing modification of C-2 azidopurine nucleosides via copper catalyzed azide-alkyne (CuAAC) ligation reactions (Scheme 4). The reactivity of a functional group on a nucleoside could very well depend on its position on the purine ring.

Successful C-6azido nucleoside-alkyne cycloaddition would produce a new class of nucleoside analogues with a C–N bond at the C-6 position i.e. adenosine analogues, similar to that found in many of the known nucleoside-based adenosine receptor agonists (Figure 2). Because, these analogues could potentially be useful drug candidates, we also intended to carry out some biological testing using the new nucleoside analogues.

This chapter describes a simple, general method of synthesis of C-6 azidopurine nucleosides, their solution properties, and their copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) reactions with various alkynes to yield C-6 triazolyl compounds. Finally, the results from biological testing against various carcinoma cell lines, using these C-6 triazolyl nucleoside analogues have been described.

Scheme 4. *Previously Reported Click Reactions with C-2 Azidopurine Nucleosides*

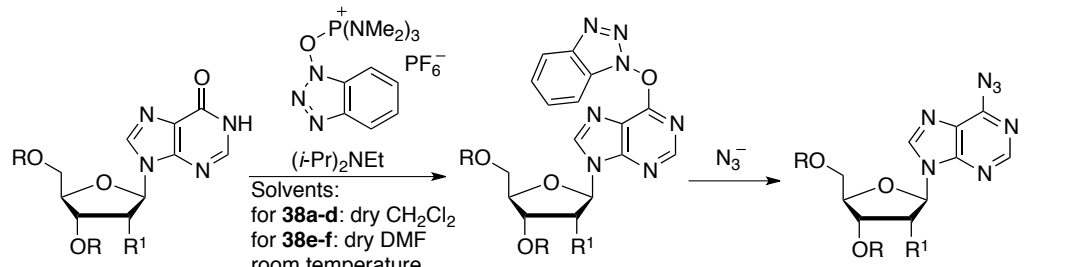


[1.2] RESULTS AND DISCUSSION

[1.2.1] Synthesis of 6-azidopurine nucleoside analogues

Recently, Lakshman et al. reported a simple and efficient synthesis of O^6-(benzotriazol-1-yl)inosine analogues, as a new class of reactive nucleosides.[21] Using this nucleoside precursors various N-6 and O-6 modified nucleosides were synthesized.[21,69,70] Considering the results obtained with these easily synthesized nucleoside analogues, which were obtained from relatively inexpensive precursors, we reasoned that they could be used to develop a general route to C-6 azidopurine nucleoside derivatives (Scheme 5). As illustrated in Scheme 5, silyl-protected 2'-deoxyinosine **38a** and inosine **38b**, as well as the unprotected nucleosides **38e** and **38f** were converted to the O^6-(benzotriazol-1-yl) derivatives using reported procedures.[21] Using similar methodology, the previously undescribed acetate-protected compounds **39c** and **39d** were also prepared.

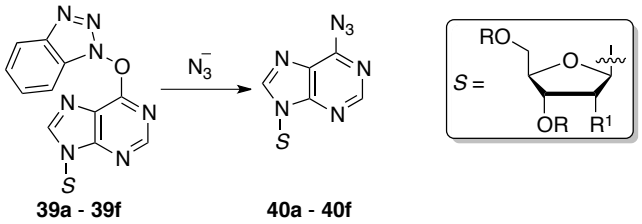
Scheme 5. *Synthesis of C-6 Azidopurine Nucleoside Derivatives Using O^6-(Benzotriazol-1-yl)inosine Derivatives as Precursors*



The conditions used for the conversion of compounds **39a-f** to C-6 azido nucleosides **40a-f** are shown in Table1. Although, these displacement reactions could be performed in DMF, we preferred to use DMSO because reactions of **39a** and **39b** in DMF produced some N^6, N^6-dimethylamino derivatives. Reactions in DMSO proceeded smoothly and in high yields, and this

simplified the purification process as well. Due to solubility and product isolation issues, the azidation reactions of unprotected nucleosides **39e** and **39f** were less simple. Polymer-supported azide, proved useful for reactions of the unprotected substrates as it removed the need for aqueous workup and product isolation via column chromatography. Reaction of deoxy derivative **39e** in water resulted in moderate conversion to the product. Since, it has already been reported that O^6-(benzotriazoly-1-yl) nucleoside analogues are relatively stable toward hydroxylic solvents such as water and alcohol under neutral conditions,[21,71] the moderate yield of **40e** may not be due to hydrolysis of **39e**. For **39f**, DMF was found to be the optimal solvent for workup and product (**40f**) isolation considerations. Alternatively, deprotection of **40a**-**40d** should also provide the corresponding unprotected derivatives, **40e** and **40f**.

Table 1. *Conditions for the Conversion of O^6-(Benzotriazol-1-yl)inosine Derivatives (**39a–f**) to the C-6 Azido Nucleosides (**40a–f**)*

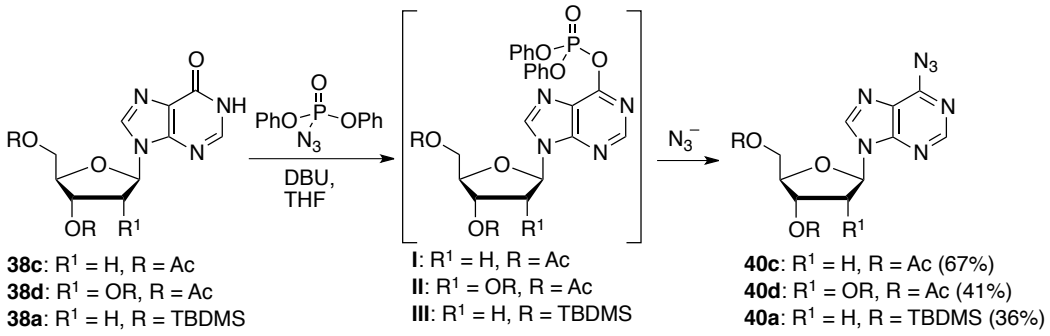


Entry	Substrate	Conditions	Product: Yield[a]
1	**39a**	NaN_3, DMSO, 40 ˚C, 2 h	**40a**: 99%
2	**39b**	NaN_3, DMSO, 40 ˚C, 3.5 h	**40b**: 96%
3	**39c**	NaN_3, DMSO, room temperature, 1 h	**40c**: 95%
4	**39d**	NaN_3, DMSO, room temperature, 1 h	**40d**: 75%
5	**39e**	Polymer-supported N_3^-, H_2O, 50 ˚C, 3.5 h	**40e**: 59%
6	**39f**	Polymer-supported N_3^-, DMF, 50 ˚C, 5 h	**40f**: 70%

[a] Yields of isolated and purified products.

Further, we designed a scheme to potentially access protected 6-azidopurine nucleosides in one step by in situ conversion of the C-6 amide carbonyl into a good leaving group. For this, we used diphenylphosphoryl azide [$(PhO)_2P(O)N_3$, DPPA] and a base. In principle, deprotonation of the amide and reaction with DPPA would produce a diphenyl phosphate intermediate that could undergo subsequent S_NAr reaction with azide anion (Scheme 6). We tested this rationale with **38c** and **38d**. Acetate-protected nucleosides **38c** and **38d** were exposed to DPPA and DBU in THF at 0 ^oC, followed by warming to 60 ^oC. The corresponding azido nucleosides **40c** and **40d** were obtained in 67% and 41% yield, respectively.

Scheme 6. *One Step Synthesis of Some C-6 Azido Nucleosides Using $(PhO)_2P(O)N_3$ and DBU*



Interestingly, a similar reaction of silylated derivative **38a** (analogus to **38c**) led to only a 36% isolated yield of **40a**. This possibly indicates some influence of the saccharide protecting group on the efficiency of the S_NAr reaction. Thus, displacement reactions on O^6-(benzotriazol-1-yl) derivatives **39a-f** by azide offer generally good access to C-6 azidopurine nucleosides.

[1.2.2] The azide-tetrazole equilibrium of 6-azidopurine nucleosides

6-Azido purine and the corresponding ribonucleoside derivatives are known to exist in an azide-tetrazole equilibrium and their slow interchange enables them to be studied by NMR technique.[48,72-74] Extensive studies on this phenomenon report, that in DMSO-d_6, 6-azidopurine as well as its N7- and N9-benzyl derivatives exist exclusively as the tetrazolyl isomers, and the

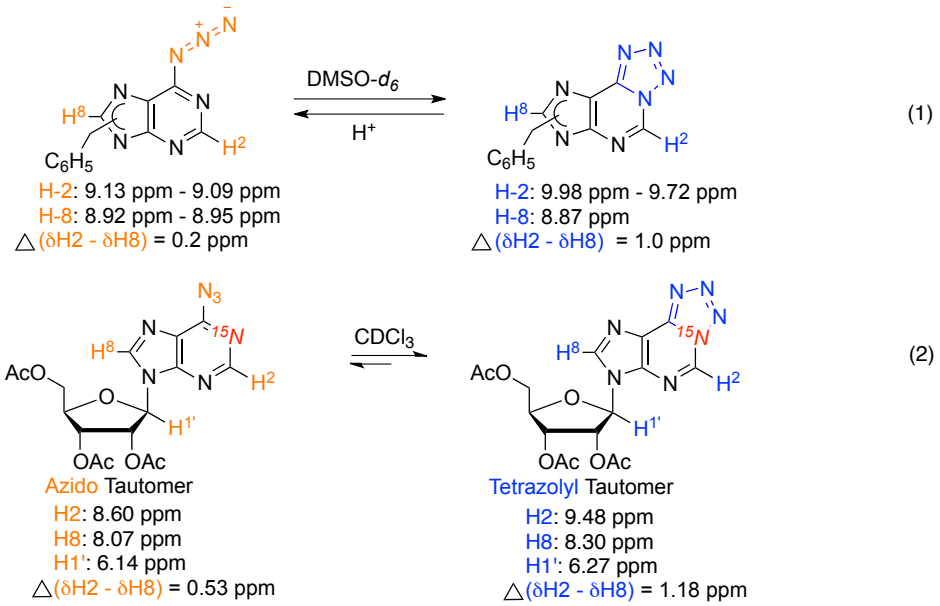
azido forms are observable only after protonation with trifluoroacetic acid (Scheme 7).[72,73] 6-Azidopurine ribonucleoside exists as the tetrazolyl isomer in the solid state, which is supported by the lack of an IR absorption at 2000-2200 cm^{-1}, characteristic of an azido functionality.[46,48]

Since we eventually wanted to modify these C-6 azido nucleosides via copper catalyzed azide alkyne ligation, we decided to evaluate the effect of solvent on the azide-tetrazole equilibrium of these azido nucleosides. These compounds can exist as the corresponding tetrazolo[5,1-*i*]purinyl isomers. This was important because as per the reported mechanism of CuAAC (Scheme 9), the reaction requires the azido tautomer for the reaction to proceed in the forward direction.[75]

We chose ^{1}H NMR spectroscopy to analyze the relative amounts of azide and tetrazolyl forms. The H-2 and H-8 resonances of the azido and tetrazolyl isomers are well resolved and diagnostic for this. As shown in Scheme 7, Temple et al.[73] have reported that 6-azido N7- and N9-benzyl purine derivatives exist only as the tetrazole tautomer in DMSO-d_6. However, upon acidification of this solution, proton resonances corresponding to the azido form were observed (Scheme 7). The H-2 and H-8 protons of the tetrazolo form appear more downfield as compared to the H-2 and H-8 protons of the azido tautomer. For the C-6 azido benzylpurine, H-2 of tetrazolyl form appears at 9.98–9.72 ppm where as the H-8 proton appears at 8.87 ppm.[73] H-2 of the azido form appears more upfield at 9.09–9.13 ppm and the H-8 proton resonance appears at 8.85–8.92 ppm.[73] The line separation between the H-2 and H-8 proton resonances of the tetrazolyl form is much larger (~1.0 ppm) as compared to the separation between the H-2 and H-8 protons of the azido form (~0.2 ppm). Thus, H-2 of the tetrazolyl isomer appears farther downfield compared to its H-8 resonance as well as the H-2 and H-8 resonances of the azido tautomer. In a recent communication, a detailed study on azide-tetrazole tautomerism of

triacetyl protected 6-azidopurine nucleoside labeled with ^{15}N at N-1 was reported (Scheme 7, eq 2).[74] This report also identifies the chemical shifts of all the protons of azido and tetrazolyl tautomer.

Scheme 7. *Azide-Tetrazole Tautomerizm of N-7 or N-9 C-6-Azidobenzyl Purine and 6-Azidopurine Nucleoside*



On the basis of these reported observations, as well as NOESY data from **40b** (in acetone-d_6) and **40d** (in $CDCl_3$) showing correlation between H-1' and H-8 (Figure 3), we determined the chemical shifts of purinyl H-2, H-8, and the sugar H-1' in the azido (A) and tetrazolyl (T) forms of compounds **40a-f**. These results are shown in Table 2. The ^1H NMR chemical shifts (in $CDCl_3$) of H-1', H-2, and H-8 in compound **40d** agrees with the published data on **40d** in $CDCl_3$ solvent (Scheme 7, eq 2).[74]

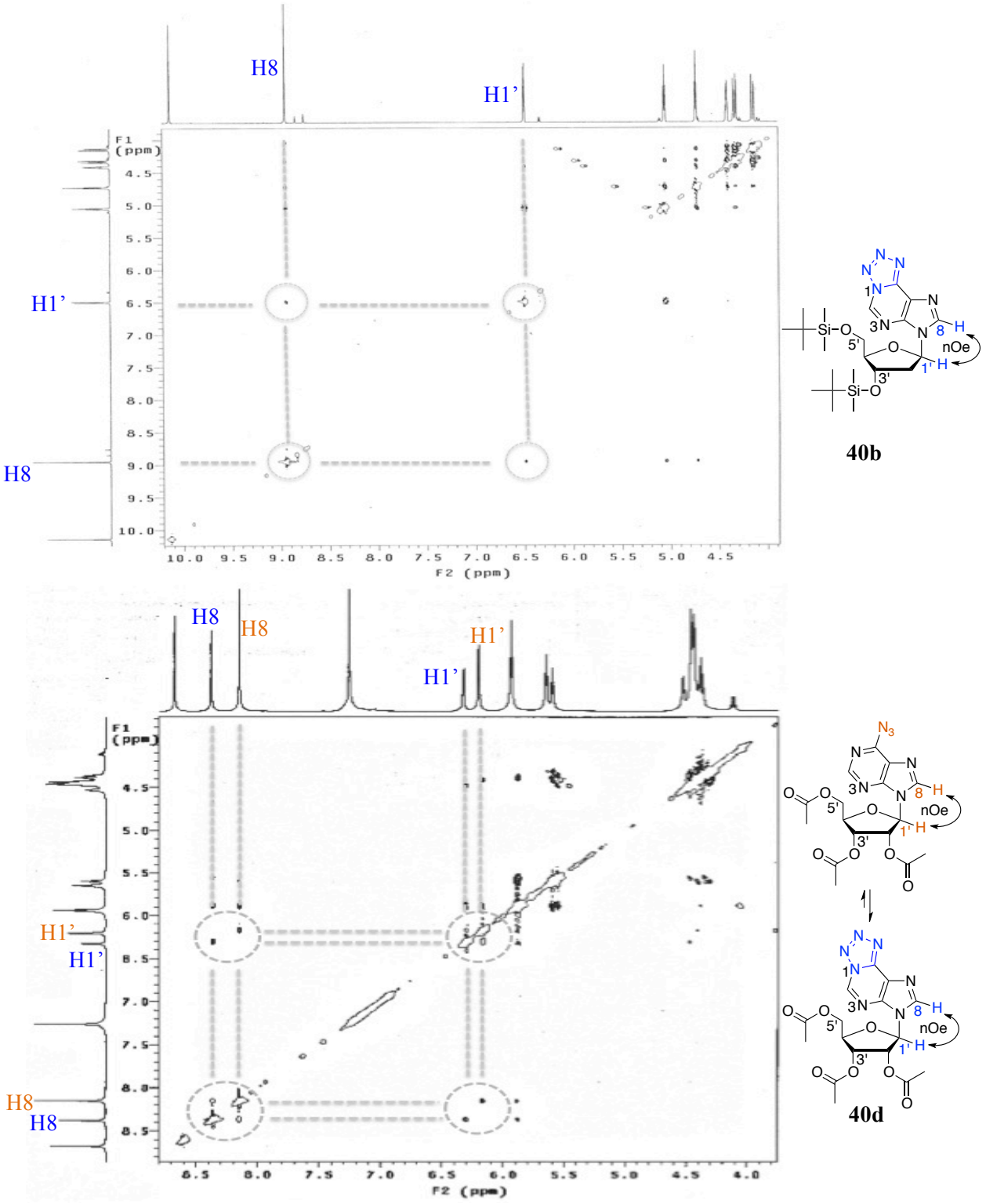
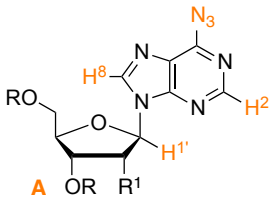
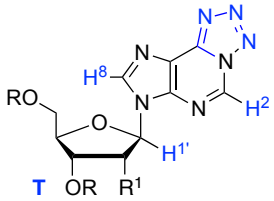


Figure 3. *nOe Correlation Between H1' and H8 Protons of **40b** (in Acetone-d_6) and **40d** (in $CDCl_3$)*

Table 2. *Chemical Shifts (δ ppm) of Purinyl H-2, H-8 and the Sugar H-1' in the Azido and Tetrazolyl Isomers of* ***40a-f***

40a: R^1 = H, R = TBDMS
40b: R^1 = OR, R = TBDMS
40c: R^1 = H, R = Ac
40d: R^1 = OR, R = Ac
40e: R^1 = H, R = H
40f: R^1 = OH, R = H



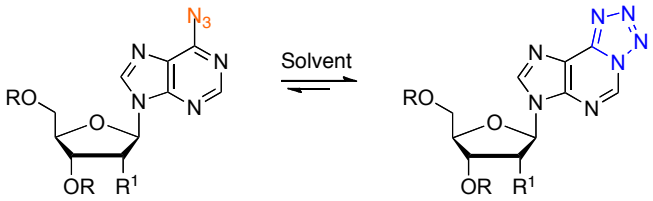


Compound	Solvent	Azido form (**A**)			Tetrazolyl form (**T**)		
		H–2	H–8	H–1'	H–2	H–8	H–1'
40a	$CDCl_3$	8.63	8.33	6.47	9.51	8.57	6.61
	THF-d_8	8.58	8.36	6.45	9.78	8.54	6.60
	CD_2Cl_2	8.63	8.33	6.47	9.51	8.57	6.61
	acetone-d_6	8.65	8.51	6.54	9.91	8.69	6.70
	DMSO-d_6	--	--	--	10.14	8.82	6.55
40b	$CDCl_3$	8.65	8.41	6.10	9.49	8.66	6.25
	THF-d_8	8.60	8.46	6.07	9.82	8.66	6.24
	CD_2Cl_2	8.64	8.40	6.09	9.52	8.67	6.25
	acetone-d_6	8.68	8.59	6.17	9.97	8.78	6.33
	DMSO-d_6	--	--	--	10.19	8.88	6.17
40c	$CDCl_3$	8.67	8.18	6.47	9.53	8.40	6.59
	THF-d_8	8.60	8.35	6.48	9.81	8.52	6.62
	CD_2Cl_2	8.65	8.19	6.48	9.54	8.42	6.60
	acetone-d_6	8.68	8.53	6.57	9.95	8.71	6.73
	DMSO-d_6	--	--	--	10.16	8.87	6.61
40d	$CDCl_3$	8.68	8.15	6.21	9.54	8.38	6.33
	THF-d_8	8.62	8.35	6.27	9.83	8.52	6.41
	CD_2Cl_2	8.67	8.16	6.22	9.56	8.41	6.36
	acetone-d_6	8.70	8.53	6.36	9.97	8.71	6.52
	DMSO-d_6	--	--	--	10.19	8.88	6.46
40e[a]	THF-d_8	8.57	8.46	6.48	9.78	8.68	6.64
	DMSO-d_6	--	--	--	10.13	8.88	6.57
40f[a]	DMSO-d_6	--	--	--	10.15	8.93	6.15

[a] Solubility constraints precluded assessment in other solvents.

To determine the proportion of the azido and tetrazolyl forms of **40a-f** in different solvents, the H-2 and H-8 resonances of the two isomers were related to their H-1' resonance. The integrals of the H-1' resonances were then used to determine the relative amounts of the two isomeric forms in each solvent. Several solvents were selected with varying dielectric constants (ε), and the proportion of each form in the different solvents is shown in Table 3. The analysis of Table 3 clearly, shows that the proportion of the tetrazolyl isomer increases with increasing solvent dielectric constant. This is consistent with the previously reported study, where 6-azido purine has been reported to exist only as tetrazolyl form in a solvent with high dielectric constant (DMSO).[72]

Table 3. *Relative Amount of the Azido (A) and Tetrazolyl (T) Isomers of **40a–f** in Various Solvents*[a]



Entry	$CDCl_3$, ε = 4.8		THF-d_8, ε =7.6		CD_2Cl_2, ε = 8.9		acetone-d_6, ε = 20.6		DMSO-d_6, ε = 46.5	
	%A	%T	%A	%T	%A	%T	%A	%T	%A	%T
40a	46.0	54.0	14.8	85.2	20.8	79.2	7.5	92.5	0.1	99.9
40b	47.6	52.4	16.5	83.5	19.7	80.3	8.2	91.8	0.1	99.9
40c	56.9	43.1	14.1	85.9	17.5	72.5	6.2	93.8	0.9	99.1
40d	61.9	38.1	16.9	83.1	31.4	68.6	7.6	92.4	1.9	98.1
40e	nd[b]	nd[b]	15.1	84.9	nd[b]	nd[b]	nd[b]	nd[b]	0.1	99.9
40f	nd[b]	nd[b]	nd[b]	nd[b]	nd[b]	nd[b]	nd[b]	nd[b]	0.9	99.1

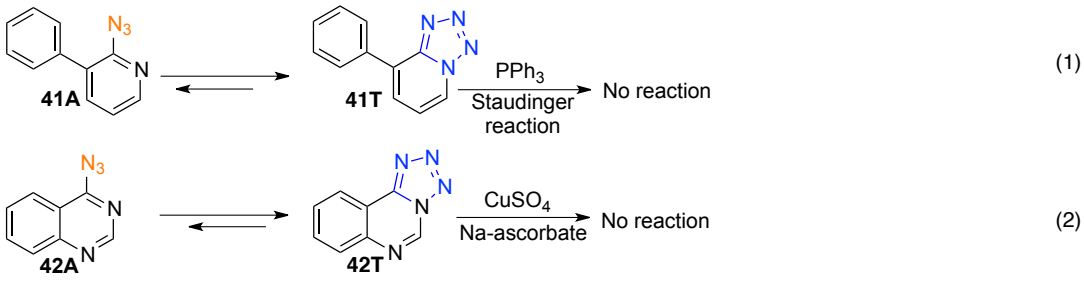
[a] The dielectric constants (ε) of the corresponding protio solvents are reported.[76] [b] Solubility constraints precluded assessment.

In chloroform, a solvent of low dielectric constant, about 40-50% of the tetrazolyl form is present. Interestingly, the acetate protected C-6 azido nucleosides **40c** and **40d** showed a slightly higher proportion of the azido form in $CDCl_3$. The result obtained for **40d** is consistent with the reported, 3:2 azide/tetrazole ratio in chloroform.[74] In THF as well as in dichloromethane, which are close in dielectric constant, the tetrazolyl form is major. Similarly, the tetrazolyl isomer is the major form in acetone and in DMSO. For unprotected **40e**, where analysis was possible in THF, a greater proportion of the azido isomer is observed in THF than in DMSO. The ratio of these isomers of **40e** is also consistent with data for the other azidopurine nucleoside derivatives shown in Table 3.

[1.2.3] Copper-catalyzed azide-alkyne ligation reaction of nucleoside azide with terminal alkynes

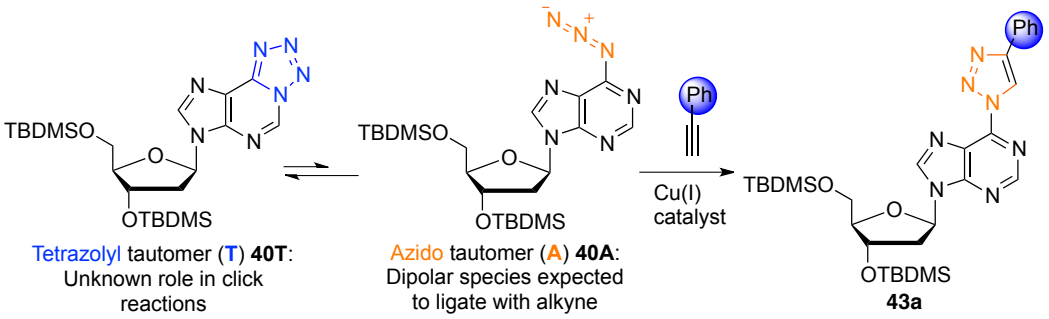
The existence of azide tetrazole equilibrium in the C-6 azido purine nucleosides led to an interesting question: *How does this tautomeric equilibrium affect copper-catalyzed "click" reactions with alkynes?* In the light of recent reports, an answer to this question was not obvious. In solution, 2-azido-3-phenylpyridine (**40A**, azido form) exists as 8-phenyltetrazolo[1,5-*a*]pyridine (**40T**, tetrazolyl form) and is unreactive towards PPh_3 in the Staudinger reaction (Scheme 8, eq 1).[77] Similary, we have found that 4-azidoquinazoline **42A** does not undergo azide-alkyne ligation under standard click reaction conditions (Scheme 8, eq 2).[78] After heating the reaction mixture, no product formation was observed either. Also, it has been speculated that some of the lower yielding azide-alkyne ligations involving a C-2 azidopurine nucleoside could be due to the presence of the tetrazolyl tautomer.[12]

Scheme 8. *Certain Tetrazolyl Tautomers are Unreactive Under Standard Reaction Conditions*



With these data in mind, we began screening conditions for the Cu-catalyzed azide-alkyne ligation[50,51] reaction between **40a** and phenylacetylene. We chose to start with the most popular reaction conditions, i.e. using the $CuSO_4$/Na-ascorbate in *t*-BuOH/H_2O.[51] To our surprise, the reaction did not go to completion after 3.5 h at room temperature and only 26% product formation was observed. More importantly, 11% reduction of the azide to the amine was observed (Table 4, entry 1), and the resulting disilyl 2'-deoxyadenosine was isolated and identified. This clearly points to the facile reducibility of the azide functionality in **40a**, which contrasts with the reactivity of simpler azides, where such reduction is generally not observed under the standard click reaction conditions. Replacing *t*-BuOH with THF or toluene did not provide any significant improvement (entries 2 and 3). However, use of a biphasic solvent system proved to be useful in suppressing the reduction of 6-azido purine nucleoside to adenosine (entries 4 and 5), and resulted in a good yield of the desired product **43a**. One-electron reduction of azide to amine is a known reaction in organic chemistry.[79,80] Reduction of copper(II) to copper(I) by sodium-ascorbate is a one electron transfer process[81] and usually, one electron transfer process occurs very efficiently in water or in solvents with high dielectric constants.[82]

Table 4. *Evaluation of Conditions for the Reaction of **4a** with Phenylacetylene*



#	Catalyst	Solvent (1:1 Mixture)	Temp, Time	Result[a,b]
1	$CuSO_4$/Na-ascorbate	*tert*-BuOH/ H_2O	rt, 3.5 h	Incomplete reaction **40a**: 63%, **43a**: 26%, reduction: 11%
2	$CuSO_4$/Na-ascorbate	THF/H_2O	rt, 6 h	Incomplete reaction **40a**: 46%, **43a**: 30%, reduction: 24%
3	$CuSO_4$/Na-ascorbate	Toluene/ H_2O	rt, 6 h	Incomplete reaction **40a**: 67%, **43a**: 22%, reduction: 11%
4	$CuSO_4$/Na-ascorbate	$CHCl_3/H_2O$	rt, 2 h	**43a**: 78% yield[c]
5	$CuSO_4$/Na-ascorbate	CH_2Cl_2/H_2O	rt, 3.5 h	**43a**: 81% yield
6	Cu(Phen)(PPh_3)Br	CH_2Cl_2/H_2O	rt, 24 h	**43a**: 46% yield
7	Cu(PPh_3)$_3$Br	CH_2Cl_2/H_2O	rt, 15 h	**43a**: 73% yield, an uncharacterized byproduct was also formed
8	CuIMes	CH_2Cl_2/H_2O	rt, 20 h	Incomplete reaction **40a**: 60%, **43a**: 29%, reduction: 11%
9	CuIPr	CH_2Cl_2/H_2O	rt, 24 h	No reaction, only **40a** present
10	CuCl	CH_2Cl_2/H_2O	rt, 5 h	**43a**: 76% yield
11	CuTC	CH_2Cl_2/H_2O	rt, 6 h	**43a**: 63% yield
12	Cu/C and 2 molar equiv Et_3N	1,4-Dioxane	rt, 15 h then 60 °C, 1.5 h	**43a**: 51%, reduction: 38%
13	Cu/C	1,4-Dioxane	rt, 23 h	No reaction, only **40a** present
14	Cu/C	CH_2Cl_2/H_2O	rt, 2.5 h	No reaction, only **40a** present

[a] In reactions that proceeded to completion, yield reported is of isolated and purified **43a**. [b] In some cases the reduction product, 3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine, was isolated and characterized. In other cases this product was detected by TLC (UV visualization) and the amount formed was estimated by ^{1}H NMR analyses of the crude reaction mixtures. [c] By TLC, reaction was less clean compared to entry 5.

The biphasic solvent system may have segregated the azido nucleoside derivative (in organic phase) from the oxidation/reduction process occurring in the aqueous medium, thus, suppressing the reduction of azido purine nucleoside to adenosine. Several other Cu catalysts shown in Figure 4 were also evaluated, and some representative results are listed in Table 4.

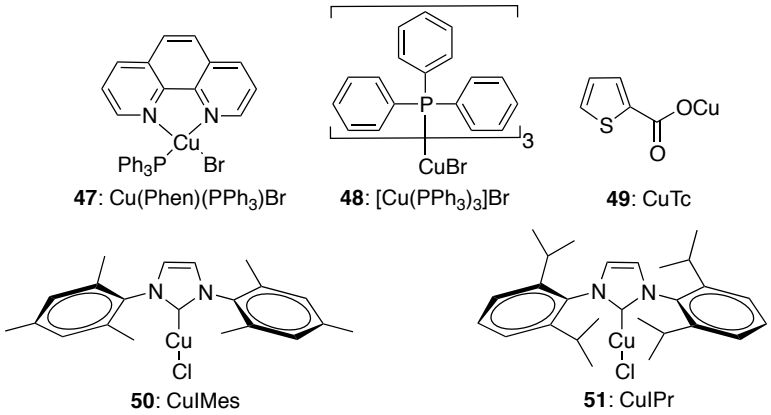
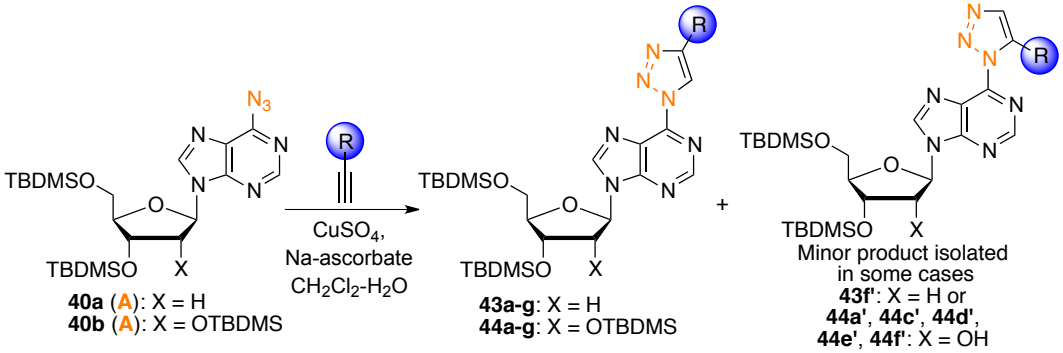
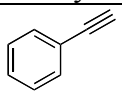
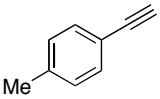
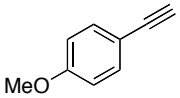
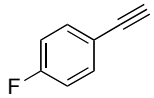
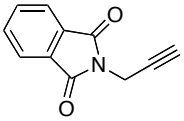
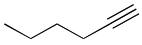


Figure 4. *Other Copper (I) Catalysts Tested for the Azide-Alkyne Ligation Reaction*

These experiments showed at least two important features of C-6 azido purine nucleosides under standard click conditions ($CuSO_4$/Na-ascorbate, *t*-BuOH/H_2O). The use of a biphasic solvent system, CH_2Cl_2/H_2O system[83] was important for successful reaction. Secondly, despite a major proportion of the tetrazolyl tautomer in this solvent system, reactions with phenylacetylene proceeded to completion smoothly. This is what was expected in the light of Le Chatelier's principle. Since reactions in CH_2Cl_2/H_2O gave best result, in terms of yield of the desired product and "cleanness" of reaction, we assessed the relative amounts of tetrazolyl and azido tautomers for **40a** and **40b** in 10% D_2O/CD_2Cl_2. In this solvent, the relative amounts of the azido (A) and tetrazolyl (T) forms of **40a** were 18.4% and 81.6%, respectively, whereas for **40b** it was 21% (A) and 79% (T), respectively. These ratios are very similar to the data obtained in CD_2Cl_2 alone (Table 3), indicating that the azide-tetrazole ratio is not substantially altered in the presence of water.

Table 5. *Copper(I) Catalyzed Cycloaddition Reaction between C6-Azido Nucleoside and Alkyne*



Entry	Substrate	Alkyne	Reaction time and Temp	Product yield[a]
1	**40a**		4.0 h, room temp	**43a**: 77%
2	**40b**		4.0 h, room temp	**44a**: 90% **44a'**: 2%[b]
3	**40a**		4.0 h, room temp	**43b**: 87%
4	**40b**		4.0 h, room temp	**44b**: 90%
5	**40a**		4.0 h, room temp	**43c**: 90%
6	**40b**		3.5 h, room temp	**44c**: 94% **44c'**: 3%[b]
7	**40a**		4.5 h, room temp	**43d**: 92%
8	**40b**		4.0 h, room temp	**44d**: 82% **44d'**: 1%[b]
9	**40a**		7.0 h, 40 ˚C	**43e**: 95%
10	**40b**		4.0 h, 40 ˚C	**44e**: 76% **44e'**: 3%[b]
11	**40a**		4.0 h, room temp	**43f**: 83% **43f'**: 6%[b]
12	**40b**		4.0 h, room temp	**44f**: 71% **44f'**: 10%[b]
13	**40a**		4.5 h, room temp	**43g**: 75%
14	**40b**		4.5 h, room temp	**44g**: 81%

[a] Yields reported are of isolated and purified products. [b] The isomeric 1,5-disubstituted tetrazole was also isolated as a minor byproduct.

We assessed the generality of the azide-alkyne ligation reaction under our optimized reaction conditions i.e. $CuSO_4$/Na-ascorbate in CH_2Cl_2/H_2O. A range of alkynes underwent successful ligation with **40a** and **40b** in good yields and within reasonably short reaction times (Table 5). Interestingly, in many cases along with the desired product, formation of a minor product was also observed, particularly within the ribonucleoside series. In many cases the minor products

were isolated and analyzed by NMR and HRMS. Surprisingly, this analysis of the minor products indicated that these were also azide-alkyne ligation products. NMR analysis could not help to identify the structures of the major and the minor products. This unexpected observation raised the question about the regiochemistry leading to the major product. In simpler systems, copper(I) catalyzed azide-alkyne ligation reaction almost always leads to 1,4-disubstituted product.

After the assessing the generality of the ligation reactions, we focused our attention on the regiochemical issue. Since, it was not possible to ascertain the regiochemistry by NMR, we attempted structure evaluation by X-ray crystallography. The minor product obtained was in low amounts to crystallize. So, we decided to crystallize one of the major isomers. From a reaction of **40a** and 4-ethynyltoluene, conducted under the optimized conditions, the major product **43b** was crystalized from hexanes. We were pleased to obtain long needle shaped crystals of **43b**. The X-ray structure (Figure 5) clearly indicated this to be the anticipated 1,4-disubstituted triazole derivative. The crystal structure shows that the purine and the triazole rings are nearly coplanar, with a *syn* conformation of the purine around the glycosidic bond, and a 3'-endo sugar ring pucker. Thus, on the basis of the NMR and HRMS data, the minor productsl must be 1,5-disubstituted regioisomers. The data analysis appropriately fits the famous quote of Sir Arthur Conan Doyle, "*When you have eliminated all which is impossible, then whatever remains, however improbable, must be the truth.*"[84]

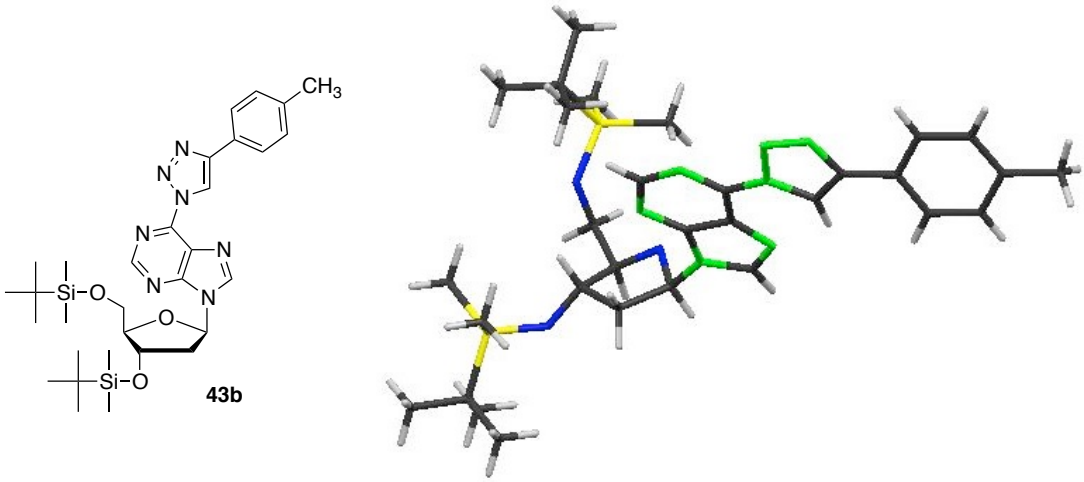


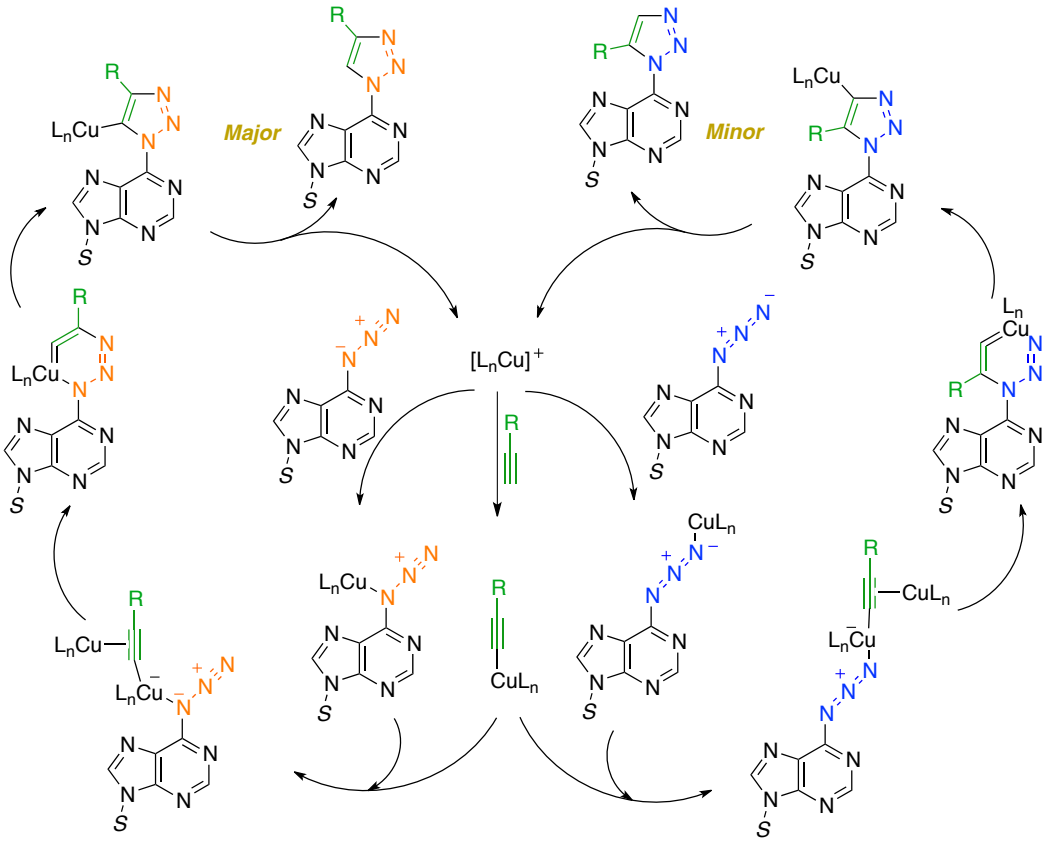
Figure 5. *X-ray Structure of the Major Isomeric Product (**43b**) from a Click Reaction Between **40a** and 4-Ethynyltoluene*

Further, to compare the catalyzed reaction with the uncatalyzed process, two different reactions were conducted. First a mixture of **40a** and 4-ethynyltoluene were heated at 85 ^{o}C in 1:3 MeOH-H_2O. This reaction was incomplete at 36 h, gave 48% of the 1,4-disubstituted triazole, 5% of the 1,5-isomer, and 18% of **40a** was recovered. A second reaction between **40a** and 4-ethynyltoluene was conducted in toluene at 65 ^{o}C. This reaction was incomplete at 120 h and showed ~10% **40a**, ~80% of the 1,4-disubstituted triazole, as well as ~10% of the 1,5-isomer (estimates based upon ^{1}H NMR analysis of the crude reaction mixture). These results indicate that the copper catalyst greatly enhances the efficiency of the azide-alkyne ligation reaction.

These results also indicate the difference in the reactivity of azido nucleosides in comparison to those of simpler azides. Since we isolated major and minor ligation products in some cases, we wondered, if mechanistically[75] (Scheme 9) a major and a minor process are in operation, leading to the two regioisomeric products. Since no product formation was observed by simply stirring 4-ethynyltoluene and **40b** in CH_2Cl_2/H_2O at room temperature for 48 h, it is likely that the minor 1,5-disubstituted products also arise via a Cu-catalyzed process (after 48 h at 100 ^{o}C, 32% of **40b**, 16% of the major, and 2.5% of the minor cycloaddition products were isolated from

this reaction). Although it is difficult to rationalize why the reaction partitions through the minor pathway, it is possible that presence of the subsitutent (R) and the nucleoside on vicinal carbons is sterically not unfavored. A plausible mechanism for the two pathways is shown in Scheme 9.

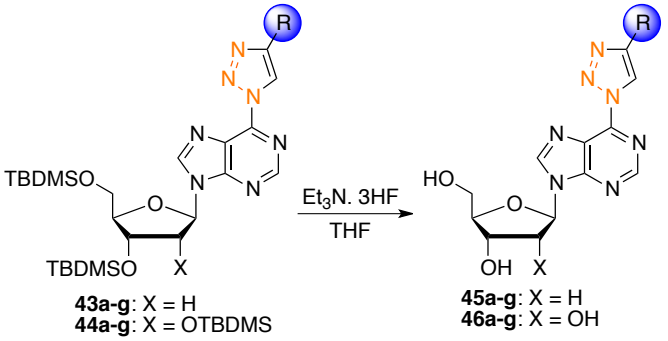
Scheme 9. *Plausible Mechanism for the Formation of Isomeric Major and Minor Ligation Products*



Finally, the biological activities of these new triazolyl nucleoside analogues were determined. Ribo- and 2'-deoxyribo nucleosides are typically of low toxicity to human cells. Compounds **43a-g** and **44a-g** were desilylated to yield the free nucleosides (Scheme 10). The desilylated compounds were tested for antiproliferative activity (range of concentrations tested was 1-100 μM, 72 h continuous exposure) against a panel of human cancer cell lines: wild-type $p53^{+/+}$ and $p53^{-/-}$ HCT116 colon carcinoma cells and paclitaxel sensitive (1A9) and resistant

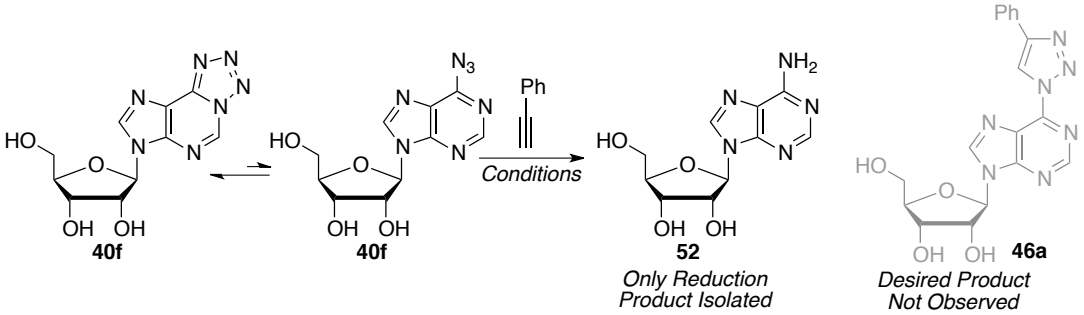
(1A9/PTX10 and 1A9/PTX22) ovarian carcinoma cells. Only weak antiproliferative or cytotoxic actions were noted for compounds **45e**, **45f**, **45g**, **46d**, and **46f**.

Scheme 10. *Desilylation of C-6 Triazolyl Nucleoside Analogues*



Subsequent to our paper, a recent report on the click reaction of an unprotected C-6 azido purine ribonucleoside is notable.[85] As shown in Scheme 11, a click reaction between 6-azido-9-(*β*-D-ribofuranosyl)purine (**40f**) and phenylacetylene led to only

Scheme 11. *Recently Reported, Attempted Click Reaction with **32f***



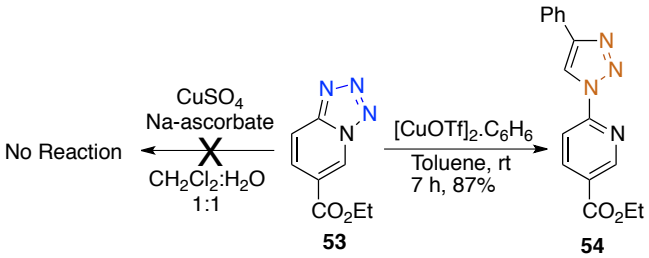
Conditions: (A) $CuSO_4$/Na-ascorbate, DMF, 80 °C, 12 h (45% **52**); (B) $CuSO_4$/Na-ascorbate, DMF, MW, 100 °C, 30 min (80% **52**); (C) $CuSO_4$/Na-ascorbate, *t*-BuOH:H_2O, rt, 2 h (75% of **52**); (D) Cu wire, CH_3CN-H_2O, 35 °C, 12 h (65% **52**)

adenosine **52**, and no desired triazole product **46a** was observed. This is consistent with our observation on the ready reducibility of C-6 azido purine nucleosides as well as the successful use of biphasic reaction conditions for successful ligations.

Subsequent to the publication of our work, successful click reactions of unreactive tetrazolyl tautomers, such as **42(T)** (Scheme 8) was also demonstrated (Scheme 12). As shown in Scheme

12, no product formation was observed under the standard click reaction conditions. However, the reaction proceeds in a facile manner with $[CuOTf]_2.C_6H_6$ catalyst (Scheme 12).[86]

Scheme 12. *Click Reaction with the Unreactive Tetrazolyl Tautomers*



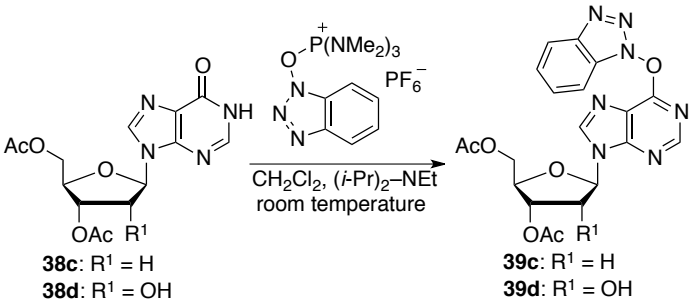
[1.3] CONCLUSION

We have developed a simple and highly efficient method to synthesize C-6 azido purine nucleoside from O^6-(benzotriazol-1-yl)inosine and 2'-deoxyinosine derivatives via S_NAr substitution with azide anion. In solution, C-6 azido purine nucleosides exist in equilibrium with the corresponding tetrazolyl forms, and the proportion of the tetrazolyl tautomer increases with increase in the solvent dielectric constant. The azide-tetrazole equilibrium of C-6 azido purine nucleosides does not affect the outcome of the azide-alkyne click reactions using $CuSO_4$/Na-ascorbate. However, successful reactions require a biphasic CH_2Cl_2/H_2O solvent system, where the competing reduction of the azide to the amine is suppressed. Click reactions with C-6 azido purine nucleosides yield two isomeric ligation products, 1,4-disubstituted and a minor 1,5-disubstituted product. This is typically not observed in case of simpler organic azides. Minor 1,5-disubstituted triazoles were isolated and characterized in some cases. The major product from a reaction between **40a** and 4-ethylnyltoluene was isolated and its structure was analyzed by X-ray crystallography. By this the structure of the major azide-alkyne ligation product was shown to be the 1,4-disubstituted triazole. To our knowledge, our studies are the first to describe a general and simple approach to the synthesis of C-6 azidopurine 2'-deoxyribo and ribonucleosides, their behavior in different organic solvents, and their use in click reactions with alkynes. The unsuccessful Cu(I)/Na-ascorbate catalyzed reaction of tetrazolo[1,5-*c*]quinazoline with terminal alkynes demonstrates markedly different behavior of azido nucleosides in general, in comparison to simpler heterocyclic compounds.

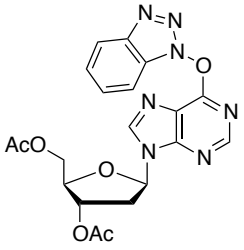
[1.4] GENERAL PROCEDURE

All the reactions were carried out in a reaction vessel flushed with nitrogen gas. Progress of reactions was monitored by TLC, using 250 μm silica plates. Column chromatographic purifications were performed on 200-300 mesh silica gel. Eluting solvents and TLC conditions along with R_f values are provided under individual compound headings. All reagents were obtained from commercial sources and were used without further purification. CH_2Cl_2 was routinely distilled over $CaCl_2$, toluene was distilled over Na, THF was distilled over $LiAlH_4$ and then over Na. Nucleoside substrates **39a**, **39b**, **39e**, and **39f** were prepared as reported previously.[21]

[1.4.1] Synthesis of O^6-benzotriazolyl derivative of acetyl protected nucleosides



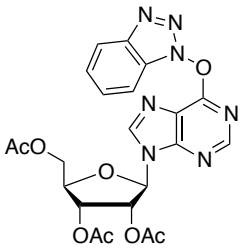
3',5'-Di-*O*-acetyl-O^6-(benzotriazol-1-yl)-2'-deoxyinosine (39c)



In a clean, dry 100 mL round-bottomed flask equipped with a stirring bar were placed 2'-deoxyinosine-3',5'-diacetate **38c** (300 mg, 0.893 mmol) and BOP (790 mg, 1.79 mmol) in anhydrous CH_2Cl_2 (8.0 mL). To this stirred mixture was added $(i\text{-Pr})_2$NEt (0.31 mL, 1.79 mmol), and the stirring was continued at room temperature for 22 h. The mixture was evaporated to dryness, and the residue was dissolved in EtOAc. The mixture was washed with water (3x) and then with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude

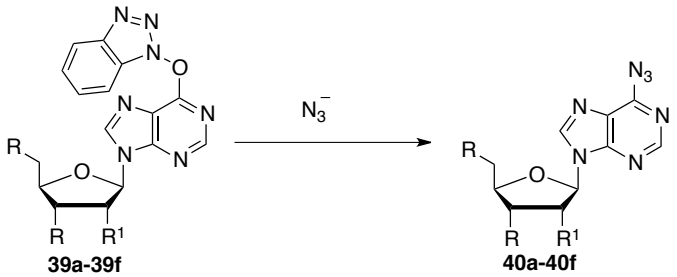
product was purified by column chromatography on silica gel using 30% EtOAc in hexanes to provide **39c** as a white, foamy solid (382 mg, 94% yield). R_f (SiO_2/10% EtOAc in hexanes) = 0.70. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (s, 1H, Ar–H), 8.33 (s, 1H, Ar–H), 8.14 (d, 1H, Ar–H, J = 8.3 Hz), 7.58-7.41 (m, 3H, Ar–H), 6.52 (t, 1H, H-1', J = 6.5 Hz), 5.46 (br s, 1H, H-3'), 4.44-4.36 (m, 3H, 1H-4', 2H-5'), 3.00 (app quint, 1H, H-2', J_{app} ≈ 7.1 Hz), 2.71 (ddd, 1H, H-2', J = 2.6, 6.0, 14.1 Hz), 2.15 and 2.10 (2s, 6H, OCOCH3). ^{13}C NMR (125 MHz, CDCl3): δ 170.5, 170.4, 159.4, 153.7, 151.9, 143.7, 143.3, 129.0, 125.1, 120.8, 108.8, 85.5, 83.1, 74.4, 63.8, 37.9, 21.1, 21.0. HRMS (ESI): calcd for $C_{20}H_{19}N_7O_6Na$ $[M + Na]^+$ 476.1295, found 476.1292.

2',3',5'-Tri-*O*-acetyl-*O*^{6}-(benzotriazol-1-yl)inosine (39d)

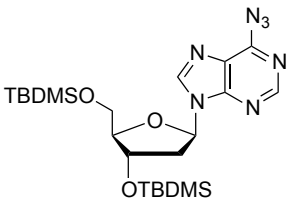


This compound was prepared by the procedure described for **39c** using **38d** (300 g, 0.761 mmol), BOP (673 mg, 1.52 mmol), anhydrous CH_2Cl_2 (8.0 mL), and (i-Pr)$_2$NEt (0.26 mL, 1.52 mmol). The crude product was purified by column chromatography on silica gel using 40% EtOAc in hexanes to provide **39d** as a white, foamy solid (353 mg, 91% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.32. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (s, 1H, Ar–H), 8.30 (s, 1H, Ar–H), 8.14 (d, 1H, Ar–H, J = 8.3 Hz), 7.57-7.46 (m, 3H, Ar–H), 6.27 (d, 1H, H-1', J = 5.1 Hz), 5.96 (t, 1H, H-2', J = 5.4 Hz), 5.60 (t, 1H, H-3', J = 5.1 Hz), 4.51-4.38 (m, 3H, H-4', 2H-5'), 2.16, 2.14, and 2.10 (3s, 9H, OCOCH3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 169.7, 169.5, 159.5, 153.8, 152.1, 143.6, 143.5, 129.0, 125.1, 120.7, 120.3, 108.8, 87.1, 80.7, 73.3, 70.6, 63.0, 53.6, 20.9, 20.7, 20.5. HRMS (ESI): calcd for $C_{22}H_{21}N_7O_8Na$ $[M + Na]^+$ 534.1349, found 534.1351.

[1.4.2] Synthesis of C-6 azido purine nucleoside derivatives

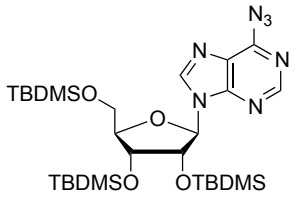


6-Azido-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl] purine (40a)



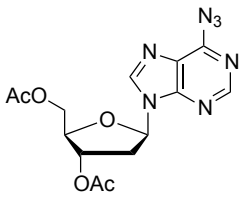
In a clean, dry 50 mL round-bottomed flask equipped with a stirring bar were placed O^6-(benzotriazol-1-yl)-2',3'-di-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyinosine **39a** (1.036 g, 1.73 mmol) and NaN_3 (326 mg, 5.0 mmol) in anhydrous DMSO (8.6 mL). The reaction mixture was flushed with nitrogen gas and stirred under a nitrogen balloon at 40 ºC for 2 h. The reaction mixture was transferred to a separatory funnel and partitioned between EtOAc and a 1:1 mixture of water-brine. The organic layer was washed with 1:1water-brinemixture (4x), then with water (3x), and finally with brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Filtration of the crude material through a silica gel plug using 20% EtOAc in hexanes solution afforded **40a** as a clear gum (871 mg, 99%). R_f (SiO_2/1%MeOH in CH_2Cl_2)=0.12. 1HNMR (500 MHz, DMSO-d_6): δ 10.14 (s, 1H, Ar–H), 8.82 (s, 1H, Ar–H), 6.57 (t, 1H, H-1', J = 6.5 Hz), 4.64 (m, 1H, H-3'), 3.91 (m, 1H, H-4'), 3.82 (dd, 1H, H-5', J = 5.2, 11.0 Hz), 3.70 (dd, 1H, H-5', J = 4.0, 11.0 Hz), 2.88 (app quint, 1H, H-2', $J_{app} \approx$ 6.0 Hz), 2.46 (m, 1H, H-2'), 0.89 and 0.82 (2s, 18H, *t*-Bu), 0.11, 0.02, and –0.001 (3s, 12H, Si-CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 145.3, 142.5, 141.5, 135.9, 120.4, 87.3, 84.2, 71.5, 62.3, 39.9, 25.7, 25.6, 17.9, 17.6, –4.8, –5.0, –5.6. HRMS (ESI): calcd for $C_{22}H_{39}N_7O_3Si_2Na$ $[M + Na]^+$ 528.2545, found 528.2534.

6-Azido-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (40b)



In a clean, dry round-bottomed flask equipped with a stirring bar were placed O^6-(benzotriazol-1-yl)-20,30,50-tri-*O*-(tert-butyldimethylsilyl)inosine **39b** (2.55 g, 3.51 mmol) and NaN_3 (684 mg, 10.53 mmol) in anhydrous DMSO (17.5 mL). The reaction mixture was flushed with nitrogen gas and stirred under a nitrogen balloon at 40 ºC for 3.5 h. The reaction mixture was transferred to a separatory funnel and partitioned between EtOAc and a 1:1 mixture of water-brine. The organic layer was washed with 1:1 water-brine mixture (4x), then with water (3x), and finally with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Filtration of the crude material through a silica gel plug using 20% EtOAc in hexanes afforded **40b** as white foam (2.14 g, 96% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.46. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.19 (s, 1H, Ar–H), 8.88 (s, 1H, Ar–H), 6.17 (d, 1H, H-1', J = 5.5 Hz), 4.79 (t, 1H, H-2', J = 4.7 Hz), 4.37 (m, 1H, H-3') 4.10-4.06 (m, 1H, H-4'), 4.02 (dd, 1H, H-5', J = 5.6, 11.0 Hz), 3.80 (dd, 1H, H-5', J = 3.0, 11.0 Hz), 0.93, 0.91, and 0.74 (3s, 27H, *t*-Bu), 0.14, 0.11, –0.05, and –0.28 (4s, 18H, Si-CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 145.3, 142.5, 141.8, 136.2, 120.3, 87.8, 85.3, 75.2, 71.6, 62.1, 25.8, 25.7, 25.4, 18.0, 17.7, 17.4, –4.6, –4.9, –5.4, –5.5, –5.6. HRMS (ESI): calcd for $C_{28}H_{53}N_7O_4Si_3Na$ $[M + Na]^+$ 658.3359, found 658.3340.

6-Azido-9-(2-deoxy-3,5-di-*O*-acetyl-*β*-D-ribofuranosyl)purine (40c).

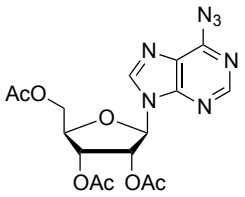


From the O^6-(Benzotriazol-1-yl)-2'-deoxyinosine diacetate (39c): In a clean, dry vial equipped with a stirring bar were placed O^6-(benzotriazol-1-yl)-2'-deoxyinosine diacetate **39c** (249 mg, 0.550 mmol) and NaN_3 (107 mg, 1.65 mmol) in DMSO (2.5 mL). The mixture was flushed with nitrogen gas and stirred at

room temperature for 1 h at which time TLC indicated the reaction to be complete. The mixture was diluted with EtOAc and transferred to a separatory funnel. The mixture was extracted with 1:1 water-brine (3x), water (3x), and finally once with brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column using 40% EtOAc in hexanes afforded **40c** as a white foamy material (195 mg, 95% yield).

From 2'-Deoxyinosine diacetate (38c): In a clean, dry reaction vial equipped with a stirring bar were placed 2'-deoxyinosine-3',5'-diacetate **38c** (500 mg, 1.487 mmol) and THF (3.0 mL). The mixture was cooled with stirring to 0 ºC in an ice bath. DPPA (0.48 mL, 2.23 mmol) and DBU (0.34 mL, 2.23 mmol) were added. The nitrogen gas-flushed mixture was allowed to stir at ice bath temperature for 5 min and then at room temperature for 10 min. Finally, the mixture was stirred in a 60 ºC sand bath for 1 h. Another aliquot of DPPA (0.48 mL, 2.23 mmol) and DBU (0.34 mL, 2.23 mmol) were added, and the reaction was continued for an additional 1 h. The mixture was evaporated to dryness, and the residue was dissolved in CH_2Cl_2 and washed with water followed by brine. Chromatographic purification on a silica gel column using 2% MeOH/50% EtOAc/48% hexanes afforded **40c** as a yellow foam (362 mg, 67%). R_f (SiO_2/80% EtOAc in hexanes) = 0.26. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.16 (s, 1H, Ar–H), 8.87 (s, 1H, Ar–H), 6.61 (t, 1H, H-1', J = 6.8 Hz), 5.50-5.41 (m, 1H, H-3'), 4.37-4.29 (m, 2H, H-4', H-5'), 4.24 (dd, 1H, H-5', J = 5.5, 11.4 Hz), 3.15 (app quint, 1H, H-2', $J_{app} \approx$ 7.1 Hz), 2.74-2.66 (m, 1H, H-2'), 2.11 and 2.01 (2s, 6H, OCOCH3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.1, 170.0, 145.4, 142.8, 141.6, 136.1, 120.6, 84.4, 82.1, 74.0, 63.4, 36.1, 20.8, 20.5. HRMS (ESI): calcd for $C_{14}H_{15}N_7O_5Na$ $[M + Na]^+$ 384.1027, found 384.1027.

6-Azido-9-(2,3,5-tri-O-acetyl-*β*-D-ribofuranosyl)purine (40d).

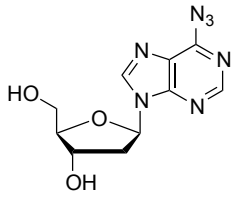


From the O^6-(Benzotriazol-1-yl)inosine triacetate (39d): In a clean, dry vial equipped with a stirring bar were placed O^6-(benzotriazol-1-yl)-inosine triacetate **39d** (281 mg, 0.550 mmol) and NaN_3 (107 mg, 1.65 mmol) in DMSO (2.5 mL). The mixture was flushed with nitrogen gas and stirred at room temperature for 1 h at which time TLC indicated the reaction to be complete. The mixture was diluted with EtOAc and transferred to a separatory funnel. The mixture was extracted with 1:1 water-brine (3x), water (3x), and finally once with brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column using 40% EtOAc in hexanes afforded **40d** as a white foamy material (173 mg, 75% yield).

From Inosine Triacetate (38d): In a clean, dry reaction vial equipped with a stirring bar were placed inosine-2',3',5'-triacetate **38d** (600 mg, 1.521 mmol) and THF (3.6 mL). The mixture was cooled with stirring to 0 ºC in an ice bath. DPPA (0.49 mL, 2.28 mmol) and DBU (0.35 mL, 2.28 mmol) were added. The nitrogen gas-flushed mixture was allowed to stir at the ice bath temperature for 5 min and then at room temperature for 10 min. Finally, the mixture was stirred in a 60 ºC sand bath for 1 h. Another aliquot of DPPA (0.49 mL, 2.28 mmol) and DBU (0.35 mL, 2.28 mmol) were added, and the reaction was continued for an additional 1 h. The mixture was evaporated to dryness, and the residue was dissolved in CH_2Cl_2 and washed with water followed by brine. Chromatographic purification on a silica gel column using 60% EtOAc in hexanes afforded **40d** as yellow foam (266 mg, 41%yield). R_f (SiO_2/80%EtOAc in hexanes) = 0.35. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.19 (s, 1H, Ar–H), 8.88 (s, 1H, Ar–H), 6.46 (d, 1H, H-1', J = 5.0 Hz), 5.98 (t, 1H, H-2', J = 5.4 Hz), 5.63 (t, 1H, H-3', J = 5.3 Hz), 4.47 (br s, 1H, H-

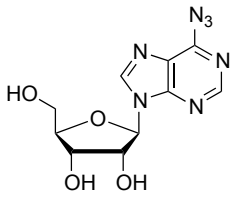
4'), 4.43 (dd, 1H,H-5', J = 2.9, 12.0 Hz), 4.30 (dd, 1H, H-5', J = 5.3, 12.0 Hz), 2.14, 2.05, and 2.04 (3s, 3H, $OCOCH_3$). ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.0, 169.4, 169.2, 145.4, 143.3, 141.3, 136.3, 120.8, 86.4, 79.8, 72.6, 69.8, 62.7, 20.5, 20.3, 20.2. HRMS (ESI): calcd for $C16H_{17}N_7O_7Na$ $[M + Na]^+$ 442.1082, found 442.1077.

6-Azido-9-(2-deoxy-*β*-D-ribofuranosyl)purine (40e)



In a clean, dry reaction vial equipped with a stirring bar were placed O^6-(benzotriazol-1-yl)-2'-deoxyinosine **39e** (150 mg, 0.406 mmol) and polymer-supported azide (530 mg, 0.406 mmol). Water (3.75 mL) was added, the reaction mixture was flushed with nitrogen gas and allowed to stir in a 50 ºC sand bath for 3.5 h. The reaction mixture was filtered and evaporated to dryness under reduced pressure. The residue was washed with Et_2O to afford **40e** as a white powder (66 mg, 59% yield). R_f (SiO_2/10% MeOH in CH_2Cl_2) = 0.2. ^1H NMR (500 MHz, DMSO-d_6): δ 10.13 (s, 1H, Ar–H), 8.88 (s, 1H, Ar–H), 6.57 (t, 1H, H-1', J = 6.5 Hz), 5.40 (d, 1H, OH, J = 4.3 Hz), 4.98 (t, 1H, OH, J = 5.4 Hz), 4.46 (m, 1H, H-3'), 3.93 (app q, 1H, H-4', $J_{app} \approx$ 4.1 Hz), 3.68-3.61 (m, 1H, H-5'), 3.59-3.53 (m, 1H, H-5'), 2.75 (app quint, 1H, H-2', $J_{app} \approx$ 6.5 Hz), 2.44 (ddd, 1H, H-2', J = 3.9, 6.3, 13.3 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 145.4, 142.5, 141.6, 135.9, 120.5, 88.2, 84.4, 70.3, 61.3, 39.8. HRMS (ESI): calcd for $C_{10}H_{11}N_7O_3Na$ $[M + Na]^+$ 300.0816, found 300.0818.

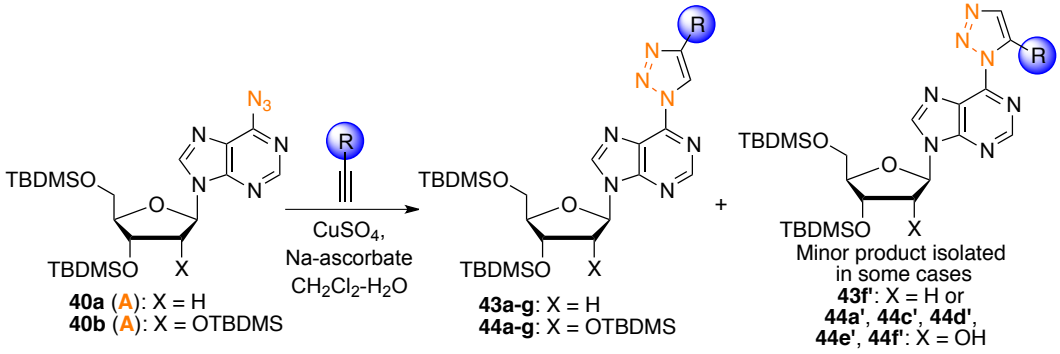
6-Azido-9-(β-D-ribofuranosyl)purine (40f)



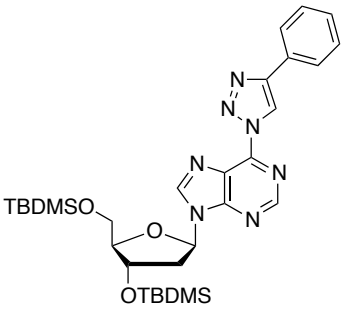
In a clean, dry reaction vial equipped with a stirring bar were placed O^6-(benzotriazol-1-yl)inosine **39f** (150 mg, 0.389 mmol) and polymer-supported azide (530 mg, 0.406 mmol). DMF (3.9 mL) was added, and the reaction mixture was flushed with nitrogen gas and allowed to stir in a 50 ºC sand bath for 5 h. The reaction mixture was filtered, and the DMF was coevaporated with toluene. The residue was washed with Et_2O to afford **40f** as a white powder (80 mg, 70% yield). R_f (SiO_2/10% MeOH in

CH_2Cl_2) = 0.19. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.15 (s, 1H, Ar–H), 8.93 (s, 1H, Ar–H), 6.15 (d, 1H, H-1', J = 5.1 Hz), 5.63 (d, 1H, OH, J = 5.6 Hz), 5.30 (d, 1H, OH, J = 5.2 Hz), 5.10 (t, 1H, OH, J = 5.3 Hz), 4.57 (q, 1H, H-2', J = 5.2 Hz), 4.20 (q, 1H, H-3', J = 4.6 Hz), 4.02 (m, 1H, H-4'), 3.76-3.68 (m, 1H, H-5'), 3.65-3.56 (m, 1H, H-5'). ^{13}C NMR (125 MHz, DMSO-d_6): δ 145.4, 142.6, 141.9, 136.1, 120.2, 88.3, 85.7, 74.5, 70.0, 60.9. HRMS (ESI): calcd for $C_{10}H_{11}N_7O_4Na$ $[M + Na]^+$ 316.0765, found 316.0765.

[1.4.3] Copper catalyzed azide-alkyne ligation reaction (CuAAC)



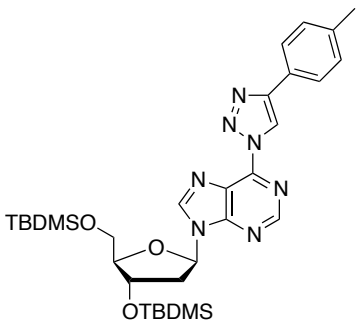
Typical Procedure for Azide-Alkyne Ligation: Synthesis of 6-(4-Phenyl-1,2,3-triaz ol-1-yl)-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (43a)



In a clean, dry vial equipped with a stirring bar were placed the azido nucleoside **40a** (240 mg, 0.474 mmol), CH_2Cl_2 (1.6 mL), and phenylacetylene (104 µL, 0.949 mmol). An aqueous solution of sodium ascorbate (0.047 mmol, 0.95 mL of freshly prepared 0.05 M solution) was added followed by an aqueous solution of $CuSO_4$ (24 µmol, 0.60 mL of freshly prepared 0.04 M solution). The mixture was stirred at room temperature for 4 h, at which time TLC indicated the reaction to be complete. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification on a silica gel

column using 20% EtOAc in hexanes afforded **43a** as an off-white foam (222 mg, 77% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.18. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.35 (s, 1H, Ar–H), 8.96 (s, 1H, Ar–H), 8.59 (s, 1H, Ar–H), 8.02 (d, 2H, Ar–H, J = 7.2 Hz), 7.49 (t, 2H, Ar-H, J = 7.6 Hz), 7.40 (t, 1H, Ar–H, J = 7.3 Hz), 6.61 (t, 1H, H-1', J = 6.4 Hz), 4.65 (m, 1H, H-3'), 4.09 (q, 1H, H-4', J = 3.2 Hz), 3.91 (dd, 1H, H-5', J = 3.8, 11.3 Hz), 3.81 (dd, 1H, H-50, J = 2.9, 11.3 Hz), 2.68 (app quint, 1H, H-2', J_{app} ≈ 6.4 Hz), 2.54 (ddd, 1H, H-2', J = 3.8, 6.1, 13.1 Hz), 0.93 and 0.92 (2s, 18H, *t*-Bu), 0.13 and 0.11 (2s, 12H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 152.3, 148.5, 144.9, 144.7, 130.1, 129.1, 128.9, 126.4, 123.4, 120.1, 88.5, 85.2, 72.1, 62.9, 41.8, 26.2, 25.9, 18.6, 18.2, –4.4, –4.6, –5.1, –5.2. HRMS (ESI): calcd for $C_{30}H_{45}N_7O_3Si_2Na$ [M + Na]$^+$ 630.3015, found 630.2999.

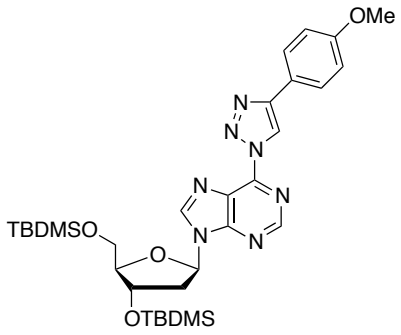
6-[4-(4-Methylphenyl)-1,2,3-triazol-1-yl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethyl-silyl)-*β*-D-ribofuranosyl]purine (43b)



Synthesized from **40a** (195 mg, 0.385 mmol) and 4-ethynyltoluene (98 μL, 0.773 mmol). Chromatography of the crude reaction mixture on a silica gel column using 10% EtOAc in hexanes yielded **43b** as a white foamy solid (209 mg, 87% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.22. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.30 (s, 1H, Ar–H), 8.95 (s, 1H, Ar–H), 8.58 (s, 1H, Ar–H), 7.90 (d, 1H, Ar–H, J = 8.0 Hz), 7.29 (d, 2H, Ar–H, J = 8.0 Hz), 6.61 (t, 1H, H-1', J = 6.3 Hz), 4.65 (m, 1H, H-3'), 4.08 (q, 1H, H-4', J = 3.2 Hz), 3.91 (dd, 1H, H-5', J = 3.9, 11.2 Hz), 3.81 (dd, 1H, H-5', J = 2.9, 11.2 Hz), 2.68 (app quint, 1H, H-2', J_{app} ≈ 6.4 Hz), 2.54 (ddd, 1H, H-2', J = 3.8, 6.1, 13.1 Hz), 2.41 (s, 3H, CH_3), 0.93 and 0.92 (2s, 18H, *t*-Bu), 0.12 and 0.11 (2s, 12H, Si–CH_3). ^{13}C NMR (125 MHz, CDCl3): δ 154.0, 152.4, 148.5, 145.0, 144.7, 138.8, 129.8, 127.2, 126.3, 123.4, 119.7,

88.5, 85.2, 72.1, 63.0, 41.8, 26.2, 26.0, 21.6, 18.6, 18.2, –4.4, –4.6, –5.1, –5.2. HRMS (ESI): calcd for $C_{31}H_{47}N_7O_3Si_2Na$ $[M + Na]^+$ 644.3171, found 644.3154.

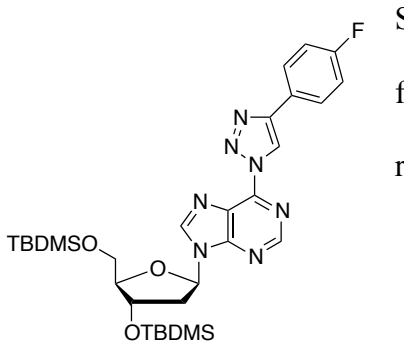
6-[4-(4-Methoxyphenyl)-1,2,3-triazol-1-yl]-9-[2-deoxy-3,5-di-*O*-(tert-butyldi-methylsilyl)-*β*-D-ribofuranosyl]purine (43c)



Synthesized from **40a** (204 mg, 0.400 mmol) and 4-ethynylanisole (102.5 μL, 0.807 mmol). Column chromatography of the crude reaction mixture a silica gel column using 10%EtOAc in hexanes yielded **43c** as a white foamy solid (231 mg, 90%yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.43. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.25 (s, 1H, Ar-H), 8.95 (s, 1H, Ar-H), 8.58 (s, 1H, Ar-H), 7.94 (d, 2H, Ar-H, J = 8.8 Hz), 7.01 (d, 2H, Ar-H, J = 8.8Hz), 6.61 (t, 1H, H-1', J = 6.4Hz), 4.65 (m, 1H,H-3'), 4.08 (q, 1H, H-4', J = 3.2 Hz), 3.91 (dd, 1H, H-5', J = 3.8, 11.3 Hz), 3.87 (s, 3H, OCH_3), 3.81 (dd, 1H, H-5', J = 2.9, 11.3 Hz), 2.67 (app quint, 1H, H-2', J_{app} ≈ 6.4Hz), 2.54 (ddd, 1H, H-2' J = 3.8, 6.1, 13.1 Hz), 0.93 and 0.92 (2s, 18H, *t*-Bu), 0.12 and 0.11 (2s, 12H, Si–CH_3). ^{13}C NMR (125

MHz, CDCl3): δ 160.2, 154.0, 152.3, 148.3, 145.0, 144.6, 127.8, 123.3, 122.7, 119.1, 114.5, 88.5, 85.1, 72.1, 62.9, 55.6, 41.8, 26.2, 25.9, 18.6, 18.2, –4.4, –4.6, –5.1, –5.2. HRMS (ESI): calcd for $C_{31}H_{47}N_7O_4Si_2Na$ $[M + Na]^+$ 660.3120, found 660.3105.

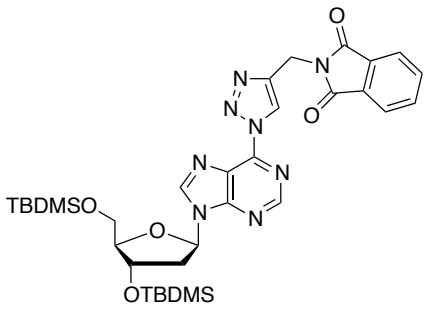
6-[4-(4-Fluorophenyl)-1,2,3-triazol-1-yl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldime-thylsilyl)-*β*-D-ribofuranosyl]purine (43d).



Synthesized from **40a** (210 mg, 0.415 mmol) and 1-ethynyl-4-fluorobenzene (95 μL, 0.830 mmol). Chromatography of the crude reaction mixture on a silica gel column using 20% EtOAc in

hexanes yielded **43d** as a yellow, crystalline solid (240 mg, 92% yield). R_f (SiO_2/40% EtOAc in hexanes) = 0.36. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.30 (s, 1H, Ar–H), 8.96 (s, 1H, Ar–H), 8.60 (s, 1H, Ar–H), 7.99 (dd, 2H, Ar–H, $J_{H,H}$ = 8.6 Hz, $J_{F,H}$ = 5.4 Hz), 7.17 (t, 2H, Ar–H, $J_{H,H}$ = $J_{F,H}$ = 8.6 Hz), 6.61 (t, 1H, H-1', J = 6.3 Hz), 4.65 (m, 1H, H-3'), 4.08 (q, 1H, H-4', J = 3.2 Hz), 3.91 (dd, 1H, H-5', J = 3.7, 11.2 Hz), 3.81 (dd, 1H, H-5', J = 2.9, 11.2 Hz), 2.68 (app quint, 1H, H-2', J_{app} ≈ 6.4 Hz), 2.54 (ddd, 1H, H-2', J = 3.8, 6.0, 13.0 Hz), 0.93 and 0.92 (2s, 18H, *t*-Bu), 0.12 and 0.11 (2s, 12H, Si–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.0 (d, $^1J_{C,F}$ = 248.1 Hz), 153.8, 152.1, 147.4, 144.6, 144.5, 128.0 (d, $^3J_{C,F}$ = 8.2 Hz), 126.0 (d, $^4J_{C,F}$ = 3.2 Hz), 123.1, 119.6, 115.9 (d, $^2J_{C,F}$ = 21.8 Hz), 88.3, 84.9, 71.9, 62.7, 41.6, 25.9, 25.6, 18.4, 18.0, –4.6, –4.8, –5.3, –5.5. HRMS (ESI): calcd for $C_{30}H_{44}FN_7O_3Si_2Na$ $[M + Na]^+$ 648.2920, found 648.2911.

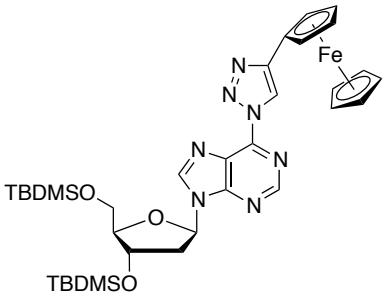
[1.3.5] 6-[4-(*N*-Phthalimidomethyl)-1,2,3-triazol-1-yl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (43e)



Synthesized from **40a** (190 mg, 0.376 mmol) and N-propargylphthalimide (139 mg, 0.751 mmol). Chromatography of the crude reaction mixture on a silica gel column using 10% EtOAc in hexanes yielded **43e** as an off-white, foamy solid (246 mg, 95% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.15. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.10 (s, 1H, Ar–H), 8.90 (s, 1H, Ar–H), 8.55 (s, 1H, Ar–H), 7.88 (dd, 2H, Ar–H, J = 3.1, 5.4 Hz), 7.73 (dd, 2H, Ar–H, J = 3.0, 5.4 Hz), 6.57 (t, 1H, H-1', J = 6.4 Hz), 5.16 (s, 2H, NCH_2), 4.64 (m, 1H, H-3'), 4.06 (q, 1H, H-4', J = 3.3 Hz), 3.89 (dd, 1H, H-5', J = 3.9, 11.2 Hz), 3.79 (dd, 1H, H-5', J = 3.1, 11.2 Hz), 2.64 (app quint, 1H, H-2', J_{app} ≈ 6.4 Hz), 2.52 (ddd, 1H, H-2', J = 3.8, 6.0, 13.0 Hz), 0.92 and 0.90 (2s, 18H, *t*-Bu), 0.11, 0.092, and 0.088 (3s, 12H, Si–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8,

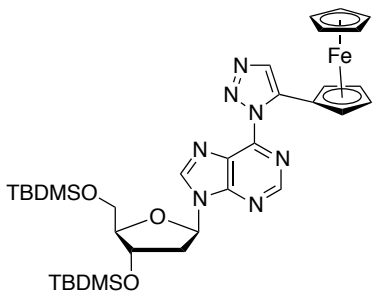
154.1, 152.2, 144.8, 143.6, 134.3, 132.3, 123.7, 123.6, 123.5, 88.5, 85.1, 72.1, 62.9, 41.8, 33.3, 26.2, 25.9, 18.6, 18.2, –4.5, –4.6, –5.2, –5.3. HRMS (ESI): calcd for $C_{33}H_{46}N_8O_5Si_2Na$ $[M + Na]^+$ 713.3022, found 713.2999.

6-(4-Ferrocenyl-1,2,3-triazol-1-yl)-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethyl-silyl)-*β*-D-ribofuranosyl]purine (4f)



Synthesized from **40a** (209 mg, 0.413 mmol) and ethynylferrocene (173 mg, 0.820 mmol). Chromatography of the crude reaction mixture on a silica gel column using 15% acetone in hexanes yielded **43f** as a brown, foamy solid (247 mg, 83% yield). R_f (SiO_2/15% acetone in hexanes) = 0.22. ^{1}HNMR (500 MHz, $CDCl_3$): δ 8.99 (s, 1H, Ar–H), 8.94 (s, 1H, Ar–H), 8.58 (s, 1H, Ar–H), 6.60 (t, 1H, H-1', J = 6.3 Hz), 4.88 (br t, 2H, ferrocenyl-H), 4.65 (m, 1H, H-3'), 4.36 (t, 2H, ferrocenyl-H, J = 1.8 Hz), 4.12 (s, 5H, ferrocenyl-H), 4.08 (q, 1H, H-4', J = 3.2 Hz), 3.91 (dd, 1H, H-5', J = 3.9, 11.2 Hz), 3.81 (dd, 1H, H-5', J = 2.9, 11.2 Hz), 2.67 (app quint, 1H, H-2', J_{app} ≈ 6.4 Hz), 2.54 (ddd, 1H, H-2', J = 3.9, 6.0, 13.0 Hz), 0.93 and 0.92 (2s, 18H, *t*-Bu), 0.12 and 0.11 (2s, 12H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 152.3, 147.9, 144.9, 144.5, 123.3, 118.8, 88.5, 85.1, 74.6, 72.1, 69.9, 69.2, 67.3, 62.9, 41.8, 26.2, 25.9, 18.7, 18.2, –4.4, –4.6, –5.1, –5.2. HRMS (ESI): calcd for $C_{34}H_{49}FeN_7O_3Si_2Na$ $[M + Na]^+$ 738.2677, found 738.2677.

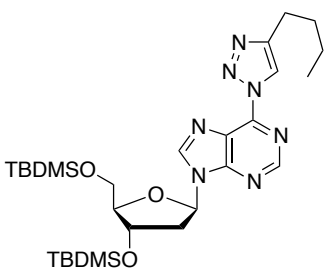
Minor Isomer: 6-(5-Ferrocenyl-1,2,3-triazol-1-yl)-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldi-methylsilyl)-*β*-D-ribofuranosyl]purine (43f').



Obtained 18.4 mg (6% yield) of **43f'** as a reddish-brown solid. R_f (SiO_2/15% acetone in hexanes) = 0.14. 1H NMR (500 MHz, $CDCl_3$): δ 8.97 (s, 1H, Ar–H), 8.55 (s, 1H, Ar–H), 7.89 (s, 1H,

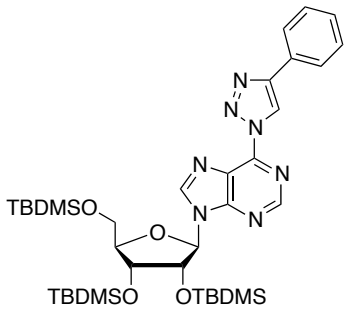
Ar–H), 6.61 (t, 1H, H-1', J = 6.5 Hz), 4.64 (m, 1H, H-3'), 4.58 (m, 2H, ferrocenyl-H), 4.27 (m, 2H, ferrocenyl–H), 4.07 (q, 1H, H-4', J = 3.1 Hz), 3.99 (s, 5H, ferrocenyl–H), 3.88 (dd, 1H, H-5', J = 3.9, 11.2 Hz), 3.80 (dd, 1H, H-5', J = 2.9, 11.2 Hz), 2.64 (app quint, 1H, H-2', $J_{app} \approx 6.4$ Hz), 2.52 (ddd, 1H, H-2', J = 3.7, 6.0, 13.0 Hz), 0.93 and 0.90 (2s, 18H, *t*-Bu), 0.12, 0.09, and 0.08 (3s, 12H, Si–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 151.9, 147.1, 145.5, 138.9, 133.3, 128.6, 88.5, 85.1, 72.1, 70.6, 70.0, 69.6, 69.5, 63.0, 41.9, 26.2, 26.0, 18.7, 18.2, –4.4, –4.6, –5.1, –5.2. HRMS (ESI): calcd for $C_{34}H_{49}FeN_7O_3Si_2Na$ $[M + Na]^+$ 738.2677, found 738.2655.

6-[4-(1-Butyl)-1,2,3-triazol-1-yl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (43g).



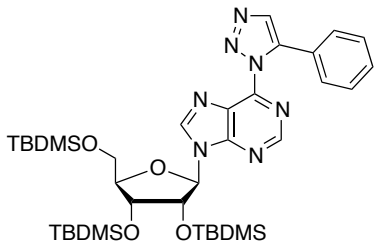
Synthesized from **40a** (190 mg, 0.375 mmol) and 1-hexyne (82.5 μL, 0.751 mmol). Chromatography of the crude reaction mixture on a silica gel column using 20% EtOAc in hexanes yielded **43g** as a white solid (166 mg, 75% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.16. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.91 (s, 1H, Ar–H), 8.81 (s, 1H, Ar–H), 8.53 (s, 1H, Ar–H), 6.58 (t, 1H, H-1', J = 6.3 Hz), 4.64 (m, 1H, H-3'), 4.07 (m, 1H, H-4'), 3.89 (dd, 1H, H-5', J = 3.9, 11.2 Hz), 3.79 (dd, 1H, H-50, J = 2.9, 11.2 Hz), 2.87 (t, 2H, butyl-CH_2, J = 7.8 Hz), 2.66 (app quint, 1H, H-2', $J_{app} \approx 6.4$ Hz), 2.50 (ddd, 1H, H-2', J = 3.8, 5.9, 13.0 Hz), 1.76 (quint, 2H, butyl–CH_2, J = 7.6 Hz), 1.44 (sextet, 2H, butyl-CH_2, J = 7.4 Hz), 0.95 (t, 3H, butyl-CH_3, J = 7.3 Hz), 0.92 and 0.90 (2s, 18H, *t*-Bu), 0.11 and 0.09 (2s, 12H, Si–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9, 152.3, 149.4, 145.1, 144.5, 123.3, 121.4, 88.5, 85.1, 72.1, 62.9, 41.7, 31.5, 26.2, 25.9, 25.5, 22.5, 18.6, 18.2, 14.0, –4.5, –4.6, –5.2, –5.3. HRMS (ESI): calcd for $C_{28}H_{49}N_7O_3Si_2Na$ $[M + Na]^+$ 610.3328, found 610.3328.

6-(4-Phenyl-1,2,3-triazol-1-yl)-9-[2,3,5-*tri*-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (44a)



Synthesized from **40b** (200 mg, 0.314 mmol) and phenylacetylene (69.0 μL, 0.628 mmol). Chromatography of the crude reaction mixture on a silica gel column using 20% EtOAc in hexanes yielded **44a** as a brown crystalline solid (210 mg, 90% yield). R_f (SiO_2/20% acetone in hexanes) = 0.49. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.34 (s, 1H, Ar-H), 8.95 (s, 1H, Ar–H), 8.64 (s, 1H, Ar–H), 8.0 (d, 2H, Ar–H, *J* = 7.5 Hz), 7.45 (t, 2H, Ar–H, *J* = 7.6 Hz), 7.36 (t, 1H, Ar-H, *J* = 7.4 Hz), 6.2 (d, 1H, H-1', *J* = 5.1 Hz), 4.65 (t, 1H, H-2', *J* = 4.6 Hz), 4.33 (t, 1H, H-3', *J* = 3.9 Hz), 4.18 (q, 1H, H-4', *J* = 3.0 Hz), 4.04 (dd, 1H, H-5', *J* = 3.5, 11.3 Hz), 3.82 (dd, 1H, H-5', *J* = 2.3, 11.3 Hz), 0.97, 0.94, and 0.79 (3s, 27H, *t*-Bu), 0.17, 0.16, 0.11, 0.10, –0.02, and –0.23 (6s, 18H, Si–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.3, 152.3, 148.4, 144.9, 130.0, 129.0, 128.7, 126.7, 123.2, 120.1, 88.6, 86.0, 76.5, 72.1, 62.6, 26.2, 25.9, 25.7, 18.7, 18.2, 18.0, –4.2, –4.4, –4.5, –4.8, –5.2. HRMS (ESI): calcd $C_{36}H_{59}N_7O_4Si_3Na$ $[M + Na]^+$ 760.3829, found 760.3826.

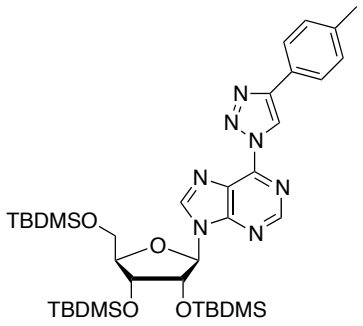
Minor Isomer: 6-(5-Phenyl-1,2,3-triazol-1-yl)-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (44a')



Obtained 4.4 mg (2% yield) of **44a'** as a brown solid. R_f (SiO_2/20% acetone in hexanes) = 0.19. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.82 (s, 1H, Ar–H), 8.55 (s, 1H, Ar–H), 7.93 (s, 1H, Ar-H), 7.36-7.28 (m, 5H, Ar-H), 6.19 (d, 1H, H-1', *J* = 5.1 Hz), 4.60 (t, 1H, H-2', *J* = 4.7 Hz), 4.31 (t, 1H, H-3', *J* = 3.8 Hz), 4.17 (m, 1H, H-4'), 4.02 (dd, 1H, H-5', *J* = 3.7, 11.5 Hz), 3.81 (dd, 1H, H-5', *J* = 2.4, 11.5 Hz), 0.95, 0.94, and 0.79 (3s, 27H, *t*-

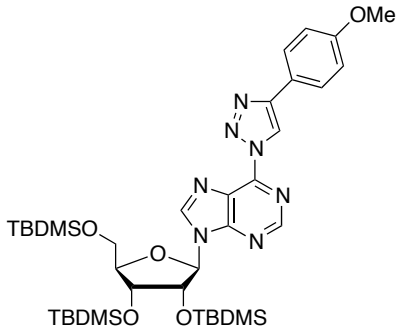
Bu), 0.13, 0.11, 0.10, –0.02, and –0.25 (5s, 18H, Si–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.5, 152.1, 146.9, 145.7, 139.5, 133.9, 129.4, 128.8, 127.7, 127.1, 88.7, 86.1, 76.5, 72.1, 62.7, 26.3, 26.0, 25.9, 18.8, 18.3, 18.0, –4.2, –4.4, –4.5, –4.8, –5.1. HRMS (ESI): calcd $C_{36}H_{59}N_7O_4Si_3Na$ $[M + Na]^+$ 760.3829, found 760.3829.

6-[4-(4-Methylphenyl)-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsil-yl)-*β*-D-ribofuranosyl]purine (44b)



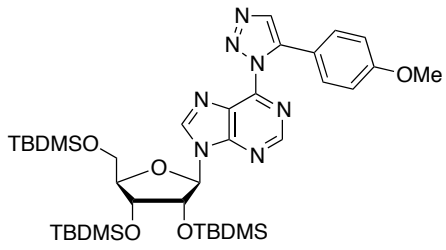
Synthesized from **40b** (200 mg, 0.314 mmol) and 4-ethynyltoluene (79.5 μL, 0.629 mmol). Chromatography of the crude reaction mixture on a silica gel column using 10% acetone in hexanes yielded **44b** as a light-yellow solid (214 mg, 90% yield). R_f (SiO_2/10% acetone in hexanes) = 0.29. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.31 (s, 1H, Ar–H), 8.96 (s, 1H, Ar–H), 8.67 (s, 1H, Ar–H), 7.90 (d, 2H, Ar–H, J = 8.0 Hz), 7.29 (d, 2H, Ar–H, J = 8.0 Hz), 6.22 (d, 1H, H-1', J = 5.2 Hz), 4.66 (t, 1H, H-2', J = 4.6 Hz), 4.33 (t, 1H, H-3', J = 3.9 Hz), 4.19 (q, 1H, H-4', J = 3.1 Hz), 4.05 (dd, 1H, H-5', J = 3.5, 11.4 Hz), 3.83 (dd, 1H, H-5', J = 2.5, 11.4 Hz), 2.41 (s, 3H, CH_3), 0.98, 0.95, and 0.80 (3s, 27H, *t*-Bu), 0.18, 0.17, 0.12, 0.11, –0.01, and –0.22 (6s, 18H, Si–CH3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.4, 152.4, 148.6, 145.1, 145.0, 138.8, 129.8, 127.3, 126.4, 123.3, 119.7, 88.7, 86.1, 76.5, 72.2, 62.7, 26.3, 26.1, 25.8, 21.5, 18.8, 18.3, 18.0, –4.2, –4.4, –4.5, –4.8, –5.1. HRMS (ESI): calcd for $C_{37}H_{61}N_7O_4Si_3Na$ $[M + Na]^+$ 774.3985, found 774.3986.

6-[4-(4-Methoxyphenyl)-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*tert*-butyldimeth-ylsilyl)-*β*-D-ribofuranosyl]purine (44c)



Synthesized from **40b** (200 mg, 0.314 mmol) and 4-ethynylanisole (81.3 μL, 0.628 mmol). Chromatography of the crude reaction mixture on a silica gel column using 20% EtOAc in hexanes yielded **44c** as a white, foamy solid (228 mg, 94% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.29. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.27 (s, 1H, Ar–H), 8.95 (s, 1H, Ar–H), 8.63 (s, 1H, Ar–H), 7.94 (d, 2H, Ar–H, *J* = 8.8 Hz), 7.01 (d, 2H, Ar–H, *J* = 8.8 Hz), 6.22 (d, 1H, H-1', *J* = 5.8 Hz), 4.66 (t, 1H, H-2', *J* = 4.7 Hz), 4.33 (t, 1H, H-3', *J* = 3.9 Hz), 4.19 (q, 1H, H-4', *J* = 3.0 Hz), 4.05 (dd, 1H, H-5', *J* = 3.6, 11.5 Hz), 3.87 (s, 3H, OCH_3), 3.83 (dd, 1H, H-5', *J* = 2.4, 11.5 Hz), 0.98, 0.95, and 0.80 (3s, 27H, *t*-Bu), 0.18, 0.17, 0.12, 0.11, –0.01, and –0.23 (6s, 18H, Si–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2, 154.4, 152.4, 148.4, 145.0, 144.9, 127.8, 123.3, 122.8, 119.2, 114.5, 88.7, 86.0, 76.5, 72.1, 62.7, 55.6, 26.3, 26.0, 25.8, 18.8, 18.3, 18.0, –4.2, –4.4, –4.5, –4.8, –5.1. HRMS (ESI): calcd for $C_{37}H_{61}N_7O_5Si_3Na$ $[M + Na]^+$ 790.3934, found 790.3933.

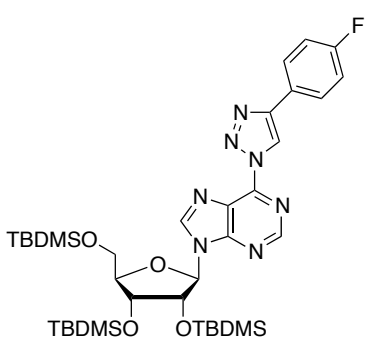
Minor isomer: 6-[5-(4-Methoxyphenyl)-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*tert*-butyl-dimethylsilyl)-*β*-D-ribofuranosyl]purine (44c')



Obtained 9.1 mg (3% yield) of **44c'** as a clear, gummy material. R_f (SiO_2/20% EtOAc in hexanes) = 0.10. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (s, 1H, Ar–H), 8.55 (s, 1H, Ar–H), 7.88 (s, 1H, Ar–H), 7.22 (d, 2H, Ar–H, *J* = 8.8 Hz), 6.83 (d, 2H, Ar–H, *J* = 8.8 Hz), 6.19 (d, 1H, H-1', *J* = 5.1 Hz), 4.60 (t, 1H, H-2', *J* = 4.7 Hz), 4.32 (t, 1H, H-3', *J* = 3.9 Hz), 4.17 (m, 1H, H-4'), 4.02 (dd,1H, H-5', *J* = 3.7, 11.5 Hz), 3.81

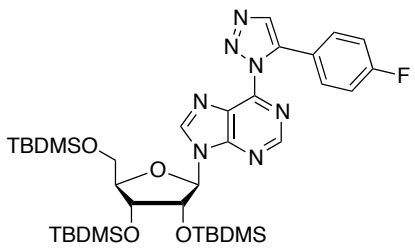
(merged with OCH_3 resonance, 1H, H-5'), 3.80 (s, 3H, OCH_3), 0.95, 0.94, and 0.79 (3s, 27H, *t*-Bu), 0.13, 0.11, 0.10, –0.02, and –0.25 (5s, 18H, Si–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.5, 154.5, 152.1, 146.9, 145.7, 139.4, 133.4, 130.2, 127.9, 119.3, 114.3, 88.7, 86.0, 76.5, 72.1, 62.7, 55.5, 26.3, 26.0, 25.8, 18.8, 18.3, 18.0, –4.2, –4.4, –4.5, –4.8, –5.1. HRMS (ESI): calcd for $C_{37}H_{61}N_7O_5Si_3Na$ $[M + Na]^+$ 790.3934, found 790.3944.

6-[4-(4-Fluorophenyl)-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethyl-silyl)-*β*-D-ribofuranosyl]purine (44d)



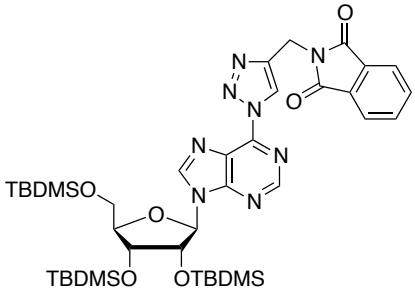
Synthesized from **40b** (200 mg, 0.314 mmol) and 1-ethynyl-4-fluorobenzene (72.0 μL, 0.629 mmol). Chromatography of the crude reaction mixture on a silica gel column using 10% EtOAc in hexanes yielded **44d** as a light-yellow, foamy solid (194 mg, 82% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.41. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.32 (s, 1H, Ar–H), 8.96 (s, 1H, Ar–H), 8.64 (s, 1H, Ar–H), 7.99 (dd, 2H, Ar–H, $J_{H,H}$ = 8.6 Hz, $J_{F,H}$ = 5.3 Hz), 7.17 (t, 2H, Ar–H, $J_{H,H}$ = $J_{F,H}$ = 8.6 Hz), 6.23 (d, 1H, H-1', J = 5.1 Hz), 4.66 (t, 1H, H-2', J = 4.6 Hz), 4.33 (t, 1H, H-3', J = 3.9 Hz), 4.19 (m, 1H, H-4'), 4.05 (dd, 1H, H-5', J = 3.3, 11.3 Hz), 3.84 (dd, 1H, H-5', J = 2.2, 11.3 Hz), 0.98, 0.95, and 0.80 (3s, 27H, *t*-Bu), 0.18, 0.17, 0.11,–0.013, and –0.23 (5s, 18H, Si–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2 (d, $^1J_{C,F}$ = 248.1 Hz), 154.5, 152.4, 147.6, 145.1, 144.9, 128.2 (d, $^3J_{C,F}$ = 8.2 Hz), 126.3 (d, $^4J_{C,F}$ = 5.1 Hz), 123.3, 119.9, 116.1 (d, $^2J_{C,F}$ = 21.8 Hz), 88.7, 86.1, 76.5, 72.1, 62.7, 26.3, 26.1, 25.8, 18.8, 18.3, 18.1, –4.2, –4.4, –4.5, –4.8, –5.1. HRMS (ESI): calcd for $C_{36}H_{58}FN_7O_4Si_3Na$ $[M + Na]^+$ 778.3734, found 778.3721.

Minor Isomer: 6-[5-(4-Fluorophenyl)-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*tert*-butyldi-methylsilyl)-*β*-D-ribofuranosyl]purine (44d')



Obtained 2.9 mg (1% yield) of **44d'** as a clear, gummy material. R_f (SiO_2/20% EtOAc in hexanes) = 0.08. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (s, 1H, Ar–H), 8.56 (s, 1H, Ar–H), 7.91 (s, 1H, Ar–H), 7.29 (dd, 2H, Ar–H, $J_{H,H}$ = 8.7 Hz, $J_{F,H}$ = 5.2 Hz), 7.01 (t, 2H, Ar–H, $J_{H,H}$ = $J_{F,H}$ = 8.7 Hz), 6.19 (d, 1H, H-1', J = 5.1 Hz), 4.58 (t, 1H, H-2', J = 4.6 Hz), 4.31 (t, 1H, H-3', J = 3.9 Hz), 4.19 (m, 1H, H-4'), 4.02 (dd, 1H, H-5', J = 3.4, 11.5 Hz), 3.81 (dd, 1H, H-5', J = 2.2, 11.5 Hz), 0.95, 0.94, and 0.79 (3s, 27H, *t*-Bu), 0.13, 0.11, 0.10, –0.02, and –0.25 (5s, 18H, Si–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.4 (d, $^1J_{C,F}$ = 250.3 Hz), 154.6, 152.1, 146.5, 145.7, 138.6, 133.9, 130.8 (d, $^3J_{C,F}$ = 8.6 Hz), 127.6, 123.3, 116.0 ($^2J_{C,F}$ = 22.0 Hz), 88.7, 86.1, 76.6, 72.1, 62.7, 26.3, 26.0, 25.8, 18.8, 18.3, 18.0, –4.2, –4.4, –4.5, –4.8, –5.1. HRMS (ESI): calcd for $C_{36}H_{58}FN_7O_4Si_3Na$ $[M + Na]^+$ 778.3734, found 778.3739.

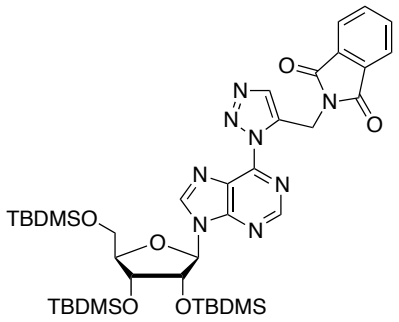
6-[4-(*N*-Phthalimidomethyl)-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*tert*-butyldi-methylsilyl)-*β*-D-ribofuranosyl]purine (44e)



Synthesized from **40b** (200 mg, 0.314 mmol) and *N*-propargylphthalimide (0.132 g, 0.628 mmol). Chromatography of the crude reaction mixture on a silica gel column using 15% EtOAc in hexanes yielded **44e** as an off-white, foamy solid (196 mg, 76% yield). R_f (SiO_2/25% EtOAc in hexanes) = 0.22. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.11 (s, 1H, Ar–H), 8.90 (s, 1H, Ar–H), 8.61 (s, 1H, Ar–H), 7.88 (dd, 2H, Ar–H, J = 2.9, 5.4 Hz), 7.72 (dd, 2H, Ar–H, J = 2.9, 5.4 Hz), 6.19 (d, 1H, H-1', J = 4.9 Hz), 5.16 (s, 2H, NCH_2), 4.63 (t, 1H, H-2', J = 4.3 Hz), 4.31 (m, 1H, H-3'),

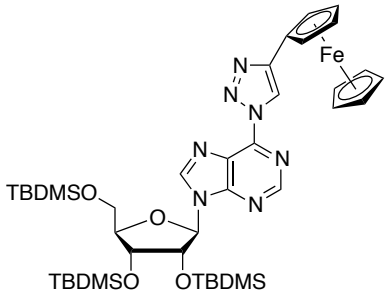
4.17 (m, 1H, H-4'), 4.03 (dd, 1H, H-5', J = 3.4, 11.7 Hz), 3.81 (dd, 1H, H-5', J = 2.4, 11.7 Hz), 0.96, 0.94, and 0.78 (3s, 27H, *t*-Bu), 0.16, 0.15, 0.10, –0.03, and –0.25 (5s, 18H, Si–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.6, 154.2, 152.1, 145.0, 144.6, 143.4, 134.1, 132.1, 123.5, 123.4, 123.2, 88.5, 85.8, 76.2, 71.9, 62.4, 33.1, 26.1, 25.8, 25.6, 18.5, 18.1, 17.8, –4.4, –4.6, –4.7, –5.0, –5.3. HRMS (ESI): calcd for $C_{39}H_{60}N_8O_6Si_3Na$ $[M + Na]^+$ 843.3836, found 843.3833.

Minor Isomer: 6-[5-(*N*-Phthalimidomethyl)-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]-purine (44e')



Obtained 8.5 mg (3% yield) of **44e'** as an off-white, gummy material. R_f (SiO_2/25% EtOAc in hexanes) = 0.10. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.95 (s, 1H, Ar–H), 8.66 (s, 1H, Ar–H), 7.86 (dd, 2H, Ar–H, J = 3.1, 5.4 Hz), 7.75 (dd, 2H, Ar–H, J = 3.4, 5.4 Hz), 7.69 (s, 1H, Ar–H), 6.26 (d, 1H, H-1', J = 5.1 Hz), 5.55 (s, 2H, NCH_2), 4.64 (t, 1H, H-2', J = 4.6 Hz), 4.34 (t, 1H, H-3', J = 3.9 Hz), 4.21-4.17 (m, 1H, H-4'), 4.04 (dd, 1H, H-5', J = 3.4, 11.5 Hz), 3.83 (dd, 1H, H-5', J = 2.2, 11.5 Hz), 0.96, 0.95, and 0.82 (3s, 27H, *t*-Bu), 0.16, 0.15, 0.12, 0.001, and –0.19 (5s, 18H, Si–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 154.7, 151.7, 146.6, 145.5, 135.2, 134.6, 134.5, 132.0, 125.7, 123.9, 88.6, 86.0, 76.6, 72.1, 62.7, 33.3, 26.4, 26.1, 25.9, 18.8, 18.3, 18.1, –4.1, –4.4, –4.5, –4.7, –5.1. HRMS (ESI): calcd for $C_{39}H_{60}N_8O_6Si_3Na$ $[M + Na]^+$ 843.3836, found 843.3830.

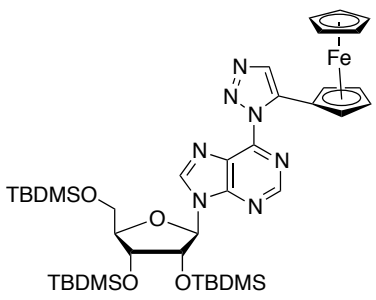
6-(4-Ferrocenyl-1,2,3-triazol-1-yl)-9-[2,3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (44f)



Synthesized from **40b** (200 mg, 0.314 mmol) and ethynylferrocene (0.132 g, 0.628 mmol). Chromatography of the crude reaction mixture on a silica gel column using 5% acetone

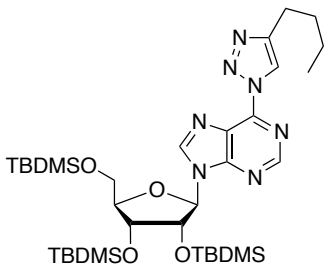
in hexanes yielded **44f** as a reddish-brown, foamy solid (189 mg, 71% yield). R_f (SiO_2/10% acetone in hexanes) = 0.18. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.99 (s, 1H, Ar–H), 8.94 (s, 1H, Ar–H), 8.64 (s, 1H, Ar–H), 6.21 (d, 1H, H-1', J = 5.1 Hz), 4.88 (br s, 2H, ferrocenyl–H), 4.65 (t, 1H, H-2', J = 4.5 Hz), 4.36 (br s, 2H, ferrocenyl–H), 4.33 (t, 1H, H-3', J = 4.0 Hz), 4.19 (m, 1H, H-4'), 4.12 (s, 5H, ferrocenyl–H), 4.05 (dd, 1H, H-5', J = 3.3, 11.5 Hz), 3.83 (dd, 1H, H-5', J = 2.0, 11.5 Hz), 0.98, 0.94, and 0.81 (3s, 27H, *t*-Bu), 0.18, 0.16, 0.11, 0.107, –0.01, and –0.20 (6s, 18H, Si–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.4, 152.4, 147.9, 145.0, 144.9, 123.3, 118.8, 88.7, 85.9, 76.4, 74.7, 72.1, 69.9, 69.2, 67.3, 62.7, 26.3, 26.0, 25.9, 18.8, 18.3, 18.0, –4.2, –4.4, –4.5, –4.7, –5.1. HRMS (ESI): calcd for $C_{40}H_{63}FeN_7O_4Si_3Na$ $[M + Na]^+$ 868.3491, found 868.3487.

Minor Isomer: 6-(5-Ferrocenyl-1,2,3-triazol-1-yl)-9-[2,3,5-bis-*O*-(*tert*-butyldimethyl-silyl)-*β*-D-ribofuranosyl]purine (44f')



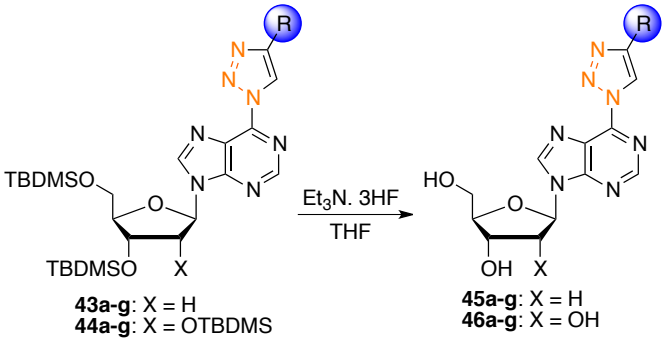
Obtained 28.3 mg (10% yield) of **44f'** as a brown solid. R_f (SiO_2/40% EtOAc in hexanes) = 0.41. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.98 (s, 1H, Ar–H), 8.60 (s, 1H, Ar–H), 7.89 (s, 1H, Ar–H), 6.22 (d, 1H, H-1', J = 5.1 Hz), 4.60 (t, 1H, H-2', J = 4.6 Hz), 4.41 (m, 2H, ferrocenyl–H), 4.32 (t, 1H, H-3', J = 4.0 Hz), 4.25 (m, 2H, ferrocenyl–H), 4.18 (q, 1H, H-4', J = 3.1 Hz), 4.02 (dd, 1H, H-5', J = 3.4, 11.5 Hz), 3.99 (s, 5H, ferrocenyl–H), 3.81 (dd, 1H, H-5', J = 2.4, 11.5 Hz), 0.943, 0.939, and 0.81 (3s, 27 H, *t*-Bu), 0.14, 0.13, 0.10, –0.005, and –0.20 (5s, 18H, Si–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.4, 152.0, 147.1, 145.7, 138.9, 133.3, 128.5, 88.7, 85.9, 76.6, 72.0, 70.0, 69.5, 69.4, 62.6, 53.6, 26.3, 26.0, 25.9, 18.8, 18.3, 18.0, –4.2, –4.4, –4.5, –4.7, –5.1. HRMS (ESI): calcd for $C_{40}H_{63}FeN_7O_4Si_3Na$ $[M + Na]^+$ 868.3491, found 868.3489.

6-[4-(1-Butyl)-1,2,3-triazol-1-yl]-9-[2,3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (44g)

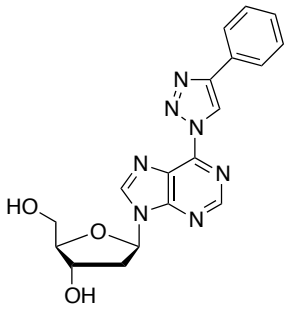


Synthesized from **40b** (200 mg, 0.314 mmol) and 1-hexyne (72.2 µL, 0.628 mmol). Chromatography of the crude reaction mixture on a silica gel column using 5% acetone in hexanes yielded **44g** as a yellow, foamy solid (184 mg, 81% yield). R_f (SiO_2/10% acetone in hexanes) = 0.22. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.92 (s, 1H, Ar–H), 8.85 (s, 1H, Ar–H), 8.59 (s, 1H, Ar–H), 6.20 (d, 1H, H-1', J = 5.1 Hz), 4.65 (t, 1H, H-2', J = 4.6 Hz), 4.32 (t, 1H, H-3', J = 3.9 Hz), 4.18 (q, 1H, H-4', J = 3.0 Hz), 4.03 (dd, 1H, H-5', J = 3.7, 11.3 Hz), 3.82 (dd, 1H, H-5', J = 2.5, 11.3 Hz), 2.88 (t, 2H, butyl-CH_2, J = 7.7 Hz), 1.77 (quint, 2H, butyl–CH_2, J = 7.6 Hz), 1.45 (sextet, 2H, butyl-CH2, J = 7.4 Hz), 0.97, 0.94, and 0.79 (overlapping 3s and t, 30H, *t*-Bu and butyl–CH_3), 0.17, 0.16, 0.11, 0.10, –0.02, and –0.24 (6s, 18H, Si–CH_3). ^{13}C NMR (125MHz, $CDCl_3$): δ 154.4, 152.4, 149.4, 145.2, 144.8, 123.3, 121.4, 88.7, 86.1, 76.4, 72.2, 62.7, 31.6, 26.3, 26.1, 25.8, 25.5, 22.5, 18.8, 18.3, 18.1, 14.0, –4.2, –4.4, –4.5, –4.8, –5.1. HRMS (ESI): calcd for $C_{34}H_{63}N_7O_4Si_3Na$ $[M + Na]^+$ 740.4142, found 740.4139.

[1.4.4] Desilylation of the click products

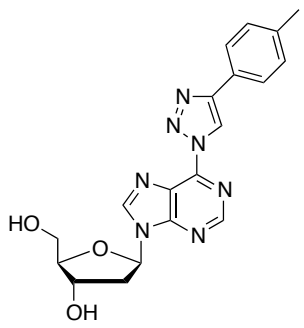


General Method for Desilylation of the Click Products: Synthesis of 6-(4-Phenyl-1,2,3-triazol-1-yl]-9-(2-deoxy-*β*-D-ribofuranosyl) purine (45a)



In a clean, dry plastic vial equipped with a stirring bar was placed the nucleoside derivative **43a** (91.2 mg, 0.150 mmol) in anhydrous THF (2.0 mL). $Et_3N.3HF$ (85 μL, 0.525 mmol) was added to the stirring mixture at room temperature. After 34 h at room temperature, TLC indicated complete consumption of the starting material at which time the mixture was evaporated to dryness under a stream of nitrogen gas. Chromatographic purification on a silica gel column using 3-5% MeOH in hexanes afforded **45a** as white powder (54.6 mg, 96% yield). R_f (SiO_2/10% MeOH in CH_2Cl_2) = 0.30. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.62 (s, 1H, Ar–H), 9.04 (s, 1H, Ar–H), 9.03 (s, 1H, Ar–H), 8.07 (d, 2H, Ar–H, J = 7.3 Hz), 7.53 (t, 2H, Ar–H, J = 7.6 Hz), 7.43 (t, 1H, Ar–H, J = 7.4 Hz), 6.57 (t, 1H, H-1', J = 6.5 Hz), 5.40 (d, 1H, OH, J = 4.2 Hz), 5.01 (t, 1H, OH, J = 5.5 Hz), 4.49 (m, 1H, H-3'), 3.94 (app q, 1H, H-4', $J_{app} \approx$ 3.6 Hz), 3.66 (m, 1H, H-5'), 3.07 (m, 1H, H-5'), 2.83 (m, 1H, H-2'), 2.43 (m, 1H, H-2', superimposed with solvent). ^{13}C NMR (125 MHz, acetone-d_6 + 4 drops of DMSO-d_6): δ 155.2, 152.7, 148.5, 147.2, 145.6, 131.2, 130.0, 129.6, 126.9, 124.5, 121.6, 89.8, 86.0, 72.1, 62.9, 41.7. HRMS (ESI): calcd for $C_{18}H_{18}N_7O_3$ $[M + H]^+$ 380.1466, found 380.1465.

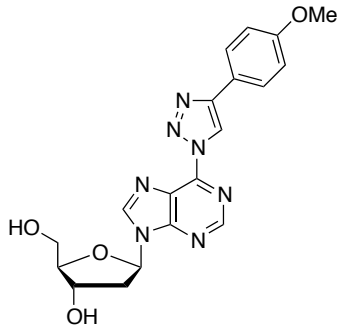
6-[4-(4-Methylphenyl)-1,2,3-triazol-1-yl]-9-(2-deoxy-*β*-D-ribofuranosyl)puri-ne (45b)



Desilylation of **43b** (93.3 mg, 0.150 mmol) with $Et_3N.3HF$ (0.15 mL, 0.901 mmol) and chromatographic purification as for **45a** afforded **45b** as a white powder (43.9 mg, 74% yield). R_f (SiO_2/10% MeOH in CH_2Cl_2) = 0.32. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.55 (s, 1H, Ar–H), 9.03 (s, 1H, Ar–H), 9.02 (s, 1H, Ar–H), 7.95 (d, 2H, Ar–H, J = 7.8 Hz),

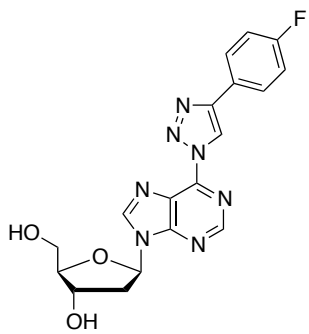
7.33 (d, 2H, Ar–H, J = 7.8 Hz), 6.57 (t, 1H, H-1', J = 6.6 Hz), 5.40 (d, 1H, OH, J = 4.1 Hz), 5.01 (t, 1H, OH, J = 5.2 Hz), 4.49 (br m, 1H, H-3'), 3.93 (app q, 1H, H-4', J_{app} = 3.8 Hz), 3.66 (m, 1H, H-5'), 3.57 (m, 1H, H-5'), 2.83 (app quint, 1H, H-2', $J_{app} \approx$ 6.5 Hz), 2.43 (ddd, 1H, H-2', J = 4.5, 6.5, 13.1 Hz). ^{13}C NMR (125 MHz, acetone-d_6 + 15 drops of DMSO-d_6): δ 154.8, 152.3, 148.0, 146.9, 145.1, 138.9, 130.2, 127.9, 126.4, 124.0, 120.8, 89.3, 85.3, 71.5, 62.3, 40.7, 21.3.HRMS (ESI): calcd for $C_{19}H_{20}N_7O_3$ $[M + H]^+$ 394.1622, found 394.1619.

6-[4-(4-Methoxyphenyl)-1,2,3-triazol-1-yl]-9-(2-deoxy-*β*-D-ribofuranosyl) purine (45c)



Desilylation of **43c** (95.7 mg, 0.150 mmol) with $Et_3N.3HF$ (85 µL, 0.525 mmol) and chromatographic purification as for **45a** afforded **45c** as white powder (50.8 mg, 83% yield). R_f (SiO_2/10% MeOH in CH_2Cl_2) = 0.32. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.50 (s, 1H, Ar–H), 9.02 (s, 1H, Ar–H), 9.01 (s, 1H, Ar–H), 7.99 (d, 2H, Ar–H, J = 8.8 Hz), 7.08 (d, 2H, Ar–H, J = 8.8 Hz), 6.57 (t, 1H,H-1', J = 6.6 Hz), 4.48 (m, 1H, H-3'), 3.93 (app q, 1H, H 4', $J_{app} \approx$ 4.0 Hz), 3.66 (dd, 1H, H-5', J = 4.6, 11.7 Hz), 3.57 (dd, 1H, H-5', J = 4.5, 11.7 Hz), 2.82 (app quint, 1H, H-2', $J_{app} \approx$ 6.5 Hz), 2.43 (ddd, 1H, H-2', J = 3.9, 6.3, 13.5 Hz). ^{13}C NMR (125 MHz, acetone-d_6 + 15 drops of DMSO-d_6): δ 160.9, 155.0, 152.6, 148.2, 147.0, 145.4, 128.1, 124.3, 123.5, 120.4, 115.3, 89.6, 85.7, 71.8, 62.6, 55.9, 41.3. HRMS (ESI): calcd for $C_{19}H_{20}N_7O_4$ $[M + H]^+$ 410.1571, found 410.1570.

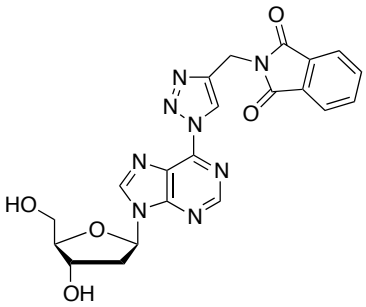
6-[4-(4-Fluorophenyl)-1,2,3-triazol-1-yl]-9-(2-deoxy-*β*-D-ribofuranosyl)purine (45d)



Desilylation of **43d** (93.9 mg, 0.150 mmol) with $Et_3N.3HF$ (85 µL, 0.525 mmol) and chromatographic purification as for **45a** afforded **45d** as white solid (50.8 mg, 83% yield). R_f (SiO_2/10% MeOH in CH_2Cl_2) = 0.37. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.62 (s, 1H, Ar–H), 9.04 (s,

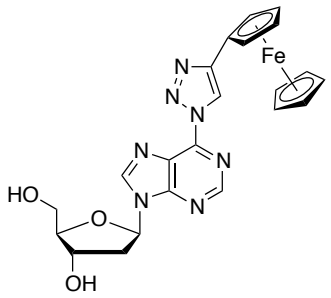
1H, Ar–H), 9.03 (s, 1H, Ar–H), 8.13 (dd, 2H,Ar–H, $J_{H,H}$ = 8.6Hz, $J_{F,H}$ = 5.5 Hz), 7.37 (t, 2H, Ar–H, $J_{H,H}$ = $J_{F,H}$ = 8.6 Hz), 6.57 (t, 1H, H-1', J = 6.3 Hz), 5.39 (br s, 1H, OH), 5.01 (br s, 1H, OH), 4.49 (m, 1H, H-3'), 3.94 (app q, 1H, H-4', J_{app} ≈ 4.1 Hz), 3.66 (dd, 1H, H-5', J = 4.5, 11.4 Hz), 3.57 (dd, 1H, H-5', J = 4.2, 11.4 Hz), 2.83 (app quint, 1H, H-2', J_{app} ≈ 6.5Hz), 2.43 (ddd, 1H, H-2', J = 3.7, 6.3, 13.3 Hz). ^{13}C NMR (125 MHz, acetone-d_6 + 10 drops of DMSO-d_6): δ 163.4 (d, $^{1}J_{C,F}$ = 245.7 Hz), 155.2, 152.6, 147.3, 147.2, 145.5, 129.0 (d, $^{3}J_{C,F}$ = 8.3 Hz), 127.6 (d, $^{4}J_{C,F}$ = 3.2 Hz), 124.5, 121.4, 116.8 ($^{2}J_{C,F}$ = 21.9 Hz), 89.7, 85.9, 72.0, 62.7, 41.5. HRMS (ESI): calcd for $C_{18}H_{17}FN_7O_3$ $[M + H]^+$ 398.1371, found 398.1386.

6-[4-(*N*-Phthalimidomethyl)-1,2,3-triazol-1-yl]-9-(2-deoxy-*β*-D-ribofuranosy-l)purine (45e)



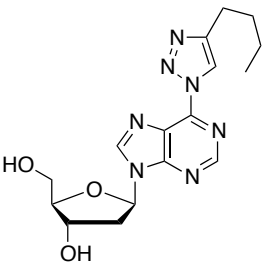
Desilylation of **43e** (112.9 mg, 0.163 mmol) with $Et_3N.3HF$ (85 μL, 0.525 mmol) and chromatographic purification as for **45a** afforded **45e** as white solid (64.5 mg, 85% yield). R_f (SiO_2/10% MeOH in CH_2Cl_2) = 0.27. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.22 (s, 1H, Ar–H), 9.00 (s, 1H, Ar–H), 8.98 (s, 1H, Ar–H), 7.92 (m, 2H, Ar–H), 7.87 (m, 2H, Ar–H), 6.54 (t, 1H, H-1', J = 6.6 Hz), 5.03 (s, 2H, NCH_2), 4.46 (m, 1H, H-3'), 3.92 (app q, 1H, H-4', J_{app} ≈ 4.0 Hz), 3.64 (dd, 1H, H-5', J = 4.5, 11.8 Hz), 3.55 (dd, 1H, H-5', J = 4.5, 11.8 Hz), 2.79 (app quint, 1H, H-2', J_{app} ≈ 6.5Hz), 2.41 (ddd, 1H, H-2', J = 3.9, 6.3, 13.3 Hz). ^{13}C NMR (125 MHz, acetone-d_6 + 15 drops of DMSO-d_6): δ 168.2, 154.8, 152.4, 147.0, 144.9, 144.2, 135.2, 132.7, 124.4, 123.9, 89.3, 85.4, 71.5, 62.4, 41.0, 33.5. HRMS (ESI): calcd for $C_{21}H_{19}N_8O_5$ $[M + H]^+$ 463.1473, found 463.1476.

6-(4-Ferrocenyl-1,2,3-triazol-1-yl)-9-(2-deoxy-*β*-D-ribofuranosyl) purine (45f) Desilylation



of **43f** (107.3 mg, 0.150 mmol) with $Et_3N.3HF$ (85 μL, 0.525 mmol) and chromatographic purification as for **45a** afforded **45f** as an orange solid (51.8 mg,71%yield). R_f (SiO_2/10% MeOH in CH_2Cl) = 0.26. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.23 (s, 1H, Ar–H), 9.02 (s, 1H, Ar–H), 9.01 (s, 1H, Ar–H), 6.57 (t, 1H, H-1', J = 6.6 Hz), 4.95 (br t, 2H, ferrocenyl–H, J = 1.5 Hz), 4.48 (m, 1H, H-3'), 4.40 (br t, 2H, ferrocenyl–H, J = 1.5 Hz), 4.10 (s, 5H, ferrocenyl–H), 3.94 (app q, 1H, H-4', J_{app} ≈ 4.3 Hz), 3.66 (dd, 1H, H-5', J = 4.6, 11.7 Hz), 3.57 (dd, 1H, H-5', J = 4.4, 11.7 Hz), 2.81 (app quint, 1H, H-2', J_{app} ≈ 6.5 Hz), 2.43 (ddd, 1H, H-2', J = 4.0, 6.3 13.3 Hz). ^{13}C NMR (125 MHz, acetone-d_6 + 10 drops of DMSO-d_6): δ 155.3, 152.8, 148.2, 147.1, 145.8, 124.5, 120.4, 90.0, 86.2, 76.1, 72.3, 70.6, 70.0, 68.0, 63.0, 41.9. HRMS (ESI): calcd for $C_{22}H_{21}FeN_7O_3Na$ $[M + Na]^+$ 510.0948, found 510.0948.

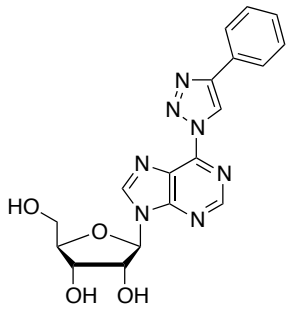
6-[4-(1-Butyl)-1,2,3-triazol-1-yl]-9-(2-deoxy-*β*-D-ribofuranosyl)purine (45g)



Desilylation of **43g** (88.2 mg, 0.150 mmol) with $Et_3N.3HF$ (85 μL, 0.525 mmol) and chromatographic purification as for **45a** afforded **45g** as a clear, gummy material (38.0 mg, 70% yield). R_f (SiO_2/10% MeOH in CH_2Cl_2) = 0.35. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.98 (s, 1H, Ar–H), 8.97 (s, 1H, Ar–H), 8.96 (s, 1H, Ar–H), 6.55 (t, 1H, H-1', J = 6.6 Hz), 5.39 (d, 1H, OH, J = 4.4 Hz), 4.99 (t, 1H, OH, J = 5.5 Hz), 4.47 (m, 1H, H-3'), 3.93 (app q, 1H, H-4', J_{app} ≈ 4.0 Hz), 3.65 (m, 1H, H-5'), 3.56 (m, 1H, H-5'), 2.84-2.76 (m, 3H, H-2' and butyl-CH_2), 2.42 (ddd, 1H, H-2', J = 3.9, 6.3, 13.3 Hz), 1.64 (quint, 2H, butyl-CH_2, J = 7.5 Hz), 1.38 (sextet, 2H, butyl-CH_2, J = 7.4Hz), 0.93 (t, 3H, butyl-CH_3, J = 7.3 Hz). ^{13}C NMR (125 MHz, acetone-d_6 + 15 drops of DMSO-d_6): δ 154.7,

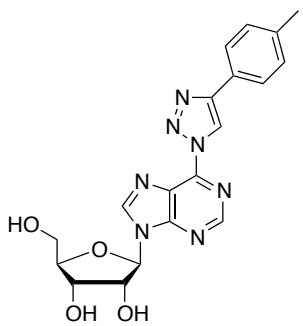
152.4, 149.0, 146.7, 145.3, 123.8, 122.5, 89.3, 85.4, 71.5, 62.4, 41.0, 31.8, 25.4, 22.6, 14.1. HRMS (ESI): calcd for $C_{16}H_{22}N_7O_3$ $[M + H]^+$ 360.1779, found 360.1791.

6-(4-Phenyl-1,2,3-triazol-1-yl)-9-(*β*-D-ribofuranosyl)purine (46a)



Desilylation of **44a** (110.7 mg, 0.150 mmol) with $Et_3N.3HF$ (0.12 mL, 0.75 mmol) and chromatographic purification on a silica gel column using 3-7% MeOH in hexanes afforded **46a** as a white, fluffy solid (57.3 mg, 96% yield). R_f (SiO_2/10% MeOH in CH_2Cl_2) = 0.28. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.62 (s, 1H, Ar–H), 9.09 (s, 1H, Ar–H), 9.05 (s, 1H, Ar–H), 8.05 (d, 2H, Ar–H, *J* = 7.3 Hz), 7.53 (t, 2H,Ar–H, *J* = 7.5 Hz), 7.43 (t, 1H, Ar-H, *J* = 7.6 Hz) 6.15 (d, 1H, H-1', *J* = 4.9 Hz), 5.62 (d, 1H, OH, *J* = 5.6 Hz), 5.28 (d, 1H, OH, *J* = 5.1 Hz), 5.14 (t, 1H, OH, *J* = 5.1Hz), 4.65 (m, 1H, H-2'), 4.24 (m, 1H, H-3'), 4.03 (m, 1H, H-4'), 3.74 (m, 1H, H-5'), 3.62 (m, 1H, H-5'). ^{13}C NMR (125 MHz, THF-d_8 + 4 drops of DMSO-d_6): δ 155.5, 152.7, 148.5, 147.2, 146.0, 131.6, 129.8, 129.3, 126.9, 124.7, 121.2, 90.4, 87.7, 76.5, 71.9, 62.6. HRMS (ESI): calcd for $C_{18}H_{18}N_7O_4$ $[M + H]^+$ 396.1415, found 396.1416.

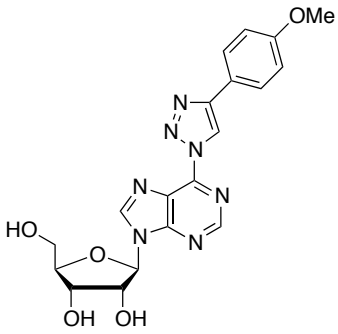
6-[4-(4-Methylphenyl)-1,2,3-triazol-1-yl]-9-(*β*-D-ribofuranosyl)purine (46b)



Desilylation of **44b** (112.8 mg, 0.15 mmol) with $Et_3N.3HF$ (0.12 mL, 0.75 mmol) and chromatographic purification as for **46a** afforded **46b** as a white solid (59.2 mg,96% yield). R_f (SiO_2/10% MeOH in CH_2Cl_2) = 0.28. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.56 (s, 1H, Ar–H), 9.08 (s, 1H, Ar–H), 9.04 (s, 1H, Ar–H), 7.96 (d, 2H, Ar–H, *J* = 7.8 Hz), 7.33 (d, 2H, Ar–H, *J* = 7.8 Hz), 6.15 (d, 1H, H-1', *J* = 4.9 Hz), 5.62 (d, 1H, OH, *J* = 5.8 Hz), 5.28 (d, 1H, OH, *J* = 5.1 Hz), 5.14 (t, 1H, OH, *J* = 5.3 Hz), 4.65 (m, 1H, H-2'), 4.24 (m, 1H, H-3'), 4.02 (m, 1H, H-4'), 3.74 (m, 1H, H-5'), 3.62 (m, 1H, H-5'), 2.37 (s, 3H, CH_3). ^{13}C NMR (125 MHz,

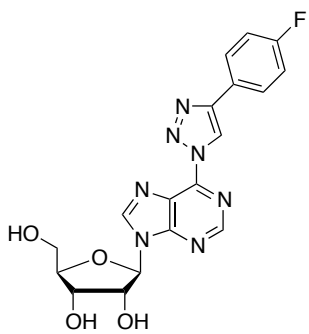
THF-d_8 + 4 drops of DMSO-d_6): δ 155.5, 152.7, 148.6, 147.1, 145.9, 139.0, 130.4, 128.8, 126.8, 124.7, 120.7, 90.5, 87.7, 76.4, 71.9, 62.6, 21.5. HRMS (ESI): calcd for $C_{19}H_{20}N_7O_4$ $[M + H]^+$ 410.1571, found 410.1572.

6-[4-(4-Methoxyphenyl)-1,2,3-triazol-1-yl]-9-(*β*-D-ribofuranosyl)purine (46c)



Desilylation of **44c** (115.2 mg, 0.150 mmol) with $Et_3N.3HF$ (0.12 mL, 0.75 mmol) and chromatographic purification as for **46a** afforded **46c** as a white solid (51.3 mg, 81% yield). R_f (SiO_2/10% MeOH in CH_2Cl_2) = 0.30. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.51 (s, 1H, Ar–H), 9.07 (s, 1H, Ar–H), 9.04 (s, 1H, Ar–H), 8.01 (d, 2H, Ar–H, J = 8.8 Hz), 7.08 (d, 2H, Ar–H, J = 8.8 Hz), 6.15 (d, 1H, H-1', J = 5.4 Hz), 4.65 (t, 1H, H-2', J = 5.0 Hz), 4.23 (t, 1H, H-3', J = 4.5 Hz), 4.03 (app q, 1H, H-4', $J_{app} \approx$ 4.9 Hz), 3.83 (s, 3H, OCH_3), 3.74 (dd, 1H, H-5', J = 3.9, 11.7 Hz), 3.62 (dd, 1H, H-5', J = 3.9, 11.7 Hz). ^{13}C NMR (125 MHz, THF-d_8 + 4 drops of DMSO-d_6): δ 161.2, 155.5, 152.7, 148.5, 147.2, 145.9, 128.2, 124.6, 124.0, 120.1, 115.3, 90.3, 87.6, 76.5, 71.8, 62.5, 55.8. HRMS (ESI): calcd for $C_{19}H_{20}N_7O_5$ $[M + H]^+$ 426.1520, found 426.1521.

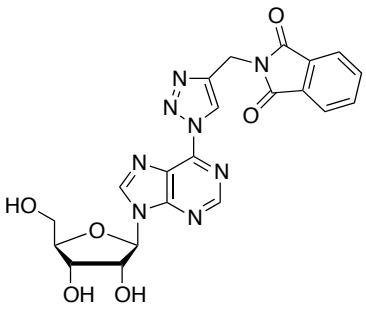
6-[4-(Fluorophenyl)-1,2,3-triazol-1-yl]-9-(*β*-D-ribofuranosyl)purine (46d) Desilylation of **44d**



(113.4 mg, 0.15 mmol) with $Et_3N.3HF$ (0.12 mL, 0.75 mmol) and chromatographic purification as for **46a** afforded **46d** as a white solid (44.0 mg, 71% yield). R_f (SiO_2/10% MeOH in CH_2Cl_2) = 0.26. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.63 (s, 1H, Ar–H), 9.08 (s, 1H, Ar–H), 9.05 (s, 1H, Ar–H), 8.13 (dd, 2H, Ar–H, $J_{H,H}$ = 8.9 Hz, $J_{F,H}$ = 5.5 Hz), 7.37 (t, 2H, Ar–H, $J_{H,H} = J_{F,H}$ = 8.9 Hz), 6.15 (d, 1H, H-1', J = 5.1 Hz), 5.62 (d, 1H, OH, J = 5.8 Hz), 5.28 (d, 1H, OH, J = 5.3 Hz), 5.14 (t, 1H, OH, J = 5.3 Hz), 4.65 (m, 1H, H-2'), 4.24 (m,

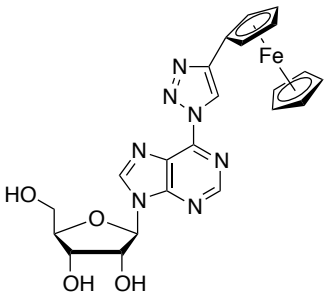
1H, H-3'), 4.03 (m, 1H, H-4'), 3.74 (m, 1H, H-5'), 3.62 (m, 1H, H-5'). ^{13}C NMR (125 MHz, THF-d_8 + 4 drops of DMSO-d_6): δ 163.7 (d, $^{1}J_{C,F}$ = 246.3 Hz), 155.6, 152.7, 147.6, 147.3, 145.8, 128.9 (d, $^{3}J_{C,F}$ = 8.2 Hz), 128.0 (d, $^{4}J_{C,F}$ = 3.2 Hz), 124.7, 121.2, 116.7 (d, $^{2}J_{C,F}$ = 21.8 Hz), 90.4, 87.7, 76.5, 71.8, 62.5. HRMS (ESI): calcd for $C_{18}H_{17}FN_7O_4$ $[M + H]^+$ 414.1321, found 414.1319.

6-[4-(*N*-Phthalimidomethyl)-1,2,3-triazol-1-yl]-9-(*β*-D-ribofuranosyl)purine (46e)



Desilylation of **44e** (115.0 mg, 0.15 mmol) with $Et_3N.3HF$ (0.12 mL, 0.75 mmol) and chromatographic purification as for **46a** afforded **46e** as a white solid (61.7 mg, 85% yield). R_f (SiO_2/10% MeOH in CH_2Cl_2) = 0.26. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.22 (s, 1H, Ar–H), 9.05 (s, 1H, Ar–H), 8.99 (s, 1H, Ar–H), 7.94-7.91 (m, 2H, Ar–H), 7.89-7.86 (m, 2H, Ar–H), 6.12 (d, 1H, H-1', J = 5.1 Hz), 5.03 (s, 2H, NCH_2), 4.60 (t, 1H, H-2', J = 5.2 Hz), 4.21 (t, 1H, H-3', J = 4.3 Hz), 4.01 (app q, 1H, H-4', $J_{app} \approx$ 3.8 Hz), 3.72 (dd, 1H, H-5', J = 3.6, 12.0 Hz), 3.60 (dd, 1H, H-5', J = 3.8, 12.0 Hz). ^{13}C NMR (125 MHz, THF-d_8 + 4 drops of DMSO-d_6): δ 168.3, 155.5, 152.7, 147.3, 145.7, 144.5, 135.2, 133.5, 124.6, 124.5, 124.1, 90.2, 87.6, 76.5, 71.8, 62.5, 33.8. HRMS (ESI): calcd for $C_{21}H_{19}N_8O_6$ $[M + H]^+$ 479.1422, found 479.1432.

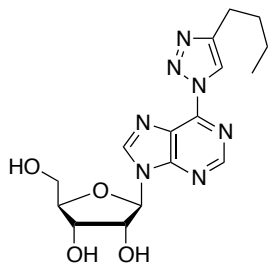
6-(4-Ferrocenyl-1,2,3-triazol-1-yl)-9-(*β*-D-ribofuranosyl)purine (46f)



Desilylation of **44f** (126.9 mg, 0.15 mmol) with $Et_3N.3HF$ (0.12 mL, 0.75 mmol) and chromatographic purification as for **46a** afforded **46f** as an orange solid (73.4 mg, 97% yield). R_f (SiO_2/10% MeOH in CH_2Cl_2) = 0.28. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.23 (s, 1H, Ar–H), 9.07 (s, 1H, Ar–H), 9.02 (s, 1H, Ar–H), 6.14 (d, 1H, H-1', J = 5.1 Hz), 4.95 (br t, 2H, ferrocenyl–H), 4.64 (t, 1H, H–2', J = 4.9 Hz), 4.41 (br t, 2H, ferrocenyl–H),

4.23 (t, 1H, H-3', J = 4.4 Hz), 4.10 (s, 5H, ferrocenyl–H), 4.03 (app q, 1H, H–4', $J_{app} \approx$ 3.9 Hz), 3.74 (dd, 1H, H-5', J = 3.9, 11.8 Hz), 3.62 (dd, 1H, H-5', J = 3.9, 11.8 Hz). ^{13}C NMR (125 MHz, THF-d_8 + 4 drops of DMSO-d_6): δ 155.5, 152.7, 148.0, 147.1, 145.8, 124.5, 120.0, 90.4, 87.6, 76.5, 76.3, 71.8, 70.5, 69.7, 62.5. HRMS (ESI): calcd for $C_{22}H_{22}FeN_7O_4$ $[M + H]^+$ 504.1077, found 504.1060.

6-[4-(1-Butyl)-1,2,3-triazol-1-yl]-9-(*β*-D-ribofuranosyl)purine (46g)



Desilylation of **44g** (107.7 mg, 0.15 mmol) with $Et_3N.3HF$ (0.12 mL, 0.75 mmol) and chromatographic purification as for **46a** afforded **46g** as a white solid (53.5 mg, 95% yield). R_f (SiO_2/10% MeOH in CH_2Cl_2) = 0.28. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.03 (s, 1H,Ar–H), 8.99 (s, 1H,Ar–H), 8.97 (s, 1H,Ar–H), 6.12 (d, 1H, H-1', J = 5.1 Hz), 5.60 (br s, 1H, OH), 5.27 (br s, 1H, OH), 5.12 (br s, 1H, OH), 4.63 (t, 1H, H-2', J = 4.7 Hz), 4.22 (t, 1H, H-3', J = 4.2 Hz), 4.01 (app q, 1H, H-4', $J_{app} \approx$ 3.8 Hz), 3.72 (dd, 1H, H-5', J = 3.4, 11.7 Hz), 3.61(dd, 1H, H-5', J = 3.2, 11.7Hz), 2.80 (t, 2H, butyl-CH2, J = 7.6 Hz), 1.70 (quint, 2H, butyl-CH2, J = 7.5 Hz), 1.39 (sextet, 2H, butyl-CH_2, J = 7.4 Hz), 0.94 (t, 3H, butyl-CH_3, J = 7.3 Hz). ^{13}C NMR (125 MHz, THF-d_8 + 4 drops of DMSO-d_6): δ 155.3, 152.7, 149.2, 146.9, 146.0, 124.4, 122.4, 90.4, 87.7, 76.4, 71.9, 62.6, 32.4, 26.1, 23.3, 14.4. HRMS (ESI): calcd for $C_{16}H_{22}N_7O_4$ $[M + H]^+$ 376.1728, found 376.1731.

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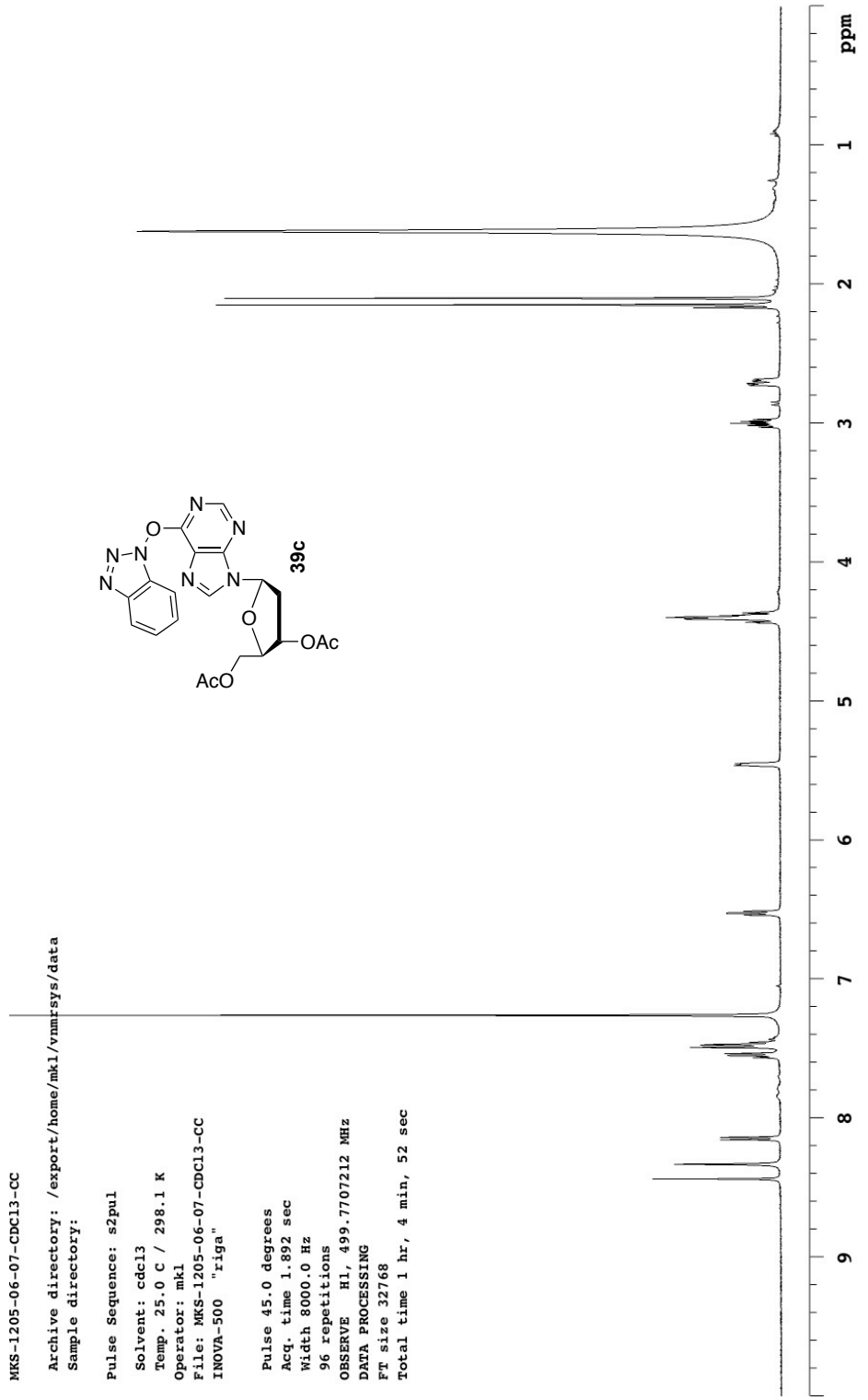
APPENDIX I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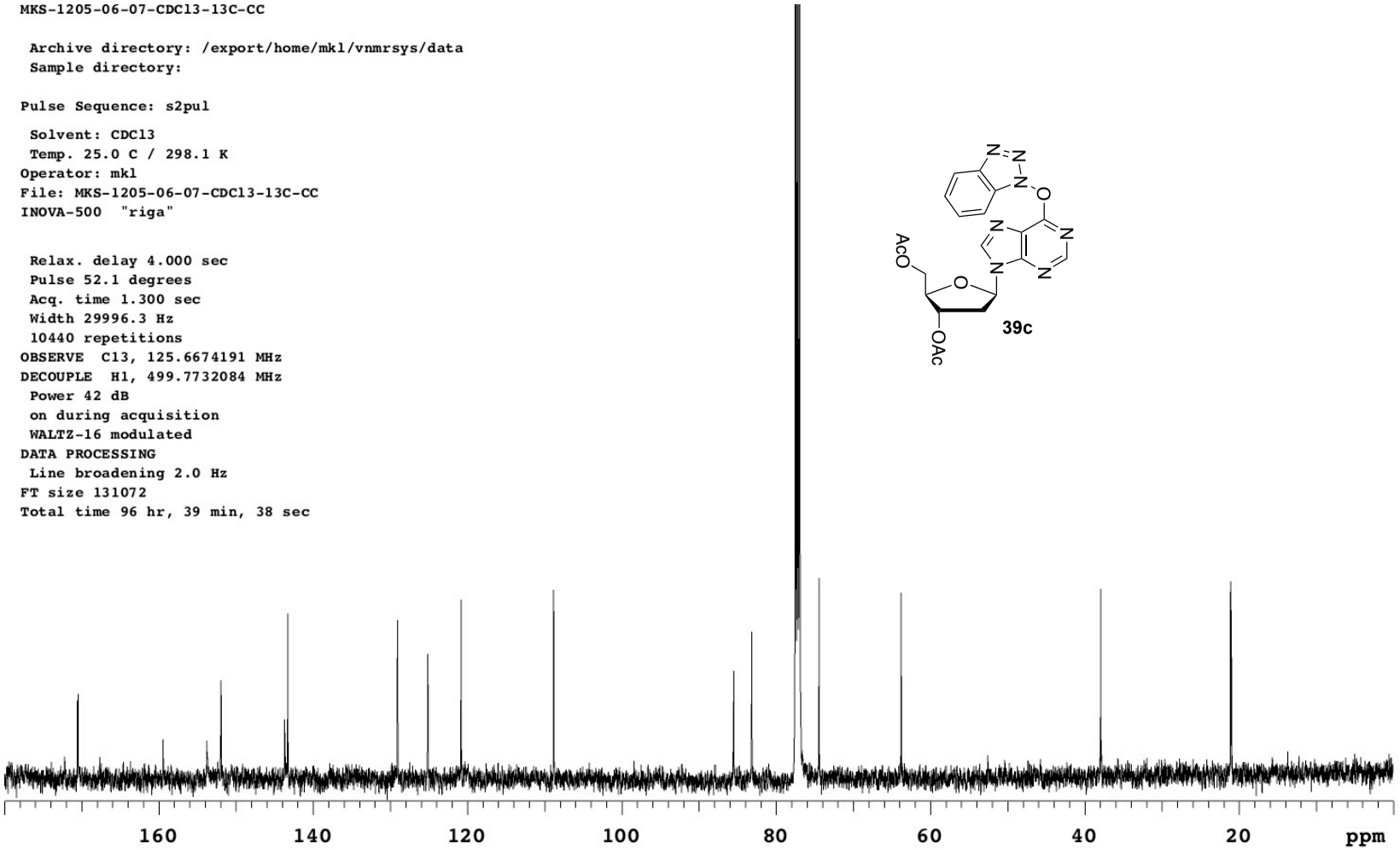
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DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
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OAc
39c
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140
120
100
80
60
40
20
ppm

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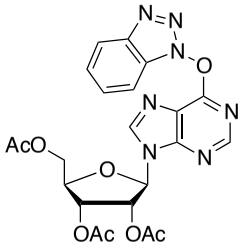

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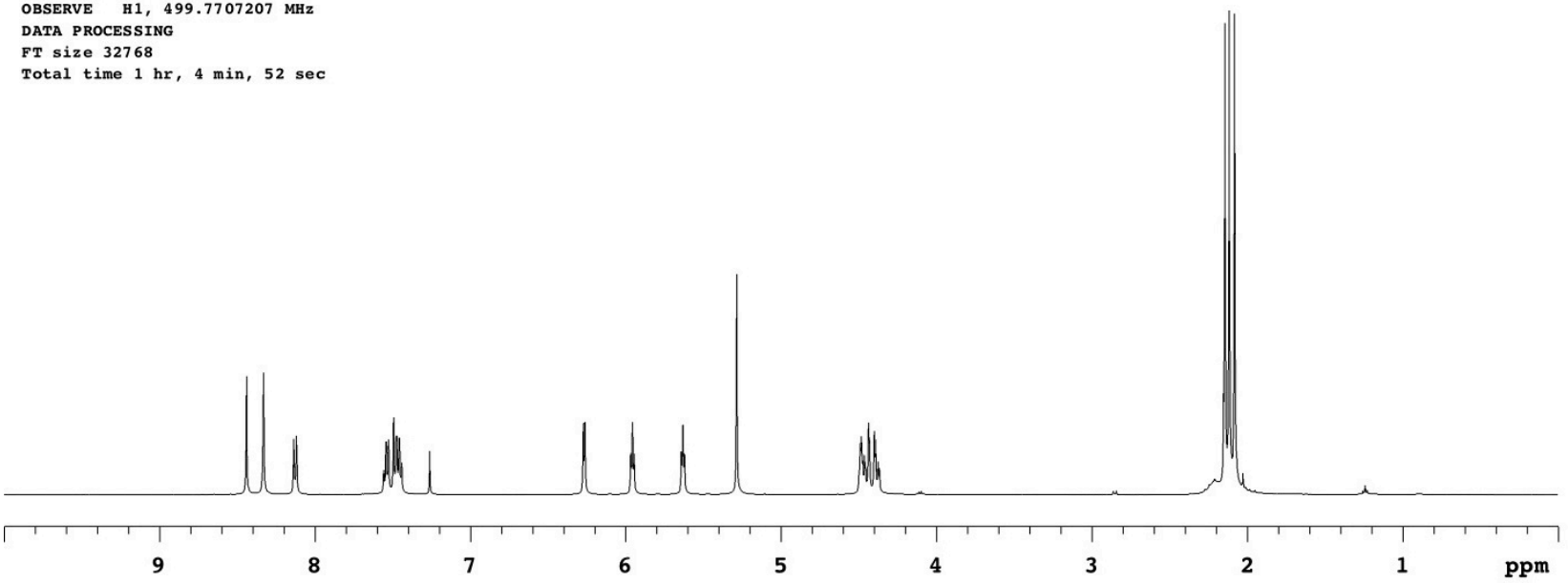

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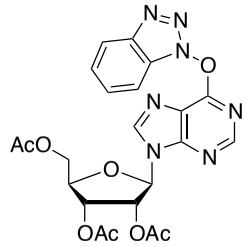

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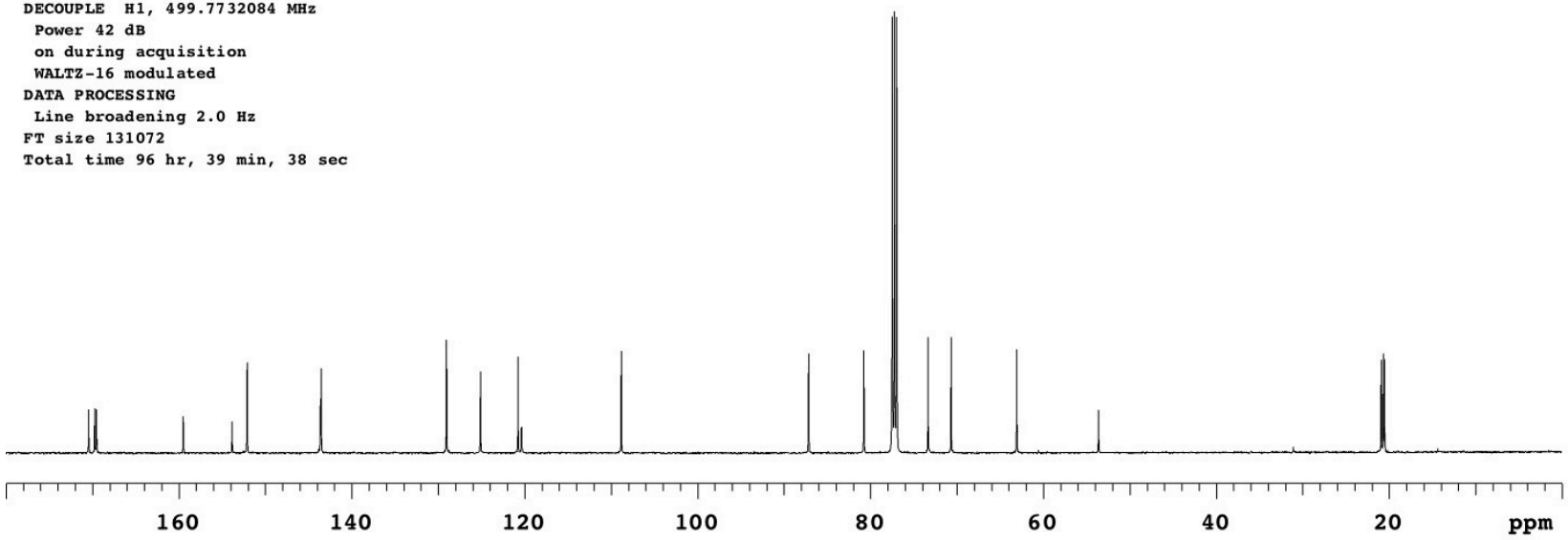

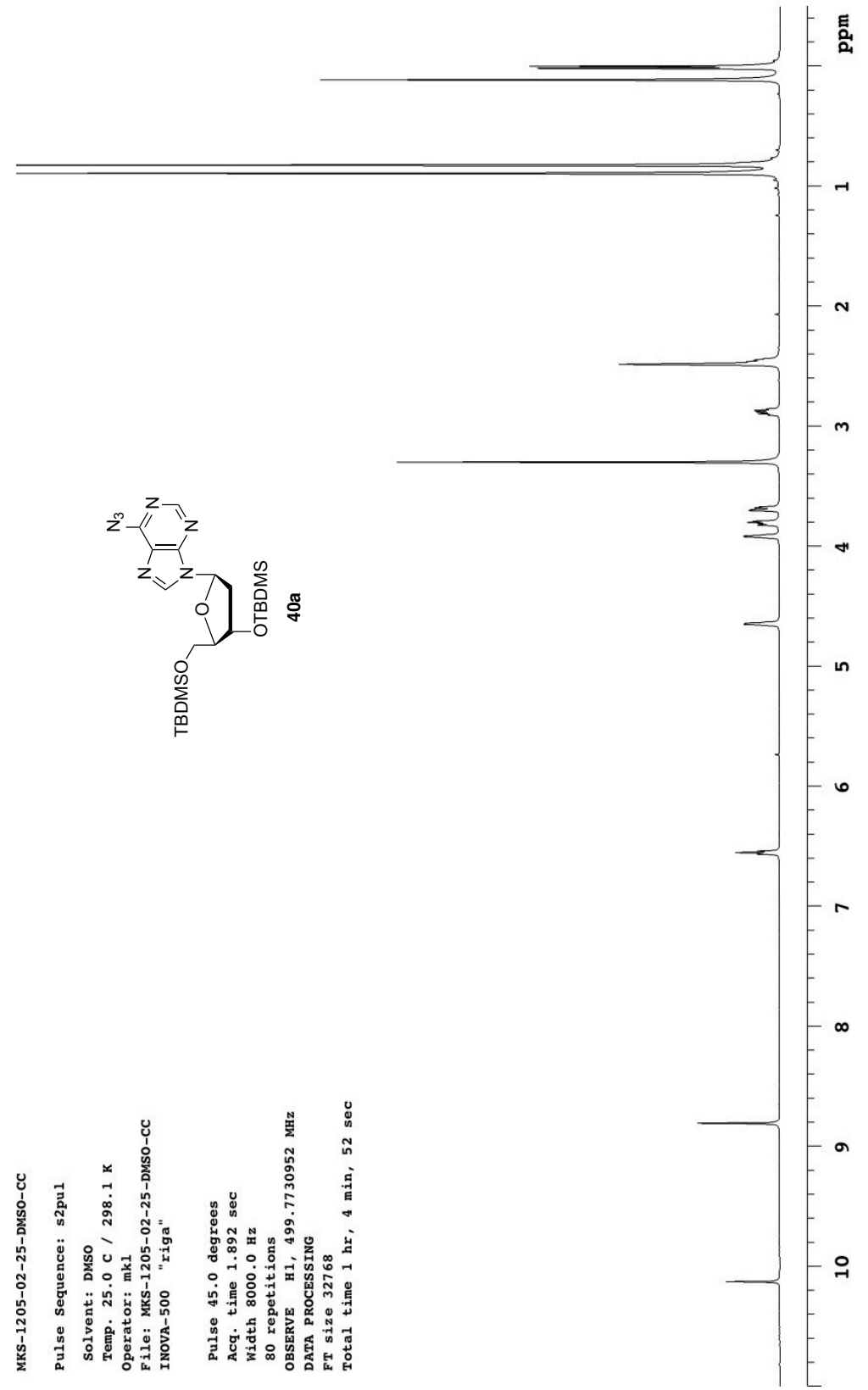
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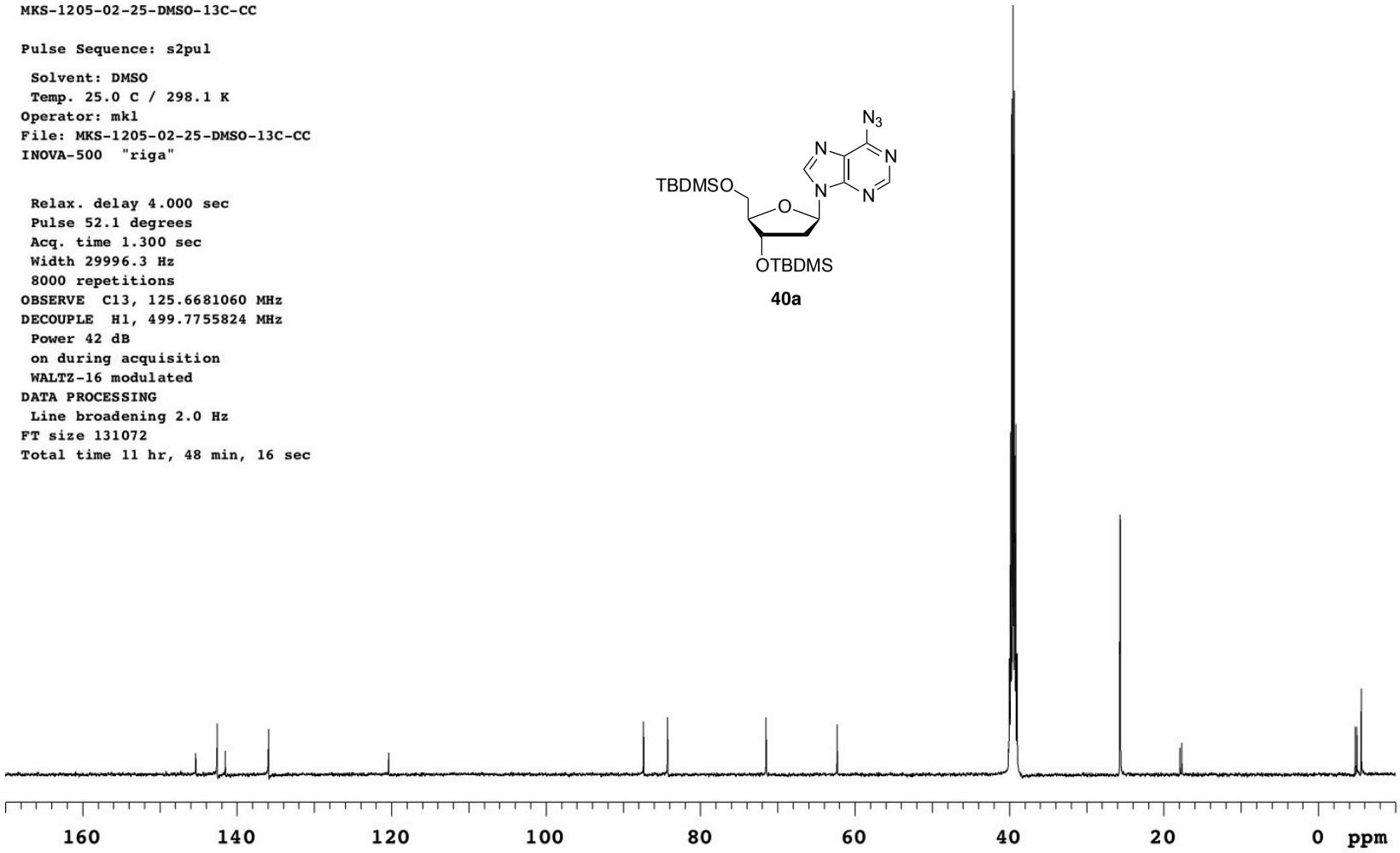
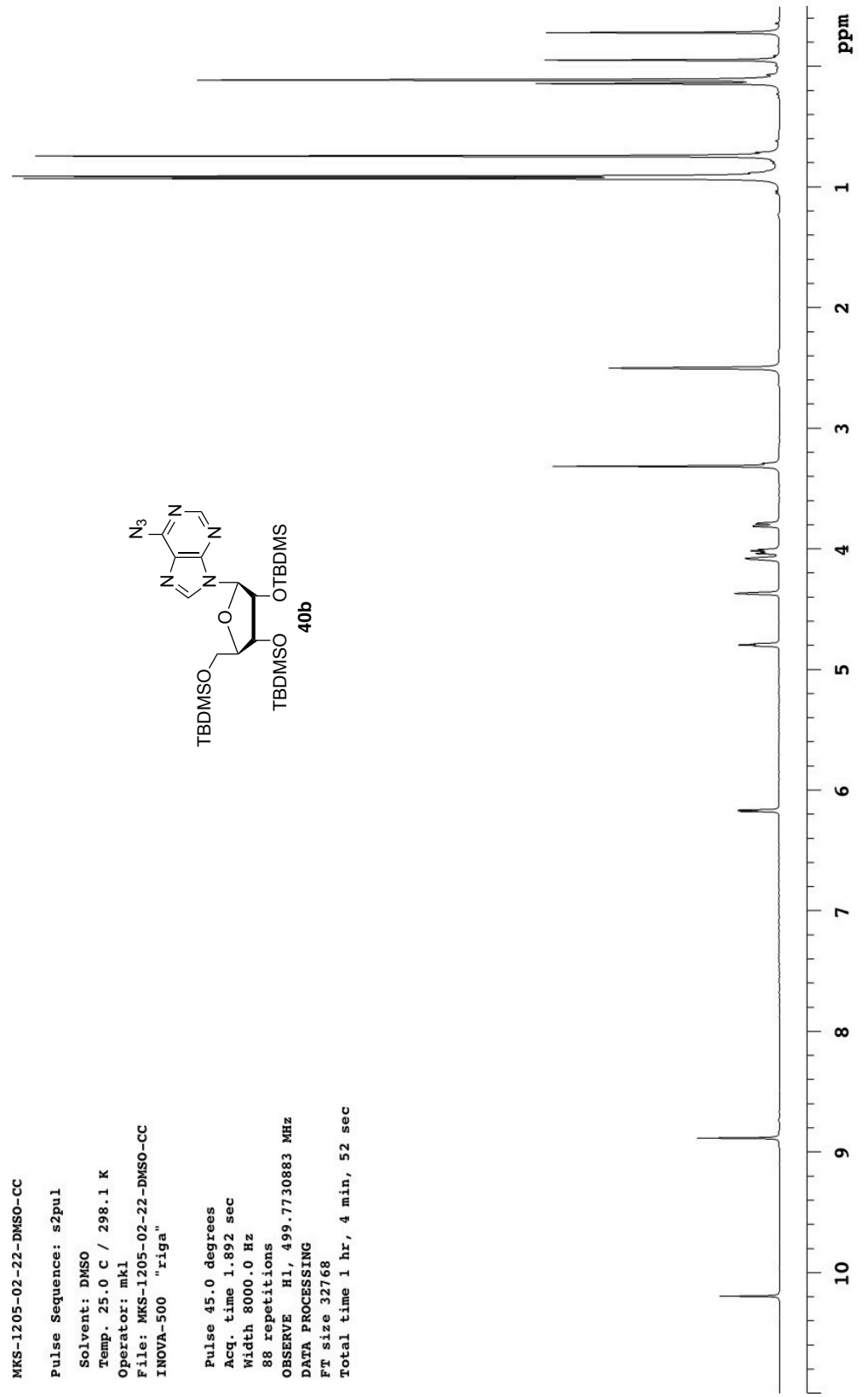
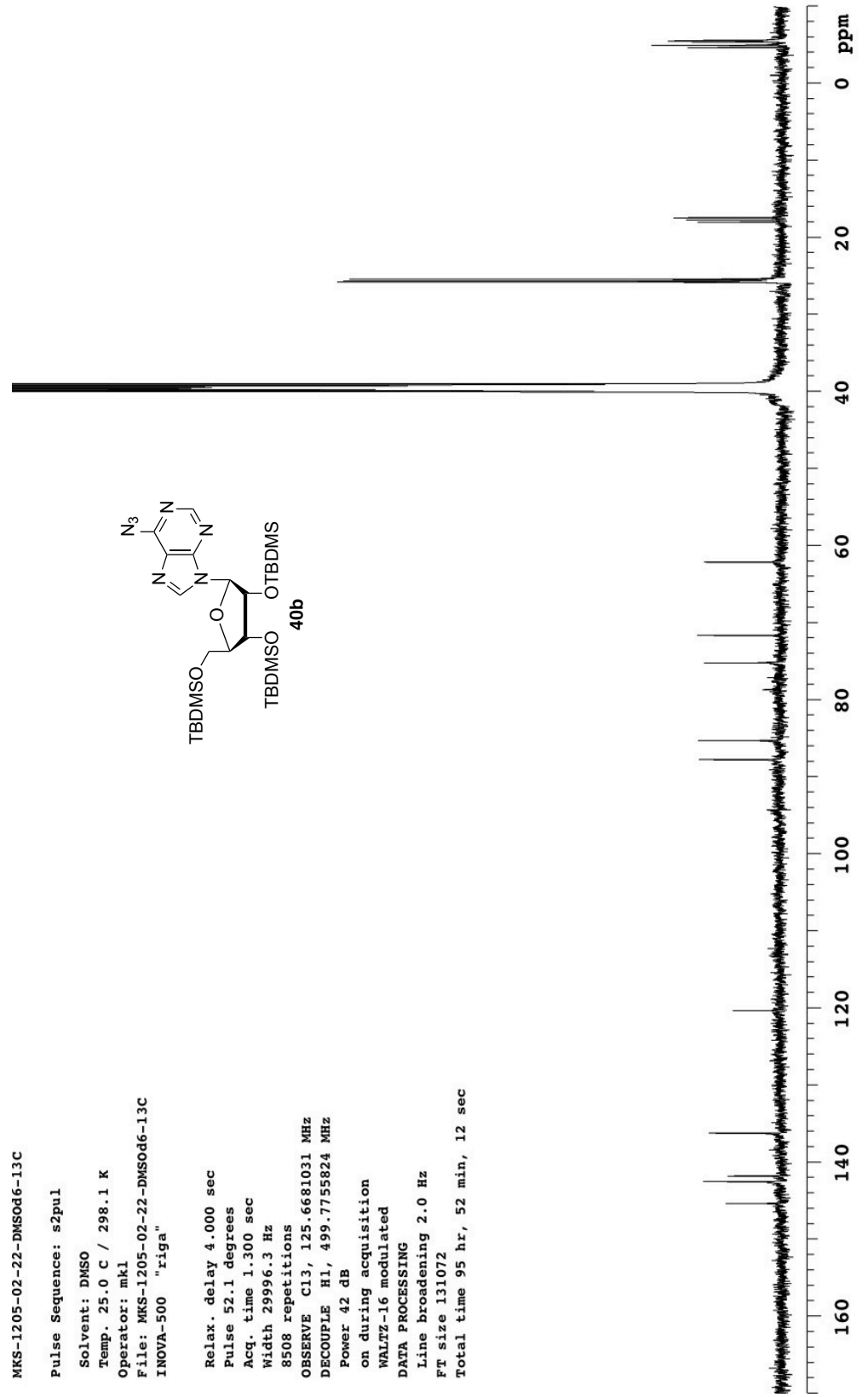
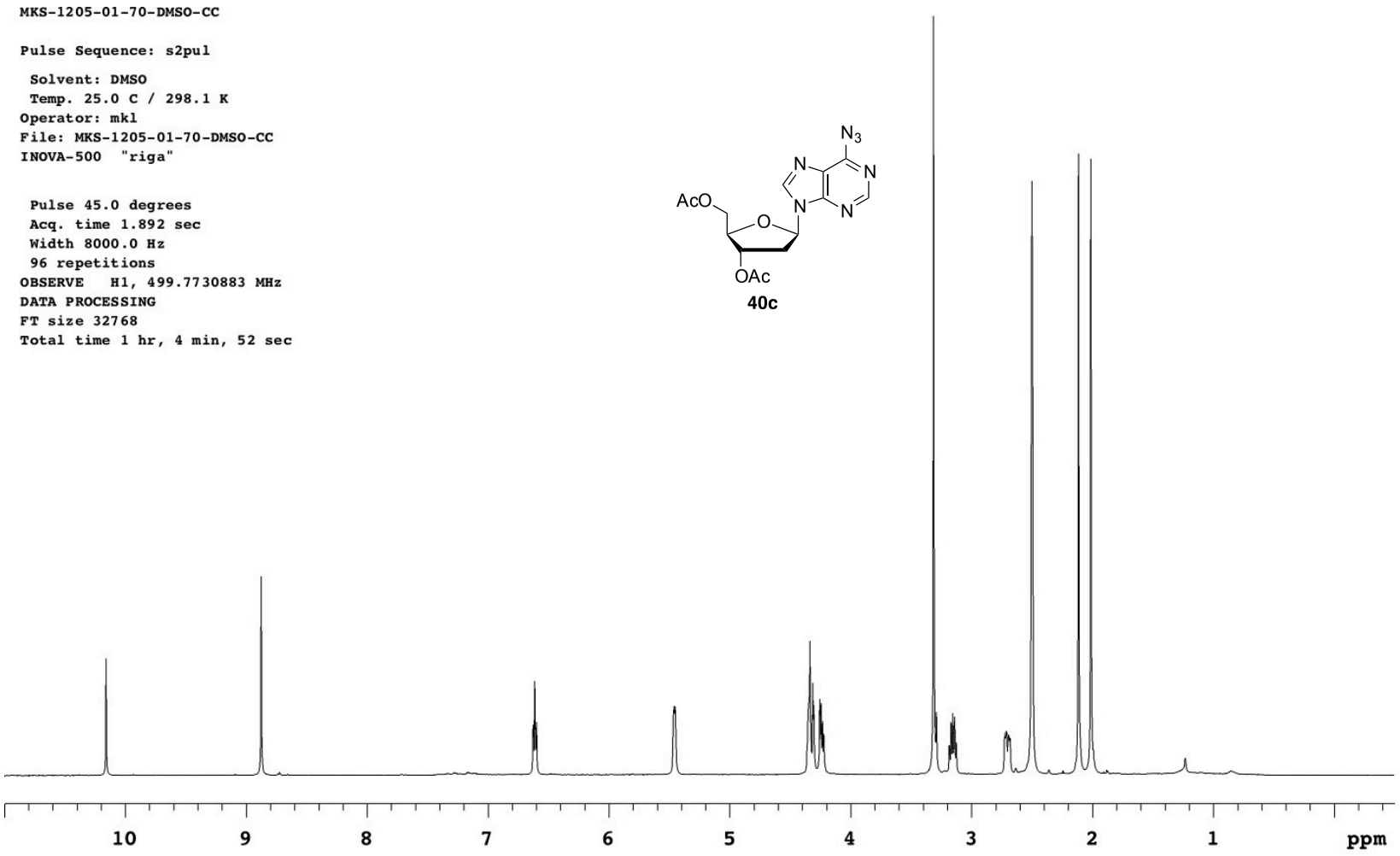
TBDMSO
OTBDMS
40a
10
9
8
7
6
5
4
3
2
1
ppm

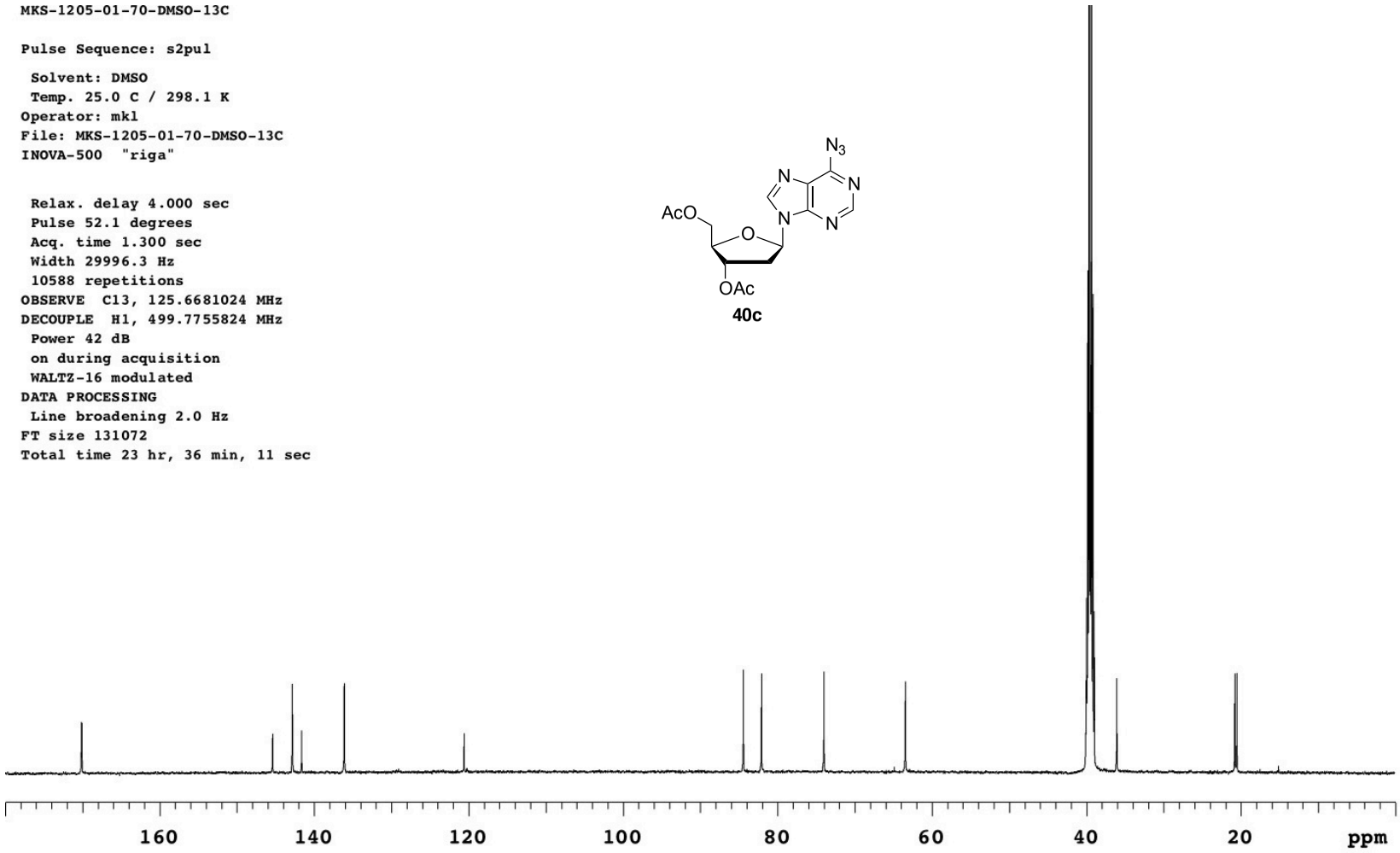

MKS-1205-02-25-DMSO-13C-CC
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-02-25-DMSO-13C-CC
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
8000 repetitions
OBSERVE C13, 125.6681060 MHz
DECOUPLE H1, 499.7755824 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 11 hr, 48 min, 16 sec
TBDMSO
OTBDMS
N3
160
140
120
100
80
60
40
20
0
ppm

40a


MKS-1205-02-22-DMSO-CC
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-02-22-DMSO-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
88 repetitions
OBSERVE H1, 499.7730883 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
N3
TBDMSO
TBDMSO
OTBDMS
40b
10
9
8
7
6
5
4
3
2
1
ppm


MKS-1205-02-22-DMSOd6-13C
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-02-22-DMSOd6-13C
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
8508 repetitions
OBSERVE C13, 125.6681031 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 95 hr, 52 min, 12 sec
N3
TBDMSO
OTBDMS
TBDMSO
40b
160
140
120
100
80
60
40
20
0 ppm


MKS-1205-01-70-DMSO-CC
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-01-70-DMSO-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
96 repetitions
OBSERVE H1, 499.7730883 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
N3
N
N
N
N
AcO
O
OAc
40c
10
9
8
7
6
5
4
3
2
1
ppm


MKS-1205-01-70-DMSO-13C
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-01-70-DMSO-13C
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
10588 repetitions
OBSERVE C13, 125.6681024 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 23 hr, 36 min, 11 sec
N3
N
N
N
N
AcO
O
OAc
160
140
120
100
80
60
40
20
ppm

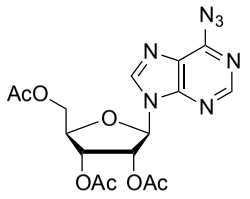
40c

MKS-1205-01-69-DMSO-CC

Pulse Sequence: s2pul

Solvent: DMSO
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-01-69-DMSO-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
104 repetitions
OBSERVE H1, 499.7730883 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



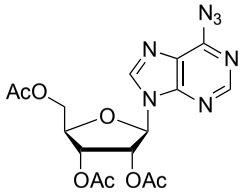
40d

MKS-1205-01-69-DMSO-13C

Pulse Sequence: s2pul

Solvent: DMSO
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-01-69-DMSO-13C
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
13288 repetitions
OBSERVE C13, 125.6681024 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 23 hr, 36 min, 11 sec



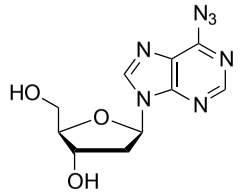
40d

MKS-1205-02-16-DMSO-AfterWash

Pulse Sequence: s2pul

Solvent: DMSO
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-02-16-DMSO-AfterWash
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
84 repetitions
OBSERVE H1, 499.7730864 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



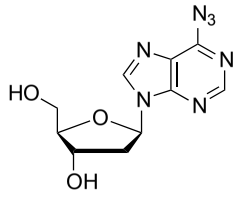
40e

MKS-1205-02-16-DMSO-13C

Pulse Sequence: s2pul

Solvent: DMSO
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-02-16-DMSO-13C-1
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
10944 repetitions
OBSERVE C13, 125.6681013 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 23 hr, 36 min, 11 sec



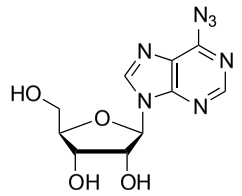
40e

MKS-1205-02-15-DMSO-3rdWash

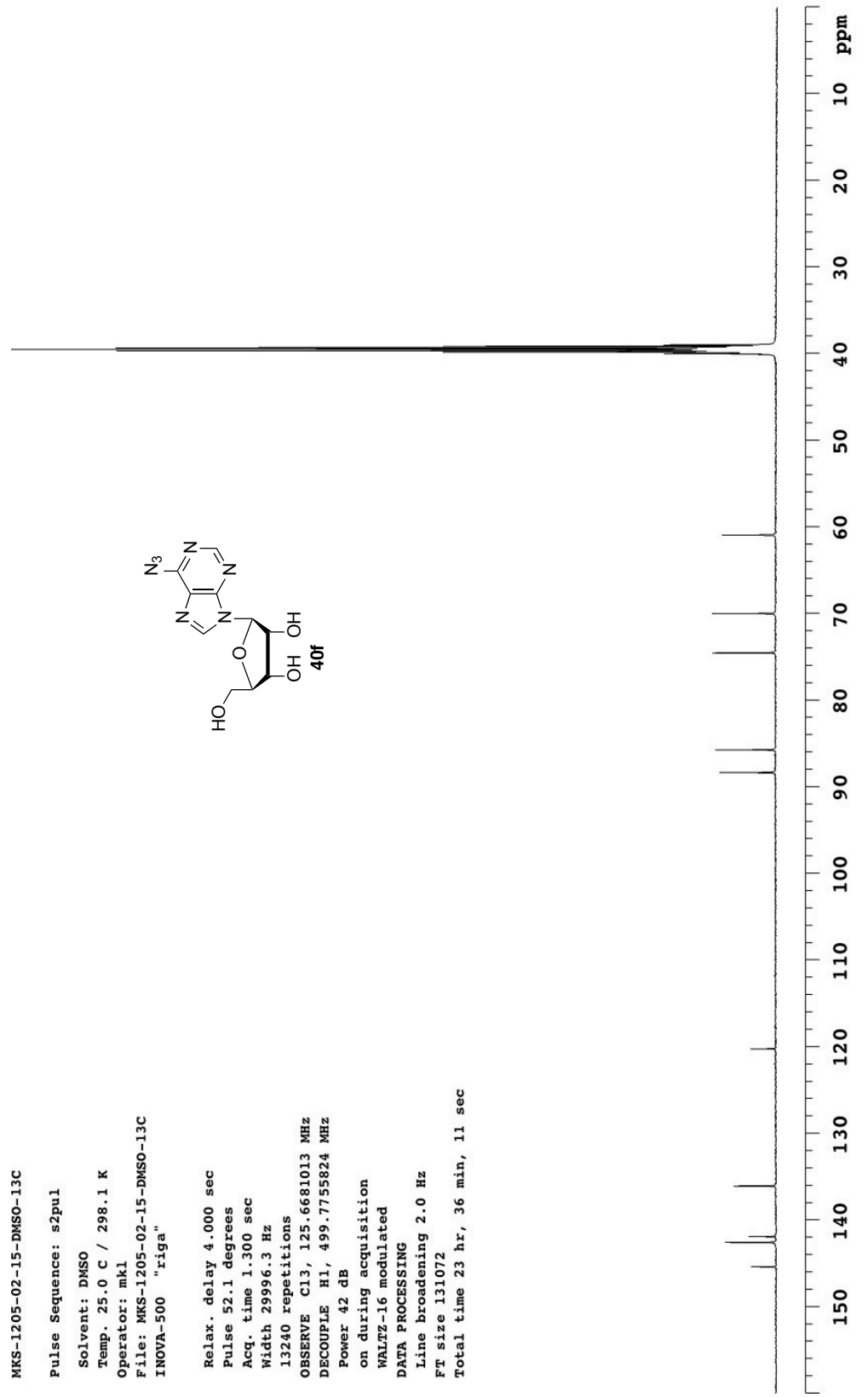
Pulse Sequence: s2pul

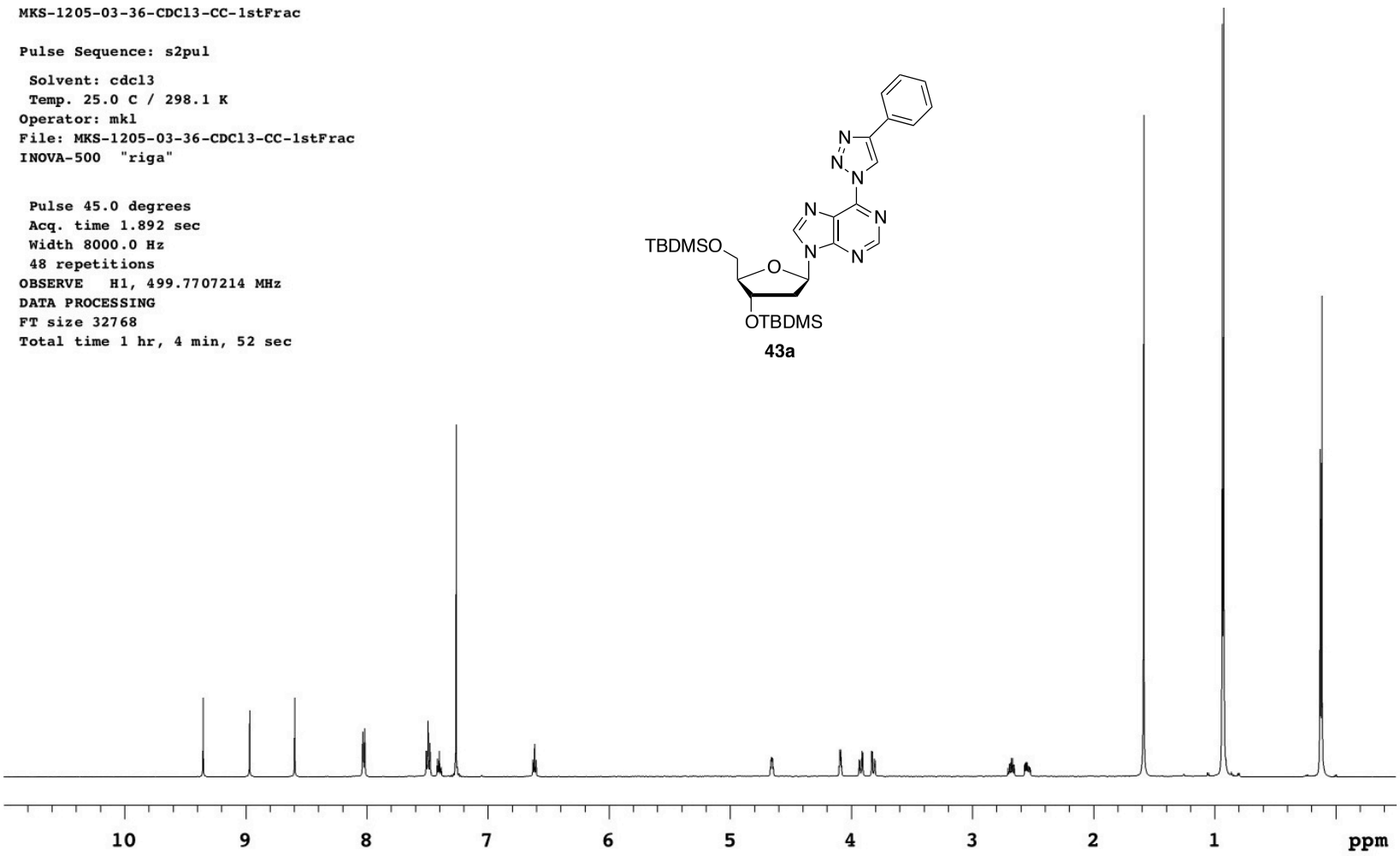
Solvent: DMSO
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-02-15-DMSO-3rdWash
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
76 repetitions
OBSERVE H1, 499.7730869 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



40f


MKS-1205-02-15-DMSO-13C
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-02-15-DMSO-13C
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
13240 repetitions
OBSERVE C13, 125.6681013 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 23 hr, 36 min, 11 sec
40f
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

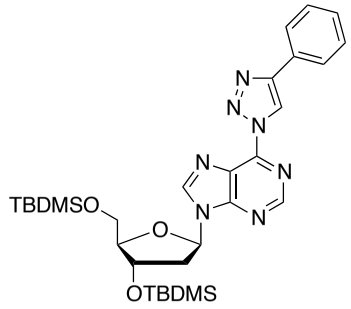

MKS-1205-03-36-CDCl3-CC-1stFrac
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-36-CDCl3-CC-1stFrac
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
48 repetitions
OBSERVE H1, 499.7707214 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
TBDMSO
OTBDMS
43a
10
9
8
7
6
5
4
3
2
1
ppm

MKS-1205-03-36-CDCl3-13C

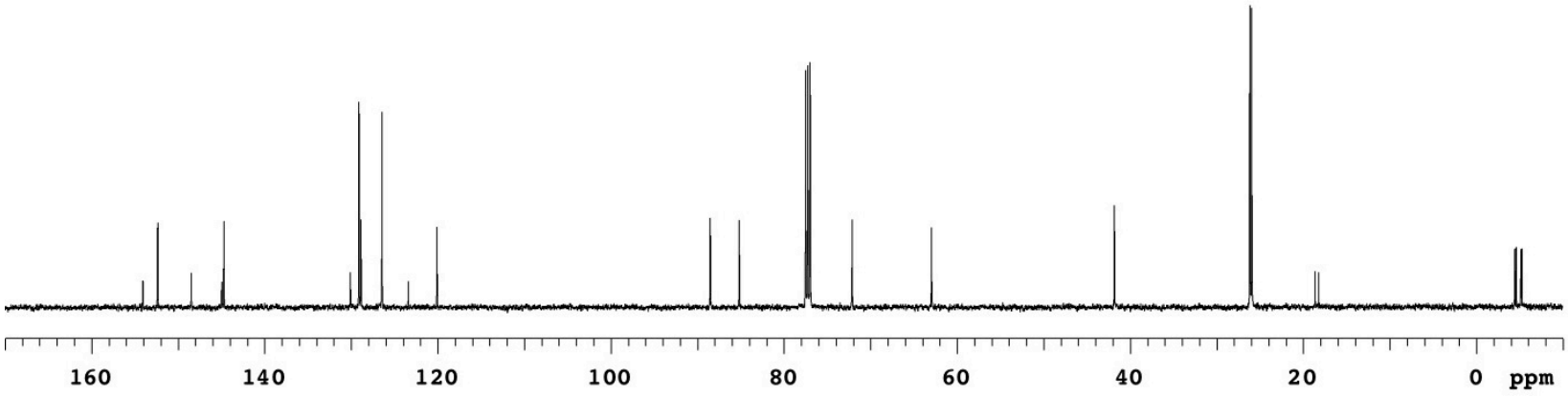
Pulse Sequence: s2pul

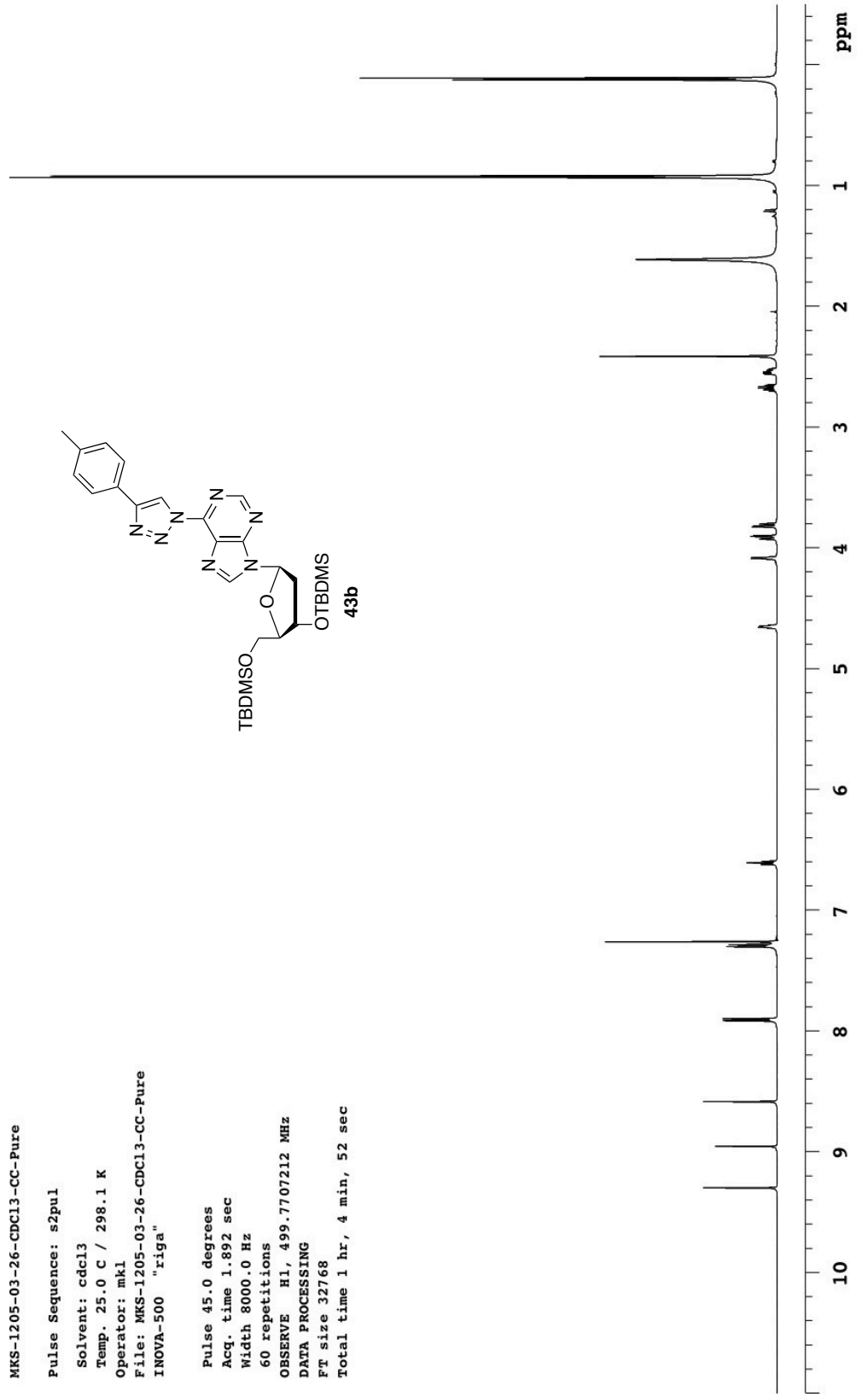
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-36-CDCl3-13C
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
788 repetitions
OBSERVE C13, 125.6674194 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 11 hr, 48 min, 16 sec



43a



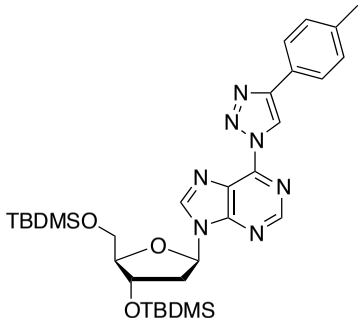

MKS-1205-03-26-CDCl3-CC-Pure
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-26-CDCl3-CC-Pure
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
60 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
TBDMSO
OTBDMS
43b
10
9
8
7
6
5
4
3
2
1
ppm

MKS-1205-03-26-CDCl3-13C-CC

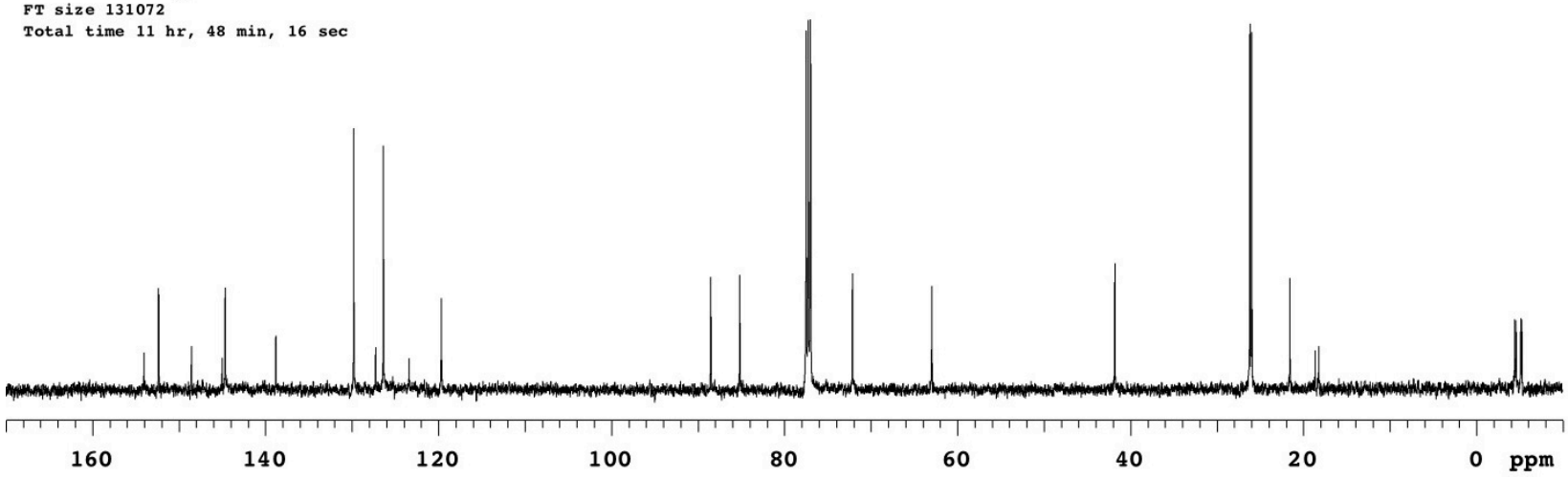
Pulse Sequence: s2pul

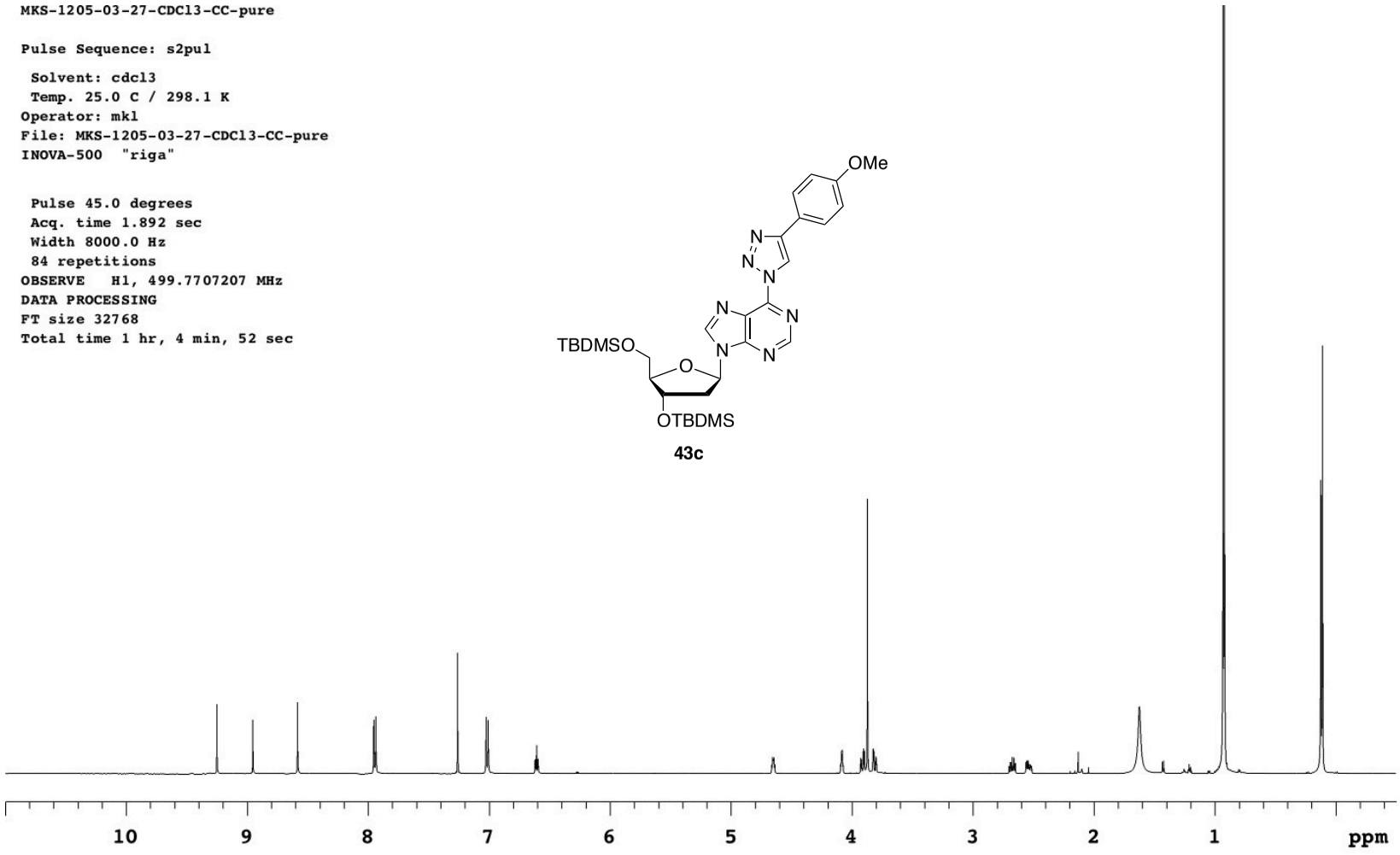
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-26-CDCl3-13C-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
928 repetitions
OBSERVE C13, 125.6674188 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 11 hr, 48 min, 16 sec



43b



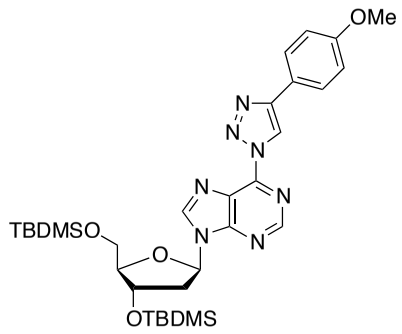

MKS-1205-03-27-CDCl3-CC-pure
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-27-CDCl3-CC-pure
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
84 repetitions
OBSERVE H1, 499.7707207 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
OMe
TBDMSO
OTBDMS
43c
10
9
8
7
6
5
4
3
2
1
ppm

MKS-1205-03-27-CDCl3-13C

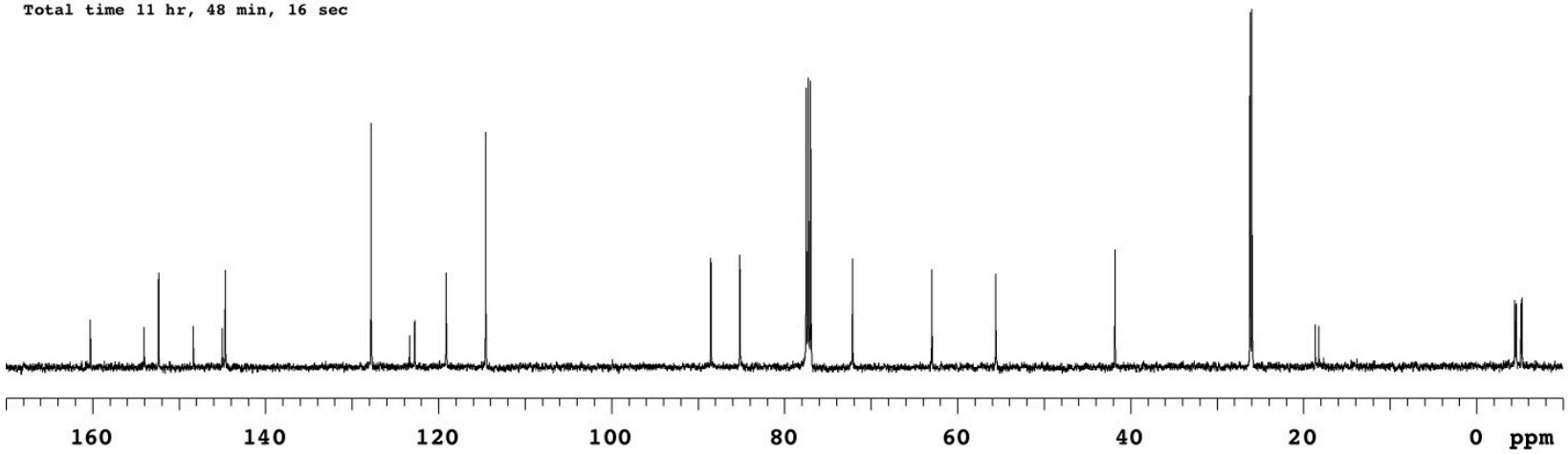
Pulse Sequence: s2pul

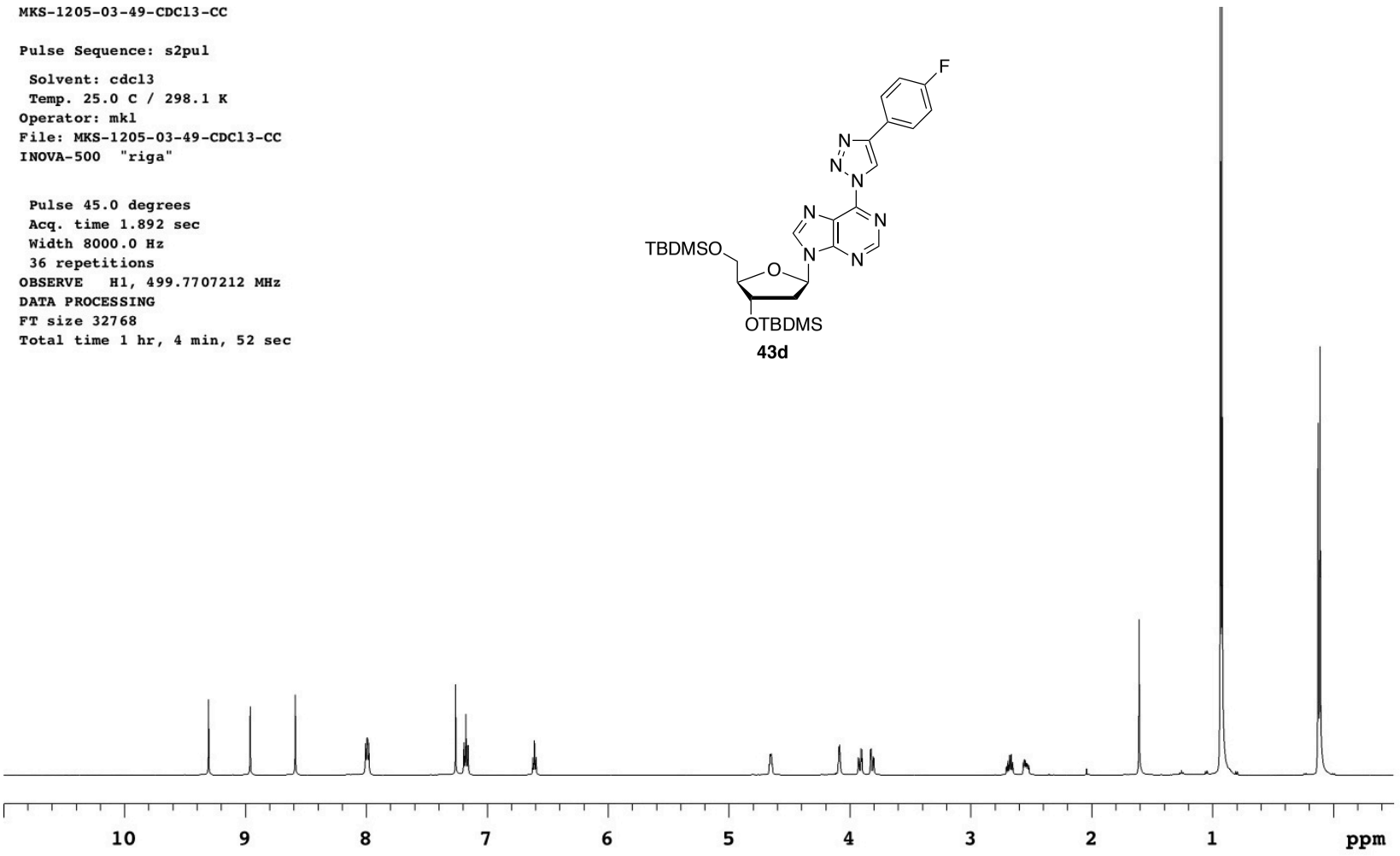
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-27-CDCl3-13C
INOVA-500 "riga"

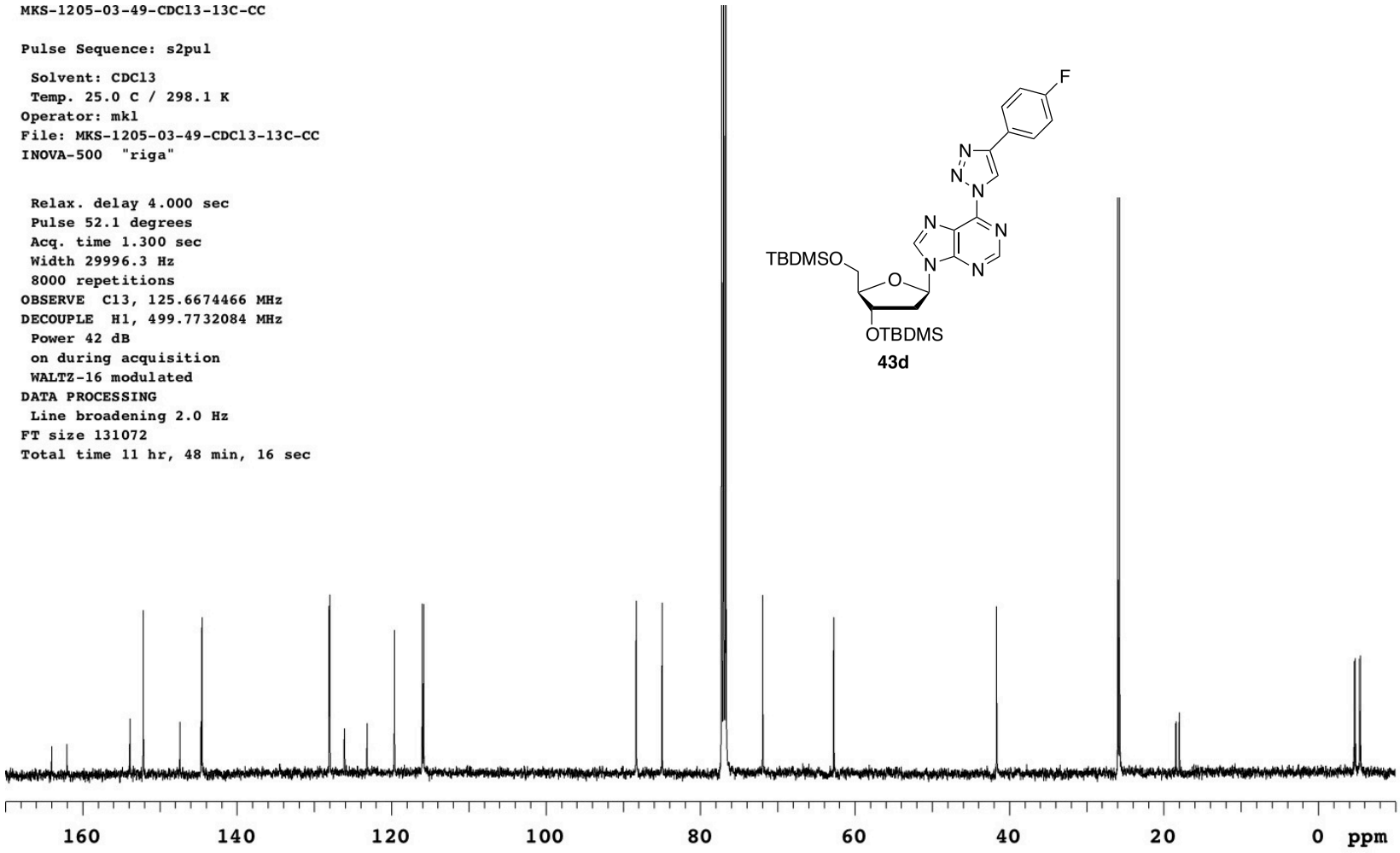
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
1028 repetitions
OBSERVE C13, 125.6674188 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 11 hr, 48 min, 16 sec



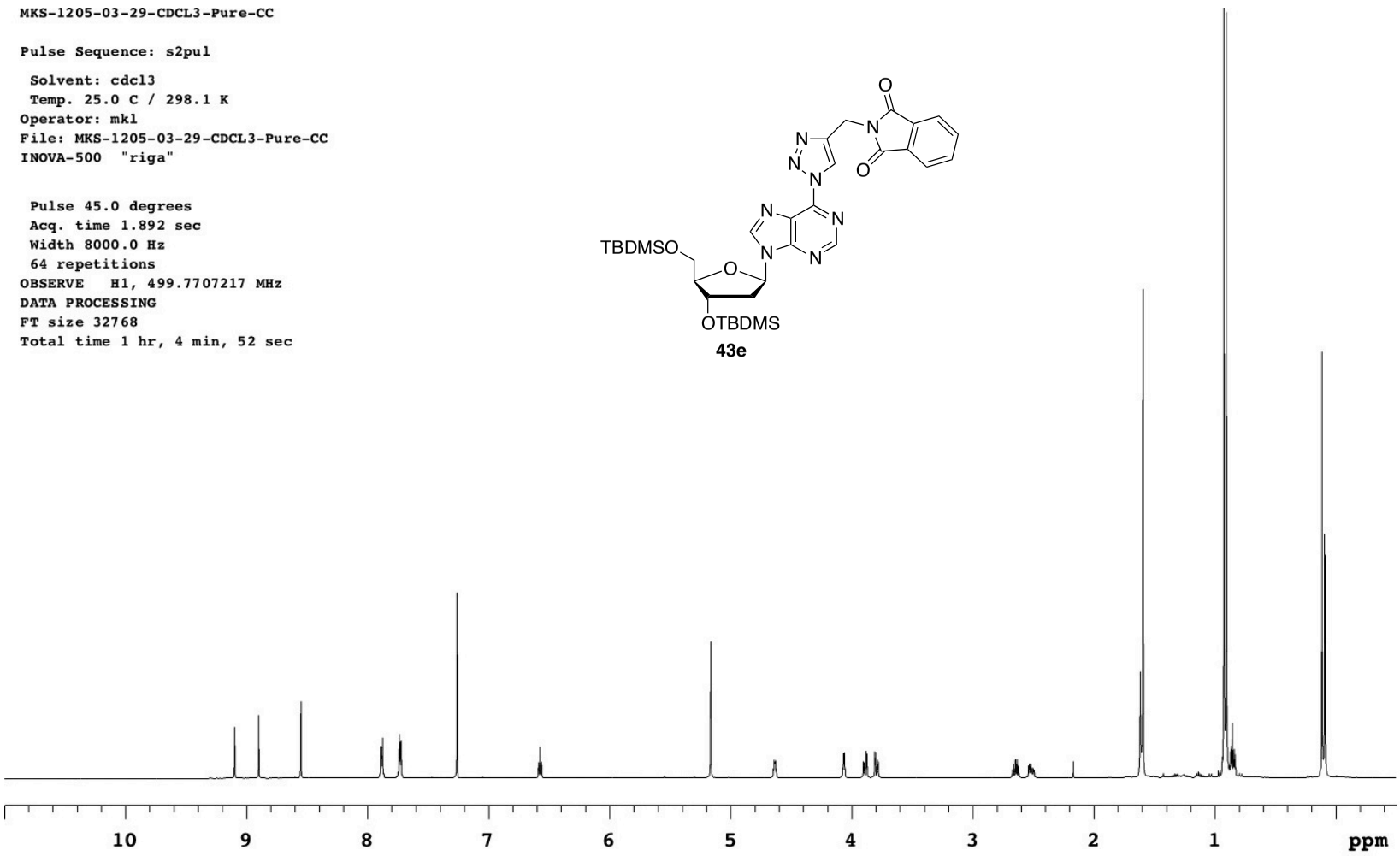
43c




MKS-1205-03-49-CDCl3-CC
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-49-CDCl3-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
36 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
F
N
N
N
N
N
N
N
TBDMSO
O
OTBDMS
43d
10
9
8
7
6
5
4
3
2
1
ppm


MKS-1205-03-49-CDCl3-13C-CC
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-49-CDCl3-13C-CC
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
8000 repetitions
OBSERVE C13, 125.6674466 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 11 hr, 48 min, 16 sec
F
N
N
N
N
N
N
TBDMSO
O
OTBDMS
160
140
120
100
80
60
40
20
0
ppm

43d

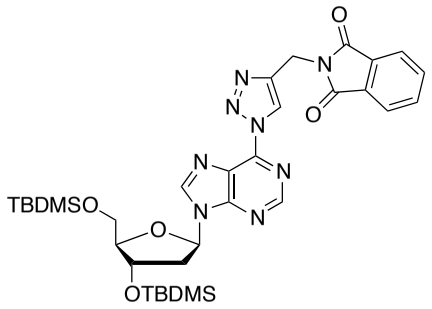

MKS-1205-03-29-CDCL3-Pure-CC
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-29-CDCL3-Pure-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
TBDMSO
OTBDMS
43e
10
9
8
7
6
5
4
3
2
1
ppm

MKS-1205-03-29-CDCl3-13C-CC

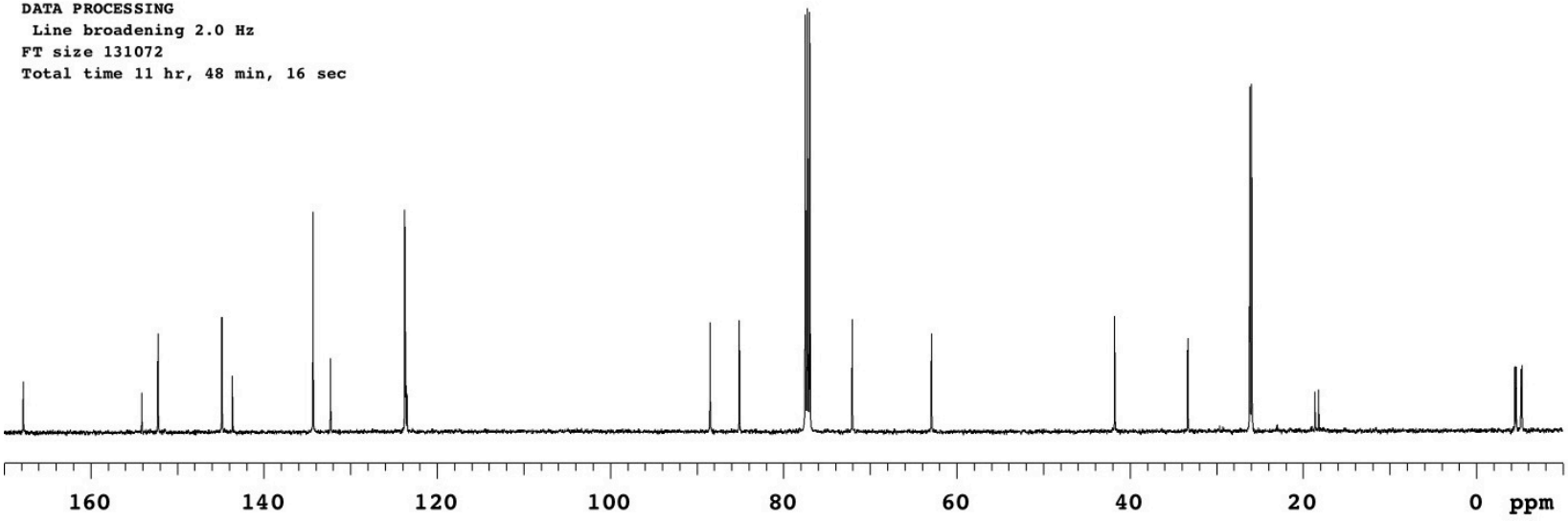
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-29-CDCl3-13C-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
8000 repetitions
OBSERVE C13, 125.6674190 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 11 hr, 48 min, 16 sec



43e

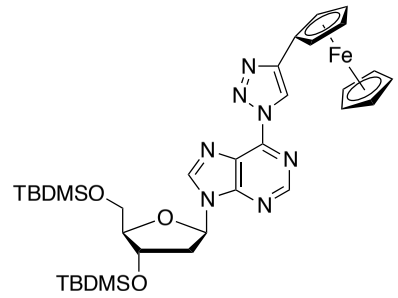


MKS-1205-03-53-CDCl3-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-53-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
100 repetitions
OBSERVE H1, 499.7707209 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



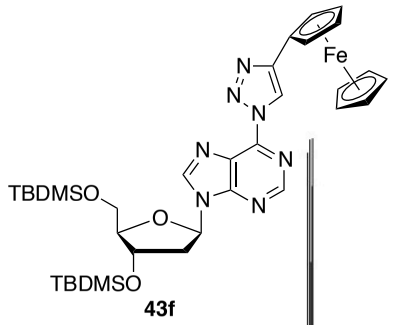
43f

MKS-1205-03-53-CDCl3-13C-CC

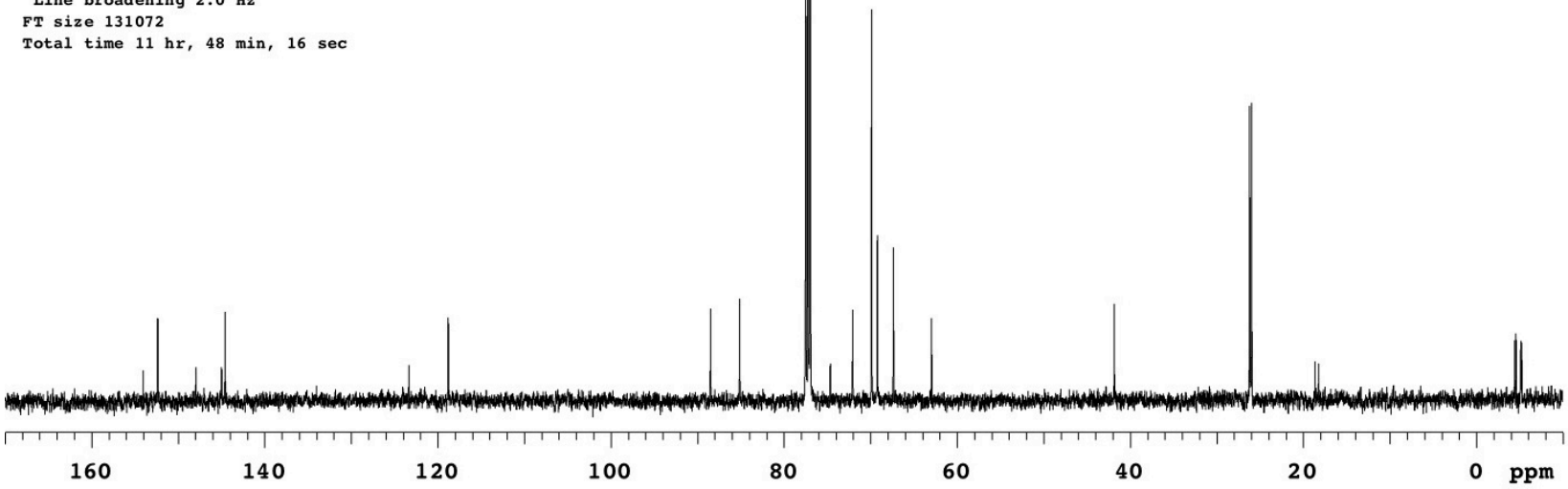
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-53-CDCl3-13C-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
784 repetitions
OBSERVE C13, 125.6674190 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 11 hr, 48 min, 16 sec



43f



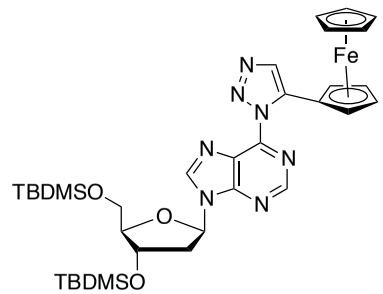
MKS-1205-03-53-CDCl3-2ndFrac-CC

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

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-53-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
92 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



43f'

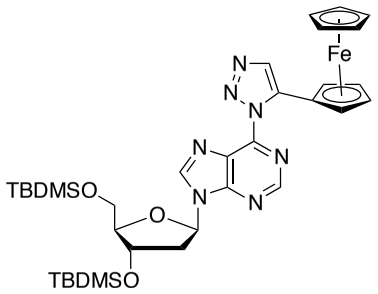
MKS-1205-03-53-CDCl3-13C-2ndFrac

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

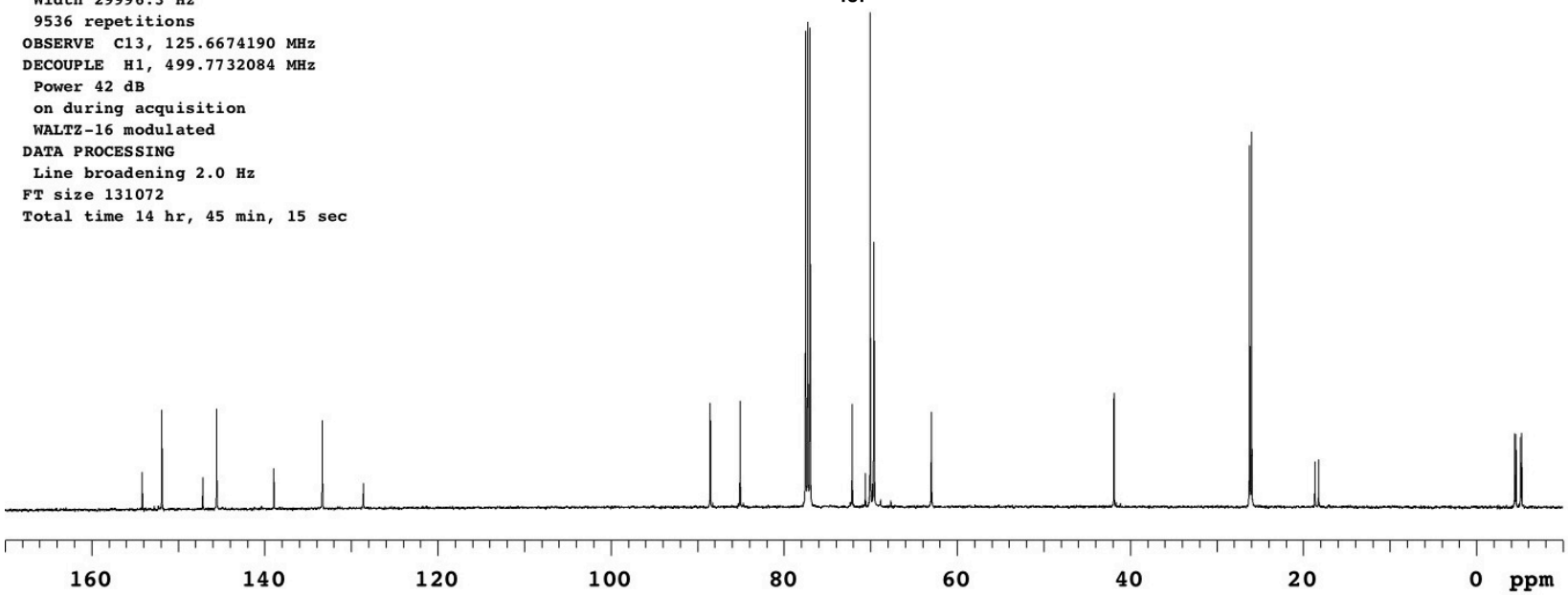
Pulse Sequence: s2pul

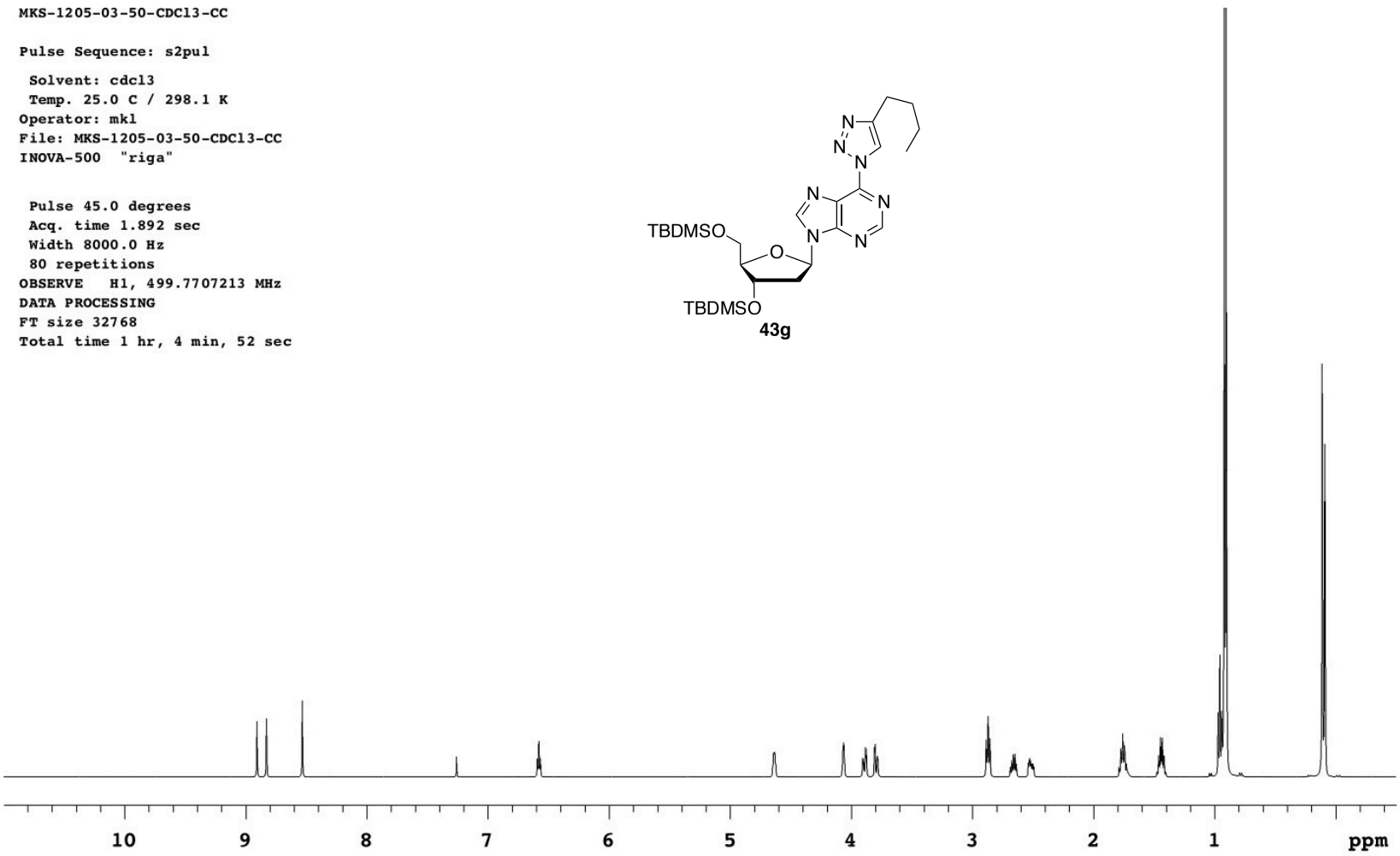
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-53-CDCl3-13C-2ndFrac
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
9536 repetitions
OBSERVE C13, 125.6674190 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



43f'



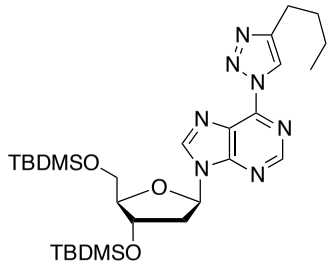

MKS-1205-03-50-CDCl3-CC
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-50-CDCl3-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
80 repetitions
OBSERVE H1, 499.7707213 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
TBDMSO
TBDMSO
43g
10
9
8
7
6
5
4
3
2
1
ppm

MKS-1205-03-50-CDCl3-13C-CC

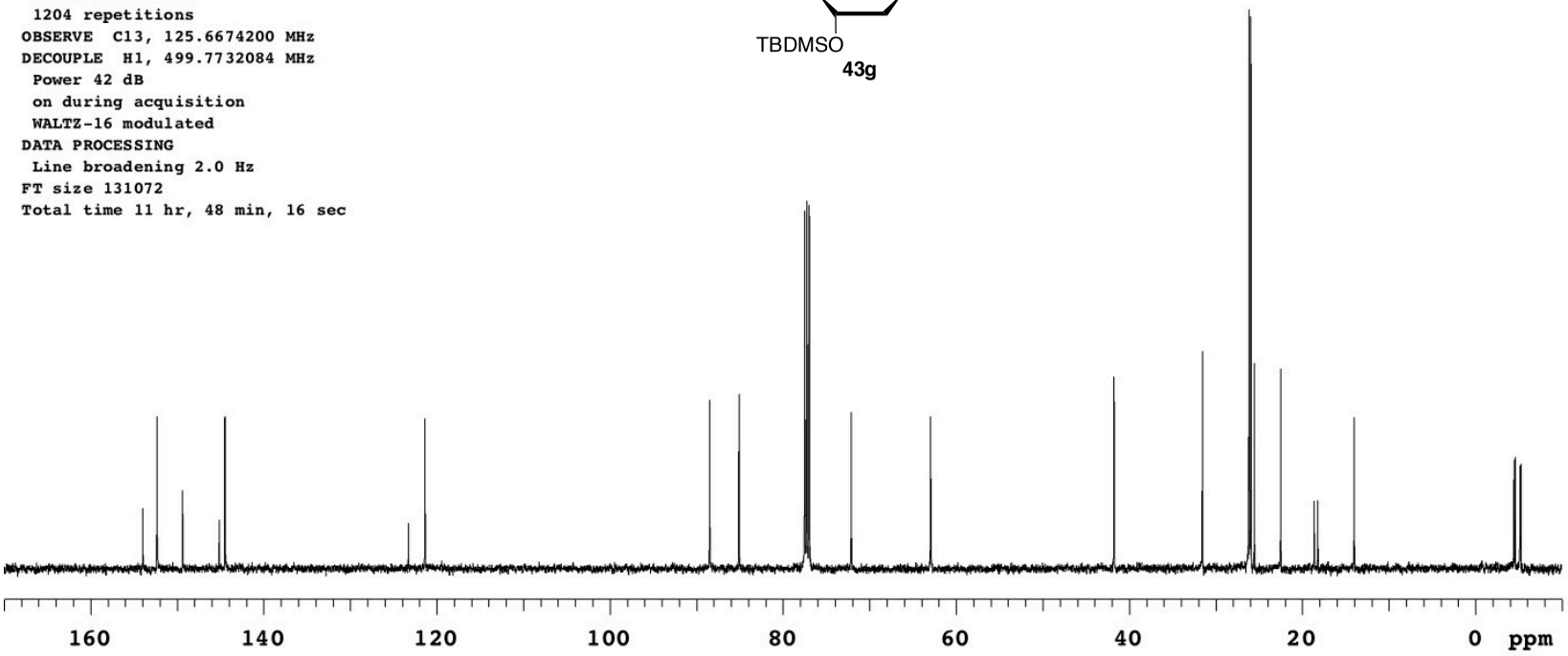
Pulse Sequence: s2pul

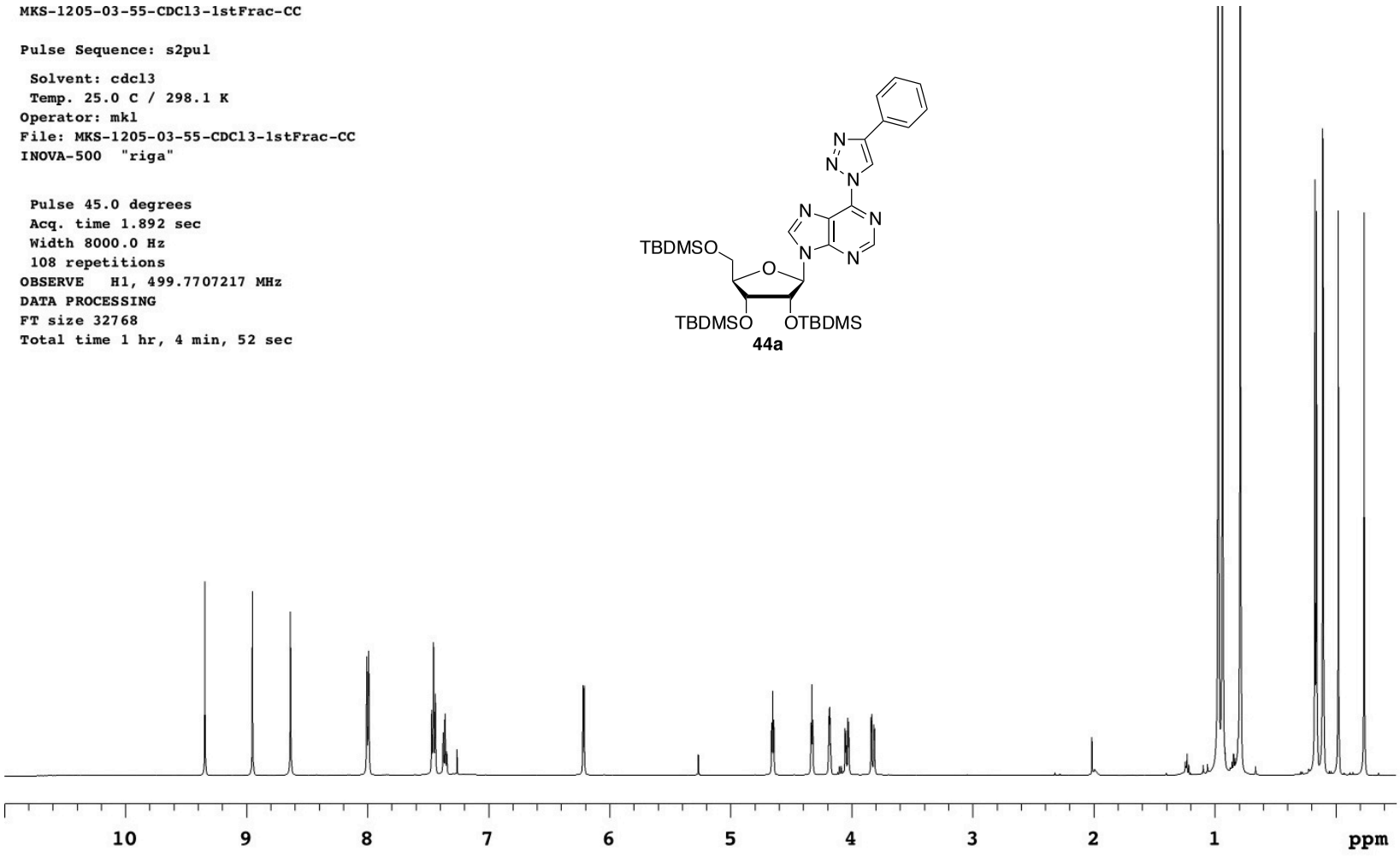
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-50-CDCl3-13C-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
1204 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 11 hr, 48 min, 16 sec



43g



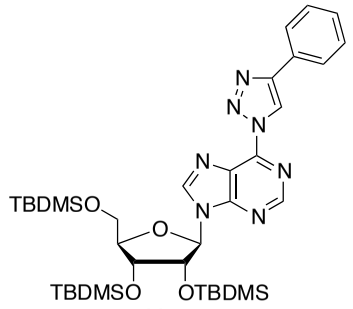

MKS-1205-03-55-CDCl3-1stFrac-CC
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-55-CDCl3-1stFrac-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
108 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
TBDMSO
TBDMSO
OTBDMS
44a
10
9
8
7
6
5
4
3
2
1
ppm

MKS-1205-03-55-CDCl3-13C-1stFrac-CC

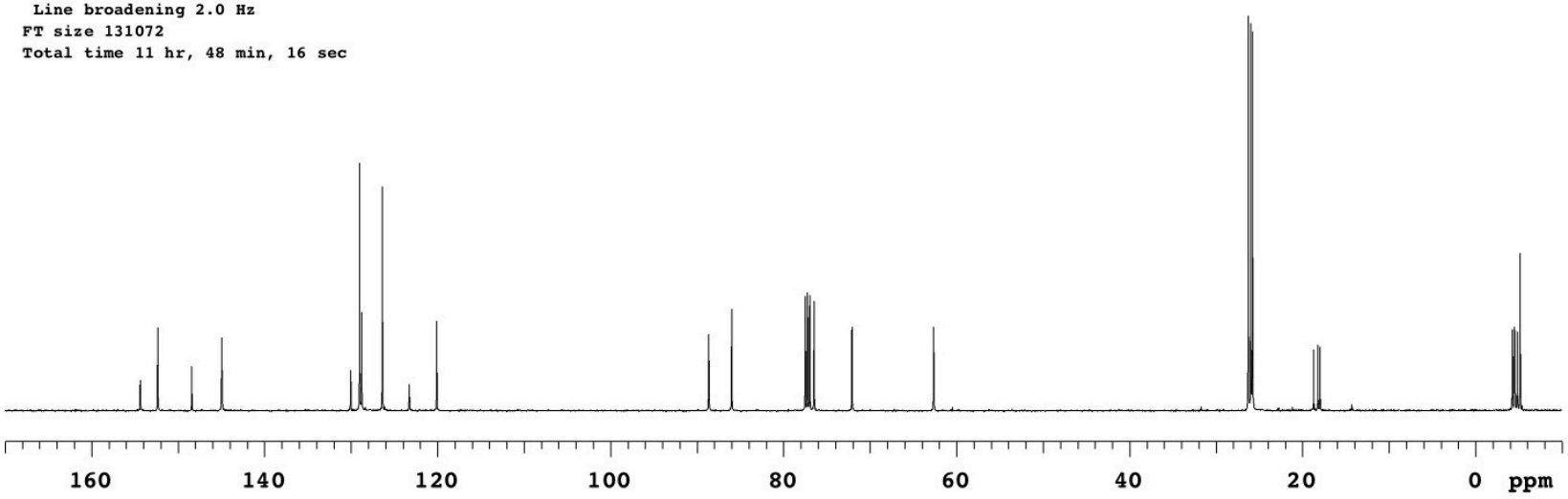
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-55-CDCl3-13C-1stFrac-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
1392 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 11 hr, 48 min, 16 sec



44a



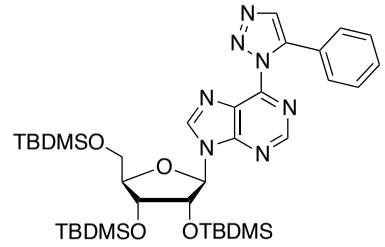
MKS-1205-03-55-CDCl3-2ndFrac-CC

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

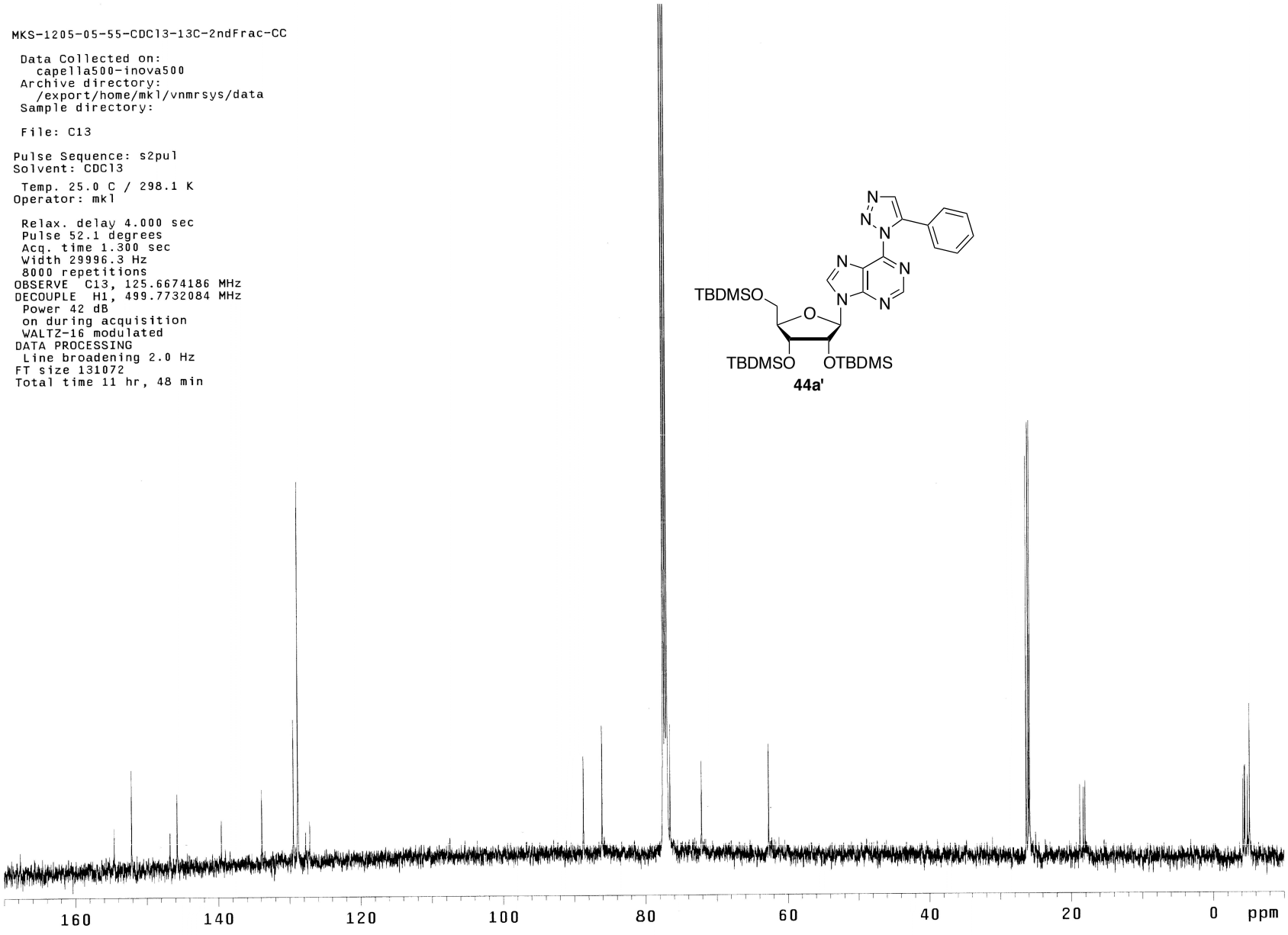
Pulse Sequence: s2pul

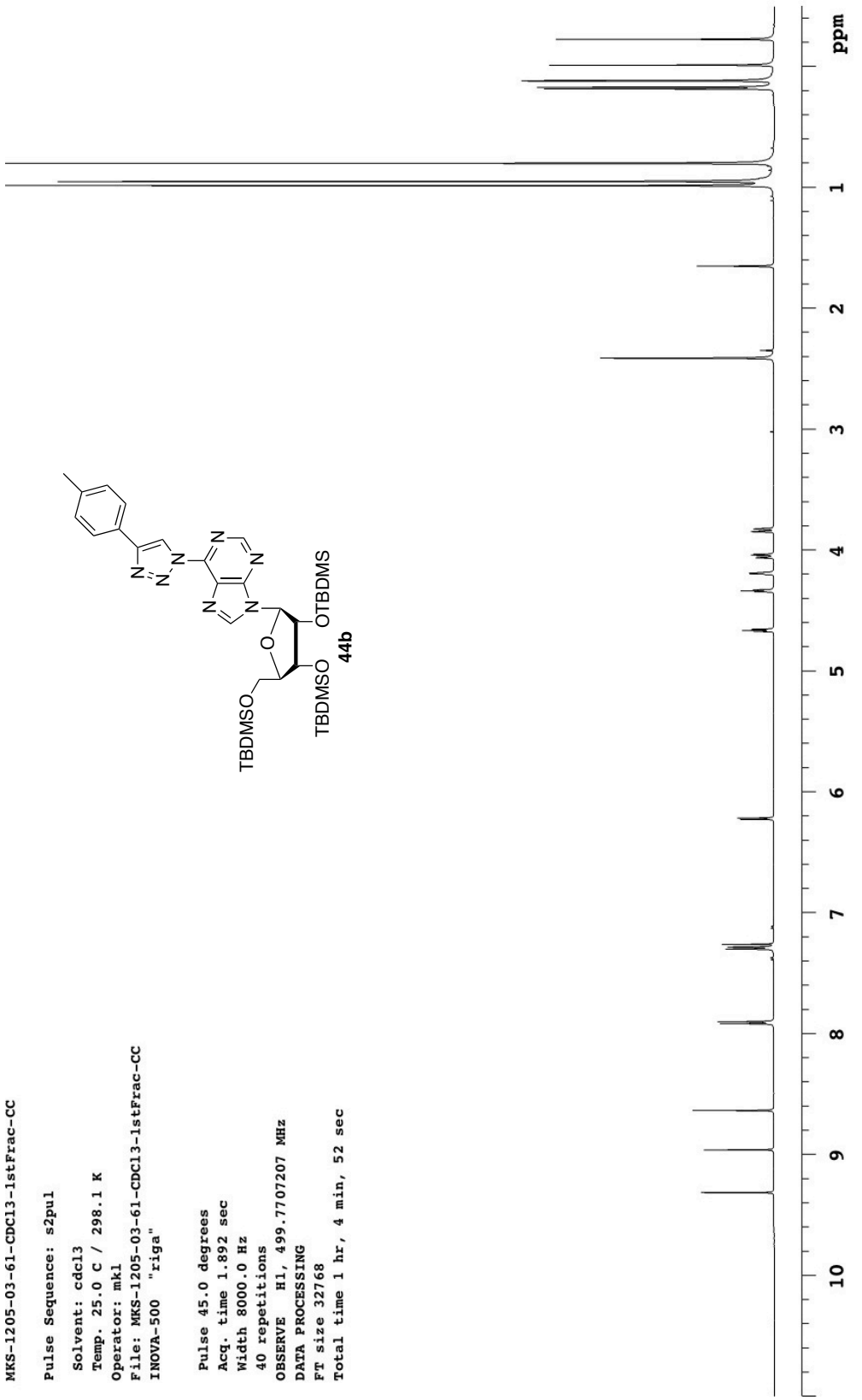
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-55-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
80 repetitions
OBSERVE H1, 499.7707214 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



44a'


MKS-1205-05-55-CDCl3-13C-2ndFrac-CC
Data Collected on:
capella500-inova500
Archive directory:
/export/home/mkl/vnmrsys/data
Sample directory:
File: C13
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
8000 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 11 hr, 48 min
TBDMSO
TBDMSO
OTBDMS
44a'
160
140
120
100
80
60
40
20
0
ppm

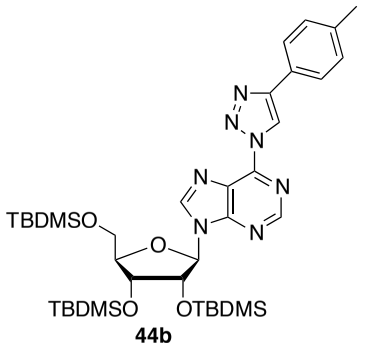

MKS-1205-03-61-CDCl3-1stFrac-CC
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-61-CDCl3-1stFrac-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
40 repetitions
OBSERVE H1, 499.7707207 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
TBDMSO
TBDMSO
OTBDMS
44b
ppm

MKS-1205-03-61-CDCl3-13C-1stFrac-CC

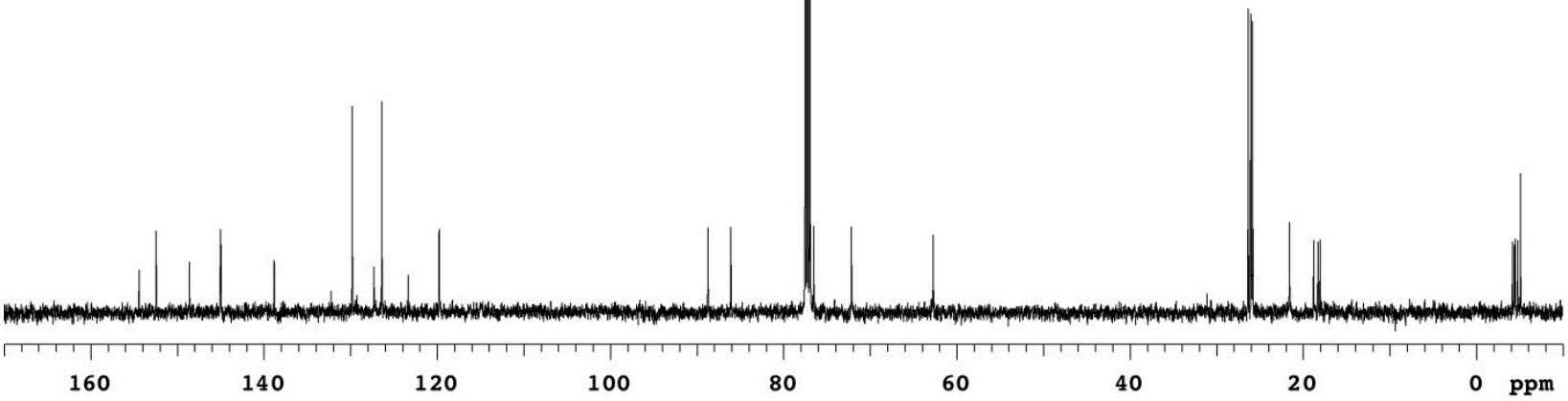
Pulse Sequence: s2pul

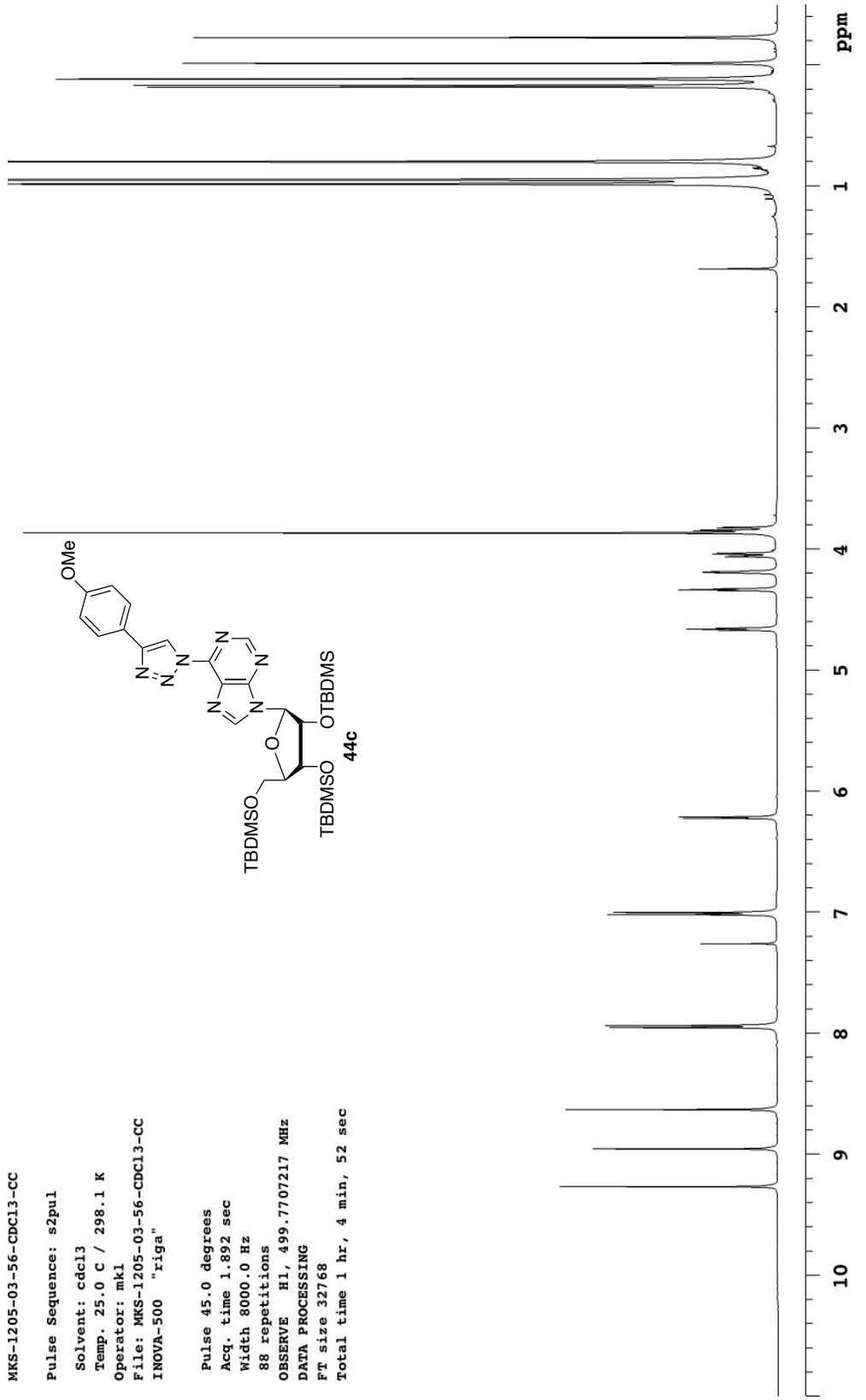
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-61-CDCl3-13C-1stFrac-CC
INOVA-500 "riga"

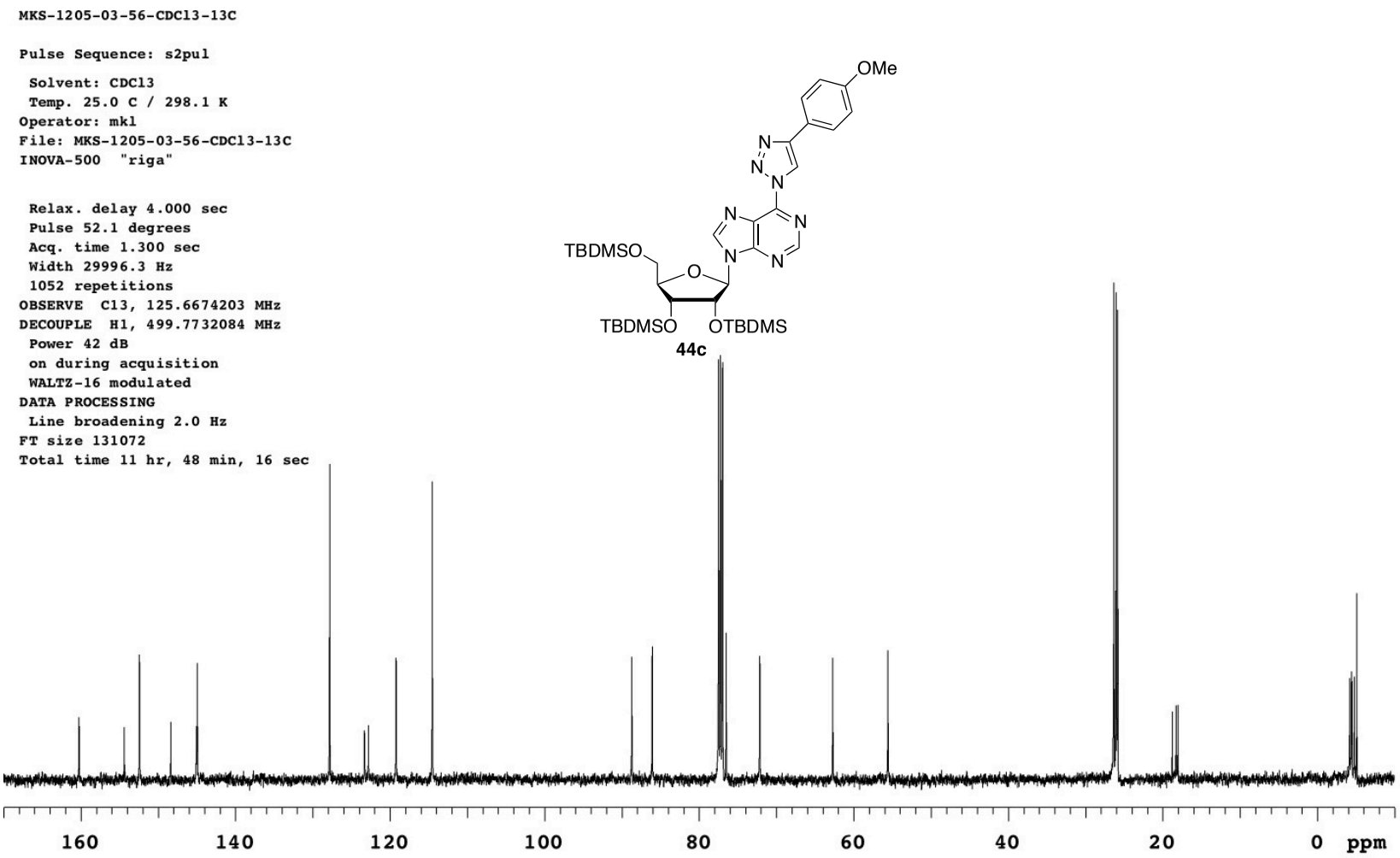
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
1000 repetitions
OBSERVE C13, 125.6674184 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 1 hr, 28 min, 50 sec

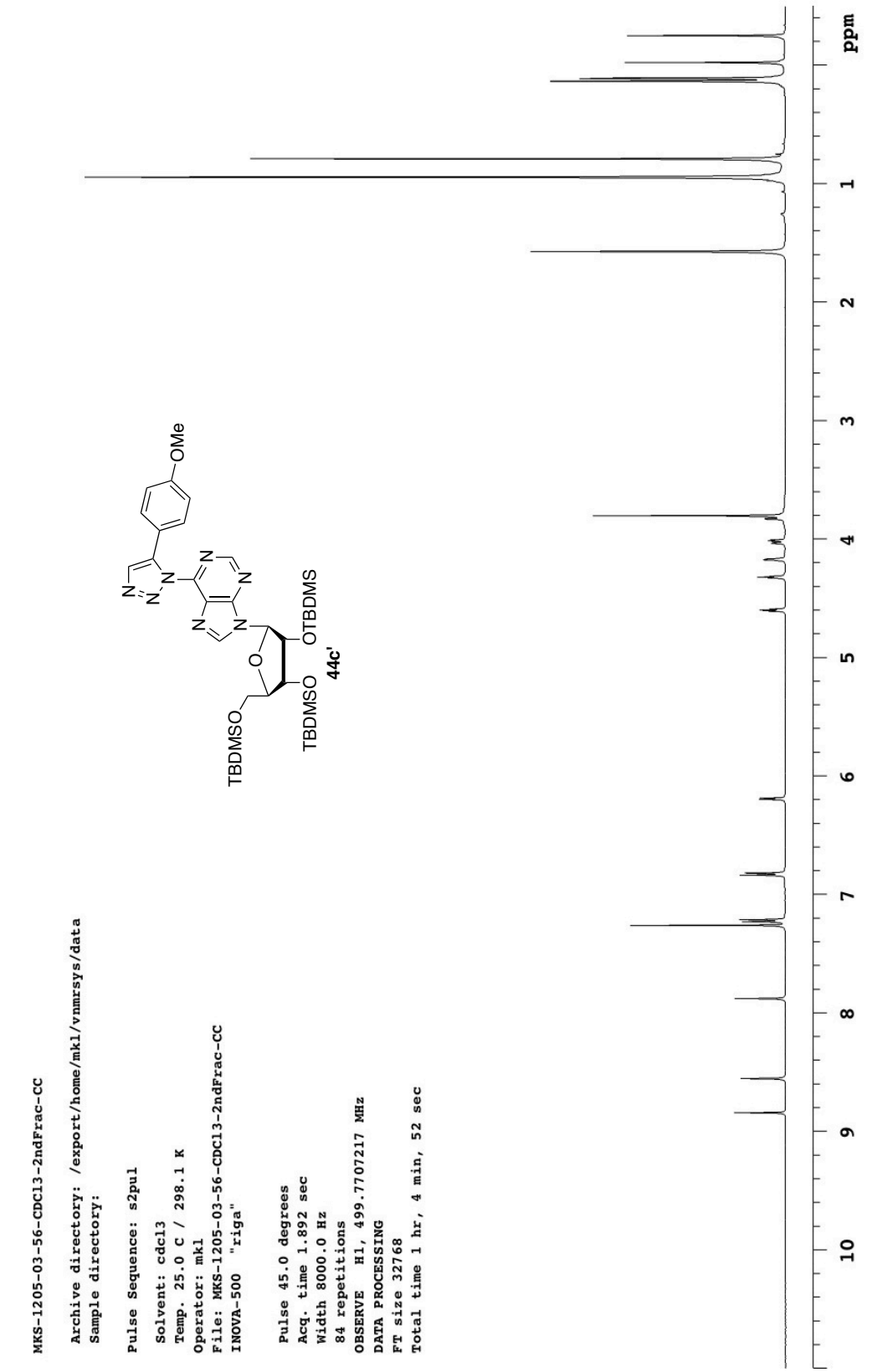


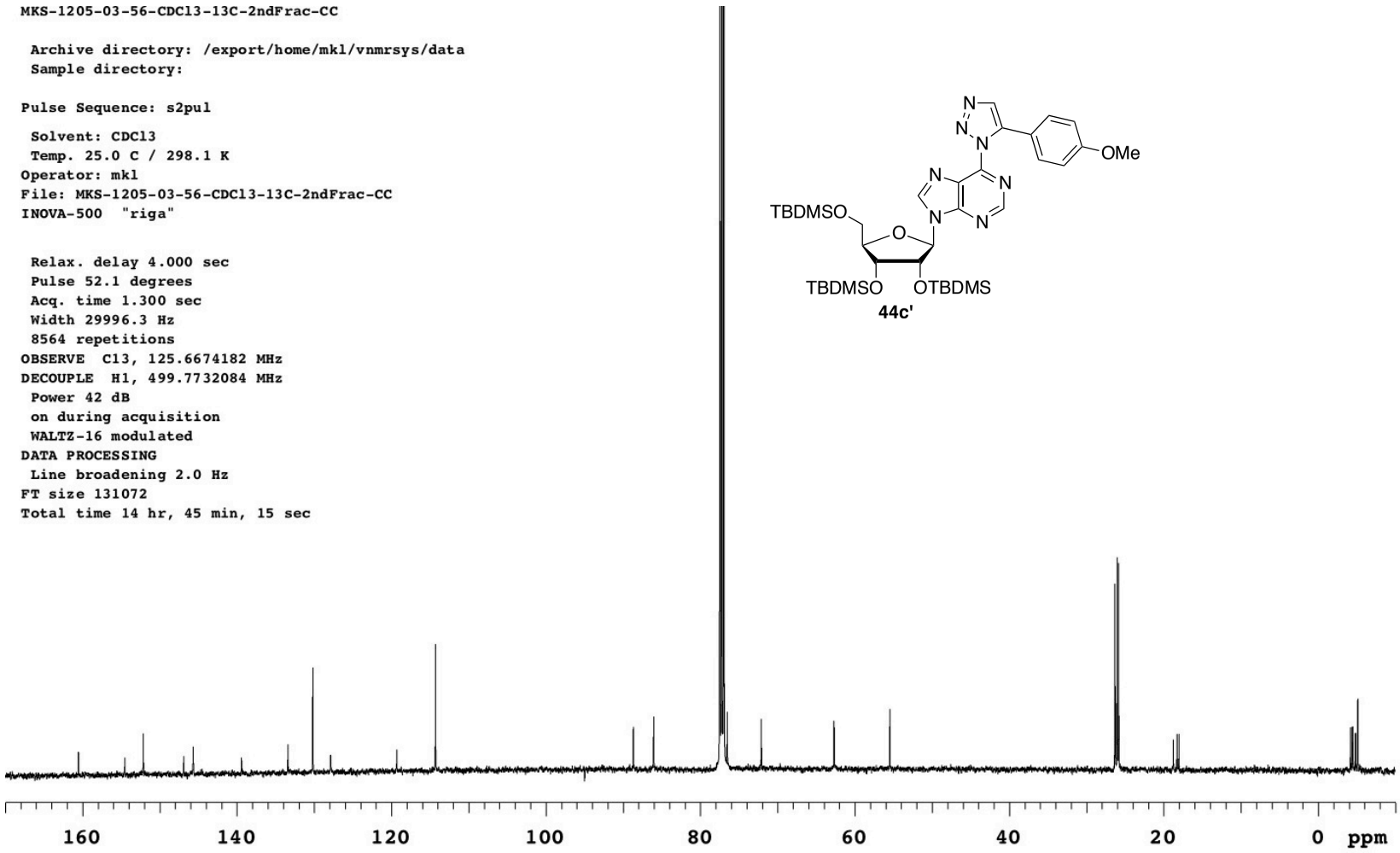
44b

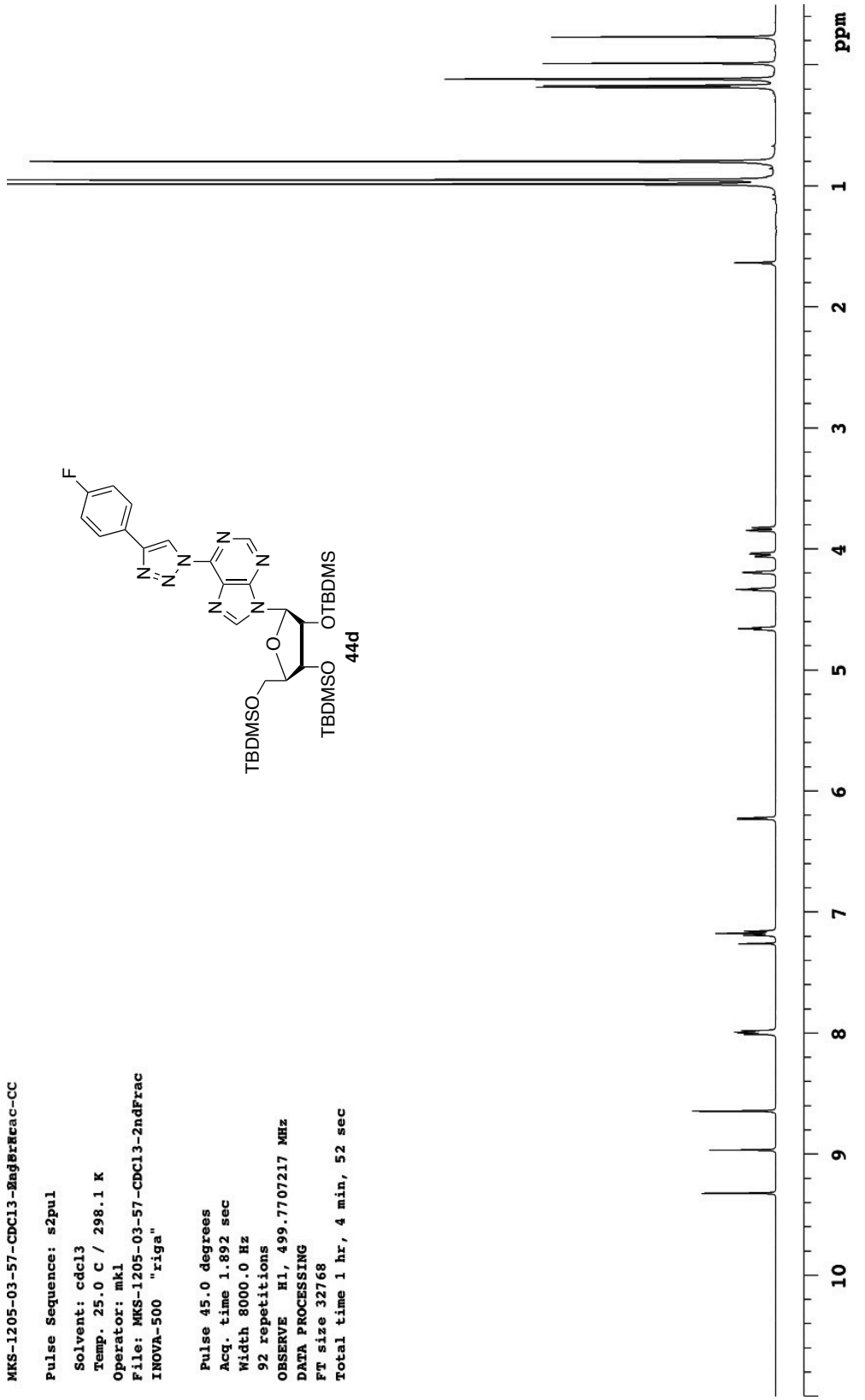


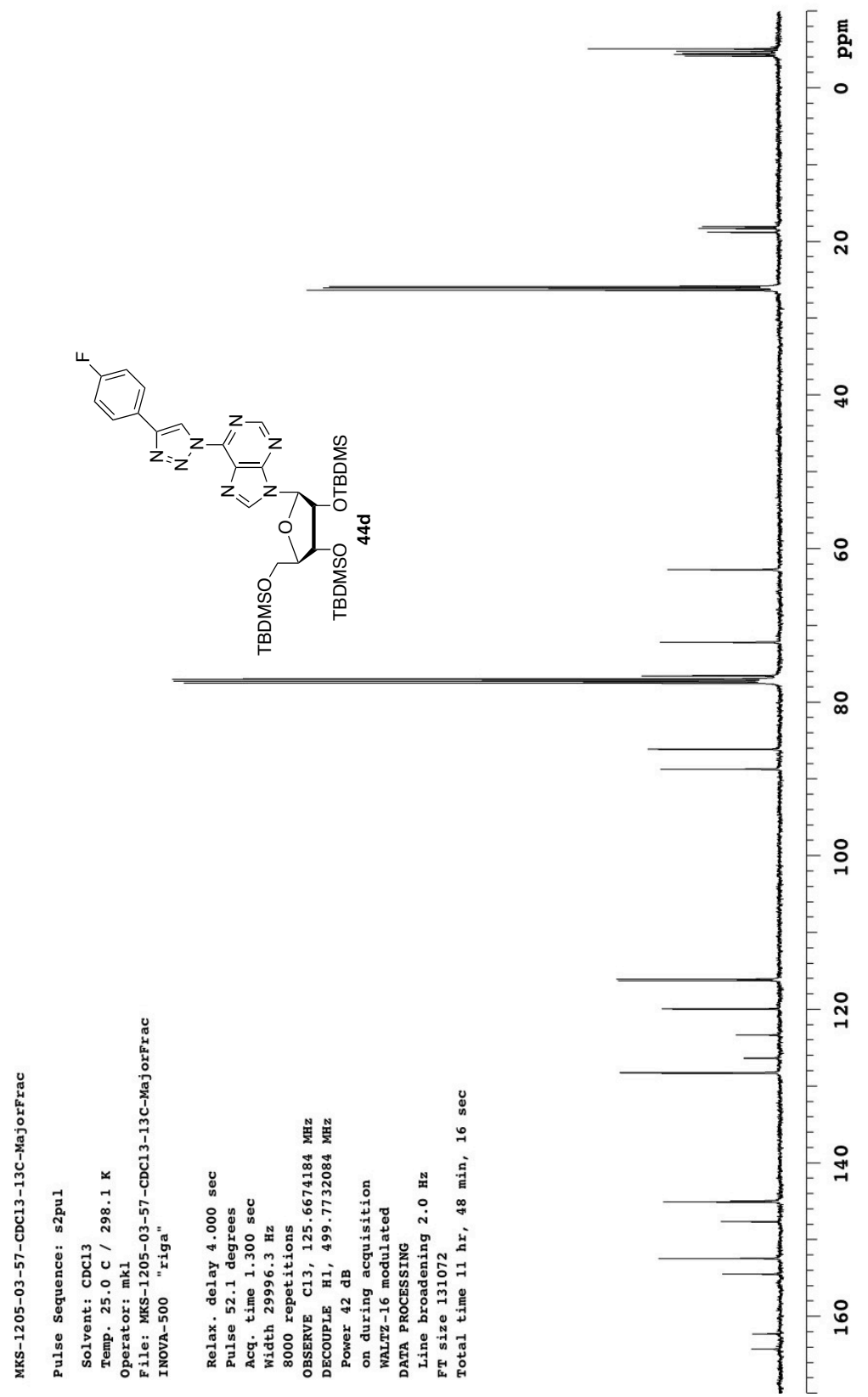

MKS-1205-03-56-CDCl3-CC
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-56-CDCl3-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
88 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
OMe
TBDMSO
TBDMSO
OTBDMS
44c
ppm

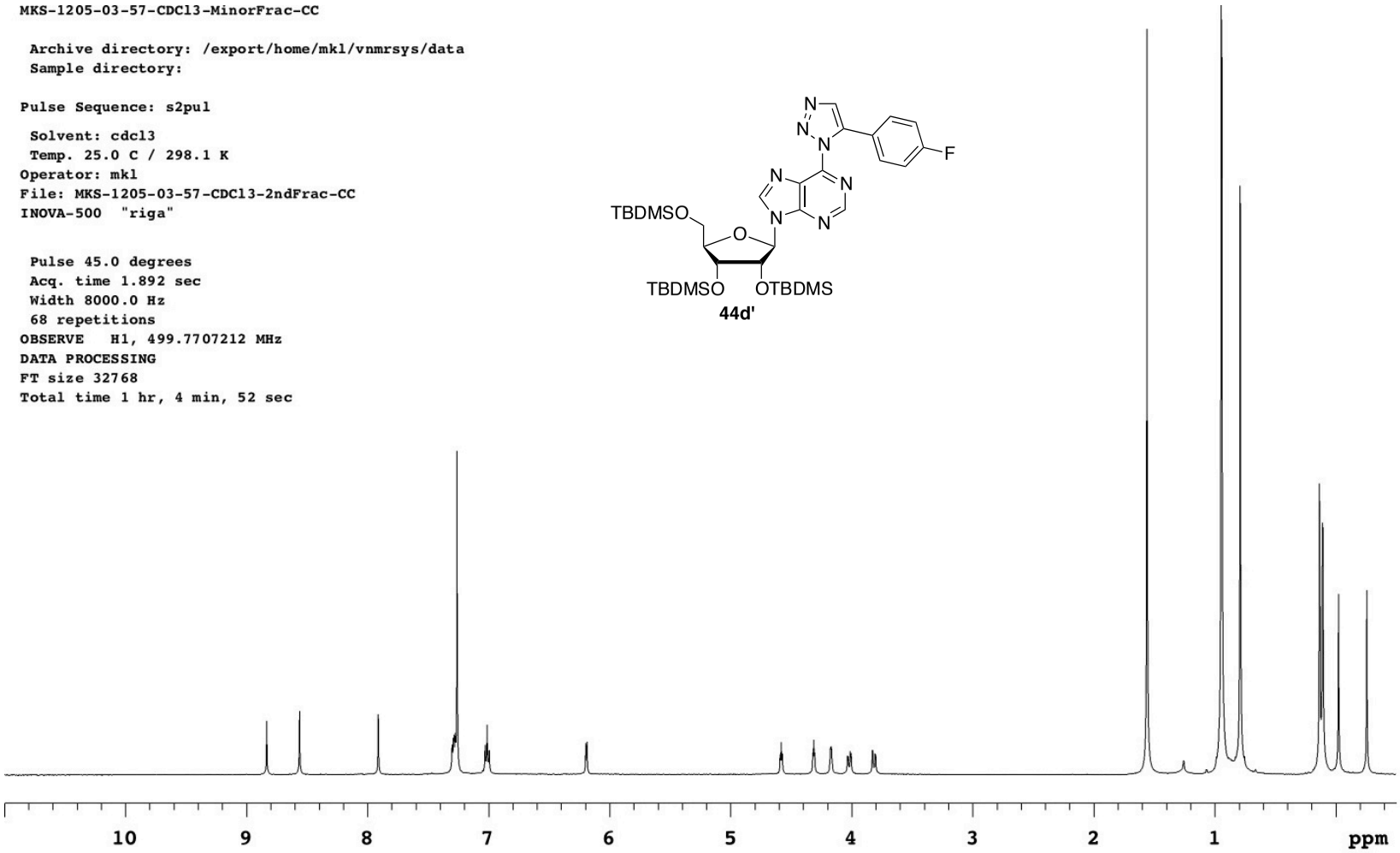

MKS-1205-03-56-CDCl3-13C
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-56-CDCl3-13C
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
1052 repetitions
OBSERVE C13, 125.6674203 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 11 hr, 48 min, 16 sec
OMe
N
N
N
N
N
N
N
TBDMSO
O
TBDMSO
OTBDMS
44c
160
140
120
100
80
60
40
20
0
ppm

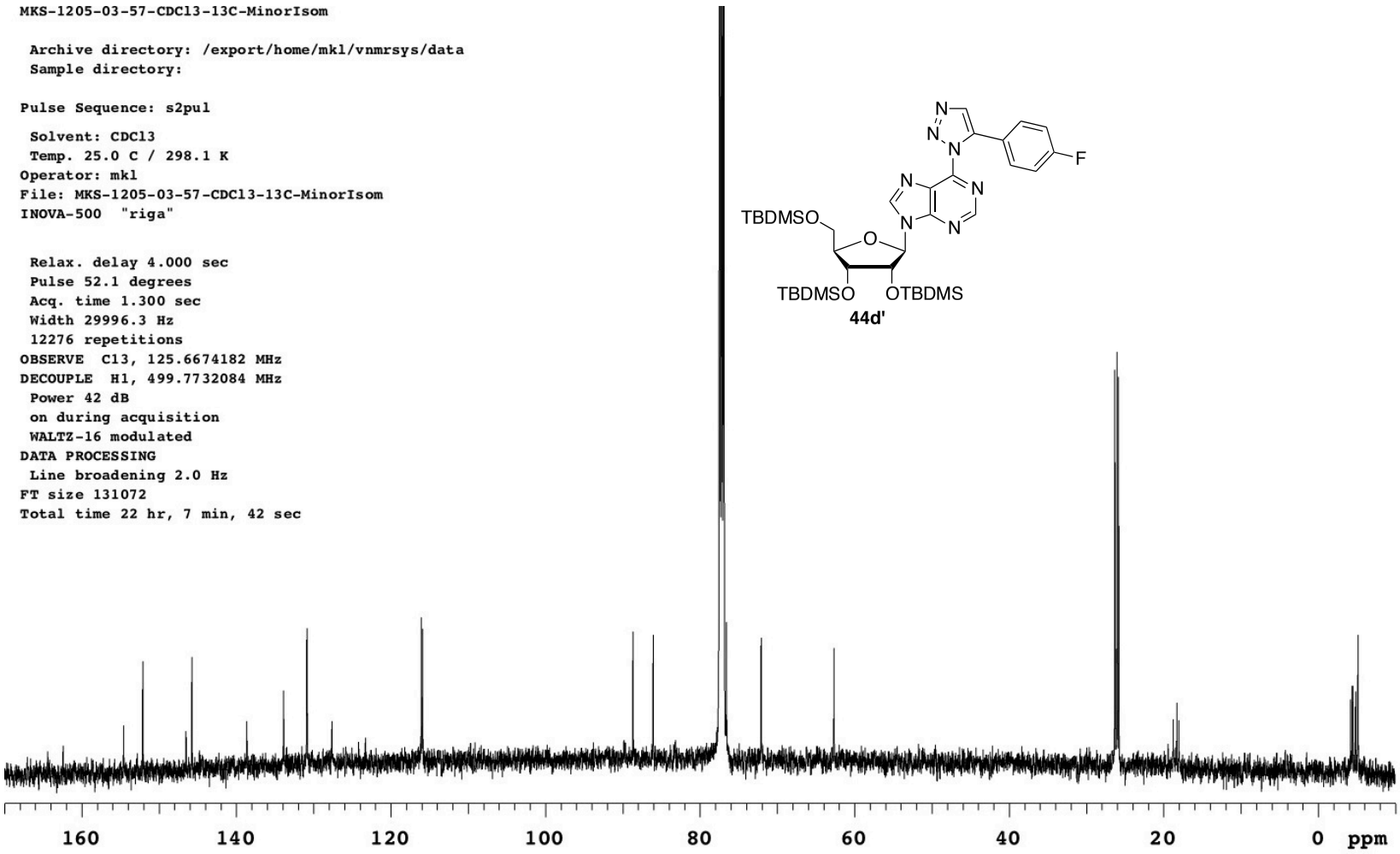

MKS-1205-03-56-CDCl3-2ndFrac-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-56-CDCl3-2ndFrac-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
84 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
OMe
TBDMSO
TBDMSO
OTBDMS
44c'
10
9
8
7
6
5
4
3
2
1
ppm


MKS-1205-03-56-CDCl3-13C-2ndFrac-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-56-CDCl3-13C-2ndFrac-CC
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
8564 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 14 hr, 45 min, 15 sec
N
N
N
OMe
N
N
N
N
TBDMSO
O
TBDMSO
OTBDMS
44c'
160
140
120
100
80
60
40
20
0
ppm


MKS-1205-03-57-CDCl3-BnglBrHcac-CC
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-57-CDCl3-2ndFrac
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
92 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
F
N
N
N
N
N
N
O
TBDMSO
TBDMSO
OTBDMS
44d
10
9
8
7
6
5
4
3
2
1
ppm


MKS-1205-03-57-CDCl3-13C-MajorFrac
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-57-CDCl3-13C-MajorFrac
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
8000 repetitions
OBSERVE C13, 125.6674184 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 11 hr, 48 min, 16 sec
F
N
N
N
N
N
N
O
TBDMSO
TBDMSO
OTBDMS
44d
160
140
120
100
80
60
40
20
0
ppm


MKS-1205-03-57-CDCl3-MinorFrac-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-57-CDCl3-2ndFrac-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
68 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
TBDMSO
TBDMSO
OTBDMS
F
44d'
10
9
8
7
6
5
4
3
2
1
ppm

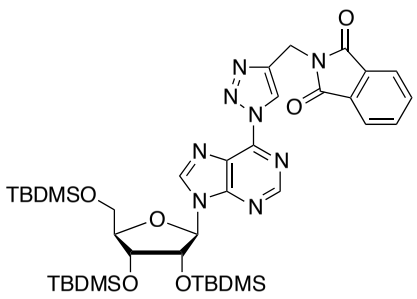

MKS-1205-03-57-CDCl3-13C-MinorIsom
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-57-CDCl3-13C-MinorIsom
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
12276 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 22 hr, 7 min, 42 sec
TBDMSO
TBDMSO
OTBDMS
F
44d'
160
140
120
100
80
60
40
20
0
ppm

MKS-1205-03-59-CDCl3-1stFrac,-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-59-CDCl3-1stFrac.-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7707211 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



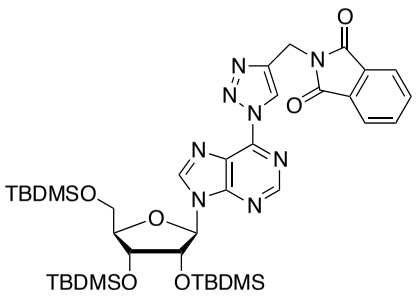
44e

MKS-1205-03-59-CDCl3-13C-1stFrac.-CC

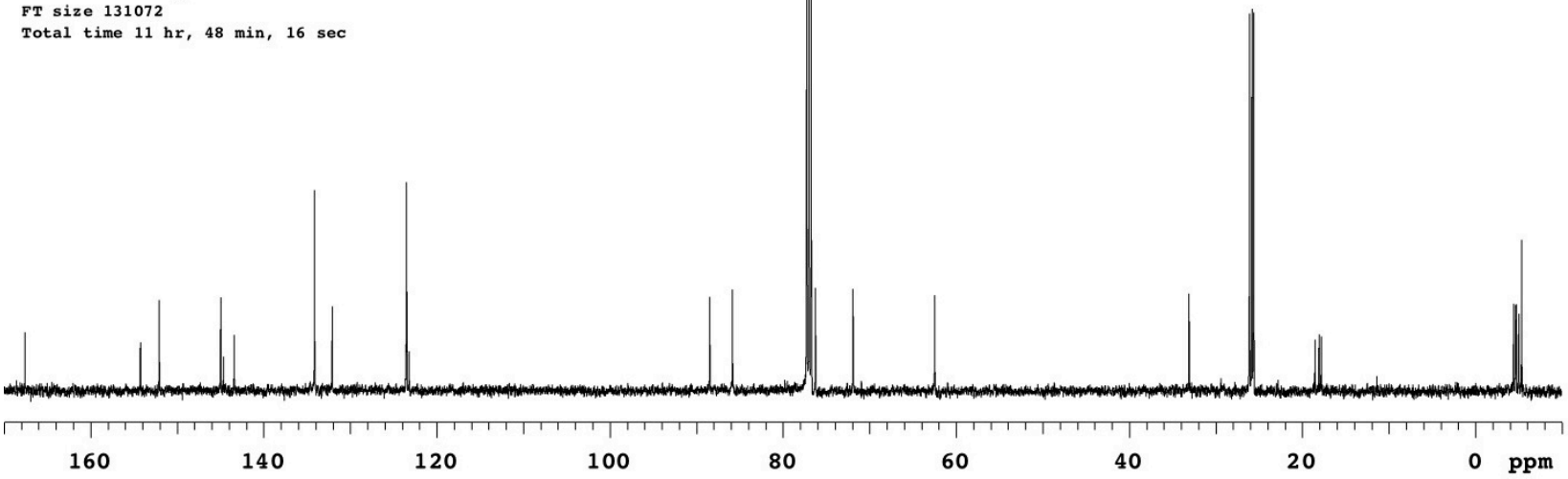
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-59-CDCl3-13C-1stFrac.-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
1004 repetitions
OBSERVE C13, 125.6674466 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 11 hr, 48 min, 16 sec



44e



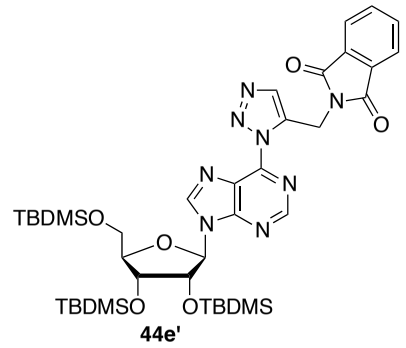
MKS-1205-03-59-CDCl3-2ndFrac-CC

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

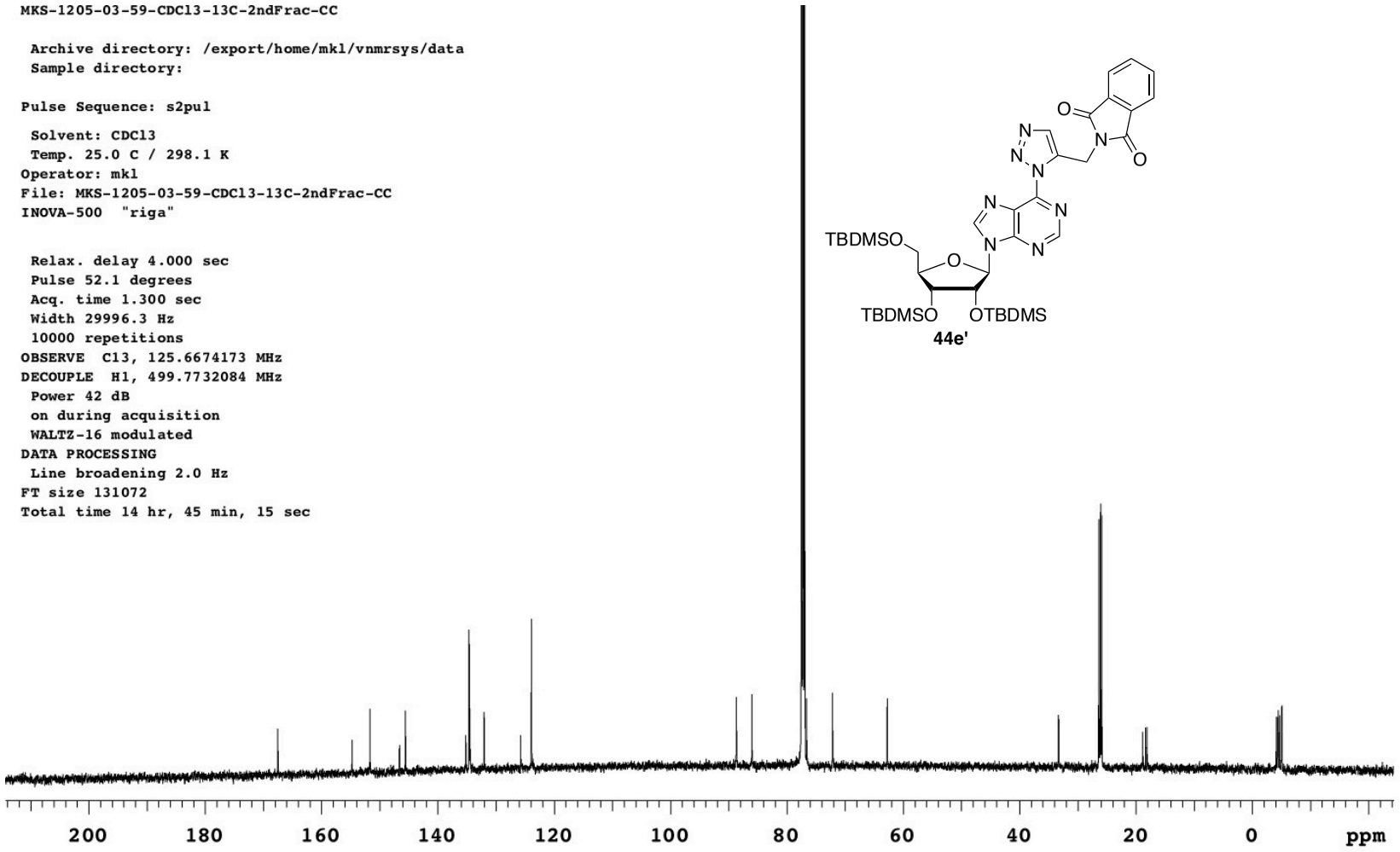
Pulse Sequence: s2pul

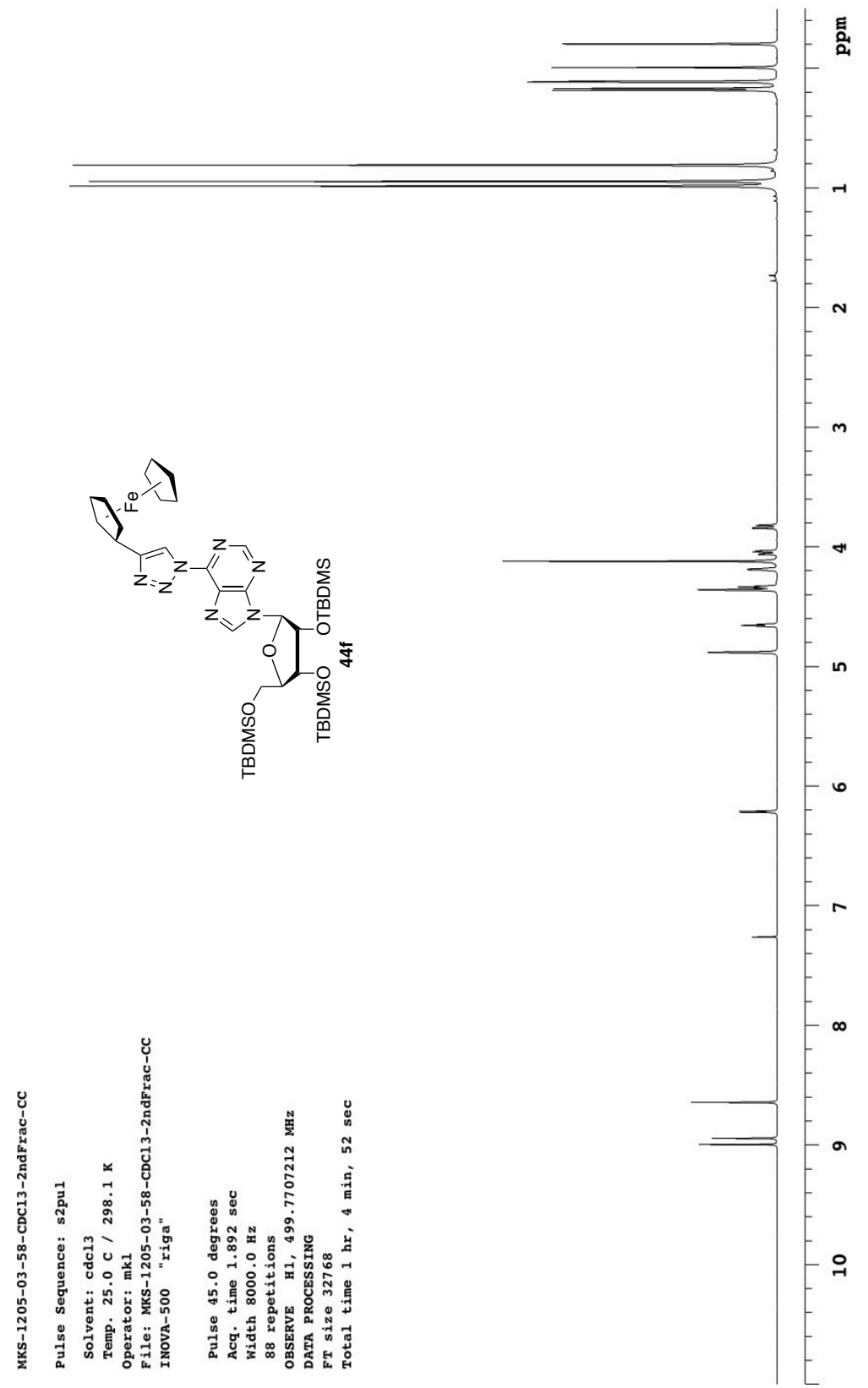
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-59-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
60 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



44e'


MKS-1205-03-59-CDCl3-13C-2ndFrac-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-59-CDCl3-13C-2ndFrac-CC
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, 125.6674173 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
TBDMSO
TBDMSO
OTBDMS
44e'
200
180
160
140
120
100
80
60
40
20
0
ppm

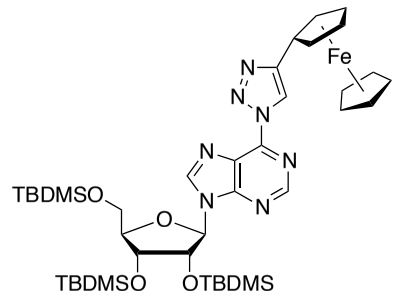

MKS-1205-03-58-CDCl3-2ndFrac-CC
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-58-CDCl3-2ndFrac-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
88 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
Fe
N
N
N
N
N
N
N
O
TBDMSO
TBDMSO
OTBDMS
44f
10
9
8
7
6
5
4
3
2
1
ppm

MKS-1205-03-58-CDCl3-13C-majorisom.

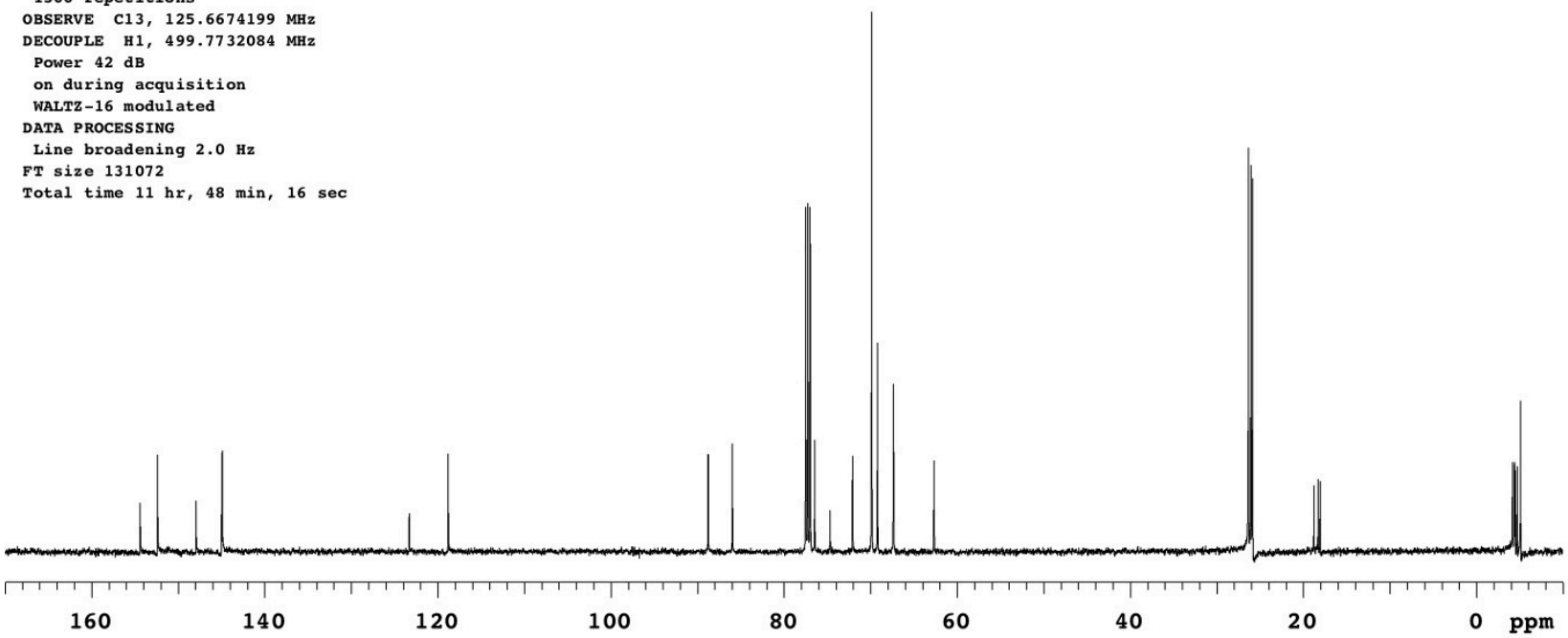
Pulse Sequence: s2pul

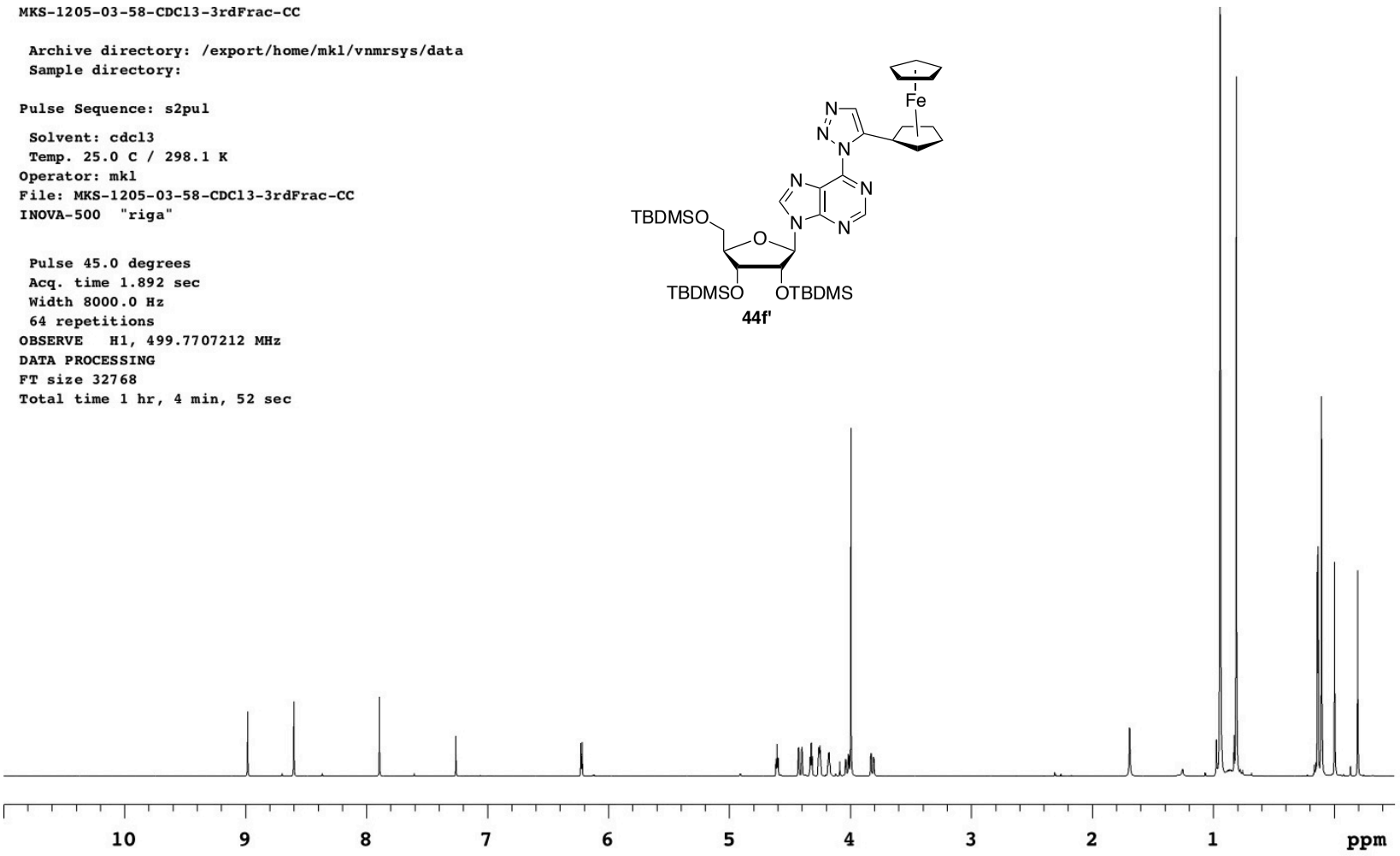
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-58-CDCl3-13C-majorisom.
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
1500 repetitions
OBSERVE C13, 125.6674199 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 11 hr, 48 min, 16 sec



44f




MKS-1205-03-58-CDCl3-3rdFrac-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-58-CDCl3-3rdFrac-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
TBDMSO
TBDMSO
OTBDMS
Fe
44f'
10
9
8
7
6
5
4
3
2
1
ppm

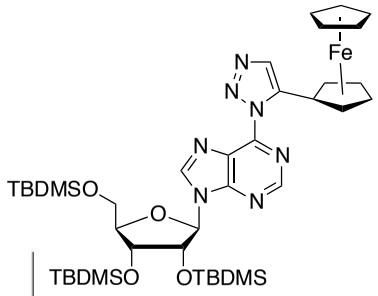
MKS-1205-03-58-CDCl3-13C-2ndFrac-CC

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

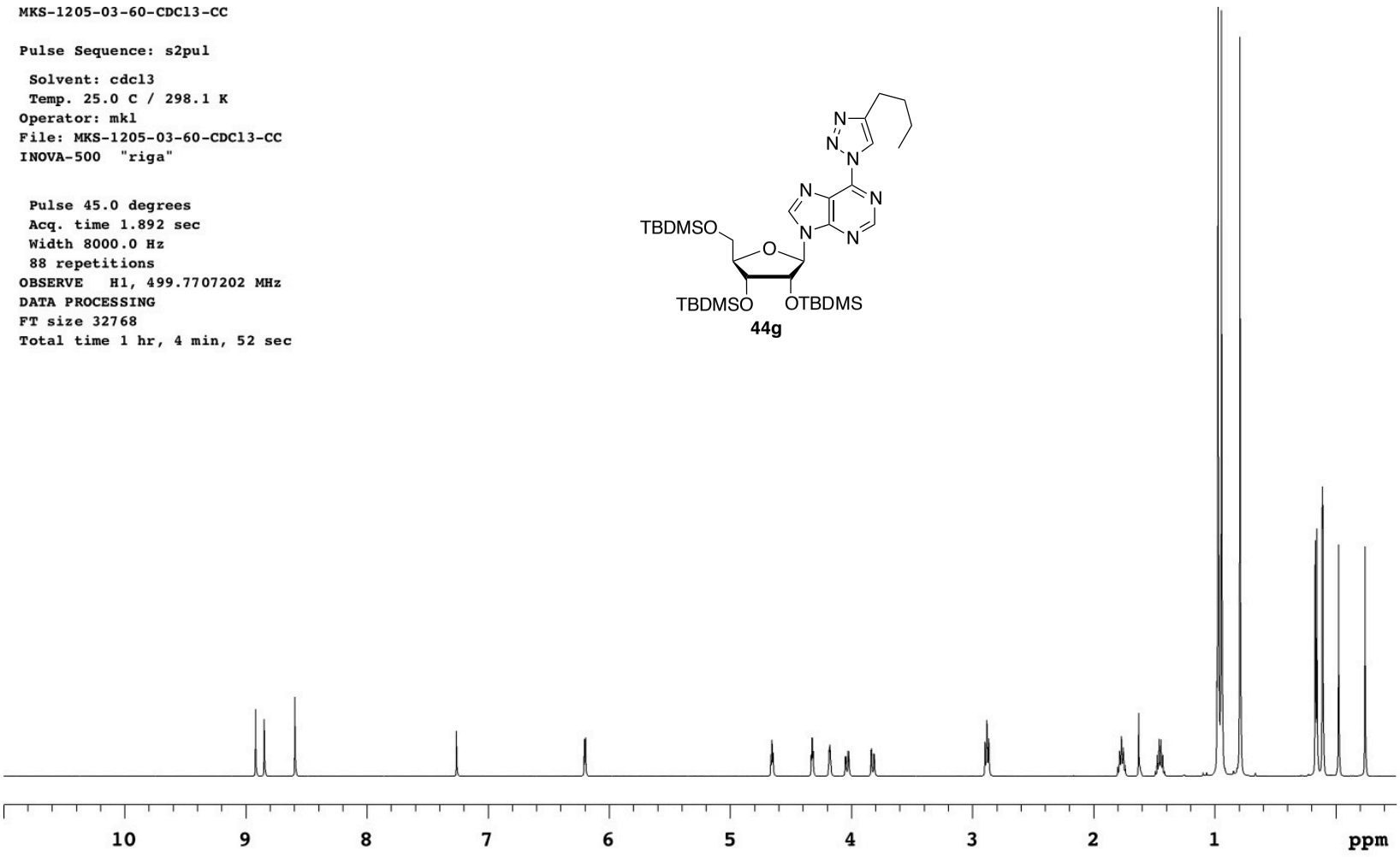
Pulse Sequence: s2pul

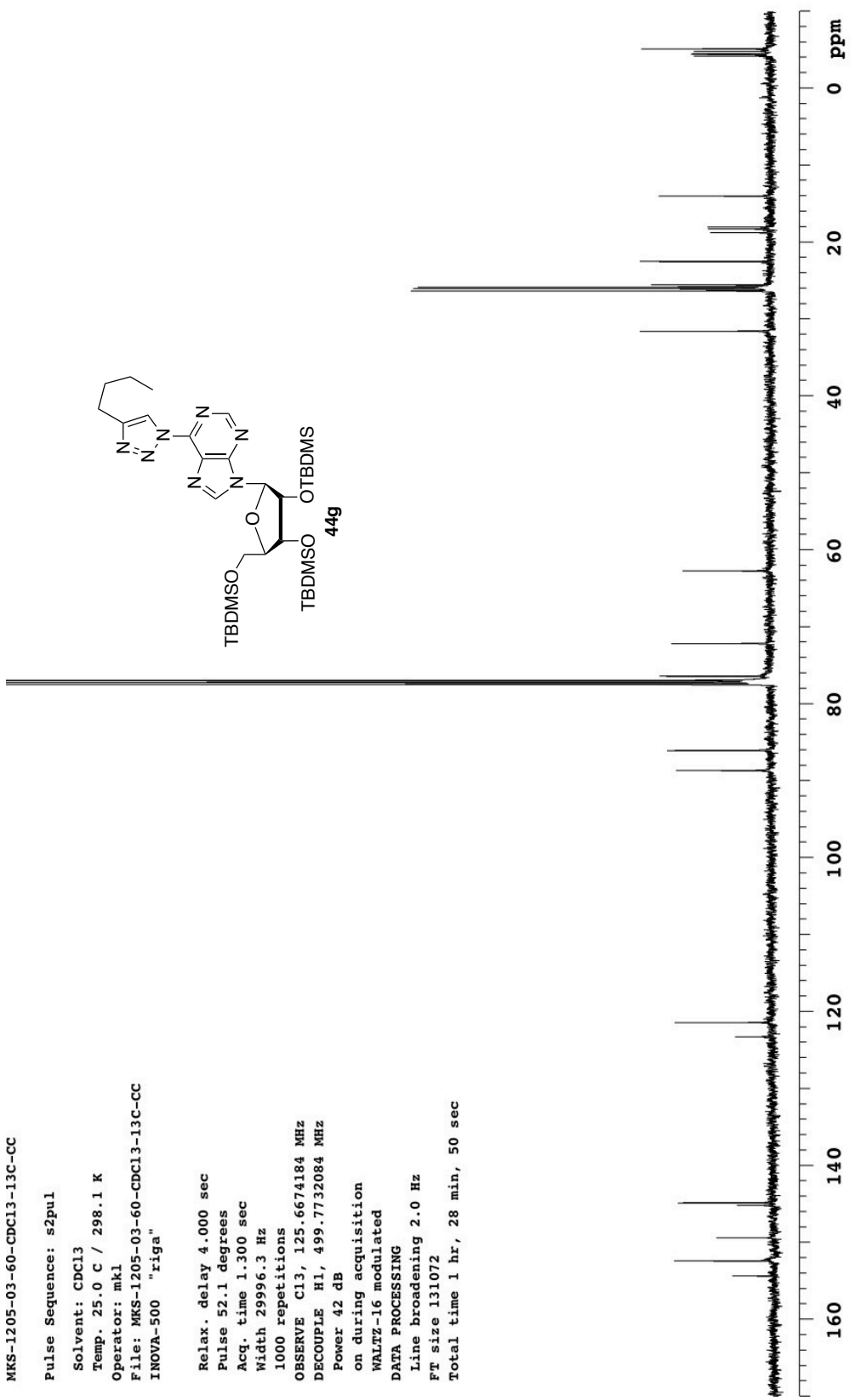
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-58-CDCl3-13C-3rdFrac-CC
INOVA-500 "riga"

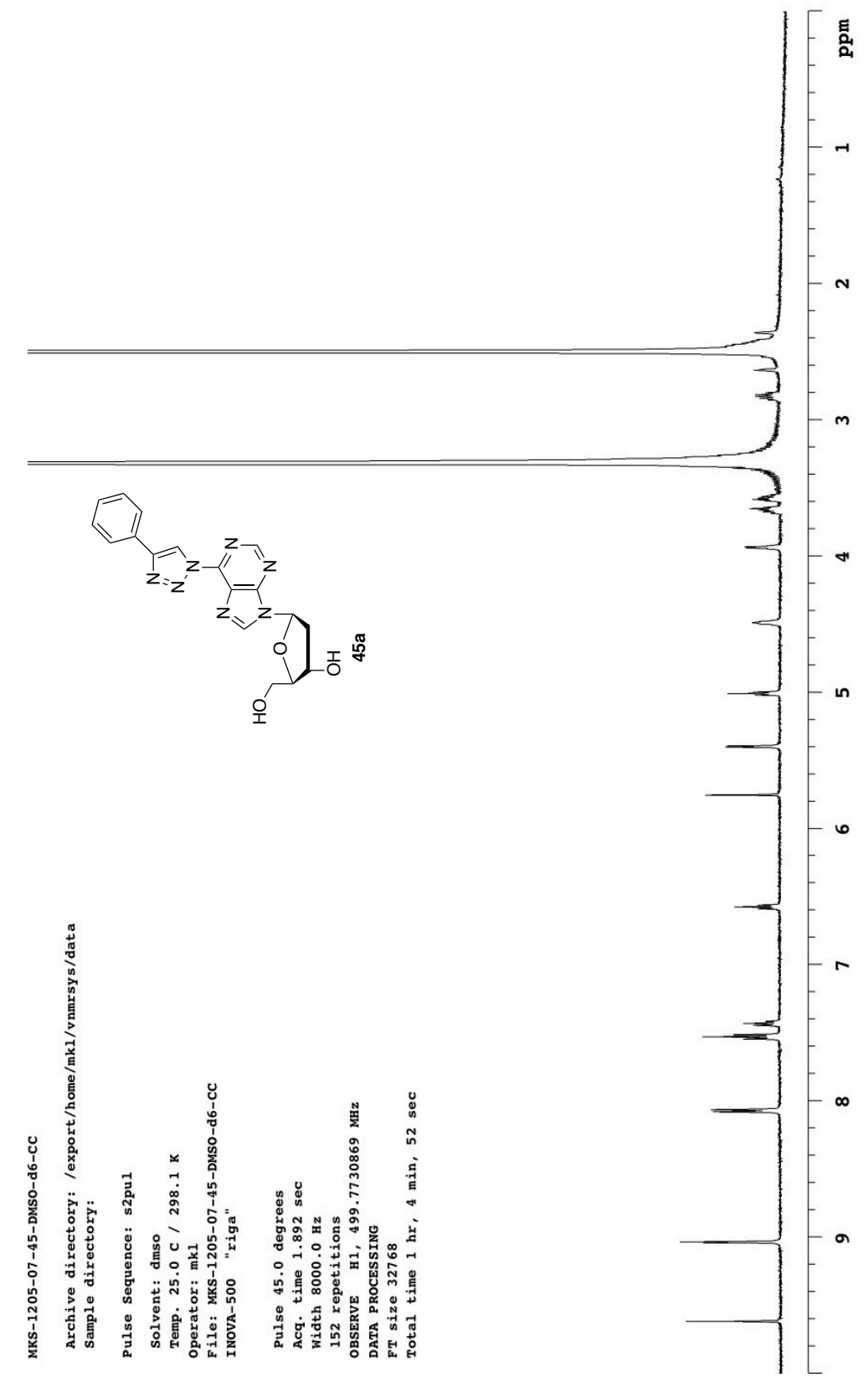
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
11052 repetitions
OBSERVE C13, 125.6674191 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 17 hr, 42 min, 14 sec



44f'


MKS-1205-03-60-CDCl3-CC
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-60-CDCl3-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
88 repetitions
OBSERVE H1, 499.7707202 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
TBDMSO
TBDMSO
OTBDMS
44g
10
9
8
7
6
5
4
3
2
1
ppm


MKS-1205-03-60-CDCl3-13C-CC
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-03-60-CDCl3-13C-CC
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
1000 repetitions
OBSERVE C13, 125.6674184 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 1 hr, 28 min, 50 sec
TBDMSO
TBDMSO
OTBDMS
44g
160
140
120
100
80
60
40
20
0
ppm


MKS-1205-07-45-DMSO-d6-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-45-DMSO-d6-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
152 repetitions
OBSERVE H1, 499.7730869 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
HO
OH
45a
9
8
7
6
5
4
3
2
1
ppm

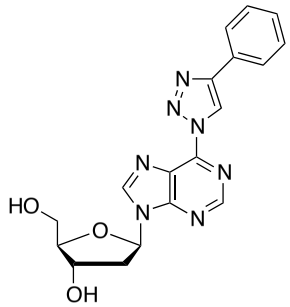
MKS-1205-07-45-Acetoned6+15dropsDMSOd6-13C-CC

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

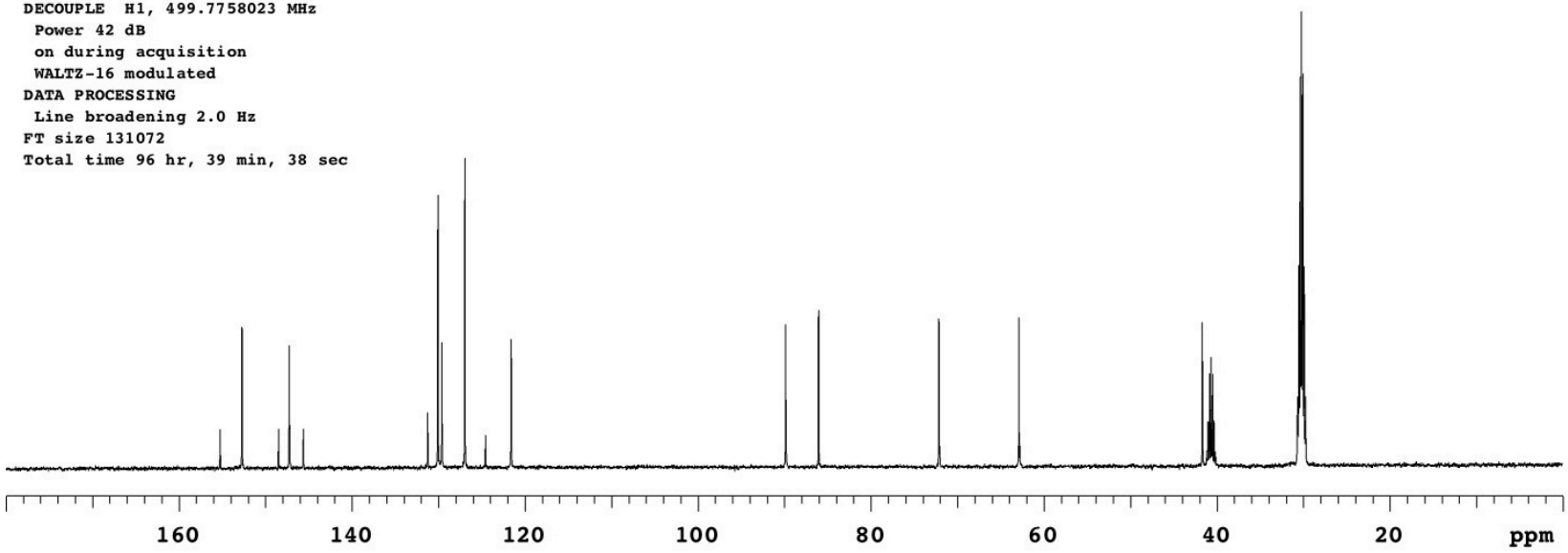
Pulse Sequence: s2pul

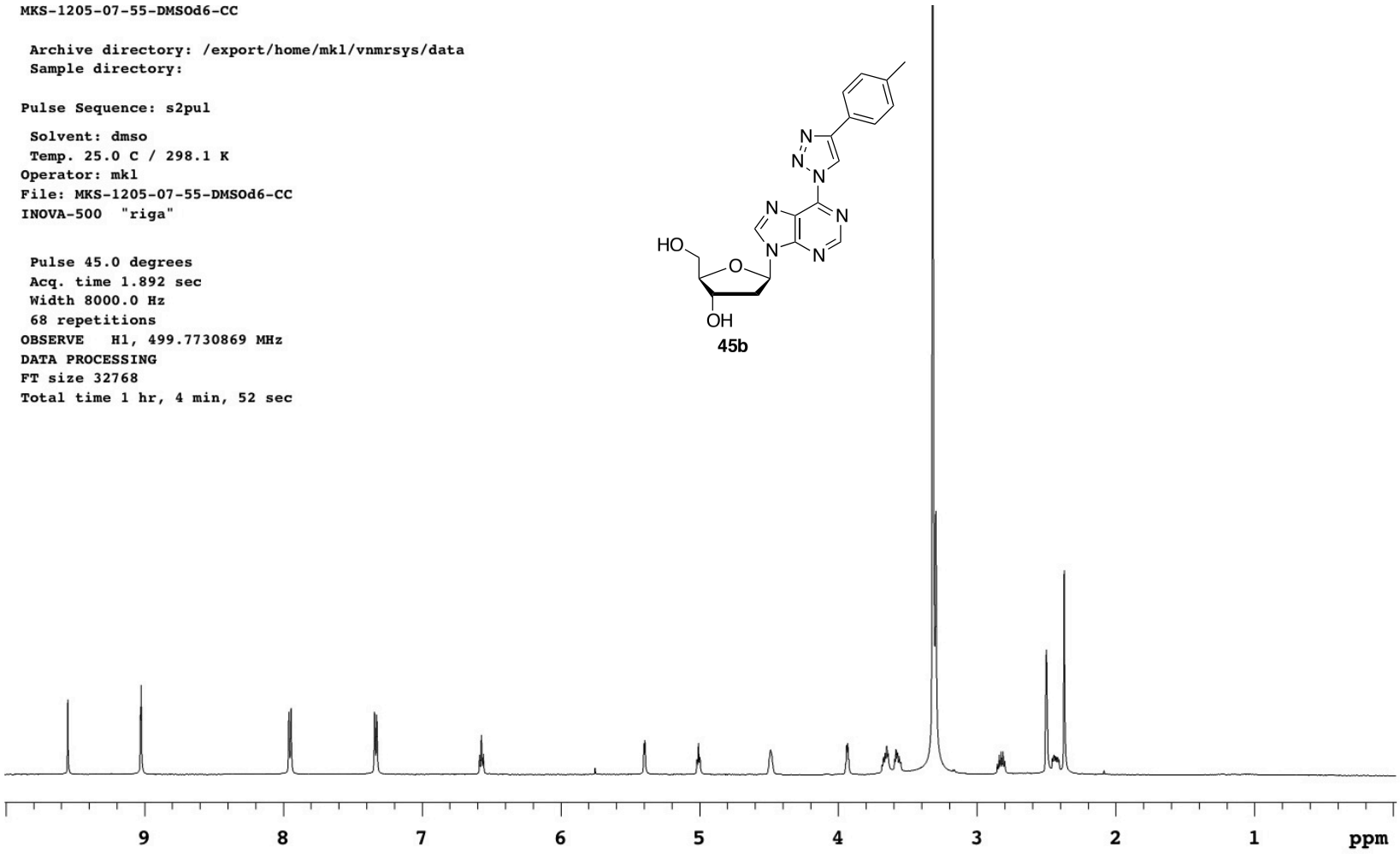
Solvent: acetone
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-45-Acetoned6+15dropsDMSOd6-13C-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
6252 repetitions
OBSERVE C13, 125.6679743 MHz
DECOUPLE H1, 499.7758023 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec



45a




MKS-1205-07-55-DMSOd6-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-55-DMSOd6-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
68 repetitions
OBSERVE H1, 499.7730869 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
HO
O
OH
N
N
N
N
N
N
45b
9
8
7
6
5
4
3
2
1
ppm

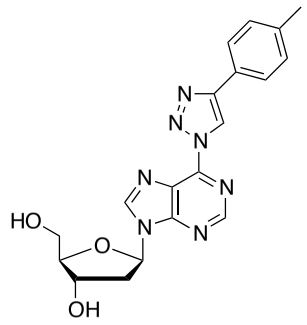
MKS-1205-07-55-Acetoned6+15dropsDMSOd6-13C-CC

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

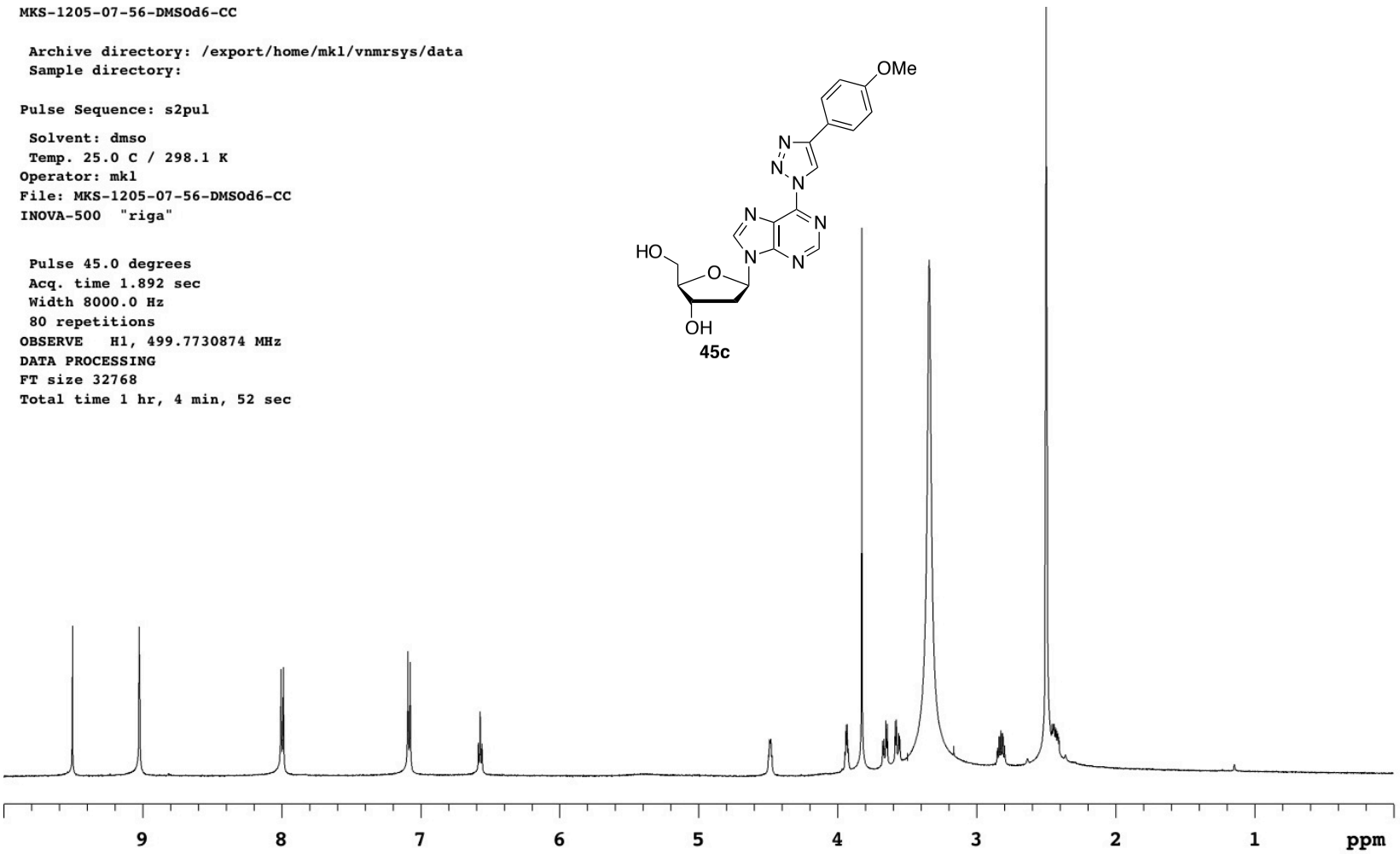
Pulse Sequence: s2pul

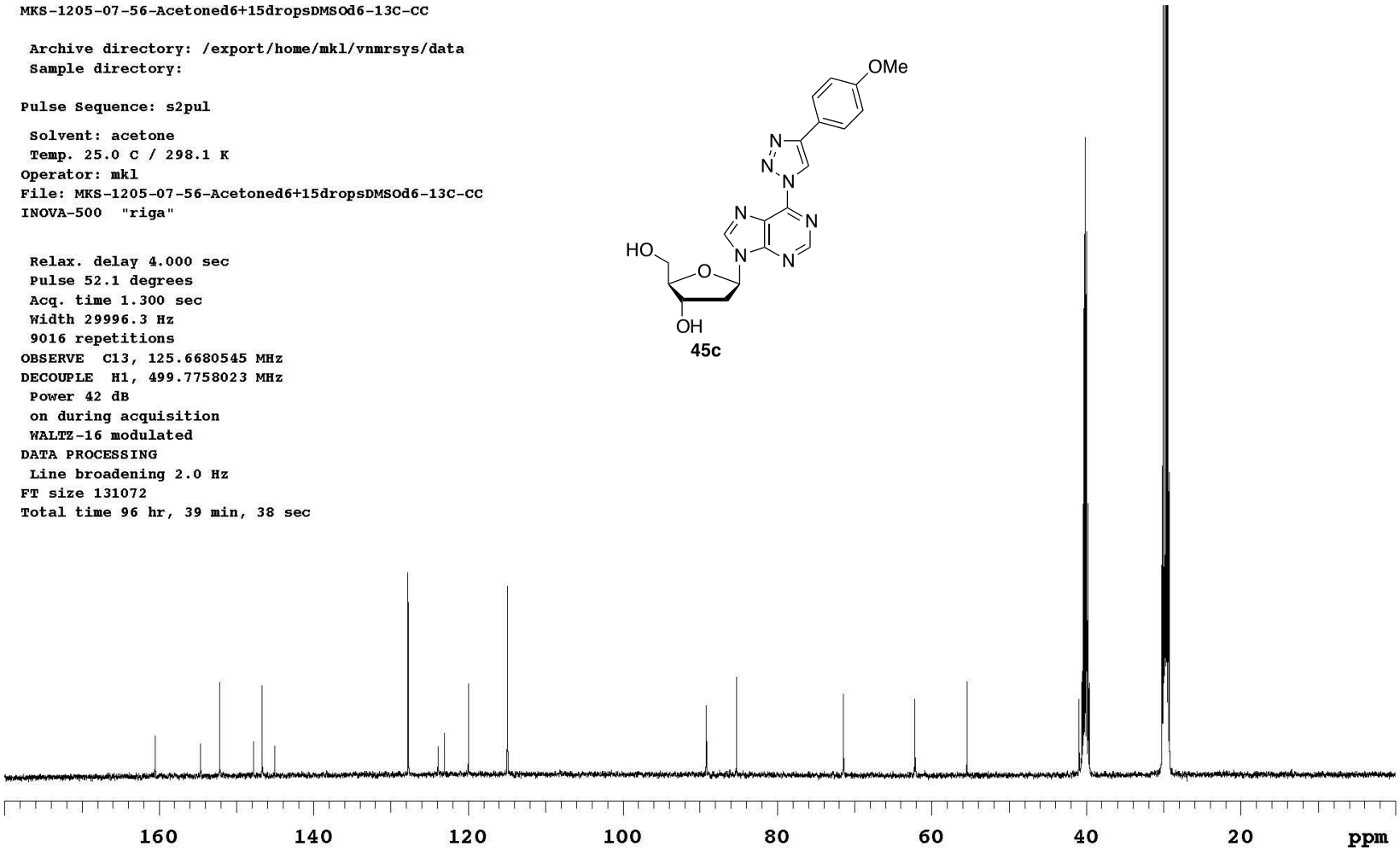
Solvent: acetone
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-55-Acetoned6+15dropsDMSOd6-13C-CC
INOVA-500 "riga"

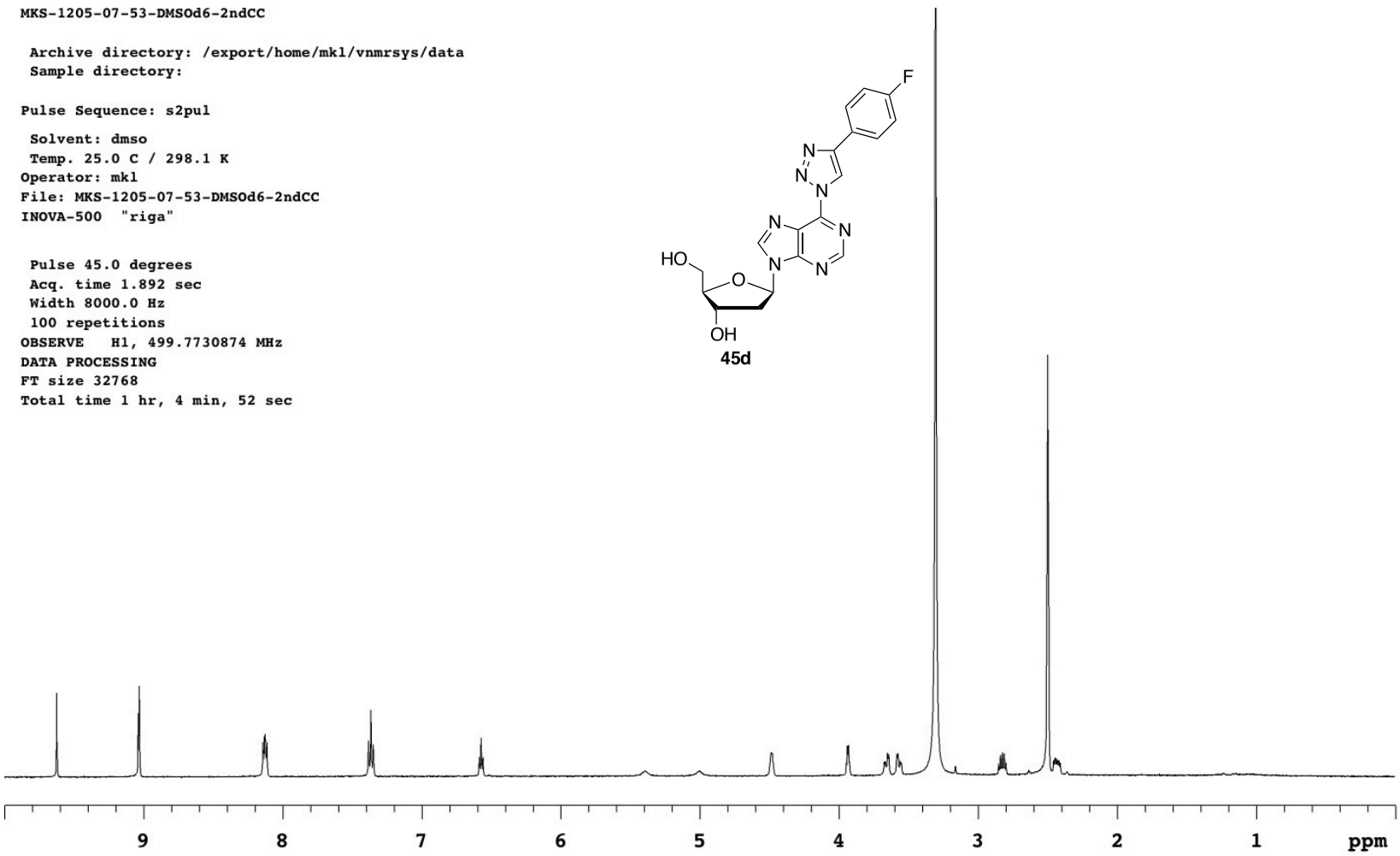
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
1156 repetitions
OBSERVE C13, 125.6680921 MHz
DECOUPLE H1, 499.7758023 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec

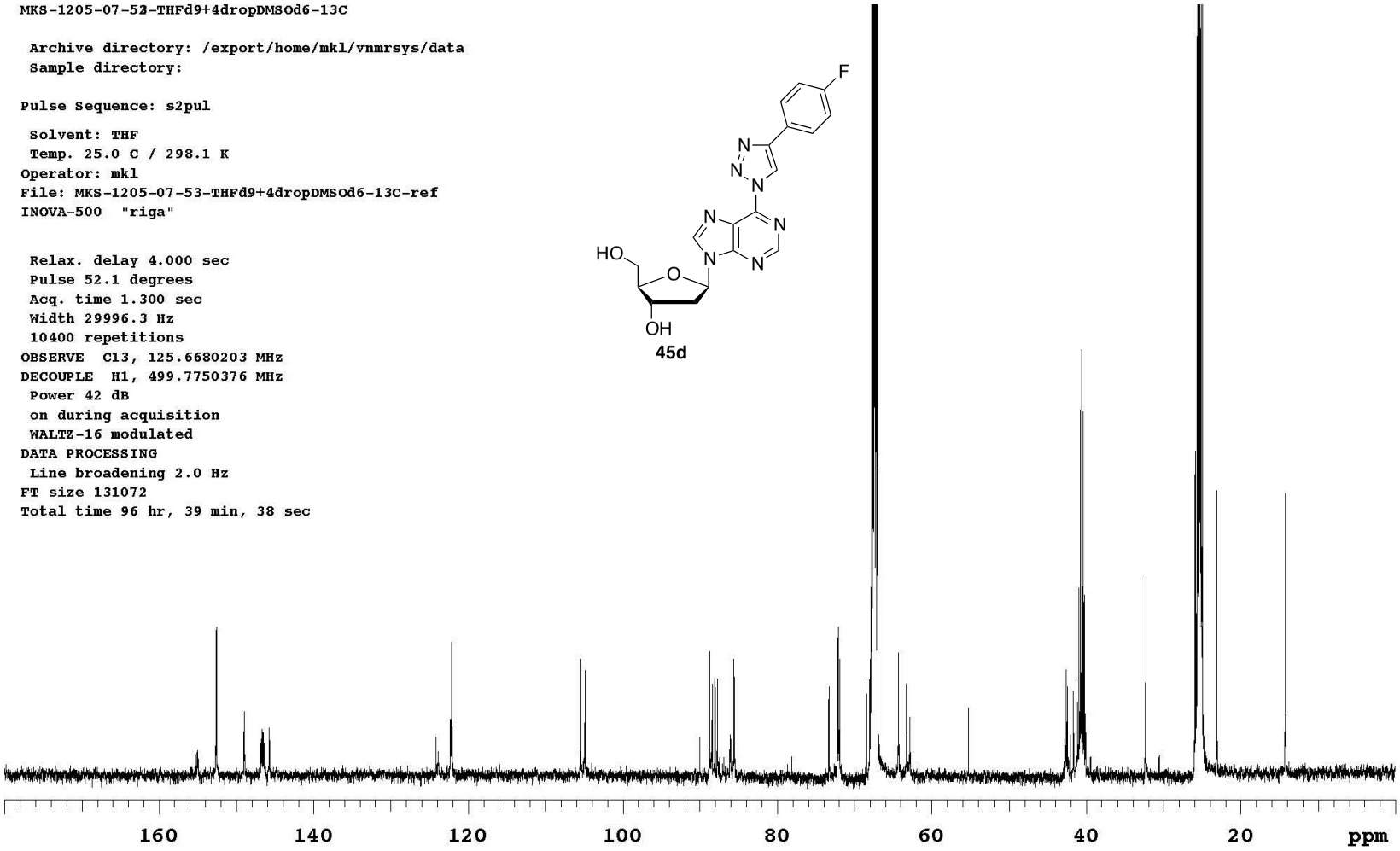


45b


MKS-1205-07-56-DMSOd6-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-56-DMSOd6-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
80 repetitions
OBSERVE H1, 499.7730874 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
OMe
HO
OH
45c
9
8
7
6
5
4
3
2
1
ppm


MKS-1205-07-56-Acetoned6+15dropsDMSOd6-13C-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: acetone
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-56-Acetoned6+15dropsDMSOd6-13C-CC
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
9016 repetitions
OBSERVE C13, 125.6680545 MHz
DECOUPLE H1, 499.7758023 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec
OMe
N
N
N
N
N
N
N
HO
O
OH
45c
160
140
120
100
80
60
40
20
ppm


MKS-1205-07-53-DMSOd6-2ndCC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-53-DMSOd6-2ndCC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
100 repetitions
OBSERVE H1, 499.7730874 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
F
N
N
N
N
N
N
HO
O
OH
45d
9
8
7
6
5
4
3
2
1
ppm


MKS-1205-07-53-THFd9+4dropDMSOd6-13C
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: THF
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-53-THFd9+4dropDMSOd6-13C-ref
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
10400 repetitions
OBSERVE C13, 125.6680203 MHz
DECOUPLE H1, 499.7750376 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec
F
N
N
N
N
N
N
HO
O
OH
45d
160
140
120
100
80
60
40
20
ppm

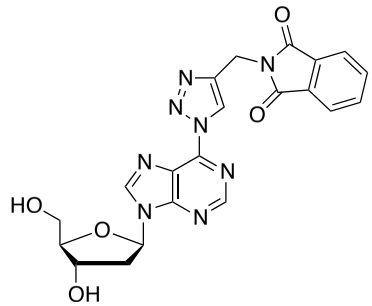
MKS-1205-07-57-DMSOd6-CC

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

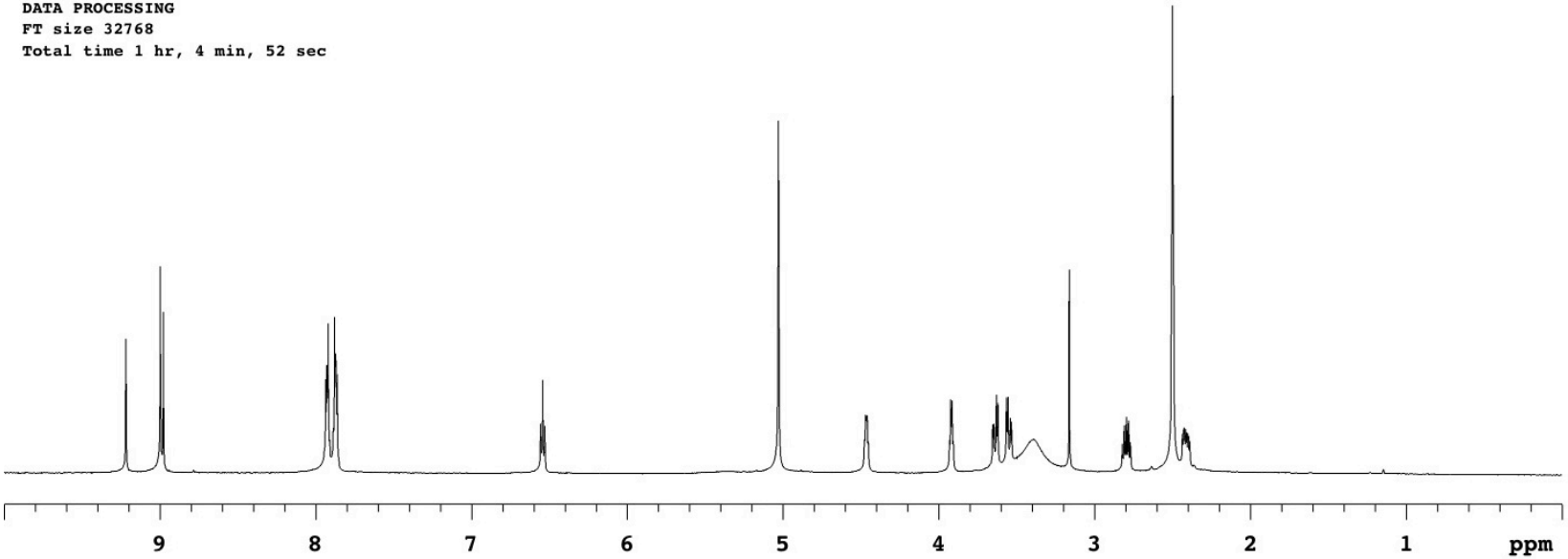
Pulse Sequence: s2pul

Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-57-DMSOd6-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
72 repetitions
OBSERVE H1, 499.7730879 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



45e



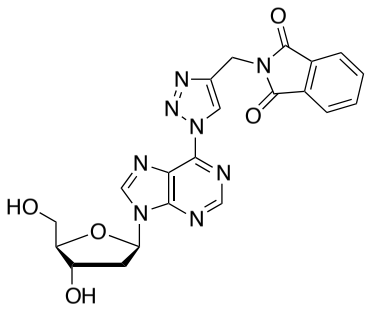
MKS-1205-07-57-Acetoned6+15dropsDMSOd6-13C-CC

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

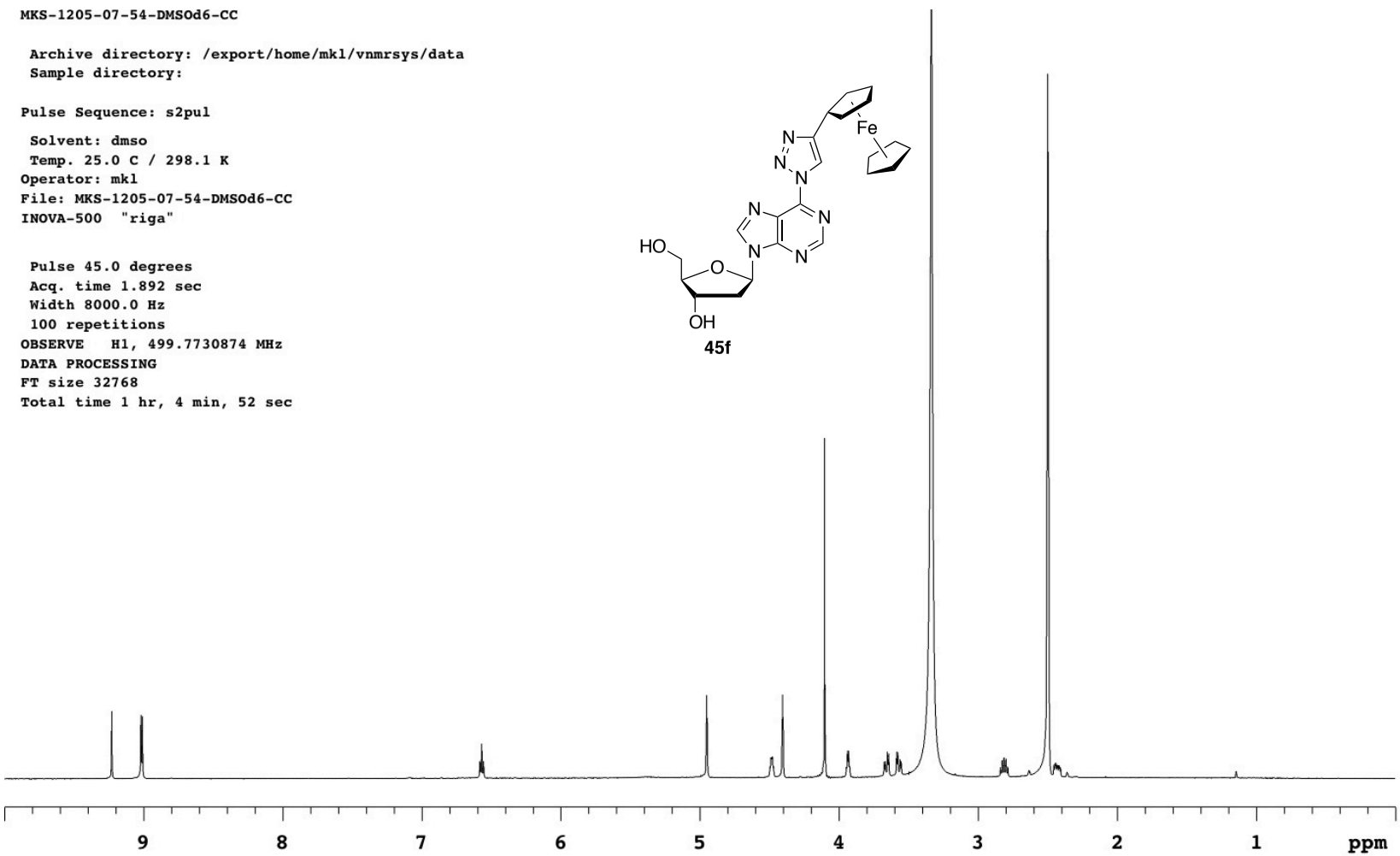
Pulse Sequence: s2pul

Solvent: acetone
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-57-Acetoned6+15dropsDMSOd6-13C-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
1024 repetitions
OBSERVE C13, 125.6680852 MHz
DECOUPLE H1, 499.7758023 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec



45e


MKS-1205-07-54-DMSOd6-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-54-DMSOd6-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
100 repetitions
OBSERVE H1, 499.7730874 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
HO
O
OH
N
N
N
N
N
N
Fe
45f
9
8
7
6
5
4
3
2
1
ppm

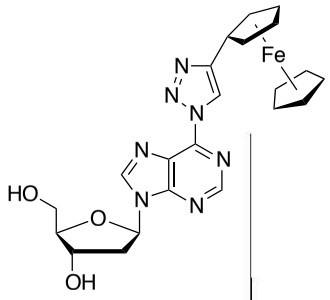
MKS-1205-07-54-Acetoned6+4dropsDMSOd6-13C-CC

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

Pulse Sequence: s2pul

Solvent: acetone
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-54-Acetoned6+4dropsDMSOd6-13C-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
1480 repetitions
OBSERVE C13, 125.6680106 MHz
DECOUPLE H1, 499.7758023 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec



45f

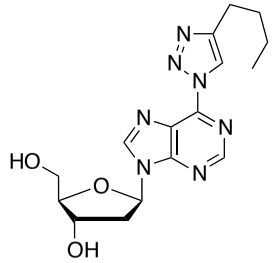
MKS-1205-07-52-DMSOd6-2ndFrac-CC

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

Pulse Sequence: s2pul

Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-52-DMSOd6-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
80 repetitions
OBSERVE H1, 499.7730869 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



45g

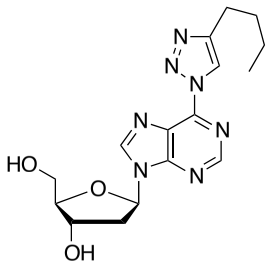
MKS-1205-07-1hexyne-Acetoned6+10dropsDMSOd6

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

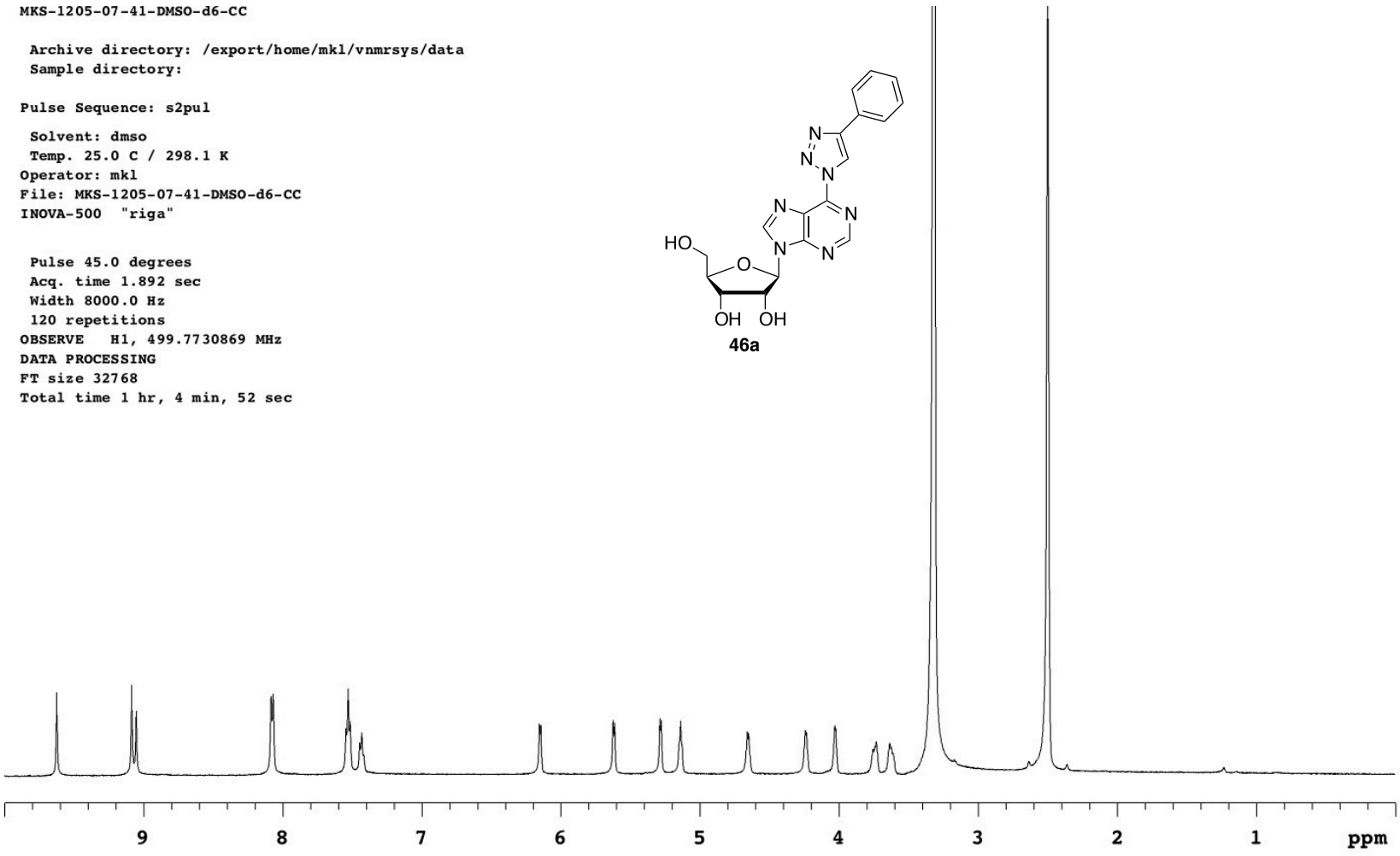
Pulse Sequence: s2pul

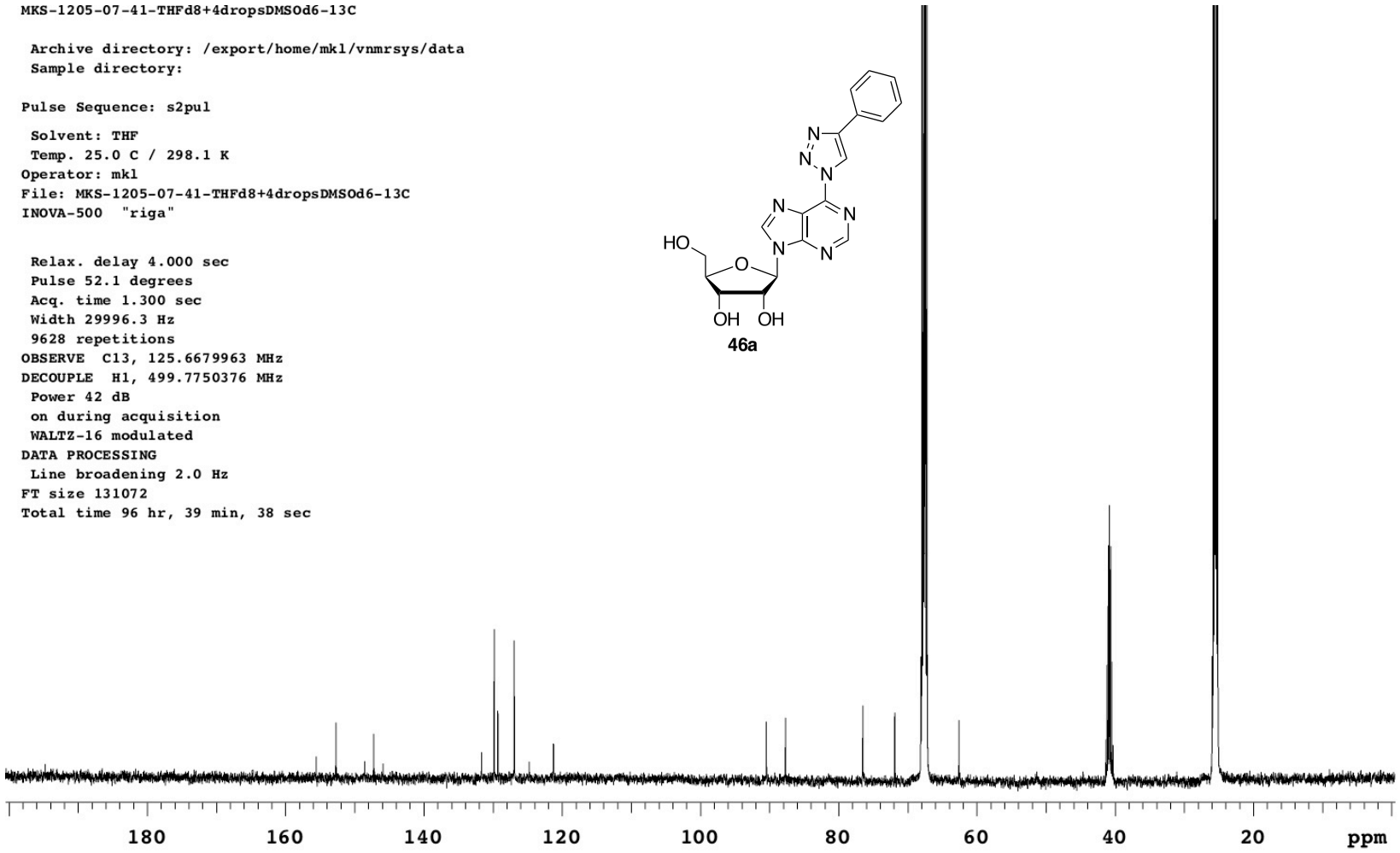
Solvent: acetone
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-52-1hexyne-13CAcetoned6+10dropsDMSOd6
INOVA-500 "riga"

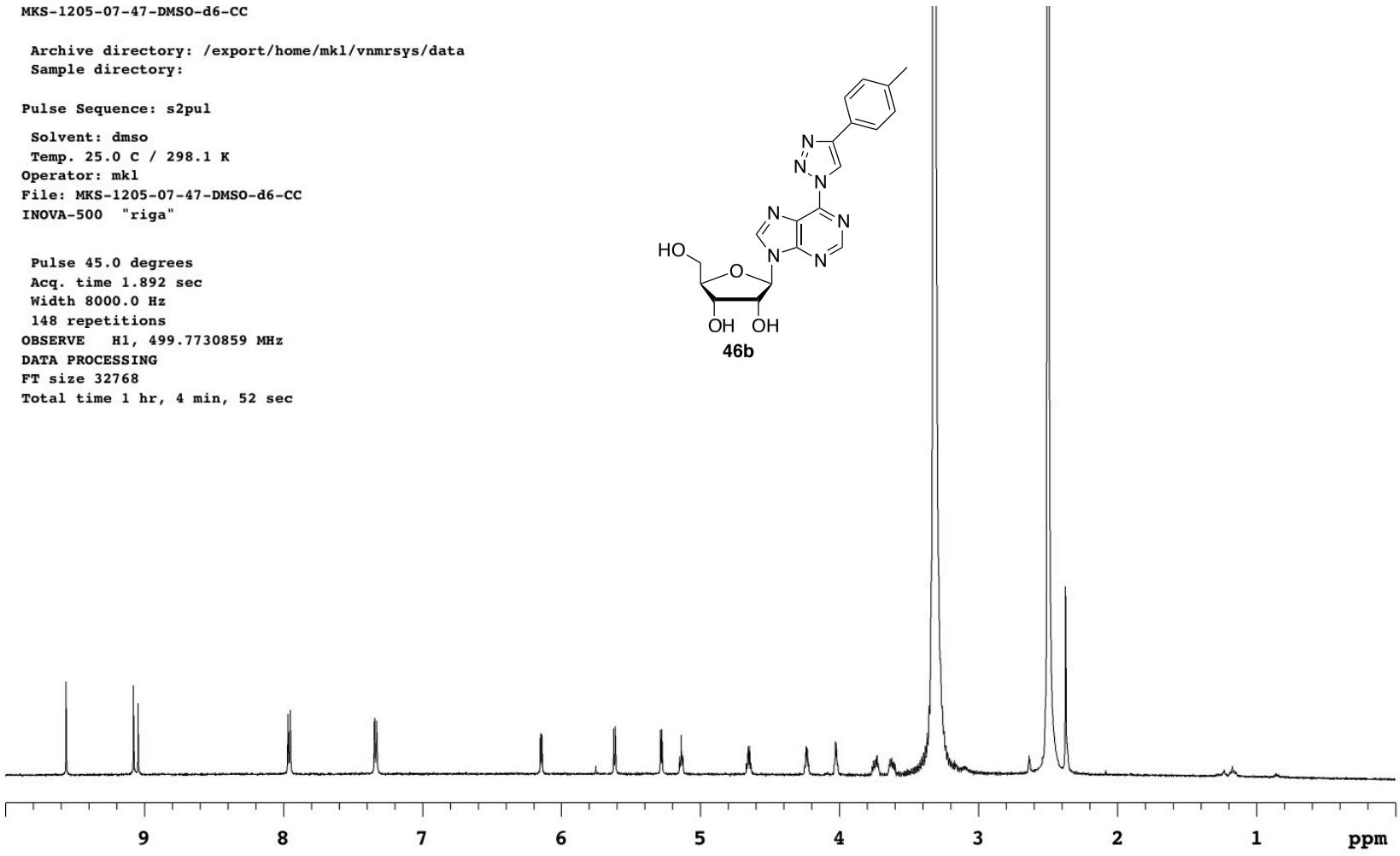
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
26384 repetitions
OBSERVE C13, 125.6680671 MHz
DECOUPLE H1, 499.7758023 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec

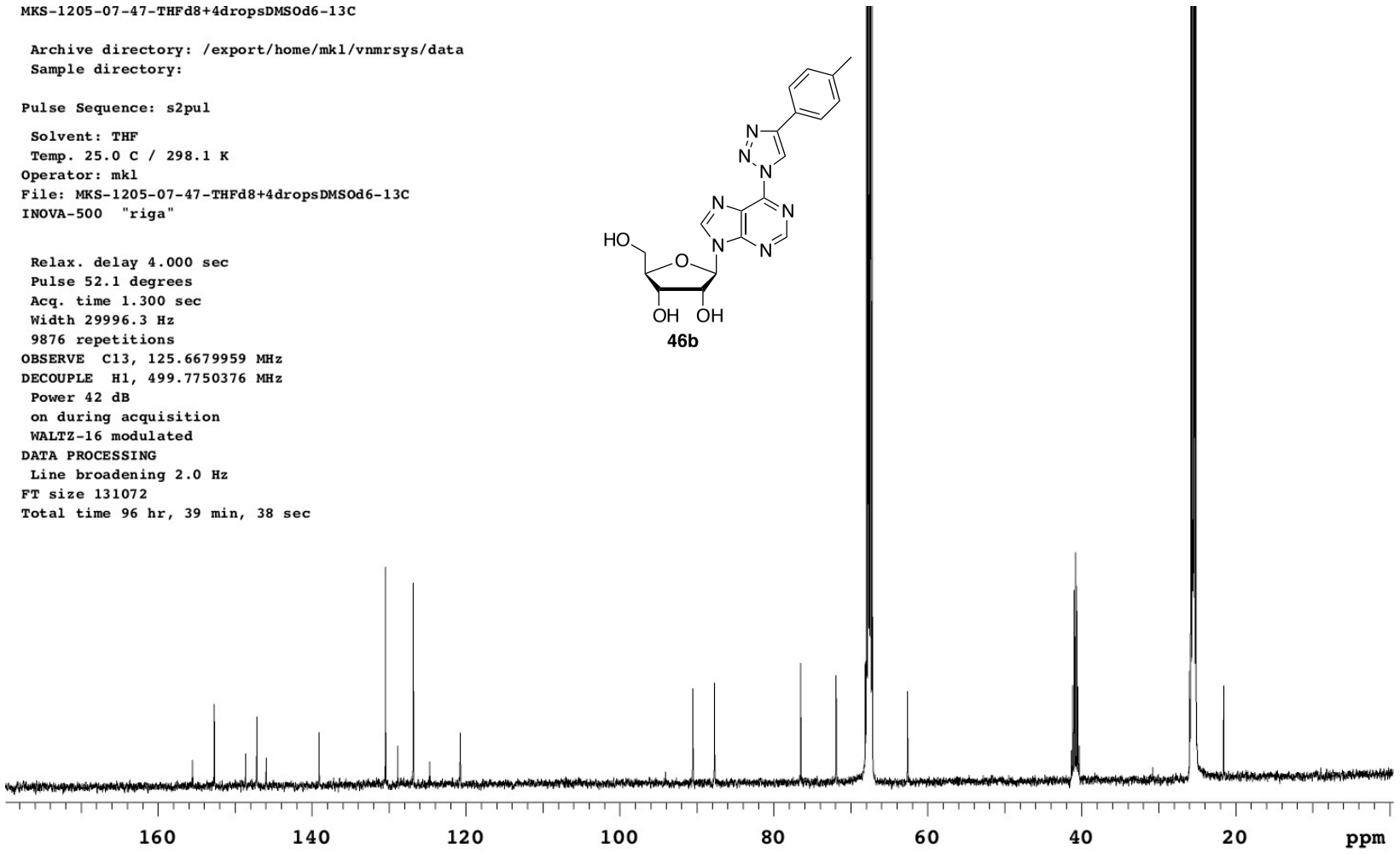


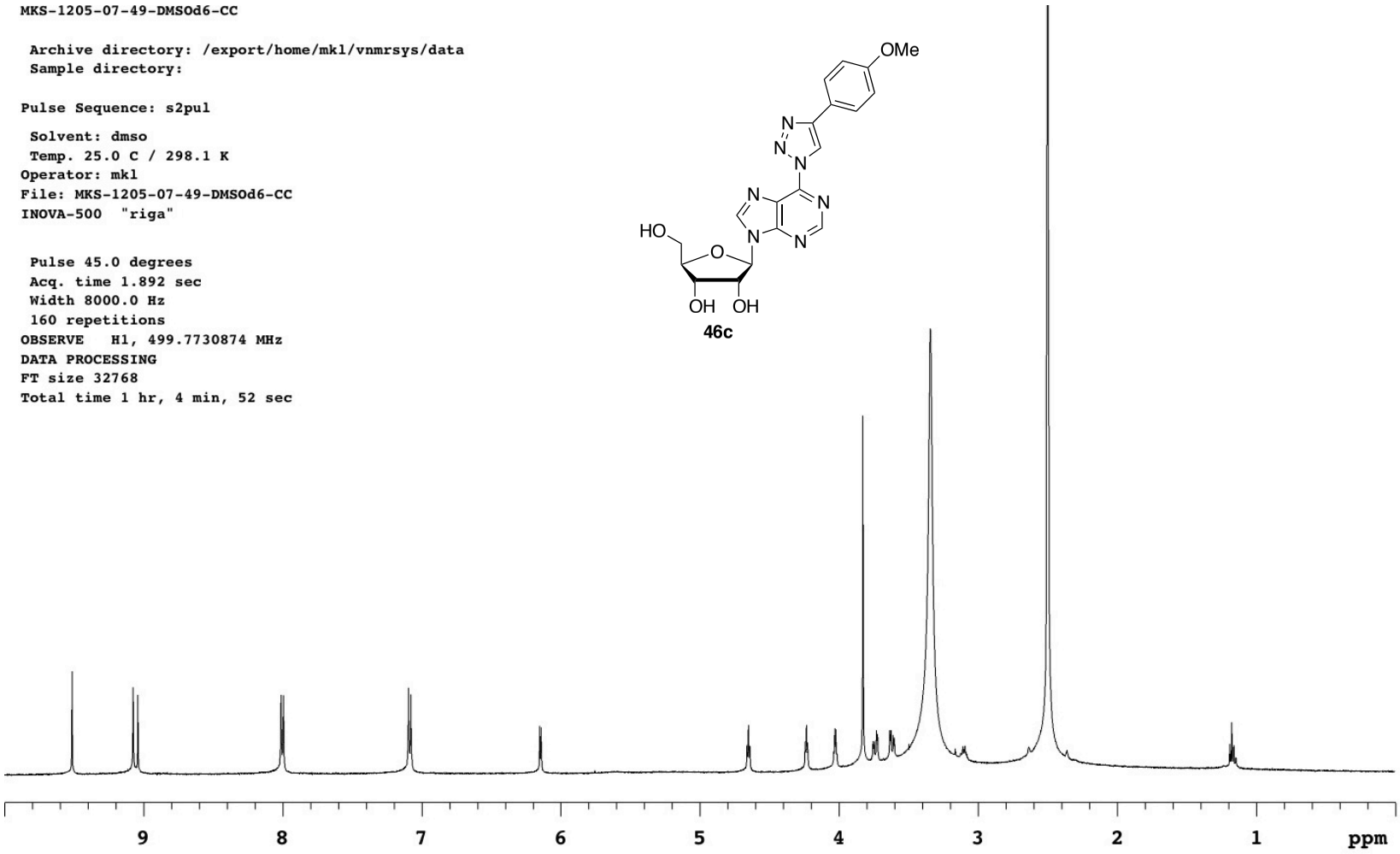
45g

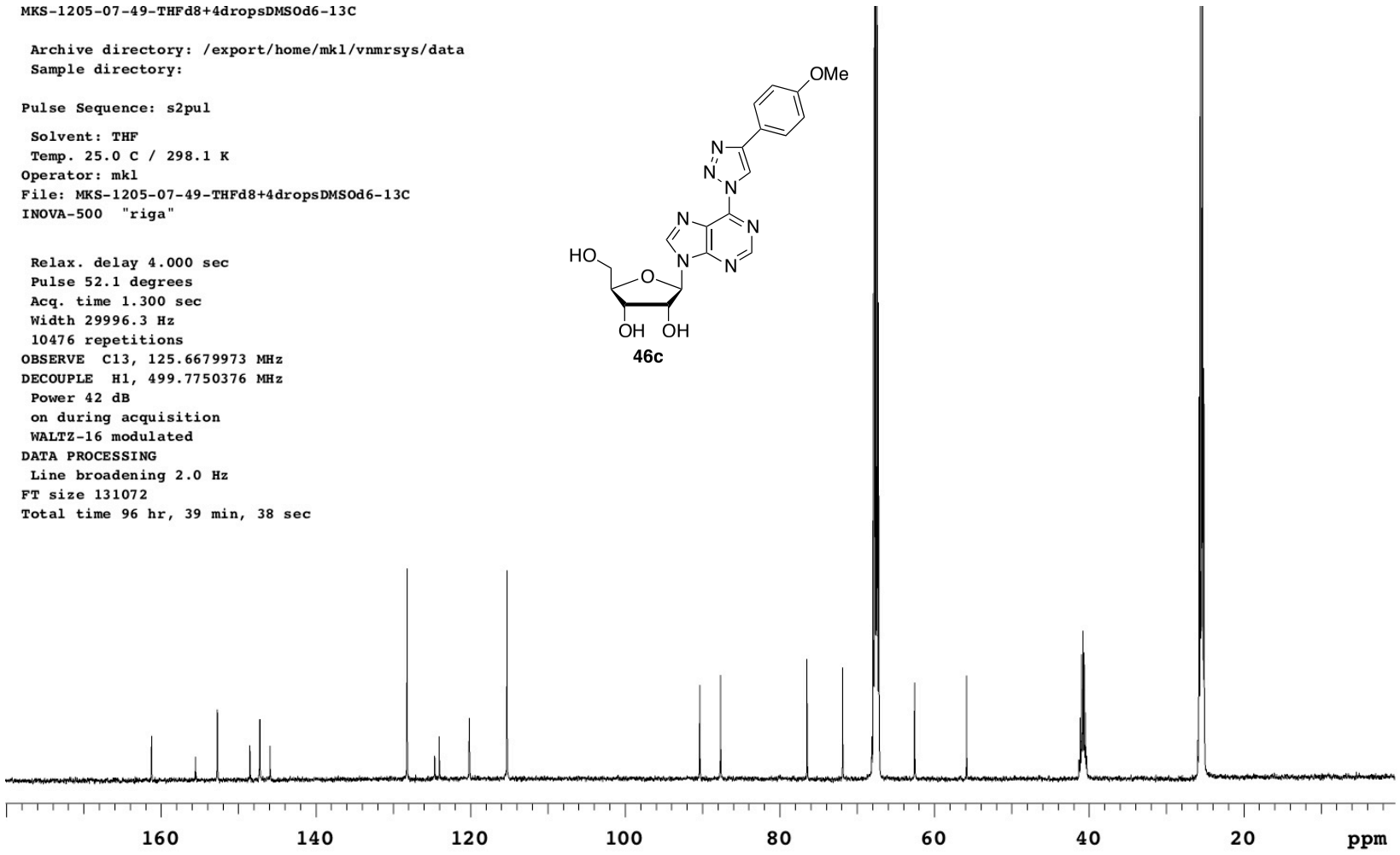

MKS-1205-07-41-DMSO-d6-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-41-DMSO-d6-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
120 repetitions
OBSERVE H1, 499.7730869 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
HO
O
OH
OH
N
N
N
N
N
N
46a
9
8
7
6
5
4
3
2
1
ppm

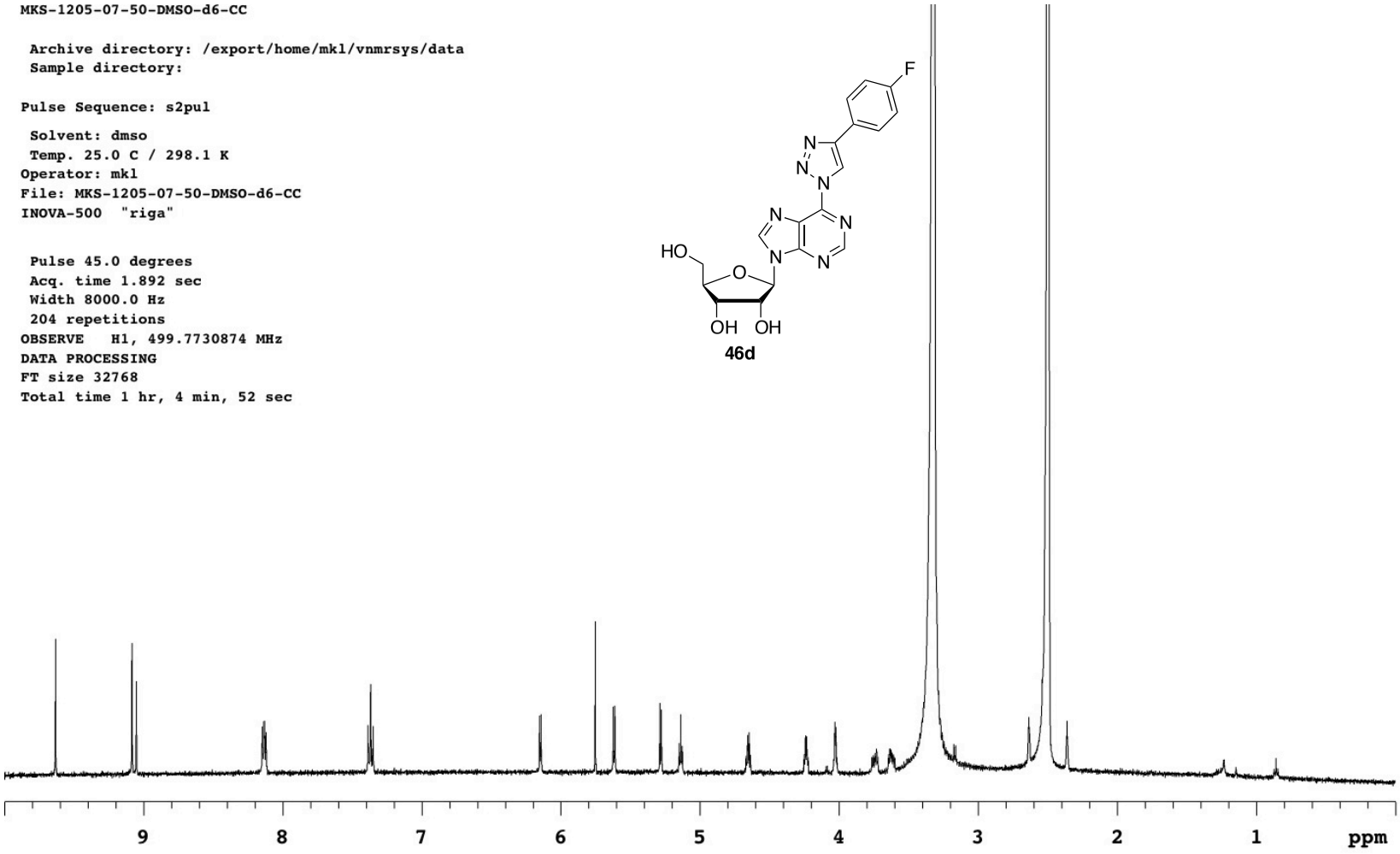

MKS-1205-07-41-THFd8+4dropsDMSOd6-13C
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: THF
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-41-THFd8+4dropsDMSOd6-13C
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
9628 repetitions
OBSERVE C13, 125.6679963 MHz
DECOUPLE H1, 499.7750376 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec
HO
O
OH
OH
N
N
N
N
N
N
46a
180
160
140
120
100
80
60
40
20
ppm

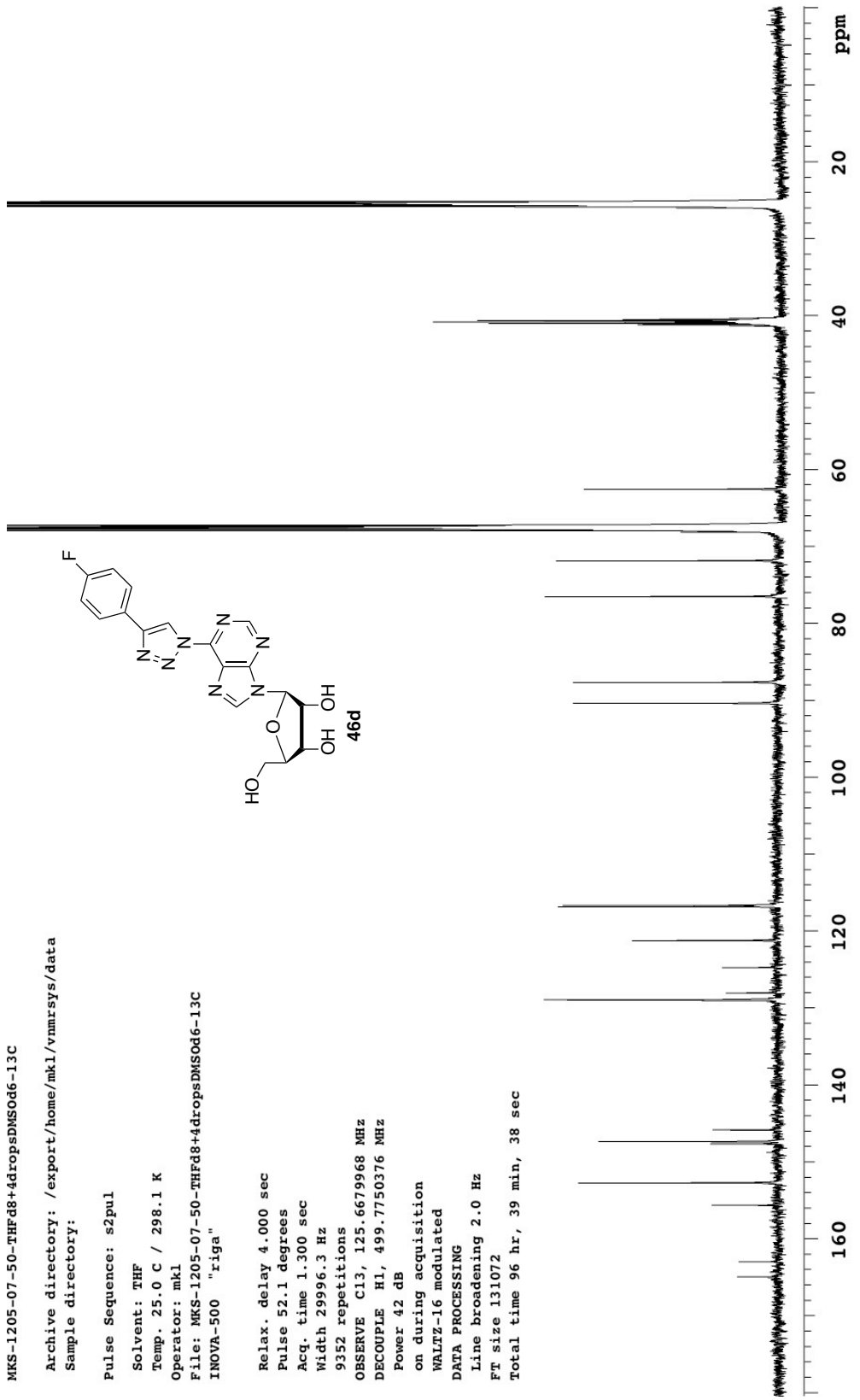

MKS-1205-07-47-DMSO-d6-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-47-DMSO-d6-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
148 repetitions
OBSERVE H1, 499.7730859 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
HO
O
OH OH
N
N
N
N
N
N
46b
9
8
7
6
5
4
3
2
1
ppm

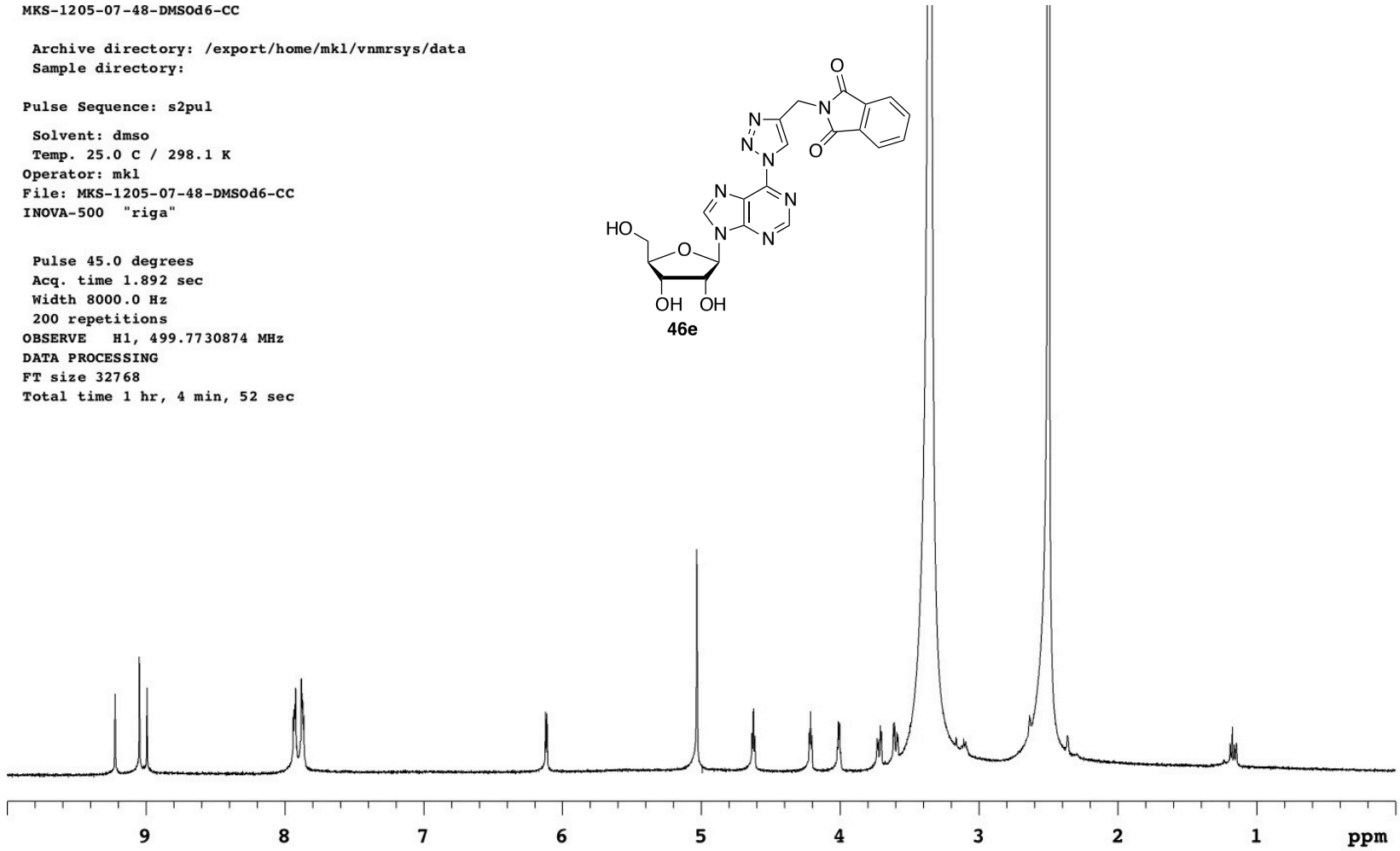

MKS-1205-07-47-THFd8+4dropsDMSOd6-13C
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: THF
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-47-THFd8+4dropsDMSOd6-13C
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
9876 repetitions
OBSERVE C13, 125.6679959 MHz
DECOUPLE H1, 499.7750376 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec
HO
OH OH
46b
160
140
120
100
80
60
40
20
ppm

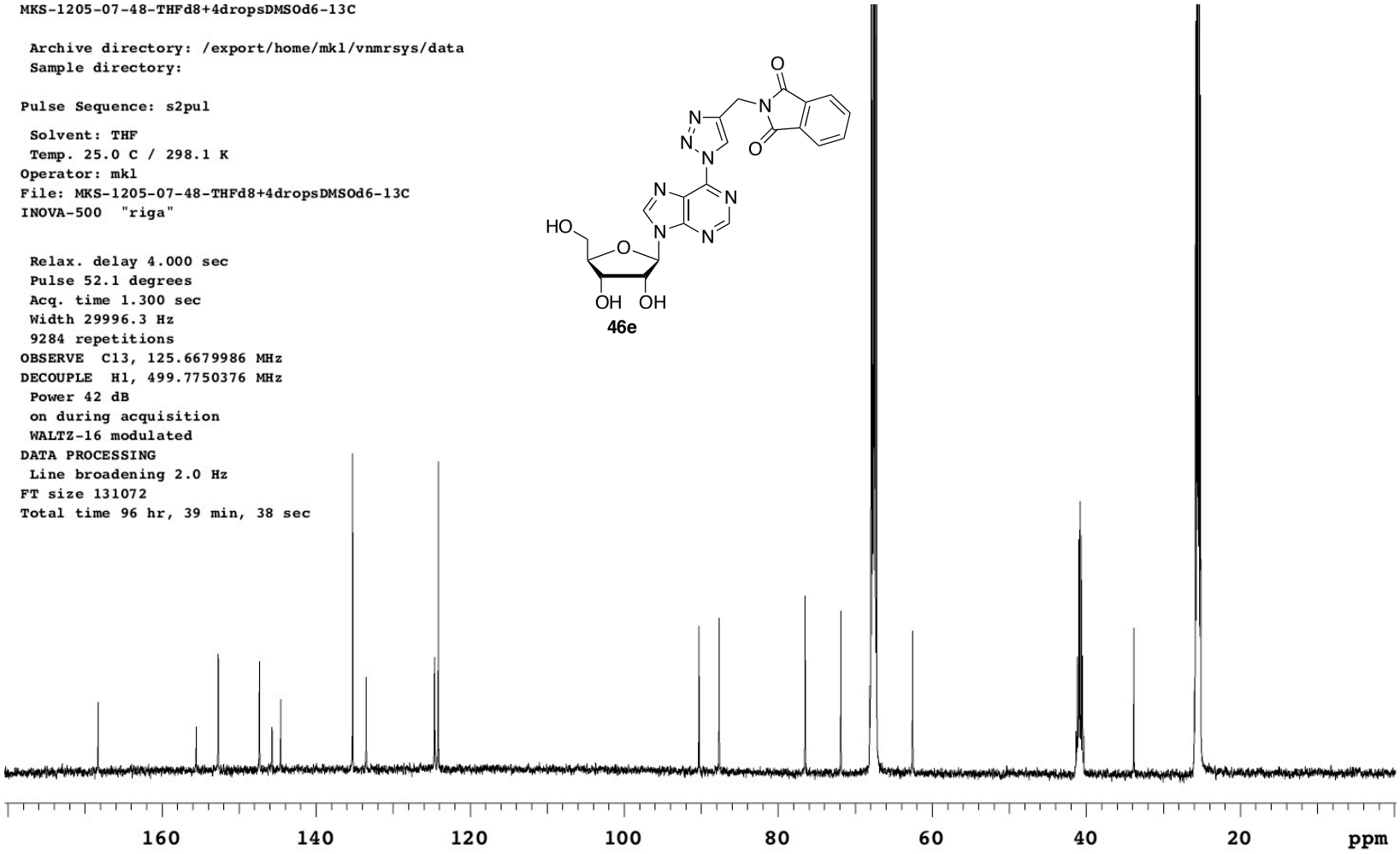

MKS-1205-07-49-DMSOd6-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-49-DMSOd6-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
160 repetitions
OBSERVE H1, 499.7730874 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
OMe
N
N
N
N
N
N
N
HO
O
OH
OH
46c
9
8
7
6
5
4
3
2
1
ppm

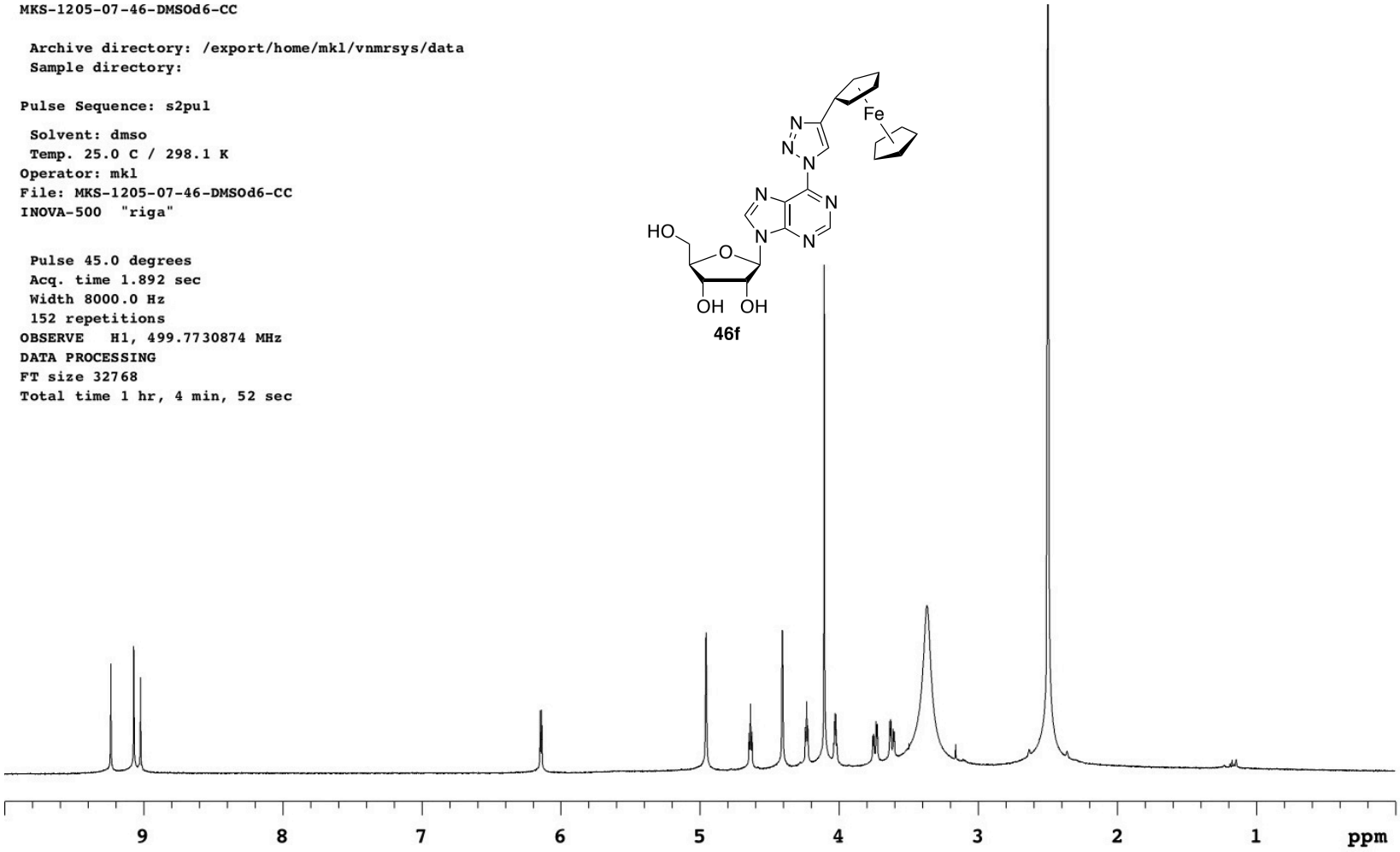

MKS-1205-07-49-THFd8+4dropsDMSOd6-13C
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: THF
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-49-THFd8+4dropsDMSOd6-13C
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
10476 repetitions
OBSERVE C13, 125.6679973 MHz
DECOUPLE H1, 499.7750376 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec
OMe
N
N
N
N
N
N
HO
O
OH
OH
46c
160
140
120
100
80
60
40
20
ppm

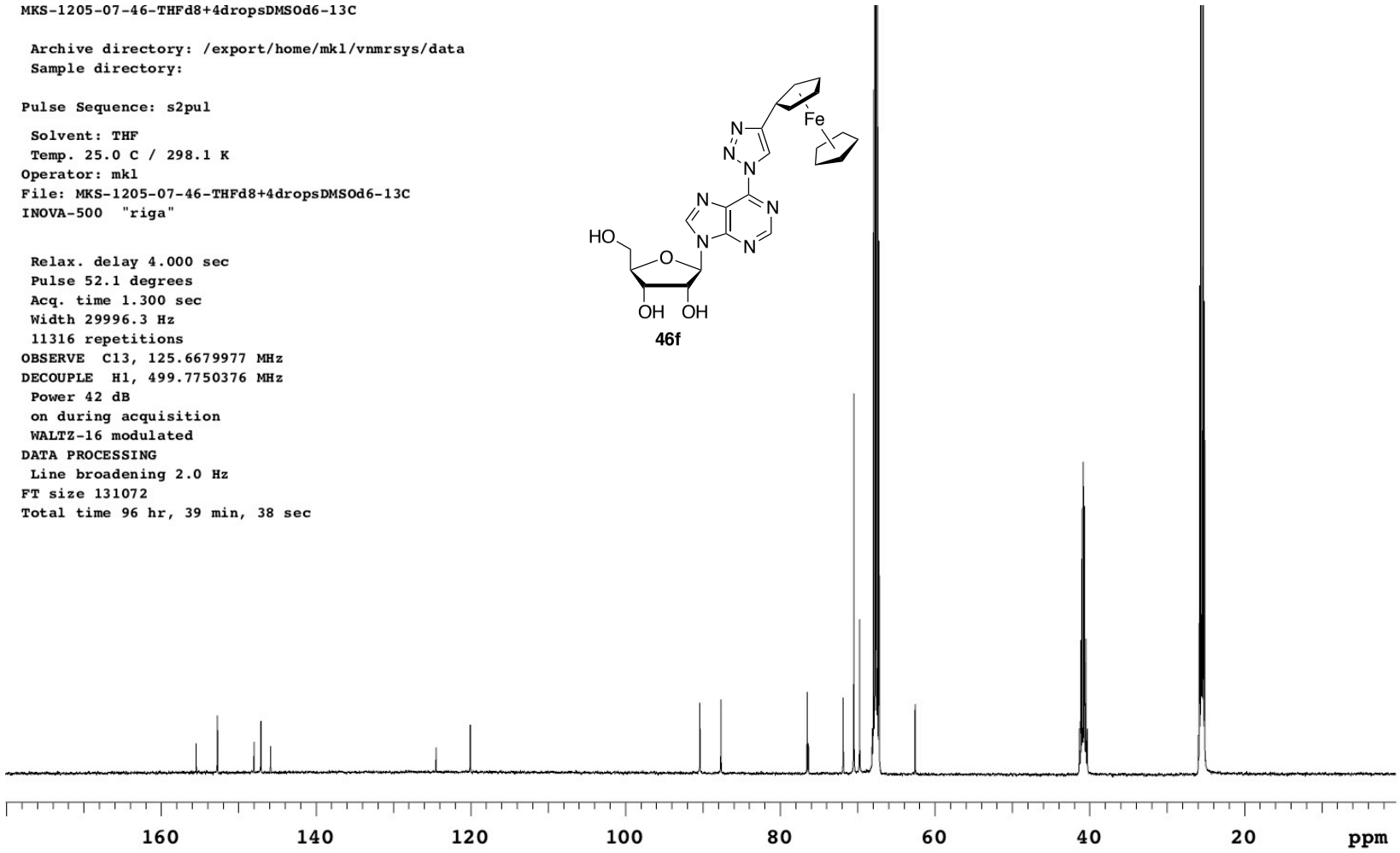

MKS-1205-07-50-DMSO-d6-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-50-DMSO-d6-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
204 repetitions
OBSERVE H1, 499.7730874 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
F
N
N
N
N
N
N
HO
O
OH
OH
46d
9
8
7
6
5
4
3
2
1
ppm


MKS-1205-07-50-THFd8+4dropsDMSOd6-13C
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: THF
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-50-THFd8+4dropsDMSOd6-13C
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
9352 repetitions
OBSERVE C13, 125.6679968 MHz
DECOUPLE H1, 499.7750376 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec
F
N
N
N
N
N
N
O
HO
OH
OH
46d
160
140
120
100
80
60
40
20
ppm


MKS-1205-07-48-DMSOd6-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-48-DMSOd6-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
200 repetitions
OBSERVE H1, 499.7730874 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
HO
O
OH
OH
N
N
N
N
N
N
O
O
46e
9
8
7
6
5
4
3
2
1
ppm


MKS-1205-07-48-THFd8+4dropsDMSOd6-13C
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: THF
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-48-THFd8+4dropsDMSOd6-13C
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
9284 repetitions
OBSERVE C13, 125.6679986 MHz
DECOUPLE H1, 499.7750376 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec
HO
OH OH
46e
160
140
120
100
80
60
40
20
ppm


MKS-1205-07-46-DMSOd6-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-46-DMSOd6-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
152 repetitions
OBSERVE H1, 499.7730874 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
HO
O
OH
OH
N
N
N
N
N
N
Fe
46f
9
8
7
6
5
4
3
2
1
ppm


MKS-1205-07-46-THFd8+4dropsDMSOd6-13C
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: THF
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-46-THFd8+4dropsDMSOd6-13C
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
11316 repetitions
OBSERVE C13, 125.6679977 MHz
DECOUPLE H1, 499.7750376 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec
HO
O
OH
OH
N
N
N
N
N
N
Fe
46f
160
140
120
100
80
60
40
20
ppm

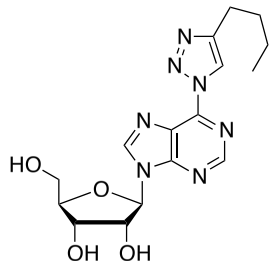
MKS-1205-07-51-DMSOd6-CC

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

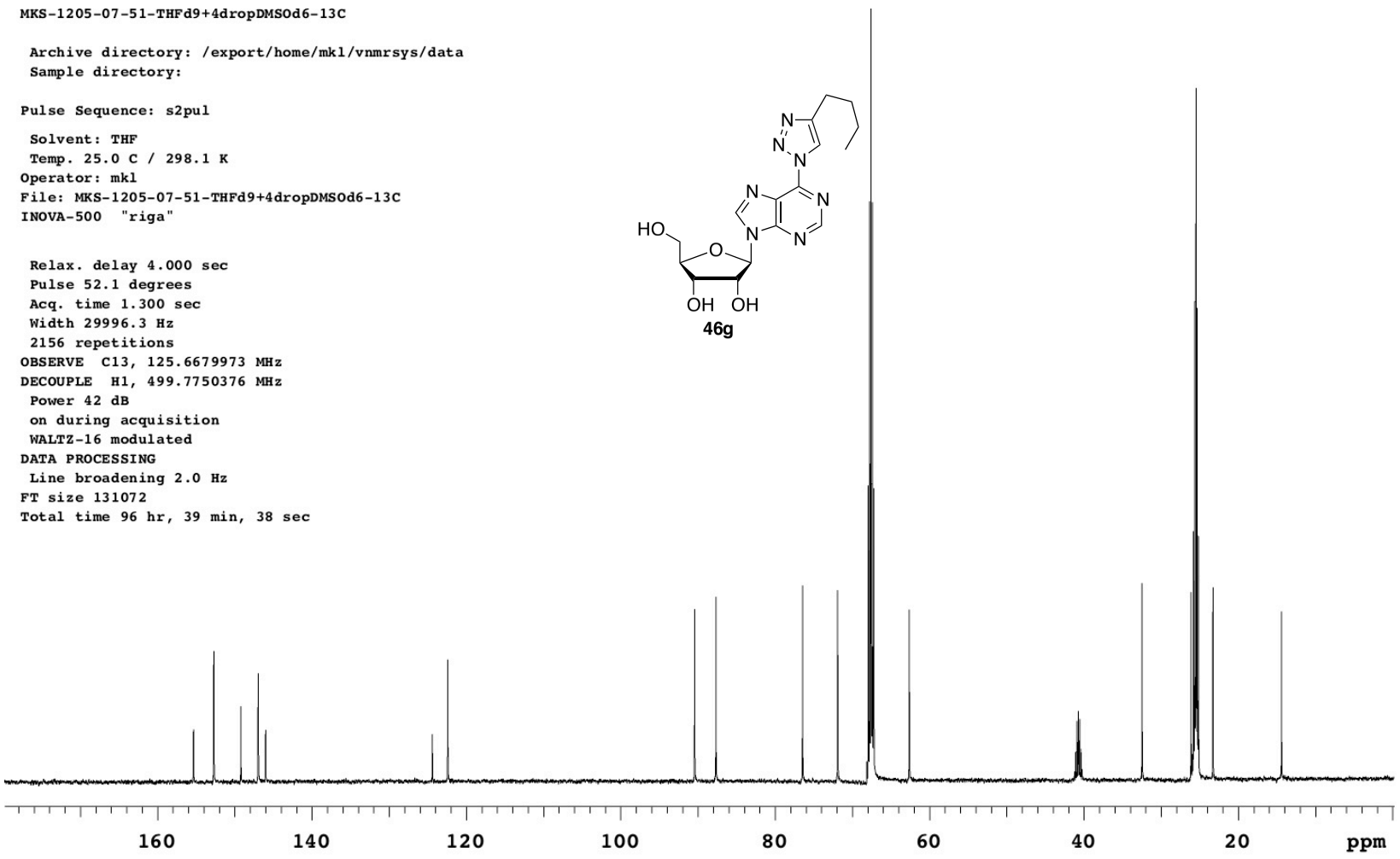
Pulse Sequence: s2pul

Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-51-DMSOd6-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
80 repetitions
OBSERVE H1, 499.7730868 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



46g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Sample directory:
Pulse Sequence: s2pul
Solvent: THF
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-51-THFd9+4dropDMSOd6-13C
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
2156 repetitions
OBSERVE C13, 125.6679973 MHz
DECOUPLE H1, 499.7750376 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec
HO
OH OH
46g
160
140
120
100
80
60
40
20
ppm

CHAPTER 2

A FACILE AND EFFICIENT METHOD FOR CONVERSION OF ALDOXIMES TO NITRILES

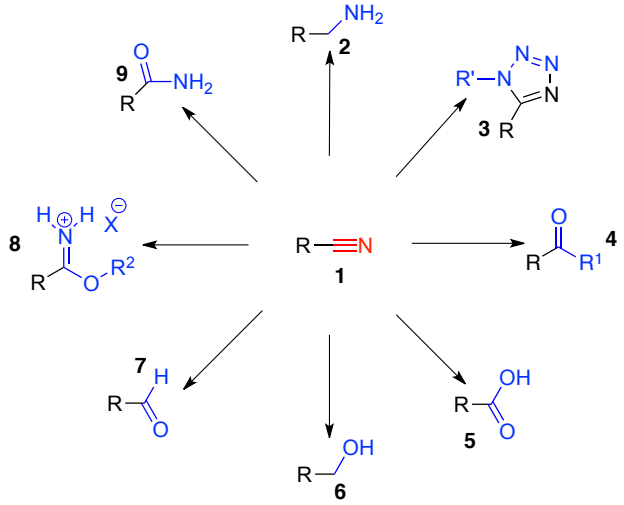
CHAPTER 2

A FACILE AND EFFICIENT METHOD FOR CONVERSION OF ALDOXIMES TO NITRILES

[2.1] INTRODUCTION

The nitrile group serves as a precursor for the synthesis of important functional groups such as amine, carboxylic acid, tetrazole, triazole etc. (Scheme 1).[1] Also, the nitrile group is present in various natural products, pharmaceuticals, agrochemicals and novel materials (Figure 1).[2-9] In several bioactive molecules, the cyano group plays an important role in hydrogen bonding with certain biological receptors.[10]

Scheme 1. *Conversion of the Nitrile Moiety to Various Useful Functionalities*



Dehydration of aldoximes is one of the most commonly used methods for the synthesis of nitriles.[11-23] Among reported methods, recently Augustine et al. discovered an efficient method for converting aldoximes to nitriles using propylphosphonic acid (Scheme 2, eq 1).[24] Rad et al. used *N*-(*p*-toluenesulphonyl)imidazole for the conversion of aldoxime to nitrile (eq 2).[25]

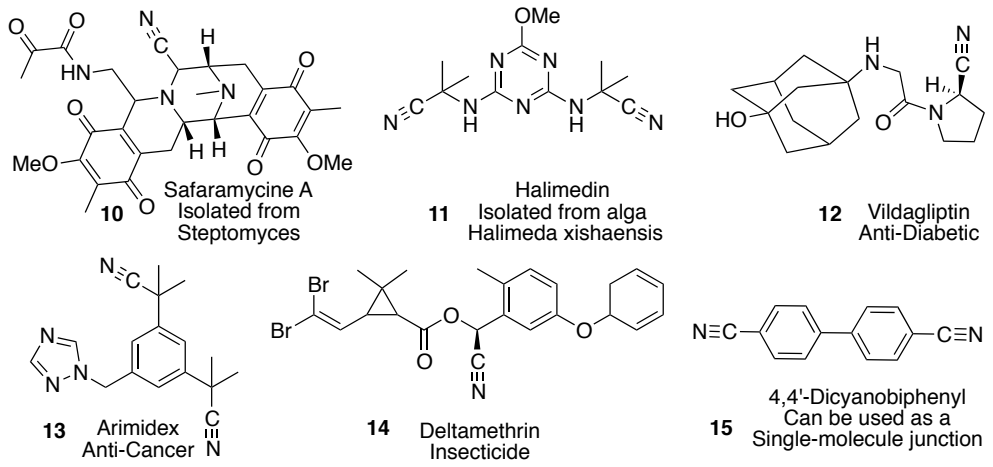
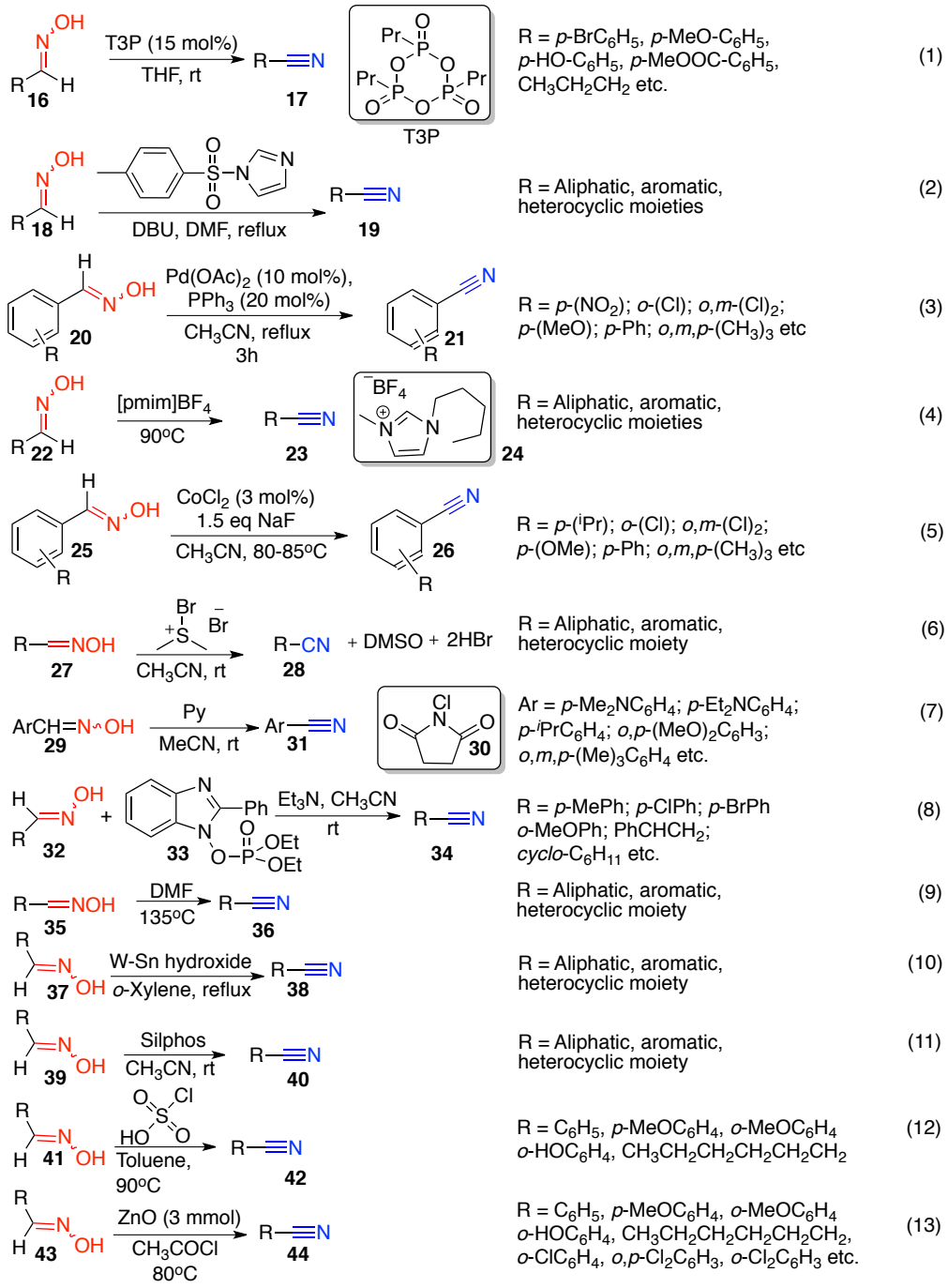


Figure 1. *Some Useful Molecules containing the Nitrile Moiety*

Kim et al. reported a palladium-catalyzed synthesis of nitriles from aldoximes (eq 3).[26] Saha et al. gave an account of aldoxime dehydration using an ionic liquid (eq 4).[27] Cobalt(II) catalyzed dehydration of aldoximes to nitrile has been described by Tamilselvan et al. (eq 5).[28] In a communication by Yadav's group, bromodimethylsulphonium bromide (BDMS) was used for the conversion of aldoximes and primary amides to nitriles (eq 6).[29] Using *N*-chlorosuccinamide and pyridine, Gucma et al. achieved conversion of aldoxime to nitrile (eq 7).[30] Use of phosphoric acid diethyl ester 2-phenylbenzimidazol-1-yl ester for aldoxime oxidation was communicated by the Kokare group (eq 8).[31] Supsana et al. reported dimethyl formamide (DMF) catalyzed thermal dehydration of aldoximes to nitrile (eq 9).[10] In a unique work by Yamaguchi et al. a heterogeneous catalyst, tungsten-tin mixed hydroxide, was used to convert aldoxime to nitrile (eq 10).[32] Silphos [$PCl_{3-n}(SiO_2)_n$], a heterogeneous phosphine reagent mediated conversion of oximes to nitriles was reported by Iranpoor group (eq 11).[33] An efficient method of dehydrating aldoxime to nitrile was published by Li et al. using chlorosulfonic acid (eq 12).[34] Sarvari et al. communicated a solvent free method to oxidize aldoxime to nitrile using ZnO/CH_3COCl (eq 13).[35]

Scheme 2. *Some Recently Published Methods for Dehydration of Aldoxime to Nitrile*



Many of the reported methods use harsh reaction conditions such as high reaction temperature, acidic and/or corrosive reaction conditions. Harsh reaction conditions cannot be applied to fragile, multifunctional molecule such as nucleosides. Hence, we became interested in evaluating the nucleoside modification methodology developed in our lab, for the synthesis of

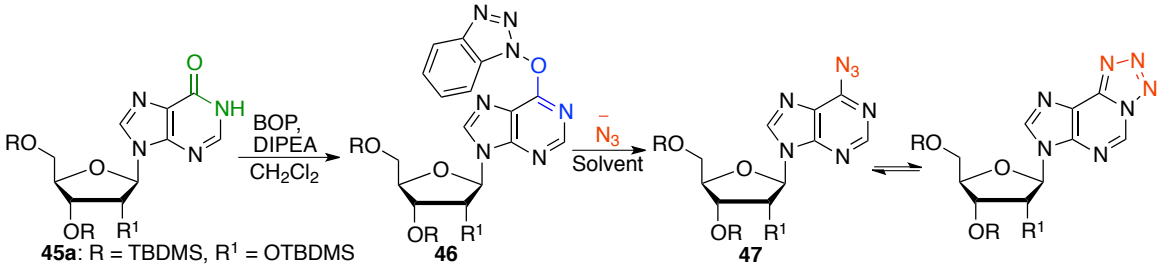
nitriles under mild reaction conditions using 1*H*-benzotriazol-1-yloxytris(dimethyl-amino)phosphonium hexafluorophosphate (BOP) as dehydrating agent.[36]

[2.2] RESULTS AND DISCUSSION

[2.2.1] Optimization and substrate scope

In the previous chapter we described a simple synthesis of C-6 azido nucleosides from benzotriazolyl derivatives of nucleosides. C-6 benzotriazolyl purine nucleosides can easily be prepared by simple reaction of 1*H*-benzotriazol-1-yloxytris(dimethyl-amino)phosphonium hexafluorophosphate (BOP) with inosine or 2'-deoxyinosine (Scheme 3).[37] The formation of the C-6 azido nucleoside (Scheme 3) proceeds via displacement of benzotriazolyloxy (BtO^-) group by N_3^- by the S_NAr mechanism. The reaction conditions for displacement by N_3^- [37] and other nucleophiles[38] indicate the ready leaving group ability of BtO^- anion.

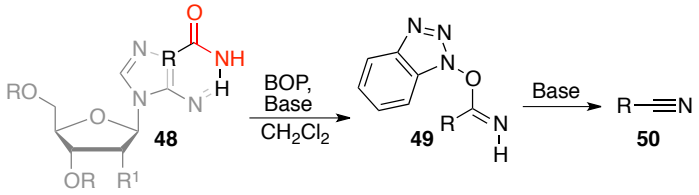
Scheme 3. *Synthesis of C-6 Azido Nucleosides Via Reaction of BOP with Inosine*



45a: R = TBDMS, R^1 = OTBDMS
45b: R = TBDMS, R^1 = H
45c: R = Ac, R^1 = OAc
45d: R = Ac, R^1 = H
45e: R = H, R^1 = OH
45f: R = H, R^1 = H

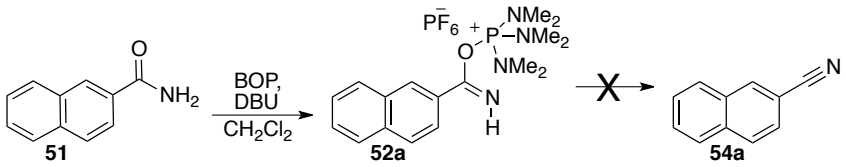
From these two observations, that is the facile formation of O^6-(benzotriazol-1-yl) intermediates and the good leaving group ability of BtO^-, we envisioned development of reaction conditions for the dehydration of amides to nitriles (Scheme 4).

Scheme 4. *Proposed Synthesis of Nitriles from Amides*



We tested our hypothesis by initially reacting benzamide with BOP and DBU. To our surprise we did not obtain the desired nitrile. The reaction stopped at phosphonium ion intermediate stage (Scheme 5). The phosphonium ion intermediate **52a** was isolated and analyzed by ^{1}H NMR (dimethylamine resonance: δ 2.83, $^3J_{P,H}$ = 10.2 Hz).[39] Even with heating, the reaction could not be forced to go to completion. We were intrigued by this result because in one report, (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate PyBOP with $(i\text{-Pr})_2$NEt in CH_2Cl_2 at 40 ºC has been used for dehydrating amides to nitriles.[23] Considering this report and our observation, we wondered if aldoximes, which are more acidic than alcohols,[40,41] could be dehydrated to nitriles using commercially available BOP and a base. Comparatively, BOP is cheaper than PyBOP. In a recent report it was shown that use of PPh_3/I_2 in CH_2Cl_2 produced nitriles in high yields, within short reaction times.[42]

Scheme 5. *Attempted Synthesis of Nitriles from Amide*

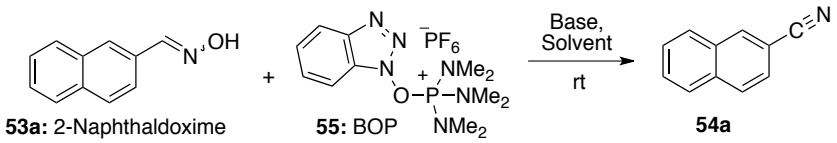


In our hands, a trial reaction of 2-naphthaldoxime with PPh_3/I_2, under the reported conditions showed incomplete reaction in 5 h. In order to get complete consumption of the starting material, the reaction was allowed to proceed for an extended period, at which time formation of some 2-naphthaldehyde was also observed (resonance at δ 10.17 ppm in the ^{1}H NMR) along with desired nitrile. Thus, formation of aldehydes may be a complicating problem in the dehydation of other aldoximes using PPh_3/I_2. Therefore, we decided to investigate our idea of using BOP for the aldoxime dehydration with the belief that mild, efficient methods would be necessary for relatively fragile substrates.

This chapter describes a simple synthesis of nitriles from aldoximes using BOP. One issue that remained on our minds was that, upon reaction with aldoxime, BOP will produce hexamethylphosphoramide (HMPA), a suspected nasal carcinogen.[43] To circumvent this problem, we also considered the use of the tosylate of HOBt (Bt-OTs) for the conversion of aldoxime to nitrile. An attempt to gain some mechanistic insight into the reaction of BOP with aldoxime in the presence of base, DBU was also undertaken. Finally, we have applied this methodology as one of the three steps in a short and efficient synthesis of adeninyl ribofuranonitrile, a compound that has demonstrated useful antiviral activity.[31]

We began our investigation for the optimal reaction conditions by screening different solvents and bases. For the initial optimization, 2-naphthaldoxime and with 2 molar equivalents of BOP were used (Table 1). As seen from Table 1, fast conversion of 2-naphthaldoxime to 2-cyanonaphthalene was observed in the reaction with BOP and DBU in CH_2Cl_2 (Table 1, entry 3). Reactions in THF and DMF were also complete within reasonable time periods, and were suitable for this reaction (entries 1 and 2). Reaction in $CHCl_3$ did not proceed cleanly (entry 4) and therefore the product was not isolated. Reaction with a weaker base $(i\text{-Pr})_2\text{NEt}$ (pK_b 2.6) gave excellent conversion (entry 6), but the reaction was very slow compared with the stronger base DBU (pK_b 2.0). DMF proved to be an inferior solvent when $(i\text{-Pr})_2\text{NEt}$ was used as base (entry 5). There is no reaction in the absence of base (entries 7 and 8). Thus, a suitable base is important for the reaction.

Table 1. *Optimization of the Dehydration Reaction of 2-Naphthaldoxime Using BOP*



53a: 2-Naphthaldoxime **55:** BOP **54a**

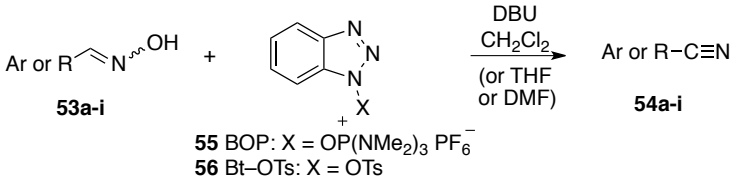
	Base, Solvent	Time	Yield[a]
1	2.3 molar equiv DBU, THF	3.5 h	91%
2	2.3 molar equiv DBU, DMF	3.5 h	93%
3	2.3 molar equiv DBU, CH_2Cl_2	1 h	95%
4	2.3 molar equiv DBU, $CHCl_3$	1 h	NA[b]
5	2.3 molar equiv (i-Pr)$_2$NEt, DMF	19 h	Inc[c]
6	2.3 molar equiv (i-Pr)$_2$NEt, CH_2Cl_2	20 h	90%
7	no base, CH_2Cl_2	6 days	NR[d]
8	no base, DMF	45 h	NR[d]

[a] Where reported, yield is of isolated and purified product. [b] Although this reaction was complete within 1 h, the reaction was not clean and therefore the product was not isolated. [c] The aldoxime was still present although product formation was observed. [d] No product formation was observed and aldoxime was still present.

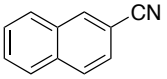
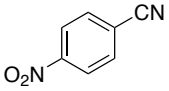
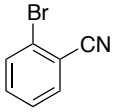
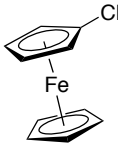
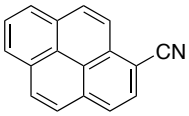
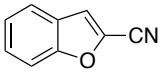
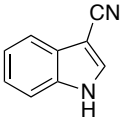
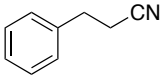
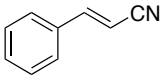
The optimal conditions were used to test the generality of this reaction with a variety of aldoximes. The aldoximes were synthesized by conventional methods involving the use of NH_2OH•HCl and aqueous Na_2CO_3, K_2CO_3, or NaOH. The results are presented in Table 2. While performing some reactions in CH_2Cl_2 at elevated temperature we found some unusual products resulting from the reaction between the 1-hydroxybenzotriazole formed and CH_2Cl_2 (Scheme 6, eq 1). Such reactions are known in literature.[44] Thus, reactions requiring higher temperatures were performed in THF as solvent, and to show the generality, some of these

reactions were performed in THF (Table 2, entries 3, 4 and 7). Reaction of pyrene-1-carbaldoxime was performed in DMF due to solubility reasons (entry 5).

Table 2. *Generality of the Dehydration Methodology Using BOP or Bt-OTs and DBU*[a]



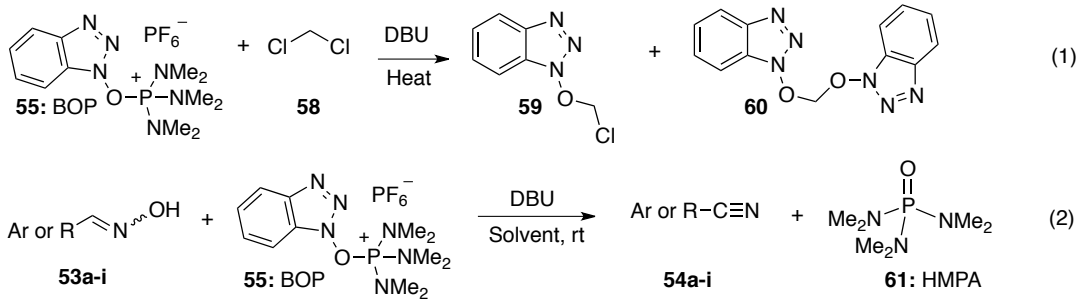
55 BOP: X = $OP(NMe_2)_3$ PF_6^-
56 Bt–OTs: X = OTs

Entry	Product	Reagent	Time, Temp	CΞN $\bar{\nu}$	Product, Yield[b]
1		BOP	45 min, rt	2225 cm^{-1}	**54a:** 95%
		Bt–OTs	25 min, rt		**54a:** 95%
2		BOP	45 min, rt	2233 cm^{-1}	**54b:** 96%
		Bt–OTs	30 min, rt		**54b:** 95%
3		BOP[c]	60 min, 50 ˚C	2224 cm^{-1}	**54c:** 84%
		Bt–OTs[c]	30 min, rt		**54c:** 80%
4		BOP[c]	90 min, rt	2223 cm^{-1}	**54d:** 97%
		Bt–OTs[c]	60 min, rt		**54d:** 89%
5		BOP[d]	45 min, rt	2213 cm^{-1}	**54e:** 96%
		Bt–OTs[d]	30 min, rt		**54e:** 90%
6		BOP	45 min, rt	2228 cm^{-1}	**54f:** 85%
		Bt–OTs	30 min, rt		**54f:** 85%
7		BOP[c]	120 min, rt	2224 cm^{-1}	**54g:** 72%
		Bt–OTs[c]	45 min, rt		**54g:** 42%
					57: 50%[e]
8		BOP	45 min, rt	2246 cm^{-1}	**54h:** 86%
		Bt–OTs	30 min, rt		**54h:** 73%
9		BOP	35 min, rt	2216 cm^{-1}	**54i:** 92%
		Bt–OTs	20 min, rt		**54i:** 92%

[a] Reactions were conducted on a 1 mmol scale except in the case of the pyrene oxime (entry 5) where reaction with Bt–OTs was conducted on the 0.75 mmol scale. [b] Yield of isolated and purified products. [c] Reaction was performed in THF. [d] Reaction was performed in DMF. [e] In this reaction with Bt-OTs, in addition to indole-3-carbonitrile **54g** the 1-(*p*-toluenesulfonyl)-indole-3-carbonitrile **57** was also isolated in 50% yield.

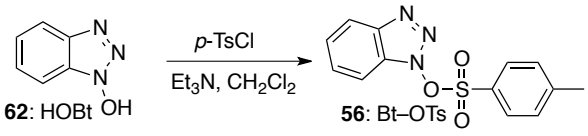
Evidently, reactions with BOP proceeded smoothly (Table 2). However, BOP produces an equivalent amount of hexamethylphosphoramide [HMPA, $(Me_2N)_3PO$] as byproduct (Scheme 6, eq 2). HMPA is a known nasal carcinogen in rats.[43] Elimination of HMPA as byproduct would make this methodology more useful for the synthesis of compounds of biological significance.

Scheme 6. *Reaction of BOP with CH_2Cl_2 and Aldoxime*



Various reagents were evaluated as potential dehydrating agents but we settled on 1*H*-benzotriazol-1-yl-4-methylbenzenesulfonate (Bt–OTs). This reagent is easily prepared in large quantities from low cost, commercially available reagents. Also, synthesis of Bt–OTs is known in the literature.[45-48]

Scheme 7. *Synthesis of 1H-Benzotriazol-1-yl-4-methylbenzenesulfonate (Bt–OTs)*



To our knowledge, Bt–OTs has not been used for dehydration of aldoximes. The dehydration reactions of aromatic, aliphatic, and heterocyclic oximes with Bt–OTs, under conditions developed for BOP, were just as efficient. Results from the reactions with Bt–OTs are also shown in Table 2. Both BOP and Bt–OTs gave good to excellent yields of aromatic, aliphatic, and heterocyclic nitriles. Unprotected indole oxime reacted readily with BOP and DBU to produce the corresponding nitrile in good yield. However, reaction of this oxime with

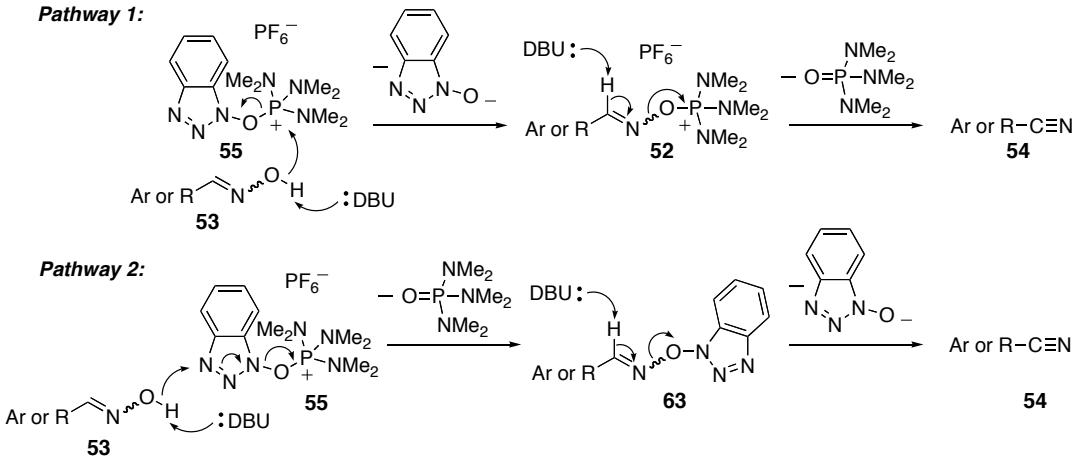
Bt–OTs and DBU gave a chromatographically separable mixture of carbonitrile **54g** (42% entry 7) and the corresponding *N*-tosyl derivative[49] **57** (50%). Such *N*-sulfonylation has been observed during amide formation.[48] Aldoxime of 3-phenyl-1-propanal also produced the corresponding nitrile derivative **54h** (entry 8) in good yield, despite the generally lower acidity of alkyl aldoximes.[40] In terms of functional group tolerance, dehydration of aldoximes can be carried out with in the presence of nitro, organometallic, and free amino moieties (entries 2, 4, and 7) as well as *ortho* substituents on an aryl ring (entries 3 and 5).

[2.2.2] Mechanistic investigation of the dehydration of aldoximes with BOP

An attempt was made to obtain some mechanistic insight into the reaction of aldoximes with BOP and DBU. Described in Scheme 7 are two mechanistic possibilities. In pathway 1, reaction of deprotonated oxime could occur at the phosphorus atom of BOP, giving rise to a new phosphonium species. On the other hand, in pathway 2, a S_N2' like attack at the nitrogen atom of BOP could directly produce HMPA, a phosphoramide very different from the phosphonium species formed in pathway 1. Therefore, we hypothesized that these two different phosphorus atom containing species should be distinguished by $^{31}P\{^1H\}$ NMR.

To elucidate the reaction pathway, a series of control reactions were performed. First, a reaction of 2-naphthaldoxime and DBU was conducted in CH_2Cl_2 in the absence of BOP. As expected, no reaction was observed over a period of 2 hrs and only starting material was present. This indicates the necessity for presence of BOP in these dehydration reactions. In presence of BOP, the reaction between 2-naphthaldoxime and DBU was complete within 1 hr.

Scheme 8. *Two Possible Pathways for the Reaction of Aldoxime with BOP in Presence of DBU*



Next, a reaction between 2-naphthaldoxime and BOP was conducted in CD_2Cl_2 using DBU, and progress of reaction the reaction was monitored by $^{31}P\{^1H\}$ NMR (Figure 2). In CD_2Cl_2, the phosphorus resonance in BOP appears at δ 44.1 ppm relative to 85% H_3PO_4 as external standard (the PF_6^- septet appears at δ –143.9 ppm). Upon addition of DBU, no new signal for a new phosphonium species was observed even after a short reaction time of 5 min, but only formation of HMPA was observed at δ 25.8 ppm (pure HMPA appears at δ 25.4 ppm in CD_2Cl_2). Finally, after 100 min, the reaction mixture was spiked with 1 molar equiv of HMPA. An increase in the signal intensity δ 25.8 ppm was observed, confirming the HMPA resonance.

The dehydration reaction of *o*-bromobenzaldoxime and BOP in the presence of DBU needed somewhat forcing conditions (Table 2, entry 3). Thus, we conducted a second $^{31}P\{^1H\}$ NMR experiment with *o*-bromobenzaldoxime to observe for any new phosphonium ion resonance. Unfortunately, in this case as well, no new phosphonium signal was observed.

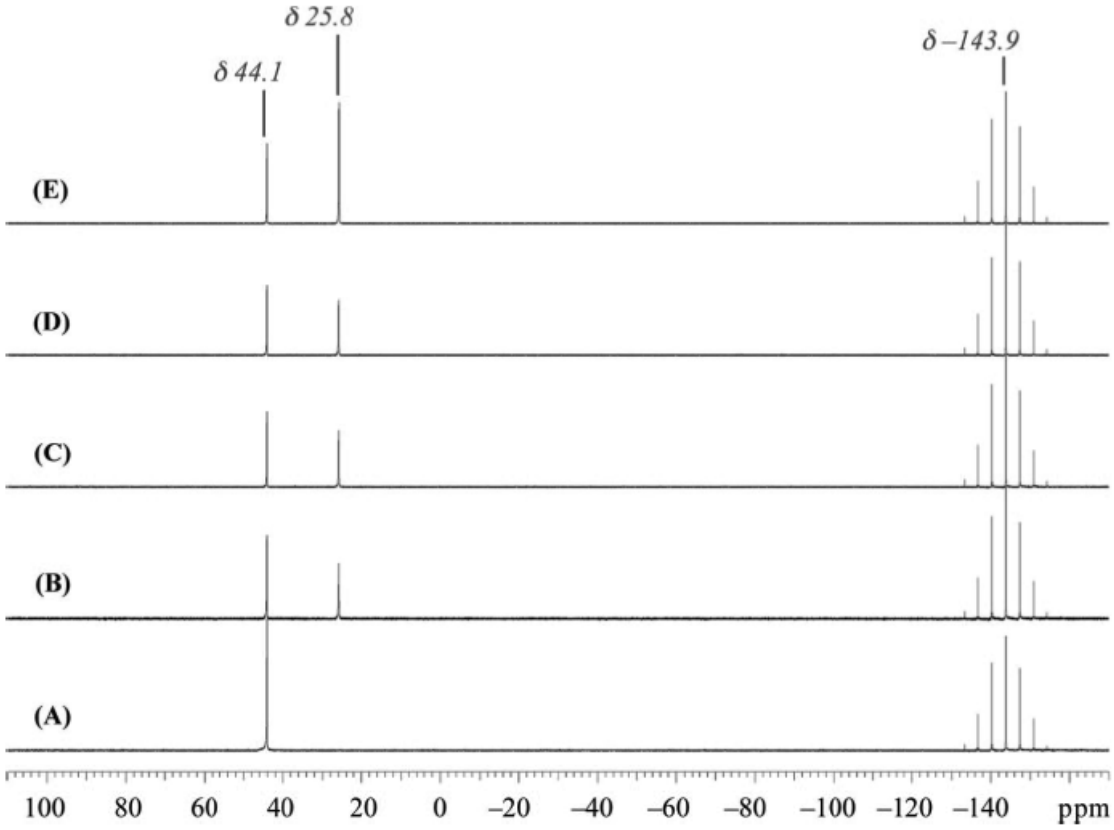


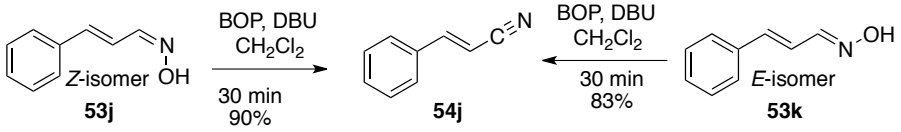
Figure 2. *Monitoring the course of the reaction between 2-naphthaldoxime, BOP (2 molar equiv), and of DBU (2.3 molar equiv) in CD_2Cl_2 using $^{31}P\{^1H\}$ NMR: (A) naphthaldoxime (0.2 M in CD_2Cl_2) + BOP; (B) 5 min after addition of DBU; (C) 45 min after addition of DBU; (D) 100 min after addition of DBU; and (E) reaction mixture spiked with HMPA (1.0 molar equiv)*

On the basis of these experiments, if a phosphonium salt is indeed an intermediate in this reaction (pathway 1 in Scheme 7), it is either formed in low concentrations, or is very reactive, or short lived, and hence, not easily observed via $^{31}P\{^1H\}$ NMR. Carboxylic acids[47] and amide functionalities of nucleosides[36] have been shown to react with BOP via a phosphonium derivative. However, the reaction of aldoximes with BOP appears to follow an alternate pathway, e.g. pathway 2 in Scheme 7, involving rapid formation of HMPA without intermediacy of a new phosphonium species.

The relative rates of dehydration of *E*- and *Z*-oximes under these reaction conditions was then evaluated with the isomeric oximes of cinnamaldehyde. The *E*- and *Z*-oximes of

cinnamaldehyde were synthesized and separated by silica column chromatography and characterized by NMR.[50] Reaction of *Z*-isomer with BOP and DBU was complete within 30 min, with a 90% isolated yield of **10** (Scheme 8). Reaction of the *E*-isomer with BOP and DBU under similar reaction conditions was also complete within 30 min, with a 83% isolated yield of **10**. This experiment indicates that, under our reaction conditions, the stereochemistry of the oxime does not seem to influence the ease of the dehydration reaction.

Scheme 9. *Dehydration of E- and Z-isomers of Cinnamaldehyde Oximes*

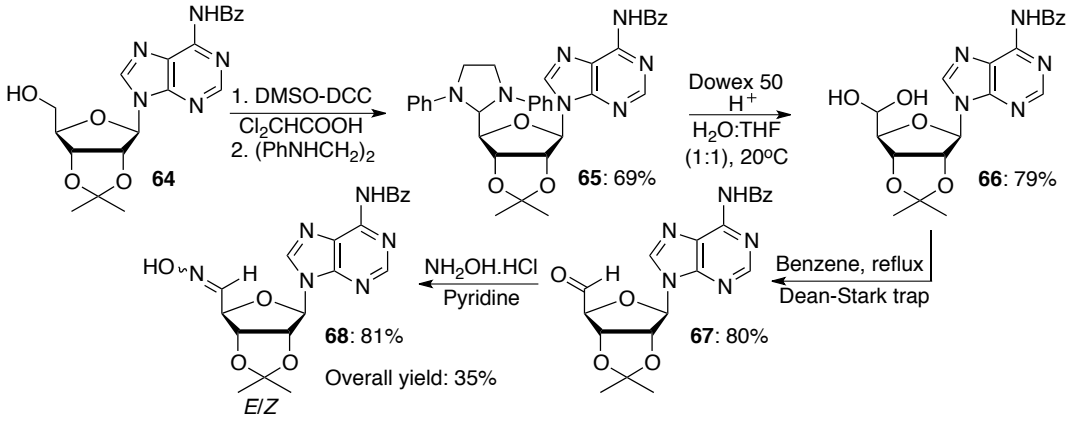


[2.2.3] Application of this new methodology to the synthesis of a nucleoside nitrile

Adeninyl ribofuranonitrile has shown encouraging antiviral activity against vesicular stomatitis virus (VSV, EC_{50} 1.2 μg/mL) and human cytomegalovirus (HCMV, EC_{50} 1.4 μg/mL). Hence we chose to evaluate this methodology for the synthesis of adeninyl ribofuranonitrile from the commercially available 2',3'-acetonide of adenosine.

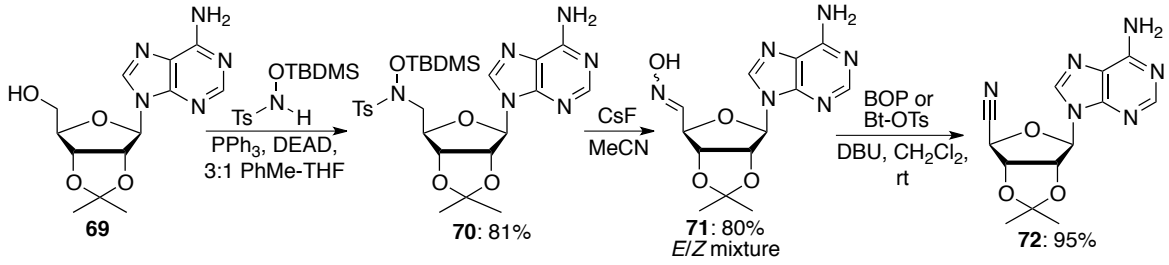
The synthesis of *E*/*Z* 5'-carbaldoximes **68**, the requisite precursor for the dehydration, from 2',3'-acetonide protected adenosine is known.[51] However, the synthesis of nucleoside oximes is cumbersome. As shown in Scheme 10, the amino group of the nucleoside requires protection and the oxidation of the 5'-hydroxyl group has to be carried out via a *N,N'*-diphenylethylenediamino intermediate **65**, which produces the aldehyde hydrate **66**, upon hydrolysis. This aldehyde hydrate has to be azeotroped with benzene before synthesizing the nucleoside aldoximes **68** (Scheme 10).[52]

Scheme 10. *Classical Method of Synthesis of E/Z 5'-Carbaldoxime of Adenosine*



Considering the inconvenience with the classical method of synthesis of the nucleoside 5'-oximes, we chose a completely different route (Scheme 11). The oxime of the nucleoside **71** was synthesized by applying a recently reported methodology, involving *O*-(*tert*-butyldimethylsilyl)-*N*-tosylhydroxylamine.[50] Thus, the 5′-hydroxyl group of commercially available **69** was converted to the *N*-tosyl-*O*-silylhydroxylamine via a Mitsunobu reaction, to give **70** in 81% yield. In the presence of a nitrogen nucleophile, Mitsunobu reactions at C-5' position of adenosine nucleoside is known to proceed smoothly without the protection of C-6 amino group.[53,54]

Scheme 11. *Our Strategy of Synthesis of E/Z 5'-Carbaldoxime of Adenosine Followed by Dehydration*

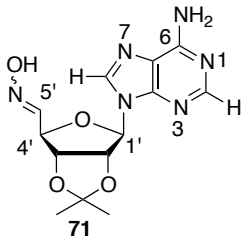


Desilylation of **70** using CsF, gave an *E*/*Z* mixture of isomeric oximes **71** in 80% yield via tautomerization of a nitroso intermediate. In Table 3, the observed chemical shifts of some key protons in **71** have been compared with the reported chemical shifts of those protons.[51]

Table 3. *Parallel Between the Reported and Observed Chemical Shifts of Some Protons of (E/Z) Nucleoside Oxime* ***71***[a]

71	Chemical Shift (ppm)				
	H–1'	H–5'	N–OH	H–2	H–8
E-isomer (reported)	6.25	7.34	11.14	8.17	8.27
Z-isomer (reported)	6.27	6.33	11.37	8.15	8.31
E-isomer (observed)	6.25	7.35	11.13	8.17	8.27
Z-isomer (observed)	6.27	6.34	11.36	8.15	8.31

[a] ^{1}H NMR recorded in DMSO-d_6 solvent.



71
E/*Z* mixture

The reaction between the nucleoside oxime **71** (*E*/*Z* mixture) and 2.0 molar equivalents of BOP and 2.3 molar equivalent of DBU base resulted in the smooth formation of 5'-adeninylribofuranonitrile **72** in 95% yield within 45 mins. Similarly, exposure of **71** with 2.0 molar equiv of Bt–OTs and 2.3 molar equiv of DBU also led to the formation of **72** in 93% yield in 35 min. Thus, the dehydration reaction of *E/Z* mixture of nucleoside oximes with both BOP and Bt–OTs proceeds smoothly leading to the corresponding nitrile in comparable yields.

Unlike the aldoxime of indole (Table 2, entry 7), no formation of *N*-sufonylated adenosine was observed when C-6 amino unprotected nucleoside oxime **71** was reacted with with Bt–OTs. Thus, the overall yield of **72** over 3 steps was 61% with BOP and 60% with Bt–OTs. Compound **72** has been synthesized previously from adeninyl methyl ribofuranuronate via the amide in 46% yield.[55]

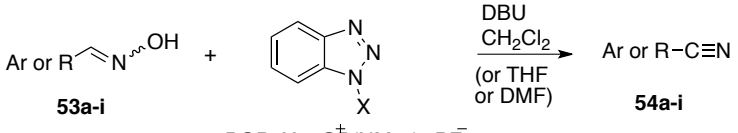
[2.3] CONCLUSION

Use of BOP or Bt–OTs proved to be very cost effective, simple, and efficient for dehydrating aldoximes to nitriles using DBU as base. Most reactions proceeded at room temperature in CH_2Cl_2. Other solvents like THF or DMF could also be used if the reaction requires heating, or solubility of aldoxime is an issue. Finally, a new three-step strategy to synthesize adeninyl ribofuranonitrile (as it's 2',3'-acetonide) from 2',3'-acetonide protected adenosine was developed. This new procedure uses only one protecting group, and simple removal of this acetonide protecting group should yield the fully deprotected compound. This approach can potentially also be used for modification of other nucleoside derivatives as well. The strategy of directly converting alcohols into oximes via Mitsunobu reaction in combination with this new dehydration method is expected to find wide use in the synthesis of organic nitriles.

[2.4] GENERAL PROCEDURE

Except two, all the nitriles listed in Table 2 of Chapter 2 are commercially available. Characterization data for cyanoferrocene[56] and 1-cyanopyrene[57] have been reported in the literature.

[2.4.1] General procedure for synthesis of nitriles



55 BOP: X = $O\overset{+}{P}(NMe_2)_3$ PF_6^-
56 Bt–OTs: X = OTs

Using BOP

In an oven-dried, two-necked, 50 mL round-bottomed flask, equipped with a stirring bar was placed a solution of the oxime (1.0 mmol) and BOP (2.0 mmol) in anhydrous CH_2Cl_2 (5.0 mL). The mixture was stirred at room temperature for 5 minutes and then DBU (2.3 mmol) was added dropwise to the stirring mixture over 2 minutes. The reaction mixture became a clear homogeneous solution after addition of DBU. The reaction was monitored by TLC, and upon complete consumption of the starting material the mixture was diluted with EtOAc and washed with water (2x) followed by brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by column chromatography.

Deviation from this procedure: (a) Dehydration reactions of *o*-bromobenzaldoxime, ferrocene carbaldoxime, and indole-3-carbaldoxime were performed in THF, and dehydration of pyrene-1-carbaldoxime was performed in DMF.

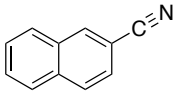
Using Bt–OTs

Into an oven-dried, two-necked, 50 mL round-bottomed flask, equipped with a stirring bar was placed a solution of the oxime (1.0 mmol) and Bt–OTs (0.5786 g, 2.0 mmol) in anhydrous

CH_2Cl_2 (5.0 mL). The mixture was stirred at room temperature for 5 minutes and then DBU (2.3 mmol) was added dropwise to the stirring mixture over 2 minutes. The reaction was monitored by TLC technique, and upon complete consumption of the starting material the reaction mixture was diluted with EtOAc and washed with water (2x) followed by brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by column chromatography.

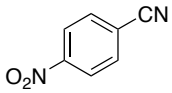
Deviation from this procedure: (a) Dehydration reactions of *o*-bromobenzaldoxime, ferrocene carbaldoxime, and indole-3-carbaldoxime were performed in THF where as dehydration of pyrene-1-carbaldoxime was performed at 0.75 mmol scale, in DMF.

2-Naphthonitrile (54a)



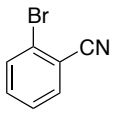
Synthesized from **53a** (171 mg, 1.0 mmol) and BOP (973 mg, 2.2 mmol) or Bt–OTs (636 mg, 2.2 mmol). Chromatography of the crude reaction mixture on a silica gel column using 5% EtOAc in hexanes yielded **54a** as a white solid (BOP: 145 mg, 95% yield; Bt–OTs: 145 mg, 95%). R_f (SiO_2/10% EtOAc in hexanes) = 0.35. ^{1}H NMR ($CDCl_3$): δ 8.25 (s, 1H, Ar–H), 7.90-7.95 (m, 3H, Ar–H), 7.69-7.62 (m, 3H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 139.6, 134.1, 132.2, 129.1, 129.0, 128.4, 128.0, 127.6, 119.2, 109.4.

4-Nitrobenzonitrile (54b)



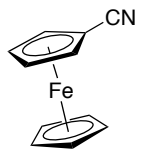
Synthesized from **53b** (166 mg, 1.0 mmol) and BOP (884 mg, 2.0 mmol) or Bt–OTs (578 mg, 2.0 mmol). Chromatography of the crude reaction mixture on a silica gel column using 15% EtOAc in hexanes yielded **54b** as a white solid (BOP: 142 mg, 96% yield; Bt–OTs: 141 mg, 95%). R_f (SiO_2/30% EtOAc in hexanes) = 0.5. ^{1}H NMR ($CDCl_3$): δ 8.36 (d, 2H, Ar–H, J = 8.8 Hz), 7.88 (d, 2H, Ar–H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$): δ 150.3, 133.7, 124.5, 118.6, 117.0.

2-Bromobenzonitrile (54c)



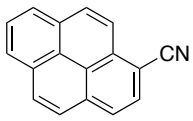
Synthesized from **53c** (200 mg, 1.0 mmol) and BOP (884 mg, 2.0 mmol) or Bt–OTs (578 mg, 2.0 mmol). Chromatography of the crude reaction mixture on a silica gel column using 5% EtOAc in hexanes yielded **54c** as a white solid (BOP: 153 mg, 84%; Bt–OTs: 145 mg, 80%). R_f (SiO_2/10% EtOAc in hexanes) = 0.20. ^{1}H NMR ($CDCl_3$): δ 7.69 (dd, 1H, Ar–H, J = 1.1, 7.9 Hz), 7.67 (dd, 1H, Ar–H, J = 1.8, 7.5 Hz), 7.48-7.41 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 134.5, 134.0, 133.4, 127.8, 125.5, 117.3, 116.1.

Cyanoferrocene (54d)



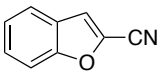
Synthesized from **53d** (229 mg, 1.0 mmol) and BOP (884 mg, 2.0 mmol) or Bt–OTs (578 mg, 2.0 mmol). Chromatography of the crude reaction mixture on a silica gel column using 15% EtOAc in hexanes yielded **54d** as an orange crystalline solid (BOP: 205 mg, 97%; Bt–OTs: 188 mg, 89%). R_f (SiO_2/30% EtOAc in hexanes) = 0.5. ^{1}H NMR ($CDCl_3$): δ 4.67 (s, 2H, Ar–H), 4.40 (s, 2H, Ar–H), 4.35 (s, 5H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 120.4, 71.9, 70.9, 70.8, 52.1.

1-Cyanopyrene (54e)



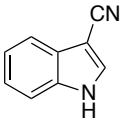
Synthesized from **53e** (184 mg, 0.75 mmol) and BOP (442 mg, 1.0 mmol) or Bt–OTs (289 mg, 1.0 mmol). Chromatography of the crude reaction mixture on a silica gel column using 3% EtOAc in hexanes yielded **54e** as light yellow solid (BOP: 218 mg, 96%; Bt–OTs: 204 mg, 90%). R_f (SiO_2/30% EtOAc in hexanes) = 0.18. ^{1}H NMR ($CDCl_3$): δ 8.43 (d, 1H, Ar–H, J = 9.0 Hz), 8.21-8.32 (m, 5H, Ar–H), 8.06-8.16 (m, 3H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 134.1, 132.9, 130.8, 130.5, 130.4, 130.3, 129.5, 127.0, 126.4, 126.8, 126.7, 124.4, 124.0, 123.9, 123.5, 118.8, 105.6.

2-Cyanobenzofuran (54f)



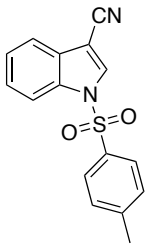
Synthesized from **53f** (161 mg, 1.0 mmol) and BOP (884 mg, 2.0 mmol) or Bt–OTs (578 mg, 2.0 mmol). Chromatography of the crude reaction mixture on a silica gel column using 5% EtOAc in hexanes yielded **54f** as white solid (BOP: 121 mg, 85%; Bt–OTs: 121 mg, 85%). R_f (SiO_2/15% EtOAc in hexanes) = 0.42. ^{1}H NMR ($CDCl_3$): δ 7.68 (d, 1H, Ar–H, J = 7.9 Hz), 7.56 (d, 1H, Ar–H, J = 8.2 Hz), 7.51 (t, 1H, Ar–H, J = 7.8 Hz), 7.46 (s, 1H, Ar–H), 7.37 (t, 1H, Ar–H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 155.9, 128.6, 127.5, 125.7, 124.7, 122.7, 118.6, 112.3, 112.0.

1*H*-indole-3-carbonitrile (54g)



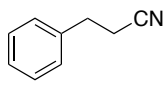
Synthesized from **53g** (160 mg, 1.0 mmol) and BOP (884 mg, 2.0 mmol) or Bt–OTs (578 mg, 2.0 mmol). Chromatography of the crude reaction mixture on a silica gel column using 5% acetone in hexanes yielded **54g** as white solid (BOP: 102 mg, 72%; Bt–OTs: 60 mg, 42%). R_f (SiO_2/100% CH_2Cl_2) = 0.33. ^{1}H NMR (DMSO-d_6): δ 12.2 (s, 1H, N–H), 8.25 (s, 1H, Ar–H), 7.63 (d, 1H, Ar–H, J = 7.8 Hz), 7.55 (d, 1H, Ar–H, J = 7.4 Hz), 7.28 (t, 1H, Ar–H, J = 7.5 Hz), 7.23 (t, 1H, Ar–H, J = 7.4 Hz). ^{13}C NMR (DMSO-d_6): δ 135.1, 134.4, 126.7, 123.3, 121.6, 118.3, 116.3, 112.9, 84.1.

1-(*p*-Toluenesulfonyl)indole-3-carbonitrile (57)



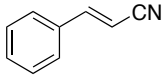
This side product was isolated from the reaction between **53g** and Bt–OTs. This is a known compound.[49] The compound **57** was isolated as white solid (71 mg, 50%). R_f (SiO_2/30% EtOAc in hexanes) = 0.47. ^{1}H NMR ($CDCl_3$): δ 8.1 (s, 1H, Ar–H), 8.0 (d, 1H, Ar–H, J = 8.4 Hz), 7.82 (d, 2H, Ar–H, J = 8.3 Hz), 7.69 (d, 1H, Ar–H, J = 7.8 Hz), 7.44 (t, 1H, Ar–H, J = 8.3 Hz), 7.38 (d, 1H, Ar–H, J = 7.9 Hz), 7.30 (d, 2H, Ar–H, J = 8.1 Hz),2.38 (s, 3H, CH_3).

3-Phenylpropanenitrile (54h)



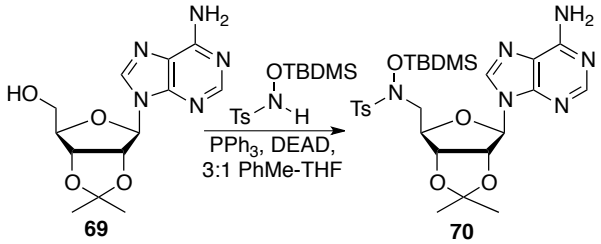
Synthesized from **53h** (149 mg, 1.0 mmol) and BOP (884 mg, 2.0 mmol) or Bt–OTs (578 mg, 2.0 mmol). Chromatography of the crude reaction mixture on a silica gel column using 5% Acetone in hexanes yielded **54f** as light yellow, clear liquid (BOP: 111 mg, 85%; Bt–OTs: 96 mg, 73%). R_f (SiO_2/10% EtOAc in hexanes) = 0.15. ^{1}H NMR ($CDCl_3$): δ 7.37 (t, 2H, Ar–H, J = 7.0 Hz), 7.31 (d, 1H, Ar–H, J = 7.3 Hz), 7.26 (t, 2H, Ar–H, J = 7.5 Hz), 2.98 (t, 2H, CH_2, J = 7.3), 2.65 (t, 2H, CH_2, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 138.2, 129.0, 128.4, 127.4, 119.3, 31.7, 19.5.

***E*-Cinnamonitrile (54i)**



Synthesized from **53i** (129 mg, 1.0 mmol) and BOP (884 mg, 2.0 mmol) or Bt–OTs (578 mg, 2.0 mmol). Chromatography of the crude reaction mixture on a silica gel column using 8% EtOAc in hexanes yielded **54i** as clear liquid (BOP: 119 mg, 92%; Bt–OTs: 119 mg, 92%). R_f (SiO_2/15% EtOAc in hexanes) = 0.23. ^{1}H NMR ($CDCl_3$): δ 7.46-7.39 (m, 6H, Ar–H), 5.88 (d, 1H, CH, J = 16.6 Hz). ^{13}C NMR ($CDCl_3$): δ 150.8, 133.7, 131.4, 127.5, 118.3, 96.6.

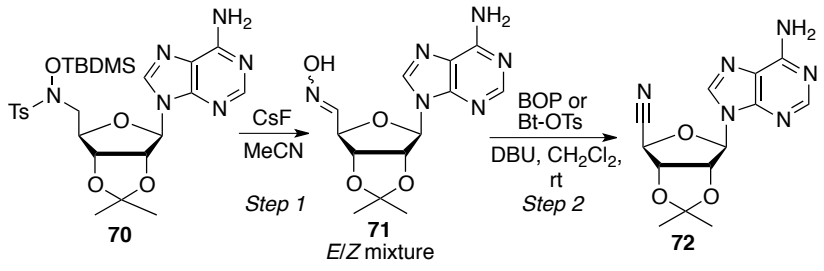
5'-Deoxy-5'-[*N*-(*tert*-butyldimethylsilyloxy)-*N*-(*p*-toluenesulfonyl)]amino-2',3-*O*-(isopropylidene)adenosine (70)



In a 100 mL oven-dried, round-bottomed flask equipped with a stirring bar were placed 2',3'-*O*-(isopropylidene)adenosine **69** (0.75 g, 2.44 mmol), *O*-(*tert*-butyldimethylsilyl)-*N*-

tosylhydroxylamine (TsNHOTBDMS, 1.10 g, 3.66 mmol) and PPh_3 (1.28 g, 4.88 mmol). Anhydrous toluene (12 mL) and THF (4 mL) were added and reaction mixture was cooled to 0 ˚C with stirring. DEAD (576 µL, 3.66 mmol) was added dropwise. The reaction mixture was stirred at 0 ˚C for 1 h and then allowed to warm to room temperature. After 5 h, TLC showed complete consumption of starting material **69**. The reaction mixture was diluted with EtOAc, and washed with saturated aq $NaHCO_3$ followed by water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The product was loaded onto a silica gel column using CH_2Cl_2 and eluted with 15% EtOAc in CH_2Cl_2 followed by 40% EtOAc in CH_2Cl_2. Compound **70** was obtained as white, foamy solid (1.163 g, 81% yield). R_f (SiO_2/50% EtOAc in CH_2Cl_2) = 0.16. ^{1}HNMR ($CDCl_3$): δ 8.37 (s, 1H, Ar-H), 7.86 (s, 1H, Ar-H), 7.58 (d, 2H, Ar-H, *J* = 8.2 Hz), 7.27 (d, 2H, Ar-H, *J* = 8.2 Hz), 6.03 (d, 1H, H-1', *J* = 1.7 Hz), 5.94 (br s, 2H, NH_2), 5.56 (dd, 1H, H-2', *J* = 1.7, 6.3 Hz), 5.15 (dd, 1H, H-3', *J* = 2.7, 6.3 Hz), 4.50 (dt, 1H, H-4', *J* = 2.7, 6.9 Hz), 3.43 (m, 1H, H-5'), 2.91 (m, 1H, H-5'), 2.41 (s, 3H, *p*-toluyl CH_3), 1.58 and 1.38 (2s, 6H, isopropylidine CH_3), 0.89 (s, 9H, *tert*-Bu), 0.34, 0.24 (2s, 6H, $SiCH_3$). ^{13}C NMR ($CDCl_3$): δ 155.8, 153.1, 149.3, 145.0, 140.5, 129.9, 129.5, 120.5, 114.3, 91.8, 84.3, 84.1, 83.6, 58.0, 27.2, 26.2, 25.6, 21.8, 18.5, –4.1, –4.3. HRMS (ESI) calculated for $C_{26}H_{38}N_6O_6SSi$ $[M]^+$ 590.2343, found 590.2354.

1'-Adenin-9-yl-2',3'-*O*-(isopropylidene)-*β*-D-ribofuranurononitrile (72)



Step 1. Compound **70** (1.32 g, 2.22 mmol) was dissolved in anhydrous CH_3CN (22 mL) and CsF (0.674 g, 4.43 mmol) was added. The reaction mixture was stirred at 60 ˚C for 1.5 h at which time TLC showed complete consumption of starting material **70**. Saturated aq. NH_4Cl was added to the cooled reaction mixture and the mixture was extracted with EtOAc. The organic layer was washed with water followed by brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was loaded onto a dry-packed silica gel column and eluted using 30% acetone in hexanes. Compound **71** (*E*/*Z* mixture) was obtained as white powder (0.569 g, 80% yield). R_f (SiO_2/4% MeOH in CH_2Cl_2) = 0.03. HRMS calculated for $C_{13}H_{16}N_6O_4$ (M^+) 320.1233, found 320.1238. The NMR data for this *E*/*Z* mixture has been reported[51].

Step 2 using BOP. In an oven-dried, 50 mL two-necked round-bottomed flask equipped with a stirring bar was placed a solution of **71** (0.320 g, 1.00 mmol) and BOP (0.885 g, 2.00 mmol) in anhydrous CH_2Cl_2 (5.0 mL). The mixture was stirred at room temperature for 5 min and then DBU (344 μL, 2.30 mmol) was added dropwise over 2-3 minutes to the stirring solution. The reaction mixture became clear after addition of DBU. After 45 min, TLC showed complete consumption of starting material **71**. The reaction mixture was diluted with EtOAc and washed with water (2x) followed by brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was chromatographed on a silica gel column using 2% EtOH in CH_2Cl_2 as eluting solvent (the chromatography was repeated a second time). Compound **72** obtained as white solid (0.288 g, 95% yield).

Step 2 using Bt–OTs. In an oven-dried, 50 mL two-necked round-bottomed flask equipped with a stirring bar was placed a solution of **71** (0.277 g, 0.864 mmol) and Bt–OTs (0.500 g, 1.727 mmol) in anhydrous CH_2Cl_2 (5.0 mL). The mixture was stirred at room temperature for 5 min

and then DBU (297 μL, 1.987 mmol) was added dropwise over 2 minutes to the stirring solution. The reaction mixture became clear after addition of DBU. After 35 min, TLC showed complete consumption of the starting material **71**. The reaction mixture was diluted with EtOAc and washed with water (2x) followed by brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was chromatographed on a silica gel column using 2% EtOH in CH_2Cl_2 as eluting solvent (the chromatography was repeated a second time). Compound **72** was obtained as a white solid (0.246 g, 93% yield). R_f (SiO_2/4% MeOH in CH_2Cl_2) = 0.27. ^{1}HNMR ($CDCl_3$): δ 8.39 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 6.20 (s, 1H, H-1'), 5.83 (d, 1H, H-2', J = 5.7 Hz), 5.79 (dd, 1H, H-3', J = 1.4, 5.7 Hz), 5.64 (br s, 2H, NH_2), 4.98 (d, 1H, H-4', J = 1.4 Hz), 1.58 and 1.43 (2s, 6H, isopropylidine CH_3). ^{13}C NMR ($CDCl_3$): δ 155.8, 153.5, 149.7, 140.1, 120.2, 116.2, 115.0, 92.0, 84.9, 84.1, 75.5, 26.7, 25.2. HRMS (ESI) calculated for $C_{13}H_{14}N_6O_3$ $[M]^+$ 302.1127, found 302.1134

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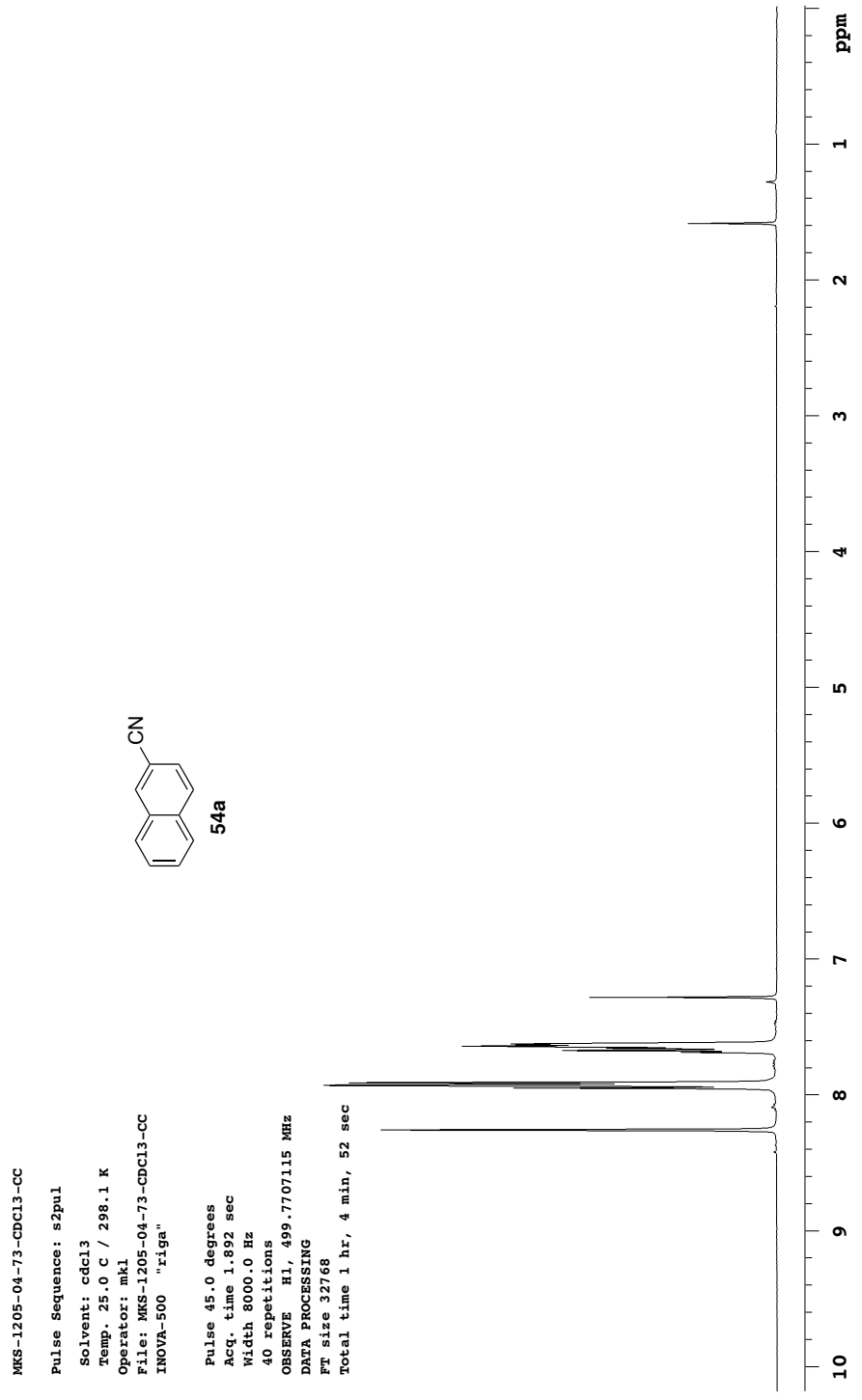
APPENDIX II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CN
54a
10
9
8
7
6
5
4
3
2
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ppm

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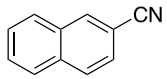

54a

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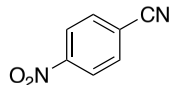

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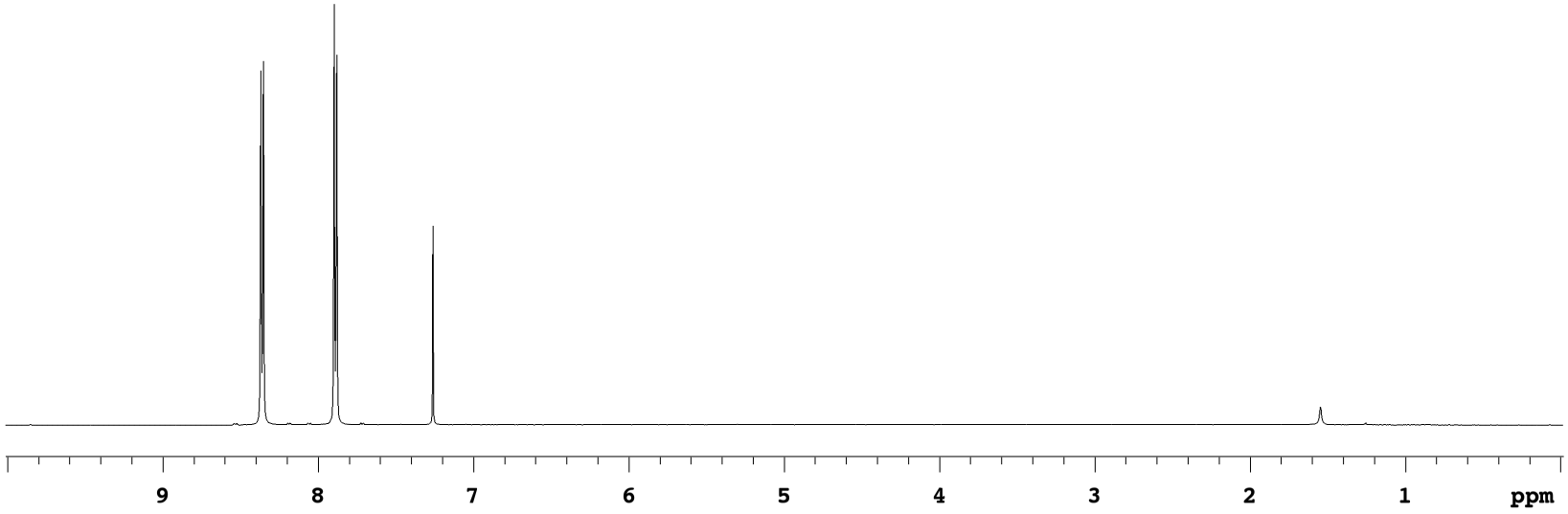

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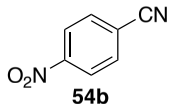

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INOVA-500 "riga"

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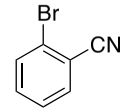
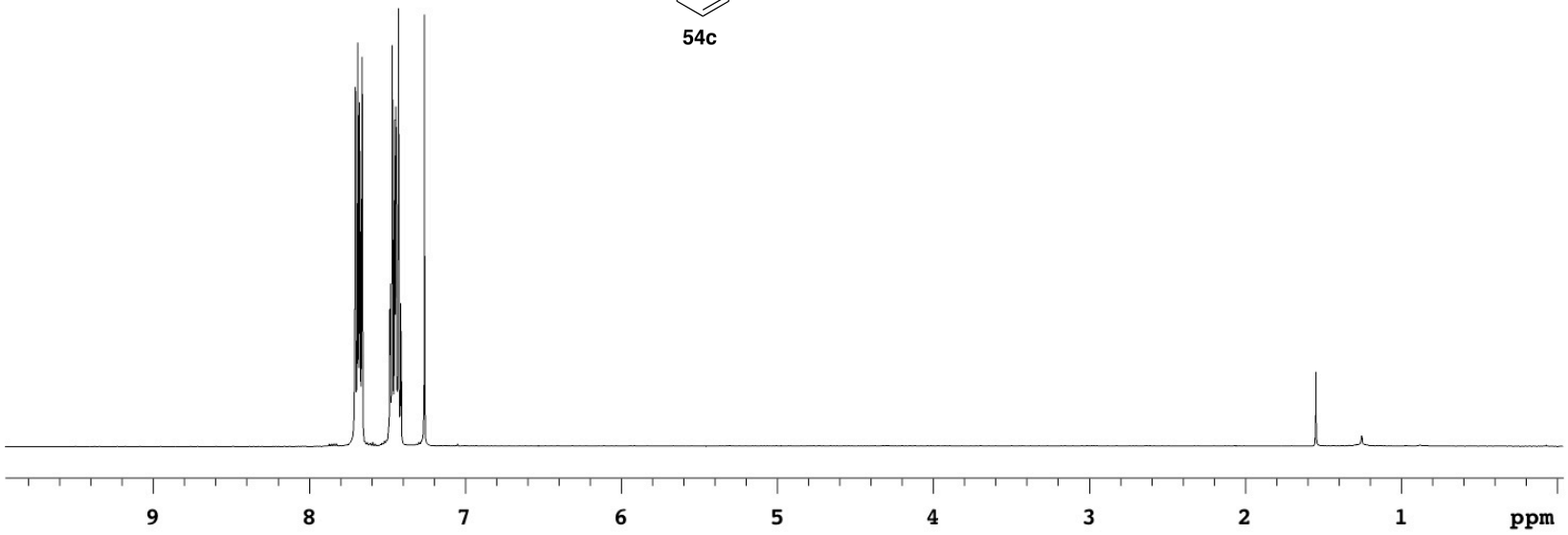
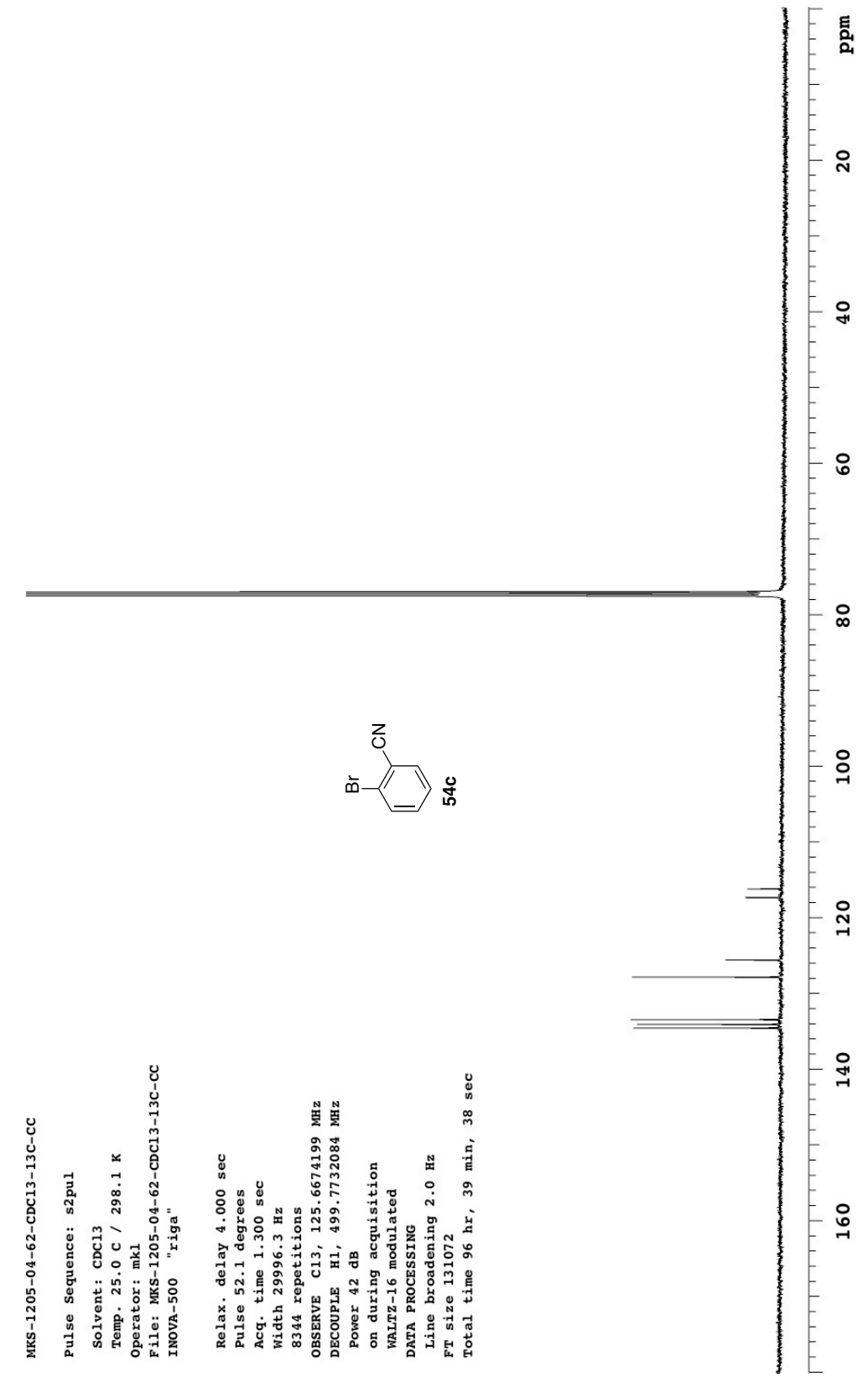


54c



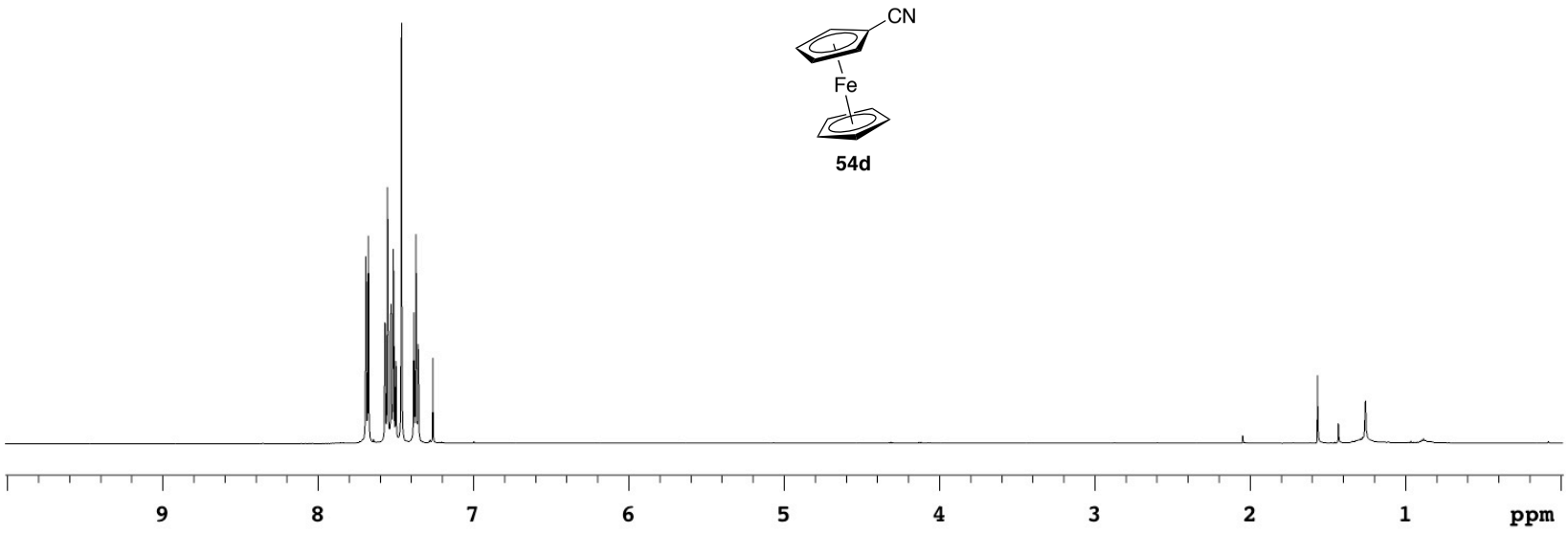

MKS-1205-04-62-CDCl3-13C-CC
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-04-62-CDCl3-13C-CC
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
8344 repetitions
OBSERVE C13, 125.6674199 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec
Br
CN
54c
160
140
120
100
80
60
40
20
ppm

MKS-1205-04-58-CDCl3-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-04-58-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
56 repetitions
OBSERVE H1, 499.7707207 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



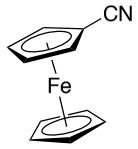
54d

MKS-1205-04-58-CDCl3-13C-CC

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-04-58-CDCl3-13C-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
9052 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 96 hr, 39 min, 38 sec



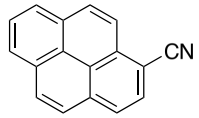
54d

MKS-1205-04-74-CDCl3-2ndFrac-CC

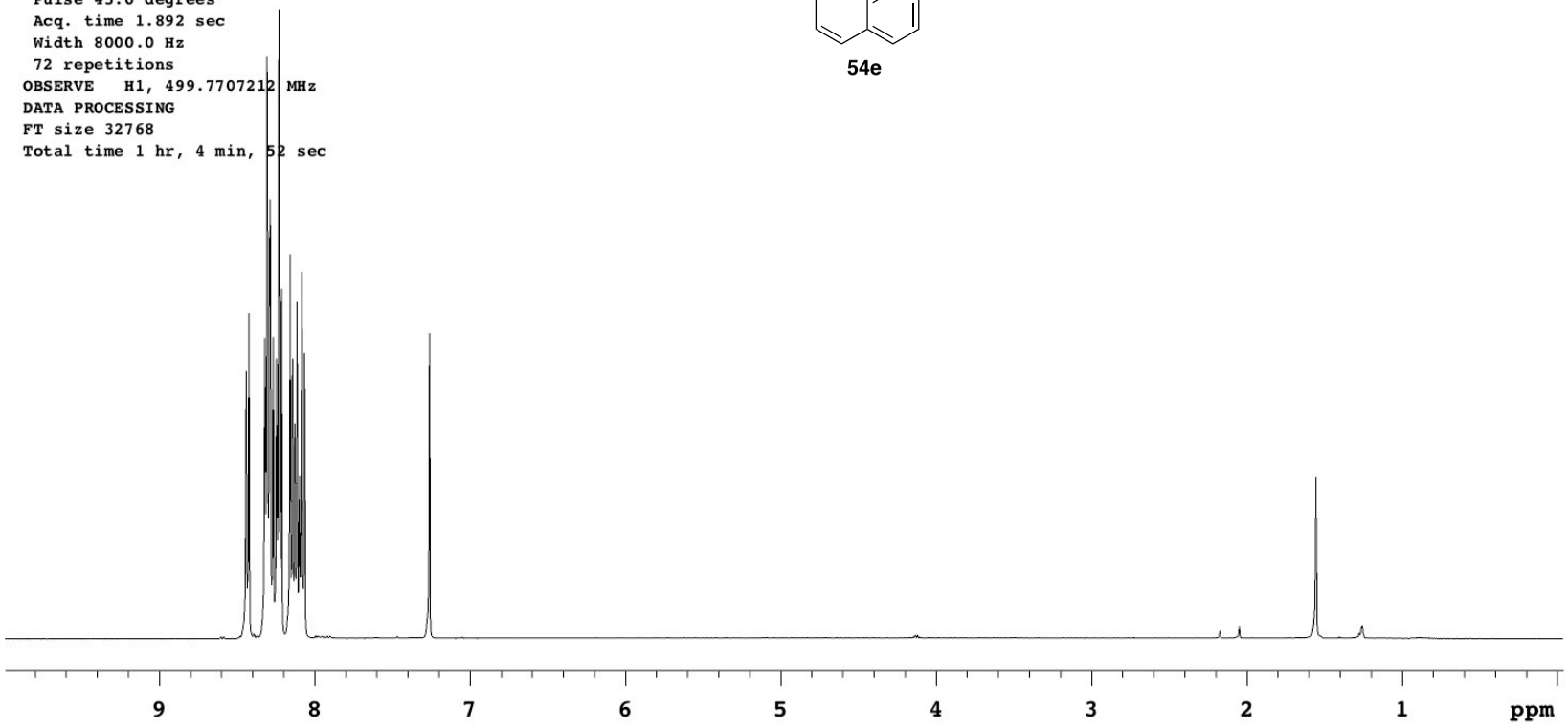
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-04-74-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
72 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



54e

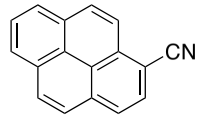


MKS-1205-04-74-CDCl3-13C-2ndFrac-CC

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-04-74-CDCl3-13C-2ndFrac-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
9964 repetitions
OBSERVE C13, 125.6674489 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 96 hr, 39 min, 38 sec



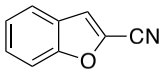
54e

MKS-1205-04-58-CDCl3-CC

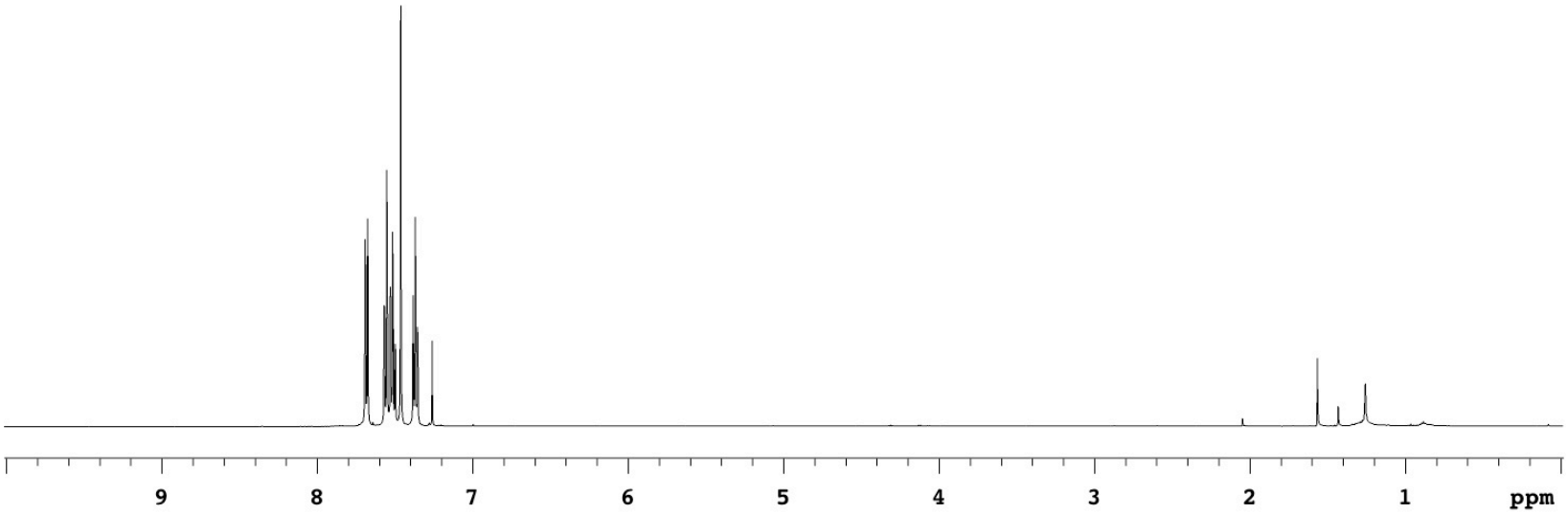
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-04-58-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
56 repetitions
OBSERVE H1, 499.7707207 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



54f

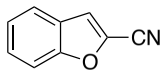


MKS-1205-04-58-CDCl3-13C-CC

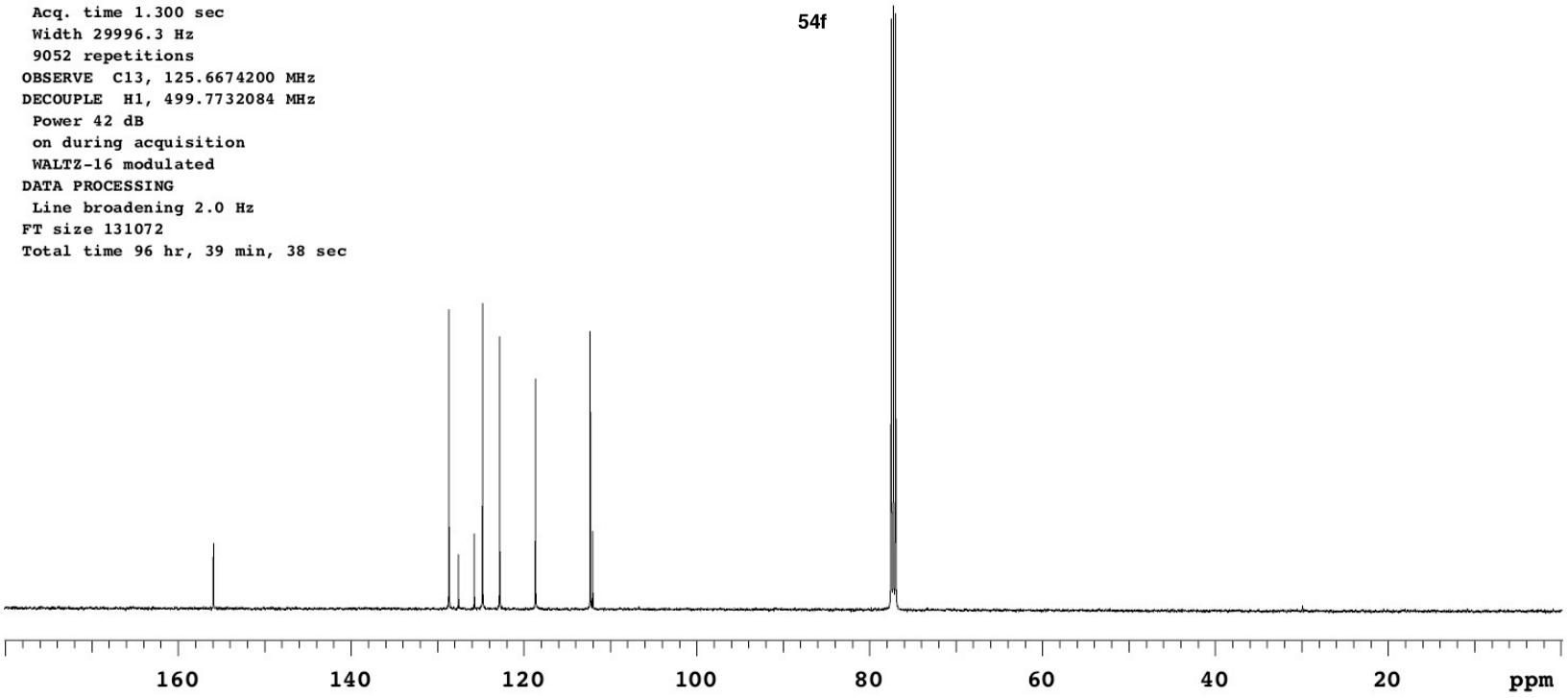
Pulse Sequence: s2pul

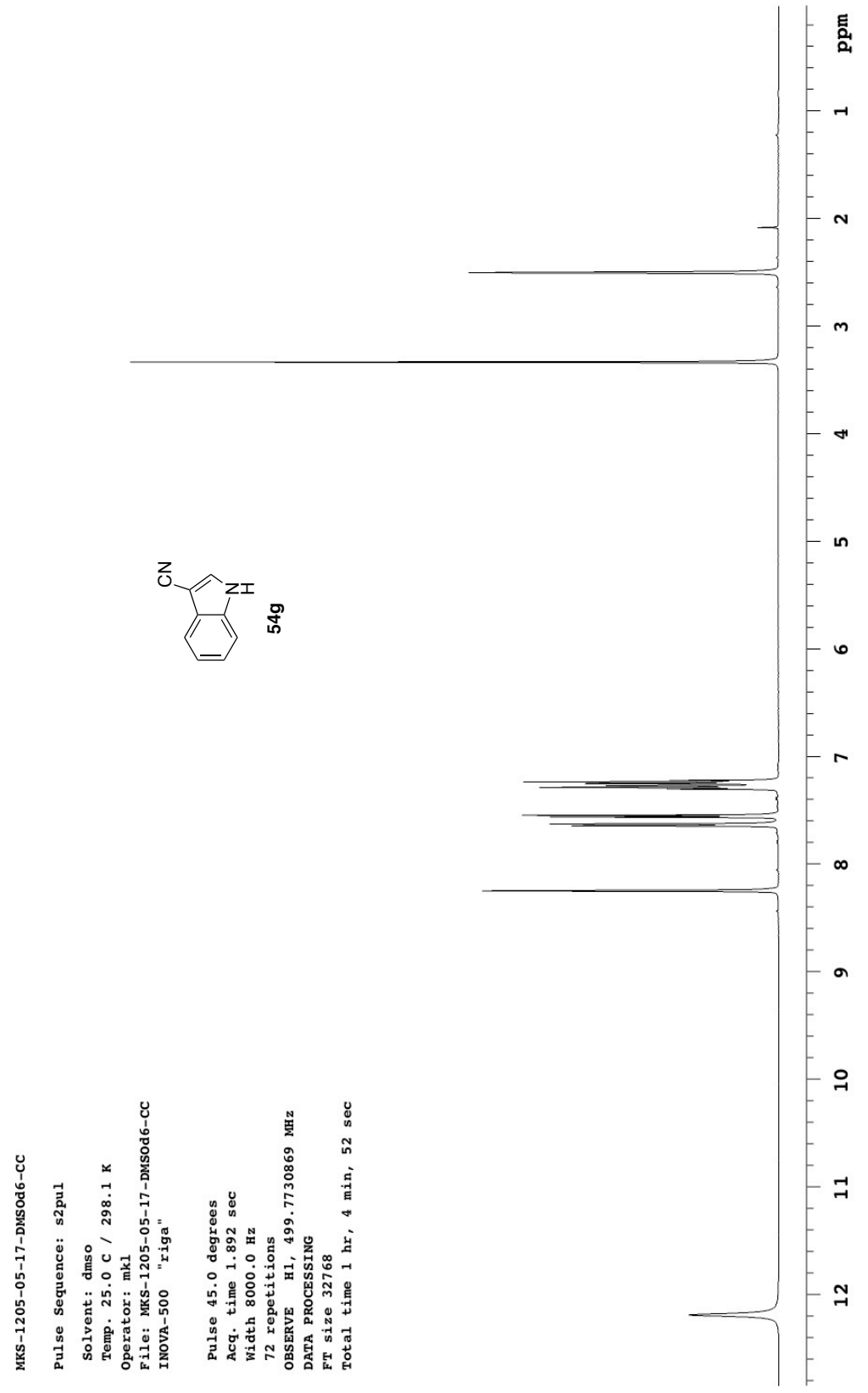
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-04-58-CDCl3-13C-CC
INOVA-500 "riga"

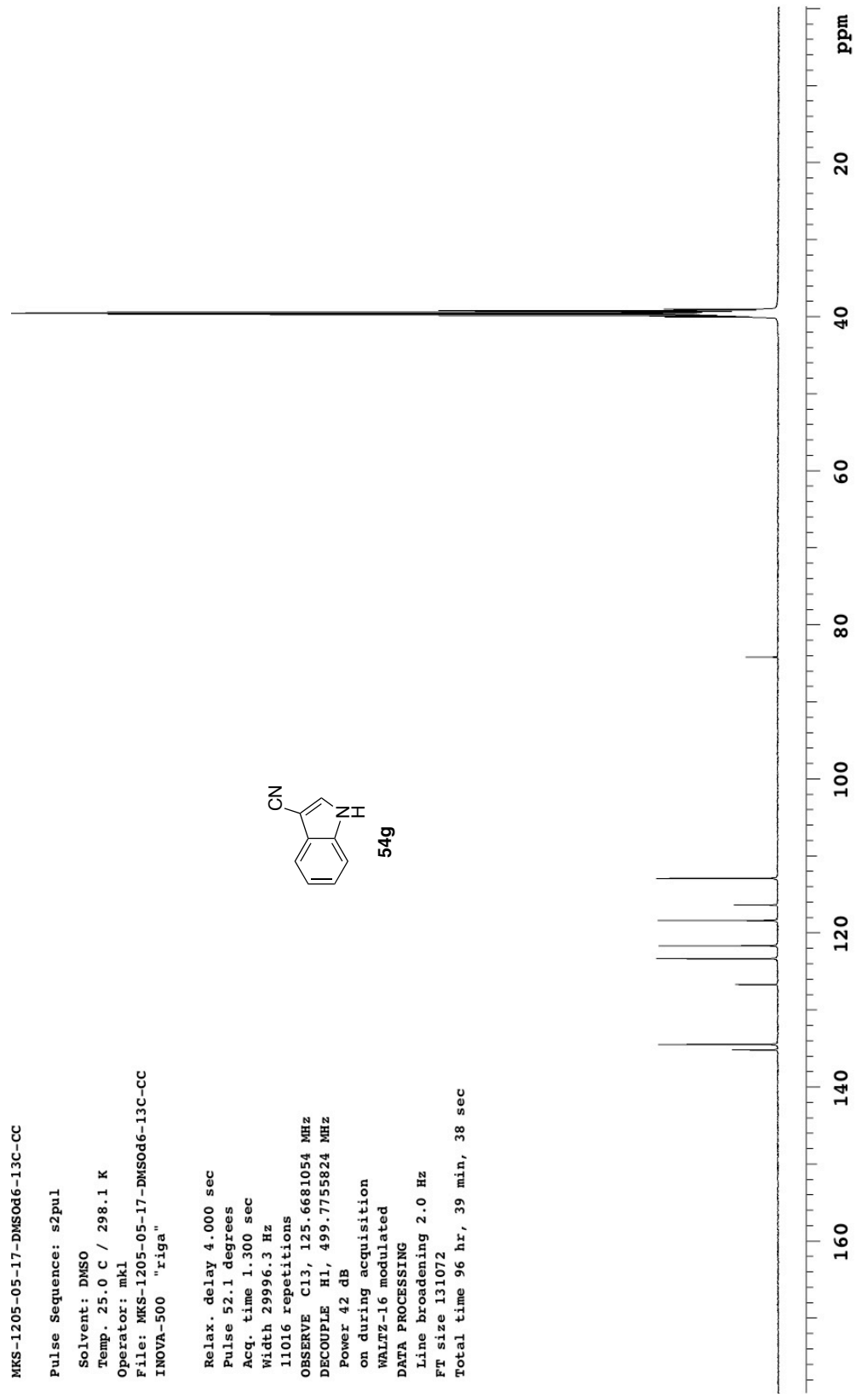
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
9052 repetitions
OBSERVE C13, 125.6674200 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec



54f




MKS-1205-05-17-DMSOd6-CC
Pulse Sequence: s2pul
Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-05-17-DMSOd6-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
72 repetitions
OBSERVE H1, 499.7730869 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
CN
N
H
54g
12
11
10
9
8
7
6
5
4
3
2
1
ppm


MKS-1205-05-17-DMSOd6-13C-CC
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-05-17-DMSOd6-13C-CC
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
11016 repetitions
OBSERVE C13, 125.6681054 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 96 hr, 39 min, 38 sec
CN
N
H
54g
160
140
120
100
80
60
40
20
ppm

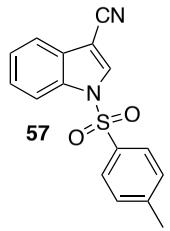
MKS-1205-07-25-II-CDCl3-1stFracPure-CC

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

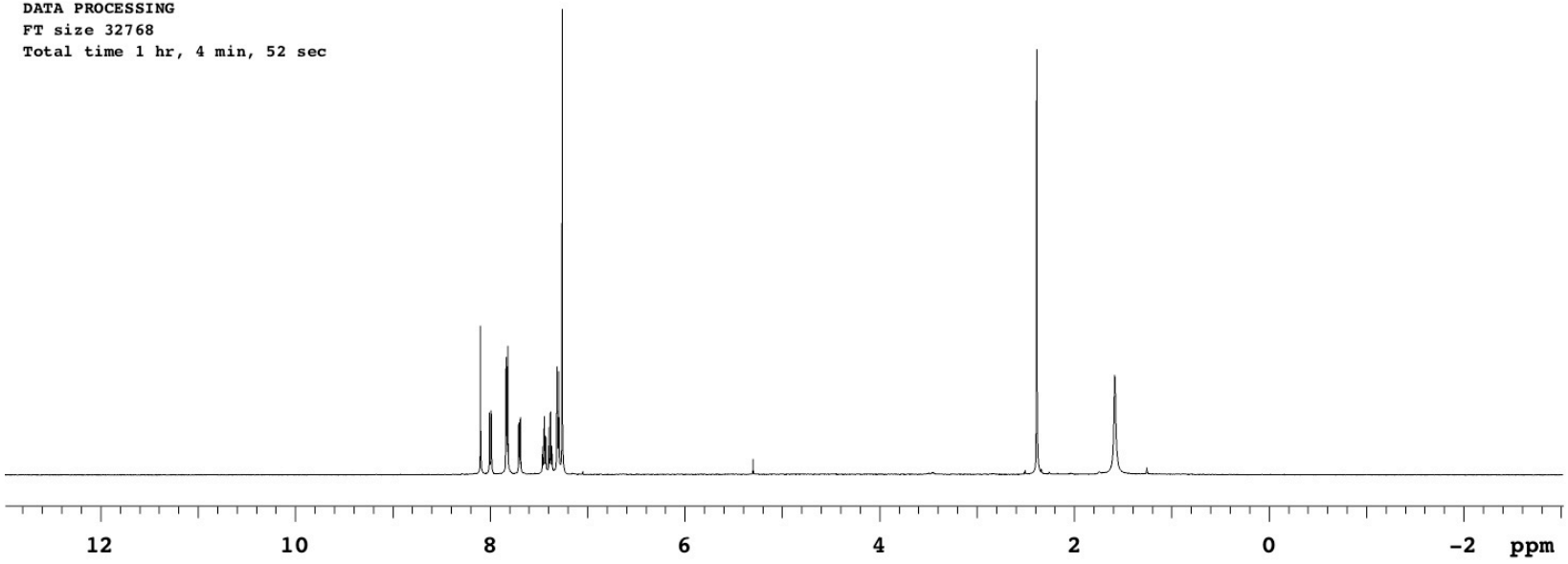
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-25-II-CDCl3-1stFracPure-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
44 repetitions
OBSERVE H1, 499.7707207 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



57

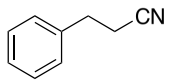


MKS-1205-05-16-CDCl3-CC

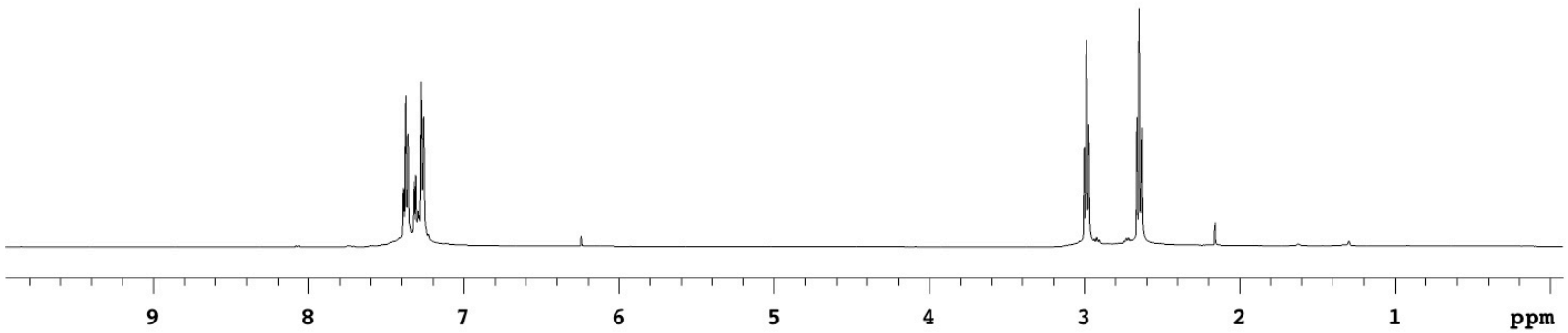
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-05-16-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 10000.0 Hz
132 repetitions
OBSERVE H1, 499.7707095 MHz
DATA PROCESSING
FT size 65536
Total time 1 hr, 4 min, 52 sec



54h

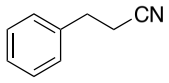


MKS-1205-05-16-CDCl3-13C-CC

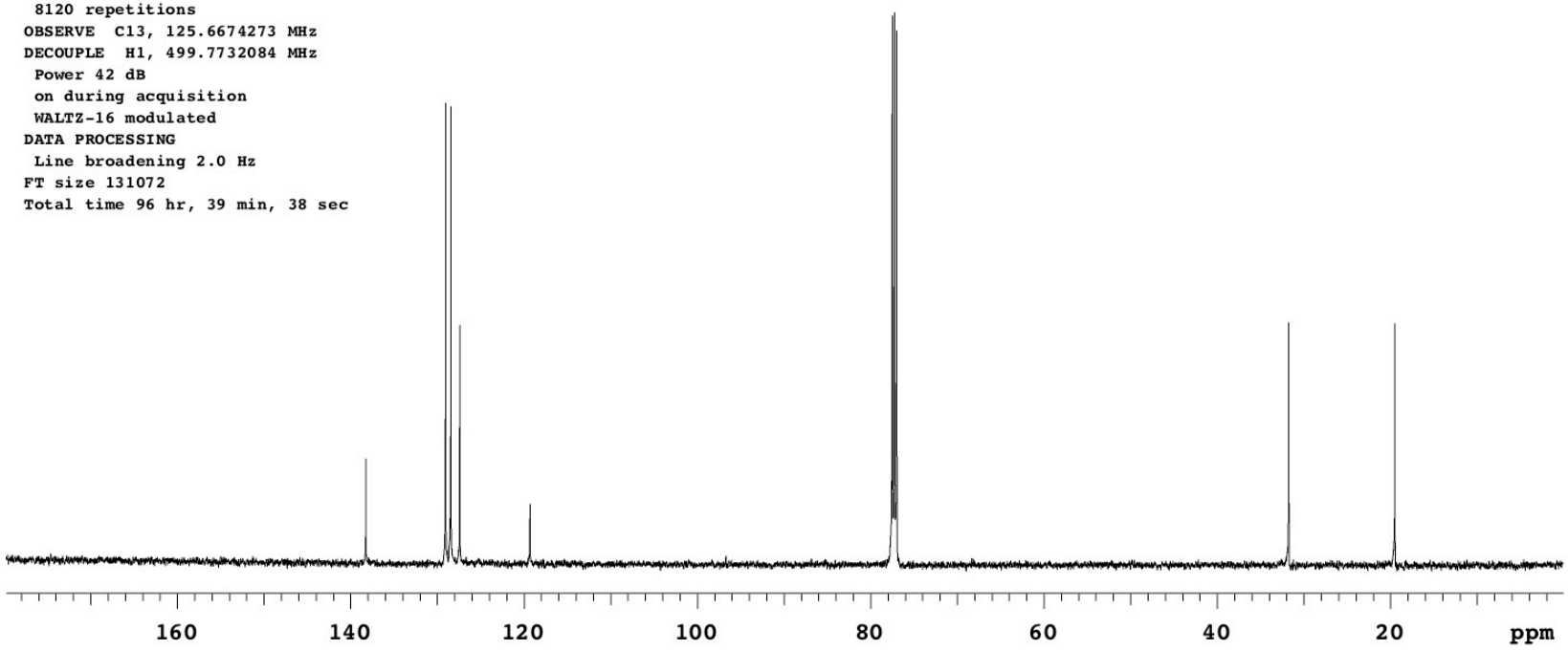
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-05-16-CDCl3-13C-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
8120 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 96 hr, 39 min, 38 sec



54h



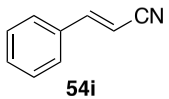
MKS-1205-07-09-CDCl3-CC

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

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-09-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



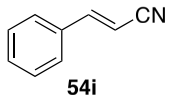
54i

MKS-1205-07-09-CDCl3-13C-CC

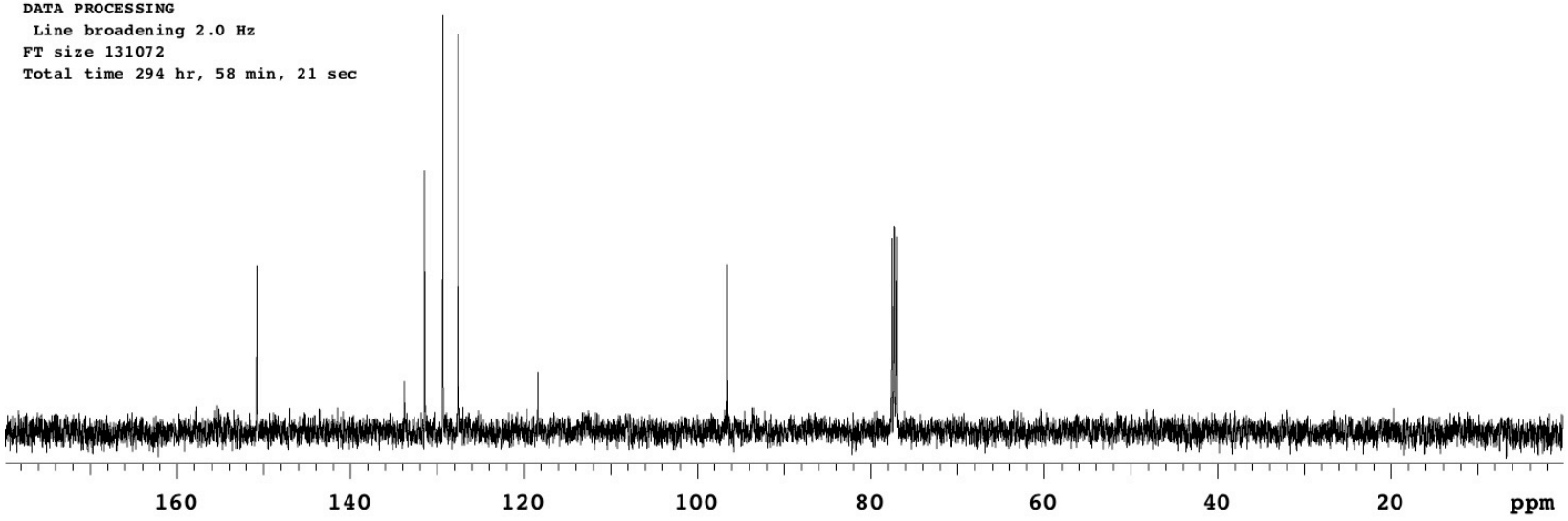
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-07-09-CDCl3-13C-CC
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, 125.6674200 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 294 hr, 58 min, 21 sec



54i



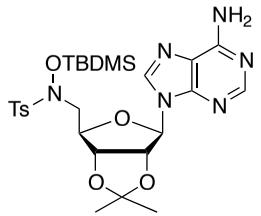
MKS-1205-05-44-CDCl3-CC

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

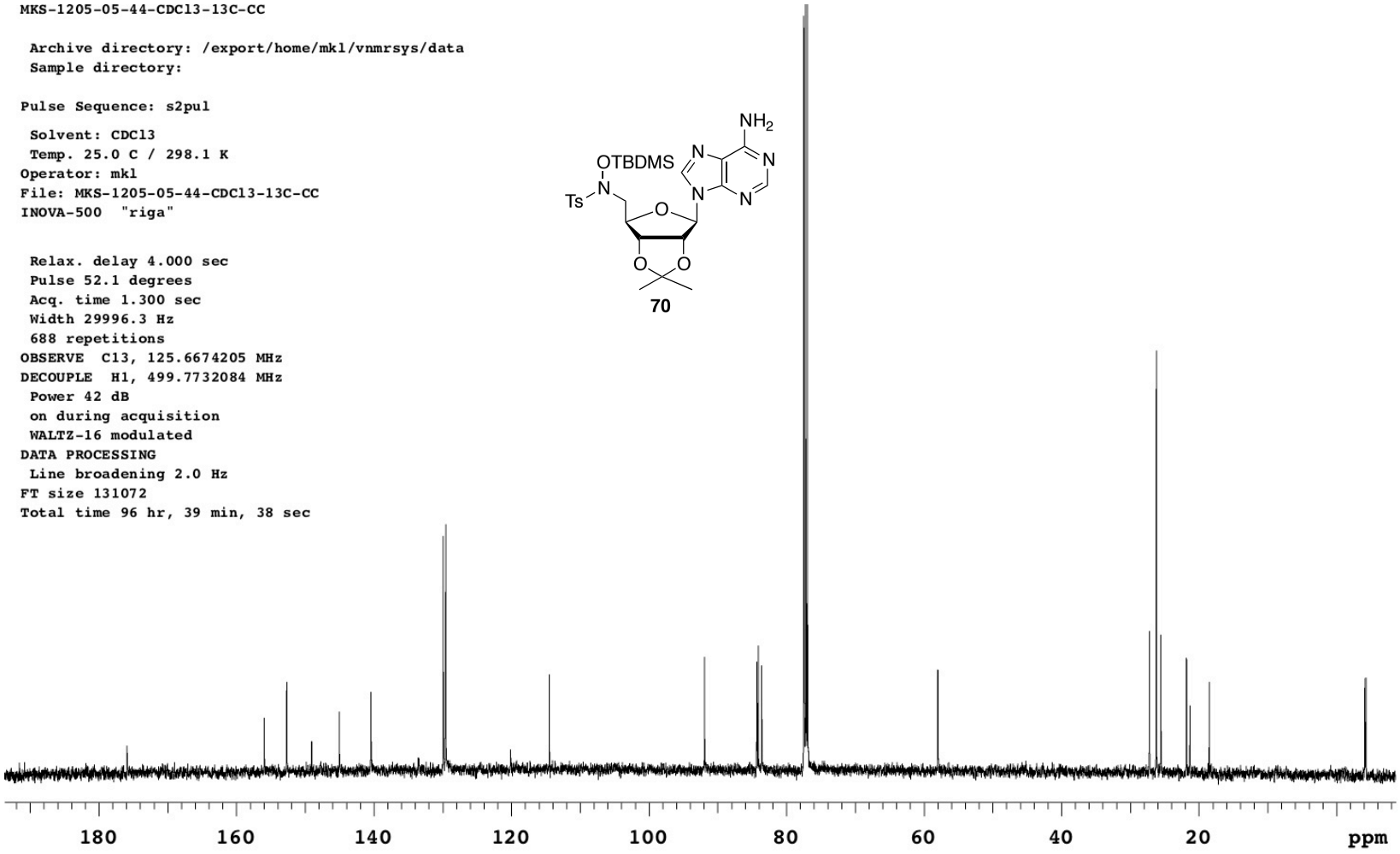
Pulse Sequence: s2pul

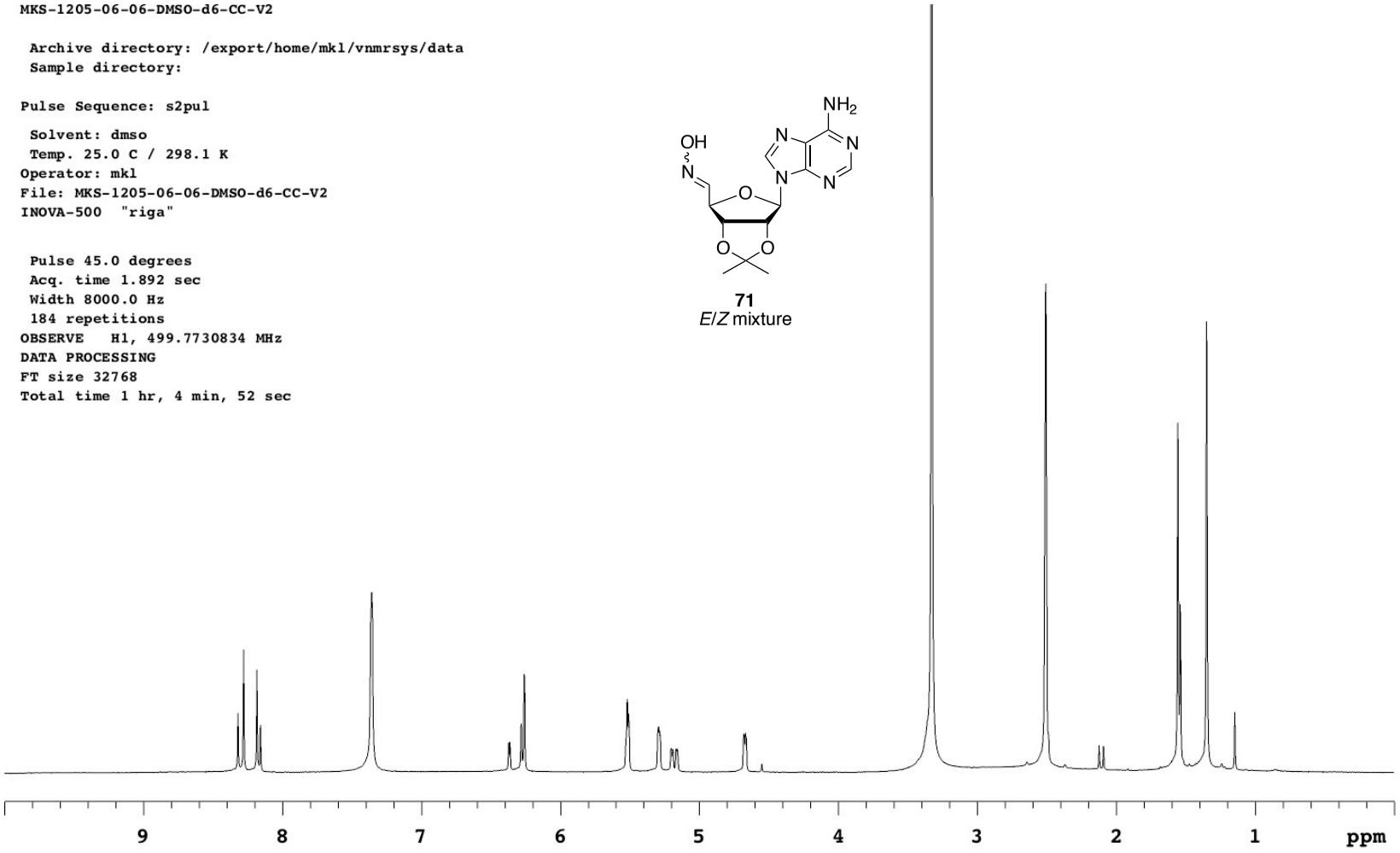
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-05-44-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 10000.0 Hz
88 repetitions
OBSERVE H1, 499.7707095 MHz
DATA PROCESSING
FT size 65536
Total time 1 hr, 4 min, 52 sec

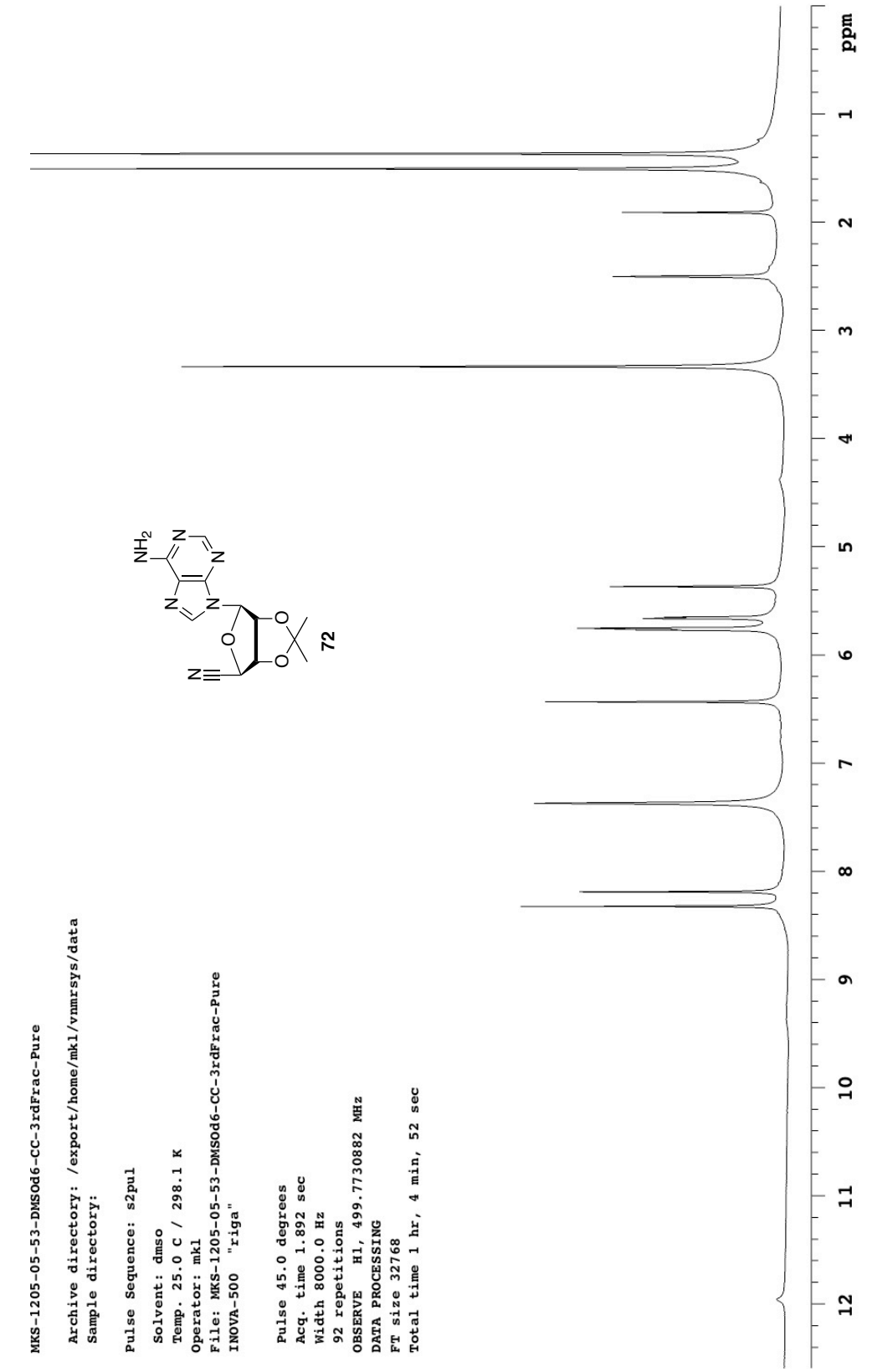


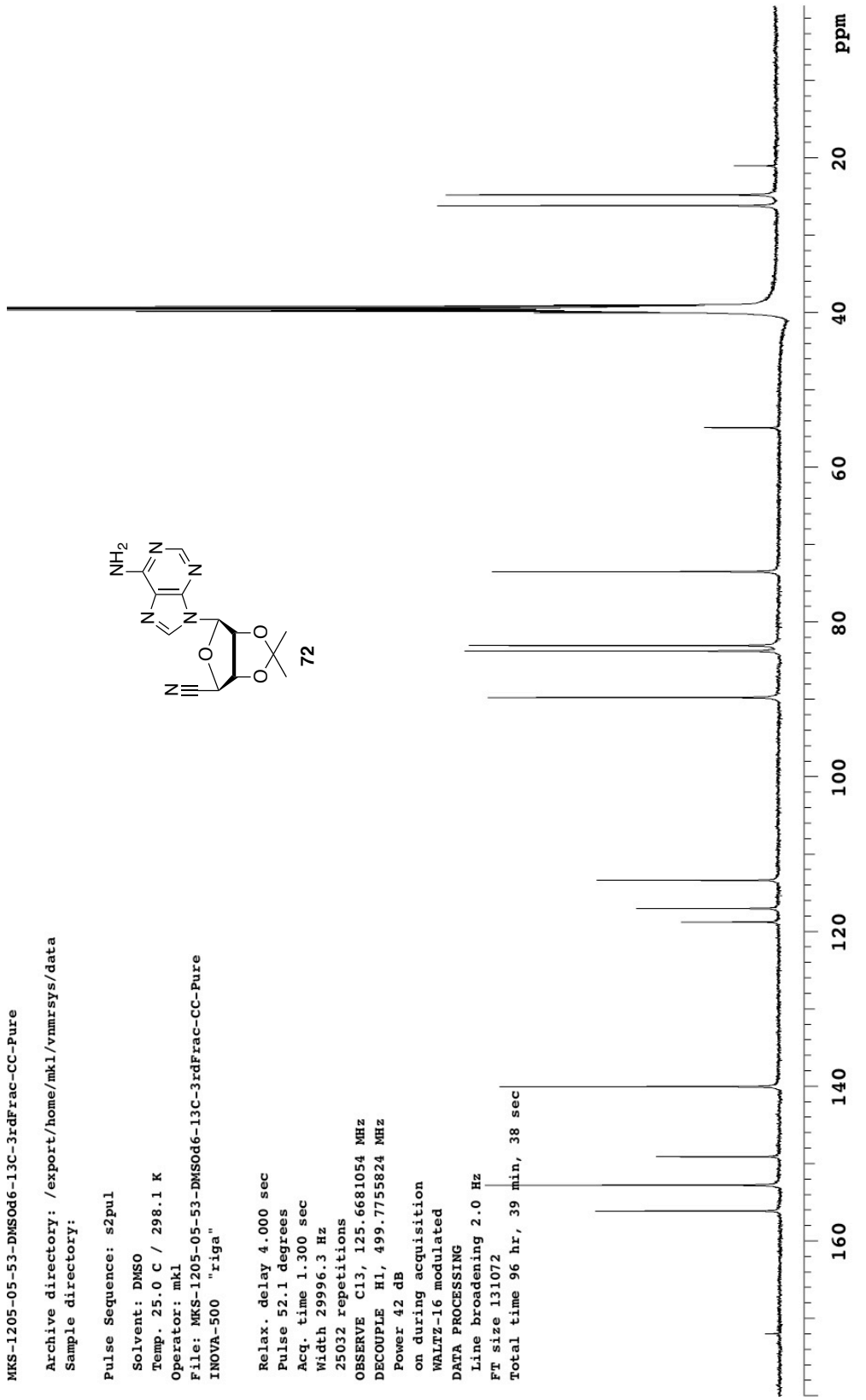
70


MKS-1205-05-44-CDCl3-13C-CC
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-05-44-CDCl3-13C-CC
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
688 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 96 hr, 39 min, 38 sec
NH2
OTBDMS
N
Ts
O
70
180
160
140
120
100
80
60
40
20
ppm



71
E/*Z* mixture


MKS-1205-05-53-DMSOd6-CC-3rdFrac-Pure
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: dmso
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-05-53-DMSOd6-CC-3rdFrac-Pure
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
92 repetitions
OBSERVE H1, 499.7730882 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec
NH2
N
N
N
N
O
O
O
O
N
72
12
11
10
9
8
7
6
5
4
3
2
1
ppm


MKS-1205-05-53-DMSOd6-13C-3rdFrac-CC-Pure
Archive directory: /export/home/mkl/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-05-53-DMSOd6-13C-3rdFrac-CC-Pure
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
25032 repetitions
OBSERVE C13, 125.6681054 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 96 hr, 39 min, 38 sec
NH2
N
N
N
N
O
O
O
N
72
160
140
120
100
80
60
40
20
ppm

CHAPTER 3

A NEW METHOD FOR SYNTHESIS OF 1,2,3-BENZOTRIAZOL-1-YL ETHERS: ANALYSIS OF THE REACTION MECHANISM AND APPLICATIONS IN ORGANIC SYNTHESIS

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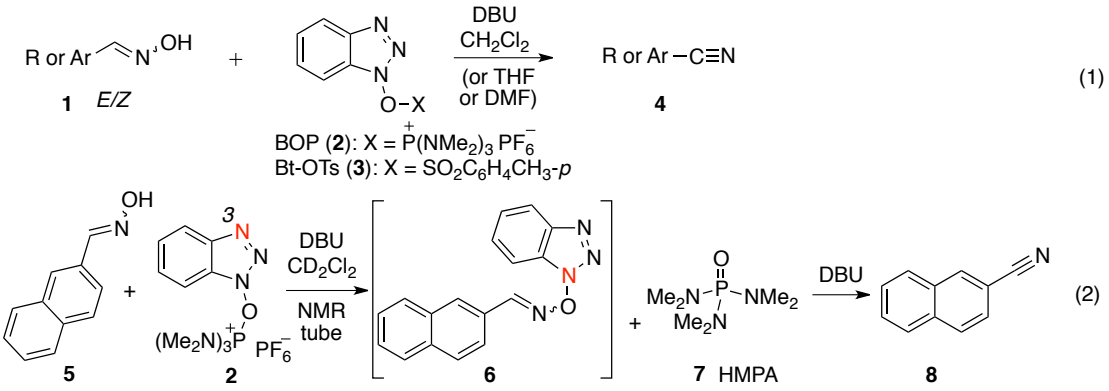
[3.1] INTRODUCTION

In Chapter 2, we described the dehydration of aldoximes using 1*H*-benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) and 1*H*-benzotriazol-1-yl-4-methylbenzenesulfonate (Bt–OTs), using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base, in solvents such as CH_2Cl_2, THF and DMF (Scheme 1, eq 1).

Scheme 1. *Dehydration of Aldoximes to Nitrile*

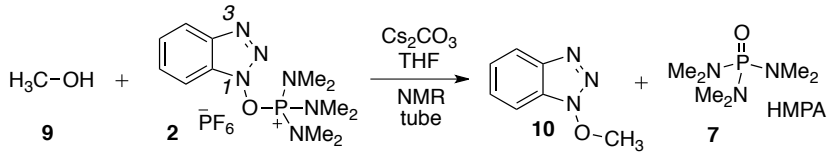


In this chemistry we showed that no new phosphonium ion signal was observed by $^{31}P\{^{1}H\}$ NMR when 2-naphthaldoxime was exposed to 2 molar equiv of BOP and 2.3 molar equiv of DBU, in CD_2Cl_2 (Scheme 1, eq 2).[1] Absence of a new phosphonium ion signal indicated the possibility of direct attack of the oxime anion at the N3 nitrogen of the triazole ring in BOP. This observation led to the idea that the reaction of BOP with 2-naphthaldoxime may proceed by

direct attack of the oxime oxygen atom at the N3 nitrogen of benzotriazole in BOP rather than initial attack at phosphorus atom of BOP (Scheme 1, eq 2).

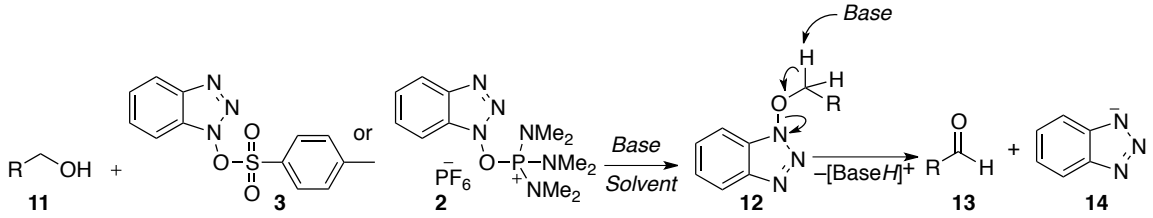
Recently, Lakshman et al. reported that the reaction between BOP and excess of methanol in THF in the presence of Cs_2CO_3, when monitored by $^{31}P\{^1H\}$ NMR, showed rapid formation of HMPA, but no new phosphinium ion signal was observed in the process (Scheme 2).[2] This observation also indicated the possibility of direct attack by alkoxide anion at the N3 nitrogen of the triazole ring in BOP. Therefore, this led us to consider the S_N2' pathway as a plausible operative mechanism in oxime dehydration.

Scheme 2. *Reaction of Methanol with BOP*



On the basis of these observations, we therefore postulated that primary alcohols could react with a benzotriazole derivative such as BOP or Bt–OTs in presence of a base. We also speculated that aldehyde **13** could be formed from such a reaction via intermediate **12** (Scheme 3). The last elimination step is dependent upon the acidity of the proton alpha to hydroxyl group and the ability of the leaving group to depart. In such an event, a question was about the mechanism of the reaction between alcohol and Bt–OTs or BOP.

Scheme 3. *Proposed Oxidation of Alcohol to Aldehyde Using BOP or Bt–OTs*



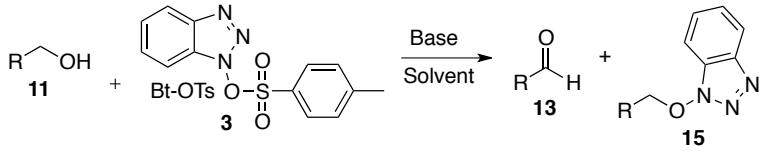
In this chapter we explore the synthesis of 1,2,3-benzotriazol-1-yl ethers of different alcohols ($R^1R^2CH–OBt$), the mechanism of their formation, their application towards metal free C–N, C–C and C–O bond formation, and potential utility as a benzylic hydroxyl-protecting group.

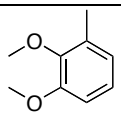
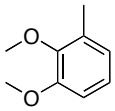
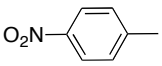
[3.2] RESULTS AND DISCUSSION

[3.2.1] Optimization of reaction and substrate scope

It was our initial hypothesis that if indeed primary alcohols underwent reaction with Bt–OTs or with BOP, then the reaction could potentially be used for oxidation of primary alcohols to aldehydes (Scheme 3). We began testing this hypothesis using 2,3-dimethoxybenzyl alcohol. When 2,3-dimethoxybenzyl alcohol was reacted with Bt–OTs in presence of DBU, desired 2,3-dimethoxybenzaldehyde was not obtained. Instead, formation of a new entity was observed, which was identified as the benzotriazolyl ether of 2,3-dimethoxybenzyl alcohol (Table 1, entry 1).

Table 1. *Attempted Oxidation of Alcohols Using BtOTs*[a]



Entry	R =	Base, Solvent	Time[b]	Temp. (^{o}C)	Yield[c]
1		DBU, THF	2.5 h	rt	**13:** 0% **15a:** 87%
2		LDA, THF	13 h	rt to 50 ^{o}C	Inc[d]
3		DBU, THF	1.5 h	rt	**13:** 20% **15b:** 0%

[a] Reaction conducted at 0.2 mmol of alcohol in 0.5 mL of solvent. [b] Reaction was monitored by TLC. [c] Reported yield is of isolated and purified product. [d] Presence of starting material and product formation was observed by TLC, no isolation was performed.

A similar reaction with lithium diisopropylamide (LDA) as base resulted in a trace amount of aldehyde, as observed by ^{1}H NMR (Table 1, entry 2). Thus, increasing the strength of the base from DBU to LDA did not improve the reaction efficiency. In both trials (entries 1 and 2), attempted oxidation of the electron-rich benzylic alcohol stopped at the benzotriazolyl ether

formation. This implies that the elimination step is much more difficult than the etherification step.

We then decided to increase the acidity of the benzylic proton by making the aryl ring electron deficient. We used *p*-nitrobenzyl alcohol for this reaction (Table 1, entry 3) and DBU as base. The oxidation reaction went to completion in a facile manner at room temperature and resulted in formation of the corresponding aldehyde. However, the isolated yield of the desired aldehyde was only 20% (Table 1, entry 3).

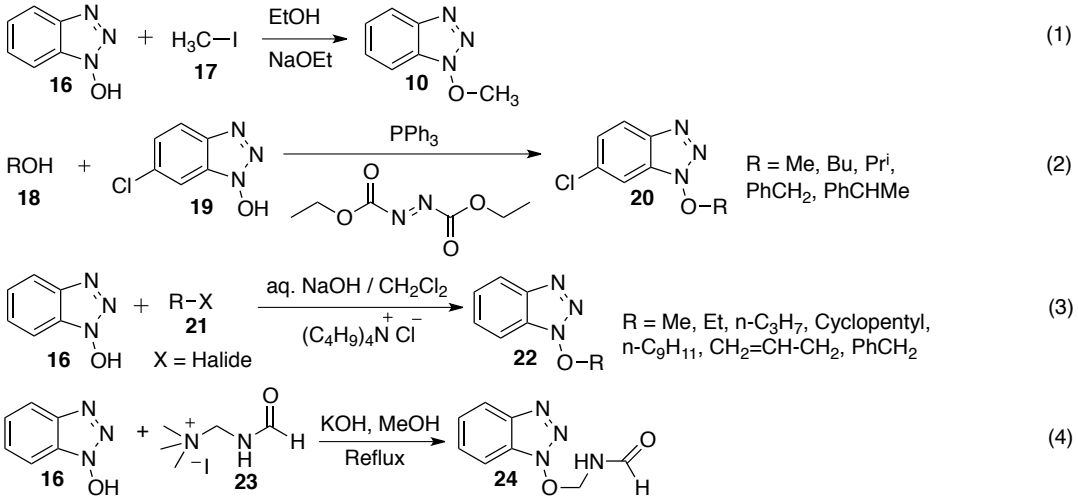
From results of Table 1, development of a simple oxidation protocol for the primary alcohols via 1,2,3-benzotriazolyl ethers was not feasible. However, alcohols with sufficiently acidic alpha protons such as *p*-nitrobenzyl alcohol, undergo oxidation to the aldehyde using weak base such as DBU (Table 1, entry 3), albeit in low yield. Notably, attempted reactions of 2,3-dimethoxybenzyl alcohol resulted in the easy formation of corresponding 1,2,3-benzotriazolyl ether (Table 1, entries 1 and 2). The facile formation of benzotriazolyl ethers in good yields caught our attention.

Thus, we conducted a search of the literature to find whether benzotriazolyl ethers are known entities. Further searches were conducted to understand how such ethers were prepared and what their utilities were. This search revealed that R–OBt ethers are known. However, neither Bt–OTs nor BOP has been used for the synthesis of benzotriazolyl (Bt) ether of an alcohol (R–OBt). Also, we did not find any literature report on the synthetic utility of these R–OBt ethers. Therefore, we decided to develop a new synthetic protocol to synthesize R–OBt ethers using Bt–OTs or BOP and to discover synthetic utilities of the benzotriazolyl ethers of some alcohols.

Older methods for synthesis of RO–Bt ethers are summarized in Scheme 4. One of the earliest methods to synthesize alkoxybenzotriazole was reported by Brady et al.[3] In this method,

1-hydroxybenzotriazole (HOBt) was etherified using iodomethane in EtOH using NaOEt (Scheme 4, eq 1).[3]

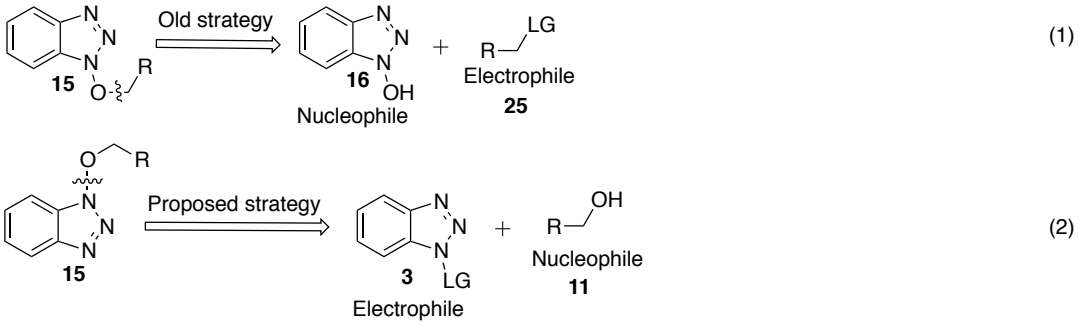
Scheme 4. *Reported Methods for Synthesis of RO–Bt Ethers*



Grochowski et al. applied the Mitsunobu approach, where the benzotriazolyl ethers were synthesized by activation of alcohol under Mitsunobu conditions followed by nucleophilic attack by benzotriazolyloxy (BtO^-) anion (Scheme 4, eq 2).[4] The third method is a simple S_N2 reaction between HOBt and an alkyl halide, under phase transfer conditions (Scheme 4, eq 3).[5] Sasaki et al. synthesized 1-(formamidomethyloxy)benzotriazole by nucleophilic substitution of a trimethylamino group with HOBt (Scheme 4, eq 4).[6]

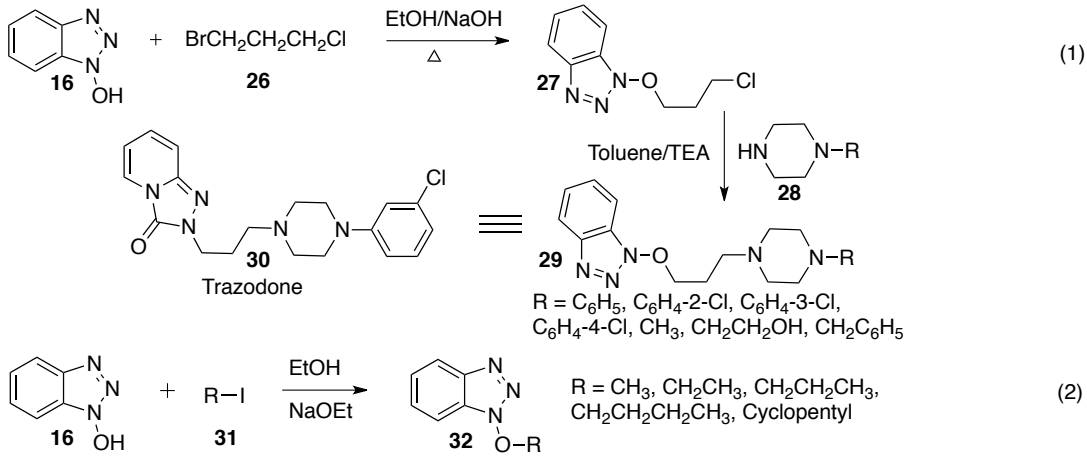
Compared to the literature methods, it appeared that our discovery would be a simpler technique, requiring inexpensive reagents. Further, current methods for the synthesis of benzotriazolyl (Bt) ethers (Scheme 4), utilize HOBt as a nucleophile. In contrast, in our approach the benzotriazole moiety seems to function as an electrophile. The basic difference between our proposed method and older methods of synthesis of R–OBt ethers can easily be understood from simple retrosynthetic analysis shown in Scheme 5.

Scheme 5. *Retrosynthetic Analysis of R–OBt Ether Synthesis*



Development of a new method to synthesize R–OBt ethers is likely to have biological significance, since many benzotriazolyl derivatives are pharmacologically important. For example, substituted benzotriazoles have been evaluated as inhibitors of respiratory syncytial virus[7] and halogenated benzotriazoles have been shown to inhibit helicase activity of hepatitis C.[8] Specifically, some benzotriazolyl ethers have been prepared as analogues of trazodone, an antidepressant (Scheme 6, eq 1).[9] Chao et. al. synthesized several derivatives of 1-alkoxy-1,2,3-benzotriazole as a potential new fungicidal agents (Scheme 6, eq 2).[10]

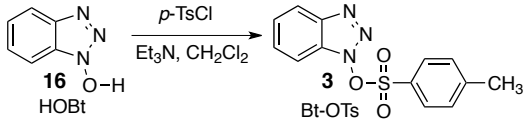
Scheme 6. *Synthesis of Some Biologically Important R–OBt Ethers*



Between the two electrophilic benzotriazolyl derivatives BOP and Bt–OTs, the latter was deemed preferable for our chemistry because BOP produces HMPA, a known nasal carcinogen.[11] Synthesis of Bt–OTs is simple[12] (Scheme 7) requiring only HOBt ($18.4/mol) and TsCl

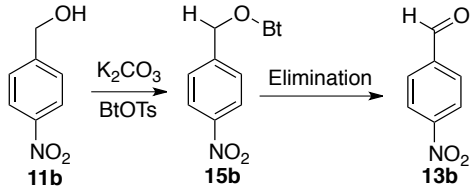
($9.3/mol). Alcohols, needed for the reactions are readily available and enantiopure alcohols can also be easily accessed.

Scheme 7. *Synthesis of Benzotriazol-1-yl-4-methylbenzene Sulfonate (Bt–OTs)*



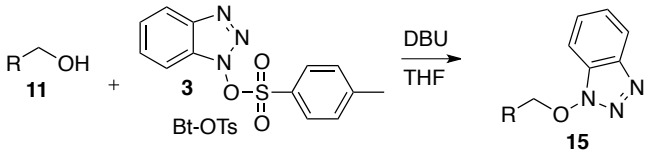
On the basis of the foregoing, we evaluated the synthesis of benzotriazolyl ethers from various alcohols (Table 2). Synthesis of the R–OBt ether from electron-rich benzylic alcohol (Table 2, entry 1) was simpler as compared to that from an electron-deficient alcohol (Table 2, entry 2). Due to the higher acidity of the benzylic proton in the benzotriazolyl ether of *p*-nitrobenzyl alcohol, formation of the corresponding aldehyde was a competing side reaction (Scheme 8).

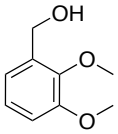
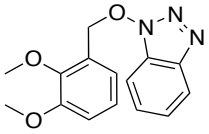
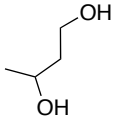
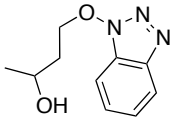
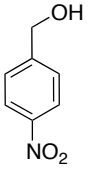
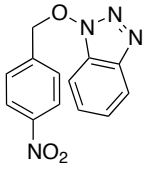
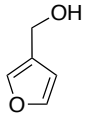
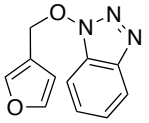
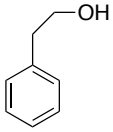
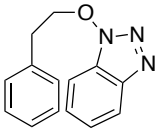
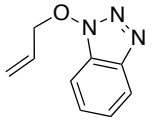
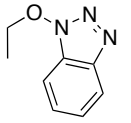
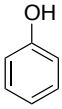
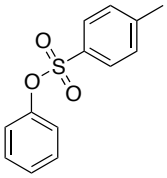
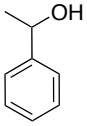
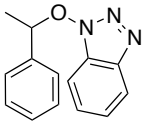
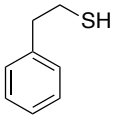
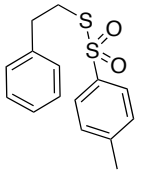
Scheme 8. *Possible Pathway for Oxidation of p-Nitrobenzyl Alcohol*



The aldehyde byproduct (**13b**) was observed even when the reaction was carried out using K_2CO_3 instead of DBU. Thus, use of K_2CO_3 did not prevent the elimination step (Scheme 8). This led to a slight modification in the reaction procedure for *p*-nitrobenzyl alcohol. For the synthesis of this ether, 1.5 mol eq of Bt–OTs (instead of 1.1 mol eq) solution in THF and 1.1 mol eq of DBU (instead of 1.5 mol eq) base were added dropwise over a period of 1.5 h. This small modification of the reaction procedure in case of *p*-nitrobenzyl alcohol helped improved the yield from 40% to 68% (Table 2, entry 2).

Table 2. *Synthesis of Benzotriazolyl Ethers of Alcohols*[a]



#	Alcohol	Product	Time	Yield[b]	#	Alcohol	Product	Time	Yield[b]
1			2.5 h	87%	6			4 h	48%
2			6 h	68%	7			4 h	67%
3			8 h	90%	8			3 h	73%
4			3 h	85%	9			3 h	84%
5			24 h	59%	10			24 h	Inc[c]

[a] Reactions were conducted at 2.5 to 6 mmol of alcohols. Concentration of reaction mixture was 0.2 M with respect to the alcohol in THF. [b] Yields of isolated and purified products. [c] Reaction was incomplete.

Benzotriazolyl ethers of a variety of alcohols were obtained in good to excellent yields (Table 2). Reaction of sterically encumbered 1-phenylethanol, a secondary alcohol, with Bt–OTs was slower as compared to those of the primary alcohols (Table 2, entry 5). The difference in the rate of reaction between primary and secondary alcohols with Bt–OTs (entries 1–4, and 5) encouraged us to investigate the selectivity of this etherification reaction. Thus, the reaction of 1,3-butanediol with Bt–OTs (1.1 mol eq) using 1.5 mol eq of DBU in THF was investigated. As expected, reaction at the primary hydroxyl group of 1,3-butanediol was faster than that of the

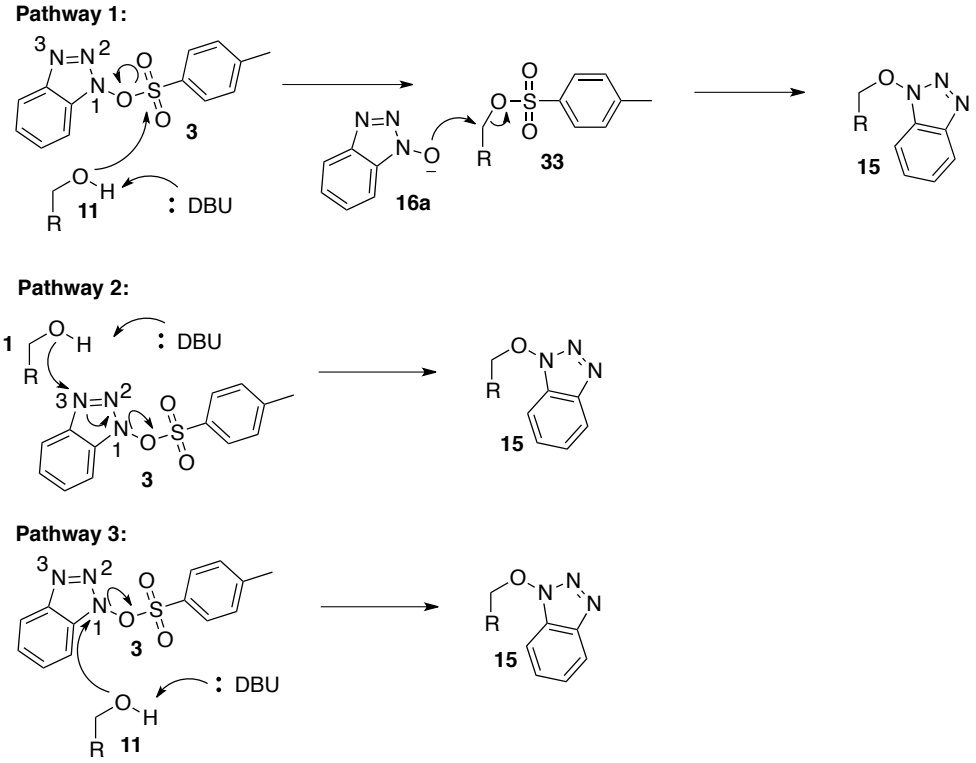
secondary hydroxyl center (entry 7). Benzotriazolyl ethers of a heterocyclic alcohol, 3-furylmethanol (entry 6) and allylic alcohol (entry 8) were also synthesized.

Interestingly, phenol did not react with Bt–OTs to give corresponding benzotriazolyl derivative (Table 2, entry 9) instead phenyl tosylate was formed. Similarly, reaction of benzyl mercaptan with Bt–OTs gave the tosyl derivative (Table 2, entry 10). The formation of tosylate esters of phenol (entry 9) and thiol (entry 10) may have occurred on account of two reasons. (i) In accordance with HSAB (hard and soft acids and bases) principle, soft nucleophiles prefer attack at a softer electrophilic site whereas hard nucleophiles prefer attack at a hard electrophilic site. Both, phenoxide and benzyl mercaptide anions being soft nucleophiles may prefer to attack at the softer electrophilic center i.e. sulfonate sulfur atom of Bt–OTs. (ii) This etherification could occur in two steps, i.e. first direct attack of alcohol on sulfur atom of Bt–OTs followed by the S_N2 attack of benzotriazolyloxy anion (BtO^-) on an in situ formed alkyl tosylate (R–OTs), resulting in the R–OBt ether. In case of phenol and benzyl mercaptan, the intermediate sulphonate will not undergo displacement readily. This may be the reason for the reaction to stop after the first step in these cases. These observations gave us solid reasons to investigate the mechanism of this etherification reaction.

[3.2.2] Mechanism of the ether forming reaction

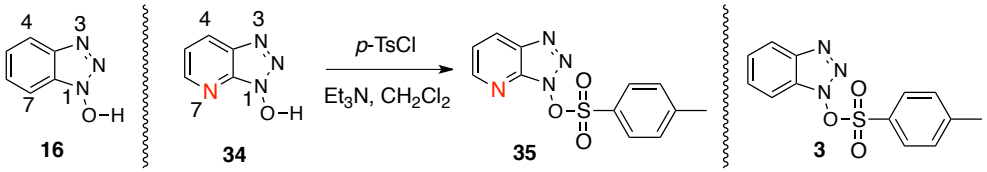
As shown in Scheme 9, the reaction can follow three possible pathways. In Pathway 1, the deprotonated alcohol could attack at the sulfur atom of the sulfonate ester leading to the alcohol sulfonate. Another S_N2 attack by the benzotriazolyoxy anion (**16a**) on the alkylsulfonate ester (**33**) can result in the desired product **15**. In Pathway 2, the desired Bt ether can be produced via a S_N2' like attack at the N3 nitrogen atom of Bt–OTs, which we initially thought was the case. In Pathway 3, Bt ether formation can occur via direct S_N2 attack at the N1 atom of Bt–OTs.

Scheme 9. *Possible Pathways of Reaction Between Bt-OTs and an Alcohol*



To gain greater insight into the reaction mechanism we decided to use a simple and inexpensive method first, i.e. by desymmetrization of the benzene ring of benzotriazole moiety in Bt–OTs. For this we chose 1-hydroxy-7-azabenzotriazole (HOAt, **34**) and synthesized At–OTs **35**,[12] an analogue of Bt–OTs **3** (Scheme 10).

Scheme 10. *Synthesis of At-OTs an Analogue of Bt-OTs*

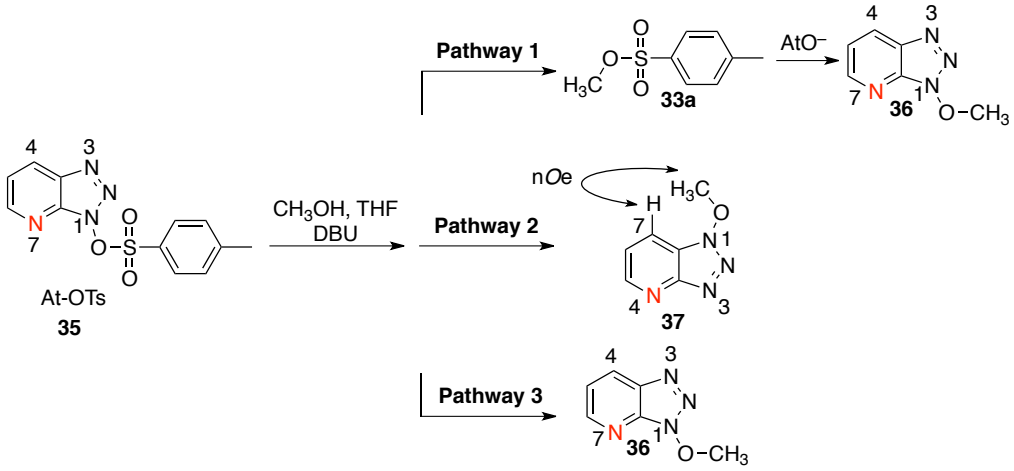


At–OTs was synthesized by reacting, HOAt with *p*-TsCl in CH_2Cl_2, with Et_3N as base (Scheme 10).[12] The presence of the N7 nitrogen atom was deemed unlikely to influence the reaction mechanism. Thus, At–OTs is expected to follow a reaction pathway similar to Bt–OTs

in the etherification reaction. However, due to dissymmetry of the azatriazolyl moiety in At–OTs, the products arising form the nucleophilic attack of the alcohol at N1 or N3 would be different. Therefore, ^{1}H NMR analysis of the products from reaction between an alcohol and At-OTs could reveal whether attack occurs at the N1 or N3.

As shown in Scheme 11, etherification of CH_3OH with At-OTs in THF, using DBU as base can give rise to two possible products, **36** (via pathways 1 and 3) and **37** (via pathway 2). If pathways 1 and/or 3 and 2 compete, then a mixture of products **36** and **37** would be the formed (Scheme 11). In such a case, ^{1}H NMR of the crude reaction mixture should show two sets of signals from the two products. If the isolated product is **37**, then a NOESY (nuclear overhauser enhancement spectroscopy) experiment may show n*O*e (nuclear overhauser effect) between the aromatic C-7 proton and methyl group. Such n*O*e would not be seen with **36**.

Scheme 11. *An Attempt to Understand the Etherification Mechanism by nOe Analysis*

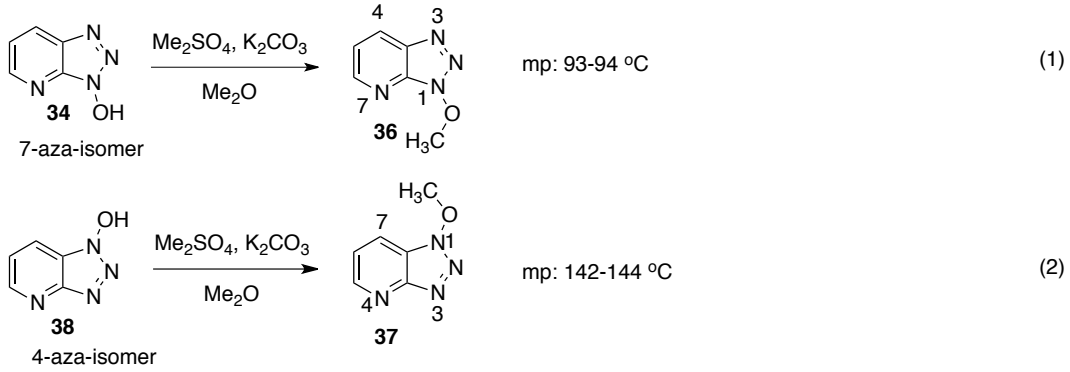


The ^{1}H NMR of the crude mixture (Scheme 11) from a reaction of At-OTs and CH_3OH showed only one set of product resonances. The NOESY experiment on the isolated and purified product from this reaction did not show any n*O*e signal between the aromatic proton and the methyl group. Although, a n*O*e signal would have supported structure **37**, the absence of n*O*e

does not negate this structure. But, this does indicate possible structure **36**, i.e. pathways 1 and/or 3.

To further investigate the mechanism, a new experiment was designed. We synthesized CH_3O–At ether by a method reported by Carpino et al. that would only yield the 7-aza isomer **36**.[13] As shown in Scheme 12, Carpino et al. have reported methylation of 4 and 7-aza-isomers of HOAt. In their ^1H NMR data, the methyl group in the 7-aza-isomer (**36**, Scheme 12, eq 1) appeared at δ 4.49 ppm and that of the 4-aza-isomer (**37**, Scheme 12, eq 2) appeared at δ 4.44 ppm.

Scheme 12. *Methylation of 7 and 4-Aza-isomers of HOAt*

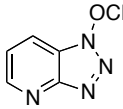
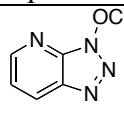
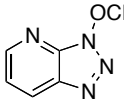


Reportedly, the aromatic protons of the 7-aza-isomer appeared as doublets of a doublet and the difference in the proton resonance of Ar–H6 and Ar–H4 protons is 0.35 ppm, and the difference in the proton resonance of Ar–H5 and Ar–H4 protons is 0.96 ppm. Also, they reported the melting points of compound **36** as 93-94 ˚C and that of compound **37** as 142-144 ˚C.[13] Therefore, the large difference in melting points between 4 and 7-aza-isomers could also help to characterize the product of our reaction.

Analysis of the product from the reaction between At–OTs and CH_3OH (Scheme 11) showed a methyl resonance at 4.47 ppm. All aromatic protons appeared as a doublets of doublets and the difference in the proton resonance of Ar–H6 and Ar–H4 protons was found to be 0.35 ppm, and the difference in the proton resonance of Ar–H5 and Ar–H4 protons was found to be 0.96 ppm

(Table 3). Clearly, the chemical shift difference of the 7-aza isomer synthesized in this reaction matches with the chemical shift difference of the product isolated from the reaction of At–OTs and MeOH (Table 3).

Table 3. *Aromatic Proton Resonance of 6 and 7-Aza Isomers*

Compound	Aromatic Resonance (ppm)	Δδ (ppm)
 **37** Carpino et al.[13]	8.80 8.04 7.52	8.80 – 8.04 = 0.76 8.04 – 7.52 = 0.52 8.80 – 7.52 = 1.28
 **36** Carpino et al.[13]	8.75 8.40 7.43	8.75 – 8.40 = 0.35 8.04 – 7.51 = 0.97 8.75 – 7.43 = 1.32
 **36** Synthesized in this work	8.73 8.37 7.41	8.73 – 8.37 = 0.36 8.37 – 7.41 = 0.96 8.73 – 7.41 = 1.32
Product from reaction of At–OTs + MeOH	8.67 8.31 7.36	8.67 – 8.31 = 0.36 8.31 – 7.36 = 0.95 8.67 – 7.36 = 1.31

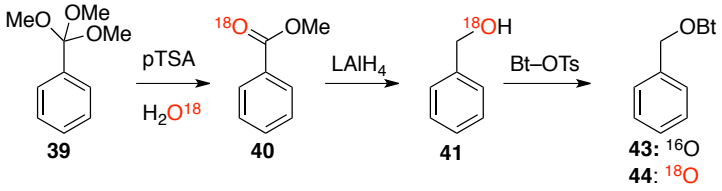
Although this was not unequivocal, the observed melting point of the isolated product was found to be 94.5-95.5 ºC. This is consistent with the literature melting point of the 7-aza-isomer (93-94 ºC). We also synthesized an authentic sample of **36** by reacting the 7-aza HOAt isomer with Me_2SO_4 by following the literature procedure (Scheme 12).[13] The methyl resonance of authentic 7-aza-isomer **36** synthesized by the method reported by Carpino et al., appeared at 4.47 ppm and the observed melting point of this white solid (**36**) was 94-95 ºC.

This detailed analyses clearly showed that pathway 2 in Scheme 11, our originally proposed mechanism, was not operational. The reaction was proceeding via either pathway 1 or pathway

3 or both. The next issue was to unambiguously identify the course of reaction between pathways 1 and 3.

To address this matter, we decided to use ^{18}O labeling of benzyl alcohol. Here we can use ^{13}C NMR and HRMS (high resolution mass spectrometry) analysis techniques. For the ^{13}C analysis, the ^{18}O isotope is known to cause slight shielding effect on the ^{13}C atom it is attached to, as compared to ^{16}O.[14,15] Therefore, a ^{13}C NMR study could reveal whether incorporation of ^{18}O occurred in the benzotriazolyl ether product. HRMS analysis should also confirm the incorporation of ^{18}O into the benzotriazolyl ether. These experiments would help clear the ambiguity centered on pathways 1 and 3. We started the labeling studies with the synthesis of ^{18}O labeled benzyl alcohol ($C_6H_5CH_2{}^{18}OH$) by a known method (Scheme 13).[16]

Scheme 13. *Synthesis of ^{18}O Labeled Benzyl Alcohol*

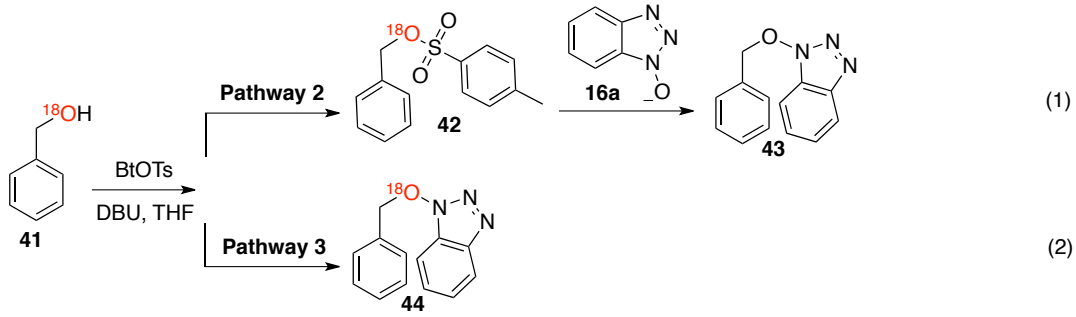


The labeled benzyl alcohol **41** was then used to synthesize the corresponding benzotriazolyl ether by the methodology developed above, i.e. by reacting $C_6H_5CH_2{}^{18}OH$ and Bt–OTs in THF, with DBU as base (Scheme 14). This product was then compared to the Bt ether of unlabeled benzyl alcohol ($C_6H_5CH_2$–OBt) synthesized as above (Table 2), using unlabeled benzyl alcohol.

^{13}C NMR showed some difference in the chemical shifts of the benzylic carbon of $C_6H_5CH_2$–OBt derived from ^{18}O benzyl alcohol (δ = 82.76 ppm) and that from unlabeled benzyl alcohol (δ = 82.82 ppm). However, ^{13}C NMR of a 1:1 mixture of $C_6H_5CH_2$–^{18}OBt and $C_6H_5CH_2$–OBt showed only one resonance (δ = 82.80 ppm) corresponding to the benzylic carbon, and not two very closely separated ones. This may indicate that the etherification reaction goes via pathway

1 (Scheme 14, eq 1). However, it is also possible that the chemical shift difference between the benzylic carbon atoms of labeled $C_6H_5CH_2$–^{18}OBt and unlabelled $C_6H_5CH_2$–OBt ether is so small that the difference was not observed by ^{13}C NMR. The HRMS analysis of the isolated product from reaction between $C_6H_5CH_2$–^{18}OH and Bt–OTs showed no ^{18}O labeling. The HRMS (ESI) showed $[M + H]^+$ of 226.0970 in comparison to the calculated $[M + H]^+$ 228.1017 for ^{18}O labeled product and 226.0975 for ^{16}O labeled compound. This supports the two-step pathway for the etherification reaction of an alcohol with Bt–OTs in THF using DBU (Scheme 14, eq 1).

Scheme 14. *Reaction between ^{18}O labeled Benzyl Alcohol and Bt-OTs*



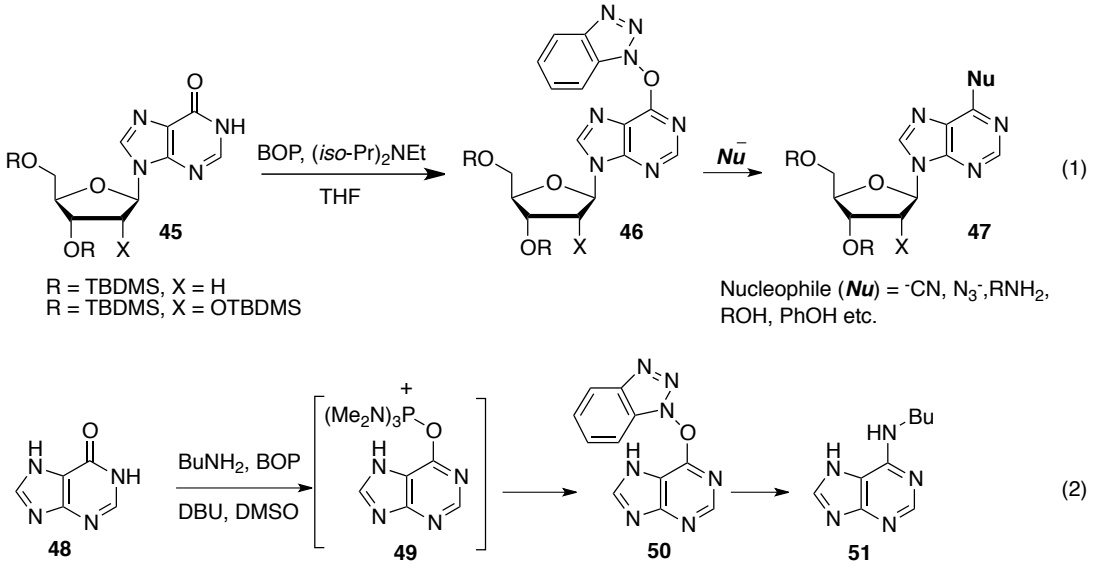
[3.2.3] Synthetic applications of benzotriazolyl ethers

So far synthesis of hydroxybenzotriazolyl ethers from alcohols and their mechanism of formation has been discussed. We next investigated the potential applications of these ethers in organic synthesis. Research from our laboratory and those of others have shown benzotriazolyloxy anion (BtO^-) to be a leaving group (Scheme 15).[17-20] For example, we have reported that reaction between 1*H*-benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) and hypoxanthine nucleosides in the presence of a base, produces the corresponding O^6-benzotriazol-1-yl nucleoside derivatives (Scheme 15, eq 1).[17] From these compounds, benzotriazolyloxy (BtO^-) anion can easily be displaced with a nucleophile (Scheme 15).[17-20] This indicates the activation of an amide C(sp^2)–O bond (Scheme 15, eq 1).[17,18]

Similarly, Wan et al. reported the C(sp^2)–O bond activation of heterocyclic amides via benzotrizolyl intermediates and they also showed that benzotriazolyoxy anion (BtO^-) is a good leaving group (Scheme 15, eq 2).[19]

The reaction in each of these cases proceeds via S_NAr displacement of benzotriazolyloxy anion. BOP is a well-known peptide-coupling reagent.[21] Also, 1*H*-benzotriazol-1-yl-4-methylbenzenesulfonate (Bt–OTs) has been evaluated as a peptide-coupling reagent.[12] In peptide coupling reactions, with both ragents the benzotriazolyloxy anion (BtO^-) acts as a leaving group from an acyl carbon.[22]

Scheme 15. *Benzotriazolyoxy Anion (BtO^-) as Leaving Group and C(sp^2)–O Bond Activation*

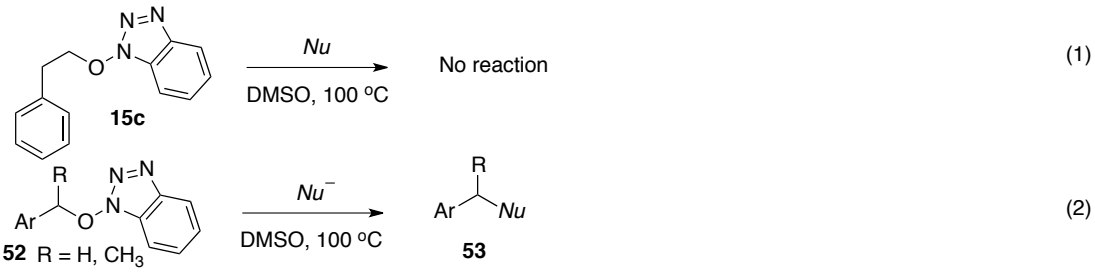


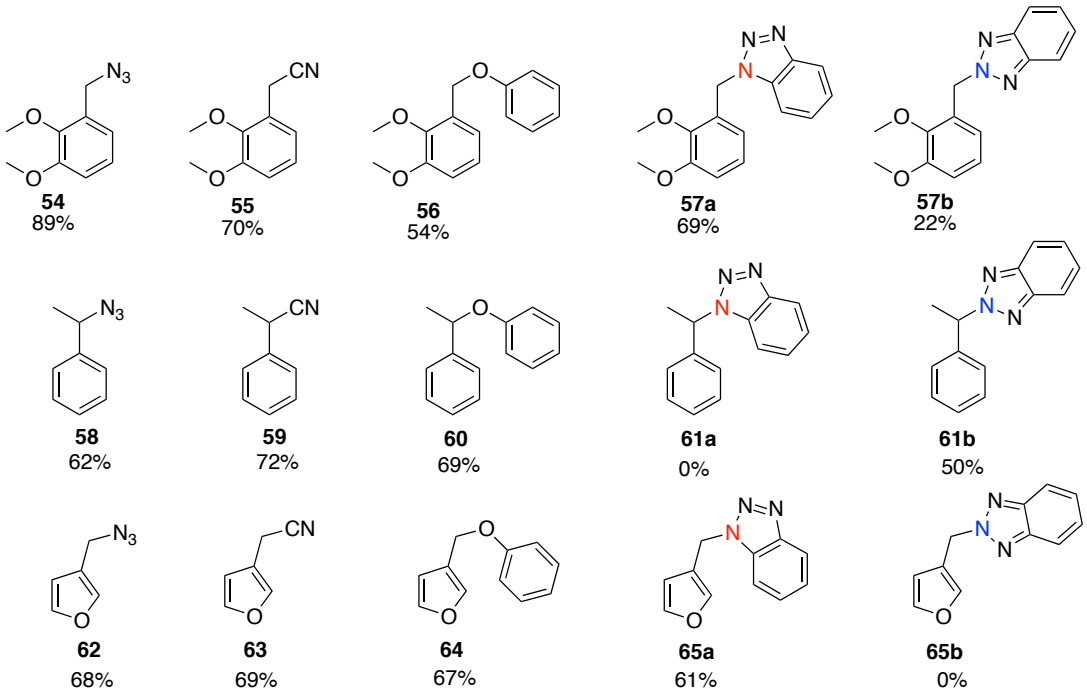
On the basis of these examples, we decided to query the direct displacement of the BtO^- anion from sp^3-hybridized carbons of $ArCH_2$–OBt ethers via nucleophilic substitution reaction. To date, BtO^- anion has never been shown to act as a leaving group from an sp^3 hybridized carbon atom.

Due to solubility reasons, DMSO was selected as solvent for reactions with inorganic nucleophiles. Also, polar aprotic solvents like DMSO stabilize S_N2 polar transition states.[23] Thus, substitution reactions were conducted in anhydrous DMSO at 100 ˚C. For this study azide,

cyanide, phenol, and benzotriazole were selected as nucleophiles. Reactions were performed with both benzylic and aliphatic benzotriazolyl ethers. No product formation observed in case of a benzotriazolyl ether from the aliphatic 2-phenyl ethanol (Scheme 16, eq 1). However, benzotriazolyl ethers of benzylic alcohols underwent substitution reactions (Scheme 16, eq 2).

Scheme 16. *Substitution of Benzotriazolyl Anion with Various Nucleophiles*





*For details see experimental section.

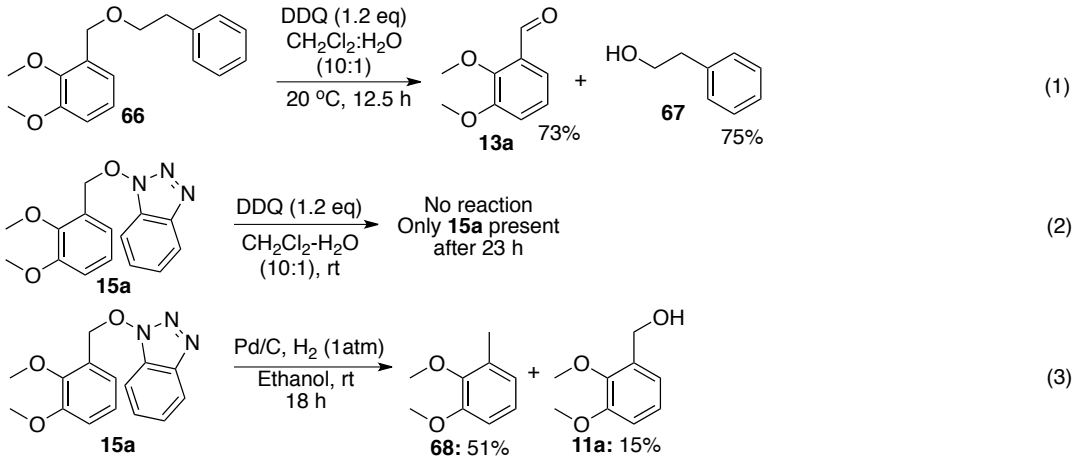
Benzotriazolyl ethers of a primary benzylic alcohol (Scheme 16, **54-57b** and **62-65b**) and of a secondary benzylic alcohol (Scheme 16, **58-61b**) underwent efficient substitution with the different nucleophiles. The resonance stabilized, weaker phenoxide nucleophile also provided the corresponding ethers in moderate to good yields. Reactions with 1*H*-benzotriazole (BtH)

resulted in symmetrical and unsymmetrical products due to nucleophilic attack by two different nitrogen atoms. Reactions of benzotriazolyl ether of the secondary benzylic alcohol with the different nucleophiles tended to produce styrene (TLC analysis) along with the desired product. A heteroaromatic substrate also underwent substitution to give the desired products (**62-65b**).

Further, we decided to test the applicability of benzotriazole as a new protecting group for benzylic alcohols. Despite the availability of a variety of protecting groups for a hydroxyl functionality,[24] new protecting groups offering different selectivities are sometimes required, specially in the synthesis of complex products. Electron-rich, benzylic alcohols are commonly used as hydroxyl protecting group, and are easily removed by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation (Scheme 17, eq 1).[25]

Reaction of benzotriazolyl ether of 2,3-dimethoxybenzyl alcohol with DDQ did not result in the formation of 2,3-dimethoxybenzaldehyde (Scheme 17, eq 2). However, the benzotriazolyl moiety could be removed using Pd/C and hydrogen gas (Scheme 17, eq 3). This indicates that benzotriazole can potentially be used as a protecting group. But further testing, particularly for removal and generality are necessary.

Scheme 17. *Reactions of Electron-Rich Benzylic Ethers with DDQ and Pd/C*



[3.3] CONCLUSION

In conclusion, we have discovered a new, simple, mild, and good-yielding method for the synthesis of a variety of benzotriazolyl ethers from a range of alcohols. Detailed mechanistic analysis of this reaction was performed by synthetic experiments, isotopic labeling, and by various NMR techniques. This investigation revealed that the etherification reaction is possibly a two-step process. The mechanism of the reaction seems to proceed via two back-to-back displacement reactions. Step1 involves a direct attack of the deprotonated alcohol at the sulfur atom of the sulfonate ester leading to the alcohol sulfonate and in Step 2 the benzotriazolyloxy anion (BtO^-) generated in Step 1, attacks the alkylsulfonate ester resulting in the desired benzotriazolyl ether. This refuted our initial belief that the benzotriazolyl moiety in Bt–OTs can act as an electrophile and participate in S_N2' like reactions. We have also shown the applicability of benzylic benzotriazolyl ethers for the formation of C–C, C–O and C–N bonds via simple substitution reactions. This is the first report to show the C–O bond activation of benzyl alcohols for substitution reactions with a variety of nucleophiles, via formation of an ether. In addition, an attempt has been made to show the applicability of benzotriazolyl ethers as hydroxyl protecting groups.

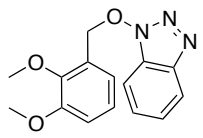
[3.4] GENERAL PROCEDURE

[3.4.1] Synthesis of benzotriazolyl ethers of alcohols using Bt-OTs

In a 50 mL oven-dried, round-bottomed flask equipped with a stirring bar were placed alcohol (1.0 mmol), 1*H*-benzotriazol-1-yl-4-methylbenzenesulfonate (Bt-OTs, 1.2 mmol) in anhydrous THF (5 mL). To this stirring solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.5 mmol). Reaction progress was monitored by TLC analysis. After, complete consumption of the starting material. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was chromatographed on a silica gel column using a suitable eluting solvent.

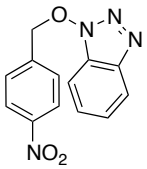
Deviations from the general procedure are mentioned under the synthetic procedure of the individual compounds.

1-(2,3-Dimethoxybenzyloxy)-1*H*-benzotriazole (15a)



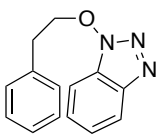
Synthesized from 2,3-dimethoxybenzyl alcohol, (**11a**, 0.58 g, 3.45 mmol) using Bt–OTs (1.10 g, 3.80 mmol) and DBU (0.77 mL, 5.2 mmol), in anhydrous THF (17 mL). Reaction progress was monitored by TLC and after 2.5 h the reaction was complete. The crude product obtained after workup was chromatographed on a silica gel column using 20% EtOAc in hexanes as eluting solvent. Compound **15a** was obtained as white solid (0.862 g, 87% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.29. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, 1H, Ar-H, J = 8.4 Hz), 7.41-7.36 (m, 2H, Ar-H), 7.33 (br t, 1H, Ar-H, J = 6.5 Hz), 7.01-6.95 (m, 2H, Ar-H), 6.89 (dd, 1H, Ar-H, J = 1.6, 7.3 Hz), 5.57 (s, 2H, CH_2), 3.88 (s, 3H, CH_3), 3.87 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 148.9, 143.5, 128.1, 127.9, 127.1, 124.6, 124.3, 123.7, 120.2, 114.6, 109.1, 77.8, 61.6, 56.1. HRMS (ESI) *m/z* calcd for $C_{15}H_{16}N_3O_3$ $[M + H]^+$ 286.1186, found 286.1194

1-(*p*-Nitrobenzyloxy)-1*H*-benzotriazole (15b)



In a 100 mL oven dried, round-bottomed flask equipped with a stirring bar were placed *p*-nitrobenzyl alcohol **11b** (0.612 g, 4 mmol), Bt–OTs, (**3**, 1.735 g, 1.5 mmol) in anhydrous THF (40 mL). The reaction mixture was cooled in an ice bath. To the stirring, cold solution was added DBU (0.65 mL, 4.4 mmol) dropwise over the period of 1.5 h. Reaction progress was monitored by TLC and after 6 h the reaction was complete. The crude product obtained after workup was chromatographed on a silica gel column using 50% CH_2Cl_2 in hexanes as eluting solvent. Compound **15b** was obtained as light yellow liquid (0.734 g, 68% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.12. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, 2H, Ar-H, J = 8.5 Hz), 8.00 (d, 1H, Ar-H, J = 8.3 Hz), 7.61 (d, 1H, Ar-H, J = 8.5 Hz), 7.43 (t, 1H, Ar-H, J = 7.6 Hz), 7.36 (t, 1H, Ar-H, J = 8.0 Hz), 7.32 (d, 1H, Ar-H, J = 8.2 Hz), 5.65 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.8, 143.5, 140.2, 130.5, 128.5, 127.7, 125.0, 124.2, 120.6, 108.5, 80.7. HRMS (ESI) *m/z* calcd for $C_{13}H_{11}N_4O_3$ $[M + H]^+$ 271.0826, found: 271.0823.

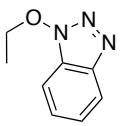
1-(2-Pheny-1-ethoxy)-1*H*-benzotriazole (15c)



Synthesized from 2-phenylethanol (**11c**, 0.34 mL, 2.86 mmol) using **3** (0.995 g, 3.44 mmol) and DBU (0.64 mL. 4.28 mmol) in anhydrous THF (15 mL). The reaction progress was monitored by TLC and after 8.0 h the reaction was complete. The crude mixture obtained after workup was chromatographed on a silica gel column using 5% EtOAc in hexanes as eluting solvent. The product was re-purified with 3% EtOAc in hexanes. Compound **15c** was obtained as clear liquid (0.611 g, 90% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.34. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.0 (d, 1H, Ar-H, J = 8.4 Hz), 7.45 (t, 1H, Ar-H, J = 8.0 Hz), 7.38-7.34 (m, 3H, Ar-H), 7.31-7.27 (m, 4H, Ar-H), 4.77 (t, 2H, CH_2, J = 6.8

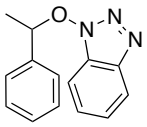
Hz), 3.20 (t, 2H, CH_2, J = 6.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.5, 136.6, 129.0, 128.8, 128.0, 127.3, 127.0, 124.7, 120.2, 108.7, 81.0, 34.6. HRMS (ESI) *m/z* calcd for $C_{14}H_{14}N_3O$ [M + H]$^+$: 240.1131, found 240.1137.

1-(Ethoxy)-1*H*-benzotriazole (15d)



Synthesized from ethanol (**11d**, 0.28 mL, 3.63 mmol) using Bt–OTs (0.954 g, 3.3 mmol) and DBU (0.74 mL. 4.9 mmol) in anhydrous THF (16.5 mL). The reaction progress was monitored by TLC and after 3.0 h the reaction was complete. Without any workup, the reaction mixture was chromatographed on a silica gel column using 4% EtOAc in hexanes as eluting solvent. Compound **15d** was obtained as clear liquid (0.457g, 85% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.33. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, 1H, Ar-H, J = 8.5 Hz), 7.58 (d, 1H, Ar-H, J = 8.4 Hz), 7.51 (t, 1H, Ar-H, J = 7.7 Hz), 7.39 (t, 1H, Ar-H, J = 7.6 Hz), 4.63 (q, 2H, CH_2, J = 7.1 Hz), 1.49 (t, 3H, -CH_3, J = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.4, 128.0, 127.6, 124.6, 120.0, 108.7, 76.6, 13.7. HRMS (ESI) *m/z* calcd for $C_8H_{10}N_3O$ [M + H]$^+$ 164.0818, found 164.0797.

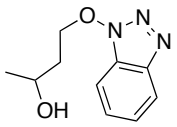
1-(1-Phenylethoxy)-1*H*-benzotriazole (15e)



Synthesized from 1-phenylethanol (**11e**, 0.6 mL, 5.0 mmol) using Bt–OTs (1.73 g, 6.0 mmol) and DBU (1.12 mL. 7.5 mmol) in anhydrous THF (25 mL). Reaction progress was monitored by TLC and after 24 h the reaction was complete. The crude product obtained after workup was chromatographed on a silica gel column using 5% acetone in hexanes as eluting solvent. Compound **15e** was obtained as clear oily liquid (0.700g, 59% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.19. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, 1H, Ar–H, J = 8.1 Hz), 7.36 (m, 2H, Ar–H), 7.31-7.24 (m, 5H, Ar–H), 7.13 (d, 1H, Ar–H, J = 8.2 Hz), 5.76 (q, 1H, CH, J = 6.6 Hz), 1.86 (d, 3H, CH_3, J = 6.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 138.4,

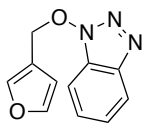
129.9, 128.7, 128.4, 127.8, 127.7, 125.6, 124.4, 120.1, 109.1, 89.1, 20.1. HRMS (ESI) *m/z* calcd for $C_{14}H_{14}N_3O$ $[M + H]^+$ 240.1131, found 240.1121.

1-(3-Hydroxy-1-butoxy)-1*H*-benzotriazole (15f)



Synthesized from 1,3-butanediol (**11f**, 0.045 mL, 0.5 mmol) using Bt–OTs (0.159 g, 0.55 mmol) and DBU (0.11 mL, 0.75mmol) in anhydrous THF (2.5 mL). Reaction progress was monitored by TLC and after 4 h the reaction was complete. Without any workup, the crude reaction mixture was chromatographed on a silica gel column using 15% EtOAc in hexanes as eluting solvent. Compound **15f** was obtained as white solid (0.0501g, 48% yield). R_f (SiO_2/40% EtOAc in hexanes) = 0.10. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, 1H, Ar-H, *J* = 8.4 Hz), 7.60 (d, 1H, Ar-H, *J* = 8.4 Hz), 7.52 (t, 1H, Ar-H, *J* = 7.6 Hz), 7.39 (t, 1H, Ar-H, *J* = 7.7 Hz), 4.66-4.76 (m, 2H, CH_2), 4.24 (br m, 1H, CH), 2.08 (m, 1H), 1.95 (m, 1H), 1.80 (d, 1H, OH, *J* = 4.3 Hz), 1.33 (d, 3H, CH_3, *J* = 6.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.5, 128.2, 127.4, 124.9, 120.2, 108.9, 78.4, 64.6, 37.3, 24.1. HRMS (ESI) *m/z* calcd for $C_{10}H_{14}N_3O_2$ $[M + H]^+$ 208.1081, found 208.1084.

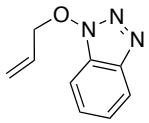
1-(3-Furanmethoxy)-1*H*-benzotriazole (15g)



Synthesized from 3-furanmethanol (**11g**, 0.27 mL, 3.16 mmol) using Bt–OTs (0.831 g, 2.87 mmol) and DBU base (0.47 mL, 3.13mmol) in anhydrous THF (15 mL). Reaction progress was monitored by TLC and after 4 h the reaction was complete. The crude product obtained after workup was chromatographed on a silica gel column using 4% EtOAc in hexanes as eluting solvent. Compound **15g** was obtained as brownish solid (0.414 g, 67% yield). R_f (SiO_2/40% EtOAc in hexanes) = 0.38. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, 1H, Ar-H, *J* = 8.2 Hz), 7.40 (t, 1H, Ar-H, *J* = 7.6 Hz), 7.38 (s, 1H, Ar-H), 7.32 (m, 3H, Ar-H),

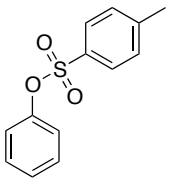
6.46 (s, 1H, Ar-H), 5.45 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.2, 143.6, 128.3, 128.0, 124.7, 120.2, 118.2, 110.9, 108.9, 73.3. HRMS (ESI) *m/z* calcd for $C_{11}H_{10}N_3O_2$ $[M + H]^+$ 216.0768, found 216.0757.

1-(Allyloxy)-1*H*-benzotriazole (15h)



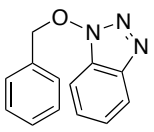
Synthesized from allyl alcohol (**11h**, 0.22 mL, 3.3 mmol) using Bt–OTs (0.868 g, 3.0 mmol) and DBU (0.67 mL, 4.5 mmol) in anhydrous THF (15 mL). The reaction progress was monitored by TLC and after 3 h the reaction was complete. The crude product obtained after workup was chromatographed on a silica gel column using 4% EtOAc in hexanes as eluting solvent. Compound **15h** was obtained as clear oily liquid (0.376 g, 73% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.38. ^1H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, 1H, Ar-H, *J* = 8.4 Hz), 7.50 (d, 1H, Ar-H, *J* = 8.3 Hz), 7.43 (t, 1H, Ar-H, *J* = 7.8 Hz), 7.30 (t, 1H, Ar-H, *J* = 8.2 Hz), 6.05 (m, 1H, CH), 5.29-5.25 (m, 2H, CH_2), 4.96 (d, 2H, CH_2, *J* = 6.8 Hz) . ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.4, 130.1, 125.0, 127.9, 124.6, 123.5, 120.1, 108.9, 81.2. HRMS (ESI) *m/z* calcd for $C_9H_{10}N_3O$ $[M + H]^+$ 176.0818, found 176.0811.

Phenyl-*p*-toluenesulfonate (33a)[26]



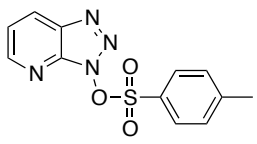
Synthesized from phenol (**11i**, 0.0094 g, 0.1 mmol) using Bt–OTs (0.0347 g, 0.12 mmol) and DBU base (22 μL, 0.15 mmol) in anhydrous THF (0.5 mL). The reaction progress was monitored by TLC and after 3 h the reaction was complete. The crude product obtained after workup was chromatographed on a silica gel column using 5% EtOAc in hexanes as eluting solvent. Compound **33a** was obtained as white crystalline solid (0.021g, 84% yield). R_f (SiO_2/10% EtOAc in hexanes) = 0.18. ^1H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.31-7.22 (m, 5H, Ar-H), 6.98 (d, 2H, Ar-H, J = 8.0 Hz) 2.45 (s, 3H, CH_3). ^1H NMR is in accordance with the reported ^1H NMR ($CDCl_3$) data.

1-(Benzyloxy)benzotriazole (44)



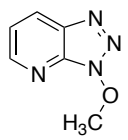
Synthesized from benzyl alcohol (**43**, 0.1 mL, 0.966 mmol) using Bt–OTs (0.335 g, 1.16 mmol) and DBU (0.21 mL, 1.45 mmol) in anhydrous THF (5 mL). Reaction progress was monitored by TLC and after 1.5 h the reaction was complete. The crude product obtaiened after workup was chromatographed on a silica gel column using 5% EtOAc in hexanes as eluting solvent. Compound **44** was obtained as thick, clear liquid (0.198 g, 91% yield). R_f (SiO_2/20% EtOAc in hexanes) = 0.39. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, 1H, Ar-H, J = 8.2 Hz), 7.37-7.28 (m, 7H, Ar-H), 7.17 (d, 1H, Ar-H, J = 8.1 Hz), 5.53 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.5, 133.3, 130.2, 130.0, 129.0, 128.1, 127.9, 124.6, 120.2, 108.9, 82.8. HRMS (ESI) *m/z* calcd for $C_{13}H_{12}N_3O_2$ $[M+H]^+$ 226.0975, found 226.0970.

7-Azabenzotriazol-1-yl-*p*-toluenesulfonate (35)[27]



A 50 mL round-bottom flask equipped with a stirring bar was charged with a suspension of HOAt (0.680 g, 5.0 mmol) in CH_2Cl_2 (12 mL) was added Et_3N (1.0 mL, 7.0 mmol) at room temperature and HOAt dissolved after the addition of base. The mixture was then cooled in ice bath. After 10 min, *p*-TsCl was added in small portions to the stirring mixture in ice bath under N_2 atm. The reaction mixture was stirred in the same ice bath without adding fresh ice and allowed to come up to the room temperature. Complete consumption of the starting material was observed by TLC analysis after 1 h. The reaction mixture was filtered through a plug of silica using CH_2Cl_2. Pure product was obtained by recrystallization from CH_2Cl_2/hexanes. The product **35**, was isolated as a white, crystalline solid (1.074 g, 74%). R_f (SiO_2/20% EtOAc in hexanes) = 0.1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.77 (dd, 1H, Ar-H, J = 1.3, 4.5 Hz), 8.38 (dd, 1H, Ar-H, J = 1.4, 8.3 Hz), 7.88 (d, 2H, Ar-H, J = 8.4 Hz), 7.46-7.42 (m, 3H, Ar-H), 2.51 (s, 3H, CH_3).

1-(Methoxy)-7-azabenzotriazole (36)[13]



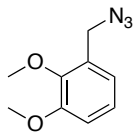
In a 50 mL round-bottom flask were placed HOAt (0.350 g, 2.57 mmol) and K_2CO_3 (1.030 g, 3.6 mmol) in anhydrous acetone (10 mL), Me_2SO_4 (0.45 mL, 3.6 mmol) was added and the mixtre was stirred at room temperature. Reaction progress was monitored by TLC and after 1.5 h the reaction was complete. The reaction was filtered through a plug of basic alumina using CH_2Cl_2. The crude product so obtained was chromatographed on a silica gel column using 20% EtOAc in hexanes as eluting solvent. Compound **36** was obtained as a white, crystalline solid (0.258 g, 66%). R_f (SiO_2/20% EtOAc in hexanes) = 0.12. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (dd, 1H, Ar-H, J = 1.3, 4.3 Hz), 8.38 (dd, 1H, Ar-H, J = 1.3, 8.3 Hz), 7.41 (dd, 1H, Ar-H, J = 4.4, 8.3 Hz), 4.47 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.4, 139.5, 135.4, 129.5, 120.8, 68.4.

[3.4.2] General procedure for nucleophilic substitution reactions of benzotriazolyl ethers of benzylic alcohols

In a clean dry vial equipped with a stirring bar, was placed a mixture of the appropriate benzotriazolyl ether (1.0 mmol) and a suitable nucleophile (2.0 mmol) in DMSO (2.5 mL) . The reaction mixture was stirred at 100 ^{o}C and the reaction progress was monitored by TLC. When complete consumption of the starting material was observed, the reaction mixture was diluted with Et_2O and washed with a 1:1 mixture of water and brine (x3) followed by deionized water (x3) and again with brine. The organic layer was died over Na_2SO_4 and concentrated under reduced pressure. The crude product was chromatographed on a silica gel column using a suitable eluting solvent.

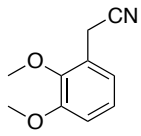
Deviations from the general procedure are mentioned under the synthetic procedures for the individual compounds.

1-(Azidomethyl)-2-3-dimethoxybenzene (54)



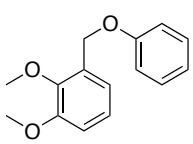
Synthesized from compound **15a** (0.143 g, 0.5 mmol) and NaN_3 (0.065 g, 1.0 mmol) in anhydrous DMSO (1.25 mL). After 2.5 h, TLC analysis showed complete consumption of the starting material. After workup, the crude product was chromatographed on a silica gel column using 10% EtOAc in hexanes as eluting solvent. Compound **54** was obtained as clear liquid (0.086 g, 89%). R_f (SiO_2/20% EtOAc in hexanes) = 0.5. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 (t, 1H, Ar-H, J = 7.9 Hz), 6.92 (d, 1H, Ar-H, J = 8.1 Hz), 6.90 (d, 1H, Ar-H, J = 7.8 Hz), 4.37 (s, 2H, CH_2), 3.90 (s, 3H, CH_3), 3.87 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.8, 147.5, 129.3, 124.2, 121.8, 113.0, 61.1, 55.8, 49.9. HRMS (EI^+) calcd for $C_9H_{11}N_3O_2$ $[M + H]^+$ 194.0924, found 194.0879.

2-(2,3-Dimethoxphenyl)acetonitrile (55)



Synthesized from **15a** (0.057 g, 0.2 mmol) and NaCN (0.0196 g, 0.4 mmol) in anhydrous DMSO (0.5 mL). After 1 h, TLC analysis showed complete consumption of the starting material. After workup, the crude product was chromatographed on a silica gel column using 10% EtOAc in hexanes as eluting solvent. Compound **55** was obtained as clear liquid (0.025 g, 70%). R_f (SiO_2/20% EtOAc in hexanes) = 0.27. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (t, 1H, Ar-H, J = 7.9 Hz), 6.95 (d, 1H, Ar-H, J = 7.7 Hz), 6.91 (d, 1H, Ar-H, J = 8.2 Hz), 3.91 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 3.71 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 146.9,124.5, 124.3, 121.1, 118.3, 112.9, 60.7, 56.0, 18.7. HRMS (ESI) *m/z* calcd for $C_{10}H_{11}NO_2Na$ $[M + Na]^+$ 200.0682, found 200.0684.

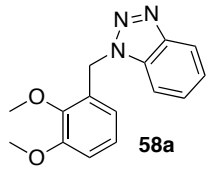
1,2-Dimethoxy-3-(phenoxymethyl)benzene (56)



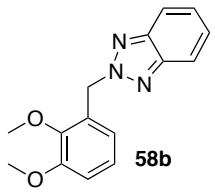
Synthesized from **15a** (0.143 g, 0.5 mmol), Cs_2CO_3 (0.326 g, 1.0 mmol) and phenol (0.094 g, 1.0 mmol) in DMSO (1.25 mL) . After 2.5 h, TLC analysis

showed complete consumption of the starting material. After workup, the crude product was chromatographed on a silica gel column using 10% EtOAc in hexanes as eluting solvent. Compound **56** was obtained as clear liquid (0.066 g, 54%). R_f (SiO_2/20% EtOAc in hexanes) = 0.47. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (t, 2H, Ar-H, *J* = 7.6 Hz), 7.14 (m, 2H, Ar-H), 7.07 (d, 2H, Ar-H, *J* = 8.6 Hz), 7.02 (t, 1H, Ar-H, *J* = 7.3 Hz), 6.95 (dd, 1H, Ar-H, *J* = 3.5, 5.9 Hz), 5.19 (s, 2H, CH_2), 3.95 (s, 3H, CH_3). 3.93 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 147.0, 128.6, 127.5, 124.6, 124.0, 121.3, 120.0, 112.9, 110.2, 61.1, 56.0, 46.8. HRMS (ESI) *m/z* calcd for $C_{15}H_{16}O_3Na$ $[M + Na]^+$ 267.0992, found 267.1003.

1-(2,3-Dimethoxybenzyl)-1*H*-benzotriazole (57a) and 2-(2,3-dimethoxybenzyl)-2*H*-benzotriazole (57b)



58a



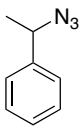
58b

Synthesized from **15a** (0.057 g, 0.2 mmol), Cs_2CO_3 (0.130 g, 0.4 mmol) and benzotriazole (0.0476 g, 0.40 mmol) in DMSO (0.5 mL). After 4 h, TLC analysis showed complete consumption of the starting material. After workup, the crude product was chromatographed on a silica gel column using 10% EtOAc in hexanes as eluting solvent. Compound **57b**, the minor component was eluted first and was obtained as a clear, gummy material (0.012 g, 20%). R_f (SiO_2/20% EtOAc in hexanes) = 0.27. Compound **57a**, the major product, eluted next was also obtained as clear, gummy material (0.039 g, 69%). R_f (20% EtOAc in hexanes) = 0.14. ^{1}H NMR (500 MHz, $CDCl_3$): **57a** δ 8.04 (d, 1H, Ar-H, *J* = 8.3 Hz), 7.52 (d, 1H, Ar-H, *J* = 8.3 Hz), 7.41 (t, 1H, Ar-H, *J* = 7.6 Hz), 8.04 (t, 1H, Ar-H, *J* = 7.6 Hz), 6.97 (t, 1H, Ar-H, *J* = 8.0 Hz), 6.87 (d, 1H, Ar-H, *J* = 8.1 Hz), 6.73 (d, 1H, Ar-H, *J* = 7.7 Hz), 5.87 (s, 2H, CH_2), 3.86 (s, 3H, CH_3), 3.82 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 147.0, 146.3, 133.1, 128.6,

127.4, 124.5, 124.0, 121.2, 120.0, 112.9, 110.2, 61.1, 56.0, 46.8. HRMS (ESI) calcd for $C_{15}H_{16}N_3O_2$ $[M + H]^+$ 270.1237, found 270.1238.

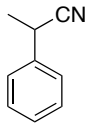
^{1}H NMR (500 MHz, $CDCl_3$): **57b** δ 7.86 (dd, 2H, Ar-H, *J* = 3.1, 6.5 Hz), 7.36 (dd, 2H, Ar-H, *J* = 3.1, 6.5 Hz), 7.02 (t, 1H, Ar-H, *J* = 8.0 Hz), 6.90 (d, 1H, Ar-H, *J* = 8.0 Hz), 6.83 (d, 1H, Ar-H, *J* = 7.7 Hz), 5.95 (s, 2H, CH_2), 3.87 (s, 3H, CH_3), 3.84 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 147.3, 144.7, 128.8, 126.4, 124.4, 121.7, 118.3, 113.1, 61.1, 56.0, 55.1. HRMS (ESI) calcd for $C_{15}H_{16}N_3O_2$ $[M + H]^+$ 270.1237, found 270.1236.

1-Phenylethyl azide (58)[28]



Synthesized from **15e** (0.120 g, 0.5 mmol) and NaN_3 (0.065 g, 1.0 mmol) in DMSO (1.25 mL). After 12 h, TLC analysis showed complete consumption of the starting material. After workup, the crude product was chromatographed on a silica gel column using 10% EtOAc in hexanes as eluting solvent. Compound **58** was obtained as brownish solid (0.046 g, 62%). R_f (SiO_2/20% EtOAc in hexanes) = 0.33. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.34 (m, 4H, Ar-H), 7.29-7.26 (m, 1H, Ar-H), 4.90 (q, 1H, CH, *J* = 6.4 Hz), 1.50 (d, 3H, CH_3, *J* = 6.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.0, 128.8, 127.8, 125.7, 70.7, 25.5.

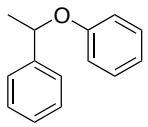
2-Phenylpropionitrile (59)



Synthesized from **15e** (0.120 g, 0.5 mmol) and NaCN (0.049 g, 1.0 mmol), in DMSO (1.25 mL). After 28 h, TLC analysis showed complete consumption of the starting material. After workup, the crude product was chromatographed on a silica gel column using 50% CH_2Cl_2 in hexanes as eluting solvent. Compound **59** was obtained as clear, oily liquid (0.048 g, 72%). R_f (SiO_2/100% CH_2Cl_2) = 0.56. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.41 (m, 5H, Ar-H), 3.90 (q, 1H, CH, *J* = 7.3 Hz), 1.65 (d, 3H, CH_3, *J* = 7.3 Hz). ^{13}C NMR (125 MHz,

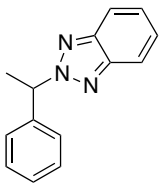
$CDCl_3$): δ 137.3, 129.4, 128.3, 126.9, 121.8, 31.5, 21.7. HRMS (ESI) calcd for C_9H_9NNa [M + Na]$^+$ 154.0627, found 154.0621.

1-(Phenoxyethyl)benzene (60)



In a clean dry vial equipped with a stirring bar, was placed phenol (0.094 g, 1.0 mmol) in MeOH (0.5 mL). To this solution NaOMe (0.057 g, 1.05 mmol) was added and the mixture was stirred for 15 min at room temperature. MeOH was removed under reduced pressure and the product was dried. To the vial containing the sodium phenoxide so prepared was added compound **15e** (0.120 g, 0.50 mmol) and DMSO (1.25 mL). The reaction mixture was capped and stirred at 100 ºC. After 14 h, TLC analysis showed complete consumption of the starting material. After workup, the crude product was chromatographed on a silica gel column using 40% CH_2Cl_2 in hexanes as eluting solvent. Compound **60** was obtained as clear liquid (0.069 g, 69%). R_f (SiO_2/100% CH_2Cl_2) = 0.64. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, 2H, Ar-H, *J* = 7.2 Hz), 7.33 (t, 2H, Ar-H, *J* = 7.5 Hz), 7.26 (m, 1H, Ar-H), 7.20 (m, 2H, Ar-H), 6.87 (m, 3H, Ar-H), 5.31 (q, 1H, CH, *J* = 6.4 Hz), 1.64 (d, 3H, CH_3, *J* = 6.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.2, 143.4, 129.5, 128.8, 127.6, 125.7, 120.8, 116.1, 76.1, 24.7. HRMS (EI$^+$) calcd for $C_{14}H_{14}O$ [M]$^+$ 199.1117, found 199.1079.

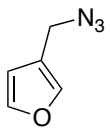
1-(1-phenylethyl)-2*H*-benzo[1,2,3]triazole (61b)



Synthesized from **15e** (0.120 g, 0.50 mmol), Cs_2CO_3 (0.325 g, 1.0 mmol) and 1*H*-benzotriazole (0.094 g, 1.0 mmol) in DMSO (1.25 mL). TLC analysis after 40 h showed some starting material remaining. After workup, the crude product was chromatographed on a silica gel column using 5% EtOAc in hexanes as eluting solvent. Compound **61b** was obtained as colorless, thick liquid (0.051 g, 50%). R_f (SiO_2/20% EtOAc in hexanes) = 0.42. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, 1H, Ar-H, *J* = 8.2 Hz), 7.35 (m, 2H, Ar-

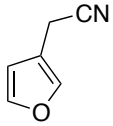
H), 7.30 - 7.23 (m, 5H, Ar-H), 7.11 (d, 1H, Ar-H, J = 8.1 Hz), 5.74 (q, 1H, CH, J = 6.6 Hz), 1.85 (d, 3H, CH_3, J = 6.6 Hz). HRMS (ESI) calcd for $C_{14}H_{14}N_3$ $[M + H]^+$ 224.1182, found 224.1176.

3-(Azidomethyl)furan (62)[29]



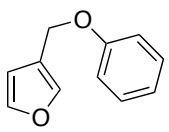
Synthesized from **15f** (0.107 g, 0.5 mmol) and NaN_3 (0.065 g, 1.0 mmol) in DMSO (1.25 mL). After 14 h, TLC analysis showed complete consumption of the starting material. After workup, the crude product was chromatographed on a silica gel column using 20% CH_2Cl_2 in hexanes as eluting solvent. Compound **62** was obtained as volatile clear liquid (0.042 g, 68%). R_f (SiO_2/50% CH_2Cl_2 in hexanes) = 0.5. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (s, 1H, Ar-H), 7.44 (app t, 1H, Ar-H, J = 1.5 Hz), 6.42 (s, 1H, Ar-H), 4.20 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.1, 141,1, 119.7, 110.3, 45.8.

2-(Furan-3-yl)acetonitrile (63)



Synthesized from **15f** (0.107 g, 0.5 mmol) and NaCN (0.049 g, 1.0 mmol) in DMSO (1.25 mL). After 20 h, TLC analysis showed complete consumption of the starting material. After workup, the crude product was chromatographed on a silica gel column using 20% CH_2Cl_2 in hexanes as eluting solvent. Compound **63** was obtained as light yellow, volatile (0.037 g, 69%). R_f (SiO_2/50% CH_2Cl_2 in hexanes) = 0.4. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 6.39 (s, 1H, Ar-H), 3.54 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.3, 140.5, 117.5, 114.6, 110.4, 14.4. HRMS (EI^+) calcd for C_6H_5NO $[M + H]^+$ 108.0444, found 108.0402.

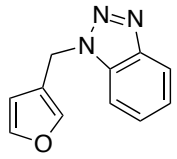
3-(Phenoxymethyl)furan (64)



In a clean dry vial equipped with a stirring bar, was placed phenol (0.094 g, 1.0 mmol) in MeOH (0.5 mL). To this solution NaOMe (0.057 g, 1.05 mmol) was added and the mixture was stirred for 15 min at room temperature. MeOH was removed under

reduced pressure and the product was dried. To the vial containing the sodium phenoxide was added compound **15f** (0.108 g, 0.50 mmol) and DMSO (1.25 mL). The reaction mixture was stirred at 100 ºC. After 15 h, TLC analysis showed complete consumption of the starting material. After workup, the crude product was chromatographed on a silica gel column using 10% CH_2Cl_2 in hexanes as eluting solvent. Compound **64** was obtained as light-brown thick, liquid (0.059 g, 67%). R_f (SiO_2/100% CH_2Cl_2) = 0.72. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 7.30 (t, 2H, Ar-H, *J* = 8.0 Hz), 6.99-6.96 (m, 3H, Ar-H), 6.50 (s, 1H, Ar-H), 4.94 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 143.7, 141.0, 129.7, 121.6, 121.3, 115.0, 62.0. HRMS (EI^+) calcd for $C_{11}H_{10}O_2$ $[M + H]^+$ 175.0754, found 175.0715.

1-(Furan-3-ylmethyl)-1*H*-benzotriazole (65a)



Synthesized from **15f** (0.107 g, 0.50 mmol) and 1*H*-benzotriazole (0.094 g, 1.0 mmol), was added DMSO (1.25 mL). After 18 h, TLC analysis showed complete consumption of the starting material. After workup, the crude product was chromatographed on a silica gel column using 20% CH_2Cl_2 in hexanes as eluting solvent. Compound **65a** was obtained as brownish, oily liquid (0.061 g, 61%). R_f (SiO_2/100% CH_2Cl_2) = 0.48. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, 1H, Ar-H, *J* = 8.2 Hz), 7.38-7.27 (m, 5H, Ar-H), 6.42 (s, 1H, Ar-H), 5.42 (s, 2H, -CH_2-). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.3, 143.6, 143.5, 128.4, 128.1, 124.7, 120.3, 118.3, 111.0, 109.0, 73.4.

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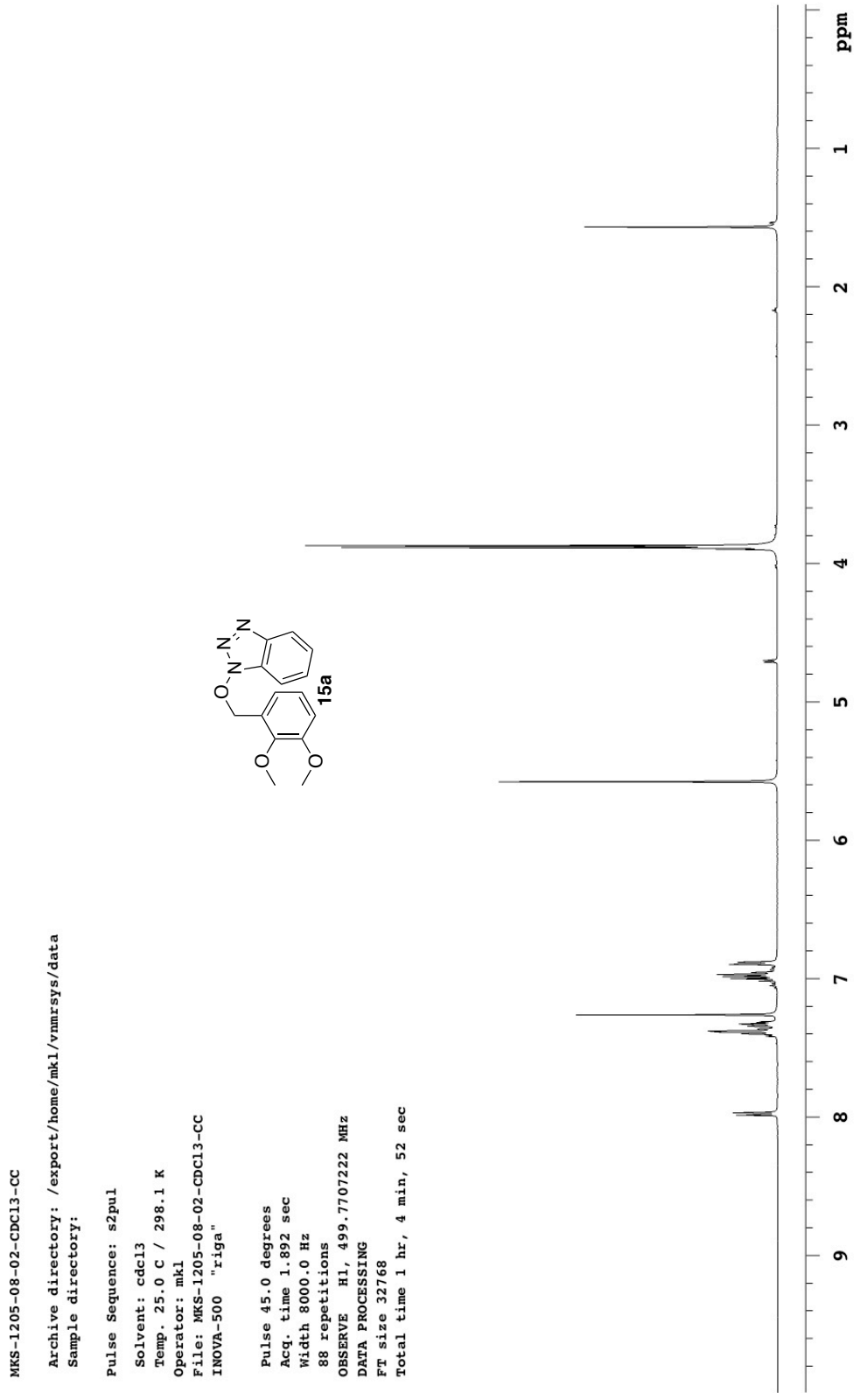
APPENDIX III



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INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
640 repetitions
OBSERVE C13, 125.6674232 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
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Line broadening 0.2 Hz
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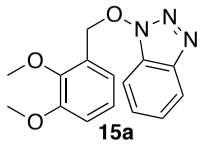
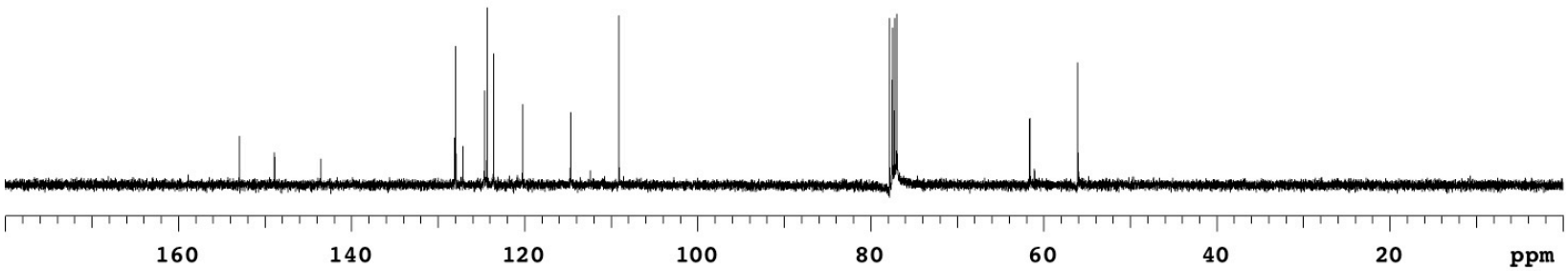
Total time 2 hr, 27 min, 5 sec



15a



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Pulse 45.0 degrees
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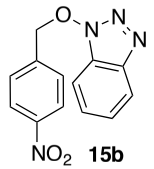


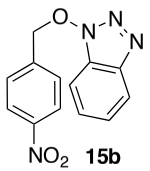
15b

MKS-1205-12-17-CDCl3-13C-CC-pure

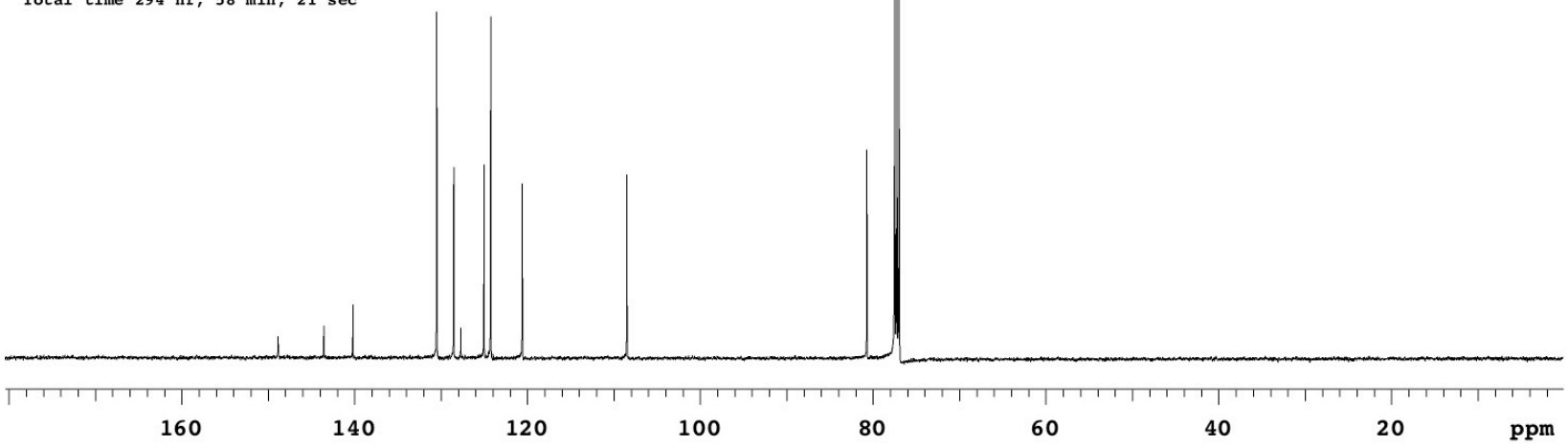
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-12-17-CDCl3-13C-CC-pure
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
10632 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 294 hr, 58 min, 21 sec



15b

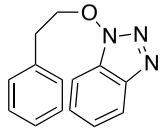


MKS-1205-08-51-CDCl3-CC

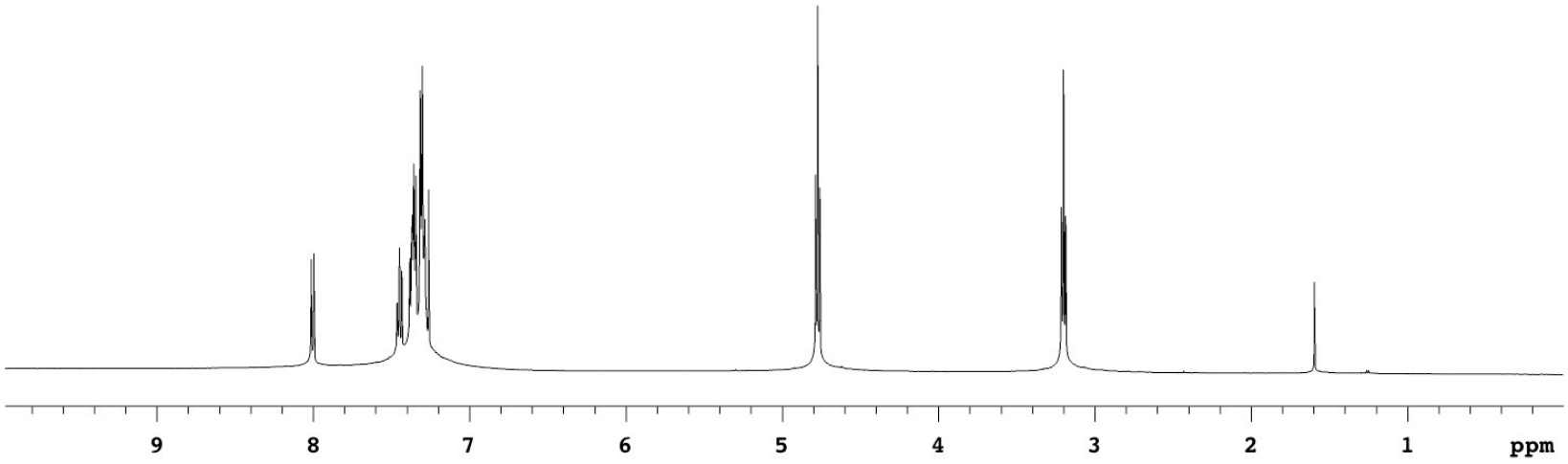
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-08-51-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
48 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



15c

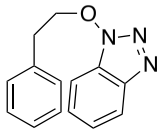


MKS-1205-08-51-CDCl3-13C-CC

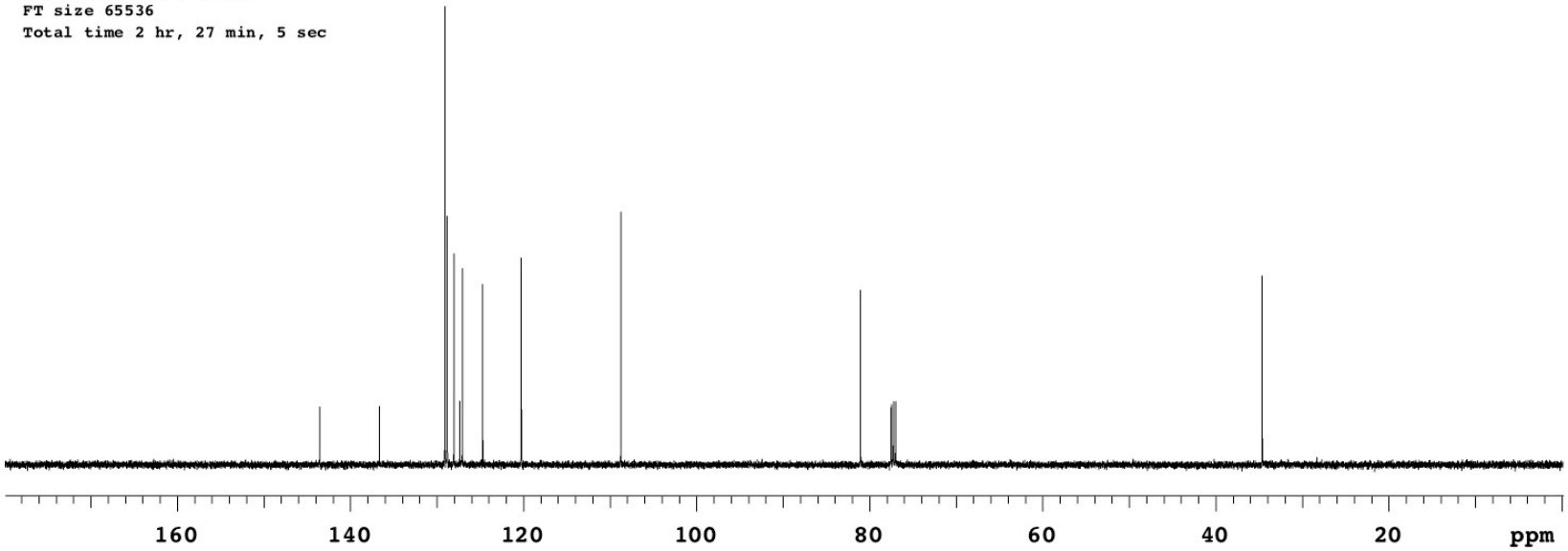
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-08-51-CDCl3-13C-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
96 repetitions
OBSERVE C13, 125.6674382 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 hr, 27 min, 5 sec



15c

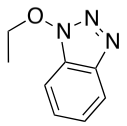


MKS-1205-08-53-CDCl3-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-08-53-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
52 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



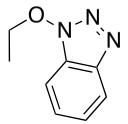
15d

MKS-1205-08-53-CDCl3-13C-CC

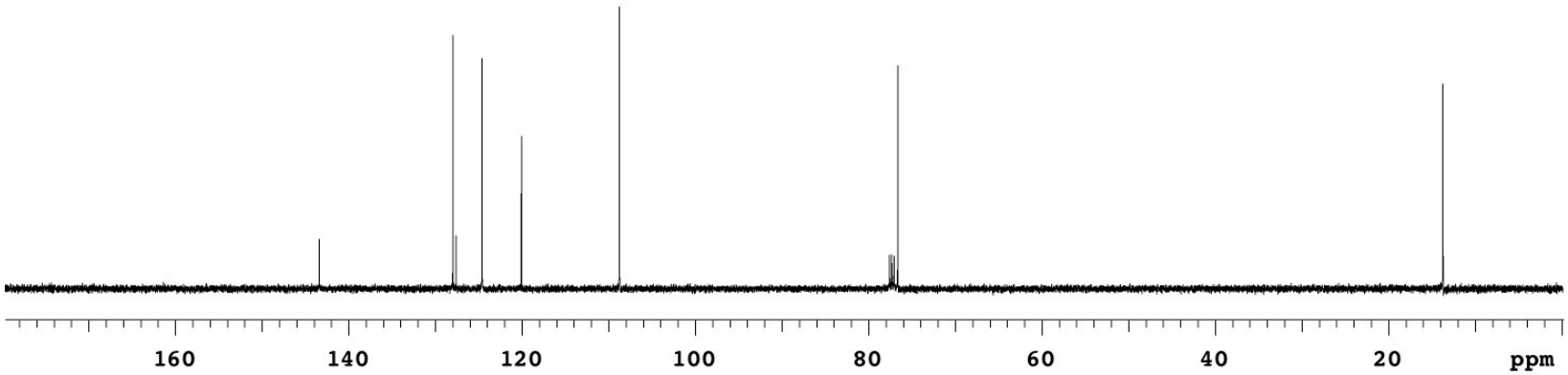
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-08-53-CDCl3-13C-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
52 repetitions
OBSERVE C13, 125.6674382 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 hr, 27 min, 5 sec



15d

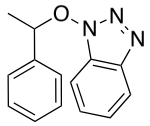


MKS-1205-11-05-CDCl3-2ndCC-repeat

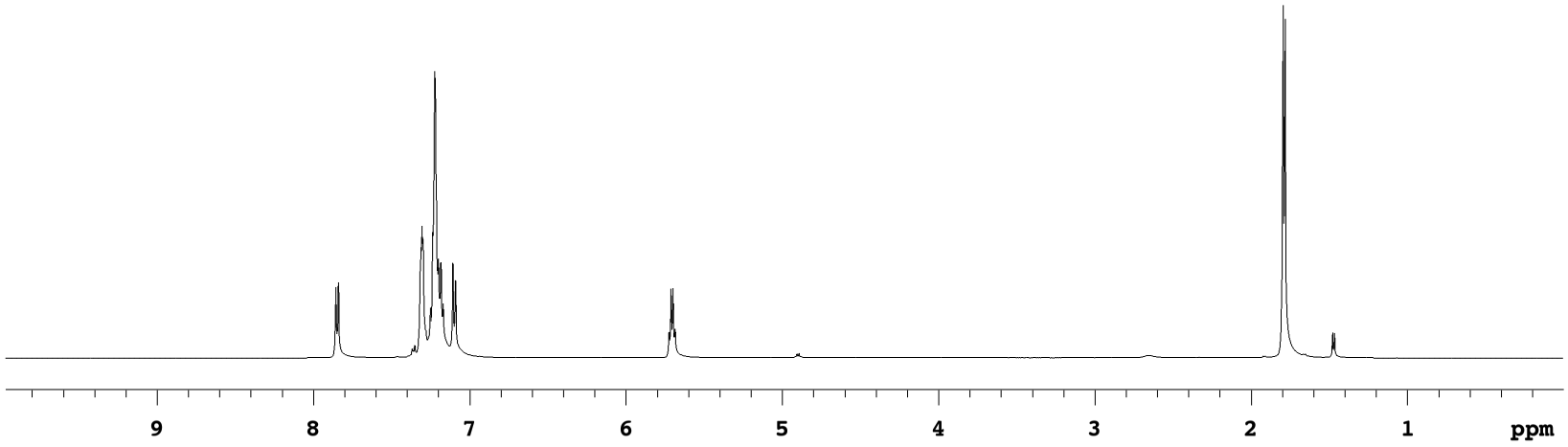
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-11-05-CDCl3-2ndCC-repeat
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
84 repetitions
OBSERVE H1, 499.7707222 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 20 sec



15e

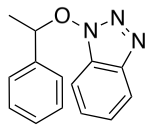


MKS-1205-11-05-CDCl3-13C-2ndCC-repeat

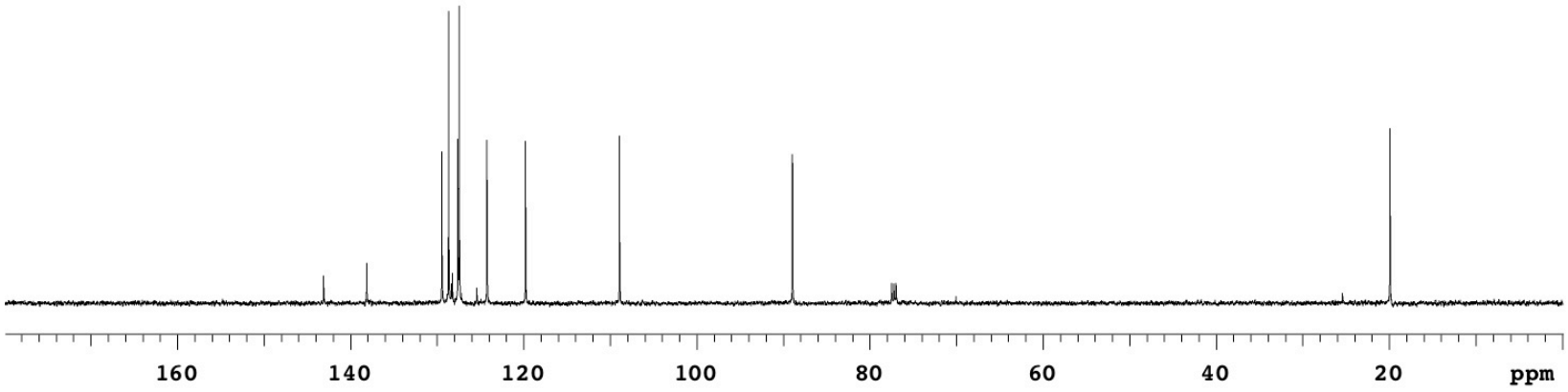
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-11-05-CDCl3-13C-2ndCC-repeat
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
24 repetitions
OBSERVE C13, 125.6674484 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 294 hr, 58 min, 21 sec



15e

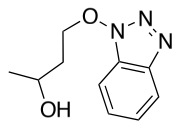


MKS-1205-11-61-CDCl3-3rdFrac-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-11-61-CDCl3-3rdFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
68 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 20 sec



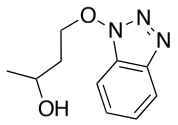
15f

MKS-1205-11-61-CDCl3-13C-2ndFrac-CC

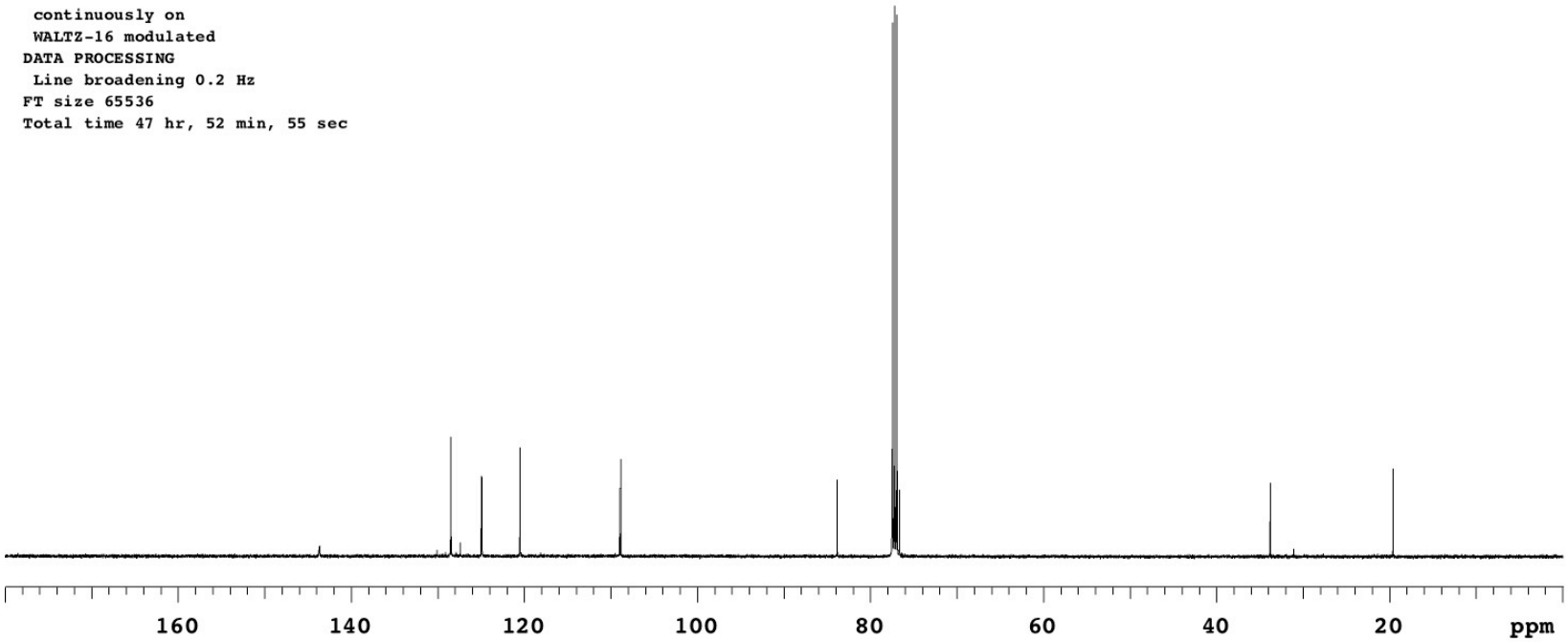
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-11-61-CDCl3-13C-2ndFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
34224 repetitions
OBSERVE C13, 125.6674271 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 47 hr, 52 min, 55 sec



15f

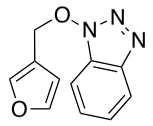


MKS-1205-12-13-CDCl3-CC

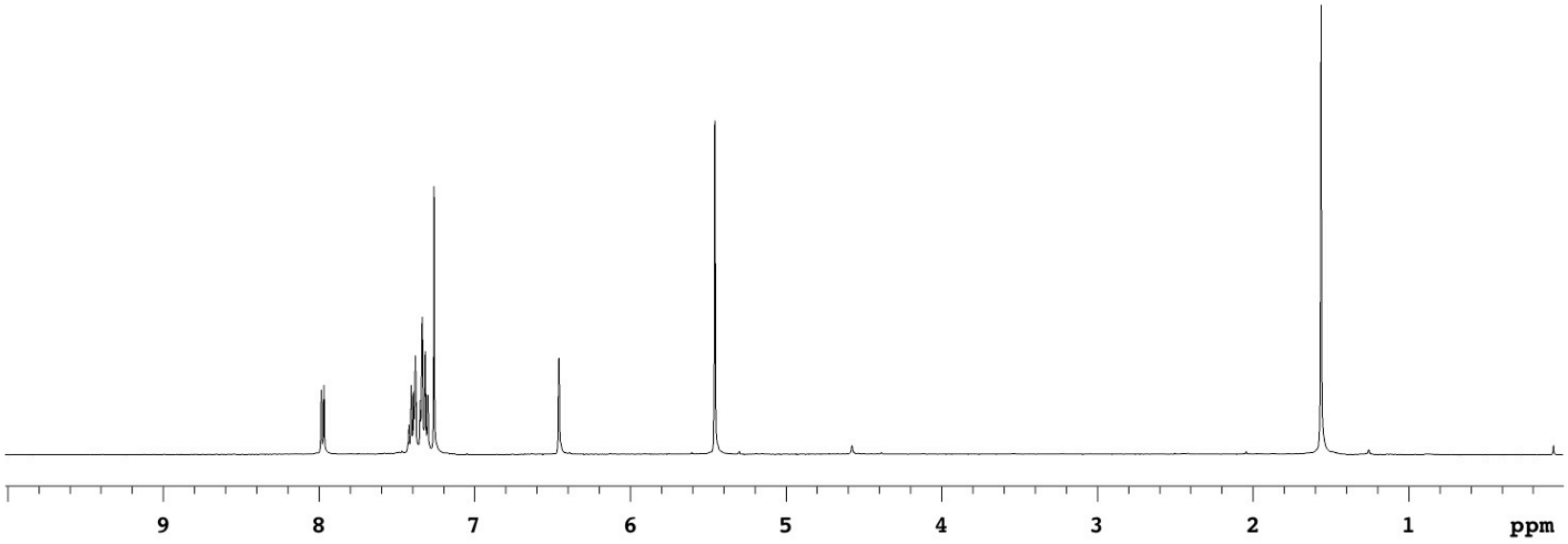
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-12-13-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
48 repetitions
OBSERVE H1, 499.7707202 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 20 sec



15g

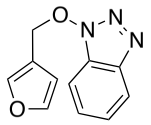


MKS-1205-09-47-CDCl3-13C-CC

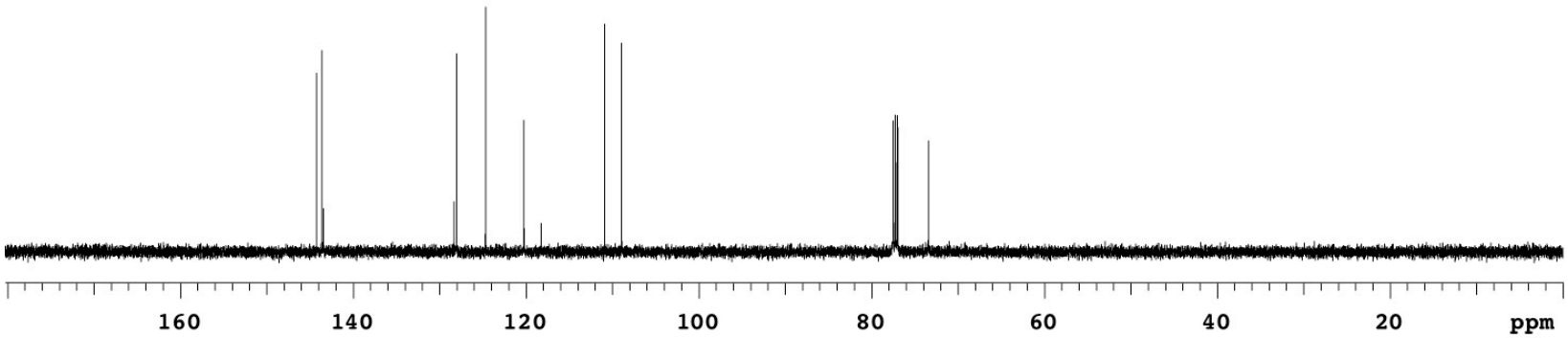
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-09-47-CDCl3-13C-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
368 repetitions
OBSERVE C13, 125.6674240 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
FT size 65536
Total time 2 hr, 27 min, 5 sec



15g

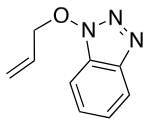


MKS-1205-13-AllylBtEther-CDCl3-CC

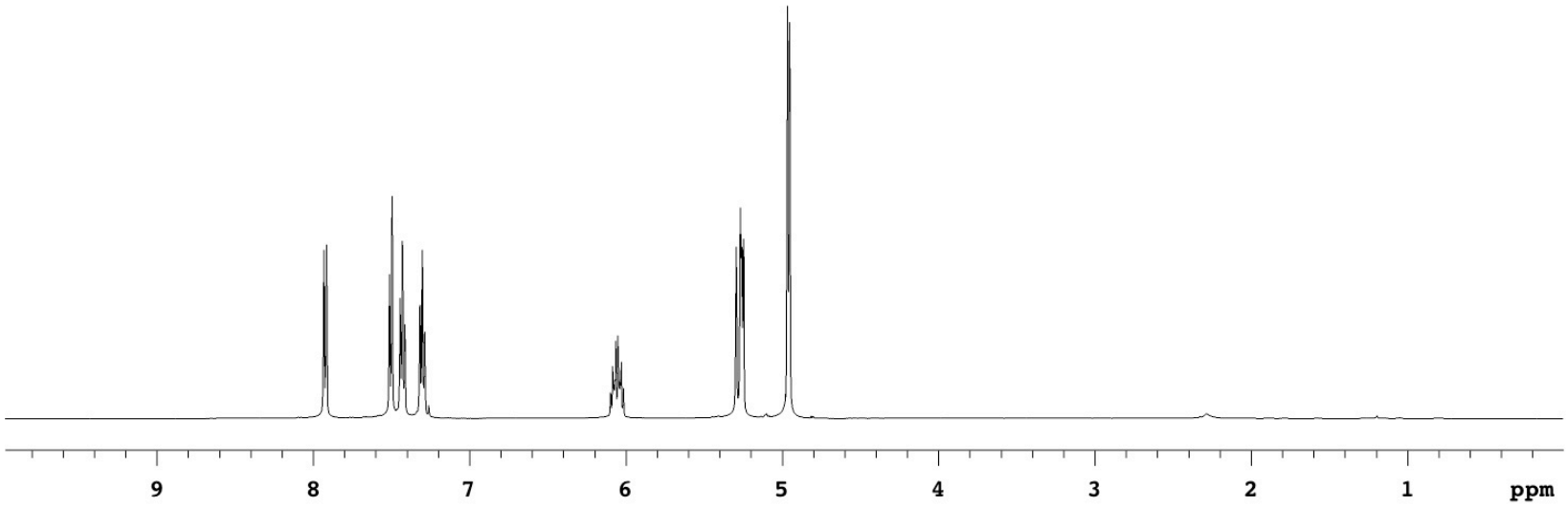
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-13-AllylBtEther-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



15h

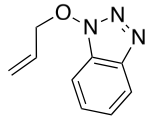


MKS-1205-13-AllylBtEther-13C-CDCl3-CC

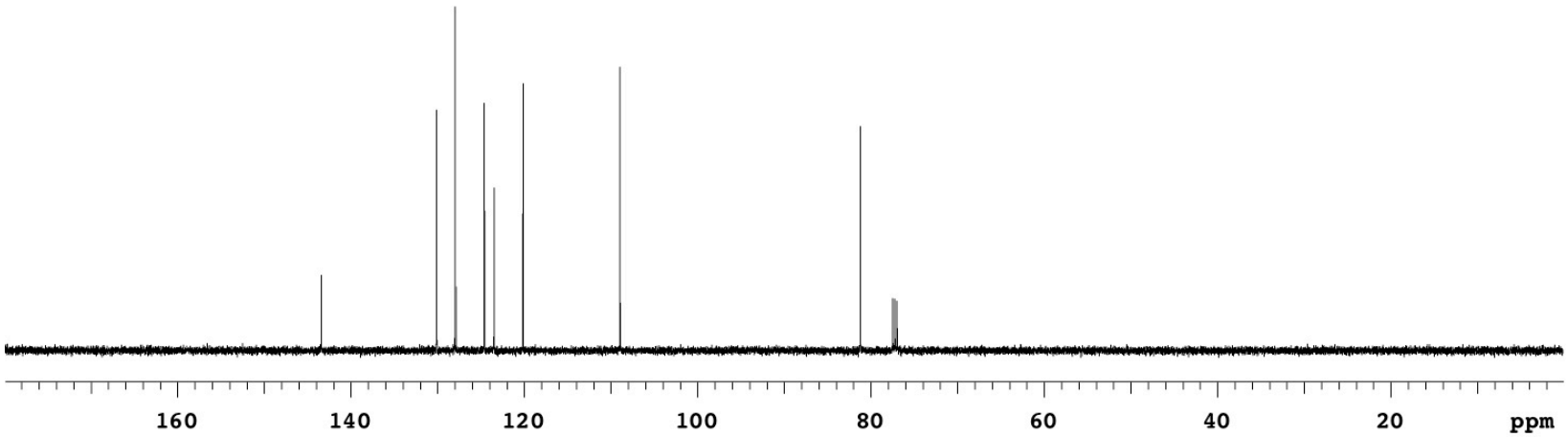
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-13-AllylBtEther-13C-CDCl3-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
64 repetitions
OBSERVE C13, 125.6674385 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 hr, 27 min, 5 sec



15h

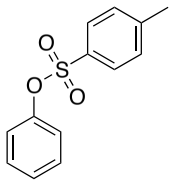


MKS-1205-13-54-CDCl3-CC

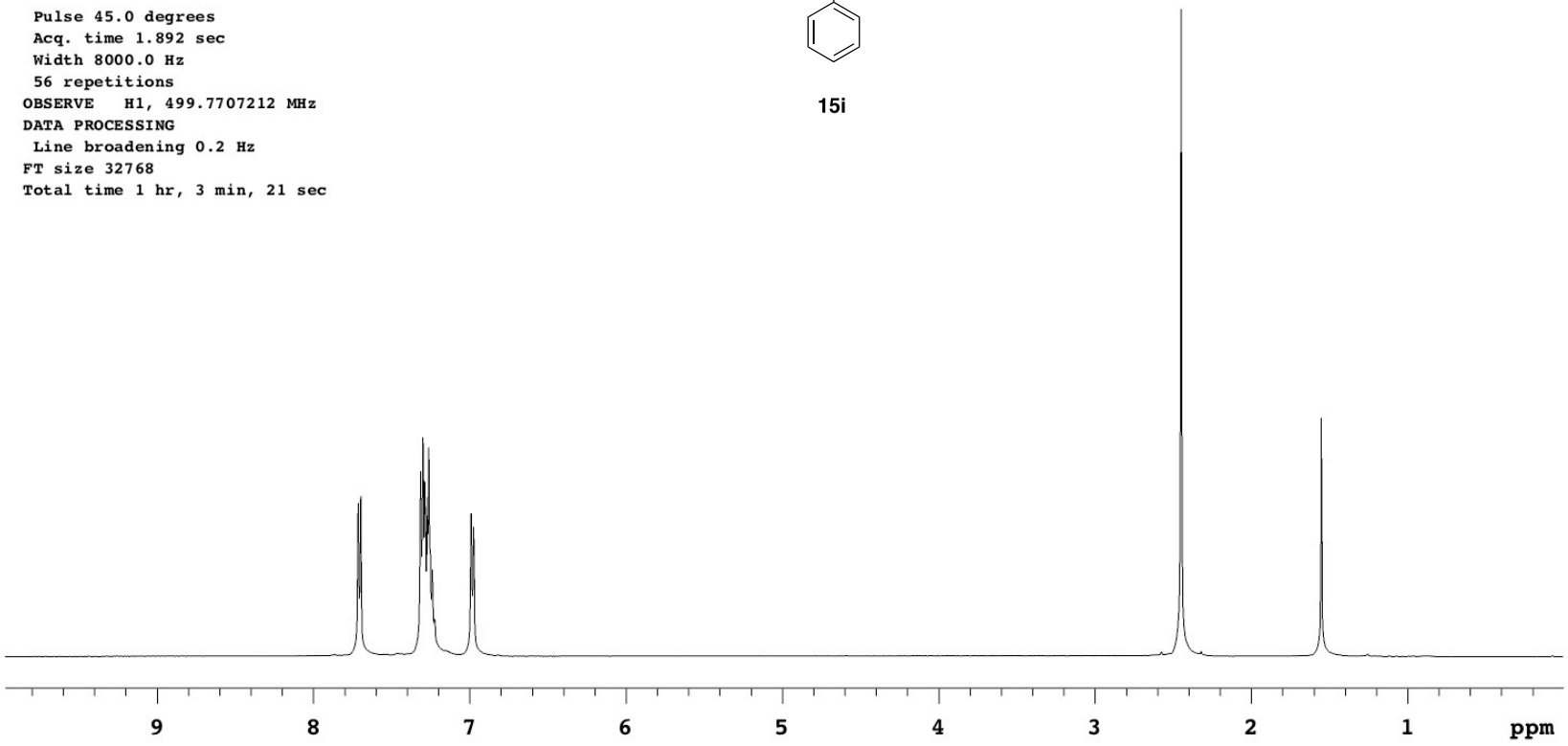
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-54-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
56 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



15i

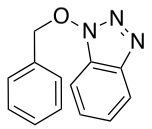


MKS-1205-12-73-CDCl3-CC

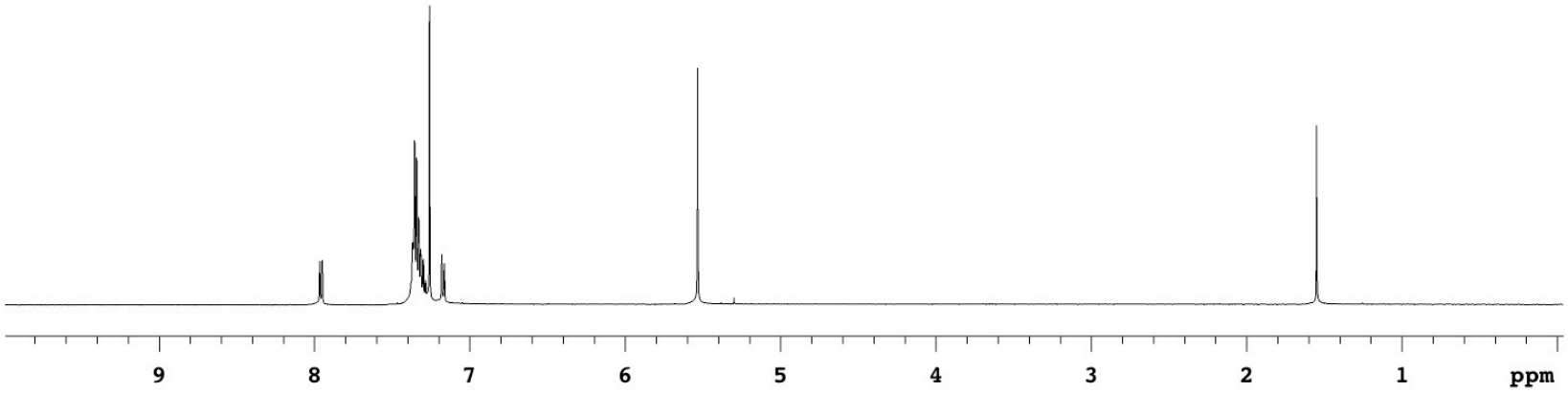
Pulse Sequence: s2pul

Solvent: cdcl3
Ambient temperature
Operator: mkl
File: MKS-1205-12-73-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
112 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



43

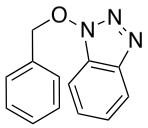


MKS-1205-12-73-13C-repeat-CDCl3-CC

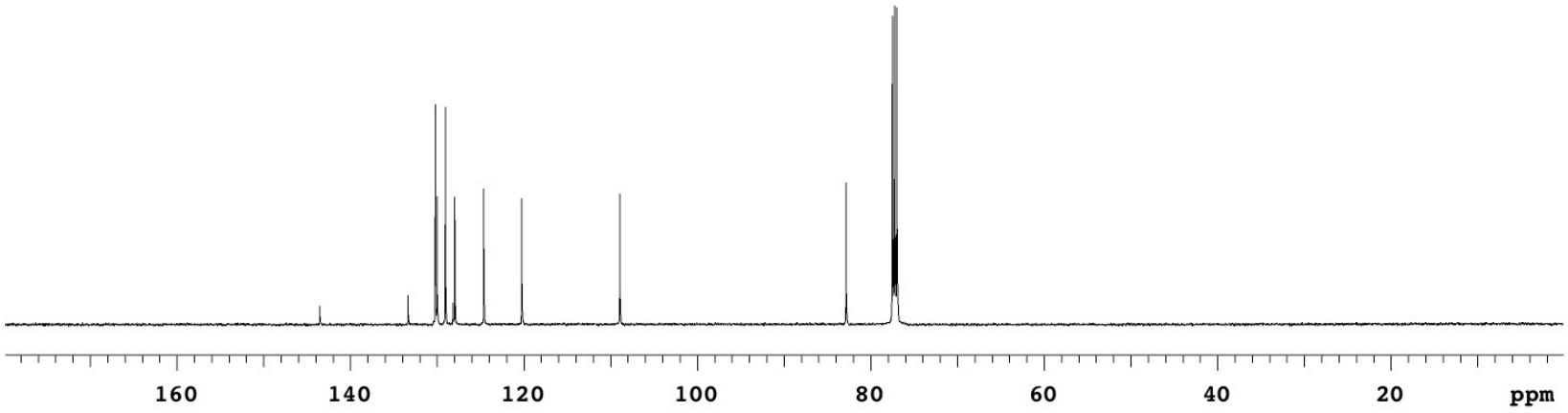
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-12-73-13C-repeat-CDCl3-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
10028 repetitions
OBSERVE C13, 125.6674197 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 294 hr, 58 min, 21 sec



43

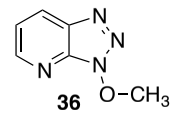


MKS-1205-13-58-CDCl3-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-58-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
76 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



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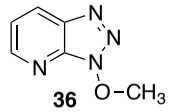
MKS-1205-13-58-CDCl3-13C-CC-rep

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-58-CDCl3-13C-CC-rep
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
2048 repetitions
OBSERVE C13, 125.6674202 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 hr, 27 min, 5 sec



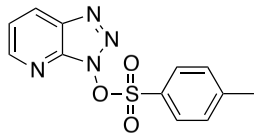
36

MKS-1205-12-67-CDCl3-crystallized

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-12-67-CDCl3-crystallized
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
76 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



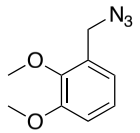
35

MKS-1205-12-36-CDCl3-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-12-36-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
44 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



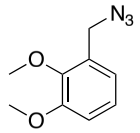
54

MKS-1205-12-36-13C-CDCl3-CC

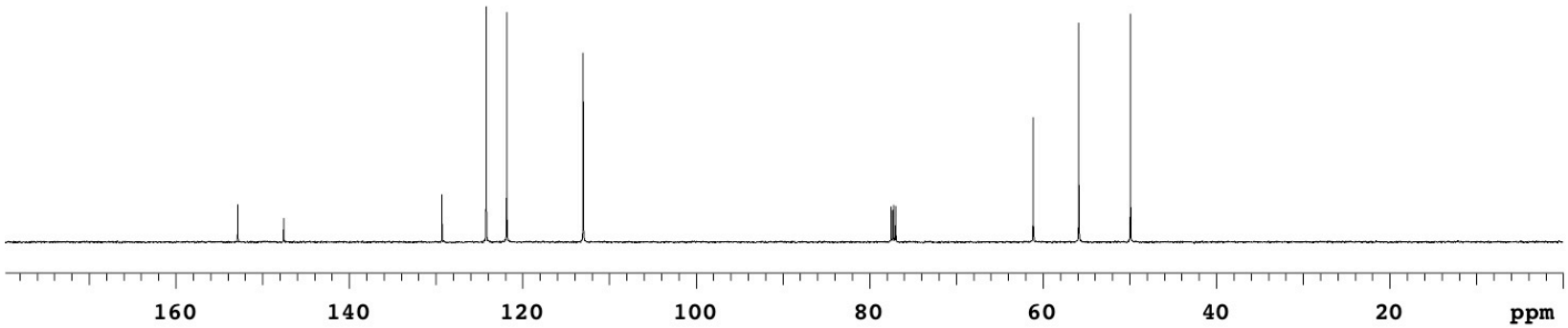
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-12-36-13C-CDCl3-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
268 repetitions
OBSERVE C13, 125.6674360 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 294 hr, 58 min, 21 sec



54

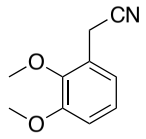


MKS-1205-11-74-CDCl3-2ndCC

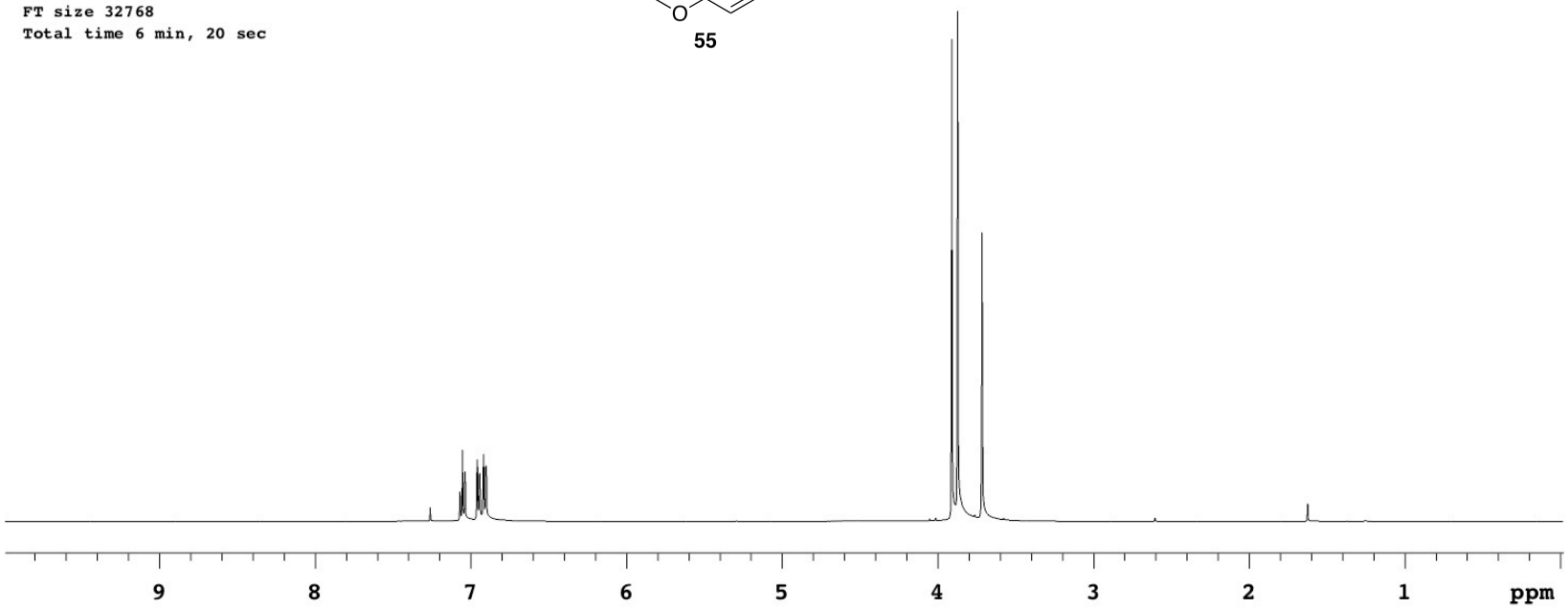
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-11-74-CDCl3-2ndCC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
80 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 20 sec



55

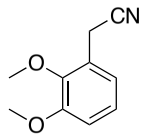


MKS-1205-11-74-CDCl3-13C-CC

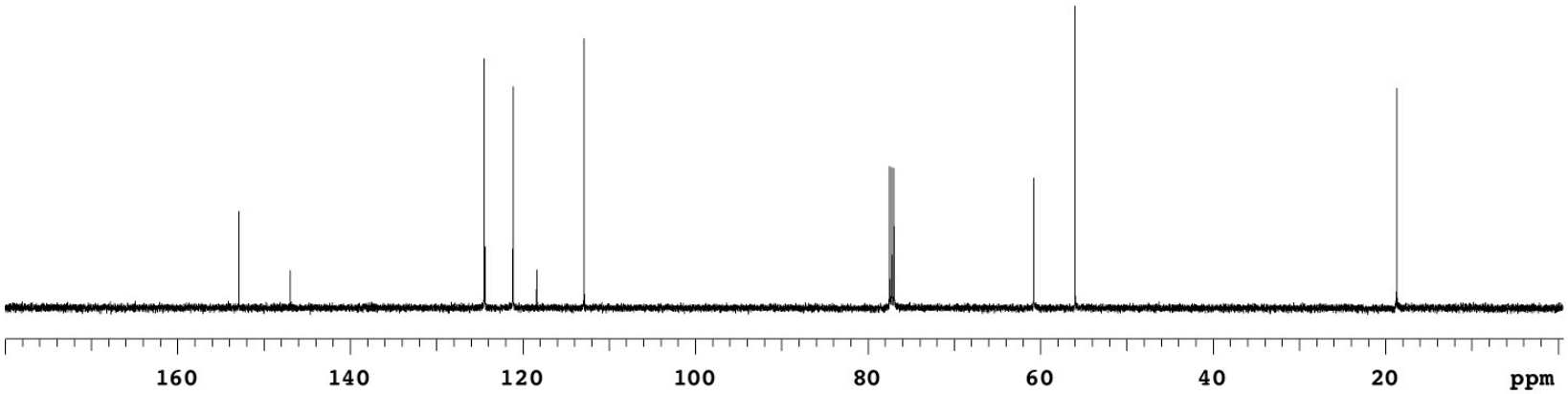
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-11-74-CDCl3-13C-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
780 repetitions
OBSERVE C13, 125.6674271 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 hr, 27 min, 5 sec



55

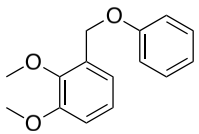


MKS-1205-12-32-CDCl3-1stFrac-CC

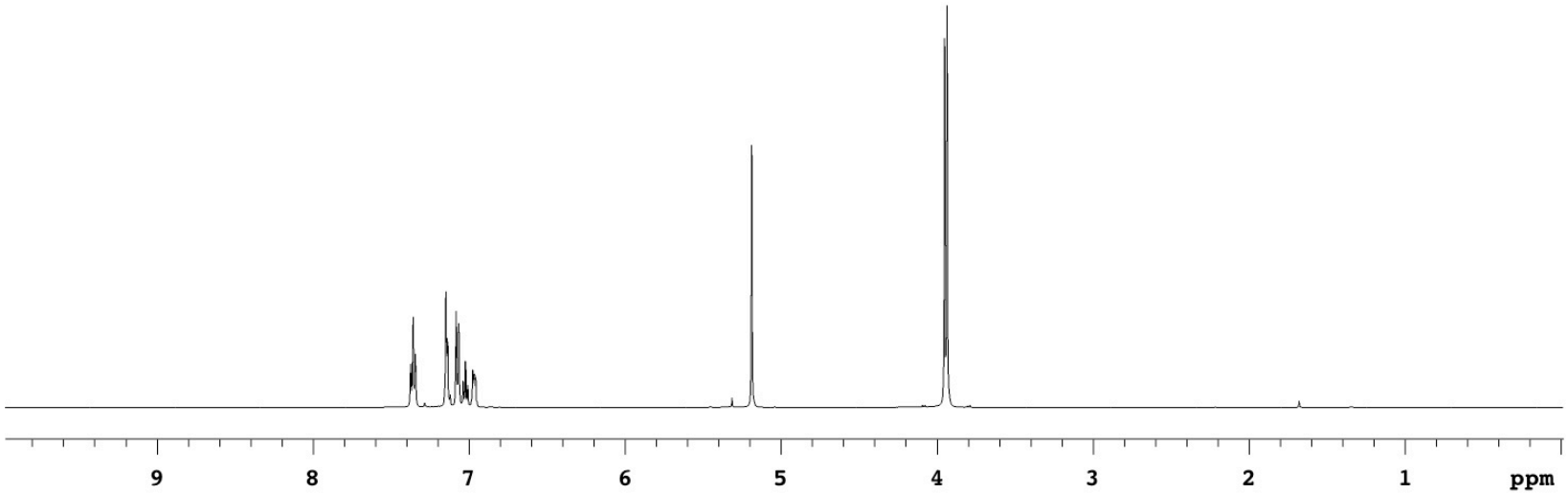
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-12-32-CDCl3-1stFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
60 repetitions
OBSERVE H1, 499.7707095 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



56

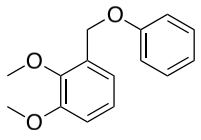


MKS-1205-12-32-CDCl3-13C-1st-Frac-CC

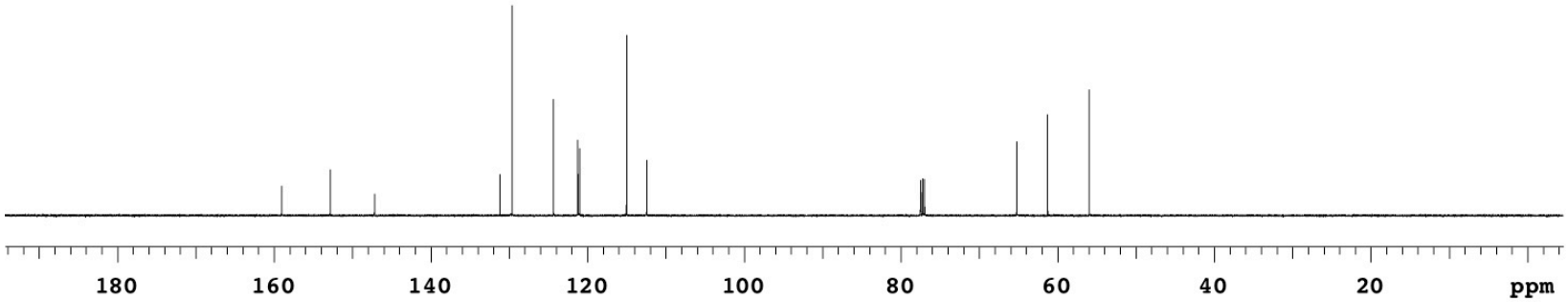
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-12-32-CDCl3-13C-1st-Frac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
560 repetitions
OBSERVE C13, 125.6674324 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 hr, 27 min, 5 sec



56

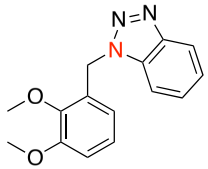


MKS-1205-12-30-CDCl3-2ndFrac-CC-Repeat

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-12-30-CDCl3-2ndFrac-CC-Repeat
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
56 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 20 sec



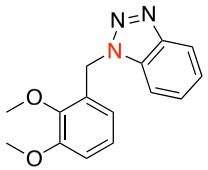
57a

MKS-1205-12-30-CDCl3-13C-2nd-Frac-CC-repeat

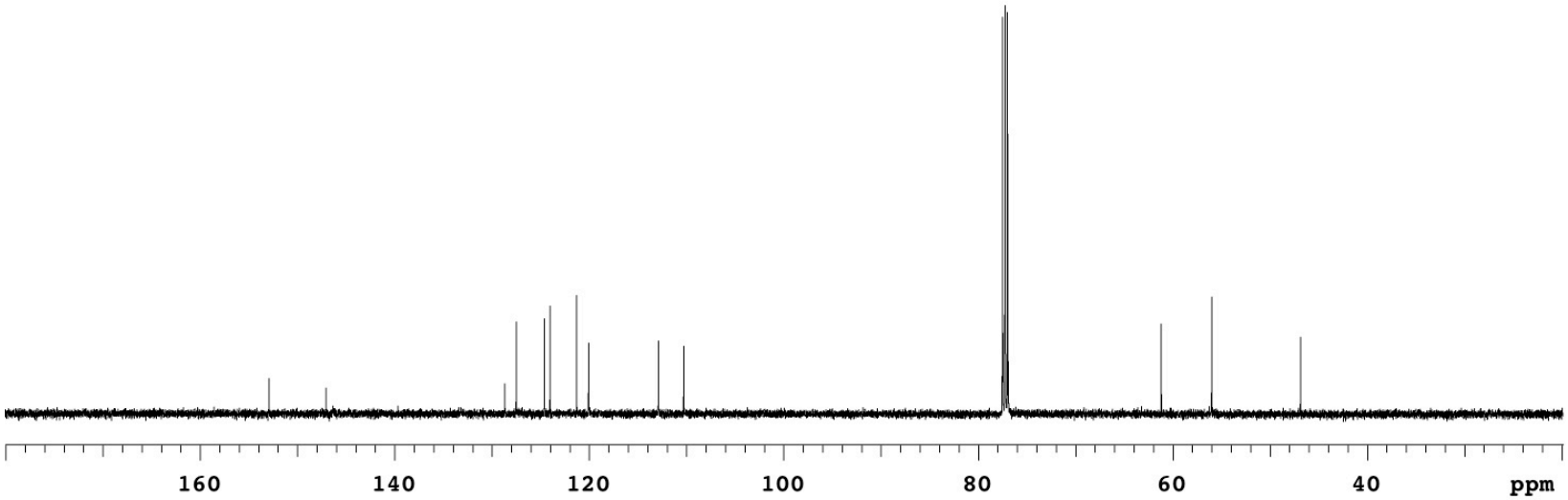
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-12-30-CDCl3-13C-2nd-Frac-CC-repeat
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
2048 repetitions
OBSERVE C13, 125.6674194 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 hr, 27 min, 5 sec



57a

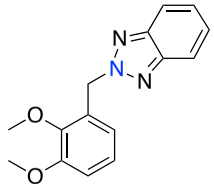


MKS-1205-12-30-CDCl3-1stFrac-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-12-30-CDCl3-1stFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
60 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 20 sec



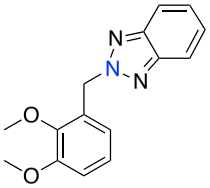
57b

MKS-1205-12-30-CDCl3-13C-1st-Frac-CC

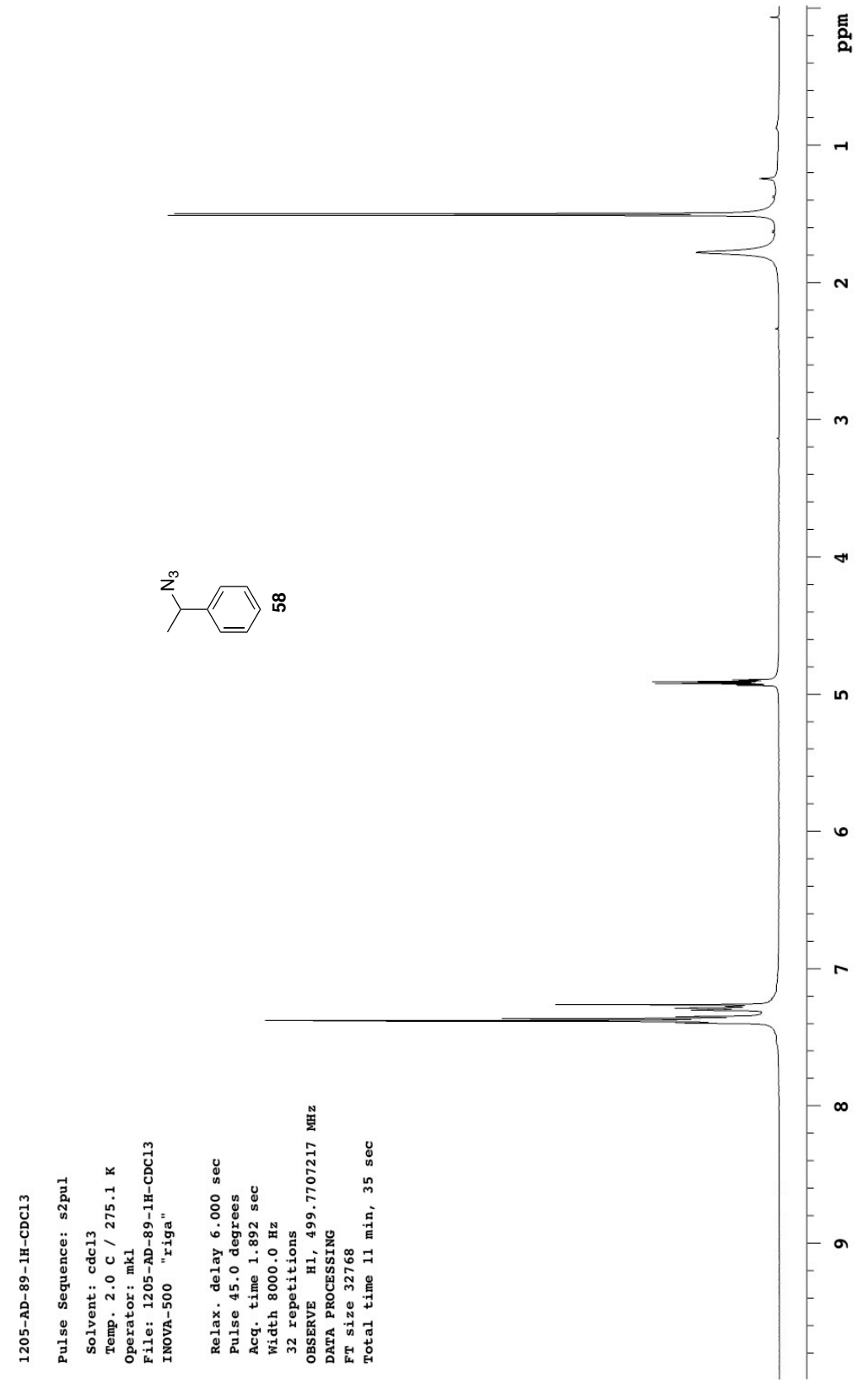
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-12-30-CDCl3-13C-1st-Frac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
2048 repetitions
OBSERVE C13, 125.6674232 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 hr, 27 min, 5 sec



57b

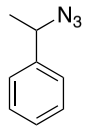

1205-AD-89-1H-CDCl3
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 2.0 C / 275.1 K
Operator: mkl
File: 1205-AD-89-1H-CDCl3
INOVA-500 "riga"
Relax. delay 6.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 11 min, 35 sec
N3
58
9
8
7
6
5
4
3
2
1
ppm

1205-AD-89-13C-CDCl3

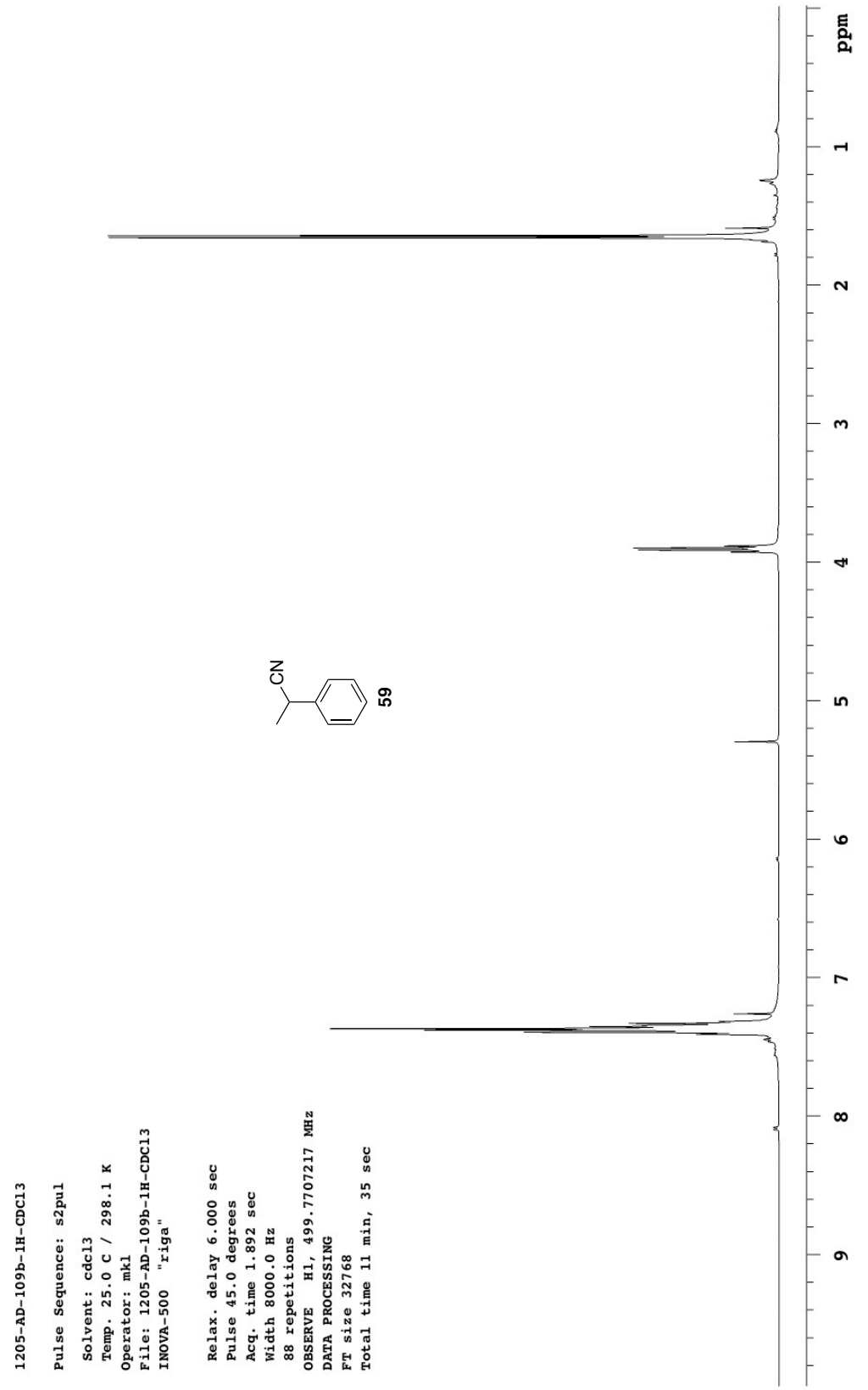
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 2.0 C / 275.1 K
Operator: mkl
File: 1205-AD-89-13C-CDCl3
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 62.6 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
13260 repetitions
OBSERVE C13, 125.6674160 MHz
DECOUPLE H1, 499.7732084 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 119 hr, 42 min, 18 sec



58

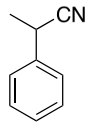

1205-AD-109b-1H-CDCl3
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: 1205-AD-109b-1H-CDCl3
INOVA-500 "riga"
Relax. delay 6.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
88 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 11 min, 35 sec
CN
59
9
8
7
6
5
4
3
2
1
ppm

1205-AD-109b-13C-CDCl3

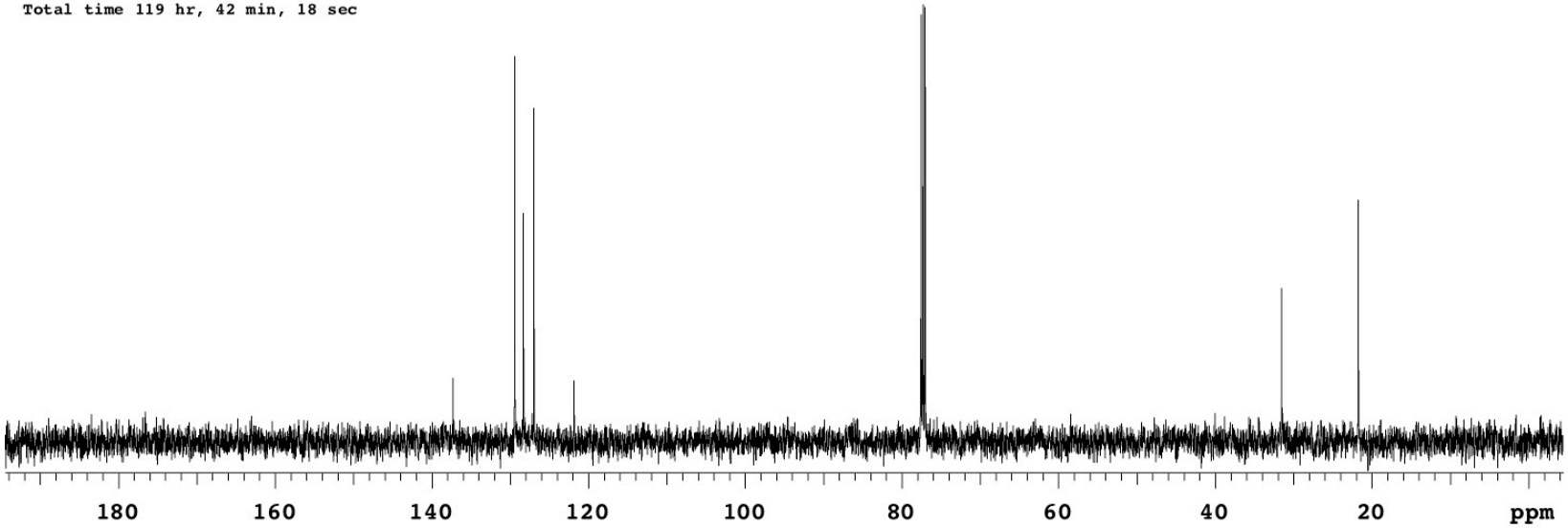
Pulse Sequence: s2pul

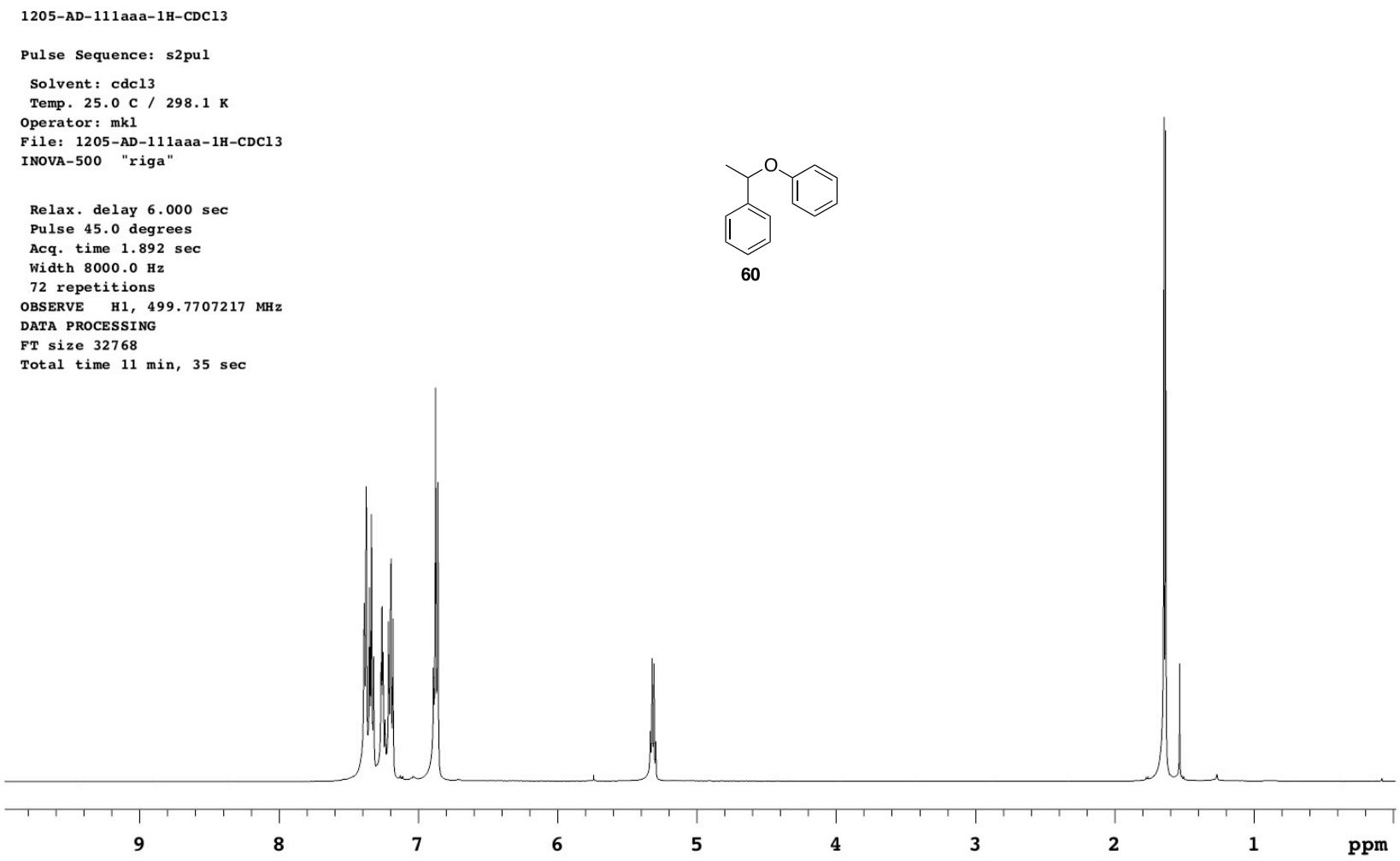
Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: 1205-AD-109b-13C-CDCl3
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 62.6 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
60 repetitions
OBSERVE C13, 125.6674160 MHz
DECOUPLE H1, 499.7732084 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 119 hr, 42 min, 18 sec



59



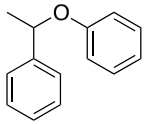

1205-AD-111aaa-1H-CDCl3
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: 1205-AD-111aaa-1H-CDCl3
INOVA-500 "riga"
Relax. delay 6.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
72 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 11 min, 35 sec
O
60
9
8
7
6
5
4
3
2
1
ppm

1205-AD-111aaa-13C-CDCl3

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: 1205-AD-111aaa-13C-CDCl3
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 62.6 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
35120 repetitions
OBSERVE C13, 125.6674202 MHz
DECOUPLE H1, 499.7732084 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 119 hr, 42 min, 18 sec



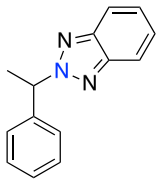
60

1205-AD-187b-1H-CDCl3

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: 1205-AD-187b-1H-CDCl3
INOVA-500 "riga"

Relax. delay 6.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
28 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 11 min, 35 sec



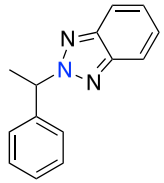
61b

1205-110d-13C-CDCl3

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: 1205-110d-13C-CDCl3
INOVA-500 "riga"

Relax. delay 6.000 sec
Pulse 62.6 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
6920 repetitions
OBSERVE C13, 125.6674160 MHz
DECOUPLE H1, 499.7732084 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 203 hr, 2 min, 18 sec



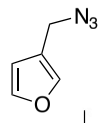
61b

1205-AD-107b-1H-CDCl3

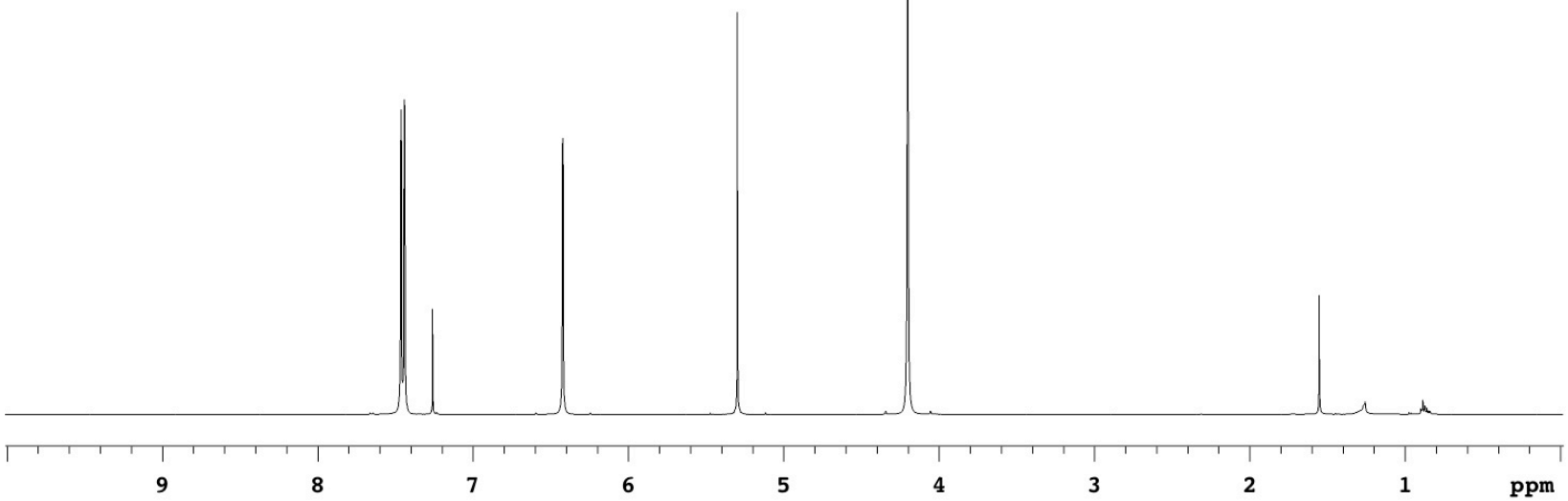
Pulse Sequence: s2pul

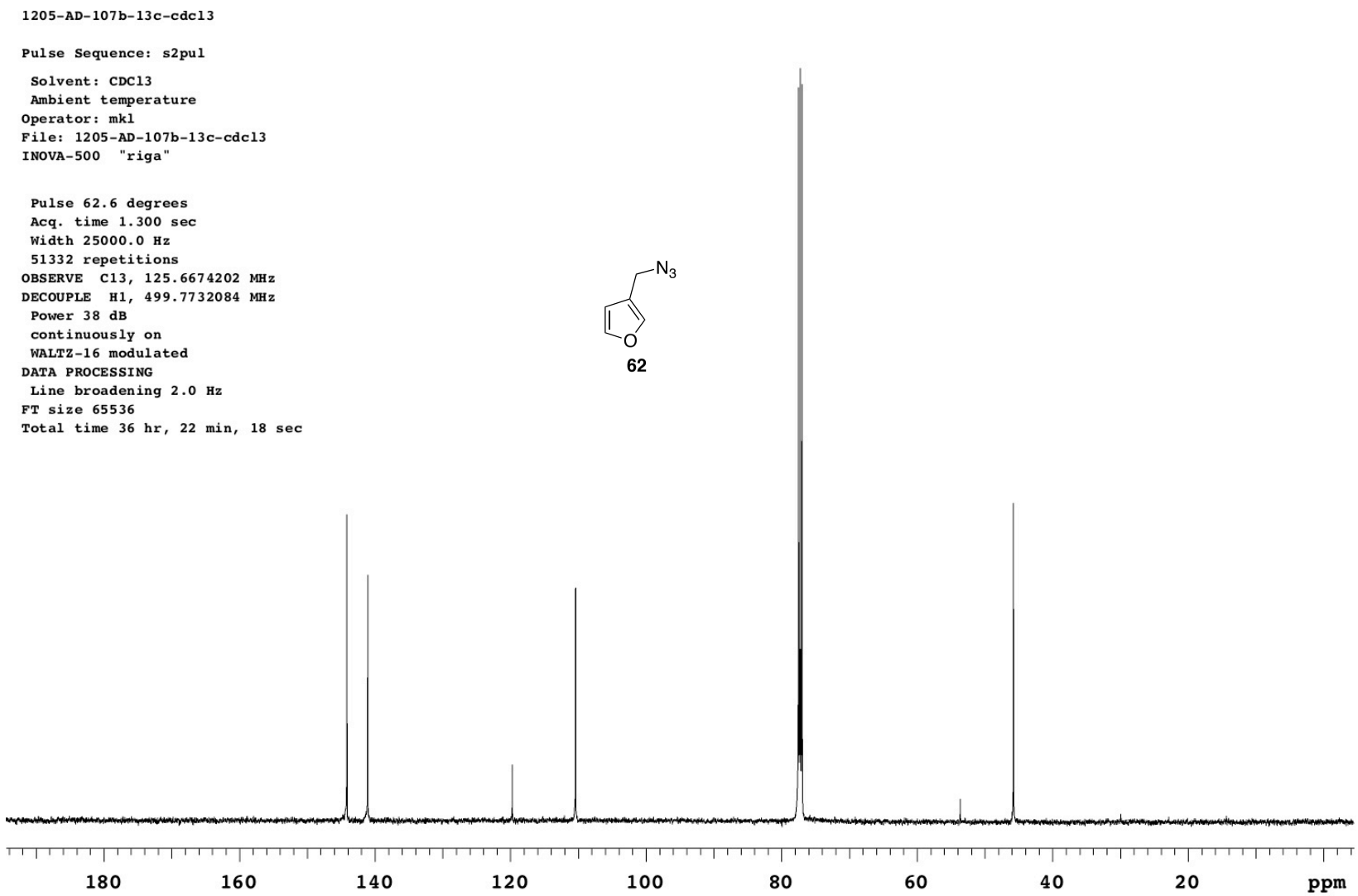
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: 1205-AD-107b-1H-CDCl3
INOVA-500 "riga"

Relax. delay 6.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
56 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 11 min, 35 sec



62

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Solvent: CDCl3
Ambient temperature
Operator: mkl
File: 1205-AD-107b-13c-cdcl3
INOVA-500 "riga"
Pulse 62.6 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
51332 repetitions
OBSERVE C13, 125.6674202 MHz
DECOUPLE H1, 499.7732084 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 36 hr, 22 min, 18 sec
N3
O
62
180
160
140
120
100
80
60
40
20
ppm

1205-AD-108b-1H-CDCl3

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: 1205-AD-108b-1H-CDCl3
INOVA-500 "riga"

Relax. delay 6.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
36 repetitions
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DATA PROCESSING
FT size 32768
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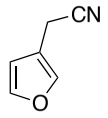

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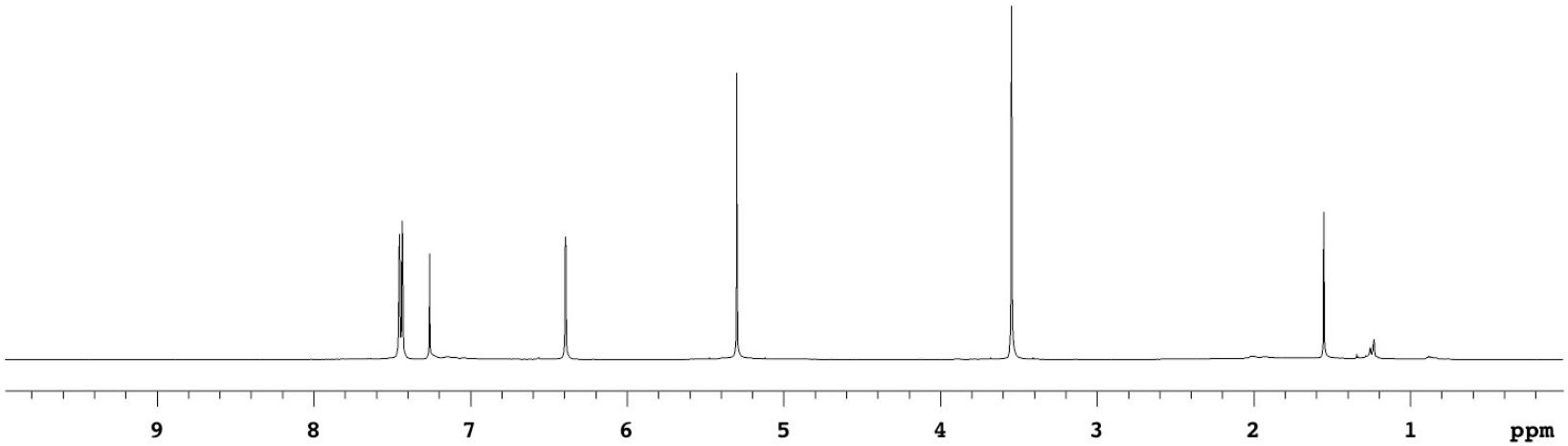

1205-AD-108b-13C-CDCl3

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Temp. 25.0 C / 298.1 K
Operator: mkl
File: 1205-AD-108b-13C-CDCl3
INOVA-500 "riga"

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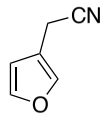
Pulse 62.6 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
17628 repetitions
OBSERVE C13, 125.6674202 MHz
DECOUPLE H1, 499.7732084 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 119 hr, 42 min, 18 sec



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Operator: mkl
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INOVA-500 "riga"

Relax. delay 6.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
88 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
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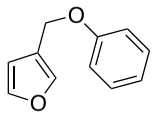
Total time 11 min, 35 sec



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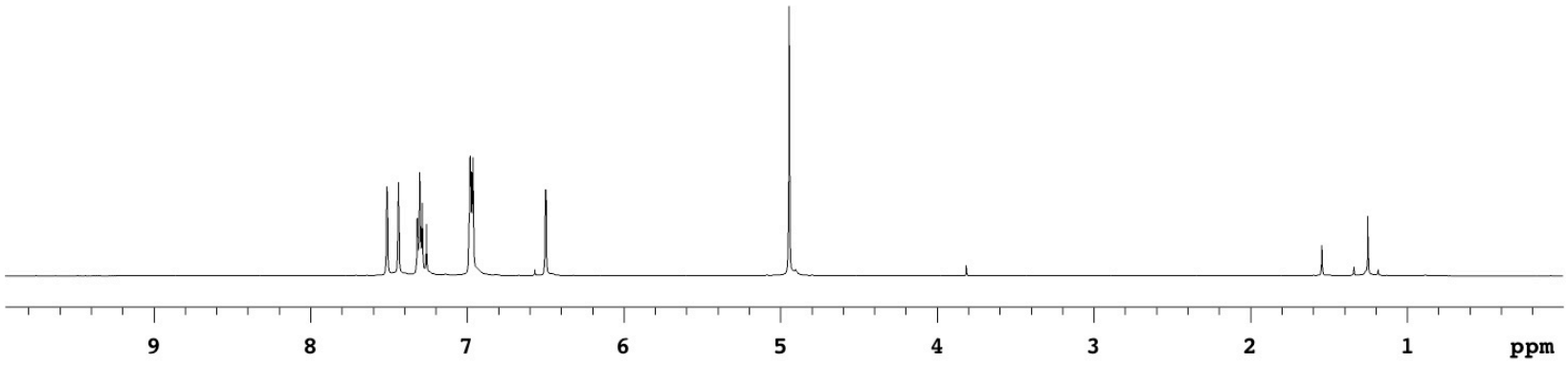

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Pulse Sequence: s2pul

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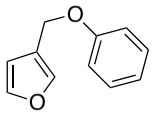
Operator: mkl
File: 1205-AD-112a-13C-CDCl3
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 62.6 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
10390 repetitions
OBSERVE C13, 125.6674160 MHz
DECOUPLE H1, 499.7732084 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 147 hr, 28 min, 58 sec



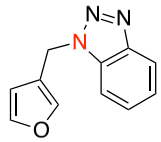
64

1205-AD-106-solid-1H-CDCl3

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: 1205-AD-106-solid-1H-CDCl3
INOVA-500 "riga"

Relax. delay 6.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
48 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 11 min, 35 sec



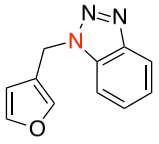
65a

1205-AD-106b-13C-CDCl3

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: 1205-AD-106b-13C-CDCl3
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 62.6 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
11132 repetitions
OBSERVE C13, 125.6674160 MHz
DECOUPLE H1, 499.7732084 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 119 hr, 42 min, 18 sec



65a

CHAPTER 4

BENZOTRIAZOLYL ETHERS OF BENZYLIC ALCOHOLS: NOVEL SUBSTRATES FOR C–C CROSS-COUPLING WITH ARYL BORONIC ACIDS

CHAPTER 4

BENZOTRIAZOLYL ETHERS OF BENZYLIC ALCOHOLS: NOVEL SUBSTRATES FOR C–C CROSS-COUPLING WITH ARYL BORONIC ACIDS

[4.1] INTRODUCTION

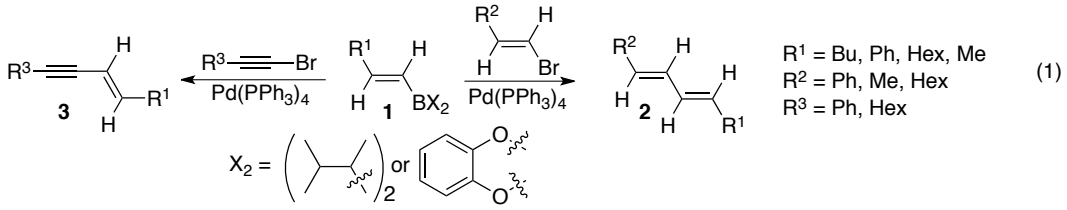
The history of metal-mediated coupling of two organic molecules via C–C bond formation dates back to the mid 19th century. Reported in 1855, the Wurtz homo-coupling of alkyl halides using sodium metal is one of the earliest documented coupling reactions.[1] Wurtz's method requires a stoichiometric amount of sodium metal.

In the 21st century, sustainable development and atom economy are the buzzwords in the chemical community, and metal catalysis seems to meet these two prerequisites of an efficient synthetic methodology. The idea of palladium-catalyzed cross-coupling reaction was first reported and systematically investigated by Prof. Richard Heck in 1968 and then onwards.[2] Heck's palladium catalyzed arylation of olefins[3] was motivated by the seminal work of P. Fitton, who reported the oxidative addition of Pd(0) across an aryl–halogen bond to give arylpalladium halide.[4] Heck's innovative idea of using palladium as catalyst for cross-coupling reactions paved the way for development of different organometallic coupling partners for such reactions that now include organozinc (Negishi),[5] organotin (Stille),[6] organoboron (Suzuki-Miyaura),[7] organomagnesium (Kumada),[8] and organosilane (Hiyama)[9] reagents.

The valuable contribution of palladium catalyzed cross-coupling reactions was recognized with the 2010 Nobel Prize to Richard Heck, Ei-ichi Negishi, and Akira Suzuki for *"palladium-*

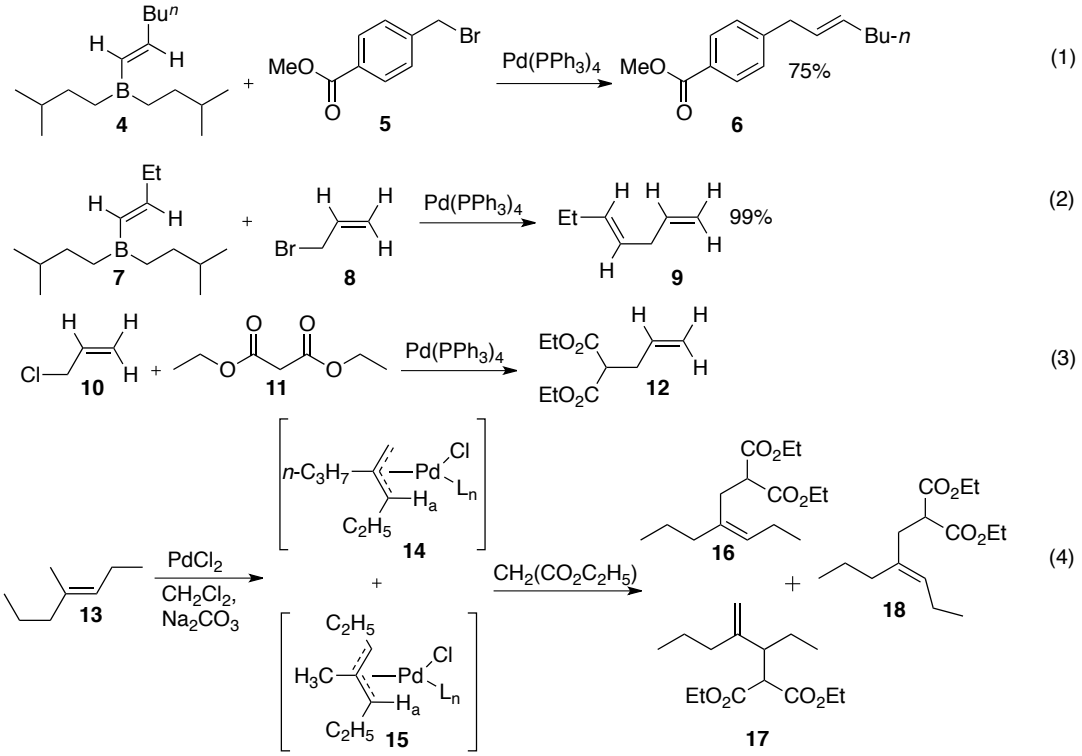
catalyzed cross-couplings in organic synthesis".[2] In 1979, N. Miyaura and A. Suzuki reported the first palladium-catalyzed $C(sp^2)$–$C(sp^2)$ cross-coupling reaction between an organoboron compound and an organic halide (Scheme 1).[7,10]

Scheme 1. *Palladium Catalyzed Cross-Coupling of Alkenyl or 1-Alkynyl Bromide with (E)-1- Alkenylboranes*



The following year they reported the palladium-catalyzed cross-coupling reaction between 1-alkenyl borane and allylic or benzylic bromide (Scheme 2, eqs 1-2).[11] Prior to this, the use of π-allyl palladium complexes as electrophilic partners in reactions with certain nucleophiles such as

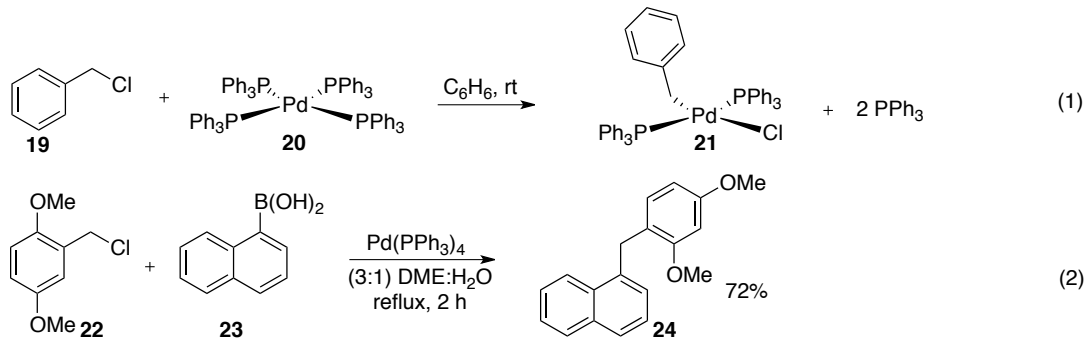
Scheme 2. *Palladium Mediated Cross-Coupling of Allylic or Benzylic* π-Complexes *with (E)-1-Alkenylborane*



enamine, and anions of diethyl malonate, and ethyl acetoacetate was published by J. Tsuji in 1965 (Scheme 2, eq 3).[12] Later on, catalytic versions of this reaction were reported.[13,14] In 1973, Trost et al. reported a complete regio- and stereoselective alkylation of alkyl-substituted π-allyl palladium complexes (Scheme 2, eq 4).[15]

In general, alkyl,[16,17] alkenyl,[18] alkynyl,[18] allyl,[19] aryl[20] and benzyl[21,22] halides are most commonly used as electrophilic coupling partners for Suzuki cross-coupling reactions. The reactivities of allyl and benzyl coupling partners is different from those of alkenyl and alkynyl coupling partners due to the differences in the hybridization state of the carbon atoms undergoing the coupling. In 1969, P. Fitton and coworkers reported the first example of palladium insertion into a benzylic carbon-halogen bond (Scheme 3, eq 1).[23] However, to our knowledge, it was only in 1994, that the first cross-coupling reaction using a boronic acid nucleophile and a benzylic halide as an electrophilic partner was reported (Scheme 3, eq 2).[24]

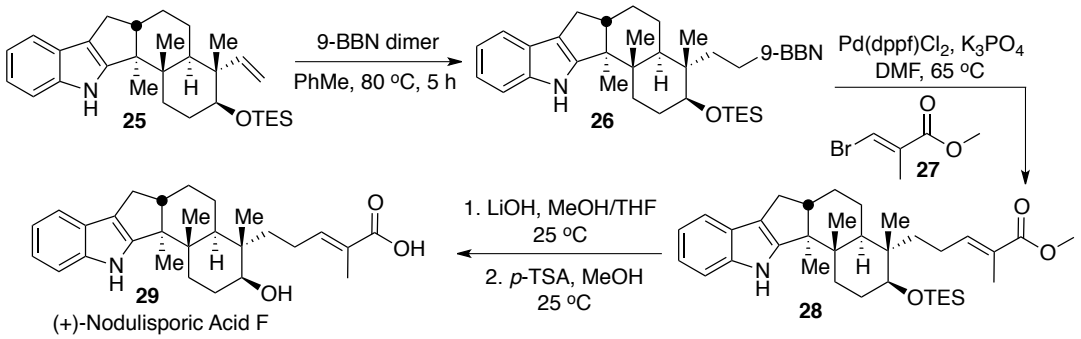
Scheme 3. *Early Examples of Palladium Insertion into Benzylic Carbon-Halogen Bonds and Coupling with a Boronic Acid*



In the past three decades, the palladium-catalyzed Suzuki cross-coupling reaction for carbon-carbon bond formation has become a cornerstone of metal catalysis in organic synthesis.[25] This simple, stereo and regioselective, environmentally benign method has helped chemists assemble complex molecular frameworks including those towards the total synthesis of natural products of medicinal value (Scheme 4).[26,27] Apart from medicinal chemistry and chemical biology[28] Suzuki

cross-coupling reaction is routinely used in process research and development,[29] materials chemistry and nanotechnology.[30]

Scheme 4. *Total Synthesis of (+)-Nodulisporic Acid F Involving Stereoselective Suzuki Cross-Coupling*[27]



The use of boronic acids as the nucleophilic coupling partner in cross-coupling reactions has further boosted the industrial application of this methodology. Compared to other organometallic nucleophilic coupling partners such as Zn, Sn, Mg, and Al, a variety of boronic acids are easily available from commercial sources. Also, boronic acids are non-pyrophoric, and are air and moisture stable. Thus, they can be easily handled on the bench top. In addition, boronic acids are generally compatible with a wide range of functional groups and the reaction byproducts from these are environmentally benign. The popular electrophilic coupling partners for boronic acids are, allylic or benzylic halides, which can be generally, hydrolytically unstable, are lychrymators and can be skin irritants. Also, many benzyl halides are known mutagens (Figure 1).[31,32]

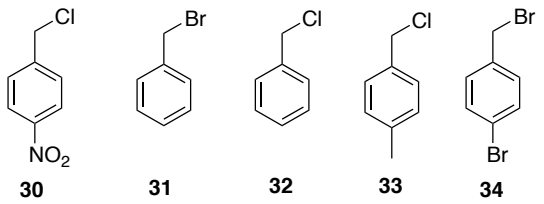


Figure 1. *Some Mutagenic Benzyl Halides*

Considering the widespread industrial and academic application of the Suzuki cross-coupling reaction, it is useful to develop alternate electrophilic couping partners. Some of the recently developed alternatives to benzyl halides are benzylic acetate[33], carbonate[34-36] and phosphate[37] coupling partners.

Cross-coupling reaction of a benzylic coupling partner and an arylboronic acid, results in the formation of diarylmethane products. Diarylmethanes are common structural units in many biolocally active molecules and pharmaceuticals.[38-40] In addition, methylene linked diaryl moieties are frequently encountered in supramolecular chemistry such as in catananes and rotaxanes (Figure 2).[41,42]

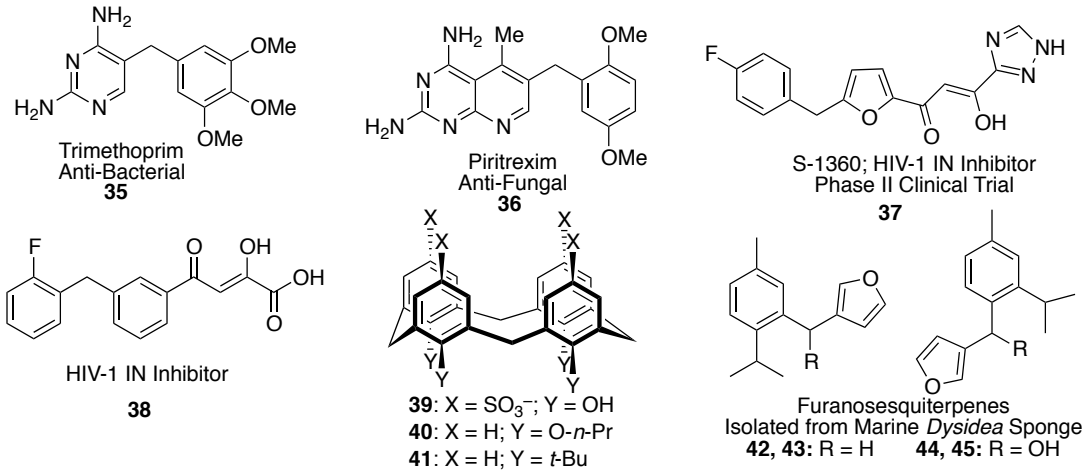


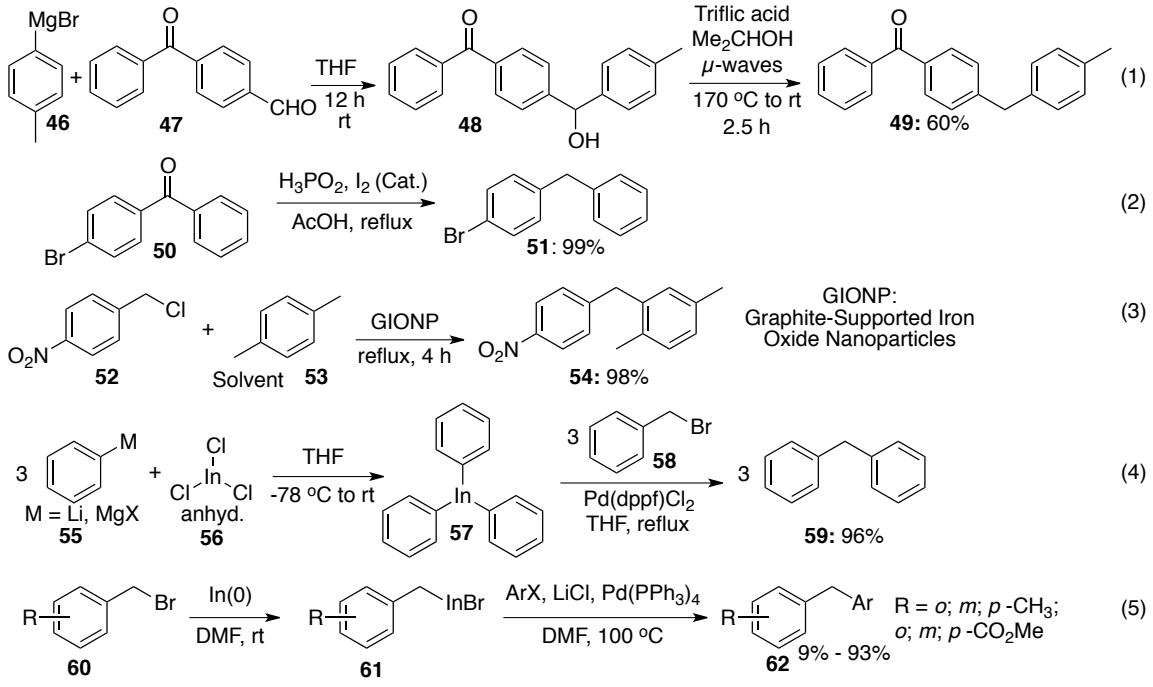
Figure 2. *Bioactive Biaryl and Heterobiaryl Compounds, Biaryl Catananes, and Natural Products*

Besides transition metal-catalyzed coupling,[43] typically diarylmethanes can also be synthesized by [1] reduction of diarylketones[44,45] or diaryl carbinols[46] (Scheme 5, eqs 1 and 2), and [2] Friedel-Crafts alkylation (Scheme 5, eq 3).[47]

As shown in Scheme 5, Provot et al. reported an acid-catalyzed reduction of carbinols via disproportionation reaction of a diarylmethylisopropyl ether intermediate (eq 1). They also demonstrated the chemoselective reduction of a diarylcarbinol in the presence of a diaryl ketone.

Though useful, application of highly reactive Grignards or aryllithium intermediates can be incompatible with many functional groups. Reduction of diaryl ketones in the presence of strong acids may not be suitable for fragile substrates (eq 2). Also, the reduction of diarylketones protocol often requires an electron-rich benzene ring, especially when hydride donors are used as reducing agents. Similarly, the Friedel-Crafts reaction requires an electron-rich aryl nucleophile for the alkylation reaction to proceed efficiently (eq 3).

Scheme 5. *Alternative Methods for Synthesis of Diarylmethanes*



In another report, a single example of diarylmethane synthesis by coupling of triphenylindium with benzyl bromide was reported (eq 4).[48] In a complimentary strategy, in a recent communication benzyl indium reagents were coupled with aryl iodides to access various diarylmethanes (eq 5).[49] This method is limited by the commercial availability of aryl iodides, and the yields are low (9% to 35%) in reactions with heteroaryl benzylic and electron-rich aryl iodides.[49] The method utilizing benzyl indium reagent as a coupling partner (eq 5) is opposite to

the trend in the Friedel-Crafts alkylation (eq 3) and reduction of diarylketones (eq 1) where electron-rich substrates give higher yields.

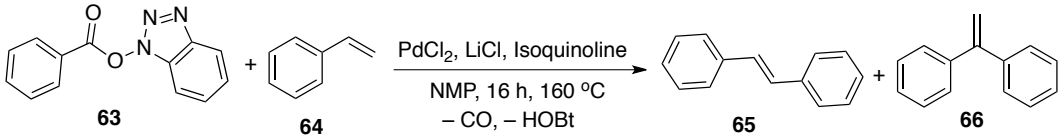
Palladium-catalyzed Suzuki-Miyaura cross coupling of halides and pseudohalides such as, benzylic carbonates, phosphates and acetates, with boronic acids has emerged as a powerful method for the synthesis of diarylmethanes. Boronic acids, provide excellent functional-group tolerance, reactions proceed under relatively mild conditions, and provide predictable connectivity.

In this chapter we describe a new application of the benzotriazolyl ethers for the synthesis of diarylmethane derivatives via palladium-catalyzed cross-coupling with boronic acids.

[4.2] RESULTS AND DISCUSSION

As shown in Chapter 3, the leaving group ability of the benzotriazolyloxy (BtO^-) anion from a sp^2 hybridized carbon has been widely exploited in nucleophilic substitution reactions (Chapter 3, Scheme 13).[50-52] To our knowledge, there is only one report, where BtO^- anion has been used as a leaving group in a palladium-catalyzed reaction. This was in a decarbonylative olefination using a benzotriazolyl benzoate ester (Scheme 6),[53] a system in which the carbonyl carbon is also sp^2 hybridized.

Scheme 6. *Decarbonylative Heck Olefination of a Benzotriazolyl Benzoate Ester*



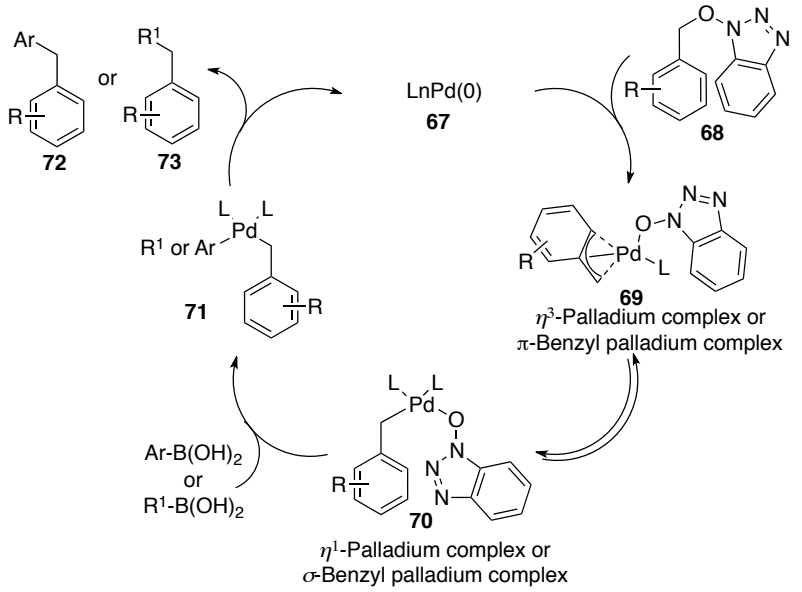
Based upon the results in Chapter 3, BtO^- appears to demonstrate pseudohalide like behavior. Other allyl and benzyl pseudohalides such as carbonates, acetates, and phosphates have been shown to efficiently undergo Suzuki cross-coupling reactions.[33-37]

Based on this collective data, we hypothesized that departure of BtO^- from benzotriazolyl ethers of allyl and benzyl alcohols, under metal-catalyzed conditions, could potentially lead to Suzuki cross-coupling applications. Such reactions could possibly proceed either via π-benzyl palladium complexes or via σ-benzyl palladium complexes (Scheme 7). A recent report by Lipshutz et al. on use of allylic phenyl ethers as electrophilic coupling partner in Suzuki-cross coupling reaction further bolstered our hypothesis (Scheme 8).[54]

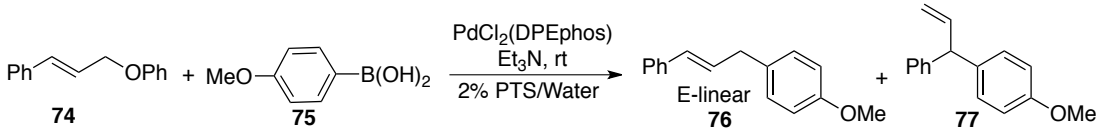
The investigation started with the selection of $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(PPh_3)_4$ as Pd sources, as well as two ligands; XPhos and SPhos, for the initial experiments (Figure 3). The reason for

using XPhos and SPhos as supporting ligands for our initial studies can be understood from the plausible mechanism shown in Scheme 7.[55,56]

Scheme 7. *Plausible Reaction Pathway Involving π- or σ-Benzyl Palladium Complex*



Scheme 8. *Reaction of p-Methoxyphenylboronic Acid with a Substituted Allylic Phenyl Ether*



The first step in the catalytic cycle is the oxidative-addition leading to the formation of a π-benzyl palladium complex (**69**), eventually **69** could rearrange to **70** which would possibly undergo transmetallation. For the oxidative-addition step to occur ligands dissociation from the catalyst must occur, to form coordinatively saturated π-benzyl palladium complex (**69**). Stability of σ-benzyl palladium complex (**70**) is very critical for the success of transmetallation step and eventually for this reaction. A chelating phosphine ligand may form a stable η^3-benzyl palladium complexes that may slow down or stop the reaction progress. Studies on π-allyl palladium complexs have shown that the required σ-allyl palladium complex for the transmetalation step is stabilized by bulky ligands such as pincer ligands (Figure 3).[57,58] Also, a

computational study on allyl palladium complexs reported that σ-allyl palladium complexs are more stable as compared to η^3-allyl palladium complex in the presence of a chelating ligand such as tridentate phosphine ligand (Figure 3).[59] From these studies it was clear that the ligand of choice for benzylic substrates should be able to stabilize the σ-benzyl palladium complexes not only by virtue of it's steric bulk but also via chelation and still be labile enough to dissociate before the transmetallation step.

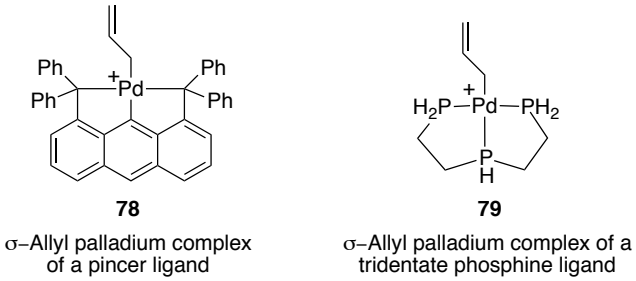


Figure 3. *Some σ-Allyl Palladium Complexes*

Based upon the recent studies by Buchwald et al. the biphenyl ligands seemed to possess these features i.e. steric bulk and possibility of stabilizing the σ-benzyl palladium complex via labile secondary interactions. The report by Buchwald group described the extra stability provided to σ-aryl palladium complex via palladium–arene interaction with the non-phosphine-containing ring of the ligand (Figure 4).[60] Thus, we chose XPhos (cone angle ~256º) and SPhos (cone angle ~240º) as ligands for initial optimization studies.[61]

Also, we decided to investigate use of SPhos and XPhos as supporting ligands because application of biarylphosphine ligands in Suzuki cross-coupling reactions of allylic or benzylic systems is seldom reported. Majority of the reports on Suzuki cross-coupling reactions of allylic or benzylic electrophilic coupling partners utilize diphosphine ligands like DPPF, DPEphos, etc.[33-36,54] Use of other monodentate ligands for Suzuki cross-coupling reaction of benzylic and allylic derivatives have also been reported.[37,62-64]

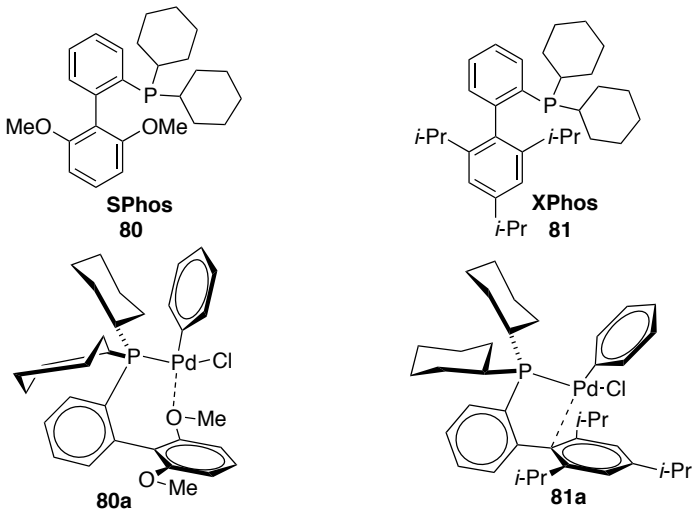
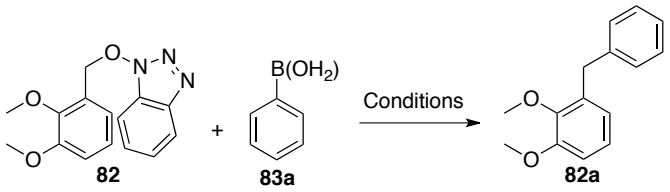


Figure 4. *Supporting Ligands SPhos and XPhos, and Stabilization of Oxidative Addition Complex Via Interaction of Palladium Center with Non-Phosphine Containing Ring of the Lingands*[60]

The benzotriazolyl ether of 2,3-dimethoxybenzyl alcohol (**82**) was used as the electrophilic coupling partner with phenylboronic acid for the initial work. The desired benzotriazolyl ether **82** was readily prepared from a reaction of 2,3-dimethoxybenzyl alcohol with 1*H*-benzotriazole-1-yl-4-methylbenzene sulfonate (Bt–OTs) in THF using DBU (see Chapter 3, Table 2). We began testing our C–C bond-formation hypothesis by reacting **82** with phenylboronic acid, using XPhos as supporting ligand.

As shown in Table 1, the reaction was first performed at room temperature using $Pd_2(dba)_3$ but no product formation was observed after 14.5 h. The second reaction was also carried out at room temperature, but with $Pd(OAc)_2$ as the metal source (entry 2). In this case, TLC showed some product formation. Hence, the reaction mixture was heated at 50 ^oC. However, starting material **82** remained unconsumed after 18 h at this temperature (entry 2). Nevertheless, the isolated yield of the desired product from this reaction was 54%. The next reaction was conducted at 100 ^oC, and although the desired product was obtained in good yield, the reaction took 18 h to reach completion (entry 3).

Table 1. *Optimization of the Cross-Coupling Reaction of Benzotriazolyl Ether **82** with PhB(OH)$_2$*[a]



Entry	Catalyst	Ligand (mol %)	Base	Time, Temp.	Yield[b]
1	$Pd_2(dba)_3$	XPhos (20)	Cs_2CO_3	14.5 h / rt	NR[c]
2	$Pd(OAc)_2$	XPhos (20)	Cs_2CO_3	24 h / rt to 50 °C	54%
3	$Pd(OAc)_2$	XPhos (20)	Cs_2CO_3	18 h / 100 °C	90%
4	$Pd(OAc)_2$	XPhos (20)	Ag_2O	22 h / 100 °C	NR[c]
5	$Pd(OAc)_2$	SPhos (20)	Cs_2CO_3	5 h / 100 °C	84%
6	$Pd(OAc)_2$	SPhos (20)	Ag_2O	22 h / 100 °C	NR[c]
7	$Pd(OAc)_2$	SPhos (20)	CsF	18 h / 100 °C	Inc[d]
8	$Pd(OAc)_2$	SPhos (20)	K_3PO_4	24 h / 100 °C	Inc[d]
9	$Pd(OAc)_2$	SPhos (20)	$K_3PO_4.H_2O$	22 h / 100 °C	Inc[d]
10	$Pd(OAc)_2$	SPhos (20)	K_3PO_4 + 2.0 eq H_2O	1 h / 100 °C	88%
11	$Pd(OAc)_2$	SPhos (20)	K_3PO_4 + 2.0 eq H_2O	26 h / 100 °C	Inc[d, e]
12	$Pd(OAc)_2$	SPhos (10)	K_3PO_4 + 2.0 eq H_2O	4 h / 100 °C	78%
13	---	SPhos (20)	K_3PO_4 + 2.0 eq H_2O	26 h / 100 °C	NR[c]
14	$Pd(PPh_3)_4$	---	K_3PO_4 + 2.0 eq H_2O	2.5 h / 100 °C	83%
15	$Pd(PPh_3)_4$	---	0.5 mL aq. Na_2CO_3 (0.2 M), degassed	26 h / 100 °C	57%
16	$Ni(COD)_2$	SPhos (20)	K_3PO_4 + 2.0 eq H_2O	16 h / 100 °C	NR[c]
17	$Ni(COD)_2$	PPh_3 (30)	K_3PO_4 + 2.0 eq H_2O	16 h / 100 °C	NR[c]
18	$Ni(COD)_2$	PCy_3 (30)	K_3PO_4 + 2.0 eq H_2O	26 h / 100 °C	NR[c]
19	$Pd(OAc)_2$	SPhos (20)	K_3PO_4 + 2.0 eq H_2O	24 h / 100 °C	Inc[c, f]

[a] Conducted at 100 °C with a 0.14 M solution of **82** in toluene, using 10 mol% Pd catalyst, 2 mol eq base, and 2 molar equiv. **83a**. [b] Yield of isolated and purified products. [c] No reaction.
[d] Incomplete reaction, product formation was observed by TLC, but starting material was present. [e] Reaction performed with 1.2 mol eq of phenylboronic acid instead of 2.0 molar equiv. [f] Reaction was performed in acetonitrile

In an attempt to reduce the reaction time, the base was changed from Cs_2CO_3 to Ag_2O, but this did not help (entry 4). Gratifyingly, use of SPhos inplace of XPhos reduced the reaction

time to 5 h and yielded a purer product (entry 5). Further changes in the reaction conditions did not seem to improve the reaction rate and/or product yield (entries 6-9).

Use of K_3PO_4 in conjunction with 2.0 equivalents of H_2O reduced the reaction time from 5 h to 1 h, and the desired product was obtained in 88% yield (entry 10). Changing the catalyst:ligand ratio from 1:2 to 1:1 increased the reaction time to 4 h with a slightly diminished yield of the desired product to 78% (entry 12). In order to ascertain that catalyst was necessary for the reaction to proceed, one reaction was conducted in the absence of the palladium metal (entry 13). No product formation was observed in this case. Use of $Pd(PPh_3)_4$ gave the desired product in a yield comparable to the SPhos/$Pd(OAc)_2$ reaction, also within a reasonable time (compare entries 14 and 10).

The outcome of reactions in entries 8, 9, and 10 clearly demonstrate that addition of water to the reaction mixture enhances the reaction efficiency. Encouraged by these results we performed a reaction in 0.5 mL of aqueous Na_2CO_3, but this reaction was slow to reach completion (26 h), yielding only 57% of the desired product (entry 15). Use of $Ni(COD)_2$ catalyst for these reactions did not yield in any product (entries 16-18). Changing the solvent from toluene to acetonitrile resulted in incomplete reaction (entry 19).

Throughout the optimization process a significant amount of boronic acid homocoupling product was observed, an undesired side reaction in many C–C bond-forming reactions.[65-67] The homocoupling of phenylboronic acids has been shown to occur due to the dissolved oxygen in the reaction solvent.[67] Thus, to optimize the reaction conditions 2.0 molar equiv. of phenylboronic acid was typically used. One reaction was conducted with 1.2 molar equiv. of phenyl boronic acid, and as expected, this reaction did not show complete consumption of the benzotriazolyl ether **82** even after 26 h (entry 11).

Supporting ligands play a vital role in any metal-catalyzed transformation and choice of a suitable ligand is critical for its success, or for improving catalyst performance. Therefore, after establishing the optimal metal source, base, and temperature for the cross-coupling, the reaction was reexamined with different biarylphosphine ligands (Figure 4). Ligand effects can be reasoned on the basis of their steric and electronic properties.

In metal complexes containing phosphine and carbonyl ligands, the steric and electronic effects of a monodentate phosphine ligand can be rationalized by the Tolman cone angle (θ) and by the infrared carbonyl stretching frequency ($\bar{\nu}$), respectively.[68] Ligands having higher θ values are relatively bulkier, i.e. they are spatially more demanding, as compared to those with lower θ values. The parameter $\bar{\nu}$ is a measure of the σ-donating ability of a ligand, i.e. how much electron density is transmitted from the ligand to the metal center. The value of $\bar{\nu}$ for a particular ligand may vary depending upon the metal and its oxidation state. In contemporary times, with the advent of a variety of structurally elaborate ligands such as biarylphosphines (Buchwald ligands), bidentate ligands, and *N*-heterocyclic carbenes (NHCs), steric parameter calculations using the Tolman model have proven difficult. Alternative approaches have therefore been introduced. One such approach to measure the steric bulk is ‘‘percent buried volume’’ (%V_{bur}), which is defined as "*the percent of the total volume of a sphere occupied by a ligand. The sphere has a defined radius and has the central metal atom at the core"*.[61]

Table 2, enumerates the reported Tolman cone angle (θ) and ‘‘percent buried volume’’ (%V_{bur}) of the biarylphosphine ligands surveyed in our ligand optimizations.[61,69] All the phosphine ligands screened here with the exception of JohnPhos, are analogues of $P(Cy)_2Ph$ (Table 2, entry 8), which in turn is analogue of $P(Cy)_3$ (Table 2, entry 10). JohnPhos is an

analogue of P(*t*-Bu)$_2$Ph (Table 2, entry 9), which in turn is an analogue of P(*t*-Bu)$_3$ (Table 2, entry 11).

Table 2. *Steric Properties of Selected Phosphine Ligands*[61,69]

Entry	Ligand	θ /°	%V_{bur} for Au–P length at 2.28 Å
1	XPhos	256	53.1
2	SPhos	240	49.7
3	RuPhos	---	---
4	Cy JohnPhos	226	46.7
5	JohnPhos	246	50.9
6	DavePhos	---	---
7	**90**	---	---
8	P(Cy)$_2$Ph	159	32.7
9	P(*t*-Bu)$_2$Ph	170	---
10	P(Cy)$_3$	170 ($\bar{\nu}$ = 2056.4 cm^{-1})	
11	P(*t*-Bu)$_3$	182 ($\bar{\nu}$ = 2056.1 cm^{-1})	

From the carbonyl stretching frequency data of P(Cy)$_3$ [$\bar{\nu}$ = 2056.4 cm^{-1}] and P(*t*-Bu)$_3$ [$\bar{\nu}$ = 2056.1 cm^{-1}] it is implied that the σ-donating ability of both these ligands would be similar (entries 10 and 11). Since, the ligands used in this study are analogues of P(Cy)$_3$ or P(*t*-Bu)$_3$ and the biarylphosphine ligands screened here differ only with regard to the substituents on the nonphosphine containing ring, it is assumed that ligands used for this study would not differ greatly in their σ-donating ability. Thus, an attempt has been made to explain the outcome of the ligand screening (Figure 5) based on their steric bulk (Table 2) and the interaction of the metal center (Pd) with the nonphosphine-containing ring (Figure 4).

As shown in Figure 5, although all the ligands tested for the cross-coupling reaction afforded good yields of product **82a** there were some notable differences. Efficiency of SPhos was compared to other similar ligands. As can be seen in Figure 5, although XPhos gave a good

product yield, the reaction time was much longer. This may be on account of its ~7% higher steric bulk than SPhos (Table 2, entry 2). Whereas θ and $\%V_{bur}$ for RuPhos is not known, the isopropyl groups in place of methoxyls of SPhos, likely renders RuPhos sterically bulkier than SPhos. This may slow down the oxidative addition or transmetallation steps. RuPhos was in fact inferior to SPhos. Also, in RuPhos, the large steric bulk around the oxygen atoms of the nonphosphine-containing ring may interfere with Pd-arene interactions (Figure 5), which is important for the stability of the η^1-benzyl palladium complex.[60] Interestingly, ~6% reduction in the steric bulk of SPhos and removal of two methoxy groups from the nonphosphine containing ring i.e. moving from SPhos to Cy-JohnPhos did not seem to adversely affect the efficiency of the reaction. Replacement of the cyclohexyl groups with *t*-butyl groups on phosphorus, i.e. use of JohnPhos in place of Cy-JohnPhos, reduced the catalyst efficiency. This may again be due to an increase in steric bulk from Cy-JohnPhos to JohnPhos (increase of 9%). JohnPhos is ~2.5% bulkier than SPhos as well and does not have electron-donating groups on the nonphosphine-containing ring that can potentially stabilize the σ-benzylpalladium complex.

DavePhos seems to meet both criteria; moderate steric bulk and electron-rich nonphosphine ring, but to our surprise, it performed poorly. This may be due to a higher stability of the σ-benzylpalladium complex via chelation with the dimethylamino nitrogen on the *ortho* position of nonphosphine containing ring of DavePhos. This could have slowed down the reaction rate. This plausible explanation about the low efficiency of DavePhos is supported by the results with ligand **90**. Ligand **90**, invented in Prof. Lakshman's laboratories,[70] is an isomer of DavePhos. In **90**, the dimethylamino group is present at *para* position of the nonphosphine containing ring, this eliminates the possibility of nitrogen chelating to the metal center and at the same time provides

enough electron density to the nonphosphine benzene ring to stabilize the σ-benzyl palladium complex via labile Pd-arene interactions.

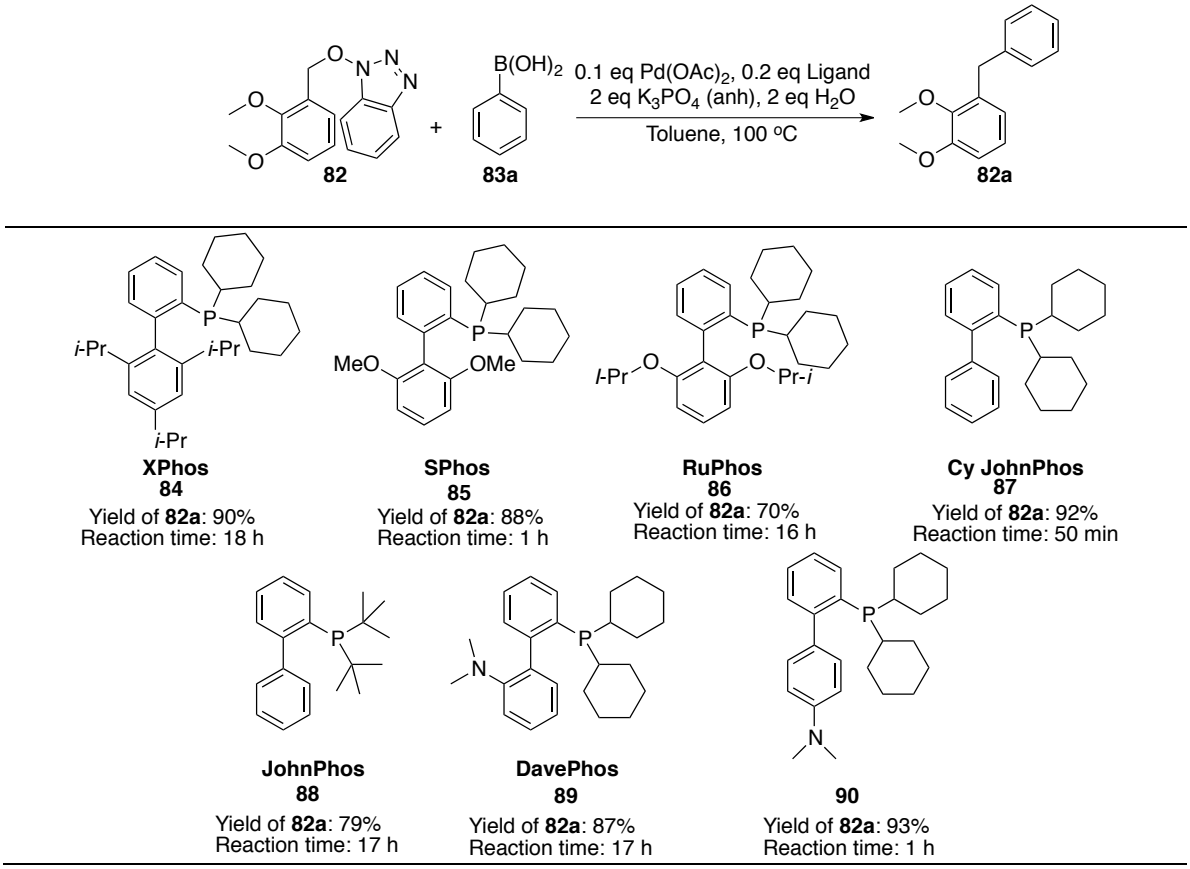
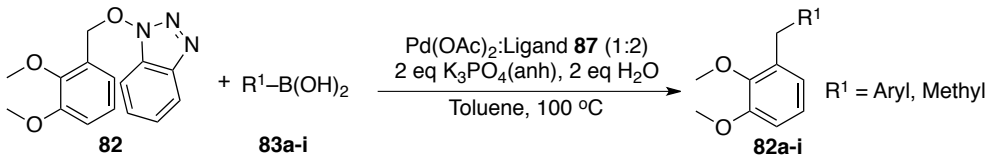


Figure 5. *Ligands Used in Further Optimizations*

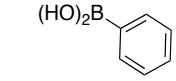
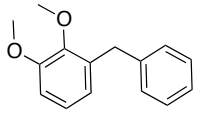
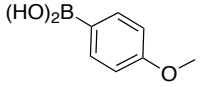
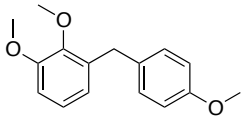
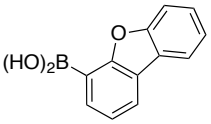
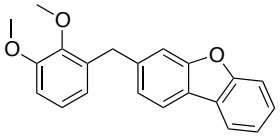
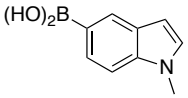
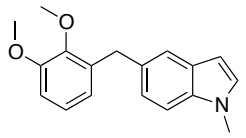
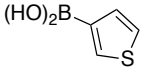
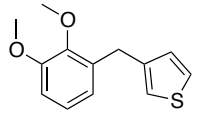
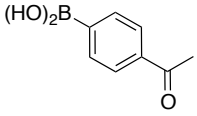
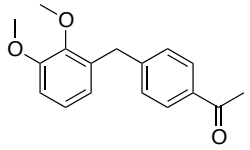
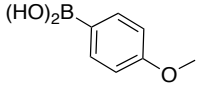
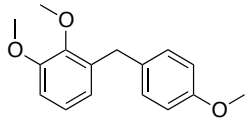
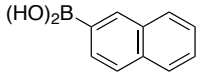
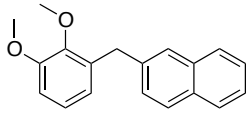
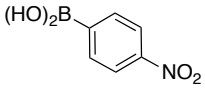
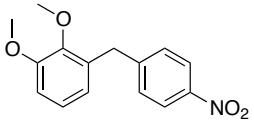
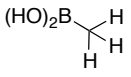
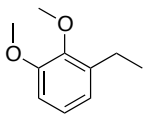
From this analysis, based on the stereoelectronic properties of the screened ligands, **90** could perform better than all other ligands tested under the reaction conditions. However, considering the commercial availability (**90** is not commercially available) and due to cost constrains Cy-JohnPhos ($14.6/mmol) was chosen over SPhos ($30.7/mmol) and **90** for further studies.

With optimal reaction conditions established for the cross coupling of the benzotriazolyl ether of 2,3-dimethoxybenzyl alcohol **82** and phenylboronic acid **83a**, the reaction was then tested for generality against a variety of boronic acids, **83a-i**. As illustrated in Table 3, satisfactory success was achieved with electron-neutral, electron-rich, and importantly electron-deficient boronic acids. Reaction with electron-neutral and electron-rich boronic acids resulted

Table 3.1. *Suzuki Cross-Coupling of the Benzotriazolyl Ether of 2,3-Dimethoxybenzyl Alcohol with Various Boronic Acids*



82 **83a-i** **82a-i**

Entry	R^1–$B(OH)_2$	$Pd(OAc)_2$ mol%	Time (h)	Product	% Yield[a]
1[b]		10	0.83		92
2[b]		10	0.83		90
3[b]		10	1.7		92
4[b]		10	16		25
5[c]		10	16		44[d]
6[e]		10	16		57
7[b]		2	4.5		93
8[b]		2	2		64
9[f]		2	16		29[d]
10[g]		5	14		45

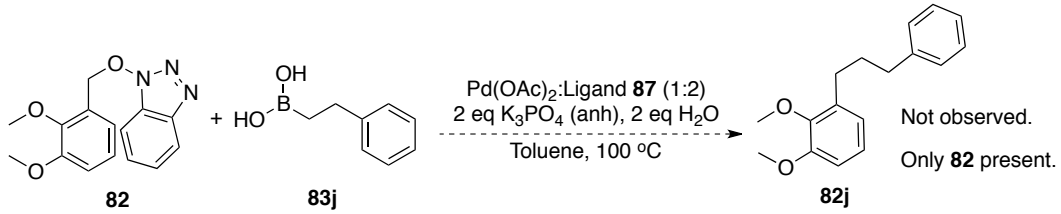
[a] Yields are of isolated and purified products. [b] Reaction was performed with 0.7 mmol of **82**. [c] Reaction was performed with 0.07 mmol **82**. [d] Reaction was incomplete and **82** was present. [e] Reaction was performed with 0.25 mmol of **82**. [f] Reaction was performed with 0.4 mmol of **82.** [g] Reaction was performed with 0.5 mmol of **82**.

in the desired products in good yields (Table 3, entries 1 and 2). Further, reactions with heteroaryl phenylboronic acids produced the desired product in good to moderate yields (entries 3-5). Moving further we tried coupling reaction of the electron-deficient *p*-acetylphenyl boronic acid (entry 6).

The reaction with electron deficient boronic acid is particularly challenging due to difficult transmetallation step. The reaction with *p*-acetylphenyl boronic acid was slow, but the desired product was isolated in good yield nevertheless (entry 6).

Our next goal was to reduce the catalyst loading. Some reactions were run at lower catalyst loading of 2 mol% $Pd(OAc)_2$. The reactions with electron-rich (compare entries 2 and 7) and electron-neutral (compare entries 1 and 8) boronic acids were slower at lower catalyst loading. However, good yields of the desired products were obtained in each case. Reaction with highly electron-deficient *p*-nitrophenylboronic acid at 2 mol% catalyst loading faired very poorly and the isolated yield of the desired product was low (compare entries 6 and 9). Also, electron-deficient arylboronic acids are more susceptible to homocoupling.[71] We also conducted a Suzuki cross-coupling reaction with methyl boronic acid. Much to our surprise we were able to isolate the desired product in a respectable yield (entry 10). This one carbon homologation reaction was conducted at 5 mol% $Pd(OAc)_2$.

Scheme 9. *Attempted Coupling of the Benzotriazolyl Ether of 2,3-Dimethoxybenzyl Alcohol and an Alkyl Boronic Acid Consisting β-Hydrogen Atoms*

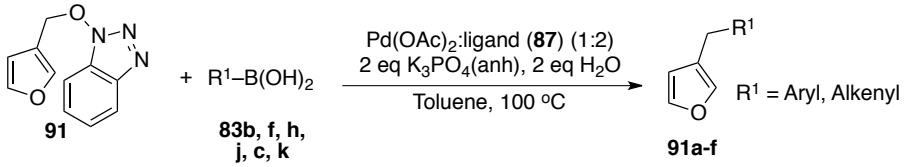


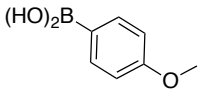
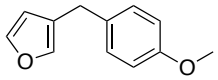
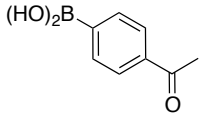
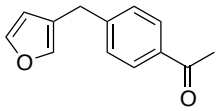
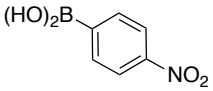
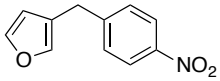
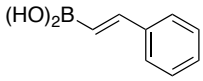
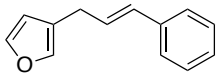
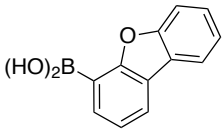
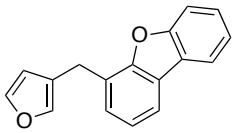
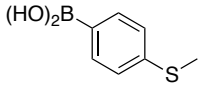
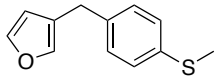
Motivated by these results a reaction with phenethylboronic acid was performed (Scheme 9). Unfortunately, formation of desired product was not observed. This may be a result of faster *β*-

hydride elimination of the transmetallated palladium complex, compared to the reductive elimination.

Next, we moved to the reactions of the benzotriazolyl ether of a heteroaromatic alcohol, 3-furanmethanol. It is very well known that furan has lower aromatic stabilization energy compared to a benzene ring.[72]

Table 3.2. *Suzuki Cross-Coupling of Benzotriazolyl Ether of 3-Furanmethanol with Different Boronic Acids*



Entry	R^1–$B(OH)_2$	$Pd(OAc)_2$ mol%	Time (h)	Product	% Yield[a]
11[b]		10	0.83		95
12[c]		10	12		64
13[b]		10	19		40[d]
14[c]		10	3.5		40
15[e]		2	3.5		89
16[e]		2	5		80

[a] Yield reported is of isolated and purified product. [b] Reaction performed with 0.07 mmol **91**. [c] Reaction performed with 0.2 mmol **91**. [d] Reaction was incomplete, starting material **91** present. *e* Reaction was performed with 0.7 mmol of **91**.

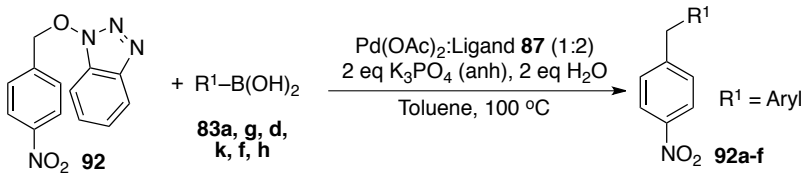
Thus, formation of η^3-palladium complex (like **69**, Scheme 7) with benzotriazolyl ether of 3-furanmethanol could possibly be easier as compared to benzotriazolyl ether **82,** which could make cross coupling with **91** more efficient than with **82**.

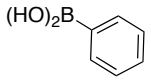
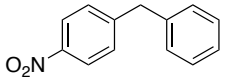
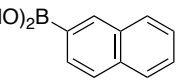
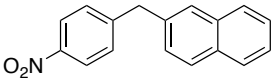
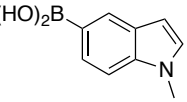
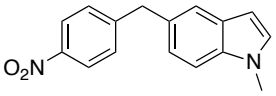
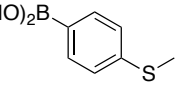
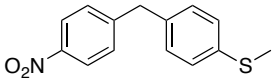
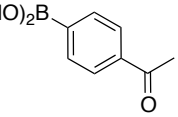
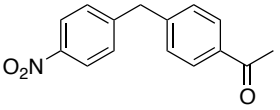
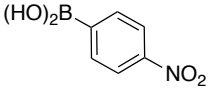
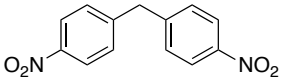
As expected, excellent yields of the desired products were obtained with electron-rich boronic acids (Table 3.2, entries 11, 14, 15). However, to our surprise electron-deficient boronic acids did not produce the cross-coupled products in good yield (Table 3.2, entries 12, 13). Similarly, an alkenylboronic acid resulted in a poor yield of the desired product (entry 16). Contrary to our expectations, **91** performed moderately with electron-deficient boronic acids (Compare Table 3.2 entries 11 and 13 with Table 3.1 entries 6 and 9). These unanticipated results encouraged us to further test the limits of this interesting, but unexplored group of electophilic, Suzuki cross-coupling partners.

Therefore, we decided to try a more challenging substrate, the benzotriazolyl ether of *p*-nitrobenzyl alcohol (**92**). As shown in Scheme 7, if the first step in the cross-coupling reaction with the benzylic coupling partner may require formation of a π-benzyl or a η^3-benzyl palladium complex (**69**). This requires disruption of aromaticity and electron-donation from the aromatic ring of the benzyl ligand. Obviously, the *p*-nitro group in benzotriazolyl ether of **92** would not favor the electron-donation from the aromatic ring. Possibly making the formation of corresponding η^3-benzyl palladium complex difficult. This is what, we thought, made the substrate **92**, a challenging coupling partner.

To our surprise, the reactions of **92** with electron-neutral (Table 3.3, entries 17 and 18), heteroaromatic (Table 3.3, entry 19), electron-rich (Table 3.3, entry 20) and electron-deficient boronic acids (Table 3.3, entry 21) resulted in good to excellent yield of the desired coupling product. In fact, these reactions were just as efficient as those with benzotriazolyl ether of 2,3-dimethoxybenzyl alcohol (compare Table 3.1 entries 1, 4 and 6 with Table 3.3 entries 17, 19 and 21). The reason for the unexpected reaction efficiency with **92** is not clear at this point.

Table 3.3. *Suzuki Cross-Coupling of the Benzotriazolyl Ether of p-Nitrobenzyl Alcohol with Different Boronic Acids*



Entry	R^1–$B(OH)_2$	$Pd(OAc)_2$ mol%	Time (h)	Product	% Yield[a]
17[b]		10	0.83		40
18[b]		10	1.5		88
19[c]		10	5		35
20[b]		10	1		91
21[c]		10	14		51
22[b]		10	24		30[d]

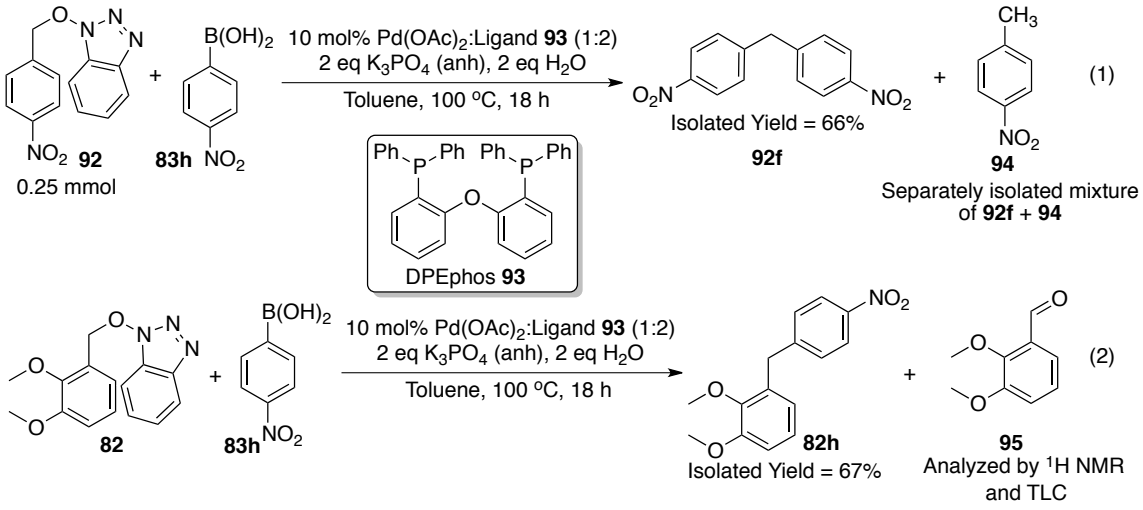
[a] Yield is of isolated and purified product. [b] Reaction was performed with 0.07 mmol of **92**. [c] Reaction was performed with 0.25 mmol of **92**. [d] Reaction was incomplete and starting material was present, isolated product was not pure.

Cross-coupling reactions of these benzotriazolyl ethers with some of the boronic acids produced low yields (Table 3.1, entries 4, 5 and 9; Table 3.2, entries 12, 13 and 14; Table 3.3, entries 17, 19 and 22). Particularly, reactions of each of these benzotriazolyl ethers (**82**, **91**, **92)** as coupling partners with highly electron deficient *p*-nitrophenylboronic acid produced poor yield of the desired cross-coupled product and the isolated compound was impure. These were the two issues with this methodology that we set out to solve next. We also wondered if the new reaction conditions that would be developed for reactions with *p*-nitrophenylboronic acid might help improve other low yielding reactions (Table 3.1, entries 4 and 5; Table 3.2, entries 12 and 13; Table 3.3, entries 17 and 19). For this purpose we again chose the seemingly difficult

combination of coupling partners i.e. benzotriazolyl ether of *p*-nitrobenzyl alcohol and *p*-nitrophenylboronic acid. A trend that was observed in the reactions with *p*-nitrophenylboronic acid was the precipitation of palladium black. Although this was also observed in other cases, those reaction went to completion in those cases nevertheless. Hence, we started thinking along the lines of maintaining palladium homogeneously in the reaction mixture for longer period of time. For this various reaction conditions were tried; using the electron-rich biaryl phosphine ligand (BrettPhos), running the reactions at lower temperature to see if the palladium-ligand complex produced palladium black at high reaction temperature, and also different solvents. Unfortunately, none of these changes in reaction conditions helped solve the problem.

Finally, we decided to use a bis-coordinating ligand, DPEphos [(oxydi-2,1-phenylene)bis(diphenylphosphine)]. Gratifyingly, a reaction of the two most electron deficient partners, **92** and **83h**, went to completion within 18 hr (Scheme 10).

Scheme 10. *Suzuki Cross-Coupling of the Benzotriazolyl Ethers **92** and **82** with p-Nitrophenylboronic Acid Using DPEphos as Supporting Ligand*

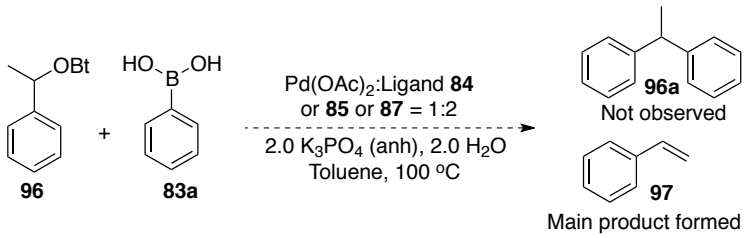


The desired product was isolated in 66% yield after two column chromatographies. Interestingly, by ^{1}H NMR analysis one of the impurities isolated as a mixture with some desired product, appears to be *p*-nitrotoluene by ^{1}H NMR analysis (Scheme 10, eq 1). This suggests that

some process similar to protodehalogenation, commonly observed in cross-coupling reactions with aryl halides,[73] may be operative with benzotriazolyl ethers as well. Encouraged by the efficient coupling of **92** and **83h**, a coupling reaction of **92** and **83h** was successfully performed using DPEphos as a supporting ligand (Scheme 10, eq 2). These successful reactions (Scheme 10, eq 1 and 2) indicate that use of DPEphos (%V_{bur} for Au–P length at 2.28 Å: 41.3) as supporting ligand in other low yielding reactions could potentially help reduce the catalyst loading while maintaining the reaction efficiency.

Next, we wondered if this methodology could be applied to benzotriazolyl ethers of secondary alcohols. To test this possibility, a reaction between benzotriazolyl ether of 1-phenylethanol and phenylboronic acid was attempted, under the reaction conditions developed above (Table 3.1). The reaction showed consumption of the starting material, but no formation of the desired product was observed (Scheme 11).

Scheme 11. *Attempted Cross-Coupling of the Benzotriazolyl Ether of a Secondary Alcohol*

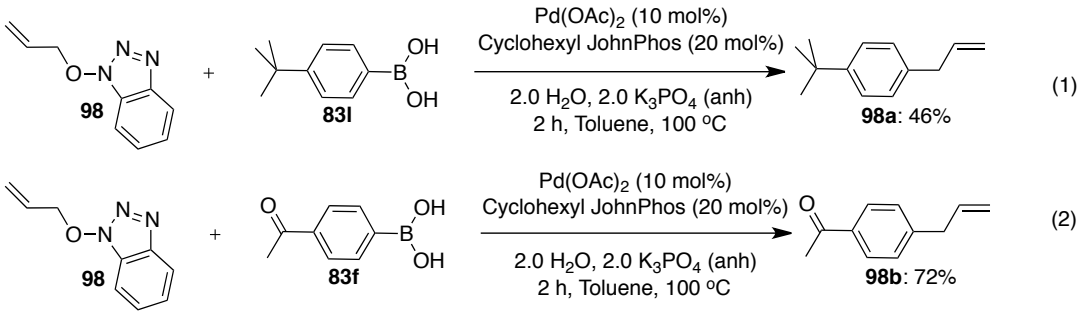


The only product observed in this reaction was styrene, indicating a facile *β*-hydride elimination under these conditions. This was not altogether unexpected. Attempt to suppress the *β*-hydride elimination via use of SPhos and XPhos failed.

Finally, possible development of methodology for the allylation of aromatic compounds using the benzotriazolyl ether of allyl alcohol was evaluated. Reaction between benzotriazolyl ether of allyl alcohol **98** and electronically-neutral boronic acid **83l** as well as electron-deficient boronic acid **83f** was attempted under the reaction conditions established above (Table 3.1). Both

reactions yielded the desired products **98a** and **98b** in moderate to good yield (Scheme 12). Some of the crude material spilled while preparing the dry slurry for the column chromatography of the reaction mixture and this is the reason for the lower yield of the product **98a**.

Scheme 12. *Allylation of Aromatic Compounds*



[4.3] CONCLUSION

In conclusion, the Suzuki-Miyaura cross-coupling reaction between benzylic benzotriazolyl ethers and arylboronic acid was investigated as a novel and unknown reaction of such ethers. Initial screening of reaction conditions revealed that addition of water to the reaction mixture increases the rate of reaction without affecting its efficiency. This also indicates hydrolytic stability of the benzotriazolyl ethers of benzylic alcohols and the eventual possibility of carrying out such reactions in water. This would possibly eliminate the need for organic solvents, making this cross-coupling reaction environmentally friendly.

The performmance of various biarylphosphine ligands was analyzed based on their Tolman cone angle (θ) and percent buried volume ($\%V_{bur}$). Analysis of the stereoelectronic properties revealed that a birylphosphine ligand with moderate steric bulk and with enough electron density on the non phosphine-containing ring could stabilize the σ-benzyl palladium intermediates via labile palladium-arene interactions. Therefore, ligands such as SPhos, Cy-JohnPhos, DavePhos etc. are likely better for catalysts involved with C–C bond formations described here.

Suzuki cross-coupling reactions of the benzotriazolyl ethers of an electron-rich and an electron-deficient benzyl alcohol, and that of a heteroaryl alcohol were efficiently carried out. The reactivities of each benzotriazolyl ether with different boronic acids i.e. electronically-neutral, electron-rich, and electron-deficient are generally comparable. Thus, the reactivity of these benzotriazolyl ethers under the described reaction conditions seems to be relatively independent of the electronics of the aromatic ring in the benzotriazolyl ether. Some of these cross-coupling reactions were successfully and efficiently carried out at a lower catalyst loading of 2 mol% $Pd(OAc)_2$.

Successful C(sp^3)-C(sp^3) cross coupling was achieved in the reaction of the benzotriazolyl ether of 2,3-dimethoxybenzyl alcohol with methylboronic acid. However, a similar reaction with a boronic acid containing of β-hydrogen atoms failed to produce the desired product. Nevertheless, the successful reaction with methylboronic acid cues toward the possible application of this methodology to other alkylboronic acids devoid of a β–hydrogen atom.

Better success in the cross-coupling reaction between benzotriazolyl ether of *p*-nitrobenzyl alcohol and the highly electron-deficient *p*-nitrophenylboronic acid was achieved by using DPEphos as supporting ligand. Plausibly, yields of other reactions can be enhanced with this ligand.

The attempted cross-coupling reaction of a benzotriazolyl ether of a secondary benzyl alcohol with phenylboronic acid failed to yield the desired product. Here, formation of styrene was observed. Styrene is formed by a β-hydride elimination from benzotriazolyl ether of a *sec*-phenylethanol.

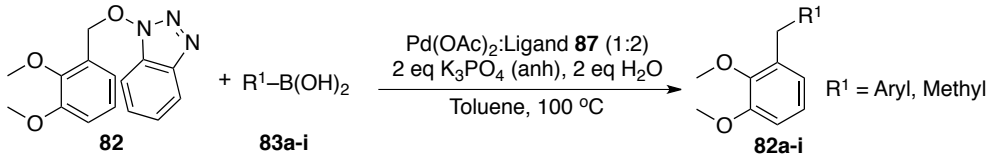
Finally, this methodology was applied for cross-coupling benzotriazolyl ether of allyl alcohol with an electronically-neutral and an electron-rich boronic acid. Moderate to good yields of the desired cross-coupled product was isolated in each case, showing the utility of this methodology to obtain a variety of allylbenzenes.

We have discovered a novel class of electrophilic benzylic/allylic coupling partners for Suzuki cross-coupling reactions. We have also explored its applicability to a whole range of boronic acids. This has opened exciting new avenues that could be explored further in the future.

[4.4] GENERAL PROCEDURE

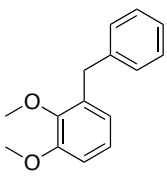
In a reaction vial equipped with a stirring bar, was placed the benzotriazolyl ether of a benzylic alcohol **82** or **91** or **92**, the boronic acid, $Pd(OAc)_2$, cyclohexyl JohnPhos, and anhydrous K_3PO_4, in anhydrous toluene. The reaction mixture was flushed with nitrogen gas and to the stirring mixture was added, deionized water. See the individual compound headings for specifics. The reaction mixture was vigorously stirred at 100 ºC, and the progress of the reaction was monitored by TLC. When complete consumption of the benzotriazolyl ether **82** or **91** or **92** was observed, the reaction mixture was filtered through a plug of silica using CH_2Cl_2, and concentrated under reduced pressure. The crude material so obtained was purified on silicagel column using a suitable eluting solvent (see compound headings for details).

[4.4.1] Cross-coupling of the benzotriazolyl ether of 2,3-dimethoxybenzyl alcohol with various boronic acids



82 **83a-i** **82a-i**

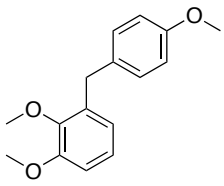
2,3-Dimethoxydiphenylmethane (82a)



Synthesized from **82** (0.150 g, 0.7 mmol), phenylboronic acid (0.170 g, 1.4 mmol), $Pd(OAc)_2$ (15.7 mg, 0.07 mmol), cyclohexyl JohnPhos (49.0 mg, 0.14 mmol), K_3PO_4 (0.297 g, 1.4 mmol) in toluene (5.0 mL) and H_2O (25 µL, 1.4 mmol). After 50 min, TLC analysis of the reaction mixture showed complete consumption of **82a**. Column chromatography was performed using 1% EtOAc in hexanes to give **82a** (0.149 g, 92%) as clear, oily liquid. R_f (SiO_2/10% EtOAc in hexanes) = 0.39. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21-7.28 (m, 4H, Ar–H), 7.17 (t, 1H, Ar–H, J = 7.1 Hz), 6.97 (t, 1H, Ar–H, J = 7.9 Hz), 6.80 (dd, 1H, Ar–

H, J = 8.1, 1.2 Hz), 6.73 (dd, 1H, Ar–H, J = 7.7, 1.2 Hz), 4.0 (s, 2H, CH_2), 3.86 (s, 3H, CH_3), 3.71 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.1, 147.4, 141.4, 135.2, 129.1, 128.5, 126.1, 124.0, 122.8, 110.8, 60.7, 55.9, 36.0. HRMS (ESI) *m/z* calcd for $C_{15}H_{17}O_2$ $[M + H]^+$: 229.1219, found 229.1223.

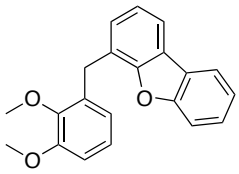
2,3,4'-Trimethoxydiphenylmethane (82b)



Synthesized from **82** (0.150 g, 0.7 mmol), *p*-methoxyphenylboronic acid acid (0.213 g, 1.4 mmol), $Pd(OAc)_2$ (15.7 mg, 0.07 mmol), cyclohexyl JohnPhos (49.0 mg, 0.14 mmol), K_3PO_4 (0.297 g, 1.4 mmol) in toluene (5.0 mL) and H_2O (25 μL, 1.4 mmol). After 50 min, TLC analysis of the reaction mixture showed complete consumption of **82**. Column chromatography was performed using 1% EtOAc in hexanes to give **82b** (0.166g, 90%) as a clear, oily liquid. R_f (SiO_2/10% EtOAc in hexanes) = 0.21.

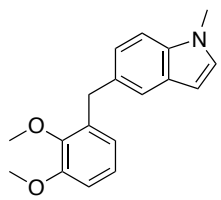
Compound **82b** was also synthesized using 2 mol% Pd catalyst loading. Following the general procedure, using **82** (0.150 g, 0.7 mmol), *p*-methoxyphenylboronic acid (0.213 g, 1.4 mmol), $Pd(OAc)_2$ (3.1 mg, 0.014 mmol), cyclohexyl JohnPhos (9.8 mg, 0.028 mmol), K_3PO_4 (0.297 g, 1.4 mmol), toluene (5.0 mL), and H_2O (25 μL, 1.4 mmol). After 4 h, TLC analysis of the reaction mixture showed complete consumption of **82**. Column chromatography was performed using 1% EtOAc in hexanes to give **82b** (0.170 g, 93%) as clear, oily liquid. R_f (SiO_2/10% EtOAc in hexanes) = 0.22. ^1H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, 2H, Ar–H, J = 8.4 Hz), 6.97 (t, 1H, Ar–H, J = 7.9 Hz), 6.82-6.78 (m, 3H, Ar–H), 6.72 (dd, 1H, Ar–H, J = 7.6, 0.9 Hz), 3.94 (s, 2H, CH_2), 3.86 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 3.72 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.0, 153.1, 147.3, 135.7, 133.5, 130.0, 124.0, 122.7, 113.9, 110.7, 60.7, 55.9, 55.4, 35.1. HRMS (ESI) *m/z* calcd for $C_{16}H_{18}O_3Na$ $[M + Na]^+$: 281.1148, found 281.1160.

4-(2,3-Dimethoxybenzyl)dibenzofuran (82c)



Synthesized from **82** (0.150 g, 0.7 mmol), dibenzofuran-4-boronic acid acid (0.297 g, 1.4 mmol), $Pd(OAc)_2$ (15.7 mg, 0.07 mmol), cyclohexyl JohnPhos (49.0 mg, 0.14 mmol), K_3PO_4 (0.297 g, 1.4 mmol) in toluene (5.0 mL), and H_2O (25 μL, 1.4 mmol). After 100 min, TLC analysis of the reaction mixture showed complete consumption of **82**. Column chromatography was performed using 1% EtOAc in hexanes to give **82c** (0.206 g, 92%) as a clear, oily liquid. R_f (SiO_2/10% EtOAc in hexanes) = 0.27. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, 1H, Ar–H, J = 7.7 Hz), 7.83 (d, 1H, Ar–H, J = 7.3 Hz), 7.62 (d, 1H, Ar–H, J = 8.2 Hz), 7.48 (t, 1H, Ar–H, J = 7.7 Hz), 7.36 (t, 1H, Ar–H, J = 7.5 Hz), 7.23-7.29 (m, 2H, Ar–H), 7.0 (t, 1H, Ar–H, J = 7.9 Hz), 6.85 (t, 2H, Ar–H, J = 8.5 Hz), 4.41 (s, 2H, CH_2), 3.90 (s, 3H, CH_3), 3.83 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 154.8, 152.9, 147.4, 133.9, 127.9, 127.0, 125.2, 124.7, 123.9,122.9, 122.71, 122.70, 120.8, 118.5, 111.8, 110.8, 60.6, 55.8, 29.5. HRMS (ESI) *m/z* calcd for $C_{21}H_{18}O_3Na$ $[M + Na]^+$: 341.1148, found 341.1153.

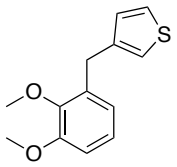
5-(2,3-Dimethoxybenzyl)-1-methyl-1*H*-indole (82d)



Synthesized from **82** (0.150 g, 0.7 mmol), *N*-methylindole-5-boronic acid (0.245 g, 1.4 mmol), $Pd(OAc)_2$ (15.7 mg, 0.07 mmol), cyclohexyl JohnPhos (49.0 mg, 0.14 mmol), K_3PO_4 (0.297 g, 1.4 mmol) in toluene (5.0 mL) and H_2O (25 μL, 1.4 mmol). After 16 h, TLC analysis of the reaction mixture showed complete consumption of **82**. Column chromatography was performed using 2% Et_2O in pentane to give **82d** (0.018 g, 25%) as a white solid. R_f (SiO_2/10% EtOAc in hexanes) = 0.23. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (s, 1H, Ar–H), 7.22 (d, 1H, Ar–H, J = 8.4 Hz), 7.10 (d, 1H, Ar–H, J = 8.4 Hz), 7.00 (d, 1H, Ar–H, J = 2.5 Hz), 6.95 (t, 1H, Ar–H, J = 7.9 Hz), 6.77 (d, 1H, Ar–H, J = 8.1

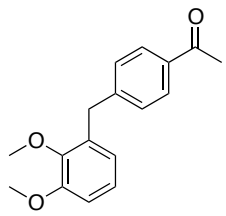
Hz), 6.74 (d, 1H, Ar–H, J = 7.7 Hz), 6.39 (d, 1H, Ar–H, J = 2.5 Hz), 4.11 (s, 2H, CH_2), 3.86 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.74 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.0, 147.4, 136.4, 135.7, 132.1, 129.0, 128.9, 123.9, 123.3, 122.9, 121.0, 110.6, 109.1, 100.8, 60.7, 56.0, 35.8, 33.0. HRMS (ESI) *m/z* calcd for $C_{18}H_{20}NO_2$ [M +H]$^+$: 282.1489, found 282.1503.

3-(2,3-Dimethoxybenzyl)thiophene (82e)



Synthesized from **82** (20.0 mg, 0.07 mmol), 3-thiopheneboronic acid (18.0 mg, 0.14 mmol), $Pd(OAc)_2$ (1.6 mg, 7.0 μmol), cyclohexyl JohnPhos (4.9 mg, 0.014 mmol), K_3PO_4 (0.0297 g, 0.14 mmol) in toluene (0.5 mL), and H_2O (2.5 μL, 0.14 mmol). After 16 h, TLC analysis of the reaction mixture showed incomplete consumption of **82**. Column chromatography was performed using 2% EtOAc in hexanes to give **82e** (7.2 mg, 44%) as a clear, liquid. R_f (SiO_2/10% EtOAc in hexanes) = 0.41. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (dd, 1H, Ar–H, J = 4.9, 3.0 Hz), 6.98 (t, 1H, Ar–H, J = 7.9 Hz), 6.95 (dd, 1H, Ar–H, J = 4.9, 1.1 Hz), 6.93 (m, 1H, Ar–H), 6.80 (dd, 1H, Ar–H, J = 8.2, 1.3 Hz), 6.76 (dd, 1H, Ar–H, J = 7.6, 1.4 Hz), 4.00 (s, 2H, CH_2), 3.86 (s, 3H, CH_3), 3.74 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.0, 147.2, 141.6, 134.8, 128.8, 125.4, 124.1, 122.5, 121.3, 110.8, 60.7, 55.9, 30.7. HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_2SNa$ [M + Na]$^+$: 257.0607, found 257.0594.

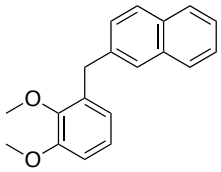
2',3'-Dimethoxy-4-acyldiphenylmethane (82f)



Synthesized from **82** (0.071 g, 0.25 mmol), *p*-acetylphenylboronic acid (0.135 g, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), cyclohexyl JohnPhos (17.5 mg, 0.05 mmol), K_3PO_4 (0.106 g, 0.5 mmol) in toluene (1.8 mL) and H_2O (9 μL, 0.5 mmol). After 14 h, TLC analysis of the reaction mixture showed complete consumption of **82**. Column chromatography was performed using 2% EtOAc in hexanes to give **82f** (13.6 mg, 72%) as a white solid. R_f (SiO_2/20% EtOAc in hexanes) = 0.31. ^{1}H NMR

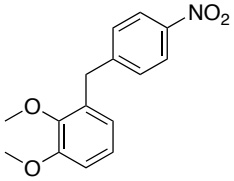
(500 MHz, $CDCl_3$): δ 7.86 (d, 2H, Ar–H, *J* = 8.1 Hz), 7.30 (d, 2H, Ar–H, *J* = 8.1 Hz), 6.99 (t, 1H, Ar–H, *J* = 7.9 Hz), 6.82 (d, 1H, Ar–H, *J* = 8.0 Hz), 6.73 (d, 1H, Ar–H, *J* = 7.5 Hz), 4.04 (s, 2H, CH_2), 3.86 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 2.56 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.9, 153.1, 147.4, 147.2, 135.3, 134.0, 129.1, 128.6, 124.1, 122.6, 111.3, 60.6, 55.9, 36.2, 36.6. HRMS (ESI) *m/z* calcd for $C_{17}H_{19}O_3$ $[M + H]^+$: 271.1329, found 271.1318.

2-(2,3-Dimethoxybenzyl)naphthalene (82g)



Synthesized from **82** (0.150 g, 0.7 mmol), 2-napthylboronic acid (0.170 g, 1.4 mmol), $Pd(OAc)_2$ (15.7 mg, 0.07 mmol), cyclohexyl JohnPhos (49.0 mg, 0.14 mmol), K_3PO_4 (0.2971 g, 1.4 mmol) in toluene (5.0 mL) and H_2O (25 μL, 1.4 mmol). After 2 h, TLC analysis of the reaction mixture showed complete consumption of **82**. Column chromatography was performed using 1% EtOAc in hexanes to give **82g** (0.123 g, 64%) as a white solid. R_f (SiO_2/20% EtOAc in hexanes) = 0.47. ^1H NMR (500 MHz, $CDCl_3$): δ 7.73-7.79 (m, 3H, Ar–H), 7.64 (s, 1H, Ar–H), 7.35-7.44 (m, 3H, Ar–H), 6.98 (t, 1H, Ar–H, *J* = 7.9 Hz), 6.81 (dd, 1H, Ar–H, *J* = 8.1, 0.7 Hz), 6.77 (d, 1H, Ar–H, *J* = 7.7 Hz), 4.17 (s, 2H, CH_2), 3.87 (s, 3H, CH_3), 3.73 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.0, 147.4, 138.9, 135.0, 133.8, 132.2, 128.0, 127.9, 127.7, 127.6, 127.2, 126.0, 125.3, 124.0, 122.8, 110.8, 60.7, 55.8, 36.1. HRMS (ESI) *m/z* calcd for $C_{19}H_{18}O_2Na$ $[M + Na]^+$: 301.1199, found 301.1227.

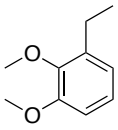
4-Nitro-2',3'-dimethoxydiphenylmethane (82h)



Synthesized from **82** (71.3 mg, 0.25 mmol), *p*-nitrophenylboronic acid (83.4 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), bis(2-diphenylphosphinophenyl)ether (DPEphos, 26.3 mg, 0.05 mmol), K_3PO_4 (0.106 g, 0.5 mmol) in toluene (1.8 mL) and H_2O (9 μL, 0.5 mmol). After 18 h, TLC analysis of the reaction mixture showed complete consumption of **82**. The reaction mixture was diluted

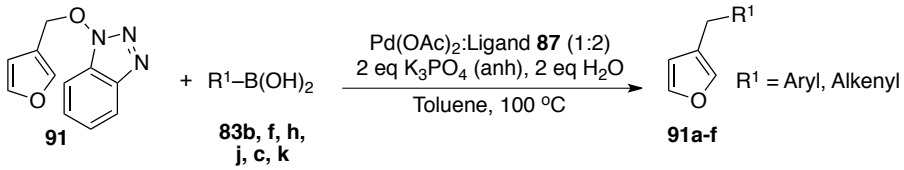
with ethyl acetate and washed with a 10% aqueous solution of sodium bisulfite. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. Column chromatography was performed using 10% Et_2O in *n*-pentane to give **82h** (45.5 mg, 67%) as a white solid. R_f (SiO_2/10% EtOAc in hexanes) = 0.20. ^1H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, 2H, Ar–H, J = 8.7 Hz), 7.36 (d, 2H, Ar–H, J = 8.7 Hz), 7.01 (t, 1H, Ar–H, J = 8.1 Hz), 6.84 (d, 1H, Ar–H, J = 8.2 Hz), 6.74 (d, 1H, Ar–H, J = 7.6 Hz), 4.07 (s, 2H, CH_2), 3.86 (s, 3H, CH_3), 3.71 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.2, 149.3, 147.4, 146.6, 133.2, 129.6, 124.2, 123.7, 122.5, 111.6, 60.6, 55.9, 36.3. HRMS (ESI) *m/z* calcd for $C_{15}H_{14}NO_4$ $[M - H]^+$: 272.0917, found 272.0649.

1-Ethyl-2,3-dimethoxybenzene (82i)

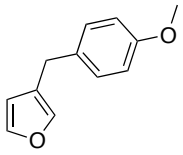


Following the general procedure, using **82** (0.143 g, 0.5 mmol), methylboronic acid (0.599 g, 1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), cyclohexyl JohnPhos (17.5 mg, 0.10 mmol), K_3PO_4 (0.212 g, 1.0 mmol), toluene (3.6 mL) and H_2O (20 μL, 1.0 mmol). After 14 h, TLC analysis of the reaction mixture showed complete consumption of **82**. Column chromatography was performed using 1% EtOAc in hexanes to give **82i** (36.9 mg, 45%) as a clear, liquid. R_f (SiO_2/10% EtOAc in hexanes) = 0.50. ^1H NMR (500 MHz, $CDCl_3$): δ 6.99 (t, 1H, Ar-H, J = 7.9 Hz), 6.80 (d, 1H, Ar-H, J = 7.6 Hz), 6.77 (d, 1H, Ar-H, J = 8.1 Hz), 3.86 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 2.67 (q, 2H, CH_2, J = 7.5 Hz), 1.21 (t, 3H, CH_3, J = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 147.1, 138.3, 124.0, 121.4, 110.1, 60.8, 55.9, 23.1, 15.3. HRMS (ESI) *m/z* calcd for $C_{10}H_{15}O_2$ $[M + H]^+$: 167.1067, found 167.1044.

[4.4.2] Suzuki cross-coupling of benzotriazolyl ether of 3-furanmethanol with various boronic acids

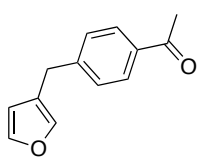


3-(*p*-Methoxybenzyl)furan (91a)[74]



Synthesized from **91** (15.1 mg, 0.07 mmol), 4-methoxyphenylboronic acid (21.3 mg, 0.14 mmol), $Pd(OAc)_2$ (1.6g, 7.0 μmol), cyclohexyl JohnPhos (4.9g, 0.014 mmol), K_3PO_4 (0.0297 g, 0.14 mmol) in toluene (0.5 mL), and H_2O (2.5 μL, 0.14 mmol). After 50 min, TLC analysis of the reaction mixture showed complete consumption of the starting material. Column chromatography was performed using 1% EtOAc in hexanes to give **91a** (12.5 mg, 95%) as a clear, oily liquid. R_f (SiO_2/10% EtOAc in hexanes) = 0.39. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (s, 1H, Ar–H), 7.20 (s, 1H, Ar–H), 7.13 (d, 2H, Ar–H, J = 8.4 Hz), 6.84 (d, 2H, Ar–H, J = 8.5 Hz), 6.23 (s, 1H, Ar–H), 3.79 (s, 3H, CH_3), 3.72 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.2, 143.2, 139.6, 132.6, 129.7, 124.9, 114.0, 111.4, 55.4, 30.5.

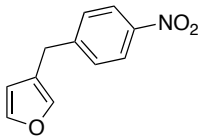
4-(3-Furaylmethyl)acetophenone (91b)



Synthesized from **91** (43.0 mg, 0.20 mmol), 4-acetylphenylboronic acid (65.6 mg, 0.40 mmol), $Pd(OAc)_2$ (4.5 mg, 0.2 mmol), cyclohexyl JohnPhos (14.0 mg, 0.04 mmol), K_3PO_4 (84.9 g, 0.4 mmol) in toluene (1.5 mL), and H_2O (7.2 μL, 0.40 mmol). After 19 h, TLC analysis of the reaction mixture showed incomplete consumption of **91**. Column chromatography was performed using 1% EtOAc in hexanes to give **91b** (25.7 mg, 64%) as a brown, oily liquid. R_f (SiO_2/10% EtOAc in hexanes) = 0.33. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, 2H, Ar-H, J = 8.2 Hz), 7.40 (s, 1H, Ar-H), 7.33 (d, 2H, Ar-

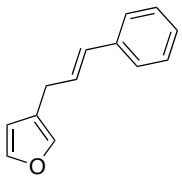
H, J = 8.2 Hz), 7.29 (s, 1H, Ar-H), 6.25 (s, 1H, Ar-H), 3.86 (s, 2H, CH_2), 2.61 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.9, 146.2, 143.5, 139.9, 135.6, 128.9, 128.8, 123.4, 111.2, 31.4, 26.8. HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O_2$ $[M + H]^+$: 201.0910, found 201.0910.

3-(4-Nitrobenzyl)furan (91c)[75]



Synthesized from **91** (15.1 mg, 0.07 mmol), 4-nitrophenylboronic acid (23.4 g, 0.14 mmol), $Pd(OAc)_2$ (1.6 mg, 7.0 μ mol), cyclohexyl JohnPhos (4.9 mg, 0.014 mmol), K_3PO_4 (29.7 mg, 0.14 mmol) in toluene (0.5 mL), and H_2O (2.5 μL, 0.14 mmol). After 19 h, TLC analysis of the reaction mixture showed incomplete consumption of **91**. Column chromatography was performed using 1% EtOAc in hexanes to give **91c** (7.9 mg, 54%) as a light yellow oil. R_f (SiO_2/10% EtOAc in hexanes) = 0.32. ^1H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, 2H, Ar-H, J = 8.6 Hz), 7.37 (s, 1H, Ar-H), 7.36 (d, 2H, Ar-H, J = 8.6 Hz), 7.26 (s, 1H, Ar-H), 6.21 (s, 1H, Ar-H), 3.88 (s, 2H, CH_2). ^{13}C NMR (500 MHz, $CDCl_3$): δ 148.2, 146.8, 143.7, 140.1, 129.5, 123.9, 122.7, 111.1, 31.3.

***trans-β*-(3-Furaylmethyl)-styrene (91d)**

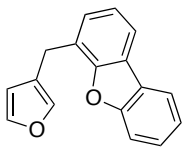


Synthesized from **91** (43.0 mg, 0.20 mmol), *trans-β*-styreneboronic acid (59.2 mg, 0.40 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), Cyclohexyl JohnPhos (14.0 mg, 0.040 mmol), K_3PO_4 (84.9 mg, 0.40 mmol) in toluene (1.5 mL), and H_2O (7.2 μL, 0.40 mmol). After 3.5 h, TLC analysis of the reaction mixture showed complete consumption of the starting material. Column chromatography was performed using 100% hexanes to give **91d** (14.8 g, 40%) as clear, oily liquid.

R_f (SiO_2/10% EtOAc in hexanes) = 0.47. ^1H NMR (500 MHz, $CDCl_3$): δ 7.39-7.28 (m, 6H, Ar–H), 7.21 (t, 1H, Ar–H, J = 7.2 Hz), 6.50 (d, 1H, CH, J = 15.7 Hz), 6.34 (m, 2H, Ar–H and CH), 3.36 (d, 2H, CH_2, J = 6.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2, 139.5, 137.6, 131.1, 128.7,

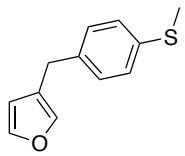
128.5, 127.3, 126.3, 123.4, 111.4, 28.7. HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O$ $[M + H]^+$: 185.0961, found 185.1056.

4-(3-Furanylmethyl)dibenzofuran (91e)



Synthesized from **91** (0.151 g, 0.7 mmol), dibenzfuran-4-boronic acid (0.297 g, 1.4 mmol), $Pd(OAc)_2$ (3.1 mg, 0.014 mmol), cyclohexyl JohnPhos (9.8 mg, 0.028 mmol), K_3PO_4 (0.297 g, 1.4 mmol) in toluene (5.0 mL) and H_2O (25 μL, 1.4 mmol). After 3.5 h, TLC analysis of the reaction mixture showed complete consumption of **91**. Column chromatography was performed using 1% EtOAc in hexanes to give **91e** (0.155 g, 89%) as a clear, oily liquid. R_f (SiO_2/10% EtOAc in hexanes) = 0.37. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, 1H, Ar–H, J = 7.7Hz), 7.83 (dd, 1H, Ar–H, J = 5.8, 2.8 Hz), 7.60 (d, 1H, Ar–H, J = 8.2 Hz), 7.47 (t, 1H, Ar–H, J = 8.2 Hz), 7.37-7.33 (m, 3H, Ar–H), 7.28 (m, 2H, Ar–H), 6.37 (s, 1H, Ar–H), 4.15 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 154.6, 143.1, 140.0, 127.4, 127.1, 124.6, 124.1, 123.2, 123.0, 122.8, 120.8, 118.8, 111.8, 111.6, 25.1. HRMS (ESI) *m/z* calcd for $C_{17}H_{13}O_2$ $[M + H]^+$: 249.0910, found 249.1445.

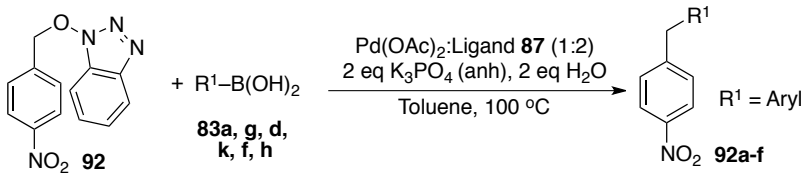
3-(4-(Methylthio)benzyl)furan (91f)



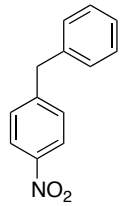
Synthesized from **91** (0.151 g, 0.7 mmol), 4-(methylthio)phenylboronic acid (0.235 g, 1.4 mmol), $Pd(OAc)_2$ (3.1 mg, 0.014 mmol), cyclohexyl JohnPhos (9.8 mg, 0.028 mmol), K_3PO_4 (0.297 g, 1.4 mmol), toluene (5.0 mL), and H_2O (25 μL, 1.4 mmol). After 1 h, TLC analysis of the reaction mixture showed complete consumption of the starting material. Column chromatography was performed using 1% EtOAc in hexanes to give **91f** (0.114 g, 80%) as a clear, oily liquid. R_f (SiO_2/10% EtOAc in hexanes) = 0.37. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (t, 1H, Ar–H, J = 1.5 Hz), 7.21 (m, 3H, Ar–H), 7.14 (d, 2H, Ar–H, J = 8.1 Hz), 6.23 (s, 1H, Ar–H), 3.73 (s, 2H, CH_2), 2.47 (s, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2, 139.6, 137.5, 135.9, 129.1, 127.2, 124.2, 111.2, 30.7, 16.3. HRMS (ESI) *m/z* calcd for $C_{12}H_{13}OS$ $[M + H]^+$: 205.0682, found 205.0503.

[4.4.3] Suzuki cross-coupling of the benzotriazolyl ether of p-nitrobenzyl alcohol with different boronic acids

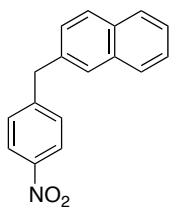


4-Nitrodiphenylmethane (92a)



Synthesized from **92** (0.1891 g, 0.7 mmol), phenylboronic acid (0.1707 g, 1.4 mmol), $Pd(OAc)_2$ (15.7 mg, 0.07 mmol), cyclohexyl JohnPhos (49.0 mg, 0.14 mmol), K_3PO_4 (0.2971 g, 1.4 mmol) in toluene (5.0 mL), and H_2O (25 µL, 1.4 mmol). After 1 h, TLC analysis of the reaction mixture showed complete consumption **92**. Column chromatography was performed using 1% EtOAc in hexanes to give **92a** (60.2 mg, 40%) as a clear, oily liquid. R_f (SiO_2/10% EtOAc in hexanes) = 0.37. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, 2H, Ar-H, J = 8.7 Hz), 7.35 (m, 4H, Ar-H), 7.28 (t, 1H, Ar–H, J = 7.3 Hz), 7.20 (d, 2H, Ar–H, J = 7.1 Hz), 4.11 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.0, 146.7, 139.3, 129.8, 129.1, 129.0, 126.9, 123.9, 41.9. HRMS (ESI) *m/z* calcd for $C_{13}H_{12}NO_2$ $[M + H]^+$: 214.0863, found 214.0861.

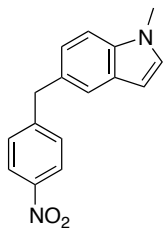
2-(4-Nitrobenzyl)naphthalene (92b)[76]



Synthesized from **92** (19.0 mg, 0.07 mmol), naphthalene-2-boronic acid (24.0 mg, 0.14 mmol), $Pd(OAc)_2$ (1.6 mg, 7.0 µmol), cyclohexyl JohnPhos (4.9 mg, 14.0 µmol), K_3PO_4 (29.7 mg, 0.14 mmol) in toluene (0.5 mL), and H_2O (2.5 µL, 0.14 mmol). After 1.5 h, TLC analysis of the reaction mixture showed complete consumption of

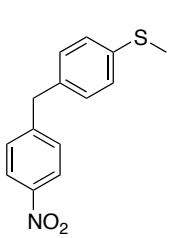
92. Column chromatography was performed using 1% EtOAc in hexanes to give **92b** (16.2 mg, 88%) as a white solid. R_f (SiO_2/20% EtOAc in hexanes) = 0.58. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (m, 2H, Ar–H), 7.78-7.83 (m, 3H, Ar–H), 7.64 (s, 1H, Ar–H), 7.51-7.45 (m, 2H, Ar–H), 7.38 (d, 2H, Ar–H, J = 8.8 Hz), 7.27 (dd, 1H, Ar–H, J = 8.4, 1.7 Hz), 4.24 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.8, 146.8, 136.8, 133.8, 132.5, 129.9, 128.7, 127.9, 127.7, 127.6, 127.3, 126.5, 126.0, 123.9, 42.1.

5-(4-Nitrobenzyl)-1-methyl-1*H*-indole (92c)



Synthesized from **92** (67.5 g, 0.25 mmol), *N*-methylindole-5-boronic acid (87.5 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), Cyclohexyl JohnPhos (17.5 mg, 0.05 mmol), K_3PO_4 (106.7 mg, 0.5 mmol) in toluene (1.8 mL), and H_2O (9 μL, 0.5 mmol). After 1.5 h, TLC analysis of the reaction mixture showed complete consumption of **92**. Column chromatography was performed using 1% EtOAc in hexanes to give **92c** (33.8 mg, 50%) as a yellowish solid. R_f (SiO_2/20% EtOAc in hexanes) = 0.27. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, 2H, Ar–H, J = 8.6 Hz), 7.43 (s, 1H, Ar–H), 7.36 (d, 2H, Ar–H, J = 8.4 Hz), 7.27 (d, 1H, Ar–H, J = 8.4 Hz), 7.06 (d, 1H, Ar–H, J = 2.9 Hz), 7.02 (d, 1H, Ar–H, J = 8.4 Hz), 6.44 (d, 1H, Ar–H, J = 2.9 Hz), 4.18 (s, 2H, CH_2), 3.79 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.3, 146.5, 135.9, 130.1, 129.7, 129.5, 129.0, 123.7, 122.9, 121.1, 109.7, 100.4, 42.0, 33.0. HRMS (ESI) *m/z* calcd for $C_{16}H_{15}N_2O_2$ $[M + H]^+$: 267.1128, found 267.1112.

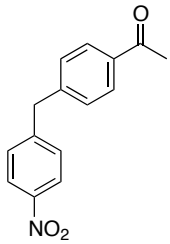
1-(Methylthio)-4(*p*-nitrobenzyl)benzene (92d)[77]



Synthesized from **92** (19.0 mg, 0.07 mmol), 4-(methylthio)phenylboronic acid (23.5 mg, 0.14 mmol), $Pd(OAc)_2$ (1.6 mg, 7.0 μmol), cyclohexyl JohnPhos (4.9 mg, 1.4 μmol), K_3PO_4 (29.7 mg, 0.14 mmol) in toluene (0.5 mL), and H_2O (2.5 μL, 0.14 mmol). After 16 h, TLC analysis of the reaction mixture showed

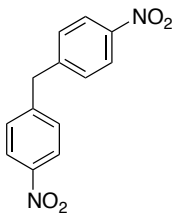
complete consumption of **92**. Column chromatography was performed using 5% EtOAc in hexanes to give **92d** (16.5 mg, 91%) as a light yellow liquid. R_f (SiO_2/10% EtOAc in hexanes) = 0.34. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, 2H, Ar–H, J = 8.5 Hz), 7.32 (d, 2H, Ar–H, J = 8.2), 7.21 (d, 2H, Ar–H, J = 8.0 Hz), 7.09 (d, 2H, Ar–H, J = 8.0 Hz), 4.03 (s, 2H, CH_2), 2.47 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.9, 137.0, 136.2, 129.8, 129.6, 127.3, 127.2, 124.0, 41.3, 16.1.

4-Acetyl-4'-nitrodiphenylmethane (92e)



Synthesized from **92** (67.5 mg, 0.25 mmol), *p*-acetylphenylboronic acid (0.1351 g, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), cyclohexyl JohnPhos (17.5g, 0.05 mmol), K_3PO_4 (0.106 g, 0.5 mmol) in toluene (1.8 mL), and H_2O (9 μL, 0.5 mmol). After 14 h, TLC analysis of the reaction mixture showed complete consumption of **92**. Column chromatography was performed using 5% EtOAc in hexanes to give **92e** (0.0325 g, 51%) as an off white solid. R_f (SiO_2/20% EtOAc in hexanes) = 0.22. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, 2H, Ar–H, J = 8.5), 7.94 (d, 2H, Ar–H, J = 8.2 Hz), 7.36 (d, 2H, Ar-H, J = 8.5 Hz), 7.29 (d, 2H, Ar–H, J = 8.4 Hz), 4.16 (s, 2H, CH_2), 2.6 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.5, 147.8, 147.2, 144.8, 136.3, 129.9, 129.4, 129.1, 124.1, 41.9, 26.7. HRMS (ESI) *m/z* calcd for $C_{15}H_{14}NO_3$ $[M + H]^+$: 256.0968, found 256.0969.

Bis(4-nitrophenyl)methane (92f)



Synthesized from **92** (67.5 mg, 0.25 mmol), *p*-nitrophenylboronic acid (83.4 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), DPEphos (17.5 mg, 0.05 mmol), K_3PO_4 (0.106 g, 0.5 mmol) in toluene (1.8 mL), and H_2O (9 μL, 0.5 mmol). After 18 h, TLC analysis of the reaction mixture showed complete consumption of **92**. The crude material was purified by silicagel column chromatography (200-

300 mesh) using 10% toluene in *n*-pentane as eluting solvent. The product was rechromatographed on a silica gel column using 10% Et_2O in *n*-pentane to give **92f** (0.0428 g, 66%) as a light yellow, crystalline solid. R_f (SiO_2/20% EtOAc in hexanes) = 0.26. ^1H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, 4H, Ar-H, J = 8.5 Hz), 7.34 (d, 4H, Ar-H, J = 8.5 Hz), 4.19 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.1, 146.8, 130.0, 124.3, 41.6. HRMS (ESI) *m/z* calcd for $C_{13}H_9N_2O_4$ $[M - H]^+$: 257.0557, found 257.0078.

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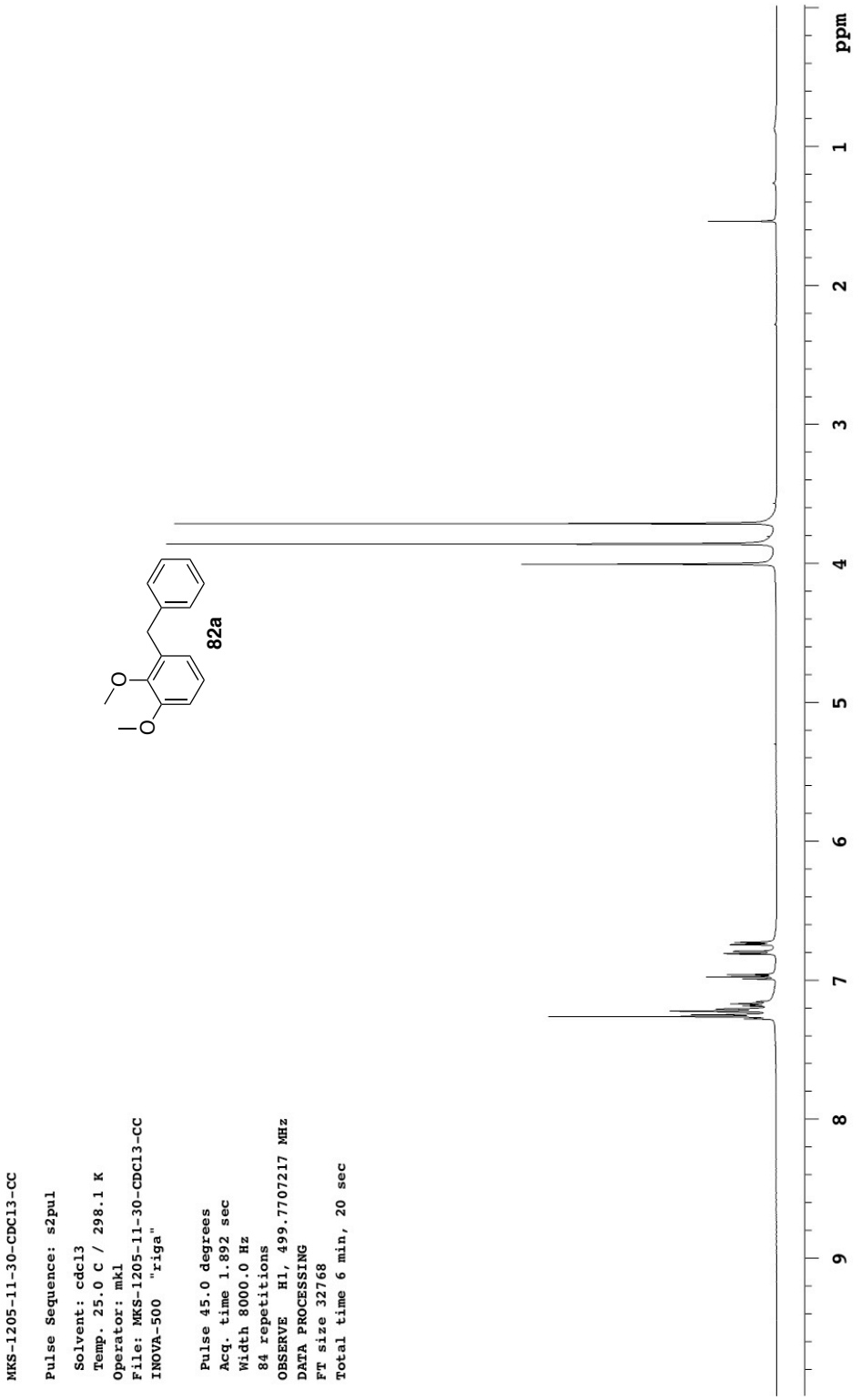
APPENDIX IV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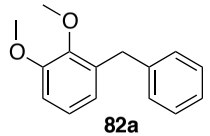
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-11-30-CDCl3-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
84 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 20 sec
82a
9
8
7
6
5
4
3
2
1
ppm

MKS-1205-11-30-13C-CDCl3-CC

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-11-30-13C-CDCl3-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
9964 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 294 hr, 58 min, 21 sec



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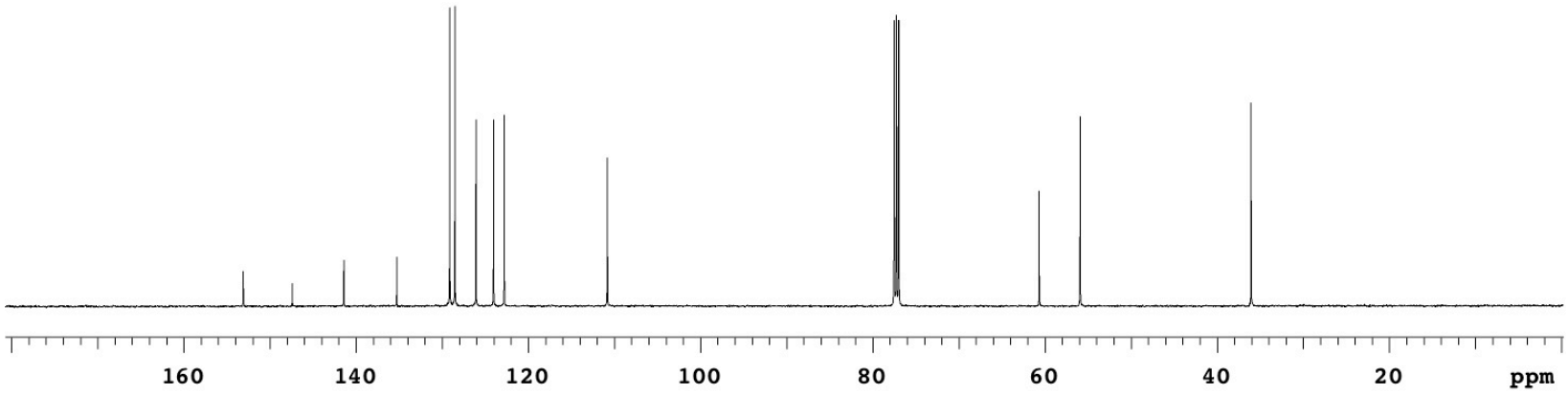

MKS-1205-11-31-CDCl3-CC

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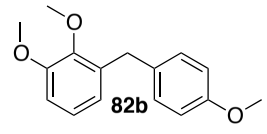
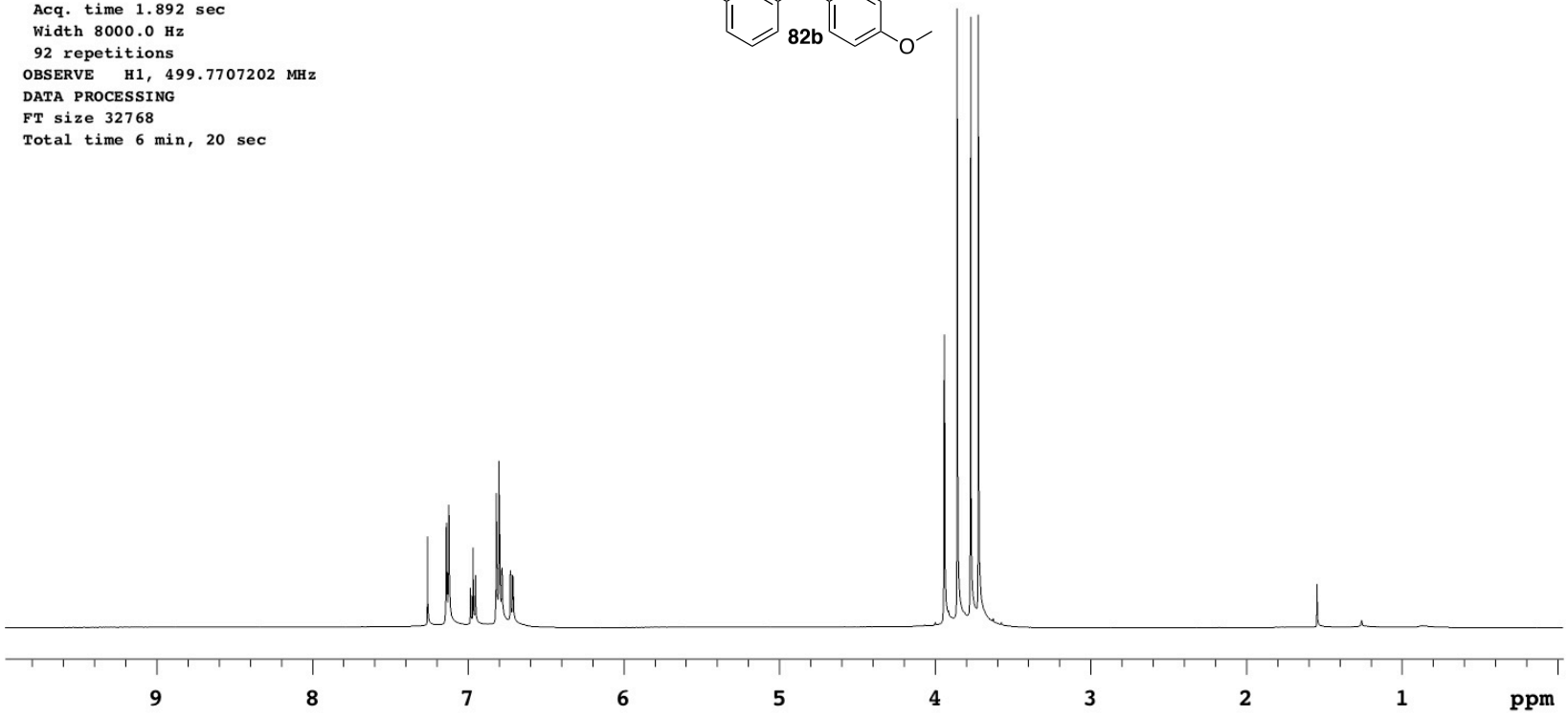
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-11-31-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
92 repetitions
OBSERVE H1, 499.7707202 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 20 sec



82b



MKS-1205-11-31-13C-CDCl3-CC

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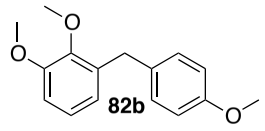
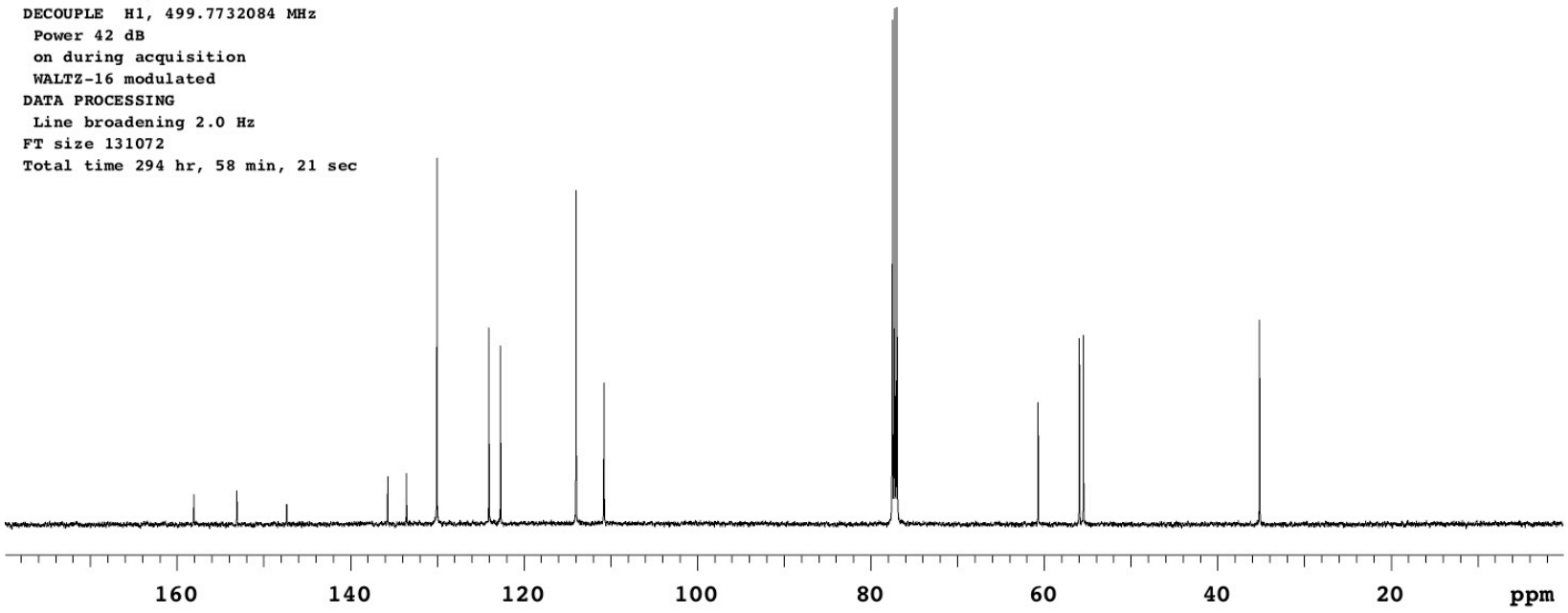
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-11-31-13C-CDCl3-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
10244 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 294 hr, 58 min, 21 sec





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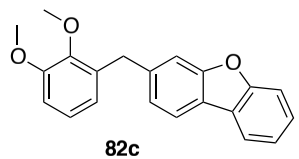
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-11-35-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
68 repetitions
OBSERVE H1, 499.7707095 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 20 sec



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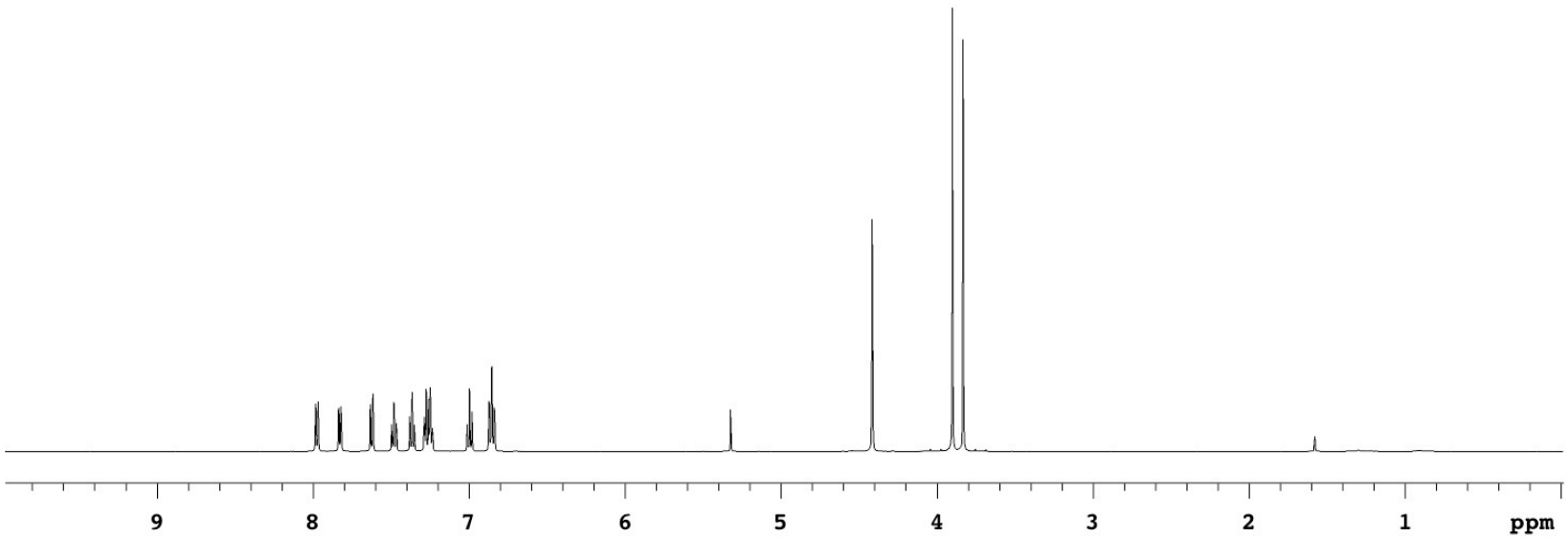
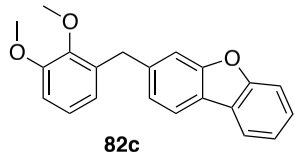


MKS-1205-11-35-CDCl3-13C-CC-rep

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-11-35-CDCl3-13C-CC-rep
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
80 repetitions
OBSERVE C13, 125.6674393 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 19 hr, 9 min, 10 sec



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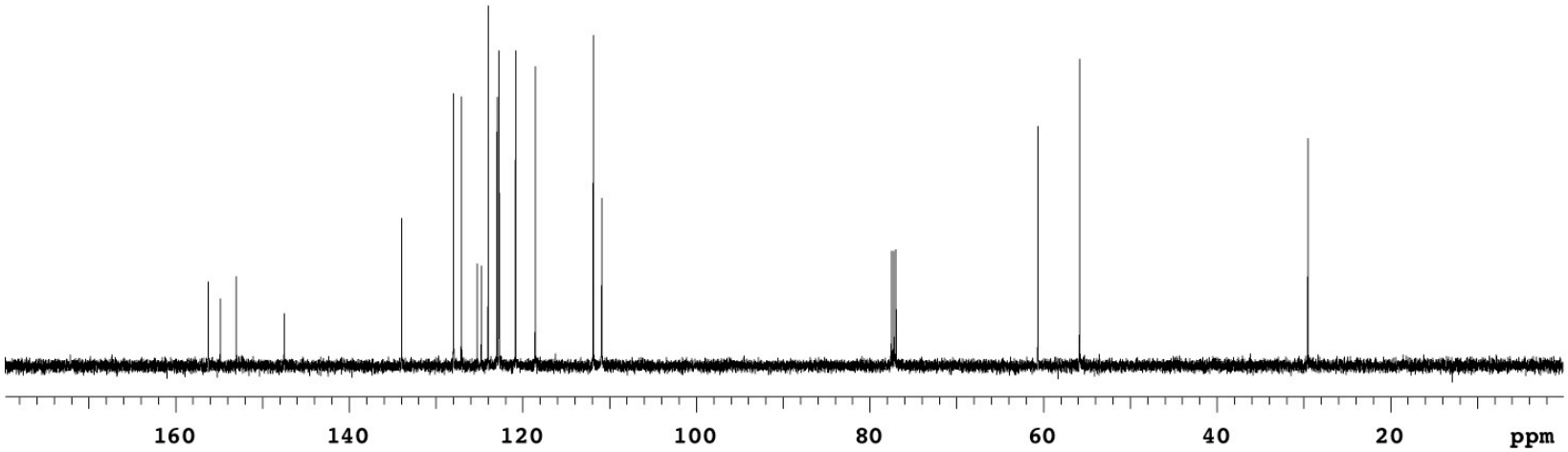
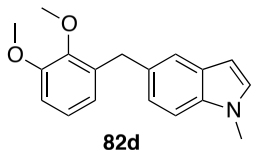


MKS-1205-13-67-CDCl3-2ndFrac-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-67-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
108 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



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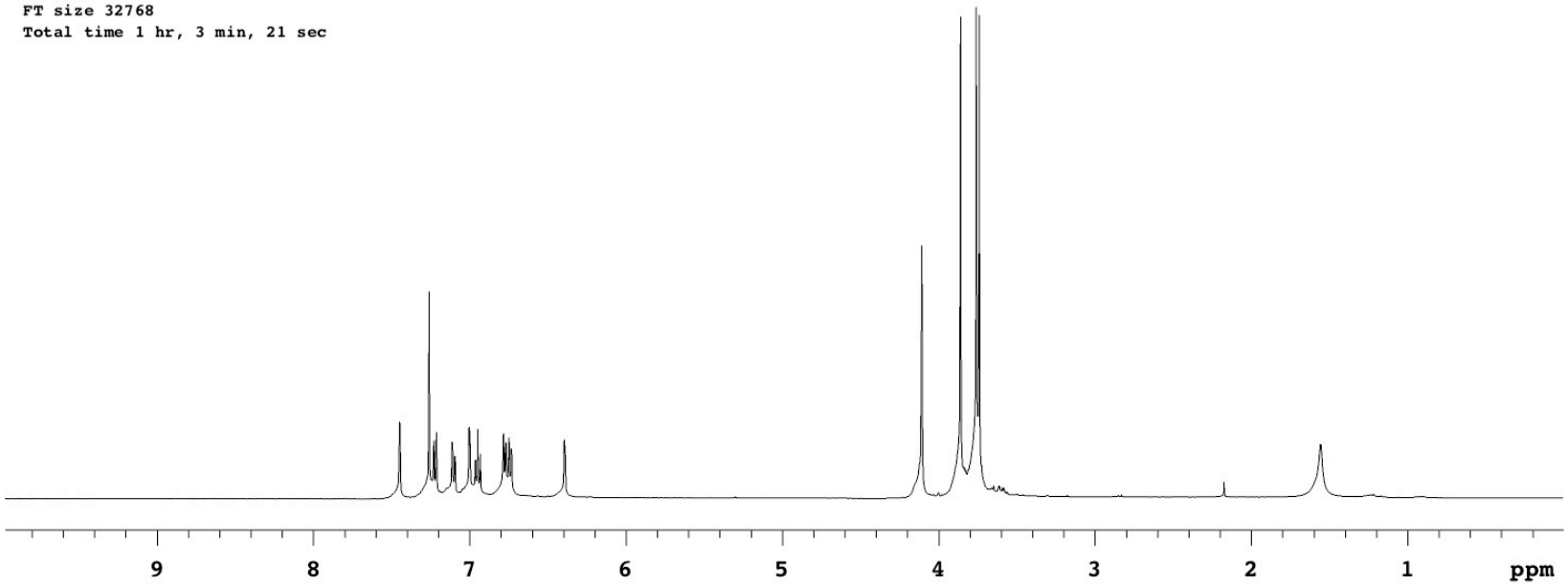
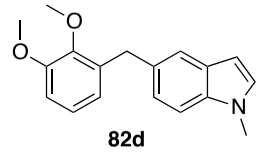


MKS-1205-13-67-CDCl3-13C-2ndFrac-CC

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-67-CDCl3-13C-2ndFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
32500 repetitions
OBSERVE C13, 125.6674187 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



82d

MKS-1205-09-35-CDCl3-2ndFrac-CC

Pulse Sequence: s2pul

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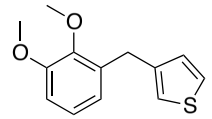
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-09-35-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
56 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



82e

MKS-1205-09-35-CDCl3-13C-2ndFrac-CC

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-09-35-CDCl3-13C-2ndFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
16344 repetitions
OBSERVE C13, 125.6674202 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
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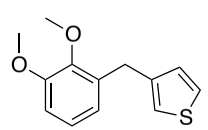


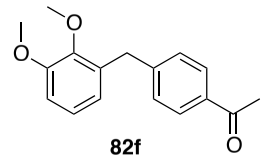
82e

MKS-1205-13-59-A-CDCl3-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-59-A-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
52 repetitions
OBSERVE H1, 499.7707214 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



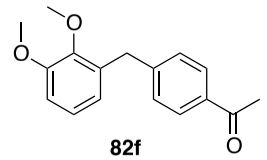
82f

MKS-1205-13-59-CDCl3-13C-A-CC

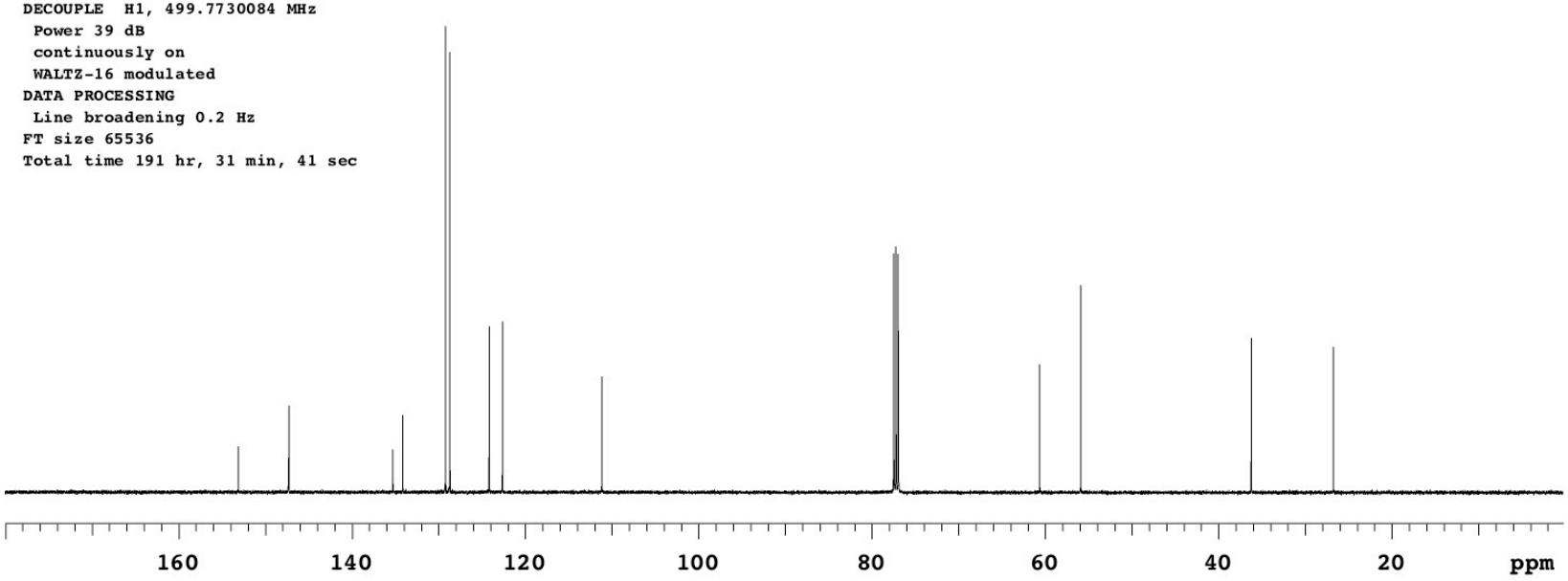
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-59-CDCl3-13C-A-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
2900 repetitions
OBSERVE C13, 125.6674225 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



82f

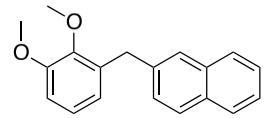


MKS-1205-12-10-CDCl3-2ndFrac-CC

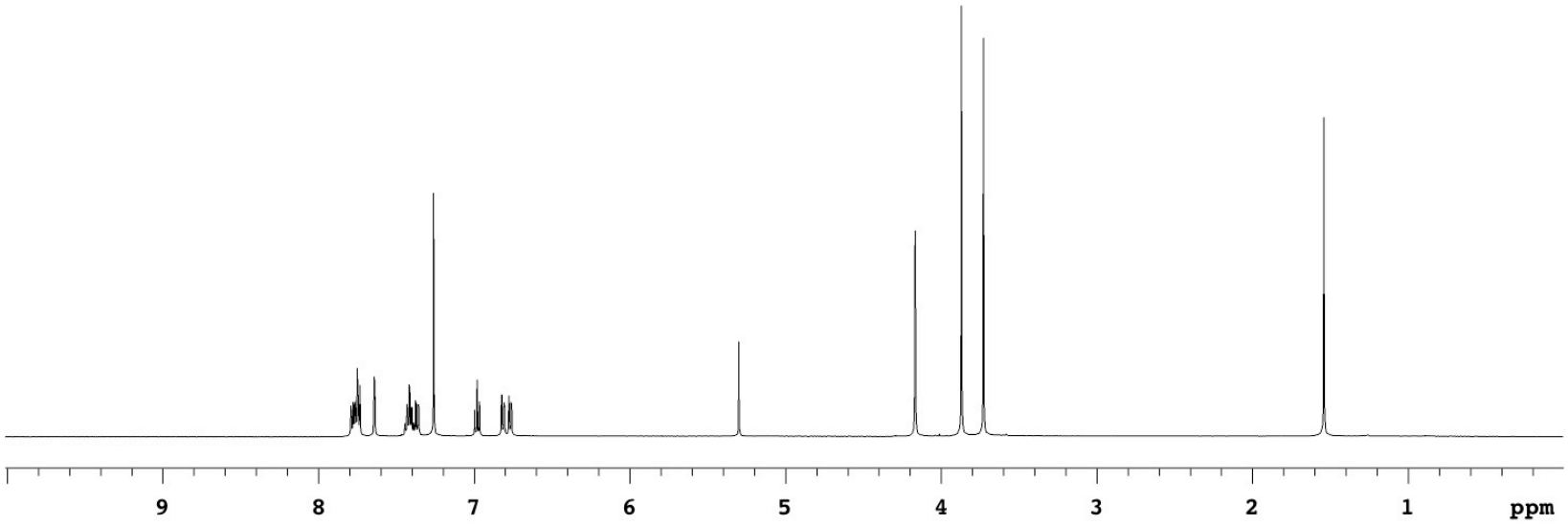
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-12-10-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
40 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 20 sec



82g

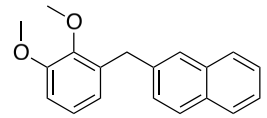


MKS-1205-12-10-CDCl3-13C-2ndFRAC-CC

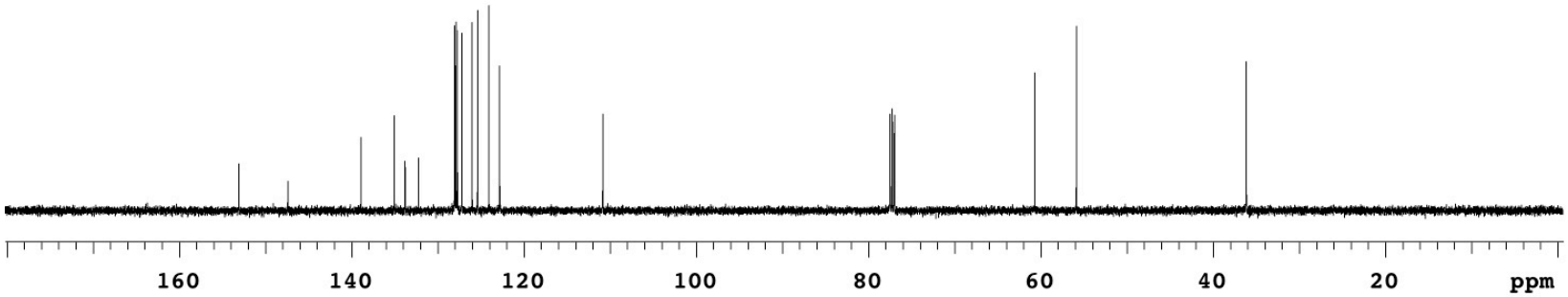
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-12-10-CDCl3-13C-2ndFRAC-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
148 repetitions
OBSERVE C13, 125.6674324 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 19 hr, 9 min, 10 sec



82g

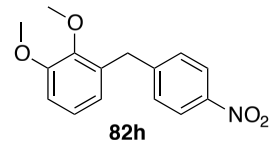


MKS-1205-13-68-CDCl3-2ndFrac-NaBiSulf

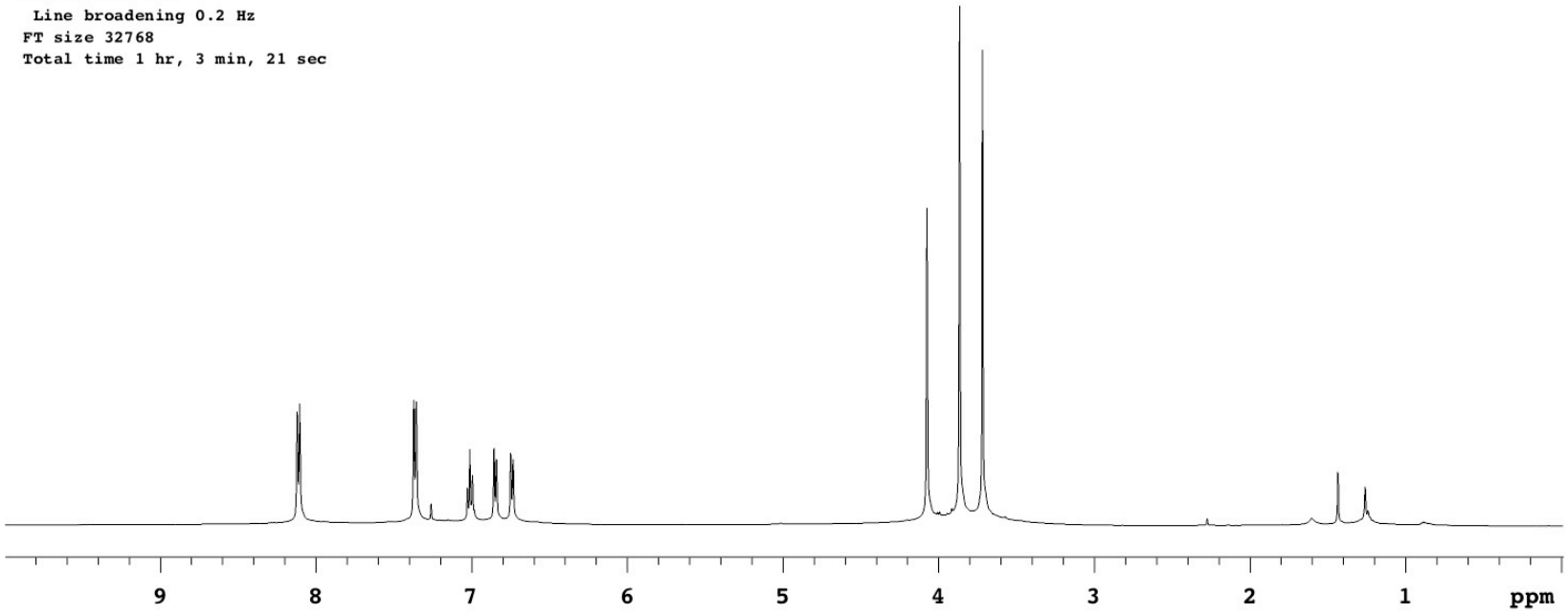
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-68-CDCl3-2ndFrac-NaBiSulf
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
80 repetitions
OBSERVE H1, 499.7707192 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



82h

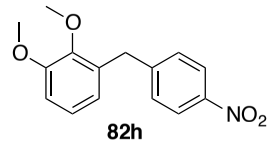


MKS-1205-13-68-CDCl3-13C-2ndFrac-NaBiSulf

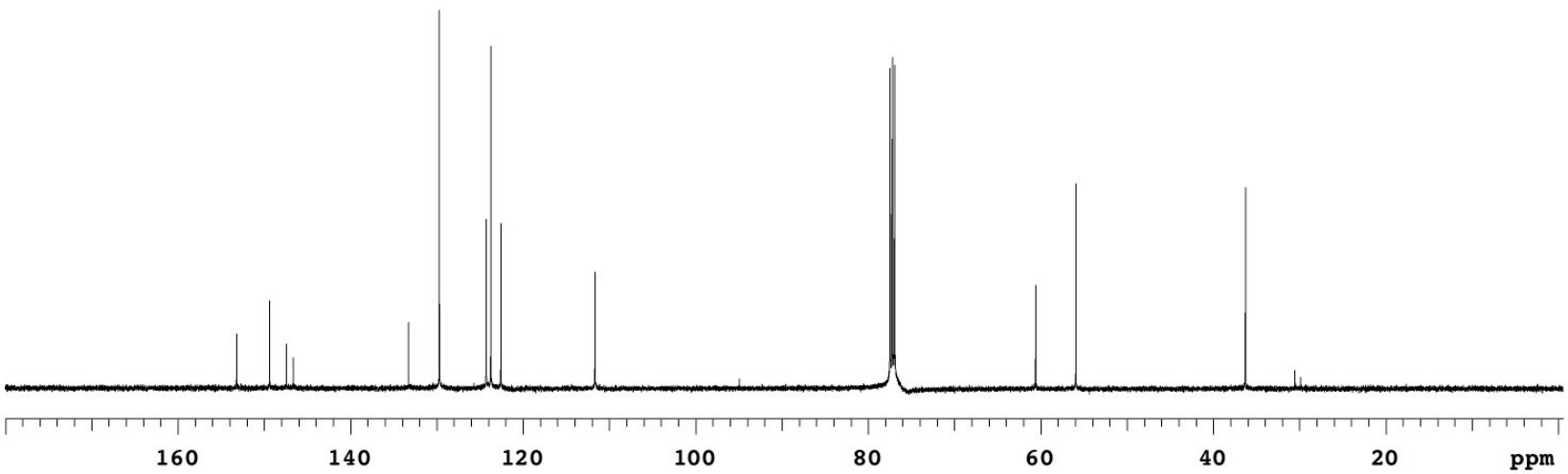
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-68-CDCl3-13C-2ndFrac-NaBiSulf
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
13336 repetitions
OBSERVE C13, 125.6674225 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 19 hr, 9 min, 10 sec



82h

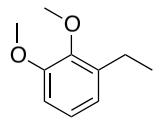


MKS-1205-12-22-CDCl3-2ndfrac-A-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-12-22-CDCl3-2ndfrac-A-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
100 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



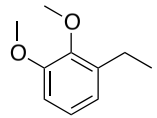
82i

MKS-1205-12-22-CDCl3-13C-2ndFrac-A-CC

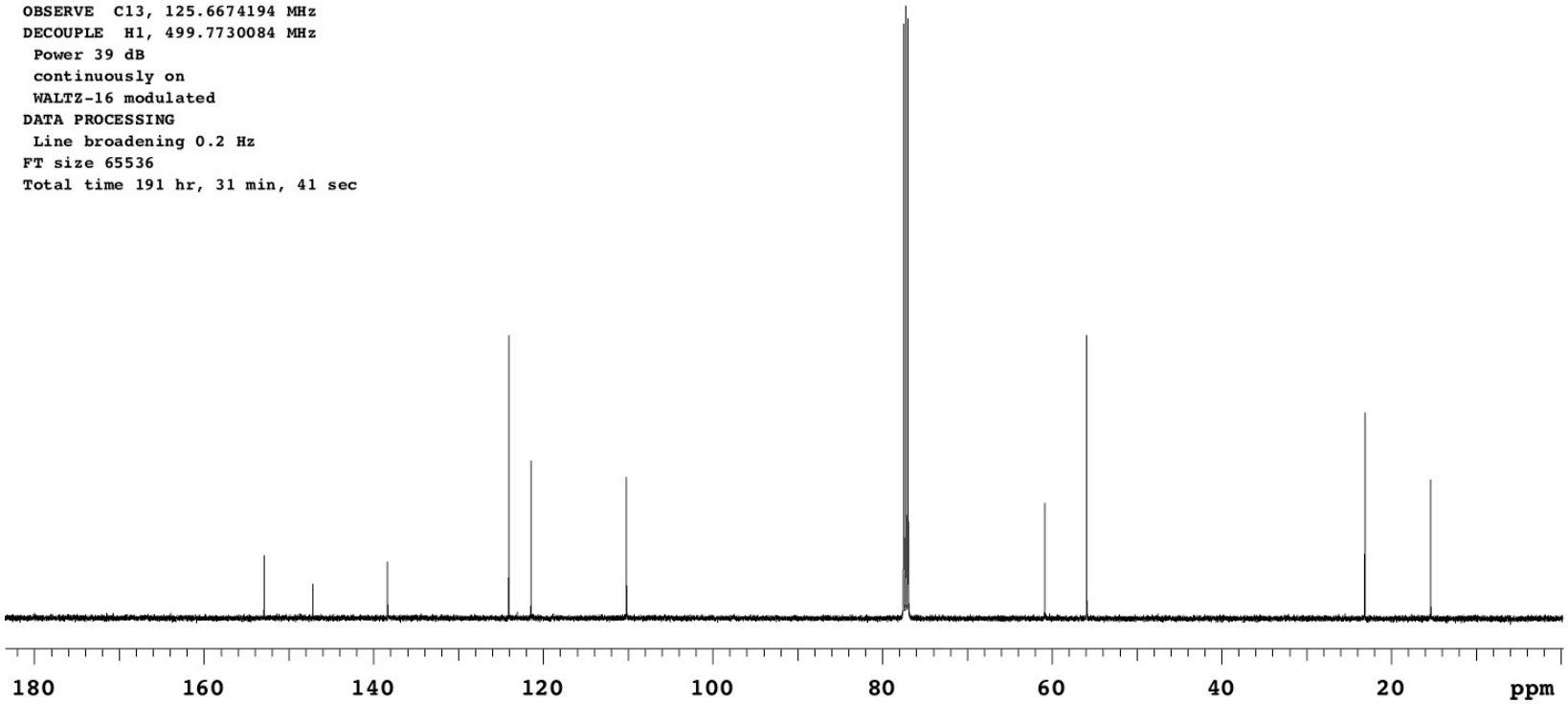
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-12-22-CDCl3-13C-2ndFrac-A-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
11108 repetitions
OBSERVE C13, 125.6674194 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



82i

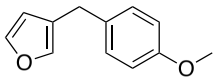


MKS-1205-13-81-CDCl3-2ndFrac-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-81-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
60 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



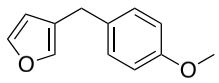
91a

MKS-1205-13-81-CDCl3-13C-2ndFrac-CC

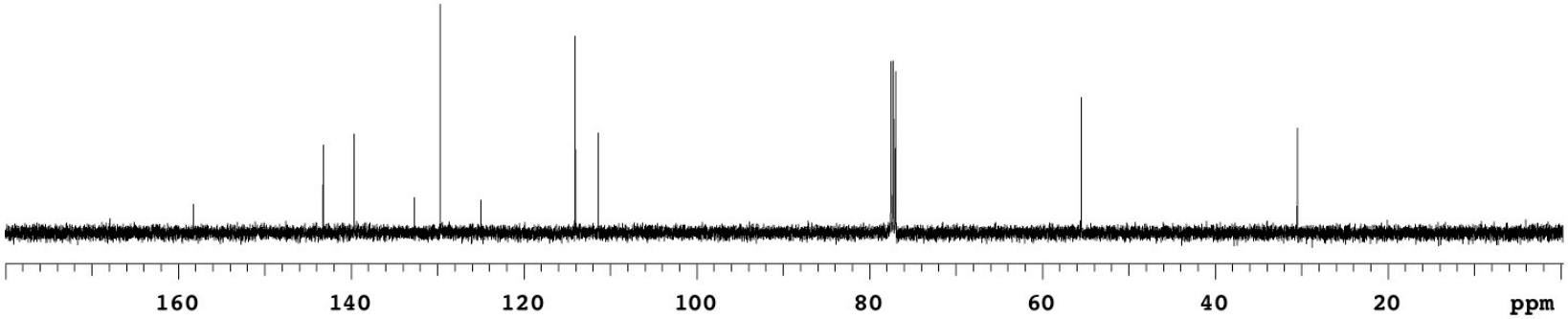
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-81-CDCl3-13C-2ndFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
120 repetitions
OBSERVE C13, 125.6674213 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



91a

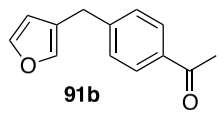


MKS-1205-13-77-CDCl3-2ndFrac-B-CC

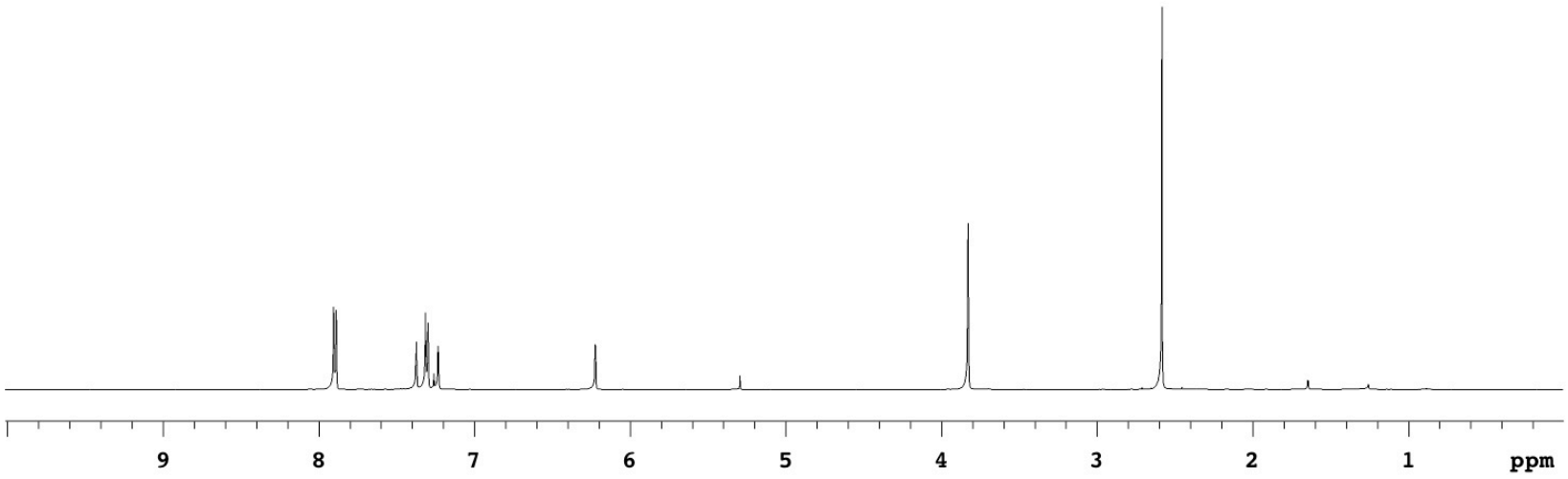
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-77-CDCl3-2ndFrac-B-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
40 repetitions
OBSERVE H1, 499.7707207 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



91b

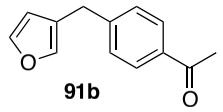


MKS-1205-13-77-CDCl3-13C-2ndFrac-B-CC

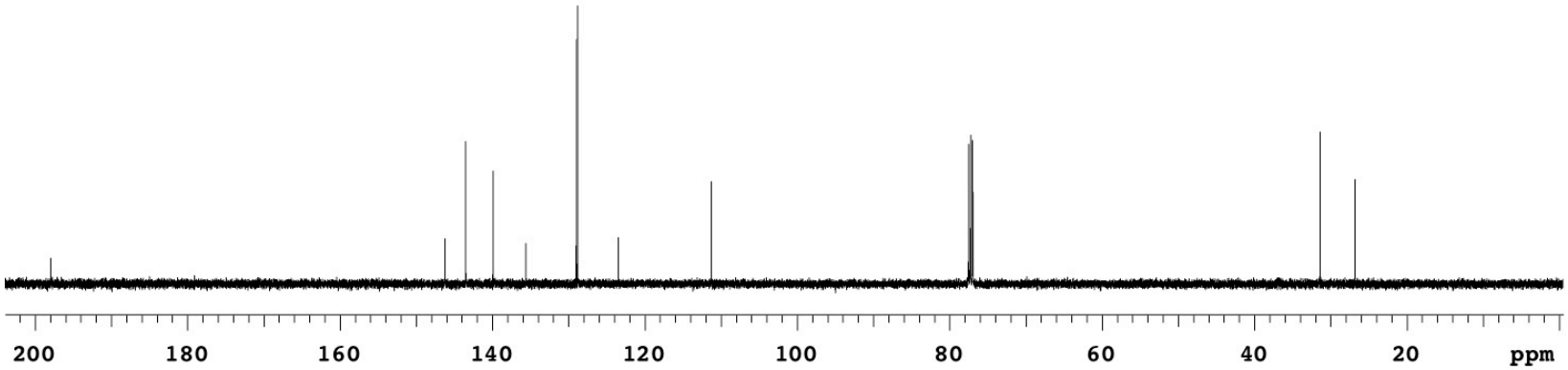
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-77-CDCl3-13C-2ndFrac-B-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
368 repetitions
OBSERVE C13, 125.6674223 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 191 hr, 31 min, 44 sec



91b

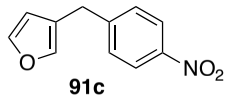


MKS-1205-09-50-CDCl3-1stFrac-CC

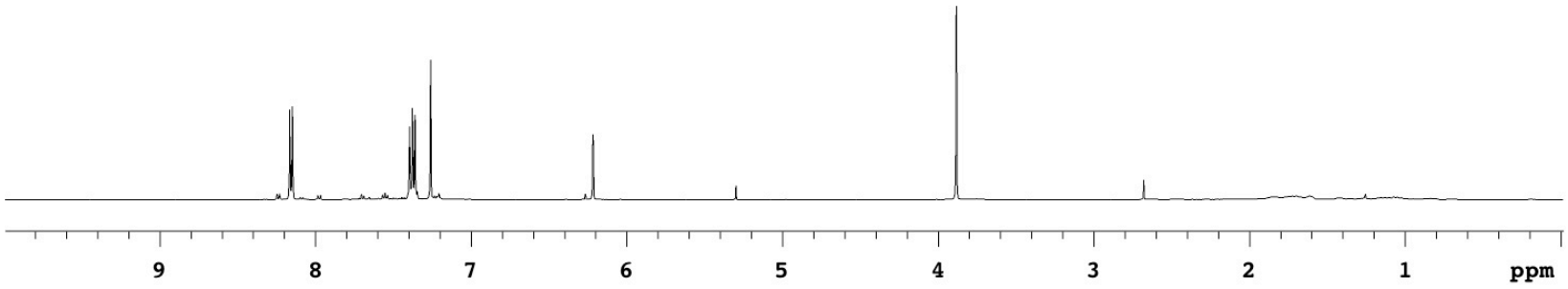
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-09-50-CDCl3-1stFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
56 repetitions
OBSERVE H1, 499.7707207 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



91c

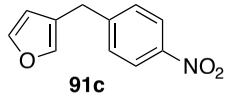


MKS-1205-09-50-CDCl3-13C-1stFrac-CC

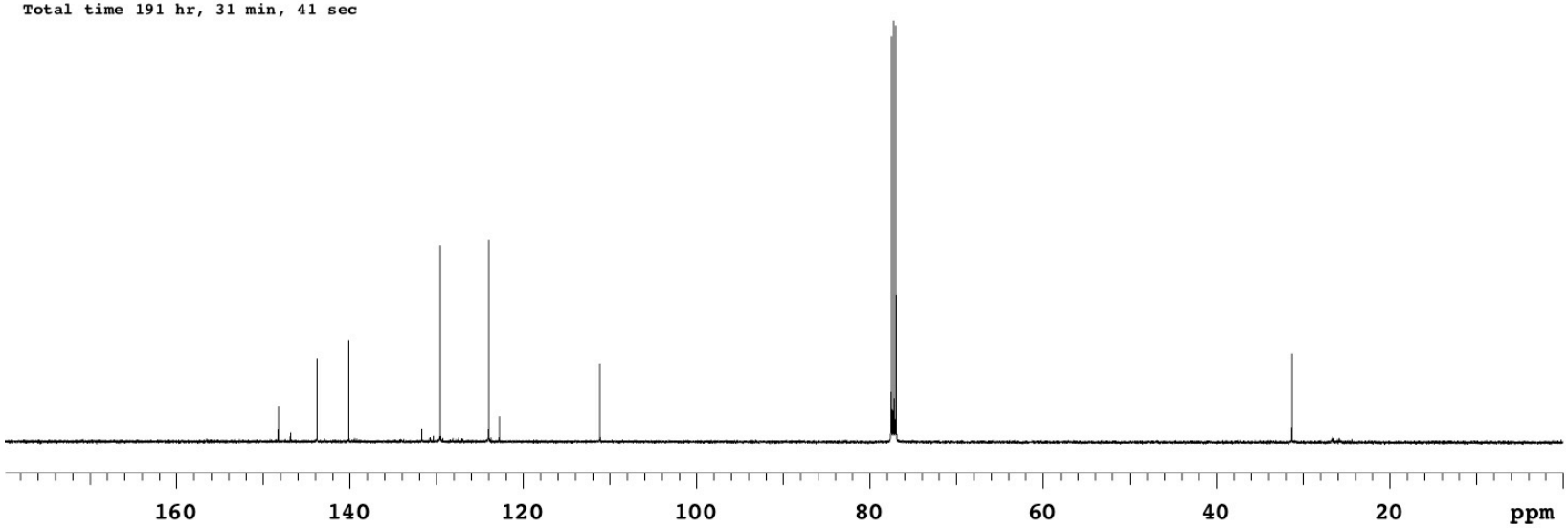
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-09-50-CDCl3-13C-1stFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
14392 repetitions
OBSERVE C13, 125.6674202 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



91c

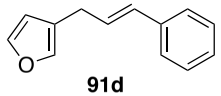


MKS-1205-12-19-CDCl3-1stFrac-rep-CC

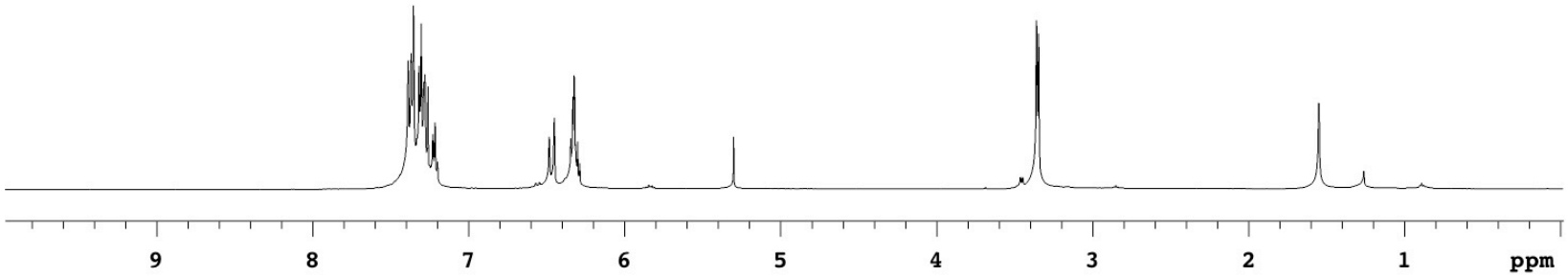
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-12-19-CDCl3-1stFrac-rep-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
124 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



91d

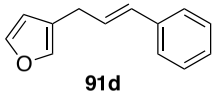


MKS-1205-12-19-CDCl3-13C-1stFrac-rep-CC

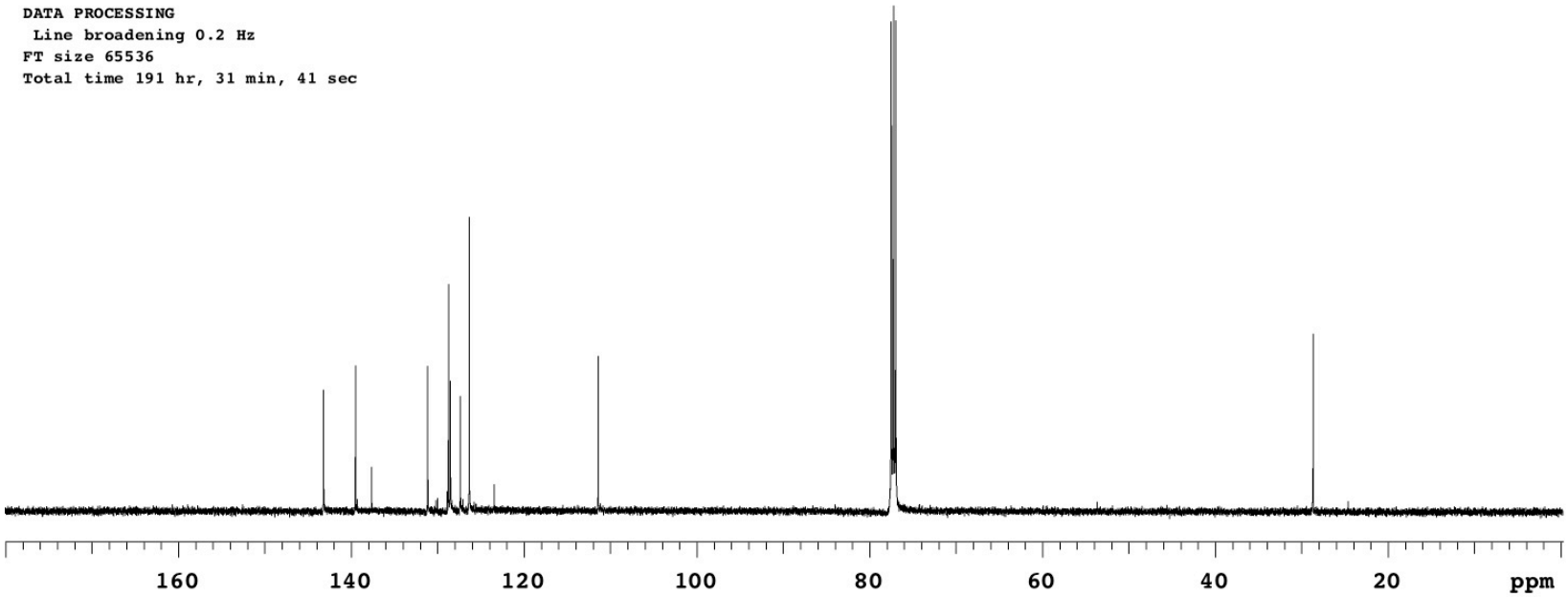
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-12-19-CDCl3-13C-1stFrac-rep-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
10024 repetitions
OBSERVE C13, 125.6674194 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



91d

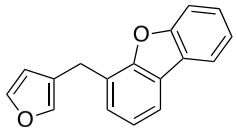


MKS-1205-12-18-CDCl3-CC-2ndFrac

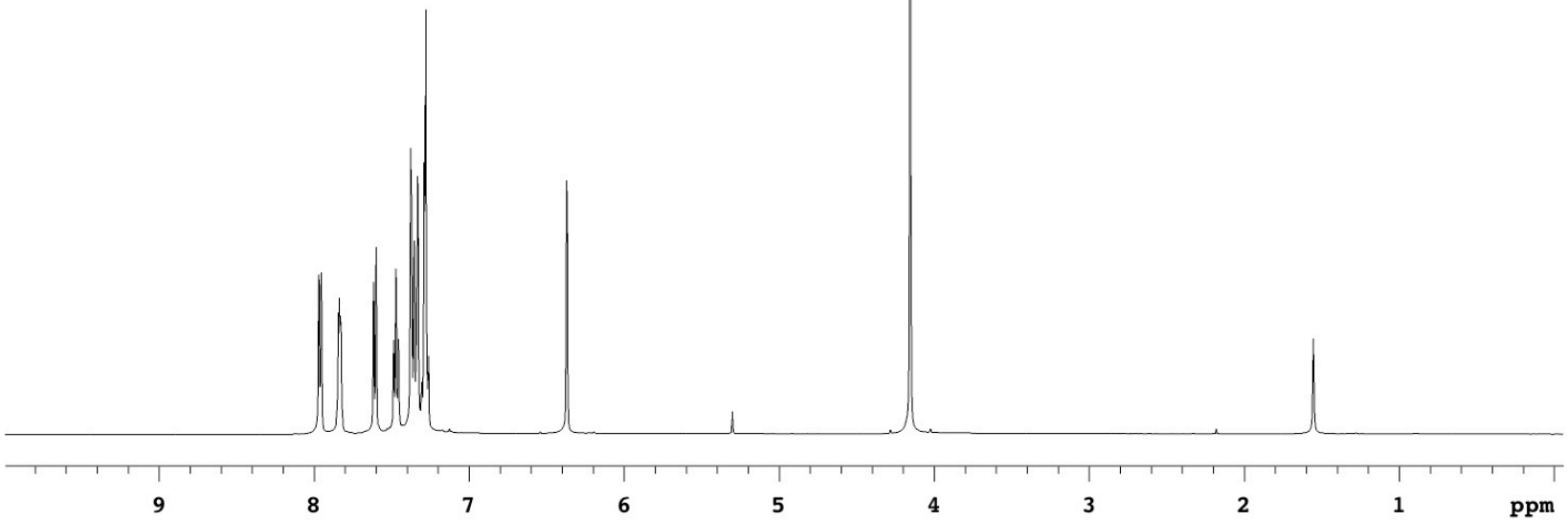
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-12-18-CDCl3-CC-2ndFrac
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
60 repetitions
OBSERVE H1, 499.7707207 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



91e

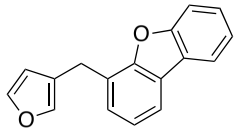


MKS-1205-12-18-CDCl3-13C-2ndFRAC-CC

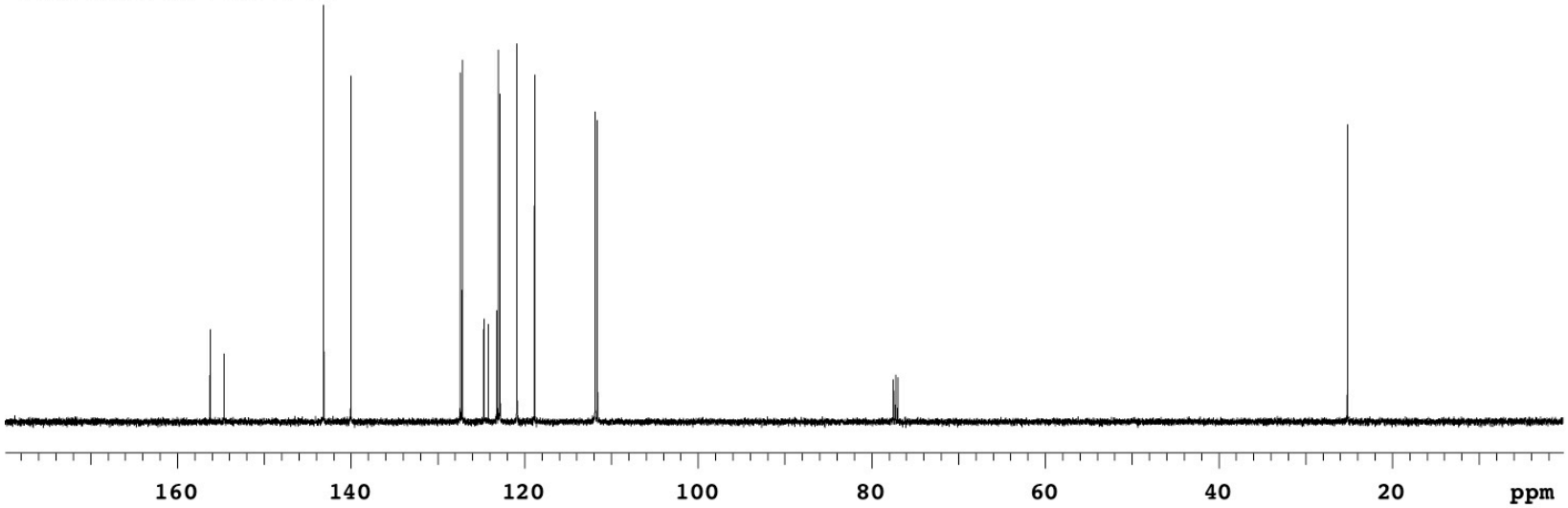
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-12-18-CDCl3-13C-2ndFRAC-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
60 repetitions
OBSERVE C13, 125.6674461 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 19 hr, 9 min, 10 sec



91e

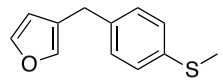


MKS-1205-12-11-CDCl3-CC-2ndFrac

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-12-11-CDCl3-CC-2ndFrac
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
76 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



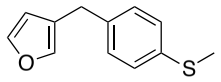
91f

MKS-1205-12-11-13C-CDCl3-2ndFrac-CC

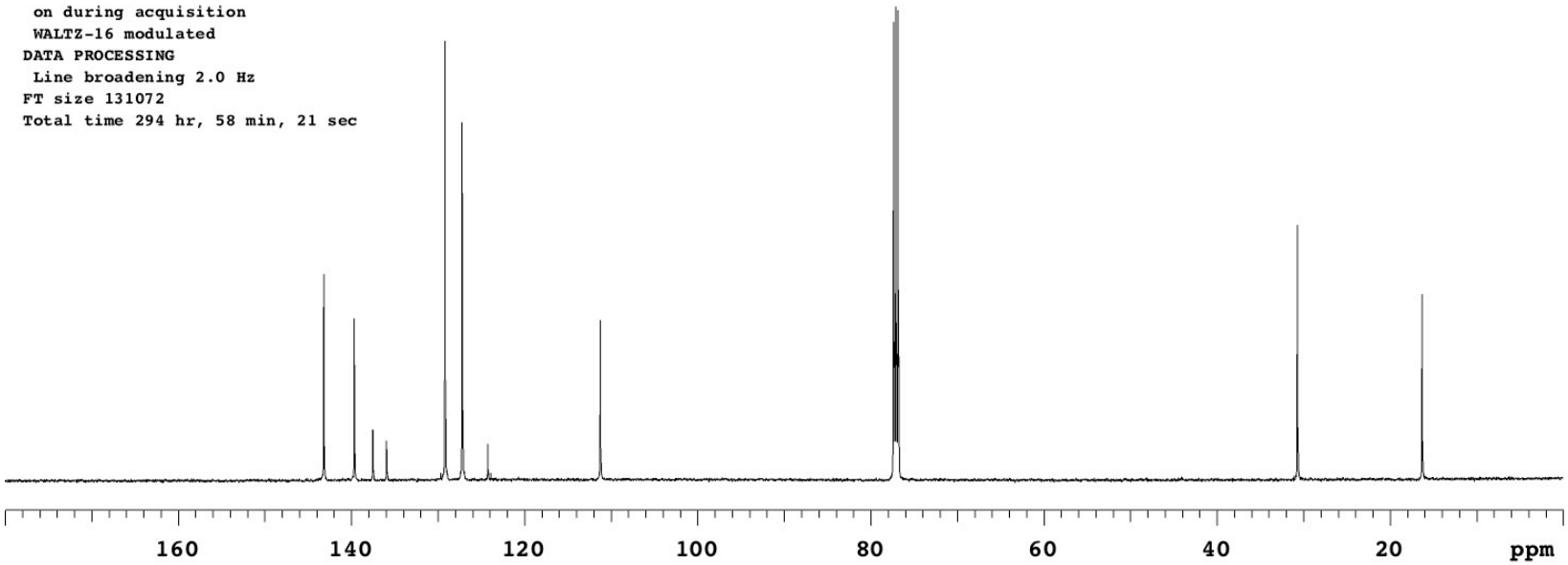
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-12-11-13C-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
42620 repetitions
OBSERVE C13, 125.6674360 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 294 hr, 58 min, 21 sec



91f

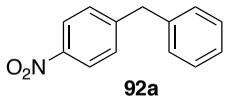


MKS-1205-11-38-A-CDCl3-CC

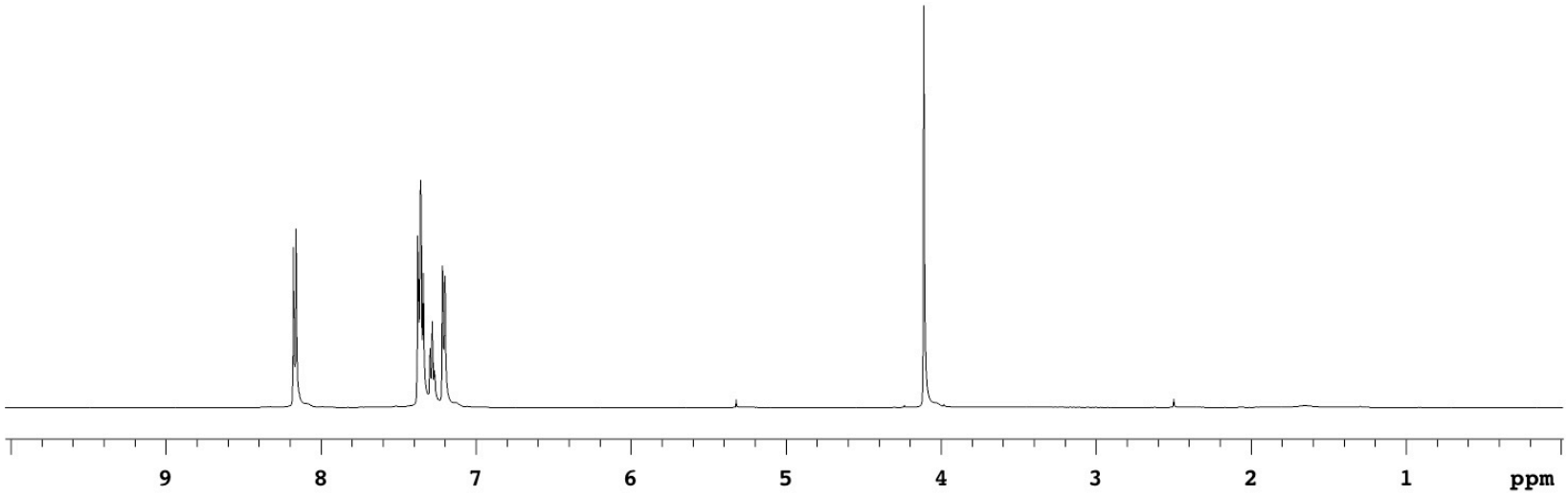
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-11-38-A-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
52 repetitions
OBSERVE H1, 499.7707095 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



92a

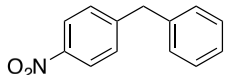


MKS-1205-11-38-CDCl3-13C-A-CC

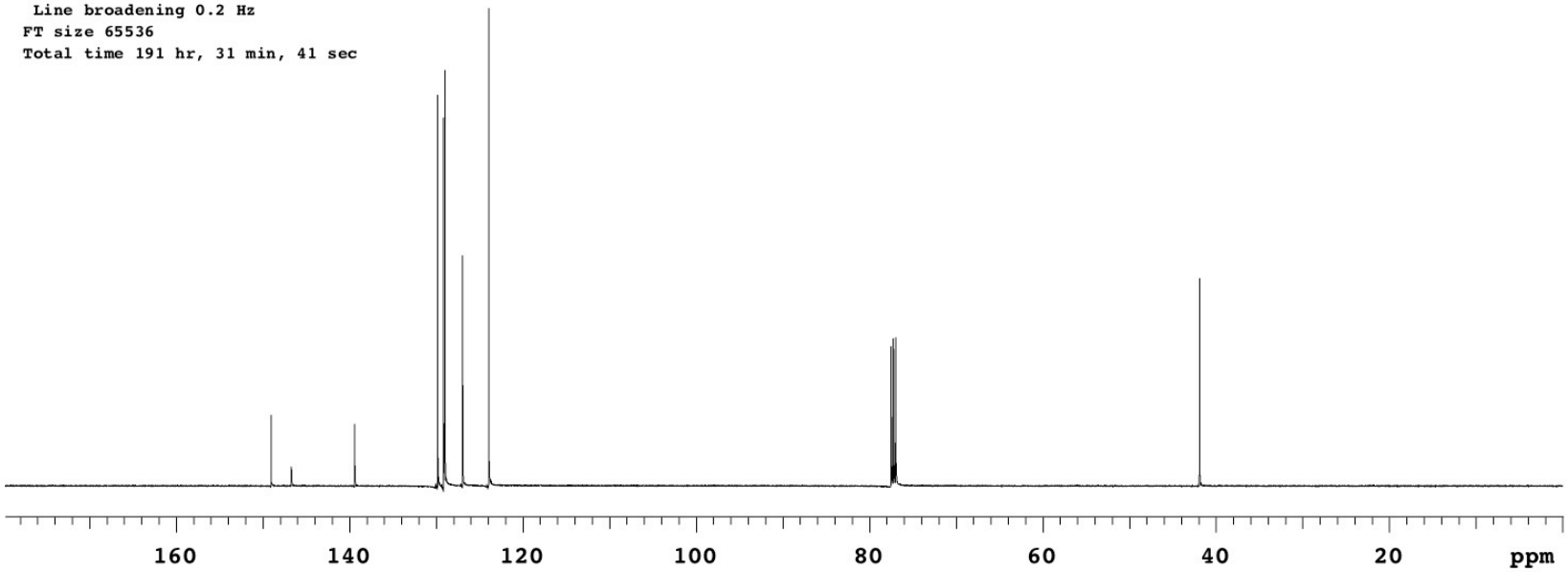
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-11-38-CDCl3-13C-A-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
11768 repetitions
OBSERVE C13, 125.6674255 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



92a

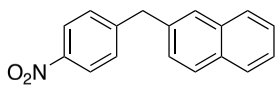


MKS-1205-09-36-CDCl3-3rdFrac-CC

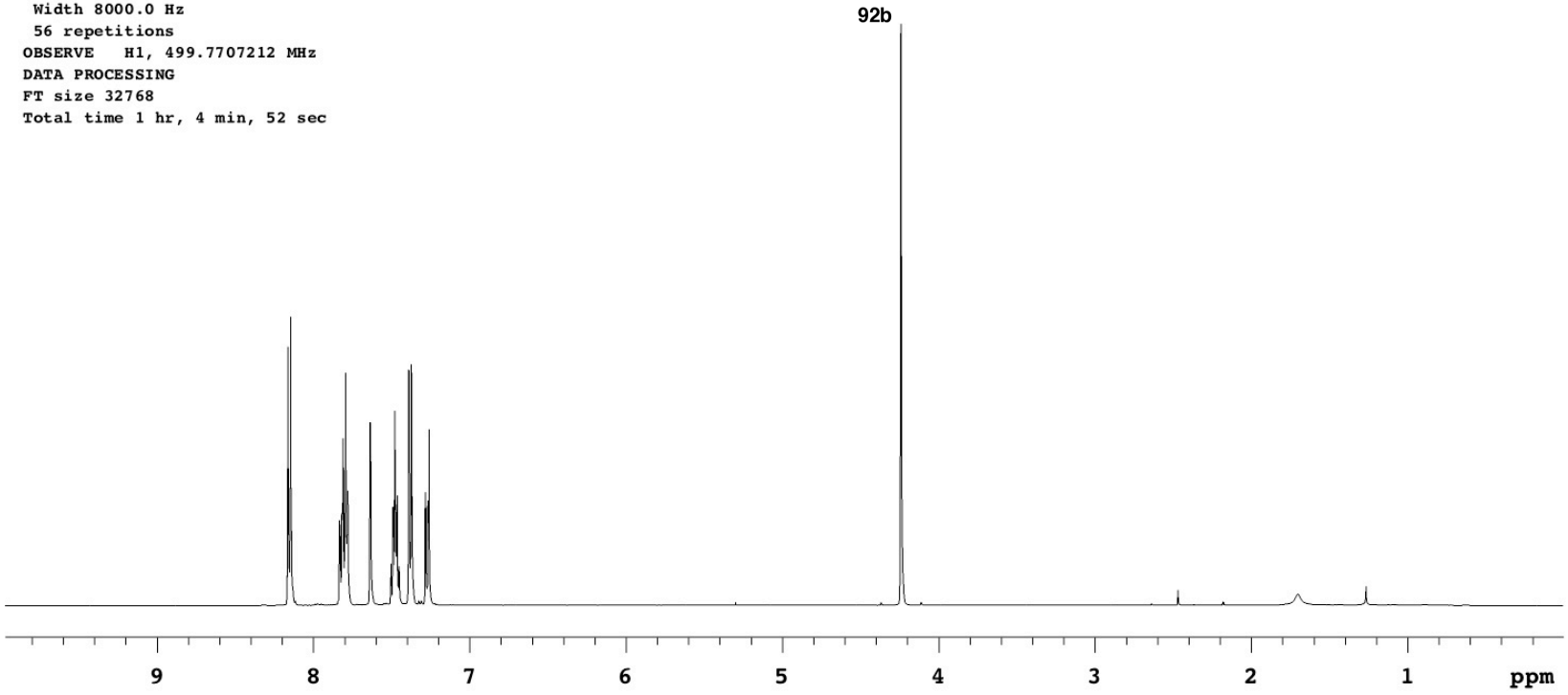
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-09-36-CDCl3-3rdFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
56 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



92b

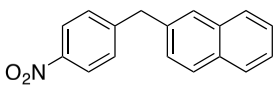


MKS-1205-09-36-CDCl3-13C-3rdFrac-CC

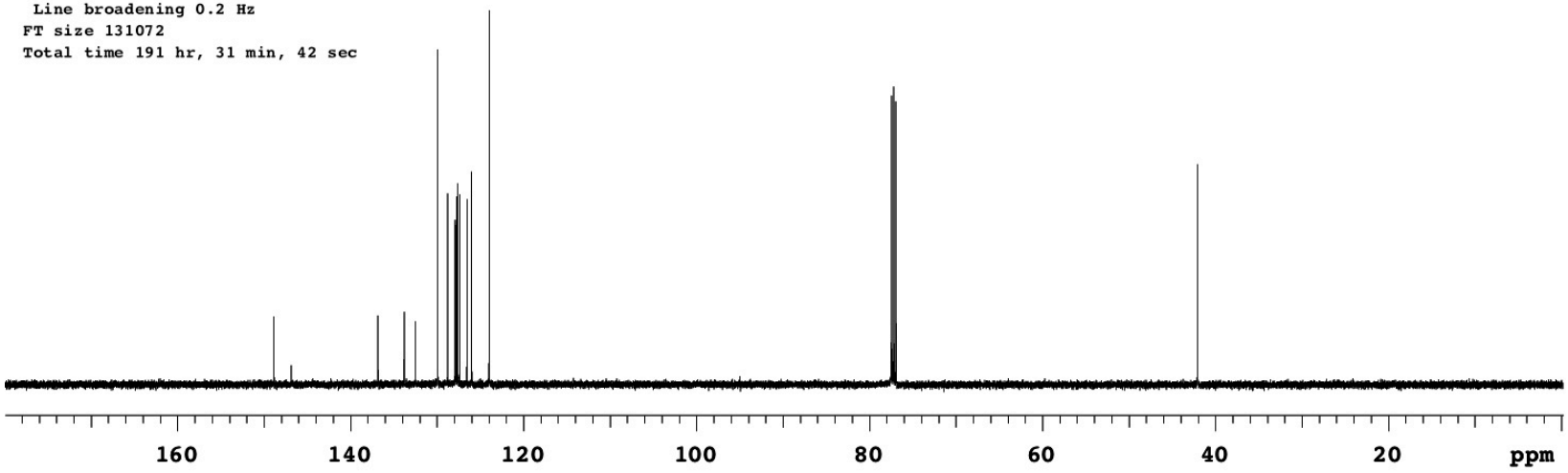
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-09-36-CDCl3-13C-3rdFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30499.4 Hz
1344 repetitions
OBSERVE C13, 125.6674226 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 191 hr, 31 min, 42 sec



92b

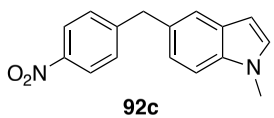


MKS-1205-13-61-CDCl3-1stFrac-2CC

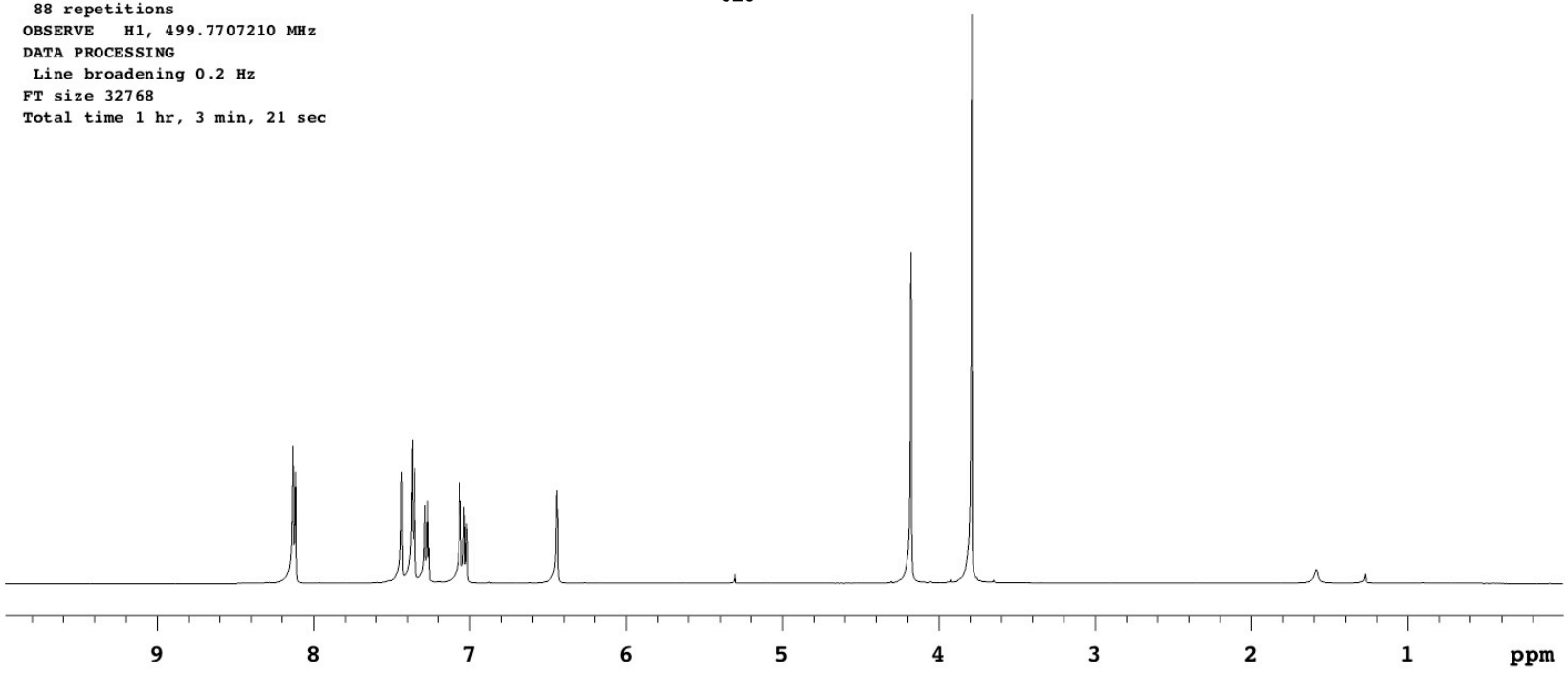
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-61-CDCl3-1stFrac-2CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
88 repetitions
OBSERVE H1, 499.7707210 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



92c

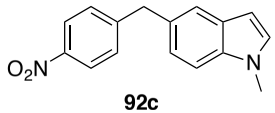


MKS-1205-13-61-CDCl3-13C-1stFrac-CC

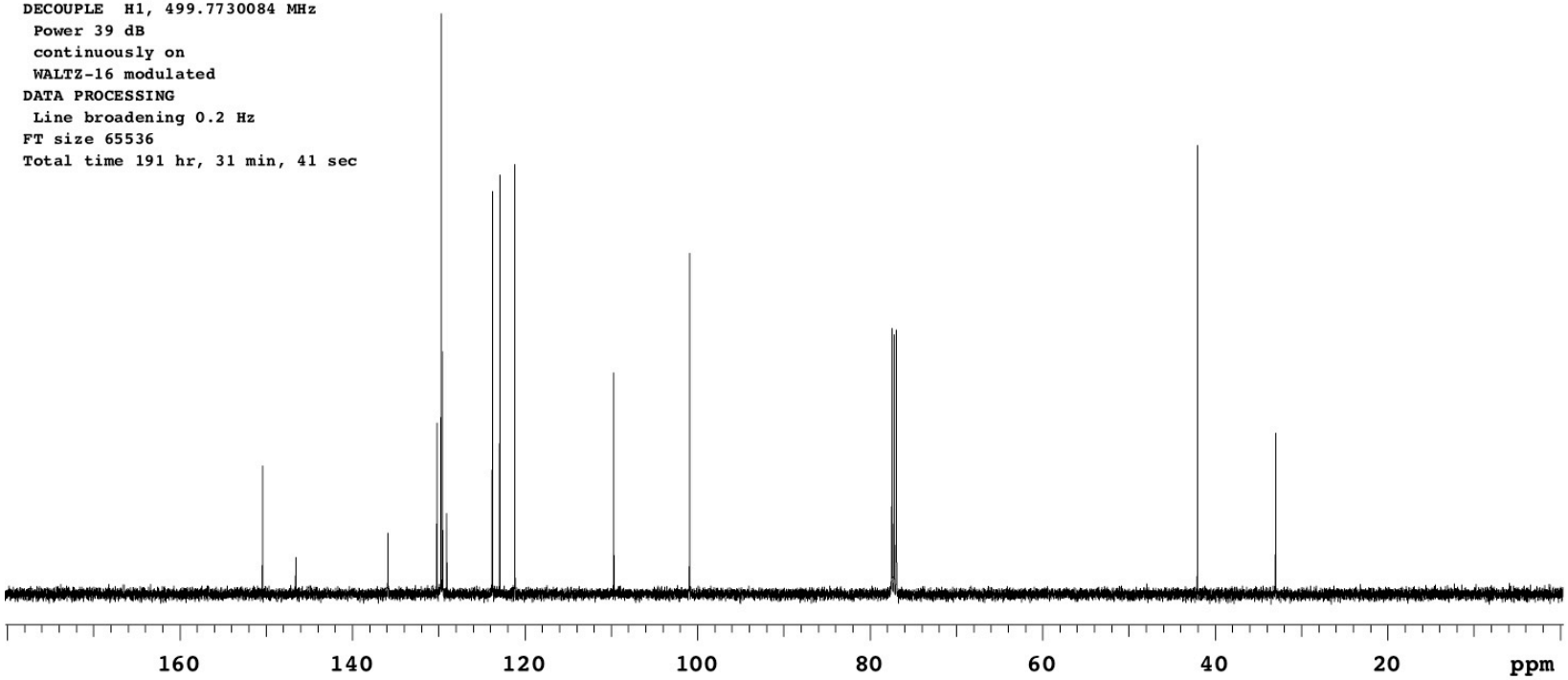
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-61-CDCl3-13C-1stFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
596 repetitions
OBSERVE C13, 125.6674286 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



92c

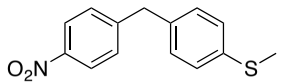


MKS-1205-09-39-CDCl3-3rdFrac-CC

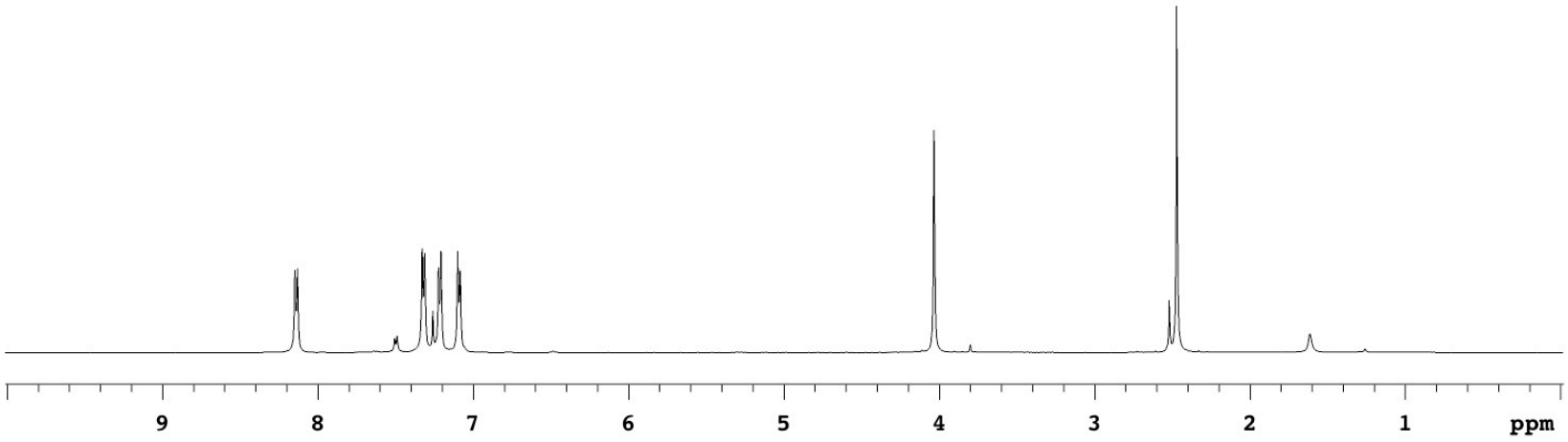
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-09-39-CDCl3-3rdFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
108 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
FT size 32768
Total time 1 hr, 4 min, 52 sec



92d

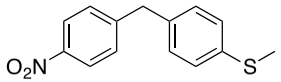


MKS-1205-09-39-CDCl3-13C-3rdFrac-CC

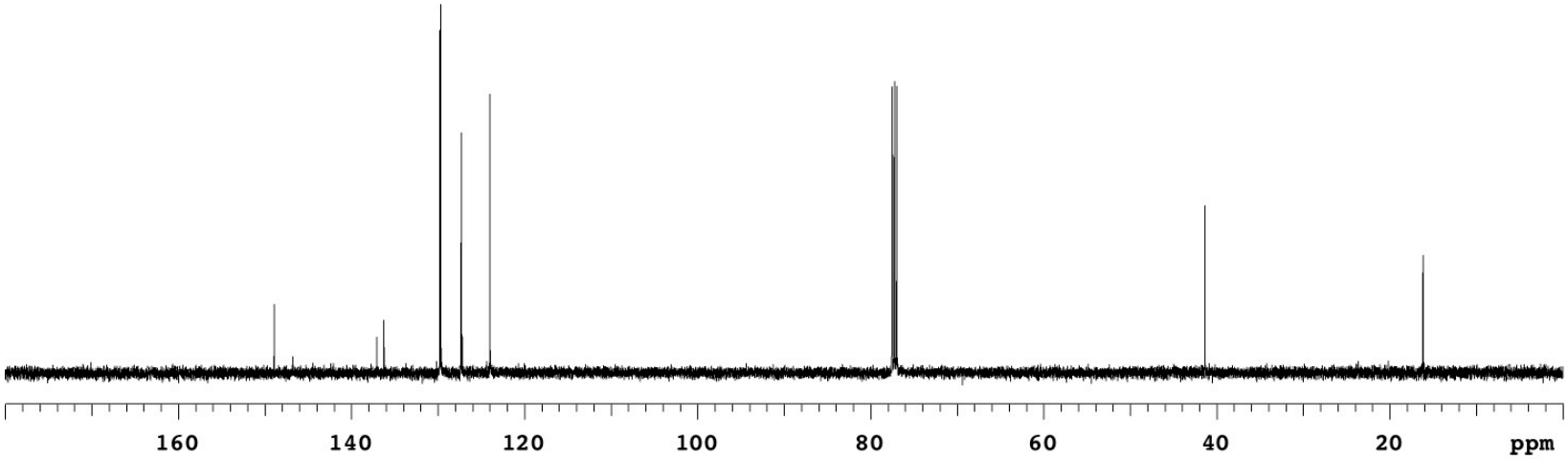
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-09-39-CDCl3-13C-3rdFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
472 repetitions
OBSERVE C13, 125.6674232 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 19 hr, 9 min, 10 sec



92d

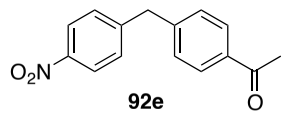


MKS-1205-13-60-A-CDCl3-CC

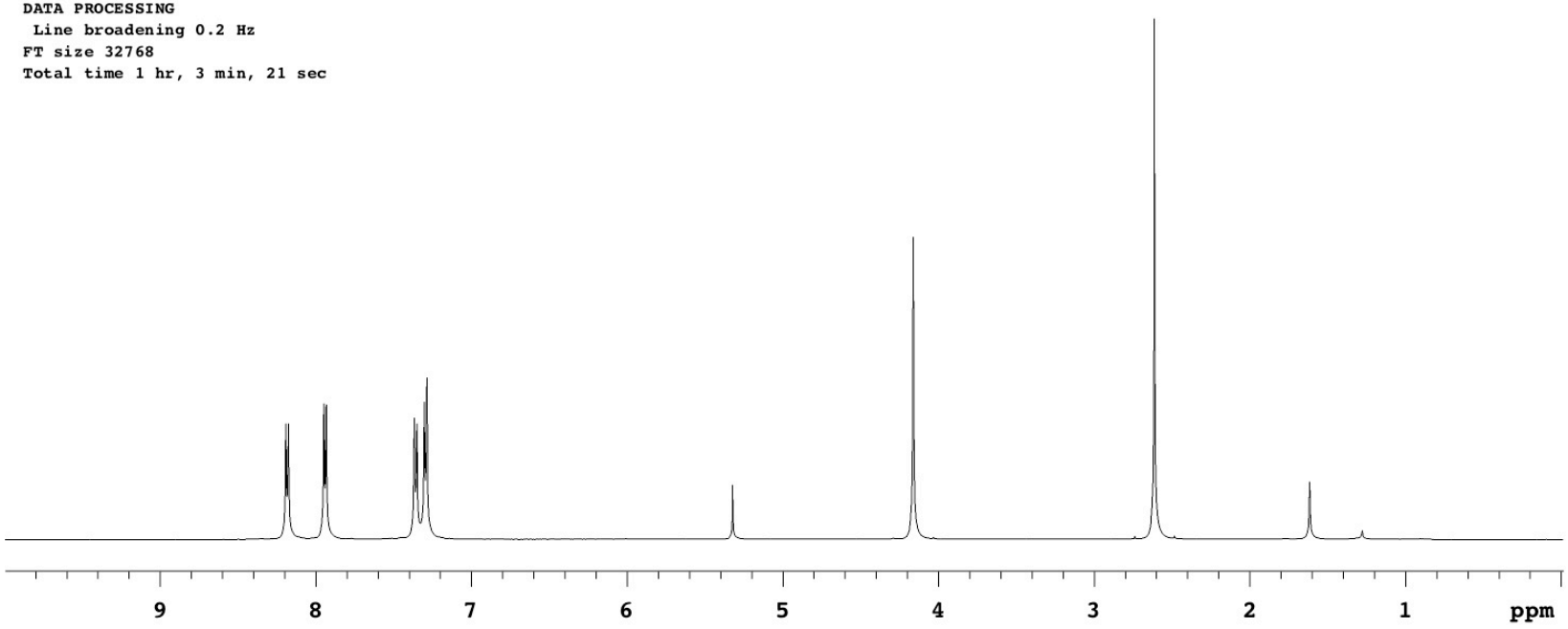
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-60-A-CDCl3-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
100 repetitions
OBSERVE H1, 499.7707095 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



92e

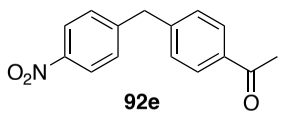


MKS-1205-13-60-A-CDCl3-13C-CC

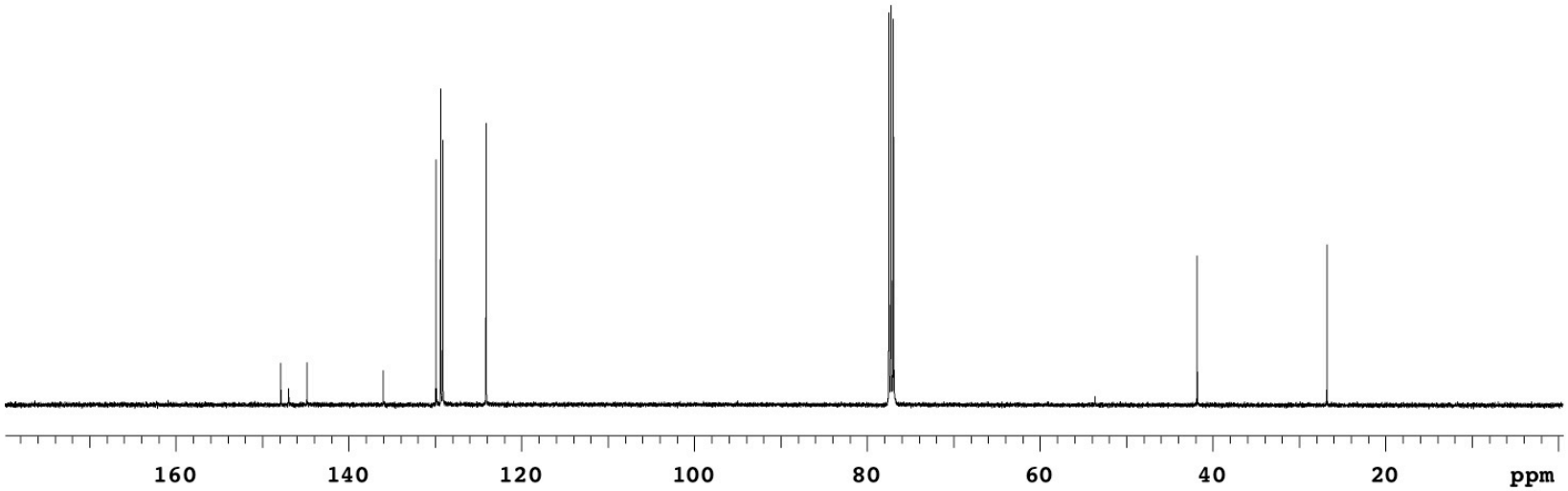
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-60-A-CDCl3-13C-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
12028 repetitions
OBSERVE C13, 125.6674210 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



92e

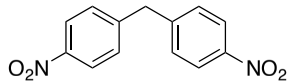


MKS-1205-13-62-CDCl3-3rdFrac-2CC

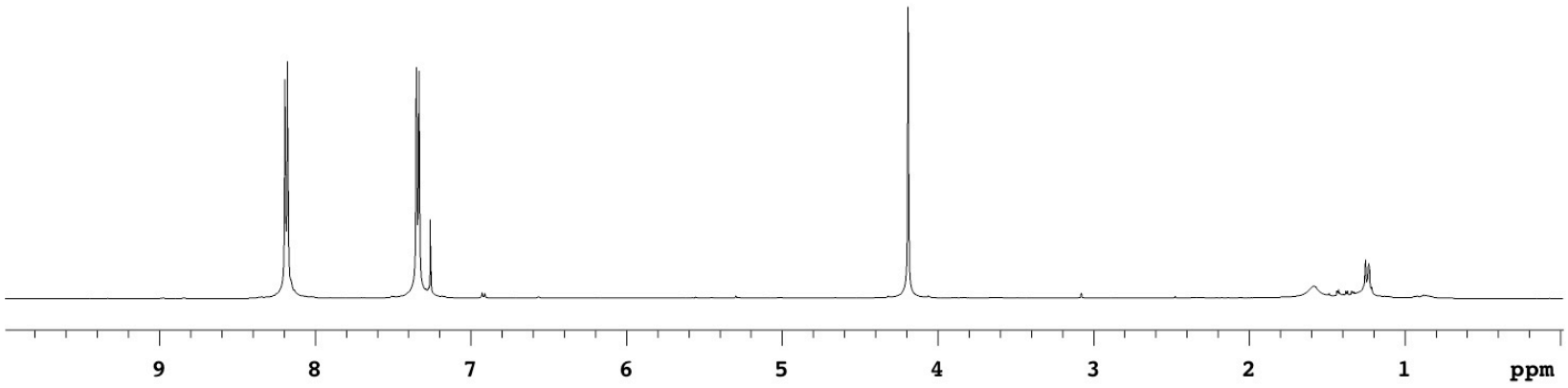
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-62-CDCl3-3rdFrac-2CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



92f

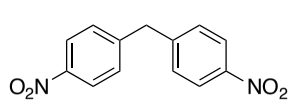


MKS-1205-13-62-CDCl3-13C-3rdFrac-2CC

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-62-CDCl3-13C-3rdFrac-2CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
14904 repetitions
OBSERVE C13, 125.6674202 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 19 hr, 9 min, 10 sec



92f

CHAPTER 5

RUTHENIUM-CATALYZED FUNCTIONALIZATION OF SP^3 CARBONS ADJACENT TO NITROGEN AND OXYGEN ATOMS OF LACTAM AND ETHERS WITH 1,2,3-1*H*-BENZOTRIAZOLES

CHAPTER 5

RUTHENIUM-CATALYZED FUNCTIONALIZATION OF sp^3 CARBONS ADJACENT TO NITROGEN AND OXYGEN ATOMS OF LACTAM AND ETHERS WITH 1,2,3-1*H*-BENZOTRIAZOLES

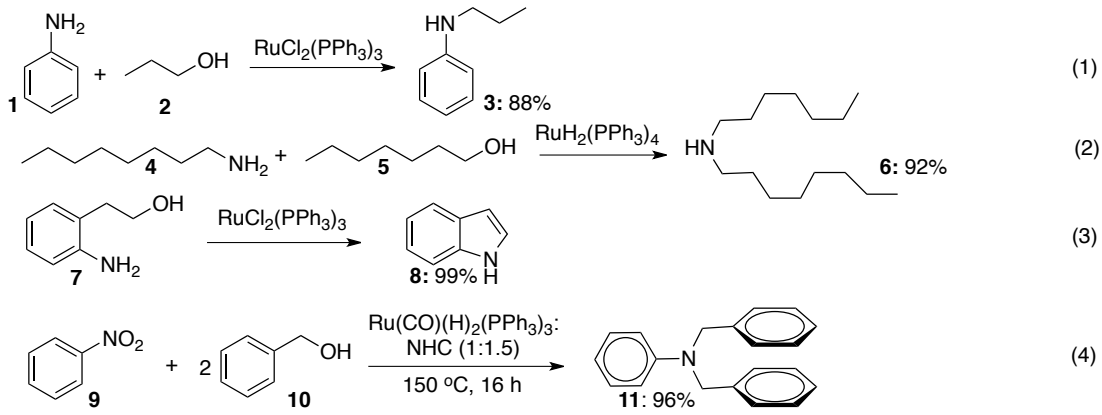
[5.1] INTRODUCTION

In contemporary organic transformations, C–H bond functionalization has attracted significant attention, due to its efficiency, economic viability and ecologically benign nature. These transformations shed light on the intrinsic characteristics of these C–H bonds in a molecule such as their reactivity.[1,2] Many transition metal catalysts, such as nickel,[3] palladium,[4] platinum,[5,6] gold,[7] rhodium,[8] iridium,[9,10] iron,[11-13] copper[14-17] are routinely used in various important transformations such as C–C and C–N bond formation reactions. Because of their robust nature many of these metal catalysts have made their way into industrial scale reactions.[18,19]

There is no doubt that each of these transition metals continues to play an important role in various organic transformations. Among diverse group of transition metal catalysts, ruthenium has carved out it's own niche, especially when it comes to carbon-carbon metathesis reactions.[20-22] Ruthenium-based catalysts are also popular in non metathesis C–C bond formation reactions.[23] Among C–heteroatom bond forming reactions, ruthenium catalyzed C–N bond formation reactions are becoming common in literature. Scheme 1 shows some of the ruthenium catalyzed C–N bond formation reactions.[24-28] Clearly, most of these methods use the oxidation of alcohol to terminal aldehyde followed by formation of imine, which in turn results in the

formation of the desired product via hydrogenation of the imine double bond with the metal hydride complex generated *in situ*.

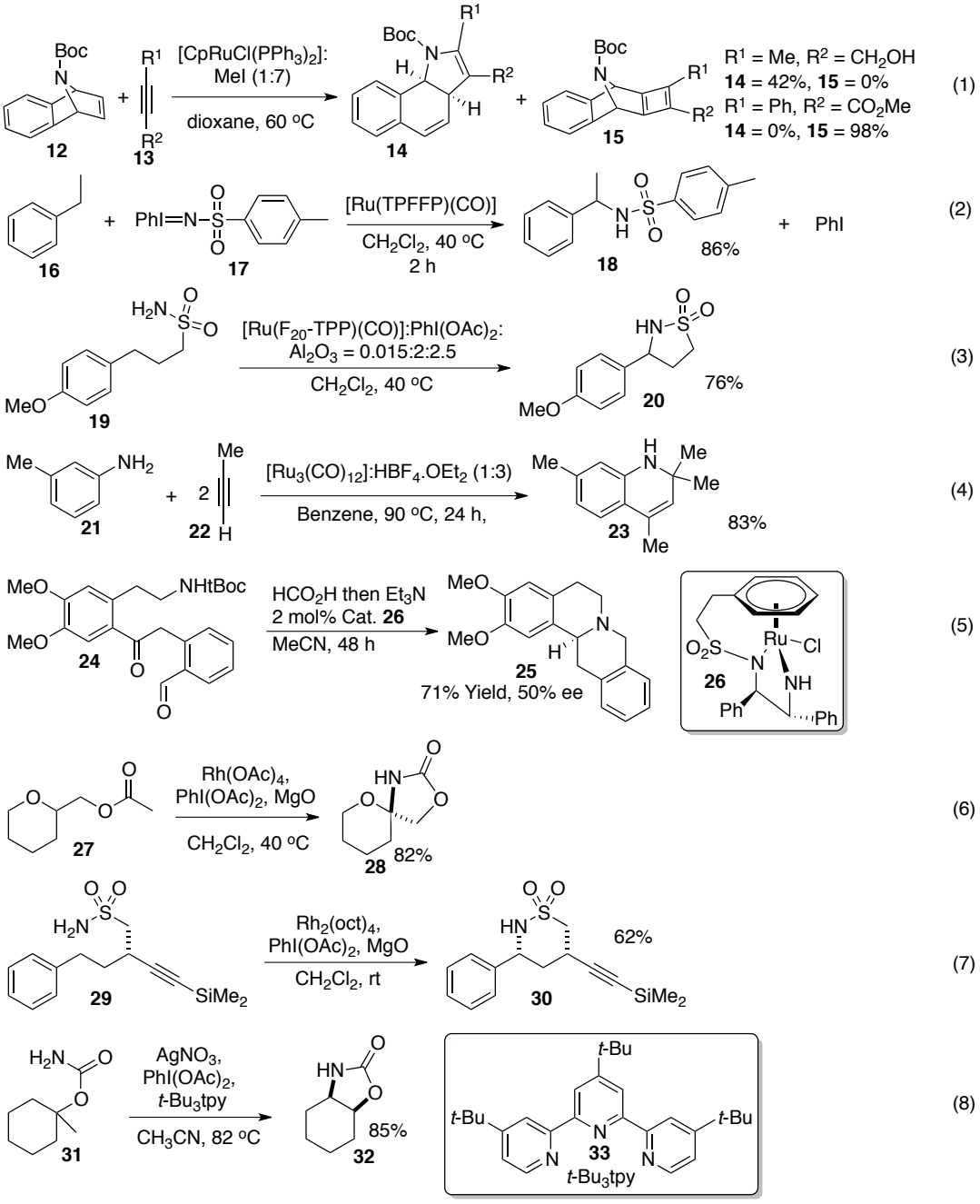
Scheme 1. *Some Ruthenium Catalyzed C–N Bond Formation Reactions*



However, reports on ruthenium catalyzed C–N bond formation via sp^3 C–H bond activation are relatively scarce.[29] Majority of the reported ruthenium catalyzed C–N bond formation methods via C–H bond activation, use primary/secondary amines or iminoiodanes PhI=NR as coupling partners. Iminoiodanes can be prepared by reacting PhI and RNH_2 (usually R = $ArSO_2$) (Scheme 2).[30-36]

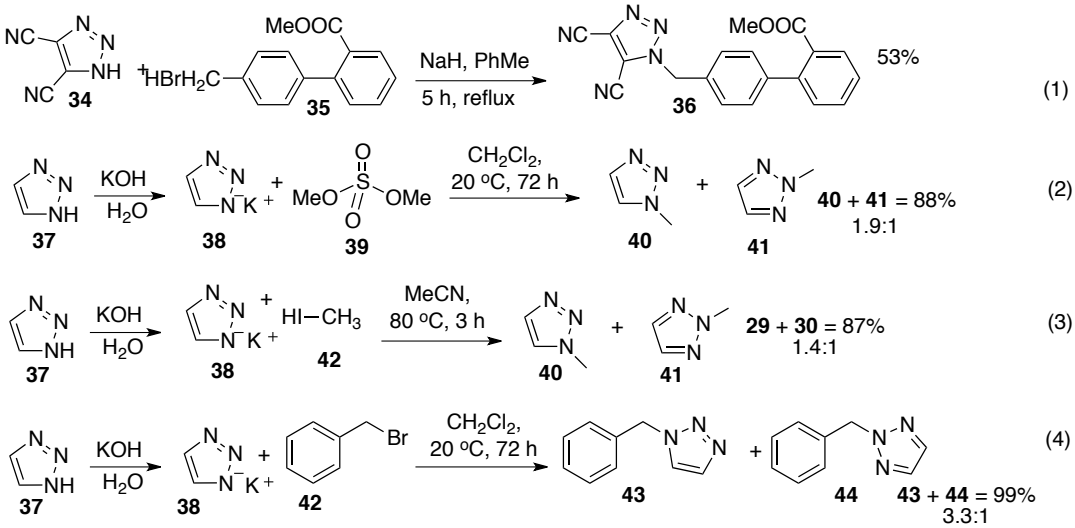
Recently, transition metal catalyzed C–N bond formation reactions with 1,2,3-triazoles as a coupling partner has gained traction due to their applicability in the field of material,[37,38] medicinal,[39-41] and biological[42-44] sciences. The advent of click chemistry has further bolstered the research on 1,2,3-triazolyl compounds. The recent reports on these special heterocyclic compounds are aimed at investigating their chemical[45,46] and biological[47-49] attributes. Considering the importance of the triazolyl derivatives, it is imperative to develop new methods to synthesize new and useful molecules with 1,2,3-triazolyl moiety. To our knowledge there are no reports on the direct ruthenium catalyzed activation of sp^3 C–H bond adjacent to nitrogen or oxygen or sulfur, followed by functionalization with 1,2,3-triazoles.

Scheme 2. *Some Metal Catalyzed C-N Bond Formation Via C-H Bond Activation*

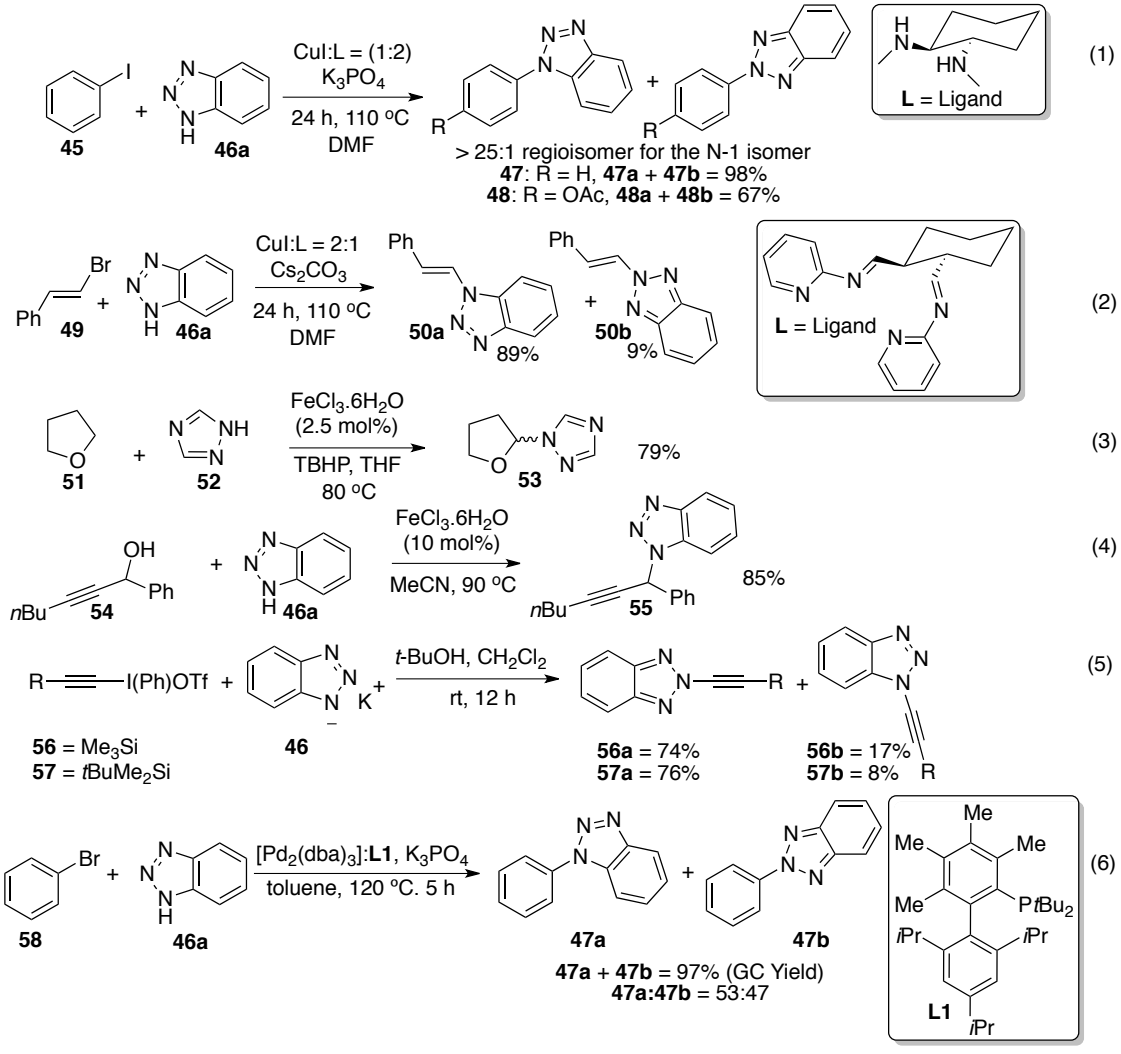


In view of the easy availability of 1,2,3-1*H*-triazoles, *N*–alkylation and *N*-arylation methods present straightforward routes to the synthesis of *N*-substituted triazoles. These conventional methods use the strategy of nucleophilic substitution with an electrophile (alkyl halide or tosylate, see Scheme 3).[50,51]

Scheme 3. *Conventional Methods for Triazole Alkylation*



Scheme 4. *Some Recently Reported C–N Bond Formation Methods Involving Triazoles*



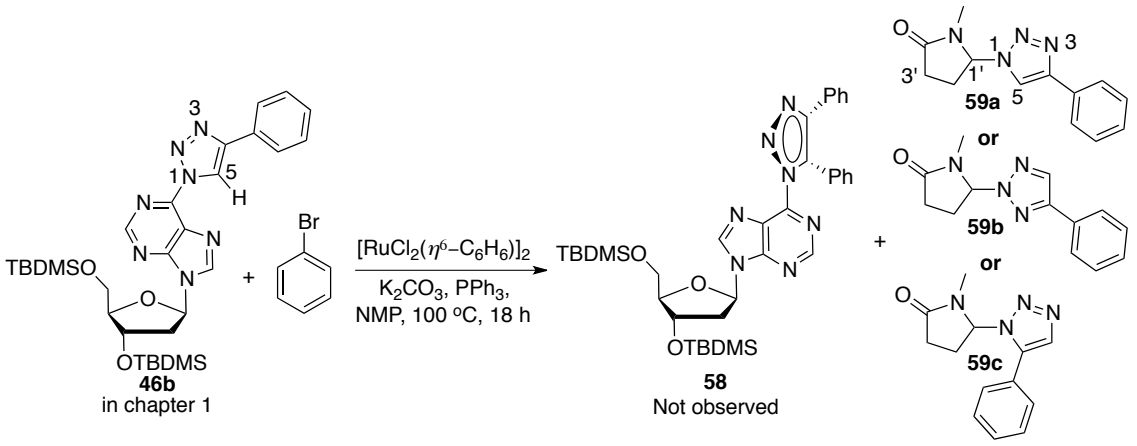
Use of strong base due to low acidity of the NH proton (1,2,3-triazole, *p*Ka: 13.9; 1,2,3-bnezotriazole, *p*Ka: 8.37) precludes applicability of this methodology to molecules with base-sensitive functionalities. Also, use of aryl and alkyl halides continues to create challenges due to health and sustainability issues.

Recently, transition metal catalysis has become a powerful technique to synthesize N-arylated and N-alkylated 1,2,3-triazoles and benzotriazoles.[52] Some of the examples of metal catalyzed C(sp^2)–N and C(sp^3)–N bond formation with triazoles is shown in Scheme 4.[53-58] In this chapter a new method for ruthenium catalyzed C(sp^3)–H bond activation in amides and ethers followed by functionalization with benzotriazoles is described.

[5.2] RESULTS AND DISCUSSION

In Chapter 1 the modification of nucleosides via CuAAC (copper catalyzed azide-alkyne cycloaddition) was described. Crystal structure analysis of the major product from the CuAAC reaction between 6-azido-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine and 4-ethynyl toluene indicated that the C-6 trizole ring and purine ring are nearly co-planer (Chapter 1, Figure 4). Also, some of the triazolyl derivatives showed moderate activity against some cancer cell lines.[59] This encouraged us to consider further modification of the triazolyl ring so as to alter the conformation relative to the purine ring by introducing steric bulk at the C-5 position of the triazolyl ring (Scheme 5). We wondered if such modification would influence the biological activity of the nucleoside triazoles but it would also create new functionalization methods for nucleosides.

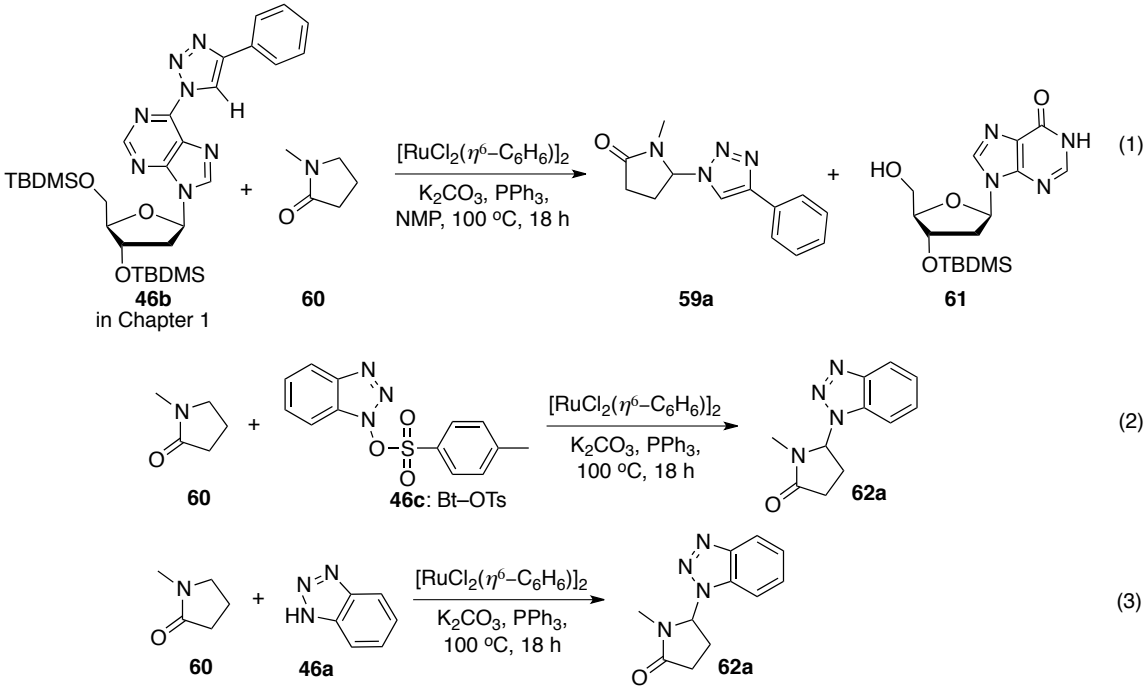
Scheme 5. *Attempted N-Directed C–H Bond Activation of the Triazolyl Ring*



On the basis of rationale, we attempted a reaction between 46**b** and bromobenzene under the reaction conditions reported by Lakshman et al.[60] However, we did not observe the formation of product **58**. To our surprise, an unexpected product **59** (**59a** or **59b** or **59c**) was isolated from the reaction mixture. Comparing the ^{1}H NMR spectra of NMP as well as that of the nucleoside triazole **46b** with the ^{1}H NMR spectra of the isolated product further confirmed that **59** is a

coupling product of NMP and the triazole portion of the nucleoside precursor. This observation was further supported by ^{13}C NMR and DEPT-135 NMRs. A weak n*O*e correlation observed between H5 proton of triazole and N-methyl proton of pyrrolidone, supported structure **59a**. This reaction was repeated without aryl halide. In this case, product **59a** was isolated and was again characterized by ^{1}H NMR, ^{13}C NMR, DEPT-135 and HMQC. ^{1}H NMR of another product isolated from this reaction indicated possible product **61** emanating from the nucleoside (Scheme 6).

Scheme 6. *C–H Bond Activation of NMP*

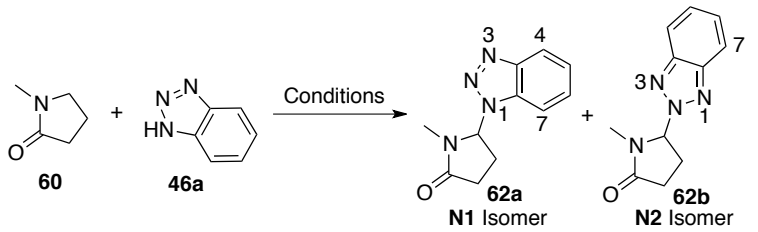


Compound **61** is known and has been very well characterized by Lakshman et al.[61] This reaction was chemically intriguing, but the triazolyl analogues of nucleosides are not a viable source of triazoles. Thus, we decided to attempt a reaction using 1*H*-benzotriazol-1-yl-4-methylbenzenesulfonate (Bt–OTs: **46c**) as a source of benzotriazole (Scheme 6, eq 2). Decent yield (51%) of the desired product **62a** was isolated in this reaction. Further, a reaction using benzotriazole as a nucleophile was attempted (Scheme 6, eq 3). The reaction between NMP and

1,2,3-1*H*-benzotriazole **46a** resulted in the formation of the product **62a**. The isolated yield of **62a**, was only 28% and triphenylphosphine oxide was also present in the isolated product. Nevertheless, we found a practical source of cyclic 1,2,3-triazole and decided to optimize the reaction conditions using 1,2,3-1*H*-benzotriazole **46a** as a nucleophile. Also, use of 1,2,3-1*H*-benzotriazole **46a** as a nucleophile was more atom economic compared to using Bt–OTs as a nucleophile.

The reaction between 1-methyl-2-pyrrolidone (NMP) **60** and 1,2,3-benzotriazole **46a** was screened under various conditions with different ruthenium salts to establish optimal reaction conditions. As shown in Table 1, the reaction produced a moderate yield of the desired, triazolyl derivative (entries 1-9). However, complete consumption of benzotriazole was observed in most of the reactions studied. Desired product isolated from the first trial reaction (entry 1) was contaminated with triphenylphosphine oxide ($O{=}PPh_3$). Based upon a recent report on ruthenium-catalyzed aerobic oxidative cyanation of tertiary amines by Murahashi et al,[62] we decided to use oxygen gas as oxidant (entry 2). The reaction showed some improvement in terms of yield (more of N-2 product was formed) and the triphenylphosphine oxide ($O{=}PPh_3$) contamination was eliminated (Table 1, entry 2). Apparently, changing the catalyst from $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ to $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$, reduced the reaction time from 18 h to 5 h. However, this occurred at the cost of reaction efficiency i.e. lower yield of the products was observed (entry 3).

Table 1. *Optimization of the C–H Bond Activation Reaction Adjacent to the Nitrogen Atom in NMP*[a]



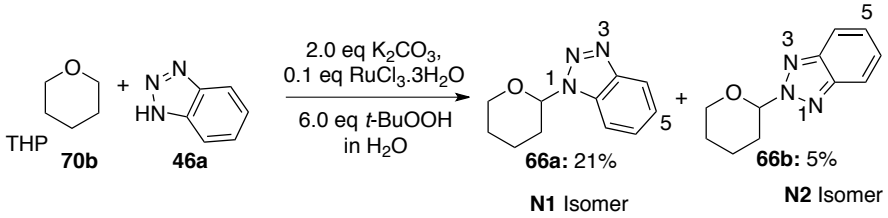
#	Catalyst	Substrate, Solvent	Reagents	Time (h) Temp. (ºC)	Yield[b]
1	$[RuCl_2(\eta^6\text{-}C_6H_6)]_2$	NMP	K_2CO_3, PPh_3	18 h, 100 ºC	**62a**: 28% **62b**: 5%
2	$[RuCl_2(\eta^6\text{-}C_6H_6)]_2$	NMP	K_2CO_3, O_2 (1 atm)	18 h, 100 ºC	**62a**: 23% **62b**: 22%
3	$[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$	NMP	K_2CO_3, O_2 (1 atm)	5 h, 100 ºC	**62a**: 16% **62b**: 12%
4	$[Ru(CO)(H)_2(PPh_3)_3]$	NMP	K_2CO_3, O_2 (1 atm)	48 h, 100 ºC	Inc[c]
5	$RuCl_3.3H_2O$	NMP	K_2CO_3, O_2 (1 atm)	16 h, 100 ºC	**62a**: 18% **62b**: 5%
6	$RuCl_3 \cdot 3H_2O$	NMP	K_2CO_3, *t*-BuOOH in H_2O (6 eq)	16 h, rt	**62a**: 41% **62b**: 9%
7[d]	$RuCl_3 \cdot 3H_2O$	NMP (6.0 mol eq)	K_2CO_3, *t*-BuOOH in H_2O (6.0 mol eq)	16 h, rt	**62a**: 40% **62b**: 28%
8[e]	$RuCl_3 \cdot 3H_2O$	NMP (3.0 mol eq), 1 mL H_2O	K_2CO_3, *t*-BuOOH in H_2O (2.5 mol eq)	18 h at rt then 4 h at 60 ºC	**62a**: 13% **62b**: 5%
9[f]	$RuCl_3 \cdot 3H_2O$	NMP (10 mol eq), 1 mL DCE	*t*-BuOOH in nonane (3.0 mol eq)	7 h at 80 ºC	**62a**: 53% **62b**: 13%
10	----------	NMP (10 mol eq), 1 mL DCE	*t*-BuOOH in nonane (3.0 mol eq)	29 h at 80 ºC	Inc[g]

[a] Reactions were conducted at 10 mol% catalyst loading, except in entry 9 where 5 mol% of catalyst was used. 1,2,3-Benzotriazole (1.0 eq) was used as the limiting reagent in each case. [b] Yield is of isolated and purified product. [c] Incomplete reaction, product formation was observed by TLC, but 1,2,3-benzotriazole was present in the reaction mixture. [d] Reaction was carried out with only 6.0 mol eq (0.3 mL) of NMP. [e] Water was used as reaction solvent. [f] 1,2-Dichloroethane (DCE) was used as solvent. [g] Reaction was incomplete, **46a** was present after 29 h.

Reaction using $[Ru(CO)(H)_2(PPh_3)_3]$ catalyst was incomplete after 48 h (entry 4). In an attempt to cut down the catalyst cost, a reaction with $RuCl_3 \cdot 3H_2O$ was attempted (entry 5). This catalyst was less efficient compared to other Ru(II) catalysts (compare entry 5 with entries 1, 2 and 3). However, upon replacing oxygen with a comparatively more powerful oxidizing agent *tert*-butylhydroperoxide (*t*-BuOOH), a significantly improved the reaction rate was observed, and the reaction could be carried out at room temperature (entry 6). Until this point (entries 1 to

6), NMP was used as solvent as well as reagent. Next, a reaction was attempted with 6.0 equivalents of NMP, but this did not seem to affect the reaction outcome (entry 7). Use of 3.0 equivalents of NMP and 2.5 equivalents of *t*-BuOOH drastically reduced the reaction yield and increased the reaction time (entry 8). So far all reactions with NMP were carried out under aqueous conditions. Since, NMP is water soluble, the aqueous conditions may pose a disadvantage for a water insoluble substrates, such as tetrahydropyran (THP) **70b**. A reaction with THP under the conditions of entry 6, yielded only 21% of the **N1** isomer and 5% of **N2** isomer (Scheme 7).

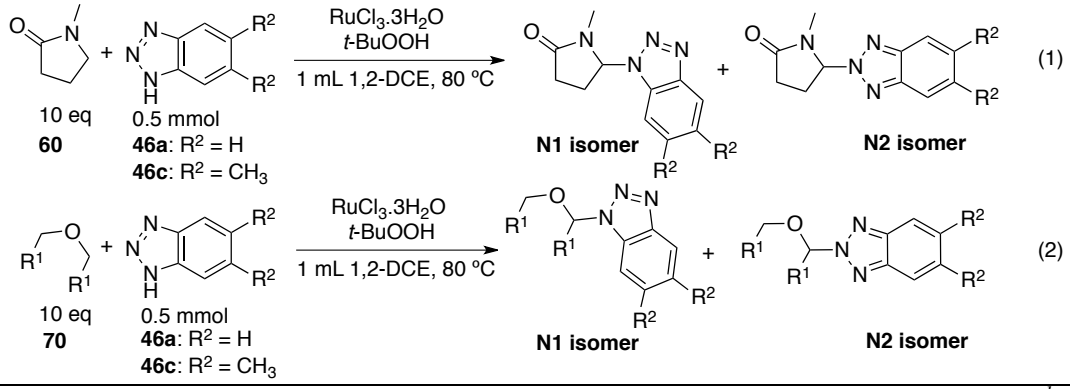
Scheme 7. *C–H Bond Activation of Tetrahydropyran (THP) Under Aqueous Conditions*

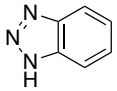
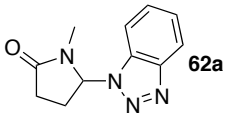
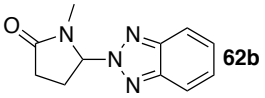
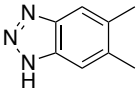
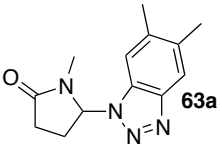
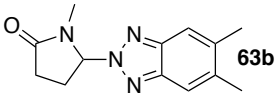
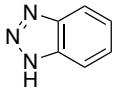
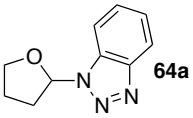
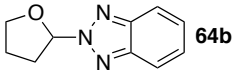
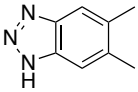
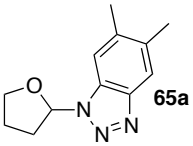
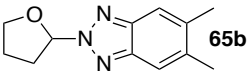
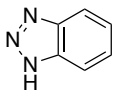
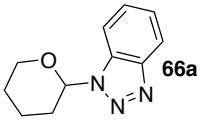
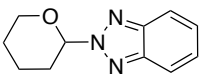
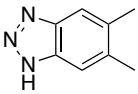
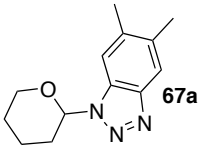
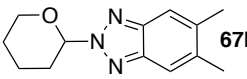
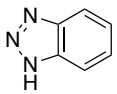
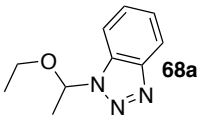
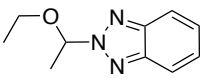
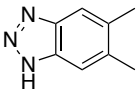
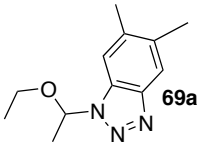
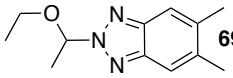


On this basis, a reaction under anhydrous conditions was then conducted with NMP in 1,2-dichloloroethane solvent (entry 9). The water-free reaction was carried out at 5 mol% of ruthenium catalyst, which is half the amount of catalyst used in entries 1 to 8. Reducing the catalyst loading slowed the reaction, but the isolated yield of the desired products was comparable with other reactions carried out under aqueous conditions (compare entry 9 with entries 6 and 7). Reactions with various other substrates were then performed (Scheme 8) using the conditions from entry 9 of Table 1.

As shown in Scheme 8 scope of this reaction was examined on NMP, THF, THP and Et_2O using two benzotriazoles. Reaction of the amide with benzotriazoles, **46a** and **46c**, resulted in the two isomeric products in good isolated yields. Reaction at the **N1** and **N2** nitrogen of the benzotriazoles resulted in the formation of these two isomeric products.

Scheme 8. *C(sp^3)–H Bond Activation of Amide and Ethers*[a]



#	Amide/ Ether	Triazole	**N1** and **N2** Regioisomeric Products		Time (h)	% Yield[b]	**N1/ N2**
1[c]			 **62a**	 **62b**	7	**62a**: 53 **62b**: 13 Total: 66	4:1
2			 **63a**	 **63b**	7	**63a**: 40 **63b**: 15 Total: 55	2.7:1
3[c, d]			 **64a**	 **64b**	6	**64a**: 61 **64b**: 20 Total: 81	3.0:1
4			 **65a**	 **65b**	6	**65a**: 45 **65b**: 23 Total: 68	1.9:1
5[c]			 **66a**	 **66b**	20	**66a**: 52 **66b**: 7 Total: 58	7.4:1
6			 **67a**	 **67b**	24	**67a**: 26 **67b**: 16 Total: 42	1.6:1
7			 **68a**	 **68b**	16	**68a**: 46 **68b**: 27 Total: 73	1.7:1
8			 **69a**	 **69b**	3.5	**69a**: 40 **69b**: 28 Total: 68	1.4:1

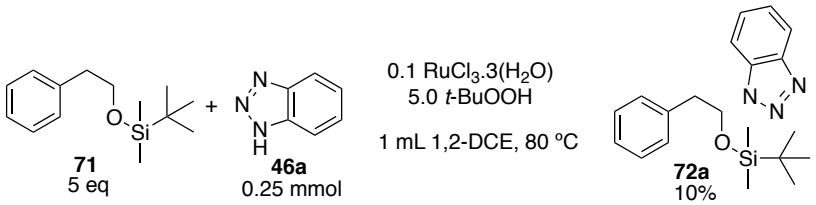
[a] Reaction was carried out with 5 mol% $RuCl_3.3H_2O$ and 0.2 g molecular sieves. [b] Yields reported are of isolated and purified products. [c] Reactions were carried out without molecular sieves. [d] Reaction was performed with 2.5 mol% of $RuCl_3$·3H2O.

The reaction of NMP with 5,6-dimethyl benzotriazole **46c** resulted in a higher yield of the **N2** isomer compared to the reaction of benzotriazole (**46a**). Reaction of tetrahydropyran (THP) with **46c** showed a similar trend. However, reactions of THF and diethylether with each of the triazoles **46a** and **46c** resulted in comparable yields of the **N2** isomer. From this analysis it appears that the amount of **N2** isomer formation is dependent on both, the triazole and amide or ether, at least under these conditions. Interestingly, the overall yield of the **N1** and **N2** isomers resulting from **46a** and **46c** with each substrate is generally comparable.

Based on the ^{1}H NMR spectra, the **N1** and **N2** regioisomers can be easily distinguished. ^{1}H NMR of the **N1** regioisomer from benzotriazole **46a** showed four sets of aromatic proton resonances whereas the **N2** isomer showed only two sets of symmetric aromatic proton signals. Similarly, the **N1** isomer from 5,6-dimethylbenzotriazole **46c** showed two sets of aromatic proton resonances whereas the **N2** regioisomer showed only one aromatic proton resonance.

Moving further this reaction was tested with alcoholsilyl ether (Scheme 9). The 1,2,3-1*H*-benzotriazole **46a** was not consumed even after 96 h. Nevertheless the reaction was quenched and the desired product was isolated, but only in 10% yield. The reaction with silyl ether can be further optimized but it clearly demonstrates the possibility for C–H bond activation at a carbinol carbon atom.

Scheme 9. *C(sp^3)–H bond activation of an organosilane*



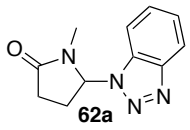
[5.3] CONCLUSION

In conclusion, a new ruthenium-catalyzed method for functionalization of a sp^3 carbon atom adjacent to nitrogen and oxygen atoms of a lactam and ethers with 1,2,3-1*H*-benzotriazole has been established. This method was shown to be applicable to silyl ether. To our knowledge, this demonstrates for the first time, applicability of C–H bond activation followed by introduction of benzotrialzolyl moiety adjacent to a lactam nitrogen atom and ether oxygen atoms.

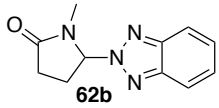
[5.4] GENERAL PROCEDURE

In a reaction vial equipped with a stirring bar, was placed benzotriazole **46a** or **46c** (0.5 mmol) and $RuCl_3 \cdot 3H_2O$ (0.05 mmol). To this mixture was added an anhydrous amide or ether (10 mol eq) followed by 1 mL of anhydrous 1,2-dichloroethane (DCE). Unless otherwise mentioned to each reaction was added 0.2 g of 4 Å molecular sieves (activated by heating overnight in an oven at 150 ºC). The reaction mixture was flushed with nitrogen gas, and to the stirring mixture was added a 5.5 M solution of *tert*-butylhydroperoxide in nonane (0.27 mmol, 1.5 mmol). The reaction mixture was stirred at 80 ºC, and progress was monitored by TLC. When complete consumption of **46a** or **46c** was observed, the reaction mixture was evaporated to dryness under reduced pressure. The crude residue so obtained was purified by chromatography on silica gel column (200-300 mesh) using a suitable eluting solvent (see compound headings below).

5-(1*H*-1,2,3-Benzotriazol-1-yl)-1-methylpyrrolidin-2-one (62a) and 5-(2*H*-1,2,3-Benzotriazol-2-yl)-1-methylpyrrolidin-2-one (62b)



62a



62b

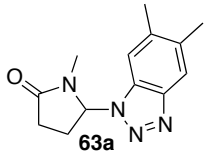
Synthesized from NMP **60** (0.48 mL, 5 mmol), benzotriazole **46a** (59.5 mg, 0.5 mmol), $RuCl_3 \cdot 3H_2O$ (6.5 mg, 0.05 mmol), 1.5 mmol (0.3 mL) anhydrous *tert*-butylhydroperoxide in 1 mL of anhydrous DCE at 80 ºC. This reaction was performed in the *absence* of 4 Å molecular sieves. After 7 h, TLC analysis showed complete consumption of **46a**. Column chromatography (230-400 mesh silica gel) was performed using 10% acetone in hexanes to give **62a** (57.0 mg, 53%) and **62b** (14.4 mg, 13%) as off white solids. R_f (SiO_2/40% EtOAc in hexanes) = **62a**: 0.06, **62b**: 0.11.

N1 Isomer 62a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, 1H, Ar–H, J = 8.6 Hz), 7.53 (t, 1H, Ar–H, J = 7.9 Hz), 7.45-7.42 (m, 2H, Ar–H), 6.49 (dd, 1H, CH, J = 2.8, 8.3 Hz), 2.97-2.90 (m, 1H,

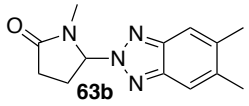
C*H*H), 2.88-2.80 (m, 1H, C*H*H), 2.70-2.64 (m, 1H, C*H*H), 2.69 (s, 3H, CH_3), 2.50-2.44 (m, 1H, C*H*H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.6, 146.8, 131.5, 128.6, 124.8, 120.8, 109.2, 74.8, 29.5, 27.8, 25.3. HRMS (ESI) *m/z* calcd for $C_{11}H_{13}N_4O$ $[M + H]^+$: 217.1084, found 217.0898.

N2 Isomer 62b: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (dd, 2H, Ar–H, *J* = 6.6, 3.1 Hz), 7.42 (dd, 2H, Ar–H, *J* = 3.1, 6.6 Hz), 6.30 (d, 1H, CH, *J* = 7.8 Hz), 3.00-3.08 (m, 1H, C*H*H), 2.74 (s, 3H, CH_3), 2.68 (m, 1H, C*H*H), 2.59-2.53 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.6, 144.7, 127.3, 118.6, 80.8, 29.0, 28.0, 26.0. HRMS (ESI) *m/z* calcd for $C_{11}H_{12}N_4ONa$ $[M + Na]^+$: 239.0903, found 239.0894.

5-(5,6-Dimethyl-1*H*-1,2,3-benzotriazol-1-yl)-1-methylpyrrolidin-2-one (63a) and 5-(5,6-Dimethyl-2*H*-1,2,3-benzotriazol-2-yl)-1-methylpyrrolidin-2-one (63b)



63a



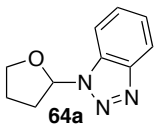
63b

Synthesized from NMP **60** (0.48 mL, 5.0 mmol), 5,6-dimethylbenzotriazole **46c** (0.074 g, 0.5 mmol), $RuCl_3 \cdot 3H_2O$ (6.5 mg, 0.05 mmol), 1.5 mmol (0.30 mL) anhydrous *tert*-butylhydroperoxide in 1 mL of anhydrous DCE at 80 ºC. The reaction was performed in the *presence* of 0.2 g of 4 Å molecular sieves. After 7 h, TLC analysis showed complete consumption of **46c**. Column chromatography (230-400 mesh silica gel) was performed using 10% acetone in hexanes to give **63a** (49.3 mg, 40%) as light-yellow solid and **63b** (18.0 mg, 15%) as an off white solid. R_f (SiO_2/20% Acetone in hexanes) = **63a**: 0.16, **63b**: 0.31.

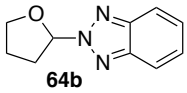
N1 Isomer 63a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (s, 1H, Ar–H), 7.14 (s, 1H, Ar–H), 6.42 (dd, 1H, CH, *J* = 3.1, 8.4 Hz), 2.94-2.87 (m, 1H, C*H*H), 2.83-2.75 (m, 1H, C*H*H), 2.67-2.61 (m, 1H, C*H*H), 2.63 (s, 3H, CH_3), 2.46-2.42 (m, 1H, C*H*H), 2.40 (s, 3H, CH_3), 2.39 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.4, 146.1, 139.0, 134.6, 130.3, 119.8, 108.5, 74.6, 29.5, 27.7, 25.0, 21.2, 20.5. HRMS (ESI) *m/z* calcd for $C_{13}H_{17}N_4O$ $[M + H]^+$: 245.1397, found 245.1389.

N2 Isomer 63b: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (s, 2H, Ar–H), 6.22 (1H, d, CH, *J* = 7.7 Hz), 3.04-2.98 (m, 1H, C*H*H), 2.69 (s, 3H, CH_3), 2.68-2.62 (m, 1H, C*H*H), 2.56-2.50 (m, 2H, C*H*H), 2.39 (s, 6H, $2CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.6, 144.1, 137.8, 116.9, 80.3, 29.1, 27.8, 25.8, 21.1. HRMS (ESI) *m/z* calcd for $C_{13}H_{17}N_4O$ $[M + H]^+$: 245.1397, found 245.1380.

1-(Tetrahydrofuran-2-yl)-1*H*-1,2,3-benzotriazole (64a) and 2-(Tetrahydrofuran -2-yl)-2*H*-1,2,3-benzotriazole (64b)



64a



64b

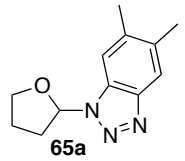
Synthesized from THF **70a** (0.56 mL, 5 mmol), benzotriazole **46a** (0.059 g, 0.5 mmol), $RuCl_3 \cdot 3H_2O$ (3.2 mg, 0.025 mmol), 1.5 mmol (0.30 mL) anhydrous *tert*-butylhydroperoxide in 1 mL of anhydrous DCE at 80 ºC. This reaction was performed in the *absence* of 4 Å molecular sieves. After 6 h, TLC analysis of the reaction mixture showed complete consumption of **46a**. Column chromatography was performed using 5% acetone in hexanes to give **64a** (0.057 g, 61%) and **64b** (0.019 g, 20%) as colorless oily liquids. R_f (SiO_2/40% EtOAc in hexanes) = **64a**: 0.31, **64b**: 0.43.

N1 Isomer 64a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, 1H, Ar–H, *J* = 8.4 Hz), 7.70 (d, 1H, Ar–H, *J* = 8.4 Hz), 7.50 (t, 1H, Ar–H, *J* = 7.4 Hz), 7.4 (t, 1H, Ar–H, *J* = 7.7 Hz), 6.51 (dd, 1H, CH, *J* = 2.3, 6.7 Hz), 4.10 (app q, 1H, C*H*H, *J* = 6.5, 7.9 Hz), 4.03 (app q, 1H, C*H*H, *J* = 6.2, 8.1 Hz), 3.19-3.13 (m, 1H, C*H*H), 2.56-2.48 (m, 1H, C*H*H), 2.44-2.34 (m, 1H, C*H*H), 2.22-2.14 (m, 1H, C*H*H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.5, 133.0, 127.7, 124.3, 120.1, 110.6, 88.1, 69.5, 31.0, 24.6. HRMS (ESI) *m/z* calcd for $C_{10}H_{12}N_3O$ $[M + H]^+$: 190.0975, found 190.0970.

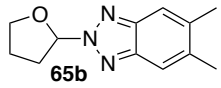
N2 Isomer 64b: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, 2H, Ar–H, *J* = 3.1, 6.6 Hz), 7.38 (dd, 2H, Ar–H, *J* = 3.1, 6.6 Hz), 6.59 (dd, 1H, CH, *J* = 2.1, 6.4 Hz), 4.34 (app q, 1H, CH*H*, *J* = 7.8,

6.1 Hz), 4.14 (app q, 1H, C*H*H, *J* = 7.7, 6.6 Hz), 2.77-2.71 (m, 1H, C*H*H), 2.56-2.45 (m, 2H, 2CH or CH_2), 2.20-2.10 (m, 1H, CH*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.4, 126.8, 118.6, 94.3, 70.4, 32.5, 24.5. HRMS (ESI) *m/z* calcd for $C_{10}H_{12}N_3O$ $[M + H]^+$: 190.0975, found 190.0975.

5,6-Dimethyl-1-(tetrahydrofuran-2-yl)-1*H*-1,2,3-benzotriazole (65a) and 5,6-dimethyl-2-(tetrahydrofuran-2-yl)-2*H*-1,2,3-benzotriazole (65b)



65a



65b

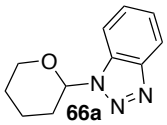
Synthesized from THF **70a** (0.56 mL, 5 mmol), benzotriazole **46c** (0.074 g, 0.5 mmol), $RuCl_3 \cdot 3H_2O$ (6.5 mg, 0.05 mmol), 1.5 mmol (0.30 mL) anhydrous *tert*-butylhydroperoxide in 1 mL of anhydrous DCE at 80 ºC. This reaction was performed in the presence of 0.2 g of 4 Å molecular sieves. After 6 h, TLC analysis showed complete consumption of **46c**. Column chromatography was performed using 5% EtOAc in hexanes to give **65a** (49.0 mg, 45%) and **65b** (25.0 mg, 23%) as white crystalline solids. R_f (SiO_2/20% EtOAc in hexanes) = **65a**: 0.18, **65b**: 0.32.

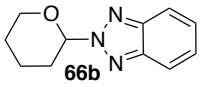
N1 Isomer 65a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (s, 1H, Ar–H), 7.41 (s, 1H, Ar–H), 6.40 (dd, 1H, CH, *J* = 2.5, 6.7 Hz), 4.04 (app q, 1H, C*H*H, *J* = 6.4, 7.9 Hz), 3.97 (app q, 1H, C*H*H, *J* = 6.3, 8.1, Hz), 3.13-3.02 (m, 1H, C*H*H), 2.48-2.23 (m, 2H, 2CH or CH_2), 2.38 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.16-2.08 (m, 1H, C*H*H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.7, 137.9, 133.9, 131.9, 118.9, 109.9, 87.7, 69.2, 30.6, 24.5, 21.0, 20.5. HRMS (ESI) *m/z* calcd for $C_{12}H_{16}N_3O$ $[M + H]^+$: 218.1288, found 218.1283.

N2 Isomer 65b: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (s, 2H, Ar–H), 6.53 (dd, 1H, CH, *J* = 2.3, 6.5 Hz), 4.49 (ddd, 1H, C*H*H, *J* = 6.1, 7.8 Hz), 4.10 (ddd, 1H, C*H*H, *J* = 6.2, 8.1 Hz), 2.75-2.68 (m, 1H, C*H*H), 2.51-2.41 (m, 2H, 2CH or CH_2), 2.37 (2, 6H, $2CH_3$), 2.15-2.07 (m, 1H, C*H*H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 143.9, 137.2, 117.0, 93.9, 70.2, 32.3, 24.5, 21.1. HRMS (ESI) *m/z* calcd for $C_{12}H_{16}N_3O$ $[M + H]^+$: 218.1288, found 218.1285.

1-(Tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-benzotriazole (66a) and 2-(tetrahydro-2*H*-pyran-2-yl)-2*H*-1,2,3benzo-triazole (66b)



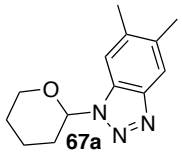


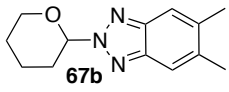
Synthesized from THP **70b** (0.5 mL, 5 mmol), benzotriazole **46a** (0.059 g, 0.5 mmol), $RuCl_3 \cdot 3H_2O$ (6.5 mg, 0.05 mmol), 1.5 mmol (0.30 mL) anhydrous *tert*-butylhydroperoxide in 1 mL of anhydrous DCE at 80 ºC. This reaction was performed in the *absence* of 4 Å molecular sieves. After 20 h, TLC analysis showed complete consumption of **46a**. Column chromatography was performed using 4% EtOAc in hexanes to give **66a** (0.053 g, 52%) as colorless oily liquid and **66b** (0.0047 g, 5%) as white solids. R_f (SiO_2/40% EtOAc in hexanes) = **66a**: 0.33, **66b**: 0.39.

N1 Isomer 66a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, 1H, Ar–H, *J* = 8.3 Hz), 7.72 (d, 1H, Ar–H, *J* = 8.3 Hz), 7.47 (t, 1H, Ar–H, *J* = 7.6 Hz), 7.36 (t, 1H, Ar–H, *J* = 7.6) 6.02 (dd, 1H, C–H, *J* = 2.3, 8.2 Hz), 3.92 (m, 1H, C*H*H), 3.77 (m, 1H, C*H*H), 2.60 (m, 1H, C*H*H), 2.19 (m, 2H, 2C*H*H or CH_2), 1.79 (m, 3H, 3C*H*H or C*H*H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.4, 132.5, 127.5, 124.2, 120.0, 111.2, 85.7, 66.4, 29.4, 25.0, 21.7. HRMS (ESI) *m/z* calcd for $C_{11}H_{14}N_3O$ $[M + H]^+$: 204.1131, found 204.1131.

N2 Isomer 66b: 7.90 (dd, 2H, Ar–H, *J* = 3.1, 6.5 Hz), 7.39 (dd, 2H, Ar–H, *J* = 3.1, 6.6 Hz), 6.04 (dd, 1H, C–H, *J* = 3.1, 6.5 Hz), 4.11 (m, 1H, C*H*H), 3.83 (m, 1H, C*H*H), 2.56 (m, 1H, C*H*H), 2.18 (m, 2H, 2C*H*H or CH_2), 1.80 (m, 2H, 2C*H*H or CH_2), 1.71 (m, 1H, C*H*H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.4, 127.0, 118.8, 90.9, 67.7, 30.1, 25.0, 21.7. HRMS (ESI) *m/z* calcd for $C_{11}H_{13}N_3ONa$ $[M + Na]^+$: 226.0951, found 226.0944.

5,6-Dimethyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-benzotriazole (67a) and 5,6-dimethyl-2-(tetrahydro-2*H*-pyran-2-yl)-2*H*-1,2,3-benzotriazole (67b)



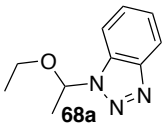


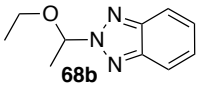
Synthesized from THP **70b** (0.5 mL, 5 mmol), benzotriazole **46c** (0.074 g, 0.5 mmol), $RuCl_3 \cdot 3H_2O$ (6.5 mg, 0.05 mmol), 1.5 mmol (0.30 mL) anhydrous *tert*-butylhydroperoxide in 1 mL of anhydrous DCE at 80 ºC. This reaction was performed in the presence of 0.2 g of 4 Å molecular sieves. After 24 h, TLC analysis showed complete consumption of **46c**. Column chromatohgraphy was performed using 5% EtOAc in hexanes to give **67a** (0.030 g, 26%) **67b** (0.019 g, 16%) as white solids. R_f (SiO_2/20% EtOAc in hexanes) = **67a**: 0.45, **67b**: 0.70.

N1 Isomer 67a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (s, 1H, Ar–H), 7.46 (s, 1H, Ar–H), 5.95 (dd, 1H, J = 2.6, 8.3 Hz), 3.90-3.45 (m, 1H, C*H*H), 3.78-3.73 (m, 1H, C*H*H), 2.60-2.54 (m, 1H, C*H*H), 2.40 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.10 (app d, 2H, 2C*H*H or CH_2, J = 9.9 Hz), 1.83-1.68 (m, 3H, 3C*H*H or C*H*H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.7, 137.9, 134.0, 131.6, 119.1, 110.5, 85.7, 67.0, 29.4, 25.1, 21.9, 21.0, 20.6. HRMS (ESI) *m/z* calcd for $C_{13}H_{18}N_3O$ [M + H]$^+$: 232.1444, found 232.1445.

N2 Isomer 67b: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (s, 2H, Ar-H), 5.96 (dd, 1H, CH, J = 2.7, 8.8 Hz), 4.09 (m, 1H, CH), 3.82-3.78 (m, 1H, CH), 2.57-2.45 (m, 1H, CH), 2.38 (s, 6H, 2CH_3), 2.19-2.11 (m, 1H, CH), 1.83-1.74 (m, 2H, CH_2), 171-1.65 (m, 2H, 2C*H*H or CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.8, 137.5, 117.0, 90.6, 67.7, 30.1, 25.0, 21.8, 21.1. HRMS (ESI) *m/z* calcd for $C_{13}H_{18}N_3O$ [M + H]$^+$: 232.1444, found 232.1444.

1-(1-Ethoxyethyl)-1*H*-1,2,3-benzotriazole (68a) and 2-(1-ethoxyethyl)-2*H*-1,2,3-benzotriazole (68b)



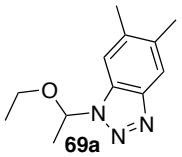


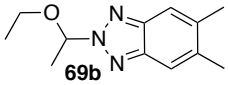
Synthesized from diethyl ether **70c** (0.52 mL, 5 mmol), benzotriazole **46a** (0.06 g, 0.5 mmol), $RuCl_3 \cdot 3H_2O$ (6.5 mg, 0.05 mmol), 1.5 mmol (0.30 mL) anhydrous *tert*-butylhydroperoxide in 1 mL of anhydrous DCE at 80 ºC. This reaction was performed in the presence of 4 Å molecular sieves. After 16 h, TLC analysis showed complete consumption of **46a**. Column chromatography was performed using 5% EtOAc in hexanes to give **68a** (0.044 g, 46%) and **68b** (0.026 g, 27%) as clear, oily liquids. R_f (SiO_2/40% EtOAc in hexanes) = **68a**: 0.31, **68b**: 0.50.

N1 Isomer 68a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, 1H, Ar–H, J = 8.4 Hz), 7.77 (d, 1H, Ar–H, J = 8.4 Hz), 7.45 (t, 1H, Ar–H, J = 7.4 Hz), 7.34 (t, 1H, Ar–H, J = 7.7 Hz), 6.23 (q, 1H, CH, J = 6.1 Hz), 3.49 (m, 1H, C*H*H), 3.22 (m, 1H, C*H*H), 1.83 (d, 3H, CH_3, J = 6.1 Hz), 1.10 (t, 3H, CH_3, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.9, 131.2, 127.5, 124.2, 120.1, 111.3, 87.1, 64.4, 21.3, 14.8. HRMS (ESI) *m/z* calcd for $C_{10}H_{14}N_3O$ $[M + H]^+$: 192.1131, found 192.1136.

N2 Isomer 68b: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, 1H, Ar–H, J = 3.2 Hz), 7.88 (d, 1H, Ar–H, J = 3.2 Hz), 7.39 (d, 1H, Ar–H, J = 3.2 Hz), 7.38 (d, 1H, Ar–H, J = 3.0 Hz), 6.06 (q, 1H, CH, J = 5.9 Hz), 3.57 (m, 1H, C*H*H), 3.34 (m, 1H, C*H*H), 1.9 (d, 3H, CH_3, J = 5.9 Hz), 1.15 (t, 3H, CH_3, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.9, 131.2, 127.5, 124.2, 120.1, 111.3, 87.1, 64.4, 21.3, 14.8. HRMS (ESI) *m/z* calcd for $C_{10}H_{13}N_3ONa$ $[M + Na]^+$: 214.0951, found 214.0954.

1-(1-Ethoxyethyl)-5,6-dimethyl-1*H*-1,2,3-benzotriazole (69a) and 2-(1-ethoxyethyl)-5,6-dimethyl-2*H*-1,2,3-benzotriazole (69b)



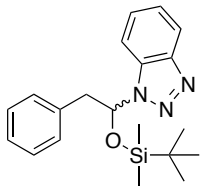


Synthesized from diethyl ether **70c** (0.52 mL, 5 mmol), benzotriazole **46c** (0.074 g, 0.5 mmol), $RuCl_3 \cdot 3H_2O$ (6.5 mg, 0.05 mmol), 1.5 mmol (0.30 mL) anhydrous *tert*-butylhydroperoxide in 1 mL of anhydrous DCE at 80 ºC. This reaction was performed in the presence of 0.2 g of 4 Å molecular sieves. After 3.5 h, TLC analysis showed complete consumption of **46c**. Column chromatography was performed using 5% EtOAc in hexanes to give **69a** (0.044 g, 40%) and **69b** (0.030 g, 28%) as clear, oily liquids. R_f (SiO_2/20% EtOAc in hexanes) = **69a**: 0.28, **69b**: 0.44.

N1 Isomer 69a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (s, 1H, Ar–H), 7.52 (s, 1H, Ar–H), 6.17 (q, 1H, CH, J = 6.1 Hz), 3.50-3.44 (m, 1H, C*H*H), 3.24-3.18 (m, 1H, C*H*H), 2.40 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 1.82 (d, 3H, CH_3, J = 6.1 Hz), 1.10 (t, 3H, CH_3, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.2, 137.8, 134.1, 130.3, 119.2, 110.7, 86.8, 64.3, 21.2, 21.0, 20.5, 14.9. HRMS (ESI) *m/z* calcd for $C_{12}H_{18}N_3O$ $[M + H]^+$: 220.1444, found 220.1436.

N2 Isomer 69b: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (s, 2H, Ar–H), 6.00 (q, 1H, CH, J = 6.0 Hz), 3.57-3.51 (m, 1H, C*H*H), 3.30-3.27 (m, 1H, C*H*H), 2.38 (s, 6H, $2CH_3$), 1.88 (d, 3H, CH_3, J = 6.0 Hz), 1.13 (t, 3H, CH_3, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.8, 137.4, 117.1, 91.2, 65.1, 21.7, 21.1, 14.9. HRMS (ESI) *m/z* calcd for $C_{12}H_{18}N_3O$ $[M + H]^+$: 220.1444, found 220.1430.

1-(1-*tert*-Butyldimethylsilyloxy)-2-phenylethyl)-1*H*-1,2,3-benzotriazole (72a)



In a reaction vial equipped with a stirring bar, was placed benzotriazole **46a** (0.03 g, 0.25 mmol), The TBDMS ether of 2-phenylethanol **71** (0.295 g, 1.25 mmol) and $RuCl_3 \cdot 3H_2O$ (0.0065 g, 0.025 mmol). To this mixture was added 0.5 mL of 1,2-DCE followed by *tert*-butyl hydroperoxide (0.23 mL, 1.25 mmol), dropwise under a nitrogen atmosphere. The mixture was stirred at 50 ºC and the reaction progress was monitored by TLC. Even after 96 h, TLC analysis of the reaction mixture showed incomplete consumption of **46a**. Nevertheless, the reaction mixture was evaporated to dryness under reduced pressure. The crude residue so obtained was purified by column chromatography (SiO_2, 200-300 mesh). Before loading the crude mixture, the column was first eluted with 10% Et_3N/hexanes. The crude mixture was then loaded on to the column by dissolving in hexanes. Elution with 1% acetone in hexanes gave **72a** (8.7 mg, 10%) as a clear, gummy material. R_f (SiO_2/20% EtOAc in hexanes) = 0.67. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, 1H, Ar–H, J = 8.4 Hz), 7.78 (d, 1H, Ar–H, J = 8.3 Hz), 7.47 (t, 1H, Ar–H, J = 8.1 Hz), 7.37 (t, 1H, Ar–H, J = 8.1 Hz), 7.27-7.22 (m, 3H, Ar–H), 7.14 (m, 2H, Ar–H), 6.57 (dd, 1H, CH, J = 4.9, 7.9 Hz), 3.47 (dd, 1H, CH, J = 7.9, 13.5 Hz), 3.31 (dd, 1H, CH, J = 4.9, 13.5 Hz), 0.73 (s, 9H, *t*-Bu), –0.15 (s, 3H, CH_3), –0.38 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.9, 135.6, 131.5, 129.9, 128.6, 128.5, 127.3, 124.2, 120.2, 111.9, 86.2, 44.3, 25.6, 18.0, –5.4, –5.7. HRMS (ESI) *m/z* calcd for $C_{20}H_{28}N_3OSi$ $[M + H]^+$: 354.1996, found 354.1986.

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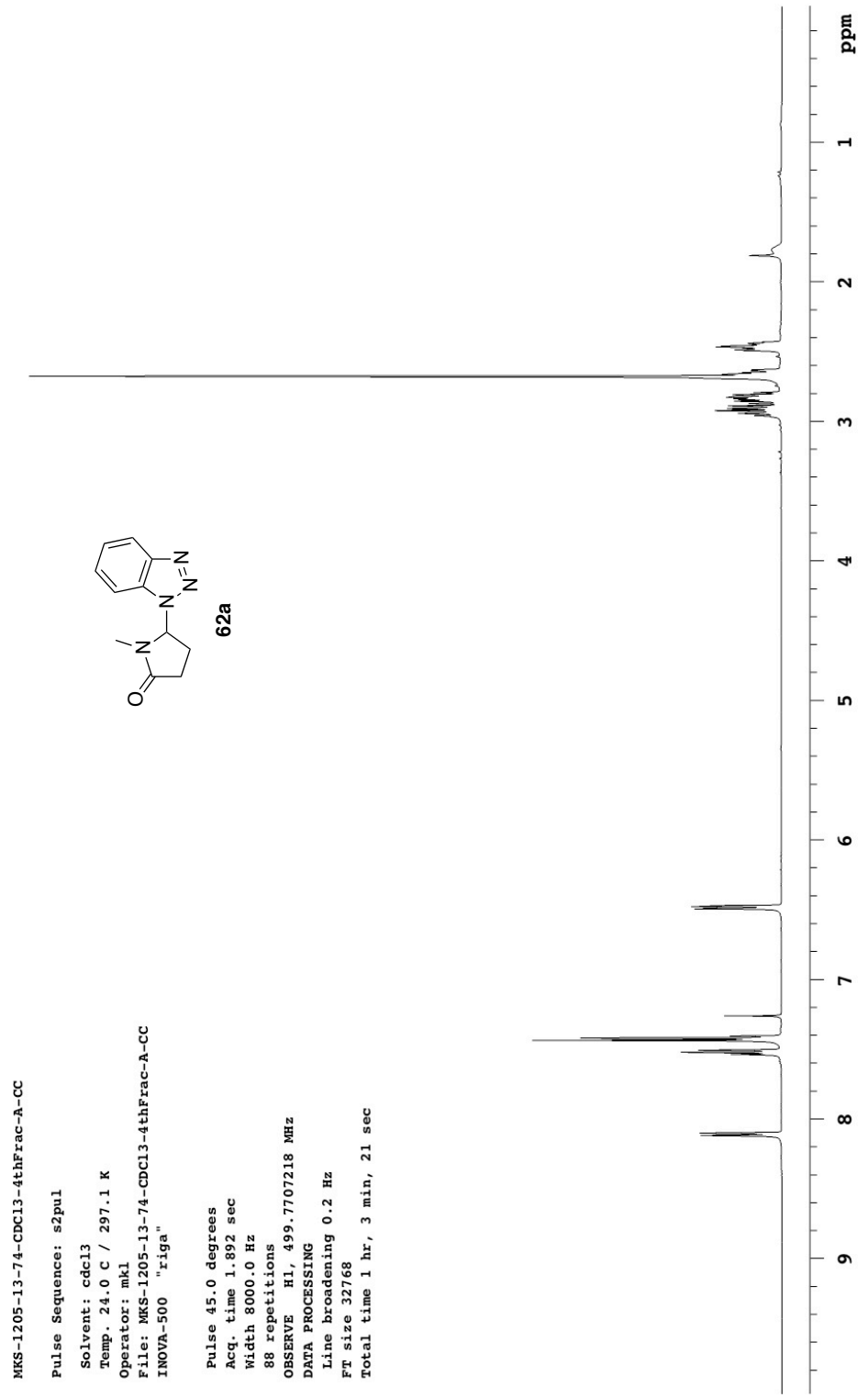
APPENDIX V

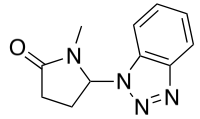

MKS-1205-13-74-CDCl3-4thFrac-A-CC
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-74-CDCl3-4thFrac-A-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
88 repetitions
OBSERVE H1, 499.7707218 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec
62a
9
8
7
6
5
4
3
2
1
ppm

MKS-1205-13-74-CDCl3-13C-4thFrac-A-CC

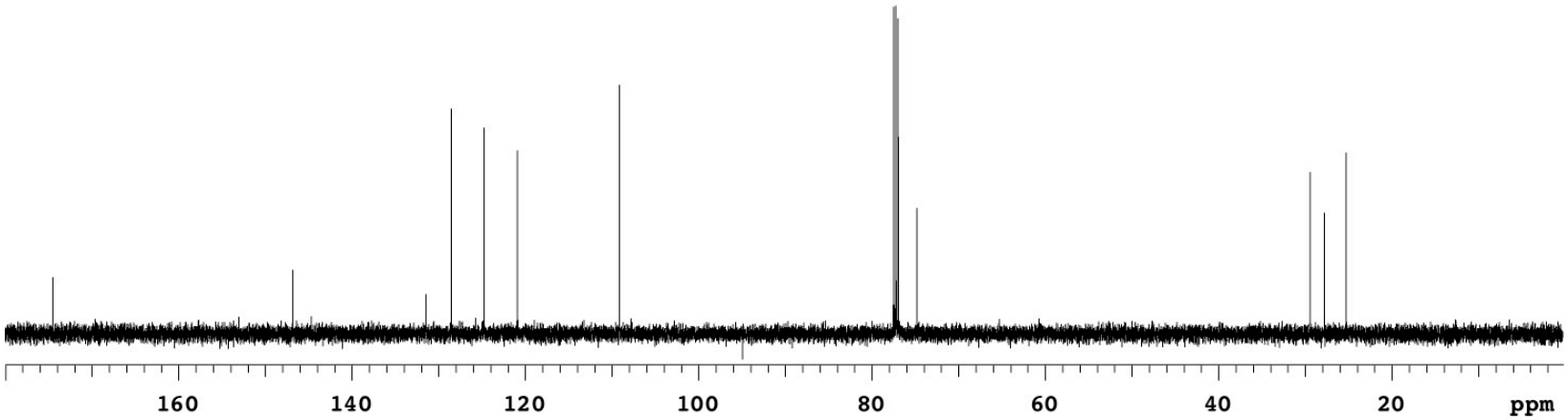
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-74-CDCl3-13C-4thFrac-A-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
232 repetitions
OBSERVE C13, 125.6674232 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



62a

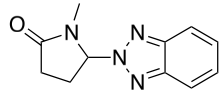


MKS-1205-13-74-CDCl3-2ndFrac-CC

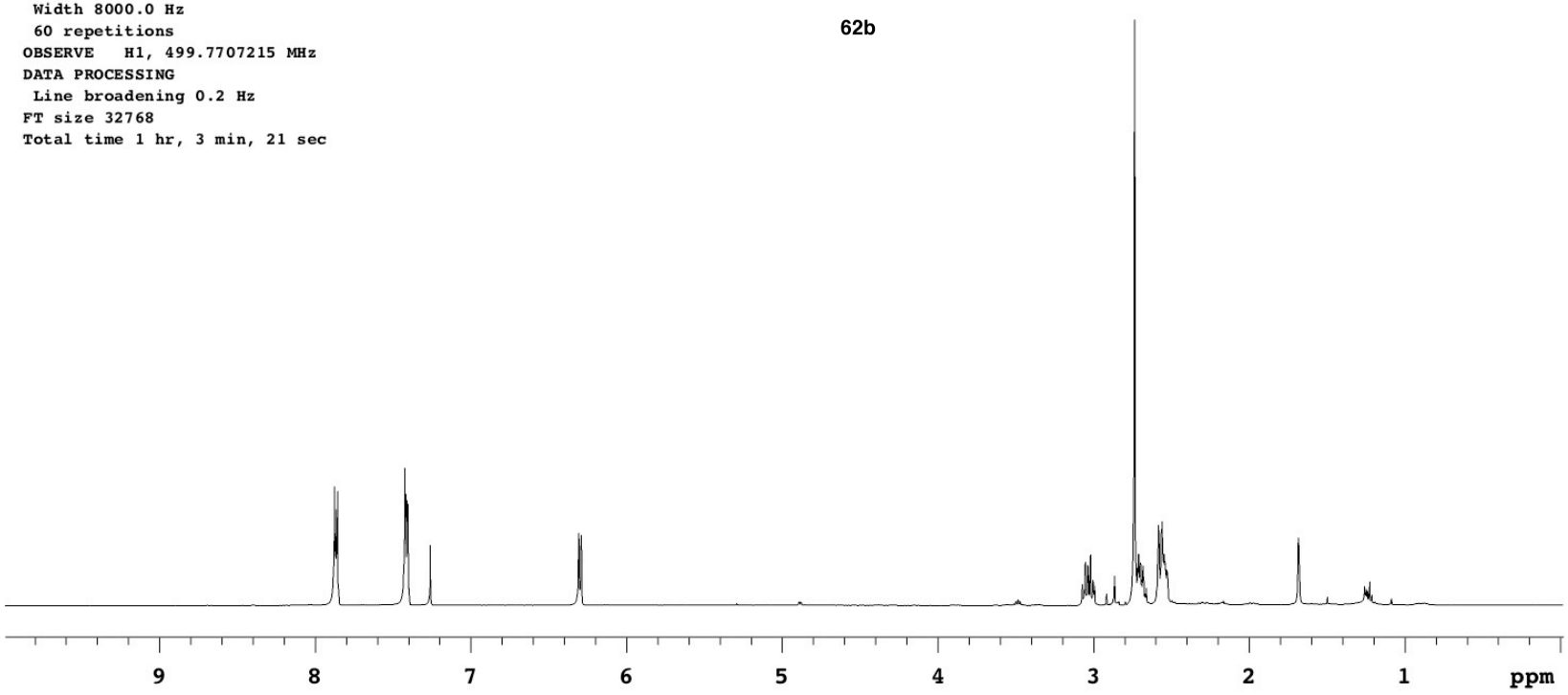
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-74-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
60 repetitions
OBSERVE H1, 499.7707215 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



62b

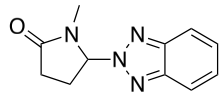


MKS-1205-13-74-CDCl3-13C-2ndFrac-CC

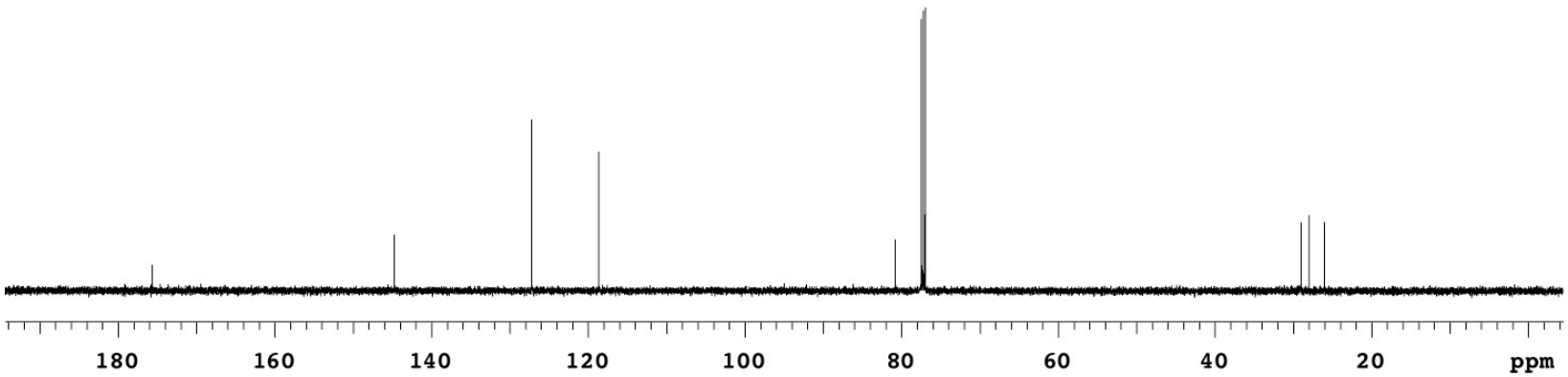
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-74-CDCl3-13C-2ndFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
624 repetitions
OBSERVE C13, 125.6674210 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



62b

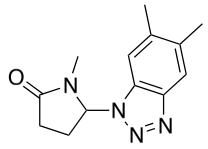


MKS-1205-13-75-CDCl3-4thFrac-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-75-CDCl3-4thFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
48 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



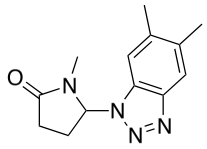
63a

MKS-1205-13-75-CDCl3-13C-4thFrac-CC

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-75-CDCl3-13C-4thFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
144 repetitions
OBSERVE C13, 125.6674251 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



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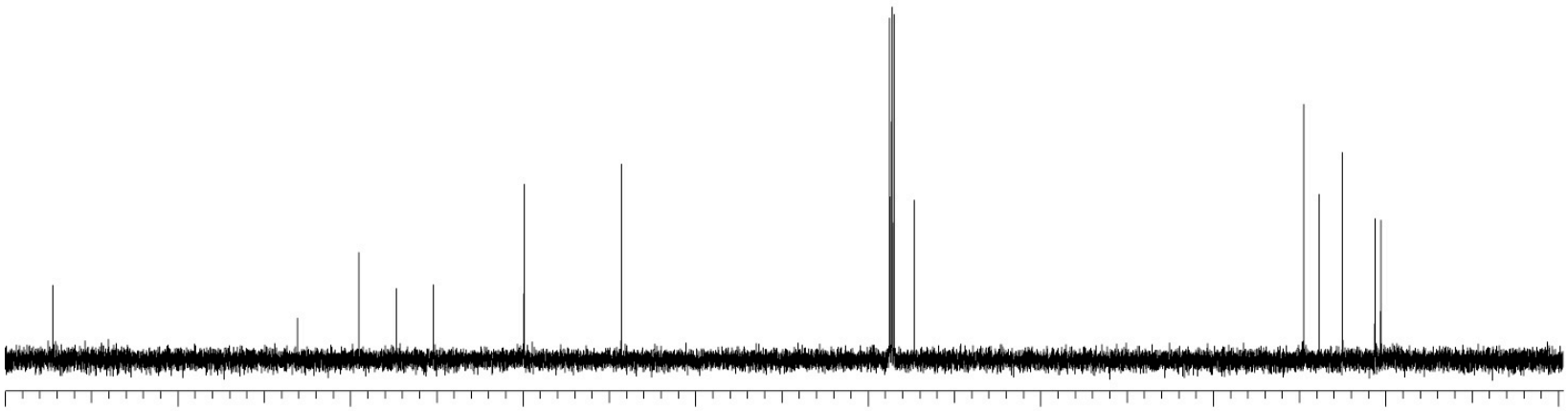
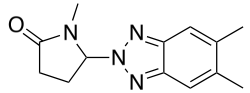


MKS-1205-13-75-CDCl3-2ndFrac-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-75-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
48 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



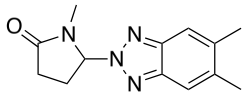
63b

MKS-1205-13-74-CDCl3-13C-2ndFrac-CC

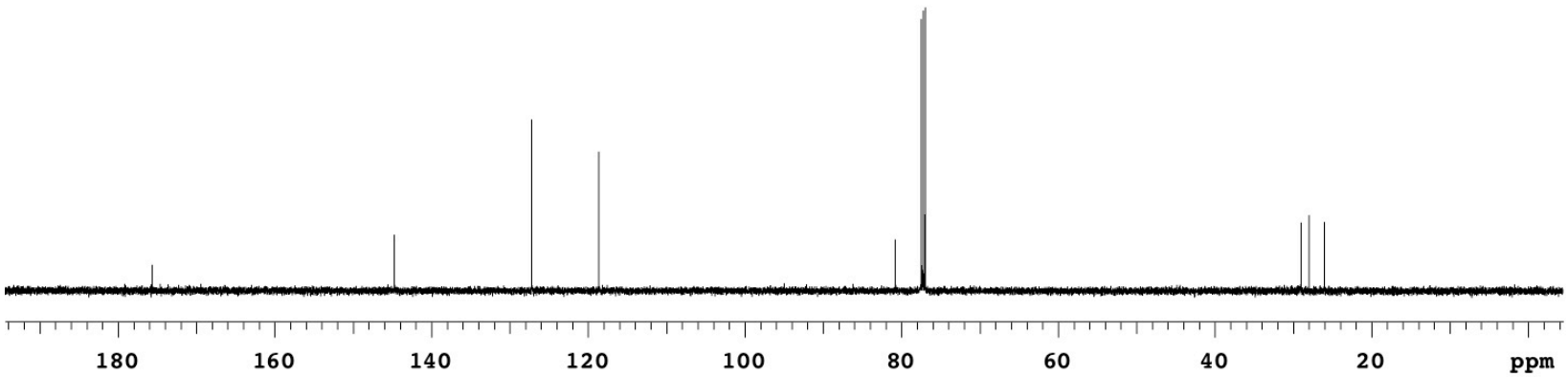
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-74-CDCl3-13C-2ndFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
624 repetitions
OBSERVE C13, 125.6674210 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



63b

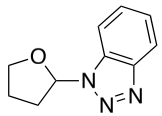


MKS-1205-13-06-CDCl3-2ndFrac-CC

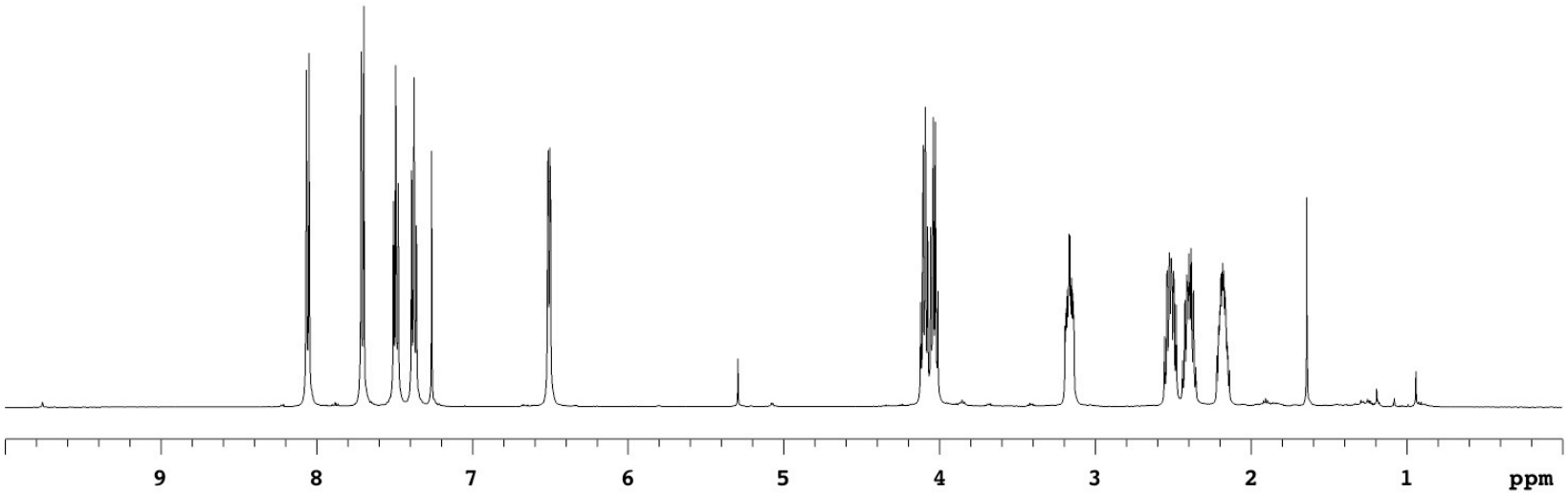
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-13-06-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
52 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



64a

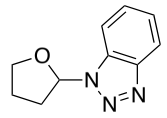


MKS-1205-13-06-CDCl3-13C-2ndFrac-CC

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-13-06-CDCl3-13C-2ndFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
2048 repetitions
OBSERVE C13, 125.6674217 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 hr, 27 min, 5 sec



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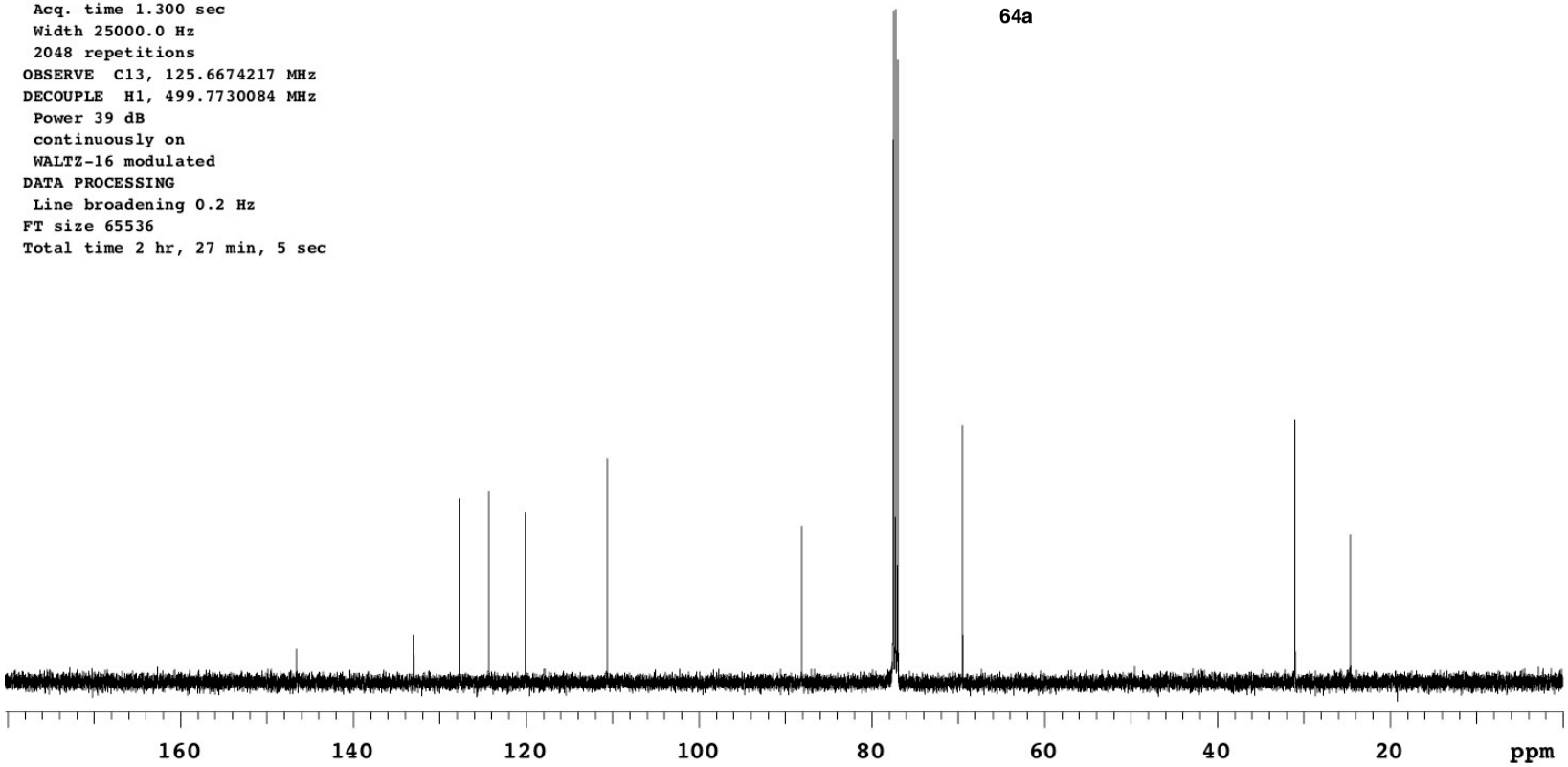
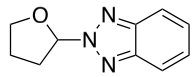


MKS-1205-13-06-CDCl3-1stFrac-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-13-06-CDCl3-1stFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
68 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



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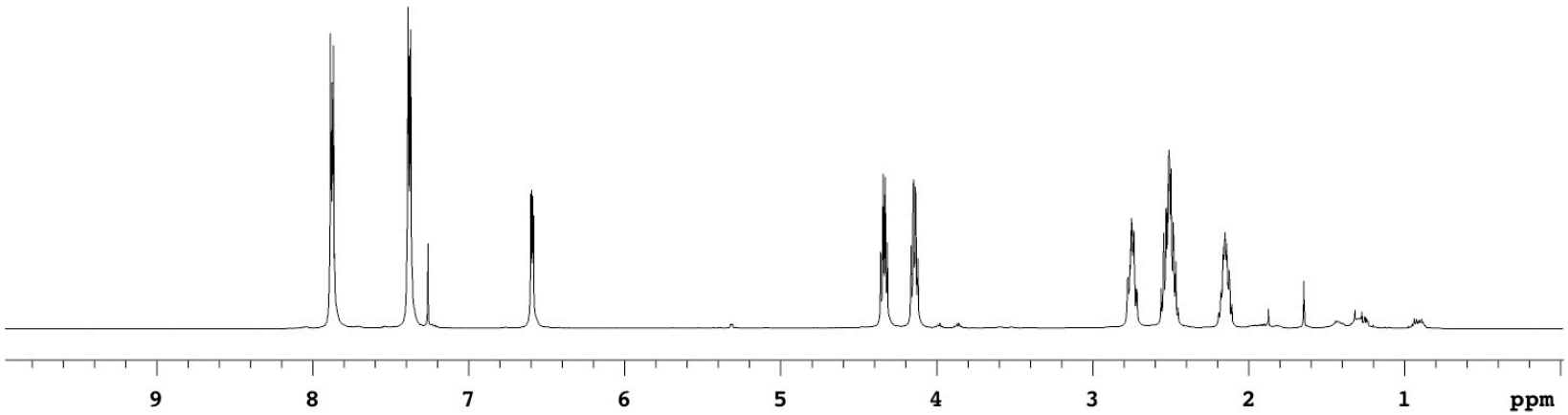
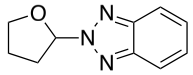


MKS-1205-13-06-13C-CDCl3-1stFrac-CC

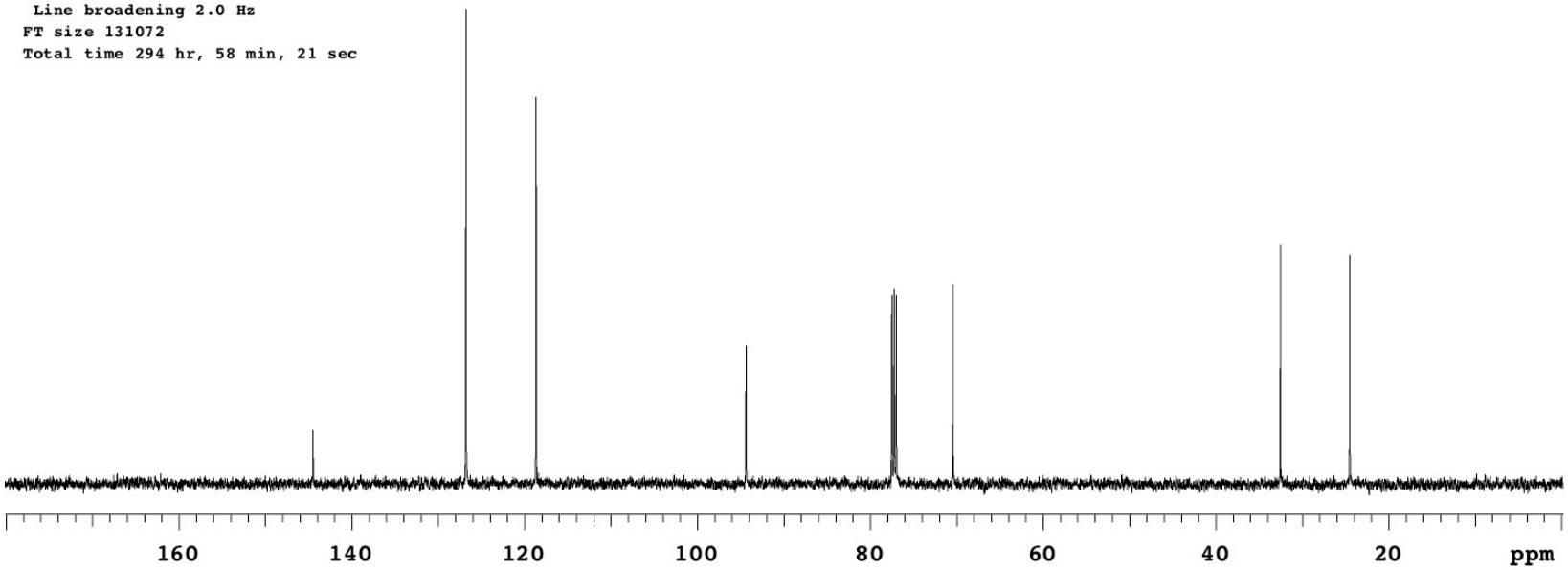
Pulse Sequence: s2pul

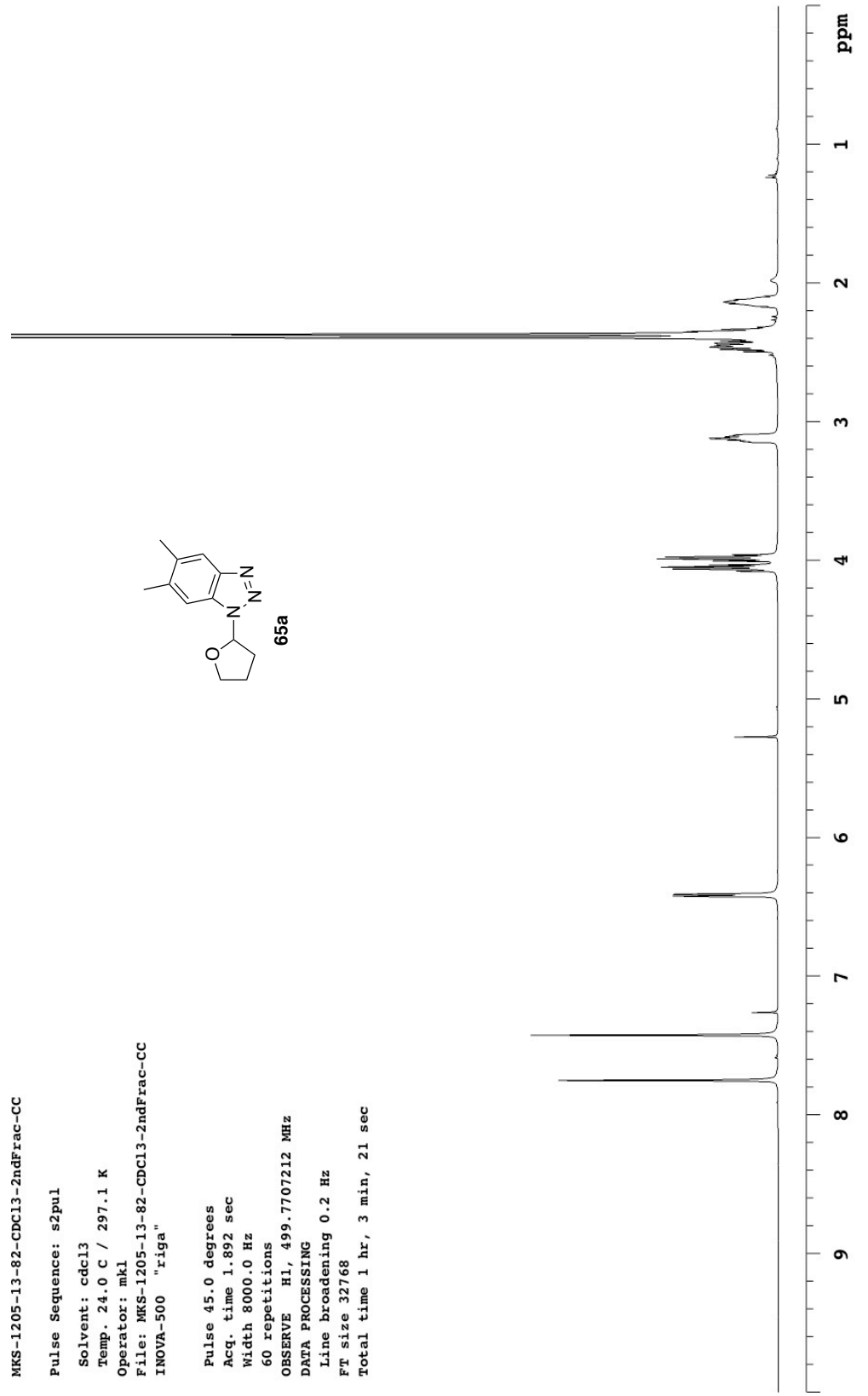
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-13-06-13C-CDCl3-1stFrac-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
144 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 294 hr, 58 min, 21 sec



64b

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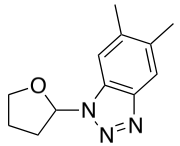
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-82-CDCl3-2ndFrac-CC
INOVA-500 "riga"
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
60 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec
65a
9
8
7
6
5
4
3
2
1
ppm

MKS-1205-13-82-CDCl3-13C-2ndFrac-CC

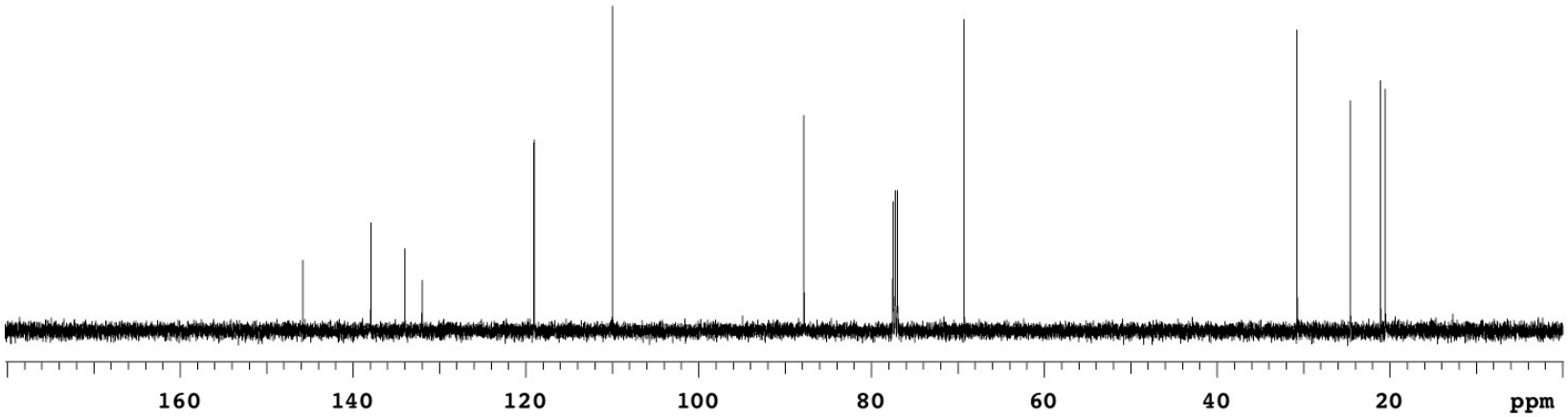
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-82-CDCl3-13C-2ndFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
80 repetitions
OBSERVE C13, 125.6674278 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



65a

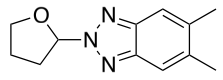


MKS-1205-13-82-CDCl3-1stFrac-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-82-CDCl3-1stFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
56 repetitions
OBSERVE H1, 499.7707221 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



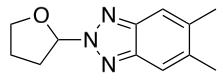
65b

MKS-1205-13-82-CDCl3-13C-1stFrac-CC

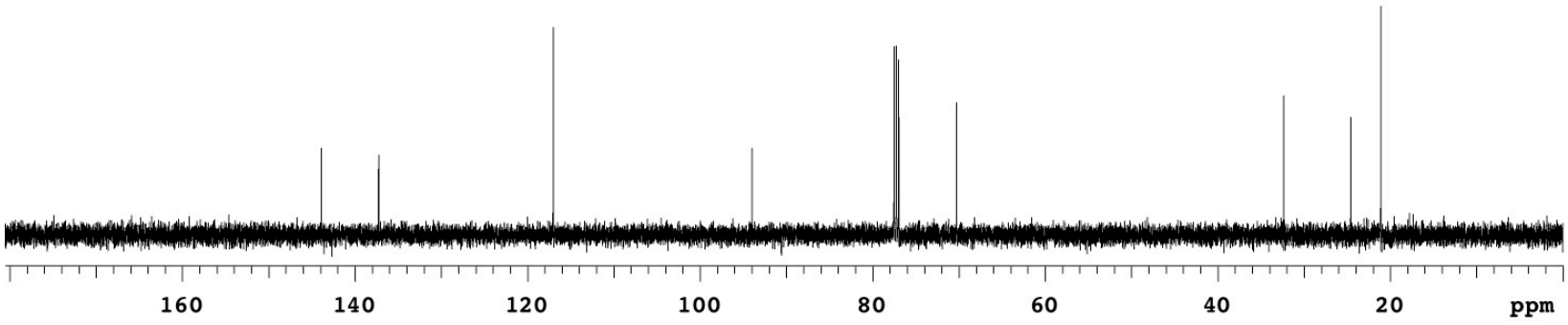
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-82-CDCl3-13C-1stFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
36 repetitions
OBSERVE C13, 125.6674232 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



65b

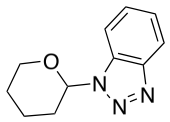


MKS-1205-13-10-CDCl3-2ndFrac-CC

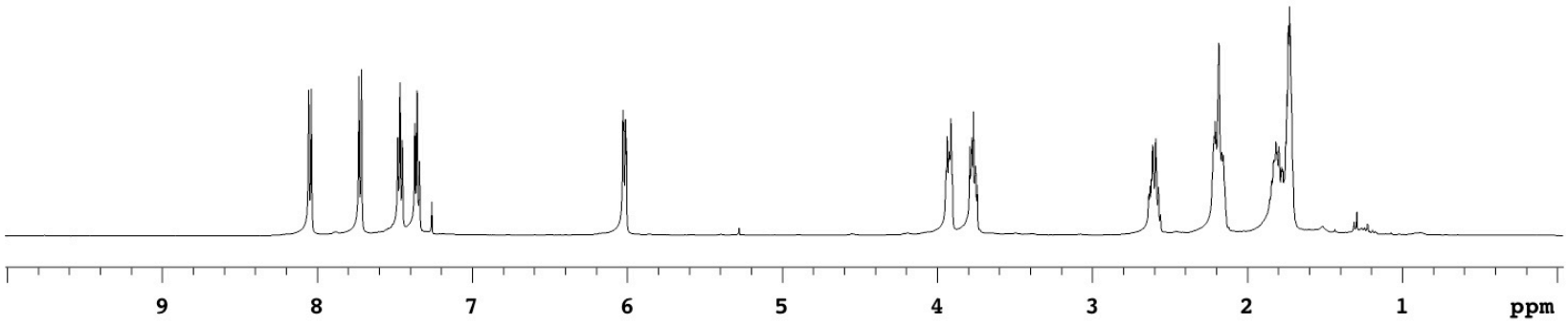
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-10-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
48 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



66a

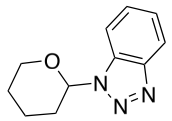


MKS-1205-13-10-CDCl3-13C-2ndFrac-CC

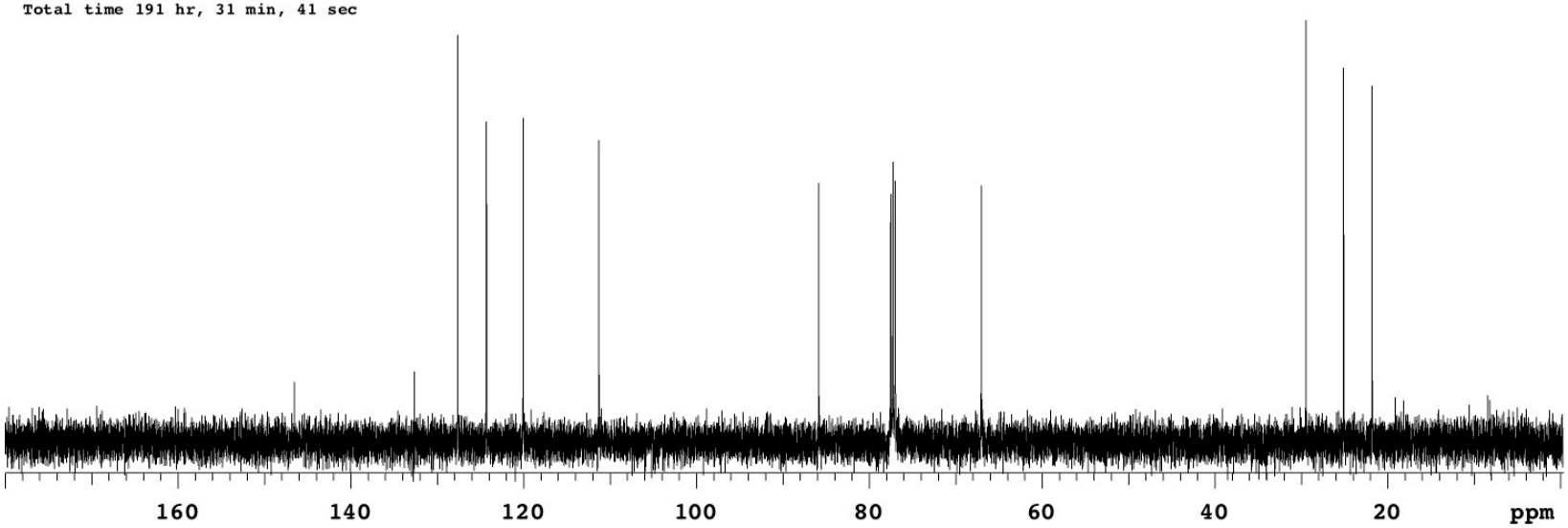
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-10-CDCl3-13C-2ndFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
60 repetitions
OBSERVE C13, 125.6674263 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



66a

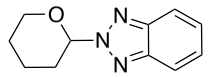


MKS-1205-13-10-CDCl3-1stFrac-CC

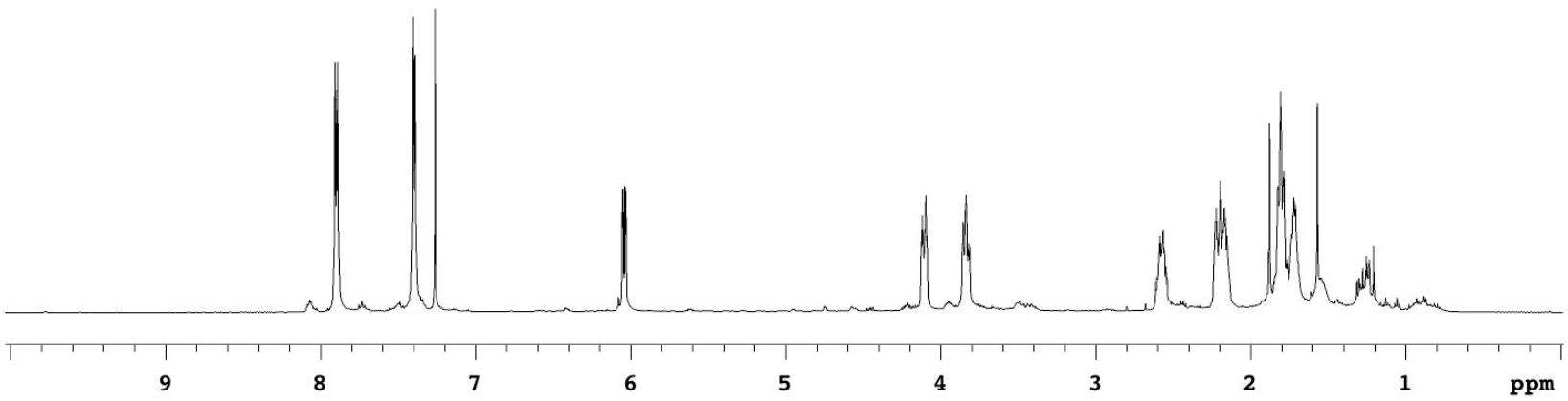
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-13-10-CDCl3-1stFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
88 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



66b

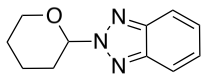


MKS-1205-13-10-CDCl3-13C-1stFrac-CC

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-10-CDCl3-13C-1stFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
1116 repetitions
OBSERVE C13, 125.6674194 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



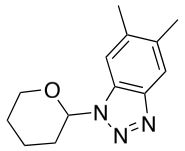
66b

MKS-1205-13-49-CDCl3-2ndFrac-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-49-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
52 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



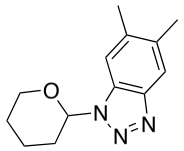
67a

MKS-1205-13-49-CDCl3-13C-2ndFrac-CC

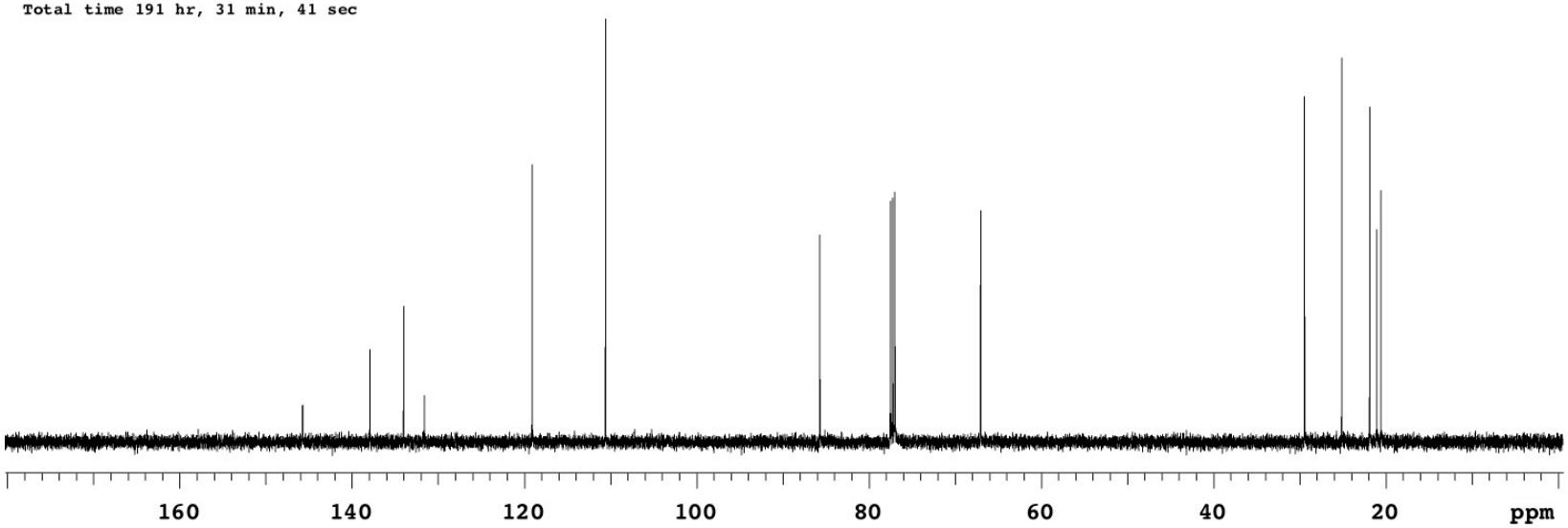
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-49-CDCl3-13C-2ndFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
320 repetitions
OBSERVE C13, 125.6674263 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



67a

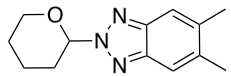


MKS-1205-13-49-CDCl3-1stFrac-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-49-CDCl3-1stFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
56 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



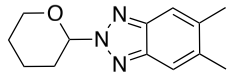
67b

MKS-1205-13-49-CDCl3-13C-1stFrac-CC

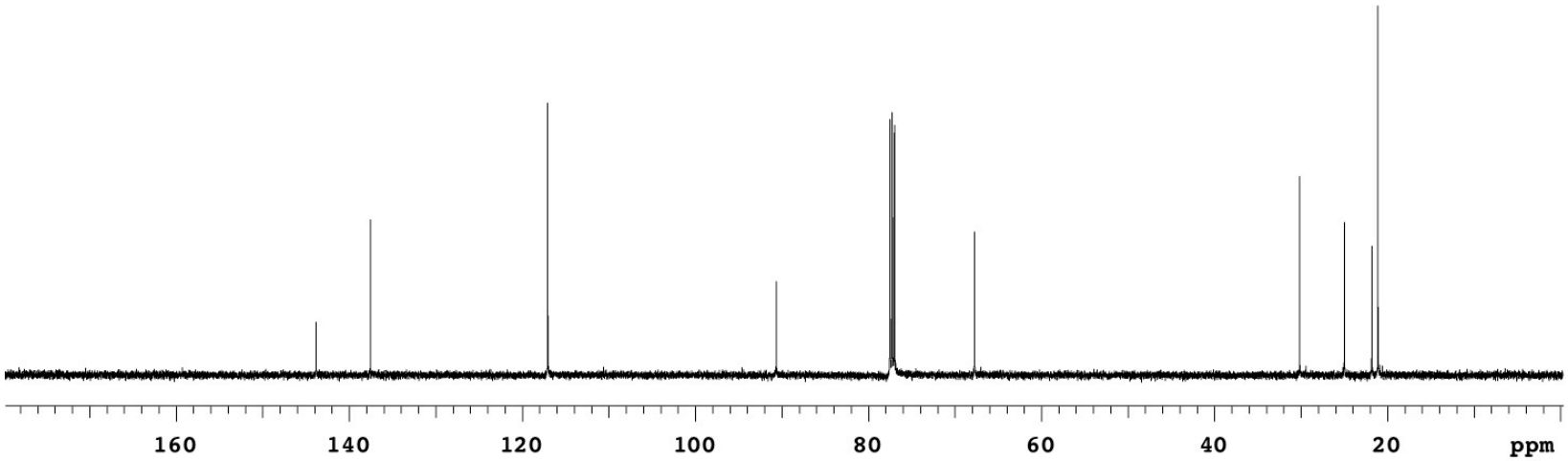
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-49-CDCl3-13C-1stFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
1240 repetitions
OBSERVE C13, 125.6674232 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



67b

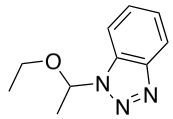


MKS-1205-13-41-CDCl3-2ndFrac-CC

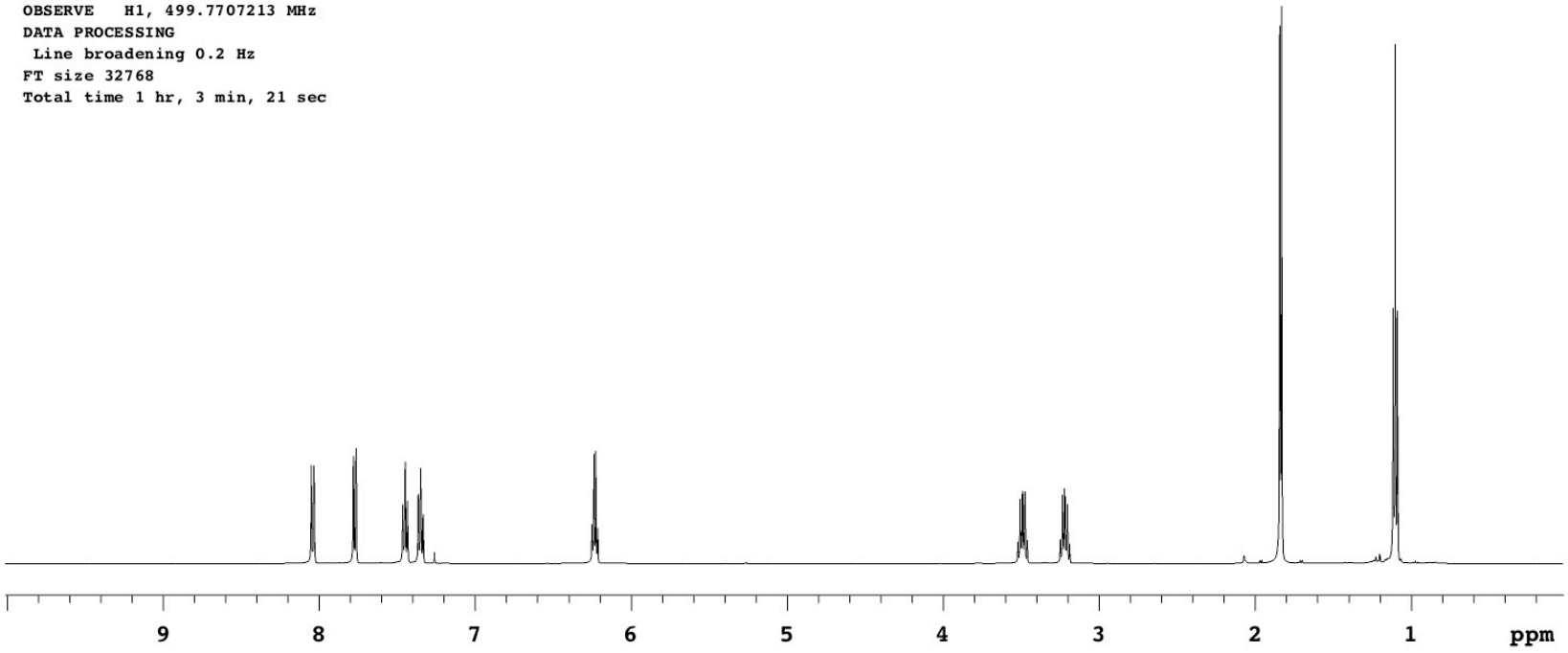
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-13-41-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
56 repetitions
OBSERVE H1, 499.7707213 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



68a

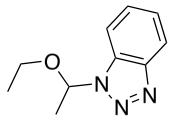


MKS-1205-13-41-CDCl3-13C-2ndFrac-CC

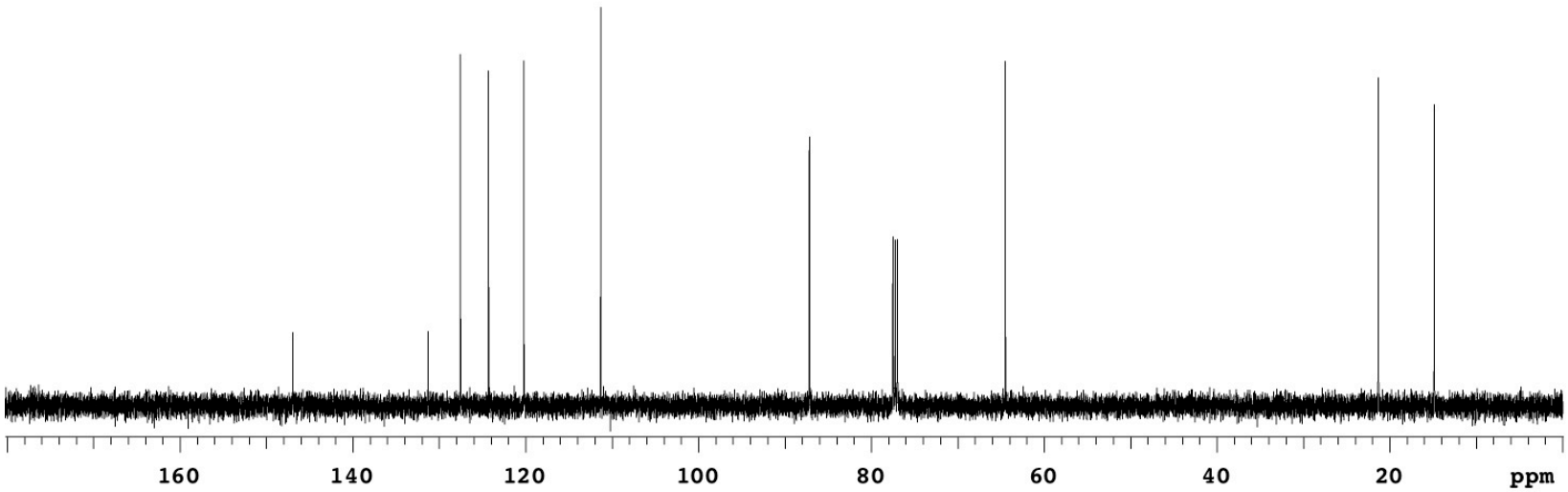
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-41-CDCl3-13C-2ndFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
40 repetitions
OBSERVE C13, 125.6674286 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



68a

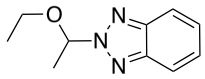


MKS-1205-13-41-CDCl3-1stFrac-CC

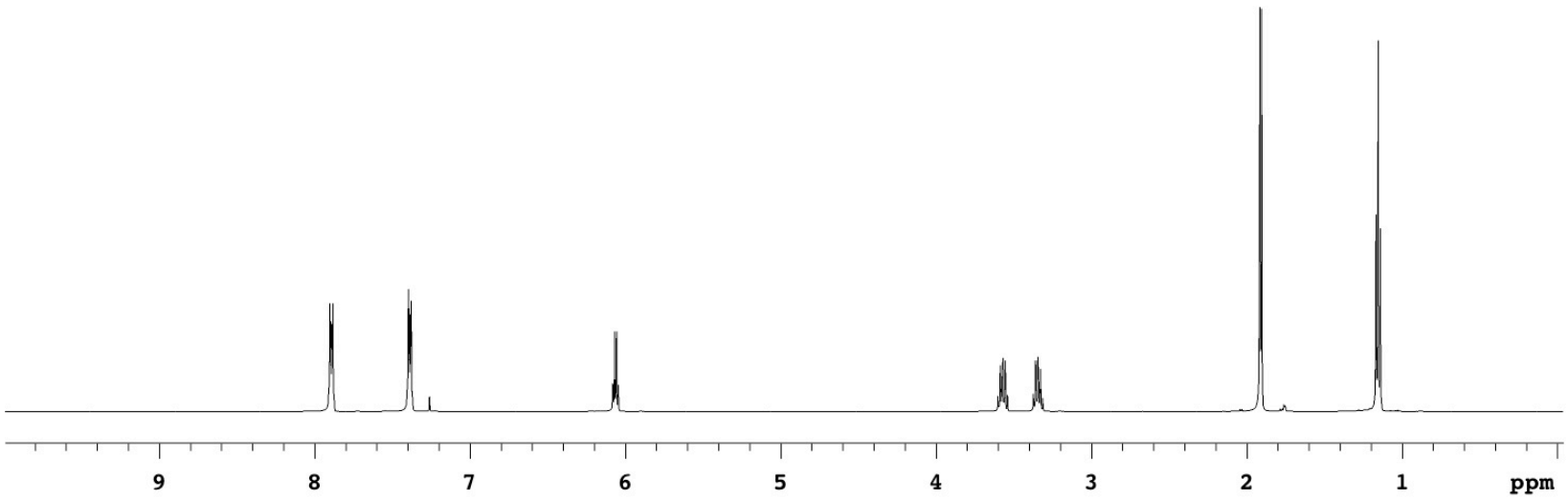
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-13-41-CDCl3-1stFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
48 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



68b

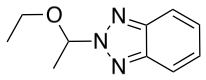


MKS-1205-13-41-CDCl3-13C-1stFrac-CC

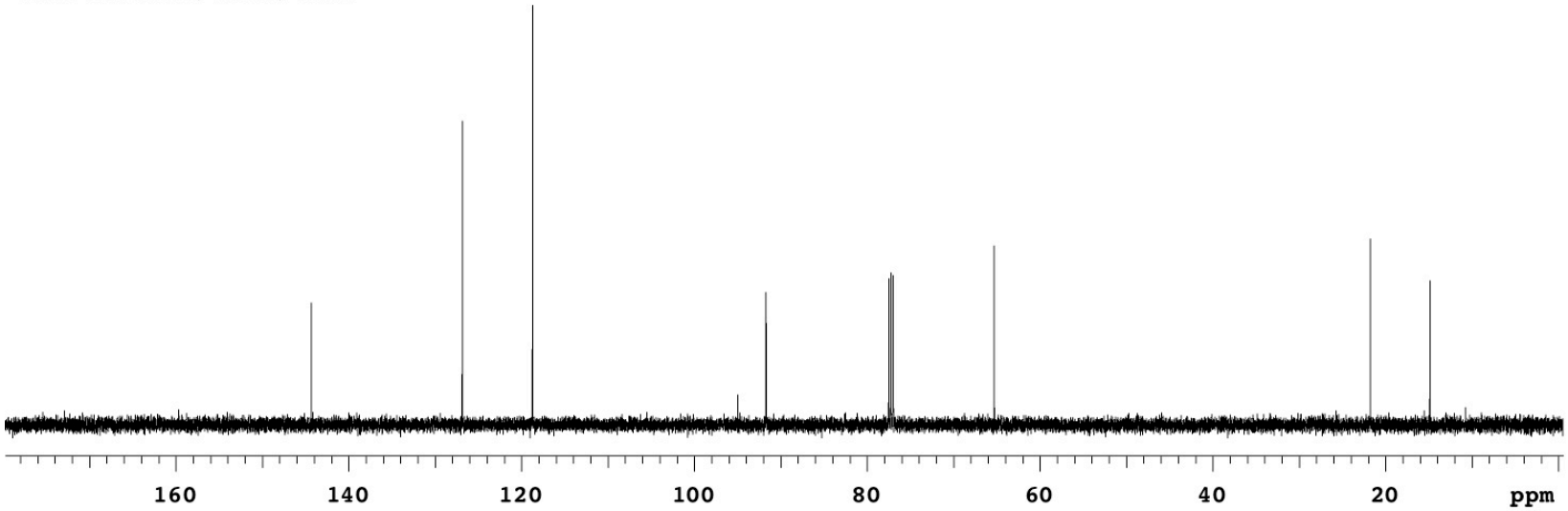
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-41-CDCl3-13C-1stFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
56 repetitions
OBSERVE C13, 125.6674223 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



68b

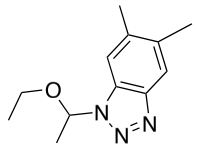


MKS-1205-13-43-CDCl3-2ndFrac-CC

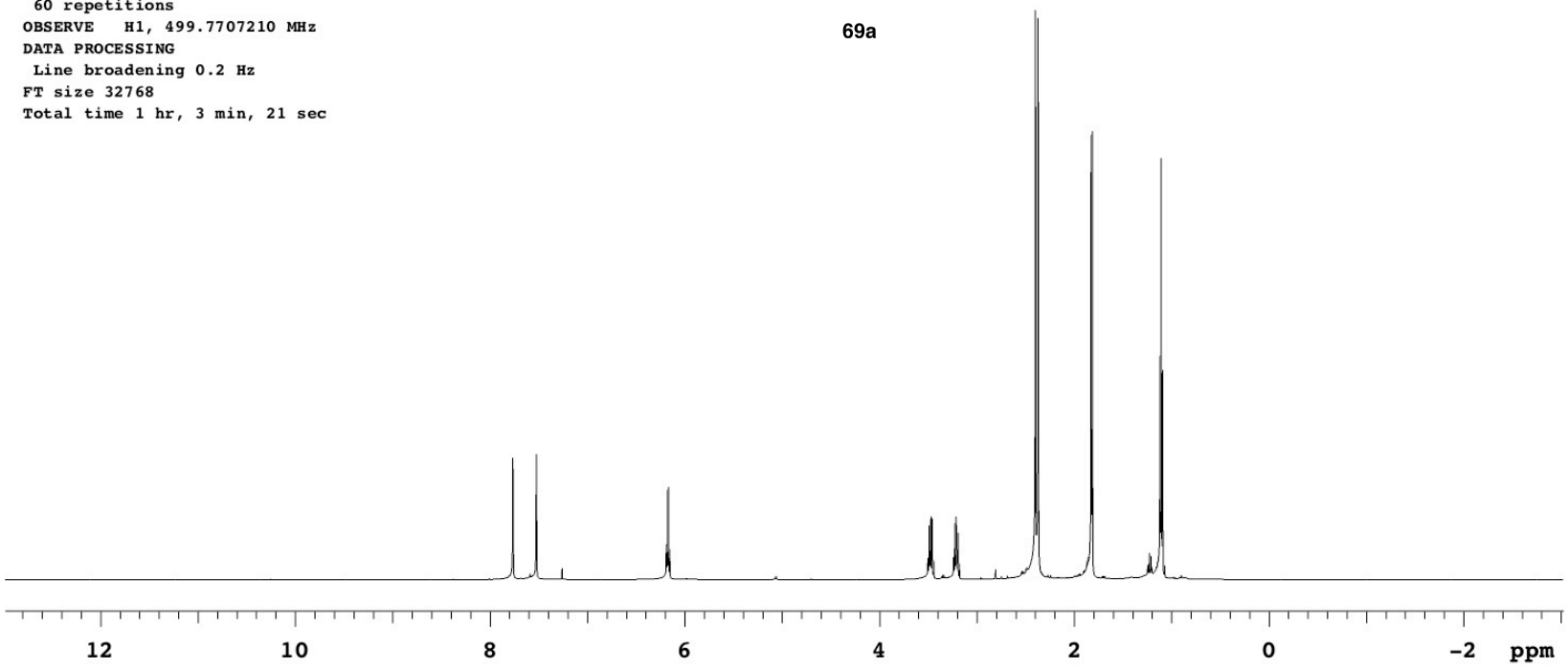
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-43-CDCl3-2ndFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
60 repetitions
OBSERVE H1, 499.7707210 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



69a

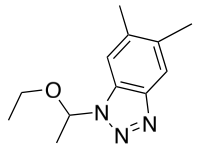


MKS-1205-13-43-CDCl3-13C-2ndFrac-CC

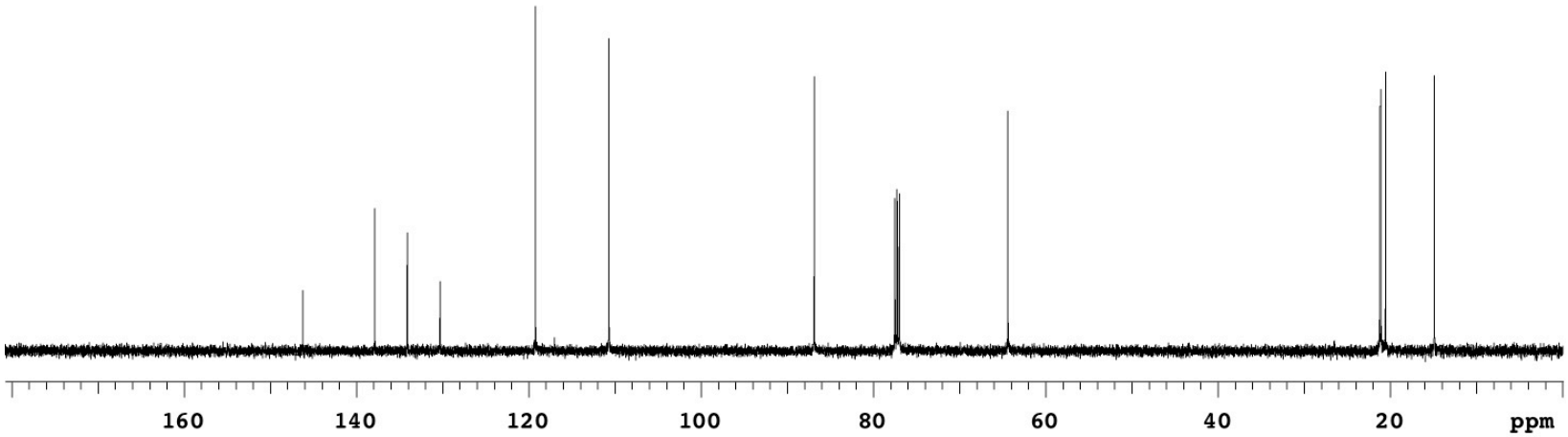
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-43-CDCl3-13C-2ndFrac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
492 repetitions
OBSERVE C13, 125.6674276 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



69a

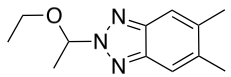


MKS-1205-13-43-CDCl3-1stFrac-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-43-CDCl3-1stFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
84 repetitions
OBSERVE H1, 499.7707210 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



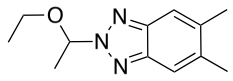
69b

MKS-1205-13-43-CDCl3-13C-1st-Frac-CC

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 24.0 C / 297.1 K
Operator: mkl
File: MKS-1205-13-43-CDCl3-13C-1st-Frac-CC
INOVA-500 "riga"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
10400 repetitions
OBSERVE C13, 125.6674187 MHz
DECOUPLE H1, 499.7730084 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 191 hr, 31 min, 41 sec



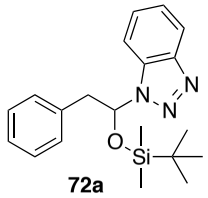
69b

MKS-1205-13-29-CDCl3-1stFrac-CC

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-13-29-CDCl3-1stFrac-CC
INOVA-500 "riga"

Pulse 45.0 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
88 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 hr, 3 min, 21 sec



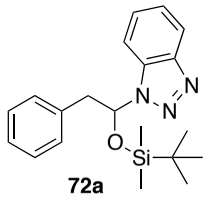
72a

MKS-1205-13-29-CDCl3-13C-1stFrac-CC

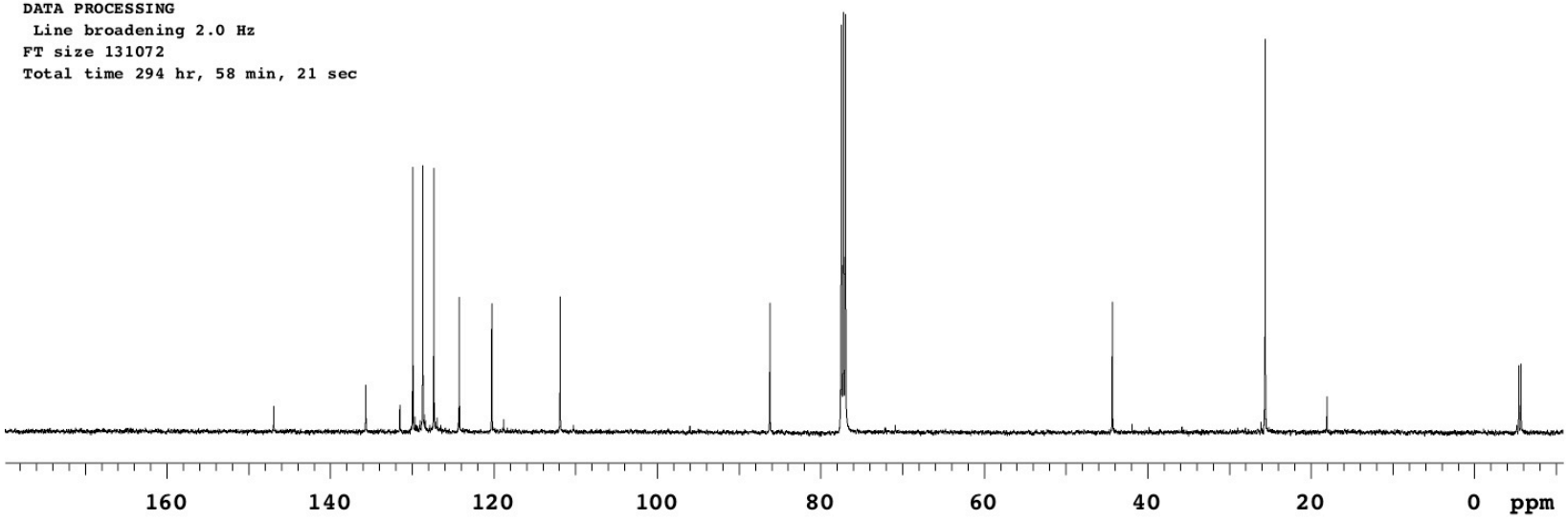
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: mkl
File: MKS-1205-13-29-CDCl3-13C-1stFrac-CC
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
9384 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 294 hr, 58 min, 21 sec



72a



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