Synthetic Studies of Bioactive Nature Products:

Azaspiracid-1 and Angelmicins

By

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ABSTRACT

Synthetic Studies of Bioactive Nature Products: Azaspiracid-1 and Angelmicins

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Adviser: Professor David R. Mootoo

The trioxadispiroketal residue in the marine biotoxin azaspiracid-1, which exists in a configuration capable of a double anomeric effect, is believed to be the thermodynamically most stable bis-acetal diastereomer. In order to get insight into how structural factors affect this equilibrium, a simplified ABC trioxadispiroketal analog of azaspiracid-1 was synthesized and subjected to equilbration and computational studies. These results suggest that while a double anomeric effect may play a major role in the stability of the trioxadispiroketal configuration in the more complex natural product, the substituion pattern of the C ring is also a contributing factor.

Angelmicins B (hibarimicin B) was first isolated from *Microbispora rosea* by Uehara and co-workers in 1993. It is a potent *v-Src* protein tyrosine kinase (PTK) inhibitor (IC_{50}=23 μM), and also shows growth inhibiting and differentiation inducing activity on human myeloid leukemia (HL-60) cell lines (IC_{50}=57 nM).

The work reported in this part of the thesis presents a divergent synthetic strategy for the angelimicin family of anthraquinoid natural products, involving conversion of a central highly oxygenated decalin intermediate to the AB and A'B' subunits. The strategy centers on an intramolecular Diels−Alder (IMDA) reaction on a triene to provide the complex highly oxygenated decalin, which is elaborated to tricyclic

AB and bicyclic A'B' subunits. The differentiating tact in the two syntheses is control of the Suárez radical fragmentation of lactol precursors by modulation of the structural rigidity of the substrate. A more flexible lactol gave the AB tricyclic framework, whereas a more rigid substrate led to the A'B' bicyclic precursor, presumably through divergent pathways from the radical produced in the initial fragmentation step.

Given the symmetry with respect to the biaryl bond of HMP-Y (hibarimicin-mutant product Y1, a biosynthesis precursor of angelmicin B), a bi-directional synthesis is attempted. The bi-directional donors for Hauser annulation and Michael-Dieckmann condensation were synthesized from known 2,3,5-trimethoxytoluene in 27% and 42% yield, respectively. When they are applied to the annulation with cyclohex-2-enone, the Hauser annulation was unsuccessful while Michael-Dieckmann condensation gave 40% yield. However, the subsequent required aromatization of Michael-Dieckmann condensation product was unsuccessful.

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This dissertation is dedicated to

My most deeply loved ones:

My Mom and Dad

My Brother and nephew

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Lists of Symbols and Abbreviations

[α]	specific rotation
Ac	acetyl
Ac_2O	acetic anhyride
Bn	benzyl
Boc	*t*-butyl carbonate or *t*-butyl carbamate
brsm	based on recovering starting materials
Bu	butyl
c	concentration
calcd.	calculated
cat.	catalytic
cm	centimeter
COSY	correlation spectroscopy
conc.	concentrated
m-CPBA	*meta*-chloroperoxybenzoic acid
δ	chemical shift
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DIB	diacetoxyiodosobenzne
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzenoquinone
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide

DMSO	dimethyl sulfoxide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
Et	ethyl
EtOAc	ethyl acetate
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilylazide
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single-quantum correlation spectroscopy
Hz	hertz
IBX	2-Iodoxybenzoic acid
IDCP	iodonium dicollidine perchlorate
imid.	imidazole
KHMDS	potassium bis(trimethylsilyl)amide
M	molar
Me	methyl
mg	milligram
MHz	megahertz
min	minutes
mmol	millimole
M.p.	melting point
MS	mass spectroscopy
m.s.	molecular sieves
μL	micro liter

NBS	N-bromosuccinimide
nM	nanomolar
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Ph	phenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
r. t.	room temperature
TBAF	tetra-n-butylammonium fluoride
TBS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

Chapter 1. Synthetic and Computational Studies on the ABC Trioxadispiroketal Subunit of the Marine Biotoxin Azaspiracid-1

1.1 Introduction and Background

Azaspiracid-1 (**1.1**), which belongs to a group of potent and structurally complex polyether biotoxins, was first detected in mussels (*mytilus edulis*) in Ireland in 1995.[1] Although the symptoms of azaspiracid poisoning are similar to those associated with the more well-known shellfish toxin, okadaic acid, the mechanism of action of the two biotoxins are believed to be different.[2, 3] The unusual activity and the structural complexity of the azaspiracids have stimulated considerable synthetic interest, the most notable study being the Nicolaou's total synthesis of azaspiracid-1, which led to correction of originally reported structure.[4] The synthesis of **ent-1.1** was subsequently reported by the Evans group.[5] In the correct structure, the alkene in ring A is located at C_7-C_8 and the configuration of the trioxadispiroketal corresponding to a double anomeric effect.[6] Our laboratory and the groups of Carter ad Forsyth, as well as have completed syntheses of the ABCD subunit[7, 8g, 9f] and several synthetic studies on less complex segments have been reported.[8, 9, 10]

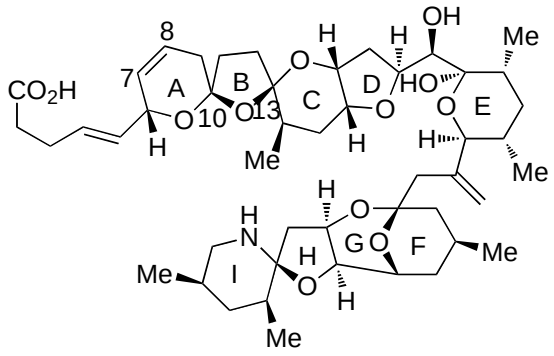
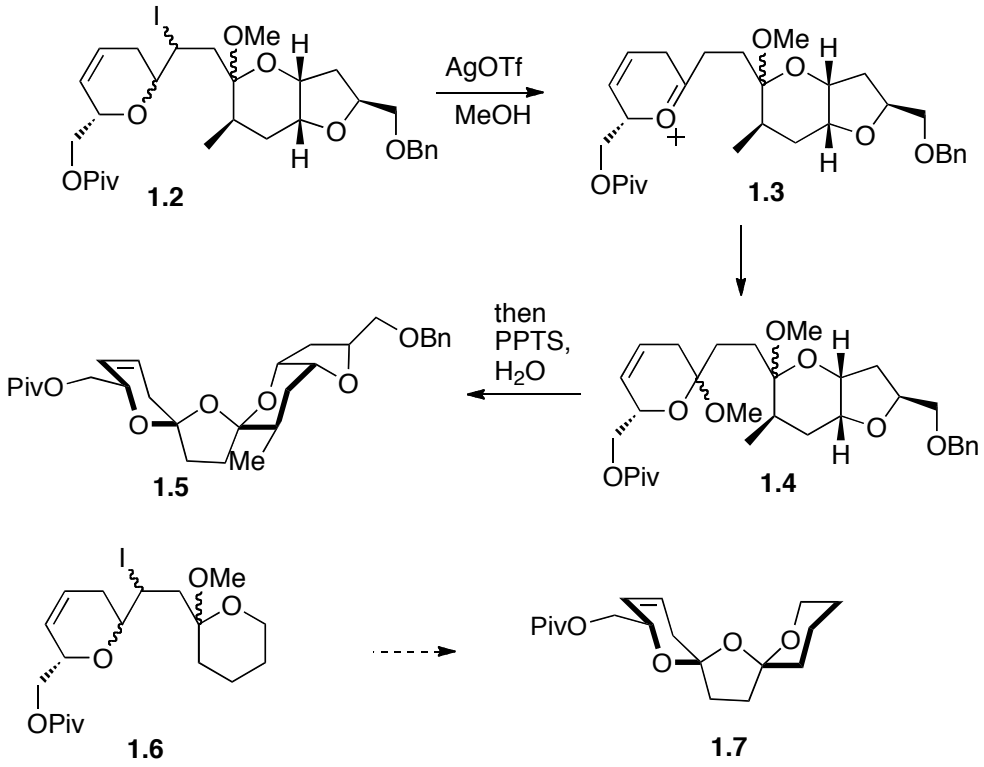


Figure 1.1 Azaspiracid-1

An interesting structure feature of the azaspiracid-1 is the configuration of the trioxadispiroketal, which is such that it allows for a conformation in which the exocyclic oxygen on both tetrahydropyranyl rings are axially positioned, i.e. a double anomeric

effect. Accordingly, it has been suggested that the naturally occurring diastereomer of azaspiracid-1 corresponds to the thermodynamically most stable motif. Indeed, it has been shown that the natural trioxadispiroketal is generated as the exclusive or major diastereomer under conditions which may allow for product equilibration.[11] In our own investigation of this issue we observed that exposure a methanolic solution of the iodide **1.2** to silver trifluoromethanesulfonate (AgOTf) followed by addition of water and pyridinium p-toluensulfonate (PPTS) to the reaction mixture afforded **1.5** as a single trioxadispiroketal product (**Scheme 1.1**).[7] This unusual spiroketalization methodology was conceived with potentially labile substrates like azaspiracids in mind and is presumed to proceed via the silver (I) mediated transformation of **1.2** the six-member-ring oxocarbenium ion **1.3**, thence an intermediate bismethyl acetal **1.4**. Under the aqueous acidic conditions, **1.4** undergoes hydrolysis, followed by dispiroketalization to give **1.5**. In order to assess the impact of the double anomeric effect on trioxadispiroketal equilibration, relative to other substituent effects, we undertook a synthetic and computational investigation on the ABC trioxadispiroketal analogue **1.7**, which contains a simplified C-ring residue.[12] These results are described herein.

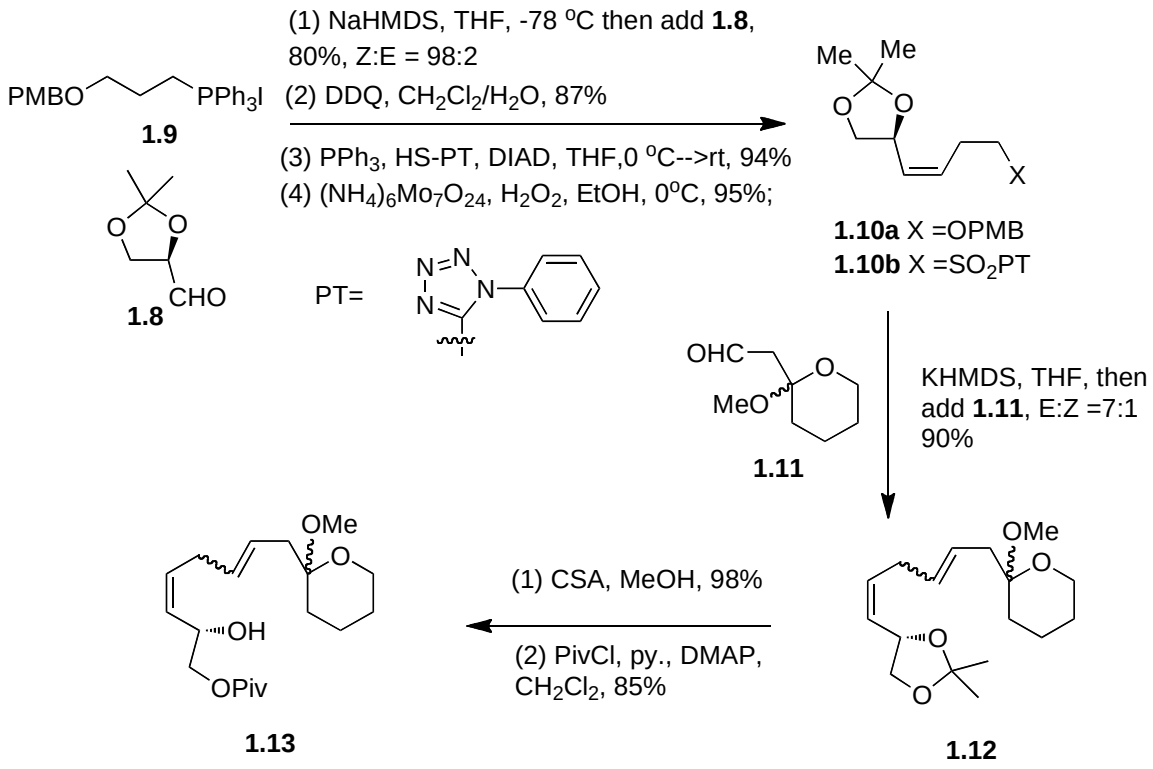


Scheme 1.1

1.2 Results and Discussion

1.2.1 Synthesis of ABC Trioxadispiroketal Analogue 1.7

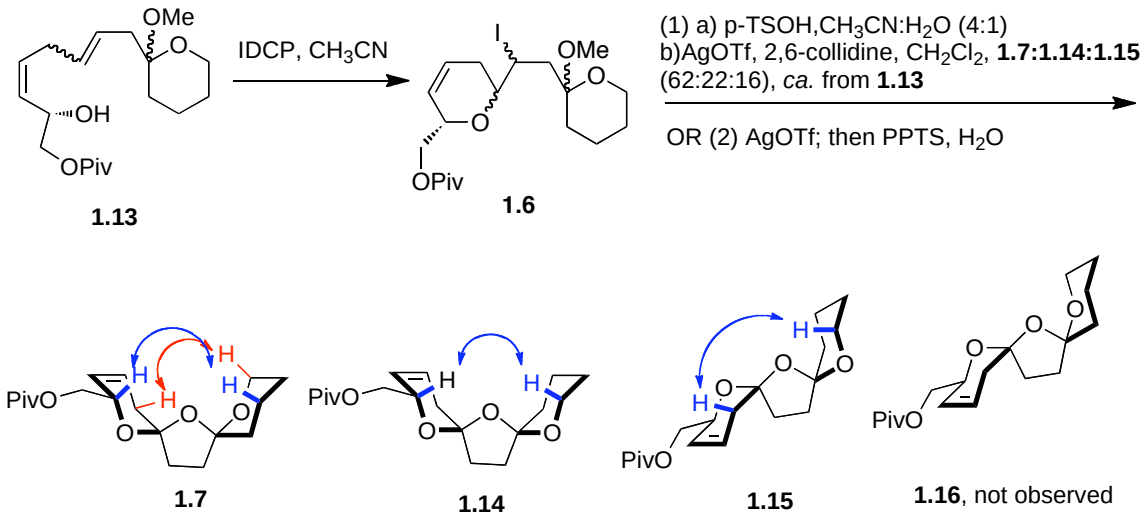
The synthesis of **1.6**, the precursor for the trioxadispiroketalization reaction started from the known aldehyde **1.8** (**Scheme 1.2**). Accordingly, sulfone **1.10b** was obtained via a standard reaction sequence form **1.8**,[13, 14] and with aldehyde **1.11**[15] was subjected to a Julia-Kocienski olefination.[16, 17] This reaction provided **1.12** in 90% yield, as a mixture of isomers (E:Z *ca* 7:1). Alcohol protecting group modification on **1.12** afforded **1.13** as a chromatographically insepareable mixture of diasteromers, (Z and E isomers with respect to the two alkenes, and an approximately 1:1 ratio of acetal anomers).



Scheme 1.2

Treatment of **1.13** with iodonium dicollidine perchlorate (IDCP), in anhydrous CH_3CN provided an unstable mixture of products (**Scheme 1.3**). NMR analysis of a partially purified sample and characterization of the eventual bis-spiroketals (*vide infra*), supported the formation of the 6-exo-trig product **1.6**, as the major component of this mixture. The crude mixture was subjected to hydrolysis of the methyl acetal using p-TsOH in wet acetonitrile. The presumed lactol product was also unstable, and the crude material was therefore treated without purification, in anhydrous CH_2Cl_2, with silver triflate. These conditions led to a 62:22:16 mixture of three bis-spiroketal isomers **1.7**:**1.14**:**1.15** in approximately 40% overall yield from **1.5**. Since the bis-spiroketalization step in the synthesis of the more complex ABCD analog **1.5** was

performed using a different reaction conditions (i.e. PPTS, MeOH-H_2O vs. CH_2Cl_2), for more accurate comparison of the results, the present synthesis was repeated following the identical conditions used for **1.5**. Thus, a solution of crude methyl acetal **1.6** in methanol was treated directly with AgOTf, following which water and PPTS were added to the reaction mixture. However, this modification had no significant effect on the overall yield of the spiroketal mixture or isomer ratio. Trioxadispiroketal **1.14** was easily separated. Compounds **1.7** and **1.15** were isolated as an inseparable mixture. Pure sample of **1.7** and **1.15** were obtained through hydrolysis of the pivalate ester, which produced a separable mixture of the derived primary alcohols, **1.7-OH** and **1.15-OH**, respectively. Re-pivaloylation of the individual alcohols provided **1.7** and **1.15**. The stereochemistry of the trioxadispiroketals was assigned by analysis of vicinal J values and exclusive nOe's **1.7** for individual isomers (**Scheme 1.3**). The major component **1.7** was found to have the trioxadispiroketal configuration that has been assigned to azaspiracid-1.



Scheme 1.3

1.2.2 Relative Stability of Anomers

Interestingly, when the NMR samples of the individual trioxadispiroketals in $CDCl_3$ were allowed to stand at 0 ^oC for several months, each sample produced a mixture of **1.7**, **1.14**, and **1.15** in a similar ratio to that obtained in the spiroketalization reaction probably due to the acidity of HCl in $CDCl_3$ from its decomposition. This suggested isomer equilibration, and that the product ratio in the AgOTf mediated spiroketalization reflected a thermodynamic ratio.

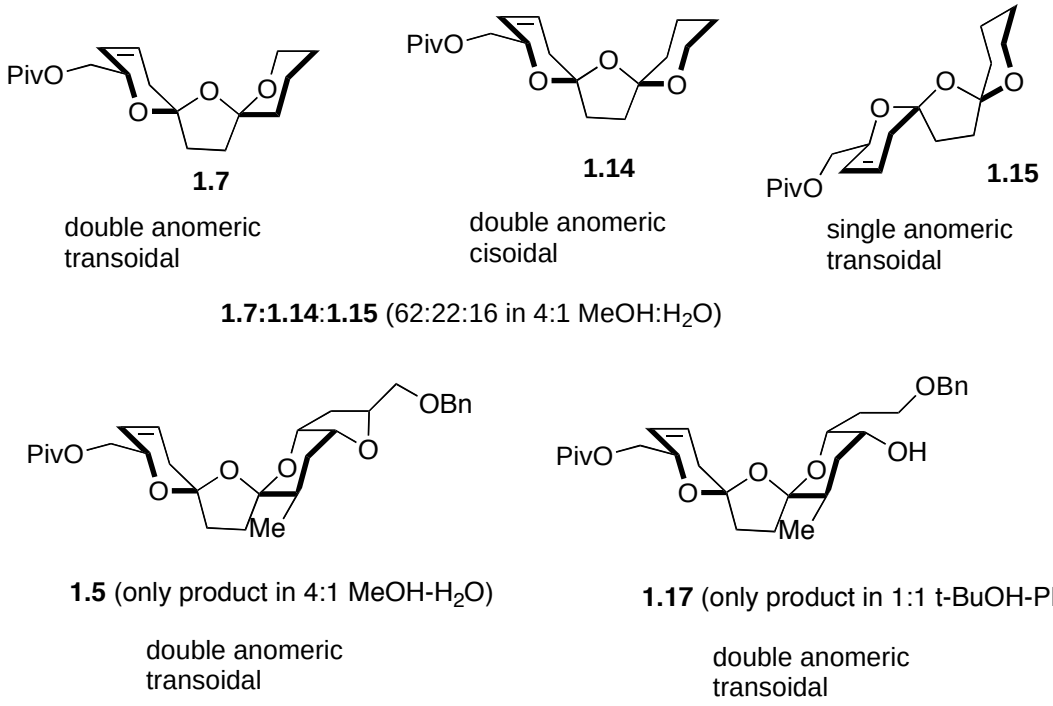
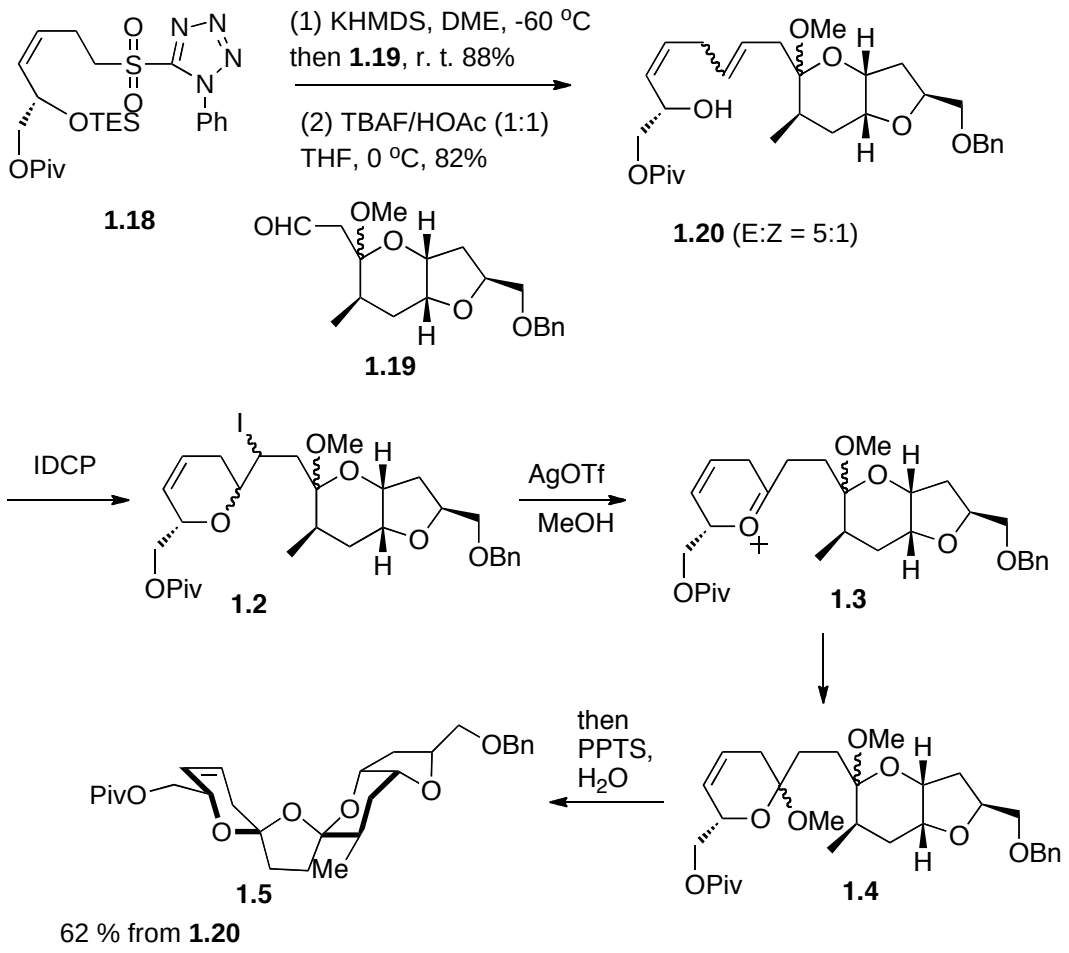


Figure 1.2 Configurational isomers of ABC and ABCD trioxadispiroketal analogues

Comparison of the apparent equilibrium ratio of the ABCD framework **1.5** with the results for the ABC systems **1.7**:**1.14**:**1.15** could shed light on the factors that affect the relative stability of the isomers of trioxadispiroketal (**Figure 1.2)**. For the ABC system, **1.7** and **1.14** which both represent a double anomeric effect are apparently favored over

1.15 and **1.16** which has a single anomeric effect (i.e. **1.7**/**1.14**:**1.15**/1.**16** = 84:16). Thus for ABC frameworks with no additional substituents on the C ring, isomers that have a greater number of anomeric effects may be intrinsically more stable. Of the two isomers that contain a double anomeric effect, **1.7**, with a *transoid* arrangement of the two oxygen subsituents on the five-membered oxacycle, appears to be favored over **1.14**, which has a *cisoid* motif. In comparison **1.5**, the ABCD analog corresponding to **1.14** is obtained as the exclusive bis-spiroketal product and compared to **1.14**, has apparently has a much higher thermodynamic bias relative to its isomers. Thus it appears that in the case of **1.5**, the additive effect of the double anomeric pattern and *transoid* arrangement of oxygen substituents on the five membered ring, is augmented by favorable conformational factors on the C ring. This argument is consistent with results obtained by Carter for the more substituted ABC analog **1.17**.[7g] In this case equilibration also favors a single configurational isomer, which may represent a synergistic interplay of a double anomeric, a *transoid* motif and the more stable flip chair conformation of the C ring.

The methodology developed herein was later applied to the synthesis of **1.5**, ABCD framework and the results were summarized in **Scheme 1.4**.[7] The diene **1.20**, the counterpart of **1.13** in our ABC framework synthesis was obtained by similar Julia-Kocienski olefination reaction as our synthesis of **1.13** between the sulfone **1.18** and aldehyde **1.19** followed by desilylation. Then the diene **1.20** was converted to the ABCD framework **1.5** in 62% yield as single isomer following the protocol developed for diene **1.13**.[7] To further understand the factors affecting the stability of anomers, a computation of relative energies of all four ABC framework anomers was conducted and described in next section.



Scheme 1.4

1.2.3 DFT B3LYP/6-31+G (d, p) Study of Relative Stability of Amomers

In order to estimate the relative energies of **1.7**:**1.14**:**1.15**:**1.16**, notwithstanding solvent effects, we next performed a DFT B3LYP/6-31+G(d, p) calculation as implemented in Gaussian 03 after a basis set search within a reasonable computational time.[18, 19] The relative energies computed for **1.7**, **1.14** and **1.15** qualitatively matched the experimental results (**Figure 1.3**). Trioxadispiroketal **1.7** which corresponds to a double anomeric effect with the anomeric oxygens on the central five membered ring in a *transoid* orientation, was 1.84 kcal/mol and 5.57 kcal/mol more stable than **1.14** and **1.15**,

which represent double anomeric-*cisoid* and a mono anomeric-*transoid* arrangements, respectively. However, the reliability of these calculations is tempered by the fact that mono anomeric-*cisoid* **1.16** which was computed to be lower in energy than **1.15**, was not observed experimentally, whereas **1.15** was.

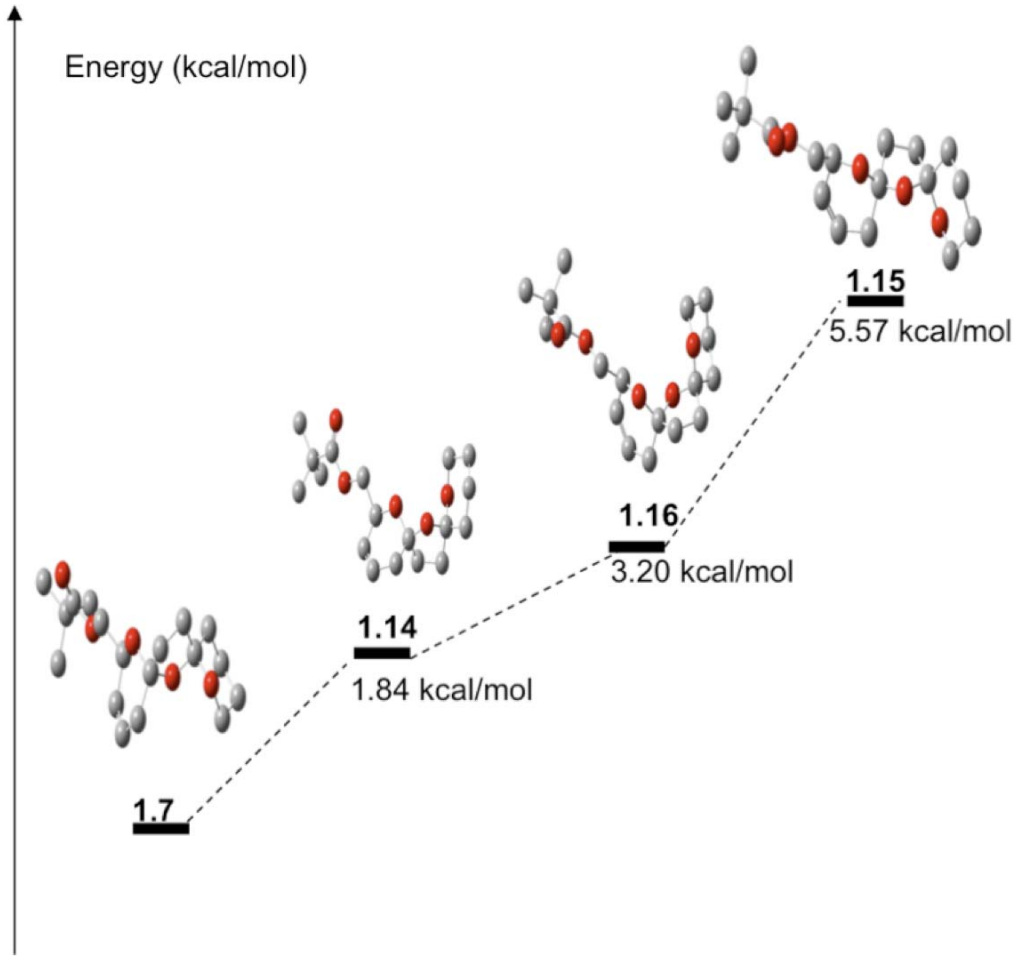


Figure 1.3 Relative B3LYP/6-31+G(d, p) energies of four ABC trioxadispiroketals

1.3 Conclusion

In conclusion, the apparent equilibrium distribution of different ABC and ABCD trioxadispiroketal analogues and computational data suggests that the double anomeric

effect is a major contributor to the stability of the trioxadispiroketal configuration in azaspiracid-1, but does not adequately account for the much greater stability of the natural isomer over other trioxadispiroketal isomers.[20] The relative arrangement of the oxygen substituents on the five membered ring and conformational effects in the C ring should also be considered. The interrogation of this hypothesis within the context of unnatural analogues of azaspiracid-1 and related trioxadispiroketal frameworks, and expansion of the novel synthetic methodology that underpins this study are in progress, and will be reported in due course.

1.4 Experimental

Unless otherwise noted, all reactions performed in organic solvents were conducted under an atmosphere of argon with oven dried glassware using standard syringe and septa technique. THF was distilled from a blue solution of sodium benzophenone ketyl. CH_2Cl_2 was distilled from phosphorus pentoxide. Anhydrous toluene, methanol, DMF and CH_3CN were purchased from Aldrich and used without purification. Analytical thin layer chromatography (TLC) was performed using Whatman silica gel HF_{254} plates or Selecto Scientific alumina B F_{254} plates and UV light, 12- molybdophosphoric acid (PMA stain), or potassium permanganate ($KMnO_4$ stain) for analysis of the developed plates. Flash column chromatography (FCC) was performed using silica gel 60 (230-400 mesh) or Brockmann I alumina gel (150 mesh). H^1-NMR spectra were recorded on a Bruker 500 MHz spectrometer in $CDCl_3$ or C_6D_6 and the chemical shifts were reported in parts per million (ppm) relative to the residue of the solvent, i.e $CD(H)Cl_3$ at 7.27 ppm or $C_6D(H)_6$ at 7.16 ppm. ^{13}C-NMR spectra were recorded on a Bruker 125 MHz spectrometer in

$CDCl_3$ or C_6D_6 and the chemical shifts were reported in parts per million (ppm) relative to the solvent peak, i.e. $CDCl_3$ at 77.23 ppm or C_6D_6 at 128.39 ppm. High resolution mass spectra (HRMS) were obtained on an Ultima Micromass Q-TOF Mass Spectrometer at the Mass Spectrometry Laboratory of University of Illinois, Urbana-Champaign.

(*S*)-4-((Z)-4-(4-Methoxybenzyloxy)-but-1-enyl)-2,2-dimethyl-1,3-dioxolane (1.10a)

Triphenylphosphine (6.69 g, 25.5 mmol) was added to a solution 1-((3-iodopropoxy)methyl)-4-methoxybenzene (5.19 g, 17.0 mmol) in dry toluene (50 mL). The mixture was refluxed for 60 h, then cooled to rt and concentrated *in vacuo* to give crude **9**. The residue was dissolved in THF (60 mL), cooled to −78 °C, and sodium hexamethyldisilylamide (28.3 mL, 0.6 M in toluene) introduced dropwise. The mixture was kept at rt for 30 min and re-cooled to −78 ^{o}C, at which time a solution of aldehyde **1.8** (2.21 g, 17.0 mmol) in THF (10 mL) was slowly added. After 30 min at −78 ^{o}C, the mixture was warmed to rt, stirred at this temperature for 1 h, then diluted with saturated aqueous NH_4Cl and extracted with Et_2O (3 x 100 mL). The combined organic phase was washed with brine and water, dried (Na_2SO_4), filtered, concentrated *in vacuo* and purified by FCC to afford **1.10a** (3.97 g, 80% over two steps). R_f = 0.40 (15% EtOAc in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.43 (s, 3H), 2.43 (dq, J=1.5, 7.0 Hz, 2H), 3.43-3.53 (m, 3H), 3.81 (s, 3H), 4.05 (dd, J=6.1, 8.1 Hz, 1H), 4.44 (s, 2H), 4.84 (dq, J=1.0, 7.5 Hz, 1H), 5.51 (tdd, J=1.5, 8.5, 10.9 Hz, 1H), 5.67 (dtd, J=0.9, 7.5, 11.0 Hz, 1H), 6.89 (m, 2H), 7.26 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.2, 27.0, 28.7, 55.5, 69.5, 69.7, 72.2, 72.9,

109.3, 114.0, 129.4, 129.4, 130.7, 131.1, 159.5. HRMS-ES: *m/z* [M+Na^+] calcd for $C_{17}H_{24}O_4Na$: 315.1572; found: 315.1584.

5-((*Z*)-4-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-but-3-enylthio)-1-phenyl-1*H*-tetrazole (1.10b)

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (3.52 g, 15.5 mmol) was added to a solution of **1.10a** (3.77 g, 12.9 mmol) in a 20/1 mixture of CH_2Cl_2/H_2O (100 mL). The mixture was stirred until TLC indicated complete disappearance of starting material, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phase was washed with brine and water, dried (Na_2SO_4), filtered, concentrated *in vacuo* and purified by FCC to afford the derived primary alcohol (1.93 g, 87%). R_f = 0.30 (30% EtOAc in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.43 (s, 3H), 1.69 (br. 1H), 2.37-2.46 (m, 2H), 3.57 (t, J=8.0 Hz, 1H), 3.67 (q, J=3.7 Hz, 2H), 4.10 (dd, J=6.1, 8.1 Hz, 1H), 4.85 (dq, J=0.7, 7.4 Hz, 1H), 5.60 (tdd, J=1.3, 8.4, 10.7 Hz, 1H), 5.69 (dtd, J=0.7, 7.5, 11.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 27.0, 31.5, 62.0, 69.7, 72.0, 109.5, 130.0, 131.2.

A solution of di-isopropyl azodicarboxylate (2.61 g, 15.5 mmol) in THF (10 mL) was added at 0 ^{o}C to a mixture of the alcohol from the previous step (2.22 g, 12.9 mmol), Ph_3P (4.06 g, 15.5 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (2.76 g, 15.5 mmol) in THF (20 mL). After 30 min, the reaction was warmed to rt and maintained at this temperature for 30 min. The mixture was then diluted with Et_2O, washed with brine and water, dried (Na_2SO_4), filtered, concentrated *in vacuo* and purified by FCC

to afford the thioether derivative (4.07g, 95%). R_f = 0.50 (20% EtOAc in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.41 (s, 3H), 2.69-2.76 (m, 2H), 3.43 (m, 2H), 3.52 (t, J=7.9 Hz, 1H), 4.04 (dd, J=6.2, 8.1 Hz, 1H), 4. 81 (dq, J=0.7, 7.5 Hz, 1H), 5.58 (tdd, J=1.3, 8.5, 10.9 Hz, 1H), 5.67 (dtd, J=0.7, 7.5, 11.0 Hz, 1H), 7.56-7.59 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 27.0, 27.6, 33.0, 69.6, 72.0, 109.6, 124.1, 130.0, 130.4, 130.8, 130.9, 136.7, 154.4.

A bright yellow mixture of 30% aqueous H_2O_2 (14.0 mL, 123 mmol) and ammonium molybdate (5.25 g, 3.56 mmol) was added dropwise, at 0 ^{o}C to a solution of the thioether from the previous step (3.93 g, 11.8 mmol) in a 1/8 mixture of THF/EtOH (30 mL). After stirring for 1 h, the reaction was diluted with Et_2O and saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase extracted with Et_2O (3 x 100 mL). The organic extract was washed with brine and water, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. FCC of the residue provided sulfone **1.10b** (3.86 g 90%) as a white solid. R_f = 0.20 (10% EtOAc in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.43 (s, 3H), 2.84 (m, 2H), 3.56 (t, J=7.9 Hz, 1H), 3.79-3.84 (m, 2H), 4.11 (dd, J=6.1, 8.1 Hz, 1H), 4.84 (q, J=6.8 Hz, 1H), 5.61-5.64 (m, 2H), 7.62-7.70 (m, 3H), 7.71 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 26.1, 27.0, 55.8, 69.5, 71.8, 109.78, 125.3, 128.3, 130.0, 131.8 (two lines), 133.2, 153.6. HRMS-ES: *m/z* [M+Na^+] calcd for $C_{16}H_{20}N_4O_4NaS$: 387.1103; found: 387.1115.

Tetrahydro-2-methoxy-2-((5Z)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-hexa-2,5-dienyl)-2*H*-pyran (1.12)

Potassium hexamethyldisiylamide (23.8 mL of a 0.5M solution in toluene, 11.9 mmol) was added dropwise, at −78 ^{o}C, to a mixture of sulfone **1.10b** (2.89 g, 7.94 mmol) in THF (50 mL). The mixture was warmed to rt and kept at this temperature for 1 h. The resulting bright yellow solution was then re-cooled to −78 ^{o}C and aldehyde **1.11** (1.65 g, 10.6 mmol) in THF (10.0 mL), slowly introduced. The reaction mixture was maintained at −78 ^{o}C for 2 h, at rt for an additional 1 h, then diluted with Et_2O and brine. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic extract was washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by FCC to afford **1.12** as a yellow oil (2.11 g, 90%). R_f = 0.80 (20% EtOAC in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.41 (m, 1H), 1.44 (s, 3H), 1.47-1.58 (m, 3H), 1.67 (m, 1H), 1.77 (tq, J=4.2, 13.3 Hz, 1H), 2.16 (dd, J=6.7, 14.6 Hz, 1H), 2.43 (dd, J=6.3, 14.5 Hz, 1H), 2.85 (t, J=6.1 Hz, 2H), 3.22 (s, 3H), 3.53 (t, J=8.0 Hz, 1H), 3.63 (m, 2H), 4.07 (dd, J=6.1, 8.0 Hz, 1H), 4.84 (dq, J=1.0, 7.5 Hz, 1H), 5.36-5.49 (m, 3H), 5.63 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.8, 25.4, 26.2, 27.0, 31.2, 33.3, 40.0, 47.6, 61.6, 67.0, 72.1, 98.7, 109.3, 125.8, 128.2, 131.1, 132.6. HRMS-ES *m/z* [M+Na^+] calcd for $C_{17}H_{28}O_4Na$: 319.1885; found: 319.1890.

(*S*,3*Z*)-8-Tetrahydro-2-methoxy-2*H*-pyran-2-yl)-2-hydroxyocta-3,6-dienyl pivalate (1.13)

A mixture of diene **1.12** (1.57 g, 5.30 mmol) and CSA (123 mg, 0.53 mmol) in dry MeOH (150 mL) was stirred at rt until TLC indicated complete disappearence of **12**. The reaction was then was quenched with solid $NaHCO_3$ and concentrated *in vacuo*.

The residue was diluted with Et_2O, washed with water, dried (Na_2SO_4), filtrated and concentrated *in vacuo*. Purification of the residue by FCC provided the derived diol (1.33 g, 98%). R_f = 0.35 (60% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (dt, J=4.3, 13.3 Hz, 1H), 1.42-1.52 (m, 3H), 1.63 (m, 1H), 1.70 (tq, J=4.2, 13.2 Hz, 1H), 2.12 (dd, J=7.1, 14.5 Hz, 1H), 2.37 (dd, J=6.7, 14.5 Hz, 1H), 2.78 (m, 2H), 3.16 (s, 3H), 3.41 (t, J=9.5, 2H), 3.48 (br. 1H), 3.51 (br., 1H), 3.55 (d, J=2.4, 1H), 3.57 (d, J=2.4 1H), 4.46 (m, 1H), 5.30-5.45 (m, 3H), 5.53 (dtd, J=0.6, 7.6, 11.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.6, 25.1, 31.1, 33.0, 39.9, 47.5, 61.5, 66.3, 68.6, 98.8, 125.4, 129.3, 131.2. HRMS-ES *m/z* [M+Na^+] calcd for $C_{14}H_{24}O_4Na$: 279.1572; found: 279.1469.

To a solution of the diol from the previous step (1.15 g, 4.50 mmol) in dry CH_2Cl_2 (60.0 mL) was added pyridine (1.78 g, 22.5 mmol), DMAP (110 mg, 0.90 mmol), and pivaloyl chloride (652 mg, 5.40 mmol). After 5 h at rt, the reaction mixture was quenched with MeOH (5.0 mL), diluted with CH_2Cl_2, washed with 0.1 M HCl, brine and water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by FCC to afford **1.13** as an oil (1.30 g, 85%). R_f = 0.30 (30% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 9H), δ 1.41 (dt, J=4.3, 13.4 Hz, 1H), 1.46-1.58 (m, 3H), 1.63 (br. 1H), 1.69 (m, 1H), 1.77 (tq, J=4.2, 13.3 Hz, 1H), 2.17 (m, 1H), 2.43 (dddd, J=0.9, 2.7, 6.6, 14.5 Hz, 1H), 2.81 (m, 1H), 2.90 (m, 1H), 3.22 (s, 3H), 3.63 (m, 2H) 4.02 (ddd, J=0.9, 7.4, 11.3 Hz, 1H), 4.08 (ddd, J=1.8, 4.0, 11.3 Hz, 1H), 4.68 (m, 1H), 5.36-5.53 (m, 3H), 5.63 (dtd, J=0.8, 7.6, 11.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.8, 25.3, 27.4, 31.2, 33.2, 39.1, 40.0,

47.6, 61.6, 66.4, 68.0, 98.8, 125.8, 128.8, 131.1, 132.2, 178.8. HRMS-ES *m/z* [M+Na^+] calcd for $C_{19}H_{32}O_5Na$: 363.2147; found: 363.2133.

Trioxadispiroketal 1.7, 1.14 and 1.15

To a solution of **1.13** (230 mg, 0.657 mmol) in dry CH_3CN (10.0 mL) was added IDCP (1.23 g, 2.62 mmol) at 0 ^oC. The mixture was warmed to rt, stirred at this temperature for 3 h, then diluted with Et_2O and 10% $Na_2S_2O_3$ in saturated aqueous $NaHCO_3$. The two phases were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The organic extract was washed with 0.1 N HCl, brine and water, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was not stable and was used directly in the next step.

For characterization purposes, in a separate experiment, one of the diastereomers of **1.6** was separated by FCC (R_f = 0.70, 15% EtOAc/petroleum ether). ^1H NMR (500 MHz, C_6D_6) 1.21 (m, 1H), 1.22 (s, 9H), 1.50 (m, 2H), 1.72 (m, 2H), 1.85 (m, 1H), 2.04 (md, J=17.2 Hz, 1H), 2.13-2.20 (m, 1H), 2.43 (dd, J=6.2, 15.5 Hz, 1H), 2.50 (dd, J=6.6, 15.5 Hz, 1H), 3.12 (s, 3H), 3.38 (td, J=3.8, 9.8 Hz, 1H), 3.45 (m, 2H), 3.59 (dd, J=3.2, 11.8 Hz, 1H), 4.30 (m, 1H), 4.41 (dt, J=4.8, 6.4 Hz, 1H), 4.50 (dd, J=8.6, 11.8 Hz, 1H), 5.21 (md, J=10.2 Hz, 1H), 5.63 (m, 1H). ^{13}C NMR (125 MHz, C_6D_6) δ 19.4, 25.6, 27.8, 29.7, 32.8, 33.6, 39.2, 44.0, 47.7, 61.8, 64.1, 71.0, 73.1, 99.6, 125.0, 127.2, 178.1.

The mixture **1.6** was not stable and was quickly dissolved in a 4/1 mixture of CH_3CN/H_2O (20.0 mL) and treated with p-toluenesulfonic acid (20.0 mg, 0.10 mmol). After 1 h, the reaction mixture was diluted with Et_2O and quenched with saturated

aqueous $NaHCO_3$. The two phases were separated, and the aqueous layer was extracted with Et_2O (3 x 50 mL). The organic extract was washed with brine and water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was co-evaporated with benzene (two times), re-dissolved in dry CH_2Cl_2 (10.0 mL) and treated with silver trifluoromethanesulfonate (675 mg, 2.62 mmol) at 0 ^oC. The mixture was warmed to rt, stirred at this temperature for 3 h, then diluted with CH_2Cl_2 and a 1/1 mixture of 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phase was washed with brine and water, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by FCC on neutral alumina to afford two fractions R_f = 0.30, 0.35 (10% EtOAc in petroleum ether), comprising trioxadispiroketal **1.14** (20 mg, 9% from **1.5**), and an inseparable mixture **1.7** and **1.15** (65 mg, 30% from **1.5**), respectively. The approximate ratio of **1.7**:**1.14**:**1.15** as determined by integration of the ^1H NMR was 62:22:16. For **1.14**: ^1H NMR (500 MHz, C_6D_6) δ 1.20 (m, 1H), 1.24 (s, 9H), 1.40 (m, 2H), 1.46 (m, 1H), 1.49 (m, 2H), 1.59 (ddd, J=4.0, 9.1, 12.3 Hz, 1H), 1.81 (tq, J=4.0, 12.7 Hz, 1H), 1.91 (dddd, J=0.9, 3.5, 4.7, 17.3 Hz, 1H), 2.14 (ddd, J= 4.0, 8.4, 12.3 Hz, 1H), 2.21 (tdd, J= 2.1, 4.2, 17.4 Hz, 1H), 2.31 (td, J= 8.6, 12.3 Hz, 1H), 3.68 (tdd, J=1.8, 4.5, 11.2 Hz, 1H), 3.97 (dt, J=2.5, 11.4 Hz, 1H), 4.28 (dd, J=4.3, 11.1 Hz, 1H), 4.34 (dd, J=6.5, 11.1 Hz, 1H), 4.80 (m ,1H), 5.60 (tdd, J=1.3, 2.5, 11.3 Hz, 1H), 5.65 (tdd, J=1.8, 5.0, 11.3Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6) δ 20.6, 25.9, 27.7, 35.0, 36.5, 37.8, 38.1, 39.3, 63.6, 66.5, 69.8, 106.1, 108.0, 125.1, 126.0, 178.0. HRMS-Es *m/z* [$M+Na^+$] calcd for $C_{18}H_{28}O_5Na$: 347.1834; found: 347.1839.

DIBAL-H (0.12 mL, 1.0 M in hexane) was added at −78 ^{o}C to a portion of the mixture of **1.7** and **1.15** (10 mg, 0.031 mmol) in CH_2Cl_2 (2.0 mL). The reaction mixture was maintained at this temperature for 30 min, then quenched with Rochelle's salt, warmed to rt, and extracted with Et_2O (4 x 10 mL). The combined organic phase was washed with brine and water, dried (Na_2SO_4), concentrated *in vacuo*, and purified by FCC on neutral alumina to afford the derived primary alcohols **1.7-OH** and **1.15-OH** (R_f = 0.28, 0.30 respectively, 15% EtOAc in petroleum ether). For **1.7-OH**: ^{1}H NMR (500 MHz, C_6D_6) δ 1.19 (m ,1H), 1.40 (m ,1H), 1.44 (m, 1H), 1.54 (dd, J=5.7, 7.1 Hz, 1H), 1.61 (dt, J=4.2, 12.7 Hz, 1H), 1.64 (m, 1H),1.85 (m ,2H), 1.94 (m, 2H), 2.03 (m, 1H), 2.08 (dddd, J= 1.4, 3.3, 5.1, 17.5 Hz, 1H), 2.29 (tdd, J=2.5, 4.0, 17.6 Hz, 1H), 3.51-3.60 (m, 3H), 3.87 (ddd, J=2.5, 9.7, 12.2 Hz, 1H), 4.45 (m, 1H), 5.51 (tdd, J=1.4, 2.7, 10.3 Hz, 1H), 5.66 (tdd, J=2.4, 5.1, 10.3 Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6) δ 20.9, 26.0, 35.4, 36.2, 37.1, 37.4, 62.2, 65.8, 71.4, 106.2, 107.6, 125.0, 126.6. For **15-OH**: ^{1}H NMR (500 MHz, C_6D_6) δ 1.11 (m, 1H), 1.32 (tq, J=4.3, 12.8 Hz, 1H), 1.42 (m, 1H), 1.55 (dt, J=4.4, 13.3 Hz, 1H), 1.73-1.90 (m, 4H), 1.96 (ddd, J=1.5, 7.3, 12.2 Hz, 1H), 2.05 (dt, J=7.9, 12.1 Hz 1H), 2.17 (tdd, J= 1.3, 5.2, 17.1 Hz, 1H), 2.23 (m, 1H), 3.46 (tdd, J=2.3, 4.7, 11.1 Hz, 1H), 3.51 (dd, J=2.9, 8.8 Hz, 1H), 3.60 (ddd, J= 4.3, 8.8, 11.4 Hz, 1H), 3.71 (ddd, J=2.5, 11.2, 12.4 Hz, 1H), 3.75 (td, J=2.8, 11.4 Hz, 1H), 4.27(m, 1H), 5.57 (dtd, J=1.3, 2.5,10.3 Hz, 1H) , 5.72 (tdd, J=2.6, 5.2, 10.4 Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6) δ 20.9, 25.8, 34.9, 35.5, 37.1, 37.4, 61.9, 66.4, 75.8, 105.3, 107.5, 124.1, 126.3.

Using the identical pivaloylation procedure that was described for preparation of **1.13**, **1.7-OH** and **1.15-OH** were individually transformed to **1.7** (7.5 mg) and **1.15**

(2.2 mg). For **1.7** : ^{1}H NMR (500 MHz, C_6D_6) δ 1.19 (m, 10H), 1.38-1.47 (m, 2H), 1.64 (dt, J= 4.2, 13.0 Hz, 1H), 1.69 (m, 1H), 1.85 (tq, J= 4.0, 12.8 Hz, 1H), 1.94 (m, 2H), 2.02 (m, 2H), 2.08 (dddd, J= 1.3, 3.3, 4.9, 17.4 Hz, 1H), 2.31 (tdd, J= 2.4, 4.1, 17.6 Hz, 1H), 3.55 (tdd, J= 2.3, 4.6, 11.3 Hz, 1H), 3.87 (ddd, J= 2.5, 9.7, 13.6 Hz, 1H), 4.15 (dd, J=4.4, 11.2 Hz, 1H), 4.31 (dd, J=6.3, 11.2 Hz, 1H), 4.62 (m, 1H), 5.57 (tdd, J=1.3, 2.7, 10.3 Hz, 1H), 5.66 (tdd, J= 2.2, 5.1, 10.3 Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6) δ 20.9, 26.0, 27.7, 35.2, 36.3, 37.1, 37.4, 39.2, 62.2, 66.5, 69.0, 106.1, 107.6, 125.4, 126.0, 177.9. HRMS-ES *m/z* [M+Na^+] calcd for $C_{18}H_{28}O_5Na$: 347.1834; found: 347.1842. For **1.15**: ^{1}H NMR (500 MHz, C_6D_6) δ 1.18 (m, 1H), 1.19 (s, 9H), 1.39 (tq, J=4.3, 12.8 Hz, 1H), 1.48 (m, 1H), 1.63 (dt, J=4.4, 13.9 Hz, 1H), 1.83 (m, 2H), 1.93-2.01 (m, 4H), 2.23 (m, 2H), 3.53 (tdd, J=2.3, 4.6, 11.0 Hz, 1H), 3.82 (ddd, J=2.6, 11.0, 13.4 Hz, 1H), 4.31 (dd, J=4.8, 9.5 Hz, 1H), 4.49 (m, 2H), 5.57 (qd, J=2.0, 10.4 Hz, 1H), 5.66 (m, 1H). ^{13}C NMR (125 MHz, C_6D_6) δ 20.9, 26.0, 27.7, 35.4, 35.6, 36.5, 37.3, 39.2, 62.0, 67.5, 72.0, 106.0, 107.4, 124.9, 125.2, 177.9. HRMS-ES *m/z* [M+Na^+] calcd for $C_{18}H_{28}O_5Na$: 347.1834; found: 347.1843.

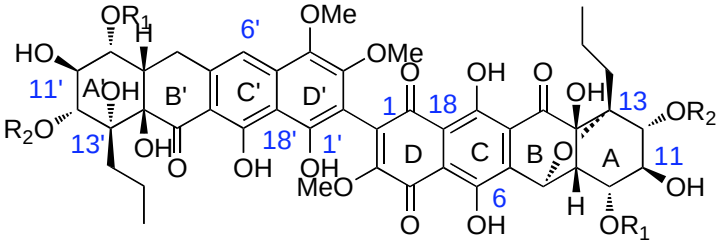
Alternative spiroketalization conditions for 1.7, 1.14 and 1.15

Hydroxydiene **1.13** (8.0 mg, 0.023 mmol) was subjected to the identical iodoetherification procedure that was described above. To a solution of the the crude product **1.6** in methanol (0.5 mL) was added AgOTf (18mg, 0.069 mmol) and the mixture was stirred for 30 min. Then PPTS (6.4 mg, 0.023 mmol) and water (0.10 mL) were added sequentially. The resulting mixture was stirred for additional 6 h and quenched by adding saturated $Na_2S_2O_3$ solution. The mixture was extracted with Et_2O (3 x 20 mL) and

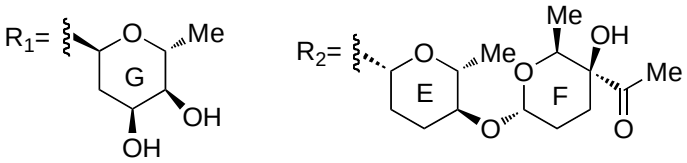
the organic extract was washed with brine and water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. H-NMR analysis of the crude product indicated a mixture of **1.7**:**1.14**:**1.15** in a respective ratio of 6:2:2.

Chapter 2. Angelmicin B (Hibarimicin B): Structure, Bioactivity, Biosynthesis and Previous Synthetic Studies

Angelmicins B (**2.1**) was first isolated form *Microbispora rosea* by Uehara and co-workers in 1993.[21] Several members of the same class of natural products (subsequently named hibarimicins) were later isolated from a different subspecies of *Microbispora rosea* subsp. *hibaria* TP-A0121.[22] Angelmicin B (hibarimicin B) (**2.1**) is one of the most complicated and largest molecules among the aromatic polyketide dimers of microbial metabolites.



Angelmicin B (hibarimicin B) (**2.1**)



Hibarimicinone (**2.2**) $R_1 = R_2 = H$

Figure 2.1 Structure of angelmicin B and hibarimicinone

2.1 Bioactivity

Angelmicin B (hibarimicin B) is a potent *v-Src* protein tyrosine kinase (PTK) inhibitor (IC_{50}=40 μg/mL or 23 μM), and the most selective congener. Angelimicin B also shows growth inhibiting and differentiation inducing activity on human myeloid leukemia (HL-60) cell lines (IC_{50}=0.10 μg/mL or 57 nM).[23] Since the effective concentration of angelmicin B (hibarimicin B) in *v-Src* PTK inhibiton is about 400-fold higher than that required for cell growth suppression and differentiation, these activities,

do not appear to be directly related. This suggests that angelmicin B (hibarimicin B) might be involved in the modulation of more than one physiological pathway.[24]

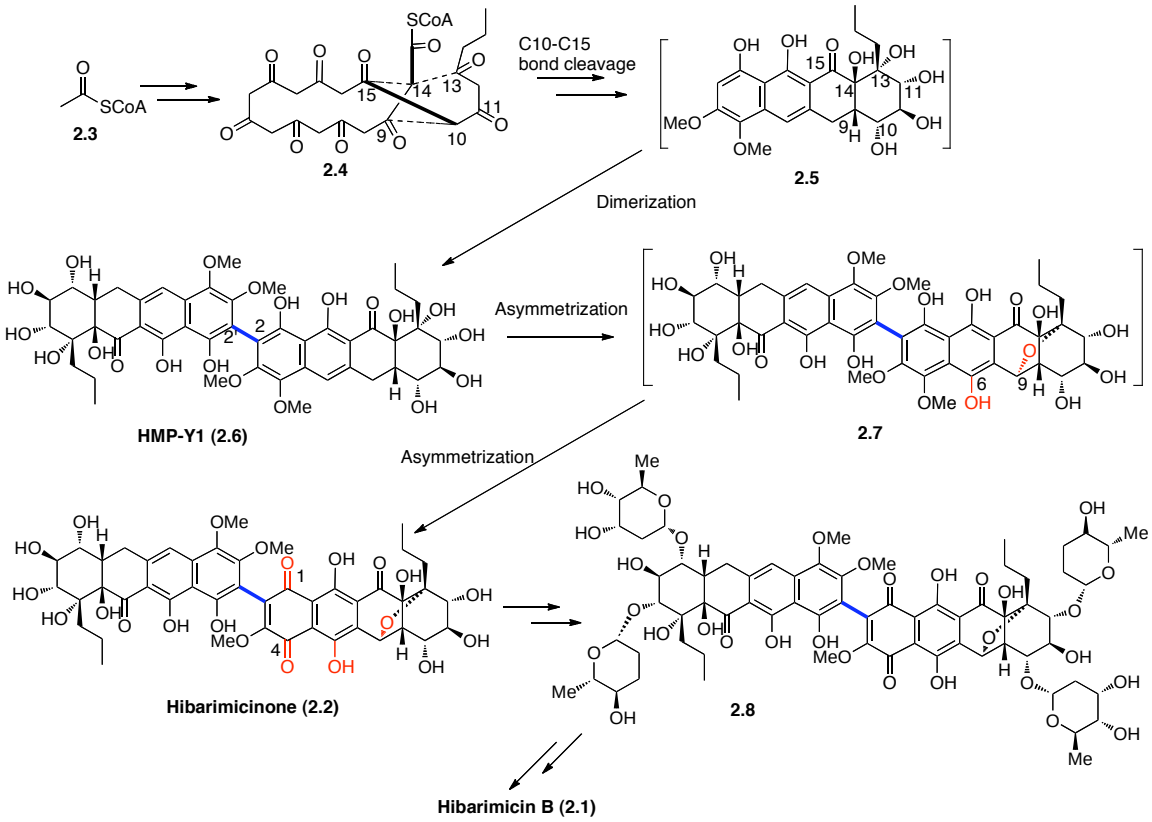
Hibarimicinone **2.2**, the aglycon part and the biosynthetic precursor of angelmicin B (hibarimicin B), is a more potent *v-Src* PTK inhibitor (IC_{50}=9.7 μg/mL or 10.5 μM), although less selective than angelmicin B (hibarimicin B), and does not induce differentiation of HL-60 cells.[23, 24] Angelmicin B (hibarimicin B) competitively inhibited ATP binding to the *v-Src* PTK, but hibarimicinone **2.2** showed noncompetitive inhibition. However, both compounds showed similar mixed types of inhibition against a *v-Src* substrate (peptide p34cdc[6-20]) binding to the *v-Src* PTK. These results again suggest that the differentiation-inducing activity of angelmicin B (hibarimicin B) is not directly associated with *v-Src* PTK inhibiting activity, and may be associated with other signaling mechanisms. [23, 24]

2.2 Structure

Angelmicin B **2.1** consists of six deoxyhexoses and an aglycon part (hibarimicinone), which has eight condensed rings and a tetrahydrofuran (THF) ring bridge with two *n*-propyl side chains.[22] It is a pseudo-symmetric dimer comprised of similar highly oxidized naphthylnapthoquinone derived cyclitol ABCD and A′B′C′D′ segments, which are connected through a D-D′ biaryl bond. The A and A′ cyclitol residues are glycosylated and the BCD and B′C′D′ segments vary in the oxidation states of the individual rings. The absolute configuration of the sugar units (E, F and G), the configuration at C13′, and the relative stereochemistry between distal rings (A and A′) are unknown. In addition, it

is unclear whether the natural structure represents a preferred atropisomer with respect to the D-D′ linkage.

2.3 Biosynthesis



Scheme 2.1

The biosynthetic origin of hibarimicins using ^{13}C-labeling experiments and co-synthesis with blocked mutants was reported 1n 2002.[25] The ^{13}C enriched hibarimicin B was isolated from the fermentation of *Microbispora rosea* subsp. *Hibaria* TP-A0121 with ^{13}C labeled sodium [1-^{13}C], [2-^{13}C], [1,2-$^{13}C_2$] acetate feeding, solvent extraction and chromatographic purification. Analysis of the ^{13}C NMR data for labeled hibarimicin B showed the enrichment of ^{13}C in the aglycon part of hibarimicin and revealed an irregular distribution of labeled acetates (**Figure 2.2**).

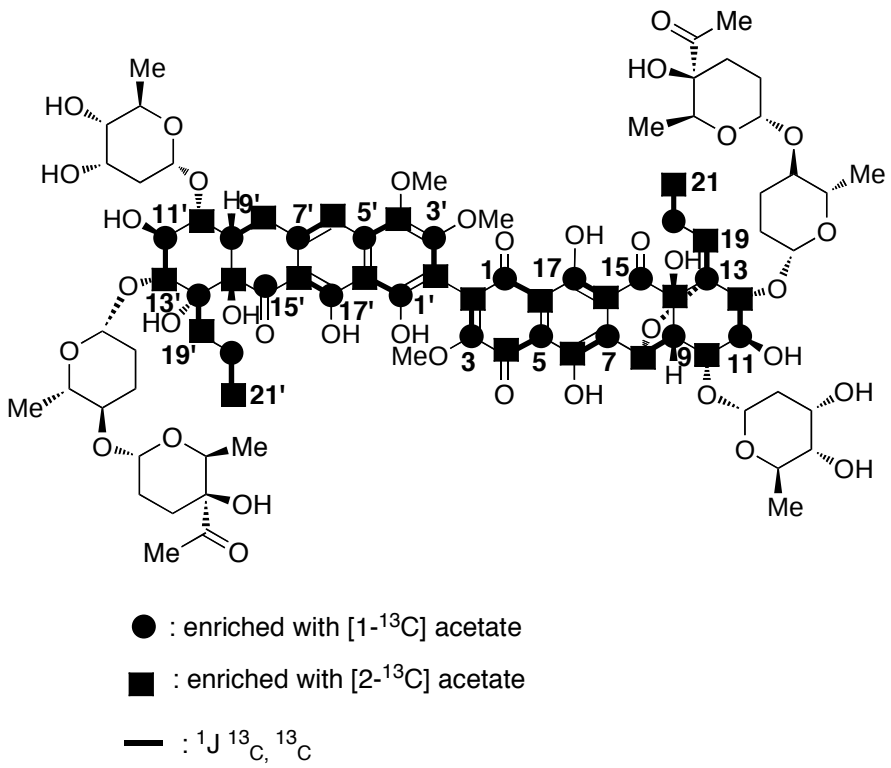
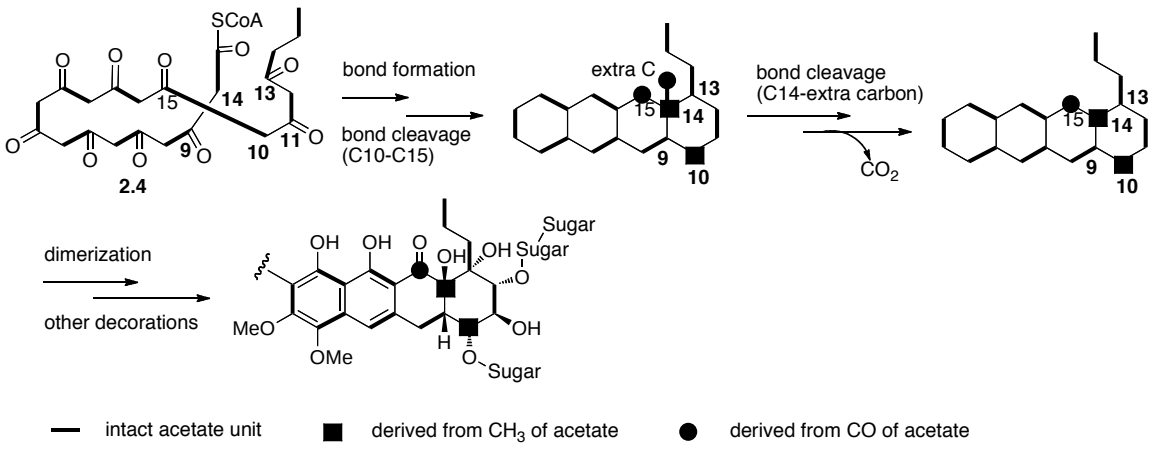


Figure 2.2 Structure of angelmicin B from ^{13}C labeled acetate feeding experiments

Alternate alignment of enriched carbons in the aglycon moiety from a [1-^{13}C] and [2-^{13}C] acetate feeding experiment revealed that aglcon part was biosynthesized through a polyketide pathway. The 2D-INADEQUATE results of hibarimicin B from [1, 2-$^{13}C_2$] acetate feeding experiments showed the symmetric distribution of two polyketide chains and they were coupled between C2-C2′ through carbons of methyl groups in acetates. This symmetric carbon skeleton indicated that the aglycon part of hibarimicin was constructed through the oxidative dimerization at C2 and C2′ positions.

Even though C-14 and C-15 were incorporated from the carbonyl and methyl groups of labeled acetates, respectively, and directly bonded each other, there were no $^{1}J\ ^{13}C$-^{13}C coupling observed between them. This was the same for C-14′ and C15′. Furthermore, C-10 was derived from carbon of the methyl group of labeled acetates and was bonded to C-9 and C-11, both derived from carbons of carbonyl of acetates, but there were no one-

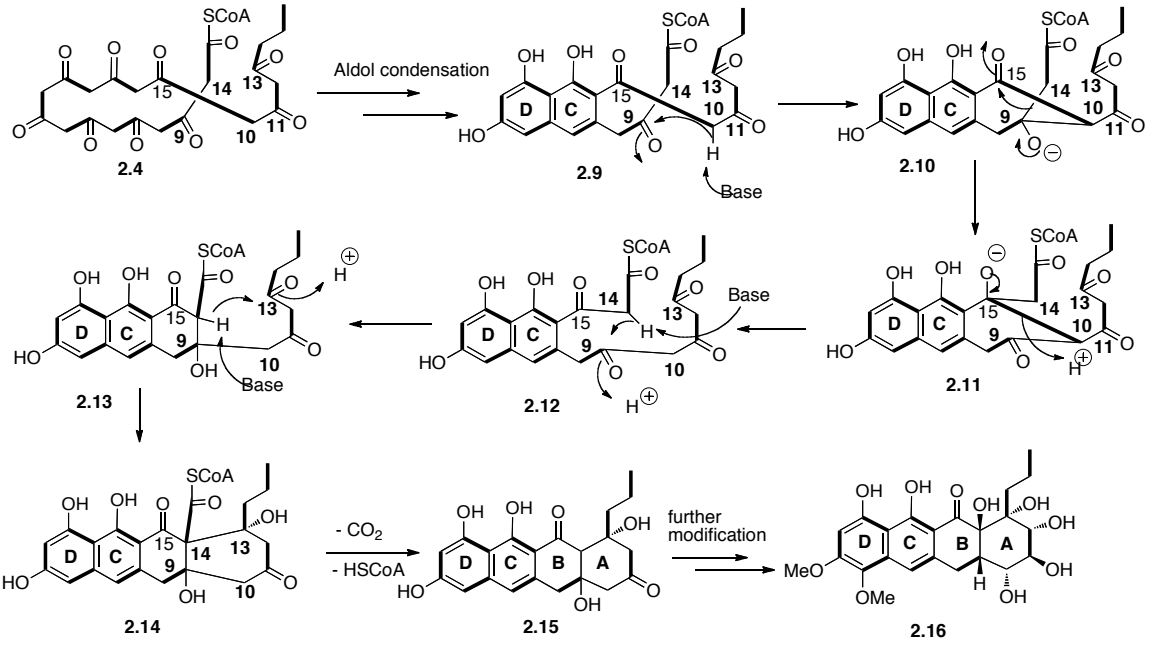
bond ^{13}C-^{13}C coupling seen. It was also the case for C-10′. The three-bond coulplings, $^{3}J_{C10,\ C15}$ and $^{3}J_{C10',\ C15'}$, were detected from the difference spectra of selective ^{13}C decoupled 1D-ADEQUATE experiment. These results showed that C-10 and C-15 and also C-10′ and C-15′ were derived from a single acetate unit, suggesting that each half of agylcon framework was originated from an undecaketide chain and then was oxidatively coupled to form the symmetric agylcon carbon skeleton. Hori and Kajiura hypothesized that starting from an undecaketide **2.4**, the half unit of the aglycon carbon framework **2.5** was constructed from a skeletal rearrangement, involving cleavage of C10-C15 bond, formation of C9-C10, C13-C14 and C14-C15 bonds, and decarboxylation at C14 as well (**Scheme 2.2)**.



Scheme 2.2

The authors did not propose a mechanism for the cleavage of C10-C15 bond and the rearrangement of the carbon framework. Here, we propose one possible mechanism, a slight modification from the one by Sulikowski (**Scheme 2.3**). After construction of the CD rings by aldol condensation, the enolate **2.9** resulting from deprotonation of C10 hydrogen attacked the C9 carbonyl. Then the fragmentation happened in cleavage of C9-

C14 bond, and 1,3 migration to form C14-C15 bond. Further fragmentation of **2.11** resulted in formation of C11-C15 bond. Next, the AB rings were constructed through C9-C14 and C13-C14 bond formation by standard enolate chemistry. The half unit of the aglycon carbon framework was accomplished by decarboxylation and further functionalization.



Scheme 2.3

Further biosynthetic studies were performed to cofirm the biosynthetic intermediates and dimerization pathway, through the isolation and structure elucidation of metabolites from blocked mutants of the *Microbispora rosea* subspecies. *Hibaria* TP-A0121. [25] Several metabolites were isolated, including HMP-Y1 **2.6** (hibarimicin-mutant product Y1) and hibarimicinone **2.2**. From sodium [1-^{13}C], [2-^{13}C], [1,2-$^{13}C_2$] acetate feeding experiment, the corresponding ^{13}C labeled HMP-Y1 **2.6** was isolated from the blocked

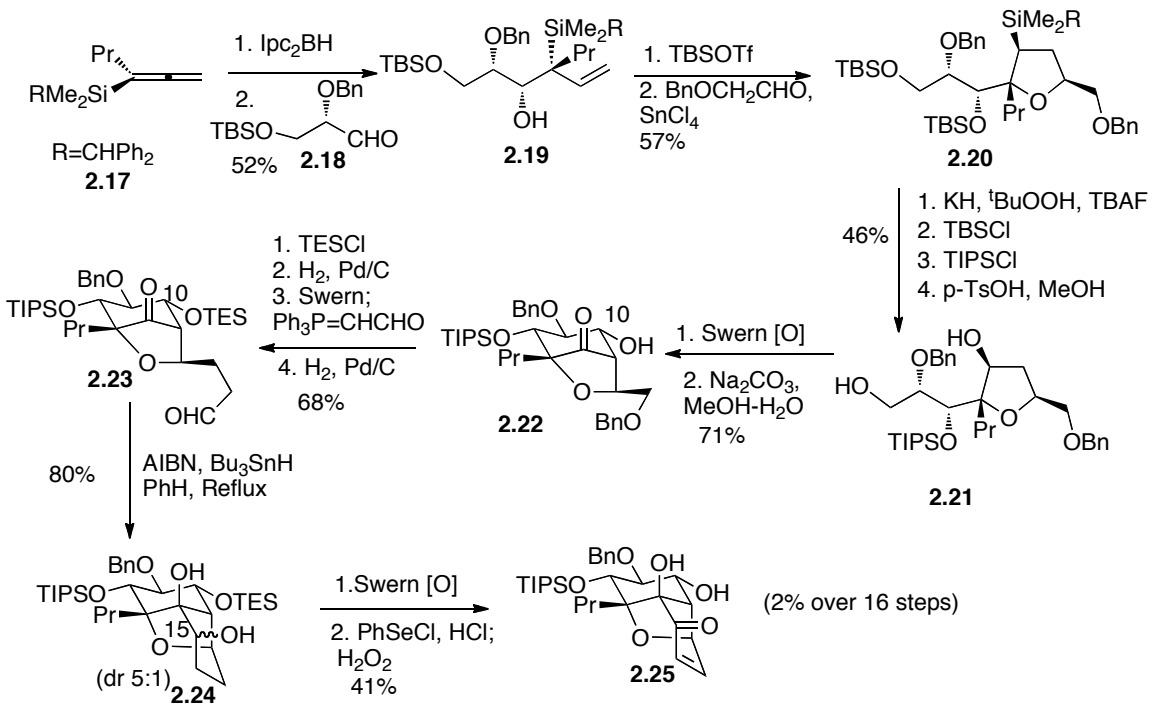
mutants and fully characterized. The 2D-INADEQUATE results of HMP-Y1 from [1, 2-$^{13}C_2$] acetate feeding experiments showed the symmetric distribution of two polyketide chains and they were coupled between C2-C2′ through carbons of methyl groups in acetates. This symmetric carbon skeleton indicated that HMP-Y1 **2.6** was possibly constructed through the oxidative dimerization at C2 and C2′ positions. Feeding the ^{13}C labeled HMP-Y1 **2.6** to *Hibaria* TP-A0121 produced ^{13}C labeled hibarimicin B **2.1**. It confirmed that HMP-Y1 **2.6** was the precursor of hibarimicin B **2.1** in its biosynthetic pathway and also demonstrated that the dimerization of the two half units occurred before the asymmetrization on the biosynthetic pathway.

Combining with the ^{13}C labeling experiment results of hibarimicin B **2.1**, the researchers assumed that the tetracycle **2.5** was oxidatively coupled through C-2 of the aromatic ring to give a symmetrical HMP-Y1 **2.6,** which was further asymmetrized to hibarimicinone **2.2** by oxidation and modification. The glycosidation of hibarimicione **2.2** finished the biosynthesis of hibarimicin B **2.1**. Thus, the HMP-Y1 **2.6** could be a valuable intermediate to synthesis of hibarimicin B **2.1** and be as an important synthetic target to correlate its stereochemistry with natural products.

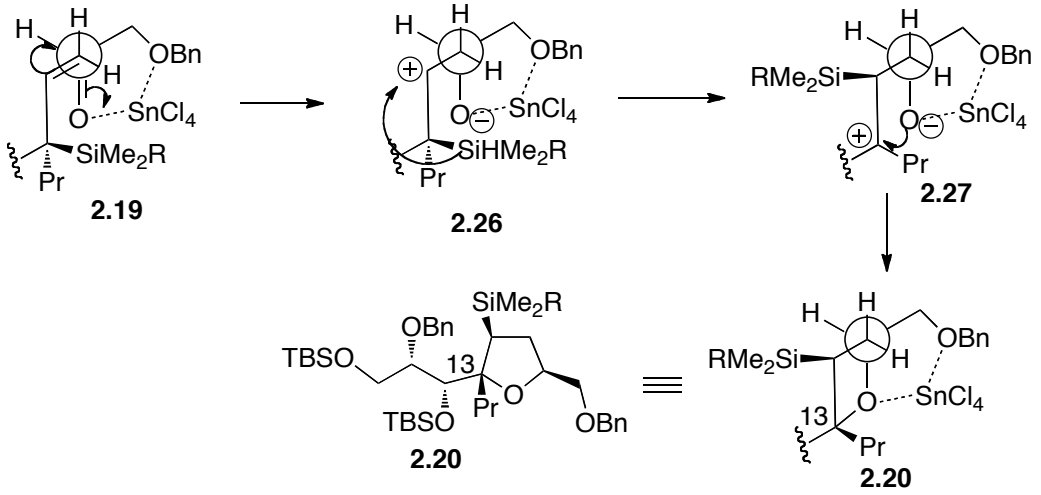
2.4 Previous synthetic studies

In 2005, Roush's group disclosed a synthesis of AB subunit of hibarimicin (Scheme **2.4**).[26b] The THF **2.20** was constructed via a [3+2] annulation in 57% yield between α-benzloxyacetylaldehyde and an allyic silane **2.19**, which was from asymmetric allylation of Fukuyama aldehyde **2.18**.[27] The mechanism of $SnCl_4$ chelated [3+2] annulation was shown in scheme **2.4**. The secondary carboncation **2.26** intermediate was undergone a

1,2-silyl shift to form a more stable tertiary carboncation **2.27**. Then the THF ring was closed from backside in **2.12** as anion-cation combined to establish the quaternary center at C-13. Tamao-Fleming oxidation of the silane in **2.20** and protecting group manipulation of the bis-silylether provided the THF-diol **2.21** in 46% yield.[28] Swern oxidation of the diol in **2.21** followed by an intramolecular aldol condensation on the resulting keto-aldehyde, led to a mixture of the bicyclic hydroxy-ketone **2.22** and the undesired C-10 epimer in 81% yield (**2.22**: **10-epi-2.22** = 1.3:1) [29, 30] The latter was converted to **2.22** quantitatively by re-exposure to the aldol reaction conditions. After protection of the C-10 hydroxyl group and selective removal of benzyl group of primary alcohol with hydrogenolysis and conversion to aldehyde by Swern oxidation, an *in situ* treatment of the aldehyde with (triphenylphosphoranylidene)acetaldehyde gave the enal, which was hydrogenated over Pd/C to afford the keto aldehyde **2.23** in 68% yield from **2.22** in 5 steps. Pinacol cyclization using Fu's method was performed upon **2.23** to give the diol mixture **2.24** (dr 5:1 at C15), which contains the carbon skeleton and the required chiral centers in AB subunit.[31] Swern oxidation of the C15 hydroxy group followed by the Sharpless-Reich procedure on the resulting ketone produced AB enone subunit **2.25**.[32] Overall, **2.25** was obtained in 2% over 16 steps from allene **2.17** and aldehdye **2.18**.



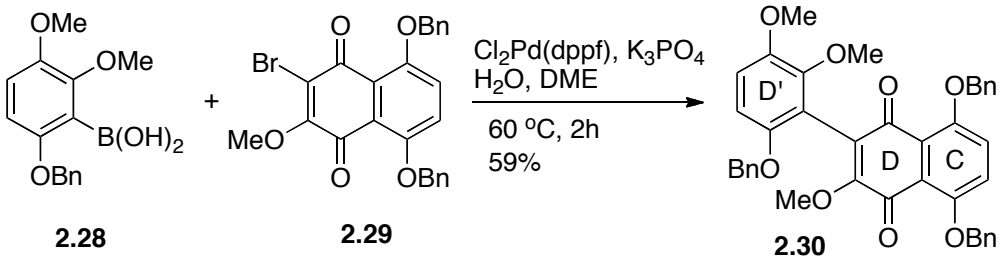
Scheme 2.4



Scheme 2.5

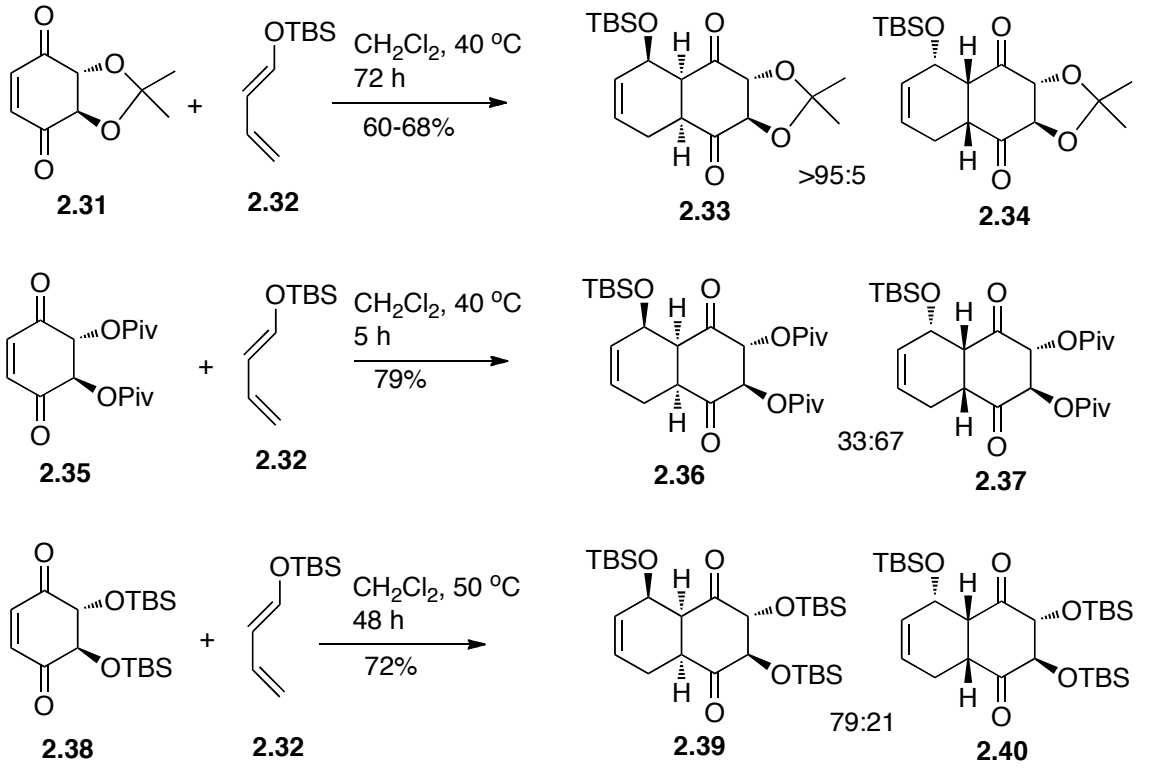
The Roush group also reported a model study for construction of the D-D′ biaryl bond.[26a] Attempts at cross-couplings of highly electron rich, highly substituted, arylhalides and triflate were unsuccessful. Eventually partnering bromonaphthoquinone **2.29** and arylboronic acid **2.28** under Suzuki conditions produced arylnaphthoquinone

2.30.[33] NMR studies and MM2 calculations of arylnaphthoquinone **2.30** showed the existence of atropisomers with an energy barrier for atropisomerization greater than 22 kcal/mol.[34] These results suggested that the natural product is possibly a single atropisomer.



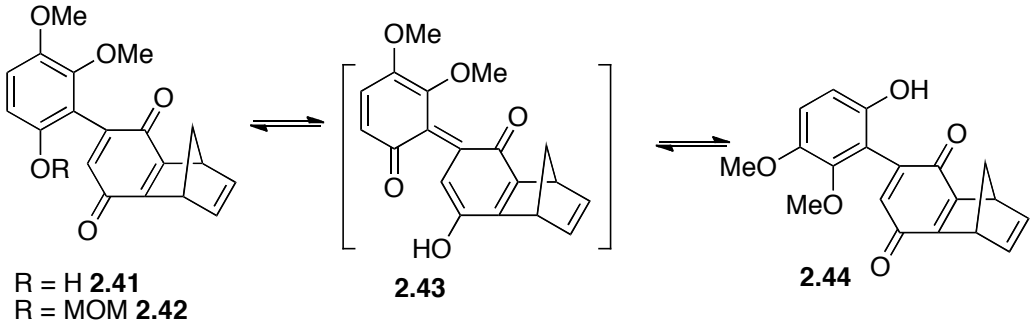
Scheme 2.6

Sulikowski's group also conducted several model studies on the AB/A′B′ subunit and the biaryl bond in hibarimicin B **2.1**.[35] The stereoselectivity in the Diels-Alder reactions of diene **2.32** and the tartaric acid derived C_2 symmetric dienophiles (**2.31**, **2.35**, **2.38**) showed strong protecting group dependence (Scheme **2.7**).[36] The acetonide protected dienophile **2.31** gave predominantly a single diastereomer **2.33** with the undesired stereochemistry of the bridge carbon of the decalin. The bis-silylether dienophile **2.38** led to an increased proportion of the desired decalin **2.40**, but this was still the minor diastereomer. The bis-pivoaloyl diene **2.35** gave the best results with a 67:33 ratio in favor of the desired diastereomer **2.37**. The authors explained the observed stereoselectivities in terms of ring strain effects in the transition state for dienophile **2.31**, and gauche interactions in the case of dienophiles **2.35** and **2.38**.



Scheme 2.7

This study also found that the biaryl model compound **2.41** underwent rapid rotation around the aryl-quinone bond while the MOM protected compond **2.42** existed as approximately 1:1 mixture of two distinct atropisomers.[35b] Th authors suggested that steric hindrance alone could not account for the difference. They concluded that the hydroxy group of **2.41** significantly lowered the rotation barrier due to stabilization of a transition state, which resembles a quinone methide intermediate **2.43**.[37]

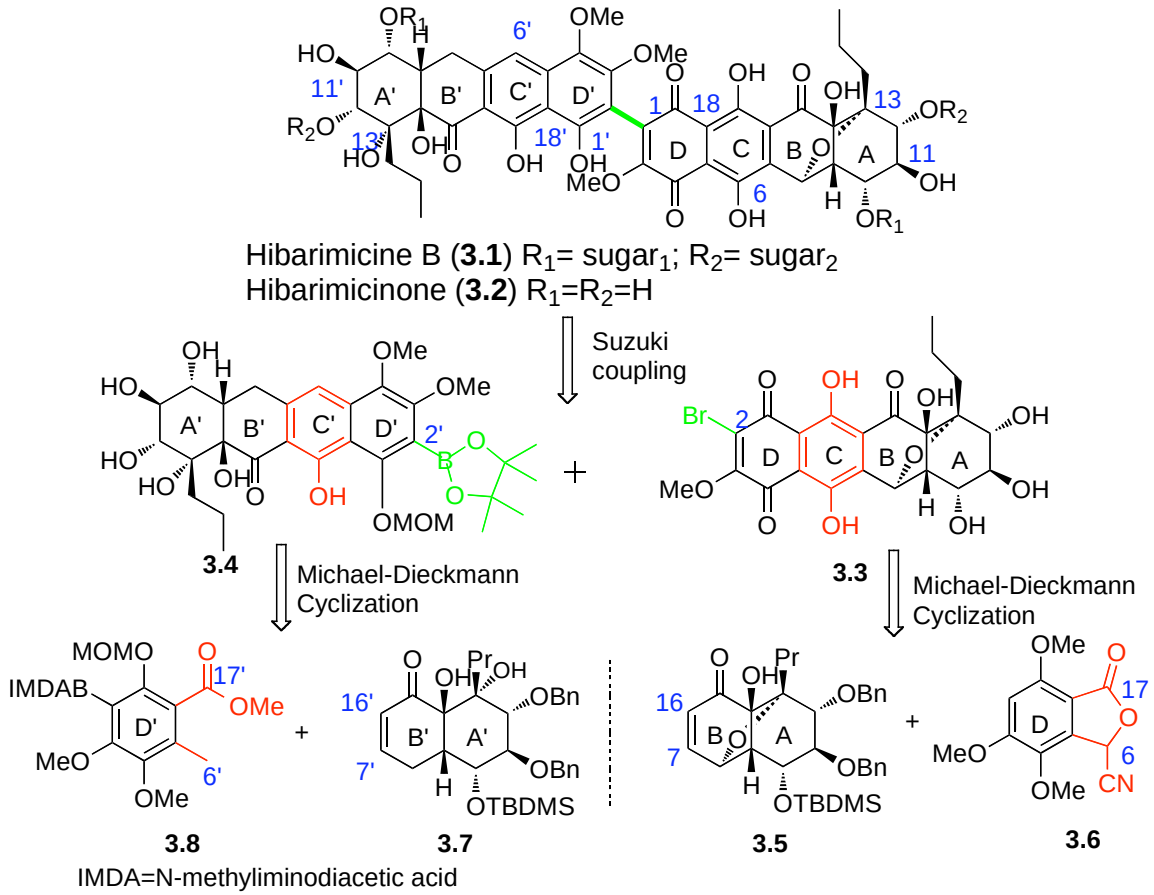


Scheme 2.8

Thus, contrasting results pertaining to the issue of atropisomer existence around the biaryl bond were reported by Roush and Sulikowski from their model studies. This controversy, the structural complexity and ambiguities combined with the intriguing biological properties make angelmicin B (hibarimicin B) a fascinating synthetic target.

Chapter 3. Synthesis of AB and A′B′ Subunit of Angelmicin B (Hibarimicin B)

3.1 Introduction

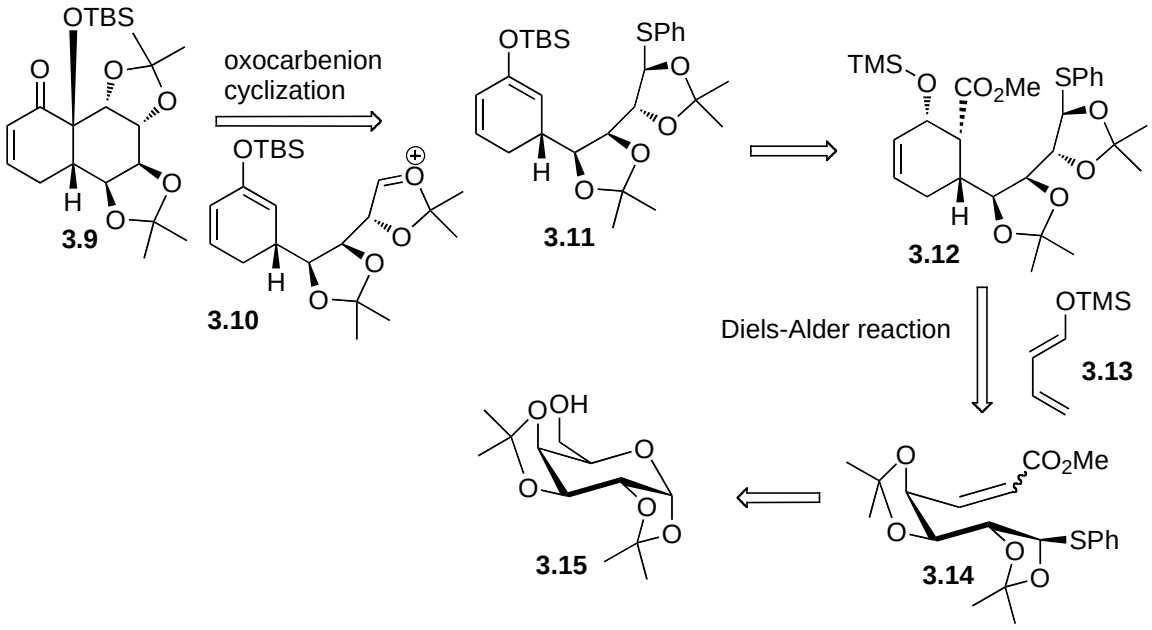


Scheme 3.1 Retrosynthetic analysis of hibarimicin B

Based on the discussion in Chapter 2, we propose that hibarimicin B (**3.1**) could be obtained from a late glycosidation of hibarimicinone **3.2**, which could be prepared through a Suzuki coupling of ABCD **3.3** ring segment and A′B′C′D′ **3.4** ring segment following a protocol developed by Roush in their CD-D′ model system study (Scheme **3.1**).[26a] C ring in ABCD **3.3** segments would be cyclized through well-studied Michael-Dieckmann reaction of Michael donor **3.6** and enone **3.5**.[38] Very similarly, A′B′C′D′ **3.4** ring segment could also be synthesized from 5-methoxyorsellinic acid derivative **3.8** and enone **3.7**.[38] In this chapter, we focused on the synthesis of the AB and A'B' enones **3.5** and **3.7**.

3.2 Model studies

Our immediate synthetic target was model compound *cis*-decalin **3.9.** A key step in the synthesis is oxocarbenium cyclization of an enol ether-thioacetal precursor **3.11**. This reaction follows from the success of related cyclization from this laboratory.[39]

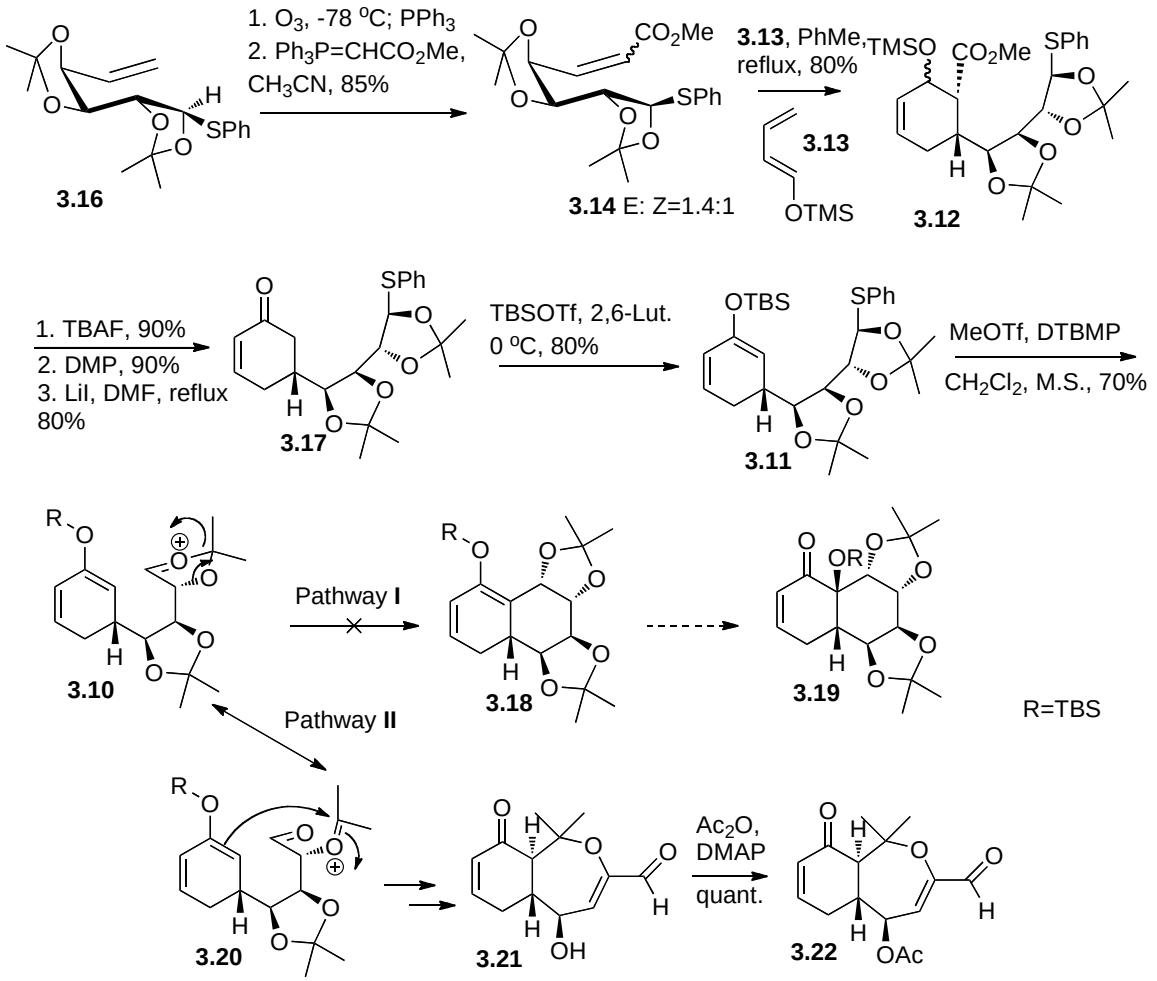


Scheme 3.2 Retrosynthetic analysis of model *cis*-decalin **3.9**

We envisaged synthesis of a model *cis*-decalin **3.9** could through an oxocarbenium ion cclization from a enol ether precursor **11** (**Scheme 3.2**). The enol ether **3.11** was expected from elaboration of a Diels-Alder adduct **3.12**. The required dienophile **3.14** could be synthesized from commercially available D-galactose derivative **3.15.**

The known alkene **3.16**[40] from a commercial D-galactopyranose **3.15** was converted to the dienophile **3.14** in 85% yield (E/Z=1.4:1), via a three step procedure, ozonolysis followed by PPh_3 reduction and Wittig olefination with PPh_3=$CHCO_2Me$. Diels-Alder

reaction of the *Z*-**3.14** with 1-trimethylsiloxybutanediene **3.13** gave mainly endo Diels Alder products.[41]



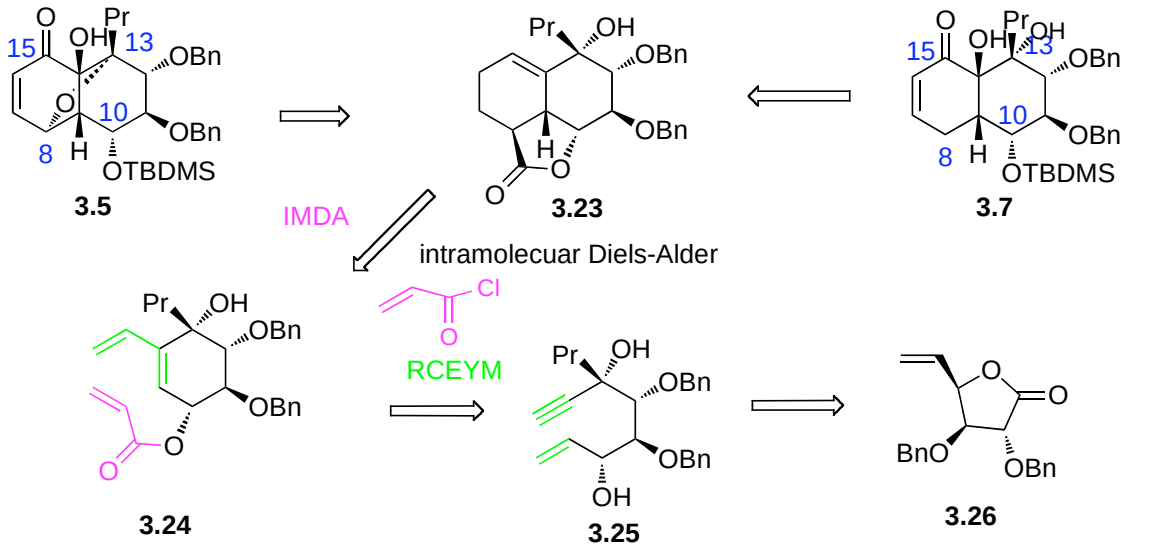
Scheme 3.3.

The major endo adducts **3.12** was determined by 2D-NOESY NMR and J coupling analysis. The stereochemistry C9′ was assigned to the same as natural compound, based on NMR analysis of the later compound **3.22**. After desilylation and Dess-Martin oxidation of Diels-Alder adduct **3.12** to β-keto ester and demethoxycarbonylation with LiI in DMF,[42] cyclohexenone **3.17** was formed in high yield and was converted to silyl enol ether **3.11** by treatment of TBSOTf (*tert*-butyldimethylsilyl triflate). Based on previous work in our laboratory, treatment of enol ether **3.11** with methyl triflate

(MeOTf) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) was expected to give our target compound **3.18**. However, the reaction produced the 7-membered ether **3.21,** instead. Varying the TBS to TMS enol ether and/or reaction conditions, the results were the same. Our speculation was that the oxocarbenium formed during the reaction did not go through pathway **I** to give the target compound **3.18**. Instead, the oxocarbenium **3.10** preferred structure **3.20** probably due to the large steric congestion between the two 2,2-dimethyl-1,3-dioxolane rings. The oxocarbenium **3.20** reacted along pathway **II** to give the 7-membered ether **3.21**. The structure of **3.21** was assigned based on the derived acetate **3.22**. In conclusion, the oxocarbenium cyclization of enol ether **3.10** resulted in bicycloether **3.21** instead of decalin **3.18**, and thus this approach was discontinued.

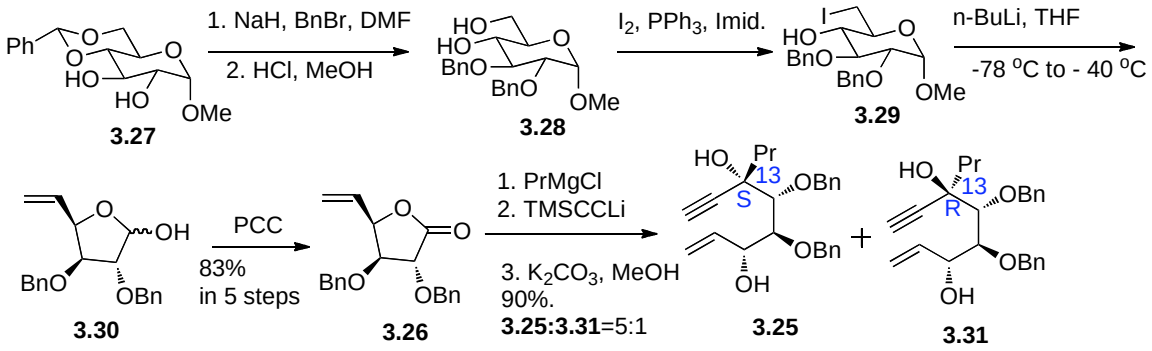
3.3 Retrosynthetic plan

We envisaged an approach to AB subunit **3.5** and A′B′ subunit **3.7** that centered on an IMDA[43] reaction on triene **3.24** to give a complex *cis*-decalin **3.23**, which is exquisitely suited for elaboration to both **3.5** and **3.7**. Precursor **3.24** appeared to be accessible from enyne **3.25** through a ring closing eneyne metathesis (RCEYM).[44, 45] The known carbohydrate derived lactone **3.26**[46] seemed to be an appropriate precursor for **3.25**.



Scheme 3.4 Retrosynthetic analysis of common intermediate decalin **3.25**

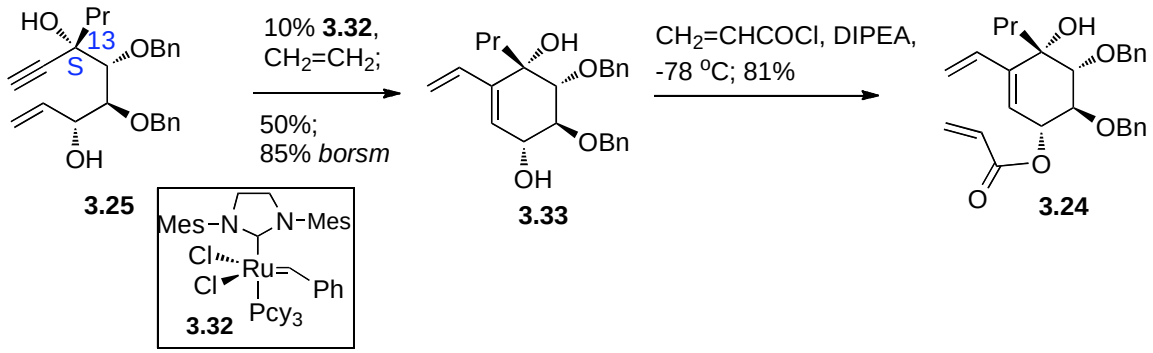
3.4 Synthesis of Diels-Alder adduct 3.23



Scheme 3.5 Synthesis of enyne **3.25**

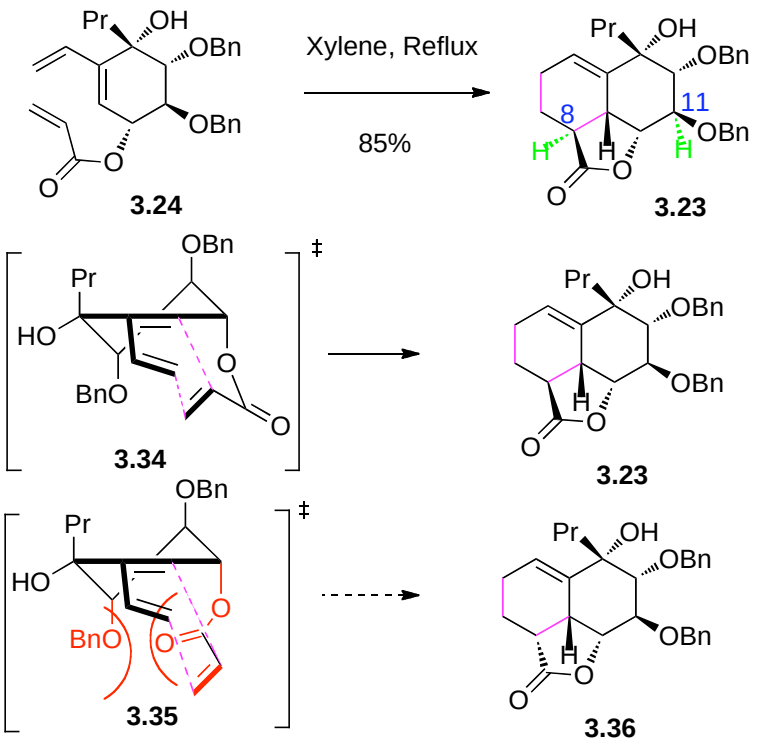
Starting from commercial avilabe D-glucose derivitive **3.27**, the known lactone **3.26** was obtained in 5 steps and 83% yield using a modified procedure as shown in scheme **3.5**. Treatment of lactone **3.26**[46] with nPrMgCl at −78 °C provided the hemiketal product, which was exposed in a separate step to TMSCCLi. Desilylation of the crude product

provided a 90% yield of **3.25** and its epimer **3.31** (respective ratio, *ca* 5:1). Similar selectivity has been observed for the addition of acetylide anions to related substrates.[47] The stereochemistry of **3.25** was confirmed by NOESY of later products (**3.23**, **3.45**) and single crystal X-ray crystallography on **3.45** (*vide infra*).



Scheme 3.6. Synthesis of triene **3.24**

RCEYM on enyne diol **3.25** was effected under Mori's conditions, using 10% Grubb's 2nd generation catalyst under an ethylene atomsphere at room temperature in CH_2Cl_2 (**Scheme 3.6**).[48] Diene **3.33** was obtained in 50% isolated yield or 85% based on recovering starting materials. Attempts to optimize this reaction by increasing the reaction temperature, varying the alcohol protecting groups or using the TMS protected acetylene were not successful.[45b,c] Ethylene atmosphere was also found to be essential. Selective esterification of diol **3.33** with acroyl chloride provided **3.24**, triene substrate for the key IMDA reaction.



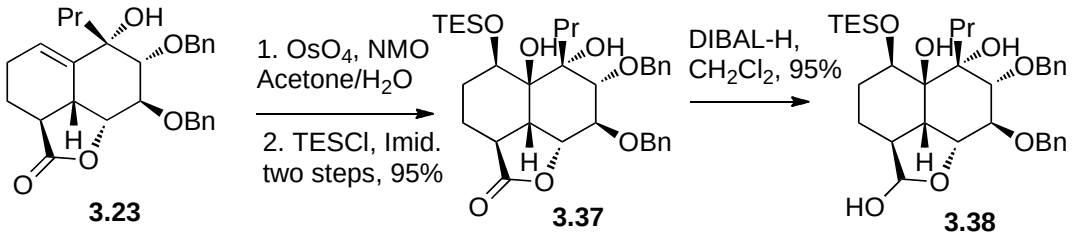
Scheme 3.7. Mechanism of the IMDA reaction.

The reaction of **3.24** in xylene at refluxing afforded the exo adduct **3.23** with the desired configuration at the ring junction (C9), as the sole Diels-Alder adduct. The structure of **3.23** was supported by 2D COSY, NOESY and HSQC experiments. High exo selectivity in IMDA reactions of related substrates has been previously noted.[49] The exo selectivity was probably due to the steric hinderance in the endo transition state (**Scheme 3.7**).

3.5 Elaboration to AB subunit

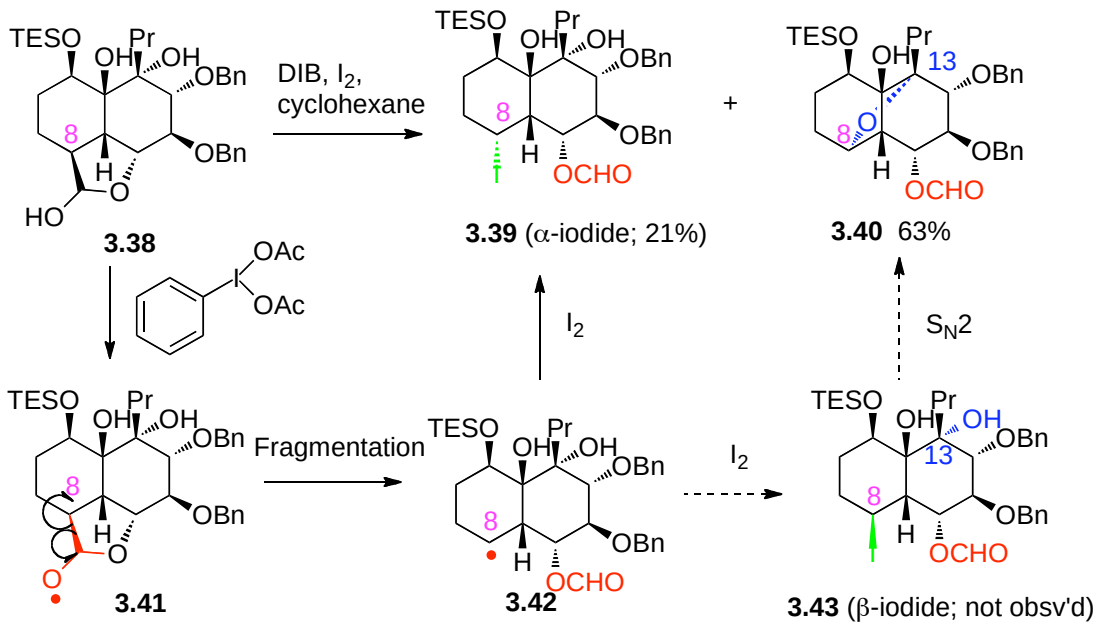
The IMDA product **3.23** was ready for elaboration to the desired target **3.5**. Thus the convex topography of **3.23** suggested that stereoselective dihydroxylation of the alkene would facilitate the introduction of the C14,15 acyloin moiety, and oxidative fragmentation of the lactone (or at the derived lactol) should pave the way for

tetrahydrofuran formation. Accordingly, treatment of **3.23** under standard dihydroxylation conditions afforded a single triol diastereomer (**Scheme 3.8**) and was selective protection of the secondary alcohol as the triethylsilyl ether, the lactone **3.37** was given in 95% yield from **3.23**.



Scheme 3.8

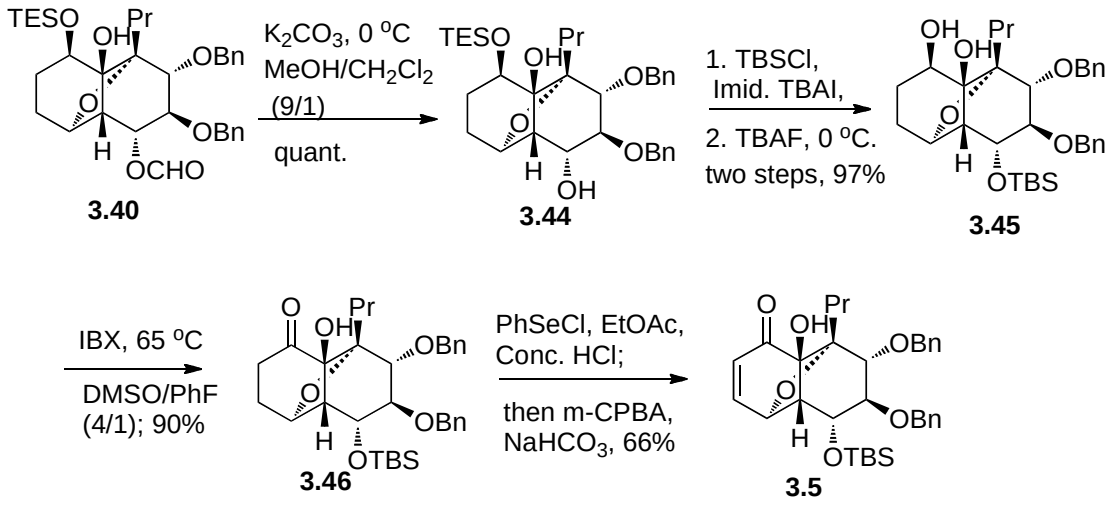
In preparation for introduction of THF ring in the final product, lactone **3.37** was reduced to a lactol **3.38** and was treated with diiodosobenzene diacetate/I_2 following the conditions developed by Suárez (**Scheme 3.9**). [14] We had anticipated a mixture of iodides



Scheme 3.9 Suárez oxidative fragementation-intramolecular etherification

3.39 and **3.43**. We were pleasantly surprised to find that the major product was in fact THF **3.40**, with a minor amount of **3.39** and no evidence for **3.43**. A small amount of lactone **3.37** was also observed. (95%, **3.40**:**3.39**:**3.37** = 6:2:1). It is possible that THF **3.40** and iodide **3.39** both arise after iodination of the C8 alkyl radical that is presumed to be the product of fragmentation of the initial oxy radical. Thus radical iodination may lead to iodides **3.39** and **3.40**, and the latter can undergo a facile intramolecular etherification to give THF **3.40**. However, the possibility that **3.39** and **3.40** may come from divergent pathways from the C8 alkyl radical cannot be excluded. [50]

Because **3.40** and **3.37** were inseparable by column chromatography, the mixture was used in the subsequent step. Thus treatment of the 6/1 ratio of **3.40**/**3.37** with K_2CO_3 in MeOH/CH_2Cl_2 (9/1) at 0 ^oC gave the tricylcic diol **3.44** and fully recovered **3.37**. After protecting group manipulation, **3.44** was converted to diol **3.45**. Single crystal X-ray crystallography of **3.45** confirmed that the stereochemistry was as required for the AB subunit of angelmicin B (hibramincin B) (**Figure 3.1**). Treatment of **3.45** with *o*-iodoxybenzoic acid (IBX) in DMSO/PhF at 65 ^oC for 20 h according to the Nicolaou procedure, gave cyclohexanone **3.46** in 90% yield.[51] In contrast to the reported reactivity of this reagent, a prolonged reaction time, higher temperatures or re-treament of **3.46** with IBX did not effect further oxidation to the cyclohexenone **3.5**. Eventually, using the Sharpless-Reich protocol[52] that was applied to a similar intermediate in the Roush synthesis, **3.5** was obtained in 66% isolated yield (72% bsrm).



Scheme 3.10 End games for enone AB **3.5**

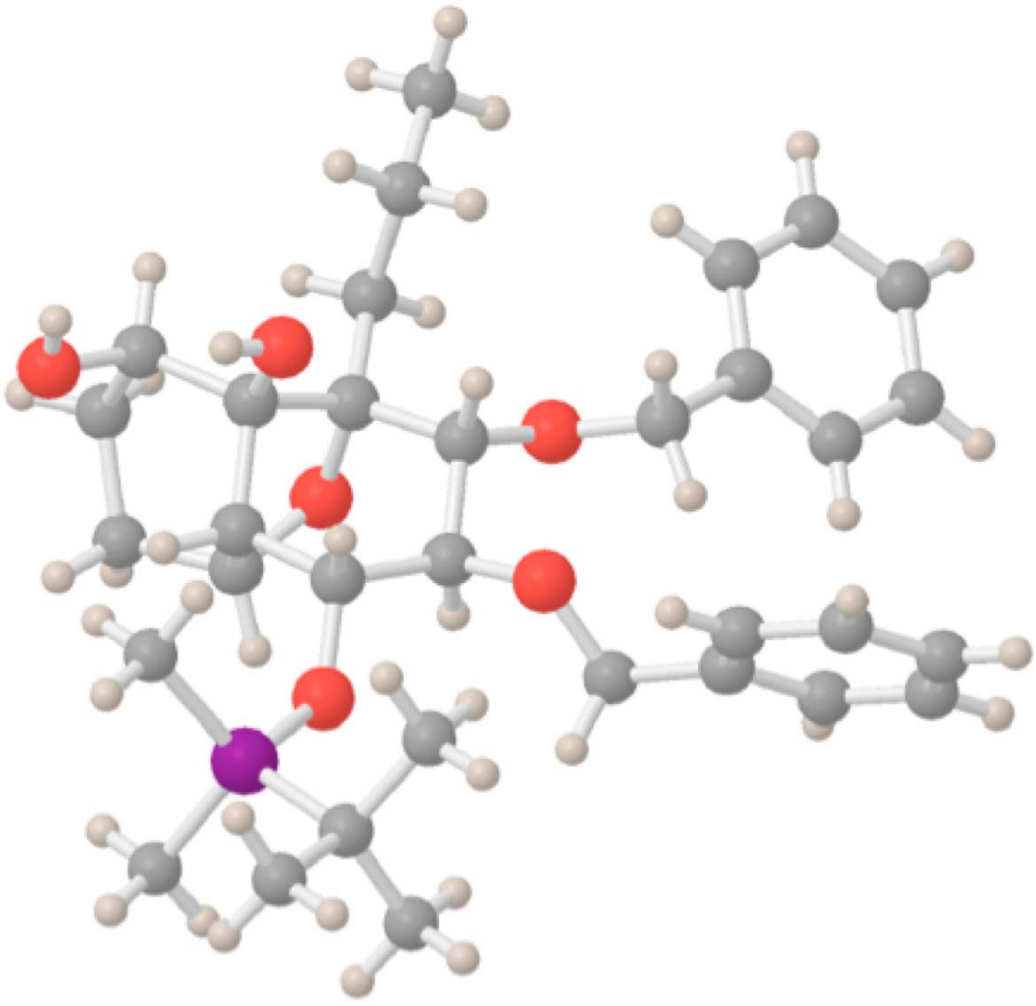
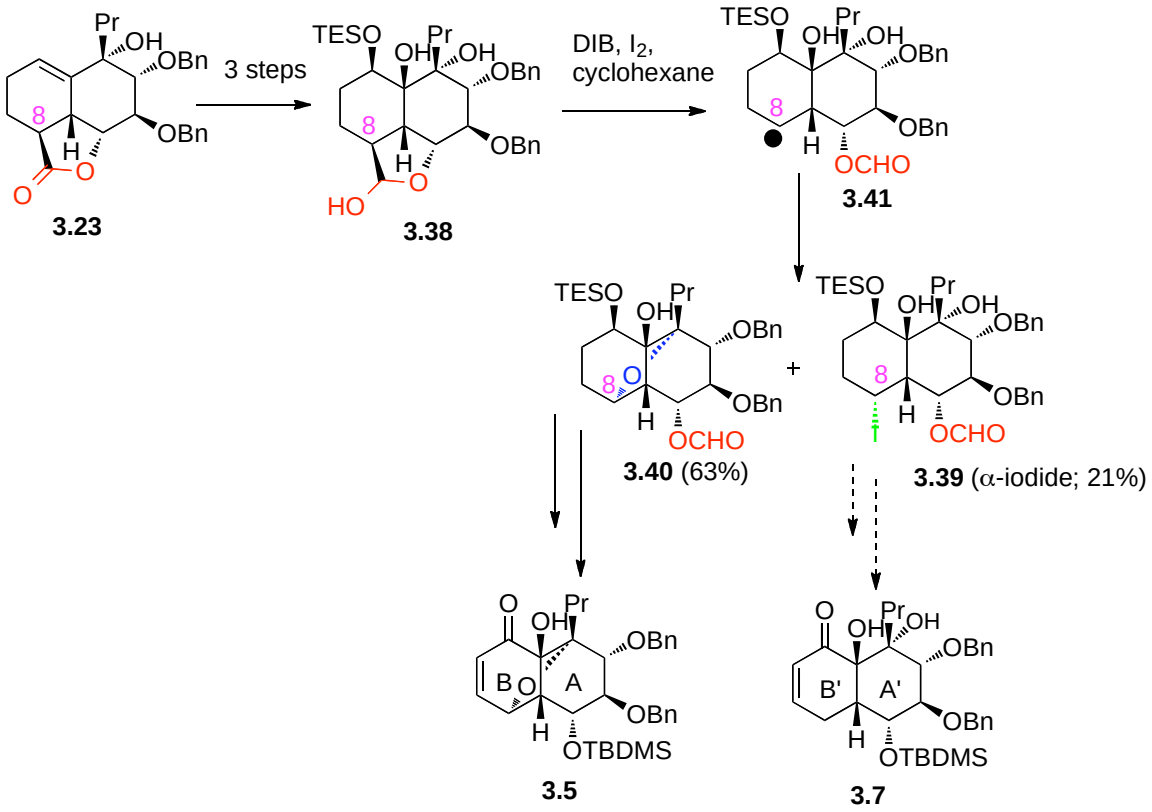


Figure 3.1 X-ray structure of the diol **3.45**

In summary, the AB ring subunit **3.5** of angelmicin B (hibramicin B) from the known lactone **3.26** through a key RCEYM/IMDA and a tandem alkoxy radical fragmetation-etherification sequence, in 15 steps and 9%, or 17 % yield (*brsm*).

3.6 Elaboration to the A′B′ subunit

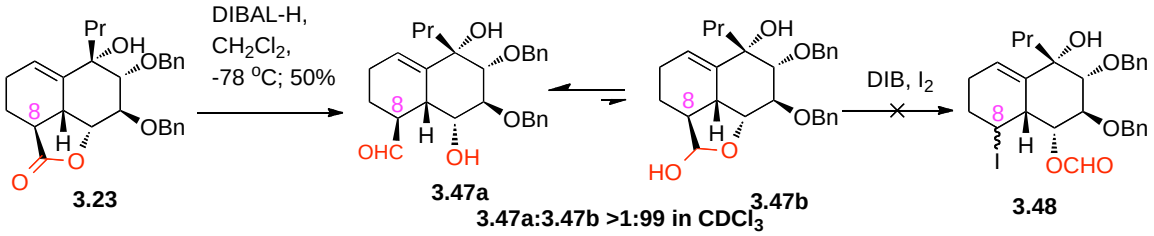


Scheme 3.11

In the previous section a synthesis of enone **3.5**, which is a potential precursor for the AB segment of angelimicin B was presented.[53] A key step in this synthesis was the transformation of the complex decalin **3.23** to the tricyclic ether **3.40**. Importantly, a minor product in this reaction was the bicyclic iodide **3.39** which can be converted to enone **3.7** for use as a precursor to the A′B′ subunit of angelimicin B. Enone **3.7** can also be used for HMP-Y1. Given its relevance to the synthesis of both HMP-Y1 and

angelimicin B we sought a more streamlined synthesis of enone **3.7**. These results are described herein.[54]

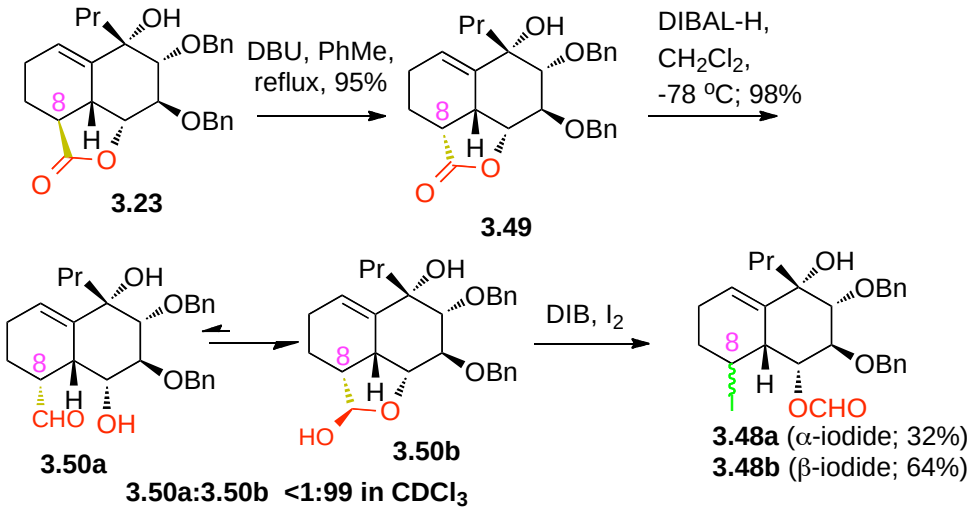
We speculated that the reaction of **3.38** with iodosobenzene diacetate proceeded via a radical fragmentation to **3.41**, which leads to **3.40** and **3.39**.[55, 56] We therefore reasoned that suppression of the pathway to the tricyclic ether **3.40**, would bias the reaction towards **3.39** and, or the epimeric iodo-derivative. Towards this end, it was decided to perform the fragmentation reaction on a lactol substrate that is more rigid than **3.38**, and therefore less prone to the cyclo-etherification. Alkene-lactol **3.47b** was considered a suitable substrate. This material was prepared by DIBAL-H reduction on **3.23**. However, the ^{1}H NMR data suggested that this compound existed primarily as the hydroxy-aldehyde **3.47a**, which raised questions about the feasibility of the planned radical fragmentation reaction. Indeed, exposure of **3.47** to iodosobenzene diacetate and iodine led to a complex mixture of intractable products.



Scheme 3.12

Lactol **3.50** was next examined as a candidate for the radical reaction because of the expectation that the lower strain in 1,3-syn bridged framework would lead to a higher proportion of the lactol tautomer **3.50b** (compared to the **3.47**). Accordingly, DBU promoted epimerization of lactone **3.23** at C8, and reduction of the resulting endo lactone **3.49** provided **3.50**. Lactol **3.50**, within the limits of ^{1}H NMR detection existed entirely as **3.50b**. Exposure of this material to the conditions for radical fragmentation afforded a 2:1

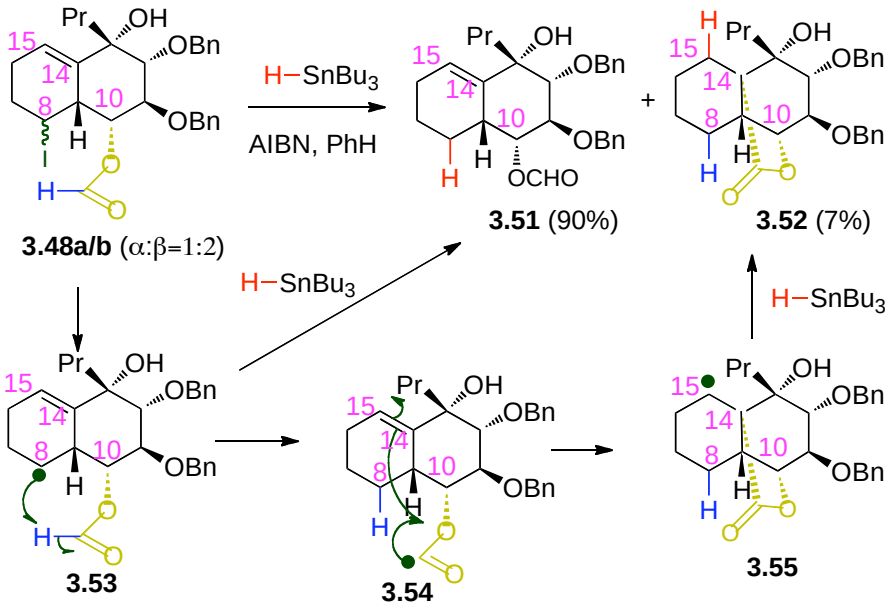
mixture of iodoformates in 96% yield. Thus the framework presented in **3.50** is delicately balanced in terms of the strain requirements for the two key steps in the radical reaction. Strain effects are not sufficiently high to prevent formation of the lactol **3.50b** that is required to trigger the fragmentation step, but channels this pathway to the desired bicyclic product by working against the competing cyclo-etherification process.



Scheme 3.13

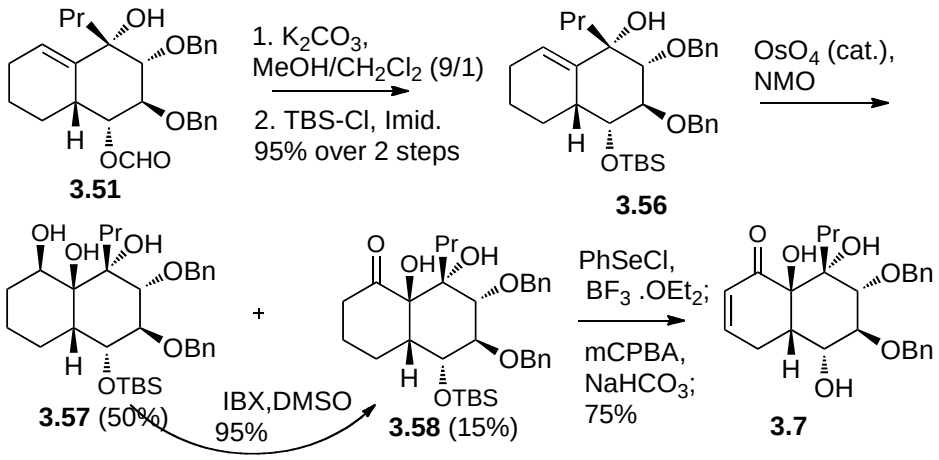
The mixture **3.48** was next elaborated to the A′B′ enone target. Treatment of **3.48** under standard deiodination conditions with Bu_3SnH and AIBN in refluxing PhH afforded the expected formate **3.51** in 90% yield together with a minor product **3.52** (7%). A possible mechanism for **3.52** proceeds through intramolecular hydrogen transfer in the first formed radical **3.53** to give the alkoxycarbonyl radical **3.54**. Instead of loss of CO_2 to give C10 carbon radical, a 5-exo-trig cyclization was undergone and resulted in carbon radical **3.55**, which extracted a hydrogen atom from $HSnBu_3$ to give **3.52**.[57, 58] This transformation may be of wider interest because **3.52** with a synthetically

formidable bridgehead quaternary center bears resemblance to a variety of naturally occurring terpenoid natural products.[59, 60]



Scheme 3.14

Standard protecting group operations on **3.51** provided **3.56** in 95% overall yield (**Scheme 3.15**). Stereoselective dihydroxylation on **3.56** afforded the expected triol **3.57** (50%) and a minor amount ketone **3.58** (15%).[61] The stereochemistry of **3.57** was confirmed by the X-ray crystal structure (**Figure 3.2**). Treatment of **3.57** with IBX gave **3.58**.[51] The overall yield of **3.58** from **3.56** was approximately 63%. The transformation of ketone **3.58** to the A′B′ **3.7** followed the Sharpless-Reich's protocol that was used on the analogous substrate in the synthesis of the AB enone **3.5**.[26, 52, 53, 62]



Scheme 3.15. End games for A′B′ enone **3.7**

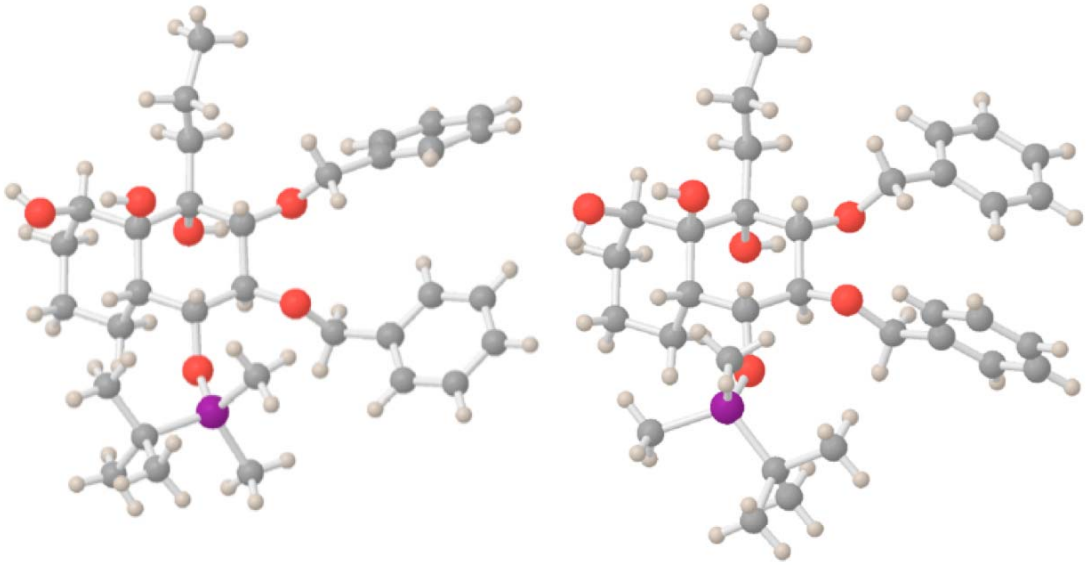


Figure 3.2. X-ray structure of triol **3.57**

3.7 Conclusion

In this chapter, after an unsuccessful oxocarbenium cyclization approach to the synthesis of decalin precursors to angelimicin B, we developed a strategy that centered on RCEYM and IMDA reactions. In summary, a tricyclic THF-bridged AB ring subunit for

angelmicin B (hibramicin B) was prepared from a known lactone through a RCEYM/IMDA sequence and a novel tandem alkoxy radical fragmetation-etherification reaction, in 15 steps and 9% or 17 % yield (*brsm*).[53] The Diels Alder adduct from this synthesis was also transformed to an A′B′ subunit for angelimicin B.[54] This synthesis complements the earlier synthesis of the AB segment, and illustrates the versatility of the Diels Alder adduct. The key differentiating reaction in the two syntheses is the Suárez fragmentation of a tricyclic lactol radical, the outcome of which was controlled by the rigidity of the lactol substrate. On a more general note, this ploy illustrates the potential of the Suárez reaction for synthesis of diverse chemical libraries.

3.8 Experimental

General. Unless otherwise noted, all reactions performed in organic solvents were conducted under an atmosphere of argon with oven-dried glassware using standard syringe and septa technique. THF was distilled from a blue solution of sodium benzophenone ketyl. CH_2Cl_2 and fluorobenzene were distilled from phosphorus pentoxide. Diisopropylethylamine (DIEPA) was distilled successively from nihydrin and KOH. Anhydrous toluene, methanol, DMSO and DMF were purchased from Aldrich and used without purification. Thin layer chromatography (TLC) was performed using Whatman silica gel HF_{254} plates or Selecto Scientific alumina B F_{254} plates and chromatograms were developed using UV light, 12-molybdophosphoric acid (PMA), or potassium permanganate ($KMnO_4$). Flash column chromatography (FCC) was performed using silica gel 60 (230-400 mesh) or Brockmann I alumina gel (150 mesh). Optical rotation was measured on a Rudolph Autopol III polarimeter. IR spectra were recorded on a Thermo Nicolet IR100 spectrometer and the vibrations were reported in wavenumbers (cm^{-1}). H^1-NMR spectra were recorded on a Bruker 500 MHz spectrometer in $CDCl_3$ or C_6D_6 and the chemical shifts were reported in parts per million (ppm) relative to the signal for the protonated solvent, i.e $CD(H)Cl_3$ at 7.27 ppm or $C_6D(H)_6$ at 7.16 ppm. ^{13}C-NMR spectra were recorded on a Bruker 125 MHz spectrometer in $CDCl_3$ or C_6D_6 and the chemical shifts were reported in parts per million (ppm) relative to the solvent peak, i.e. $CDCl_3$ at 77.23 ppm or C_6D_6 at 128.39 ppm. High resolution mass spectra (HRMS) were obtained on an Ultima Micromass Q-TOF Mass Spectrometer at the Mass Spectrometry Laboratory of Hunter college, CUNY.

Methyl 3-((4S,5S)-2,2-dimethyl-5-((4S,5R)-2,2-dimethyl-5-(phenylthio)-1,3-dioxolan-4-yl)-1,3-dioxolan-4-yl)acrylate (3.14)

A solution of thioacetal **3.16**[40] (2.29g, 6.42 mmol) in CH_2Cl_2 (50 mL) at −78 ^oC was treated with a stream of O_3. On appearance of a persistent light blue color of the reaction mixture, the flow of O_3 was stopped and to the solution was added PPh_3 (1.85, 7.06 mmol). The mixture was then slowly warmed up to room temperature and concentrated *in vacuo*. The crude aldehyde product was used in next step without purification. A small portion was purified for characterization purposes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (d, J=2.3 Hz, 1H), 7.53 (m, 2H), 7.32 (m, 2H), 7.29 (m, 1H), 5.48 (d, J=7.4 Hz, 1H), 4.59 (dd, J=1.5, 8.4 Hz, 1H), 4.50 (dd, J=2.3, 8.4 Hz, 1H), 4.04 (dd, J=1.5, 7.4 Hz, 1H), 1.59 (s, 3H), 1.47 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.09, 133.85, 131.73, 129.08, 127.60, 111.82, 111.45, 84.68, 80.87, 78.15, 76.01, 26.99, 26.55, 26.33, 25.29.

The crude aldehyde from above was dissolved in CH_3CN (15 mL) and treated with $Ph_3P{=}CHCO_2Me$ (3.43g 10.3 mmol). The solution was heated at reflux for 3 h. The mixture was poured into brine (100 mL) and extracted with Et_2O (3x50 mL). The combined organic phase was washed with brine and water, dried over Na_2SO_4, concentrated *in vacuo* and purified by FCC to afford an *E/Z* mixture of alkenes. (2.47 g, 94% yield). (E/Z=1.4/1). ***E*-3.14** alkene, R_f = 0.50, 15% EtOAc in petroleum ether. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.31 (m, 2H), 7.28 (m, 1H), 7.05 (dd, J=7.1, 15.7 Hz, 1H), 6.13 (dd, J=1.2, 15.7 Hz, 1H), 5.37 (d, J=7.2 Hz, 1H), 4.85 (dt, J=1.2, 7.1 Hz, 1H), 4.39 (dd, J=2.8, 7.1 Hz, 1H), 3.87 (dd, J=2.8, 7.2 Hz, 1H), 3.77 (s, 3H), 1.56 (s, 3H), 1.51 (s, 3H), 1.47 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.28,

142.77, 134.35, 131.67, 129.20, 127.62, 124.37, 112.09, 110.65, 85.68, 79.65, 76.84, 76.62, 51.91, 27.43, 26.95, 26.32, 25.72. ***Z*-3.14** alkene: R_f=0.64, 15% EtOAc in petroleum ether. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.31-7.26 (m, 3H), 6.48 (dd, J=6.9, 11.7 Hz, 1H), 5.94 (dd, J=1.7, 11.7 Hz, 1H), 5.72 (dt, J=1.7, 7.3 Hz, 1H), 5.39 (d, J=7.5 Hz, 1H), 4.68 (dd, J=2.0, 7.5 Hz, 1H), 3.77 (s, 3H), 3.74 (dd, J=2.0, 7.5 Hz, 1H), 1.55 (s, 3H), 1.49 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.34, 147.20, 134.04, 132.17, 129.01, 127.58, 120.92, 111.41, 109.93, 84.99, 79.37, 75.48, 75.04, 51.78, 27.48, 26.68, 26.50, 25.51.

(6*R*)-Methyl 6-((4*S*,4'*R*,5*S*,5'*R*)-2,2,2',2'-tetramethyl-5'-(phenylthio)-[4,4'-bi(1,3-dioxolan)]-5-yl)-2-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate. (3.12)

To a solution of ***Z*-3.14** (1.40g, 3.41 mmol) in PhMe (5 mL) was added 1-trimethylsiloxylbutadiene (5.90 mL, 34.1 mmol). The solution was heated at reflux for 16 h and then concentrated in *vacuo* and purified by FCC to afford the Diels-Alder adducts **3.12** (1.80 g, 95% yield). There were 4 isomers (1:0.39:0.25:0.05) based on integration of the OMe signal in the ^{1}H NMR.

(R)-5-((4S,5S)-2,2-Dimethyl-5-((4R,5R)-2,2-dimethyl-5-(phenylthio)-1,3-dioxolan-4-yl)-1,3-dioxolan-4-yl)cyclohex-2-enone. (3.17)

The above mixture (**3.12**) was dissolved in THF (8.0 mL) and MeOH (2.0 mL) and treated with TBAF (1.0 M, 6.5 mL). After TLC showed complete disappearence of starting material, water (10 mL) was added to the reaction mixture. The mixture was extracted with Et_2O (3x20 mL). The combined organic phase was washed with brine and

water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by FCC to afford the derived alcohols. (1.38 g, 84% yield). Two major components were isolated by FCC purification for characterization purpose. Less polar fraction: R_f=0.48 (20% EtOAc in petroleum ether) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.34-7.26 (m, 3H), 5.82 (m, 1H), 5.73 (m, 1H), 5.41 (d, J=7.5 Hz, 1H), 4.41 (m, 2H), 4.34 (m, 1H), 3.95 (dd, J=1.1, 7.4 Hz, 1H), 3.77 (s, 3H), 2.97 (d, J=10.8 Hz, 1H), 2.95 (t, J=4.6 Hz, 1H), 2.51 (m, 1H), 2.34 (td, J=4.7, 18.4 Hz, 1H), 2.13 (m, 1H), 1.50 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.48, 133.44, 132.63, 129.22, 129.02, 128.97, 127.99, 111.77, 109.05, 85.42, 78.82, 77.84, 74.75, 67.44, 51.98, 47.29, 34.94, 27.47, 26.81, 26.73, 26.50, 25.70. More polar fraction: R_f=0.40 (20% EtOAc in petroleum ether) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.32 (m, 2H), 7.29 (m, 1H), 5.83 (m, 1H), 5.76 (m, 1H), 5.39 (d, J=7.5 Hz, 1H), 4.59 (br. 1H), 4.30 (t, J=6.4 Hz, 1H), 4.23 (dd, J=2.1, 6.3 Hz, 1H), 4.06 (dd, J=2.1, 7.5 Hz, 1H), 3.78 (s, 3H), 2.59 (m, 2H), 2.31 (m, 1H), 2.11 (d, J=6.7 Hz, 1H), 1.51 (s, 6H), 1.49 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.39, 134.41, 131.78, 129.14, 128.44, 128.25, 127.52, 111.73, 108.67, 85.84, 78.89, 77.48, 75.08, 68.06, 52.43, 52.36, 34.77, 27.42, 26.62, 26.55, 26.16, 25.59.

To the mixture of the two isolated alcohols (1.38g, 2.87 mmol) in wet CH_2Cl_2 (70 mL) was added DMP (15 wt% in CH_2Cl_2, 16.2 mL, 5.74 mmol) and pyridine (2.27 g, 28.7 mmol). After TLC showed complete disappearence of starting material, saturated aqueous $NaHCO_3$ (35 mL), saturated aqueous $Na_2S_2O_3$ (7 mL) and Et_2O (100 mL) were added to the reaction mixture. The mixture was extracted with Et_2O (3x50 mL), and organic phase was washed with brine and water, dried (Na_2SO_4) and concentrated *in*

vacuo. The residue was purified by FCC to afford the derived β-keto-ester. (1.18 g, 86%) R_f=0.62 (20% EtOAc in petroleum ether.)

To a flask containing the β-keto-ester (170 mg, 0.355 mmol) in DMF (12 mL) was added LiI (441 mg, 3.29 mmol). The solution was heated at reflux for 2 h. After cooling to room temperature, the mixture was poured into brine (20 mL) and extracted with Et_2O (3x20 mL). The combined organic phase was washed with brine and water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FCC to afford the derived ketone (120 mg, 80% yield). R_f=0.25 (10% EtOAc in petroleum ether.) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.34 (m, 2H), 7.29 (m, 1H), 7.00 (ddd, J=2.8, 5.6, 10.0 Hz, 1H), 6.06 (d, J=10.0 Hz, 1H), 5.34 (d, J=8.0 Hz, 1H), 4.31 (dd, J=0.3, 6.2 Hz, 1H), 4.09 (dd, J=6.2, 9.8 Hz, 1H), 3.84 (dd, J=0.7, 8.0 Hz, 1H), 2.75 (td, J=5.0, 18.9 Hz, 1H), 2.62 (m, 1H), 2.46 (dd, J=3.7, 16.2 Hz, 1H), 2.30 (tdd, J=2.7, 9.2, 18.9 Hz, 1H), 2.26 (dd, J=11.9, 16.2 Hz, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.53, 149.78, 133.57, 132.27, 129.77, 129.21, 127.82, 111.68, 109.19, 85.27, 79.55, 78.42, 73.99, 41.39, 35.27, 29.72, 27.25, 26.65, 26.30, 25.74.

((R)-3-((4S,5S)-2,2-Dimethyl-5-((4R,5R)-2,2-dimethyl-5-(phenylthio)-1,3-dioxolan-4-yl)-1,3-dioxolan-4-yl)cyclohexa-1,5-dienyloxy)(tert-butyl)dimethylsilane. (3.11)

To a flask containing keone (30 mg, 0.071 mmol) in CH_2Cl_2 (1.5 mL) at 0 ^oC was added 2,6-lutidine (0.041 mL, 0.357 mmol) and TBSOTf (0.025 mL, 0.107 mmol). After TLC showed complete disappearance of starting material, 2-propanol (0.2 mL) was added. The mixture was diluted with saturated $NaHCO_3$ (5 mL) and extracted with Et_2O

(3x10 mL). The combined organic phase was washed with brine and water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was and purified by FCC to afford the derived silyl enol ether (28 mg, 75% yield). R_f = 0.80 (neutral alumina, 15% EtOAc in petroleum ether). ^{1}H NMR (500 MHz, C_6D_6) δ 7.61 (m, 2H), 7.00 (m, 2H), 6.93 (m, 1H), 5.82 (qd, J=1.8, 9.8 Hz, 1H), 5.77 (d, J=8.0 Hz, 1H), 5.74 (td, J=4.3, 9.8 Hz, 1H), 4.98 (dd, J=1.6, 4.6 Hz, 1H), 4.41 (d, J=6.2 Hz, 1H), 4.34 (dd, J=6.3, 10.5 Hz, 1H), 4.26 (d, J=7.9 Hz, 1H), 3.18 (m, 1H), 2.46 (m, 2H), 1.60 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.29 (s, 3H), 1.00 (s, 9H), 0.24 (s, 3H), 0.23 9s, 3H). ^{13}C NMR (500 MHz, C_6D_6) δ 151.58, 135.54, 132.04, 129.91, 129.59, 127.03, 112.21, 109.54, 101.63, 86.86, 80.04, 78.88, 75.08, 34.25, 27.54, 27.42, 27.29, 26.39, 26.29, 26.21, 18.75, -3.72, -3.74.

(3Z,5S,5aR,9aR)-3-Formyl-1,5,5a,6,9,9a-hexahydro-1,1-dimethyl-9-oxobenzo[c]oxepin-5-yl acetate. (3.22)

To a flask containing enol ether **3.11** (26 mg, 0.0487 mmol) in CH_2Cl_2 (2 mL) were added DTBMP (77 mg, 0.487 mmol), molecular sieves (100 mg), MeOTf (56 mg, 0.393 mmol). After stirring for 48 h, the mixture was diluted with saturated $NaHCO_3$ (5 mL) and extracted with Et_2O (3x10 mL). The combined organic phase was washed with brine and water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was subjected to FCC. The partially purified product was dissolved in EtOAc (2 mL), and treated with Ac_2O (0.1 mL) and a DMAP (ca 1 mg). After 6 h, the mixture was diluted with saturated $NaHCO_3$ (5 mL) and extracted with Et_2O (3x10 mL). The combined organic phase was washed with brine and water, dried (Na_2SO_4) and concentrated *in vacuo.* The residue purified by FCC to give **3.22**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (s, 1H), 6.94 (ddd,

J=2.2, 6.8, 10.0 Hz, 1H), 6.21 (d, J=4.8 Hz, 1H), 6.15 (dd, J=2.7, 10.0 Hz, 1H), 5.37 (dd, J=4.8, 10.8 Hz, 1H), 2.97 (m, 1H), 2.69 (td, J=6.4, 18.0 Hz, 1H), 2.42 (d, J=10.5 Hz, 1H), 2.14 (s, 3H), 2.04 (m, 1H), 1.55 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.26, 189.57, 170.42, 152.17, 146.49, 131.51, 130.13, 84.72, 75.23, 55.87, 35.14, 28.77, 28.38, 22.

(2*R*,3*R*,4*S*,5*R*,6*S*)-4,5-Bis(benzyloxy)-2-(hydroxymethyl)-6-methoxytetrahydro-2*H*-pyran-3-ol (3.28).

NaH (40% in mineral oil, 3.54 g, 88.2 mmol) and TBAI (1.31 g, 3.55 mmol) was added at 0 ^{o}C to a DMF solution containing α-D-methyl 4,6-bezylideneylglucopyranose **3.27** (10.0 g, 35.4 mmol). The mixture was kept at the temperature for 45 min and then warmed to room temperature. After 30 min, the mixture was recooled to 0 ^{o}C and benzylbromide (10.5 mL, 88.5 mmol) was added dropwise. The mixture was then warmed to room temperature. After TLC showed complete disappearence of starting material, the reaction was quenched with saturated NH_4Cl solution. The mixture was extracted with Et_2O (3 x 100 mL). The organic phase was washed with brine and water, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was azeotroped with toluene and then dissolved in methanolic HCl (100 mL). After 3 h, saturated aqueous $NaHCO_3$ was added to the mixture until the pH was 8. Most the MeOH was then removed under reduced pressure. The residue was diluted with EtOAc and washed with brine and water, dried (Na_2SO_4), filtered, and concentrated in *vacuo*. Purification of the residue by FCC gave **3.28** (12.8g, 34.2 mmol, 97% yield). R_f = 0.35 (60% EtOAc in petroleum ether). ^{1}H NMR ($CDCl_3$) δ 7.39-7.31 (m, 10H), 5.04 (d, J=11.5 Hz, 1H), 4.78

(d, J=12.0 Hz, 1H), 4.71 (d, J=11.6 Hz, 1H), 4.68 (d, J=12.0 Hz, 1H), 4.61 (d, J=3.5 Hz, 1H), 3.84-3.72 (m, 3H), 3.65-3.61 (m, 1H), 3.54-3.50 (m, 2H), 3.39 (s, 3H), 2.23 (d, J=2.5 Hz, 1H), 1.87 (d, J=5.7, 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 138.91, 138.17, 128.90, 128.74, 1128.34, 128.25, 128.17, 98.41, 81.49, 80.02, 75.60, 73.37, 70.85, 70.71, 62.79, 55.49.

Methyl 2,3-di-O-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside (3.29).

To a flask containing Ph_3P (11.6g, 44.1 mmol) and imidazole (6.94 g, 102 mmol) in dry toluene (150 mL) was added I_2 (11.2 g, 44.1 mmol). The mixture was stirred for 1 h at which time **3.28** (12.6 g, 33.7 mmol) in toluene (50 mL) was added, and the mixture was warmed to 45 ^{o}C. When TLC showed complete disappearance of starting material, the reaction was cooled to room temperature. Brine (100 mL) was added, the organic layer was separated, and the aqueous phase was extracted with Et_2O (3 x 150 mL). The organic extract was dried (Na_2SO_4), concentrated *in vacuo* and purified by FCC to afford **3.29** (16.0g, 95% yield). R_f = 0.26 (15% EtOAc in petroleum ether). ^{1}H NMR ($CDCl_3$) δ 7.39-7.32 (m, 10H), 5.04 (d, J=11.5, 1H), 4.78 (d, J=12.1 Hz, 1H), 4.68 (d, J=11.5 Hz, 1H), 4.67 (d, J=12.1 Hz, 1H), 4.65 (d, J=3.7 Hz, 1H), 3.79 (t, J=9.1 Hz, 1H), 3.55 (d, J=3.3 Hz 1H), 3.52 (m, 1H), 3.45 (s, 3H), 3.43 (ddd, J=2.3, 7.1 , 9.5 Hz, 1H), 3.31 (dt, J=2.4, 9.0 Hz, 1H), 3.26 (dd, J=7.1, 10.4 Hz, 1H), 2.16 (d, J=2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 138.8, 138.1, 129.0, 128.8, 128.3, 128.29, 128.3, 98.4, 80.9, 80.1, 75.6, 73.9, 73.4, 70.0, 55.8, 7.2.

(3*R*,4*S*,5*R*)-3,4-Bis(benzyloxy)-5-vinyldihydrofuran-2(3*H*)-one (3.26)

To a flask containing iodide **3.29** (13.4 g, 26.7 mmol) in THF at −78 ^{o}C was added n-BuLi (2.5 M in hexane, 32.0 mL, 80.1 mmol), dropwise. After 30 min, the mixture was warmed to -40 ^{o}C and was kept at this temperature until TLC showed complete disappearence of starting material. The mixture was then poured into saturated aqueous NH_4Cl and extracted with Et_2O (3x150 mL). The combined organic phase was washed with brine and water, dried over Na_2SO_4, concentrated *in vacuo* and purified by FCC to afford the derived lactol (8.70 g, 99% yield) (α/β =5/4). R_f = 0.20 (15% EtOAc in petroleum ether).

A mixture of PCC (14.5 g, 67.5 mmol), sodium acetate (5.54 g, 67.5 mmol) activated molecular sieves (14.5 g), Celite (14.5 g) and florisil (14.5 g) in CH_2Cl_2 (50 mL) was stirred at room temperature for 30 min. A solution of the lactol from the previous step (8.70 g, 26.7 mmol) in CH_2Cl_2 (50 mL) was then introduced. After TLC showed complete disappearence of starting material, the mixture was then diluted with Et_2Ö and filtered through a short column of florsil. The solvent was then removed under reduced pressure and the residue purified by FCC to afford lactone **3.26** (8.03 g, 93 % yield). R_f = 0.65 (15% EtOAc in petroleum ether). ^{1}H NMR ($CDCl_3$) δ 7.39-7.28 (m, 10H), 6.01 (ddd, J=6.3, 10.6, 17.1 Hz, 1H), 5.45 (td, J=1.2, 17.2 Hz, 1H), 5.39 (td, J=1.1, 10.7 Hz, 1H), 5.04-5.00 (m, 2H), 4.72 (d, J=11.6 Hz, 1H), 4.63 (d, J=11.9 Hz, 1H), 4.57 (d, J=11.9 Hz, 1H), 4.29 (t, J=6.3 Hz, 1H), 4.23 (d, J=6.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 172.8, 137.1, 137.0, 131.5, 128.8, 128.4, 128.4, 128.0, 119.9, 80.1, 79.9, 76.9, 72.8, 72.6. HRMS (*m/z*) calculated for $C_{20}H_{20}O_4Na$ (ESI, M + Na^+) 347.1253, found 347.1252.

(3*R*,4*S*,5*R*,6*S*)-4,5-Bis(benzyloxy)-6-ethynylnon-1-ene-3,6-diol (3.25) and **(3*R*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-ethynylnon-1-ene-3,6-diol (3.31)**

n-PrMgCl (2.0 M in Et_2O, 43.2 mL, 86.3 mmol) was added dropwise, at −78 ^oC, to a solution of lactone **3.26** (8.00 g, 24.7 mmol) in THF (100 mL). After TLC showed no starting material was left, saturated aqueous NH_4Cl solution was added. The mixture was extracted with Et_2O (3x100 mL). The combined organic phase was washed with brine and water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by FCC afforded the derived lactol (8.60 g, 23.4 mmol, 95% yield) (α/β =2/1) . R_f = 0.40 (15% EtOAc in petroleum ether).

To a flask containing trimethylsilylacetylene (3.08 mL, 22.0 mmol) in THF (20 mL) at −78 ^oC was added n-BuLi (2.5 M in hexane, 8.50 mL, 21.2 mmol). The mixture was kept at this temperature for 30 min, and then transferred dropwise at −78 ^oC, to a flask containing a THF solution of the lactol from the previous step (1.62 g, 4.40 mmol). After 30 min, the reaction mixture was slowly warmed to 0 ^oC. Saturated aqueous NH_4Cl was then added and the mixture extracted with Et_2O (3x100 mL). The combined organic phase was washed with brine and water, dried (Na_2SO_4) filtered and concentrated *in vacuo.* The crude was dissolved in methanol (100 mL) and K_2CO_3 (0.95g, 6.88 mmol). Was added to the solution. After TLC showed disappearence of the starting material, water was added. The mixture was extracted with Et_2O and the organic phase was washed with brine and water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by FCC to provided enyne diol **3.25** and its epimer **3.27** in a 5:1 ratio. (**3.25**: 1.37 g, 3.48 mmol, 79%, R_f = 0.45 10% EtOAc in petroleum ether and **3.27:** 0.27g, 0.686 mmol, 16%, R_f=0.42, 10% EtOAc in petroleum). For **3.25**: ^1H NMR

($CDCl_3$) δ 7.38-7.29 (m, 10H), 5.98 (ddd, J=5.4, 10.5, 17.2 Hz, 1H), 5.37 (td, J=1.4, 17.2 Hz, 1H), 5.22 (td, J=1.4, 10.5 Hz, 1H), 4.87 (d, J=11.0 Hz, 1H), 4.85 (d, J=11.1 Hz, 1H), 4.65 (d, J=11.1 Hz, 1H), 4.63 (d, J=11.0 Hz, 1H), 4.38 (m, 1H), 3.99 (dd, J=2.7, 5.6 Hz, 1H), 3.70 (d, J=5.6 Hz, 1H), 3.46 (s, 1H), 2.62 (d, J=8.3 Hz, 1H), 2.54 (s, 1H), 1.76 (dt, J=4.5, 12.1 Hz, 1H), 1.68 (dt, J=4.5, 11.7 Hz, 1H), 1.64-1.58 (m, 1H), 1.54-1.47 (m, 1H), 0.94 (t, J=7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 138.7, 138.2, 138.0, 128.8, 128.7, 128.7, 128.6, 128.5, 128.2, 128.1, 116.2, 84.9, 81.8, 81.2, 75.3, 74.9, 73.8, 73.1, 41.5, 17.7, 14.5. HRMS (*m/z*) calculated for $C_{25}H_{30}O_4Na$ (ESI, M + Na^+) 417.2036, found 417.2034. For **3.27** (epimer) ^1H NMR ($CDCl_3$) δ 7.36-7.27 (m, 10H), 5.99 (ddd, J= 5.4, 10.6, 17.3 Hz, 1H), 5.36 (td, J=1.0 Hz, 17.2 Hz, 1H), 5.22 (td, J=1.0, 10.6 Hz, 1H), 4.83 (d, J=11.3 Hz, 1H), 4.80 (d, J=11.2 Hz, 1H), 4.72 (d, J=11.2 Hz, 1H), 4.61 (d, J=11.2 Hz, 1H), 4.49 (br. 1H), 3.82 (dd, J=2.6, 6.0 Hz, 1H), 3.69 (d, J=6.0 Hz, 1H), 3.15 (br. 2H), 2.54 (s, 1H), 1.84 (dt, J=4.7, 12.4 Hz, 1H), 1.69 (dt, J=4.9, 11.6 Hz, 1H), 1.62-1.52 (m, 2H), 0.94 (t, J=7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 138.5, 138.3, 138.3, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 116.1, 85.5, 82.6, 81.8, 75.3, 74.9, 74.0, 73.7, 73.0, 41.2, 17.2, 14.4.

(1S,4R,5S,6R)-5,6-Bis(benzyloxy)-1-propyl-2-vinylcyclohex-2-ene-1,4-diol (3.33).

Freshly distilled CH_2Cl_2 was degassed for 1 h. Enyne diol **3.25** (0.650 g, 1.65 mmol) was dissolved in CH_2Cl_2 (50 mL, 0.033 M), and ethylene gas was bubbled through the solution for 45 min. Grubbs's 2nd generation ruthenium catalyst (0.140 g, 0.165 mmol) was then added, and ethylene was bubbled through the solution for an additional 20 min. The mixture was stirred under an atmosphere of ethylene at room temperature for 35 h. Silica gel was then added and the nixture concentrated under reduced pressure. The

residue was purified by FCC to afford **3.33** (0.325g, 50% yield or 87.5% *brsm* yield) and recovered **3.25** (0.250 g, 38%). For **3.33**: R_f = 0.30 (15% EtOAc in petroleum ether). ^{1}H NMR ($CDCl_3$) δ 7.40-7.29 (m, 10H), 6.35 (dd, J=11.0, 17.4 Hz, 1H), 5.83 (d, J=2.1 Hz, 1H), 5.53 (dd, J=1.4, 17.4 Hz, 1H), 5.13 (dd, J=1.5, 11.0 Hz, 1H), 5.07 (d, J=11.0 Hz, 1H), 4.92 (d, J=11.5 Hz, 1H), 4.77 (d, J=11.5 Hz, 1H), 4.69 (d, J=11.0 Hz, 1H), 4.19 (br. 1H), 3.79 (dd, J=7.4, 9.4 Hz, 1H), 3.56 (d, J=9.4 Hz, 1H), 2.81 (s, 1H), 2.05 (d, J=5.0 Hz, 1H), 1.71-1.61 (m, 2H), 1.11-0.95 (m, 2H), 0.78 (t, J=7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 139.4, 138.7, 137.9, 134.0, 128.9, 128.8, 128.6, 128.4, 128.1, 127.2, 116.7, 82.2, 78.9, 75.7, 75.6, 75.0, 71.4, 39.3, 17.7, 14.5. HRMS (*m/z*) calculated for $C_{25}H_{30}O_4Na$ (ESI, M + Na^+) 417.2036, found 417.2046.

(1R,4S,5R,6S)-5,6-bis(benzyloxy)-4-hydroxy-4-propyl-3-vinylcyclohex-2-en-1-yl acrylate (3.24).

Acroyl chloride (0.368 mL, 4.56 mmol) was added dropwise to a flask containing **3.33** (300 mg, 0.761 mmol) and DIPEA (1.06 mL, 6.08 mmol) in CH_2Cl_2 (10 mL) at −78 ^{o}C. After TLC showed complete disappearence of starting material, the mixture was diluted with water and extracted with Et_2O (3x150 mL). The combined organic phase was dried (Na_2SO_4) and concentrated in *vacuo*. The residue was purified by FCC to afford **3.24** (275 mg, 81%). R_f = 0.36 (10% EtOAc in petroleum ether). ^{1}H NMR ($CDCl_3$) δ 7.39-7.26 (m, 10H), 6.41 (dd, J=1.3, 17.3 Hz, 1H), 6.34 (dd, J=11.0, 17.3 Hz, 1H), 6.10 (dd, J=10.5, 17.3 Hz, 1H), 5.86 (dd, J=1.3, 10.5 Hz, 1H), 5.71 (d, J=1.4 Hz, 1H), 5.56 (d, J=8.0 Hz, 1H), 5.52 (dd, J=1.2, 17.3 Hz, 1H), 5.15 (dd, J=1.4, 11.0 Hz, 1H), 5.01 (d, J=11.1 Hz, 1H), 4.81 (d, J=11.2 Hz, 1H), 4.74 (d, J=11.3 Hz, 1H), 4.68 (d, J=11.1 Hz,

1H), 4.05 (dd, J=8.1, 9.8 Hz, 1H), 3.62 (d, J=9.8 Hz, 1H), 2.82 (s, 1H), 1.67-1.61 (m, 2H), 1.03-0.89 (m, 2H), 0.76 (t, J=7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 165.9, 140.8, 138.5, 138.0, 133.7, 131.5, 128.8, 128.7, 128.6, 128.6, 128.3, 128.2, 127.9, 124.3, 117.2, 79.4, 78.3, 75.9, 75.5, 75.2, 74.1. HRMS (*m/z*) calculated for $C_{28}H_{32}O_5Na$ (ESI, M + Na^+) 471.2141, found 471.2154.

(2a*S*,2a^1*R*,6*S*,7*R*,8*S*,8a*R*)-7,8-Bis(benzyloxy)-6-hydroxy-6-propyl-2a,2a^1,3,4,6,7,8,8a-octahydro-2*H*-naphtho[1,8-*bc*]furan-2-one (3.23)

A solution of **3.24** (240 mg, 0.535 mmol) in xylene (18 mL, 0.03 M) was heated at reflux until TLC showed less than 5% starting material left, at which time the solution was cooled to room temperature. The solvent was then removed in *vacuo* and the residue was purified by FCC to give **3.23** (204 mg, 85%). R_f = 0.23 (10% EtOAc in petroleum ether). ^{1}H NMR ($CDCl_3$) δ 7.40-7.26 (m, 10H), 5.64 (td, J=2.8, 4.2 Hz, 1H), 4.90 (d, J=11.4 Hz, 1H), 4.73 (t, J=9.0 Hz, 1H), 4.71 (d, J=11.0 Hz, 1H), 4.66 (d, J=11.4 Hz, 1H), 4.61 (d, J=11.0 Hz, 1H), 3.76 (dd, J=4.9, 9.3 Hz, 1H), 3,50 (d, J=4.9 Hz, 1H), 3.05 (s, 1H), 2.81-2.75 (m, 1H), 2.47-2.41 (m, 1H), 2.37-2.28 (m, 2H), 2.22-2.17 (m, 1H), 1.67 (tt, J=8.8, 12.6 Hz, 1H), 1.55-1.41 (m, 3H), 1.29-1.23 (m, 1H), 0.91 (t, J=7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 175.8, 139.2, 137.8, 137.3, 128.8, 128.7, 128.5, 128.4, 128.4, 128.2, 121.5, 86.8, 82.1, 80.5, 75.2, 75.0, 73.5, 42.9, 41.6, 40.7, 25.5, 21.3, 17.0, 14.5. HRMS (*m/z*) calculated for $C_{28}H_{32}O_5Na$ (ESI, M + Na^+) 471.2141, found 471.2140.

(2a*S*,2a^1*S*,5*R*,5a*S*,6*R*,7*R*,8*S*,8a*R*)-7,8-Bis(benzyloxy)-5a,6-dihydroxy-6-propyl-5-((triethylsilyl)oxy)decahydro-2*H*-naphtho[1,8-*bc*]furan-2-one. (3.37)

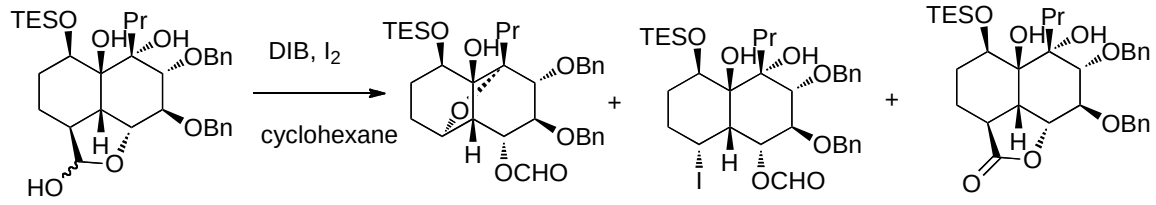
To a flask containing **3.23** (100 mg, 0.223 mmol) in acetone (2 mL) at 0 ^{o}C was added OsO_4 (0.28 mL 2.5% in ^{t}BuOH , 0.022 mmol) and N-methylmorpholine oxide (0.185 mL 50% in water, 0.892 mmol). After TLC showed complete disapperence of starting material, 2M aqueous Na_2SO_3 was added. The mixture was extracted with EtOAc (3x50 mL), and the combined organic phase was washed with brine and water, dried (Na_2SO_4), concentrated in *vacuo* and purified by FCC to afford a single dihydroxylated derivative (106 mg, 95%). R_f = 0.40 (30% EtOAc in petroleum ether). ^{1}H NMR ($CDCl_3$) δ 7.38-7.26 (m, 10H), 5.07 (d, J=10.6 Hz, 1H), 4.96 (d, J=11.0 Hz, 1H), 4.79 (t, J=7.9 Hz, 1H), 4.69 (d, J=11.0 Hz, 1H), 4.64 (d, J=10.6 Hz, 1H), 4.17 (br., 1H), 4.05 (dd, J=8.2, 9.4 Hz, 1H), 3.82 (d, J=9.5 Hz, 1H), 3.28 (ddd, J=3.5, 11.9, 15.1 Hz, 1H), 3.14 (br., 1H), 2.43 (dd, J=7.6, 15.1 Hz, 1H), 2.32 (s, 1H), 2.19-2.12 (m, 1H), 2.00-1.93 (m, 2H), 1.91-1.84 (m, 2H), 1.70 (ddd, J=4.6, 12.3, 14.6 Hz, 1H), 1.62-1.49 (m, 2H), 1.41-1.31 (m, 1H), 0.89 (t, J=7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 176.8, 138.4, 138.4, 128.7, 128.59, 128.3, 128.3, 128.1, 127.9, 83.0, 82.3, 81.7, 79.5, 76.5, 74.9, 74.6, 68.5, 47.9, 40.1, 38.4, 32.8, 19.1, 18.5, 15.2. HRMS (*m/z*) calculated for $C_{28}H_{34}O_7Na$ (ESI, M + Na^+) 505.2196, found 505.2200.

To a solution the triol from the previous step (78 mg, 0.162 mmol) and imidazole (33 mg, 0.585 mmol) in DMF (2 mL) was added chlorotriethylsilane (0.041 mL, 0.243 mmol). After TLC showed complete disappearence of starting material, the reaction mixture was diluted with Et_2O (150 mL) and washed with brine and water. The organic phase was separated, dried (Na_2SO_4), , concentrated in *vacuo* and purified by FCC to give **3.37** (96 mg, 100%). R_f=0.33 (10% EtOAc in petroleum ether). ^{1}H NMR ($CDCl_3$) δ 7.38-7.26 (m, 10H), 5.08 (d, J=10.6 Hz, 1H), 4.96 (d, J=11.1 Hz, 1H), 4.76 (d, J=7.9 Hz, 1H),

4.68 (d, J=11.1 Hz, 1H), 4.63 (d, J=10.6 Hz, 1H0, 4.15 (t, J=2.7 Hz, 1H), 4.05 (dd, J=8.4, 9.3 Hz, 1H), 3.81 (d, J=9.3 Hz, 1H), 3.23 (ddd, J=3.3, 11.7, 15.1 Hz, 1H), 3.09 (s, 1H), 2.40 (dd, J=7.6, 15.1 Hz, 1H), 2.29 (s, 1H), 2.10-2.03 (m, 1H), 1.95-1.88, (m, 2H), 1.86 (ddd, J=4.9, 12.5, 14.6 Hz, 1H), 1.70 (ddd, J=4.7, 12.3, 14.6 Hz, 1H), 1.64-1.48 (m, 2H), 1.40-1.30 (m, 1H), 1.00 (t, J=8.0 Hz, 9H), 0.89 (t, J=7.3 Hz, 3H), 0.68 (q, J=8.1, 6H). ^{13}C NMR ($CDCl_3$) δ 177.0, 138.5, 138.5, 128.6, 128.6, 128.27, 128.2, 128.1, 127.9, 83.1, 82.4, 81.8, 79.5, 76.5, 74.6, 74.5, 70.1, 48.2, 40.1, 38.5, 32.9, 19,3, 18.6, 15.2, 7.0, 5.1. HRMS (*m/z*) calculated for $C_{34}H_{48}O_7NaSi$ (ESI, M + Na^+) 619.3061, found 619.3059.

(2*S*,2a*S*,2a^1*S*,5*R*,5a*S*,6*R*,7*R*,8*S*,8a*R*)-7,8-Bis(benzyloxy)-6-propyl-5-((triethylsilyl)-oxy)-decahydro-2*H*-naphtho[1,8-*bc*]furan-2,5a,6-triol. (3.38)

To a solution of **3.37** (90 mg, 0.151 mmol) in CH_2Cl_2 (2.0 mL) at −78 ^{o}C was added DIBALH (0.81 mL, 1.0 M in hexane, 0.81 mmol). After TLC showed complete disappearence of starting material, the reaction was quenched with aqueous saturated potassium sodium tartrate and diluted with Et_2O. The mixture was stirred for 30 min at room temperature then extracted with Et_2O (3 x 50 mL). The combined organic phase was washed with brine and water, dried (Na_2SO_4), filtered, concentrated in *vacuo* and purified by FCC to afford **3.38** (86 mg, 0.144 mmol) in 95% yield. R_f=0.33 (15% EtOAc in petroleum ether). ^{13}C NMR ($CDCl_3$) δ 139.4, 138.9, 128.6, 128.4, 128.2, 127.9, 127.5, 98.3, 84.2, 83.5, 81.7, 79.2, 76.2, 75.3, 74.3, 70.5, 46.8, 43.9, 38.5, 32.8, 18.8, 15.3, 7.0, 5.2. HRMS (*m/z*) calculated for $C_{34}H_{50}O_7NaSi$ (ESI, M + Na^+) 621.3218, found 621.3225.



3.38 **3..40** **3.39** **3.37**

(1*R*,2*R*,3*S*,4*R*,4a*S*,5*R*,8*R*,8a*S*)-2,3-Bis(benzyloxy)-8a-hydroxy-1-propyl-8-((triethylsilyl)oxy)decahydro-1,5-epoxynaphthalen-4-yl formate (3.40) and **(1*R*,2*S*,3*R*,4*R*,4a*S*,5*R*,8*R*,8a*S*)-2,3-bis(benzyloxy)-4,4a-dihydroxy-8-iodo-4-propyl-5-((triethylsilyl)oxy)decahydronaphthalen-1-yl formate (3.39).**

To a solution of lactol **3.38** (80 mg, 0.13 mmol) in cyclohexane (4.0 mL, 0.03 M) was added diacetoxyiodoxybenzene (DIB) (86 mg, 0.268 mmol) and I_2 (68 mg, 0.27 mmoL). After TLC showed complete disappearance of starting material, the reaction was quenched with 10% $Na_2S_2O_3$ in saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O (3 x 50 mL) and the combined organic phase was washed with brine and water, dried (Na_2SO_4), filtered, concentrated and purified by FCC to give **3.40:3.37:3.39** in 6:1:2 ratio in 95% yield. Compounds **3.37** and **3.40** were homogeneous on TLC and the ratio was determined by ^{1}H NMR (**3.40**:**3.37** 61 mg, ca ratio 6:1, R_f=0.65, 15% EtOAc in petroleum ether); **3.39** (21 mg, R_f= 0.70, 15% EtOAc in petroleum ether). For **3.40**: ^{13}C NMR ($CDCl_3$) δ 160.85, 139.08, 139.79, 128.58, 128.44, 128.08, 127.81, 127.78, 127.58, 84.09, 84.05, 81.69, 80.49, 75.35, 75.22, 75.19, 74.06, 72.68, 48.05, 31.15, 27.99, 27.57, 17.13, 15.19, 7.02, 5.25. HRMS (*m/z*) calculated for $C_{34}H_{48}O_7NaSi$ (ESI, M + Na^+) 619.3061, found 619.3062. For **3.39** ^{1}H NMR ($CDCl_3$) δ 8.06 (s, 1H), 7.36-7.28 (m, 8H), 7.22-7.18 9(m, 2H), 5.72 (d, J=2.7 Hz, 1H), 4.21 (br., 1H), 5.12 (dd, J=5.1, 11.2 Hz, 1H),

4.93 (td, J=5.6, 13.6 Hz, 1H), 4.75 (d, J=12.0 Hz, 1H), 4.55 (d, J=12.0 Hz, 1H), 4.54 (d, J=11.5 Hz, 1H), 4.32 (d, J=11.5 Hz, 1H), 3.74 (td, J=1.8, 12.6 Hz, 1H), 2.76 (s, 1H), 2.57 (t, J=5.0 Hz, 1H), 2.48 (dq, J=5.2, 13.5 Hz, 1H), 2.17-2.13 (m, 1H), 2.06-2.01 (m, 1H), 1.87-1.81 (m, 2H), 1.62-1.57 (m, 1H), 1.53-1.49 (m, 1H), 1.35-1.18 (m, 2H), 0.89-0.85 (m, 12H), 0.54-0.48 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 159.8, 138.1, 138.0, 128.6, 128.6, 128.5, 128.2, 128.0, 127.9, 81.2, 79.8, 76.8, 76.0, 75.1, 74.8, 74.2, 72.6, 44.8, 35.4, 35.1, 33.7, 28.8, 16.8, 14.9, 7.1, 5.7. . HRMS (*m/z*) calculated for $C_{34}H_{49}O_7NaSiI$ (ESI, M + Na^+) 747.2184, found 747.2195.

1*R*,2*R*,3*S*,4*R*,4a*R*,5*R*,8*R*,8a*S*)-2,3-Bis(benzyloxy)-1-propyl-8 ((triethylsilyl)oxy)deca-hydro-1,5-epoxynaphthalene-4,8a-diol. (3.44)

To a solution of mixture of **3.40** and **3.37** (55 mg, 0.092 mmol) in MeOH (4.5 mL) and CH_2Cl_2 (0.5 mL) at 0 ^oC was added K_2CO_3 (41 mg, 0.30 mmol). After 3 h, the reaction mixture was diluted with Et_2O and saturated aqueous NH_4Cl, and extracted with Et_2O (3x50 mL). The combined organic phase was dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by FCC to afford **3.37** (7.8 mg) and diol **3.44** (45 mg, 0.079 mmol, quant. yield brsm from **3.40**). R_f=0.27 (15% EtOAc in petroleum ether). ^{1}H NMR ($CDCl_3$) δ 7.39-7.25 (m, 10H), 4.98 (d, J=11.3 Hz, 1H), 4.93 (d, J=11.8 Hz, 1H), 4.78 (d, J=11.8 Hz, 1H), 4.67 (d, J=11.3 Hz, 1H), 4.35 (d, J=4.9 Hz, 1H), 4.13 (dd, J=3.5, 8.4 Hz, 1H), 4.05 (d, J=3.9 Hz, 1H), 4.00 (d, J=8.1 Hz, 1H), 3.85 (t, J=8.3 Hz,1 H), 2.46 (s, 1H), 3.35 (d, J=3.5 Hz, 1H), 2.19-2.05 (m, 2H), 1.80-1.57 (m, 4H), 1.55-1.43 (m, 2H), 1.31-1.21 (m, 1H), 0.99 (t, J=7.9 Hz, 9H), 0.87 (t, J=7.3 Hz, 3H), 0.67 (q, J=8.0 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 139.3, 139.2, 128.9, 128.4, 128.0, 127.7, 127.5, 87.2, 84.2, 81.9, 80.4,

75.1, 75.0, 74.9, 72.9, 70.4, 49.6, 31.2, 28.1, 27.7, 17.2, 15.2, 7.0, 5.3. HRMS (*m/z*) calculated for $C_{33}H_{48}O_6NaSi$ (ESI, M + Na^+) 591.3112, found 591.3103.

(1*R*,4*R*,4a*S*,5*R*,6*R*,7*R*,8*R*,8a*S*)-6,7-Bis(benzyloxy)-8-((*tert*-butyldimethylsilyl)oxy)-5-propyldecahydro-1,5-epoxynaphthalene-4,4a-diol (3.45)

To a solution of **3.44** (40 mg, 0.070 mmol) in DMF (1 mL) was added imidazole (30 mg, 0.42 mmol), TBAI (5.2 mg, 0.014 mmol) and *t*-butyldimethylsilyl chloride (TBDMSCl) (32 mg, 0.21 mmol). After TLC showed complete disappearance of starting material, the reaction was quenched with water. The mixture was extracted with Et_2O (3 x 50 mL) and the combined organic phase was dried ($MgSO_4$), concentrated in *vacuo* and purified by FCC to afford the bis-silyl ether-tertiary alcohol derivative (47 mg, 0.69 mmol) in 98% yield. R_f=0.36 (5% EtOAc in petroleum ether). ^{1}H NMR ($CDCl_3$) δ 7.36-7.21 (m, 10H), 4.98 (d, J=10.7, 1H), 4.96 (d, J=11.1 Hz, 1H), 4.78 (d, J=11.2 Hz, 1H), 4.58 (d, J=11.4 Hz, 1H), 4.42 (d, J=4.9 Hz, 1H), 4.23 (dd, J=3.6, 8.0 Hz, 1H), 4.03 (d, J=3.7 Hz, 1H), 3.93 (d, J=8.1 Hz, 1H), 3.87 (t, J=8.1 Hz, 1H), 2.40 (s, 1H), 2.29 (d, J=3.6, 1H), 2.20-2.06 (m, 2H), 1.76 (ddd, J=5.6, 6.6, 13.5 Hz, 1H), 1.68 (dd, J=6.2, 14.8 Hz, 1H), 1.63-1.53 (m, 1H), 1.48 (dt, J=4.3, 13.0 Hz, 1H), 1.42 (dt, J=6.4, 12.8 Hz, 1H), 1.25-1.14 (m, 1H), 1.00 (t, J=8.0, 9H), 0.91 (s, 9H), 0.84 (t, J=7.3 Hz, 3H), 0.66 (q, J=8.0, 6H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 139.5, 128.4, 128.3, 127.7, 127.7, 127.4, 127.3, 87.35, 84.0, 81.7, 80.4, 75.5, 75.1, 74.8, 73.1, 72.2, 51.0, 31.3, 28.4, 27.7, 26.1, 18.2, 17.1, 15.24, 7.0, 5.3, -4.2, -4.3. HRMS (*m/z*) calculated for $C_{39}H_{62}O_6NaSi_2$ (ESI, M + Na^+) 705.3977, found 705.3980.

To a solution of the alcohol from the previous step (42 mg, 0.062 mmol) in THF (1 mL) at 0 ^{o}C was added TBAF (0.074 mL, 1.0 M in THF). After TLC showed no starting material left, the reaction was quenched with H_2O and diluted with Et_2O. The reaction mixture was extracted with Et_2O (3 x 50 mL) and the combined organic phase was dried ($MgSO_{4)}$, concentrated in *vacuo* and purified by FCC to afford diol **3.45** (34.5 mg, 0.061 mmol, 99%) as a white solid. R_f=0.15 (30% EtOAC in petroleum ether). Melting Point: 168-171 ^{o}C. ^{1}H NMR ($CDCl_3$) δ 7.35-7.21 (m, 10H), 4.98 (d, J=11.1 Hz, 1H), 4.96 (d, J=11.3 Hz, 1H), 4.78 (d, J=11.1 Hz, 1H), 4.59 (d, J=11.4 Hz, 1H), 4.44 (d, J=4.9 Hz, 1H), 4.24 (dd, J=3.7, 8.0 Hz, 1H), 4.02 (d, J=4.2 Hz, 1H), 3.94 (d, J=8.1 Hz, 1H), 3.88 (t, J=8.0 Hz, 1H), 2.51 (s, 1H), 2.24 (d, J=3.7 Hz, 1H), 2.23-2.17 (m, 1H), 2.09 (dt+br. J=3.6, 13.0 Hz, 1H+1OH), 1.78 (ddd, J=5.2, 7.2, 13.5 Hz, 1H), 1.67 (dd, J=6.4, 15.0 Hz, 1H), 1.60-1.40 (m, 3H), 1.24-1.17 (m, 1H), 0.91 (s, 9H), 0.83 (t, J=7.3, Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 139.3, 128.4, 128.3, 127.8, 127.7, 127.5, 127.4, 87.4, 84.2, 81.5, 80.2, 75.6, 75.2, 74.9, 72.0, 71.7, 50.6, 31.3, 28.0, 27.8, 16.1, 18.2, 17.2, 15.2, -4.1, -4.2. HRMS (*m/z*) calculated for $C_{33}H_{48}O_6NaSi$ (ESI, M + Na_{+}) 591.3112, found 591.3113.

(1*R*,4a*R*,5*R*,6*R*,7*R*,8*R*,8a*S*)-6,7-Bis(benzyloxy)-8-((*tert*-butyldimethylsilyl)oxy)-4a-hydroxy-5-propyloctahydro-1,5-epoxynaphthalen-4(1*H*)-one (3.46)

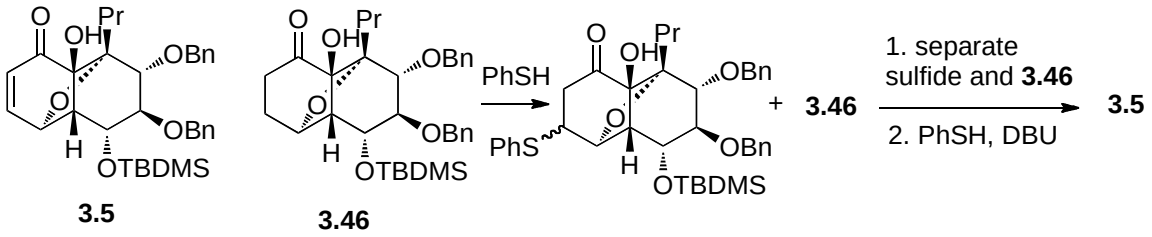
Diol **3.45** (10 mg, 0.0176 mmol) was dissolved in a mixture of fluorobenzene (PhF) (0.060 mL) and DMSO (0.240 mL). Iodoxybenzoic acid (IBX) (9.5 mg, 0.034 mmol) was added to the solution, the mixture stirred at 75 ^{o}C for 20 h, then cooled to room temperature and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted

with Et_2O (3 x 20 mL) and the combined organic phase was washed with brine and water, dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by FCC to afford **3.46** (9.0 mg, 0.0159 mmol) in 90% yield. R_f=0.50 (10% EtOAc in petroleum ether). ^{1}H NMR ($CDCl_3$) δ 7.36-7.26 (m, 10H), 4.98 (d, J=11.2 , 1H), 4.92 (d, J=11.2 Hz, 1H), 4.83 (d, J=11.2 Hz, 1H), 4.65 (d, J=4.1 Hz, 1H), 4.57 (d, J=11.2 Hz, 1H), 4.24 (dd, J=3.5, 7.8 Hz, 1H), 3.98-3.93 (m, 2H), 3.85 (s, 1H), 2.79-2.68 (m, 2H), 2.35-2.29 (m, 1H), 2.02 (dd, J=11.5, 16.0 Hz, 1H), 1.93 (d, J=3.5 Hz, 1H), 1.65 (td, J=10.8, 13.6 Hz, 1H), 1.31-1.11 (m, 3H), 0.89 (s, 9H), 0.75 (t, J=7.0 Hz, 3H), 0.09 (s, 3H), 0.05 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 209.3, 139.2, 138.9, 128.5, 128.4, 127.9, 127.6, 127.6, 127.5, 87.1, 85.1, 84.1, 81.6, 75.8, 75.5, 73.6, 71.6, 54.7, 34.3, 33.1, 31.3, 26.0, 18.1, 17.1, 15.1, -4.2, -4.3. HRMS (*m/z*) calculated for $C_{33}H_{46}O_6NaSi$ (ESI, M + Na^+) 589.2966, found 589.2960.

(1*R*,4a*R*,5*R*,6*R*,7*R*,8*R*,8a*S*)-6,7-Bis(benzyloxy)-8-((*tert*-butyldimethylsilyl)oxy)-4a-hydroxy-5-propyl-4a,5,6,7,8,8a-hexahydro-1,5-epoxynaphthalen-4(1*H*)-one (3.5)

To a solution of ketone **3.46** (26 mg, 0.045 mmol) in EtOAc (0.40 mL) at room temperature was added PhSeCl (11 mg, 0.057 mmol) followed by conc. HCl (10 μL). The resulting red-orange solution was stirred at room temperature for 6 h, during which time the solution became yellow. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with Et_2O, and the organic layer was concentrated *in vacuo* to give the crude a-selenoketone. The residue was dissolved in CH_2Cl_2 (0.5 mL), and solid $NaHCO_3$ (10 mg, 0.12 mmol) followed by *m*-CPBA (20 mg, 0.11 mmol) were added. This mixture was stirred for 20 min, during which time it turned from yellow to colorless. When TLC indicated the complete consumption of the selenide, the reaction was diluted

with Et_2O and washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by FCC provided an inseparable mixture of enone **3.5** and ketone **3.46** as colorless oil (18.8 mg, ca ratio: 8:1 as determined by HNMR, **3.5**: 66% based on recovered **3.46**). R_f=0.50 (10% EtOAc in petroleum ether).



Purification of enone 3.5

To obtain a pure sample of **3.5**, the mixture of **3.5** and **3.46** from the previous reaction was subjected to a thio-Michael addition and β-thio elimination sequence.[63,64] To a reaction vial containing 5.0 mg (**3.5:3.46=**8:1, ca 0.0079 mmol of **3.5**) was added H_2O (0.050 mL) and PhSH (0.050 mL). After stirring at rt for 40 min, the mixture was diluted with Et_2O and washed with H_2O. The organic phase was separated, dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by FCC to afford the thia Michael product (5.0 mg, ca 94 % yield from enone **3.5**) and ketone **3.46** (0.5 mg, ca 90% recovered from ketone **3.46**). For the Michael product : R_f=0.30, (10% Et_2O in petroleum ether). ^{1}H NMR ($CDCl_3$) δ 7.36-7.24 (m, 15H), 4.98 (d, J=11.2 Hz, 1H), 4.91 (d, J=11.2 Hz, 1H), 4.83 (d, J=11.2 Hz, 1H), 4.72 (d, J=3.8 Hz, 1H), 4.56 (d, J=11.2 Hz, 1H), 4.29 (dd, J=3.5, 8.0 Hz, 1H), 3.94 (m, 2H), 3.90 (t, J=8.1 Hz, 1H), 3.85 (s, 1H), 3.16 (dd, J=9.2, 18.8 Hz, 1H), 2.82 (d, J=18.8 Hz, 1H), 2.49 (d, J=3.5 Hz, 1H), 2.03 (m, 1H), 1.28-

1.25 (m, 3H), 0.90 (s, 9H), 0.74 (t, J=7.1 Hz, 3H), 0.14 (s, 3H), 0.11 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 207.3, 139.1, 138.7, 134.1, 131.1, 129.5, 128.5, 128.5, 127.9, 127.7, 127.6, 127.5, 127.47, 87.1, 85.1, 84.3, 81.6, 76.1, 75.9, 75.6, 70.9, 50.3, 47.2, 41.4, 33.6, 26.1, 18.1, 17.0, 15.1, -3.9, -4.5.

To the product from the previous step (4 mg, 0.0059 mmol) was added CH_2Cl_2 (0.050 mL) and DBU (3.5 μL, 0.022 mmol). After stirring at rt for 40 min, the reaction mixture was diluted with Et_2O and washed with saturated aqueous NH_4Cl. The organic phase was separated, dried ($MgSO_4$), concentrated in *vacuo*, and purified by FCC to afford enone **3.5** (1.6 mg, 0.0028 mmol, 48% yield). R_f=0.25 (10% Et_2O in petroleum ether). ^{1}H NMR ($CDCl_3$) δ 7.68 (dd, J=5.7, 9.2 Hz, 1H), 7.36-7.24 (m, 10H), 6.32 (dd, J=1.4, 9.2 Hz, 1H), 4.95 (d, J=11.2 Hz, 1H), 4.91 (d, J=11.2 Hz, 1H), 4.83 (d, J=11.2 Hz, 1H), 4.76 (dd, J=1.2, 5.8 Hz, 1H), 4.59 (d, J=11.2 Hz, 1H), 4.22 (dd, J=3.9, 7.9 Hz, 1H), 4.07 (d, J=8.0 Hz, 1H), 4.05 (s, 1H0, 3.98 (t, J=8.0 Hz, 1H), 2.25 (d, J=3.9 Hz, 1H), 1.96 (m, 1H), 1.26 (m, 1H), 1.08 (m, 2H), 0.89 (s, 9H), 0.74 (t, J=7.0 Hz, 3H), 0.08 (s, 3H), 0.03 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 200.2, 157.5, 139.1, 138.8, 129.0, 128.5, 128.5, 127.85, 127.7, 127.6, 127.5, 87. 1, 86.9, 82.5, 81.9, 75.7, 75.5, 71.5, 71.3, 60.8, 35.0, 26.0, 18.1, 17.2, 15.0, -4.2, -4.4. HRMS (*m/z*) calculated for $C_{33}H_{44}O_6NaSi$ (ESI, M + Na+) 587.2810, found 587.2807.

(1*S*,5*S*,6*R*,7*S*,8*R*,8a*R*)-6,7-bis(benzyloxy)-5,8-dihydroxy-5-propyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde (3.47).

To a solution of **3.23** (85 mg, 0.190 mmol) in CH_2Cl_2 (1.5mL) at −78 ^{o}C was added DIBALH (0.57 mL, 1.0 M in hexane, 0.57 mmol). After TLC showed complete disappearance of starting material, the reaction was quenched with aqueous saturated

potassium sodium tartrate and diluted with Et_2O. The mixture was stirred for 30 min at room temperature then extracted with Et_2O. The combined organic phase was washed with brine and water, dried (Na_2SO_4), filtered, concentrated in *vacuo* and purified by FCC to afford **3.47** (44 mg, 50%): R_f = 0.13 (15% EtOAc: petroleum ether); ^{1}H NMR ($CDCl_3$) δ 9.71 (d, J = 0.7 Hz, 1H), 7.40-7.33 (m, 8H), 7.27-7.24 (m, 2H), 6.10 (m, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.60 (d, J = 10.9 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.43 (d, J = 10.9 Hz, 1H), 3.94 (t, J = 2.8 Hz, 1H), 3.87 (qd, J = 1.8, 11.9 Hz, 1H), 3.57 (dd, J = 1.8, 2.6 Hz, 1H), 2.99 (m, 1H), 2.92 (d, J = 11.9 Hz, 1H), 2.88-2.84 (m, 1H), 2.66 (d, J = 1.1 Hz, 1H), 2.11 (m, 3H), 2.07-2.01 (m, 1H), 1.58-1.51 (m, 2H), 1.38-1.29 (m, 1H), 1.26-1.19 (m, 1H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 203.9, 138.0, 136.6, 135.7, 129.0, 128.8, 128.7, 128.1, 127.9, 125.6, 83.5, 75.6, 75.4, 74.1, 72.5, 71.9, 48.3, 39.0, 35.0, 23.8, 21.7, 16.5, 14.7; HRMS (*m/z*) calculated for $C_{28}H_{34}O_5Na$ (ESI, M + Na+) 473.2298, found 473.2302.

(2a*R*,2a^1*R*,6*S*,7*R*,8*S*,8a*R*)-7,8-Bis(benzyloxy)-6-hydroxy-6-propyl-2a,2a^1,3,4,6,7,8,8a-octahydro-2*H*-naphtho[1,8-*bc*]furan-2-one (3.49)

A solution of lactone **3.23** (680 mg, 1.51 mmol) and DBU (0.25 mL, 1.68 mmol) in toluene (35 mL) was heated at reflux until TLC showed less than 5% of starting material, at which time the solution was cooled to room temperature. The solvent was then removed in *vacuo* and the residue was purified by FCC to give the C-8 epimeric lactone **3.49** as white solid (650 mg, 96%): R_f = 0.30 (15% EtOAc : petroleum ether); mp: 93-96 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.38-7.28 (m, 10H), 6.10 (m, 1H), 4.95 (d, J = 11.2 Hz, 1H), 4.77 (d, J = 11.5 Hz, 1H), 4.67 (d, J = 11.5 Hz, 1H), 4.61 (t, J = 5.5 Hz, 1H), 4.58 (d, J = 11.2 Hz, 1H), 3.84 (dd, J = 4.8, 8.8 Hz, 1H), 3.48 (d, J = 8.8 Hz, 1H), 3.04-2.97 (m, 2H), 2.84

(s, 1H), 2.11-2.09 (m, 3H), 1.67-1.48 (m, 3H), 1.31-1.27 (m, 1H), 1.22-1.12(m, 1H), 0.84 (t, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 177.5, 138.2, 137.8, 132.7, 128.7, 128.6, 128.3, 128.0, 126.6, 83.1, 79.7, 78.9, 75.0, 74.8, 73.5, 41.7, 39.0, 35.6, 20.6, 19.2, 16.8, 14.6; HRMS (*m/z*) calculated for $C_{28}H_{32}O_5Na$ (ESI, M + Na+) 471.2142, found 471.2142.

(2*R*,2a*R*,2a^1*R*,6*S*,7*R*,8*S*,8a*R*)-7,8-Bis(benzyloxy)-6-propyl-2a,2a^1,3,4,6,7,8,8a-octahydro-2*H*-naphtho[1,8-*bc*]furan-2,6-diol (3.50).

To a solution of the product from the previous step **3.49** (520 mg, 1.16 mmol) in CH_2Cl_2 (7 mL) at −78 ^{o}C was added DIBAL-H (2.68 mL, 1.0 M in hexane, 2.68 mmol). After TLC showed complete disappearance of starting material, the reaction was quenched with saturated aqueous potassium sodium tartrate and diluted with Et_2O. The mixture was stirred for 30 min at room temperature then extracted with Et_2O. The combined organic phase was washed with brine and water, dried (Na_2SO_4), filtered, concentrated in *vacuo* and purified by FCC to afford **3.50** (495 mg, 94%): R_f = 0.12 (15% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$) δ 7.39-7.28 (m, 10H), 6.02 (m, 1H), 5.29 (m, 1H), 4.89 (d, J = 11.2 Hz, 1H), 4.79 (d, J = 11.6 Hz, 1H), 4.66 (d, J = 11.6 Hz, 1H), 4.60 (d, J = 11.2 Hz, 1H), 4.43 (dd, J = 5.7, 6.4 Hz, 1H), 3.68 (dd, J = 5.5, 8.0 Hz, 1H), 3.51 (br., 1H), 3.42 (d, J = 8.0 Hz, 1H), 3.01 (s, 1H), 2.78 (m, 1H), 2.45 (m, 1H), 2.07 (m, 2H), 1.74-1.68 (m, 1H), 1.66-1.58 (m, 2H), 1.50 (ddd, J = 4.5, 12.0, 13.1 Hz, 1H), 1.40-1.31 (m, 1H), 1.24-1.15 (m, 1H), 0.86 (t, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 139.0, 138.2, 135.3, 128.8, 128.6, 128.5, 128.2, 127.9, 127.8, 123.8, 101.6, 81.6, 81.5, 80.7, 75.1, 75.0, 73.4, 45.4, 42.4, 38.1, 21.6, 21.5, 16.9, 14.7; HRMS (*m/z*) calculated for $C_{28}H_{34}O_5Na$ (ESI, M + Na+) 473.2298, found 473.2299.

(1*R*,2*S*,3*R*,4*S*,8a*R*)-2,3-Bis(benzyloxy)-4-hydroxy-8-iodo-4-propyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-1-yl formate (3.48a, 3.48b).

To a solution of lactol **3.50** (490 mg, 1.09 mmol) in cyclohexane (36 mL, 0.03 M) was added diacetoxyiodobenzene (456 mg, 1.42 mmol) and I_2 (331 mg, 1.30 mmoL). After TLC showed complete disappearance of starting material, the reaction was quenched with 10% $Na_2S_2O_3$ in saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic phase was washed with brine and water, dried (Na_2SO_4), filtered, concentrated and purified by FCC to give a mixture of iodides **3.48a:3.48b** (596 mg, 95%) in ca. 2:1 ratio. For **3.48a**: R_f = 0.20 (15% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.41-7.30 (m, 8H), 7.17-7.14 (m, 2H), 6.19 (m, 1H), 5.40 (br., 1H), 4.71 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.41-4.33 (m, 3H), 3.92 (t, J = 2.6 Hz, 1H), 3.40 (dd, J = 1.1 , 2.4 Hz, 1H), 3.04 (d, 7.0 Hz, 1H), 2.79 (d, J = 0.6 Hz, 1H), 2.35-2.23 (m, 2H), 2.20- 2.11 (m, 2H), 1.90-1.84 (m, 1H), 1. 55-1.49 (m, 1H), 1.40-1.30 (m, 1H), 1.28-1.21 (m, 1H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 160.6, 137.7, 137.1, 135.9, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 124.0, 81.6, 74.6, 73.6, 73.0, 72.9, 72.5, 45.4, 39.8, 35.3, 29.5, 26.5, 16.5, 14.6; HRMS (*m/z*) calculated for $C_{28}H_{33}IO_5Na$ (ESI, M + Na+) 599.1265, found 599.1252. For **3.48b**: R_f = 0.17 (10% EtOAc : petroleum ether; ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1H), 7.41-7.31 (m, 8H), 7.17-7.13 (m, 2H), 6.09 (d, J = 5.1 Hz, 1H0, 5.58 (m, 1H), 4.71 (d, J = 12.0 Hz, 1H), 4.60-4.55 (m, 2H), 4.37 (d, J = 11.8 Hz, 1H), 4.32 (d, J = 11.8 Hz, 1H), 3.92 (t, J = 2.4 Hz, 1H), 3.32 (br., 1H), 2.87 (d, J = 1.4 Hz, 1H), 2.78 (d, J = 6.5 Hz, 1H), 2.57-2.46 (m, 1H), 2.31-2.21 (m, 2H), 2.15-2.08 (m, 1H), 1.98-1.92 (m, 1H), 1.50-1.44 (m, 1H), 1.40-1.32 (m, 1H), 1.15-1.08 (m, 1H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 160.5, 137.8,

137.2, 135.6, 128.8, 128.7, 128.6, 128.5, 128.2, 123.2, 82.3, 77.1, 75.4, 73.8, 73.5, 72.9, 38.9, 37.8, 33.3, 31.4, 28.0, 16.8, 14.6; HRMS (*m/z*) calculated for $C_{28}H_{33}IO_5Na$ (ESI, M + Na+) 599.1265, found 599.1263.

(1*R*,2*S*,3*R*,4*S*,8a*R*)-2,3-Bis(benzyloxy)-4-hydroxy-4-propyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-1-yl formate (3.51) and **(1*R*,2*S*,3*R*,4*S*,4a*S*,8a*R*)-2,3-bis(benzyloxy)-4-hydroxy-4-propyloctahydro-1*H*-1,4a-(epoxymethano)naphthalen-9-one (3.52)**.

To a flask containing the mixture **3.48a:3.48b** (614 mg, 1.066 mmol) in benzene (35 mL) at reflux, was added dropwise, a solution of tributyltin hydride (0.423 mL, 1.60 mmol) and AIBN (17.4 mg, 0.106 mmol) in benzene (23 mL). After TLC showed complete disappearance of starting material, the reaction was cooled to room temperature and diluted with brine (20 mL). The mixture was extracted with Et_2O and the combined organic phase was washed with brine and water, dried (Na_2SO_4), filtered, concentrated and purified by FCC to give formate **3.51** (430 mg, 90%) and carbonate **3.52** (33 mg, 7%). For **3.51**: R_f = 0.23 (10% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$) δ 8.08 (s, 1H), 7.39-7.30 (m, 8H), 7.22-7.20 (m, 2H), 6.13 (br., 1H), 5.09 (br., 1H), 4.60 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 11.9 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.44 (d, J = 11.9 Hz, 1H), 3.79 (t, J = 2.5 Hz, 1H), 3.45 (d, J = 1.5 Hz, 1H), 2.76 (d, J = 0.8 Hz, 1H), 2.66 (br., 1H), 2.17 (m, 1H), 2.09-2.01 (m, 1H), 1.94 (ddd, J = 1.3, 4.6, 14.7 Hz, 1H), 1.77-1.69 (m, 2H), 1.60-1.42 (m, 3H), 1.40-1.29 (m, 1H), 1.24-1.14 (m, 1H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$δ 161. 2, 137.9, 137.4, 136.7, 128.8, 128.7, 128.4, 128.1, 127.9, 124.9, 81.5, 74.9, 74.6, 74.0, 73.7, 72.7, 39.9, 33.0, 25.5, 25.2, 21.3, 16.7, 14.6; HRMS (*m/z*) calculated for $C_{28}H_{34}O_5Na$ (ESI, M + Na+) 473.2298, found 473.2302. For **3.52**: R_f =

0.40 (15% EtOAc : petroleum ether); $[\alpha]_D^{29}$ = -15.0^o (c=0.20, $CHCl_3$); IR (neat) $\bar{\nu}$ 3534, 2934, 2863, 1776, 1453, 1099, 1075, 1027; ^{1}H NMR ($CDCl_3$) δ 7.40-7.30 (m, 8H), 7.23-7.20 (m, 2H), 4.57 (s, 2H), 4.37 (d, J = 11.8 Hz, 1H), 4.29 (d, J = 11.8 Hz, 1H), 4.15 (d, J = 4.2 Hz, 1H), 3.87 (dd, J = 1.0, 4.2 Hz, 1H), 3.67 (s, 1H), 2.97 (d, J = 1.5 Hz, 1H), 2.54 (dd, J = 6.0, 11.7 Hz, 1H), 2.20 (md, J = 14.3 Hz, 1H), 1.81-1.63 (m, 5H), 1.55-1.46 (m, 2H), 1.24-1.04 (m, 4H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.6, 137.5, 137.3, 128.8, 128.7, 128.4, 128.3, 128.2, 127.9, 79.0, 76.8, 75.3, 74.9, 73.5, 72.7, 53.1, 38.6, 35.6, 26.5, 23.7, 22.9, 22.8, 17.0, 14.8; HRMS (*m/z*) calculated for $C_{28}H_{34}O_5Na$ (ESI, M + Na+) 473.2298, found 473.2304.

(1*S*,2*R*,3*R*,4*R*,4a*R*)-2,3-Bis(benzyloxy)-4-((*tert*-butyldimethyl-silyl)oxy)-1-propyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-1-ol (3.56).

To a solution of **3.51** (415 mg, 0.922 mmol) in MeOH (8.1 mL) and CH_2Cl_2 (0.9 mL) at 0 ^{o}C was added K_2CO_3 (127 mg, 0.922 mmol). After TLC showed complete disappearance of starting material, the reaction mixture was diluted with water, and extracted with Et_2O. The combined organic phase was dried ($MgSO_4$), concentrated in *vacuo* and purified by FCC to afford the derived diol (375 mg, 96%): R_f = 0.36 (15% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$) δ 7.39-7.31 (m, 8H), 7.28-7.26 (m, 2H), 6.10 (br s, 1H), 4.64-4.57 (m, 3H), 4.45 (d, J = 11.0 Hz, 1H), 3.93 (t, J = 2.7 Hz, 1H), 3.74 (qd, J = 0.4, 11.8 Hz, 1H), 3.57 (br., 1H), 2.82 (d, J = 11.8 Hz, 1H), 2.63 (s, 1H), 2.54 (br., 1H), 2.04-1.96 (m, 3H), 1.58-1.54 (m, 1H), 1.48-1.41 (m, 1H), 1.39-1.30 (m, 1H), 1.28-1.19 (m, 1H), 0.87 (t, J = 7.3 Hz, 3H); ^{1}H NMR ($CDCl_3$) δ 138.1, 137.9, 136.5,

128.9, 128.8, 128.7, 128.6, 128.1, 127.8, 126.4, 83.4, 76.4, 75.6, 74.0, 73.8, 72.5, 39.2, 35.5, 25.8, 25.4, 21.6, 16.6, 14.7.

To a solution of the product from the previous step (375 mg, 0.889 mmol) in DMF (8.0 mL) was added imidazole (294 mg, 4.32 mmol), TBAI (320 mg, 0.865 mmol) and *t*-butyldimethylsilyl chloride (651mg, 4.32 mmol). After TLC showed complete disappearance of starting material, the reaction was quenched with water. The mixture was extracted with Et_2O and the combined organic phase was dried ($MgSO_4$), concentrated in *vacuo* and purified by FCC to afford **3.56** (470 mg, 99%): R_f = 0.50 (5% EtOAc : petroleum ether); $[\alpha]_D^{28}$ = -6.2^o (c=0.85, $CHCl_3$); IR (neat) $\bar{\nu}$ 3546, 3030, 2928, 2857, 1454, 1254, 1071, 835, 773; ^{1}H NMR ($CDCl_3$) δ 7.42-7.27 (m, 10H), 6.07 (br., 1H), 4.83 (d, J = 11.7 Hz, 1H), 4.69-4.60 (m, 3H), 3.86 (br., 1H), 3.83 (d, J = 5.0 Hz, 1H), 3.68 (s, 1H), 3.54 (d, J = 5.0 Hz, 1H), 2.47 (br., 1H), 2.13-2.02 (m, 3H), 1.85-1.80 (m, 1H), 1.69-1.59 (m, 3H), 1.52-1.42 (m, 1H), 1.22-1.13 (m, 1H), 1.04-0.94 (m, 1H), 0.91 (s, 9H), 0.86 (t J = 7.3 Hz, 3H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.8, 138.3, 137.3, 128.7, 128.4, 128.1, 127.8, 127.7, 125.9, 84.5, 81.6, 75.1, 73.9, 73.7, 72.2, 38.1, 36.8, 26.7, 26.1, 25.6, 22.0, 18.3, 17.6, 14.7, -3.6, -4.7; HRMS (*m/z*) calculated for $C_{33}H_{48}O_4NaSi$ (ESI, M + Na+) 559.3214, found 559.3217.

(1*R*,2*R*,3*R*,4*R*,4a*S*,8*R*,8a*S*)-2,3-Bis(benzyloxy)-4-((*tert*-butyl-dimethylsilyl)oxy)-1-propyldecahydronaphthalene-1,8,8a-triol (3.57).

To a flask containing alkene **3.56** (465 mg, 0.867 mmol) in acetone (8 mL) at 0 ^{o}C was added OsO_4 (0.44 mL 2.5% in ^{t}BuOH , 0.043 mmol) and N-methylmorpholine oxide (0.539 mL 50% in water, 2.60 mmol). After 24 h, 2M aqueous Na_2SO_3 was added. The

mixture was extracted with EtOAc and the combined organic phase was washed with brine and water, dried (Na_2SO_4), concentrated in *vacuo* and purified by FCC to afford triol **3.57** (247 mg, 50%) and dihydroxyketone **3.58** (74 mg, 15%). For **3.57**: R_f = 0.60 (15% EtOAc : petroleum ether); mp: 149-151 ^oC; $[\alpha]_D^{27}$ = +4.7^o (c=0.45, $CHCl_3$); IR (film) $\bar{\nu}$ 3500, 3030, 2954, 2928, 2856, 1454, 1253, 1115, 1056, 873, 836, 775, 735, 698; ^1H NMR ($CDCl_3$) δ 7.35 (m, 2H), 7.31-7.23 (m, 6H), 7.16 (m, 2H), 5.00 (d, J = 10.7 Hz, 1H), 4.96 (d, J = 11.6 Hz, 1H), 4.74 (d, J = 11.6 Hz, 1H), 4.59 (d, J = 10.7 Hz, 1H), 4.24 (dd, J = 5.8, 9.7 Hz, 1H), 4.05 (td, J = 2.7, 5.3 Hz, 1H), 3.79 (t, J = 9.5 Hz, 1H), 3.72 (d, J = 9.1 Hz, 1H), 2.77 (s, 1H), 2.38 (s, 1H), 2.30 (ddt, J = 2.9, 4.8, 14.1 Hz, 1H), 1.96-1.91 (m, 1H), 1.87-1.80 (m, 3H), 1.78-1.72 (m, 2H), 1.67-1.53 (m, 3H), 1.47-1.30 (m, 2H), 0.91 (s, 9H), 0.87 (t, J = 7.3 Hz, 3H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.7. 138.8, 128.5, 128.3, 128.1, 127.8, 127.2, 127.1, 84.2, 82.6, 79.0, 76.1, 75.8, 75.2, 72.3, 70.0, 46.9, 38.5, 31.0, 26.2, 21.5, 19.2, 19.1, 18.3, 15.3, -4.2, -4.3; HRMS (*m/z*) calculated for $C_{33}H_{50}O_6NaSi$ (ESI, M + Na+) 593.3269, found 593.3273. For **3.58**, see below.

(4a*S*,5*R*,6*R*,7*R*,8*R*,8a*R*)-6,7-Bis(benzyloxy)-5-((*tert*-butyl-dimethylsilyl)oxy)-8,8a-dihydroxy-8-propyloctahydro-naphthalen-1(2*H*)-one (3.58).

Triol **3.57** (30 mg, 0.0526 mmol) was dissolved in DMSO (0.240 mL). Iodoxybenzoic acid (38 mg, 0.137 mmol) was added to the solution, the mixture stirred at 75 ^oC for 20 h, then cooled to room temperature and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic phase was washed with brine and water, dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by FCC to afford ketone **3.58** (28 mg, 95%): R_f = 0.66 (10% EtOAc : petroleum ether);^1H

NMR ($CDCl_3$) δ 7.36-7.24 (m, 8H), 7.16 (m, 2H), 5.00 (d, J = 10.9 Hz, 1H), 4.80 (d, J = 11.5 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.32 (s, 1H), 4.14 (dd, J = 5.8, 10.0 Hz, 1H), 3.91 (t, J = 9.7 Hz, 1H), 3.63 (d, J = 9.2 Hz, 1H), 3.23 (dt, J = 6.8, 13.2 Hz, 1H), 2.55 (md, J = 14.6 Hz, 1H), 2.53 (s, 1H), 2.32 (dq, J = 4.1, 13.5 Hz, 1H), 2.17 (m, 1H), 1.94 (md, J = 13.5 Hz, 1H), 1.86 (td, J = 5.0, 13.7 Hz, 1H), 1.65-1.42 (m, 3H), 1.33-1.25 (m, 1H), 1.11-1.01 (m, 1H), 0.89 (s, 9H), 0.78 (t, J = 7.3 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 214.9, 139.5, 138.5, 128.6, 128.4, 128.1, 128.0, 127.3, 127.2, 84.3, 82.3, 80.9, 79.3, 76.4, 75.5, 72.2, 55.7, 40.8, 38.0, 27.6, 26.2, 21.3, 18.3, 17.1, 15.2, -4.3, -4.4; HRMS (*m/z*) calculated for $C_{33}H_{48}O_6NaSi$ (ESI, M + Na+) 591.3112, found 591.3119.

(4a*S*,5*R*,6*S*,7*R*,8*R*,8a*R*)-6,7-Bis(benzyloxy)-5,8,8a-trihydroxy-8-propyl-4a,5,6,7,8,8a-hexahydronaphthalen-1(4*H*)-one (3.7).

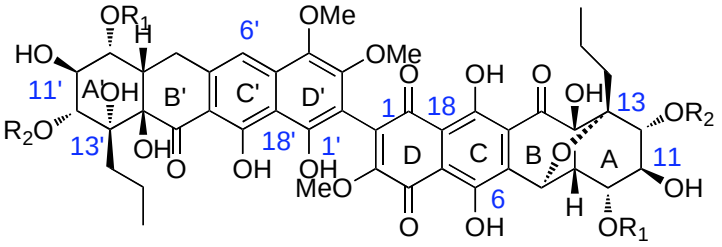
To a solution of ketone **3.58** (18 mg, 0.0316 mmol) in CH_2Cl_2 (2.0 mL) at room temperature was added PhSeCl (12 mg, 0.057 mmol) followed by $BF_3.OEt_2$ (78 μL, 0.632 mmol). The resulting red-orange solution was stirred at room temperature for 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with Et_2O, and the organic layer was concentrated *in vacuo* to give the crude a-selenoketone. The residue was dissolved in CH_2Cl_2 (0.5 mL), and solid $NaHCO_3$ (10 mg, 0.12 mmol) followed by *m*-CPBA (20 mg, 0.11 mmol) were added. This mixture was stirred for 20 min, during which time it turned from yellow to colorless. When TLC indicated the complete consumption of the selenide, the reaction was diluted with Et_2O, washed with water and brine, and the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by FCC provided the trihydroxy-enone **3.7** (11 mg, 75%): R_f = 0.33 (30% EtOAc : petroleum ether). ^1H NMR ($CDCl_3$) δ 7.40-7.29 (m, 10H), 7.12 (dm, J = 10.2 Hz,

1H), 6.23 (dd, J = 2.3, 10.2 Hz, 1H), 5.01 (d, J = 10.6 Hz, 1H), 4.99 (d, J = 11.2 Hz, 1H), 4.76 (d, J = 11. 2 Hz, 1H), 4.68 (d, J = 10.6 Hz, 1H), 4.13 (m, 1H), 4.01 (s, 1H), 3.99 (t, J = 9.8 Hz, 1H), 3.81 (d, J = 9.1 Hz, 1H), 2.91-2.83 (m, 1H), 2.60-2.52 (m, 2H), 2.22 (d, J = 2.5 Hz, 1H), 2.09 (s, 1H), 1.64 (ddd, J = 4.5, 12.3, 14.3 Hz, 1H), 1.54-1.50 (m, 1H), 1.45-1.35 (m, 1H), 1.26-1.16 (m, 1H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 201.0, 154.1, 138.7, 138.2, 128.9, 128.8, 128.2, 128.1, 128.0, 127.8, 127.7, 83.6, 82.8, 80.2, 77.6, 76.1, 75.8, 70.3, 46.0, 36.9, 27.1, 18.0, 15.2; HRMS (*m/z*) calculated for $C_{27}H_{32}O_6Na$ (ESI, M + Na+) 475.2091, found 475.2097.

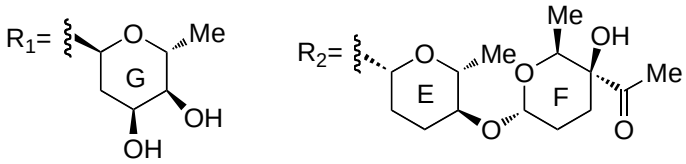
Chapter 4. Studies towards Total Synthesis of HMP-Y1

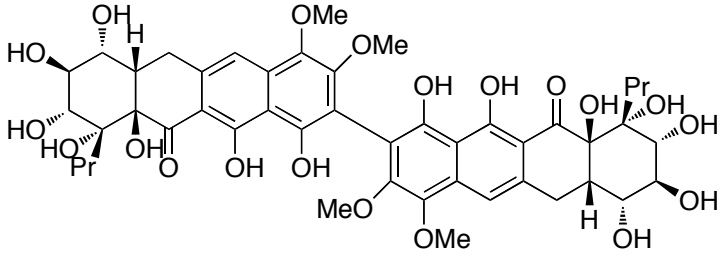
4.1 Introduction and Background

In Chapter 3 we described synthesis of the AB and A'B' segments of the angelimicin. Chapter 4 discusses the progress on the total synthesis of HMP-Y1 (**Figure 4.1)**. HMP-Y1 is an attractive target because it is symmetrical with respect to the biaryl bond, thereby making it a less challenging target than asymmetric congeners like angelimicin B. Furthermore, it may be possible to execute an oxidative desymmetrization strategy to convert HMP-Y1 to angelimicin B, as is believed to occur in the biosynthesis of angelimicin B.



Angelmicin B (hibarimicin B) (**4.1**)





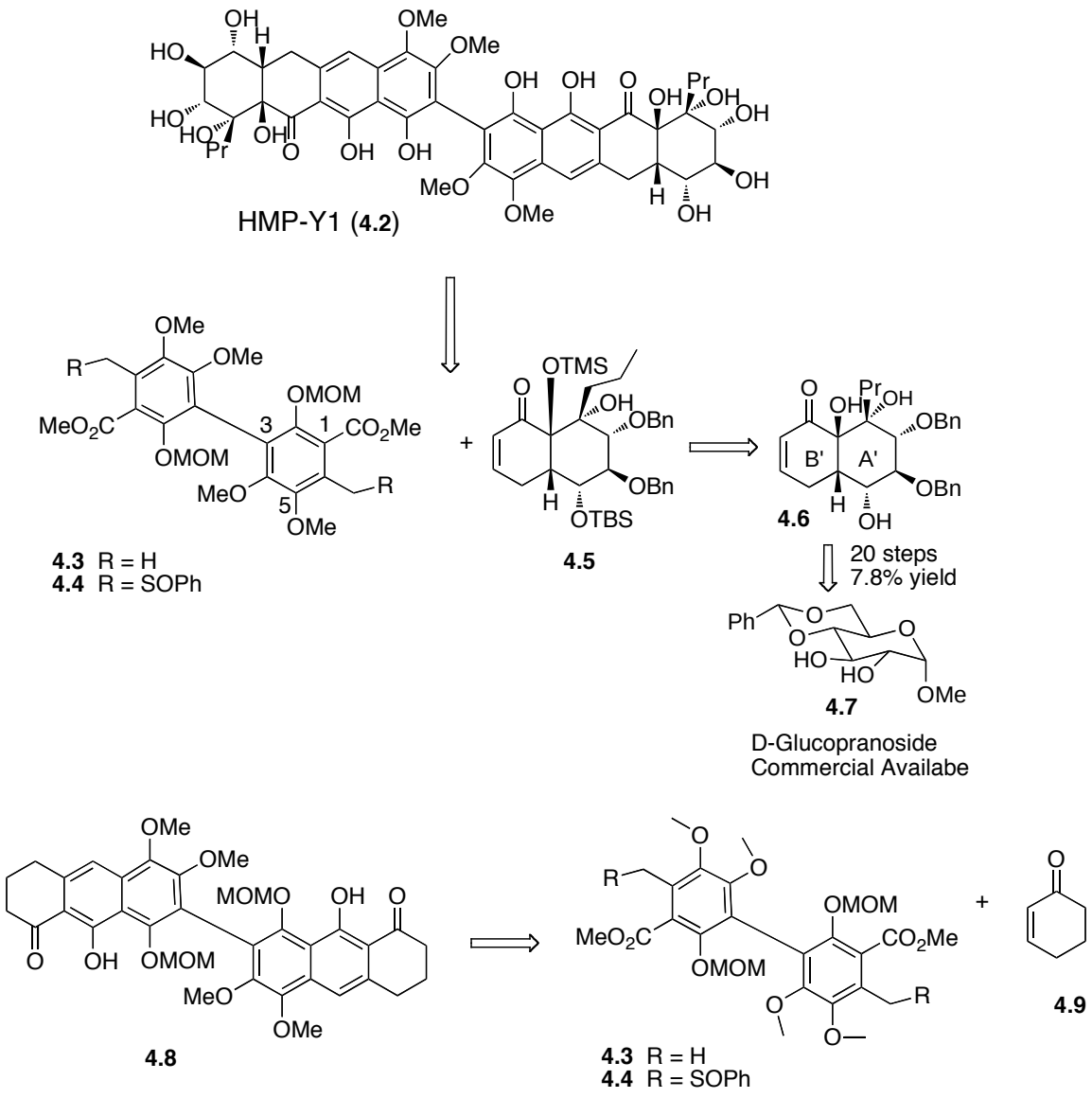
HMP-Y1 (**4.2**)

Figure 4.1 Structure of angelmicin B and HMP-Y1

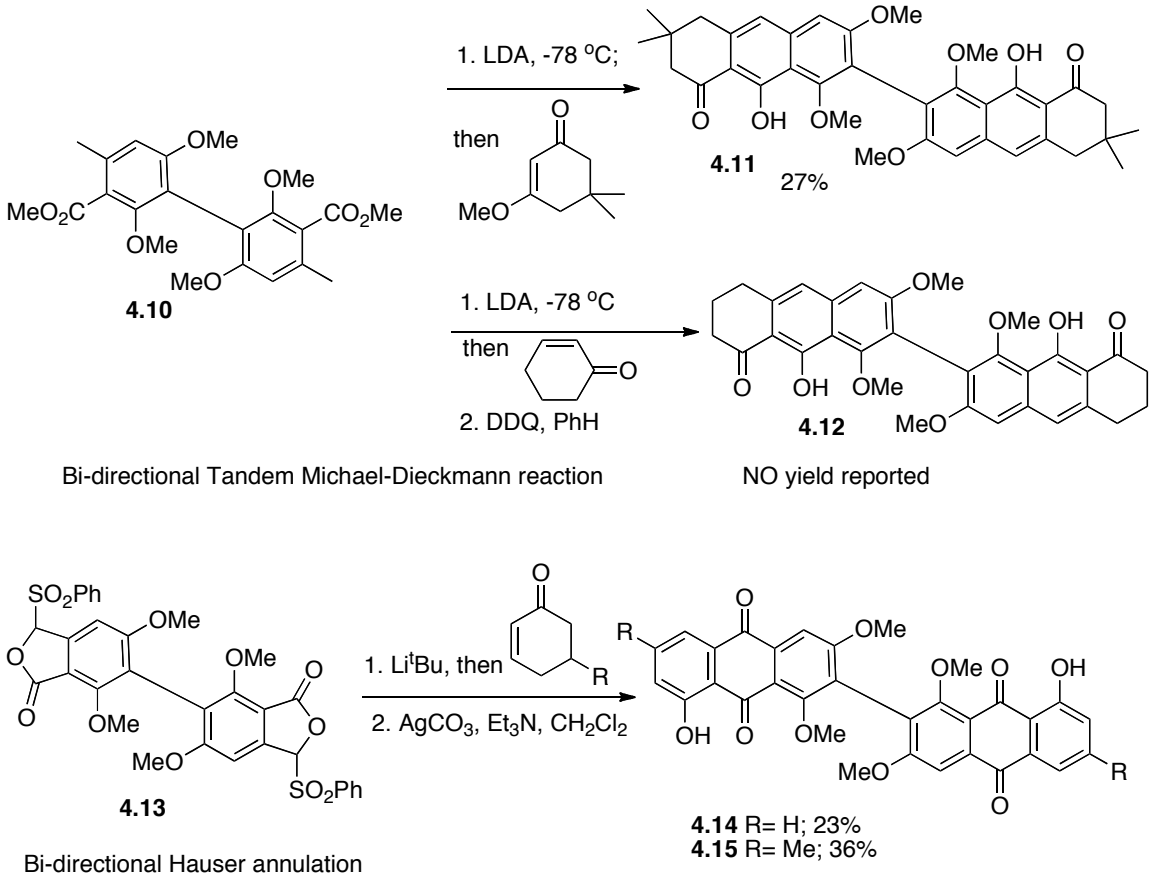
4.2 Retrosynthetic Plan

Given the symmetry with respect to the biaryl bond, we envisaged a bidirectional synthesis of HMP-Y1 (**Scheme 4.1)**. Thus **4.2** can be prepared by a Hauser annulation (R = SOPh)[65, 66] or a tandem Michael-Dieckmann condensation[67] (R=H) on the dimeric 5-methoxyorsellinates **4.4** or **4.3** respectively, and enone **4.5**, followed by aromatization of the annulated adducts. Enone **4.5** should be available by straightforward alcohol protecting group chemistry on the AB enone **4.6** that was prepared in Chapter 3. These bidirectional strategies were tested using cyclohexenone **4.9** as a model for enone **4.5**.

To the best of our knowledge, there is only one example of a bi-directional tandem-Michael-Dieckmann condensation[68] and one example of a bi-directional Hauser annulation[69] in the literature (**Scheme 4.2**). The highest yield was 36%, and unlike **4.3** and **4.4**, the bi-orsellinate substrates were unsubstituted at the 5-position. The closest cases to our case are the Michael Dieckmann reactions between 5,5-dimethyl-3-methoxy-cyclohexenone or cyclohexenone and the bis-orsellinate **4.10**, which is similar to **4.3**. However, no yield was given for one product **4.12**, and the other **4.11**, is reported without C-13 NMR. The bis-Hauser annulation was performed with the bis-phthalide **4.13**, which gave the bis-dihydroquinones **4.14** and **4.15**. For the naphthalene core in HMP-Y1, a bis-sulfoxide substrate **4.4** instead of a bis-phthalide precursor like **4.13** is required.


HMP-Y1 (4.2)
4.3 R = H
4.4 R = SOPh
4.5
4.6
20 steps
7.8% yield
4.7
D-Glucopranoside
Commercial Availabe
4.8
4.3 R = H
4.4 R = SOPh
4.9

Scheme 4.1

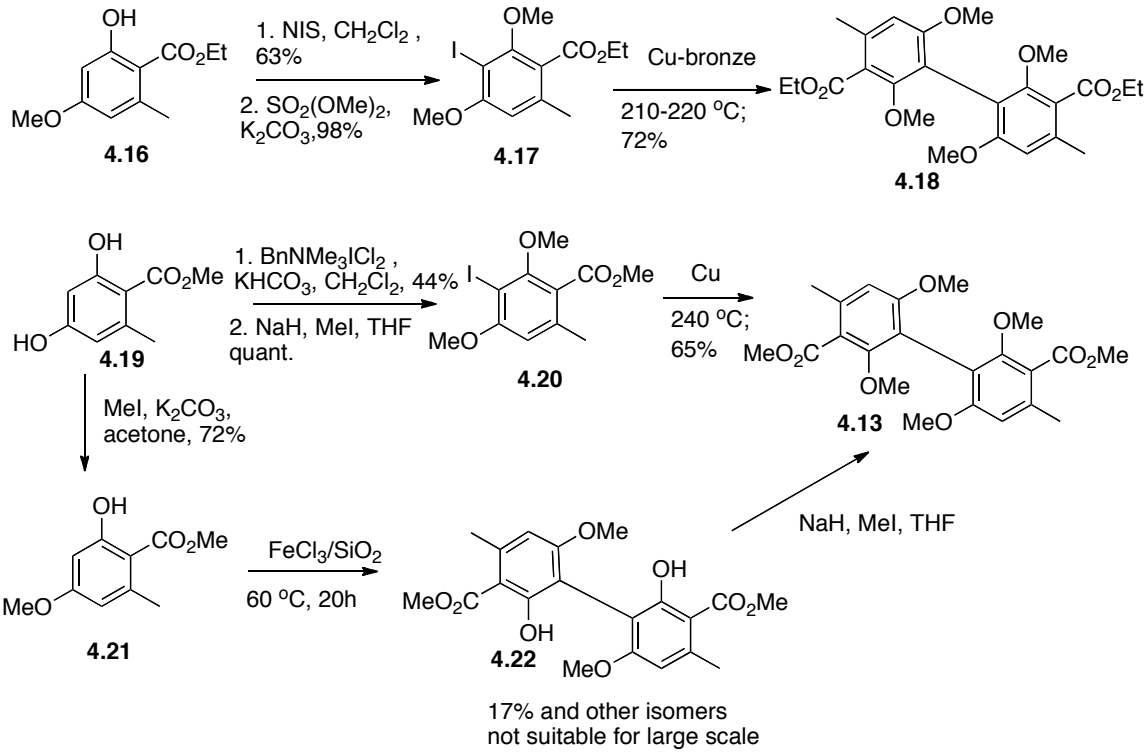


Scheme 4.2

4.3 Model Studies on Cyclohex-2-enone

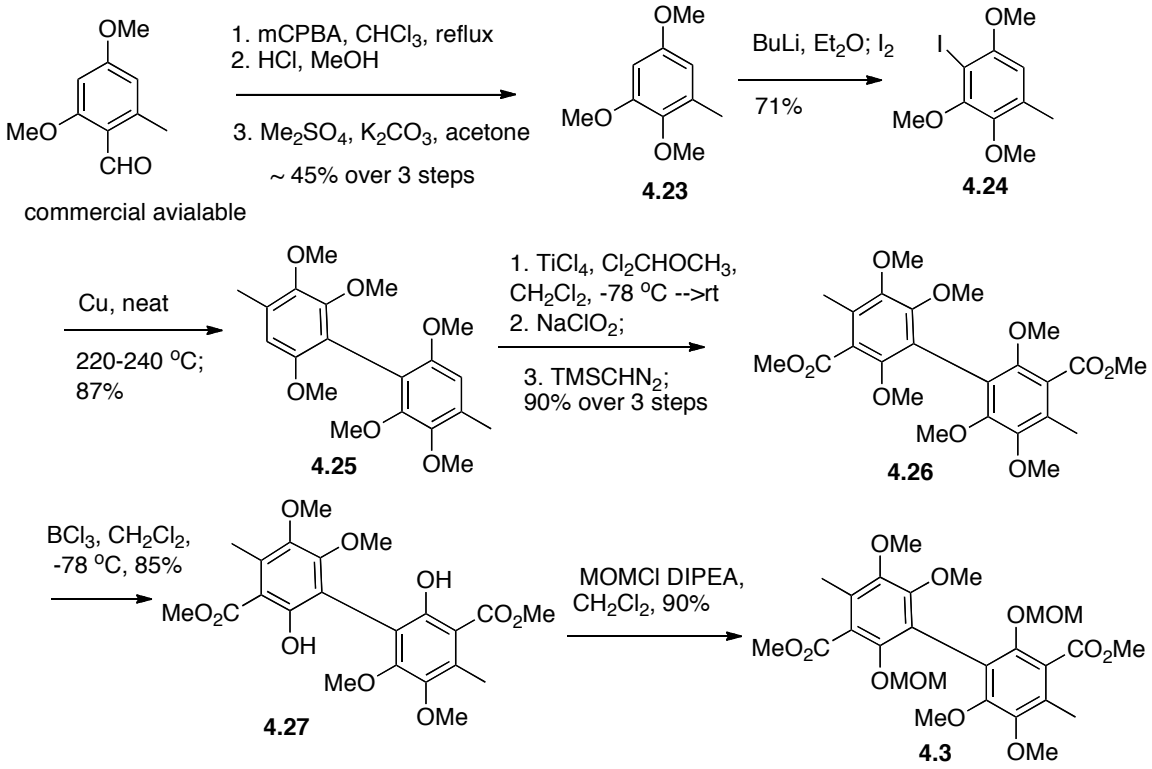
4.3.1 Precursors for Michael-Dieckmann Condensation 4.3

We envisaged using an Ullmann strategy for 3,3'-dimeric methyl 5-methoxyorsellinate **4.3**.[70] However, while this approach has been applied to dimeric orsellinates (**Scheme 4.3**), to the best of our knowledge neither the Ullmann coupling for the 5-methoxyorsellinates, nor the requisite iodinated precursors, has been reported. Therefore we decided to perform the Ullmann coupling on a less substituted precursor, and to introduce the carboxylate residue at a later stage.



Scheme 4.3

The known 2,3,5-trimethoxytoluene **4.23**[71] was synthesized from commercial available orsellinal by a modified three-step procedure in 45% yield as shown in **Scheme 4.4**.



Scheme 4.4

Regioselective iodination of 2,3,5-trimethoxytoluene **4.23** was performed through *orth*-lithation of 2,3,5-trimethoxytoluene with *n*-BuLi followed by quenching of the resulting aryllithium with I_2 which led to 4-iodo-2,3,5-trimethoxytoluene **4.24** in 71% yield without any detectable 6-iodo-2,3,5-trimethoxytoluene. Heating the very hindered aryl iodide **4.24** with copper powder at 220-240 ^{o}C under nitrogen provided the desired Ullmann product, bis-4,4'-(2,3,5-trimethoxytoluene) **4.25** in 87% yield. Compound **4.25** was formylated with Cl_2CHOCH_3 and $TiCl_4$,[72] and oxidation of the product with $NaClO_2$ and esterification of the resulting acid gave the 3,3' coupled 5-methoxyorsellinate dimer **4.26**. Overall, the fully substituted biaryl **4.26** was obtained from known 2,3,5-trimethoxytoluene **4.23** in 55% yield through five steps and three chromatography purifications. Because of anticipated problems in selectively removing the 2,2'-methyl

group in the annulated product, **4.26** was selectively de-methylated with BCl_3 to give bis-phenol **4.27**, then re-protected, and the MOM groups were installed on the bis-phenol to give **4.3**.

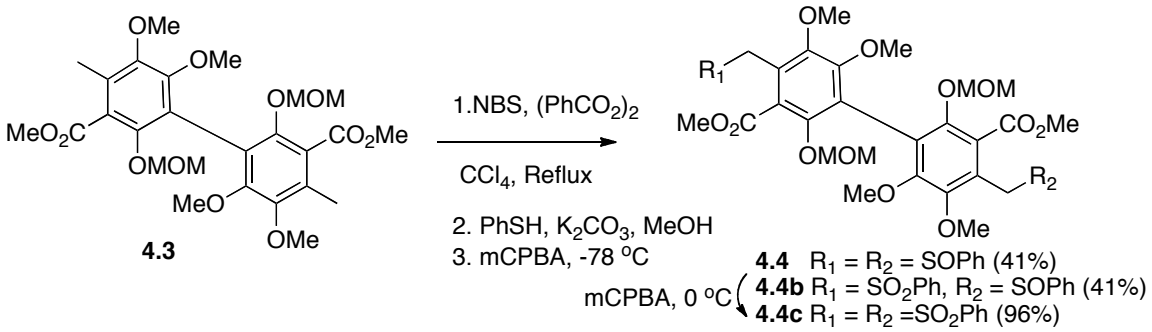
4.3.2 Precursor for Hauser Annulation

The dimeric sulfoxide **4.4** for the Hauser type annualtion was obtained in 32% yield through a three step sequence: free radical di-bromination on **4.3** with NBS, substitution of the resulting dibromide with thiophenol to give the bis-thioether, and mCPBA oxidation of the bis-thioether. The oxidation step produced an approximately 1:1 ratio of the desired bis-sulfoxide **4.4** (41%) and the mixed sulfoxide-sulfone product **4.4b** from over-oxidation (41%). ^{1}H and ^{13}C NMR analysis of bis-sulfoxide **4.4** suggested a mixture of three diastereoisomers. Thus, certain individual protons and carbons appeared as four signals, one signal each for the two C_2 symmetric chiral dimers, and two resonances for the non-equivalent nuclei in the meso dimer. For example, the proton signals for two carboxymethyl groups appeared as a 6H set of four singlets in the 3.83-3.85 ppm range, and the carbonyl carbons showed as four peaks between 167.4 and 167.5 ppm. Similar results have been observed in the literature.[69] The NMR data for sulfoxide-sulfone **4.4b** indicated a mixture of two diastereomers. The structure of **4.4b** was confirmed by oxidation of the mixture to the bis-sulfone **4.4c** (**Scheme 4.5**).

4.3.3 Attempted Hauser Annulation

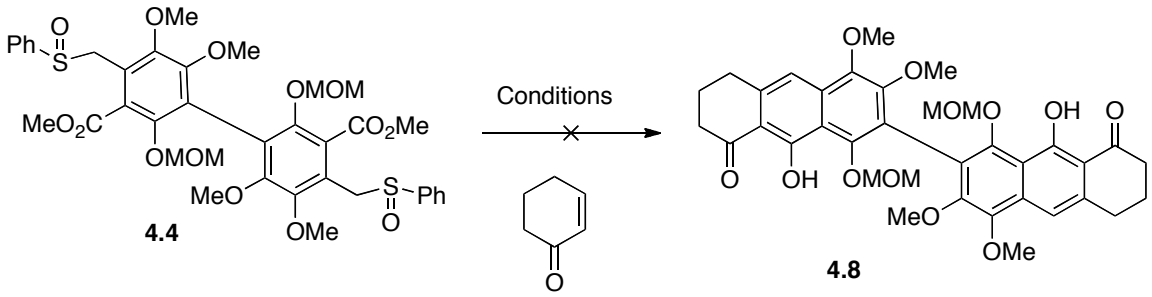
Two standard Hauser annulation conditions were first tested (**Table 4.1**).[66] Treatment of bis-sulfoxide **4.4** with LDA in THF at −78 ^{o}C followed by addition of cyclohexenone

resulted in no desired product and approximately 30% recovered **4.4**. The reaction was also unsuccessful with lithium *t*-butoxide (LTB) as the base in THF at -60 ^{o}C. It was recently reported that using DMSO as co-solvent dramatically increases the yield.[73] However, mixed solvent variations, THF/DMSO (3/1)/LTB and THF/HMPA (10/1), were also unsuccessful. Attempts at using the bis-sulfone **4.4c** instead of the bis-sulfoxide **4.4** were also not productive. This strategy was not further pursued.



Scheme 4.5

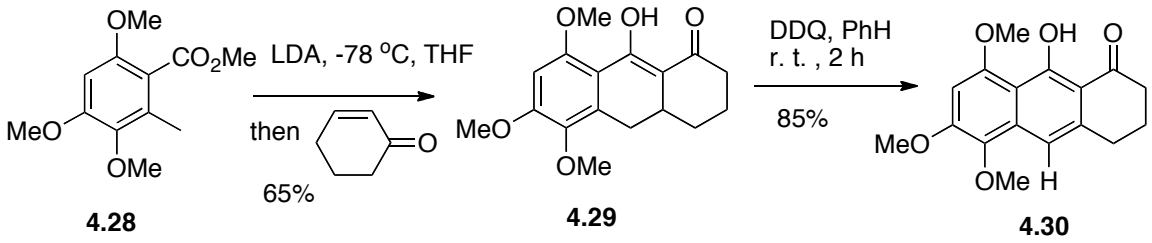
Table 4.1 Attempted Bi-directional Hauser annulation.



Entry	Conditions	Product
1	LDA, THF, −78^{o}C to rt	~30% r. s. m., 0% product
2	LTB, THF, -60 ^{o}C to rt	~70% r. s. m., 0% product
3	LTB, THF/DMSO (3/1), -60 ^{o}C to rt	~20% r. s. m. , 0% product
4	LDA, THF/HMPA (10/1), −78^{o}C to rt	~20% r. s. m., 0% product

r.s.m.: recovered starting material (bis-sulfoxide **4.4**)

4.3.4 Bi-directional Tandem-Michael-Dieckmann Condensation.

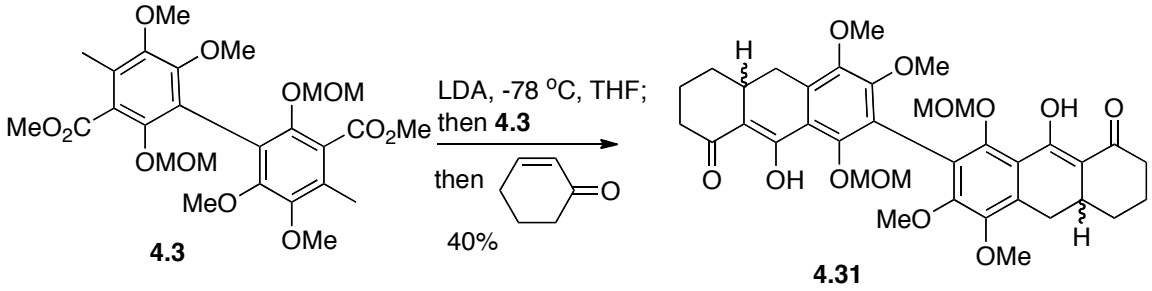


4.28 **4.29** **4.30**

Scheme 4.6

The two-step annulation approach, i.e. bi-directional tandem Michael-Dieckmann condensation followed by aromatization, was next tested. Due to the lack of experimental details in the reported example of the bi-directional reaction, conditions were first developed on the monomeric variant using the known 5-methoxyorsellinate **4.28**[74] (Scheme **4.6**). Furthermore, although orsellinates are well-known substrates in tandem Michael-Dieckmann condensations, a 5-methoxyorsellinate **4.28** has never been reported. Thus, **4.28** was treated with LDA at −78 ^{o}C in THF to form the dark red lithiated enolate. Cyclohex-2-enone was then added at −78 ^{o}C, and the mixture was warmed to room temperature. The condensation product **4.29** was obtained in 65% yield. Treatment of **4.29** in dry benzene at room temperature with DDQ over 2 h, gave the aromatized product **4.30** as a yellow solid, in 85% isolated yield. Comparison of ^{1}H NMR data for **4.29** and **4.30** showed an extra signal at 7.23 ppm for **4.30**, which indicated aromatization of the middle ring of **4.29**. There are also three signals integrating for 2H each in the upfield region in the spectrum for **4.30**, i.e. one triplet at 3.00 ppm, another triplet at 2.74 ppm and a quintet at 2.10 ppm. On the other hand, **4.29** shows eight distinguishable signals for 9H between 1.24 and 3.23 ppm. The ^{13}C NMR spectrum for **4.30** shows two less sp^3 and two extra sp^2 carbon signals compared to the data for **4.29**. Together these

data confirmed the structures of compound **4.29** and **4.30** and are helpful for analysis of the more complex bi-directional condensation product, and its aromatized derivative.



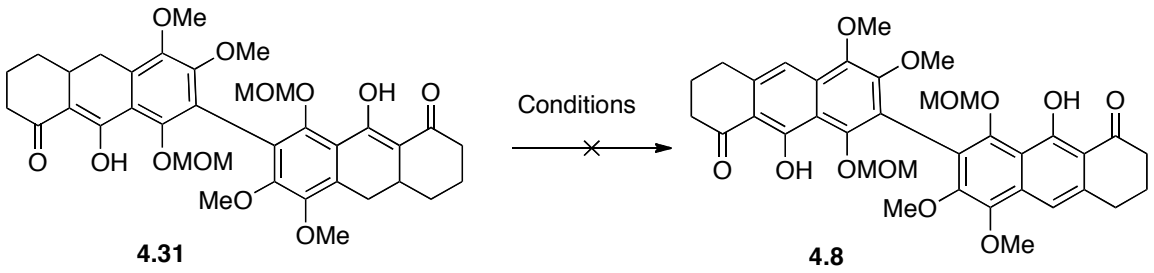
Scheme 4.7

Thus, the reaction of the bis-lithiated enolate of **4.3** and cyclohex-2-enone following the procedure developed for 5-methoxyorsellinate **4.28** provided **4.31,** the product of the bi-directional tandem Michael-Dieckmann condensation, in ~ 40% yield. ^{1}H NMR spectrum of **4.31** was compared to that of **4.29**. In the upfield region, the signal patterns are very similar but more complex for **4.31**. In the ^{13}C NMR spectra nearly all carbon signals for both compounds matched very well, though individual carbons for **4.31** comprised four peaks compared to the corresponding carbons in **4.29**, which showed as single peaks. As for the bis-sulfoxide **4.4**, this data suggests that **4.31** consists of a mixture of three diastereomers, due to the two chiral centers and the chiral axis of the 2,2' biaryl bond.

The next step was to aromatize the compound **4.31**. However, treatment of dimer **4.31** with DDQ at room temperature in dry benzene for 2 h, following the conditions that were used for the monomer **4.30**, did not lead to any noticeable change. Prolonged reaction time, or elevated temperatures resulted in decomposition. Several other aromatization procedures were attempted but were also unsuccessful (**Table 4.2**). During the final stages of our study, the Sulikowski's group reported that exposure of a very

similar substrate to **4.31** to DDQ in benzene at reflux for 5 h led to aromatization (*vide infra*). However, treatment of **4.31** under these conditions led to decomposition. Together with the Sulikowski result and our observations on the reaction of **4.31** with DDQ in benzene at different temperatures and over different time periods, suggest that the reaction time may be critical for success of this reaction.

Table 4.2. Attempted aromatization of compound **4.31 to 4.8**



4.31 **4.8**

Entry	Conditions	Product
1	DDQ, dry benzene at r. t., 2 h or 8 h	No reaction
2	DDQ, dry benzene, 50 ^{o}C, 16 h	Decomposition[a]
3	DDQ, dry benzene, reflux, 2 h	Complex mixture on TLC
4	DDQ, dry benzene, reflux, 16 h	Decomposition[a]
5	$Pd(OAc)_2$, CH_3CN (dry or wet), r. t.	Decomposition[a]
6	Ag_2CO_3 on Celite, Et_3N, CH_2Cl_2, r. t.	No reaction
7	Ag_2CO_3 on Celite, Et_3N, CH_2Cl_2, reflux	Decomposition[a]
8	Ph_3CBF_4 , CH_2Cl_2 at r. t.	Unknown compound

[a]: Disappearance of **4.31** with many spots on the TLC.

4.4 Conclusion

The bisulfoxide **4.4** for the bi-directional Hauser annulation and the dimeric 5-methoxyorsellinate **4.3** for the bi-directional tandem-Michael-Dieckmann condensation

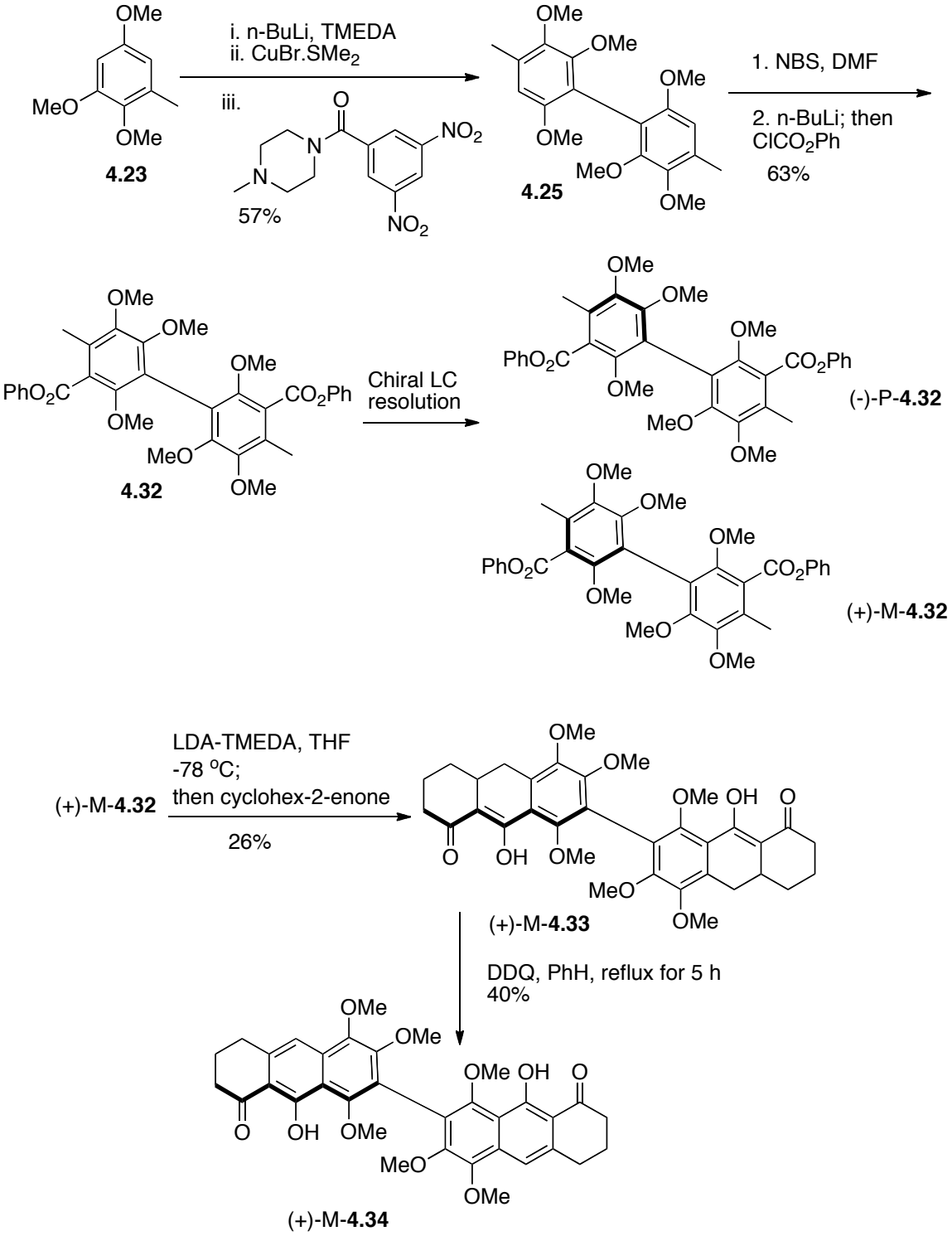
were synthesized in ten and seven steps from known 2,3,5-trimethoxytoluene **4.23** in 27% and 21% yield, respectively. The Hauser annulation with **4.4** and cyclohexenone was unsuccessful. The bi-directional tandem-Michael-Dieckmann condensation with **4.3** and cyclohexenone afforded the desired product **4.31** in 40% yield. However, the subsequent aromatization of **4.31** to **4.8** was unsuccessful while aromatization of the monomeric counterpart **4.28** to **4.29** proceeded smoothly. Comparing to Sulikowski' results, the success of the aromatization may be very sensitive to the reaction time.

4.5 Updated Literature Reported on Synthesis

At the completion of this thesis research, several synthetic studies by the Sulikowski, Tatsuta and Shair groups on hibarimincines were reported. [75] In the Sulikowski work a bi-directional tandem Michael-Dieckmann condensation that is very similar to ours was performed (**Scheme 4.8**).[75a] The main difference was in the protecting groups on the phenol and carboxylic acid residues in the Michael donor. In the Sulikowski case, the Michael donor was also optically active, whereas our material was racemic. Thus, lithiated (+)-M-**4.32** was condensed with cyclohex-2-enone to give (+)-M-**4.33** in 26% yield after optimization, which was similar to the 40% yield obtained for our reaction with **4.3** (Scheme **4.7**). Treatment of (+)-M-**4.33** with DDQ in benzene at reflux for 5 h afforded the aromatized product (+)-M-**4.34** in 40% yield. The same sequence of reactions on the (-)-P-**4.32**, provided the enantiomer of (+)-M-**4.34**. Comparison of the CD spectra of (+)-M-**4.34** to HMP-Y6 led to the assignment of HMP-Y6 and hibarimicin B atropoisomers as *aR* and *aS*, respectively. Sulikowski's synthesis of the Michael donor **4.32** was also very similar to our synthesis of **4.3**. In both cases 2,3,5-trimethoxytoluene

4.23 was used as starting material for the same biphenyl intermediate **4.25**. Our synthesis used a two-step iodination-Ullmann coupling sequence and furnished **4.25** in 62% overall yield (**Scheme 4.4**). The Sulikowski route involved a lithiation-cupration-Spring oxidative coupling and gave **4.25** in 51-63%.[76] For introduction of the caboxymethyl group in **4.25** we employed a Friedel-Crafts-like formylation-oxidation strategy whereas the Sulikowski group subjected **4.25** to bromination, followed by a lithium-halogen exchange and phenyl chloroformate quench. The enantiomers of the product in the latter case, **4.32**, were resolved by chiral liquid chromatography.

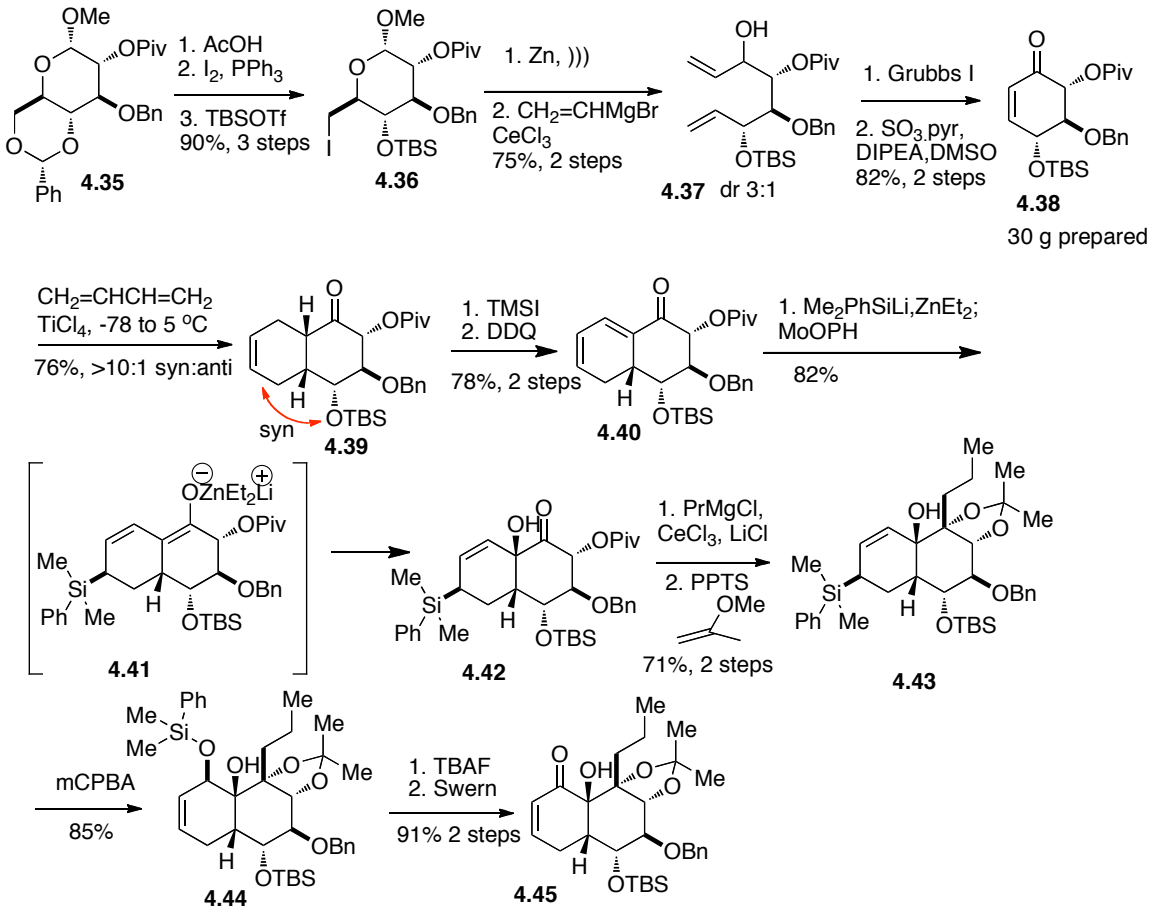
Shair's synthesis of A'B' subunit started with **4.35**, an orthogonally protected derivative of **3.27**, the same D-glucose precursor that was used in our synthesis.[75c] Iodide **4.36** was obtained from **4.35** in three standard steps in 90% yield and was converted into dien-ol **4.37** in 75% yield and 3:1 diastereoselectivity. Since the chiral center would be destroyed in later steps, no separation was needed. The enone **4.38** was obtained in two steps, RCM with the first generation Grubb's catalyst followed by Parikh-Doering oxidation on the resulting allylic alcohol. A $TiCl_4$ catalyzed contrasteric Diels-Alder reaction on **4.38** gave the key *syn* Diels-Alder product **4.39** in 76% yield and high selectivity (>10:1 *syn/anti*). The Diels-Alder adduct **4.39** was converted to the dienone **4.40** through a thermodynamic enol intermediate. The regio- and diastereoselective 1,6-conjugated addition of dimethylphenylsilyl zincate to the dienone **4.40** generated zinc enolate intermediate **4.41**.



Scheme 4.8 Sulikowshi's synthesis of model compound **4.34**

The *in situ* oxidation of **4.41** delivered *cis*-decalin **4.42** as a single regio- and diastero-isomer in 82% yield. The $CeCl_3$ promoted addition of propylmagnesium chloride to **4.42**

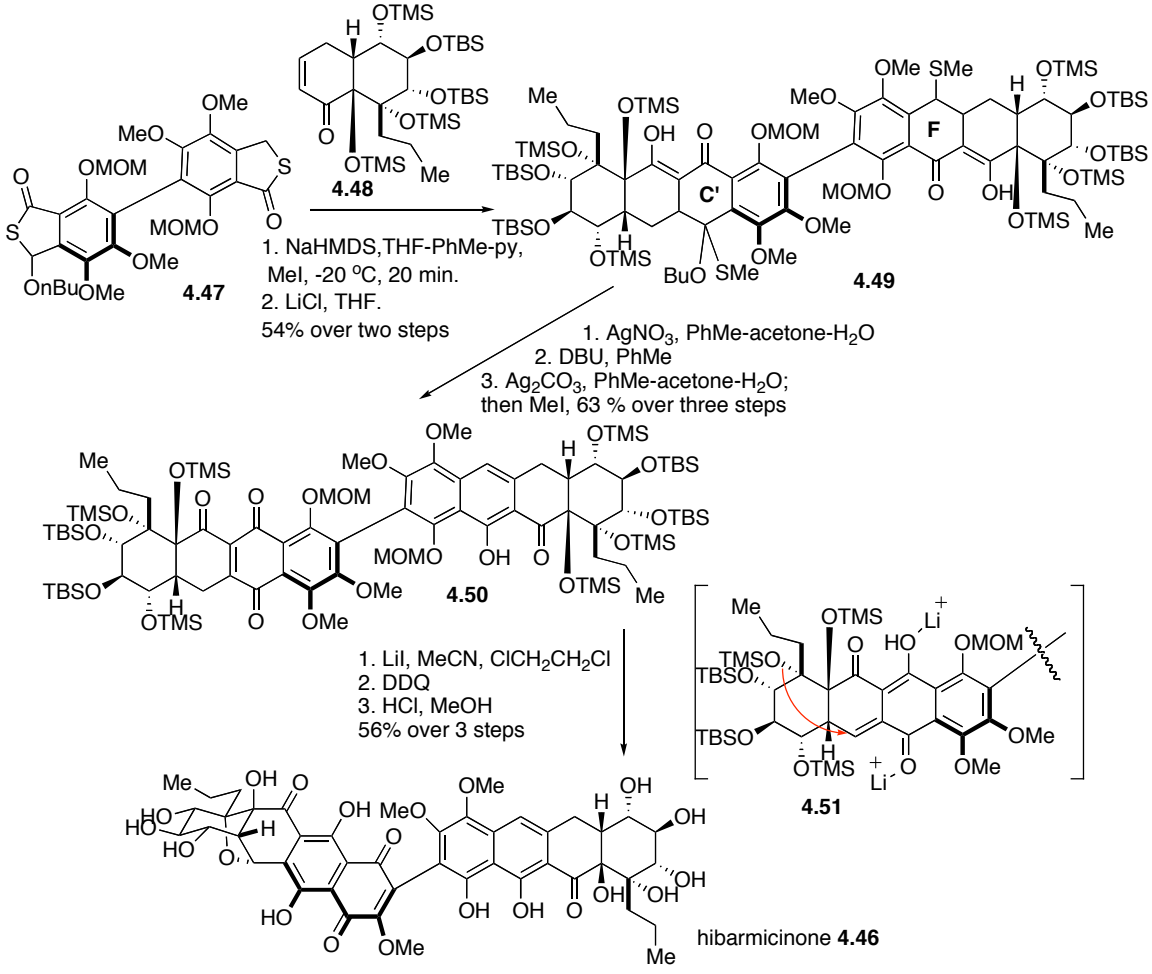
led to carbonyl addition exclusively from the convex face of the molecule, together with cleavage of pivoyl ester. The resulting diol was protected as the acetonide, affording **4.43** in 71% yield over two steps (**Scheme 4.9**). Treatment of allysilane **4.43** with m-CPBA provided **4.44** in 85% yield. Selective removal of the dimethylphenylsilyl group with TBAF and Swern oxidation of the resulting allyic alcohol delivered **4.45** in 91% yield over two steps. The overall synthesis delivered a gram of the protected A'B' subunit of hibarimicin B.



Scheme 4.9. Shair's synthesis of A'B' subunit.

The Tatsuta group reported the first total synthesis of hibarimicinone **4.46**, the aglycon part of hibarimicines and determined the absolute stereochemistry of the hibarimicinone (**Scheme 4.10**).[75b] This study revealed that the absolute stereochemistry

of AB and A'B' subunits prepared in our and Shair's initial syntheses were opposite to that in the natural product.

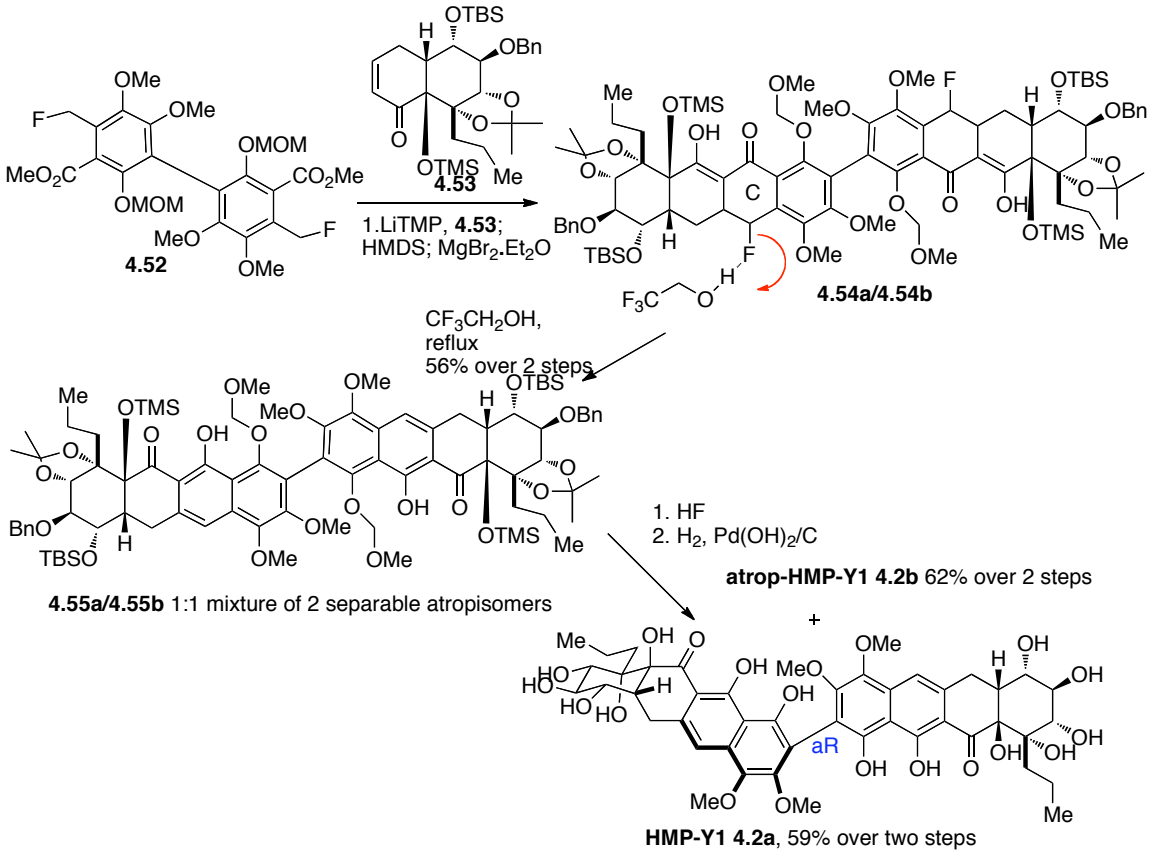


Scheme **4.10**. Tatsuta's synthesis of hibarimicinone **4.46**.

A bi-directional Michael-Dieckmann cyclization on an unsymmetrical Michael donor approach was used to construct the carbon skeleton. The mixed benzothiolactone **4.47** was annulated with enone **4.48** with NaHMDS as base in a mixed solvent containing THF, toluene and pyridine. The annulated product **4.49** was then submitted to a three-step sequence to furnish the key intermediate **4.50** in 63% yield, hydrolysis of mixed thioketal, DBU promoted tautomerization of ring C', and eliminative-aromatization in ring F. Exposure of **4.50** to excess LiI led to tetrahydrofuran formation. This reaction

presumably proceeds via the LiI promoted intramolecular conjugated addition to enone **4.51**. Subsequent DDQ oxidation and global deprotection on this product afforded hibarimicinone **4.46** in 56% overall yield from **4.50**.

More recently the Shair group reported the total syntheses of HMP-Y1 **4.2**, and hibarimicinone **4.46** using a bi-directional strategy (**Scheme 4.11**).[75d] A novel Michael-Dieckmann reaction sequence on a symmetrical bis-benzylic fluoride was developed for HMP-Y1, and a bi-directional double annulation on an unsymmetrical precursor followed by a biomimetic etherification, was developed for hibarimicinone.

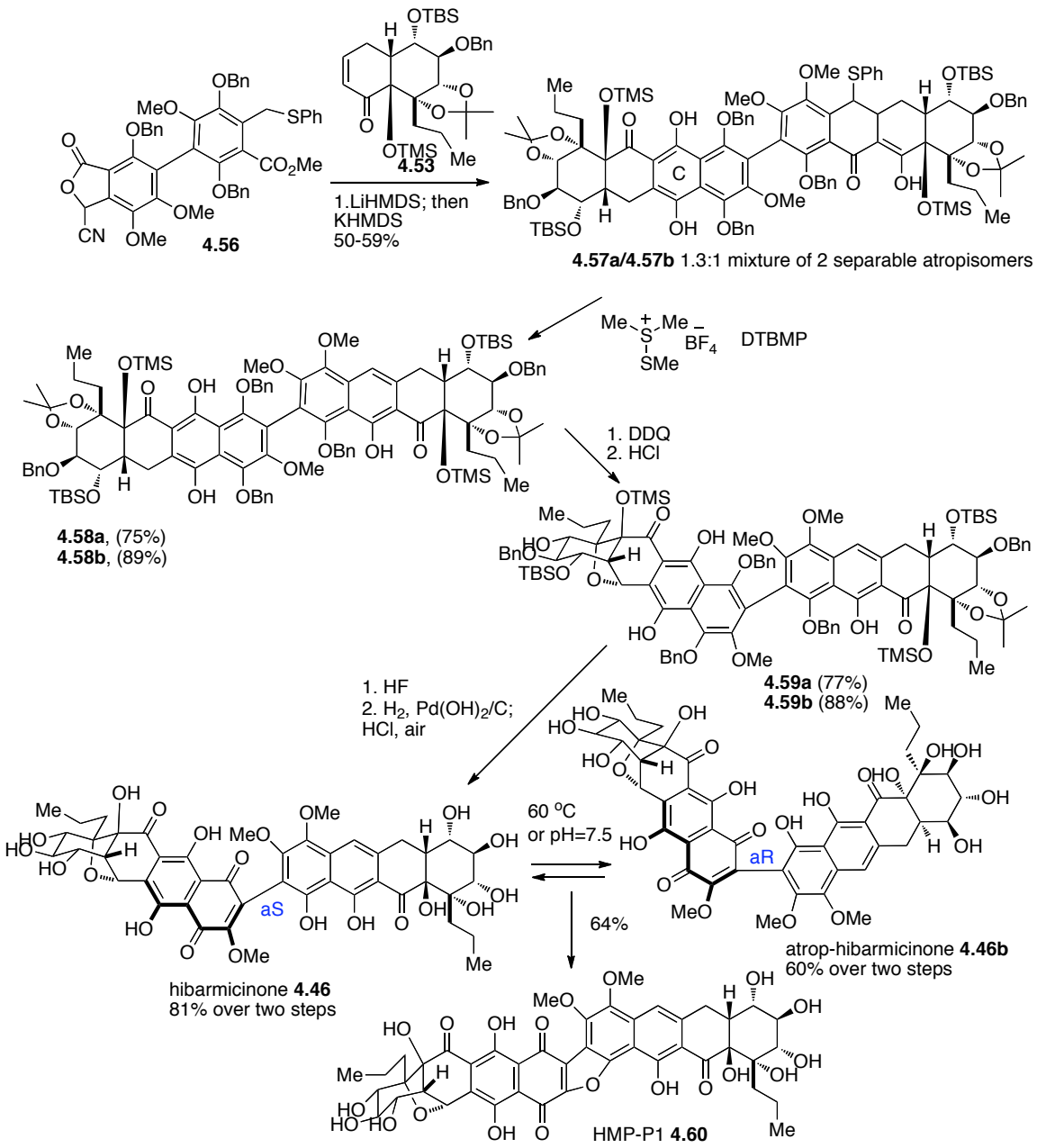


Scheme 4.11. Shair's total synthesis of HMP-Y1 **4.2a**.

The $MgBr_2.Et_2O$ promoted condensation of lithiated bis-fluoride **4.52** and enone **4.53**, the enantiomer of aforementioned **4.45**, provided mixture **4.54a**/**4.54b**. Without

purification, heating of this mixture in CF_3CH_2OH provided a separable mixture of atropisomers **4.55a** and **4.55b**, via the formal elimination of HF. The overall yield of **4.55a** and **4.55b** over two steps was 56%. Global deprotection of **4.55a** and **4.55b** with HF followed by hydrogenolysis afforded HMP-Y1 as well as atrop-HMP-Y1. By comparing NMR data and CD spectra, HMP-Y1 **4.2a** was assigned as the *aR* configuration, in agreement with Tatsuta's result.

Shair's hibarmicinone **4.46** synthesis started with the bi-directional double annulation using unsymmetrical biaryl **4.56** and enone **4.53**. The mixture was first treated with LiHMDS followed by subsequent addition of KHMDS and afforded the annulation product **4.57a** and **4.57b** as two separable atropisomers. Elimination of phenyl sulfide was accomplished with dimethyl(methylthio)sulfonium tetrafluoroborate to deliver the aromatization product **4.58a** and **4.58b**. DDQ oxidation to form the C-ring quinone and HCl promoted biomimetic etherification delivered **4.59a** and **4.59b**. Deprotection of acid sensitive groups with HF, hydrogenolysis of benzyl ethers, and exposure of the resulting compound to air provided hibarimicinone **4.46** and atrop-hibarimicinone **4.46b**. The atropisomers are relatively stable in acidic conditions, but are quickly interconverted at high pH, such as pH 7.5 buffer and are transformed into HMP-P1 **4.60**. These observations suggest that the rotational barriers about the biaryl bond in hibarmicinone are pH-dependent.



Scheme 4.12. Shair's syntheses of hibarmicinone and HMP-P1.

4.6 Experimental

2-Iodo-1,3,4-trimethoxy-5-methylbenzene (4.24).

To a solution of 2,3,5-trimethoxytoluene **4.23** (1.49 g, 8.19 mmol) in Et_2O (30 mL) at 0 ^oC, was added n-BuLi (4.6 mL, 2.5M in hexane, 11.50 mmol). The reaction mixture was then warmed to room temperature and stirred for 16 h. At this time the resulting white suspension was cooled to 0 ^oC, and a solution of I_2 (2.91g, 11.5 mmol) in Et_2O (15 mL) was added. The yellow solution was warmed to room temperature and stirred for 1 h. The reaction was quenched with aqueous $NaHSO_3$. The solution was extracted with Et_2O (3x100 mL) and the organic phase was washed with brine, H_2O, dried ($MgSO_4$), and concentrated in *vacuo*. Purification of the residue by FCC gave iodide **4.24** (1.80 g, 71%). R_f = 0.30 (5% EtOAc in petroleum ether). Mp: 42 - 44 ^oC. IR (thin film) cm^{-1}: 2935, 1583, 1470, 1392, 1237, 1101, 1010, 795. ^1H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$) δ 155.0, 153.9, 145.8, 132.9, 108.5, 81.1, 60.7, 60.6, 56.9, 16.4. HRMS (*m/z*) calculated for $C_{10}H_{13}O_3Na$ (ESI, M + Na+) 330.9807, found 330.9795.

2,2',3,3',6,6'-Hexamethoxy-4,4'-dimethyl-1,1'-biphenyl (4.25).

A mixture of iodide **4.24** (1.80 g, 5.84 mmol) and fine copper powder (3.74 g, 58.4 mmol) was heated to 220-240 ^oC under nitrogen for 3 h. The mixture was then cooled to room temperature and transferred to a Soxhlet apparatus. The extraction was effected with acetone (250 mL) for 16 h under nitrogen. The extract was concentrated and purifed by FCC to give a white solid **4.25** (910 mg, 86%). R_f = 0.50 (10% EtOAc in petroleum ether). Mp: 114-116 ^oC; Lit: 114-117 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 6.57 (s, 2H),

3.83, (s, 6H), 3.72 (s, 6H), 3.70 (s, 6H), 2.36 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 151.9, 145.4, 131.3, 116.0, 108.3, 60.4, 56.2, 16.6.

Dimethyl 2,2',5,5',6,6'-hexamethoxy-4,4'-dimethyl-[1,1'-biphenyl]-3,3'-dicarboxylate (4.26).

To a solution of biphenyl **4.25** (510 mg, 1.42 mmol) in CH_2Cl_2 (4 mL) at −78 ^{o}C, was added $TiCl_4$ (5.68 mL, 1 M in CH_2Cl_2, 5.68 mmol) and Cl_2CHOCH_3 (0.51 mL, 5.68 mmol). After 5 min, the reaction mixture was slowly warmed to room temperature and mentained at this temperature for 2 h. The reaction was then quenched with 1N HCl (10 mL). The mixture was extracted with CH_2Cl_2 (3x 50 mL) and the combined organic phase was washed with brine, water, dried (Na_2SO_4) and concentrated in v*acuo* to give the crude aldehyde. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.46 (s, 2H), 3.86 (s, 6H), 3.79 (s, 6H), 3.60 (s, 6H), 2.61 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 160.0, 156.6, 148.2, 136.2, 124.2, 120.0, 63.6, 60.8, 60.5, 13.0.

The material from the previous step was dissolved in a mixture of CH_2Cl_2 (6 mL) and CH_3CN (6 mL). To this vigorously stirred solution was added 2,3-dimethyl-2-butene (0.5 mL) and an aqueous solution (9 mL) containing NaH_2PO_4 (1.96 g, 14.2 mmol), $NaClO_2$ (511 mg, 5.68 mmol), and H_2O_2 (0.644 mL, 30% in H_2O, 5.68 mmol). After 3 h, the reaction mixture was extracted with EtOAc (3x50 mL) and the combined organic phase was washed with brine, water, dried (Na_2SO_4) and concentrated in *vacuo* to give the crude carboxylic acid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (br. 2H), 3.80 (s, 6H), 3.79 (s, 6H), 3.56 (s, 6H), 2.47 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ172.0, 153.3, 152.1, 147.8, 131.6, 123.4, 120.4, 62.3, 60.6, 60.3, 13.4.

The crude carboxylic acid was azeotroped with toluene (2x10 mL) and then re-dissolved in PhMe (15 mL) and MeOH (5 mL). $TMSCHN_2$ (2.0 mL, 2M in hexane, 4.00 mmol) was then added to the mixture at 0 ^oC. After stirrring for 1 h, the reaction was quenched with acetic acid (1 mL) and concentrated in *vacuo*. The residue was purified by FCC to give the biphenyl di-ester **4.26** (630 mg, 1.32 mmol). Recrystallization of this material from CH_2Cl_2 afforded white prisms (570 mg, 90%). Mp: 133-135 ^oC R_f = 0.50 (30% EtOAc in petroleum ether). IR (thin film) cm^{-1}: 2948, 1732, 1461, 1399, 1273, 1213, 1094, 1058. ^1H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 6H), 3.79 (s, 6H), 3.74 (s, 6H), 3.51 (s, 6H), 2.28 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 168.7, 152.9, 151.8, 130.4, 124.8, 120.7, 62.0, 60.6, 60.4, 52.5, 13.2. HRMS (*m/z*) calculated for $C_{24}H_{30}O_{10}Na$ (ESI, M + Na+) 501.1737, found 501.1739.

Dimethyl 2,2'-dihydroxy-5,5',6,6'-tetramethoxy-4,4'-dimethyl-[1,1'-biphenyl]-3,3'-dicarboxylate (4.27)

To a solution of **4.26** (1.326 g, 2.77 mmol) in dry CH_2Cl_2 (15 mL) was added BCl_3 (8.32 mL, 1 M in hexane, 8.32 mmol) at −78 ^oC. After the complete disappearance of starting material, the reaction was quenched with saturated aqueous $NaHCO_3$. The reaction mixture was diluted with extracted with EtOAc (3 x 50 mL). The combined organic phase was dried (Na_2SO_4), concentrated in *vacuo* and purified by FCC to afford **4.27 (**1.06 g, 85%) as a foaming solid. R_f = 0.40 (15% EtOAc in petroleum ether). ^1H NMR (500 MHz, $CDCl_3$) δ 11.50 (s, 2H), 3.95 (s, 6H), 3.80 (s, 6H), 3.76 (s, 6H), 2.53 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 158.0, 157.3, 144.6, 134.8, 114.3, 108.4, 60.7 (2C), 52.3, 15.1.

Dimethyl 5,5',6,6'-tetramethoxy-2,2'-bis(methoxymethoxy)-4,4'-dimethyl-[1,1'-biphenyl]-3,3'-dicarboxylate (4.3)

To a solution of bis-phenol **4.27** (1.06g, 2.41 mmol) in dry CH_2Cl_2 (15 mL) was added DIPEA (4.2 mL, 24.1 mmol) and MOMCl (1.83 mL, 24.1 mmol) at 0 ^oC. After 10 min the reaction mixture was warmed to room temperature and stirred at this temperature for 4 h. The reaction mixture was then diluted with H_2O (10 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with H_2O and brine, dried (Na_2SO_4), concentrated in *vacuo* and purified by FCC to afford **4.3** (1.17 g, 90%) as a white prism solid. R_f=0.20 (15% EtOAc in petroleum ether). IR (thin film) cm^{-1}: 2949, 1732, 1454, 1393, 1354, 1301, 1272, 1212, 1162, 1057, 1006, 930, 738. ^1H NMR (500 MHz, $CDCl_3$) δ 4.78 (d, J = 6.0 Hz, 2H), 4.74 (d, J= 6.0 Hz, 2H), 3.88 (s, 6H), 3.78 (s, 6H), 3.76 (s, 6H), 3.07 (s, 6H), 2.26 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 153.0, 148.9, 148.0, 130.4, 125.5, 121.6, 100.3, 60.4, 60.3, 56.7, 52.5, 13.3. HRMS (*m/z*) calculated for $C_{26}H_{34}O_{12}Na$ (ESI, M + Na^+) 561.1948, found 561.1945.

Dimethyl 5,5',6,6'-tetramethoxy-2,2'-bis(methoxymethoxy)-4,4'-bis((phenylsulfinyl)-methyl)-[1,1'-biphenyl]-3,3'-dicarboxylate (4.4)

To a solution of **4.3** (345 mg, 0.641 mmol) in CCl_4 (9 mL) was added NBS (136mg, 0.768 mmol), $(PhCOO)_2$ (16 mg, 0.066 mmol), NaOAc (100 mg, 1.22 mmol). After heating at reflux for 30 min, additional portions of NBS (136 mg, 0.768 mmol) and $(PhCOO)_2$ (16 mg, 0.066 mmol) were added. Heat was continued for an additional 30 min, at which time the reaction was cooled to room temperature and quenched with 10%

Na_2SO_3 (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the organic phase dried (Na_2SO_4), concentrated in *vacuo* and purified by FCC to afford the dibromo dervative (440 mg, 98%). R_f=0.25 (15% EtOAc in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (d, J = 6.0 Hz, 2H), 4.77 (d, J= 6.0 Hz, 2H), 4.67 (d, J= 9.7 Hz, 2H), 4.63 (d, J= 9.7 Hz, 2H), 3.96 (s, 6H), 3.95 (s, 6H), 3.83 (s, 6H), 3.00 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 153.2, 149.9, 148.0, 130.9, 124.8, 124.7, 100.8, 60.8, 60.3, 56.7, 52.8, 24.0.

To a solution of product from the previous step (440 mg, 0.632 mmol) in MeOH (6 mL) was added PhSH (0.322 mL, 3.16 mmol) and K_2CO_3 (872 mg, 6.32 mmol). The reaction was stirred for 16 h, then diluted with water and extracted with EtOAc (3 x 15 mL). The organic phase was dried (Na_2SO_4), concentrated in *vacuo* and purified by FCC to afford the derived bis-phenylthio ether (340 mg, 70%) as a white semi-solid. R_f = 0.35 (30% EtOAc in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 8.0 Hz, 4H), 7.27 (m, 4H), 7.20 (t, J = 7.4 hz, 2H), 4.76 (d, J = 6.0 Hz, 2H), 4.73 (d, J= 6.0 Hz, 2H), 4.37 (d, J= 12.2 Hz, 2H), 4.28 (d, J= 12.2 Hz, 2H), 3.83 (s, 6H), 3.76 (s, 6H), 3.70 (s, 6H), 2.99 (s, 6H). ^{13}C NMR (125 M Hz, $CDCl_3$) δ 167.7, 153.1, 149.8, 148.2, 136.3, 131.0, 130.9, 129.0, 126.9, 124.7, 123.5, 100.5, 61.1, 60.2, 56.8, 52.6, 30.8. HRMS (*m/z*) calculated for $C_{38}H_{42}O_{12}NaS_2$ (ESI, M + Na^+) 777.2015, found 777.2011.

To a solution of the bis-phenylthio ether (340 mg, 0.450 mmol) in CH_2Cl_2 (6 mL) at -78 ^{o}C was added NaOAc (147 mg, 3.60 mmol) and mCPBA (309 mg, 1.80 mmol). After TLC showed less than 5% starting material, the mixture was quenched with 2M Na_2SO_3 (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phase was dried (Na_2SO_4), concentrated in *vacuo* and purified by FCC to afford an approximately 1:1

ration of bis-sulfoxide **4.4** (145 mg, 41%, mixture of three diatereomers) and mixed sulfoxide-sulfone **4.4b** (147 mg, 41%, mixture of two diastereomers). For **4.4:** R_f = 0.10 (80% EtOAc in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.53 (m, 2H), 7.46 (m, 8H), 4.76-4.70 (m, 4H), 4.52-4.48 (m, 2H), 4.27-4.23 (m, 2H), 3.85-3.83 (4 singlet, 6H), 3.75-3.74 (4 singlet, 6H), 3.67-3.64 (4 singlet, 6H), 3.09-3.07 (4 singlet, 6H). ^{13}C NMR (125 M Hz, $CDCl_3$) δ 167.5 (2 signals), 167.4 (2 signals), 153.3, 153.2 (2 signals), 153.1, 150.1 (2 signals), 150.0 (2 signals), 148.8 (2 signals), 148.6 (2 signals), 143.8 (4 signals), 131.2 (4 signals), 129.1 (4 signals), 125.0, 124.7, 124.5, 124.4, 124.3 (many aromatic signals overlapped), 100.6 (2 signals), 100.5 (2 signals), 60.8 (4 signals), 60.1 (4 signals), 56.9 (4 signals), 56.2 (4 signals), 52.6 (4 signals). HRMS (*m/z*) calculated for $C_{38}H_{43}O_{14}S_2$ (ESI, M + H^+) 786.2016, found 786.2016. For **4.4b**: R_f = 0.15 (80% EtOAc in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83-7.81 (m, 2H), 7.62-7.47 (m, 8H), 4.93-4.85 (m, 2H), 4.82-4.73 (m, 4H), 4.54-4.51 (m, 1H), 4.29-4.26 (m, 1H), 3.93, 3.92 (2 singlet, 3H), 3.88, 3.86 (2 singlet, 3H), 3.77, 3.76 (2 singlet, 3H), 3.75 (2 singlet, 3H), 3.68, 3.66 (2 singlet, 3H), 3.59, 3.58 (2 singlet, 3H), 3.12, 3.11, 3.09 (4 singlet, 6H). ^{13}C NMR (125 M Hz, $CDCl_3$) δ 167.5 (2 signals), 167.4 (2 signals), 153.3, 153.2 (2 signals), 153.1, 150.5, 150.3, 149.1, 148.8, 148.7, 143.9, 139.5, 133.8, 131.3, 129.2, 129.1, 128.6, 125.6, 125.4, 125.0, 124.8, 124.7, 124.6, 124.5, 124.4, 121.7, 121.6, 100.8 (2 signals), 100.7 (2 signals), 60.9 (2 signals), 60.7 (2 signals), 60.6, 60.2 (2 signals), 60.0 (2 signals), 57.0 (3 signals), 56.3 (2 signals), 53.2, 52.9, 52.8, 52.7. HRMS (*m/z*) calculated for $C_{38}H_{43}O_{15}S_2$ (ESI, M + H^+) 803.2038, found 803.2030.

Dimethyl 5,5',6,6'-tetramethoxy-2,2'-bis(methoxymethoxy)-4,4'-bis((phenylsulfonyl)-methyl)-[1,1'-biphenyl]-3,3'-dicarboxylate (4.4c)

To a solution of **4.4**/**4.4b** (100 mg, 0.127 mmol) in CH_2Cl_2 (2 mL) at 0 ^oC was added mCPBA (87 mg, 0.508 mmol) and NaOAc (87 mg, 1.06 mmol). After TLC showed less than 5% starting material, the reaction was quenched with 2M Na_2SO_3 (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phase was dried (Na_2SO_4), concentrated in *vacuo* and purified by FCC to afford **4.4c** (100 mg, 96%) as a white solid. R_f = 0.33 (30% EtOAc in petroleum ether). ^1H NMR (500 MHZ, $CDCl_3$) δ 7.81 (d, J=7.6 Hz, 4H), 7.61 (t, J = 7.6 Hz, 2H), 7.50 (t, J = 7.6 hz, 4H), 4.90 (d, J = 13.3 Hz, 2H), 4.86 (d, J= 13.3 Hz, 2H), 4.80 (d, J= 6.0 Hz, 2H), 4.77 (d, J= 6.0 Hz, 2H), 3.91 (s, 6H), 3.73 (s, 6H), 3.56 (s, 6H), 3.11 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 153.0, 150.5, 149.1, 139.4, 133.8, 129.1, 128.6, 125.5, 125.3, 121.7, 100.8, 60.6, 60.0, 57.0, 52.9, 23.4. HRMS (*m/z*) calculated for $C_{38}H_{42}O_{16}NaS_2$ (ESI, M + Na^+) 841.1819, found 841.1812.

Bi-directional Hauser annulation studies

Procedure A: To a solution of $^iPr_2NH$ (0.090 mL, 0.638 mmol) in THF (3 mL) was added n-BuLi (0.254 mL, 2.5 M in hexane, 0.638 mmol) at −78 ^oC. After 2 h a solution of **4.4** (50 mg, 0.0634 mmol) in THF (1.5 mmL) was added to the mixture, dropwise, over 1 h. The mixture was warmed to – 40 ^oC for 1 h and then re-cooled to −78 ^oC. Cyclohex-2-enone (19 mg, 0.198 mmol) in THF (1.5 mL) was added dropwise at −78 ^oC, over 1 h, to the resulting dark yellow solution. The reaction was mentained for an additional 2 h at this temperature, and then warmed to room temperature. Stirring was continued at room temperature for 8 h, at which point the reaction was quenched with

saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc (3 x 20 mL) and the organic phase was dried (Na_2SO_4) and concentrated in *vacuo*. TLC of the residue showed a homogeneous material, which after FCC and NMR analysis was identified as the starting material **4.4**.

In another experiment, procedure A was repeated using THF/HMPA (10: 1) as the reaction solvent. Similar results were obtained in both experiments.

Procedure B: To a solution of ^tBuOH (47 mg, 0.635 mmol) in THF (3 mL) was added nBuLi (0.254 mL, 2.5 M in hexane, 0.638 mmol) at -60 ^oC. After 2 h, a solution of **4.3** (50 mg, 0.0634 mmol) in THF (1.5 mmL) was added dropwise, over 1 h to the mixture. The solution was stirred at -60 ^oC for 4 h, at which time cyclohex-2-enone (19 mg, 0.198 mmol) in THF (1.5 mL) was added dropwise, over 1 h, to the resulting dark yellow solution. After stirring at this temperature for an additional 2 h, the mixture was warmed to room temperature. Stirring was continued at room temperature for 8 h. The reaction was then quenched with saturated aqueous NH_4Cl solution and the mixture extracted with EtOAc (3 x 20 mL). The combined organic phase was dried (Na_2SO_4) and concentrated in *vacuo*. TLC of the crude residue indicated a homogeneous material, which after FCC and NMR analysis was identified as unreacted **4.3**.

In another experiment, procedure B was repeated using THF/DMSO (3: 1) as the reaction solvent. Similar results were obtained in both experiments.

Michael-Dieckmann condensation studies

9-Hydroxy-5,6,8-trimethoxy-3,4,4a,10-tetrahydroanthracen-1(2*H*)-one (4.29)

To a solution of $^{i}Pr_2NH$ (0.090 mL, 0.638 mmol) in THF (3 mL) was added n-BuLi (0.254 mL, 2.5 M in hexane, 0.638 mmol) at −78 ^{o}C. After 2 h a solution of **4.28** (50 mg, 0.210 mmol) in THF (1.5 mmL) was added to the mixture, dropwise, over 1 h. After stirring at -78 ^{o}C for an additional 4 h a dark-red solution was obtained. To this solution was added cyclohex-2-enone (24 mg, 0.25 mmol) in THF (1.5 mL) dropwise, over 1 h. After stirring an additional 2 h at -78 ^{o}C, the mixture was warmed to room temperature and mentained at this temperature for 8h. The reaction was then quenched with saturated aqueous NH_4Cl and the mixture extracted with EtOAc (3 x 20 mL). The organic phase was dried (Na_2SO_4), concentrated in *vacuo* and purified by FCC to afford **4.29** (42 mg, 65%). R_f = 0.50 (30% EtOAc in petroleum ether). ^{1}H NMR (500 MHZ, $CDCl_3$) δ 6.43 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.73 (s, 3H), 3.23 (dd, J = 15.3, 4.2 Hz, 1H), 2.53 (m, 1H), 2.41 (m, 2H), 2.14 (t, J = 14.4 Hz, 1H), 2.04 (m, 1H), 1.93 (m, 1H), 1.63 (m, 1H), 1.34 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.2, 181.6, 158.3, 157.1, 138.8, 138.0, 114.1, 109.0, 95.3, 61.0, 56.6, 55.9, 32.8, 31.4, 30.4, 30.1, 21.2.

9,9'-Dihydroxy-3,3',4,4'-tetramethoxy-1,1'-bis(methoxymethoxy)-6,6',7,7',10,10a,10', 10'a-octahydro-[2,2'-bianthracene]-8,8'(5*H*,5'*H*)-dione (4.31)

To a solution of $^{i}Pr_2NH$ (0.785 mL, 5.57 mmol) in THF (55 mL) was added n-BuLi (2.23 mL, 2.5 M in hexane, 5.57 mmol) at −78 ^{o}C. After 2 h a solution of **4.3** (300 mg, 0.557 mmol) in THF (25 mmL) was added to the LDA solution, dropwise over 2 h. The

resulting red solution was warmed to – 40 ^{o}C and kept at this temperature for 2 h, during which time the color became dark red. The soltuion was then re-cooled to −78 ^{o}C and cyclohex-2-enone (160 mg, 1.67 mmol) in THF (25 mL) was added dropwise, over 1 h. After stirring an additional 2 h at -78 ^{o}C, the reaction was warmed to room temperature, mentained at this temperature for 8 h, and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (3 x 100 mL), and the organic phase dried (Na_2SO_4 concentrated in *vacuo* and purified by FCC to afford **4.31** (150 mg, 40%) as a white gum. R_f = 0.51 (30% EtOAc in petroleum ether). IR (thin film) cm^{-1}: 2983, 1600, 1568, 1323, 1156, 1033, 1020. ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.52 (4 singlet, 2H), 4.98-4.84 (4 doublet, 4H), 3.89-3.80 (8 singlet, 12H), 3.30 (m, 2H), 2.90 (4 singlet, 6H), 2.59-2.44 (m, 6H), 2.25-2.19 (m, 4H), 2.09 (m, 2H), 1.95 (m, 2H), 1.68 (m, 2H), 1.39 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (major component): 188.5, 184.2, 155.9, 153.1, 145.2, 137.6, 123.2, 120.6, 109.1, 100.8, 60.6, 56.3, 33.0, 31.8, 30.430.2, 21.1. HRMS (*m/z*) calculated for $C_{36}H_{42}O_{12}Na$ (ESI, M + Na^+) 689.2574, found 689.2568.

Aromatization studies

9-hydroxy-5,6,8-trimethoxy-3,4-dihydroanthracen-1(2*H*)-one (4.30).

DDQ (60 mg, 0.262 mmol) was slowly added to a solution of **4.29** (40 mg, 0.131 mmol) in dry PhH (13 mL) under nitrogen. After 2 h, the reaction was quenched with $NaHSO_3$ solution (5 mL, 2 M) and the mixture extracted with EtOAc (3 x 20 mL). The organic phase was dried (Na_2SO_4), concentrated in *vacuo* and purified by FCC to afford **4.30** (34 mg, 85%) as a yellow solid. R_f = 0.40 (30% EtOAc in petroleum ether). IR (thin film) cm^{-1}: 2940, 1625, 1597, 1461, 1388, 1345, 1311, 1114. ^{1}H NMR (500 MHZ, $CDCl_3$) δ 16.00 (s, 1H), 7.23 (t, J = 1.1 Hz, 1H), 6.56 (s, 1H), 4.02 (s, 6H), 3.87 (s,

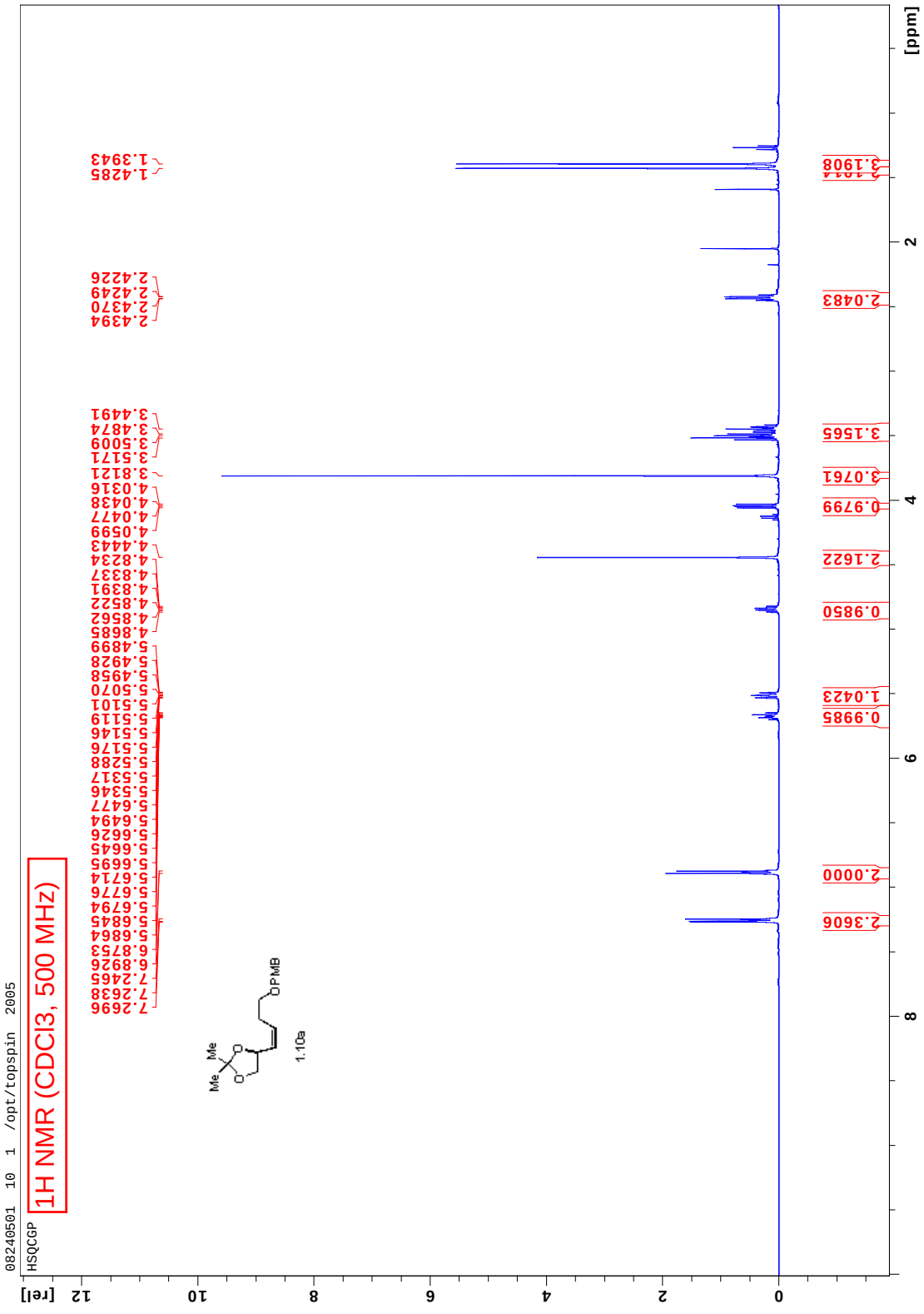
3H), 3.00 (t, J = 6.3 Hz, , 2H), 2.74 (t, J = 6.3 Hz, 2H), 2.10 (quin., J = 6.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 166.7, 157.8, 153.1, 139.7, 135.9, 134.8, 110.7, 110.1, 109.4, 94.5, 61.2, 56.8, 56.5, 39.0, 30.7, 23.0. HRMS (*m/z*) calculated for $C_{17}H_{18}O_5Na$ (ESI, M + Na^+) 325.1052, found 325.1032.

Attempted aromatization of 4.31 to 4.8

DDQ (113 mg, 0.500 mmol) was slowly added to a solution of **4.31** (67 mg, 0.100 mmol) in dry PhH (15 mL) under nitrogen. After 2 h, the reaction was quenched with $NaHSO_3$ solution (5 mL, 2 M), extracted with EtOAc (3 x 20 mL). The combined organic phase was dried (Na_2SO_4), concentrated in *vacuo* and purified by FCC to give recovered **4.31** (60 mg).

This procedure was repeated using different reaction times and temperatures. These conditions gave either recovered **4.31** and, or an intractable mixture of several products (**Table 4.2**).

APPENDIX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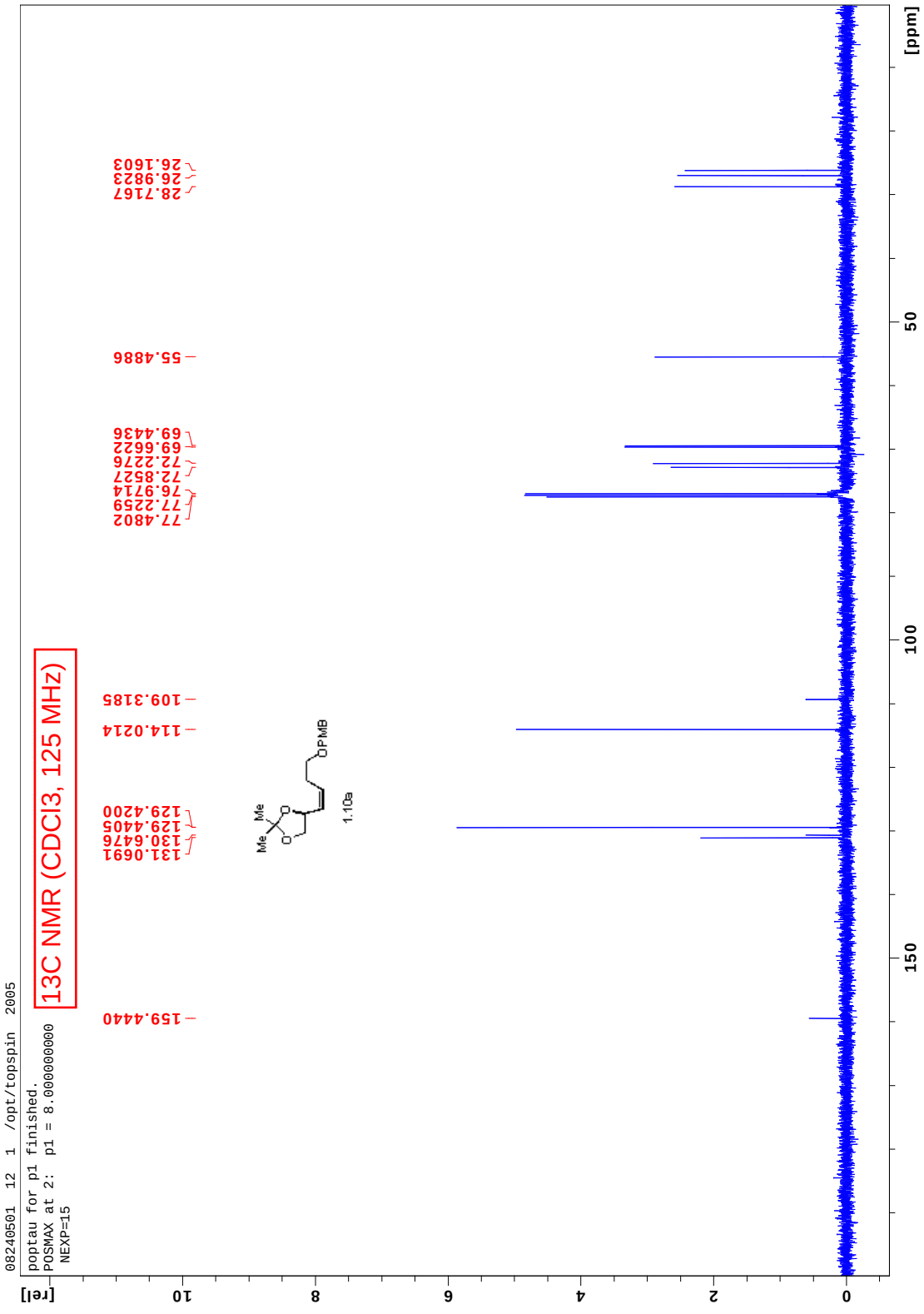
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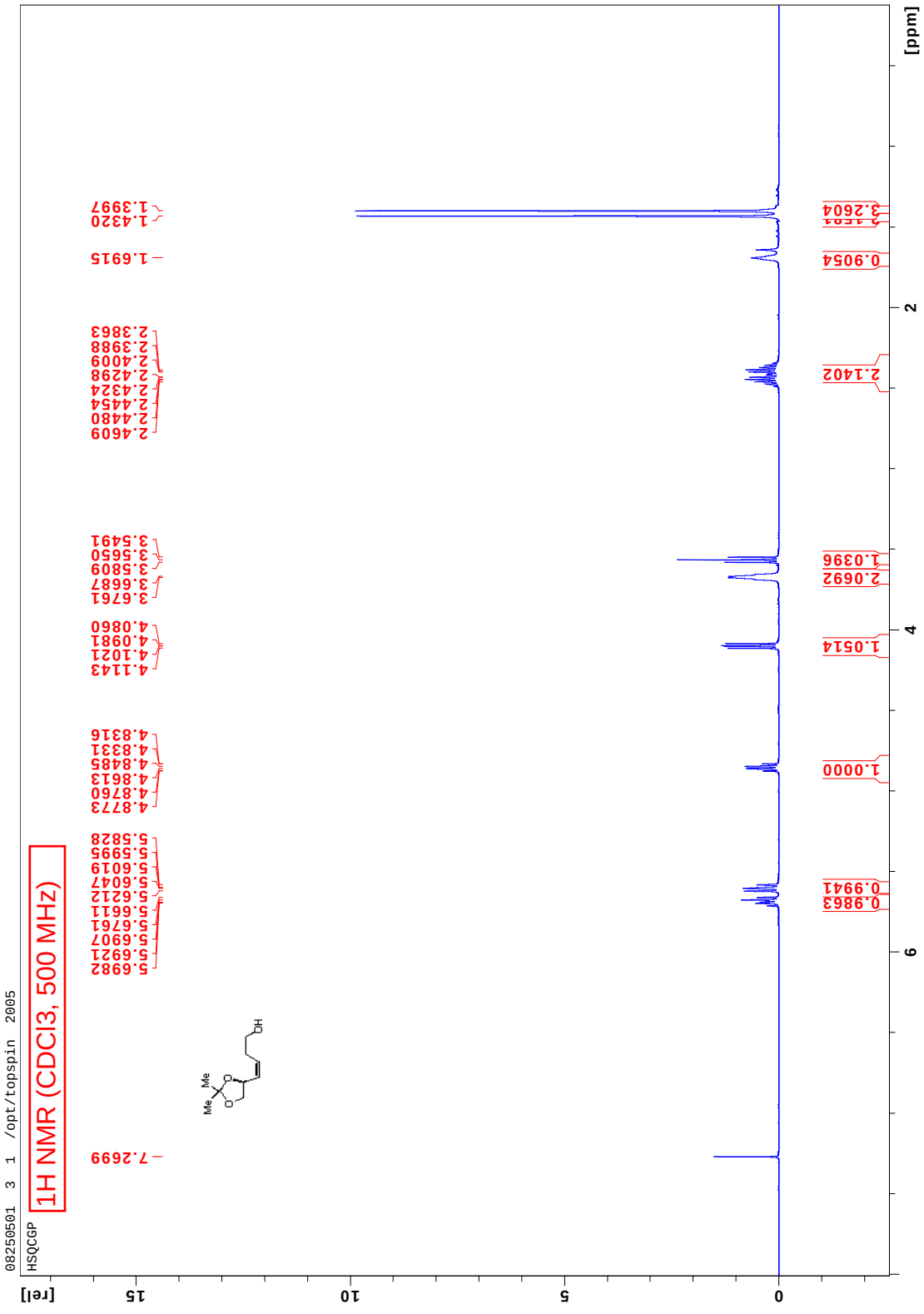
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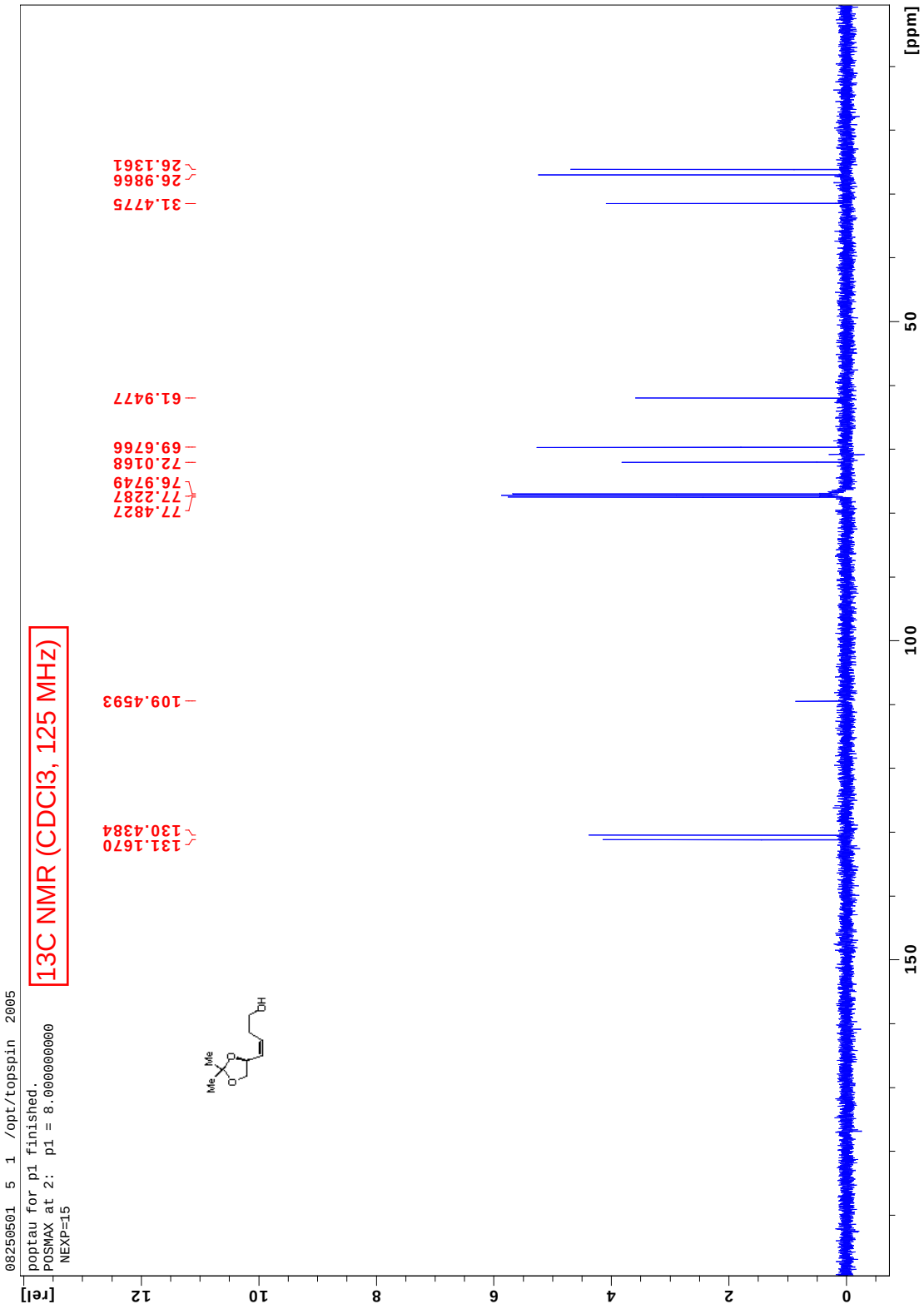
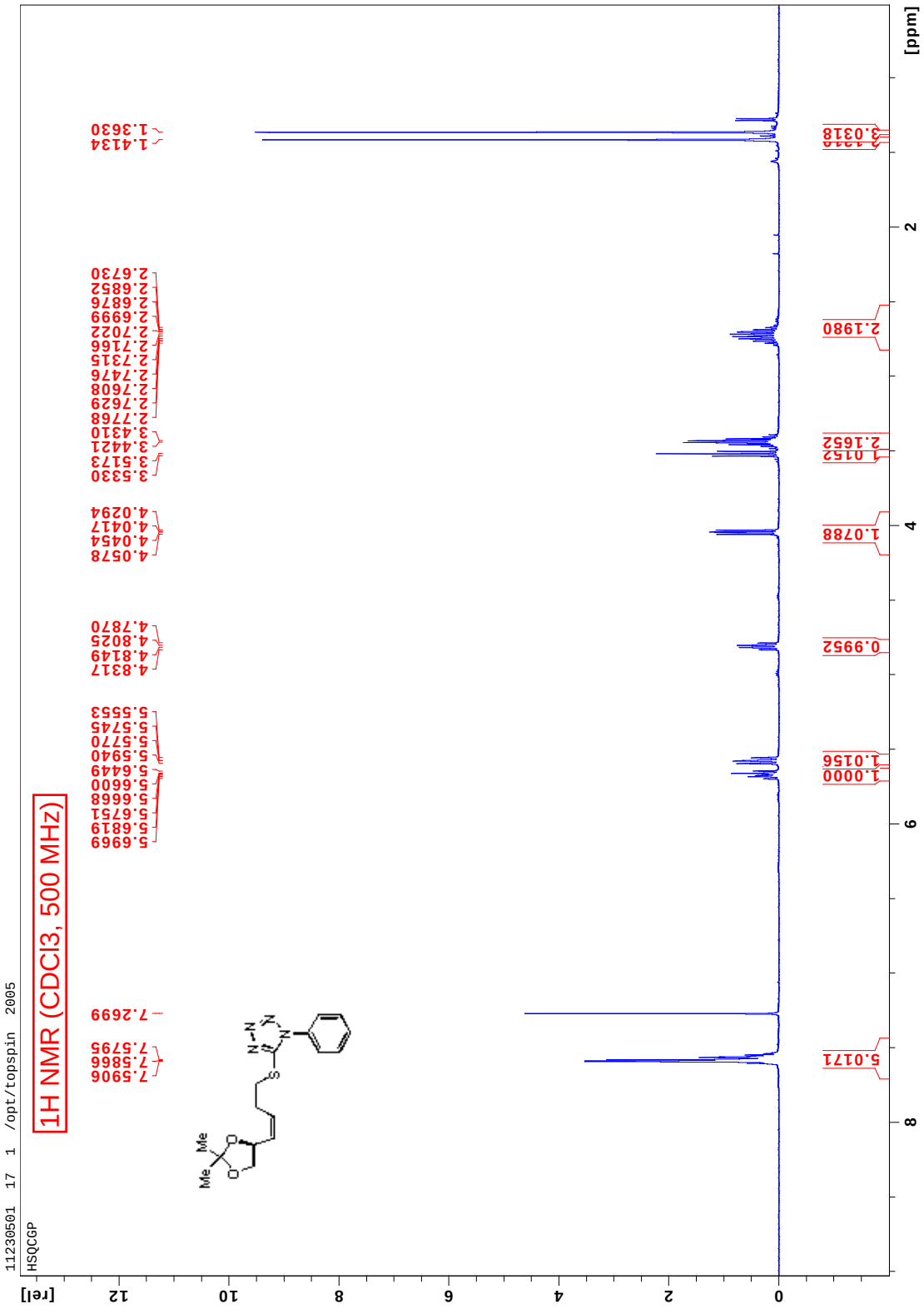
2.3863
1.6915
1.4320
1.3997
3.2604
0.9054
2.1402
1.0396
2.0692
1.0514
1.0000
0.9941
0.9863


13C NMR (CDCl3, 125 MHz)
08250501 5 1 /opt/topspin 2005
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
Me
Me
Me
OH
131.1670
130.4384
109.4593
77.4827
77.2287
76.9749
72.0168
69.6766
61.9477
31.4775
26.9866
26.1361
[rel]
0
2
4
6
8
10
12
150
100
50
[ppm]


1H NMR (CDCl3, 500 MHz)
11230501 17 1 /opt/topspin 2005
HSQCGP
[rel]
[ppm]
Me
Me
7.2699
7.5906
7.5866
7.5795
5.6969
5.6819
5.6751
5.6668
5.6600
5.6449
5.5940
5.5770
5.5745
5.5553
4.8317
4.8149
4.8025
4.7870
4.0578
4.0454
4.0417
4.0294
3.5330
3.5173
3.4421
3.4310
2.7768
2.7629
2.7608
2.7476
2.7315
2.7166
2.7022
2.6999
2.6876
2.6852
2.6730
1.4134
1.3630
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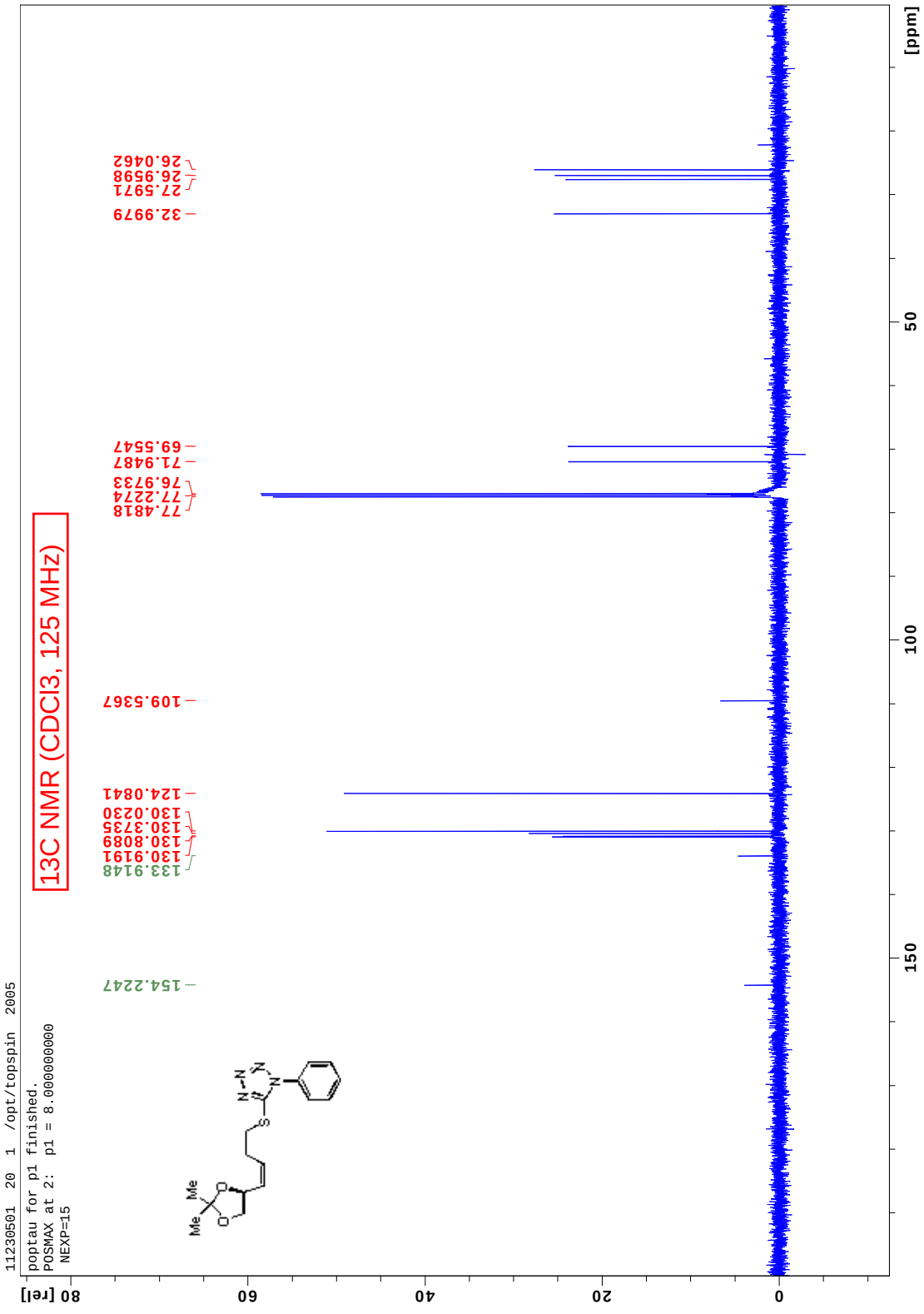
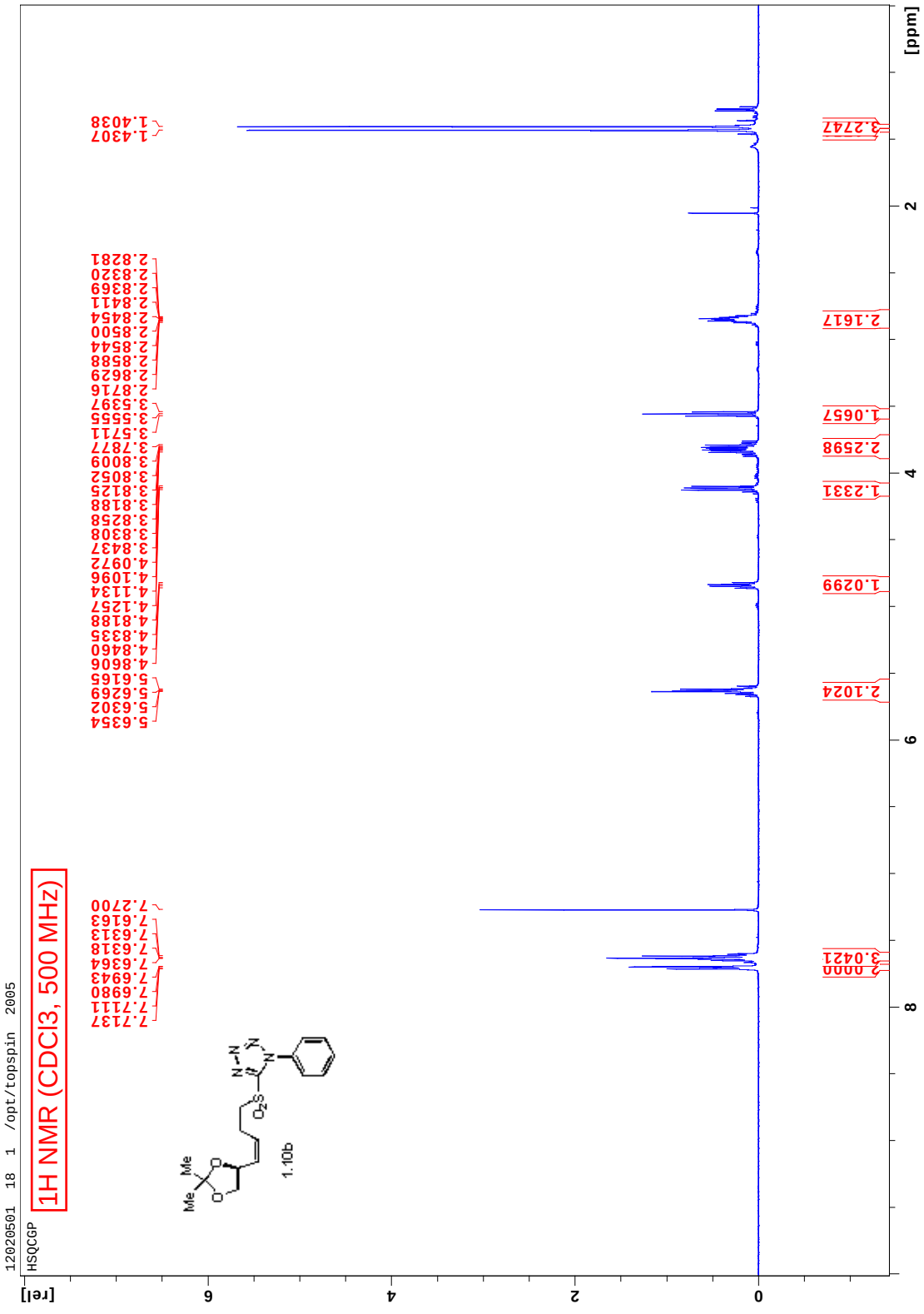
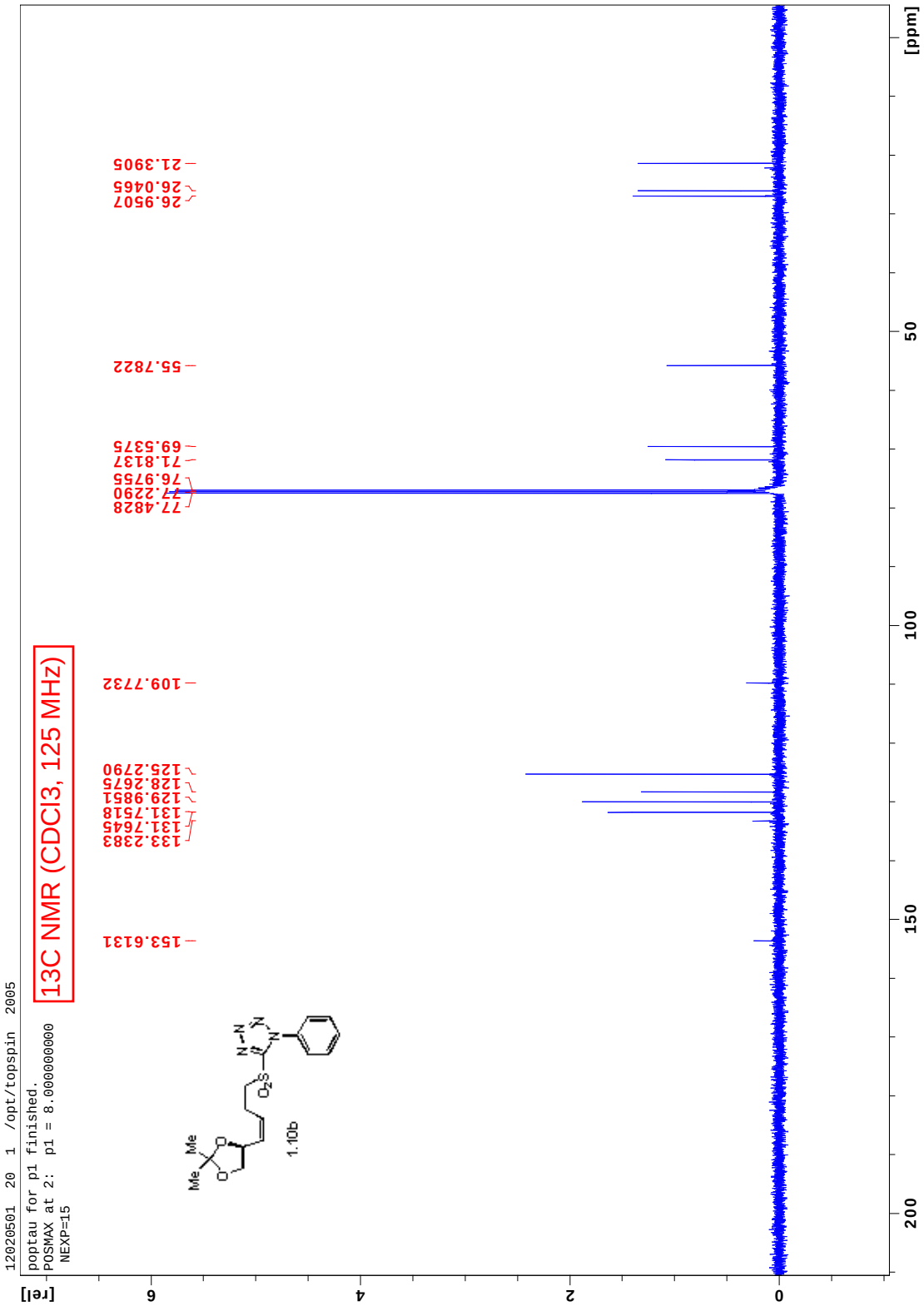
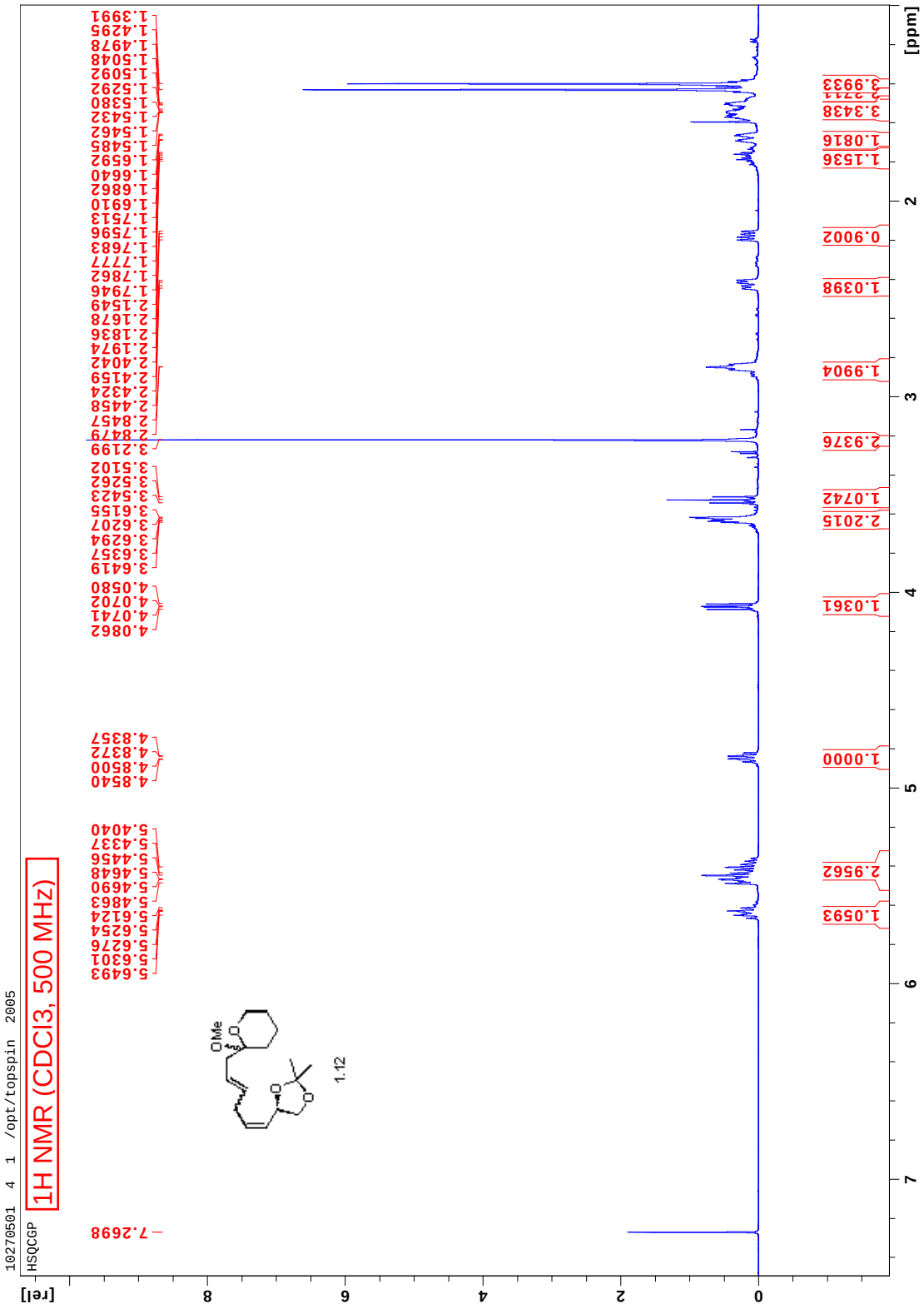
3.0318
2.1980
2.1652
1.0152
1.0788
0.9952
1.0000
1.0156


13C NMR (CDCl3, 125 MHz)
11230501 20 1 /opt/topspin 2005
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
154.2247
133.9148
130.9191
130.8089
130.3735
130.0230
124.0841
109.5367
77.4818
77.2274
76.9733
71.9487
69.5547
32.9979
27.5971
26.9598
26.0462
Me
Me
[rel]
80
60
40
20
0
150
100
50
[ppm]


1H NMR (CDCl3, 500 MHz)
HSQCGP
12020501 18 1 /opt/topspin 2005
[rel]
[ppm]
1.10b
Me
Me
O2S
3.2747
2.1617
1.0657
2.2598
1.2331
1.0299
2.1024
3.0421


13C NMR (CDCl3, 125 MHz)
12020501 20 1 /opt/topspin 2005
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
153.6131
133.2383
131.7645
131.7518
129.9851
128.2675
125.2790
109.7732
77.4828
77.2290
76.9755
71.8137
69.5375
55.7822
26.9507
26.0465
21.3905
1.10b
Me
Me
Me
[rel]
[ppm]


10270501 4 1 /opt/topspin 2005
HSQCGP
1H NMR (CDCl3, 500 MHz)
OMe
1.12
[rel]
[ppm]
7.2698
5.6493
5.6301
5.6276
5.6254
5.6124
5.4863
5.4690
5.4648
5.4456
5.4337
5.4040
4.8540
4.8500
4.8372
4.8357
4.0862
4.0741
4.0702
4.0580
3.6419
3.6357
3.6294
3.6207
3.6155
3.5423
3.5262
3.5102
3.2199
2.8479
2.8457
2.4458
2.4324
2.4159
2.4042
2.1974
2.1836
2.1678
2.1549
1.9946
1.9862
1.9777
1.9683
1.9596
1.9513
1.9310
1.8862
1.8640
1.6592
1.6485
1.5462
1.5432
1.5380
1.5292
1.5092
1.5048
1.4978
1.4295
1.3991
3.9933
3.3438
1.0816
1.1536
0.9002
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1.9904
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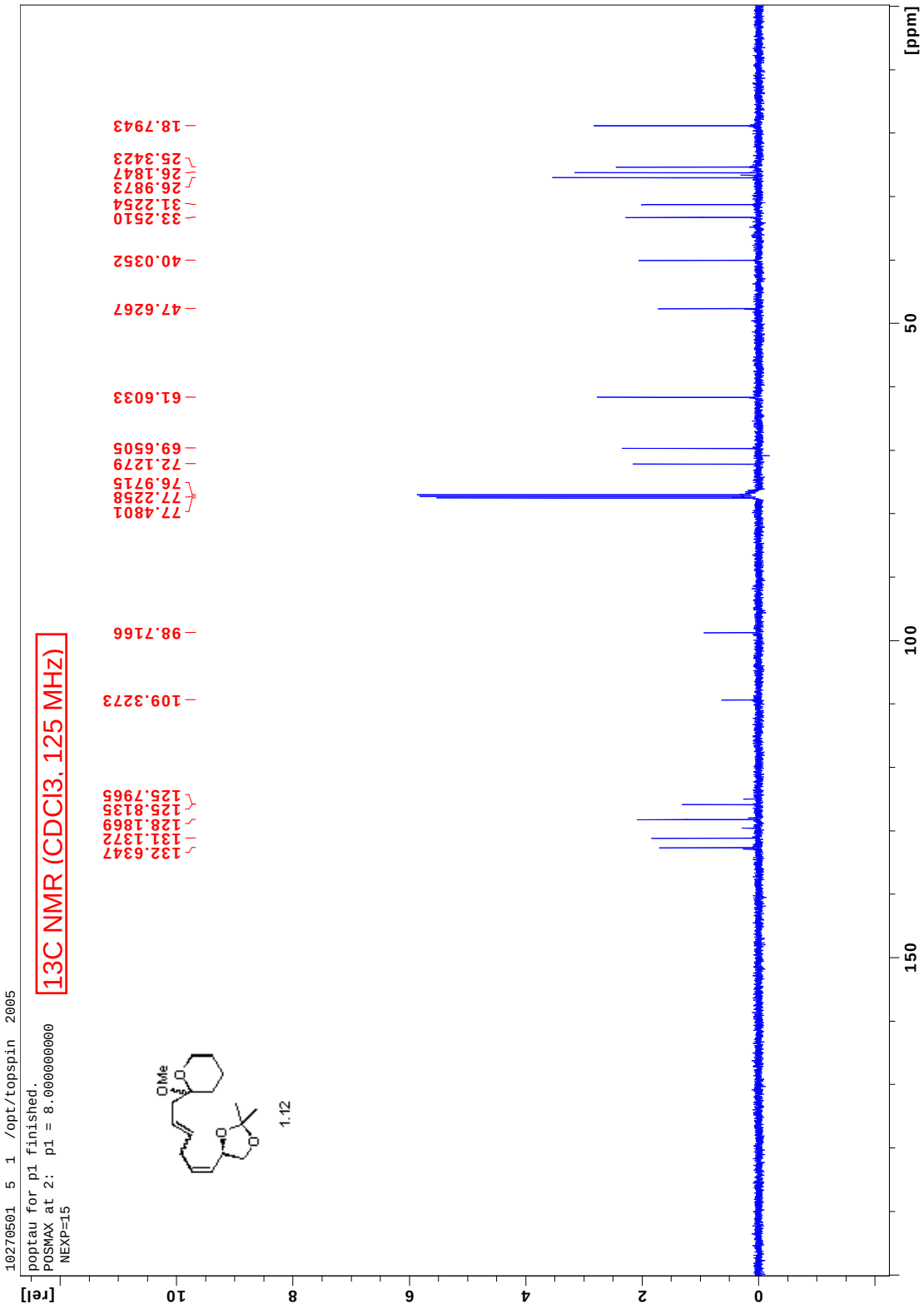
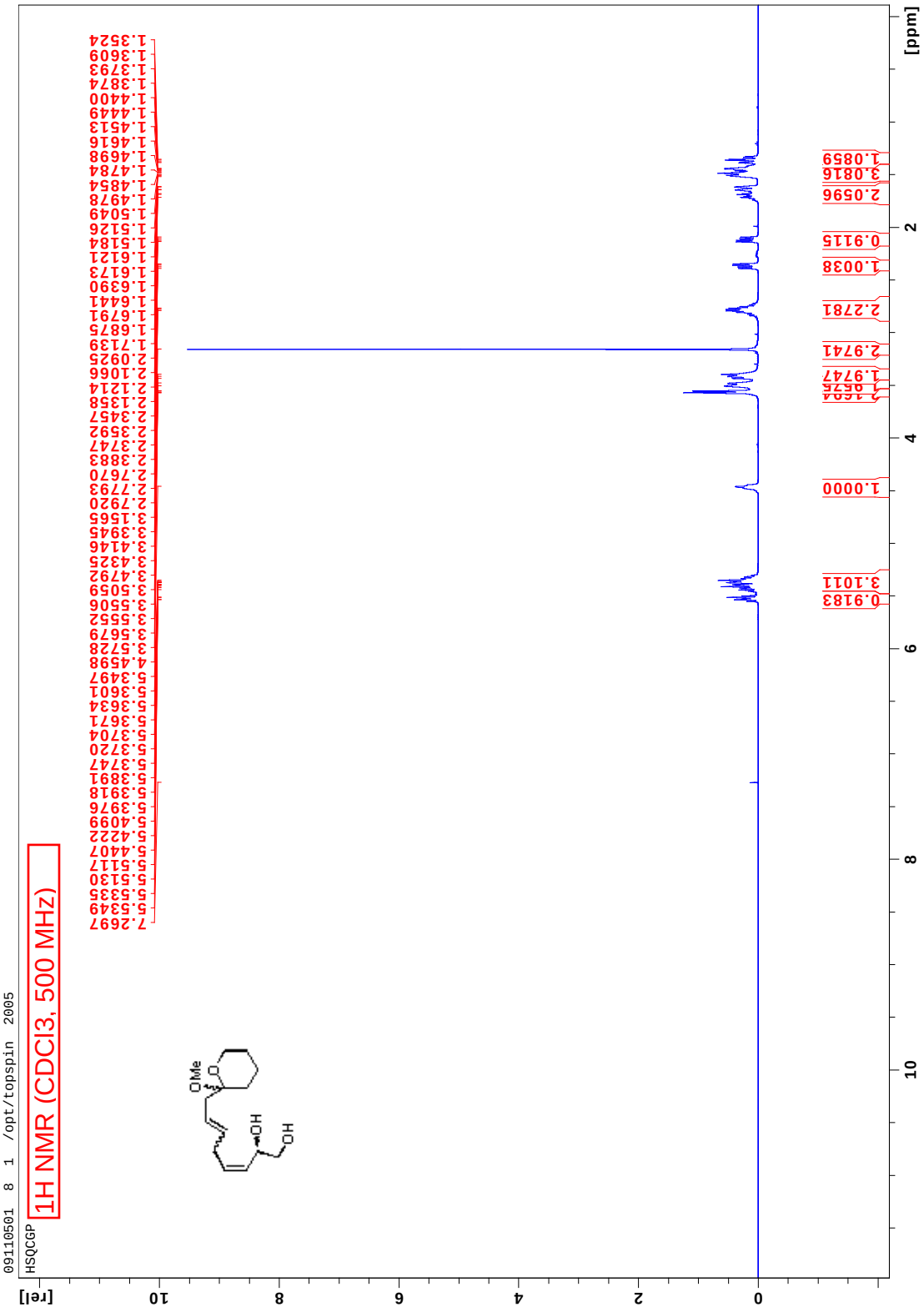
2.2015
1.0361
1.0000
2.9562
1.0593


13C NMR (CDCl3, 125 MHz)
10270501 5 1 /opt/topspin 2005
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
OMe
1.12
18.7943
25.3423
26.1847
26.9873
31.2254
33.2510
40.0352
47.6267
61.6033
69.6505
72.1279
76.9715
77.2258
77.4801
98.7166
109.3273
125.7965
125.8135
128.1869
131.1372
132.6347
[rel]
[ppm]


09110501 8 1 /opt/topspin 2005
HSQCGP
1H NMR (CDCl3, 500 MHz)
[rel]
[ppm]
OMe
OH
OH
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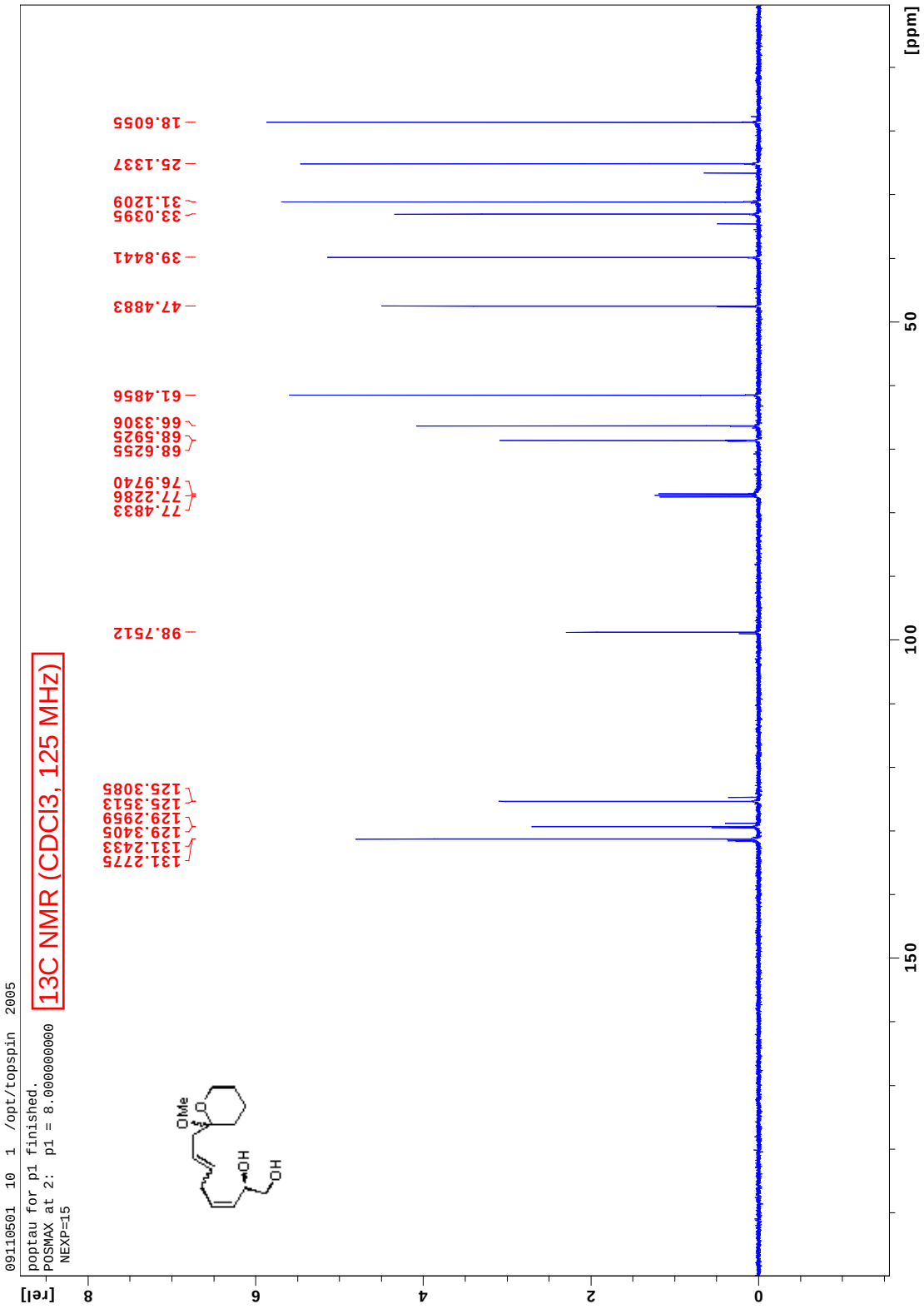
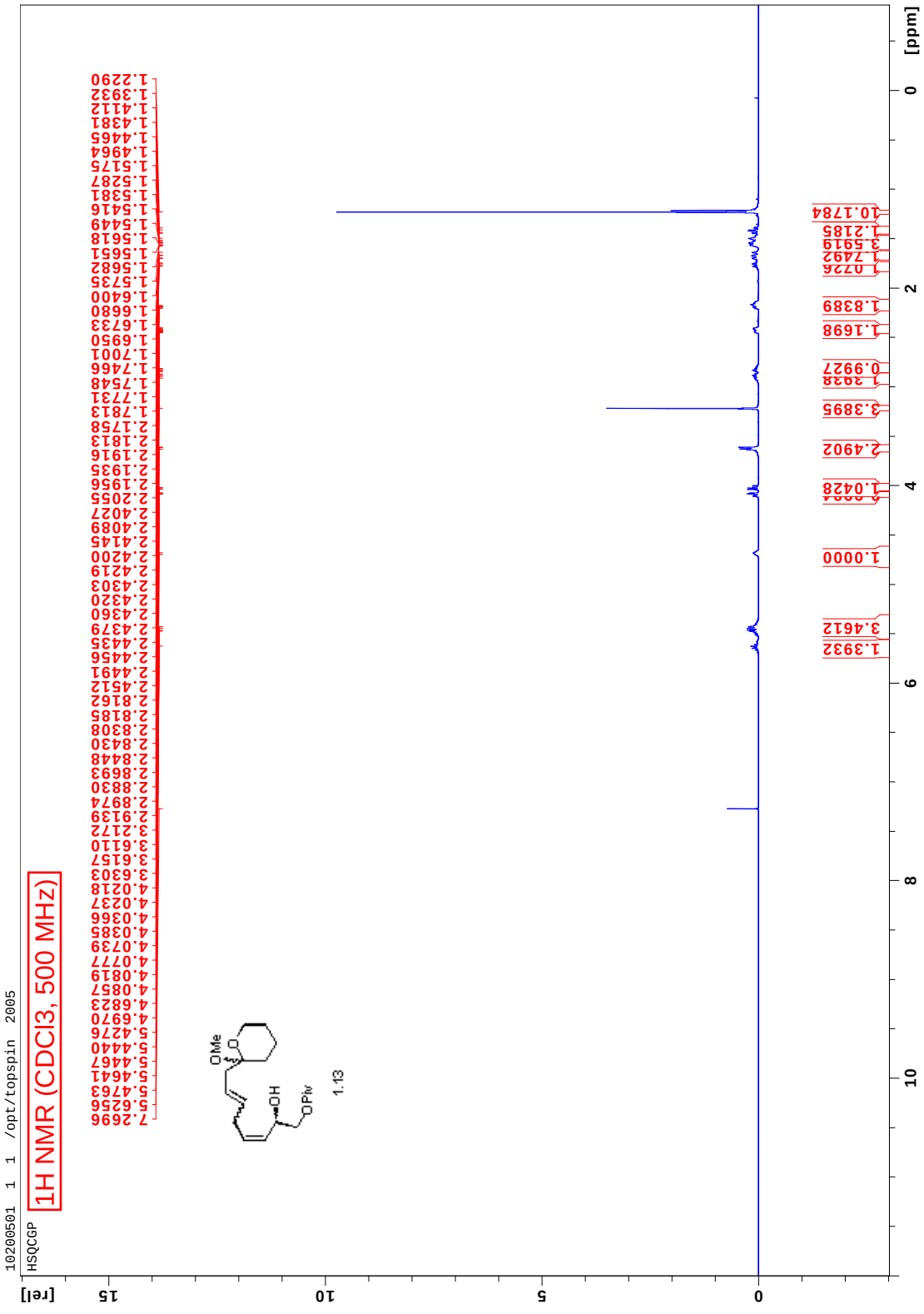
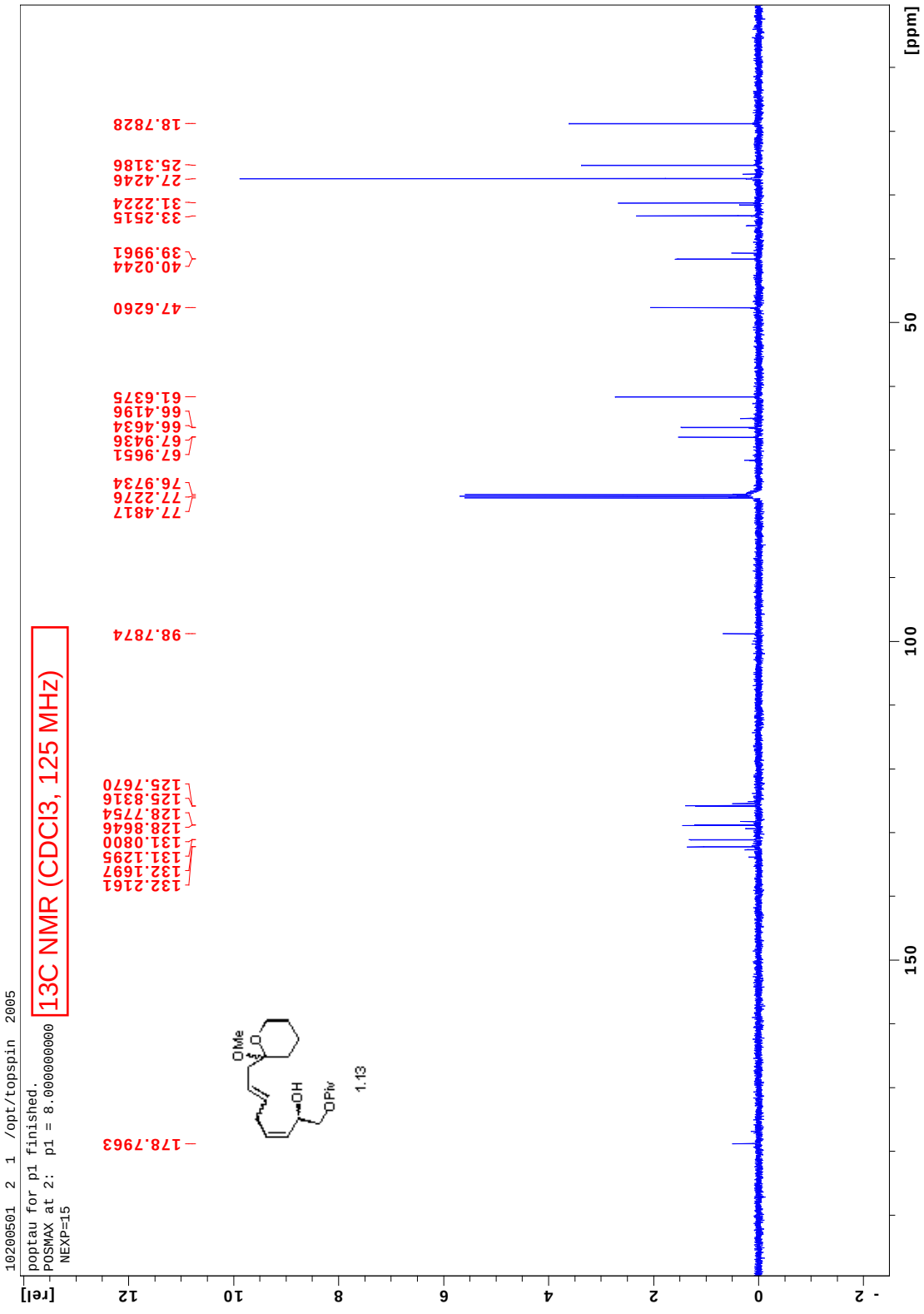
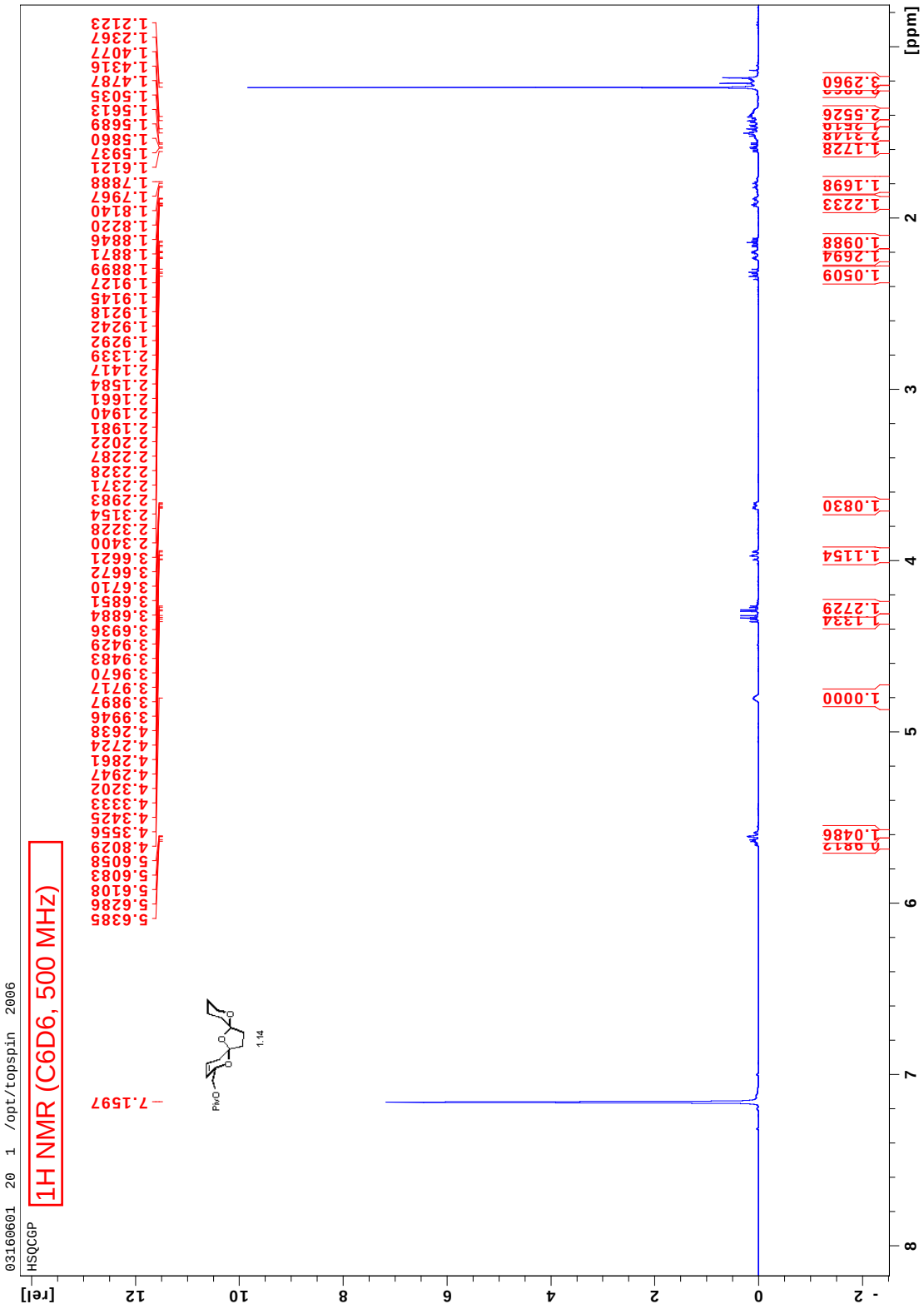
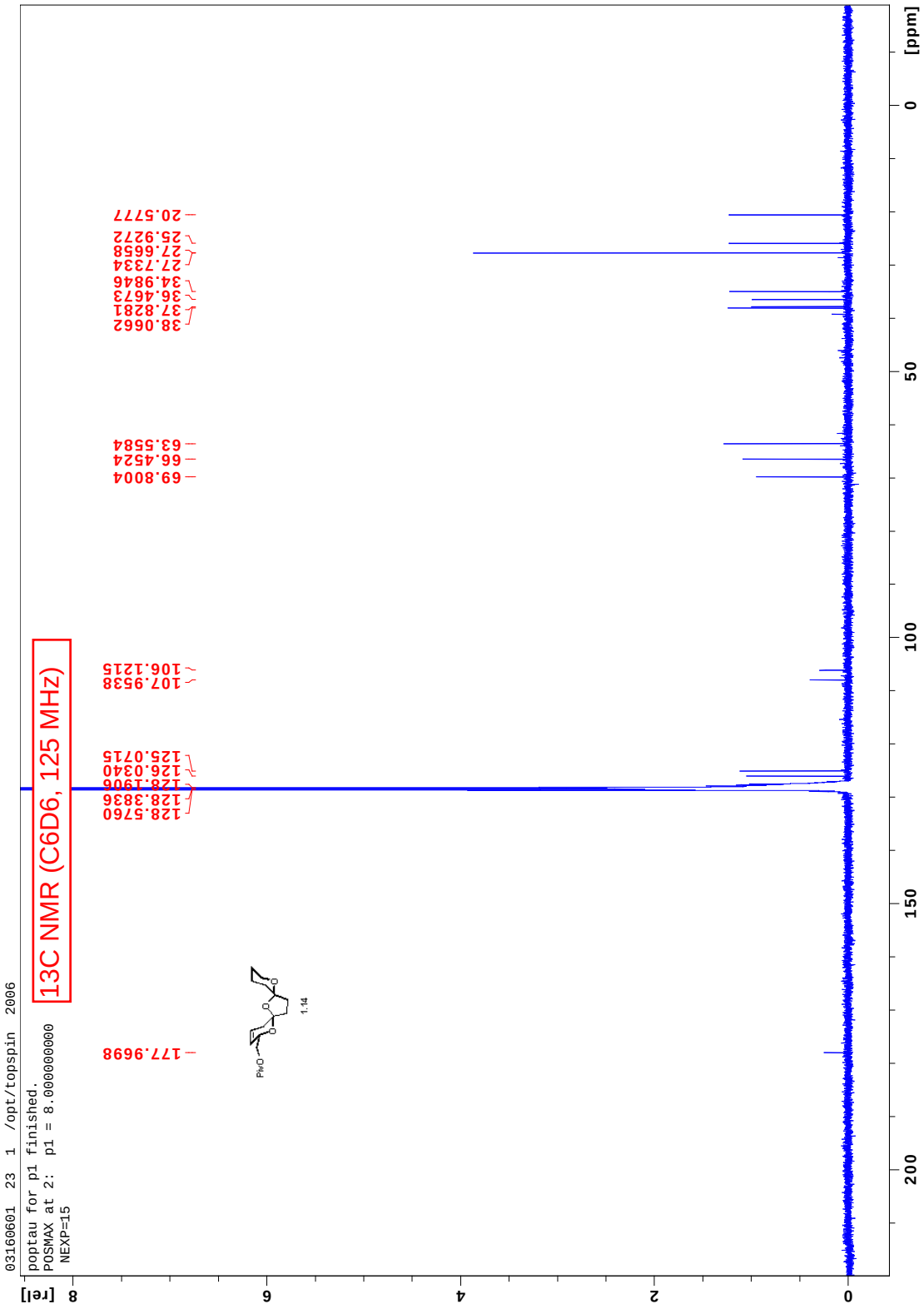
5.5349
5.5335
5.5130
5.5117
5.4407
5.4222
5.4099
5.3976
5.3918
5.3891
5.3747
5.3720
5.3704
5.3671
5.3634
5.3601
5.3497
4.4598
3.5728
3.5679
3.5552
3.5506
3.5059
3.4792
3.4325
3.4146
3.3945
3.1565
2.7920
2.7793
2.7670
2.3883
2.3747
2.3592
2.3457
2.1358
2.1214
2.1066
2.0925
1.7139
1.6875
1.6791
1.6441
1.6390
1.6173
1.6121
1.5184
1.5126
1.5049
1.4978
1.4854
1.4784
1.4698
1.4616
1.4513
1.4449
1.4400
1.3874
1.3793
1.3609
1.3524
0.9183
3.1011
1.0000
2.9741
1.9747
2.2781
1.0038
0.9115
2.0596
3.0816
1.0859

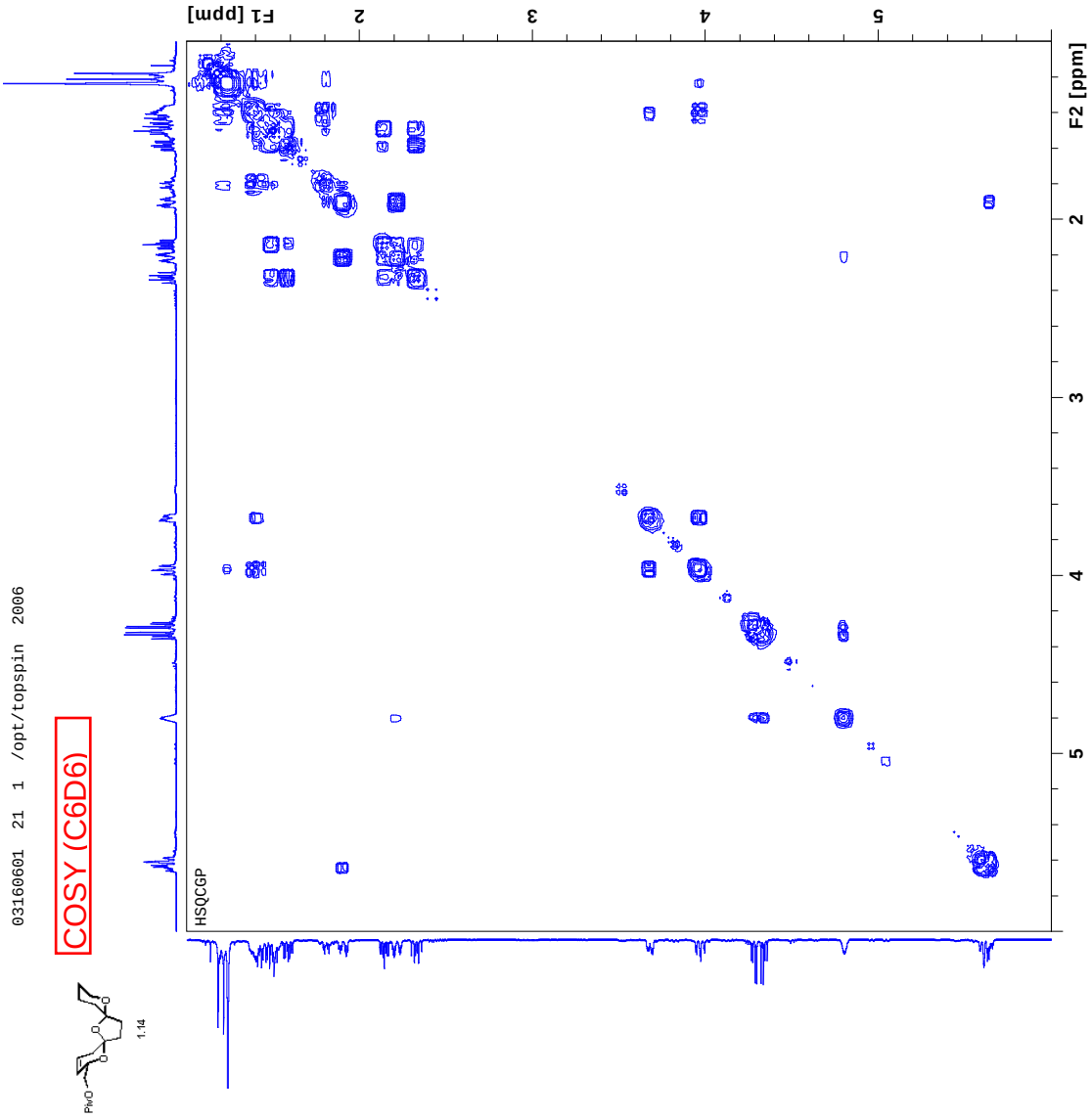

13C NMR (CDCl3, 125 MHz)
09110501 10 1 /opt/topspin 2005
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
OMe
OH
OH
18.6055
25.1337
31.1209
33.0395
39.8441
47.4883
61.4856
66.3306
68.5925
68.6255
76.9740
77.2286
77.4833
98.7512
125.3085
125.3513
129.2959
129.3405
131.2433
131.2775

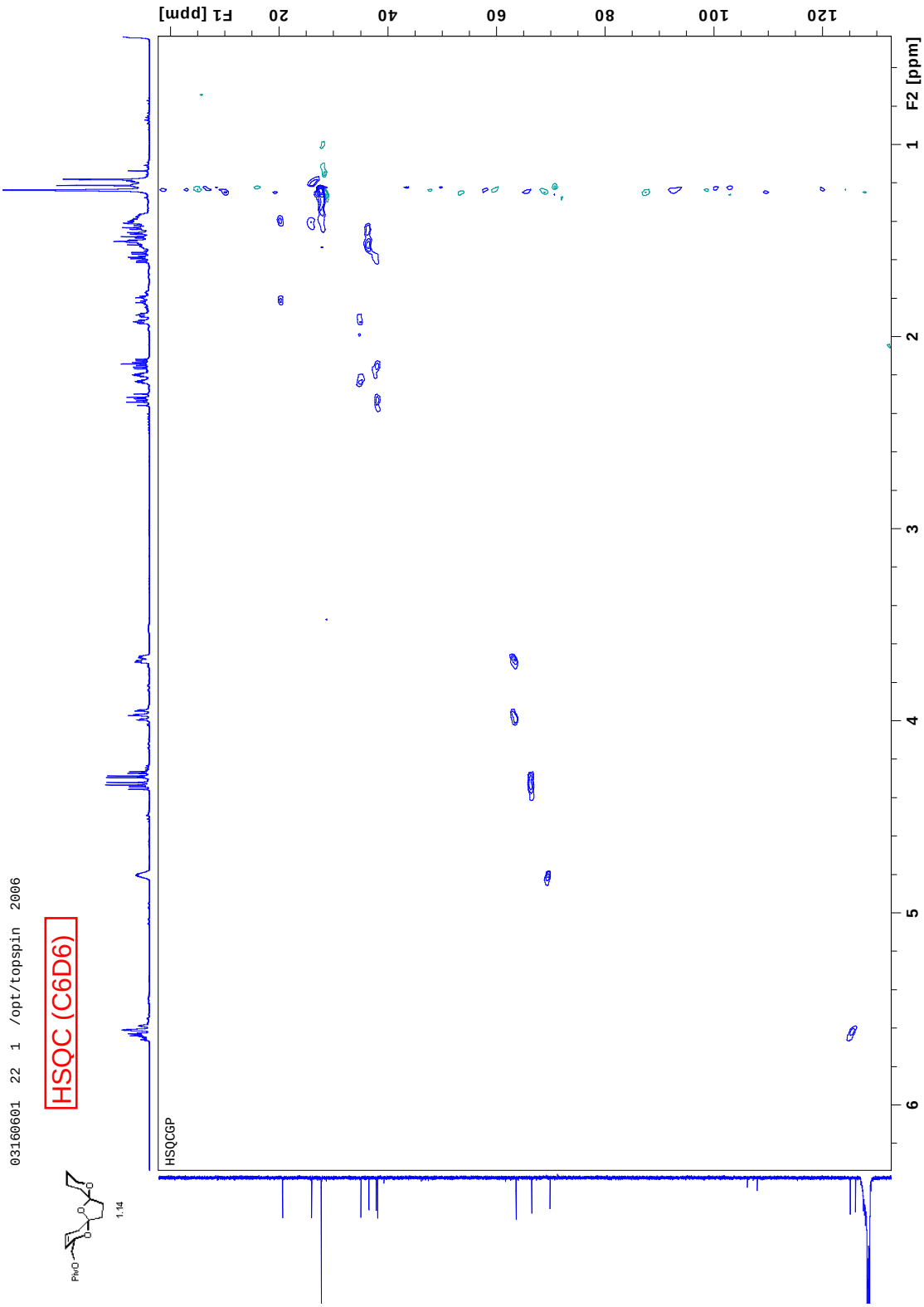

10200501 1 1 /opt/topspin 2005
HSQCGP
1H NMR (CDCl3, 500 MHz)
OMe
OH
OPiv
1.13
[rel]
[ppm]

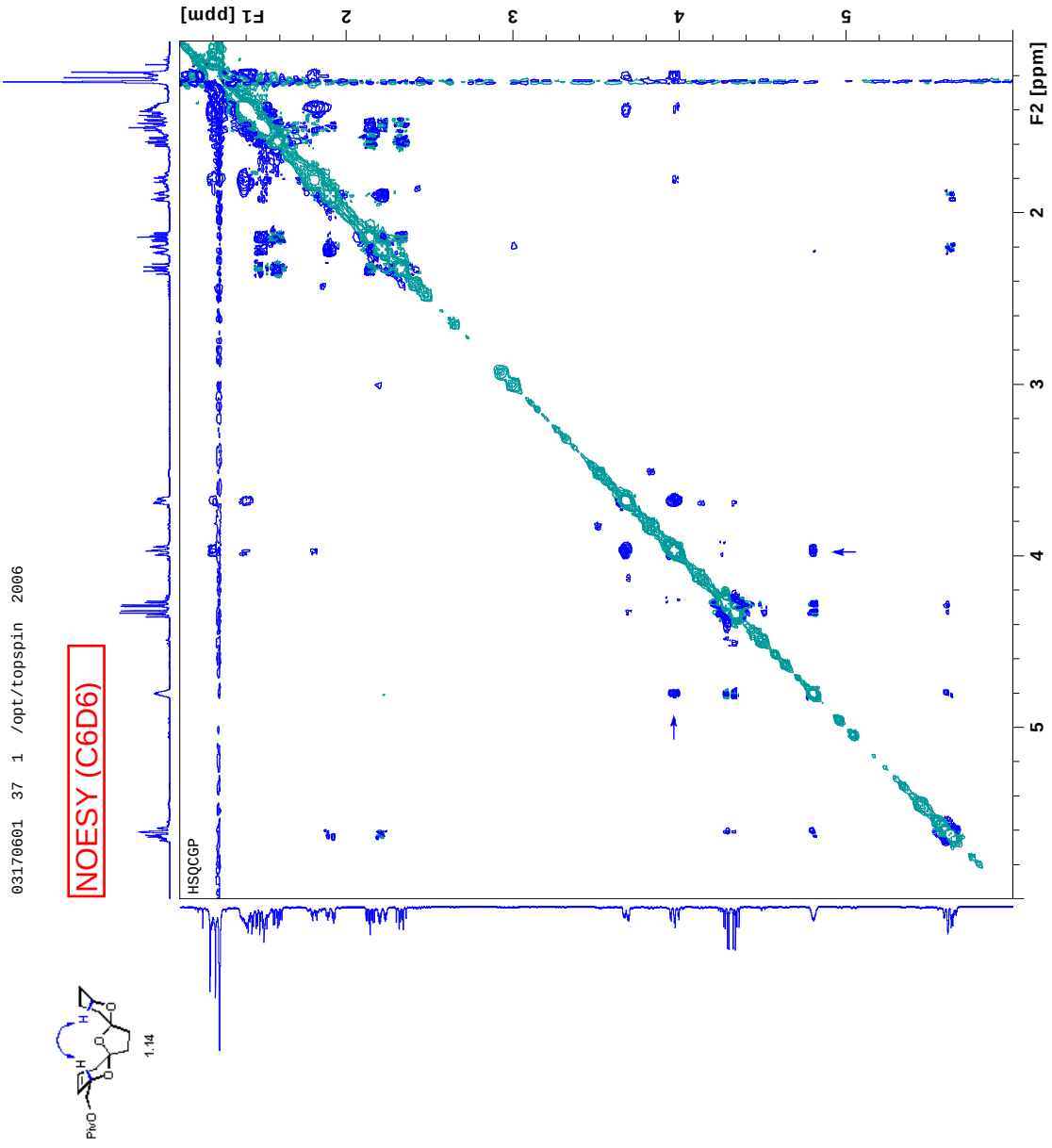

13C NMR (CDCl3, 125 MHz)
10200501 2 1 /opt/topspin 2005
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
178.7963
132.2161
132.1697
131.1295
131.0800
128.8646
128.7754
125.8316
125.7670
98.7874
77.4817
77.2276
76.9734
67.9651
67.9436
66.4634
66.4196
61.6375
47.6260
40.0244
39.9961
33.2515
31.2224
27.4246
25.3186
18.7828
OMe
OH
OPiv
1.13

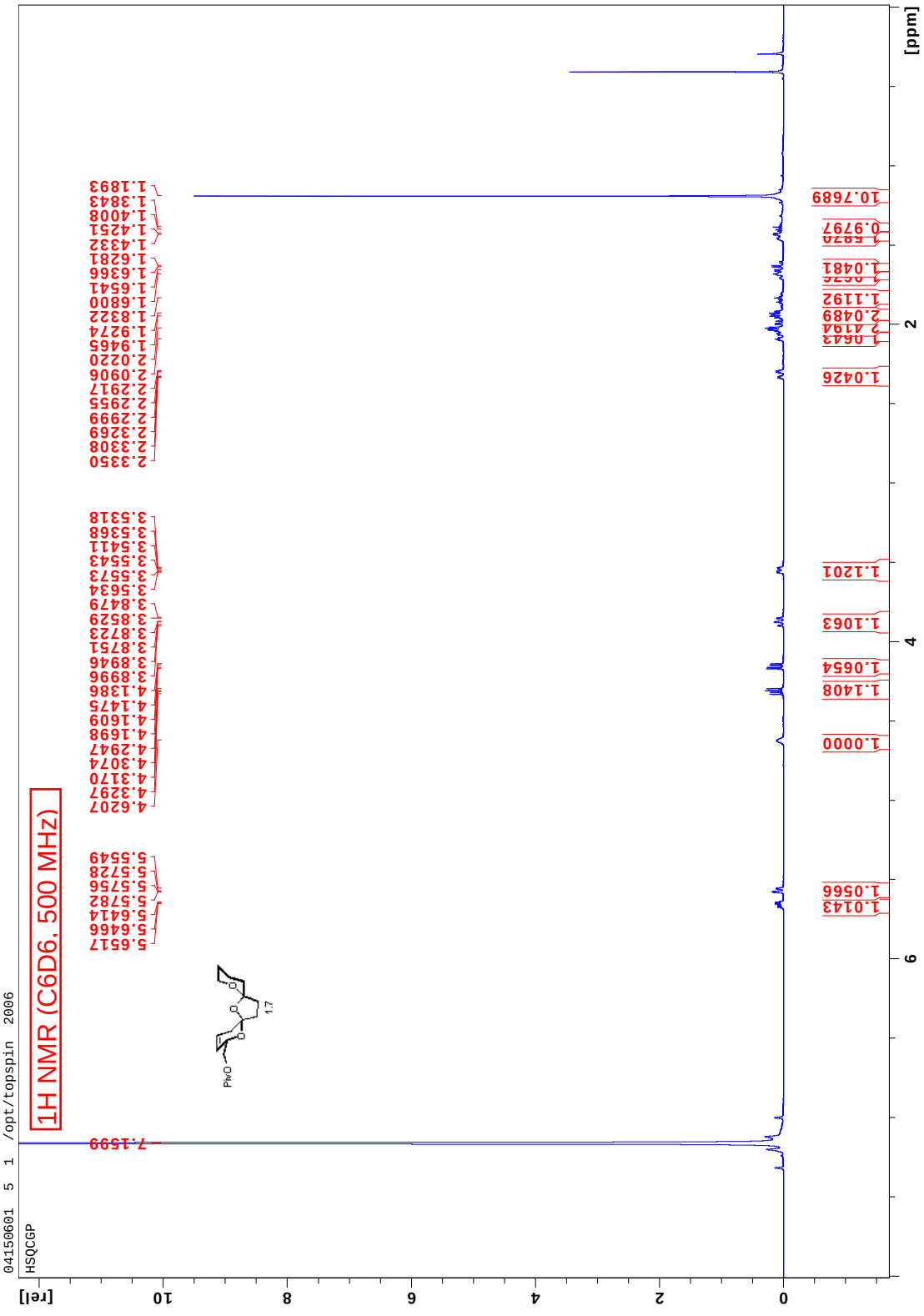

1H NMR (C6D6, 500 MHz)
HSQCGP
03160601 20 1 /opt/topspin 2006
[rel]
[ppm]
7.1597
5.6385
5.6286
5.6108
5.6083
5.6058
4.8029
4.3556
4.3425
4.3333
4.3202
4.2947
4.2861
4.2724
4.2638
3.9946
3.9897
3.9717
3.9670
3.9483
3.9429
3.9369
3.6884
3.6851
3.6710
3.6672
3.6621
3.4400
3.3228
3.3154
2.2983
2.2371
2.2328
2.2287
2.2022
2.1981
2.1940
2.1661
2.1584
2.1417
2.1339
1.9292
1.9242
1.9218
1.9145
1.9127
1.8899
1.8871
1.8846
1.8220
1.8140
1.7967
1.7888
1.6121
1.5937
1.5860
1.5689
1.5613
1.5035
1.4787
1.4316
1.4077
1.2367
1.2123
3.2960
2.5526
1.1728
1.1698
1.2233
1.0988
1.2694
1.0509
1.0830
1.1154
1.2729
1.1334
1.0000
1.0486
9.0812
PivO
1.14


13C NMR (C6D6, 125 MHz)
03160601 23 1 /opt/topspin 2006
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
177.9698
128.5760
128.3836
128.1906
126.0340
125.0715
107.9538
106.1215
69.8004
66.4524
63.5584
38.0662
37.8281
36.4673
34.9846
27.7334
27.6658
25.9272
20.5777
1.14
[rel]
[ppm]


COSY (C6D6)
03160601 21 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
2
3
4
5
1.14


HSQC (C6D6)
031600601 22 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
120
100
80
60
40
20
1
2
3
4
5
6
PivO
1.14


NOESY (C6D6)
03170601 37 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
2
3
4
5
1.14
PMO


1H NMR (C6D6. 500 MHz)
HSQCGP
04150601 5 1 /opt/topspin 2006
[rel]
[ppm]
PwO
1.7
7.1599
5.6517
5.6466
5.6414
5.5782
5.5756
5.5728
5.5549
4.6207
4.3297
4.3170
4.3074
4.2947
4.1698
4.1609
4.1475
4.1386
3.8996
3.8946
3.8751
3.8723
3.8529
3.8479
3.5634
3.5573
3.5543
3.5411
3.5368
3.5318
2.3350
2.3308
2.3269
2.2999
2.2955
2.2917
2.0906
2.0220
1.9465
1.9274
1.8322
1.6800
1.6541
1.6366
1.6281
1.4332
1.4251
1.4008
1.3843
1.1893
10.7689
0.9797
1.0481
1.1192
2.0489
2.4194
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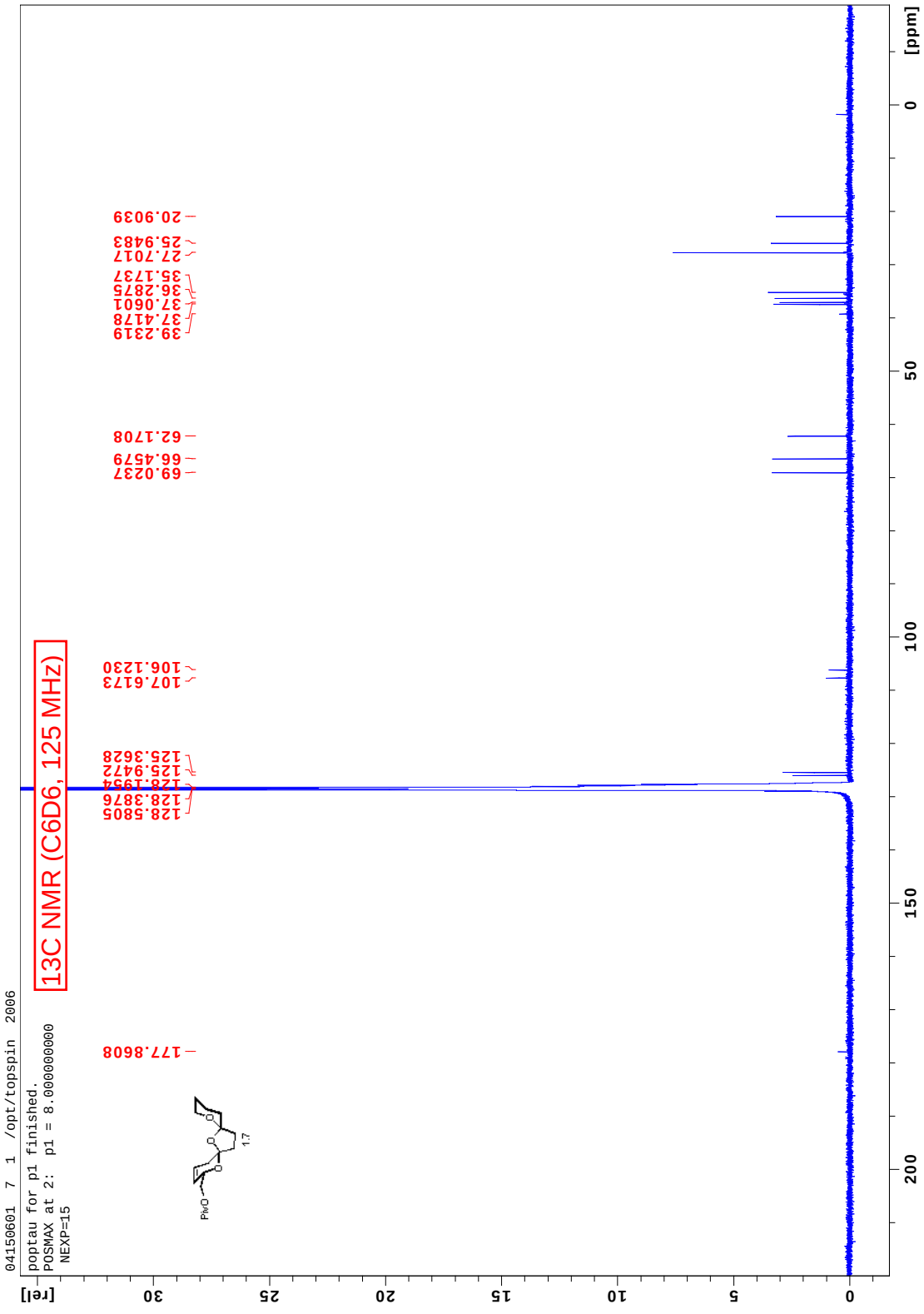
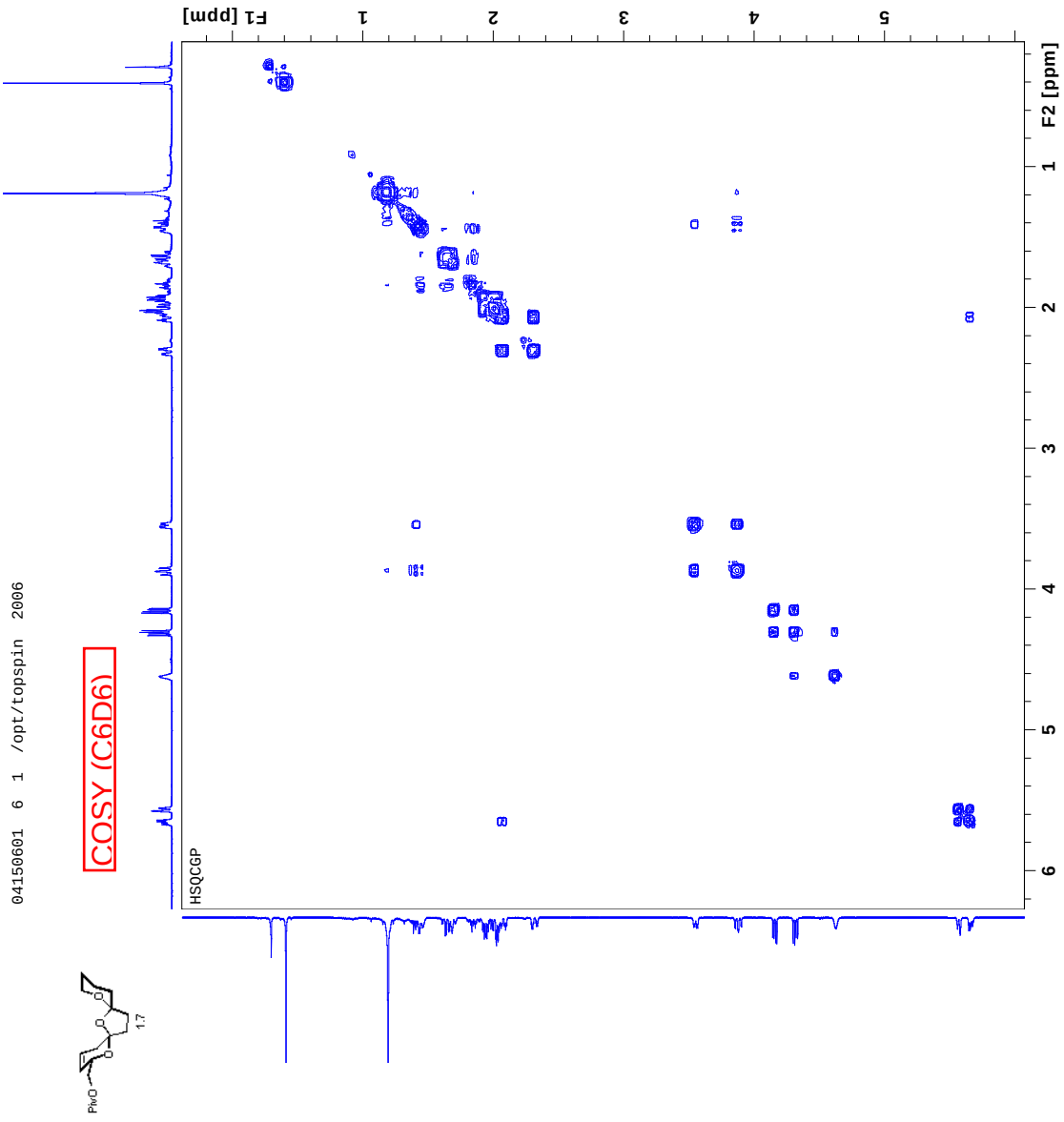
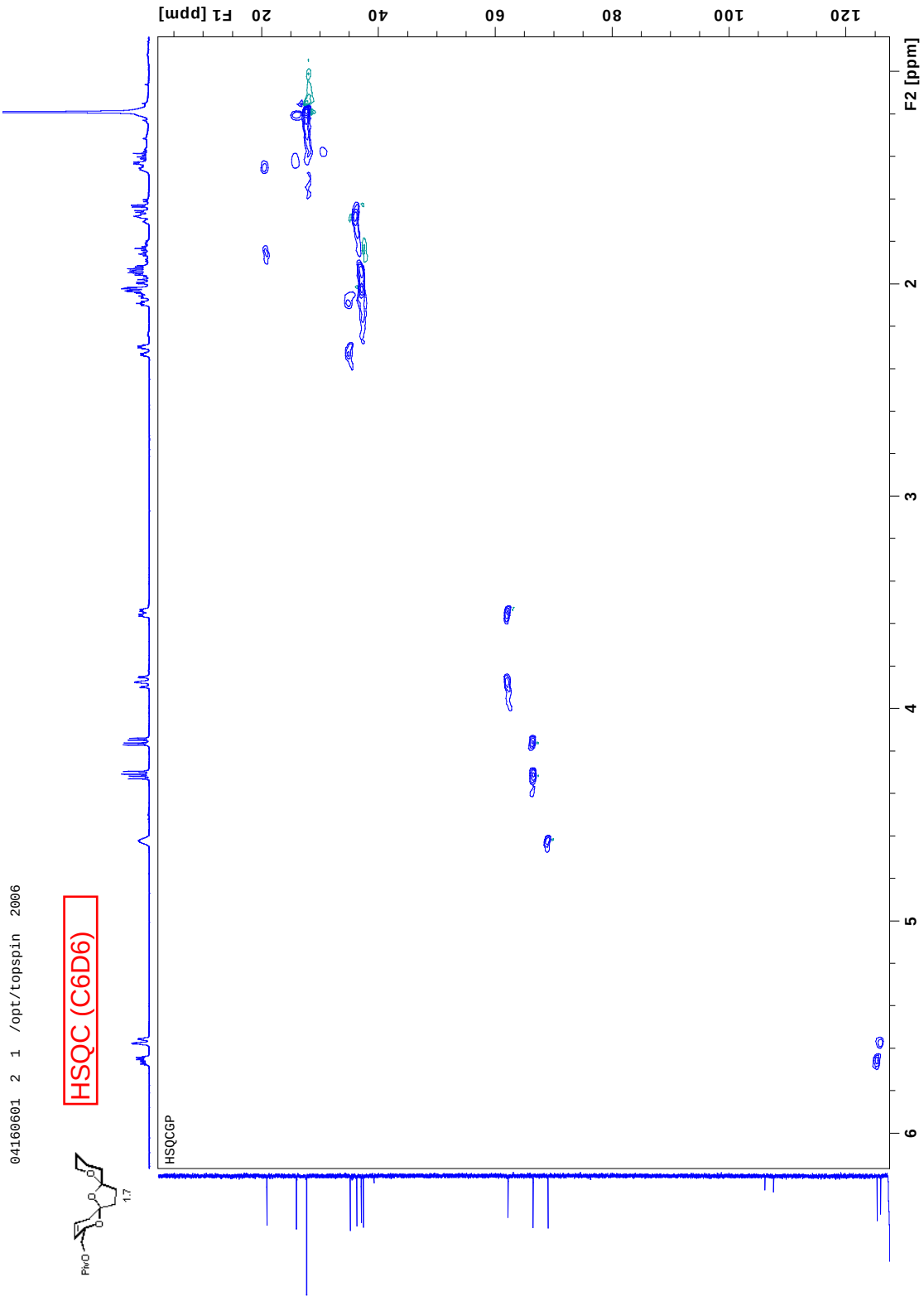
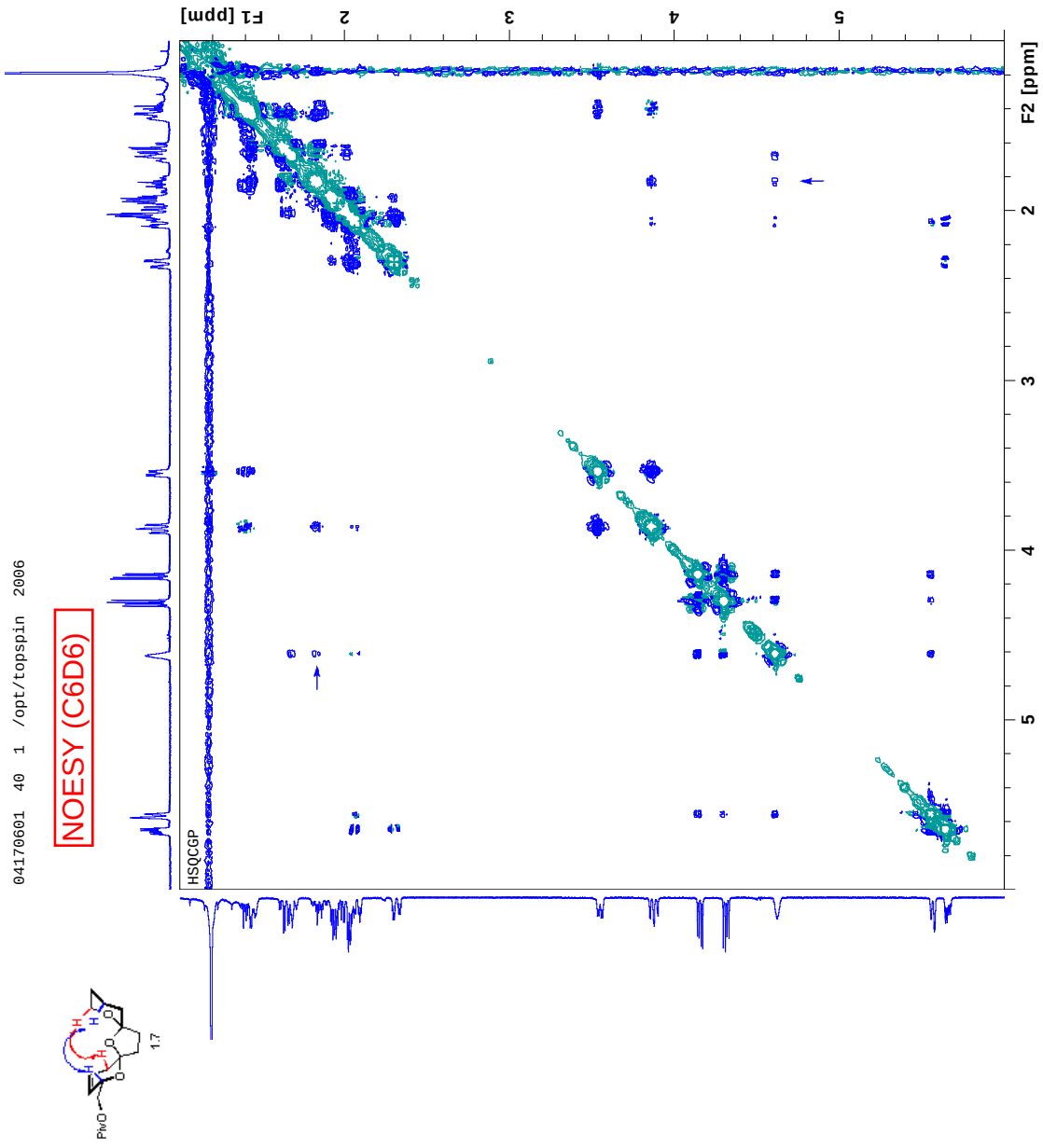
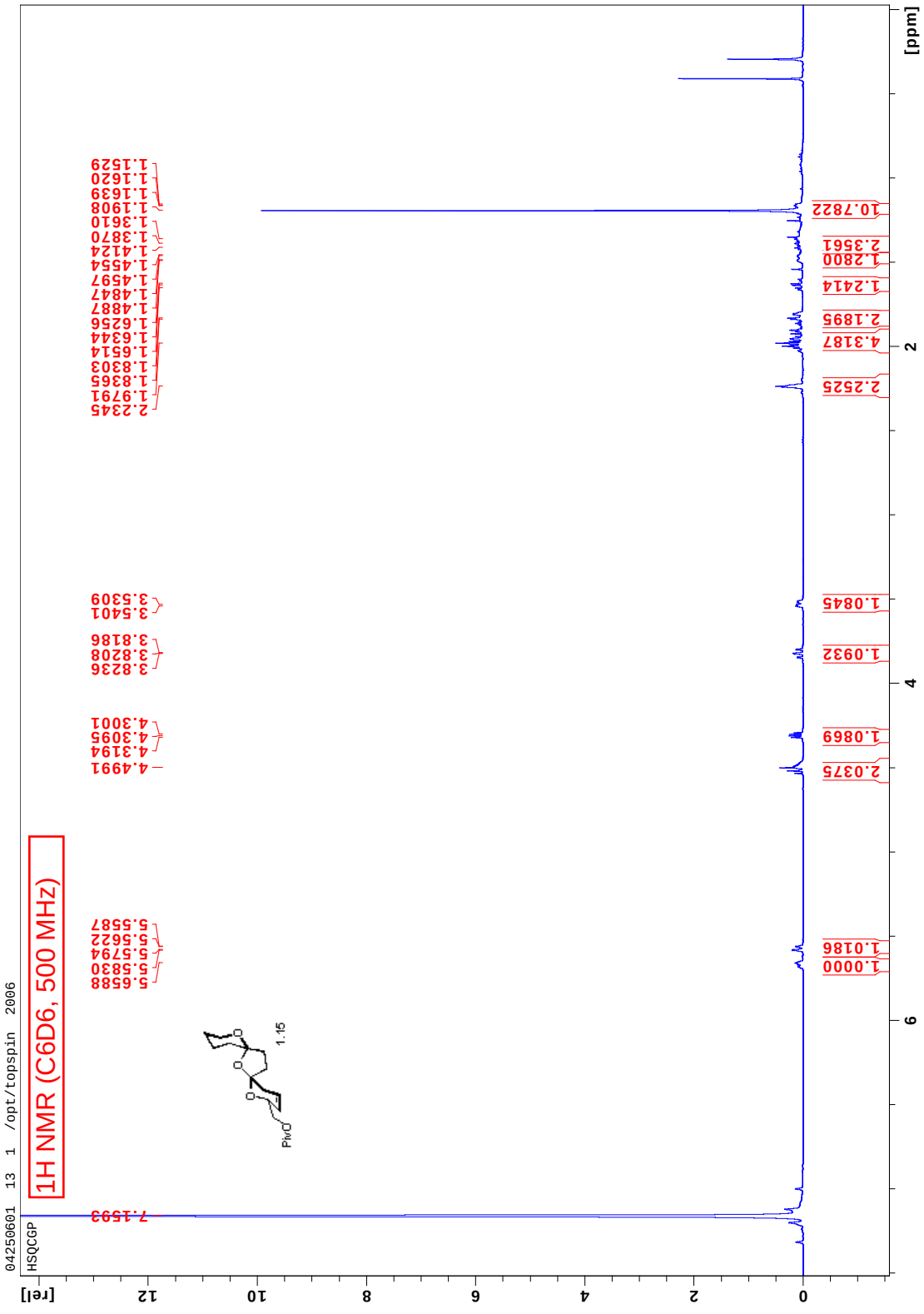
1.0426
1.1201
1.1063
1.0654
1.1408
1.0000
1.0566
1.0143

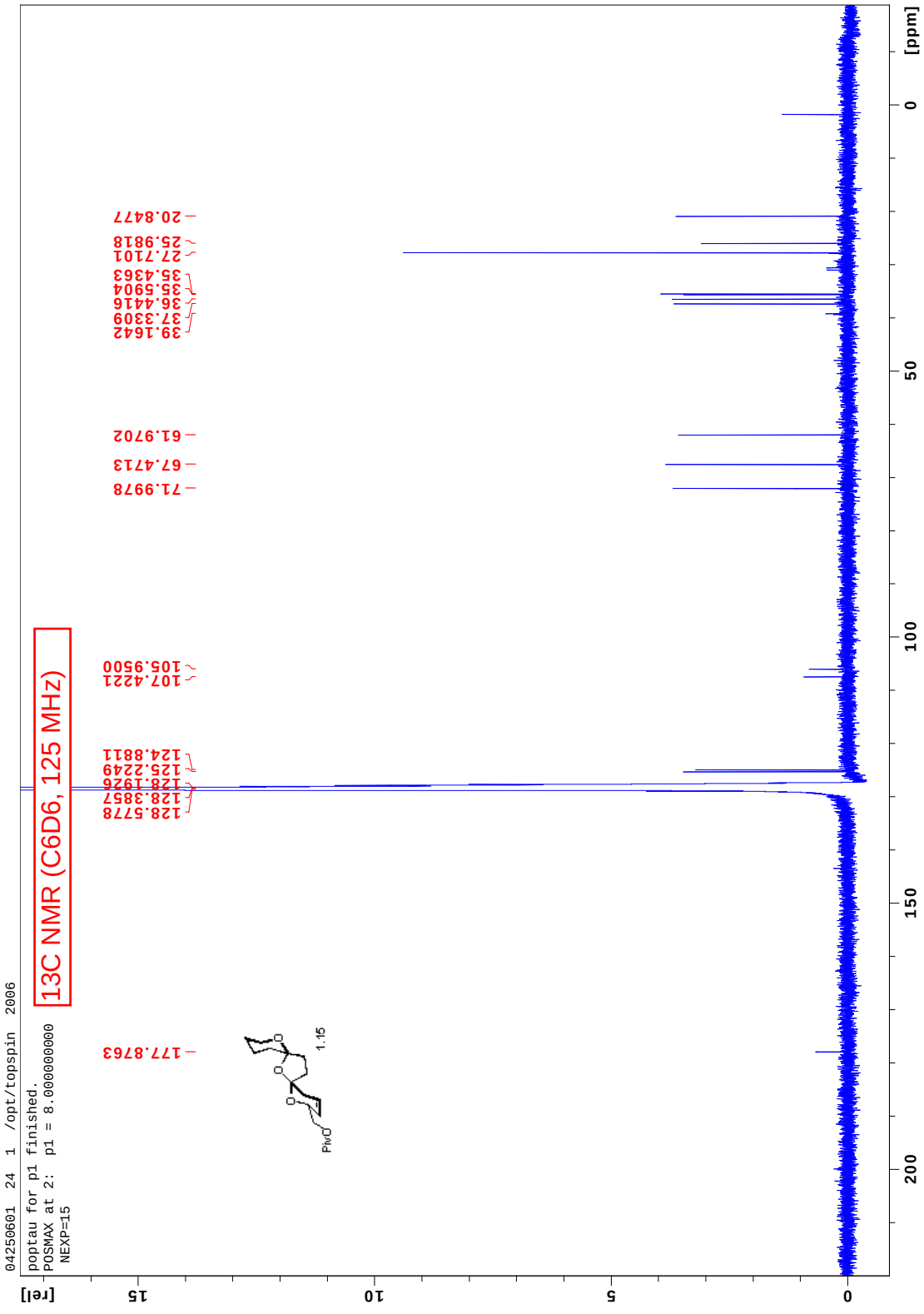

13C NMR (C6D6, 125 MHz)
177.8608
128.5805
128.3876
128.1954
125.9472
125.3628
107.6173
106.1230
69.0237
66.4579
62.1708
39.2319
37.4178
37.0601
36.2875
35.1737
27.7017
25.9483
20.9039
[rel]
[ppm]
041506O1 7 1 /opt/topspin 2006
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15

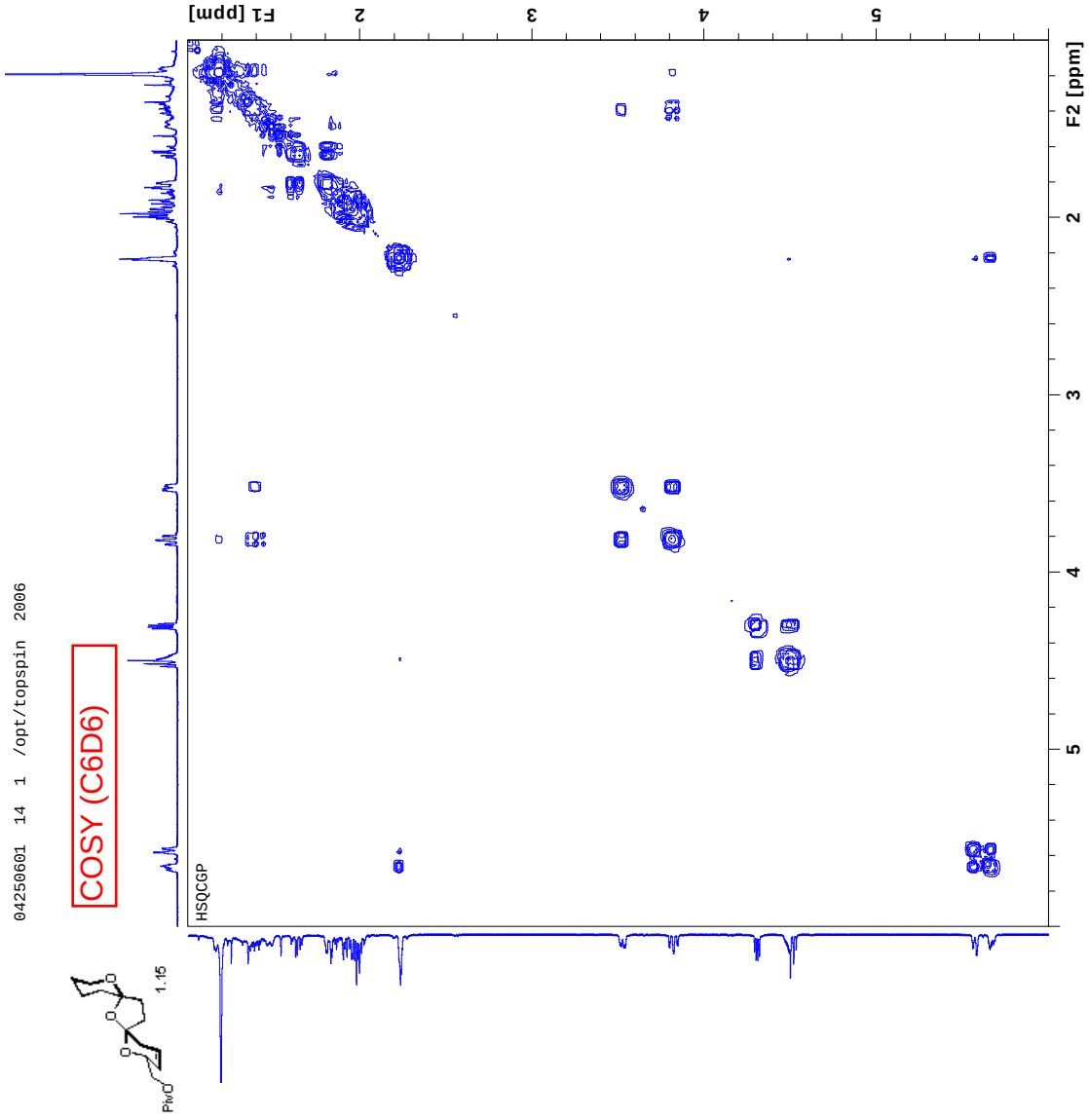

COSY (C6D6)
04150601 6 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
1
2
3
4
5
6
PivO
1.7

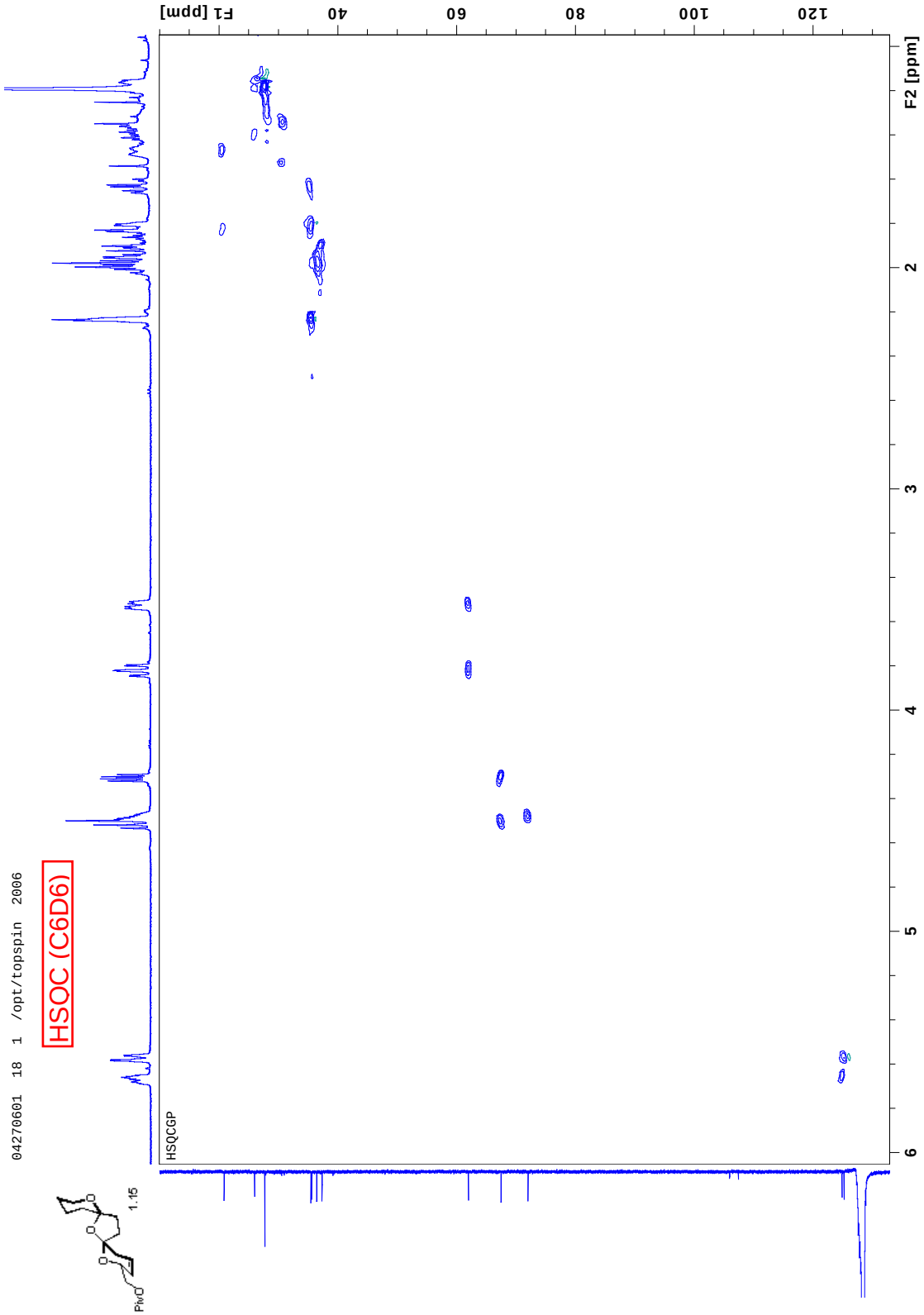

HSQC (C6D6)
041606001 2 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
120
100
80
60
40
20
2
3
4
5
6

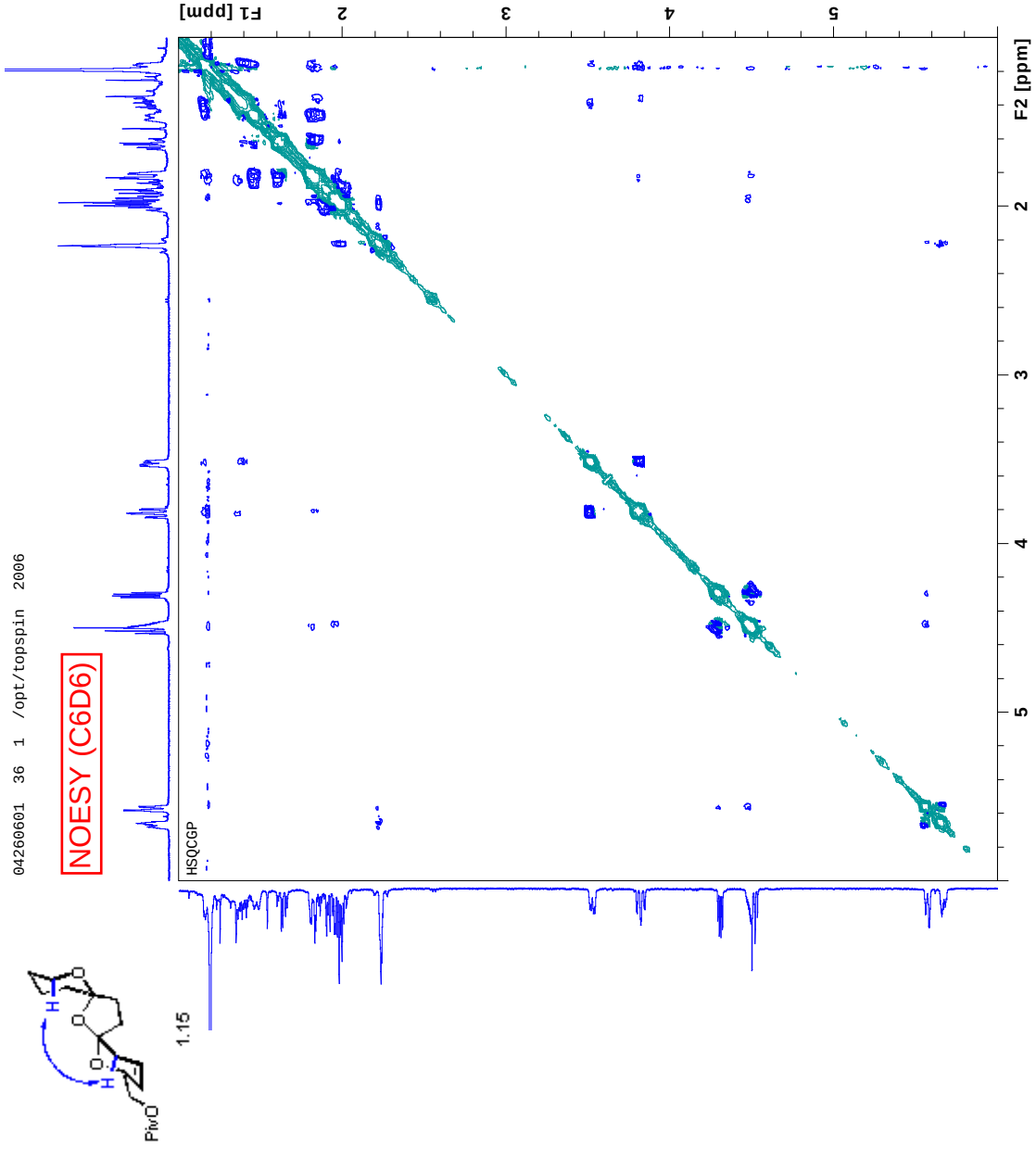

NOESY (C6D6)
04170601 40 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
2
3
4
5
PivO
1.7

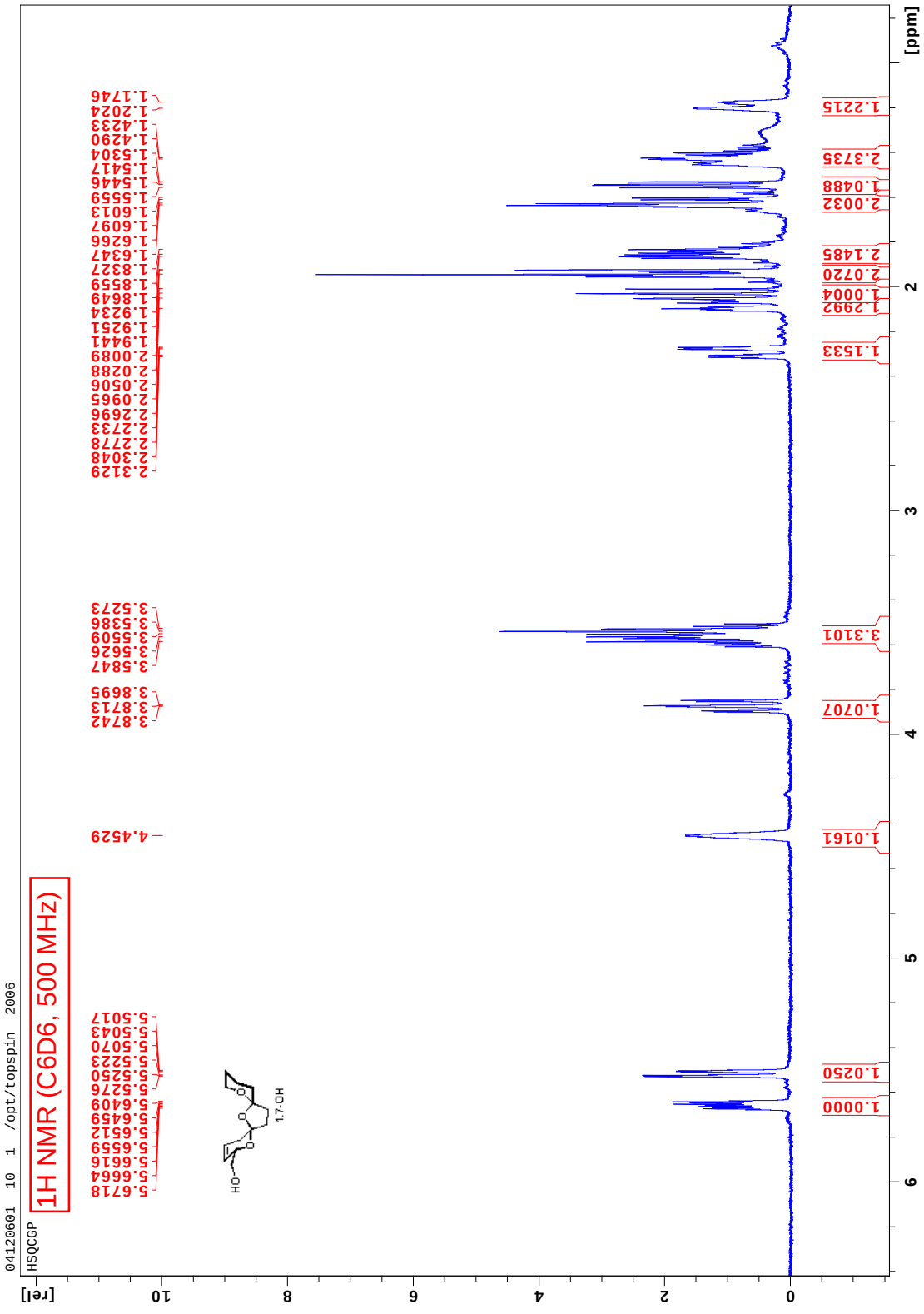

04250601 13 1 /opt/topspin 2006
HSQCGP
1H NMR (C6D6, 500 MHz)
7.1593
5.6588
5.5830
5.5794
5.5622
5.5587
4.4991
4.3194
4.3095
4.3001
3.8236
3.8208
3.8186
3.5401
3.5309
2.2345
1.9791
1.8365
1.8303
1.6514
1.6344
1.6256
1.4887
1.4847
1.4597
1.4554
1.4124
1.3870
1.3610
1.1908
1.1639
1.1620
1.1529
10.7822
2.3561
1.2800
1.2414
2.1895
4.3187
2.2525
1.0845
1.0932
1.0869
2.0375
1.0000
1.0186
PivO
1.15
[rel]
[ppm]


13C NMR (C6D6, 125 MHz)
04250601 24 1 /opt/topspin 2006
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
177.8763
128.5778
128.3857
128.1926
125.2249
124.8811
107.4221
105.9500
71.9978
67.4713
61.9702
39.1642
37.3309
36.4416
35.5904
35.4363
27.7101
25.9818
20.8477
1.15
PhrO
[rel]
15
10
5
0
200
150
100
50
0
[ppm]


COSY (C6D6)
04250601 14 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
2
3
4
5
1.15
Pb/O


HSOC (C6D6)
042706001 18 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
120
100
80
60
40
2
3
4
5
6
1.15
PhO


NOESY (C6D6)
04260601 36 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
1.15
PivO


1H NMR (C6D6, 500 MHz)
HSQCGP
04120601 10 1 /opt/topspin 2006
[rel]
[ppm]
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HO
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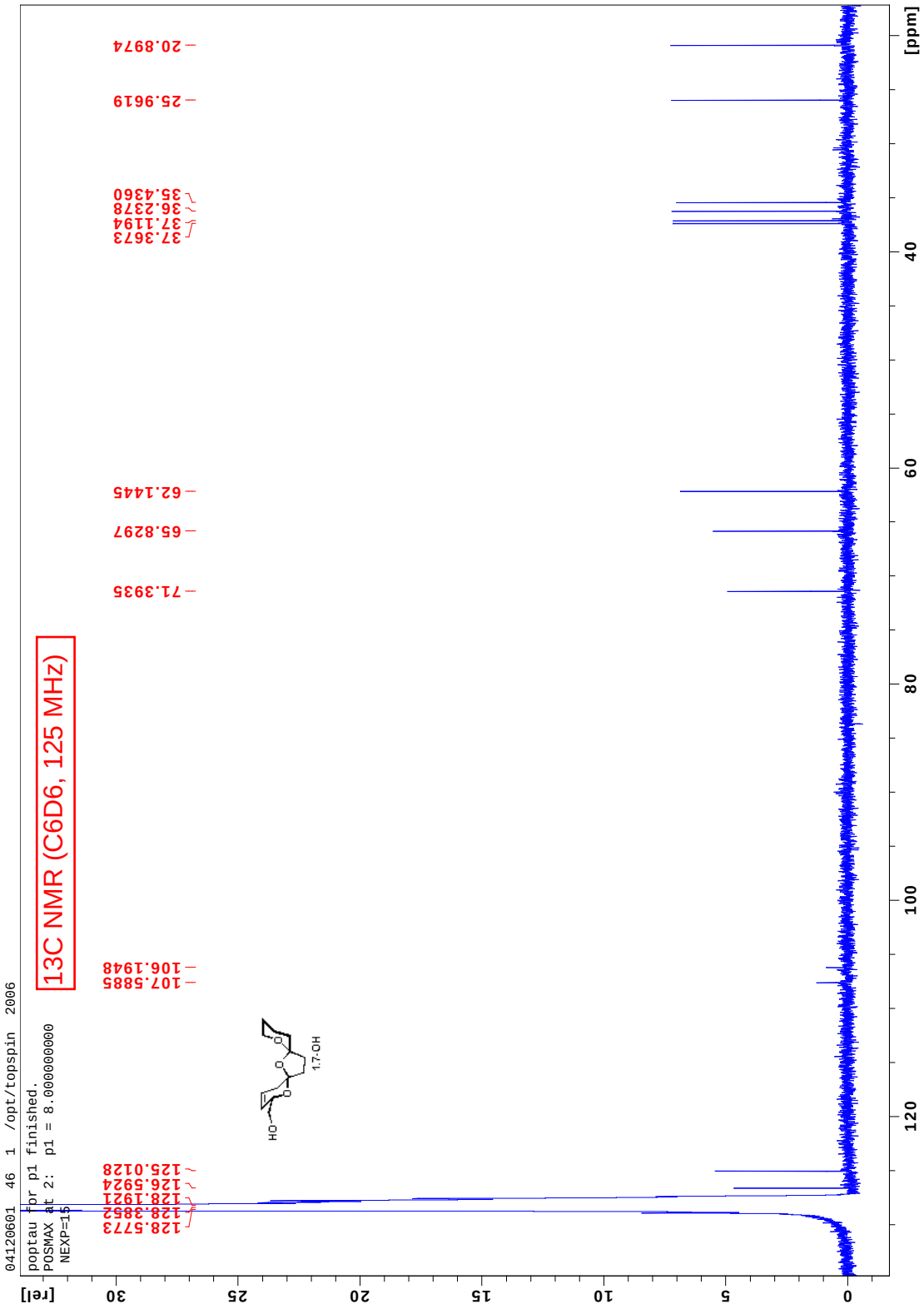
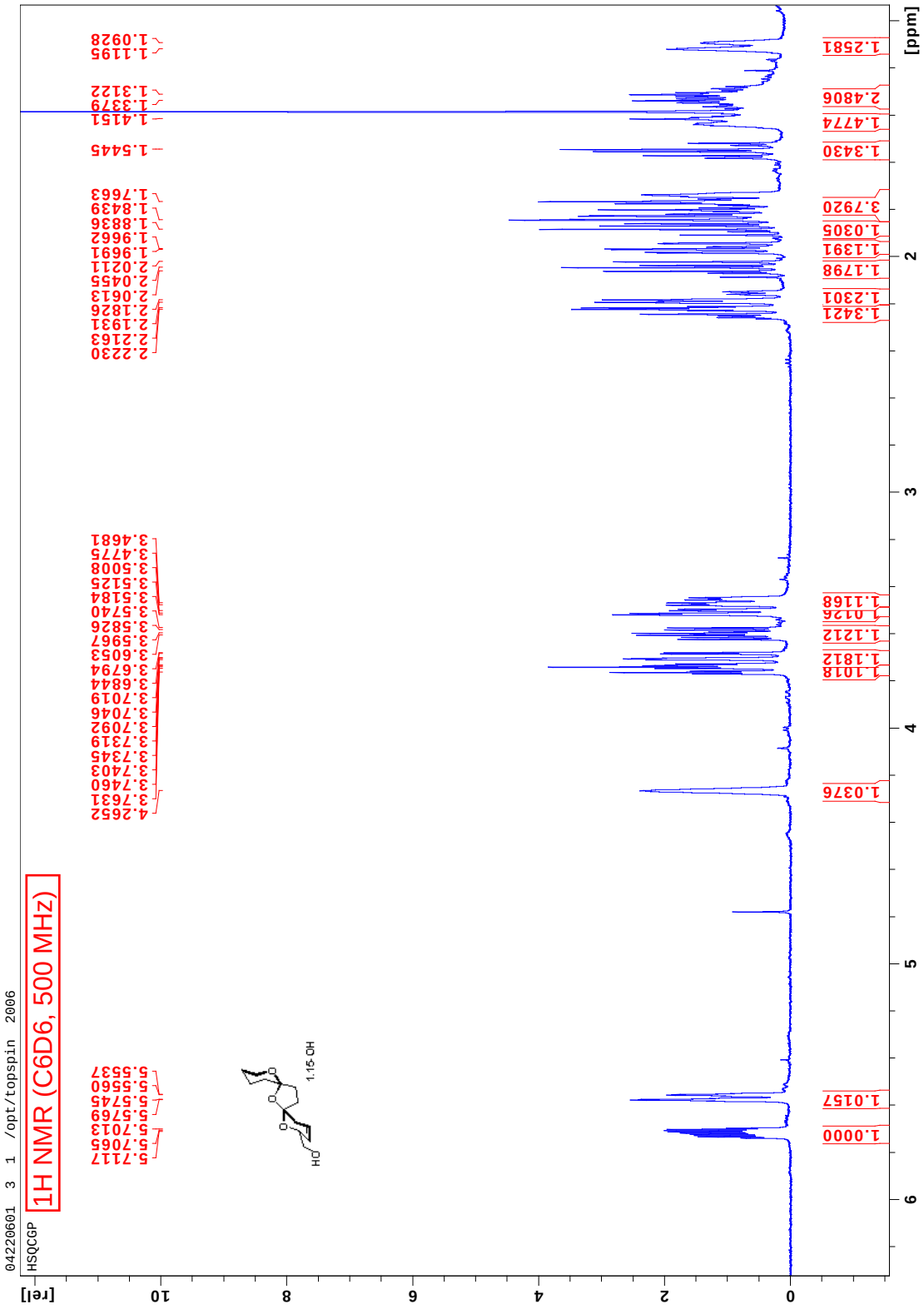
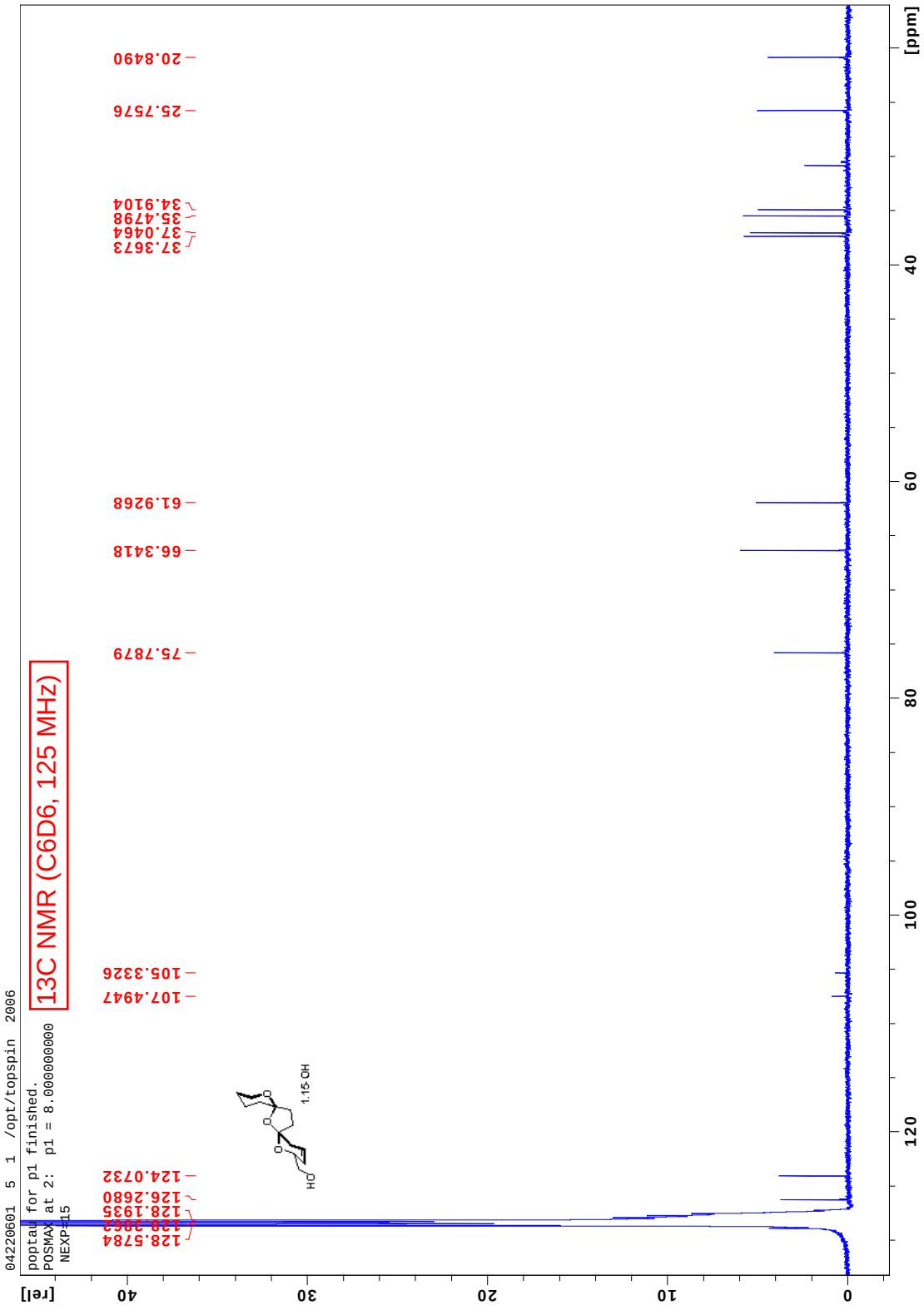
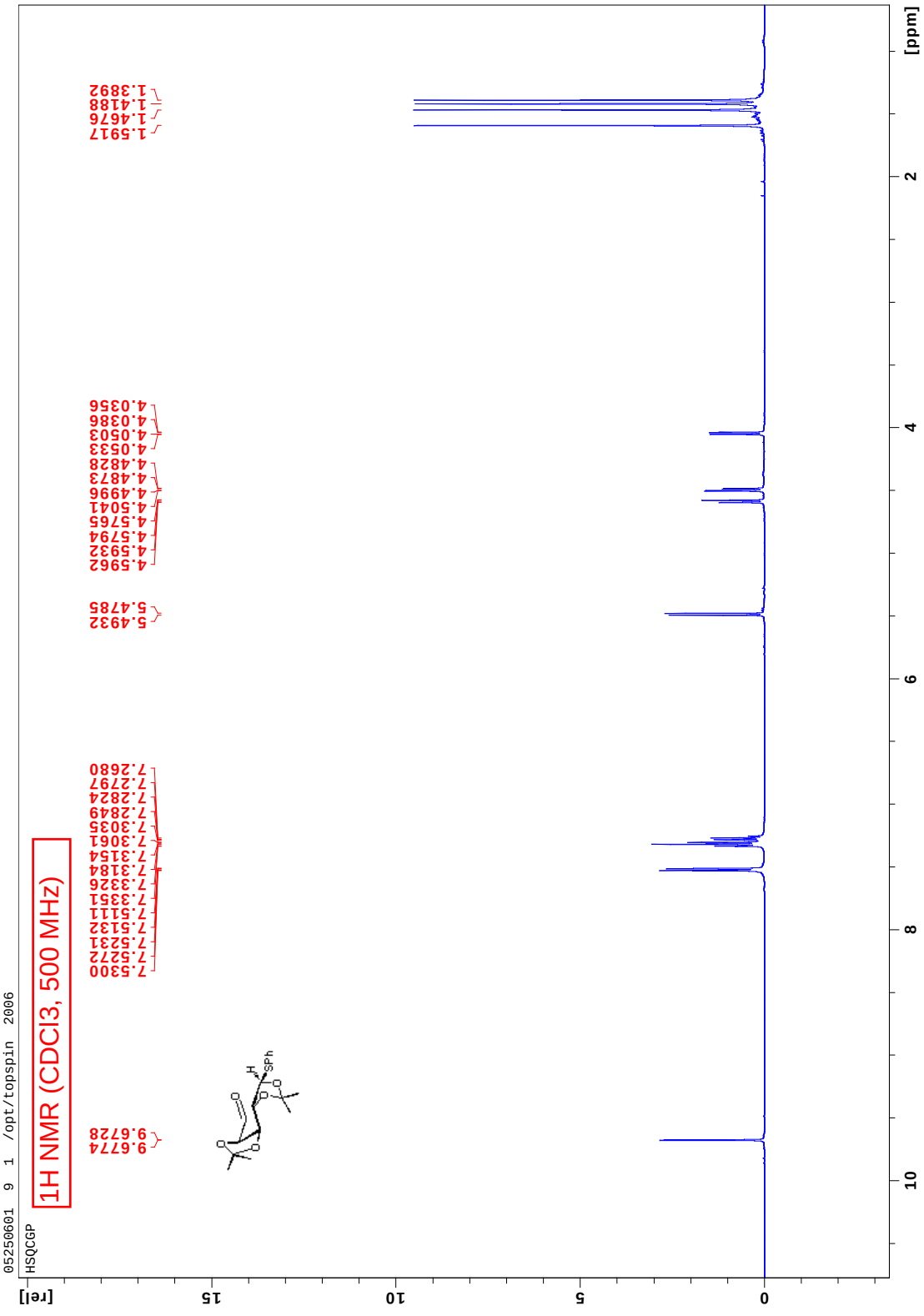
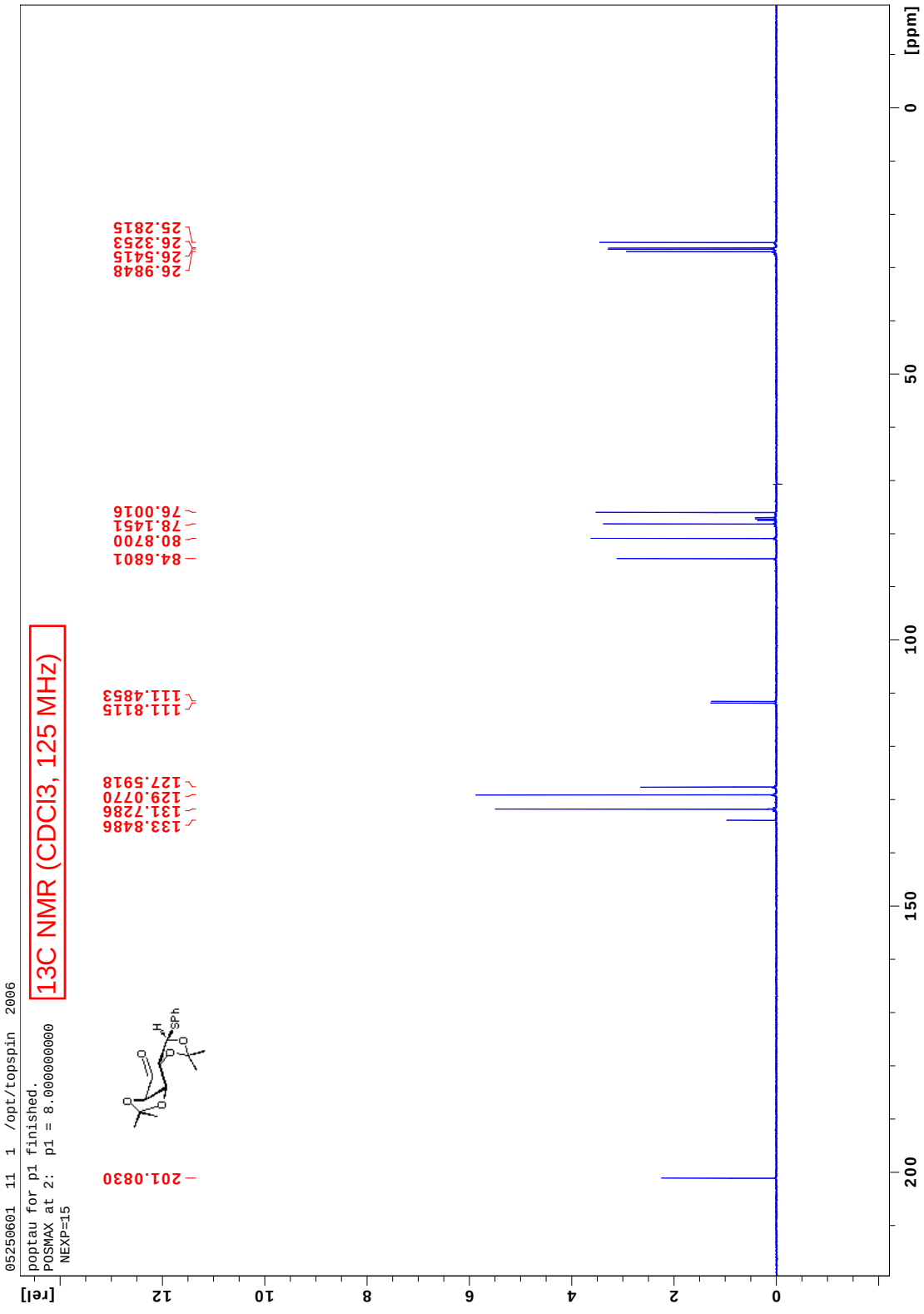
1.0250
1.0161
1.0707
3.3101
1.1533
1.2992
1.0004
2.0720
2.1485
2.0032
1.0488
2.3735
1.2215
4.4529
5.6718
5.6664
5.6616
5.6559
5.6512
5.6459
5.6409
5.5276
5.5250
5.5223
5.5070
5.5043
5.5017
3.8742
3.8713
3.8695
3.5847
3.5626
3.5509
3.5386
3.5273
2.3129
2.3048
2.2778
2.2733
2.2696
2.0965
2.0506
2.0288
2.0089
1.9441
1.9251
1.9234
1.8649
1.8559
1.8327
1.6347
1.6266
1.6097
1.6013
1.5559
1.5446
1.5417
1.5304
1.4290
1.4233
1.2024
1.1746

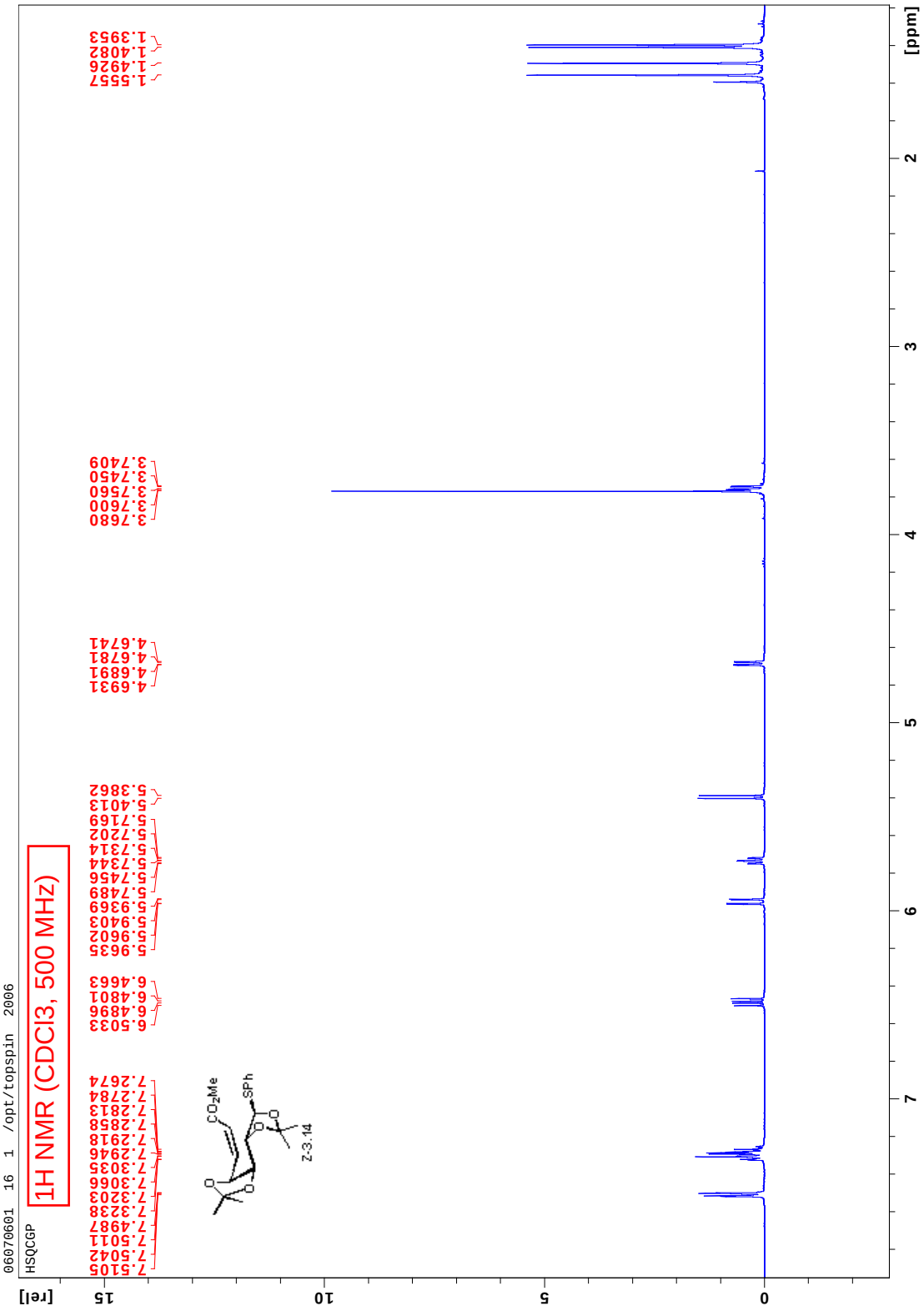

13C NMR (C6D6, 125 MHz)
20.8974
25.9619
35.4360
36.2378
37.1194
37.3673
62.1445
65.8297
71.3935
106.1948
107.5885
125.0128
126.5924
128.1921
128.3852
128.5773
1,7-OH
HO
[rel]
[ppm]
0
5
10
15
20
25
30
40
60
80
100
120
04120601 46 1 /opt/topspin 2006
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15

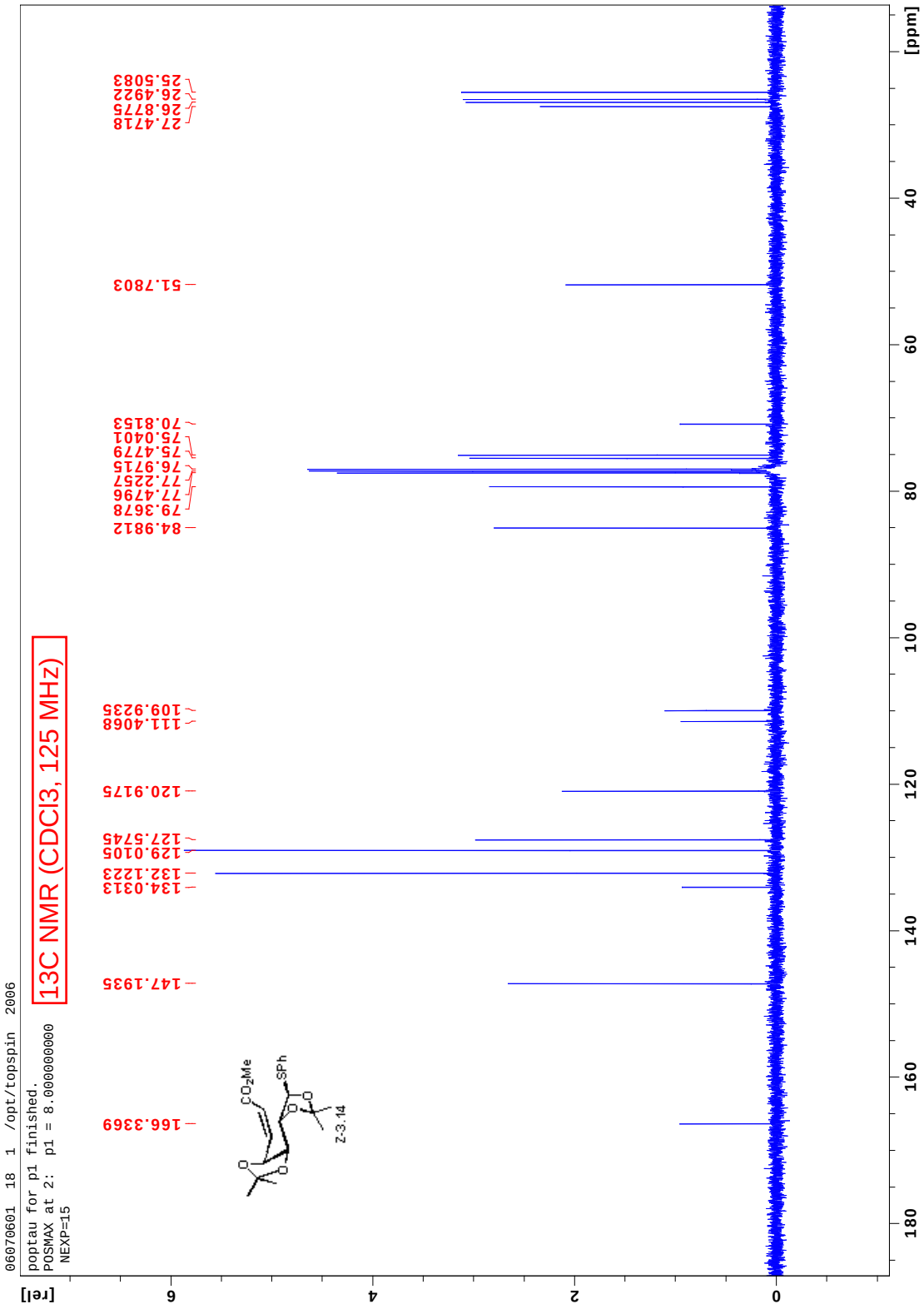

1H NMR (C6D6, 500 MHz)
HSQCGP
04220601 3 1 /opt/topspin 2006
[rel]
[ppm]
1.15 OH
HO
1.0000
1.0157
1.0376
2.4806
3.7920
5.5537
5.5560
5.5745
5.5769
5.7013
5.7065
5.7117
4.2652
3.7631
3.7460
3.7403
3.7345
3.7319
3.7092
3.7046
3.7019
3.6844
3.6794
3.6053
3.5967
3.5826
3.5740
3.5184
3.5125
3.5008
3.4775
3.4681
2.2230
2.2163
2.1931
2.1826
2.0613
2.0455
2.0211
1.9691
1.9662
1.8836
1.8439
1.7663
1.5445
1.4151
1.3379
1.3122
1.1195
1.0928
1.2581
1.4774
1.3430
1.1798
1.1391
1.0305
1.3421
1.2301
1.1212
1.1812
1.1018
1.1168
0.9126

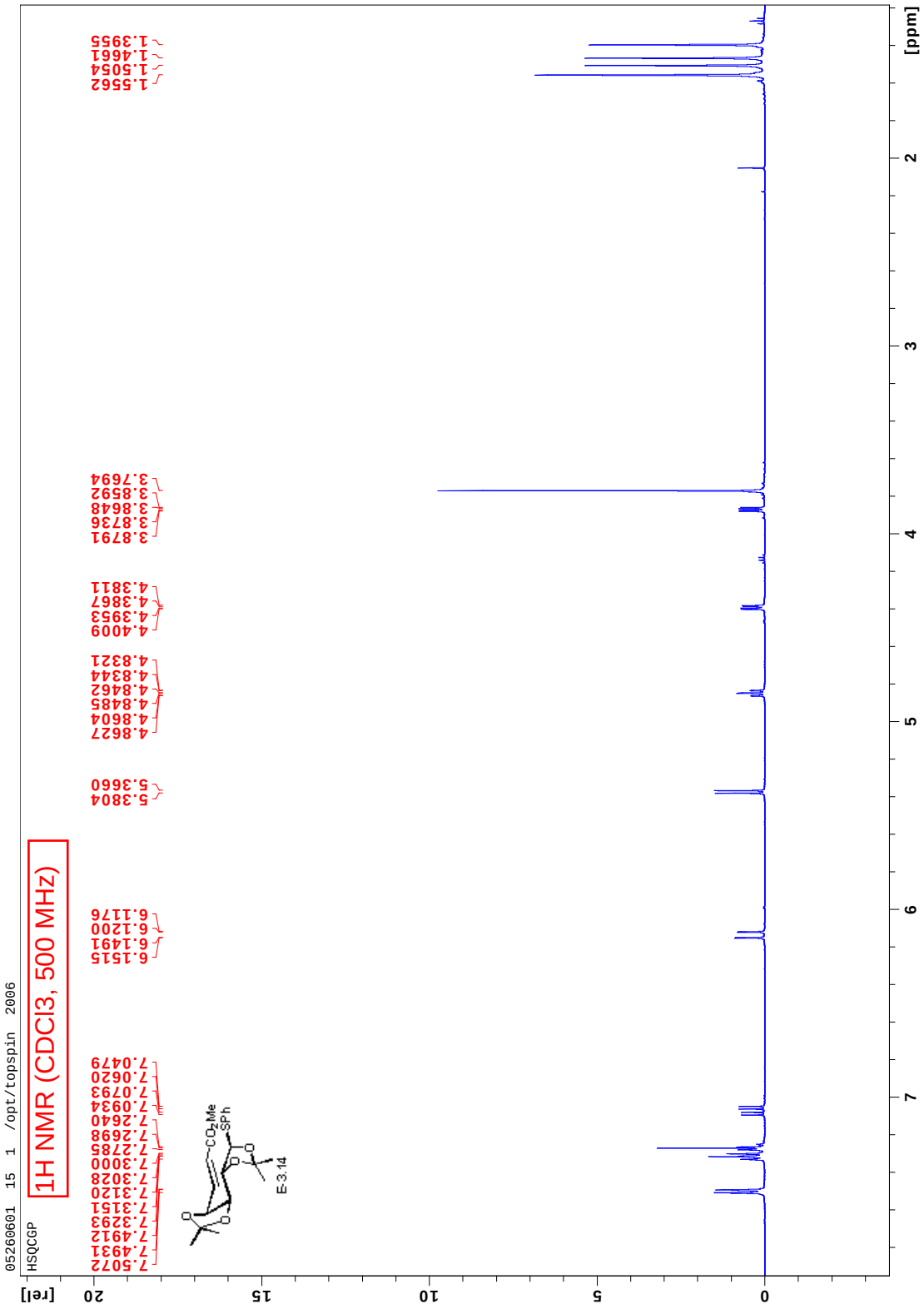

13C NMR (C6D6, 125 MHz)
04220601 5 1 /opt/topspin 2006
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
0
10
20
30
40
60
80
100
120
20.8490
25.7576
34.9104
35.4798
37.0464
37.3673
61.9268
66.3418
75.7879
105.3326
107.4947
124.0732
126.2680
128.1935
128.3962
128.5784
1.15-OH
HO

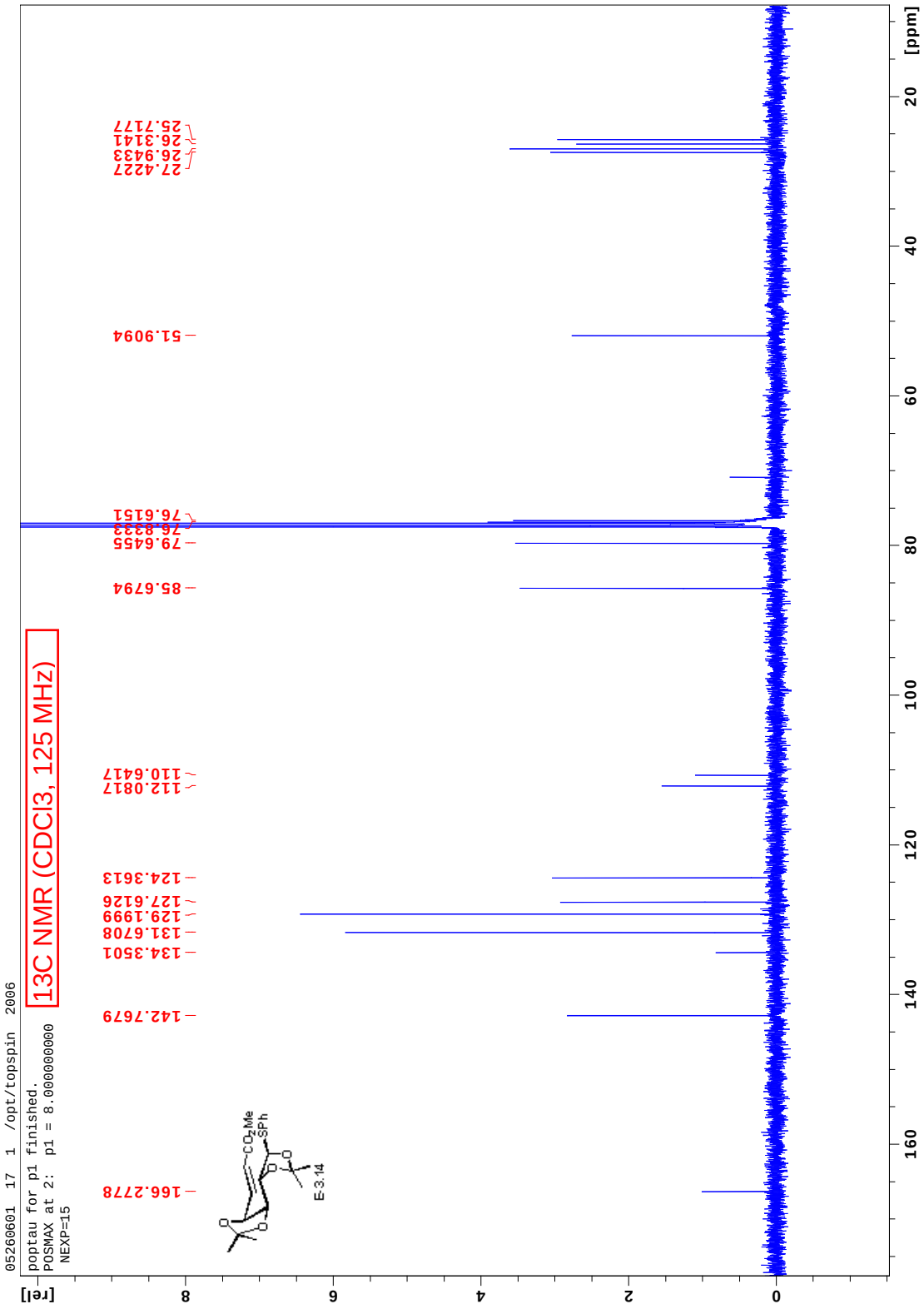

05250601 9 1 /opt/topspin 2006
HSQCGP
1H NMR (CDCl3, 500 MHz)
9.6774
9.6728
7.5300
7.5272
7.5231
7.5132
7.5111
7.3351
7.3326
7.3184
7.3154
7.3061
7.3035
7.2849
7.2824
7.2797
7.2680
5.4932
5.4785
4.5962
4.5932
4.5794
4.5765
4.5041
4.4996
4.4873
4.4828
4.0533
4.0503
4.0386
4.0356
1.5917
1.4676
1.4188
1.3892
SPh
[rel]
15
10
5
0
[ppm]
10
8
6
4
2

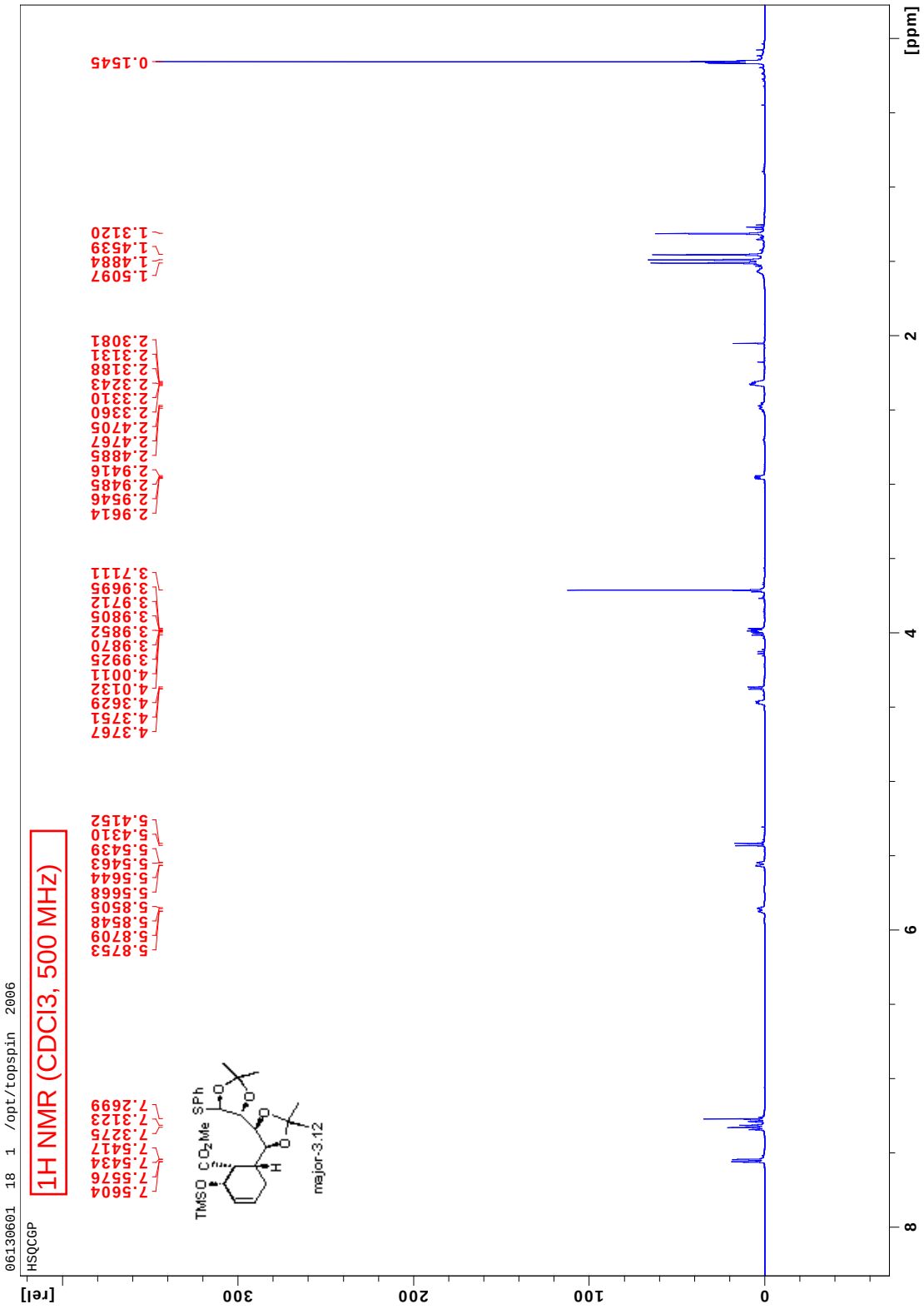

13C NMR (CDCl3, 125 MHz)
05250601 11 1 /opt/topspin 2006
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
201.0830
133.8486
131.7286
129.0770
127.5918
111.8115
111.4853
84.6801
80.8700
78.1451
76.0016
26.9848
26.5415
26.3253
25.2815
[rel]
[ppm]


1H NMR (CDCl3, 500 MHz)
HSQCGP
060706O1 16 1 /opt/topspin 2006
[rel]
[ppm]
CO2Me
SPh
Z-3.14
7.5105
7.5042
7.5011
7.4987
7.3238
7.3203
7.3066
7.3035
7.2946
7.2918
7.2858
7.2813
7.2784
7.2674
6.5033
6.4896
6.4801
6.4663
5.9635
5.9602
5.9403
5.9369
5.7489
5.7456
5.7344
5.7314
5.7202
5.7169
5.4013
5.3862
4.6931
4.6891
4.6781
4.6741
3.7680
3.7600
3.7560
3.7450
3.7409
1.5557
1.4926
1.4082
1.3953


13C NMR (CDCl3, 125 MHz)
060706O1 18 1 /opt/topspin 2006
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
166.3369
147.1935
134.0313
132.1223
129.0105
127.5745
120.9175
111.4068
109.9235
84.9812
79.3678
77.4796
77.2257
76.9715
75.4779
75.0401
70.8153
51.7803
27.4718
26.8775
26.4922
25.5083
CO2Me
SPh
Z-3.14
[rel]
[ppm]


05260601 15 1 /opt/topspin 2006
HSQCGP
1H NMR (CDCl3, 500 MHz)
E-3.14
[rel]
[ppm]
7.5072
7.4931
7.4912
7.3293
7.3151
7.3120
7.3028
7.3000
7.2785
7.2698
7.2640
7.0934
7.0793
7.0620
7.0479
6.1515
6.1491
6.1200
6.1176
5.3804
5.3660
4.8627
4.8604
4.8485
4.8462
4.8344
4.8321
4.4009
4.3953
4.3867
4.3811
3.8791
3.8736
3.8648
3.8592
3.7694
1.5562
1.5054
1.4661
1.3955


13C NMR (CDCl3, 125 MHz)
05260601 17 1 /opt/topspin 2006
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
166.2778
142.7679
134.3501
131.6708
129.1999
127.6126
124.3613
112.0817
110.6417
85.6794
79.6455
76.8323
76.6151
51.9094
27.4227
26.9433
26.3141
25.7177
E-3.14
[rel]
[ppm]


1H NMR (CDCl3, 500 MHz)
major-3.12
TMSO
CO2Me
SPh
0.1545
1.3120
1.4539
1.4884
1.5097
2.3081
2.3131
2.3188
2.3243
2.3310
2.3360
2.4705
2.4767
2.4885
2.9416
2.9485
2.9546
2.9614
3.7111
3.9695
3.9712
3.9805
3.9852
3.9870
3.9925
4.0011
4.0132
4.3629
4.3751
4.3767
5.4152
5.4310
5.5439
5.5463
5.5644
5.5668
5.8505
5.8548
5.8709
5.8753
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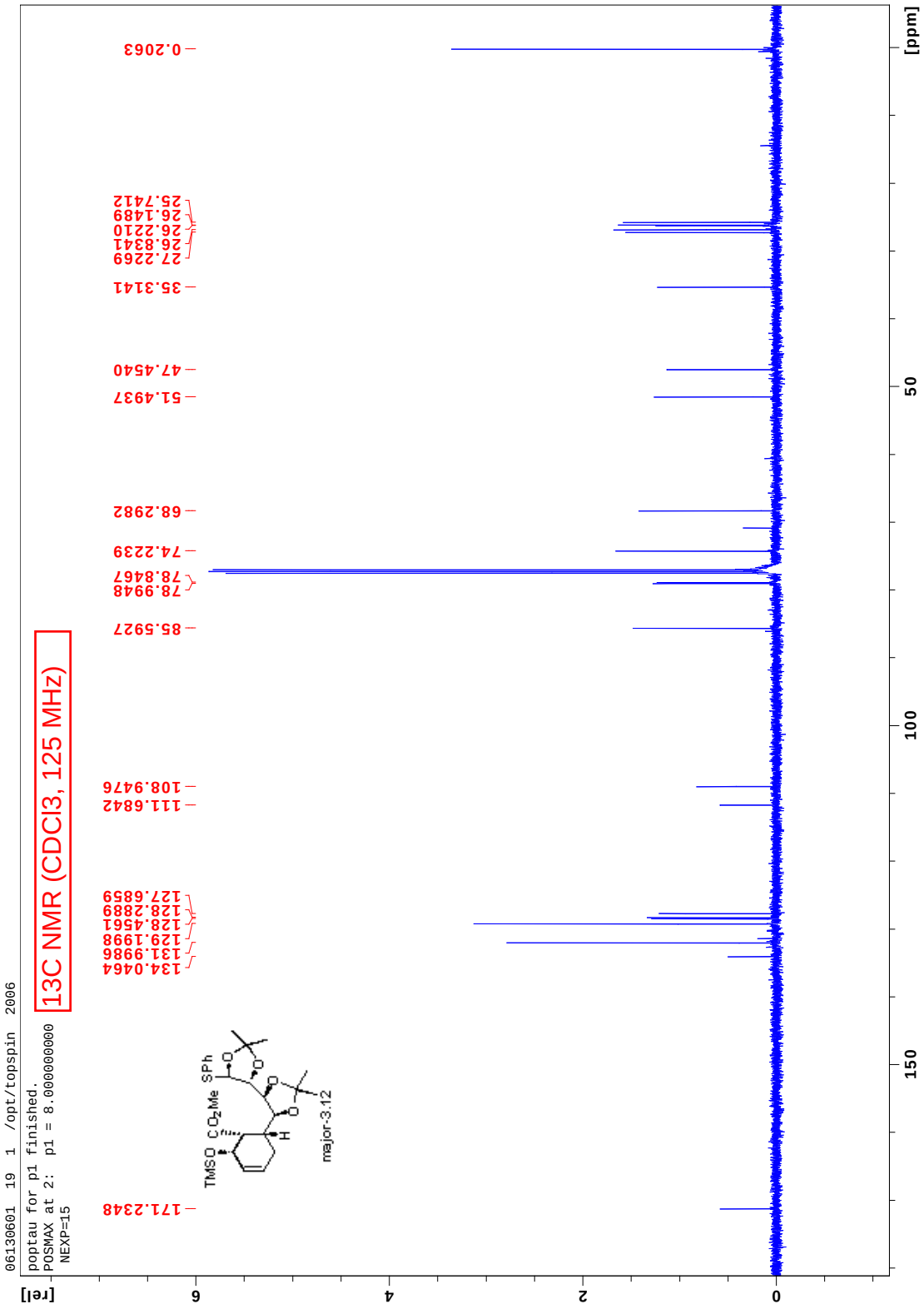
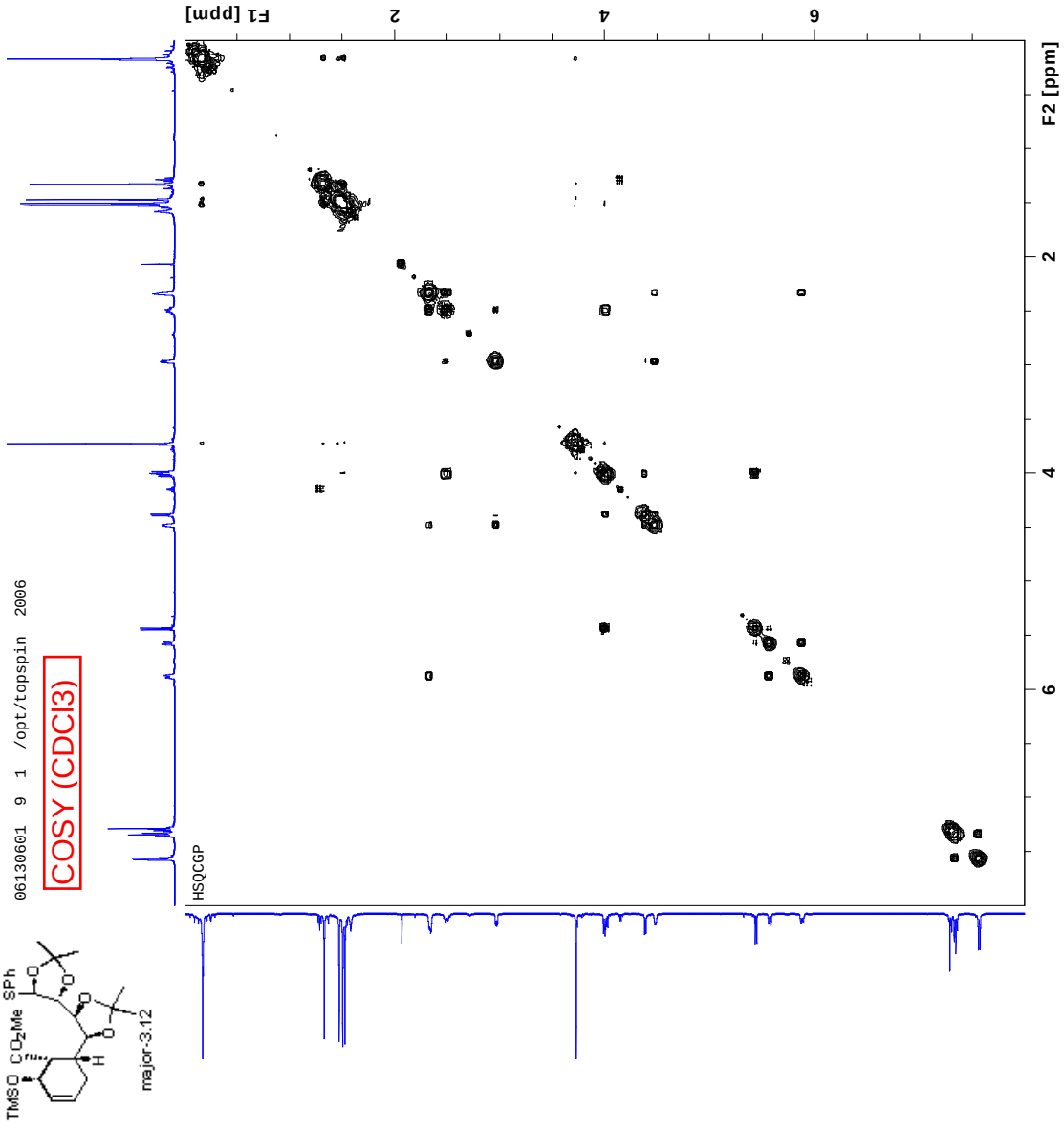
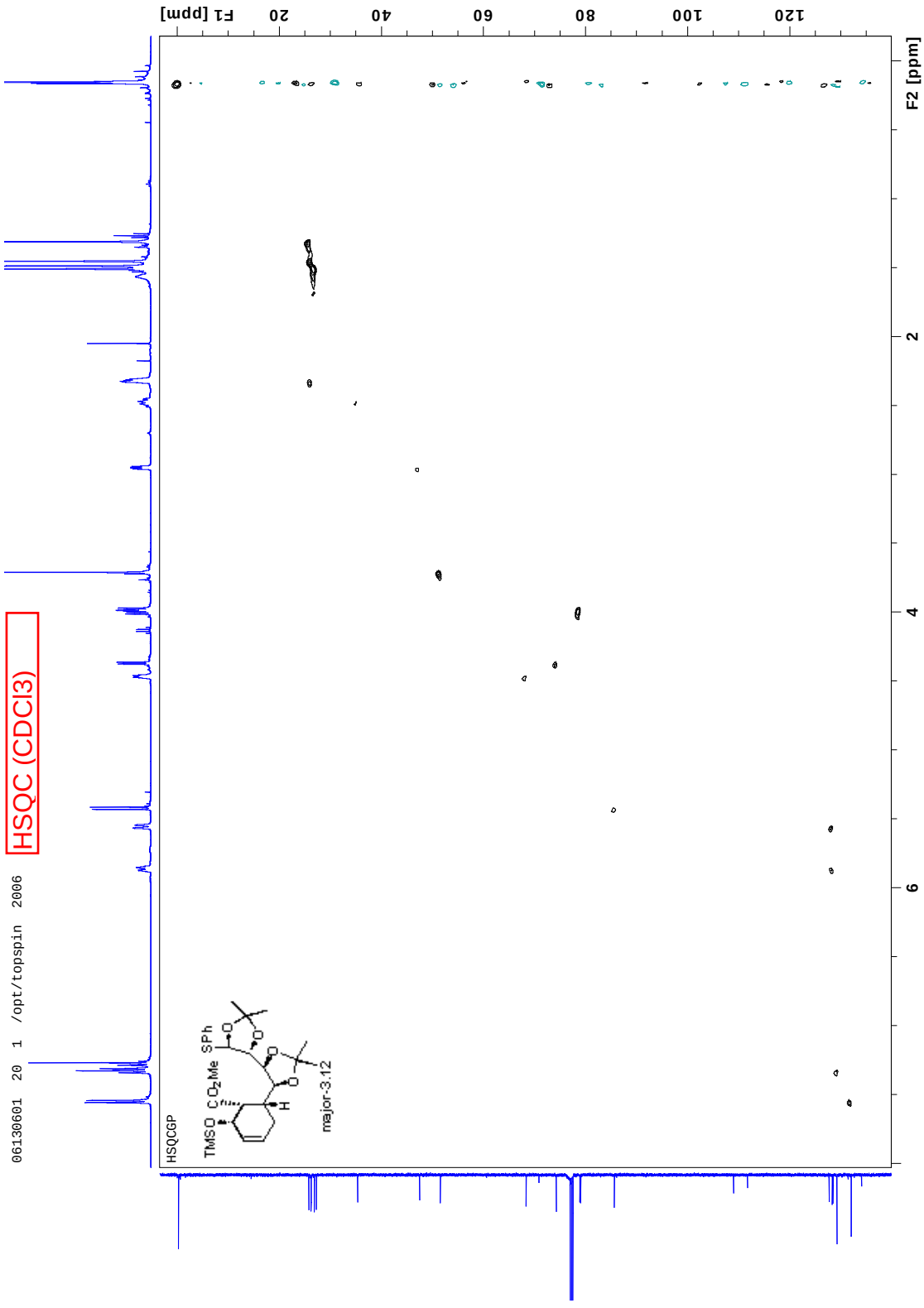
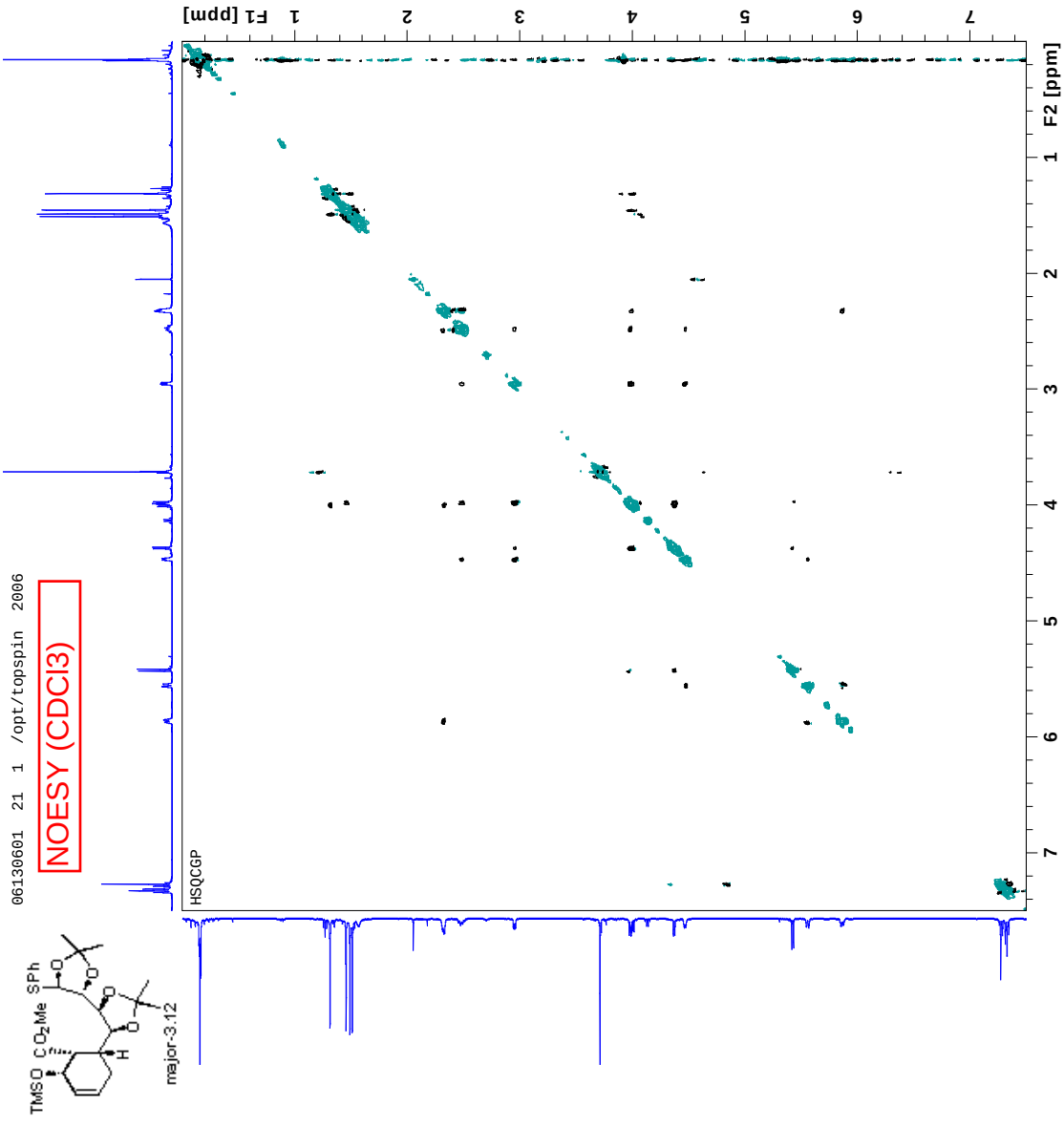
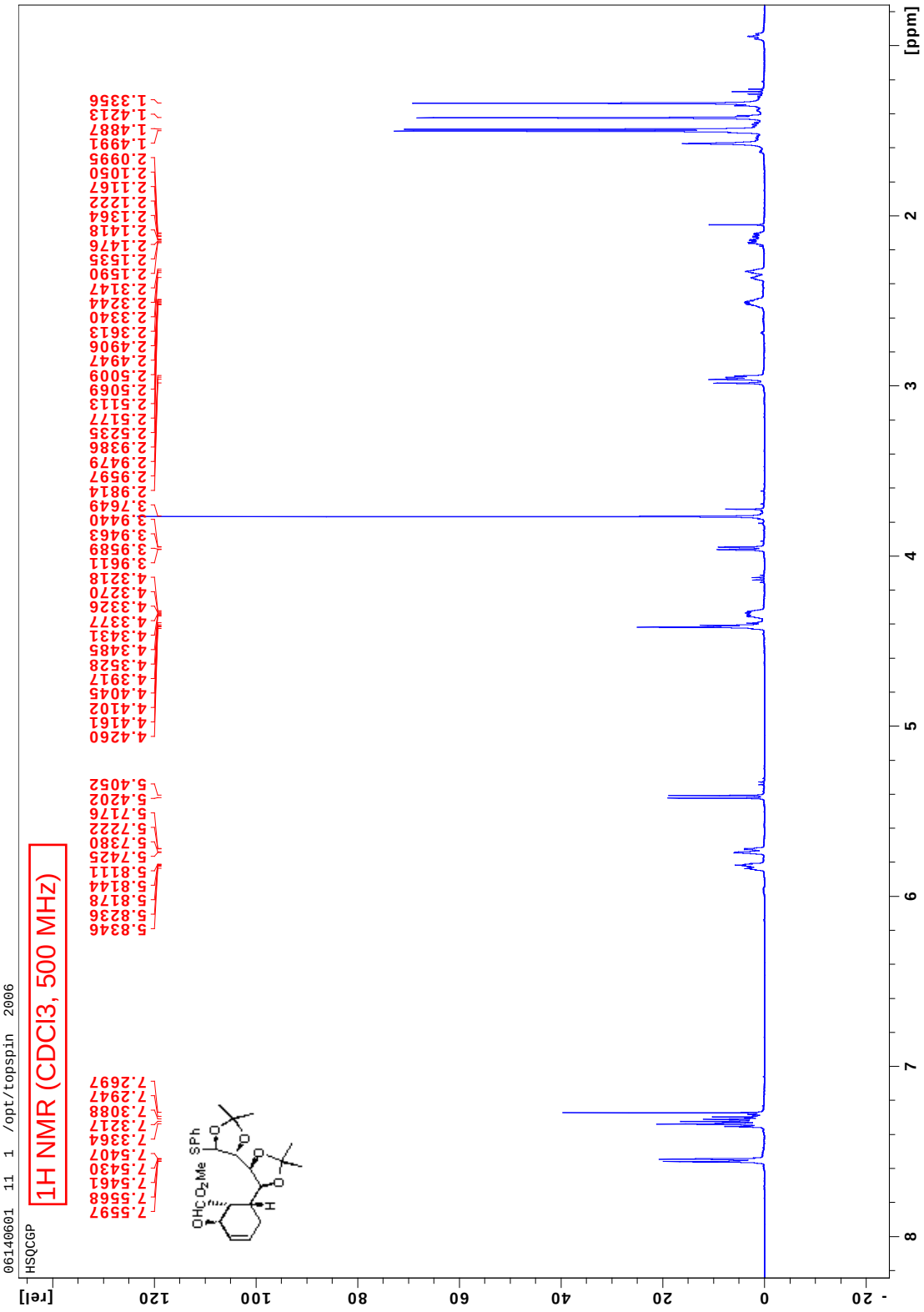
7.3123
7.3275
7.5417
7.5434
7.5576
7.5604
[rel]
[ppm]

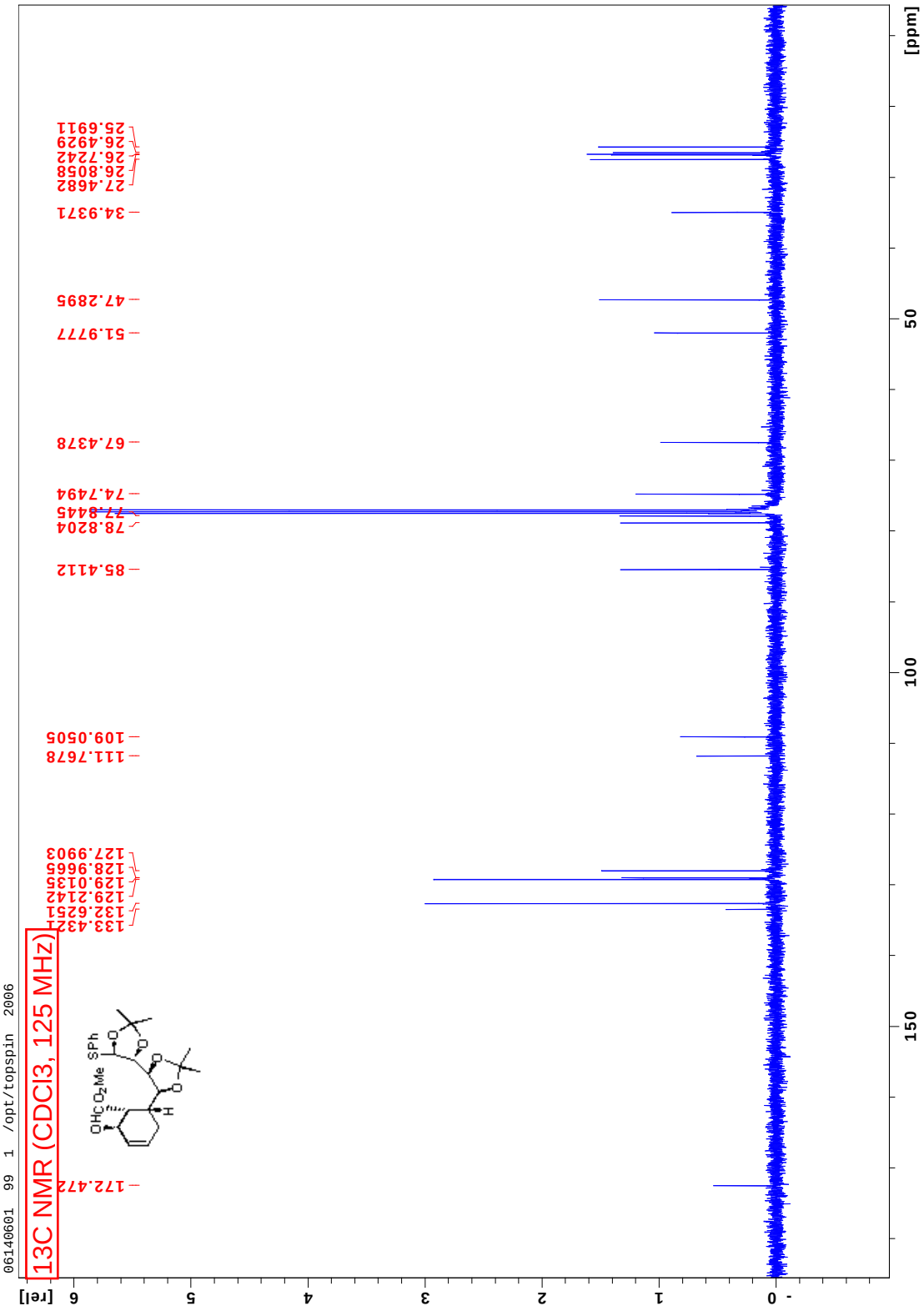

13C NMR (CDCl3, 125 MHz)
06130601 19 1 /opt/topspin 2006
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
major-3.12
TMSO
CO2Me
SPh
171.2348
134.0464
131.9986
129.1998
128.4561
128.2889
127.6859
111.6842
108.9476
85.5927
78.9948
78.8467
74.2239
68.2982
51.4937
47.4540
35.3141
27.2269
26.8341
26.2210
26.1489
25.7412
0.2063
[rel]
[ppm]

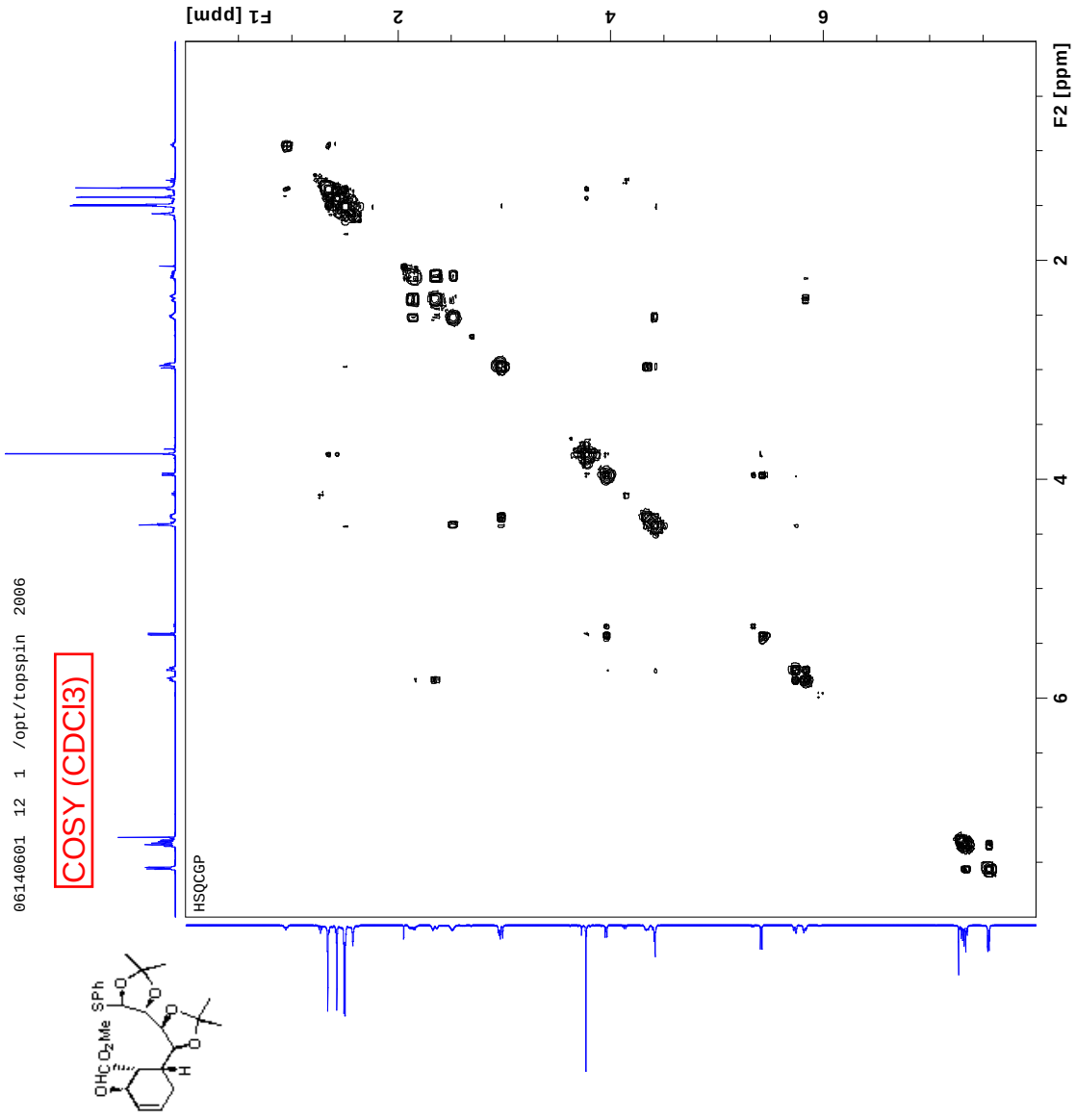

F1 [ppm]
2
4
6
F2 [ppm]
2
4
6
HSQCGP
COSY (CDCl3)
06130601 9 1 /opt/topspin 2006
TMSO CO2Me SPh
major-3:12

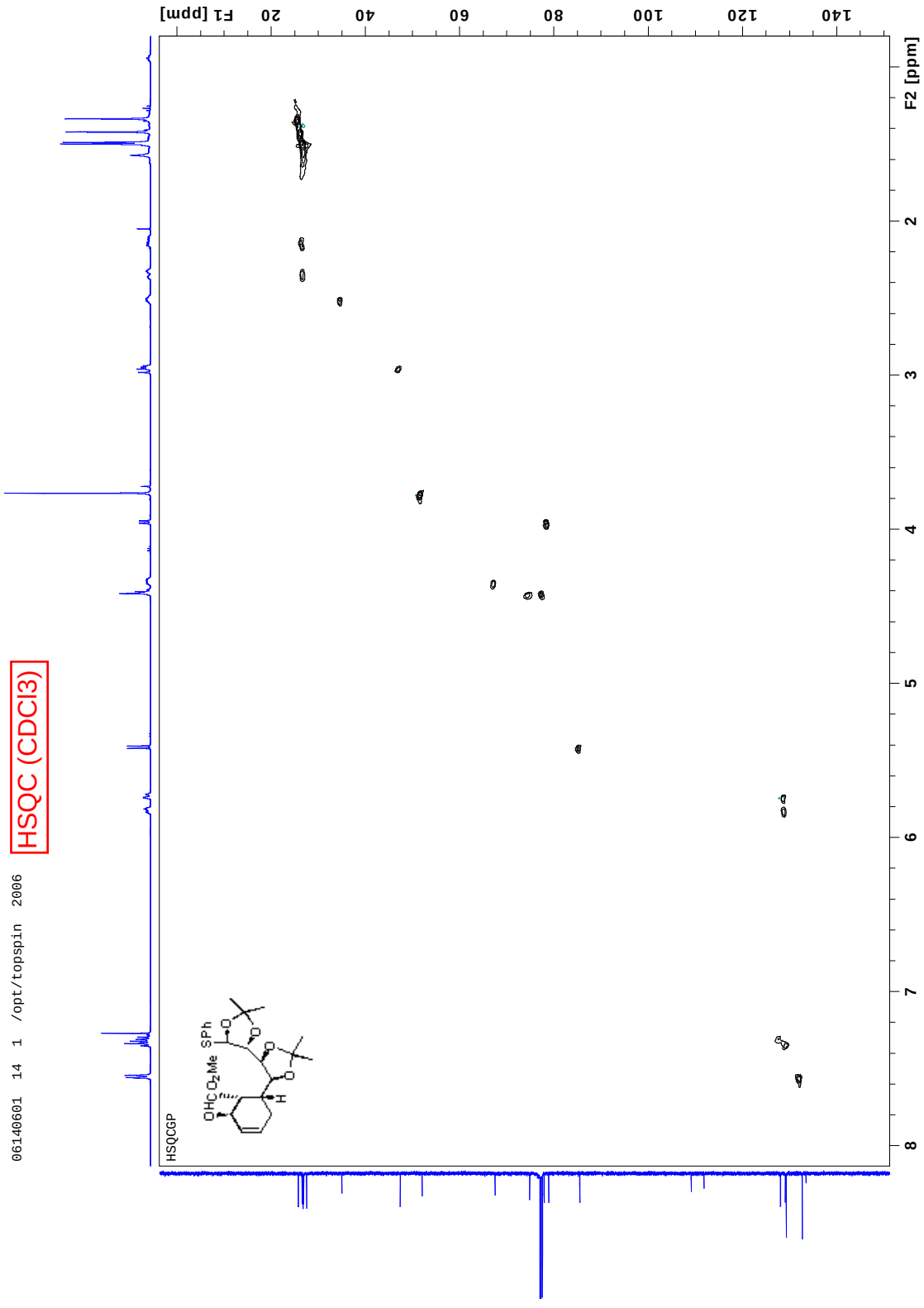

HSQC (CDCl3)
06130601 20 1 /opt/topspin 2006
HSQCGP
TMSO CO2Me SPh
major-3:12
F1 [ppm]
F2 [ppm]


NOESY (CDCl3)
06130601 21 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
major-3.12


1H NMR (CDCl3, 500 MHz)
HSQCGP
06140601 11 1 /opt/topspin 2006
[rel]
[ppm]
7.5597
7.5568
7.5461
7.5430
7.5407
7.3364
7.3217
7.3088
7.2947
7.2697
5.8346
5.8236
5.8178
5.8144
5.8111
5.7425
5.7380
5.7222
5.7176
5.4202
5.4052
4.4260
4.4161
4.4102
4.4045
4.3917
4.3528
4.3485
4.3431
4.3377
4.3326
4.3270
4.3218
3.9611
3.9589
3.9463
3.9440
3.7649
2.9814
2.9597
2.9479
2.9386
2.5235
2.5177
2.5113
2.5069
2.5009
2.4947
2.4906
2.3613
2.3340
2.3244
2.3147
2.1590
2.1535
2.1476
2.1418
2.1364
2.1222
2.1167
2.1050
2.0995
1.4991
1.4887
1.4213
1.3356
SPh
CO2Me
OH
H
O
O
O


13C NMR (CDCl3, 125 MHz)
06140601 99 1 /opt/topspin 2006
[rel]
[ppm]
172.472
133.432
132.6251
129.2142
129.0135
128.9665
127.9903
111.7678
109.0505
85.4112
78.8204
77.8445
74.7494
67.4378
51.9777
47.2895
34.9371
27.4682
26.8058
26.7242
26.4929
25.6911
SPh
OHC
CO2Me
H


COSY (CDCl3)
061406O1 12 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
2
4
6
SPh
OHC
CO2Me
H
O


HSQC (CDCl3)
06140601 14 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
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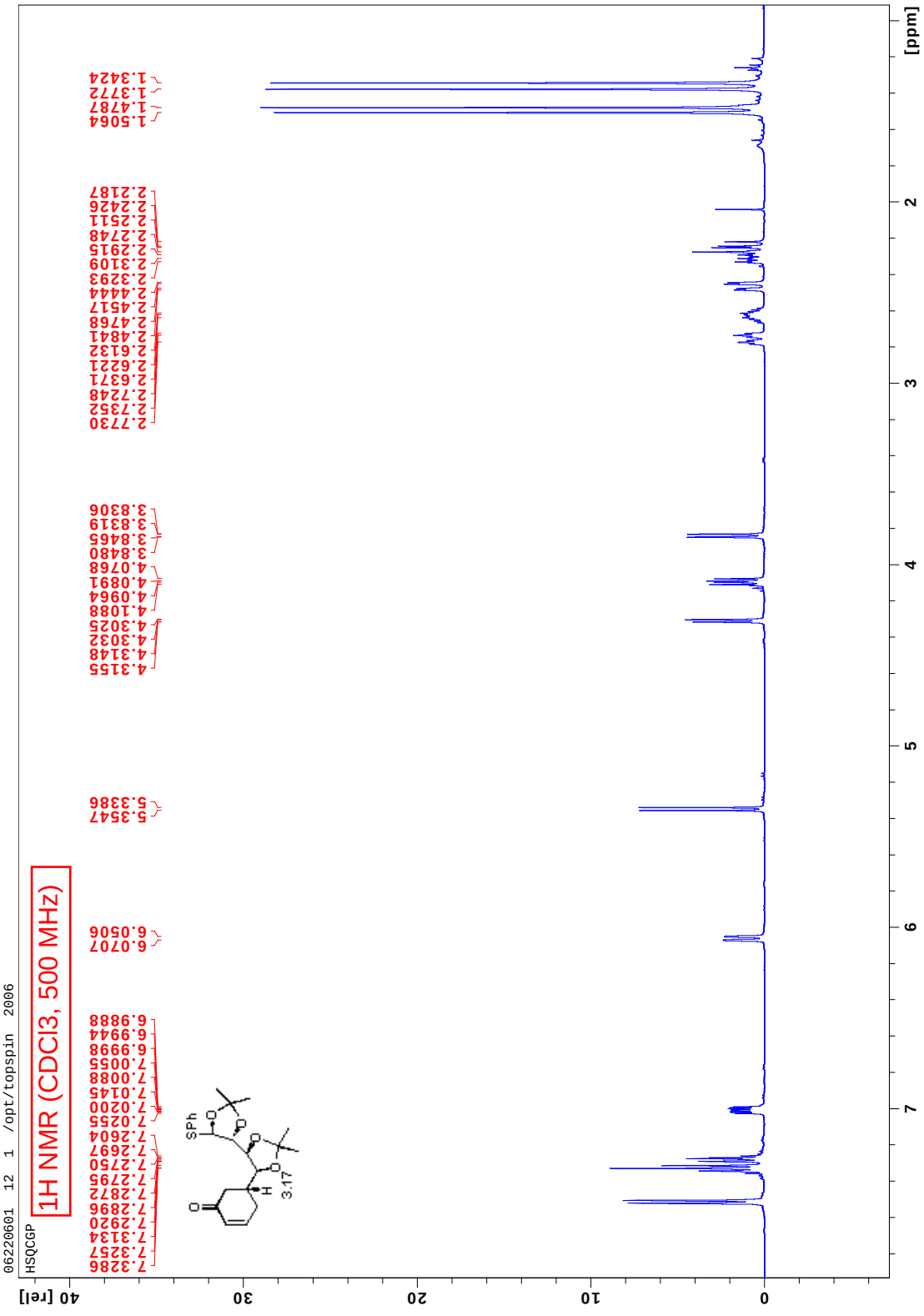
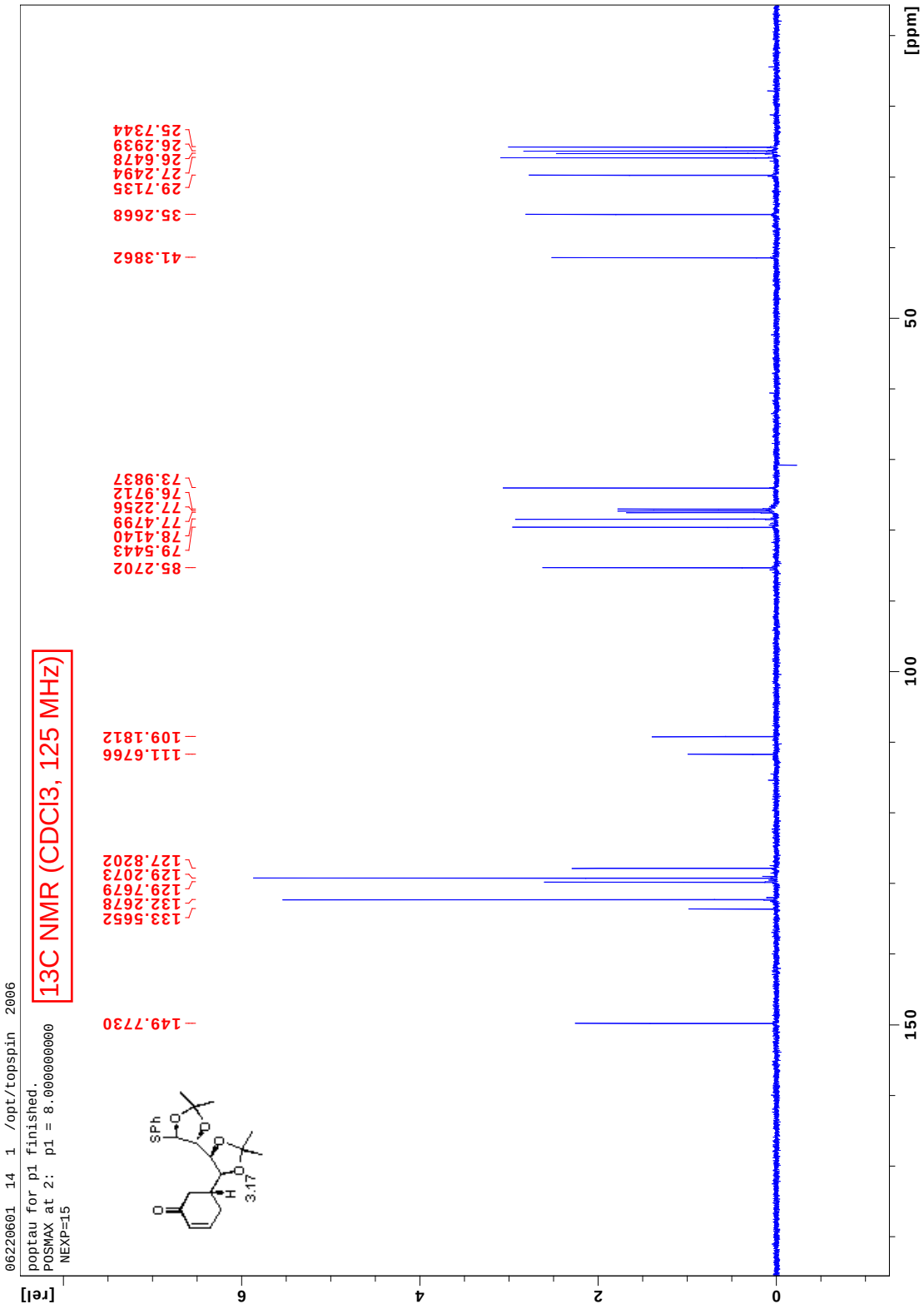
40
60
80
100
120
140
1
2
3
4
5
6
7
8
SPh
OHC
CO2Me
H


1H NMR (CDCl3, 500 MHz)
HSQCGP
06220601 12 1 /opt/topspin 2006
SPh
3.17
7.3286
7.3257
7.3134
7.2920
7.2896
7.2872
7.2795
7.2750
7.2697
7.2604
7.0255
7.0200
7.0145
7.0088
7.0055
6.9998
6.9944
6.9888
6.0707
6.0506
5.3547
5.3386
4.3155
4.3148
4.3032
4.3025
4.1088
4.0964
4.0891
4.0768
3.8480
3.8465
3.8319
3.8306
2.7730
2.7352
2.7248
2.6371
2.6221
2.6132
2.4841
2.4768
2.4517
2.4444
2.3293
2.3109
2.2915
2.2748
2.2511
2.2426
2.2187
1.5064
1.4787
1.3772
1.3424
40 [rel]
30
20
10
0
7
6
5
4
3
2
[ppm]


13C NMR (CDCl3, 125 MHz)
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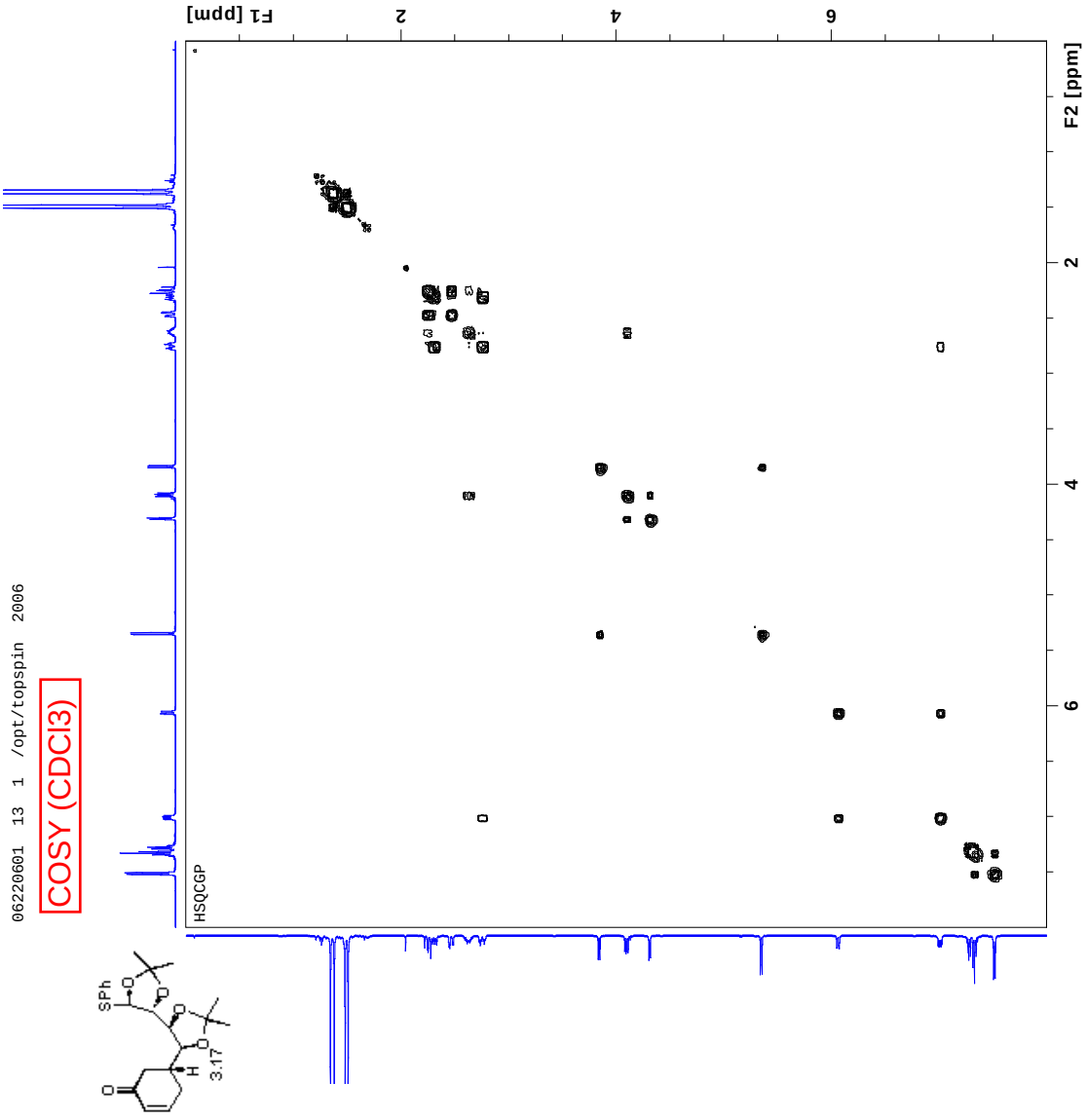
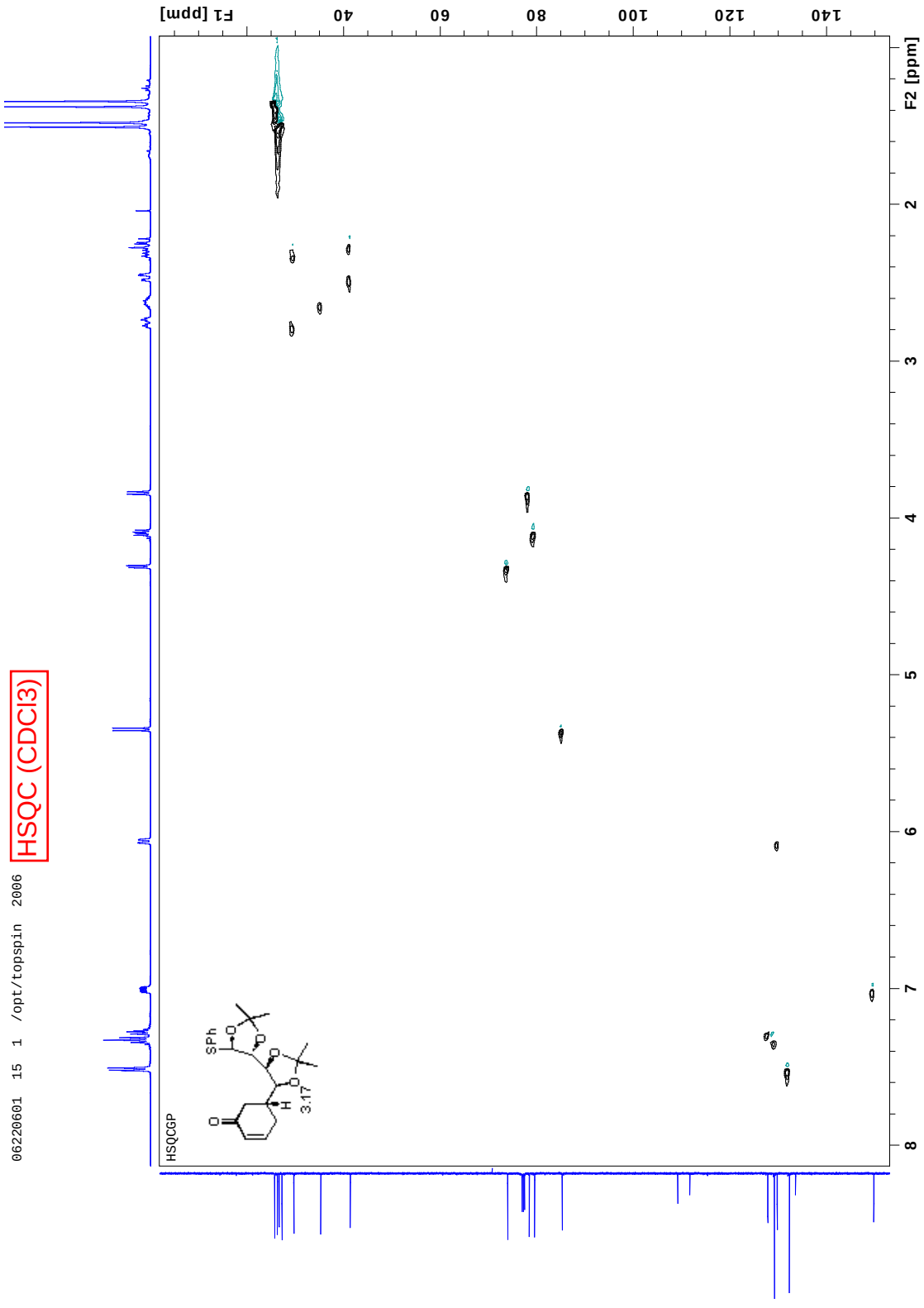
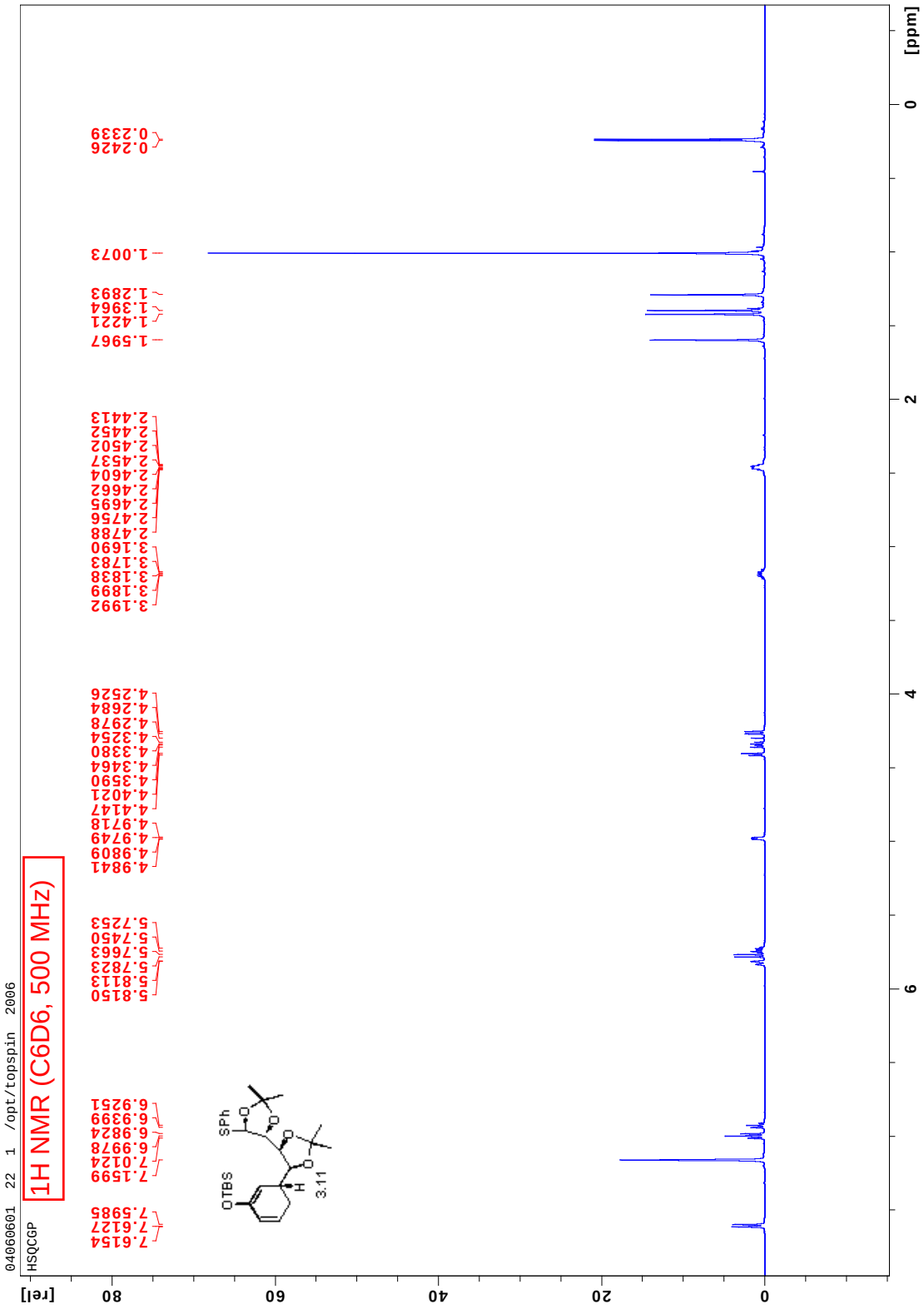
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
149.7730
133.5652
132.2678
129.7679
129.2073
127.8202
111.6766
109.1812
85.2702
79.5443
78.4140
77.4799
77.2256
76.9712
73.9837
41.3862
35.2668
29.7135
27.2494
26.6478
26.2939
25.7344
SPh
3.17
[rel]
[ppm]


COSY (CDCl3)
06220601 13 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
2
4
6
SPh
O
O
O
O
H
3.17
O


HSQC (CDCl3)
06220601 15 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
SPh
3.17


1H NMR (C6D6, 500 MHz)
04060601 22 1 /opt/topspin 2006
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60
40
20
0
[ppm]
0
2
4
6
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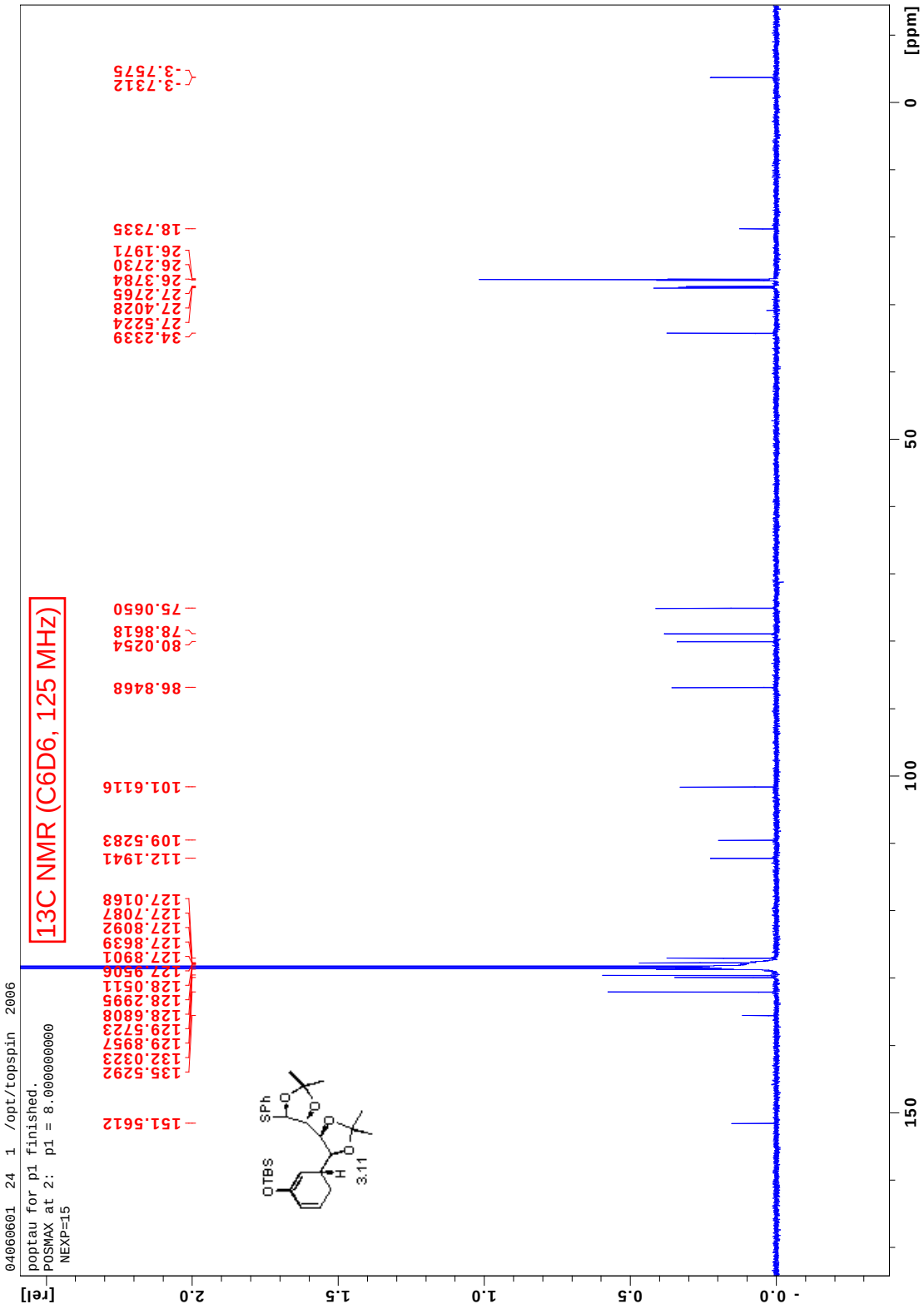
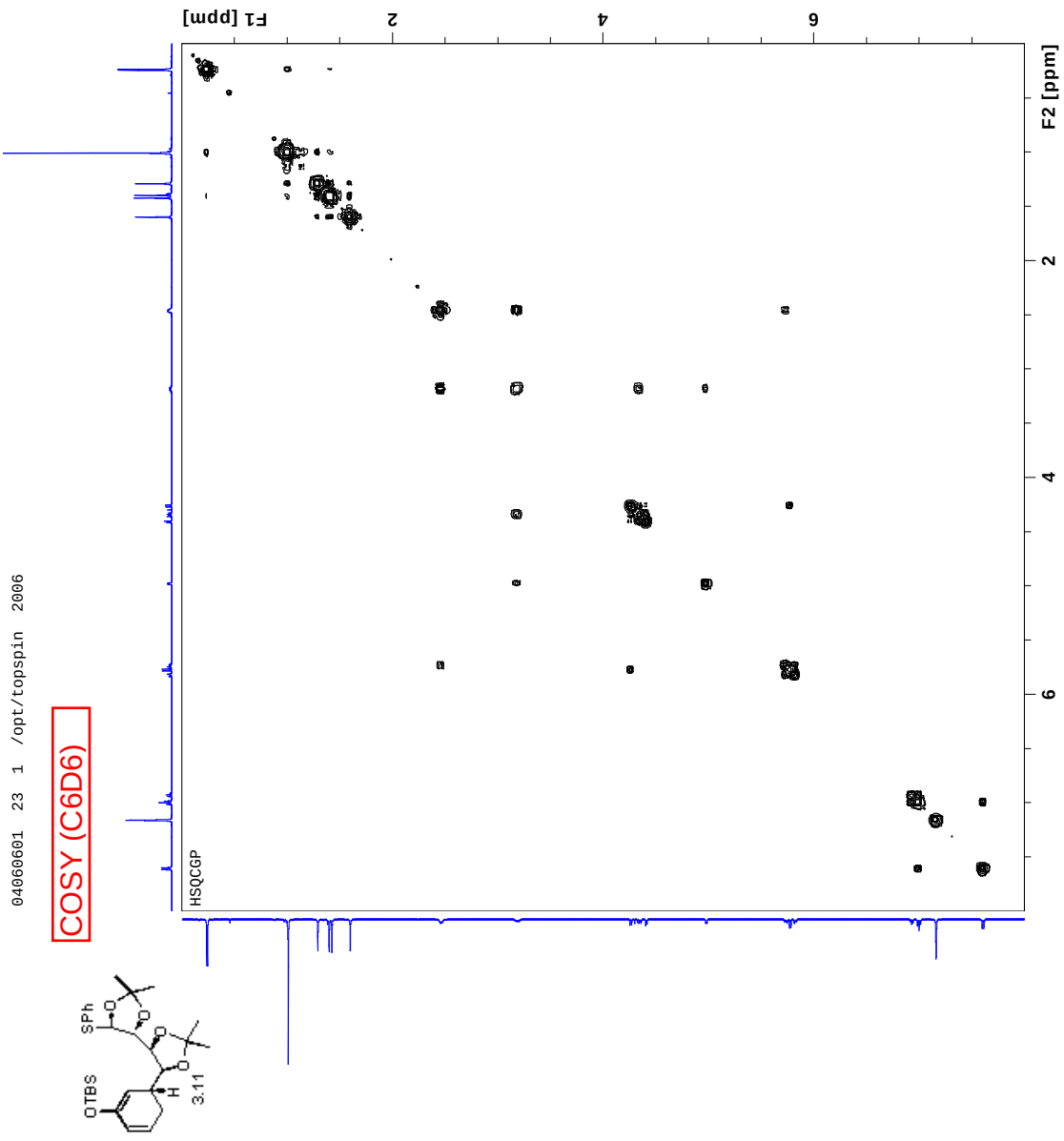
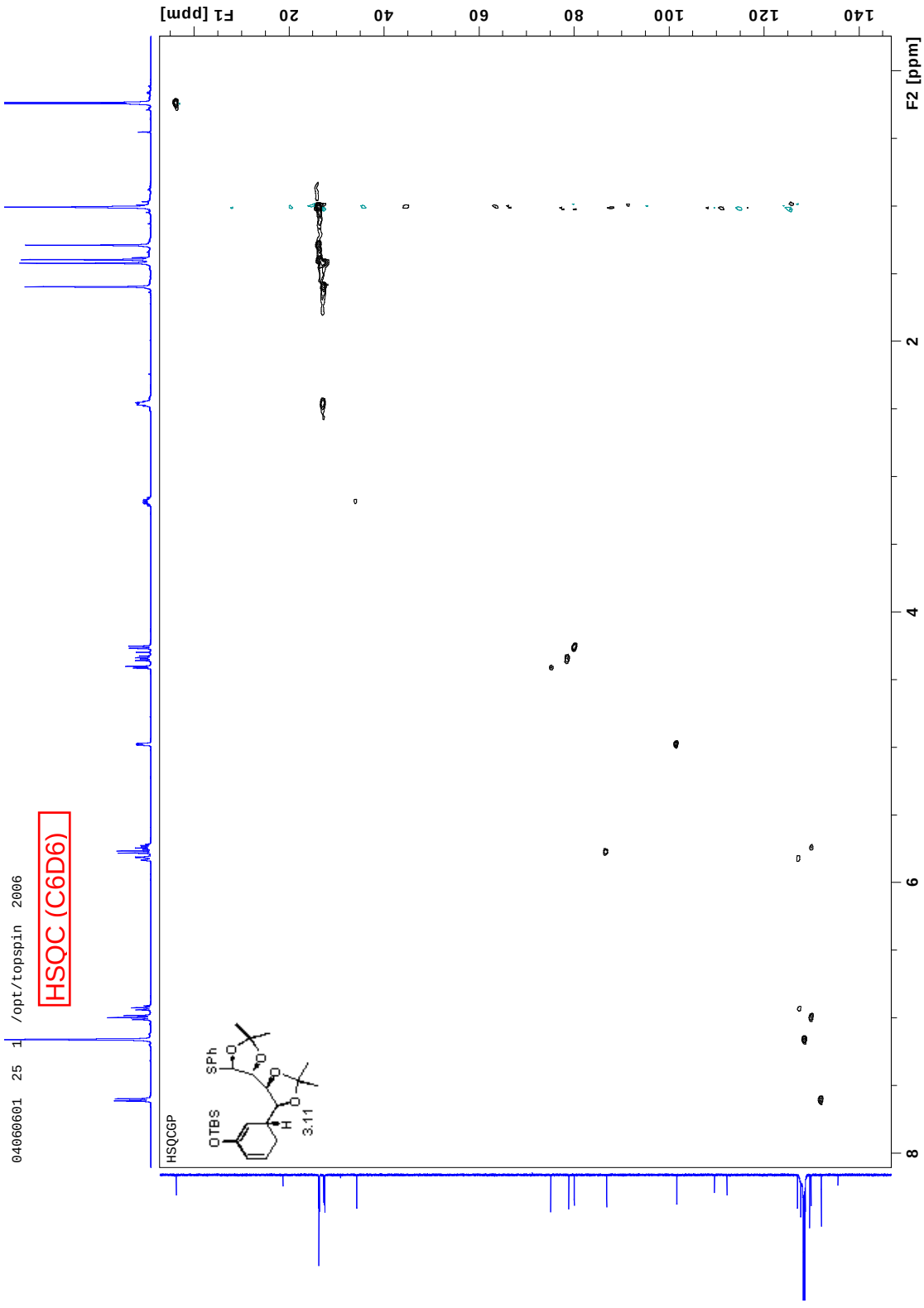
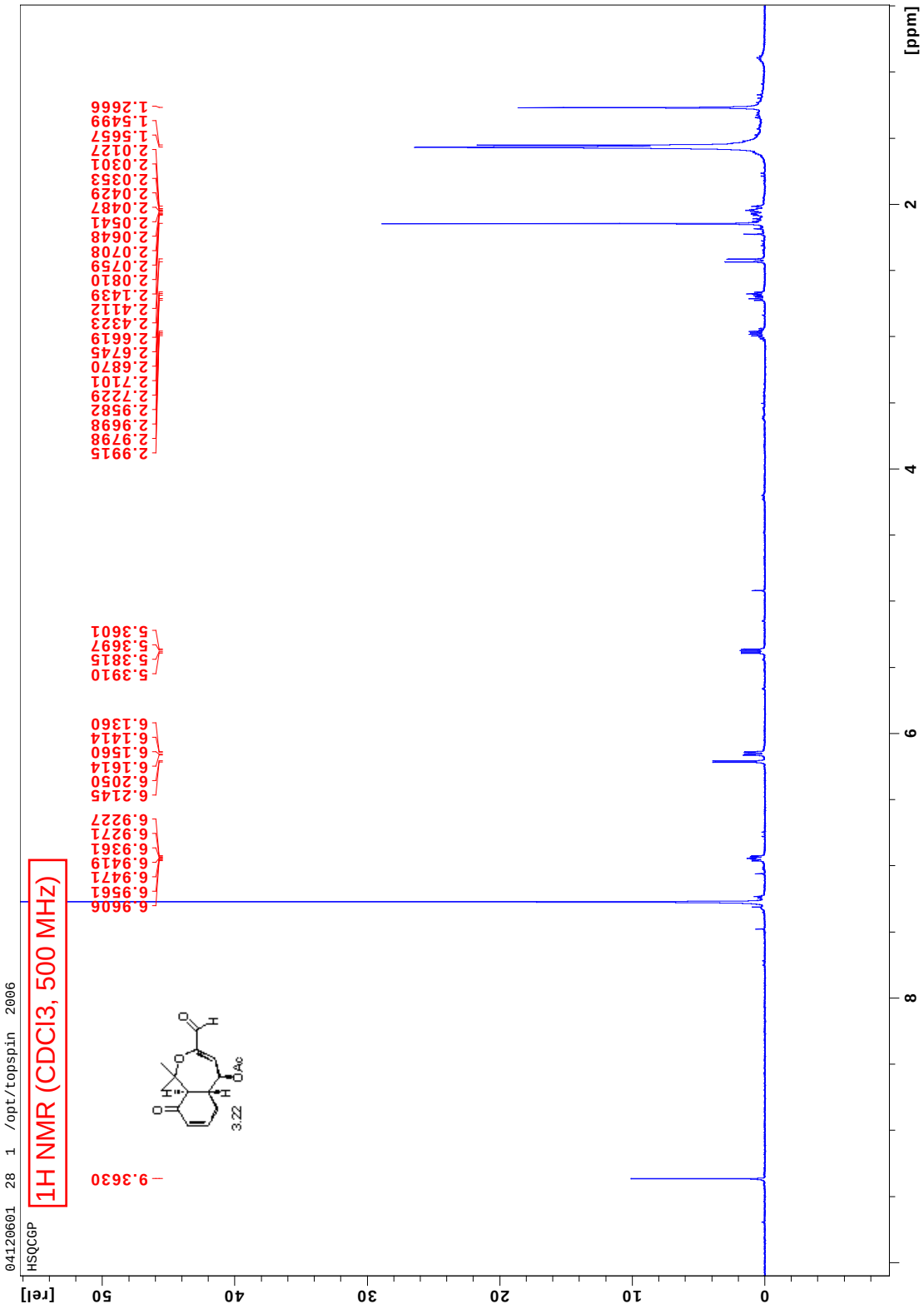
0.2426
1.0073
1.2893
1.3964
1.4221
1.5967
2.4413
2.4452
2.4502
2.4537
2.4604
2.4662
2.4695
2.4756
2.4788
3.1690
3.1783
3.1838
3.1899
3.1992
4.2526
4.2684
4.2978
4.3254
4.3380
4.3464
4.3590
4.4021
4.4147
4.9718
4.9749
4.9809
4.9841
5.7253
5.7450
5.7663
5.7823
5.8113
5.8150
6.9251
6.9399
6.9824
6.9978
7.0124
7.1599
7.5985
7.6127
7.6154
OTBS
SPh
H
3.11


13C NMR (C6D6, 125 MHz)
04060601 24 1 /opt/topspin 2006
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
OTBS
SPh
3.11
-3.7312
-3.7575
18.7335
26.1971
26.2730
26.3784
27.2765
27.4028
27.5224
34.2339
75.0650
78.8618
80.0254
86.8468
101.6116
109.5283
112.1941
127.0168
127.7087
127.8092
127.8639
127.8901
127.9506
128.0511
128.2995
128.6808
129.5723
129.8957
132.0323
135.5292
151.5612


COSY (C6D6)
040060601 23 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
2
4
6
SPh
OTBS
3.11


HSQC (C6D6)
040606O1 25 1 /opt/topspin 2006
HSQCGP
OTBS
SPh
3.11
F1 [ppm]
F2 [ppm]


1H NMR (CDCl3, 500 MHz)
04120601 28 1 /opt/topspin 2006
HSQCGP
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6.9561
6.9471
6.9419
6.9361
6.9271
6.9227
6.2145
6.2050
6.1614
6.1560
6.1414
6.1360
5.3910
5.3815
5.3697
5.3601
2.9915
2.9798
2.9698
2.9582
2.7229
2.7101
2.6870
2.6745
2.6619
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2.0487
2.0429
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2.0301
2.0127
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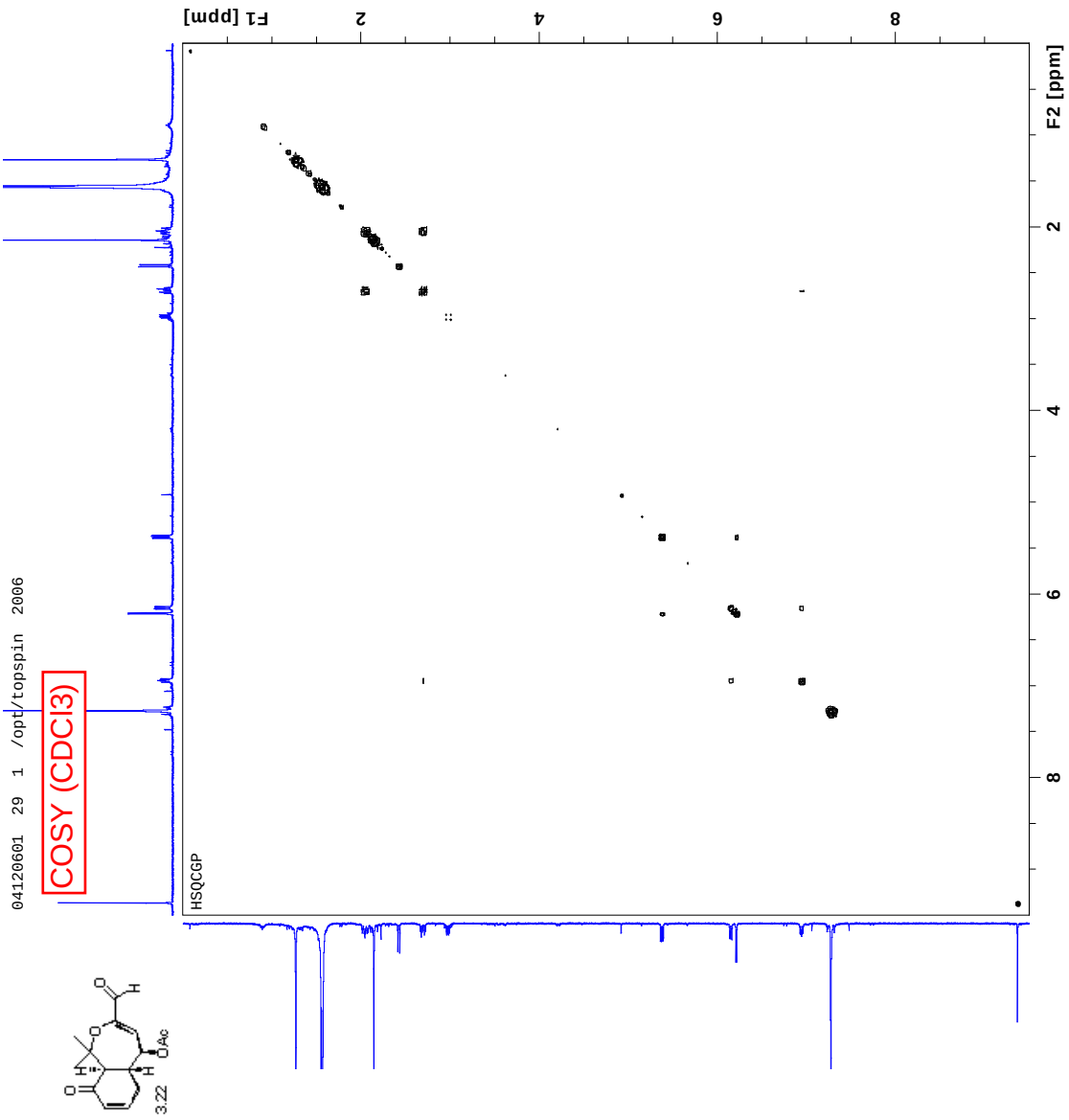
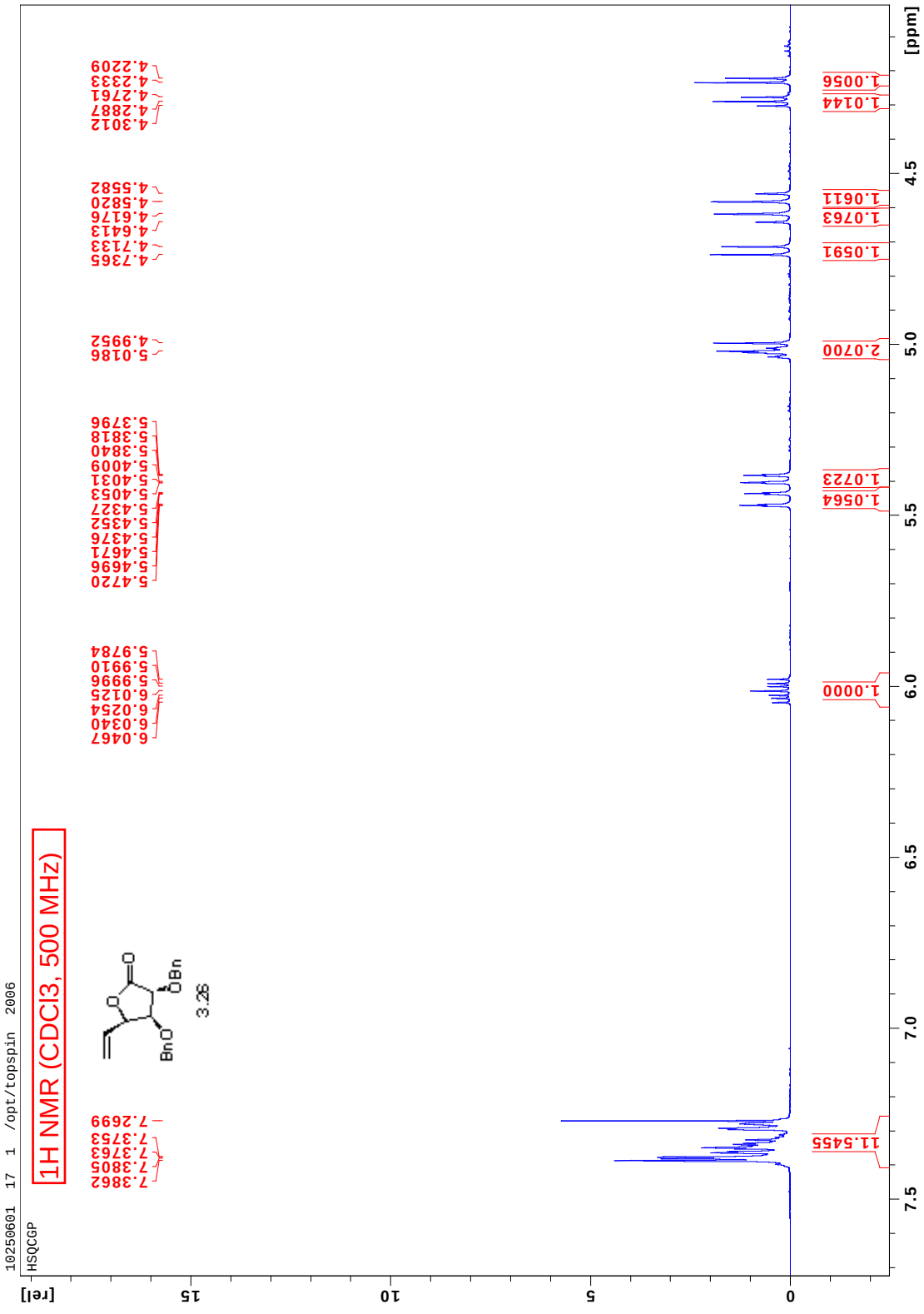
1.5499
1.2666
3.22
OAc
[rel]
[ppm]


COSY (CDCl3)
04120601 29 1 /opt/topspin 2006
HSQCGP
F1 [ppm]
F2 [ppm]
2
4
6
8
OAc
3.22


1H NMR (CDCl3, 500 MHz)
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HSQCGP
[rel]
[ppm]
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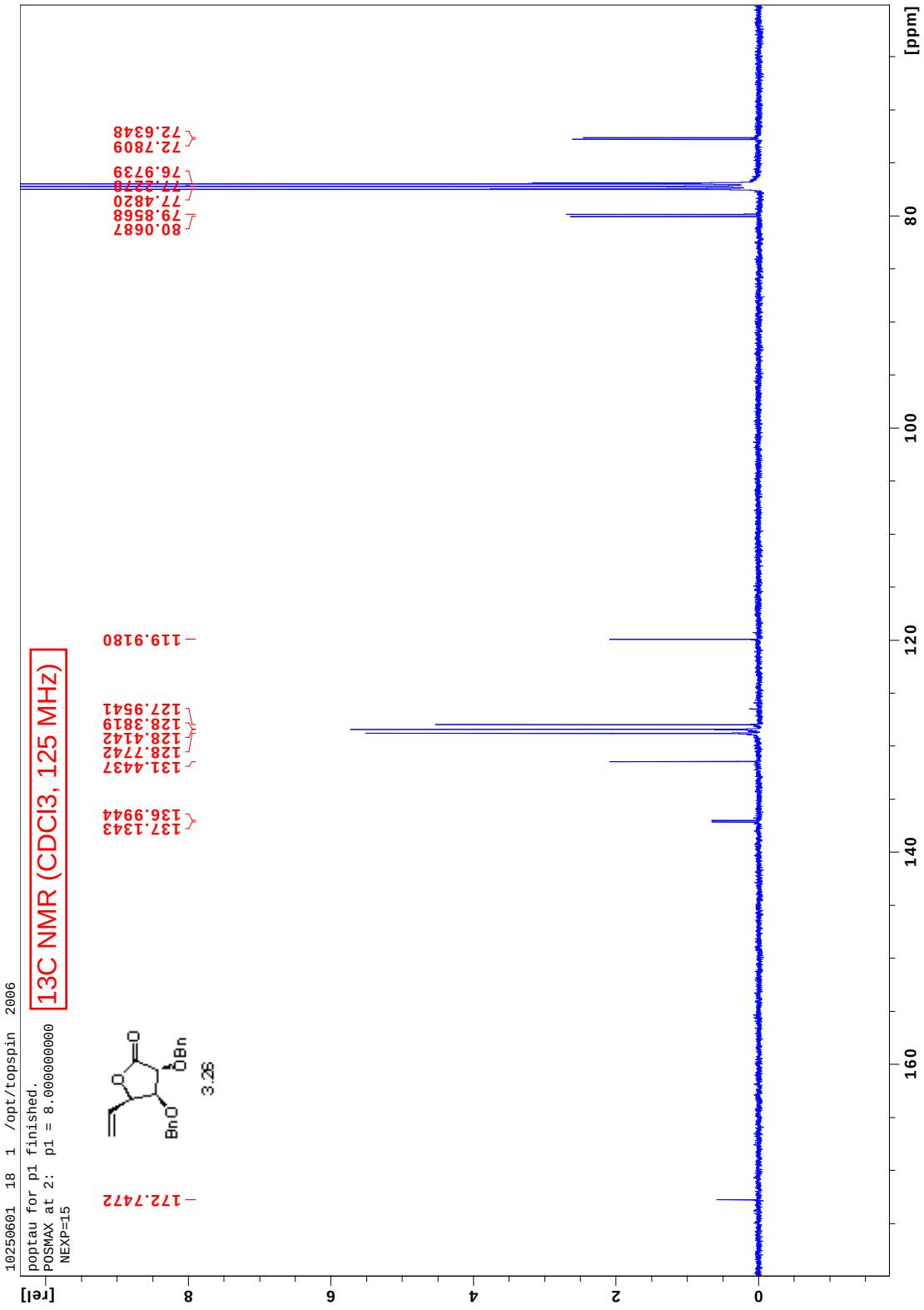
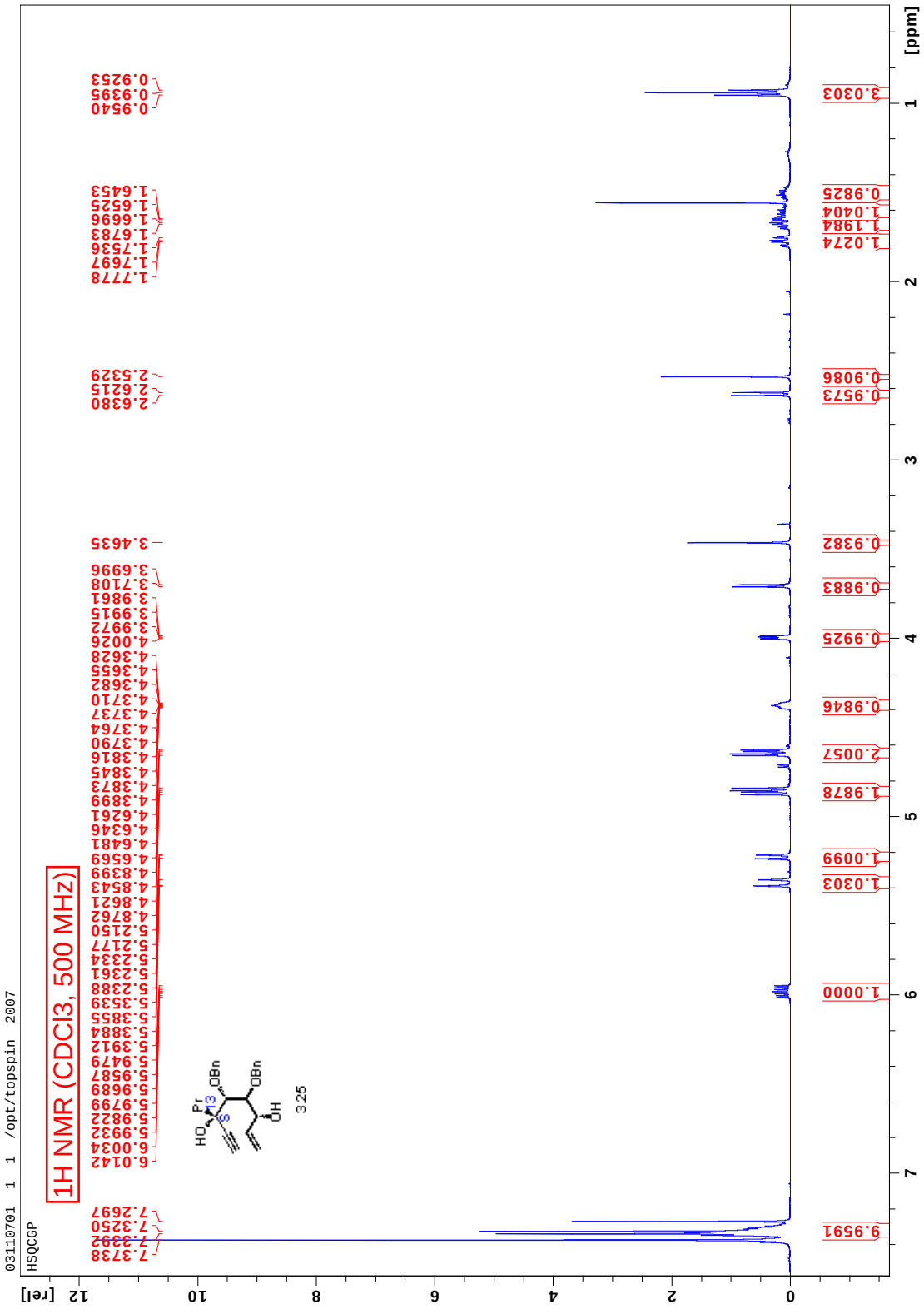
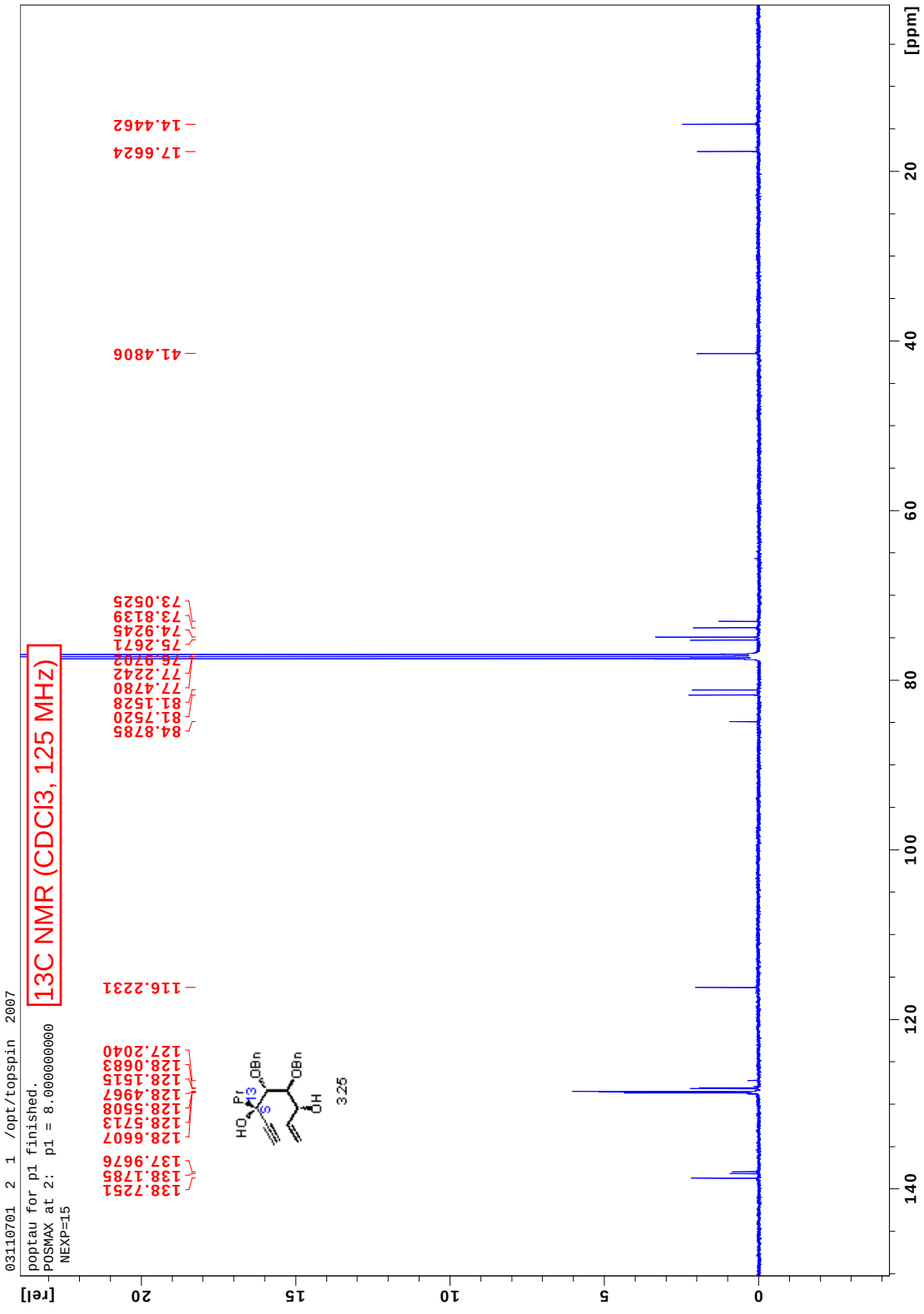
2.0700
1.0564
1.0723
1.0591
1.0763
1.0611
1.0144
1.0056
7.3862
7.3805
7.3763
7.3753
7.2699
6.0467
6.0340
6.0254
6.0125
5.9996
5.9910
5.9784
5.4720
5.4696
5.4671
5.4376
5.4352
5.4327
5.4053
5.4031
5.4009
5.3840
5.3818
5.3796
5.0186
4.9952
4.7365
4.7133
4.6413
4.6176
4.5820
4.5582
4.3012
4.2887
4.2761
4.2333
4.2209
OBn
BnO
3.26


13C NMR (CDCl3, 125 MHz)
10250601 18 1 /opt/topspin 2006
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
3.26
OBn
BnO
172.7472
137.1343
136.9944
131.4437
128.7742
128.4142
128.3819
127.9541
119.9180
80.0687
79.8568
77.4820
77.2278
76.9739
72.7809
72.6348
[rel]
[ppm]


1H NMR (CDCl3, 500 MHz)
03110701 1 1 /opt/topspin 2007
HSQCGP
[rel]
[ppm]
OBn
OBn
OH
Pr
HO
3.25


13C NMR (CDCl3, 125 MHz)
03110701 2 1 /opt/topspin 2007
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
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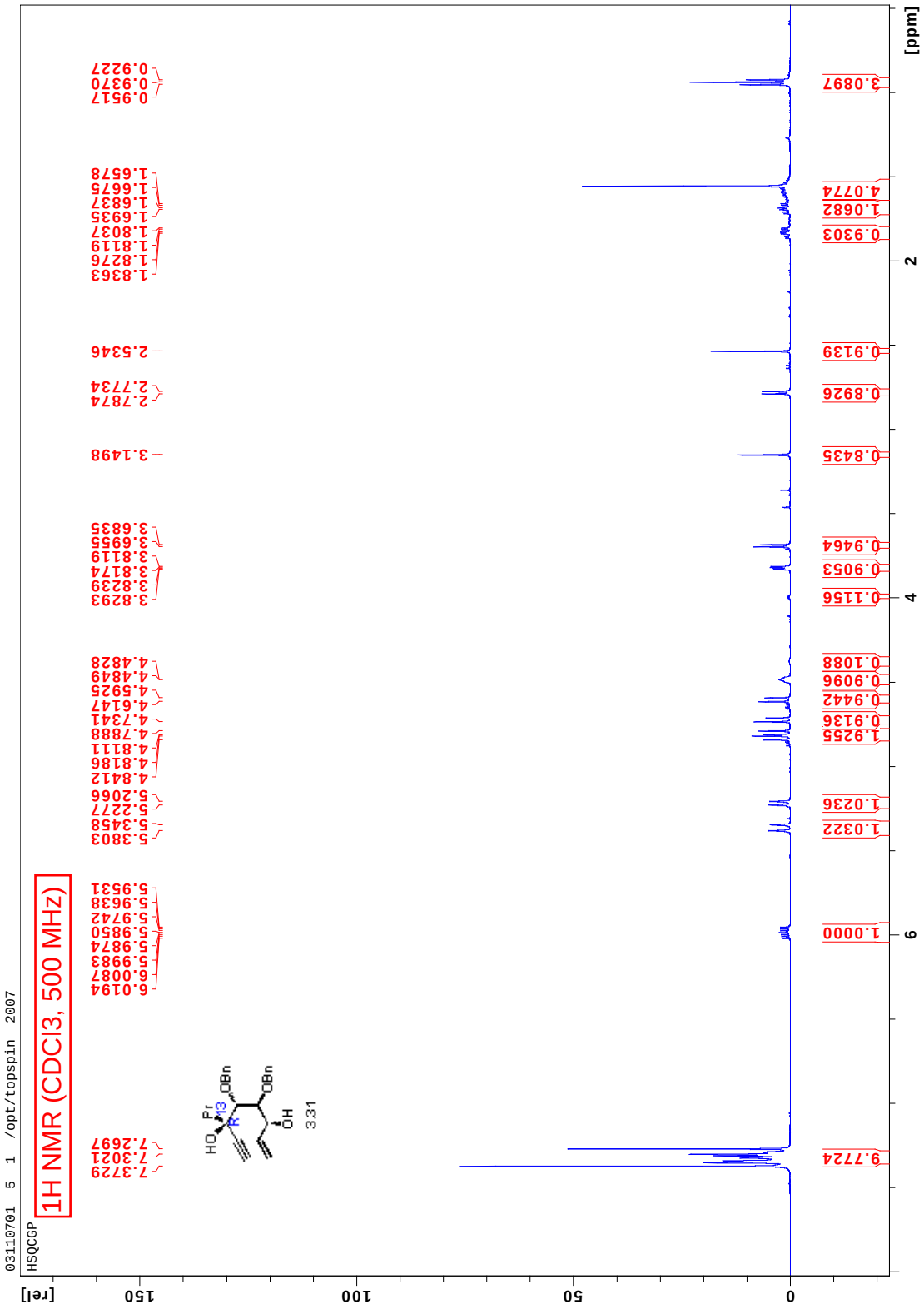
41.4806
73.0525
73.8139
74.9245
75.2671
76.9702
77.2242
77.4780
81.1528
81.7520
84.8785
116.2231
127.2040
128.0683
128.1515
128.4967
128.5508
128.5713
128.6607
137.9676
138.1785
138.7251
OBn
OBn
OH
HO
Pr
3.25


1H NMR (CDCl3, 500 MHz)
HSQCGP
03110701 5 1 /opt/topspin 2007
[rel]
[ppm]
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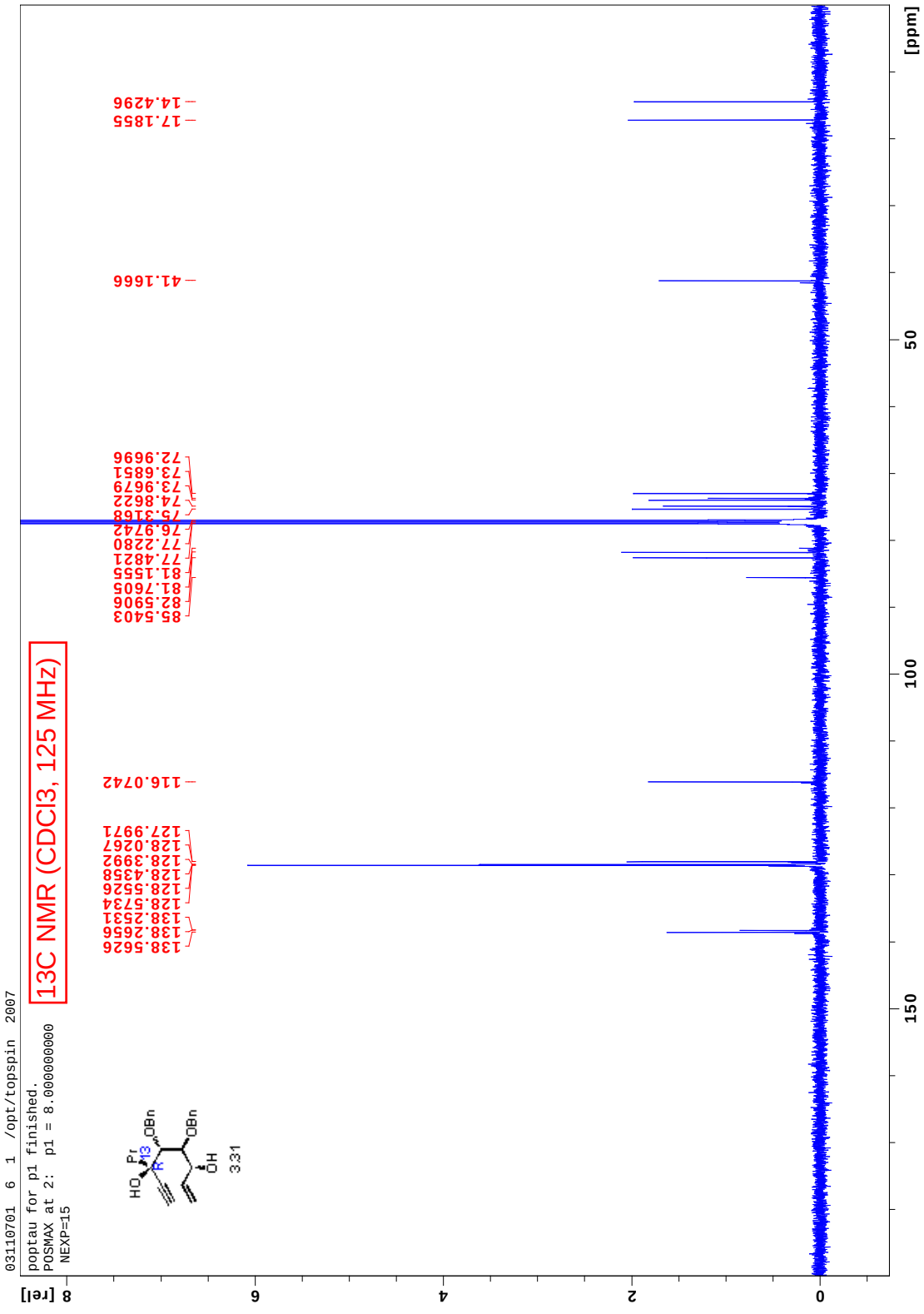
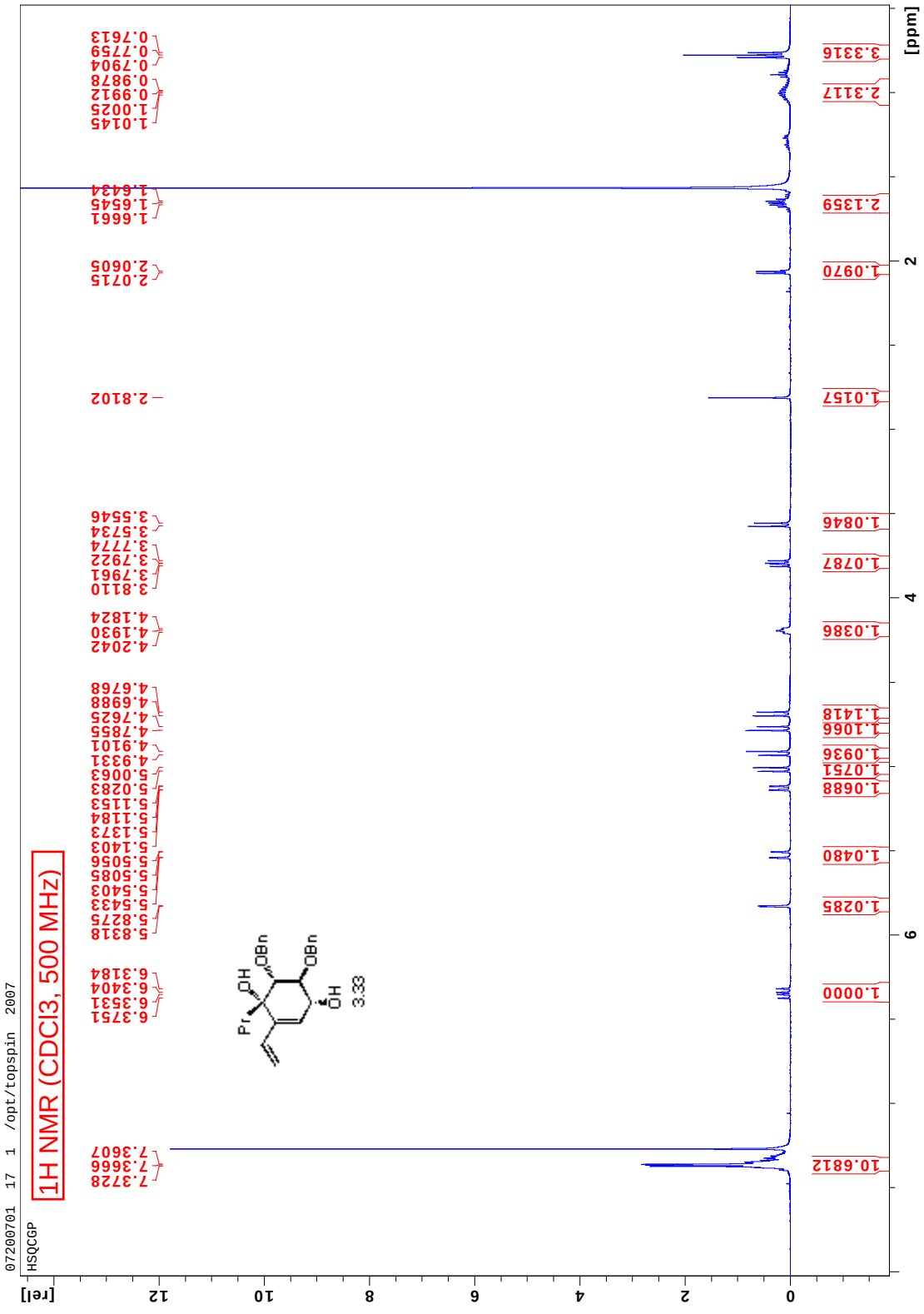
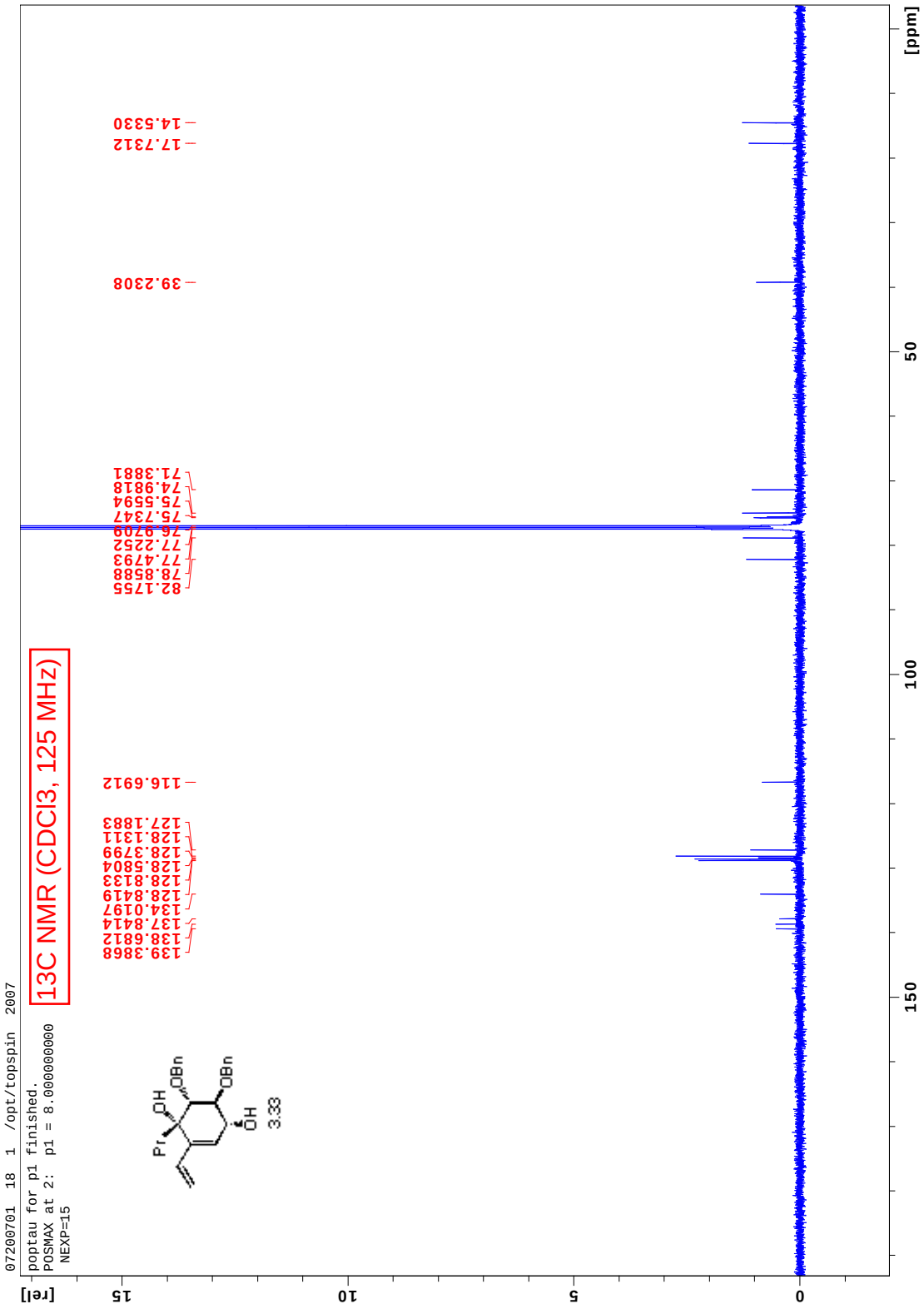
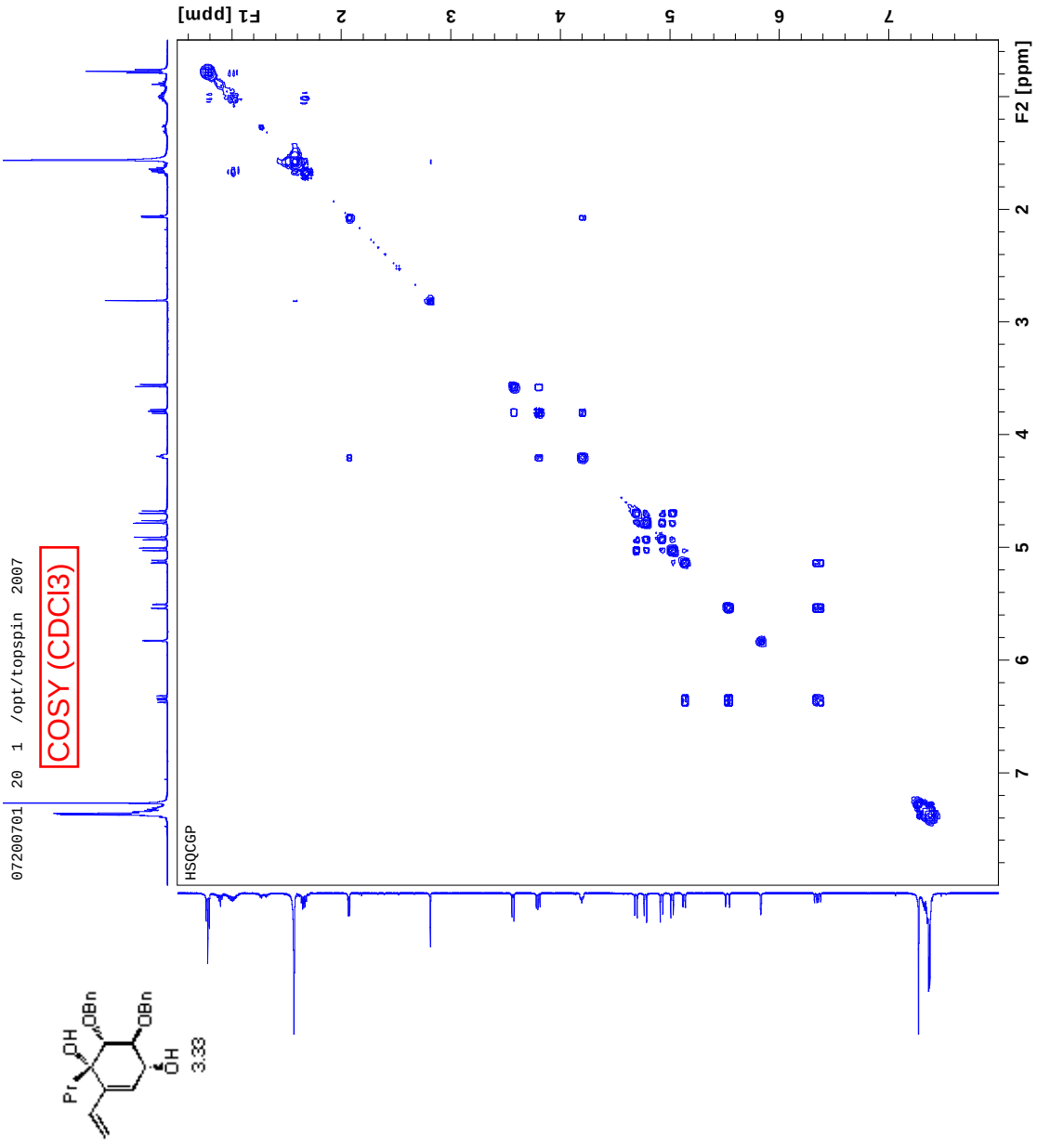
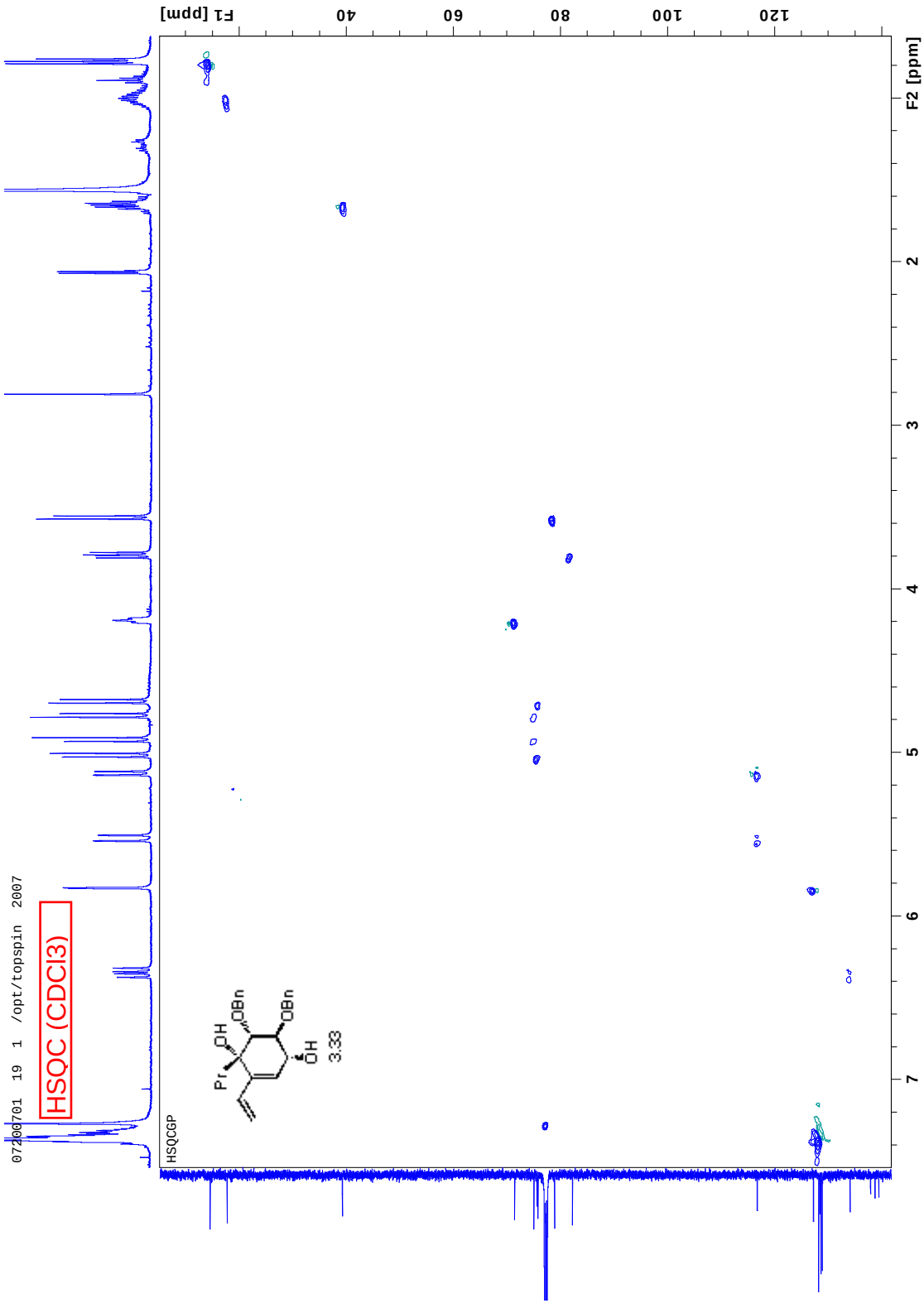
Pr
OBn
OBn
OH
3.31

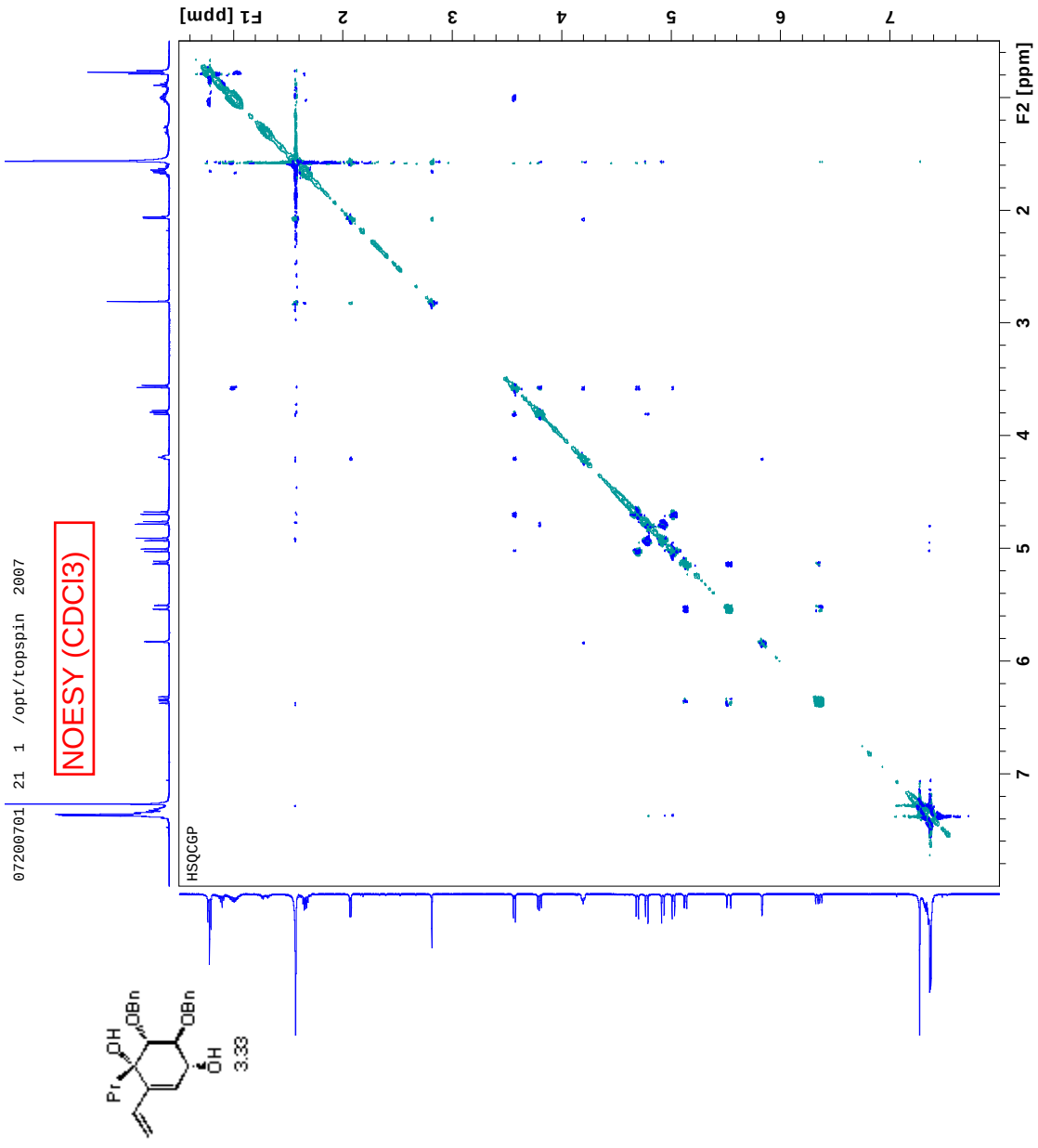

13C NMR (CDCl3, 125 MHz)
03110701 6 1 /opt/topspin 2007
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
3.31
14.4296
17.1855
41.1666
72.9696
73.6851
73.9679
74.8622
75.3168
76.9742
77.2280
77.4821
81.1555
81.7605
82.5906
85.5403
116.0742
127.9971
128.0267
128.3992
128.4358
128.5526
128.5734
138.2531
138.2656
138.5626
[rel]
[ppm]

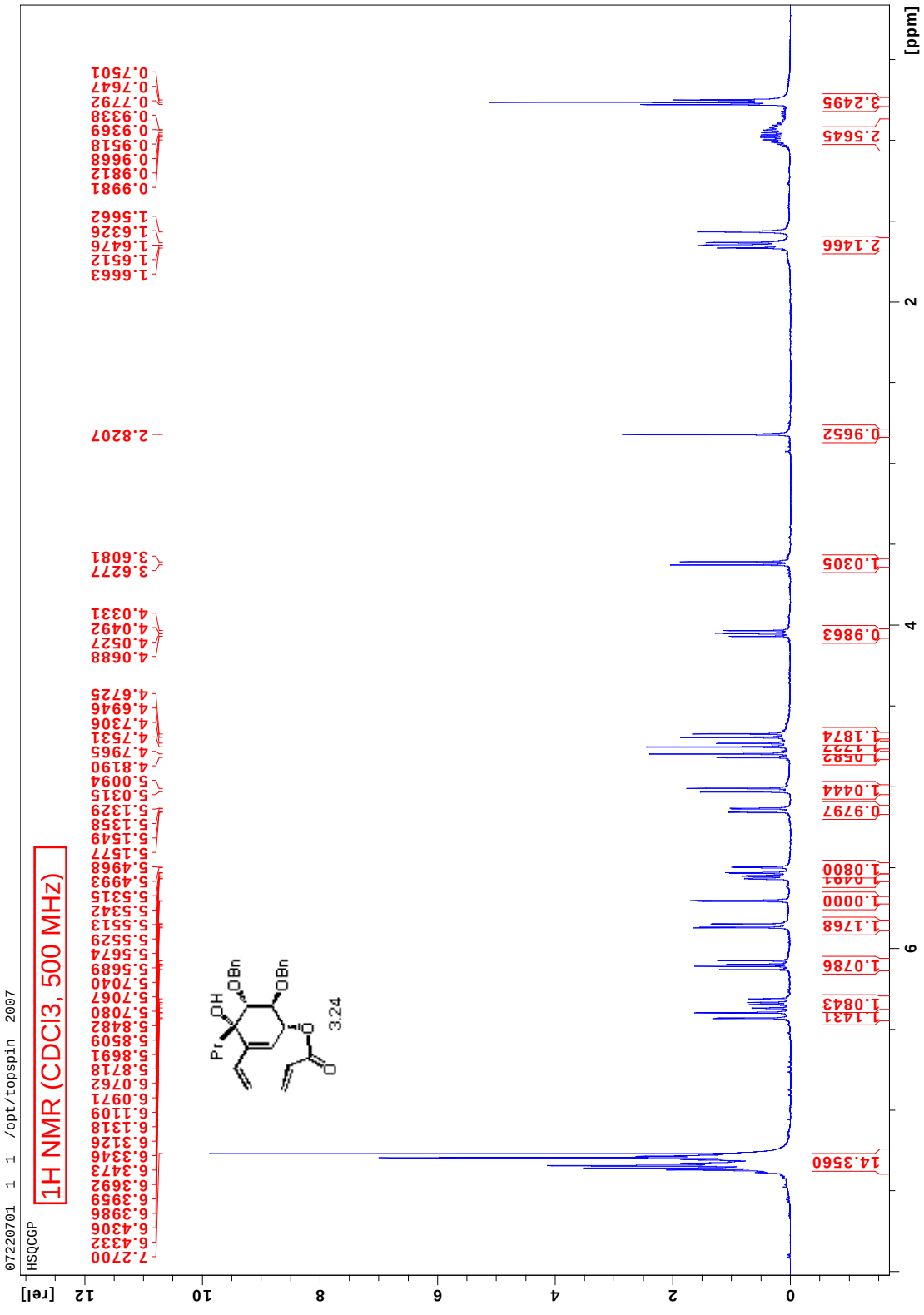

1H NMR (CDCl3, 500 MHz)
07200701 17 1 /opt/topspin 2007
HSQCGP
[rel]
[ppm]
OBn
OBn
OH
OH
Pr
3.33

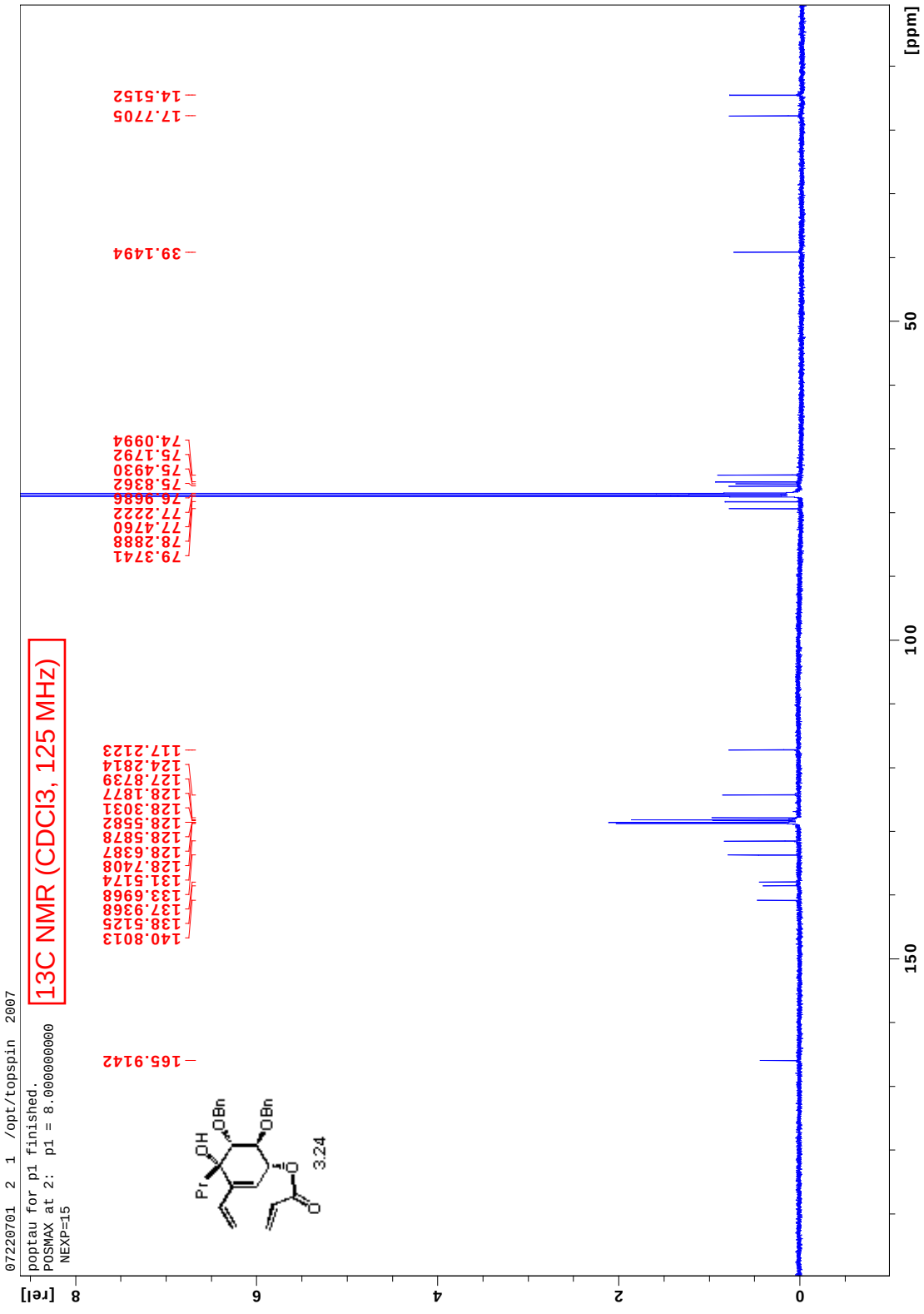

13C NMR (CDCl3, 125 MHz)
07200701 18 1 /opt/topspin 2007
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
139.3868
138.6812
137.8414
134.0197
128.8419
128.8133
128.5804
128.3799
128.1311
127.1883
116.6912
82.1755
78.8588
77.4793
77.2252
76.9709
75.7347
75.5594
74.9818
71.3881
39.2308
17.7312
14.5330
OBn
OBn
OH
Pr
OH
3:33
[rel]
15
10
5
0
150
100
50
[ppm]

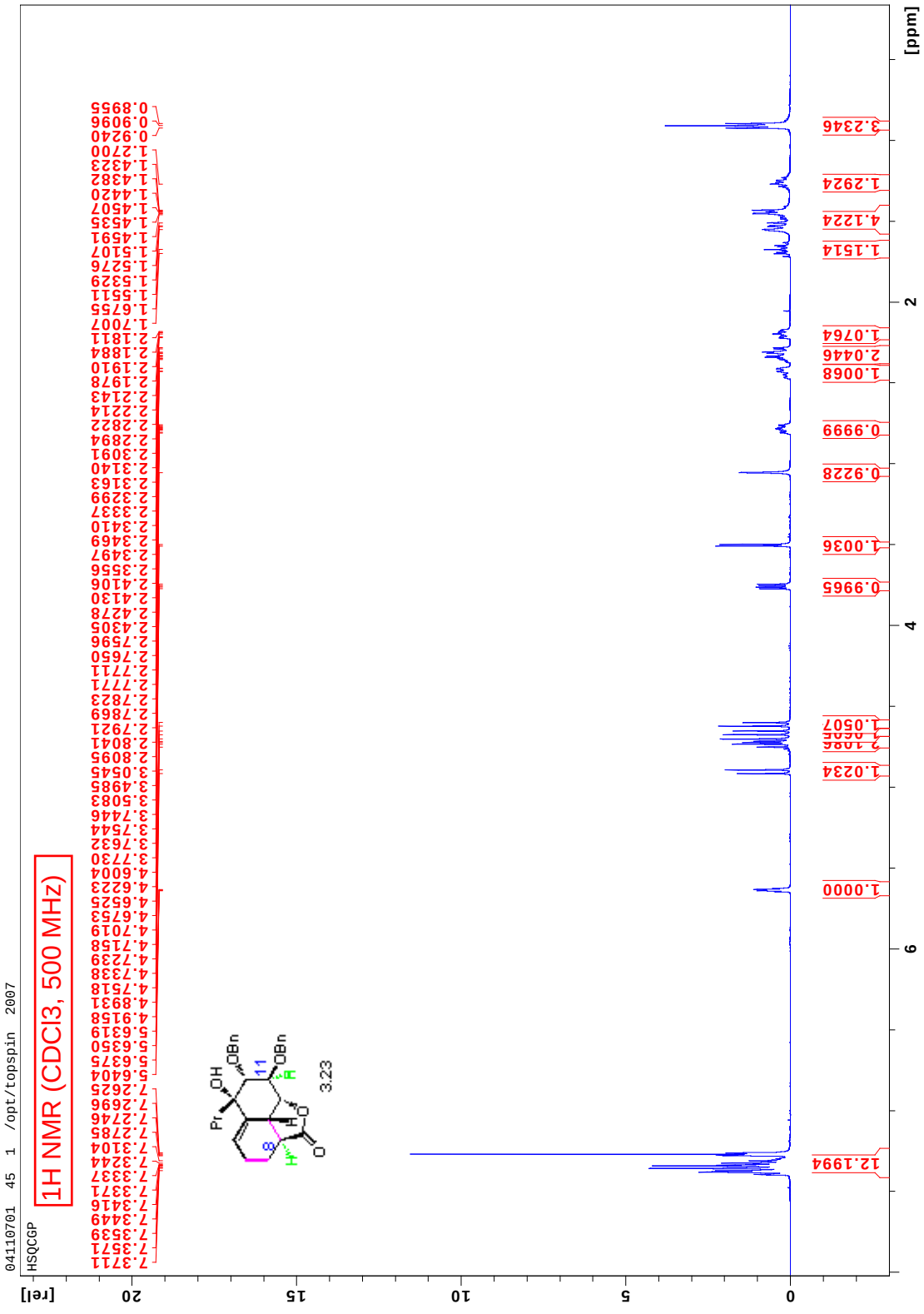

COSY (CDCl3)
07200701 20 1 /opt/topspin 2007
HSQCGP
F1 [ppm]
F2 [ppm]
OBn
OBn
OH
OH
Pr
3.33


HSQC (CDCl3)
072007701 19 1 /opt/topspin 2007
HSQCGP
F1 [ppm]
F2 [ppm]
120
100
80
60
40
1
2
3
4
5
6
7
OH
OBn
OBn
OH
Pr
3.33


NOESY (CDCl3)
07200701 21 1 /opt/topspin 2007
HSQCGP
F1 [ppm]
F2 [ppm]
OBn
OBn
OH
Pr
OH
3.33


1H NMR (CDCl3, 500 MHz)
HSQCGP
07220701 1 1 /opt/topspin 2007
[rel]
[ppm]
OH
OBn
OBn
Pr
O
O
3.24
14.3560
3.2495
2.5645
2.1466
0.9652
1.0305
0.9863
1.1874
0.9797
1.0444
1.0000
1.1768
1.0786
1.0843
2.8207


13C NMR (CDCl3, 125 MHz)
07220701 2 1 /opt/topspin 2007
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
165.9142
140.8013
138.5125
137.9368
133.6968
131.5174
128.7408
128.6387
128.5878
128.5582
128.3031
128.1877
127.8739
124.2814
117.2123
79.3741
78.2888
77.4760
77.2222
76.9686
75.8362
75.4930
75.1792
74.0994
39.1494
17.7705
14.5152
OBn
OBn
OH
Pr
O
O
3.24


1H NMR (CDCl3, 500 MHz)
HSQCGP
04110701 45 1 /opt/topspin 2007
[rel]
[ppm]
12.1994
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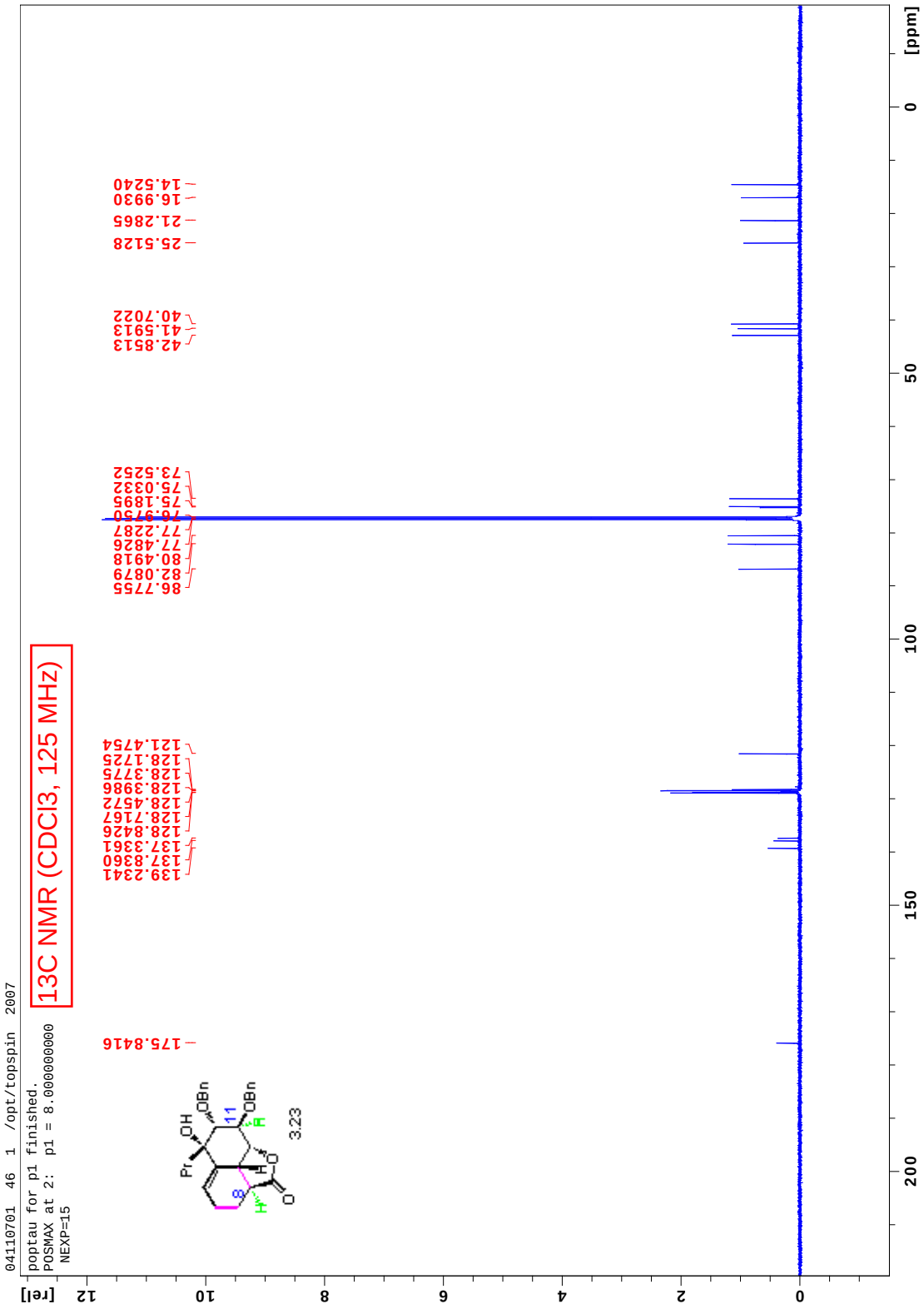
1.2924
4.1224
1.1514
1.0764
2.0446
1.0068
0.9999
0.9228
1.0036
0.9965
1.0234
1.0000
1.0507
3.23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128.8426
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128.3986
128.3775
128.1725
121.4754
86.7755
82.0879
80.4918
77.4826
77.2287
76.9750
75.1895
75.0332
73.5252
42.8513
41.5913
40.7022
25.5128
21.2865
16.9930
14.5240
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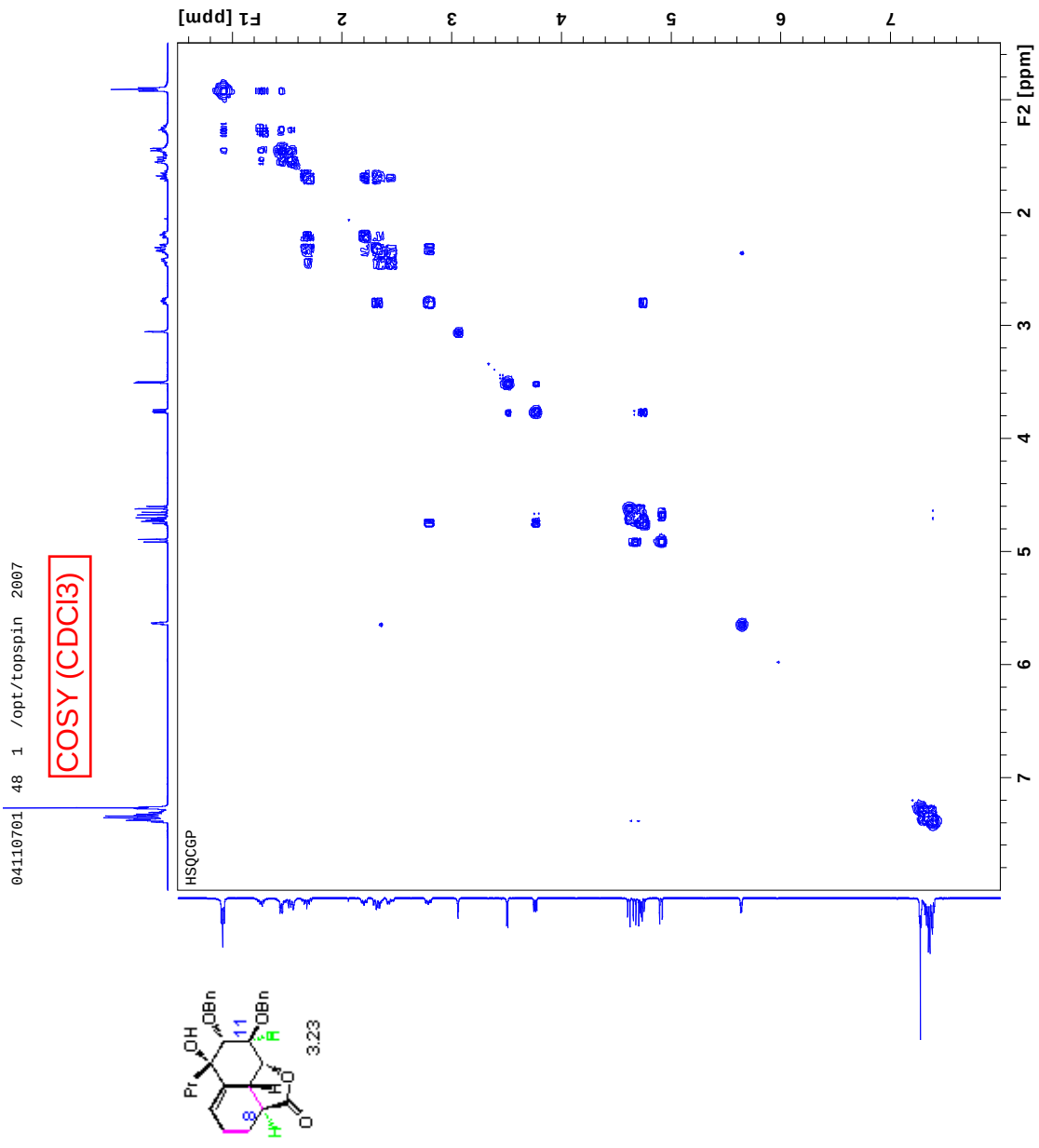
OH
OBn
Pr
H
H
O
O
11
8
3.23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04110701 48 1 /opt/topspin 2007
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F1 [ppm]
F2 [ppm]
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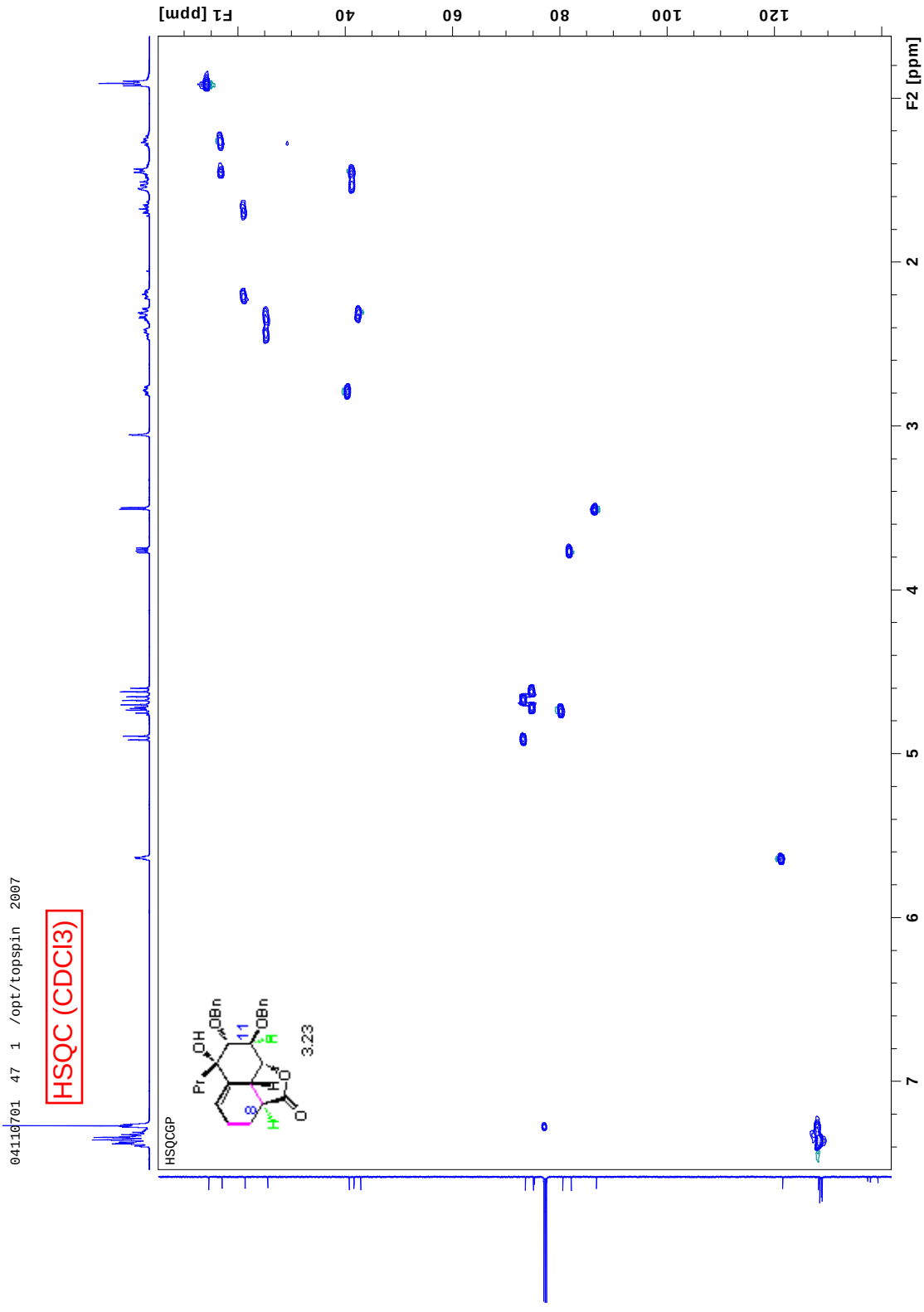
3
4
5
6
7
OBn
OBn
OH
Pr
11
H
H
O
O
8
3.23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F2 [ppm]
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100
80
60
40
2
3
4
5
6
7
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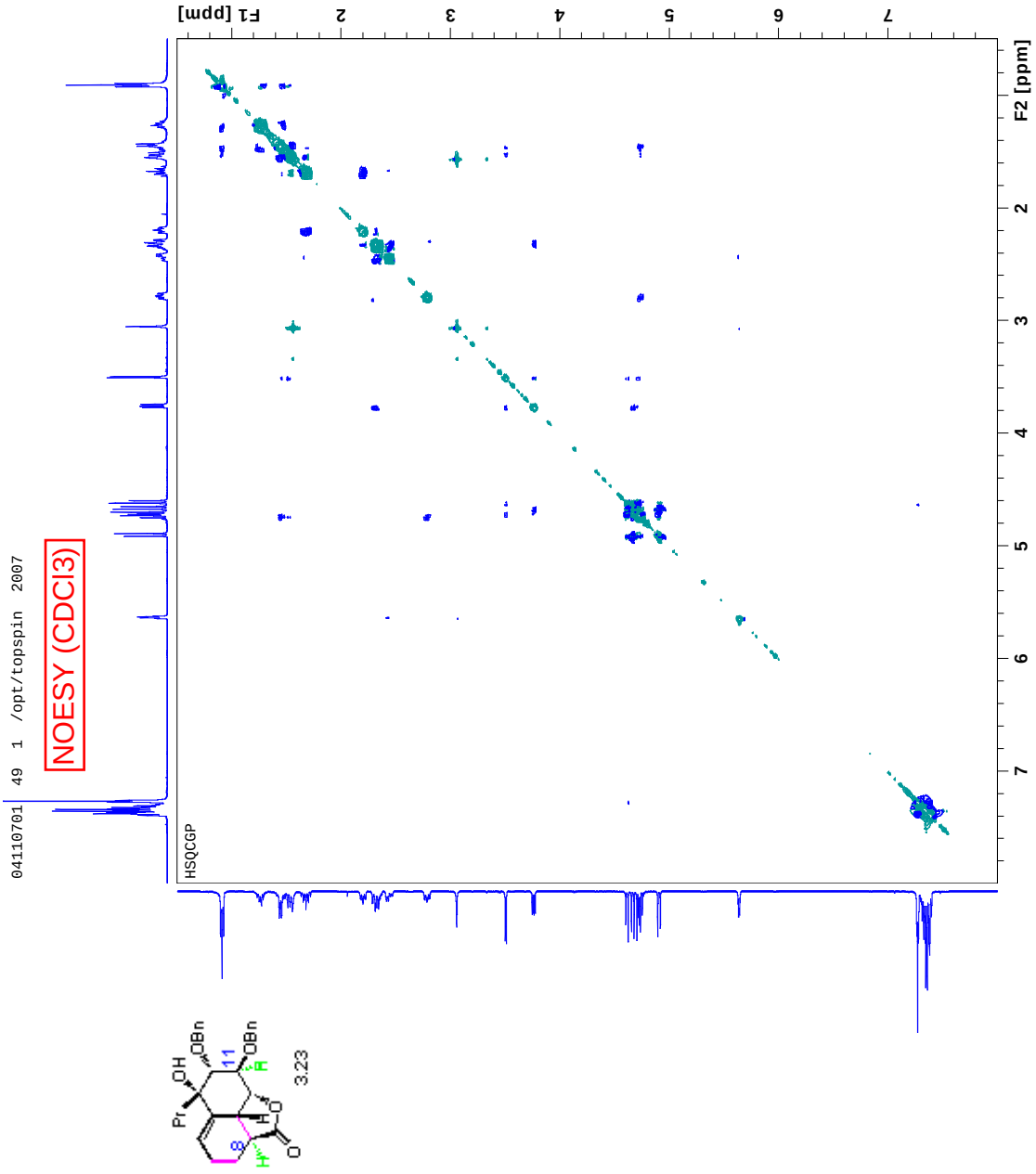
OBn
OH
Pr
3.23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F2 [ppm]
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OBn
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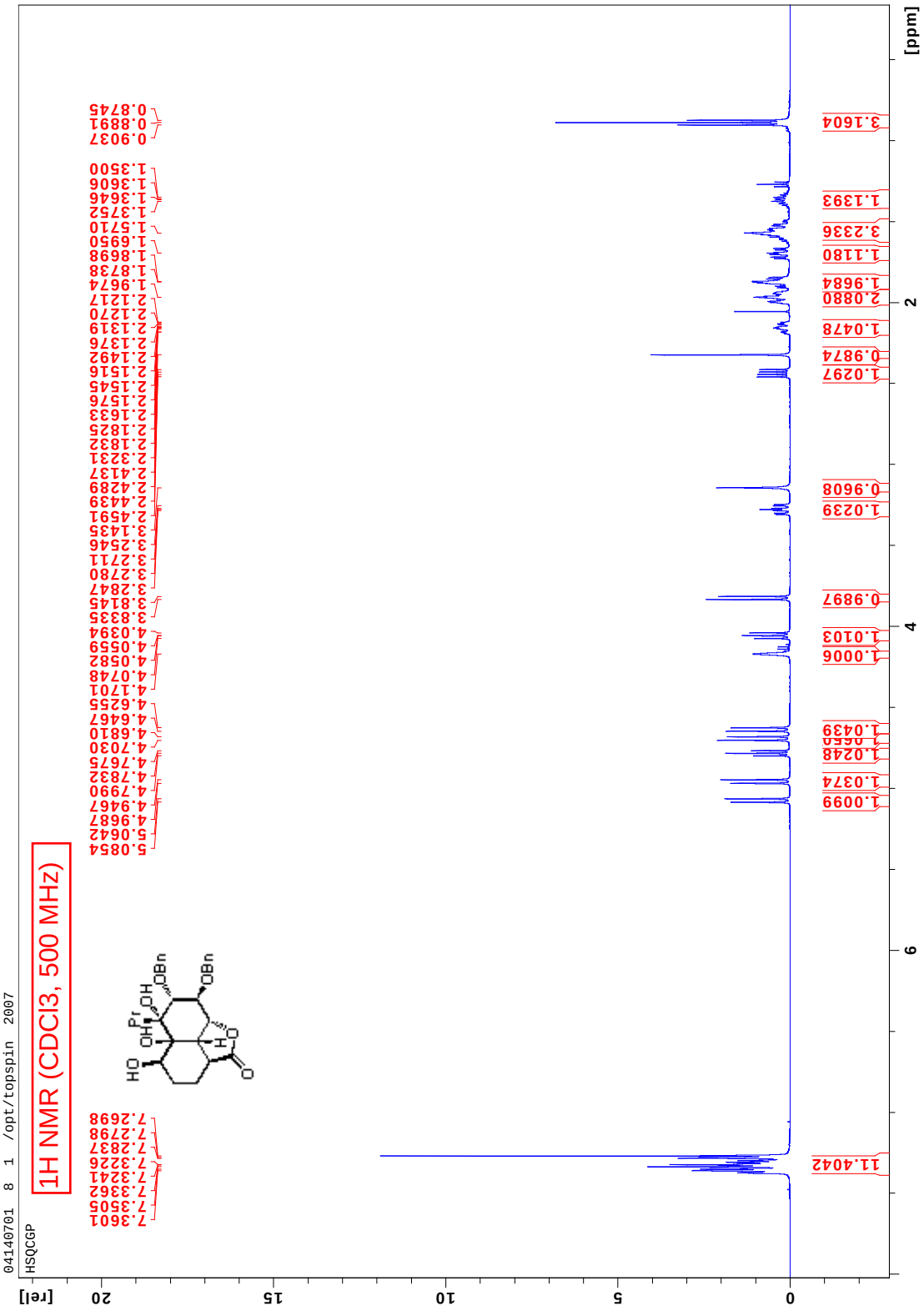
Pr
H
O
O
3.23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OBn
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OH
HO
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O
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7.3362
7.3241
7.3226
7.2837
7.2798
7.2698
5.0854
4.9687
4.9467
4.7990
4.7832
4.7675
4.7030
4.6810
4.6467
4.6255
4.1701
4.0748
4.0582
4.0559
4.0394
3.8335
3.8145
3.2847
3.2780
3.2711
3.2546
3.1435
3.0591
2.4439
2.4289
2.4137
2.3231
2.1832
2.1825
2.1633
2.1576
2.1545
2.1516
2.1492
2.1376
2.1319
2.1270
2.1217
1.9674
1.8738
1.8698
1.6950
1.5710
1.3752
1.3646
1.3606
1.3500
0.9037
0.8891
0.8745
3.1604
1.1393
3.2336
1.1180
1.9684
2.0880
1.0478
0.9874
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1.0099
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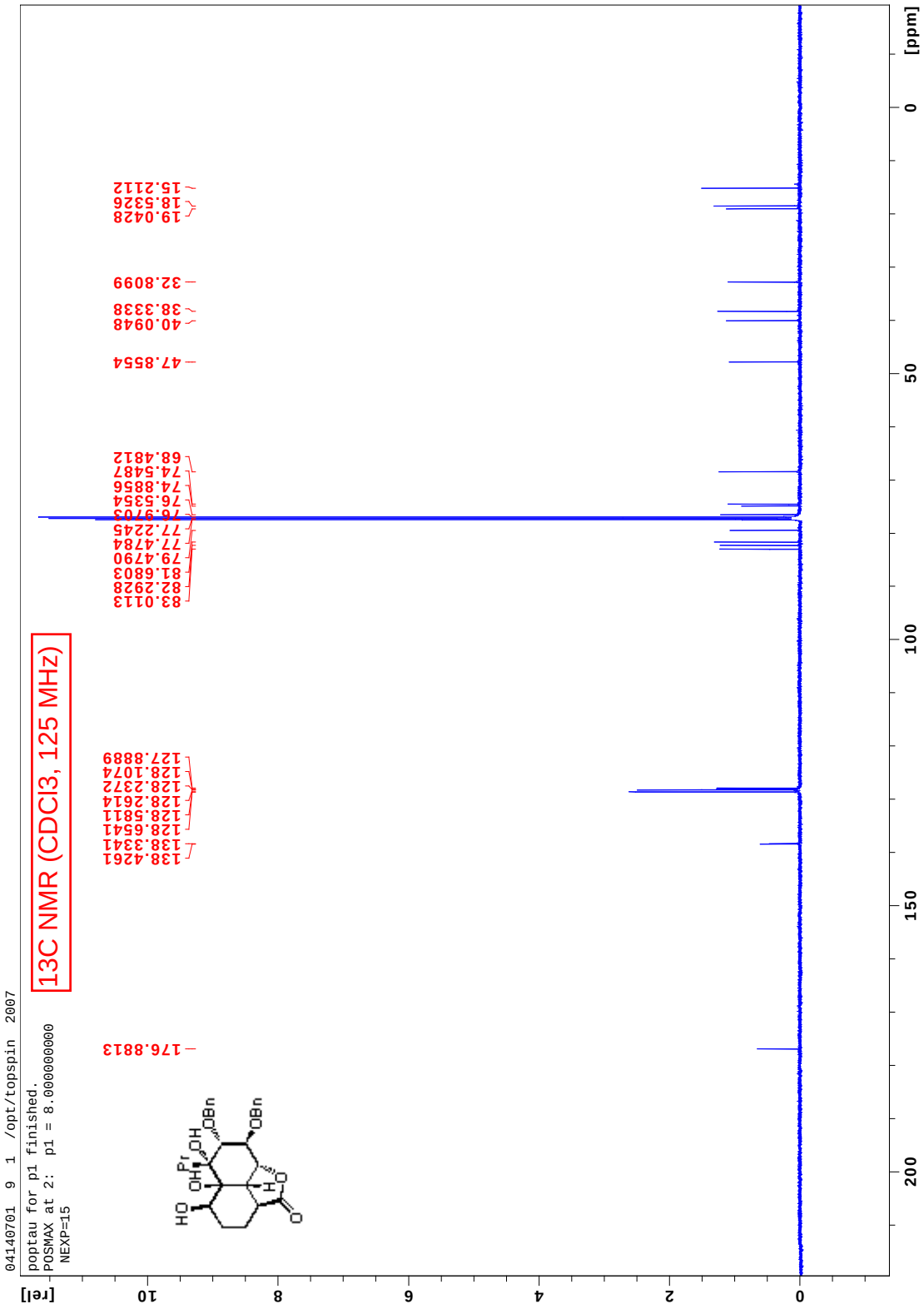
1.0248
1.0439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128.5811
128.2614
128.2372
128.1074
127.8889
83.0113
82.2928
81.6803
79.4790
77.4784
77.2245
76.9703
76.5354
74.8856
74.5487
68.4812
47.8554
40.0948
38.3338
32.8099
19.0428
18.5326
15.2112
[rel]
[ppm]
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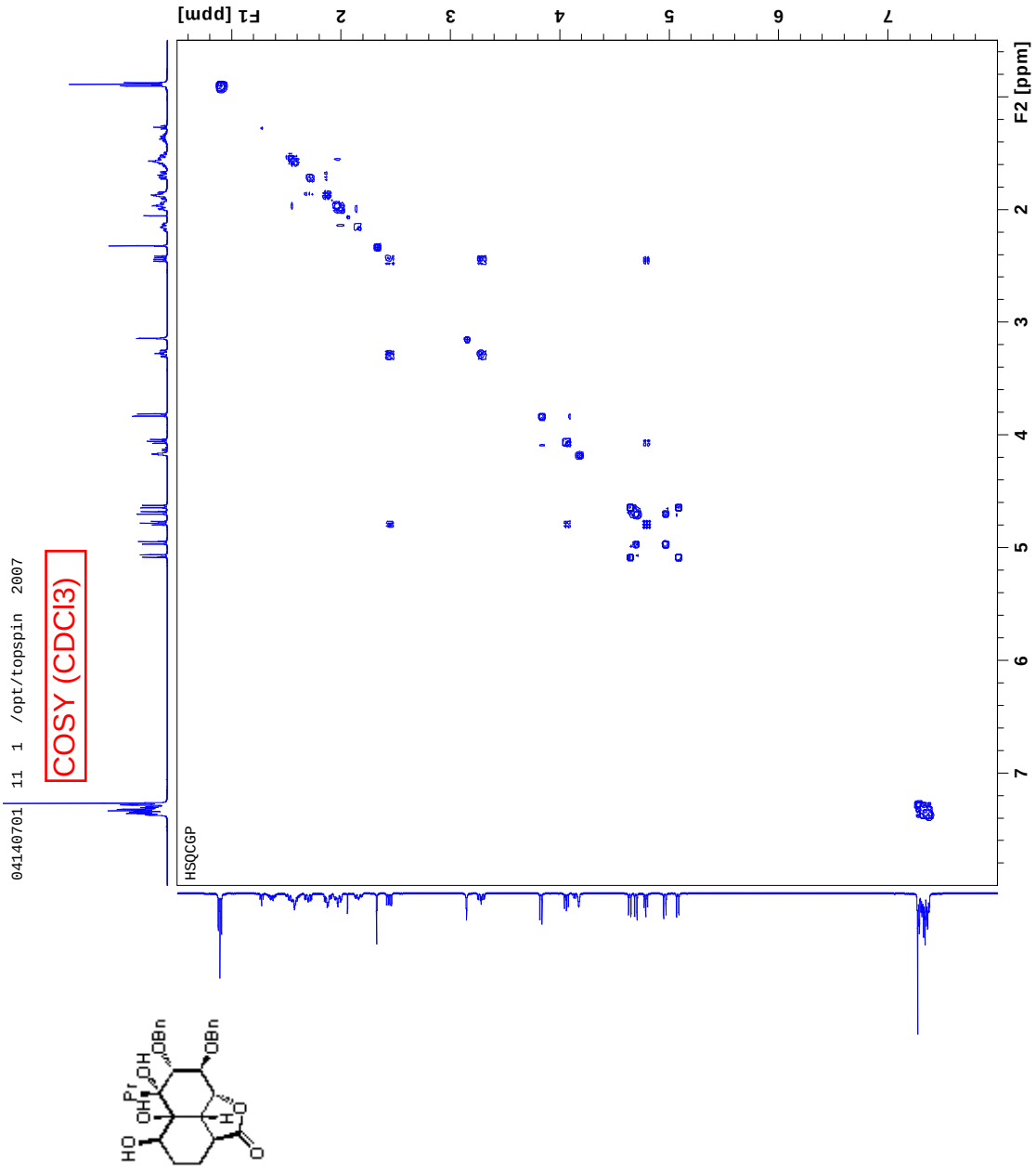
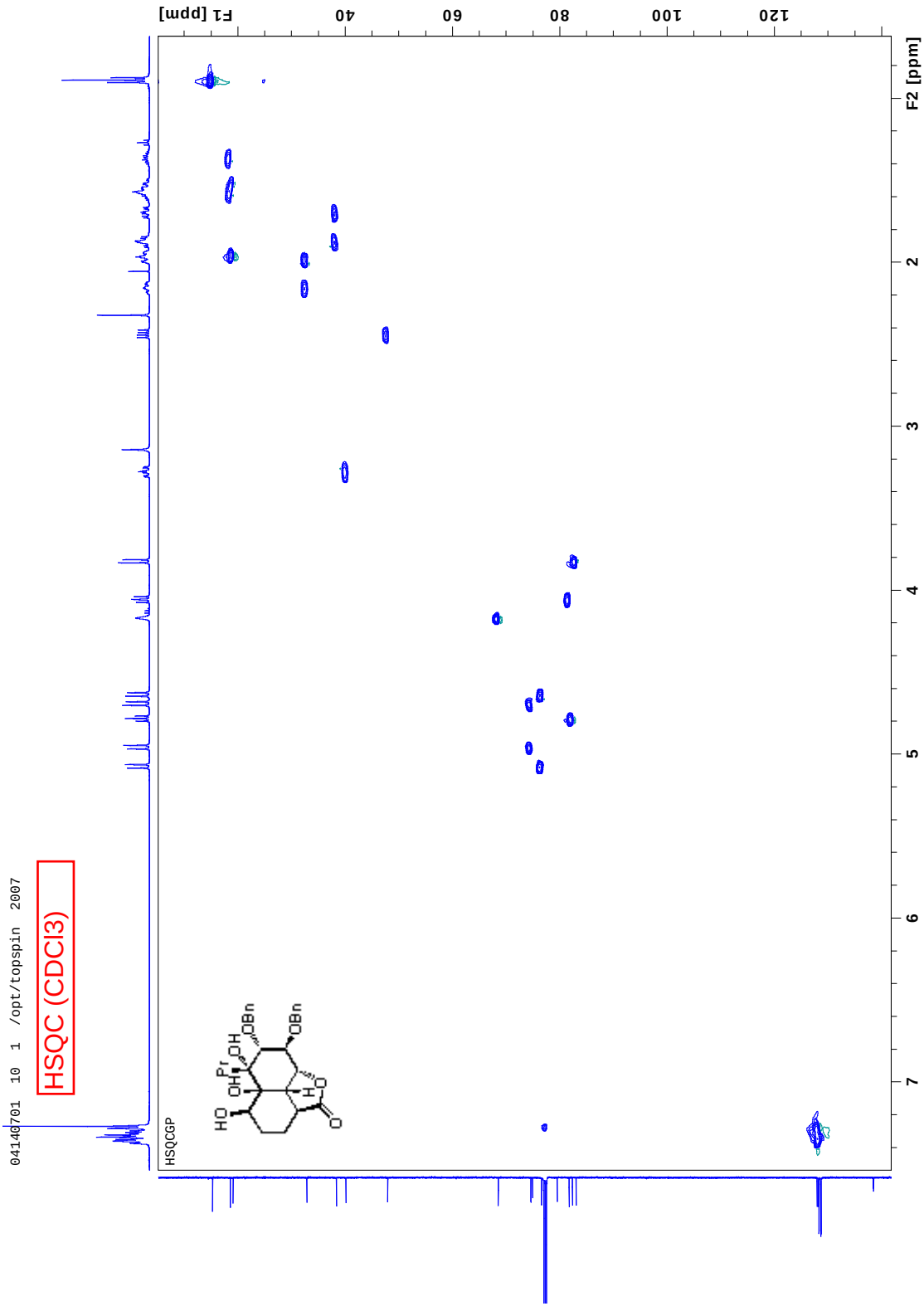
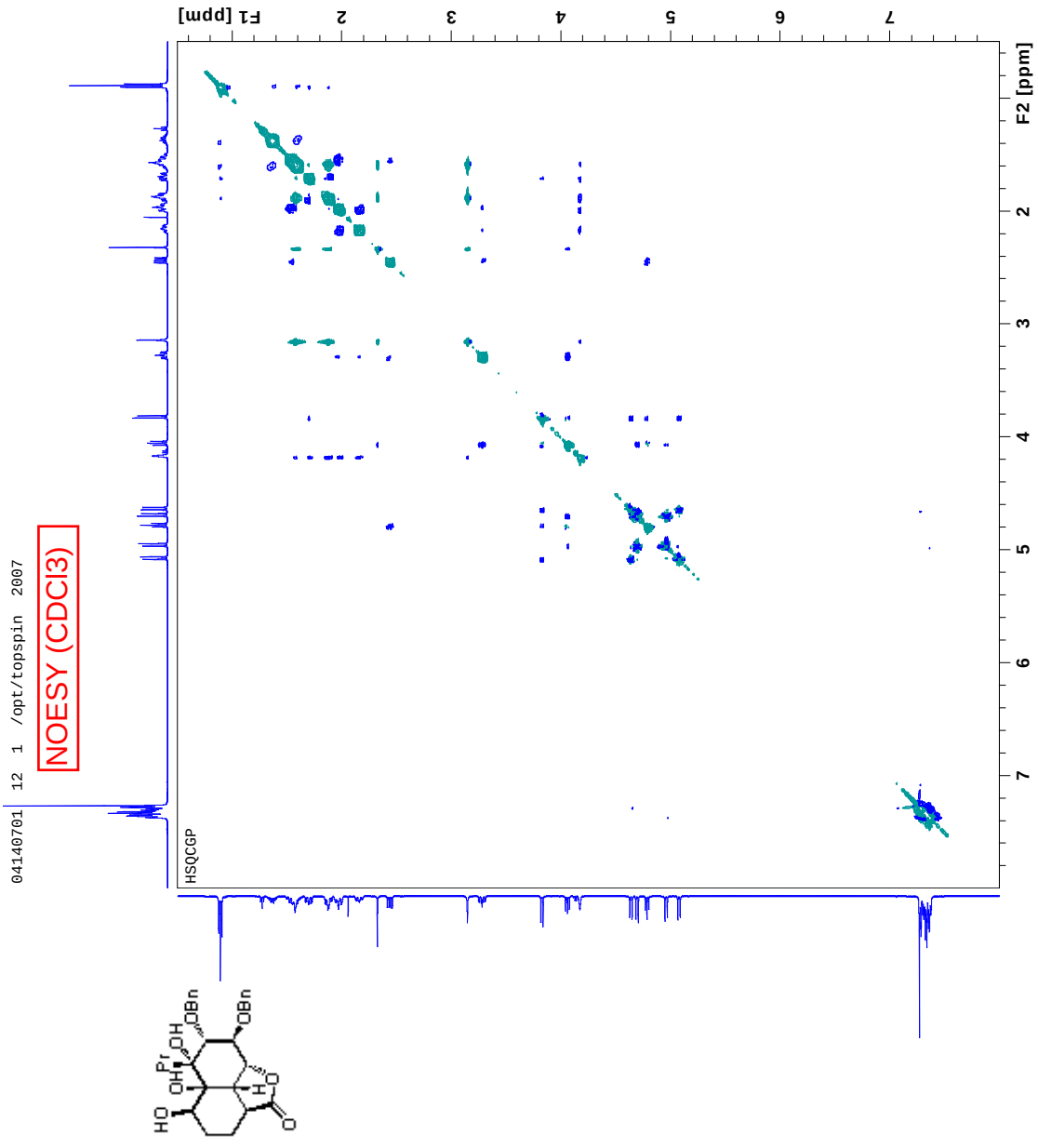
OBn
OH
OH
Pr
HO
O
O
H


COSY (CDCl3)
04140701 11 1 /opt/topspin 2007
HSQCGP
F1 [ppm]
F2 [ppm]
2
3
4
5
6
7
OBn
OBn
OH
Pr
HO
O
O


HSQC (CDCl3)
041407701 10 1 /opt/topspin 2007
HSQCGP
F1 [ppm]
F2 [ppm]
120
100
80
60
40
2
3
4
5
6
7
OBn
OBn
OH
OH
Pr
HO
O
O
H


NOESY (CDCl3)
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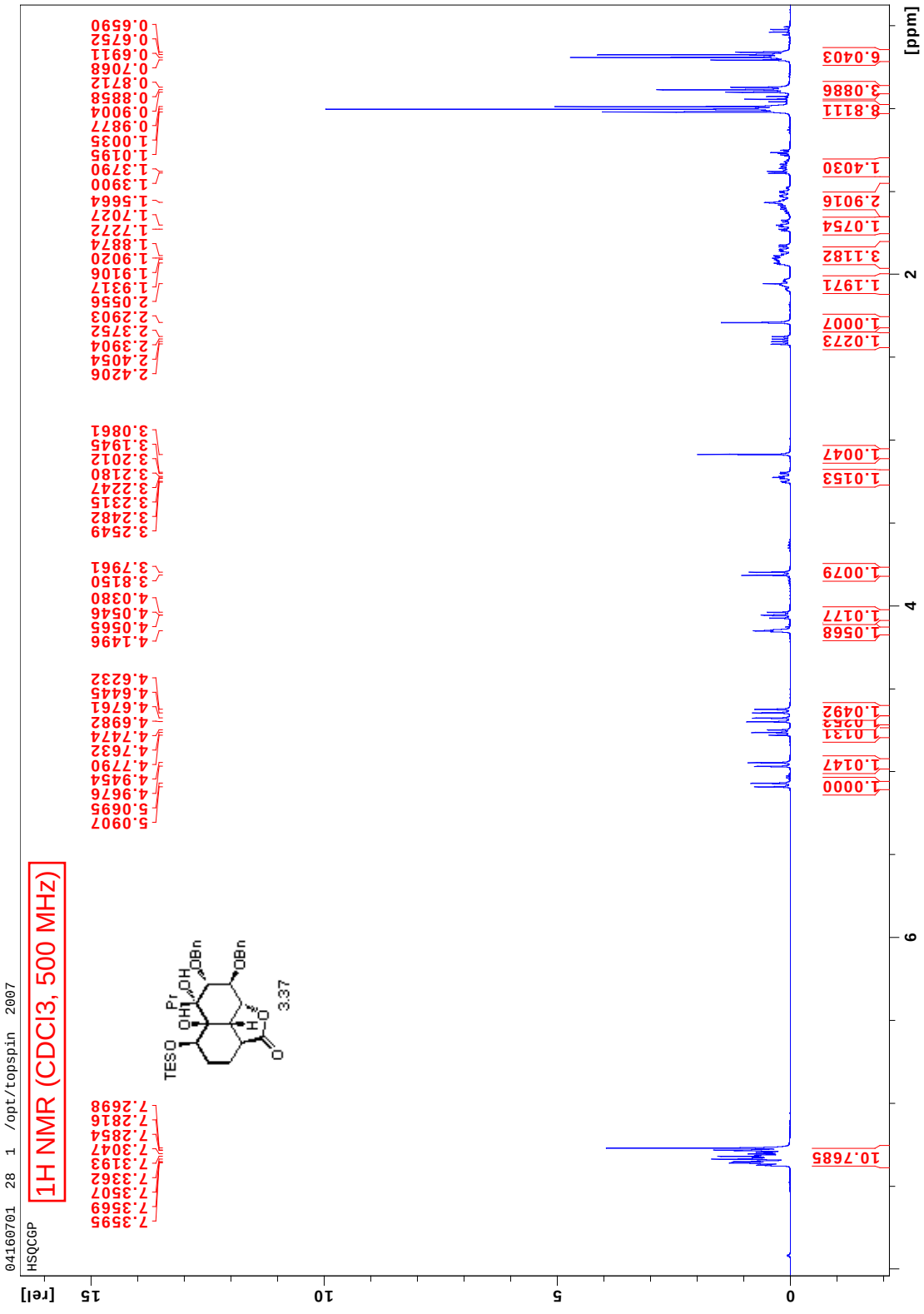
HSQCGP
F1 [ppm]
F2 [ppm]
OBn
OBn
OH
OH
HO
O
O
H


1H NMR (CDCl3, 500 MHz)
HSQCGP
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[ppm]
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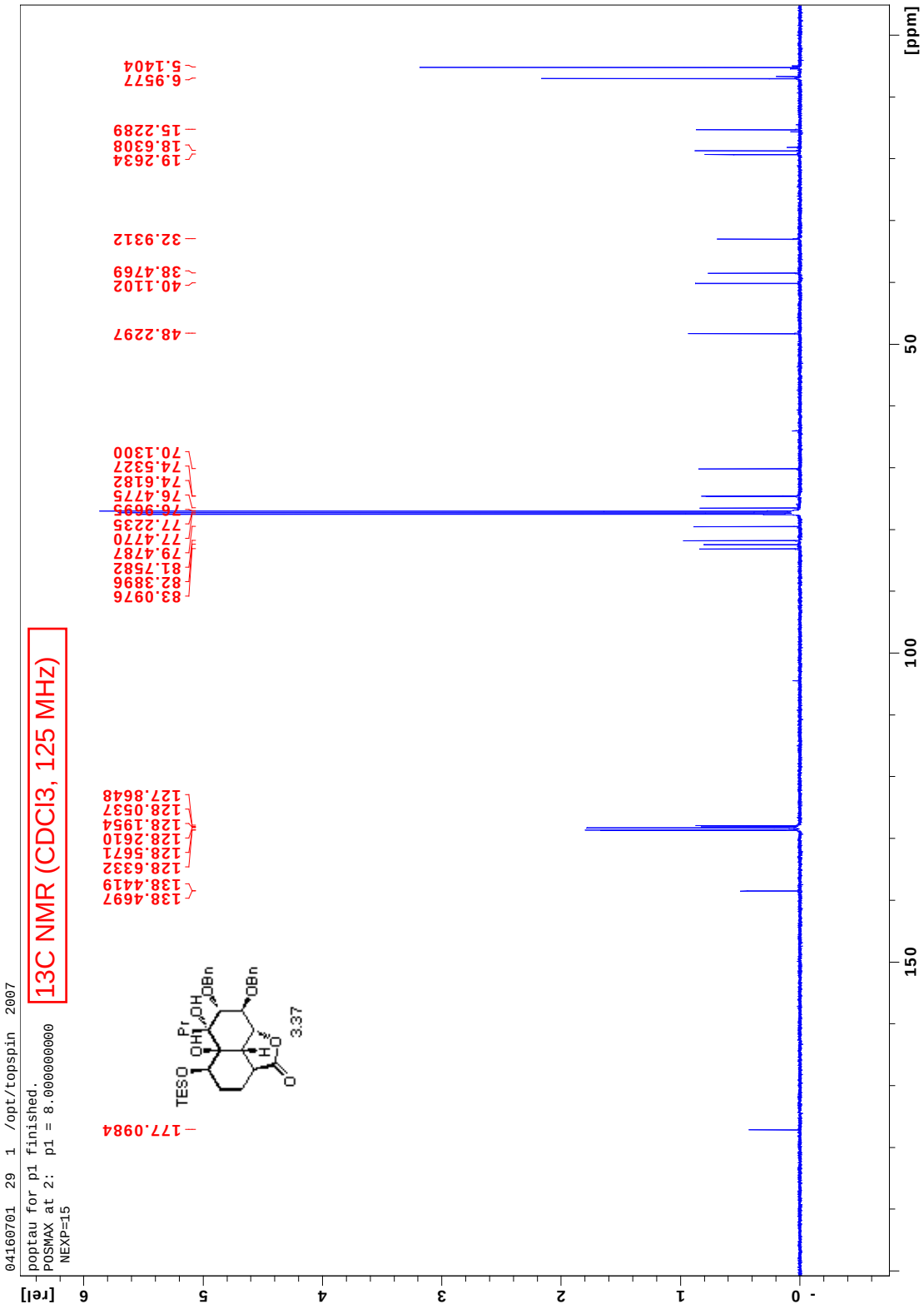
Pr
OH
OBn
OBn
3.37


13C NMR (CDCl3, 125 MHz)
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[ppm]
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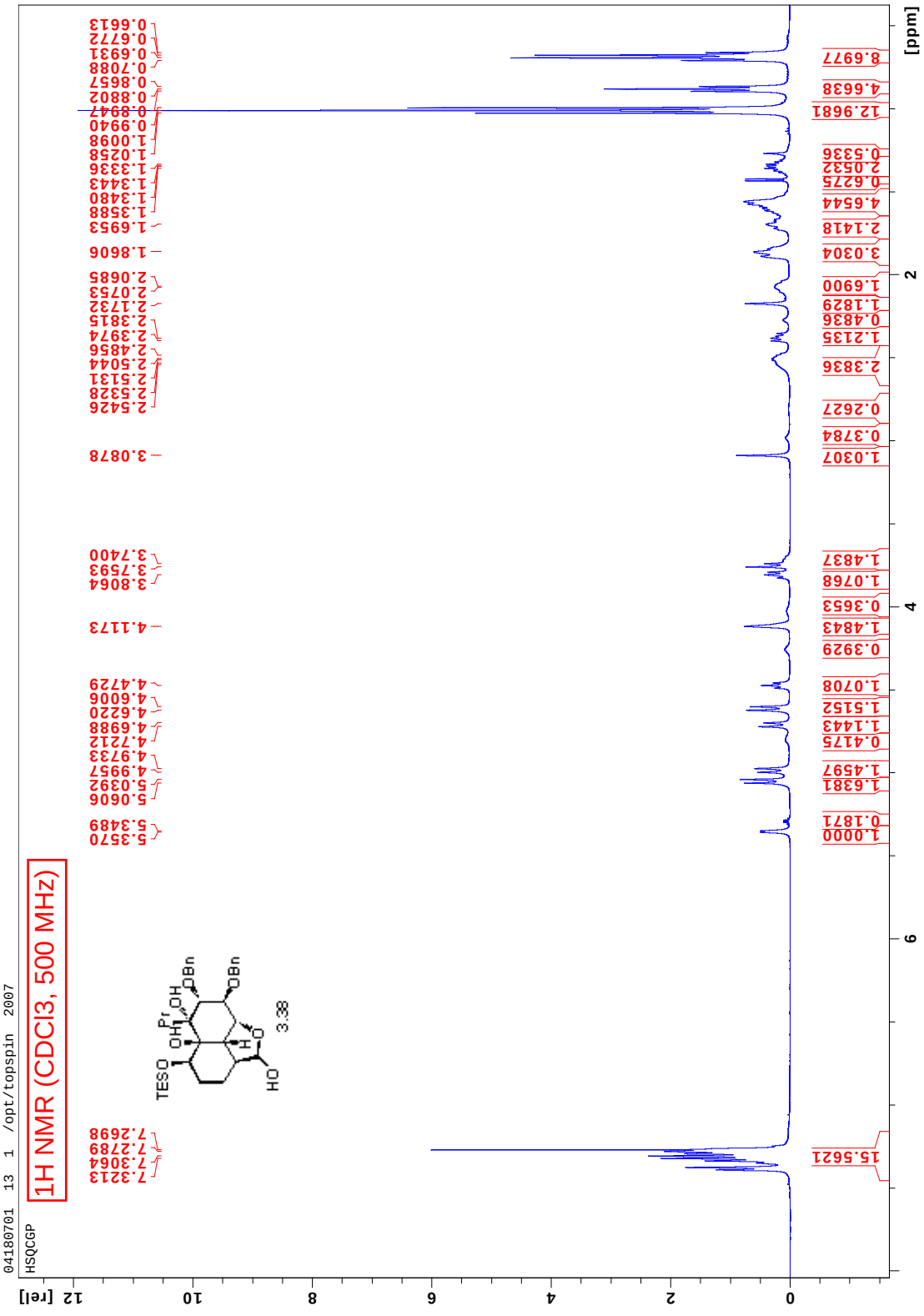
138.4419
128.6332
128.5671
128.2610
128.1954
128.0537
127.8648
83.0976
82.3896
81.7582
79.4787
77.4770
77.2235
76.9695
76.4775
74.6182
74.5327
70.1300
48.2297
40.1102
38.4769
32.9312
19.2634
18.6308
15.2289
6.9577
5.1404
TESO
OH
Pr
OH
OBn
OBn
H
O
O
3.37


1H NMR (CDCl3, 500 MHz)
HSQCGP
04180701 13 1 /opt/topspin 2007
[rel]
[ppm]
TESO
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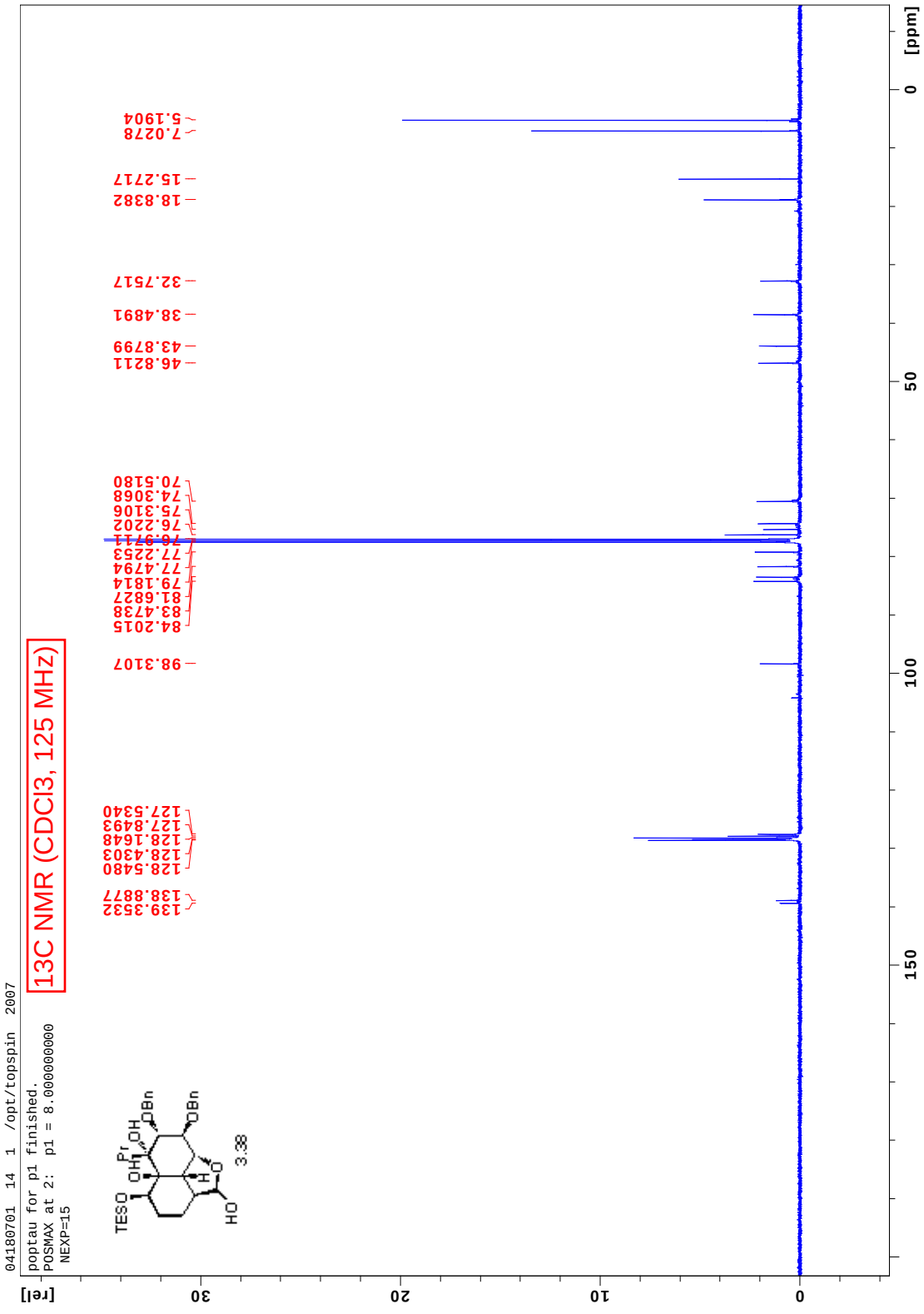
OBn
OBn
OH
HO
3.88


13C NMR (CDCl3, 125 MHz)
04180701 14 1 /opt/topspin 2007
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POSMAX at 2: p1 = 8.000000000
NEXP=15
TESO
OH
Pr
OBn
OBn
O
H
HO
3.38
[rel]
[ppm]
0
10
20
30
50
100
150
5.1904
7.0278
15.2717
18.8382
32.7517
38.4891
43.8799
46.8211
70.5180
74.3068
75.3106
76.2202
76.9711
77.2253
77.4794
79.1814
81.6827
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127.5340
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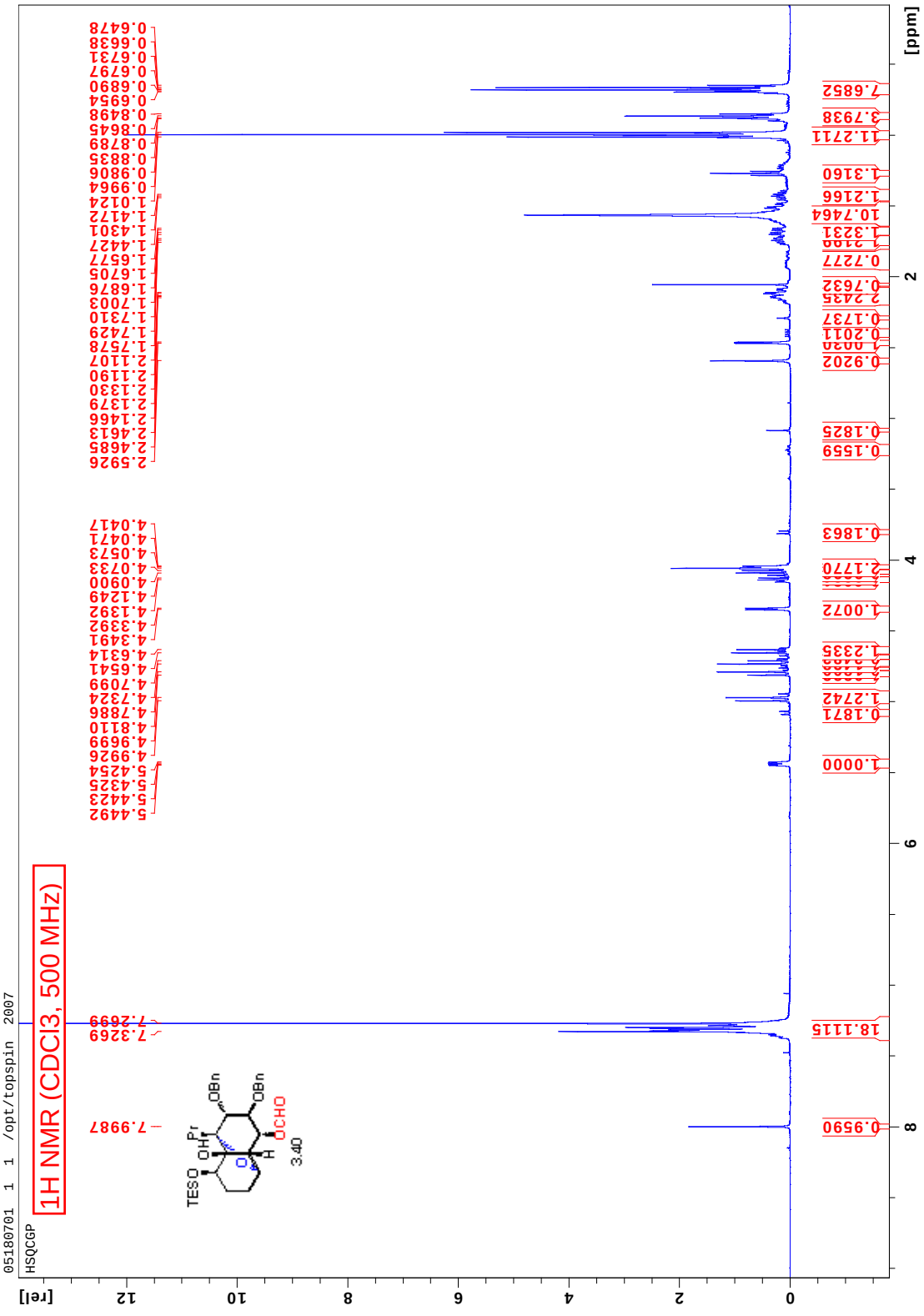
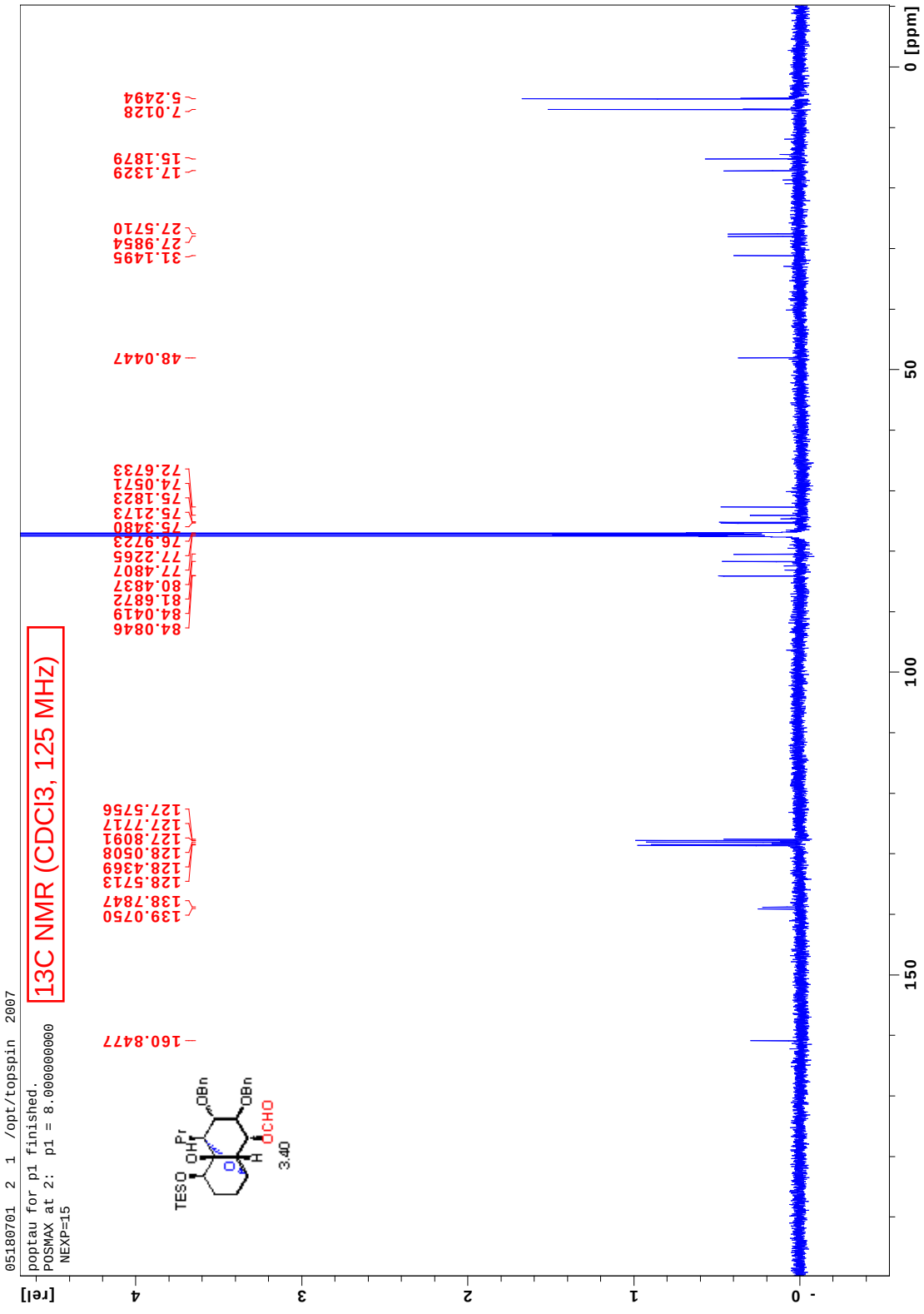
128.1648
128.4303
128.5480
138.8877
139.3532


1H NMR (CDCl3, 500 MHz)
HSQCGP
05180701 1 1 /opt/topspin 2007
[rel]
[ppm]
TESO
OH
Pr
OBn
OBn
H
OCHO
3.40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128.4369
128.0508
127.8091
127.7717
127.5756
84.0846
84.0419
81.6872
80.4837
77.4807
77.2265
76.9723
75.3480
75.2173
75.1823
74.0571
72.6733
48.0447
31.1495
27.9854
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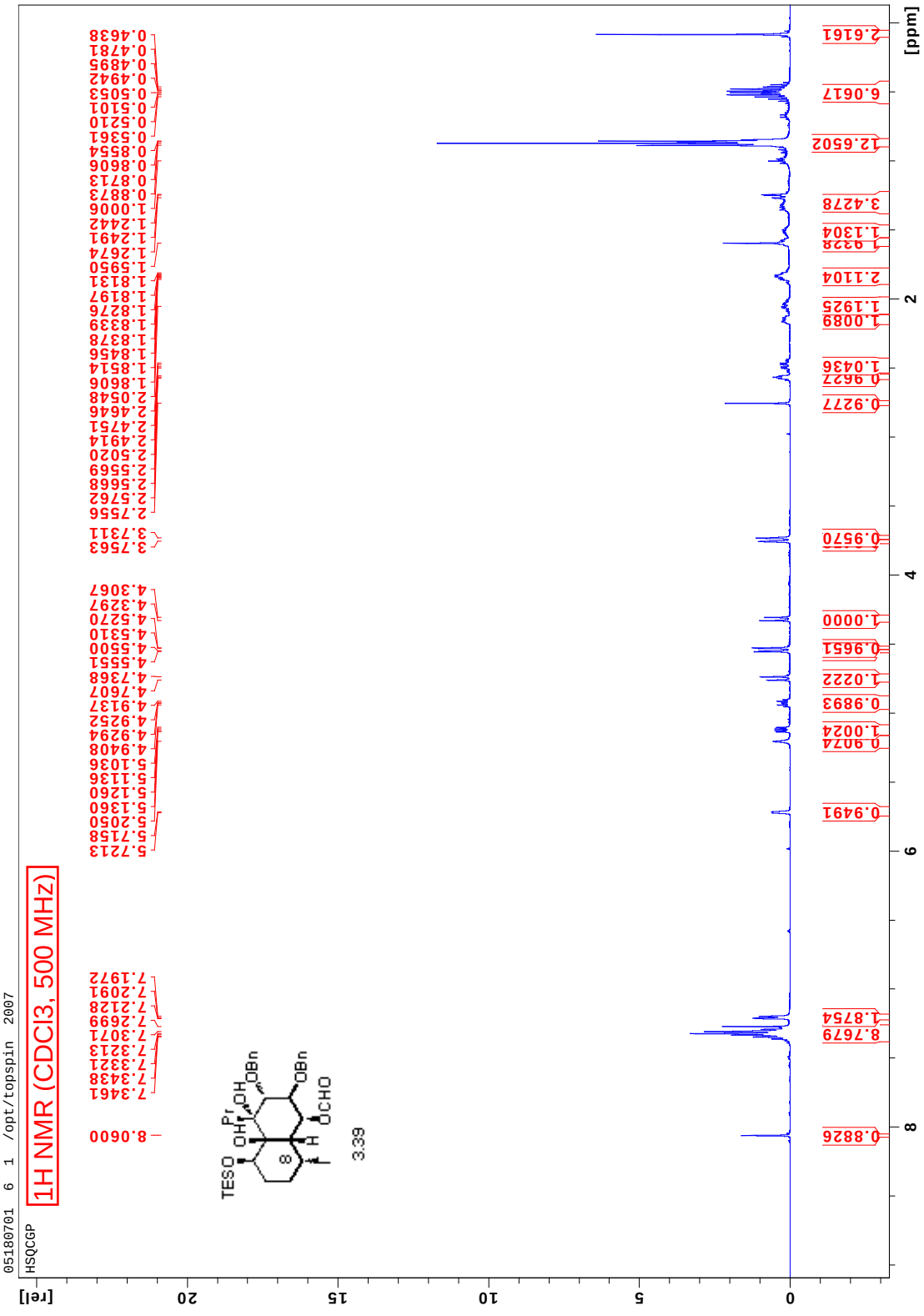
7.0128
5.2494
TESO
OH
Pr
OBn
OBn
OCHO
H
O
3.40


1H NMR (CDCl3, 500 MHz)
HSQCGP
05180701 6 1 /opt/topspin 2007
TESO
OH
iPr
OBn
OBn
H
OCHO
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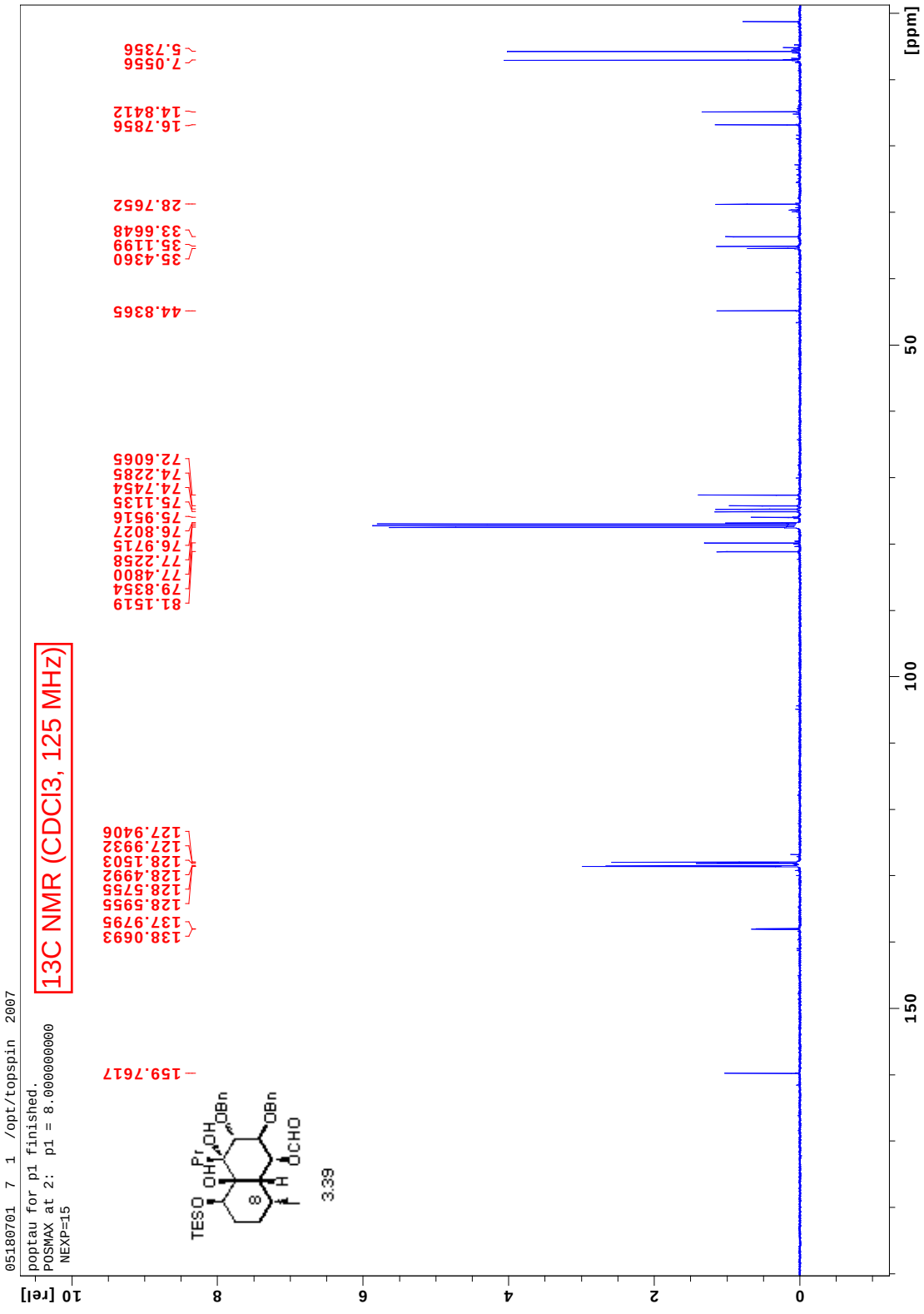
3.39
[rel]
[ppm]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128.5755
128.4992
128.1503
127.9932
127.9406
81.1519
79.8354
77.4800
77.2258
76.9715
76.8027
75.9516
75.1135
74.7454
74.2285
72.6065
44.8365
35.4360
35.1199
33.6648
28.7652
16.7856
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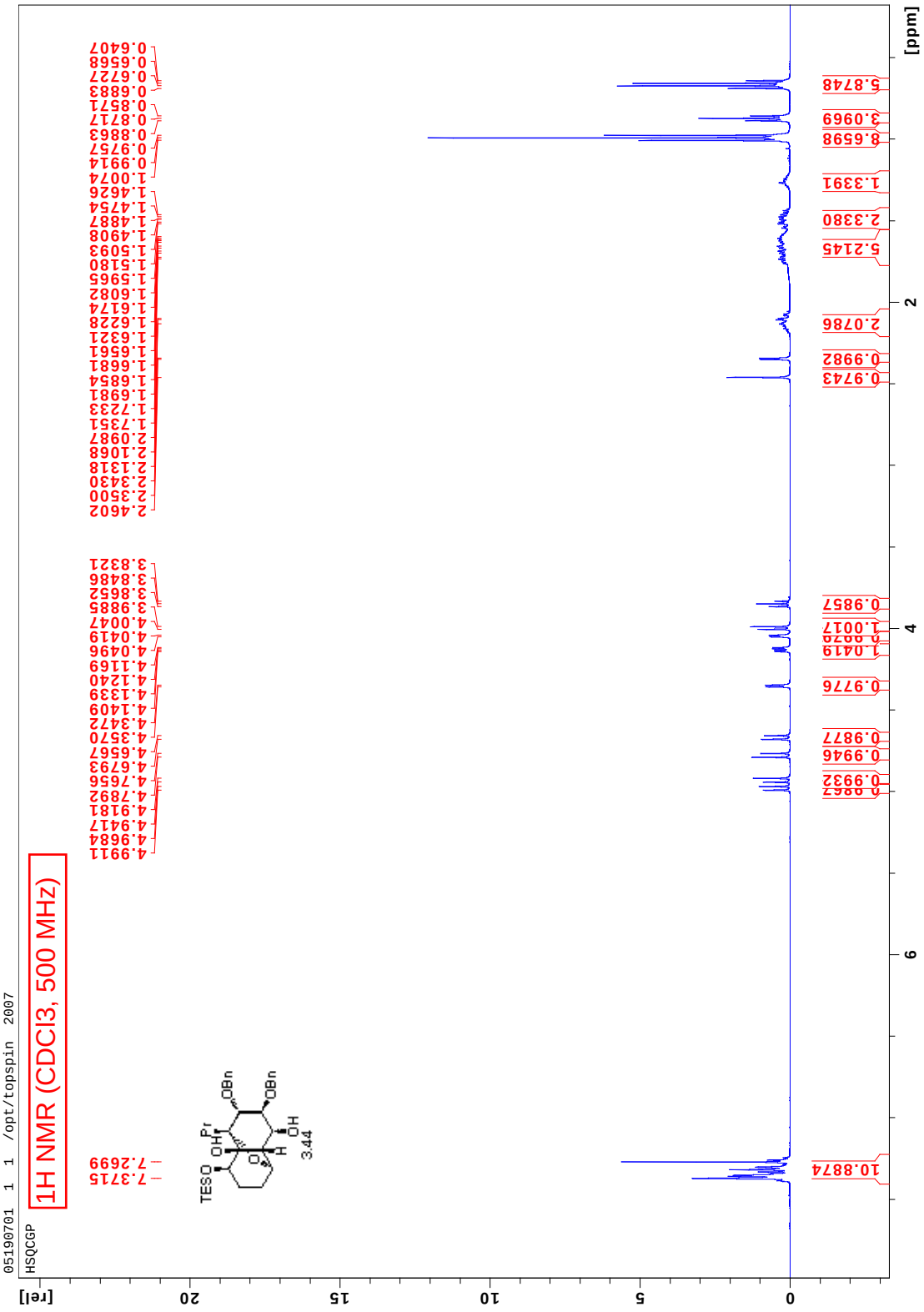
5.7356
TESO
OH
Pr
OBn
OBn
OCHO
H
8
3.39
[rel]
[ppm]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HSQCGP
05190701 1 1 /opt/topspin 2007
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[ppm]
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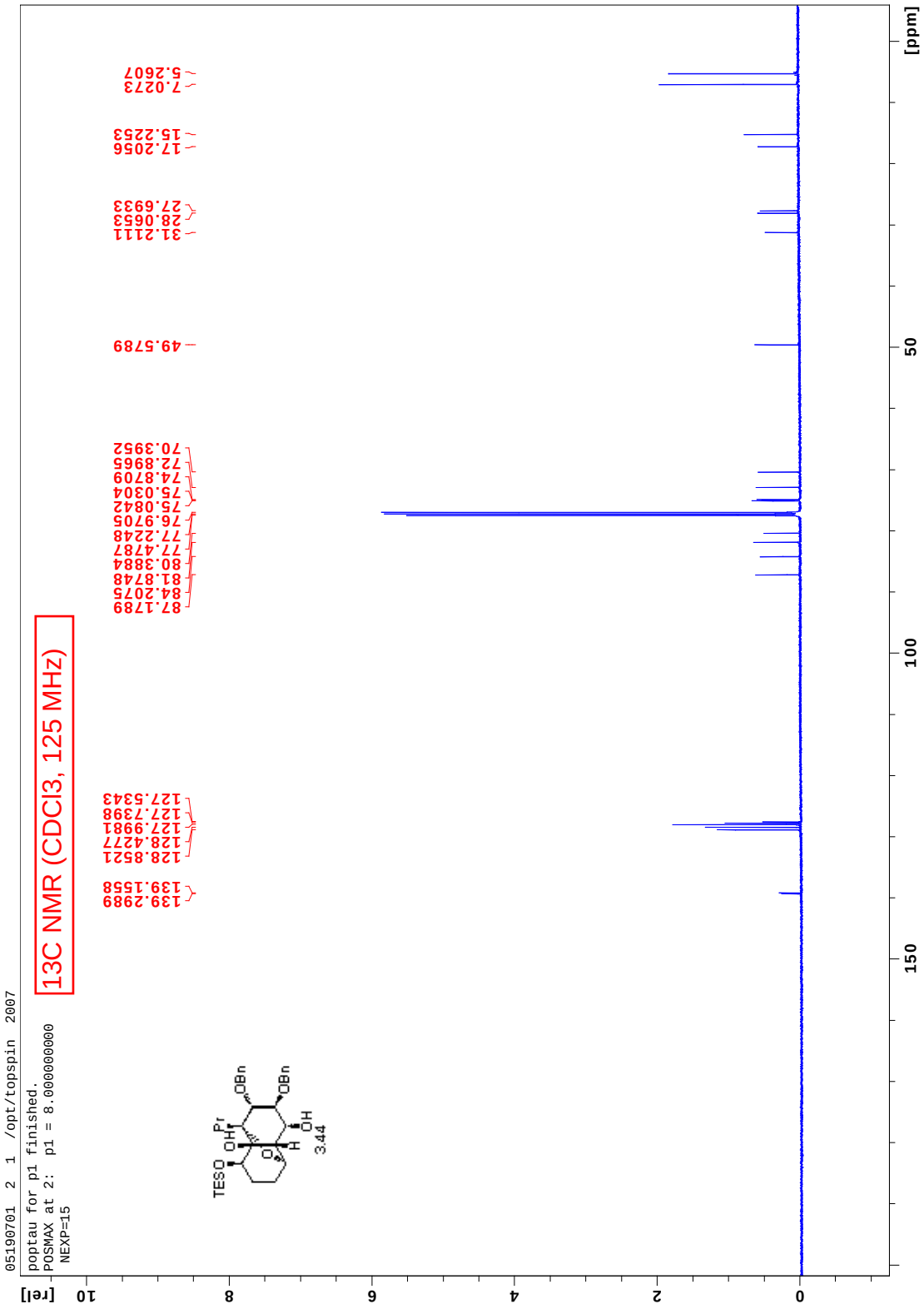
OBn
OH
OH
3.44


13C NMR (CDCl3, 125 MHz)
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poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
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127.9981
127.7398
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87.1789
84.2075
81.8748
80.3884
77.4787
77.2248
76.9705
75.0842
75.0304
74.8709
72.8965
70.3952
49.5789
31.2111
28.0653
27.6933
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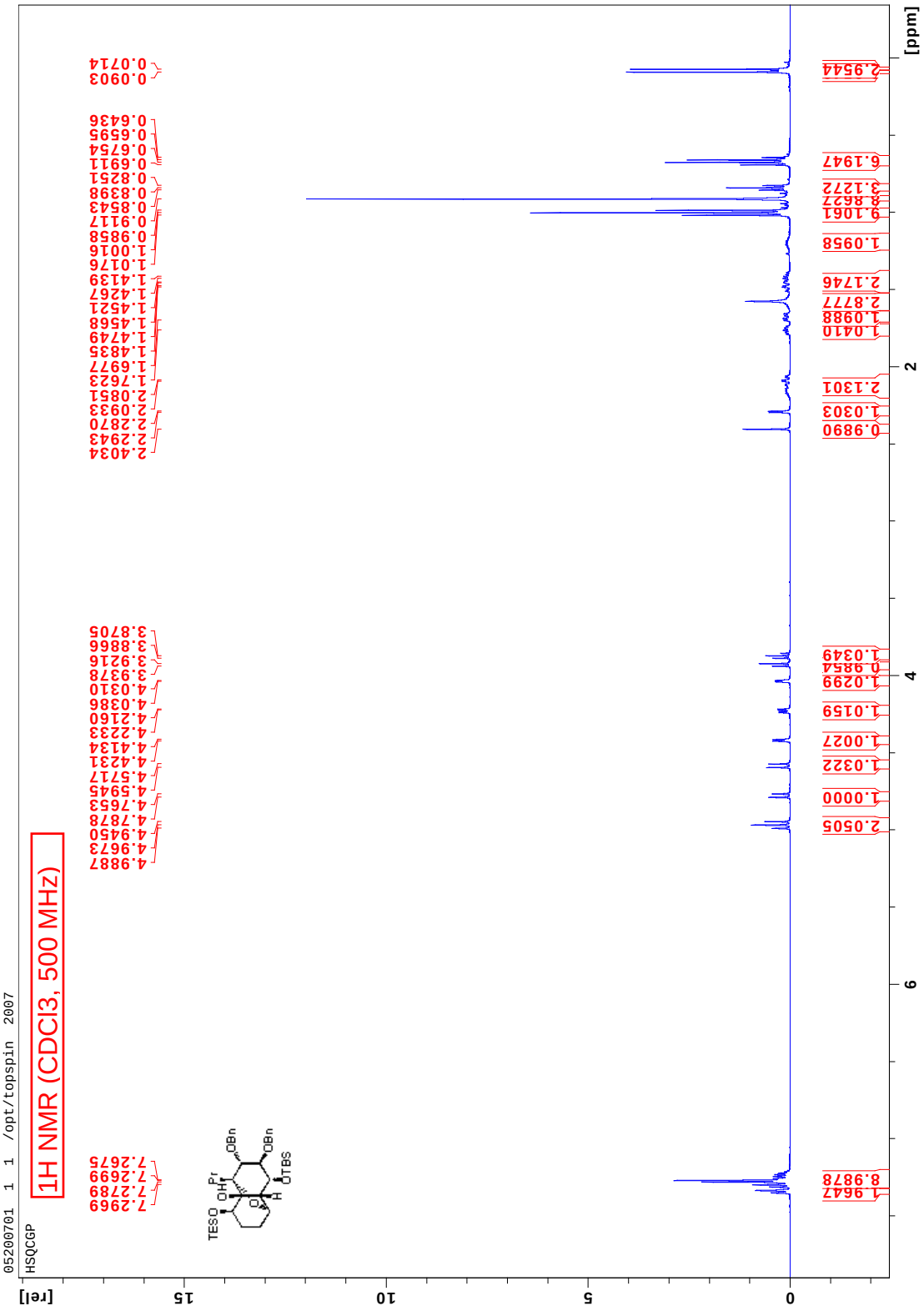
15.2253
7.0273
5.2607
TESO
OH
Pr
OBn
OBn
H
OH
3.44


1H NMR (CDCl3, 500 MHz)
HSQCGP
05200701 1 1 /opt/topspin 2007
[rel]
[ppm]
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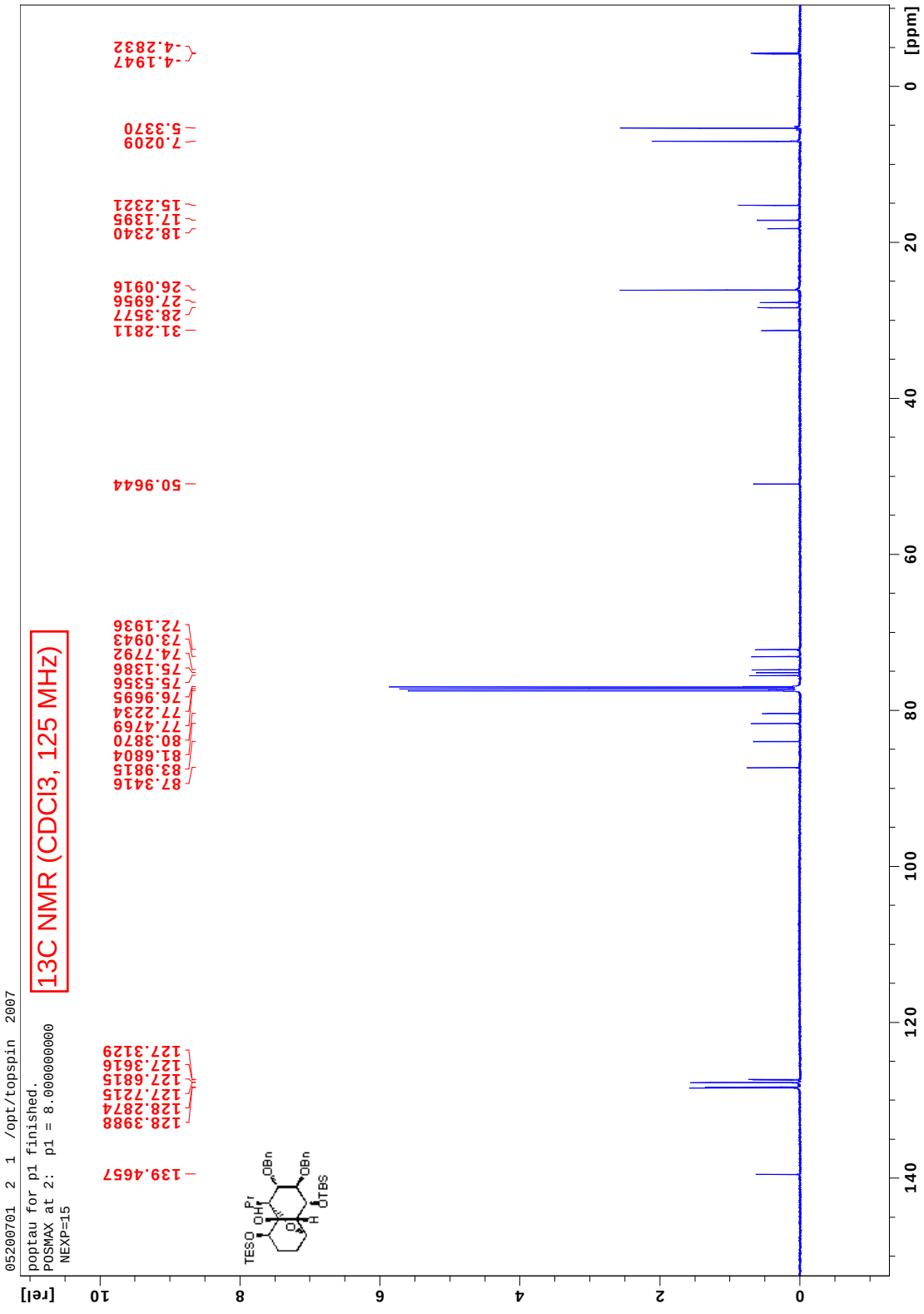
OH
Pr
OBn
OBn
O
H
OTBS


13C NMR (CDCl3, 125 MHz)
05200701 2 1 /opt/topspin 2007
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
139.4657
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127.6815
127.3616
127.3129
87.3416
83.9815
81.6804
80.3870
77.4769
77.2234
76.9695
75.5356
75.1386
74.7792
73.0943
72.1936
50.9644
31.2811
28.3577
27.6956
26.0916
18.2340
17.1395
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5.3370
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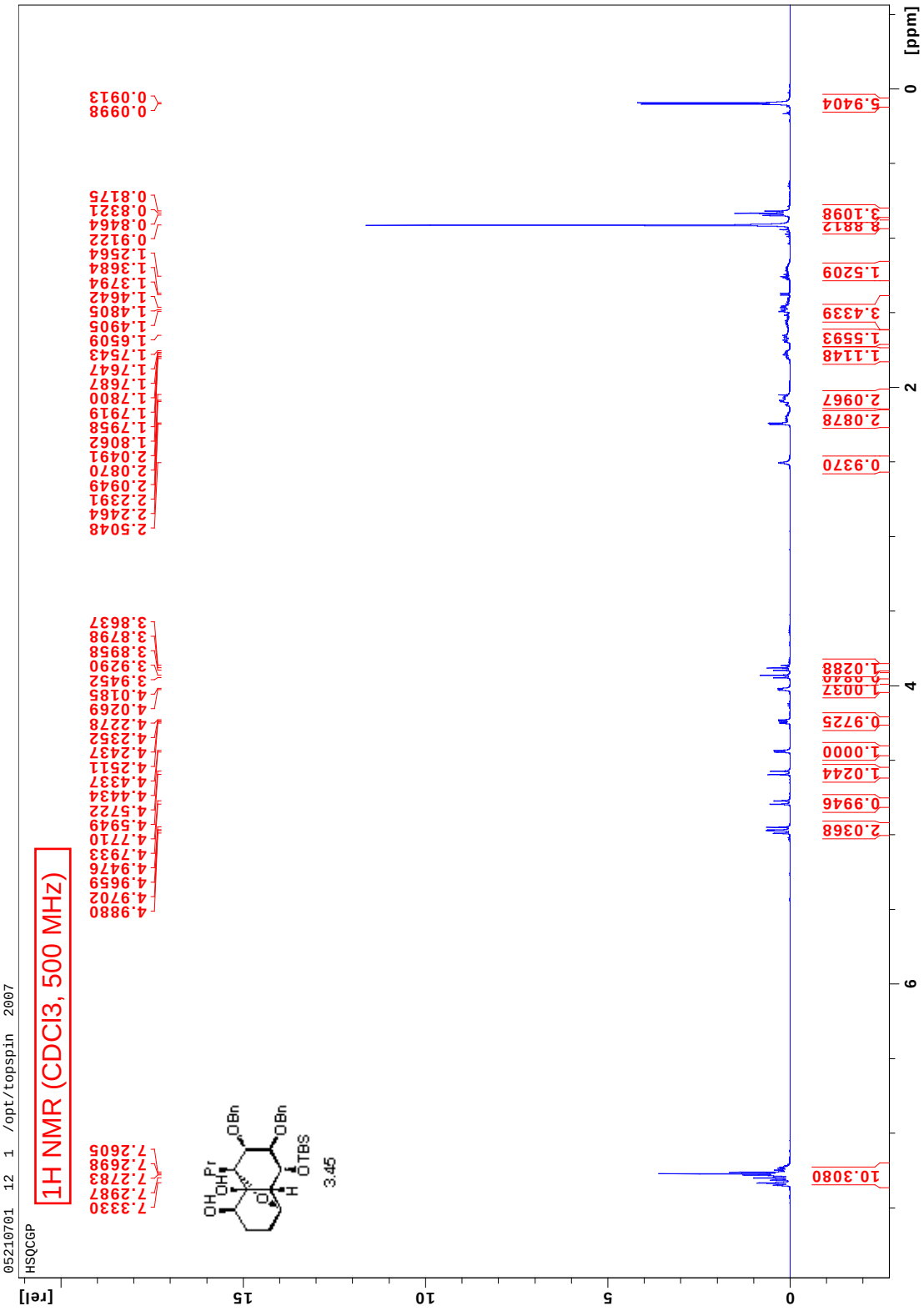
-4.2832
TESO
OH
Pr
OBn
OBn
O
H
OTBS


1H NMR (CDCl3, 500 MHz)
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[ppm]
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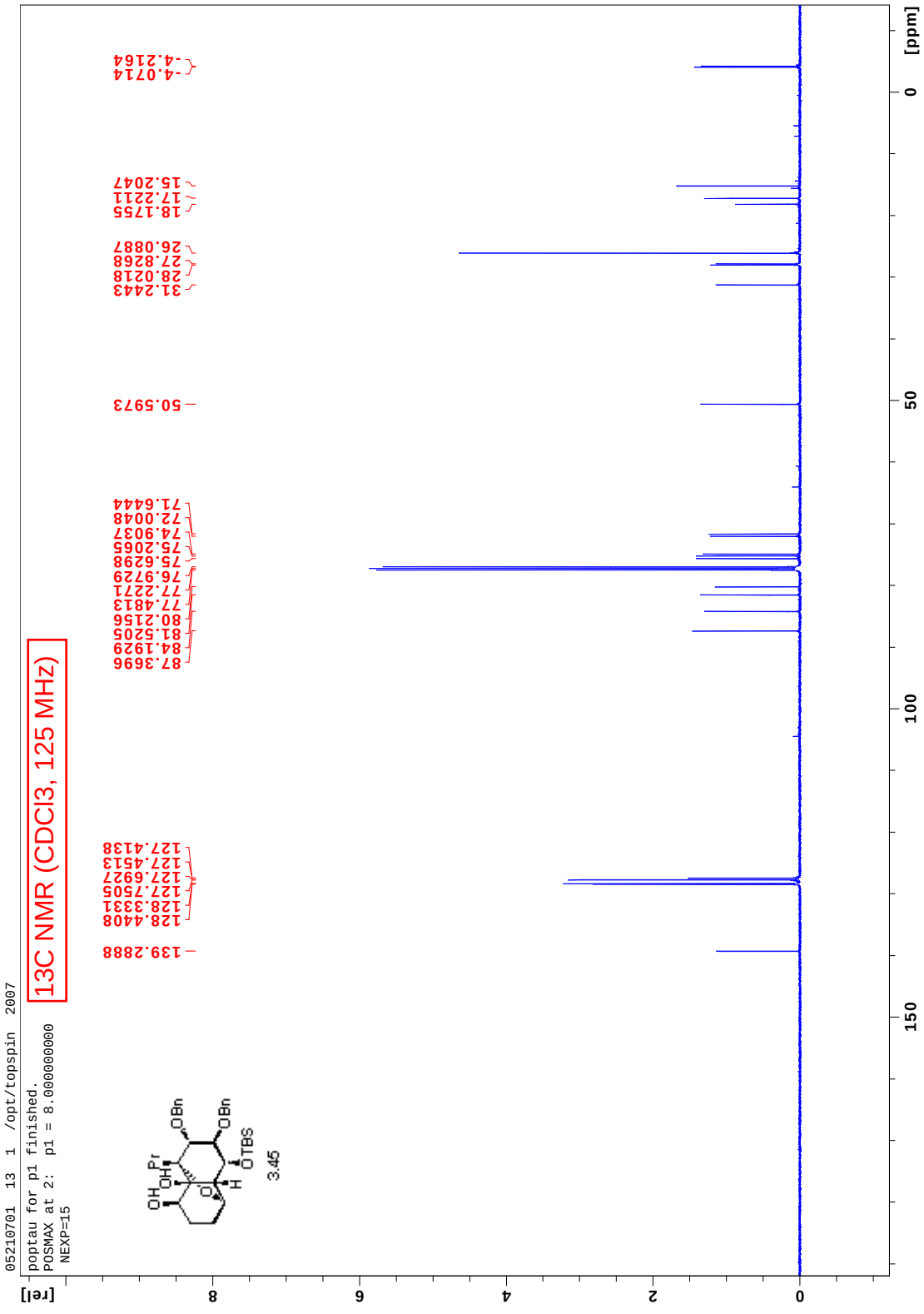
OBn
OTBS
OH
Pr
3.45


13C NMR (CDCl3, 125 MHz)
05210701 13 1 /opt/topspin 2007
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
0
2
4
6
8
0
50
100
150
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-4.2164
15.2047
17.2211
18.1755
26.0887
27.8268
28.0218
31.2443
50.5973
71.6444
72.0048
74.9037
75.2065
75.6298
76.9729
77.2271
77.4813
80.2156
81.5205
84.1929
87.3696
127.4138
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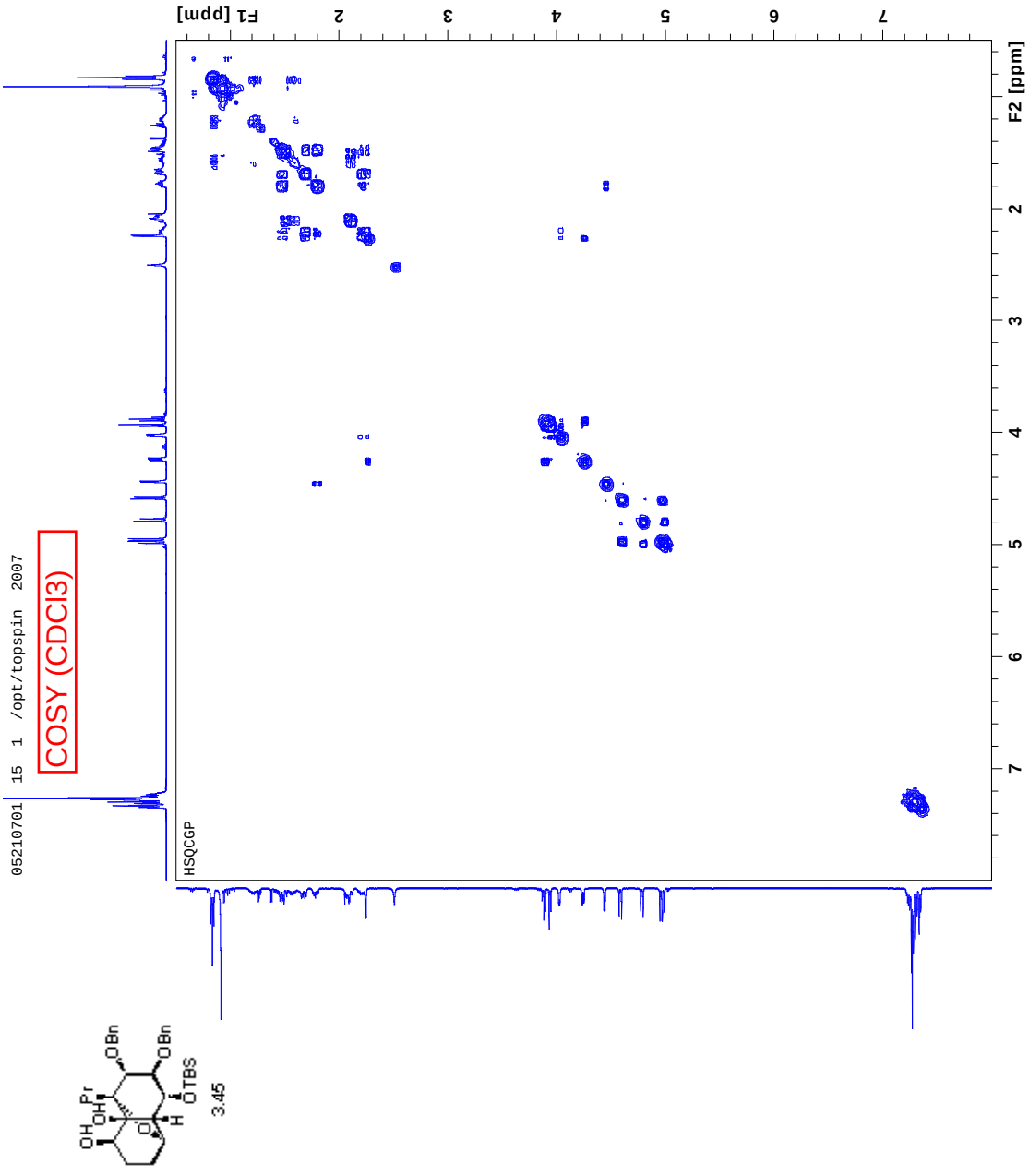
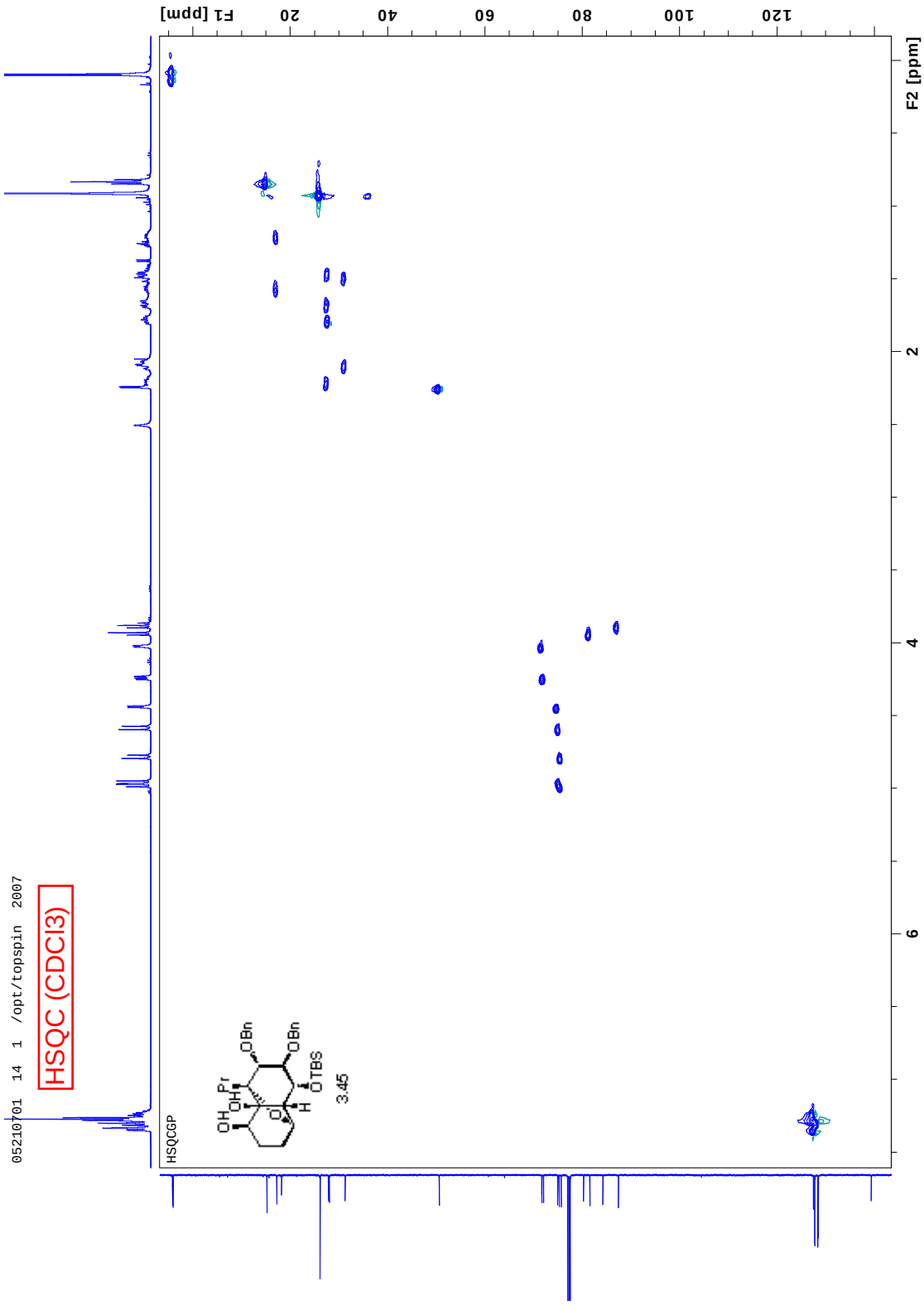
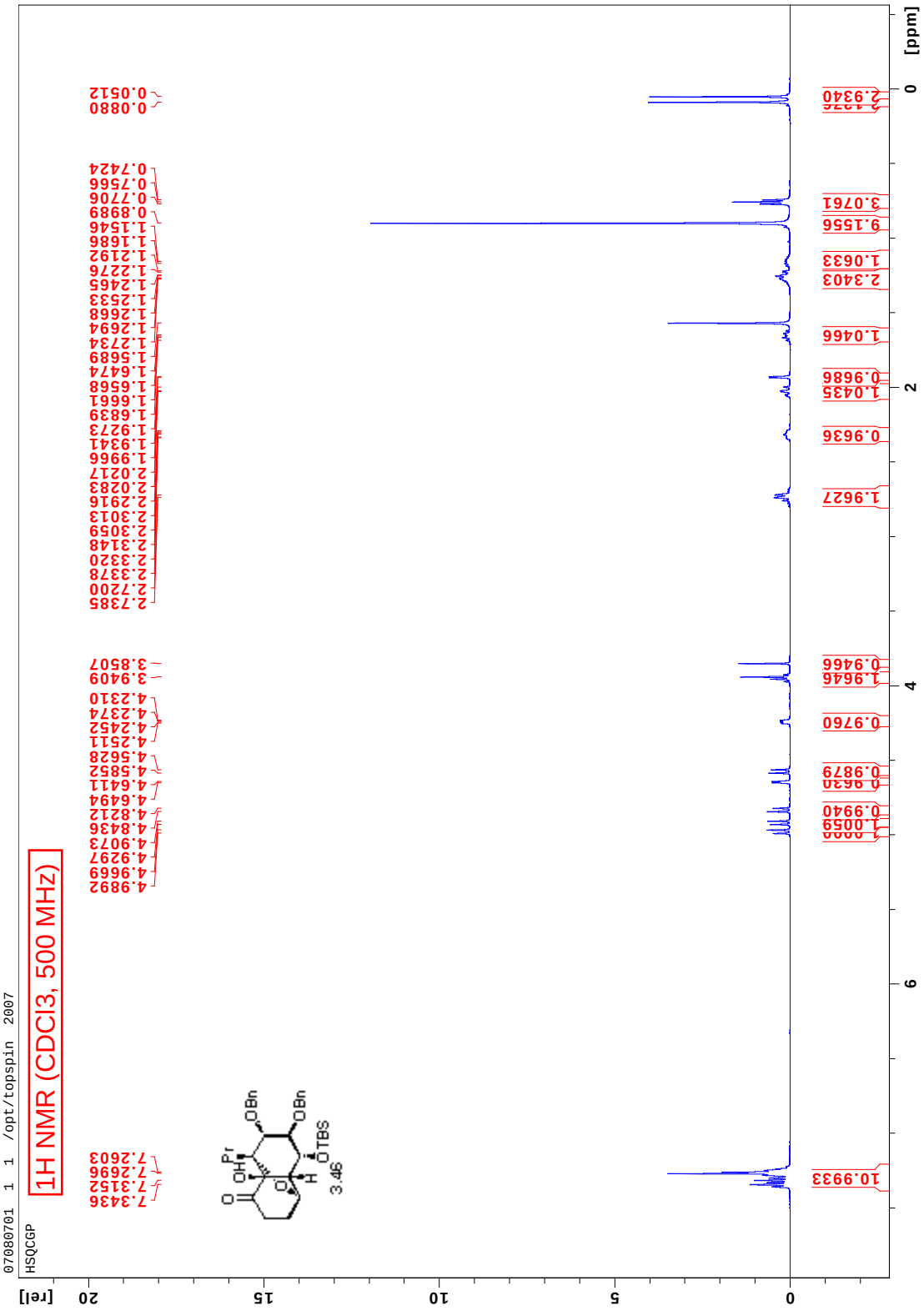
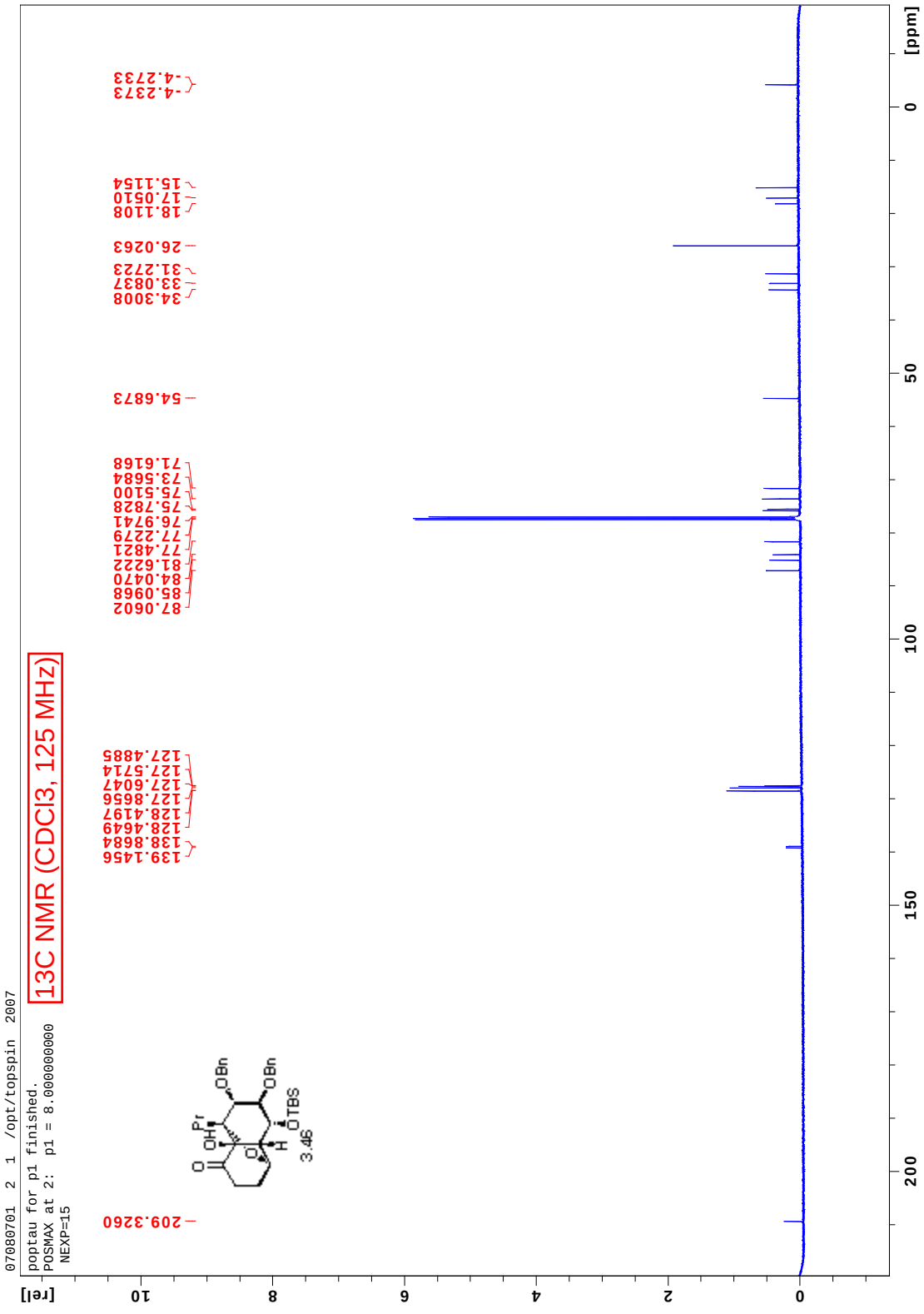
Pr
O
H
OBn
OBn
OTBS
3.45


COSY (CDCl3)
05210701 15 1 /opt/topspin 2007
HSQCGP
F1 [ppm]
F2 [ppm]
2
3
4
5
6
7
OBn
OBn
OH
OH
iPr
O
H
OTBS
3.45


HSQC (CDCl3)
05210701 14 1 /opt/topspin 2007
HSQCGP
F1 [ppm]
F2 [ppm]
20
40
60
80
100
120
2
4
6
OBn
OBn
Pr
OH
OH
O
H
OTBS
3.45


07080701 1 1 /opt/topspin 2007
HSQCGP
1H NMR (CDCl3, 500 MHz)
[rel]
[ppm]
OBn
OBn
OTBS
OH
iPr
3.46


13C NMR (CDCl3, 125 MHz)
07080701 2 1 /opt/topspin 2007
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POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
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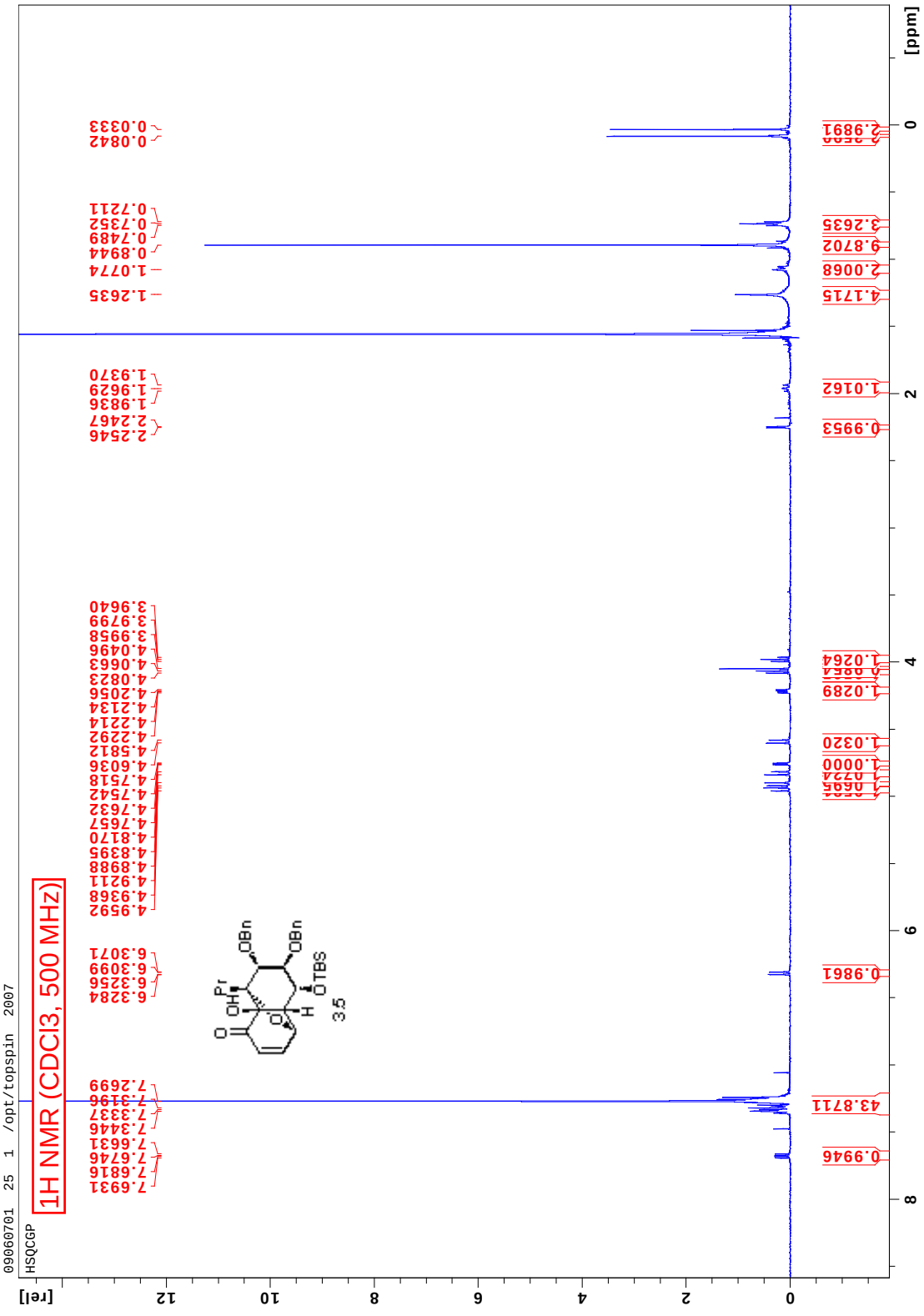
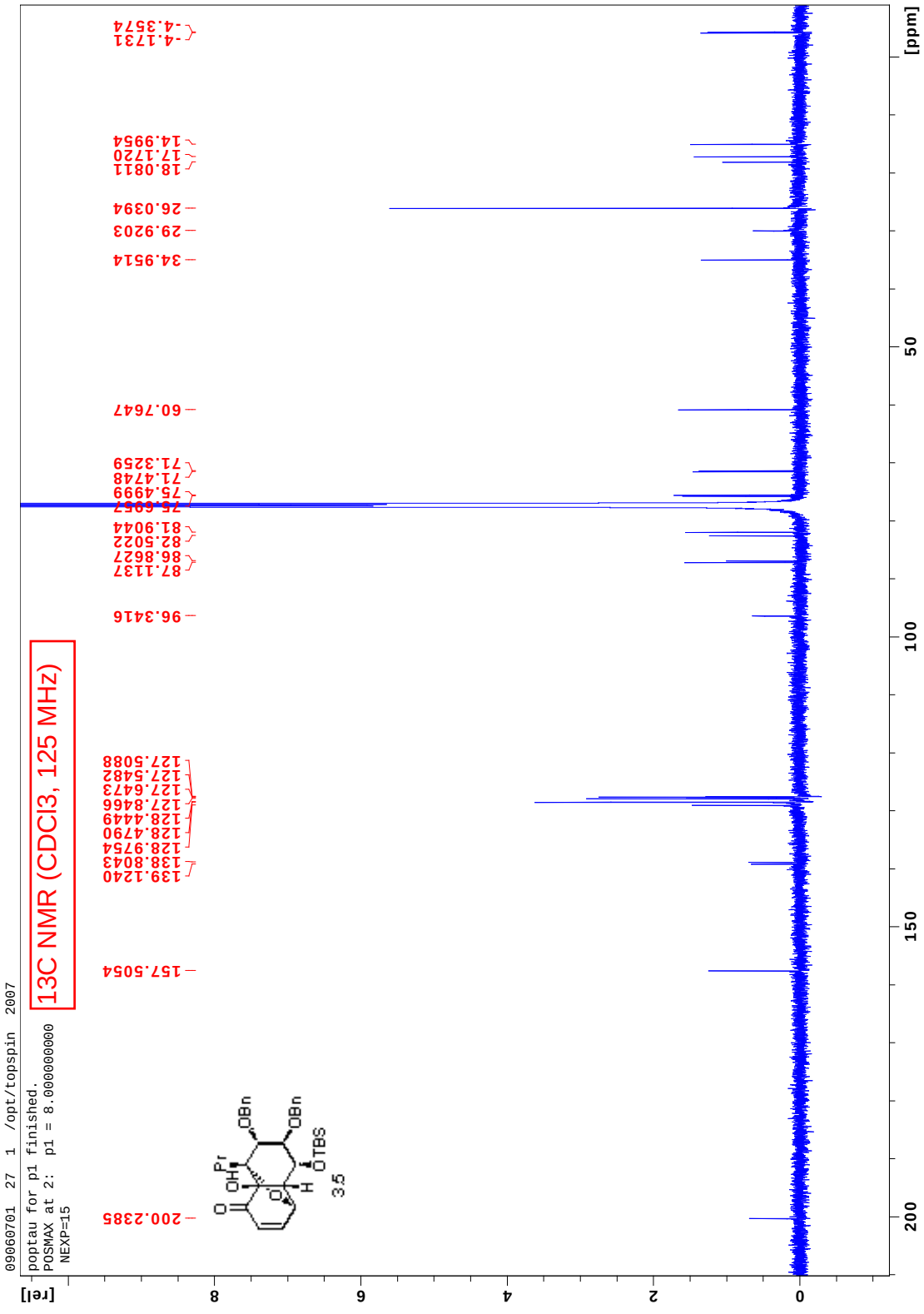
139.1456
138.8684
128.4649
128.4197
127.8656
127.6047
127.5714
127.4885
87.0602
85.0968
84.0470
81.6222
77.4821
77.2279
76.9741
75.7828
75.5100
73.5684
71.6168
54.6873
34.3008
33.0837
31.2723
26.0263
18.1108
17.0510
15.1154
-4.2373
-4.2733
OBn
OBn
OTBS
OH
Pr
O
O
H
3.46


1H NMR (CDCl3, 500 MHz)
090607O1 25 1 /opt/topspin 2007
HSQCGP
OBn
OBn
Pr
OH
O
H
OTBS
3.5
[rel]
[ppm]


13C NMR (CDCl3, 125 MHz)
090607O1 27 1 /opt/topspin 2007
poptau for p1 finished.
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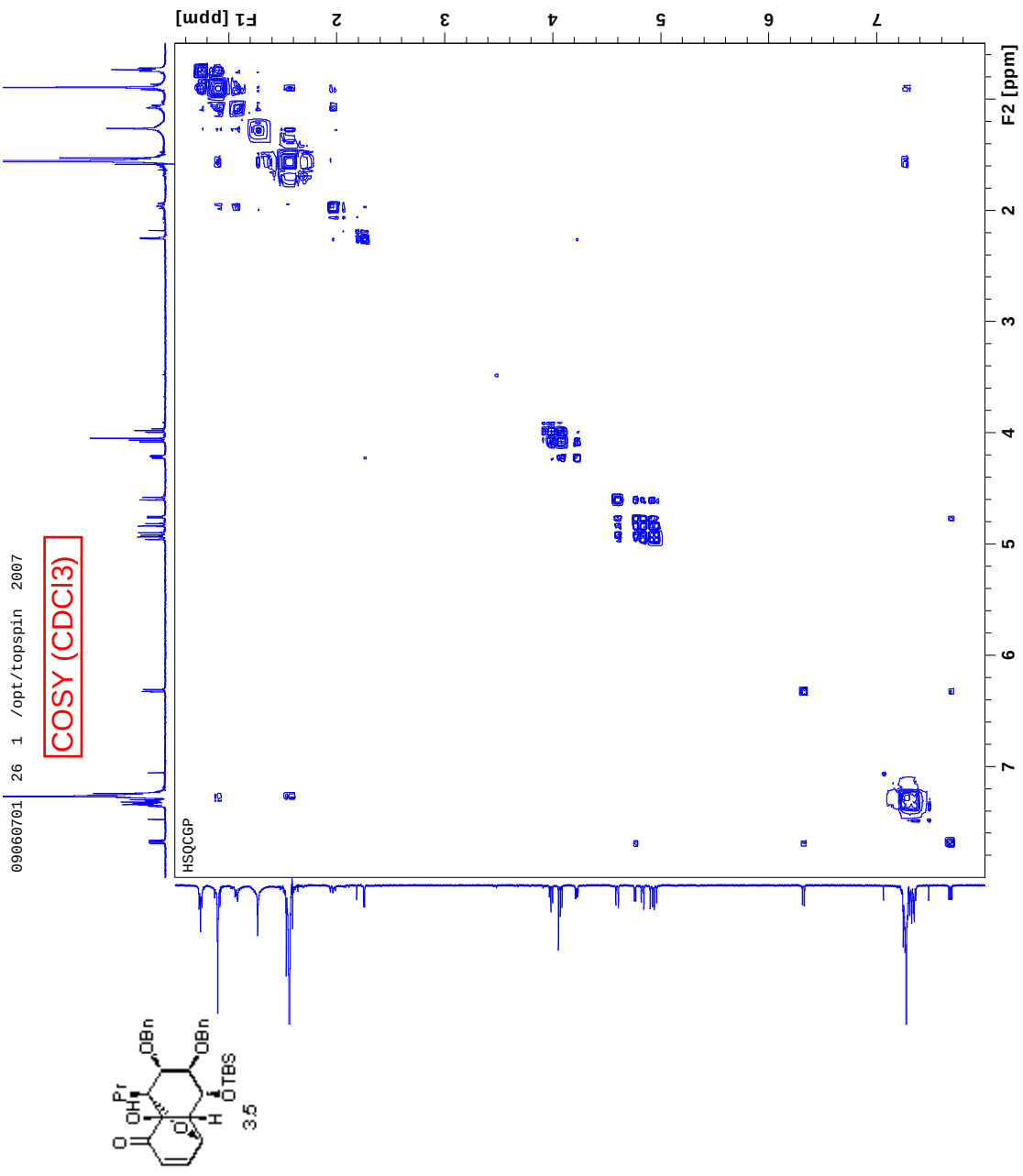
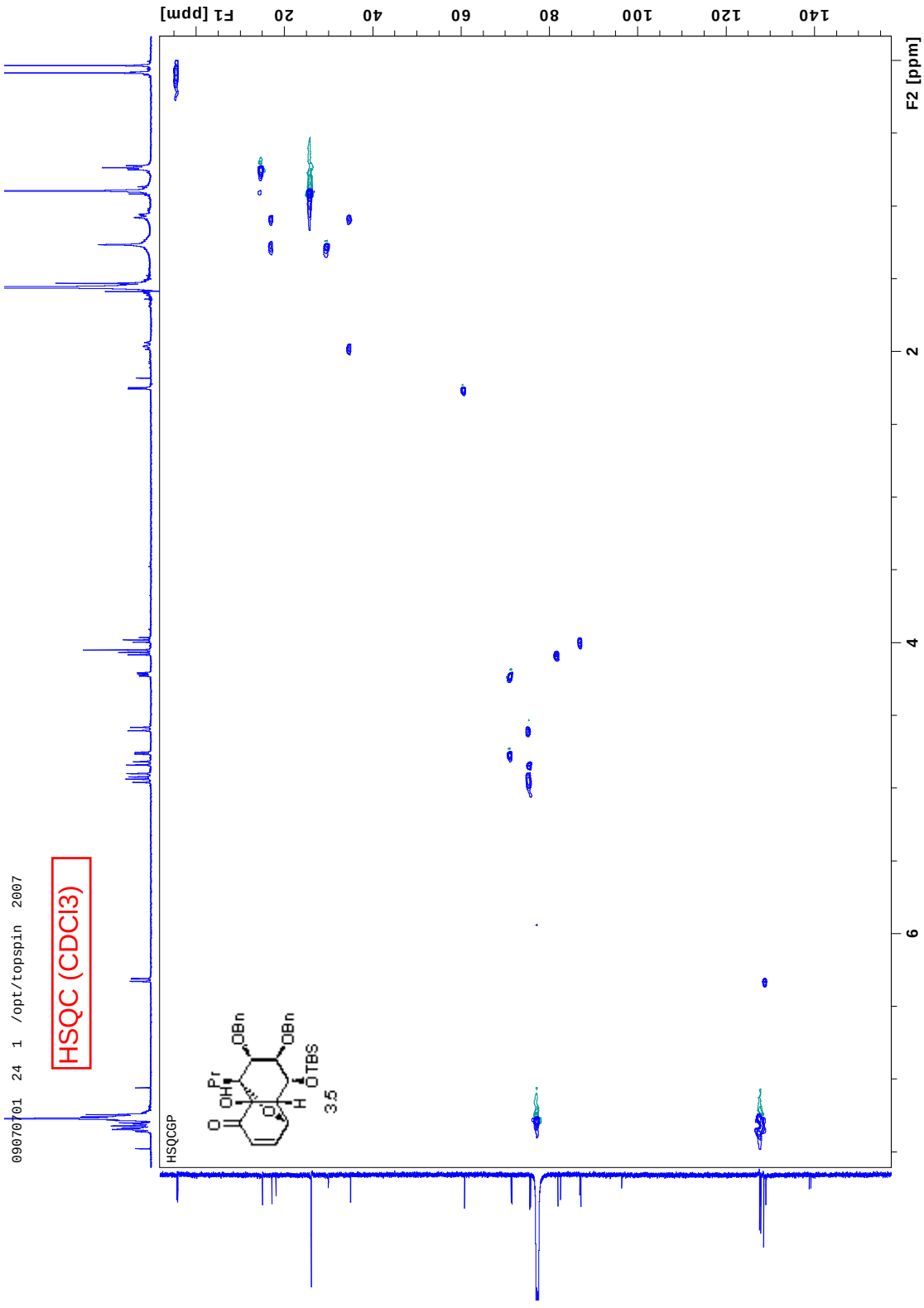
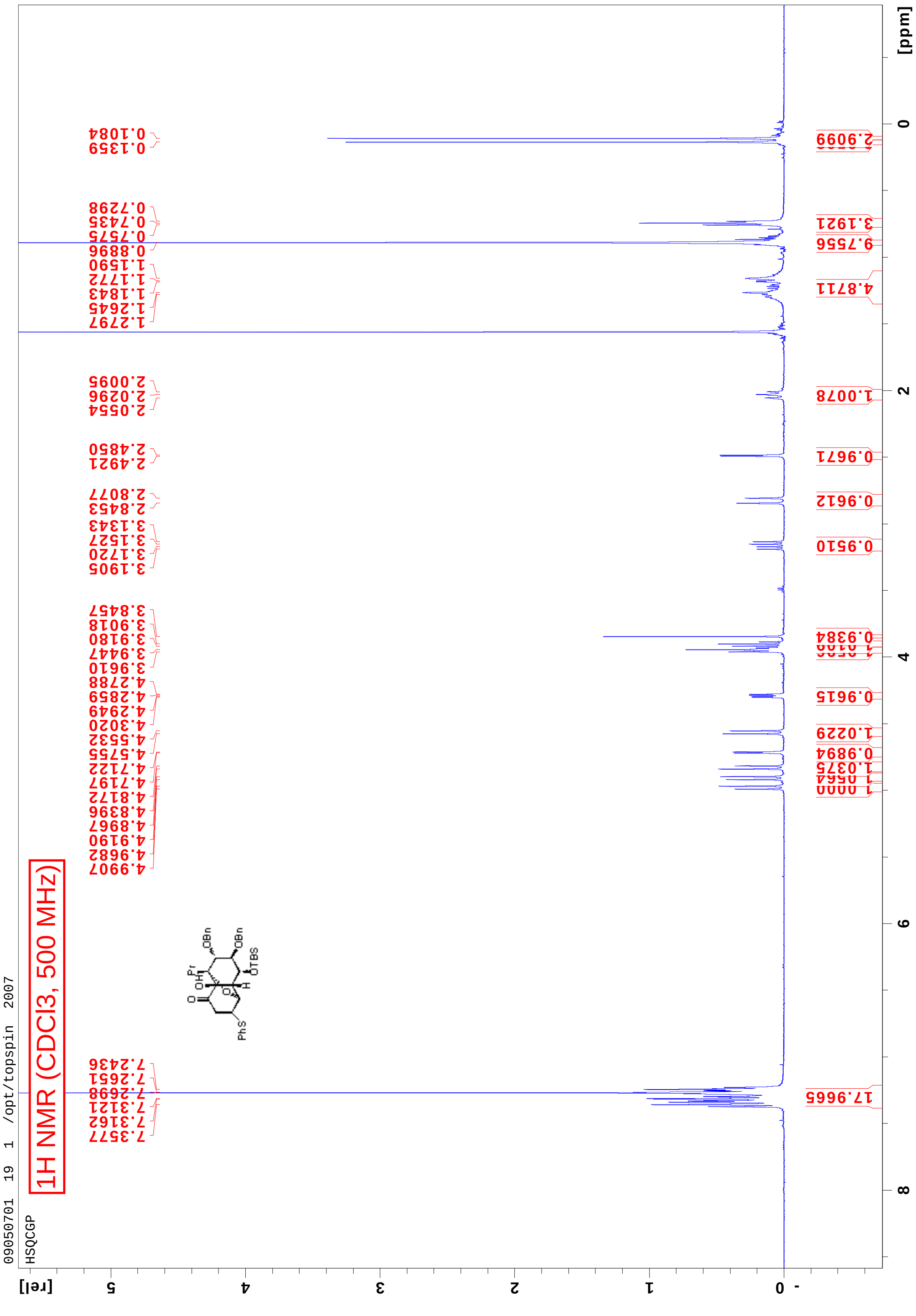
157.5054
139.1240
138.8043
128.9754
128.4790
128.4449
127.8466
127.6473
127.5482
127.5088
96.3416
87.1137
86.8627
82.5022
81.9044
76.6567
75.4999
71.4748
71.3259
60.7647
34.9514
29.9203
26.0394
18.0811
17.1720
14.9954
-4.1731
-4.3574
OBn
OBn
Pr
OH
O
H
OTBS
3.5
[rel]
[ppm]


COSY (CDCl3)
090607O1 26 1 /opt/topspin 2007
HSQCGP
F1 [ppm]
F2 [ppm]
OBn
OBn
OTBS
OH
Pr
O
O
H
3.5


HSQC (CDCl3)
HSQCGP
F1 [ppm]
F2 [ppm]
20
40
60
80
100
120
140
2
4
6
OBn
OBn
OTBS
OH
Pr
O
H
3.5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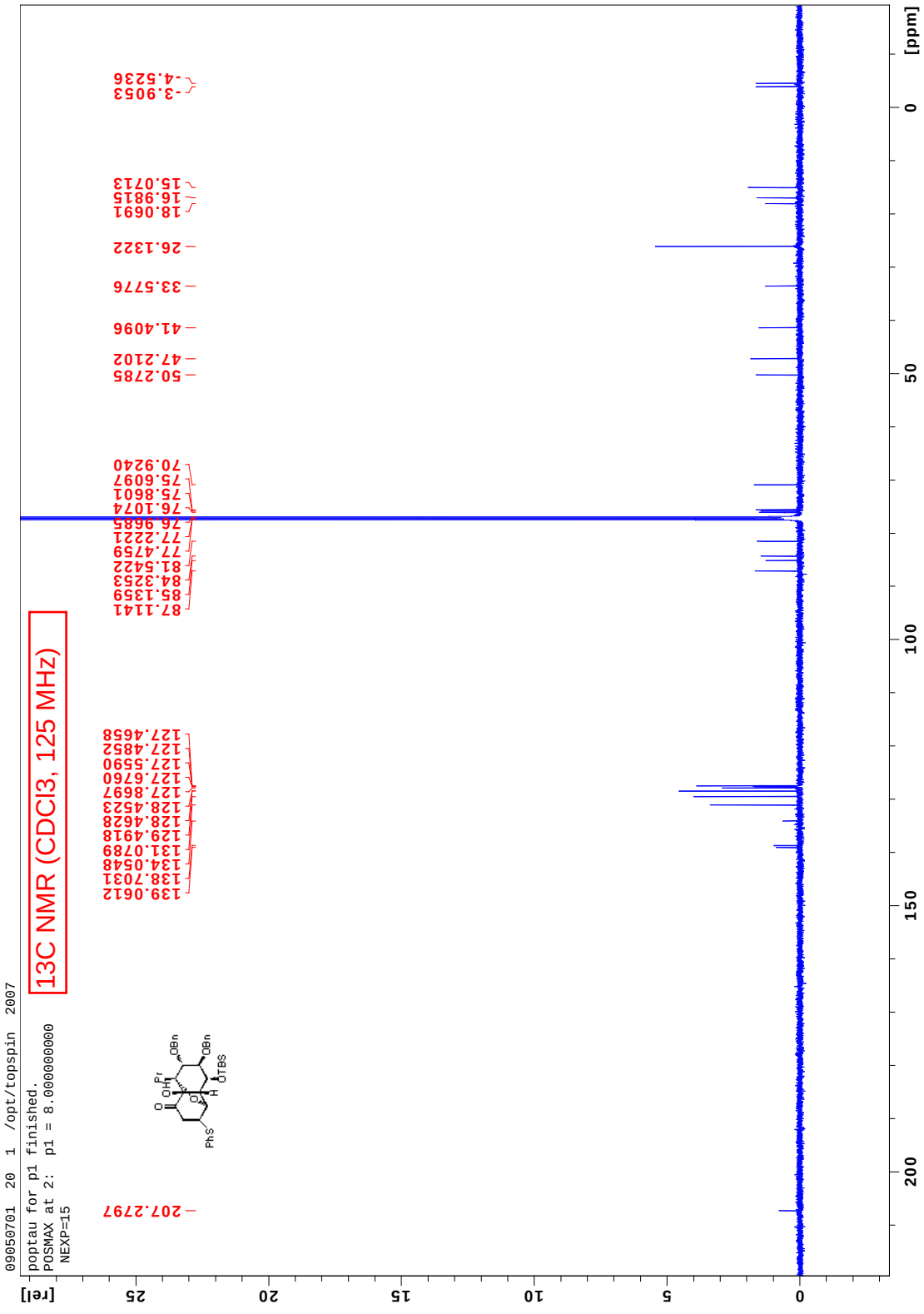
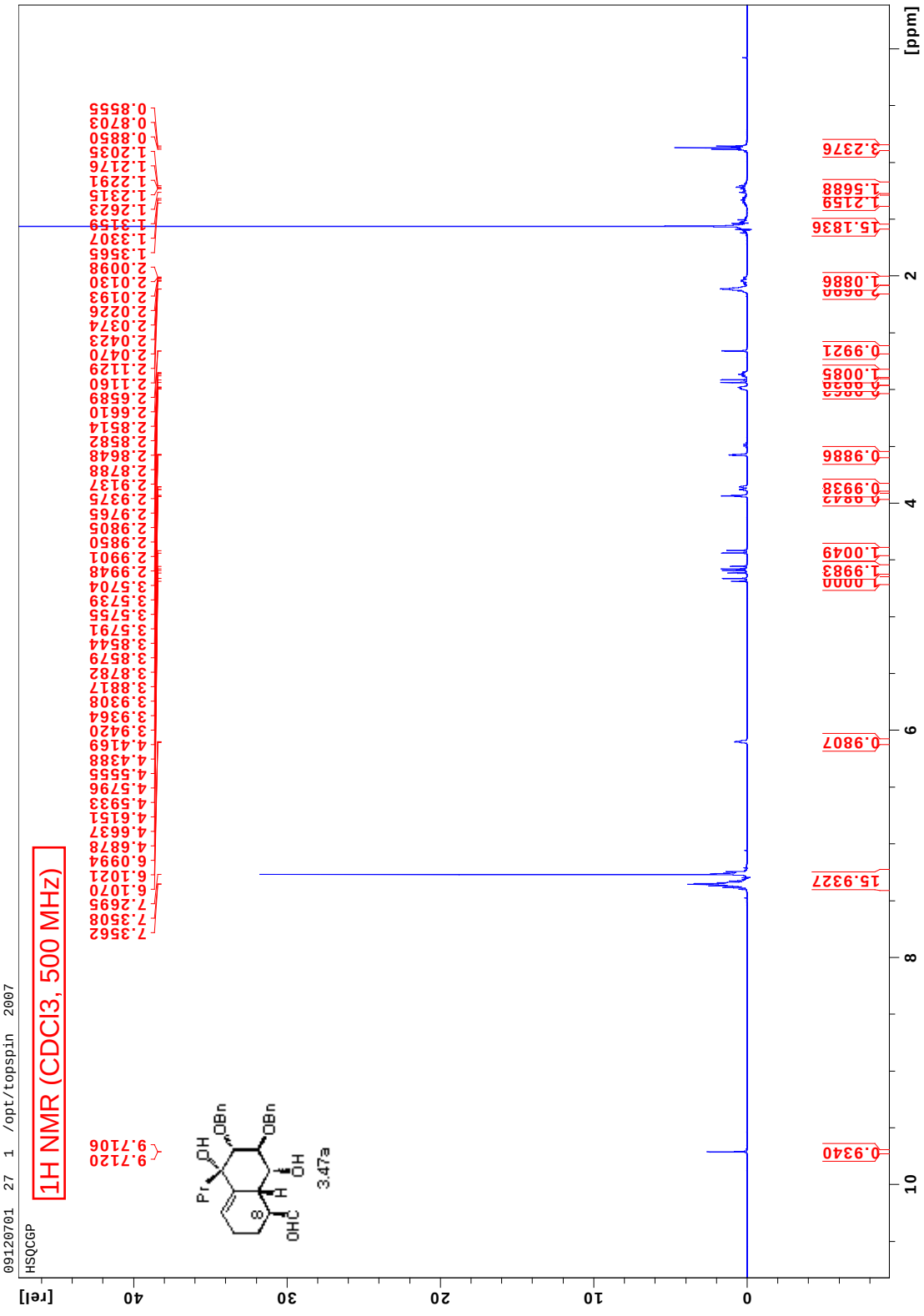
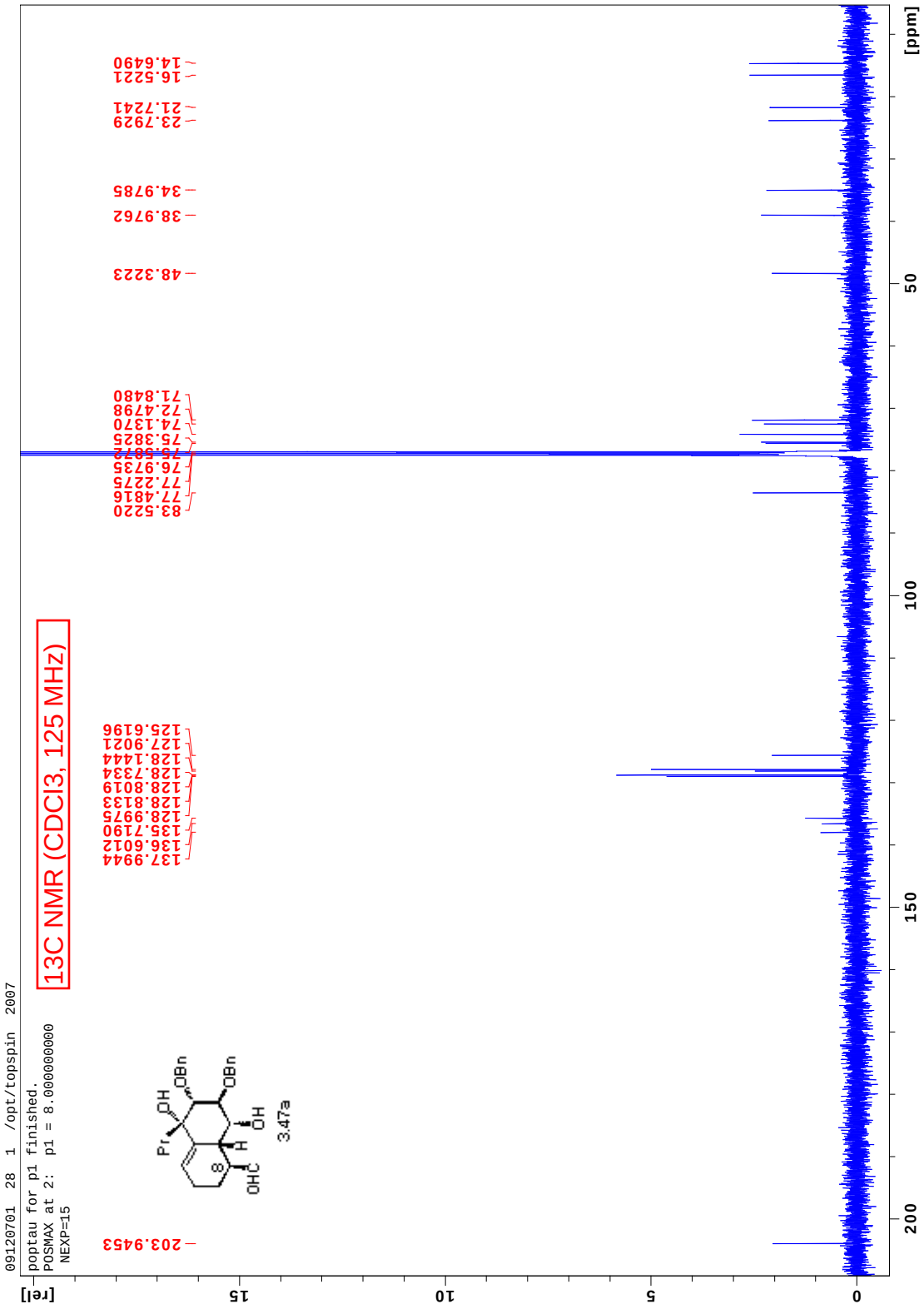
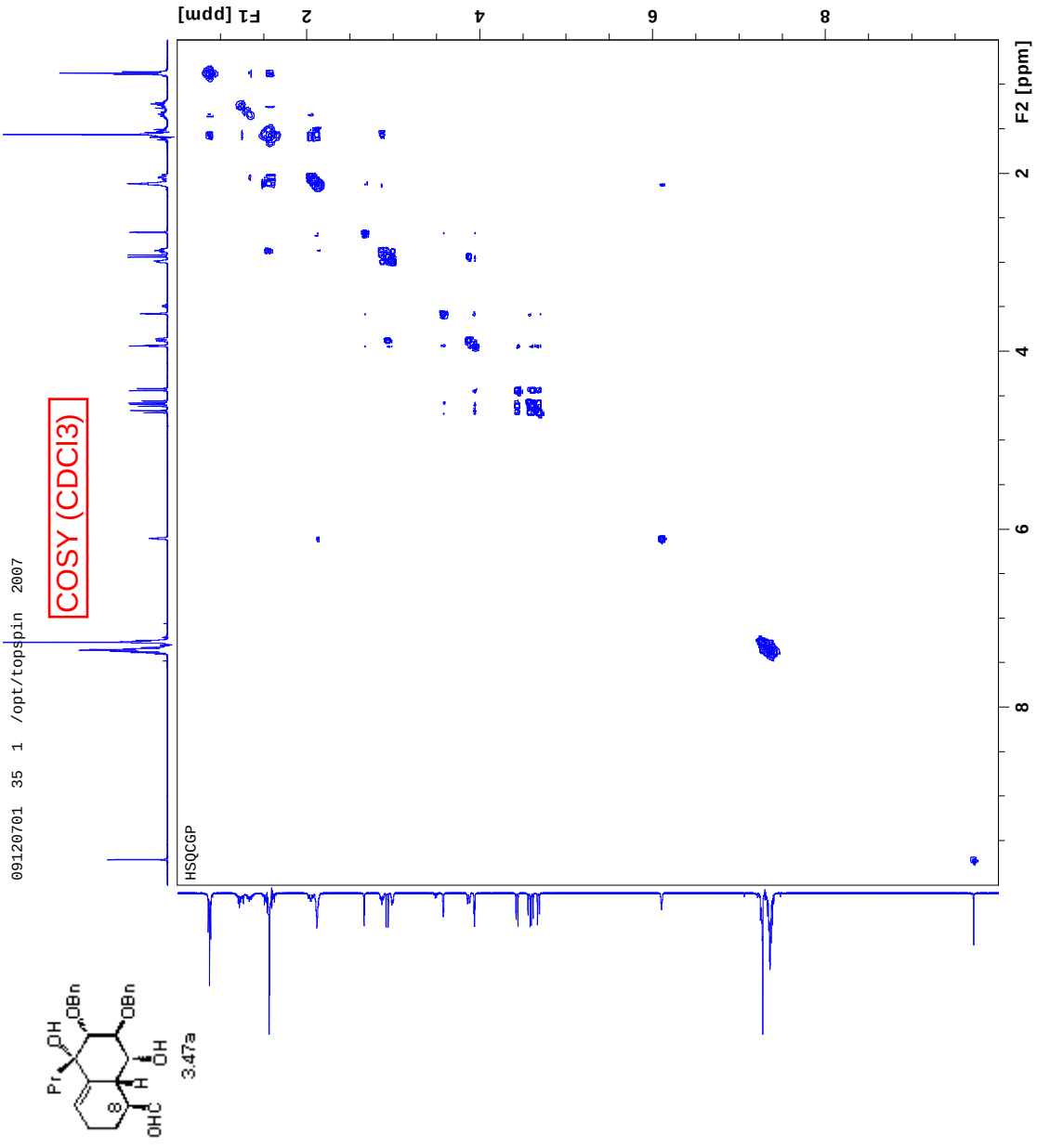
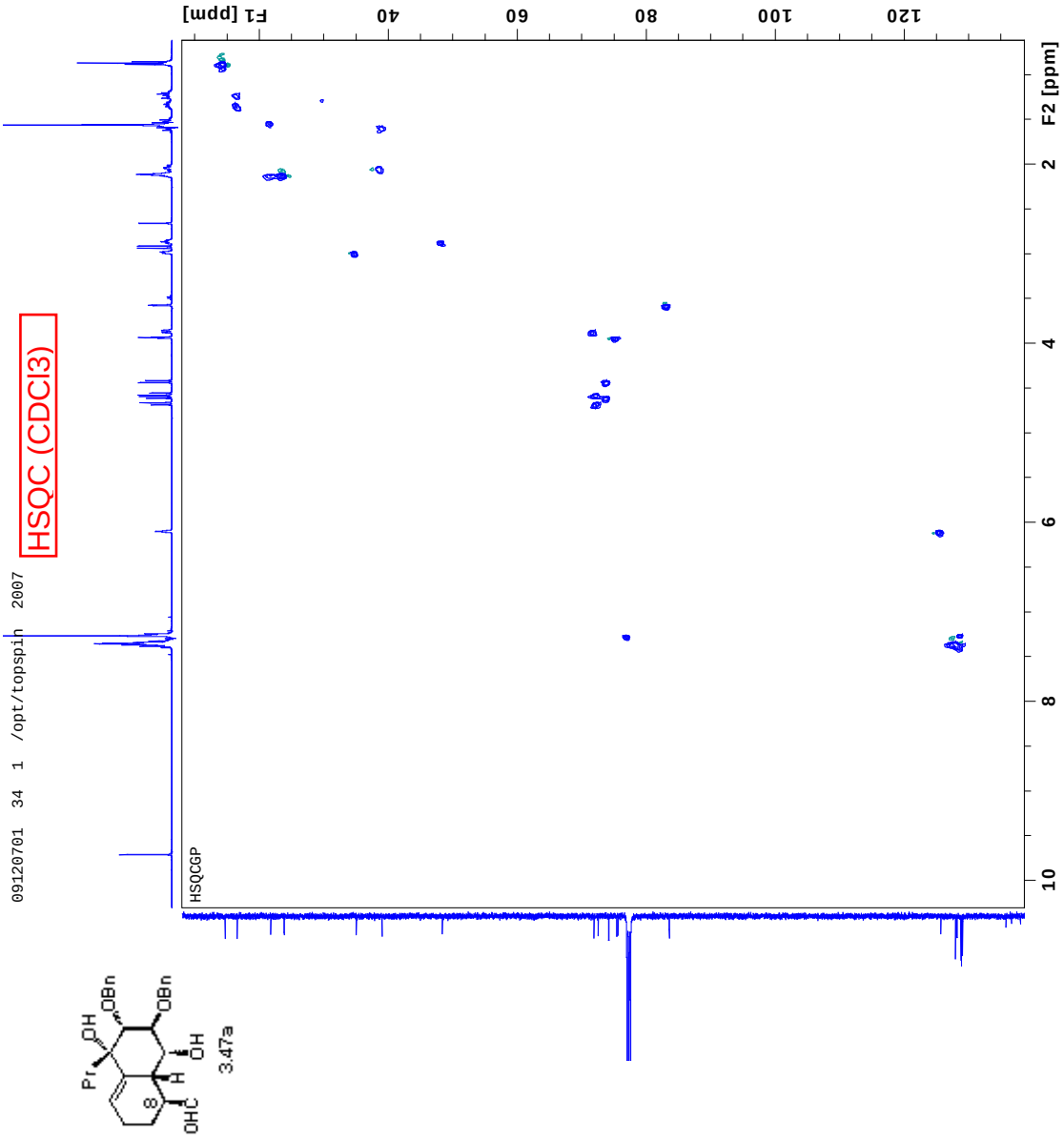
HSQCGP
1H NMR (CDCl3, 500 MHz)
7.3577 7.3162 7.3121 7.2698 7.2651 7.2436
4.9907 4.9682 4.9190 4.8967 4.8396 4.8172 4.7197 4.7122 4.5755 4.5532 4.3020 4.2949 4.2859 4.2788
3.9610 3.9447 3.9180 3.9018 3.8457
3.1905 3.1720 3.1527 3.1343
2.8453 2.8077
2.4921 2.4850
2.0554 2.0296 2.0095
1.2797 1.2645 1.1843 1.1772 1.1590
0.8896 0.7575 0.7435 0.7298
0.1359 0.1084
[ppm]
[rel]

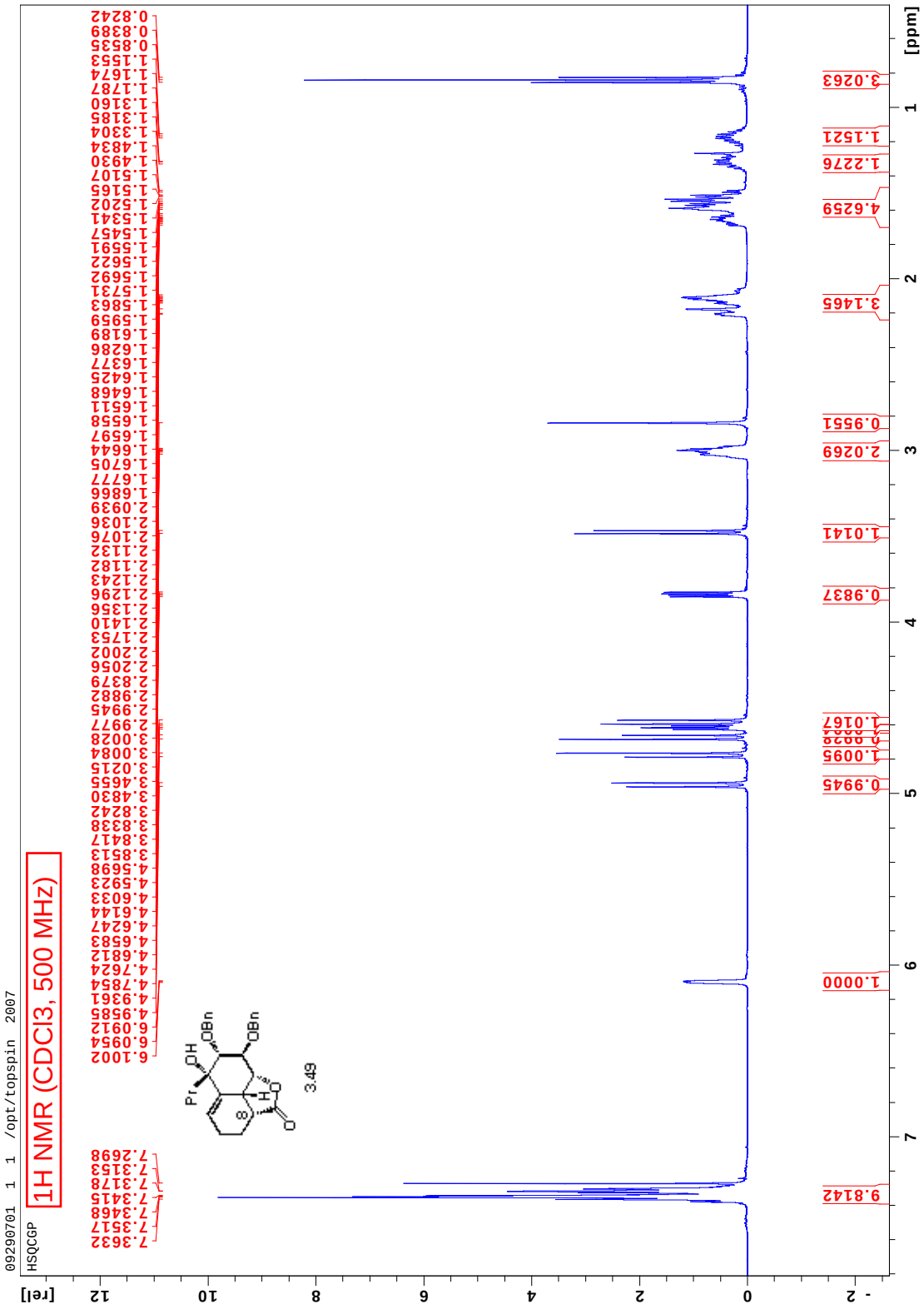

13C NMR (CDCl3, 125 MHz)
090507O1 20 1 /opt/topspin 2007
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
207.2797
139.0612
138.7031
134.0548
131.0789
129.4918
128.4628
128.4523
127.8697
127.6760
127.5590
127.4852
127.4658
87.1141
85.1359
84.3253
81.5422
77.4759
77.2221
76.9685
76.1074
75.8601
75.6097
70.9240
50.2785
47.2102
41.4096
33.5776
26.1322
18.0691
16.9815
15.0713
-3.9053
-4.5236
[rel]
25
20
15
10
5
0
200
150
100
50
0
[ppm]

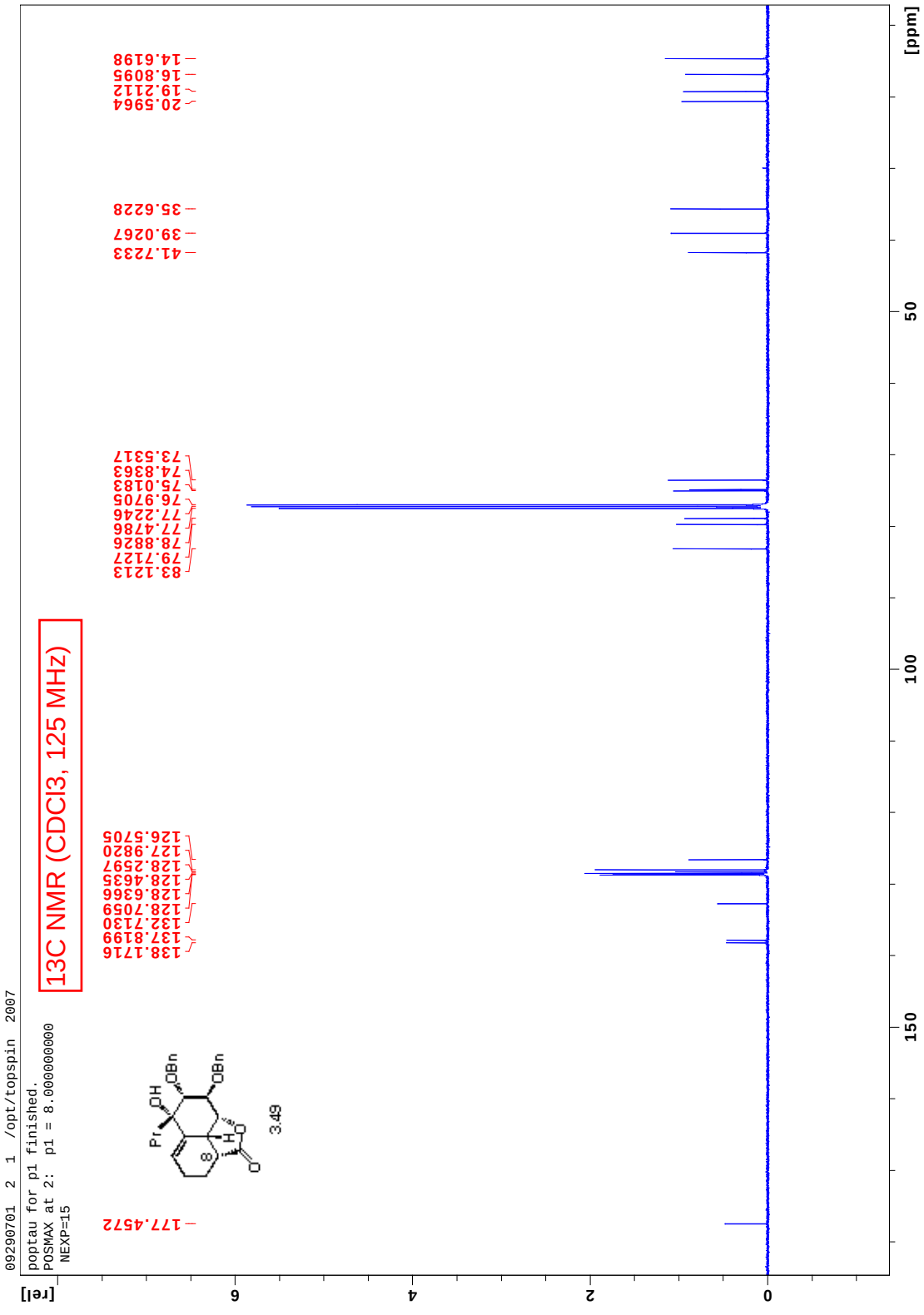

1H NMR (CDCl3, 500 MHz)
09120701 27 1 /opt/topspin 2007
HSQCGP
3.47a
[rel]
[ppm]

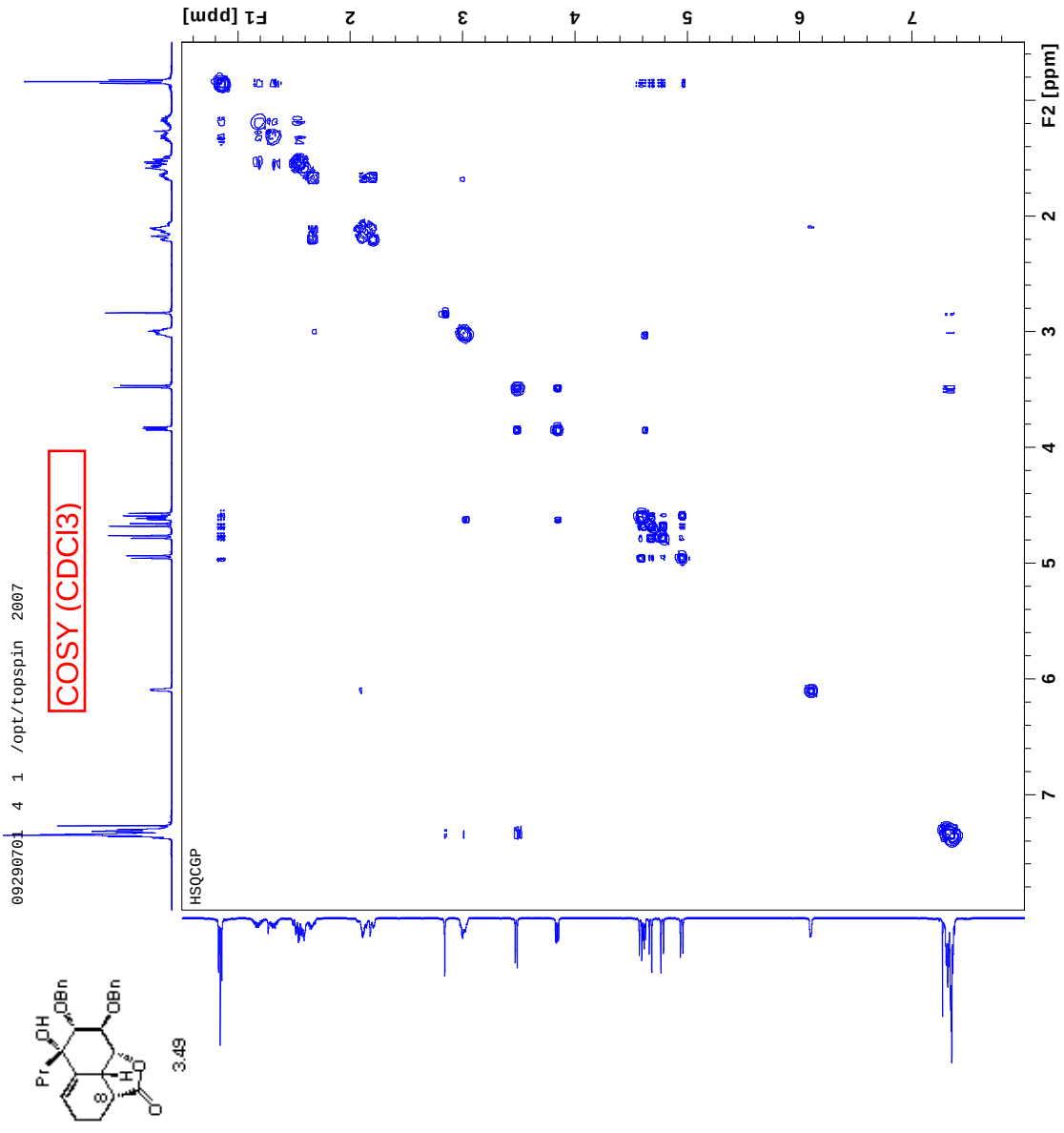

13C NMR (CDCl3, 125 MHz)
203.9453
137.9944
136.6012
135.7190
128.9975
128.8133
128.8019
128.7334
128.1444
127.9021
125.6196
83.5220
77.4816
77.2275
76.9735
76.6072
75.3825
74.1370
72.4798
71.8480
48.3223
38.9762
34.9785
23.7929
21.7241
16.5221
14.6490
3.47a
OBn
OBn
OH
OH
H
Pr
OHC
8
[rel]
[ppm]
0
5
10
15
50
100
150
200

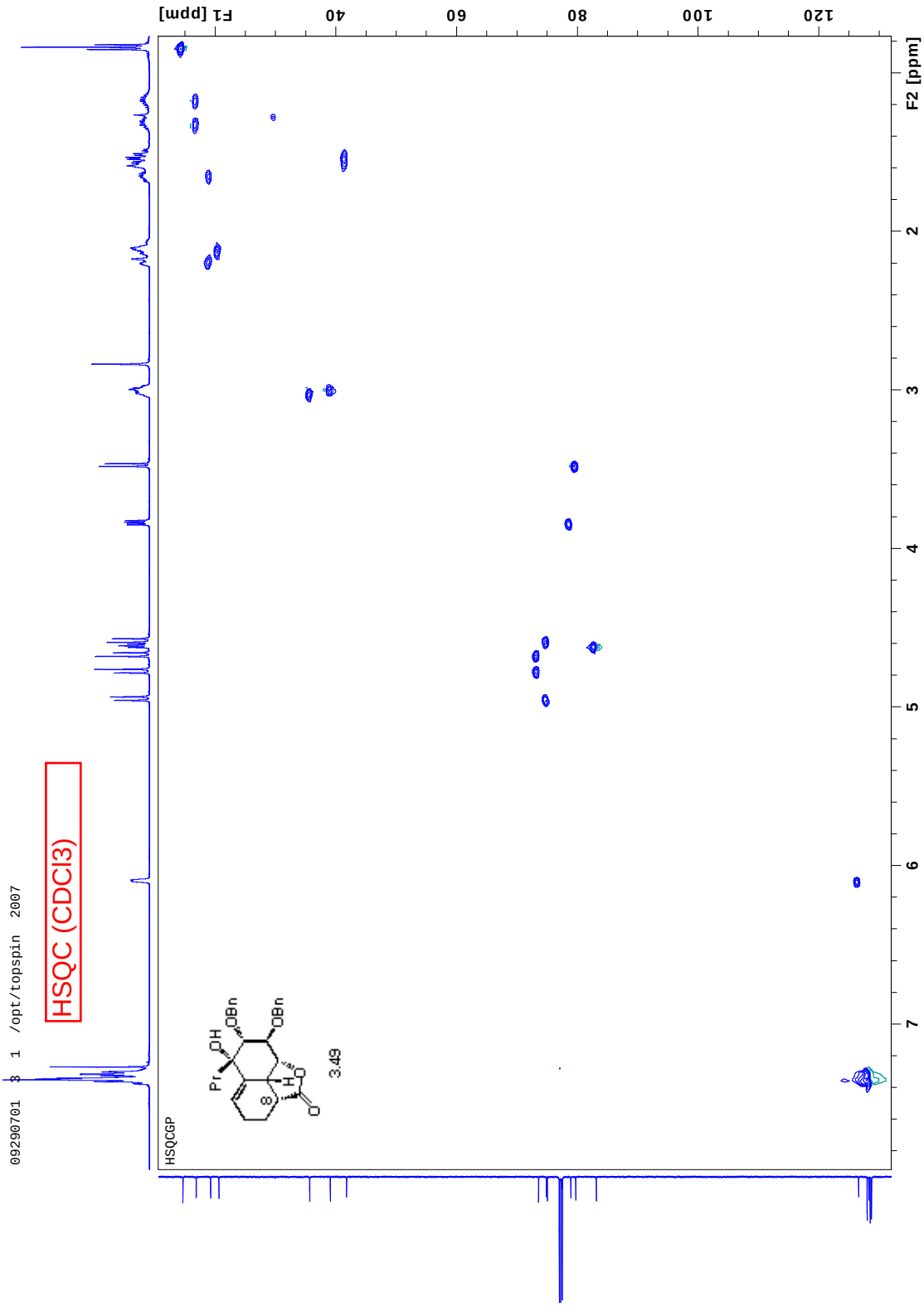

COSY (CDCl3)
09120701 35 1 /opt/topspin 2007
HSQCGP
F1 [ppm]
F2 [ppm]
2
4
6
8
3.47a
OBn
OBn
OH
OH
Pr
H
OHC

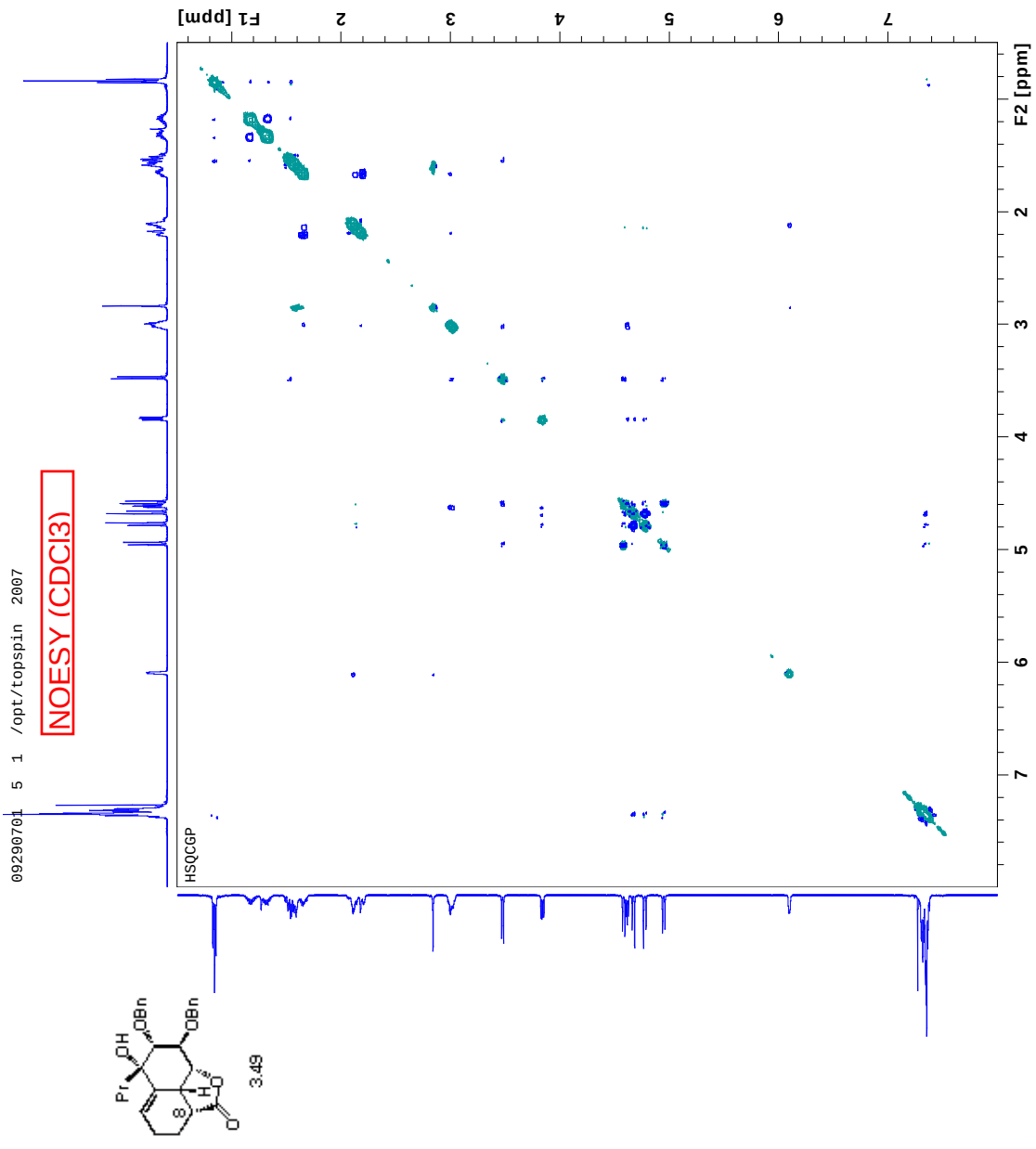

HSQC (CDCl3)
09120701 34 1 /opt/topspin 2007
HSQCGP
F1 [ppm]
F2 [ppm]
120
100
80
60
40
2
4
6
8
10
OBn
OBn
OH
OH
OHC
Pr
H
3.47a

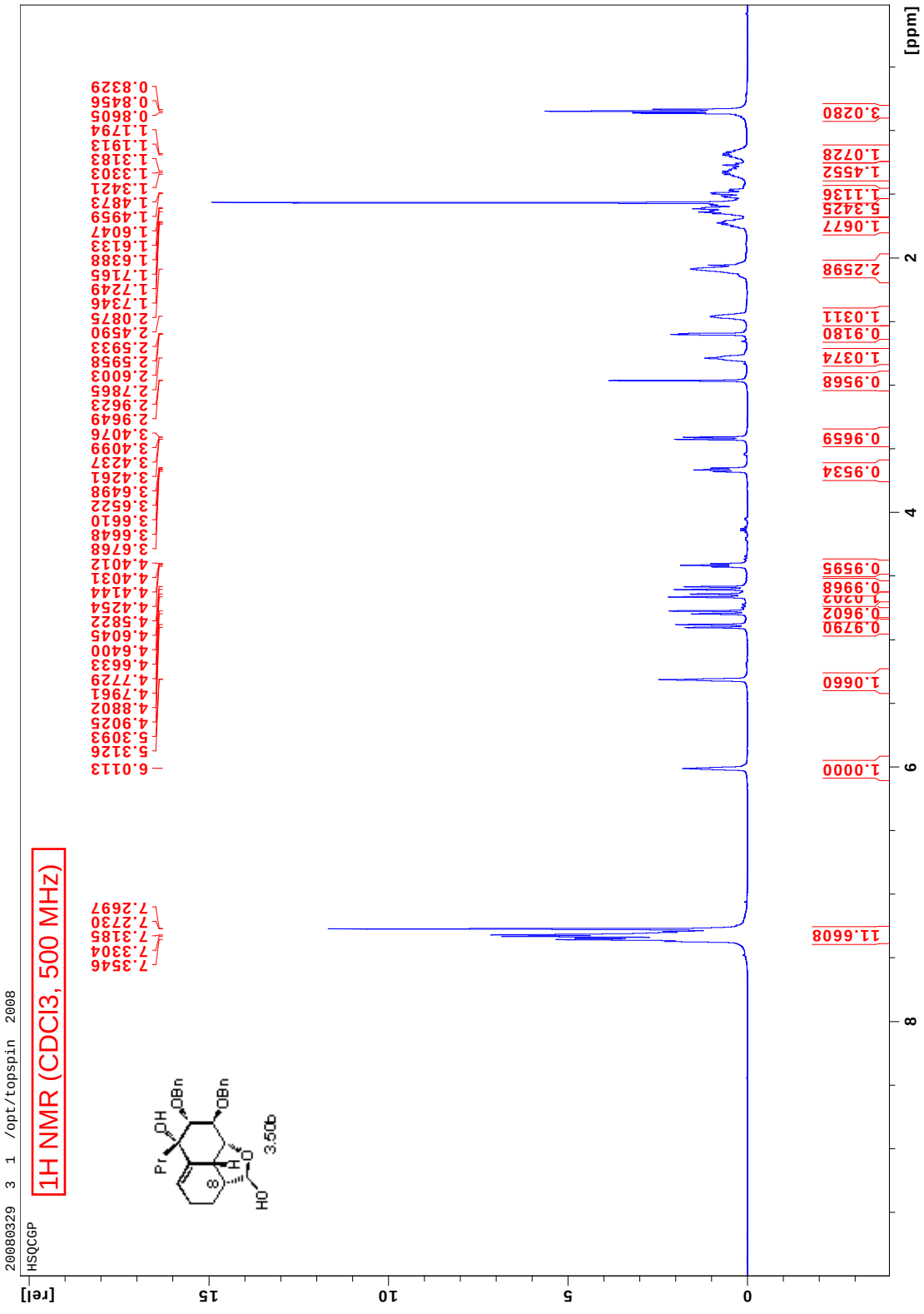

1H NMR (CDCl3, 500 MHz)
HSQCGP
09290701 1 1 /opt/topspin 2007
[rel]
[ppm]
OBn
OBn
OH
Pr
O
O
H
8
3.49


13C NMR (CDCl3, 125 MHz)
09290701 2 1 /opt/topspin 2007
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
177.4572
138.1716
137.8199
132.7130
128.7059
128.6366
128.4635
128.2597
127.9820
126.5705
83.1213
79.7127
78.8826
77.4786
77.2246
76.9705
75.0183
74.8363
73.5317
41.7233
39.0267
35.6228
20.5964
19.2112
16.8095
14.6198
3.49
OBn
OBn
OH
Pr
O
O
H
8
[rel]
0
2
4
6
150
100
50
[ppm]


COSY (CDCl3)
09290701 4 1 /opt/topspin 2007
HSQCGP
F1 [ppm]
F2 [ppm]
2
3
4
5
6
7
OBn
OBn
OH
Pr
O
O
8
3.49


HSQC (CDCl3)
F1 [ppm]
F2 [ppm]
HSQCGP
OBn
OBn
OH
Pr
3.49


NOESY (CDCl3)
09290701 5 1 /opt/topspin 2007
HSQCGP
F1 [ppm]
F2 [ppm]
OBn
OBn
OH
Pr
O
O
3.49


1H NMR (CDCl3, 500 MHz)
HSQCGP
20080329 3 1 /opt/topspin 2008
[rel]
[ppm]
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OBn
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Pr
HO
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1.0000
1.0660
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0.9602
0.9968
0.9595
0.9534
0.9659
0.9568
1.0374
0.9180
1.0311
2.2598
1.0677
5.3425
1.1136
1.4552
1.0728
3.0280
6.0113
5.3126
5.3093
4.9025
4.8802
4.7961
4.7729
4.6633
4.6400
4.6045
4.5822
4.4254
4.4144
4.4031
4.4012
3.6768
3.6648
3.6610
3.6522
3.6498
3.4261
3.4237
3.4099
3.4076
2.9649
2.9623
2.7865
2.6003
2.5958
2.5933
2.4590
2.0875
1.7346
1.7249
1.7165
1.6388
1.6133
1.6047
1.4959
1.4873
1.3421
1.3303
1.3183
1.1913
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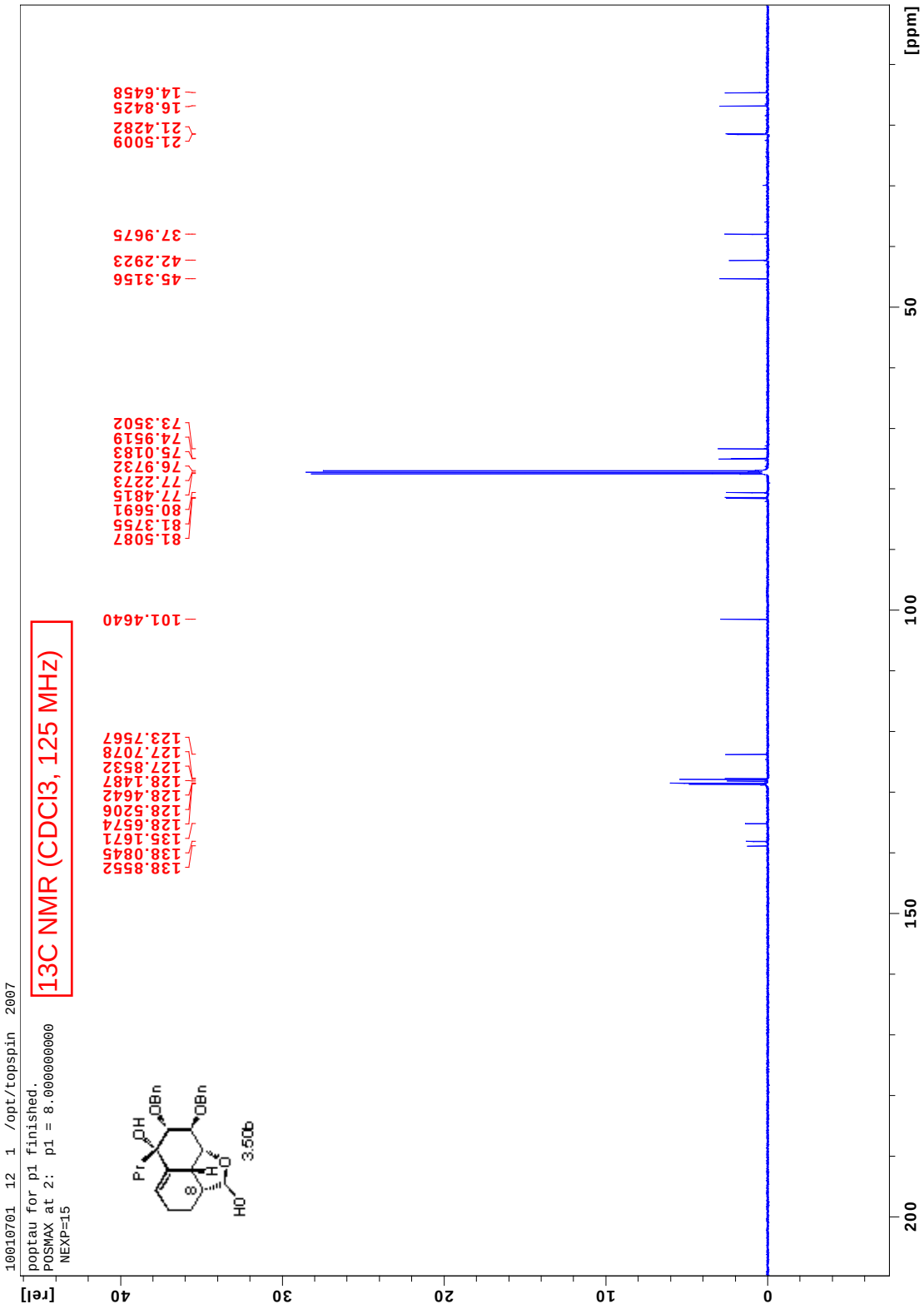
0.8605
0.8456
0.8329
7.3546
7.3304
7.3185
7.2730
7.2697


13C NMR (CDCl3, 125 MHz)
10010701 12 1 /opt/topspin 2007
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
0
10
20
30
40
50
100
150
200
138.8552
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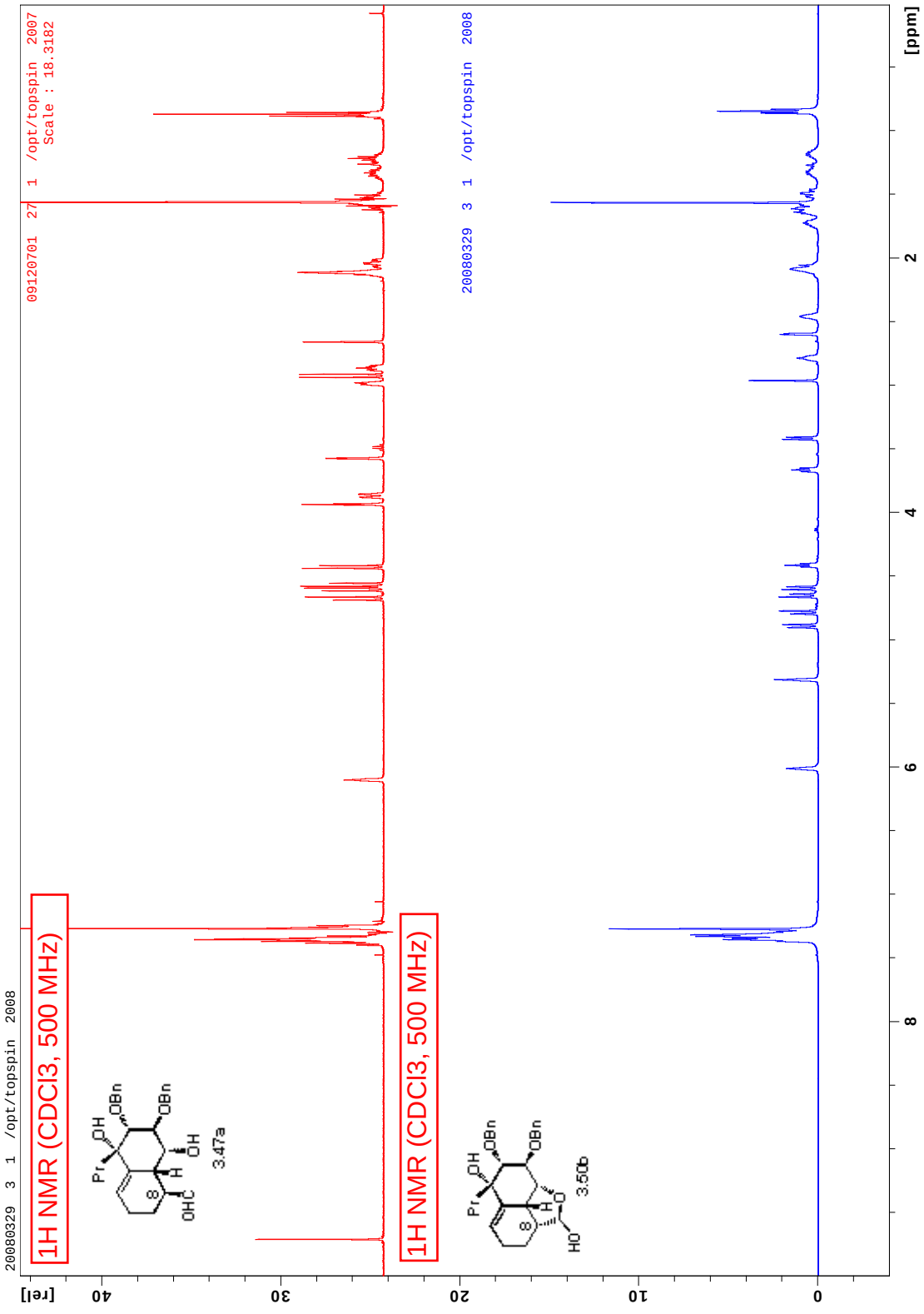
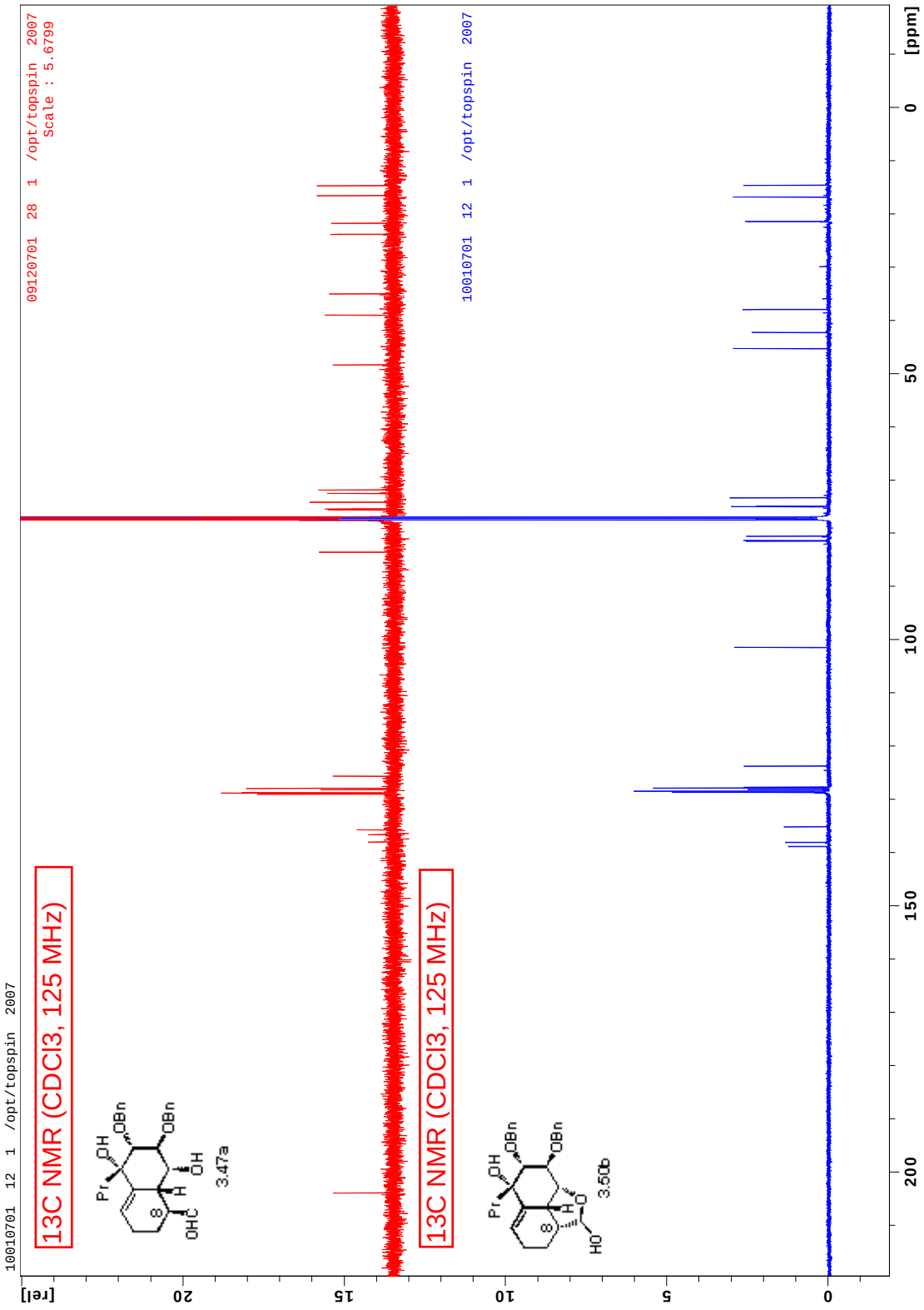
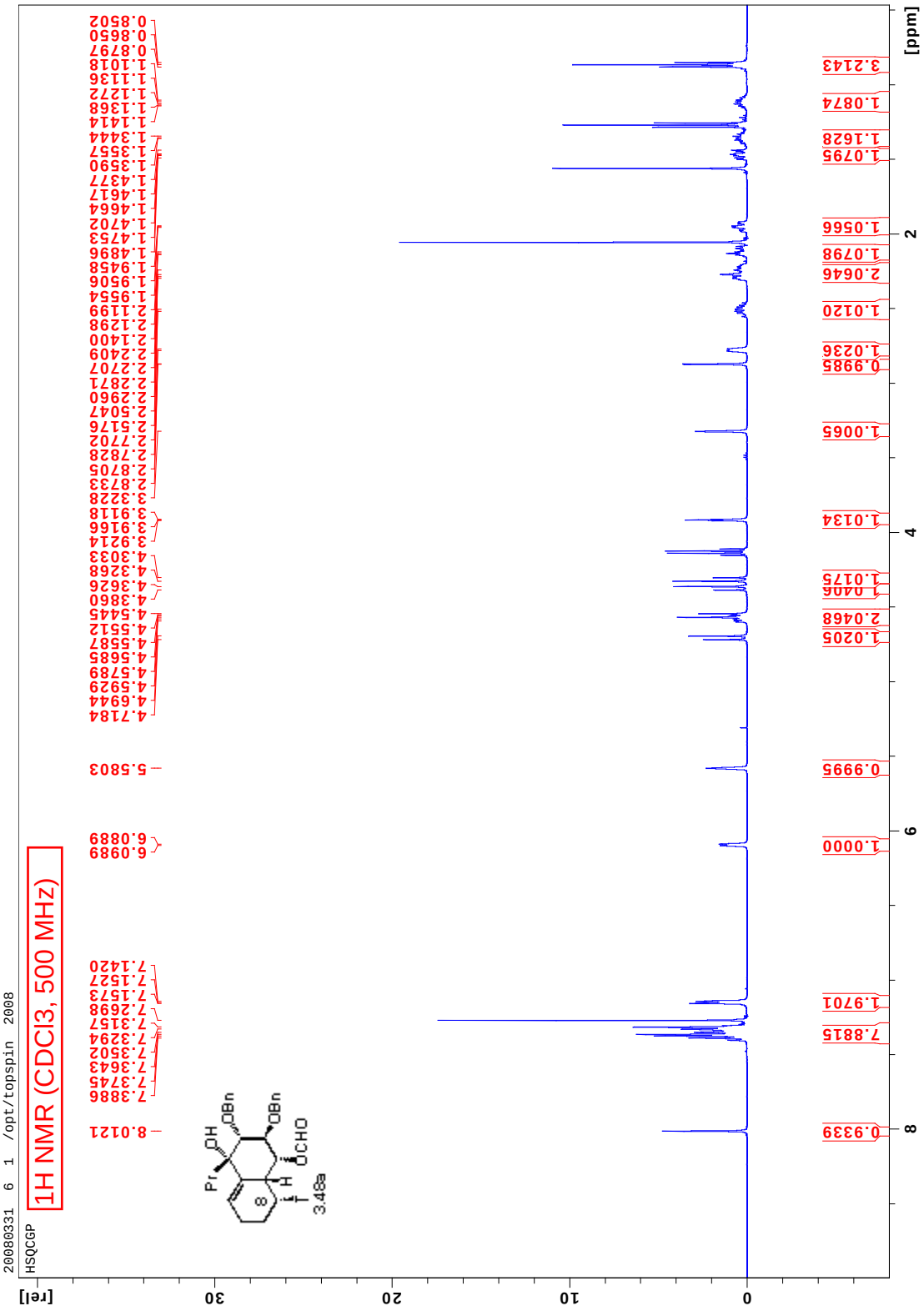
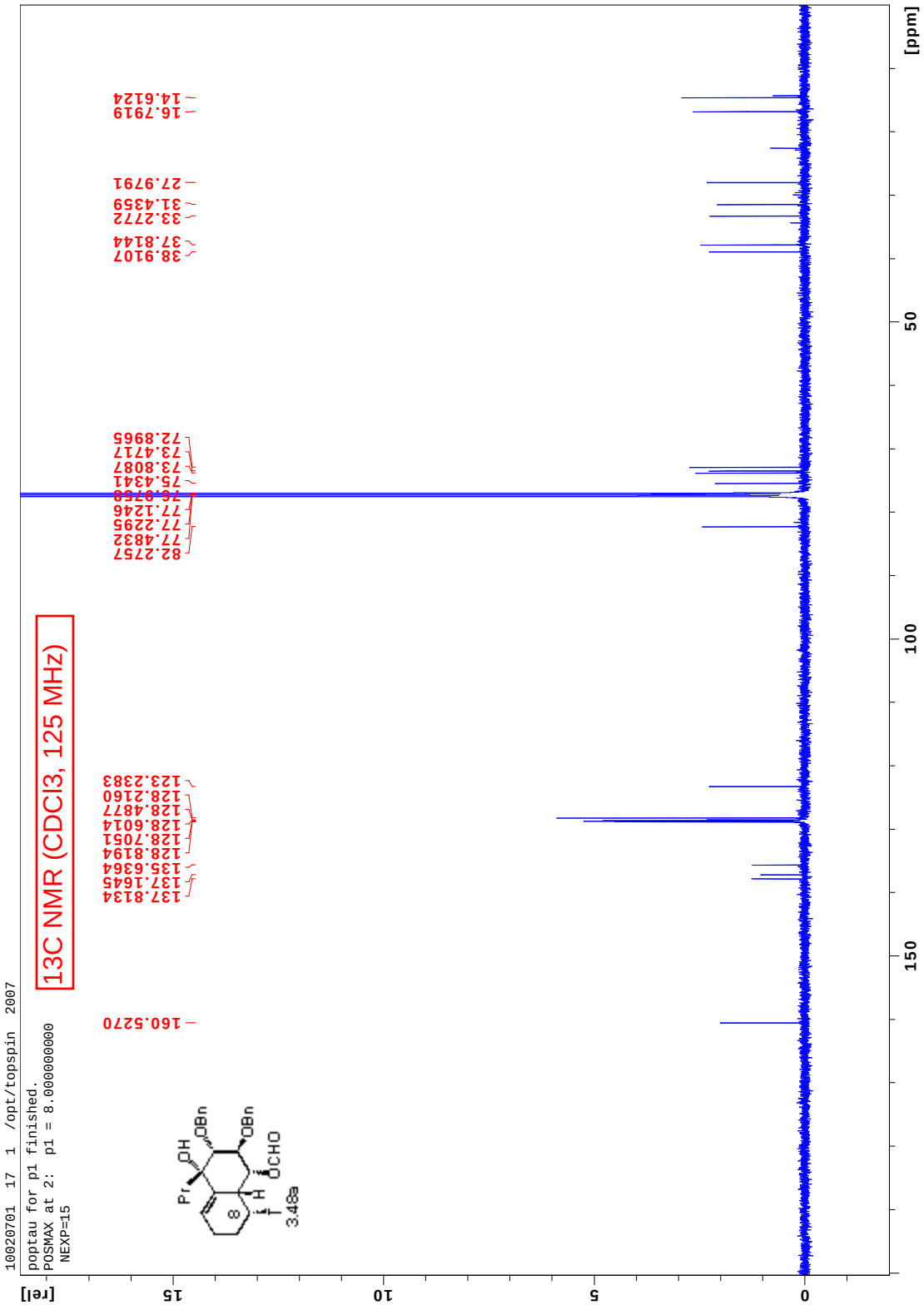
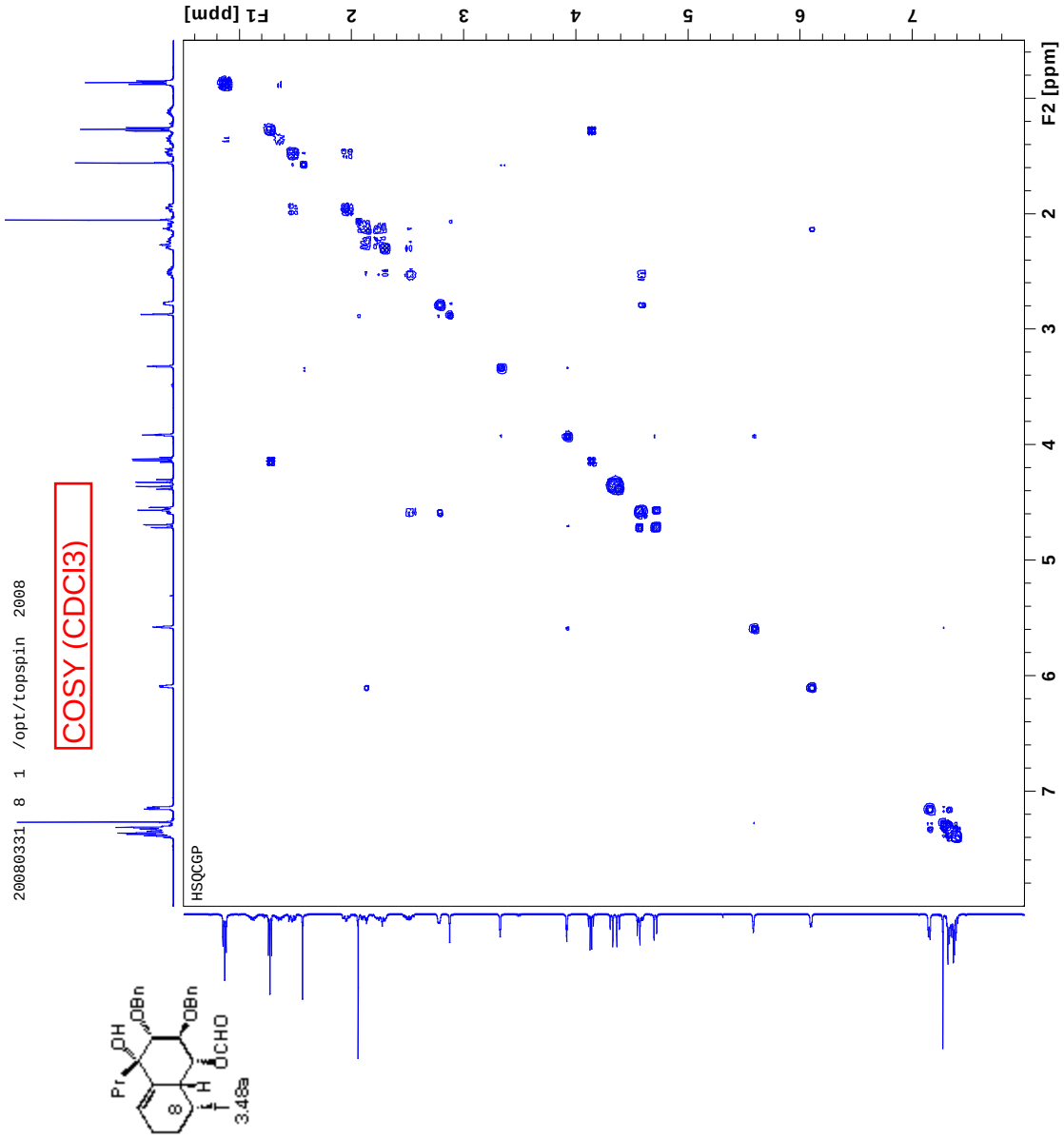
135.1671
128.6574
128.5206
128.4642
128.1487
127.8532
127.7078
123.7567
101.4640
81.5087
81.3755
80.5691
77.4815
77.2273
76.9732
75.0183
74.9519
73.3502
45.3156
42.2923
37.9675
21.5009
21.4282
16.8425
14.6458
OBn
OBn
OH
H
O
HO
3.50b

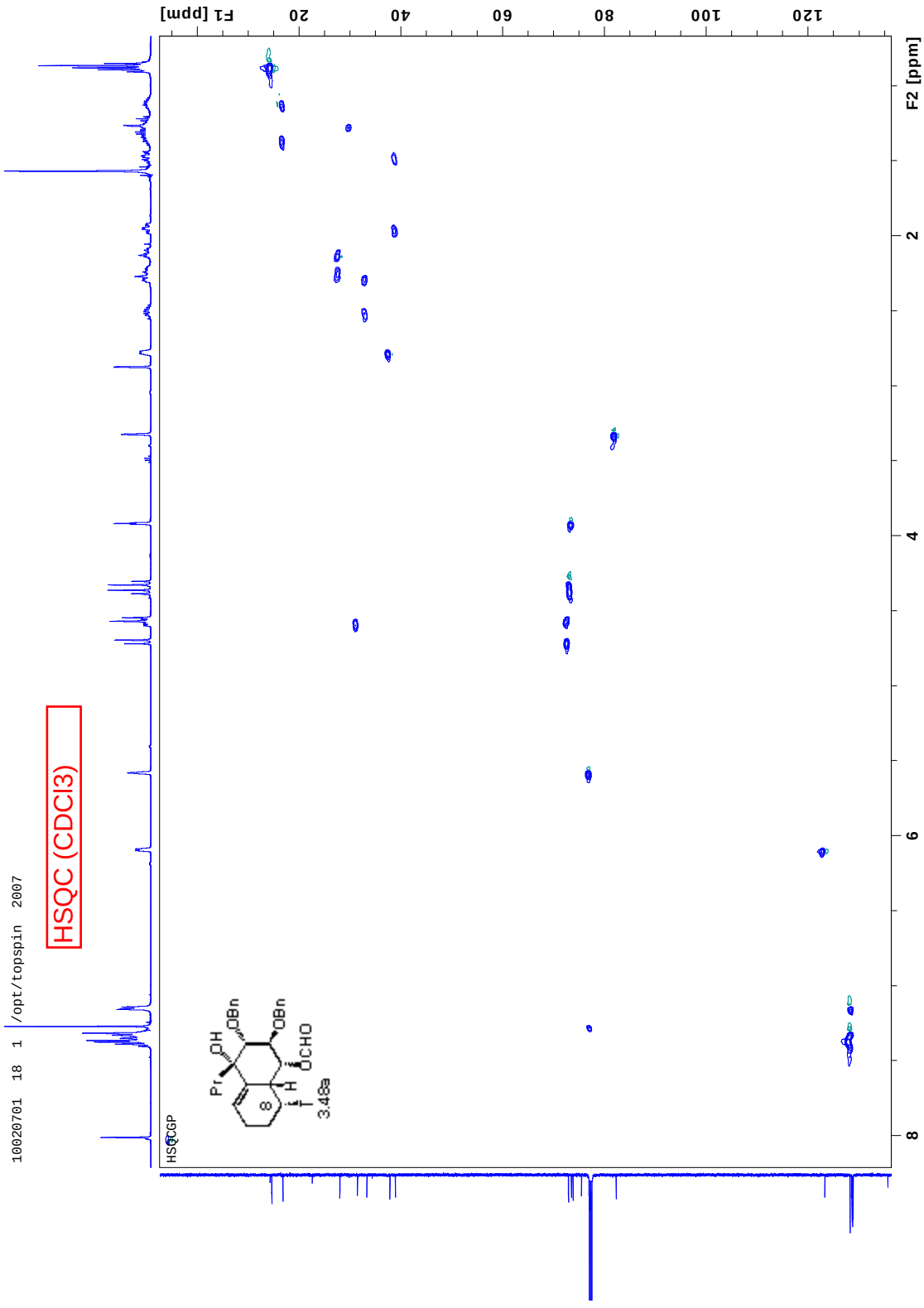

1H NMR (CDCl3, 500 MHz)
1H NMR (CDCl3, 500 MHz)
20080329 3 1 /opt/topspin 2008
09120701 27 1 /opt/topspin 2007
Scale : 18.3182
20080329 3 1 /opt/topspin 2008
[rel]
[ppm]
3.47a
3.50b

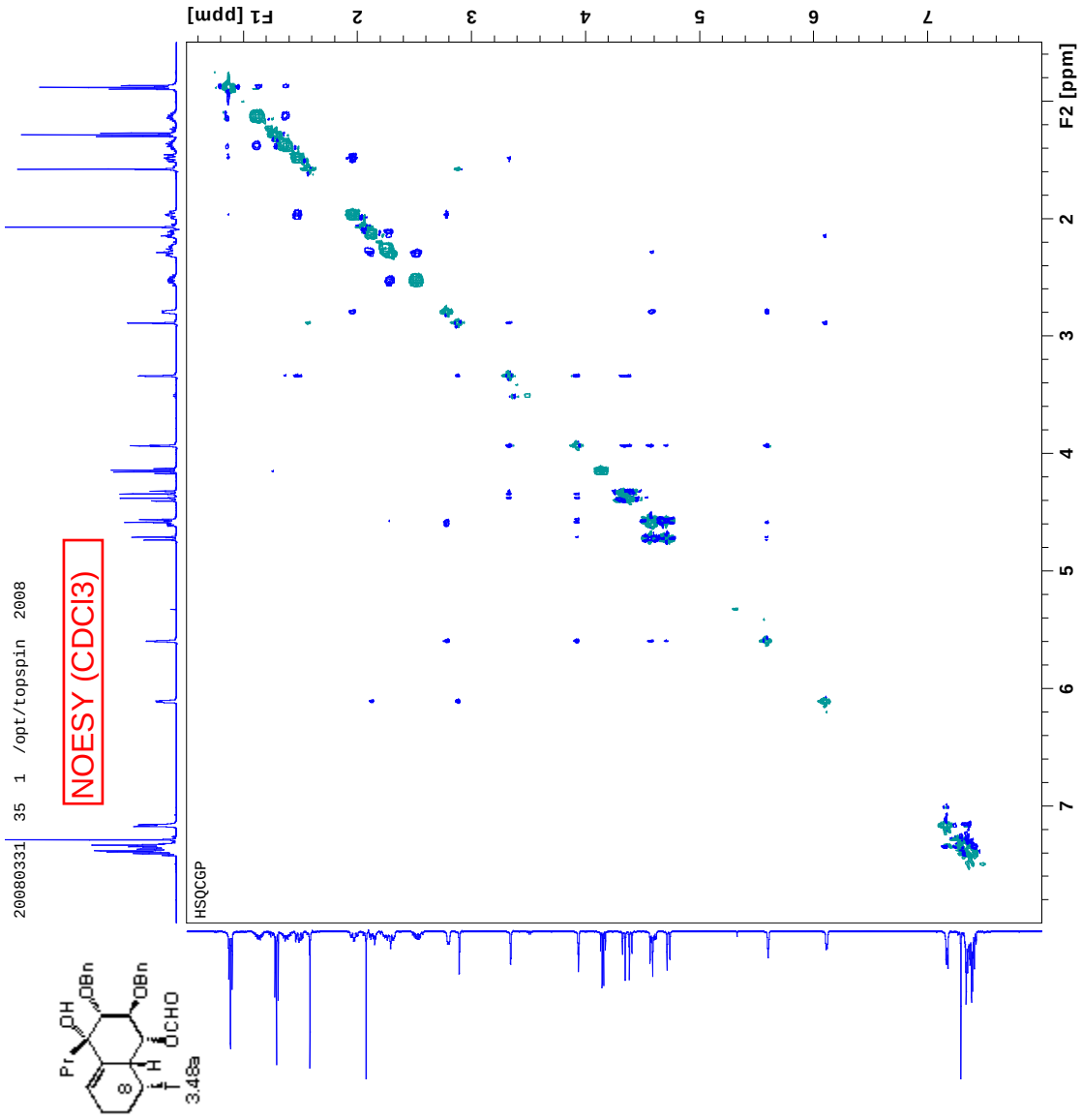

10010701 12 1 /opt/topspin 2007
13C NMR (CDCl3, 125 MHz)
3.47a
09120701 28 1 /opt/topspin 2007
Scale : 5.6799
13C NMR (CDCl3, 125 MHz)
3.50b
10010701 12 1 /opt/topspin 2007
[rel]
[ppm]

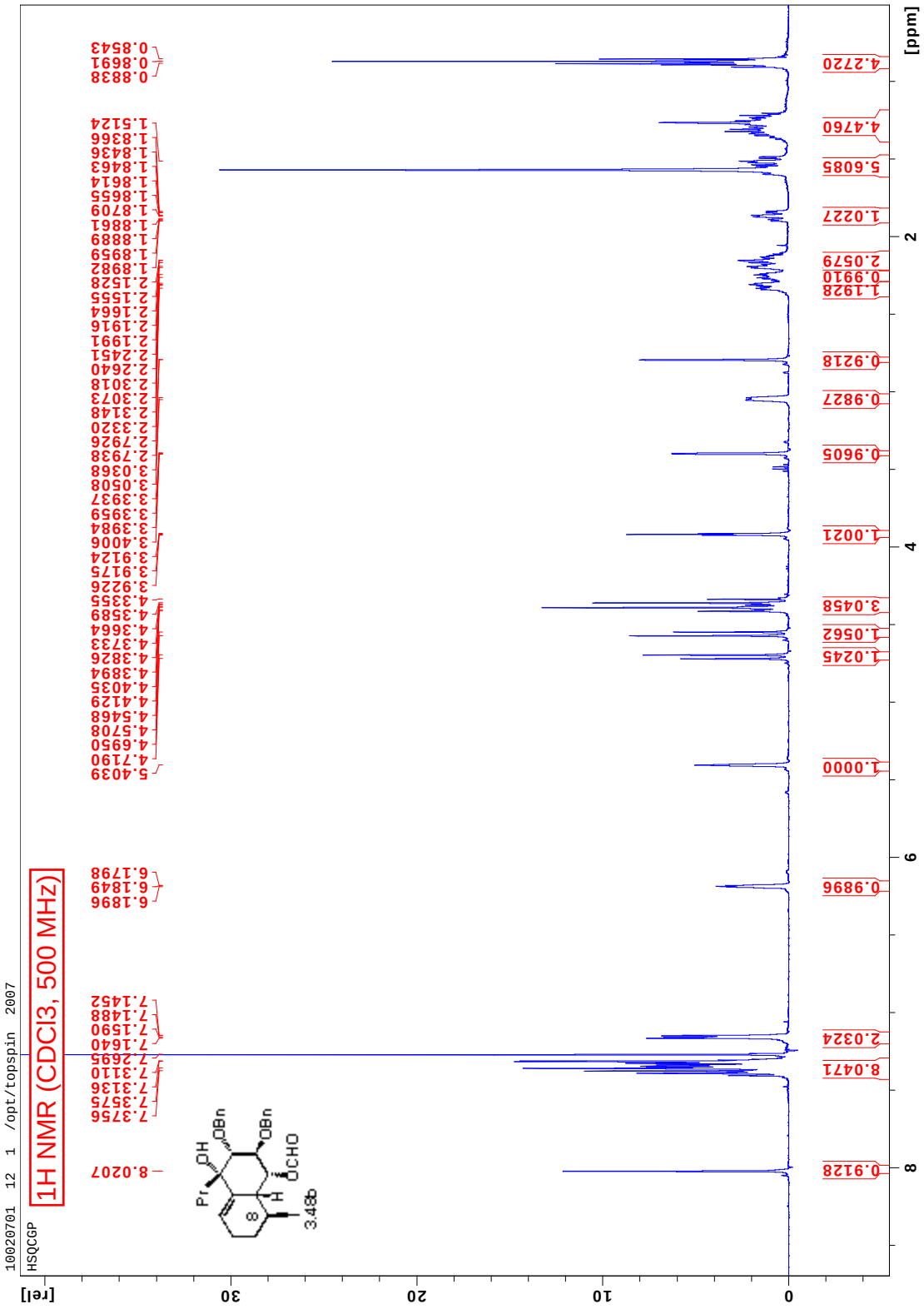

1H NMR (CDCl3, 500 MHz)
HSQCGP
20080331 6 1 /opt/topspin 2008
[rel]
[ppm]
OBn
OBn
OH
OCHO
3.48a

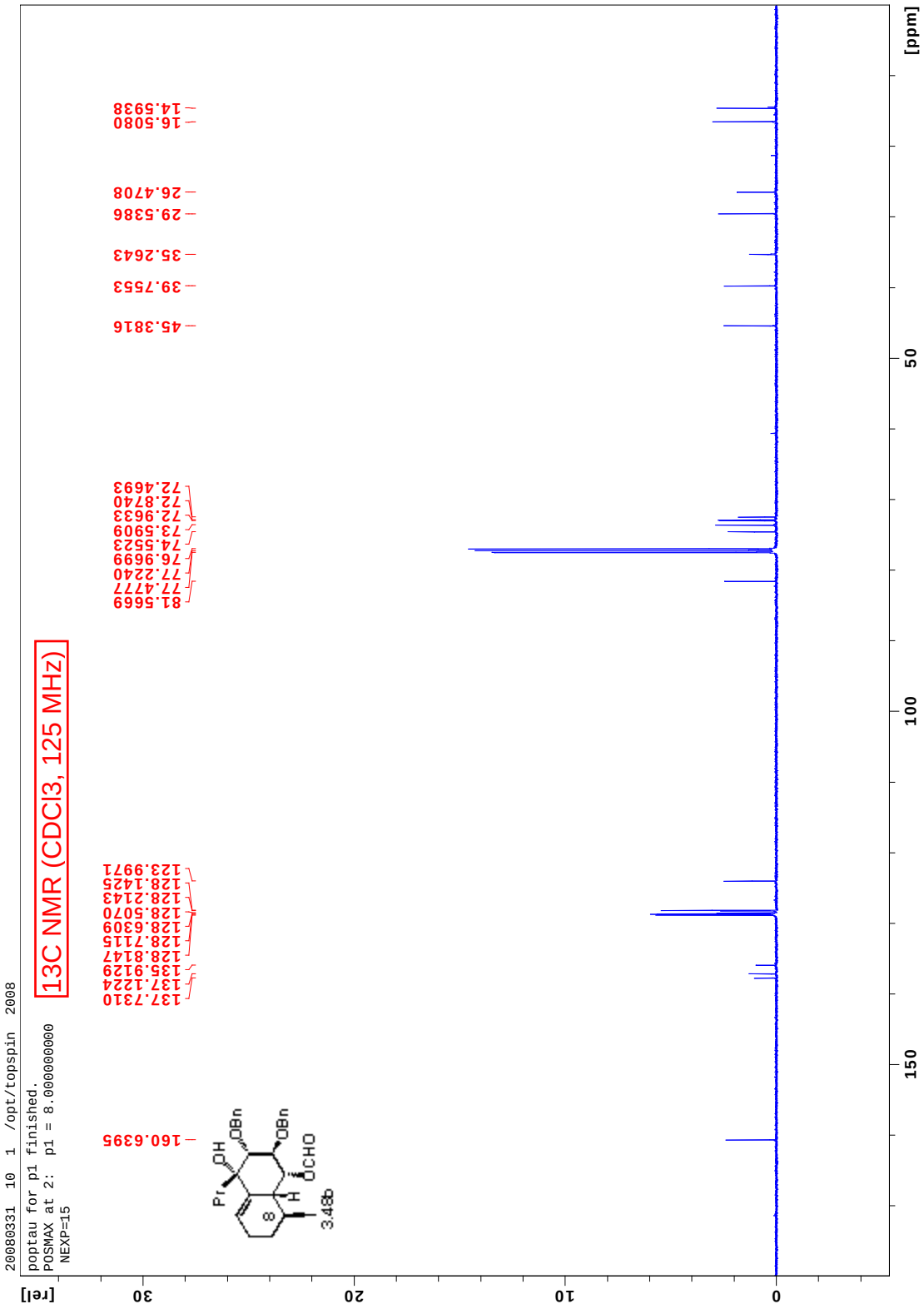

13C NMR (CDCl3, 125 MHz)
10020701 17 1 /opt/topspin 2007
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
160.5270
137.8134
137.1645
135.6364
128.8194
128.7051
128.6014
128.4877
128.2160
123.2383
82.2757
77.4832
77.2295
77.1246
76.9758
75.4341
73.8087
73.4717
72.8965
38.9107
37.8144
33.2772
31.4359
27.9791
16.7919
14.6124
OH
OBn
OBn
OCHO
Pr
H
8
3.48a


COSY (CDCl3)
20080331 8 1 /opt/topspin 2008
HSQCGP
F1 [ppm]
F2 [ppm]
OH
OBn
OBn
OCHO
H
Pr
8
3.48a


HSQC (CDCl3)
10020701 18 1 /opt/topspin 2007
HSQCGP
F1 [ppm]
F2 [ppm]
20
40
60
80
100
120
2
4
6
8
OBn
OBn
OH
OCHO
Pr
H
3.48a


NOESY (CDCl3)
20080331 35 1 /opt/topspin 2008
HSQCGP
F1 [ppm]
F2 [ppm]
2
3
4
5
6
7
OH
OBn
OBn
OCHO
H
Pr
8
3.48a


1H NMR (CDCl3, 500 MHz)
10020701 12 1 /opt/topspin 2007
HSQCGP
[rel]
[ppm]
OH
OBn
OBn
OCHO
Pr
H
3.48b


13C NMR (CDCl3, 125 MHz)
20080331 10 1 /opt/topspin 2008
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
30
20
10
0
[ppm]
150
100
50
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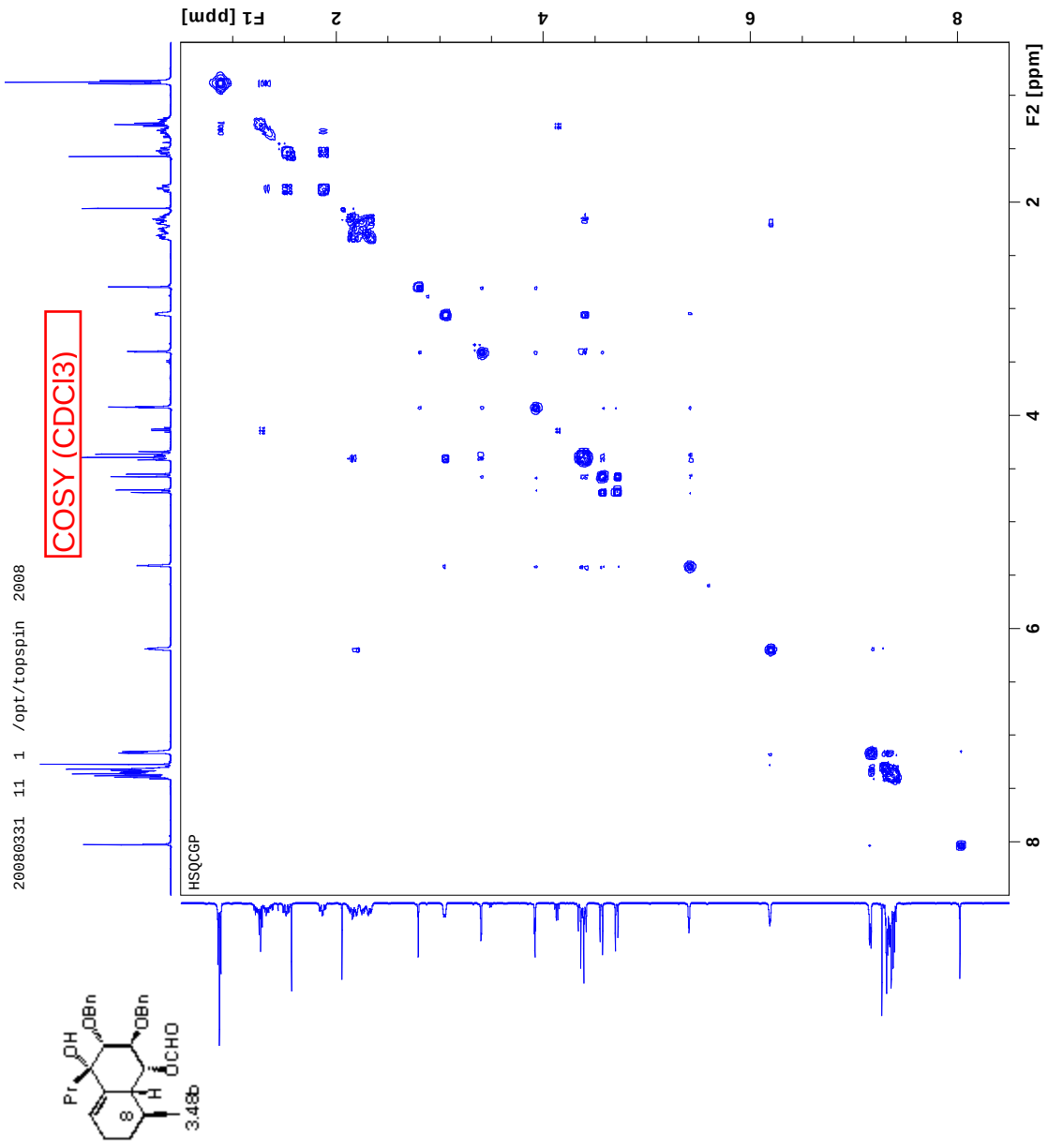
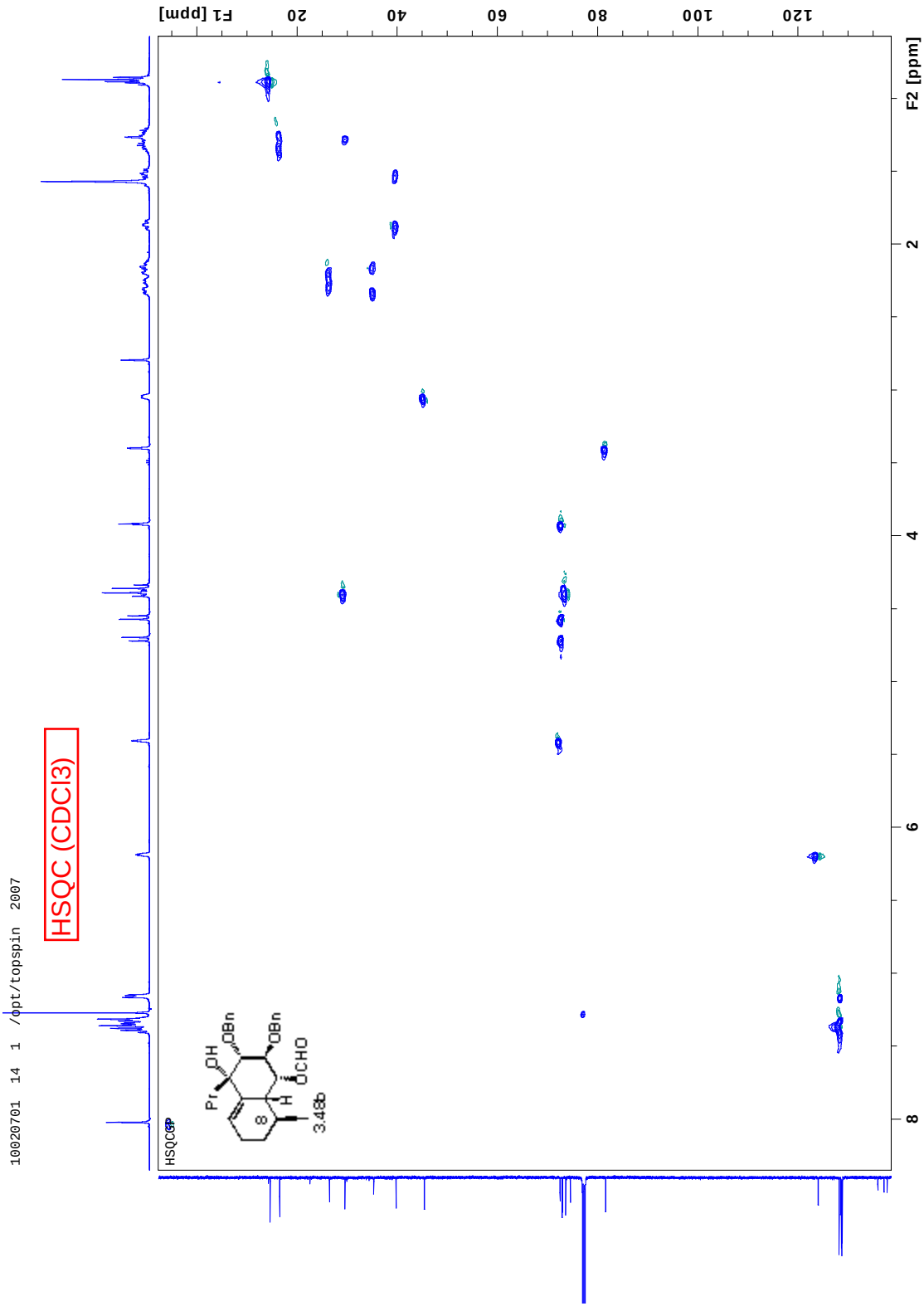
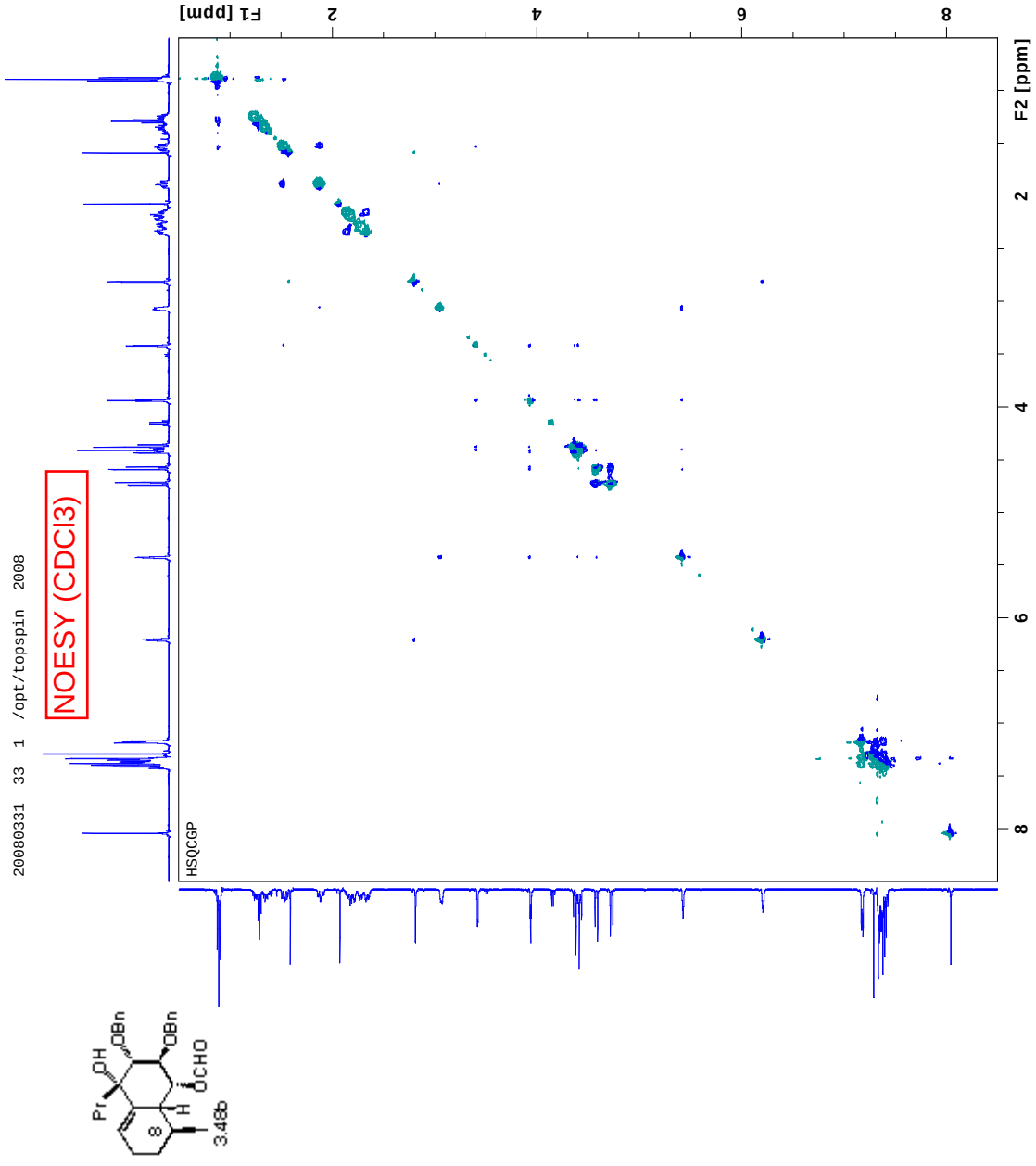
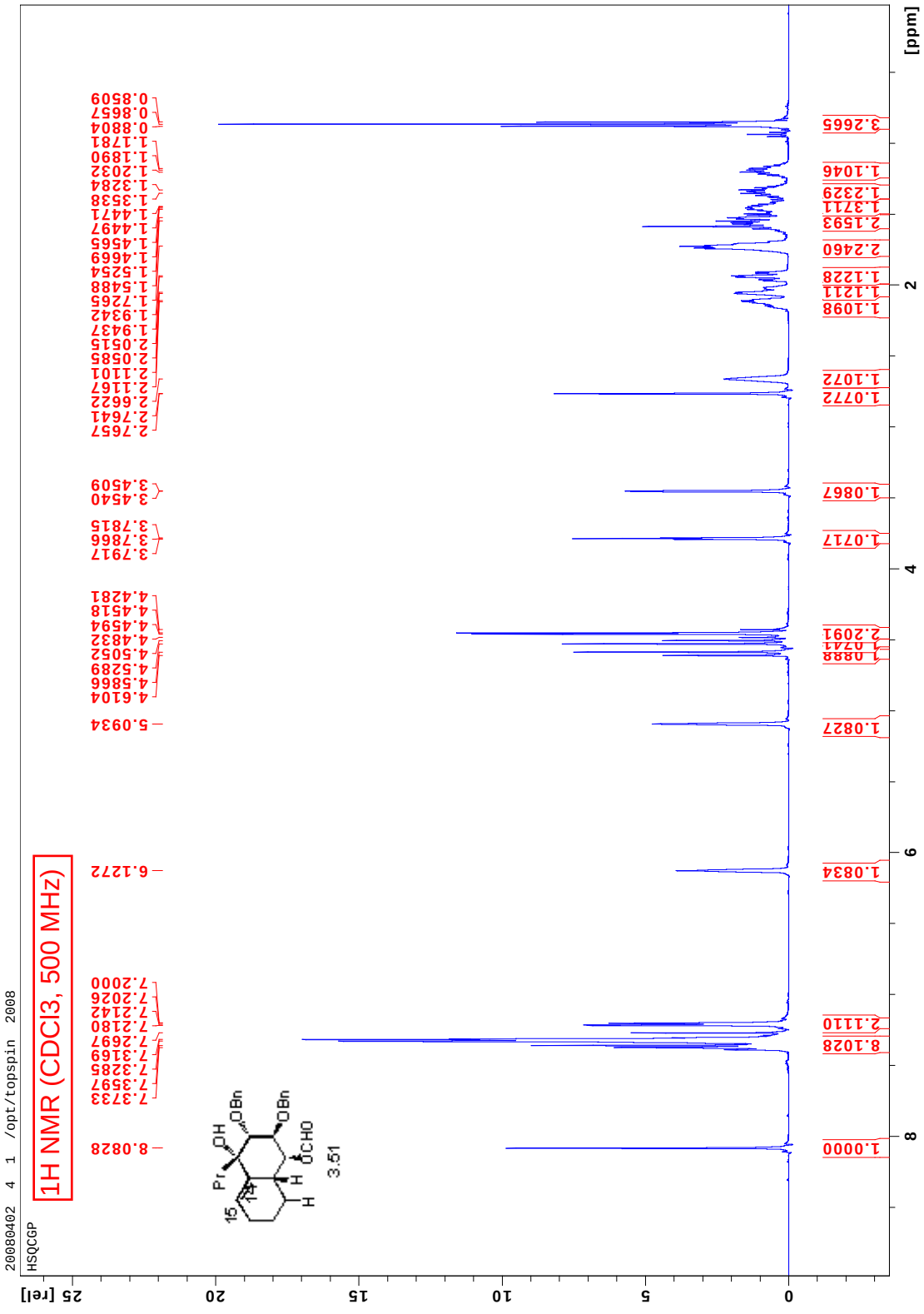
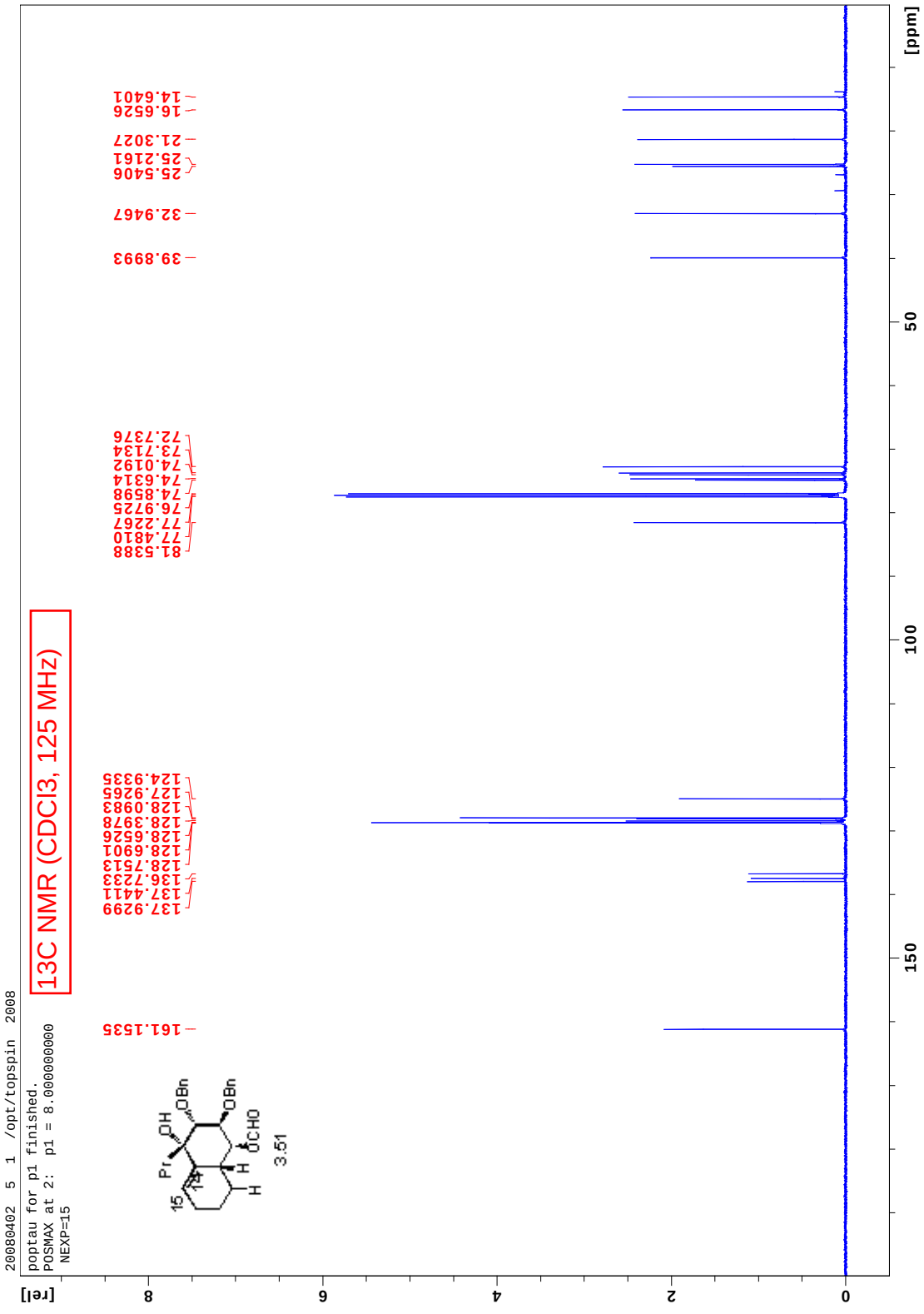
137.7310
137.1224
135.9129
128.8147
128.7115
128.6309
128.5070
128.2143
128.1425
123.9971
81.5669
77.4777
77.2240
76.9699
74.5523
73.5909
72.9633
72.8740
72.4693
45.3816
39.7553
35.2643
29.5386
26.4708
16.5080
14.5938
OH
OBn
OBn
OCHO
Pr
H
8
3.48b


COSY (CDCl3)
20080331 11 1 /opt/topspin 2008
HSQCGP
F1 [ppm]
F2 [ppm]
2
4
6
8
OH
OBn
OBn
OCHO
Pr
H
3.48b


HSQC (CDCl3)
10020701 14 1 /opt/topspin 2007
HSQCGP
F1 [ppm]
F2 [ppm]
20
40
60
80
100
120
2
4
6
8
OH
OBn
OBn
OCHO
Pr
H
3.48b


NOESY (CDCl3)
20080331 33 1 /opt/topspin 2008
HSQCGP
F1 [ppm]
F2 [ppm]
2
4
6
8
OH
OBn
OBn
OCHO
H
Pr
3.48b


1H NMR (CDCl3, 500 MHz)
20080402 4 1 /opt/topspin 2008
HSQCGP
[ppm]
[rel]
OBn
OBn
OH
OCHO
3.51


13C NMR (CDCl3, 125 MHz)
20080402 5 1 /opt/topspin 2008
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
0
2
4
6
8
50
100
150
161.1535
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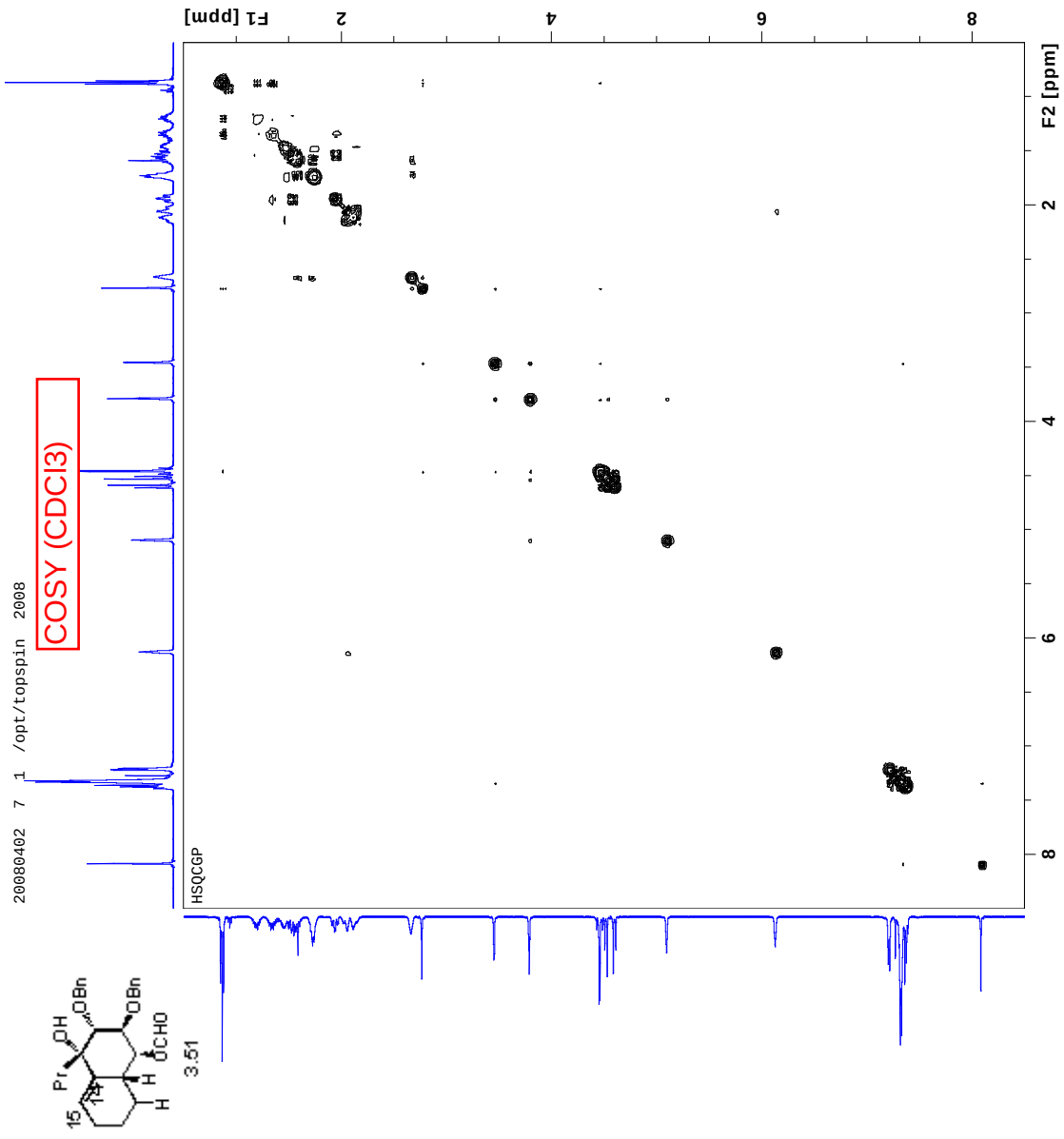
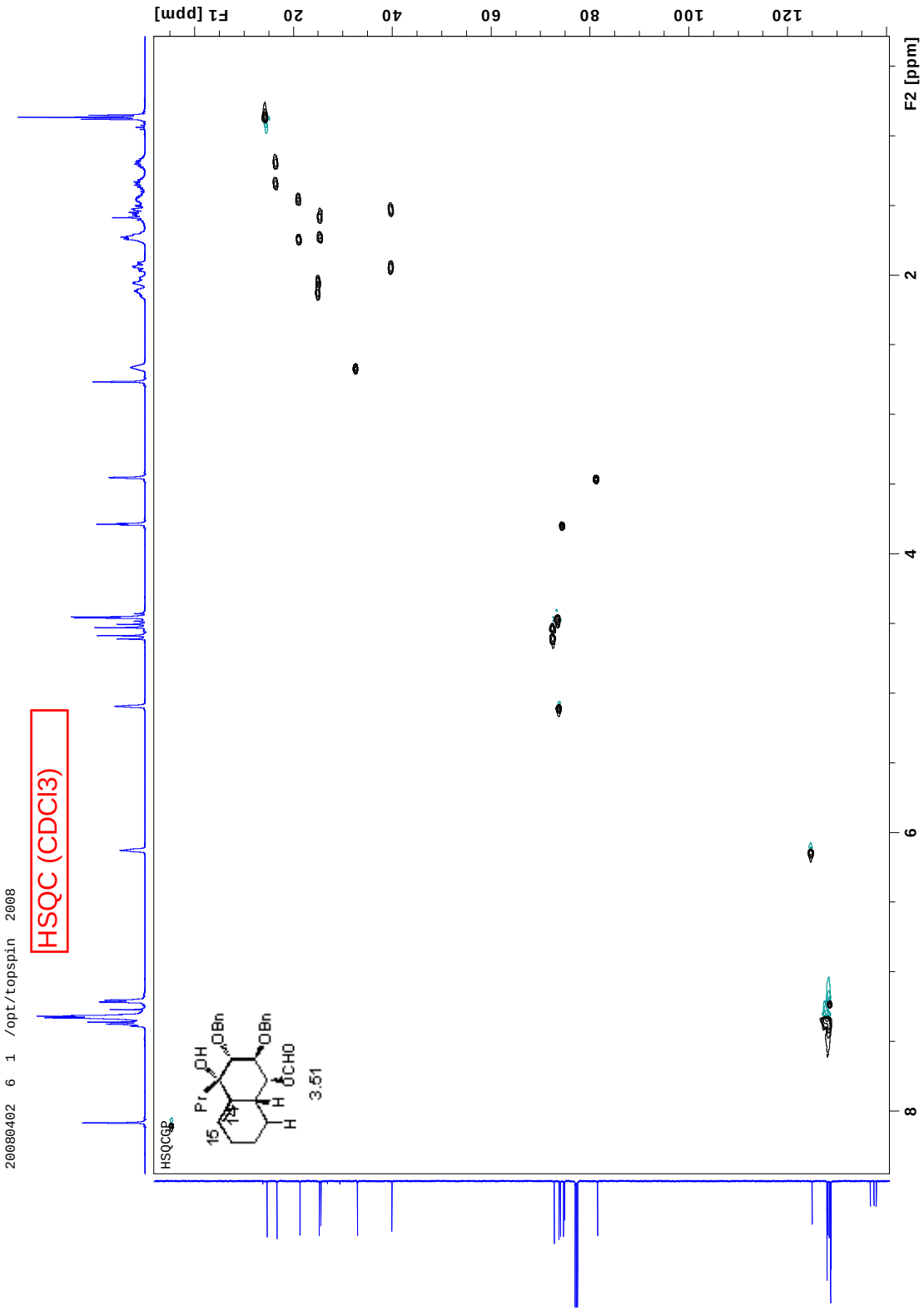
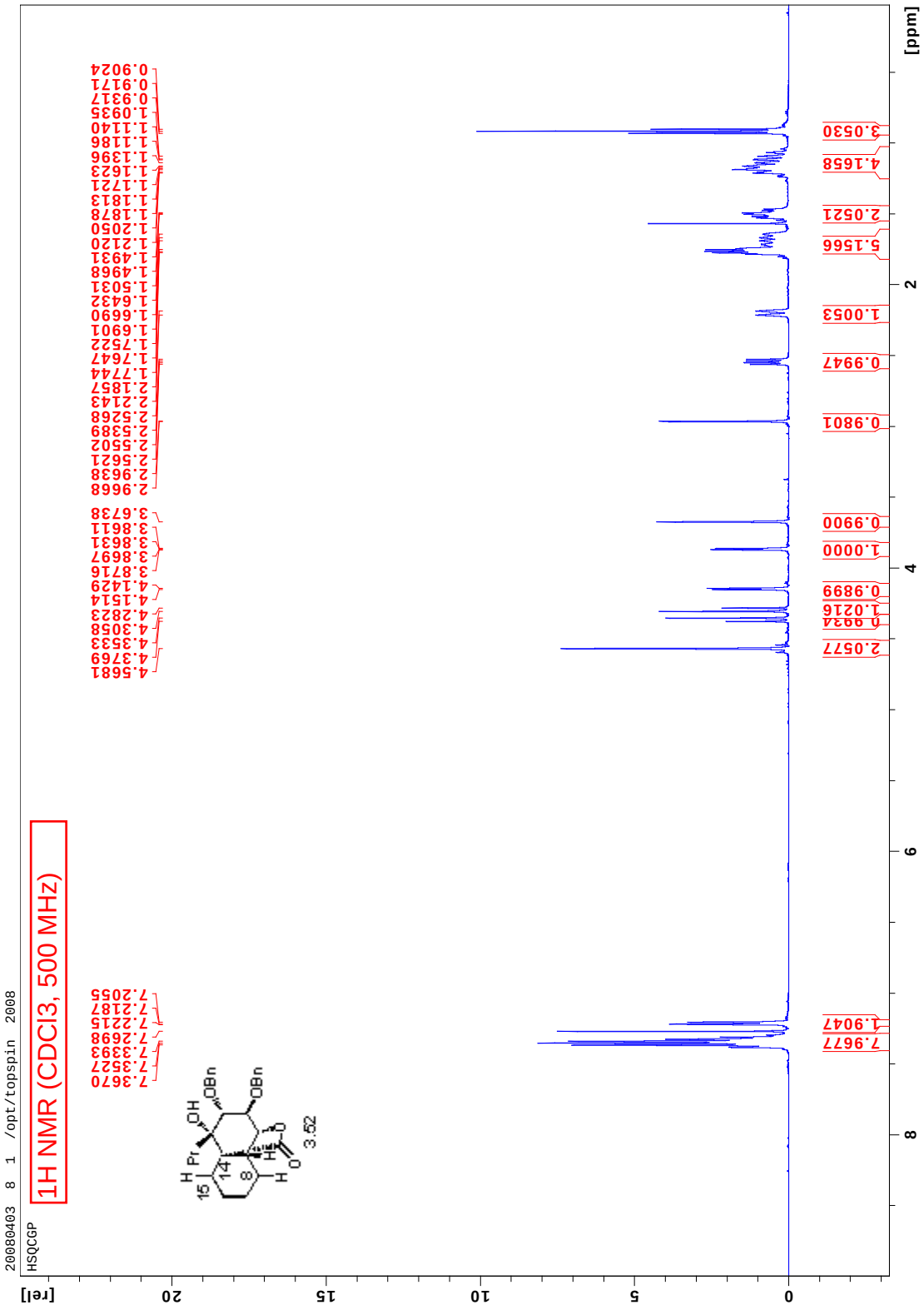
128.6901
128.6526
128.3978
128.0983
127.9265
124.9335
81.5388
77.4810
77.2267
76.9725
74.8598
74.6314
74.0192
73.7134
72.7376
39.8993
32.9467
25.5406
25.2161
21.3027
16.6526
14.6401
OBn
OBn
OH
OCHO
H
H
Pr
15
3.51


COSY (CDCl3)
20080402 7 1 /opt/topspin 2008
HSQCGP
F1 [ppm]
F2 [ppm]
2
4
6
8
3.51
OBn
OBn
OCHO
H
H
Pr
OH
15
14


HSQC (CDCl3)
20080402 6 1 /opt/topspin 2008
HSQCGP
F1 [ppm]
F2 [ppm]
OH
OBn
OBn
OCHO
3.51


1H NMR (CDCl3, 500 MHz)
HSQCGP
20080403 8 1 /opt/topspin 2008
[rel]
[ppm]
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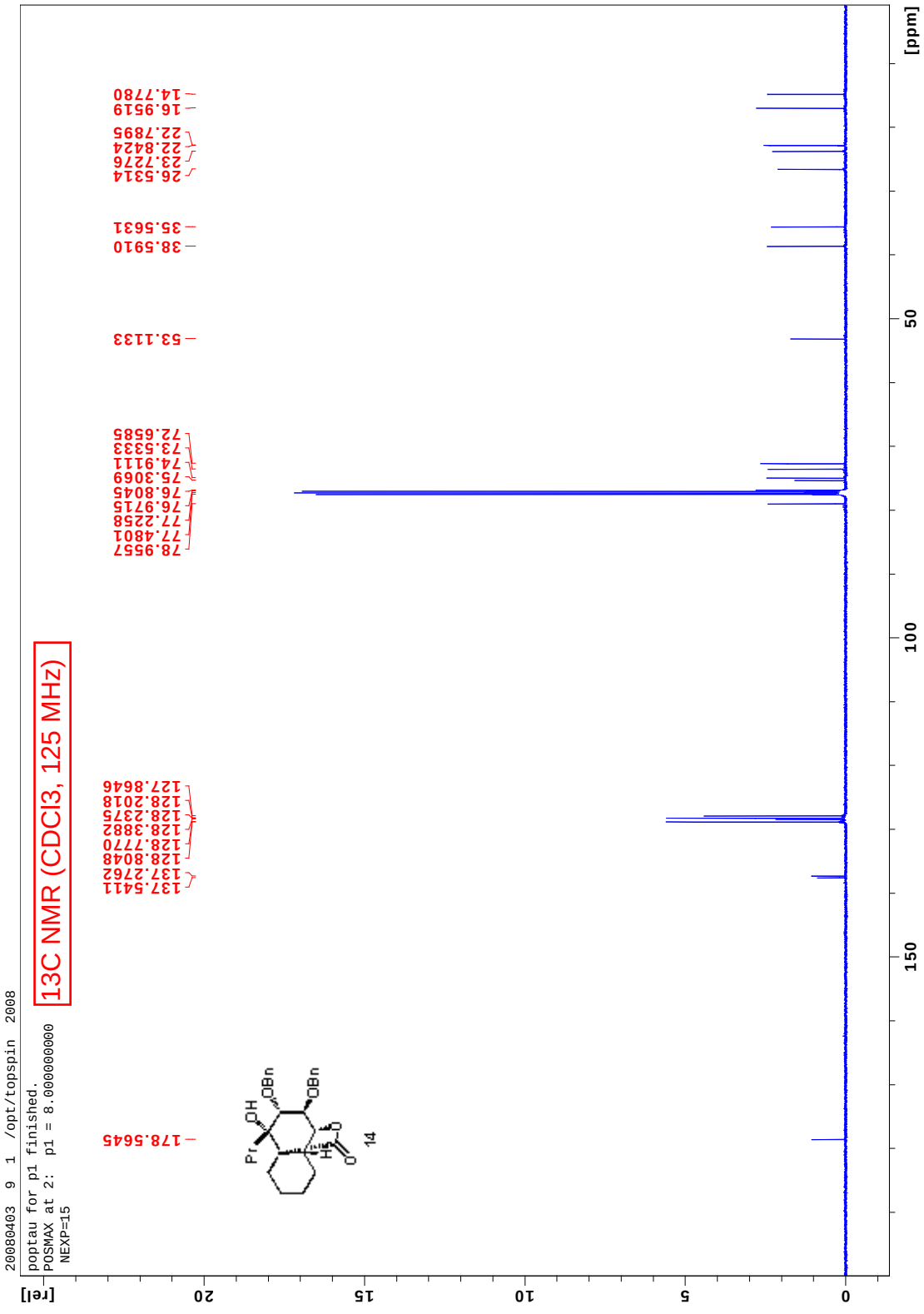
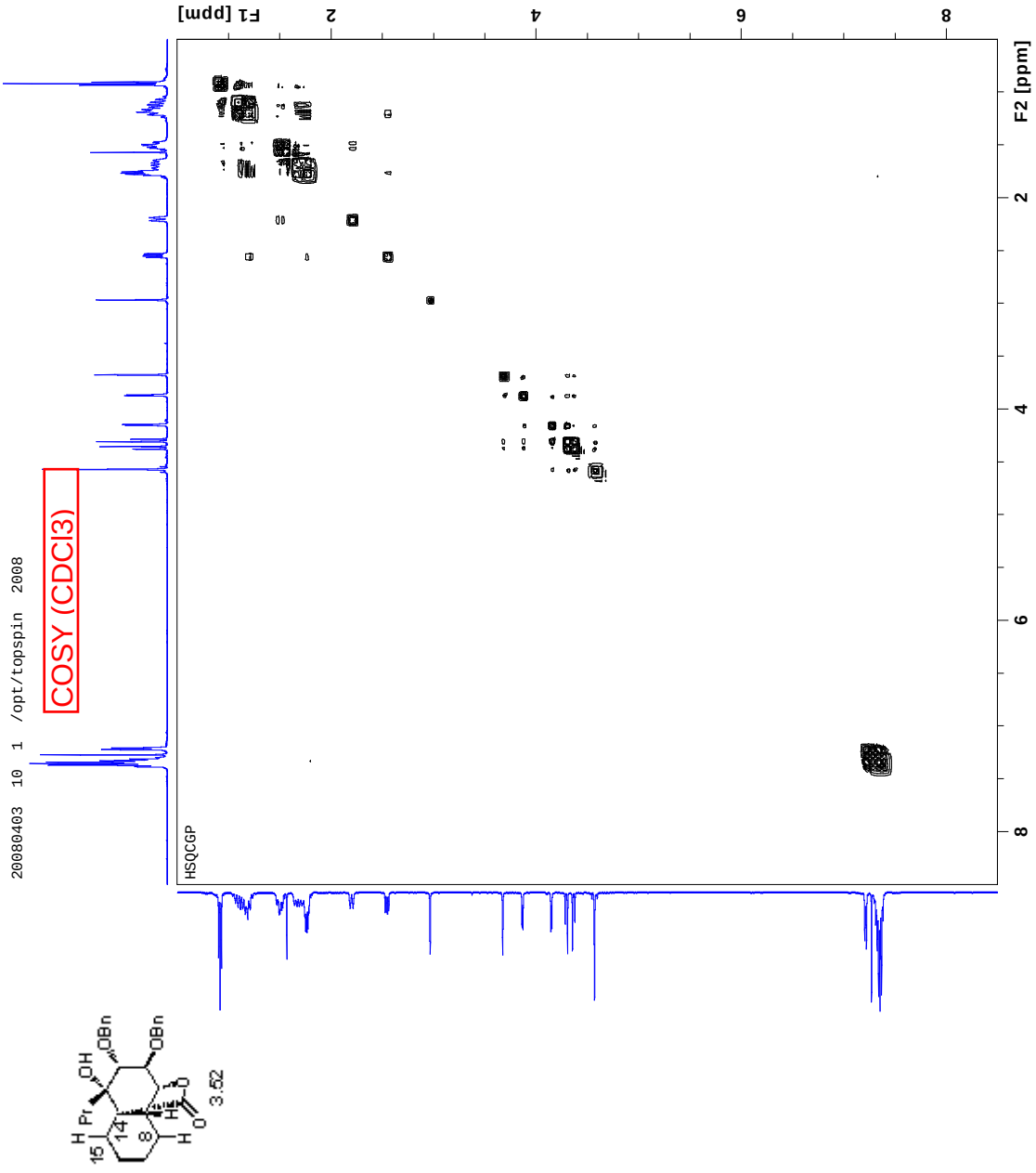
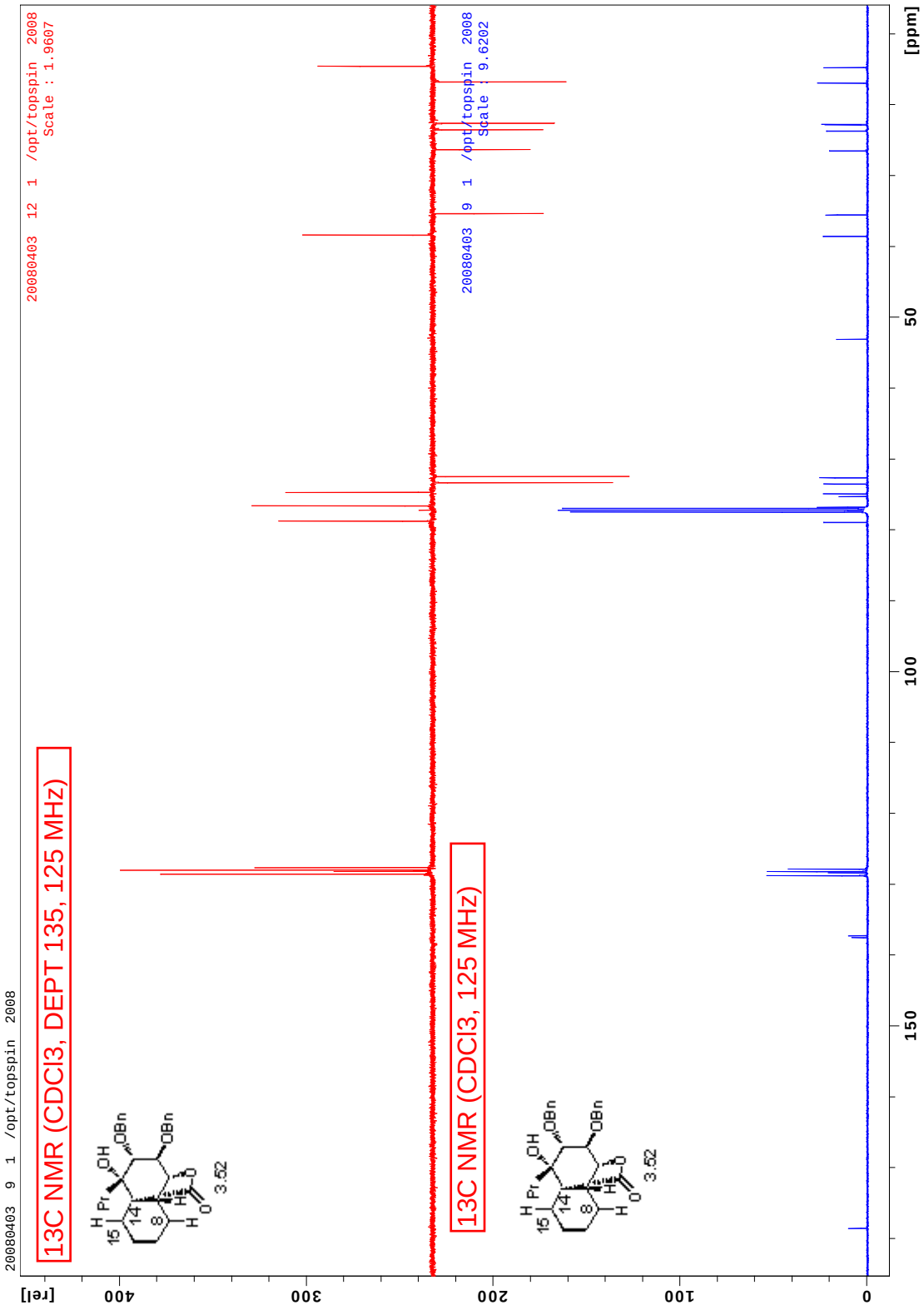
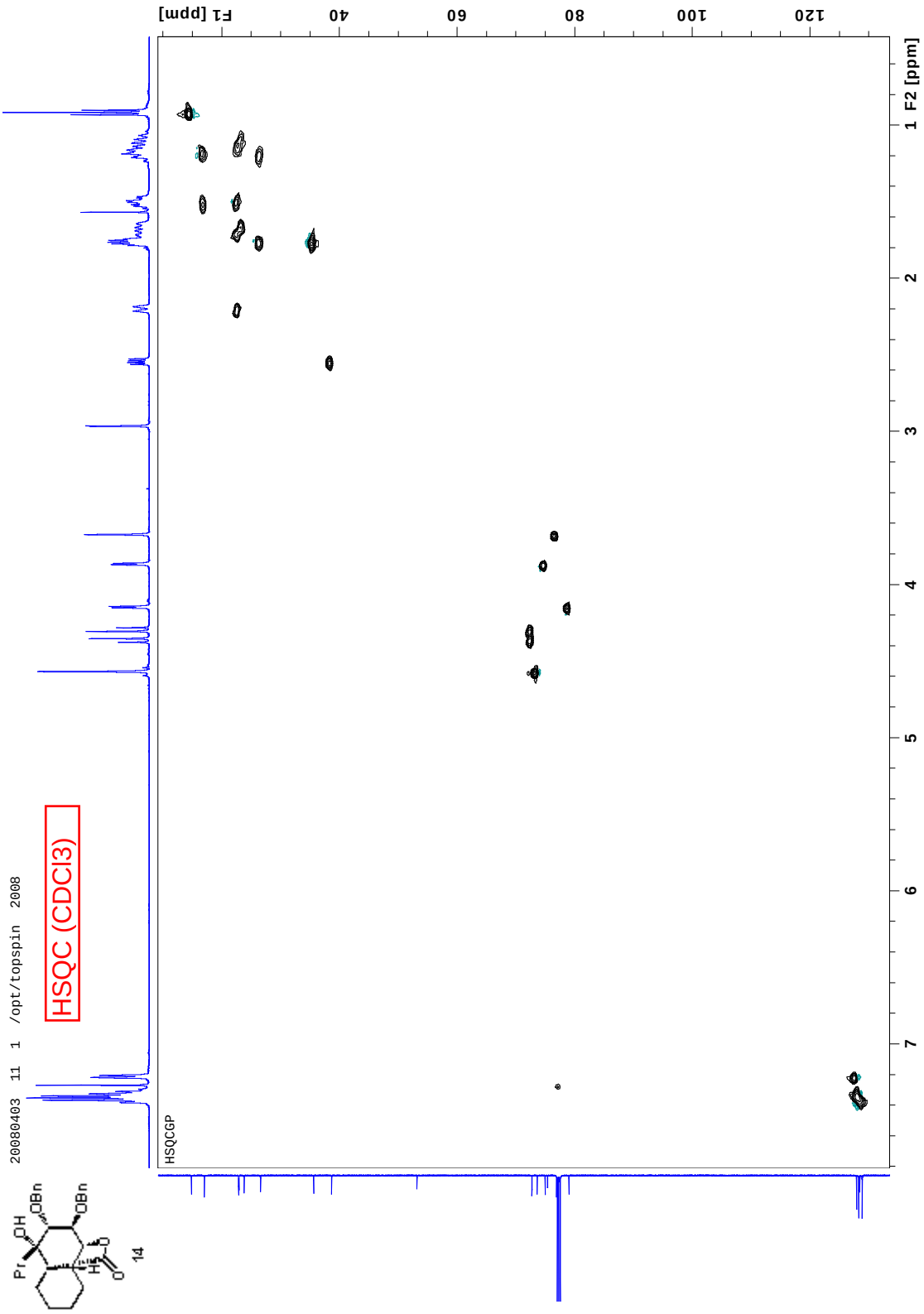
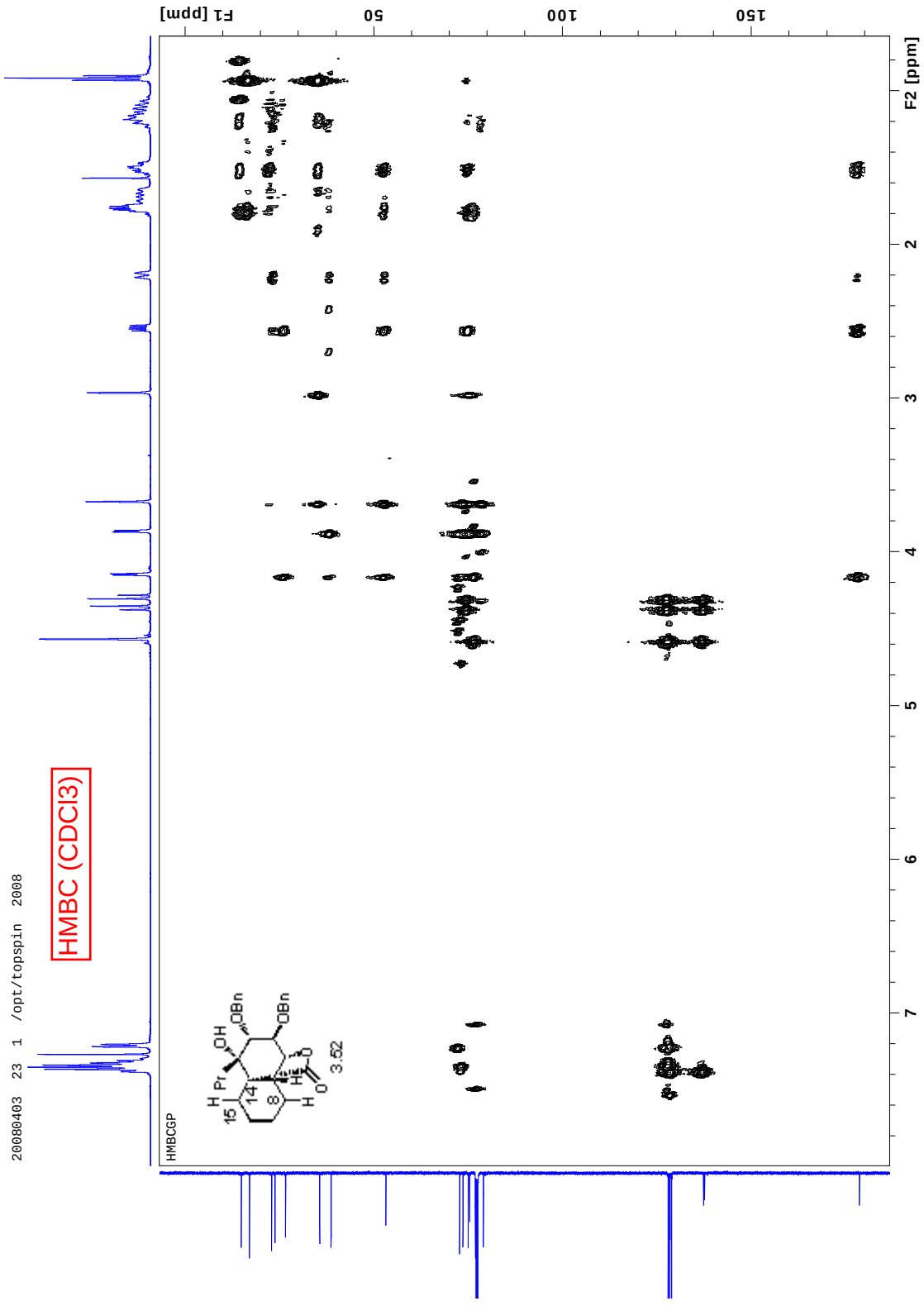
1.9047
2.0577
0.9934
1.0216
0.9899
1.0000
0.9900
0.9801
0.9947
1.0053
5.1566
2.0521
4.1658
3.0530
OBn
OBn
OH
Pr
3.52

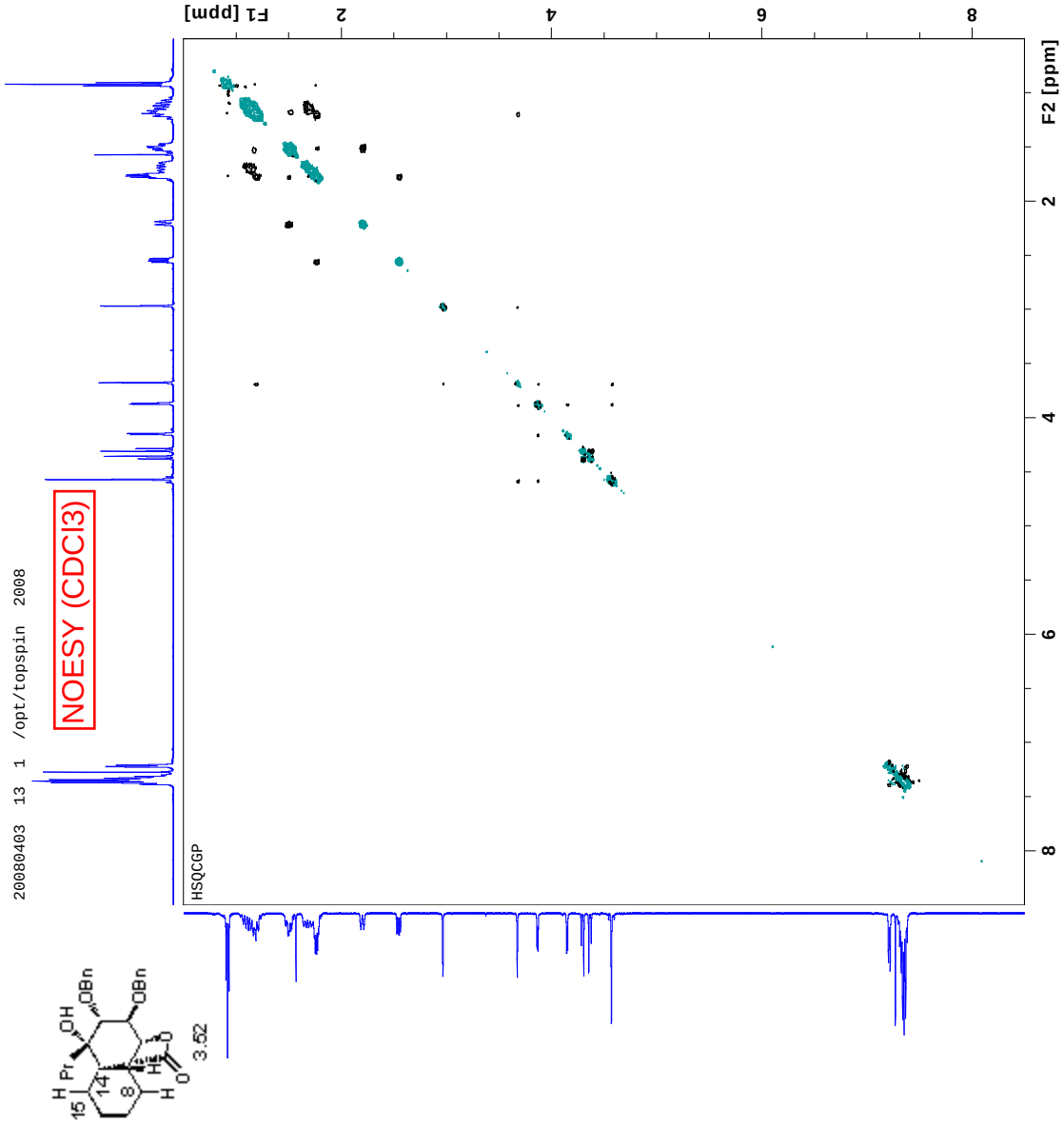

13C NMR (CDCl3, 125 MHz)
20080403 9 1 /opt/topspin 2008
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
178.5645
137.5411
137.2762
128.8048
128.7770
128.3882
128.2375
128.2018
127.8646
78.9557
77.4801
77.2258
76.9715
76.8045
75.3069
74.9111
73.5333
72.6585
53.1133
38.5910
35.5631
26.5314
23.7276
22.8424
22.7895
16.9519
14.7780
OBn
OBn
OH
Pr
H
O
O
14

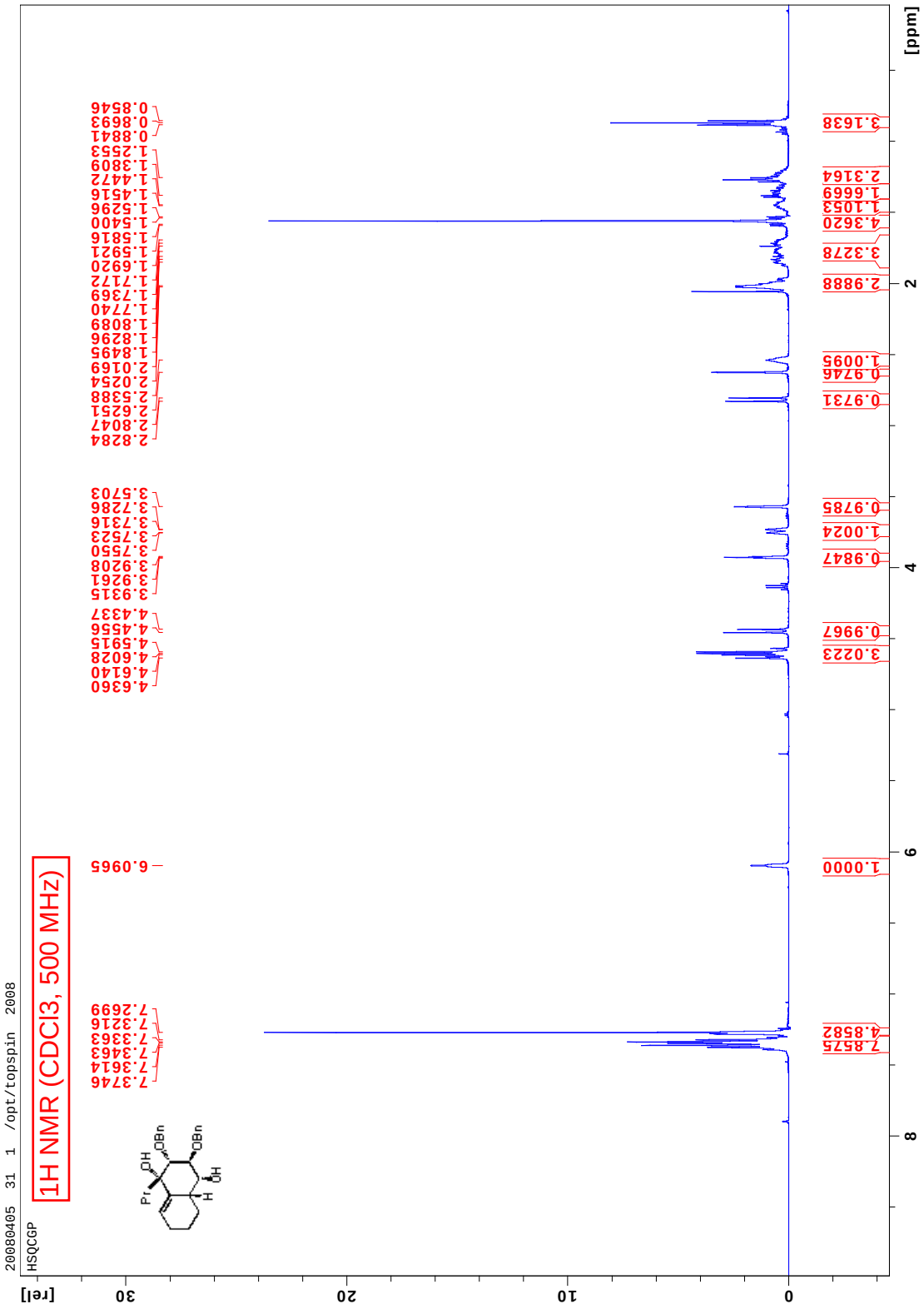

COSY (CDCl3)
20080403 10 1 /opt/topspin 2008
HSQCGP
F1 [ppm]
F2 [ppm]
2
4
6
8
OBn
OBn
OH
Pr
H
O
O
H
H
15
14
8
3.52

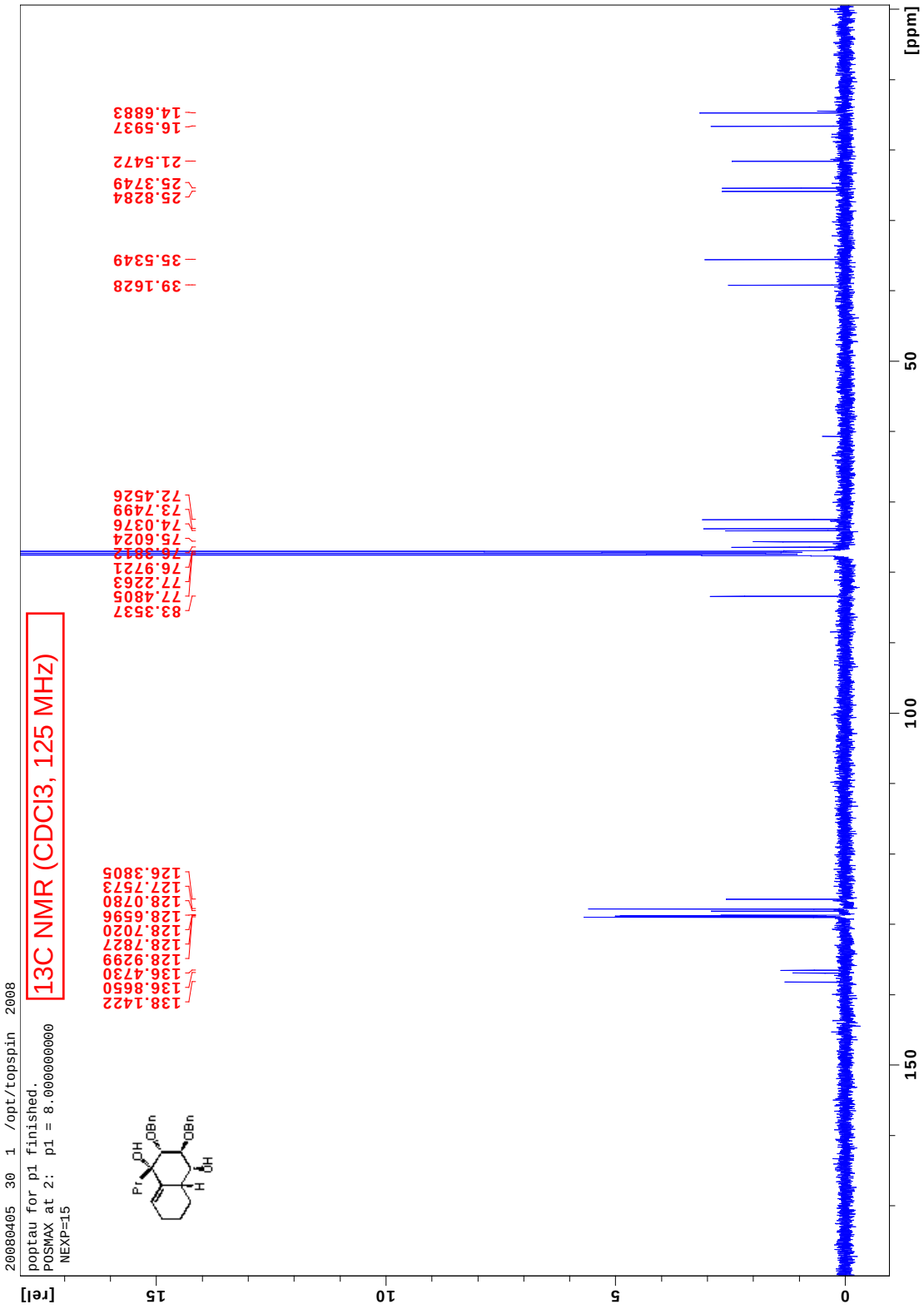

20080403 9 1 /opt/topspin 2008
13C NMR (CDCl3, DEPT 135, 125 MHz)
20080403 12 1 /opt/topspin 2008
Scale : 1.9607
13C NMR (CDCl3, 125 MHz)
20080403 9 1 /opt/topspin 2008
Scale : 9.6202
[rel]
400
300
200
100
0
150
100
50
[ppm]
OBn
OH
OBn
Pr
H
H
O
O
3.52


HSQC (CDCl3)
20080403 11 1 /opt/topspin 2008
HSQCGP
F1 [ppm]
F2 [ppm]
OH
OBn
OBn
Pr
H
O
O
14


HMBC (CDCl3)
20080403 23 1 /opt/topspin 2008
HMBCGP
F1 [ppm]
F2 [ppm]
OBn
OBn
OH
Pr
3.52


NOESY (CDCl3)
20080403 13 1 /opt/topspin 2008
HSQCGP
F1 [ppm]
F2 [ppm]
2
4
6
8
3.52
OH
OBn
OBn
Pr
H
O
H
O
H
15
14
8


1H NMR (CDCl3, 500 MHz)
HSQCGP
20080405 31 1 /opt/topspin 2008
[rel]
[ppm]
OBn
OBn
OH
OH
Pr
H


13C NMR (CDCl3, 125 MHz)
20080405 30 1 /opt/topspin 2008
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
0
5
10
15
50
100
150
14.6883
16.5937
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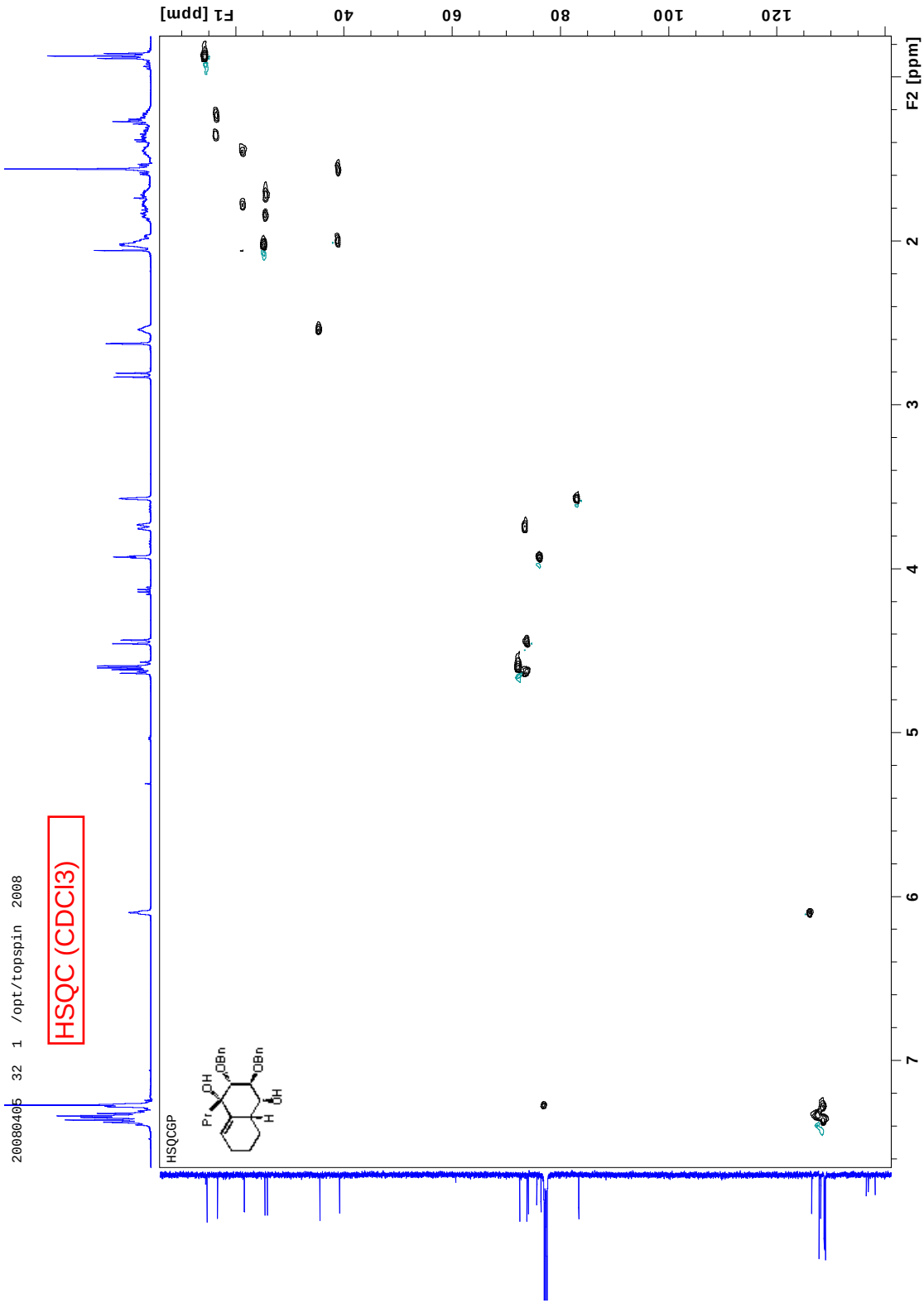
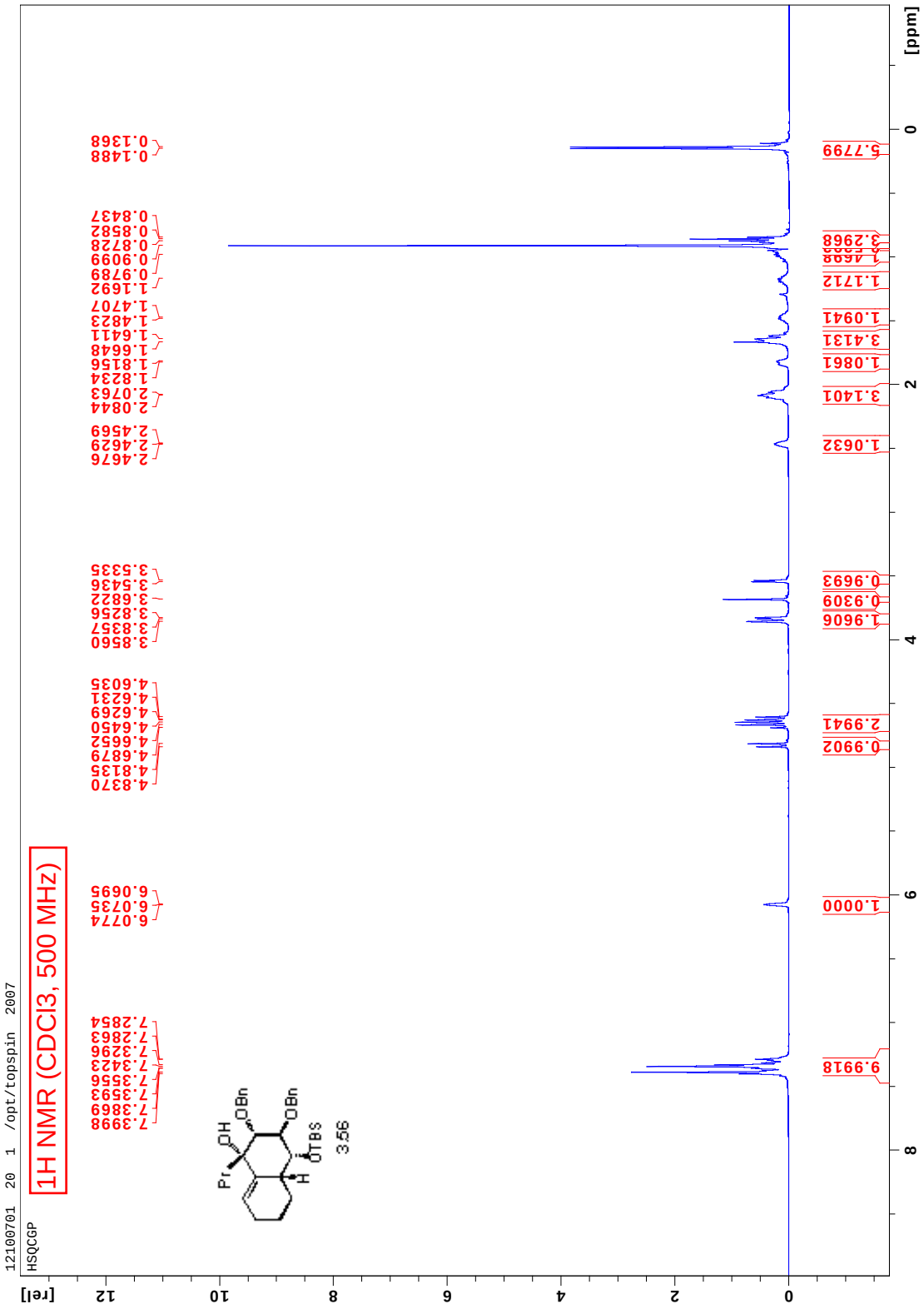
39.1628
72.4526
73.7499
74.0376
75.6024
76.3812
76.9721
77.2263
77.4805
83.3537
126.3805
127.7573
128.0780
128.6596
128.7020
128.7827
128.9299
136.4730
136.8650
138.1422
OBn
OBn
OH
OH
Pr


HSQC (CDCl3)
F1 [ppm]
F2 [ppm]
HSQCGP
OBn
OBn
OH
H
OH


12100701 20 1 /opt/topspin 2007
HSQCGP
1H NMR (CDCl3, 500 MHz)
[rel]
[ppm]
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OBn
OBn
OTBS
Pr
H
3.56
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0.9902
2.9941
1.9606
0.9309
0.9693
1.0632
3.1401
1.0861
3.4131
1.0941
1.1712
1.4698
3.2968
5.7799
0.1488
0.1368
0.8437
0.8582
0.8728
0.9099
0.9789
1.1692
1.4707
1.4823
1.6411
1.6648
1.8156
1.8234
2.0763
2.0844
2.4569
2.4629
2.4676
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3.5436
3.6822
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3.8357
3.8560
4.6035
4.6231
4.6269
4.6450
4.6652
4.6879
4.8135
4.8370
6.0695
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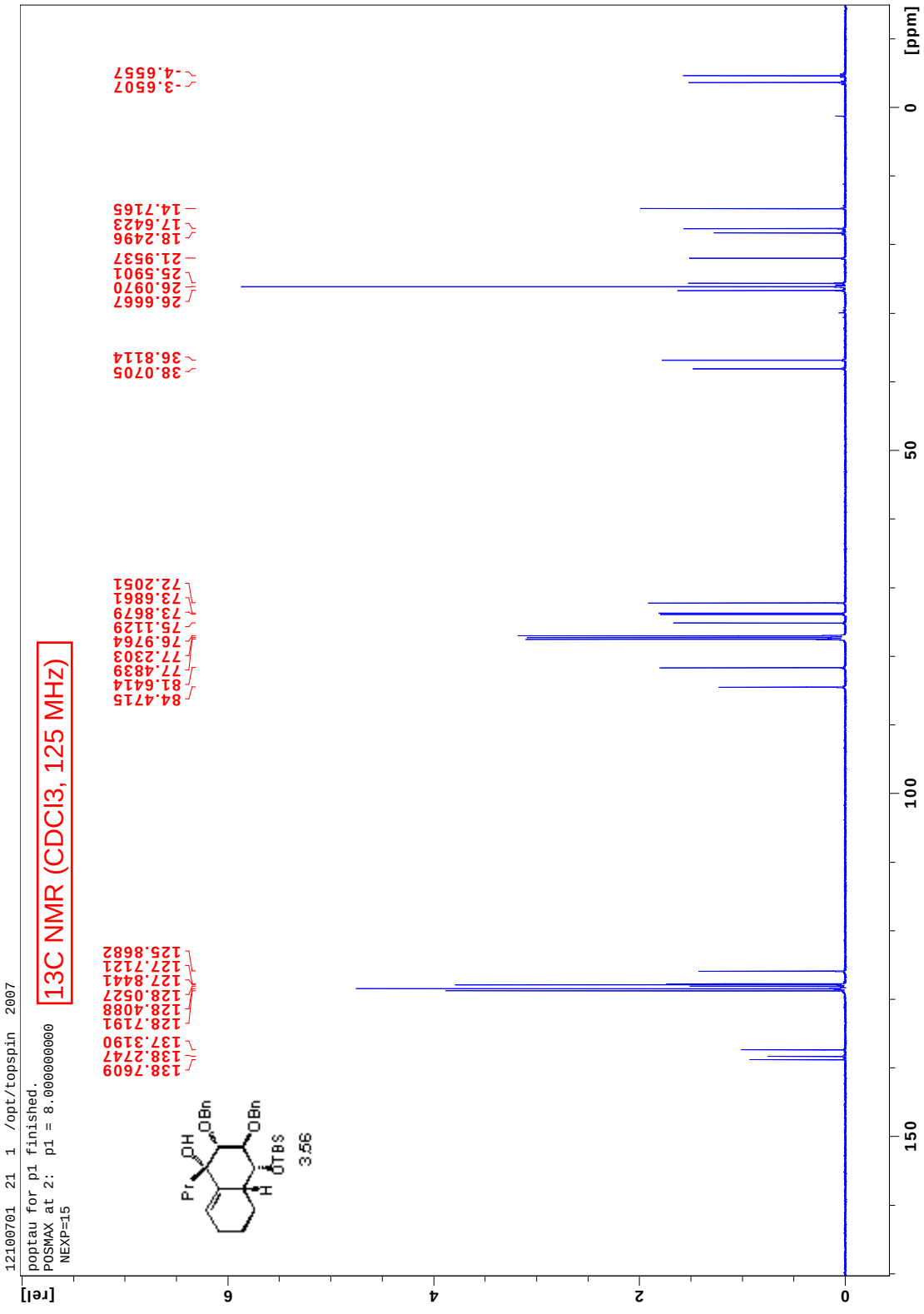
7.3593
7.3869
7.3998


13C NMR (CDCl3, 125 MHz)
12100701 21 1 /opt/topspin 2007
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
[rel]
[ppm]
0
2
4
6
50
100
150
138.7609
138.2747
137.3190
128.7191
128.4088
128.0527
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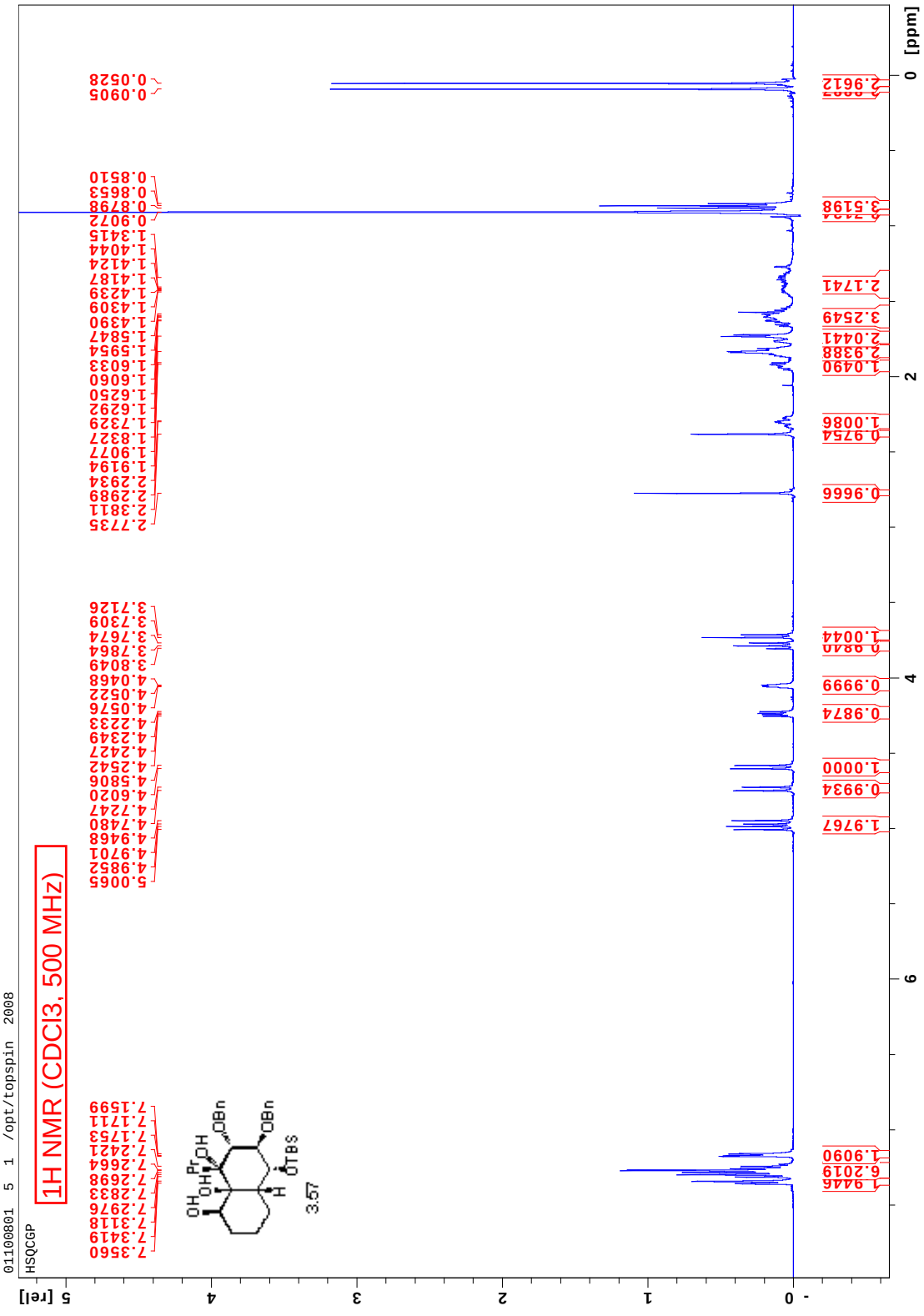
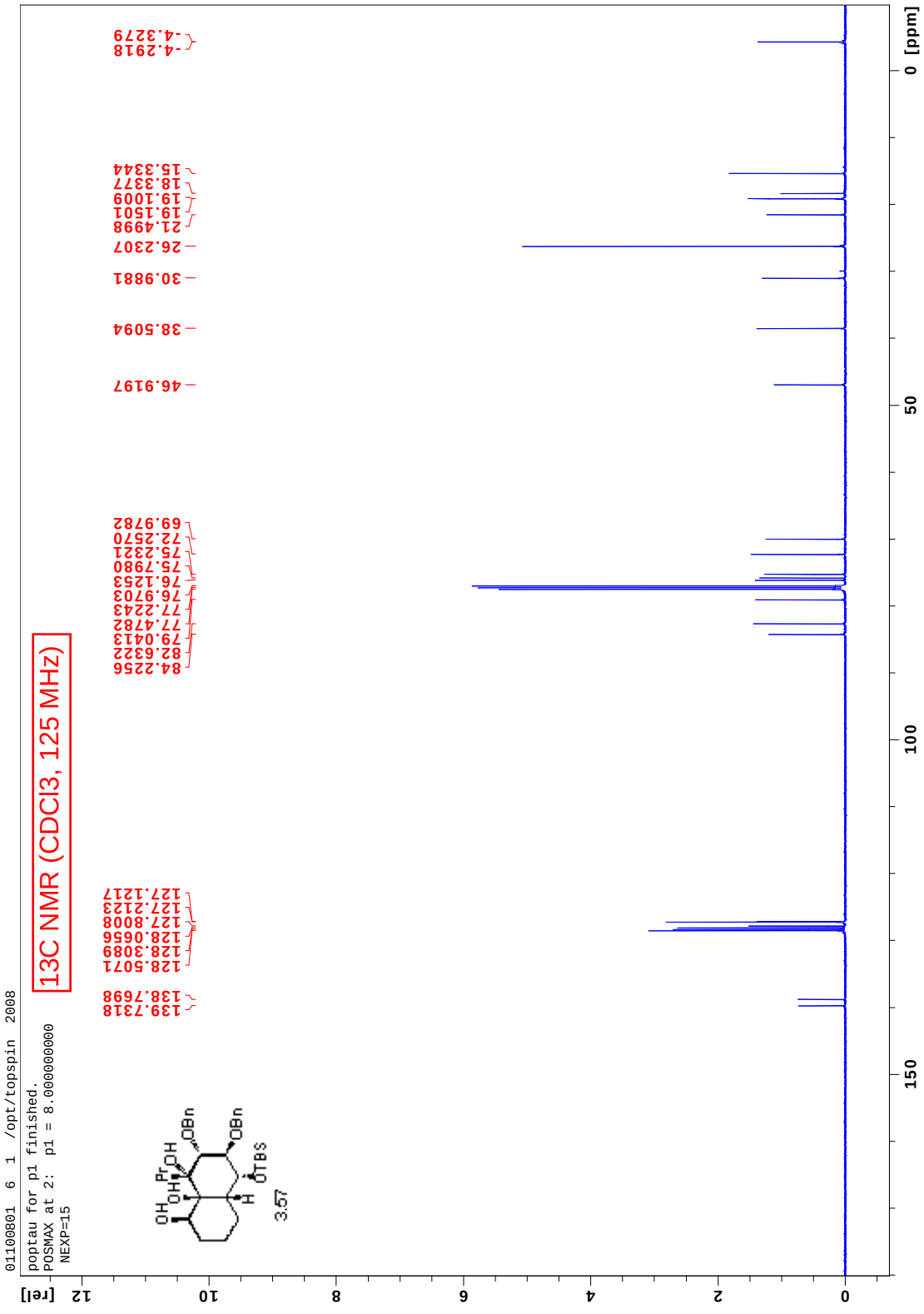
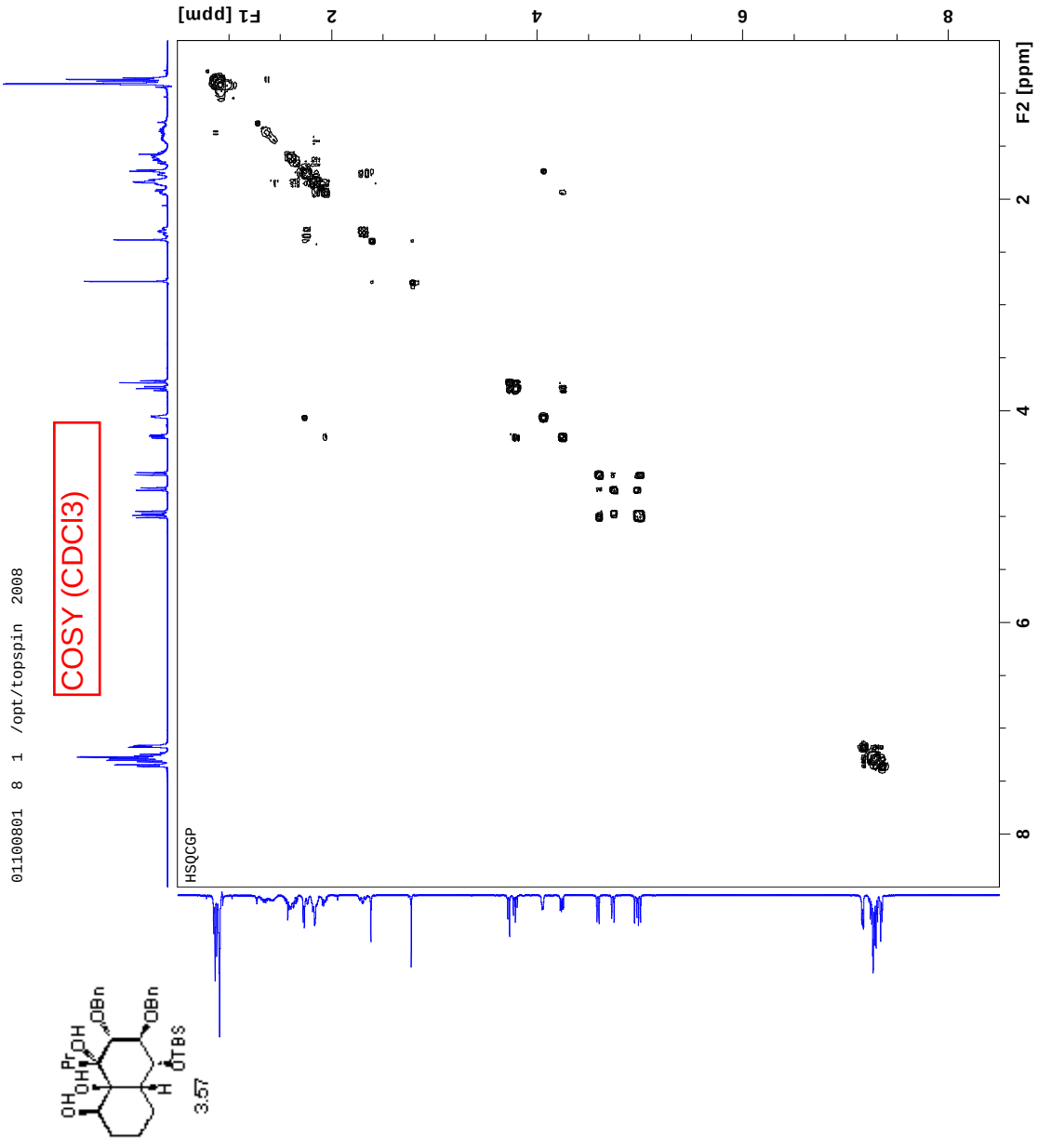
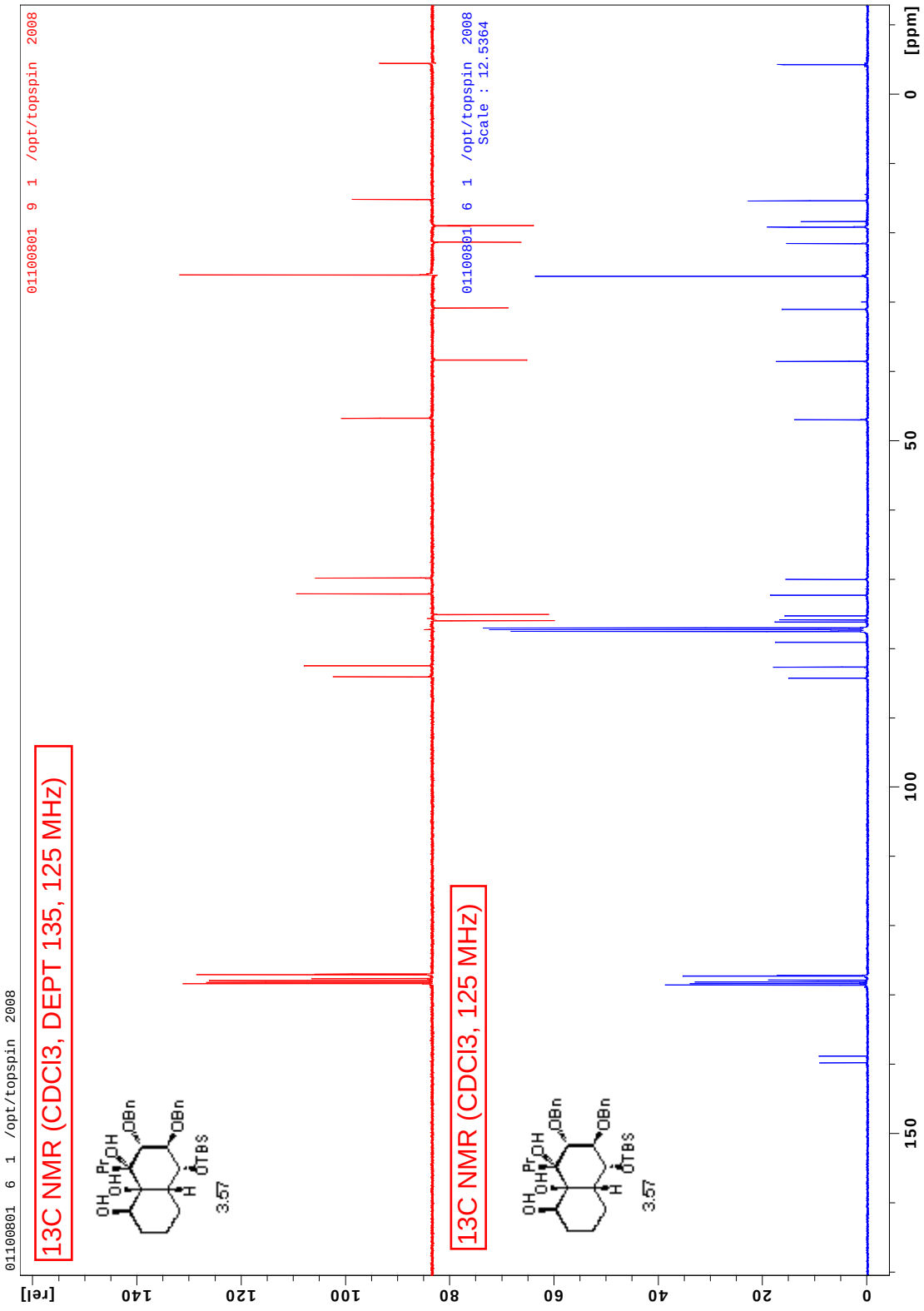
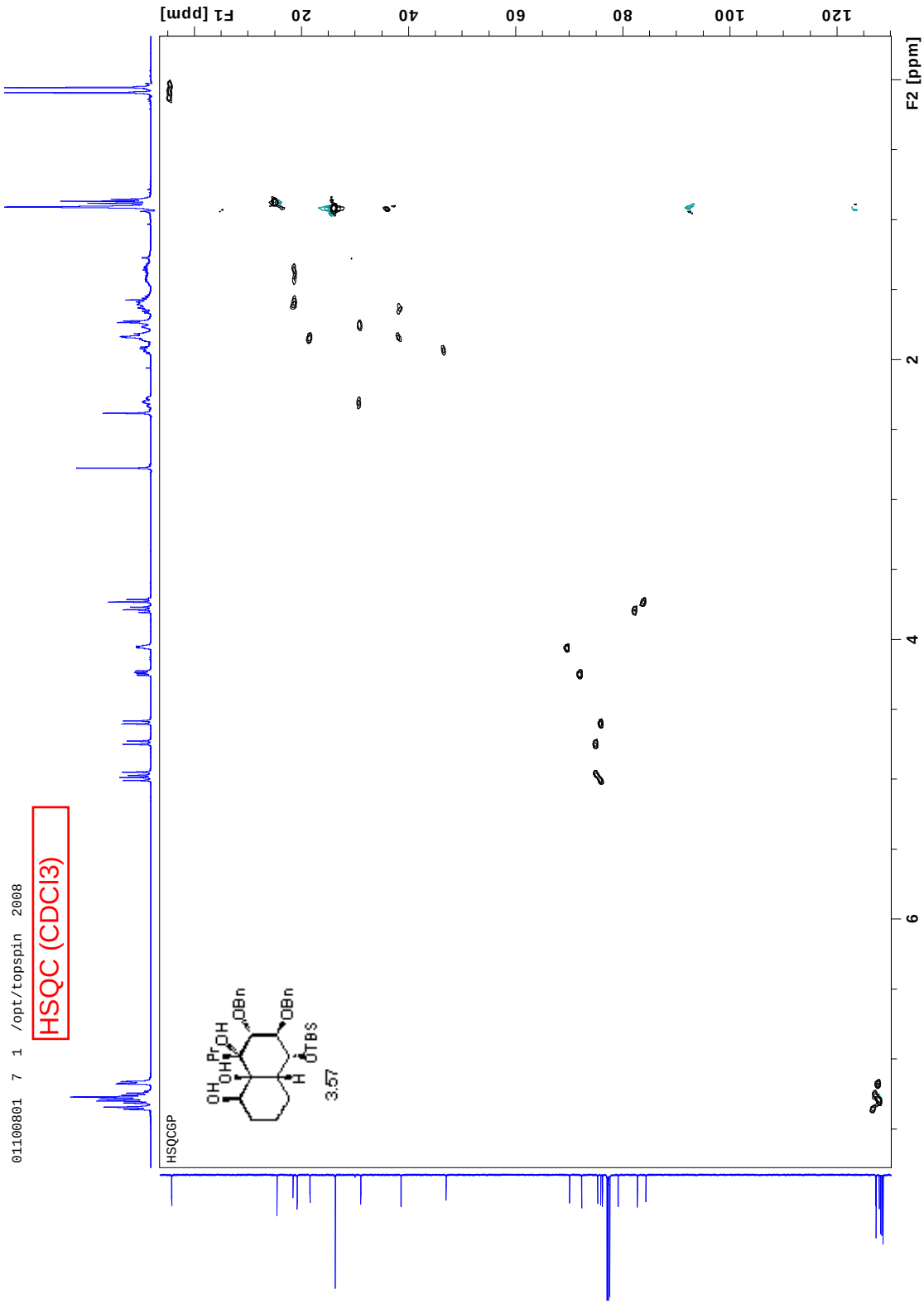
127.7121
125.8682
84.4715
81.6414
77.4839
77.2303
76.9764
75.1129
73.8679
73.6861
72.2051
38.0705
36.8114
26.6667
26.0970
25.5901
21.9537
18.2496
17.6423
14.7165
-3.6507
-4.6557
OBn
OBn
OH
OTBS
H
Pr
3.56

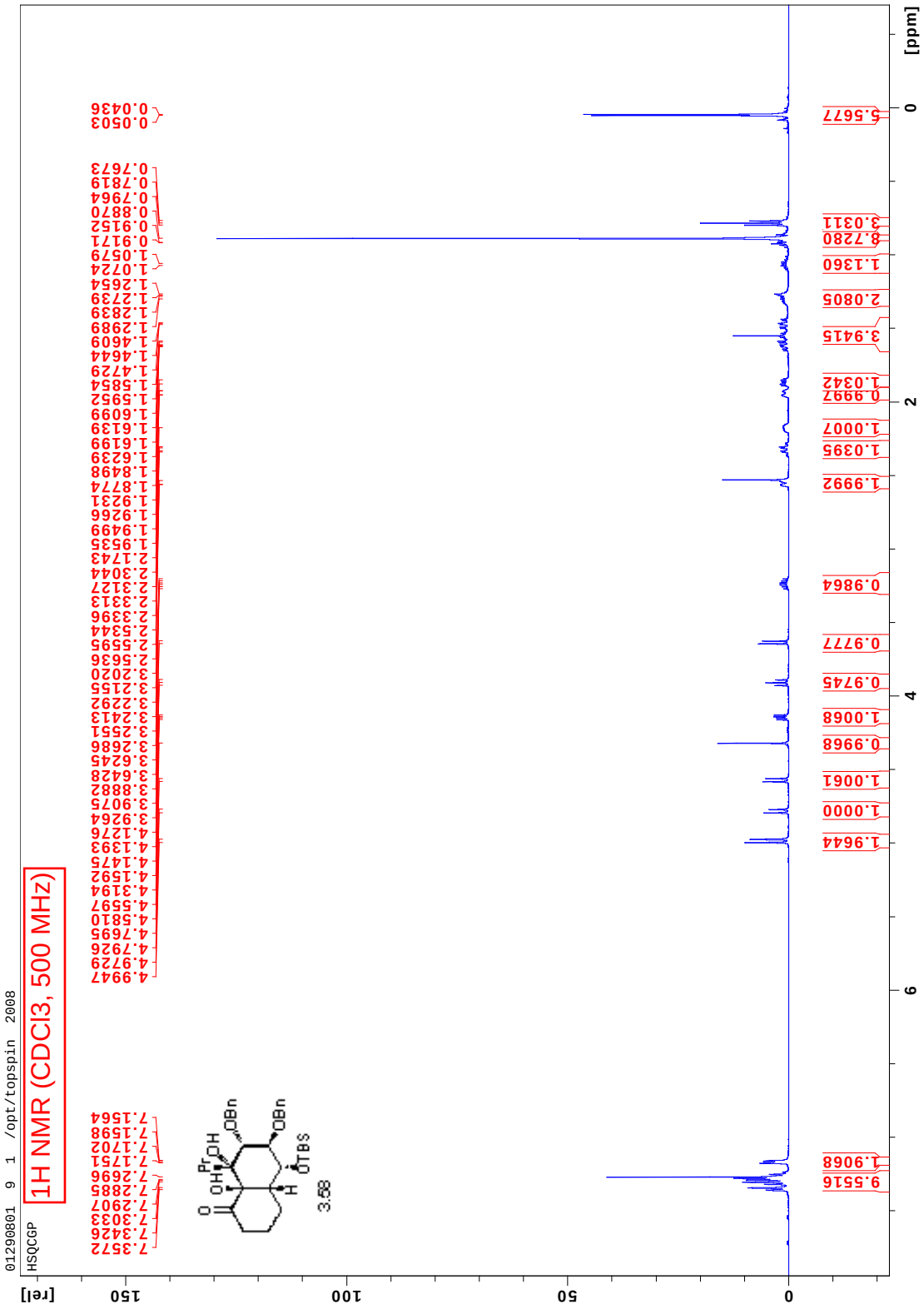

1H NMR (CDCl3, 500 MHz)
HSQCGP
01100801 5 1 /opt/topspin 2008
OBn
OBn
OTBS
3.57
[ppm]
[rel]

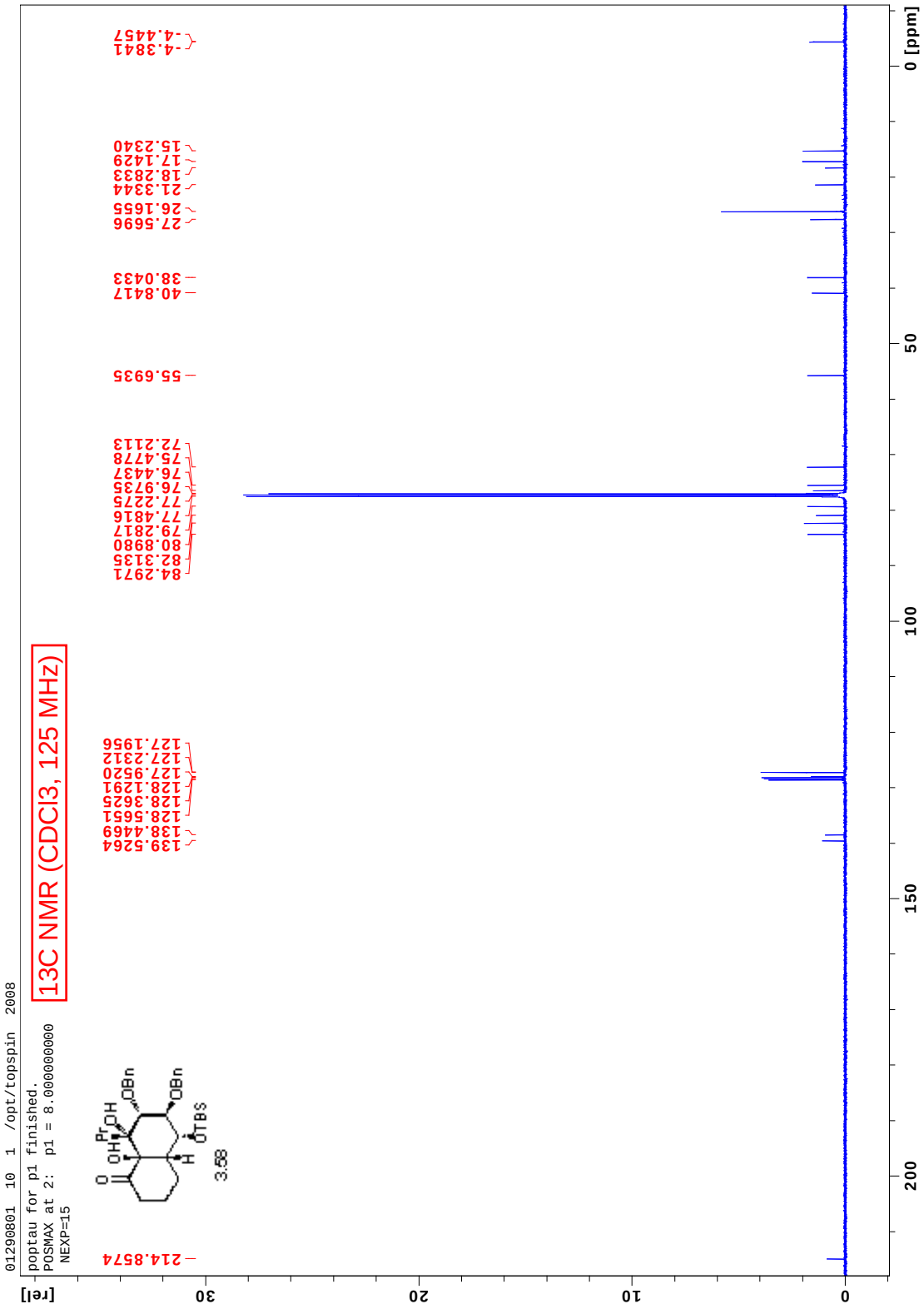

13C NMR (CDCl3, 125 MHz)
01100801 6 1 /opt/topspin 2008
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
-4.2918
-4.3279
15.3344
18.3377
19.1009
19.1501
21.4998
26.2307
30.9881
38.5094
46.9197
69.9782
72.2570
75.2321
75.7980
76.1253
76.9703
77.2243
77.4782
79.0413
82.6322
84.2256
127.1217
127.2123
127.8008
128.0656
128.3089
128.5071
138.7698
139.7318
3.57
[rel]
0 [ppm]


COSY (CDCl3)
01100801 8 1 /opt/topspin 2008
HSQCGP
F1 [ppm]
F2 [ppm]
2
4
6
8
OH
OH
Pr
OH
OBn
OBn
H
OTBS
3.57


13C NMR (CDCl3, DEPT 135, 125 MHz)
13C NMR (CDCl3, 125 MHz)
01100801 6 1 /opt/topspin 2008
01100801 9 1 /opt/topspin 2008
01100801 6 1 /opt/topspin 2008
Scale : 12.5364
[rel]
[ppm]
0
20
40
60
80
100
120
140
50
100
150
OH
OH
OBn
OBn
H
OTBS
3.57


HSQC (CDCl3)
01100801 7 1 /opt/topspin 2008
HSQCGP
F1 [ppm]
F2 [ppm]
20
40
60
80
100
120
2
4
6
OBn
OBn
OTBS
OH
OH
Pr
3.57


1H NMR (CDCl3, 500 MHz)
HSQCGP
01290801 9 1 /opt/topspin 2008
[rel]
[ppm]
OBn
OBn
OTBS
OH
3.58


13C NMR (CDCl3, 125 MHz)
01290801 10 1 /opt/topspin 2008
poptau for p1 finished.
POSMAX at 2: p1 = 8.000000000
NEXP=15
214.8574
139.5264
138.4469
128.5651
128.3625
128.1291
127.9520
127.2312
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79.2817
77.4816
77.2275
76.9735
76.4437
75.4778
72.2113
55.6935
40.8417
38.0433
27.5696
26.1655
21.3344
18.2833
17.1429
15.2340
-4.3841
-4.4457
OBn
OBn
OH
OTBS
3.68
[rel]
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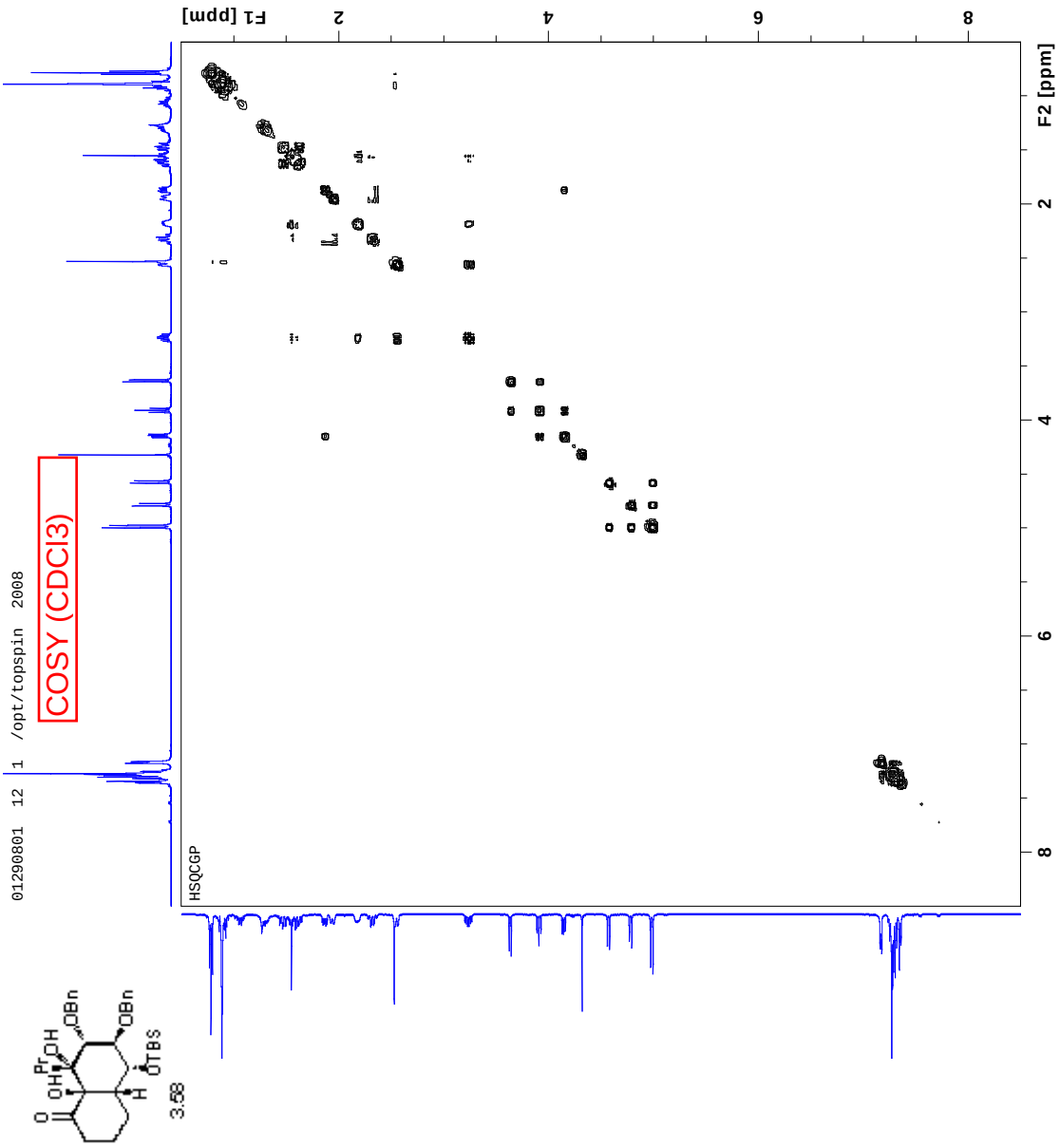
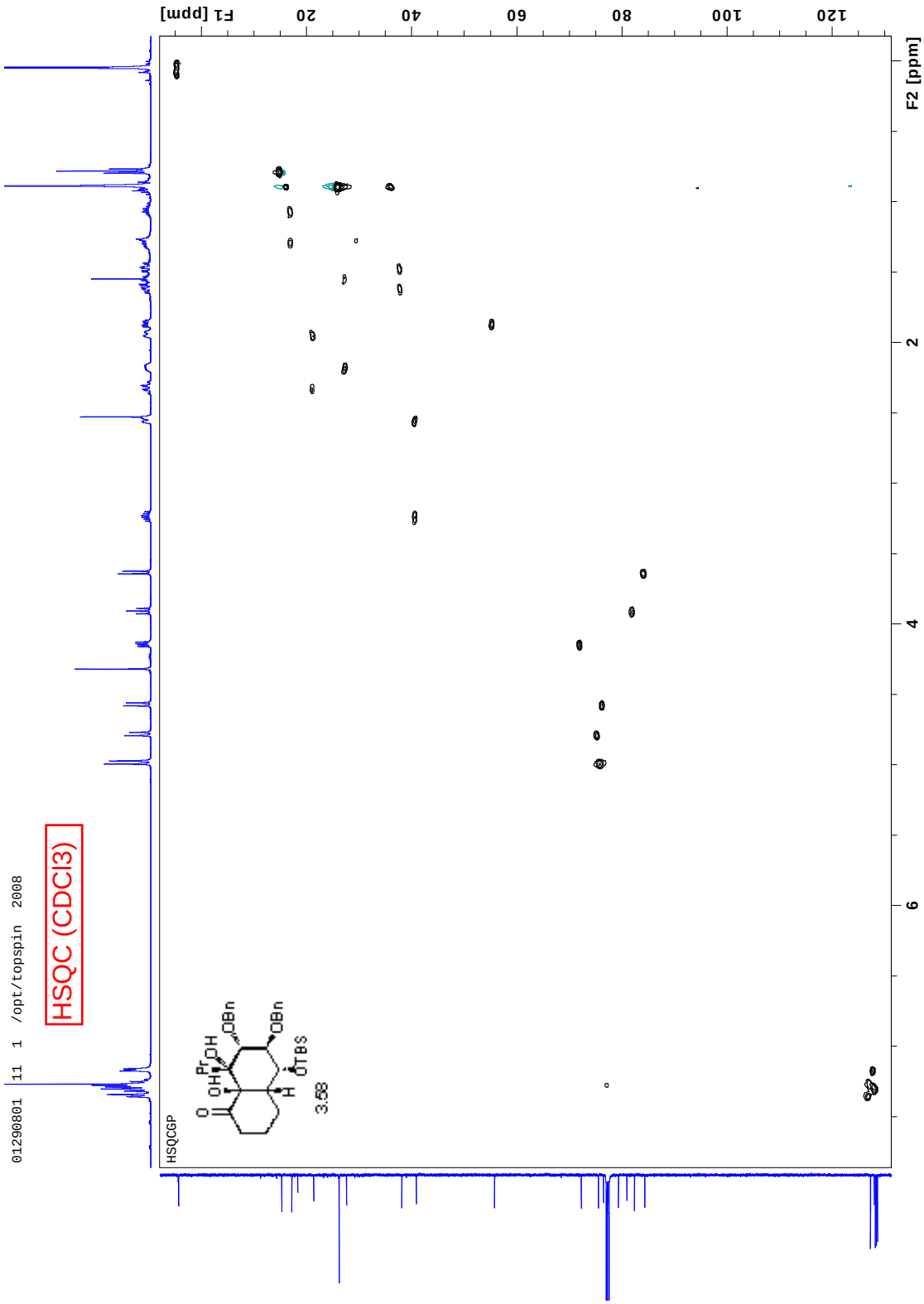
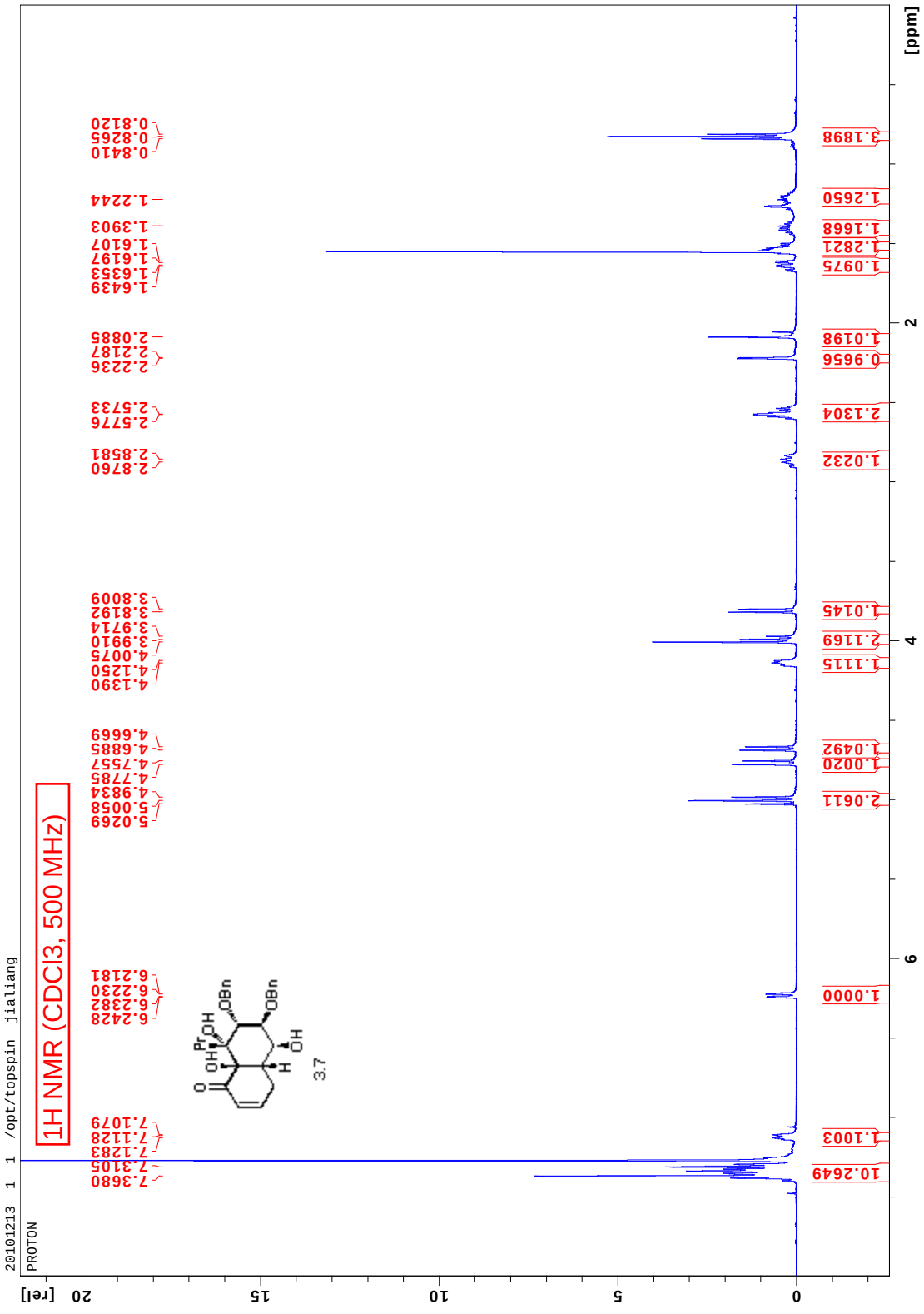
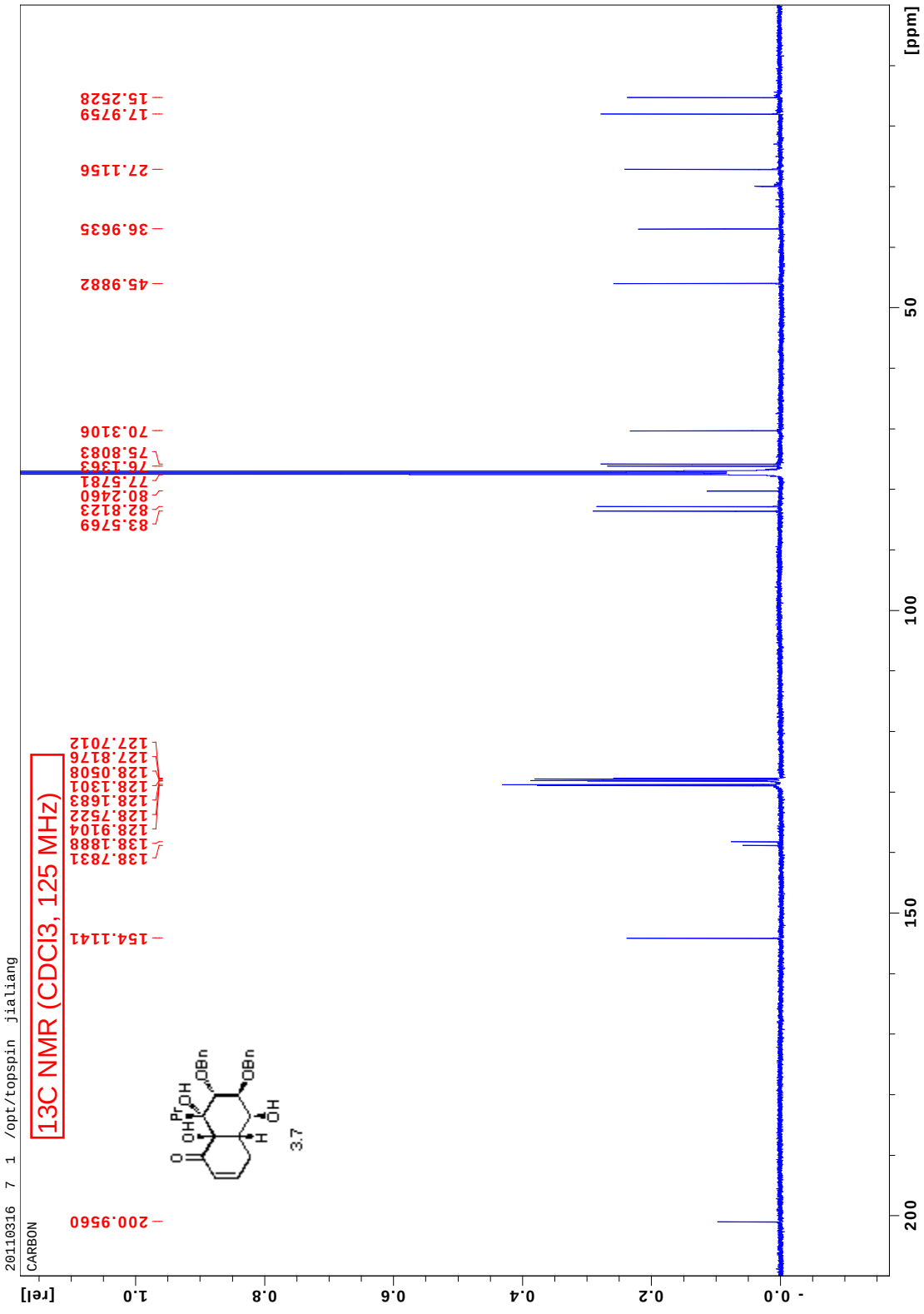
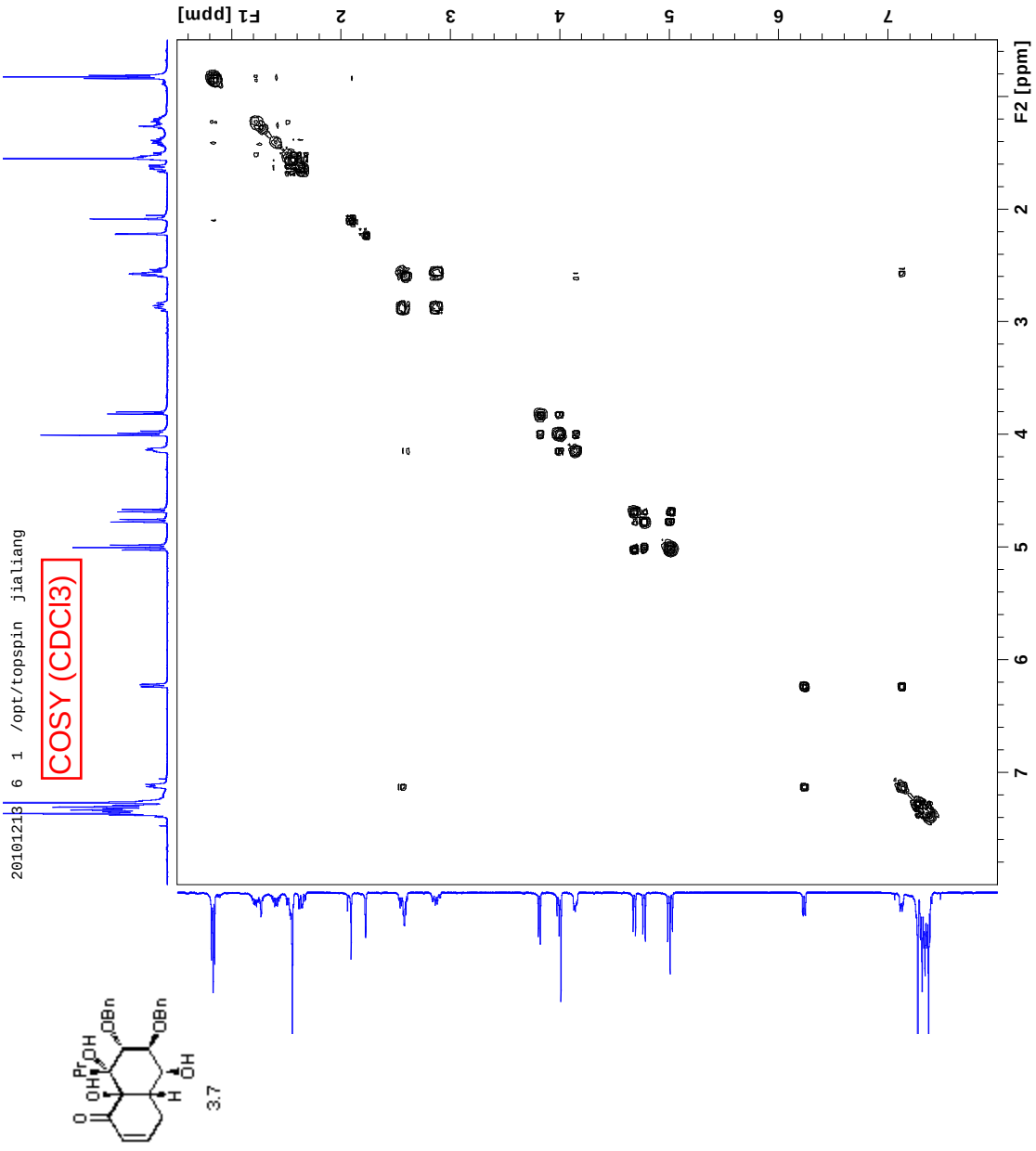
10
20
30
200
150
100
50
0 [ppm]

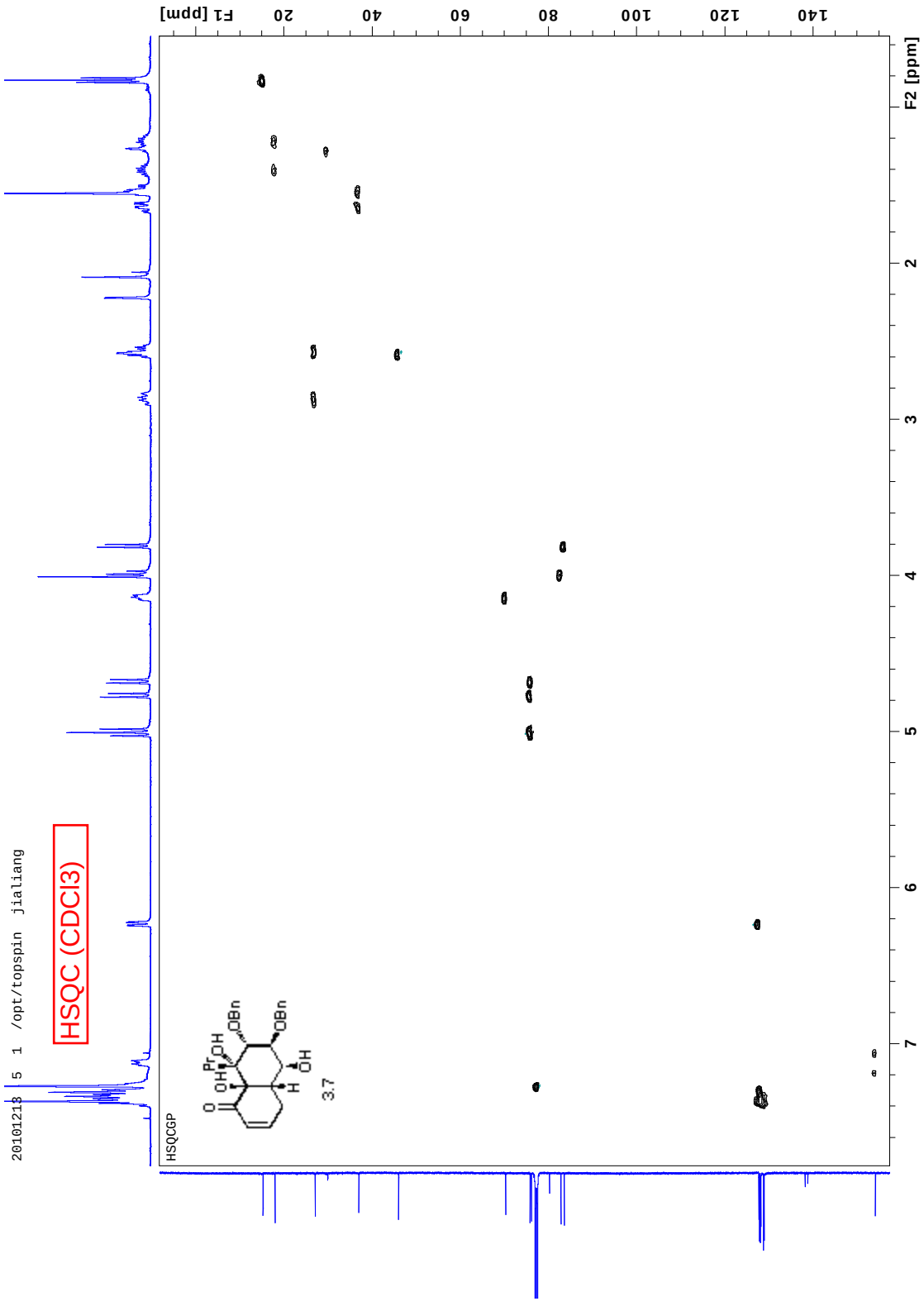

COSY (CDCl3)
HSQCGP
F1 [ppm]
F2 [ppm]
2
4
6
8
01290801 12 1 /opt/topspin 2008
OBn
OBn
OTBS
OH
3.58

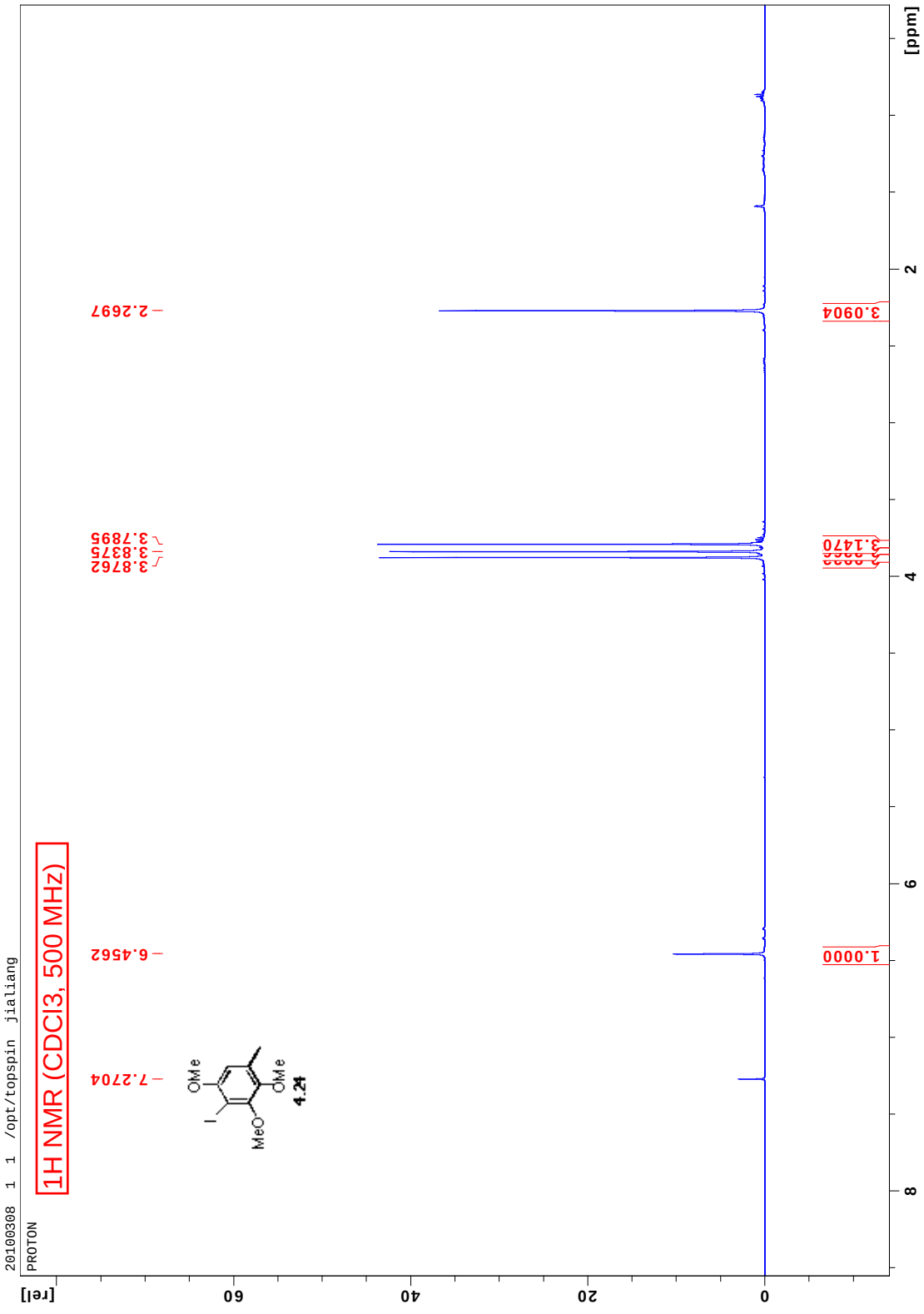

HSQC (CDCl3)
01290801 11 1 /opt/topspin 2008
HSQCGP
F1 [ppm]
F2 [ppm]
20
40
60
80
100
120
2
4
6
OBn
OBn
OH
OTBS
3.58

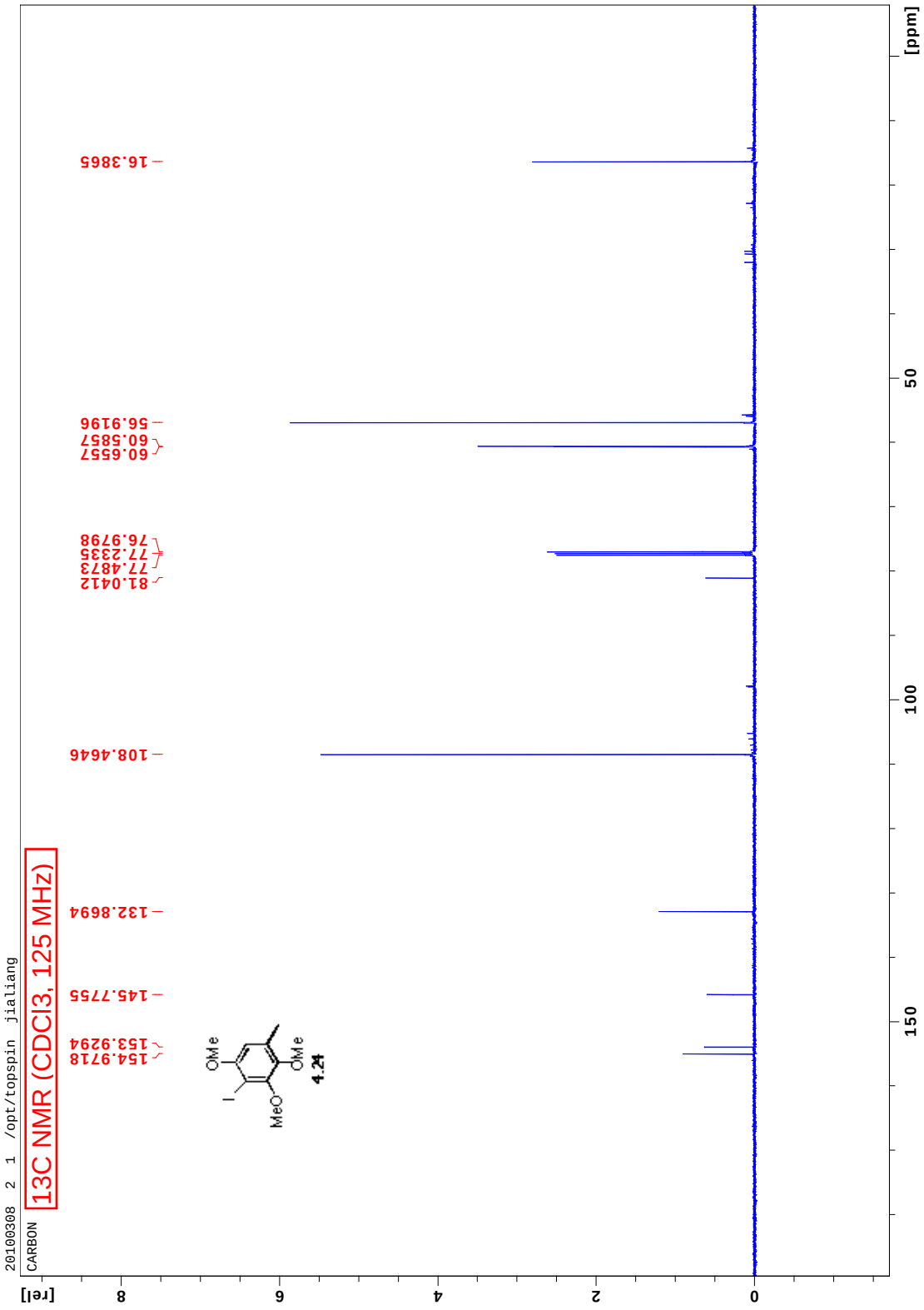

1H NMR (CDCl3, 500 MHz)
20101213 1 1 /opt/topspin jialiang
PROTON
[rel]
[ppm]
OBn
OBn
OH
OH
H
O
Pr
3.7

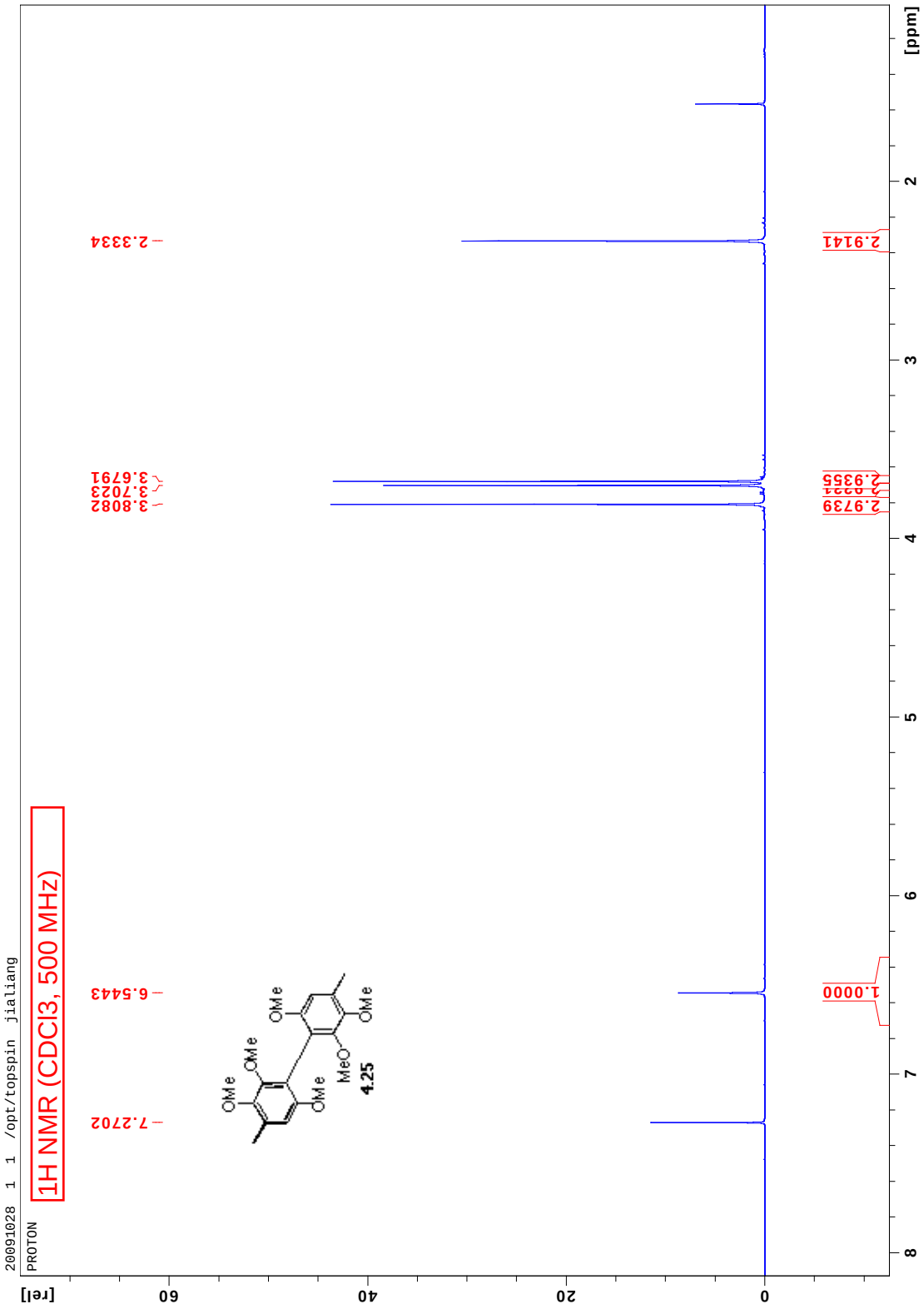

13C NMR (CDCl3, 125 MHz)
CARBON
20110316 7 1 /opt/topspin jialiang
200.9560
154.1141
138.7831
138.1888
128.9104
128.7522
128.1683
128.1301
128.0508
127.8176
127.7012
83.5769
82.8123
80.2460
77.5781
76.1363
75.8083
70.3106
45.9882
36.9635
27.1156
17.9759
15.2528
OBn
OBn
OH
OH
H
O
3.7
[rel]
1.0
0.8
0.6
0.4
0.2
0.0
[ppm]
200
150
100
50

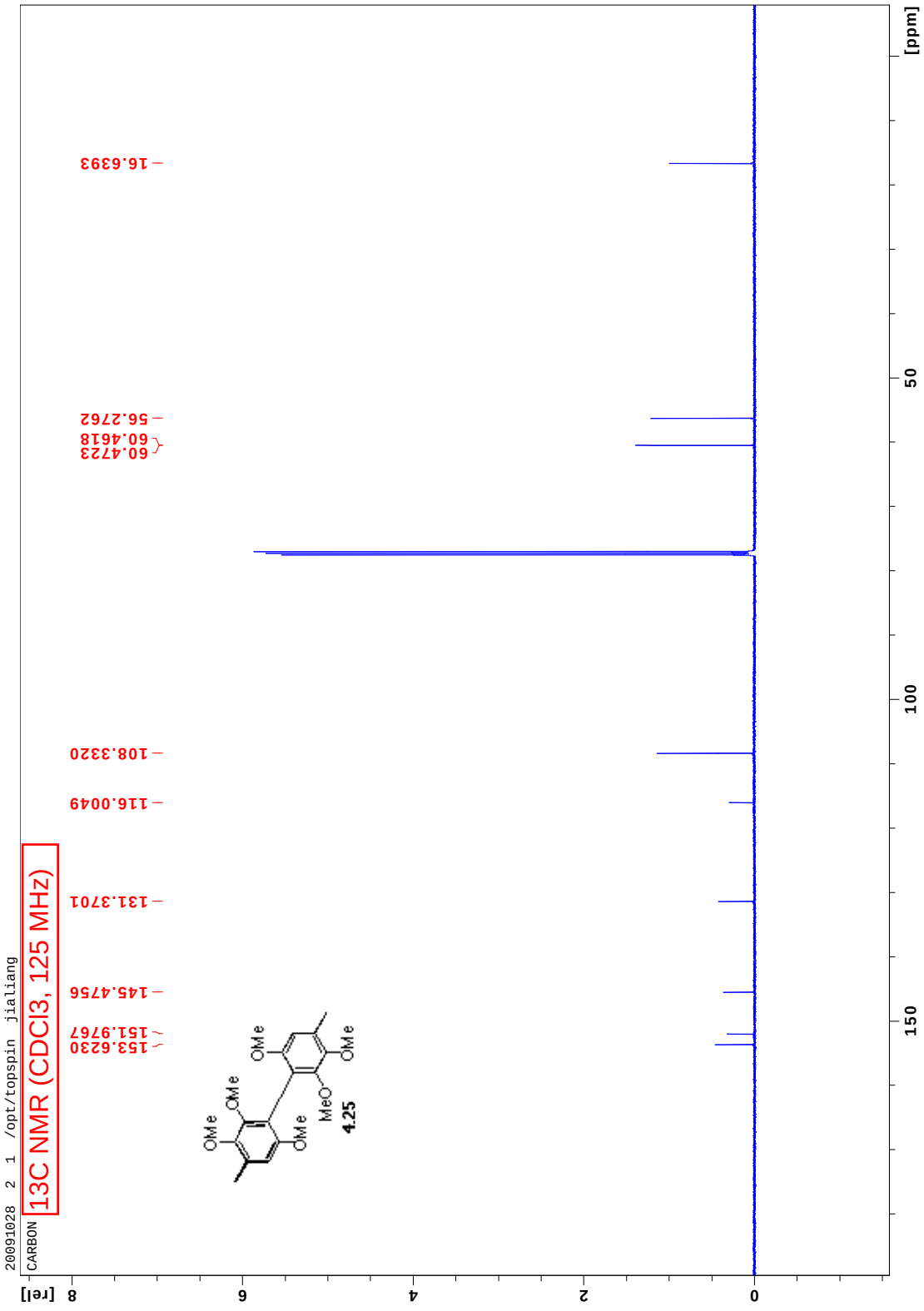

COSY (CDCl3)
20101213 6 1 /opt/topspin jialiang
F1 [ppm]
F2 [ppm]
2
3
4
5
6
7
OBn
OBn
OH
OH
O
H
3.7

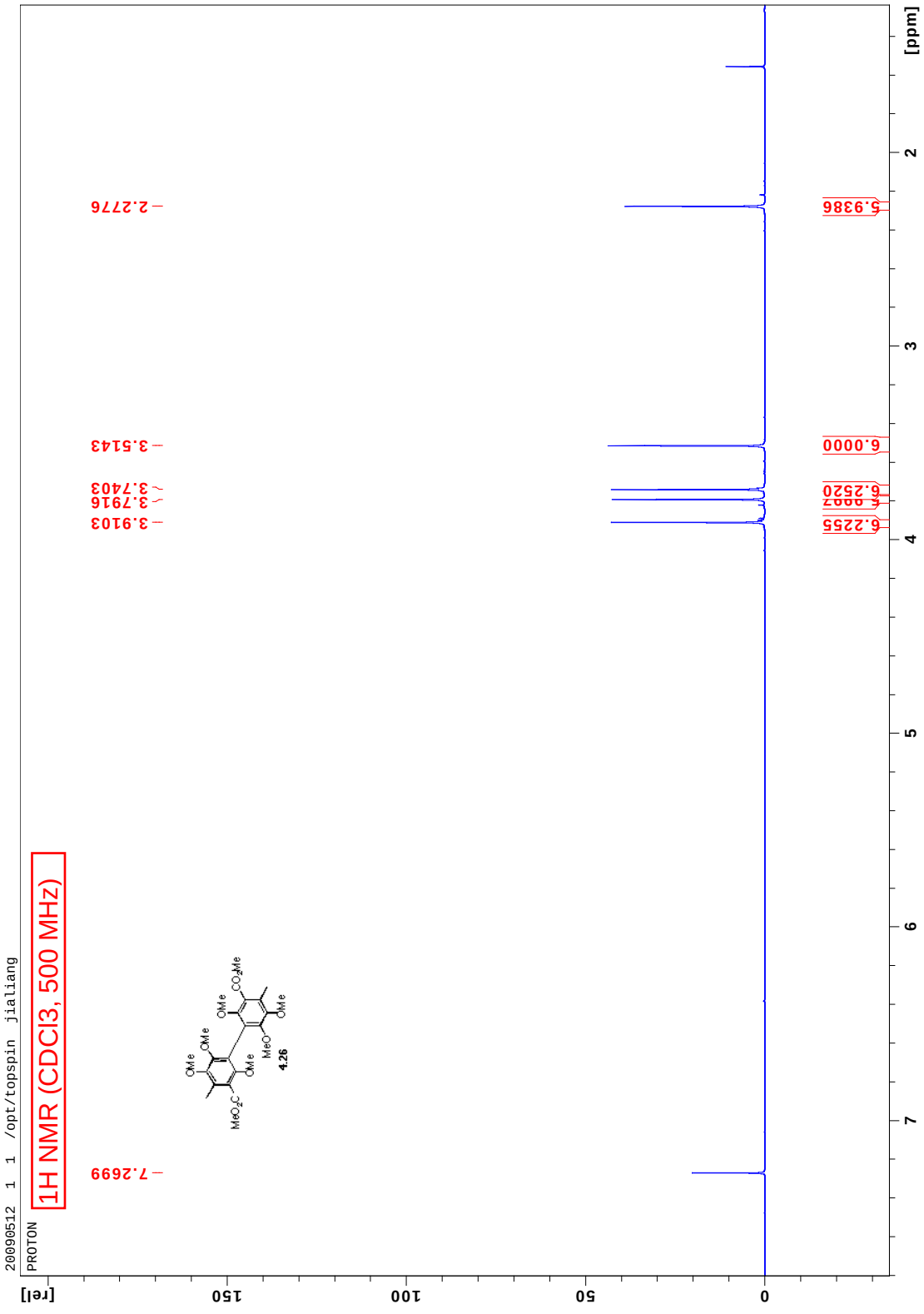

HSQC (CDCl3)
20101218 5 1 /opt/topspin jialiang
HSQCGP
F1 [ppm]
F2 [ppm]
3.7

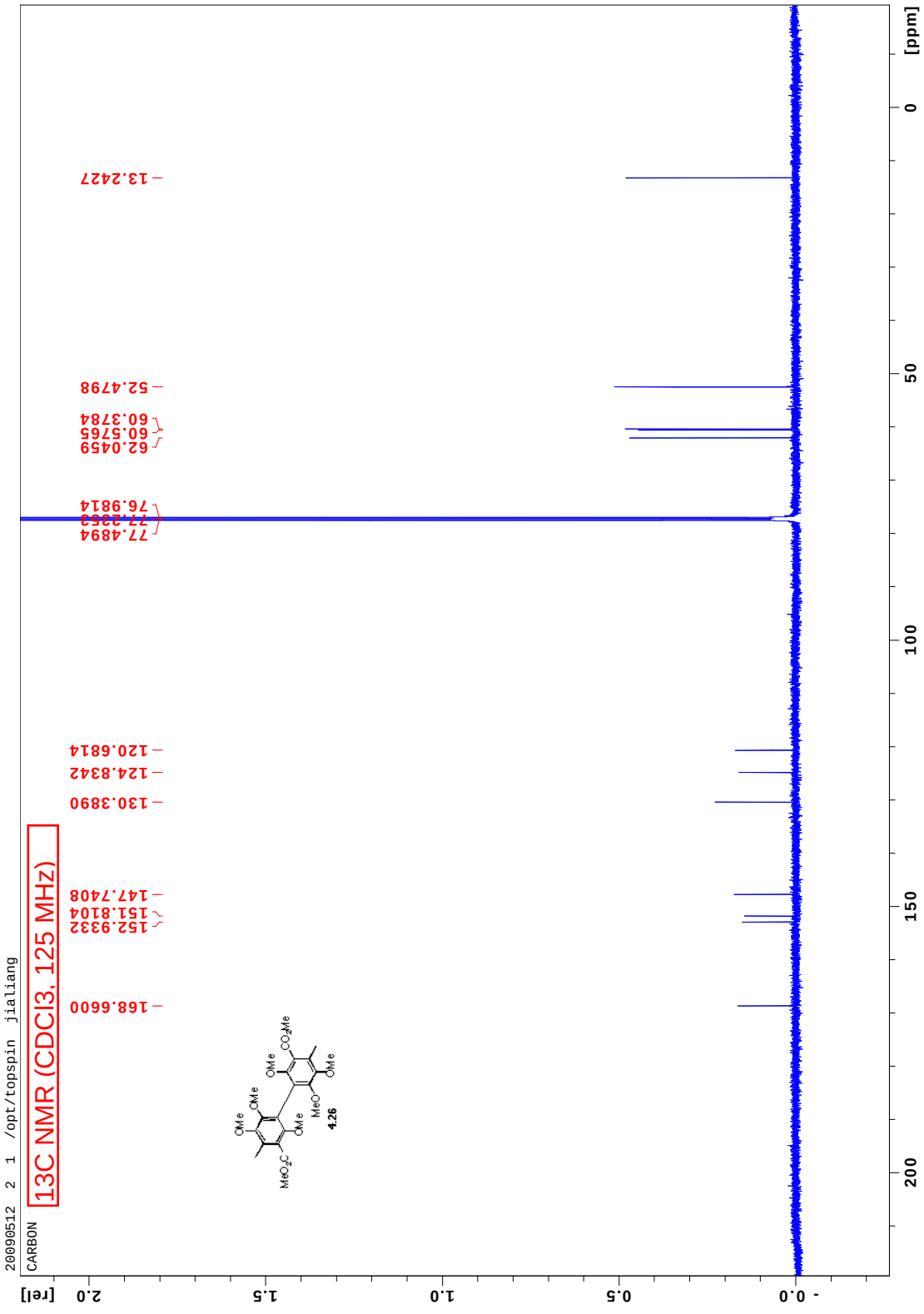

20100308 1 1 /opt/topspin jialiang
PROTON
1H NMR (CDCl3, 500 MHz)
OMe
OMe
MeO
I
4.24
7.2704
6.4562
3.8762
3.8375
3.7895
2.2697
1.0000
3.1470
3.0904
[rel]
[ppm]

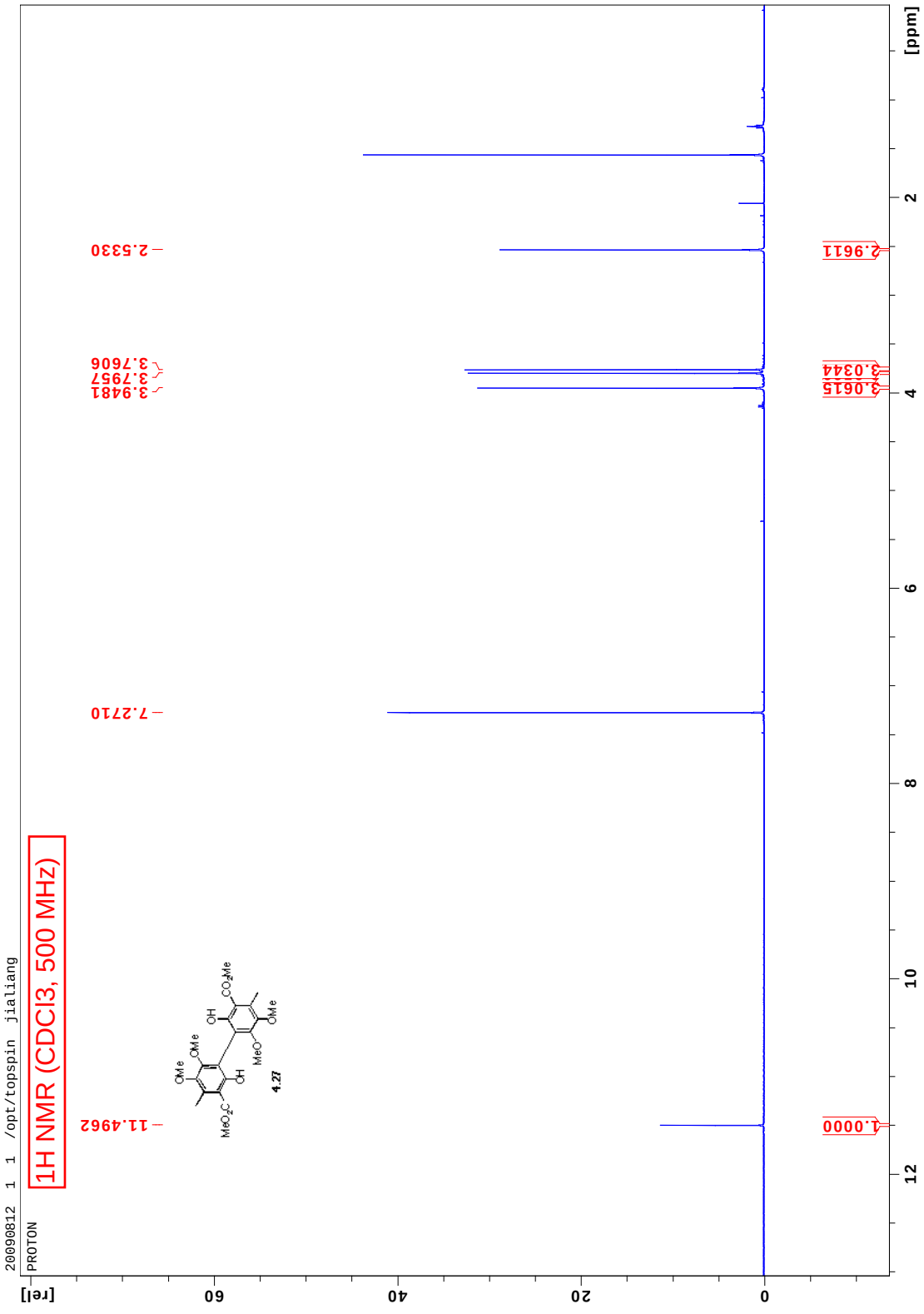

20100308 2 1 /opt/topspin jialiang
CARBON
13C NMR (CDCl3, 125 MHz)
16.3865
56.9196
60.6557
60.5857
76.9798
77.2335
77.4873
81.0412
108.4646
132.8694
145.7755
153.9294
154.9718
OMe
OMe
MeO
I
4.24
[rel]
[ppm]
0
2
4
6
8
50
100
150

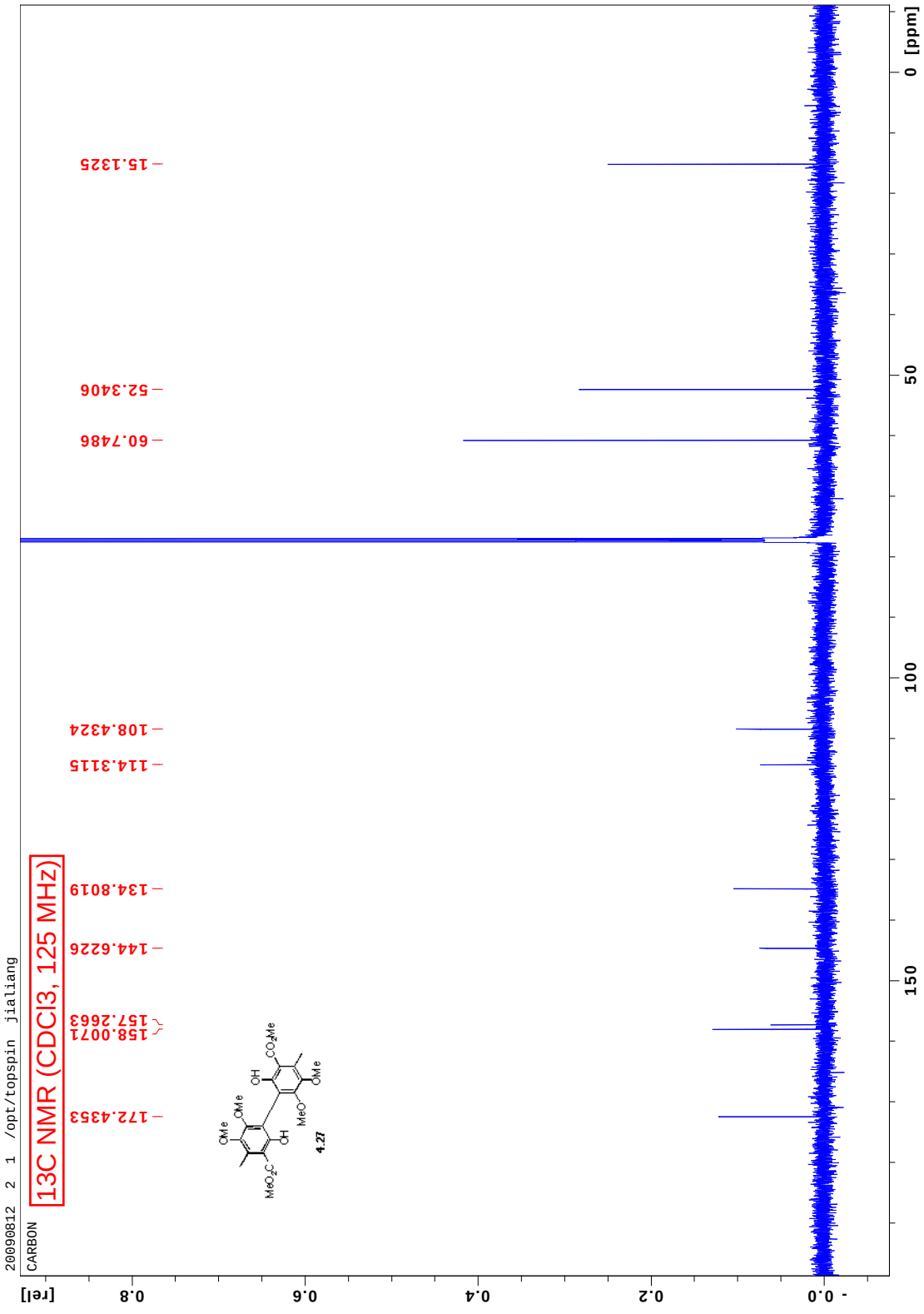

20091028 1 1 /opt/topspin jialiang
PROTON
1H NMR (CDCl3, 500 MHz)
7.2702
6.5443
3.8082
3.7023
3.6791
2.3334
2.9739
2.9355
2.9141
1.0000
4.25
OMe
OMe
OMe
OMe
MeO
OMe
[rel]
[ppm]

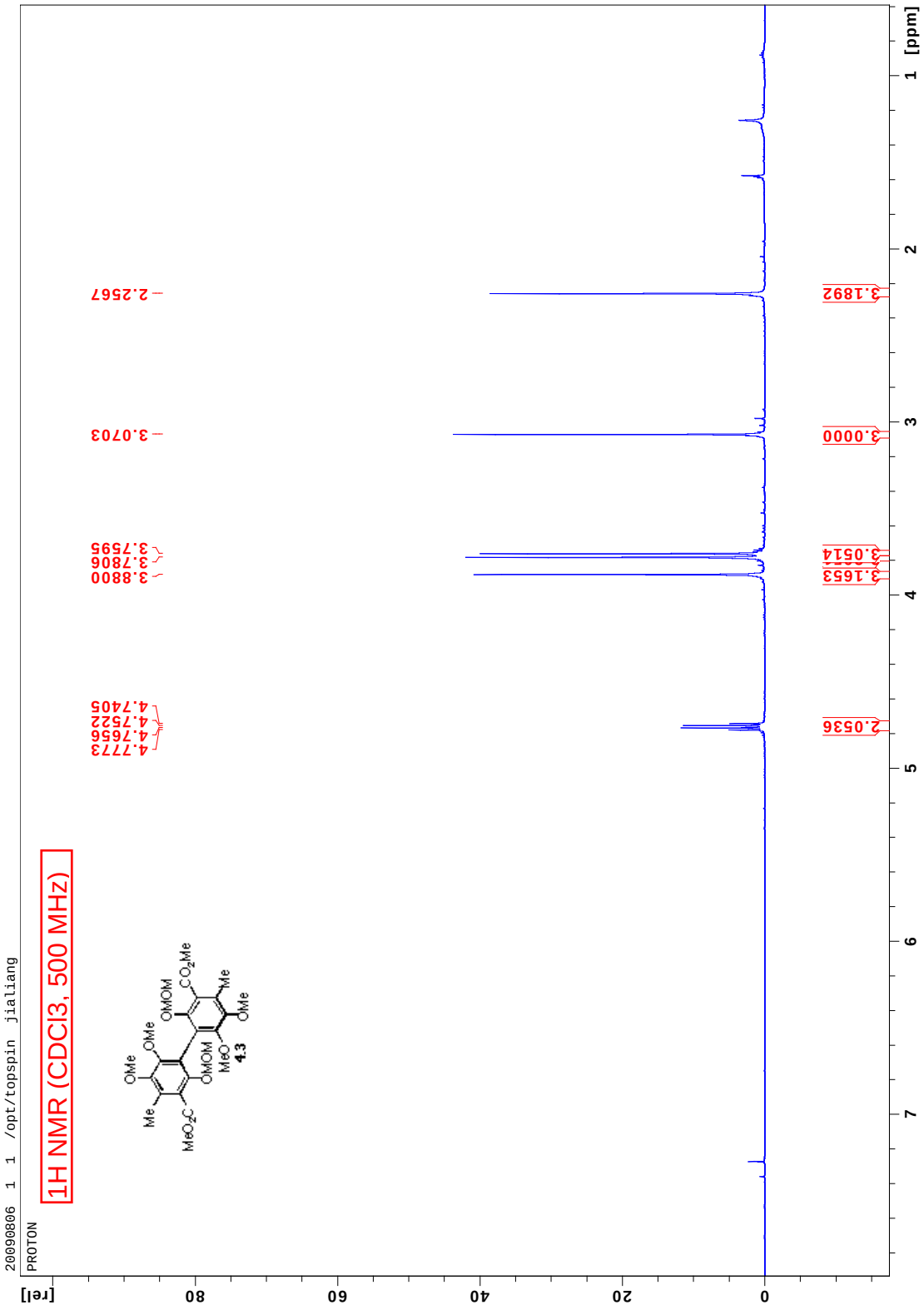

20091028 2 1 /opt/topspin jialiang
CARBON
13C NMR (CDCl3, 125 MHz)
153.6230
151.9767
145.4756
131.3701
116.0049
108.3320
60.4723
60.4618
56.2762
16.6393
OMe
OMe
OMe
OMe
OMe
MeO
4.25
[rel]
[ppm]

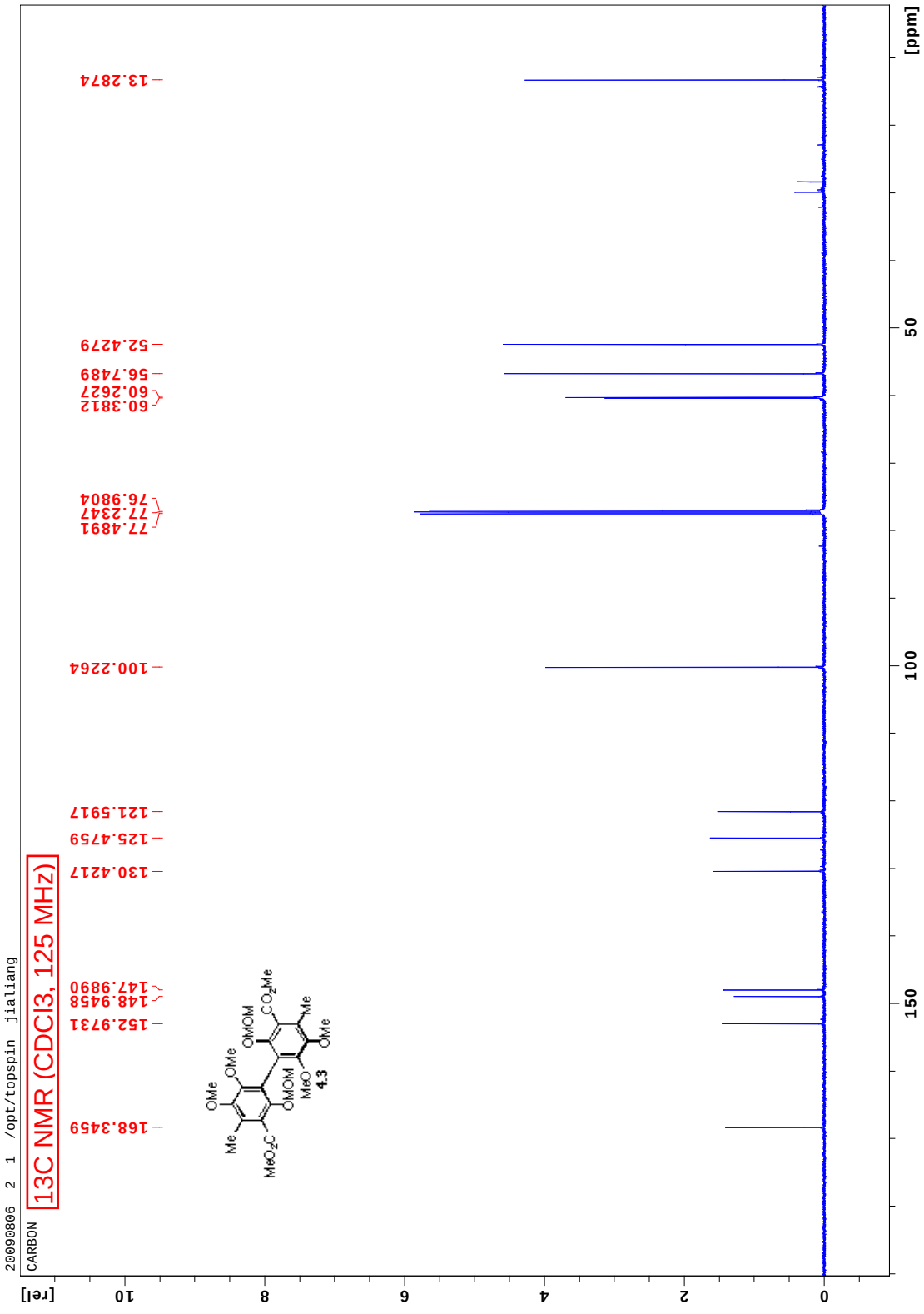

20090512 1 1 /opt/topspin jialiang
PROTON
1H NMR (CDCl3, 500 MHz)
7.2699
2.2776
3.5143
3.7403
3.7916
3.9103
5.9386
6.0000
6.2520
6.2555
4.26
[rel]
[ppm]

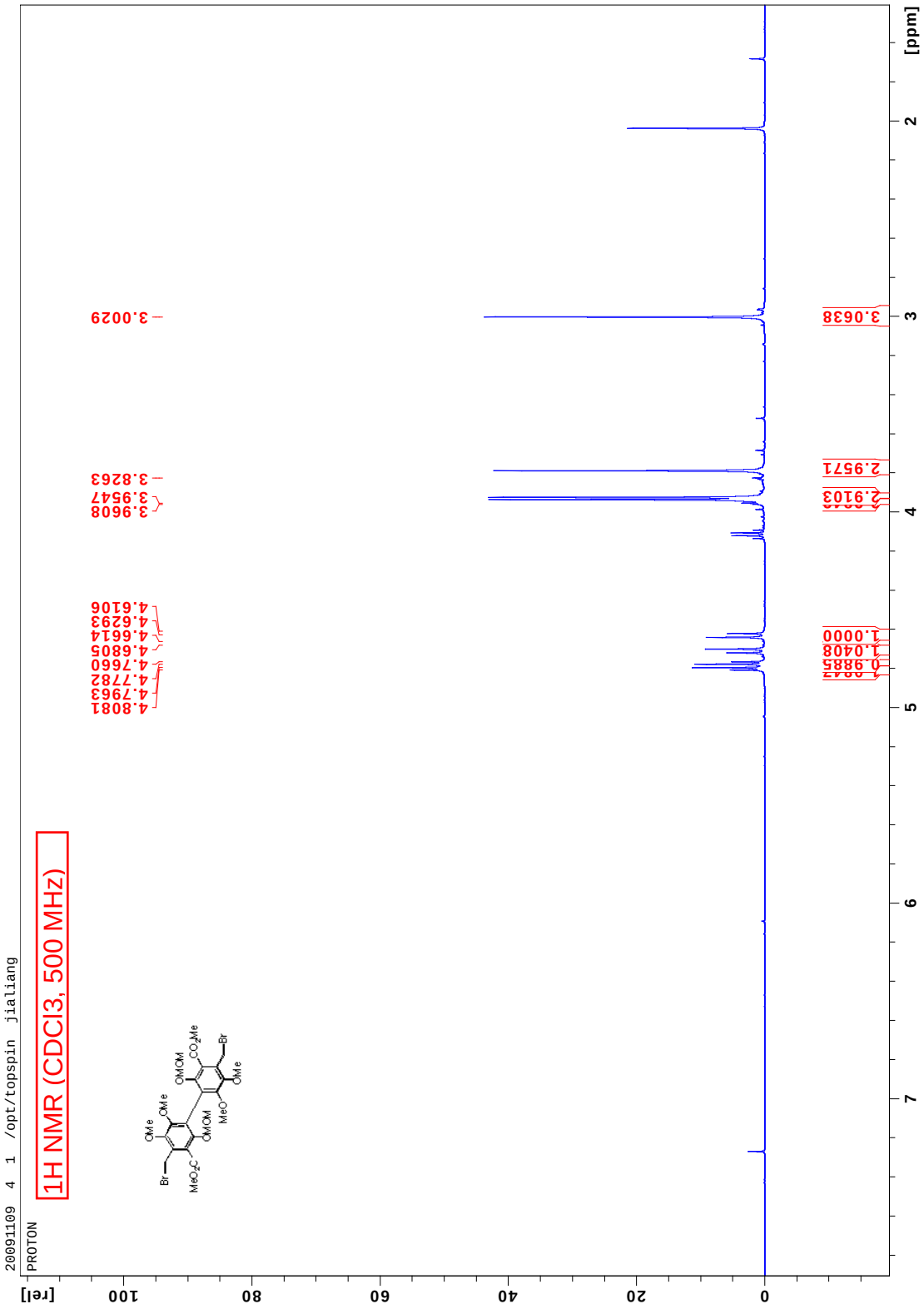

13C NMR (CDCl3, 125 MHz)
20090512 2 1 /opt/topspin jialiang
CARBON
4.26
168.6600
152.9332
151.8104
147.7408
130.3890
124.8342
120.6814
77.4894
77.2362
76.9814
62.0459
60.5765
60.3784
52.4798
13.2427
[rel]
[ppm]

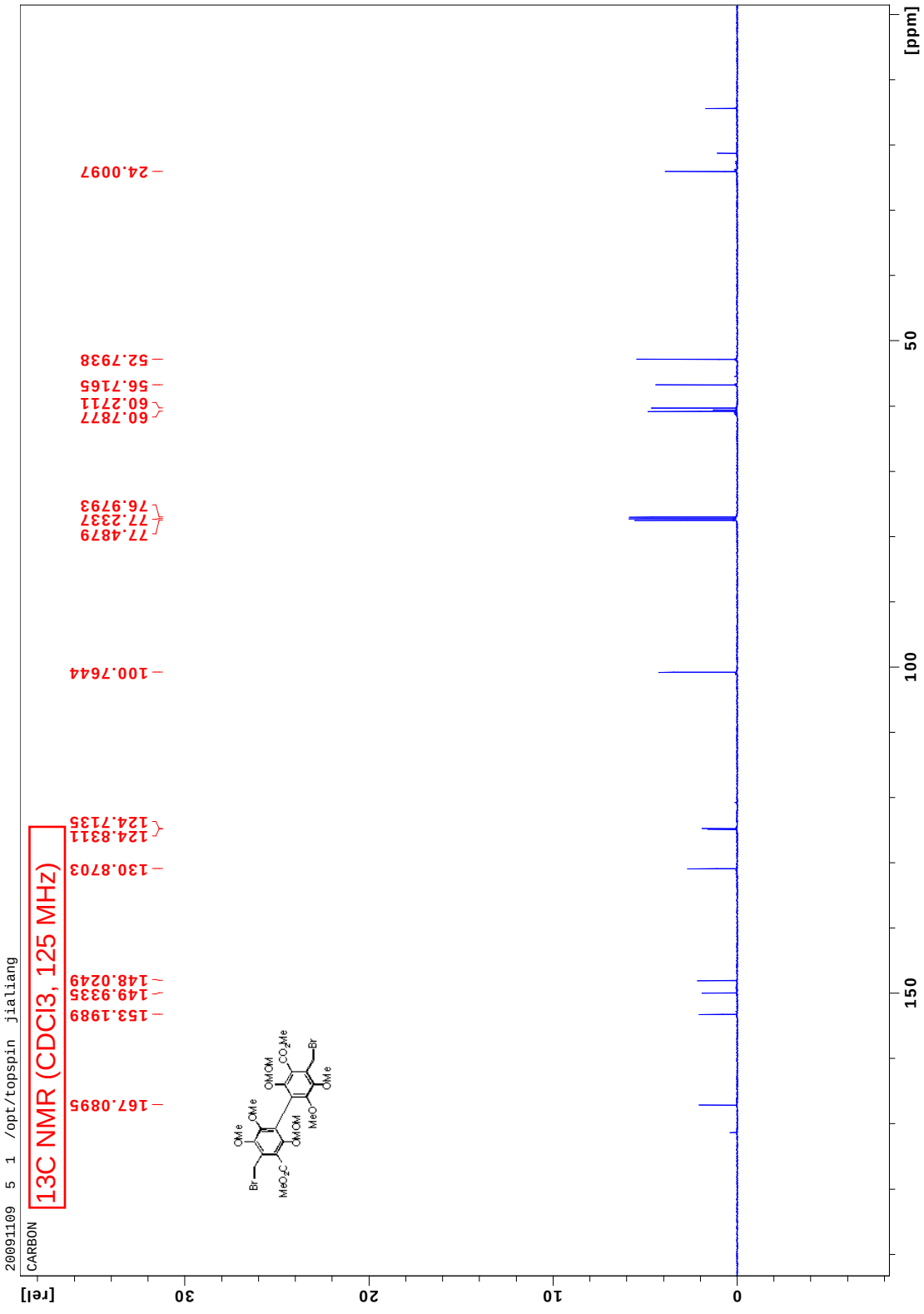

20090812 1 1 /opt/topspin jialiang
PROTON
1H NMR (CDCl3, 500 MHz)
11.4962
7.2710
3.9481
3.7957
3.7606
2.5330
1.0000
2.9611
3.0344
3.0615
4.27
[rel]
[ppm]

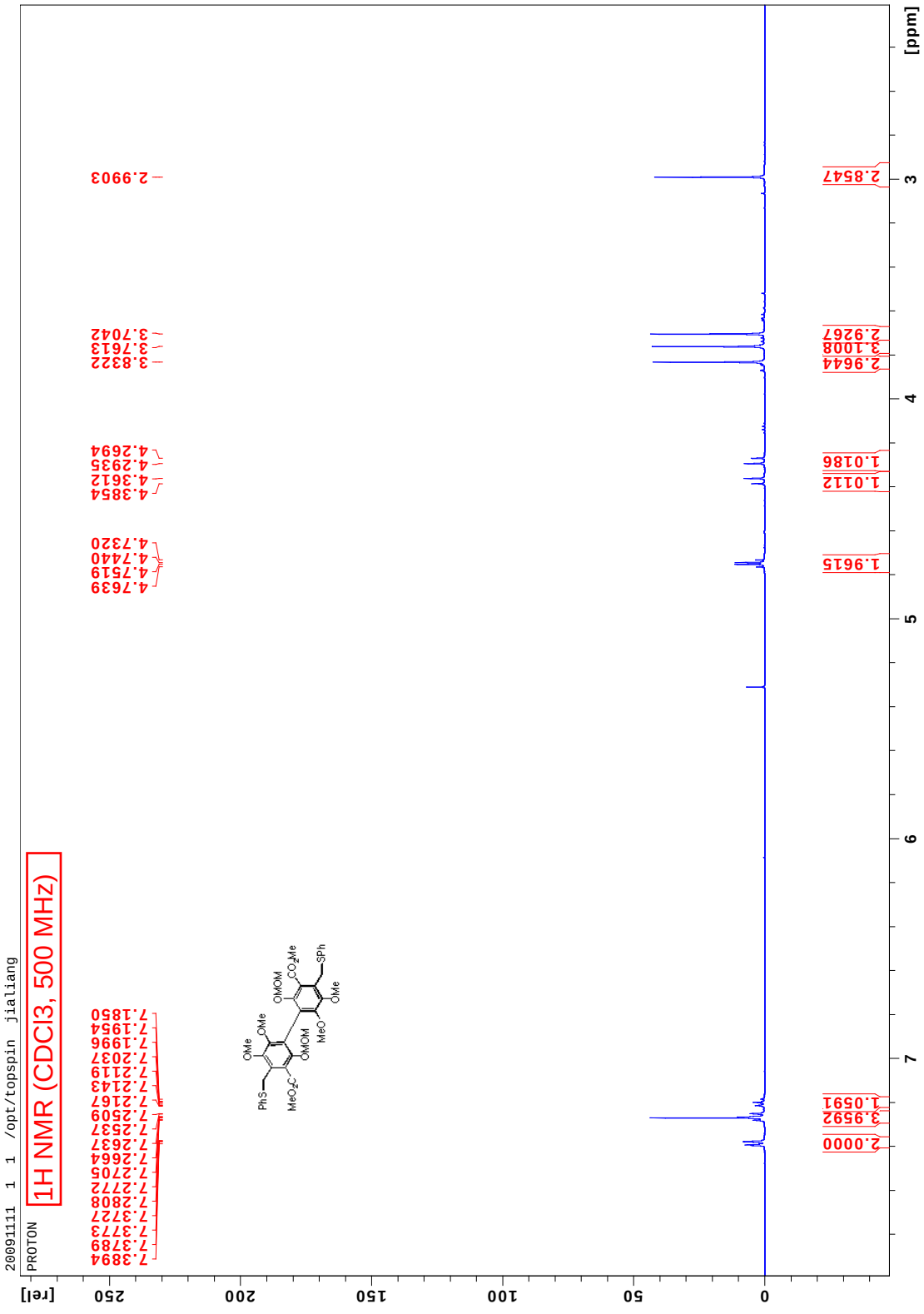

20090812 2 1 /opt/topspin jialiang
CARBON
13C NMR (CDCl3, 125 MHz)
172.4353
158.0071
157.2663
144.6226
134.8019
114.3115
108.4324
60.7486
52.3406
15.1325
4.27
[rel]
0.8
0.6
0.4
0.2
0.0
150
100
50
0 [ppm]

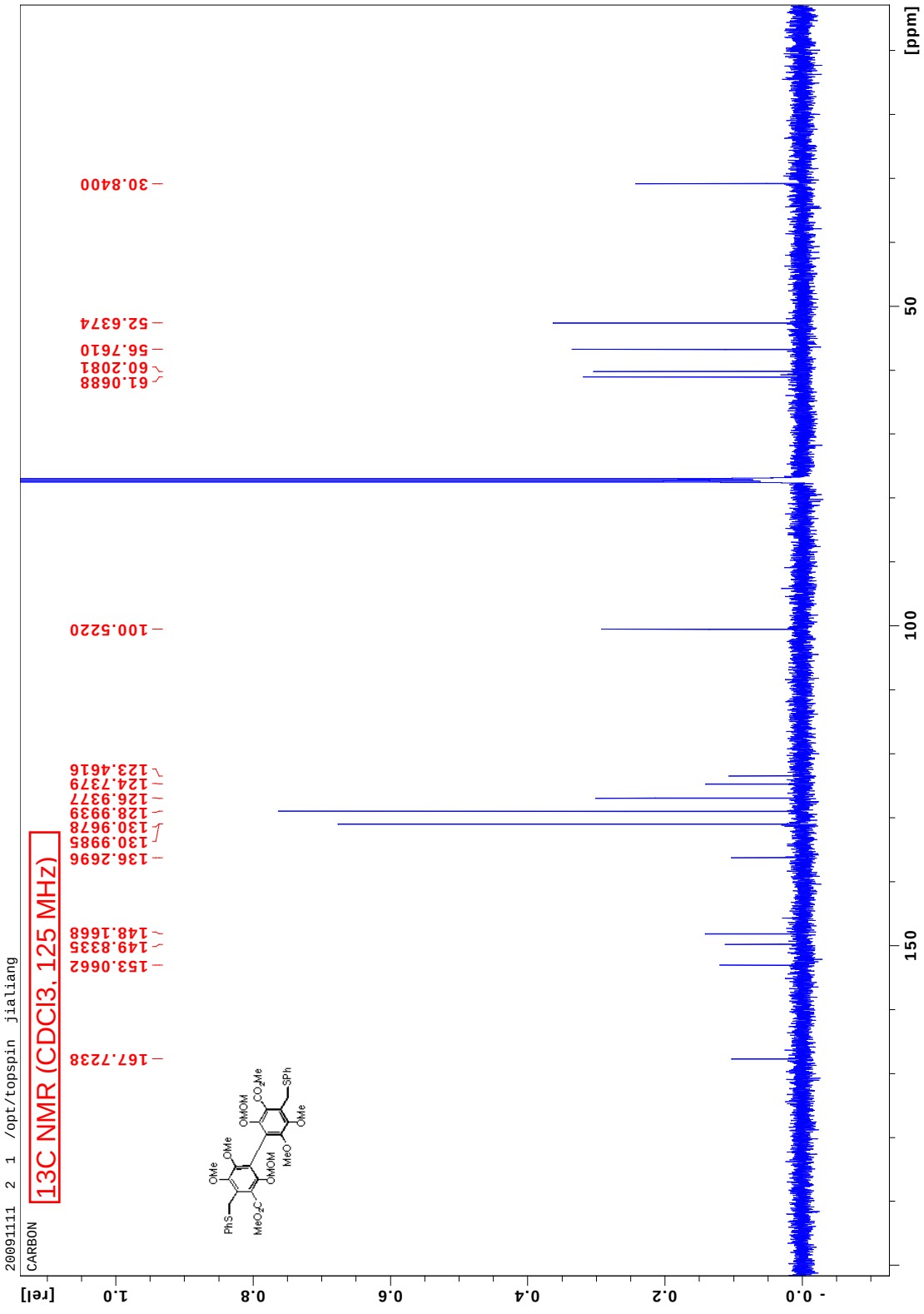

20090806 1 1 /opt/topspin jialiang
PROTON
1H NMR (CDCl3, 500 MHz)
4.7773
4.7656
4.7522
4.7405
3.8800
3.7806
3.7595
3.0703
2.2567
2.0536
3.1653
3.0514
3.0000
3.1892
4.3
[rel]
[ppm]

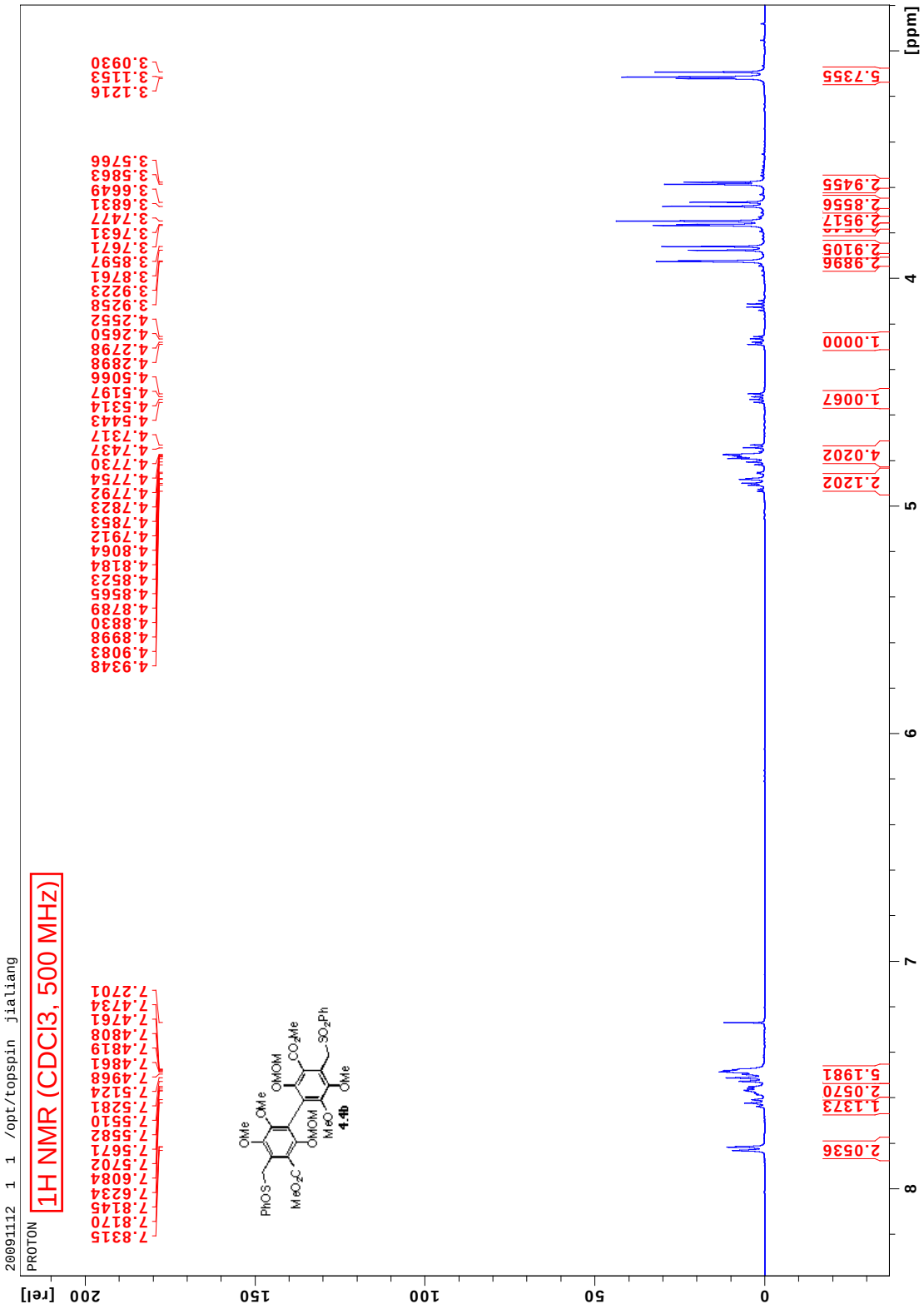

13C NMR (CDCl3, 125 MHz)
20090806 2 1 /opt/topspin jialiang
CARBON
[rel]
[ppm]
168.3459
152.9731
148.9458
147.9890
130.4217
125.4759
121.5917
100.2264
77.4891
77.2347
76.9804
60.3812
60.2627
56.7489
52.4279
13.2874
4.3

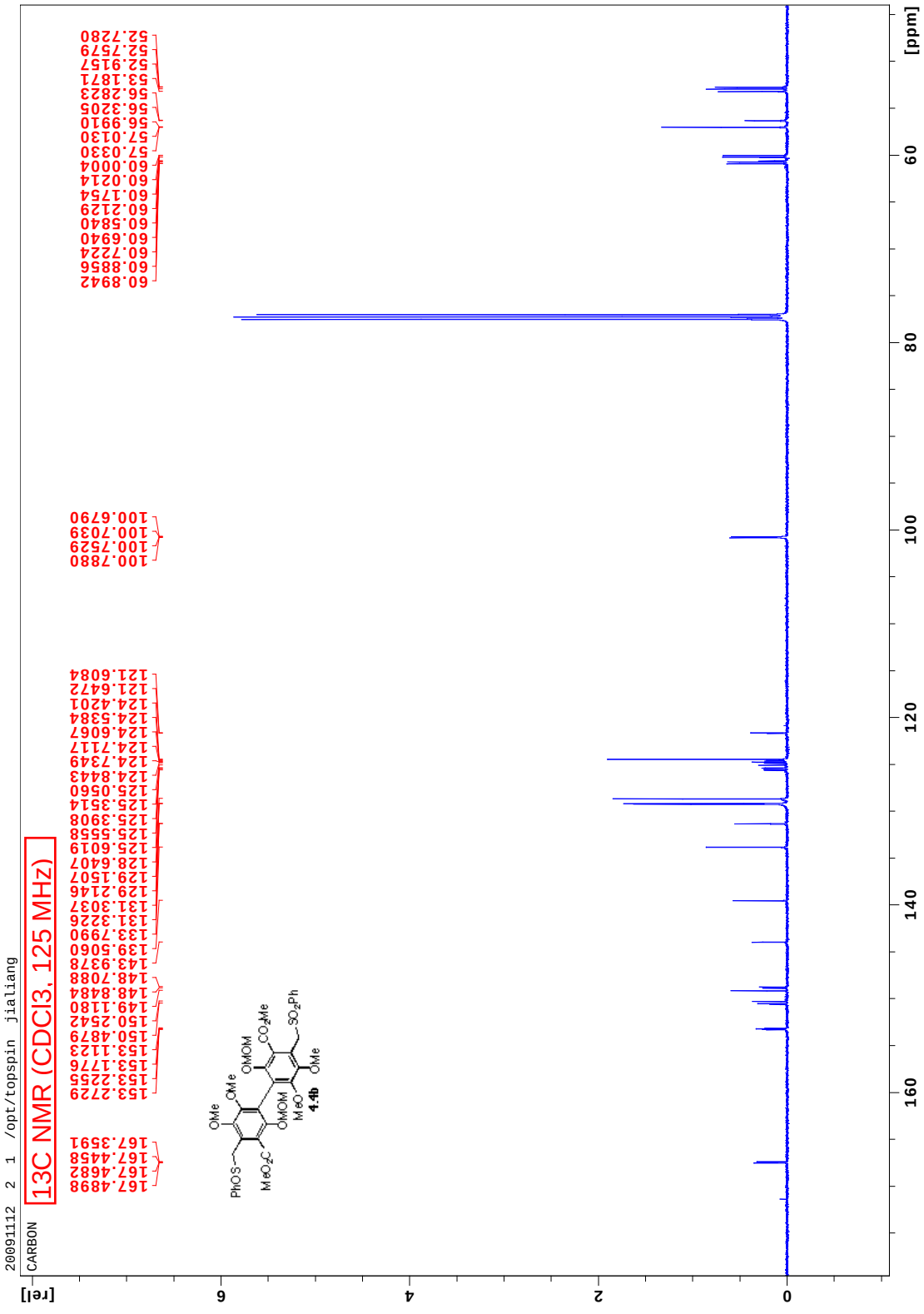

20091109 4 1 /opt/topspin jialiang
PROTON
1H NMR (CDCl3, 500 MHz)
[rel]
[ppm]
4.8081
4.7963
4.7782
4.7660
4.6805
4.6614
4.6293
4.6106
3.9608
3.9547
3.8263
3.0029
1.0000
1.0408
0.9885
2.9103
2.9571
3.0638

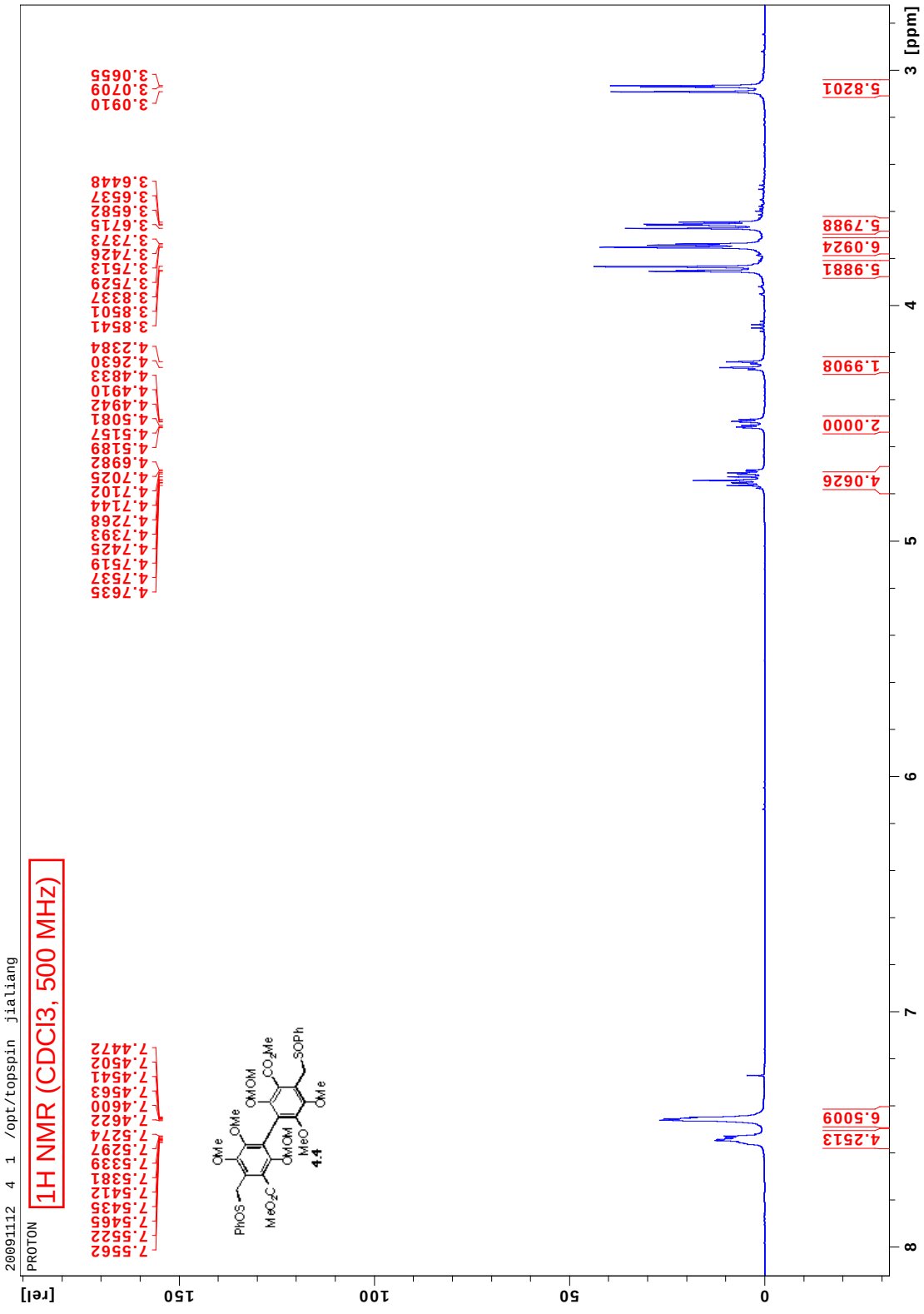

20091109 5 1 /opt/topspin jialiang
CARBON
13C NMR (CDCl3, 125 MHz)
167.0895
153.1989
149.9335
148.0249
130.8703
124.8311
124.7135
100.7644
77.4879
77.2337
76.9793
60.7877
60.2711
56.7165
52.7938
24.0097
[rel]
30
20
10
0
150
100
50
[ppm]


20091111 1 1 /opt/topspin jialiang
PROTON
1H NMR (CDCl3, 500 MHz)
[rel]
[ppm]
7.3894
7.3789
7.3773
7.3727
7.2808
7.2772
7.2705
7.2664
7.2637
7.2537
7.2509
7.2167
7.2143
7.2119
7.2037
7.1996
7.1954
7.1850
4.7639
4.7519
4.7440
4.7320
4.3854
4.3612
4.2935
4.2694
3.8322
3.7613
3.7042
2.9903
2.8547
2.9644
3.1008
2.9267
1.0186
1.0112
1.9615
1.0591
3.9592
2.0000
PhS
MeO2C
OMe
OMe
OMOM
OMOM
CO2Me
MeO
SPh
OMe


13C NMR (CDCl3, 125 MHz)
CARBON
20091111 2 1 /opt/topspin jialiang
[rel]
[ppm]
167.7238
153.0662
149.8335
148.1668
136.2696
130.9985
130.9678
128.9939
126.9377
124.7379
123.4616
100.5220
61.0688
60.2081
56.7610
52.6374
30.8400
OMe
OMe
OMOM
CO2Me
SPh
OMe
MeO
OMOM
MeO2C
PhS


20091112 1 1 /opt/topspin jialiang
PROTON
1H NMR (CDCl3, 500 MHz)
[rel]
[ppm]
4.b


20091112 2 1 /opt/topspin jialiang
CARBON
13C NMR (CDCl3, 125 MHz)
167.4898
167.4682
167.4458
167.3591
153.2729
153.2255
153.1776
153.1123
150.4879
150.2542
149.1180
148.8484
148.7088
143.9378
139.5060
133.7990
131.3226
131.3037
129.2146
129.1507
128.6407
125.6019
125.5558
125.3908
125.3514
125.0560
124.8443
124.7349
124.7117
124.6067
124.5384
124.4201
121.6472
121.6084
100.7880
100.7529
100.7039
100.6790
60.8942
60.8856
60.7224
60.6940
60.5840
60.2129
60.1754
60.0214
60.0004
57.0330
57.0130
56.9910
56.3205
56.2823
53.1871
52.9157
52.7579
52.7280
PhOS
MeO2C
OMe
OMe
OMOM
OMOM
CO2Me
MeO
SO2Ph
OMe
4.4b
[rel]
6
4
2
0
[ppm]
160
140
120
100
80
60


20091112 4 1 /opt/topspin jialiang
PROTON
1H NMR (CDCl3, 500 MHz)
4.44
[rel]
[ppm]
7.5562
7.5522
7.5465
7.5435
7.5412
7.5381
7.5339
7.5297
7.5274
7.4622
7.4600
7.4563
7.4541
7.4502
7.4472
4.7635
4.7537
4.7519
4.7425
4.7393
4.7268
4.7144
4.7102
4.7025
4.6982
4.5189
4.5157
4.5081
4.4942
4.4910
4.4833
4.2630
4.2384
3.8541
3.8501
3.8337
3.7529
3.7513
3.7426
3.7373
3.6715
3.6582
3.6537
3.6448
3.0910
3.0709
3.0655
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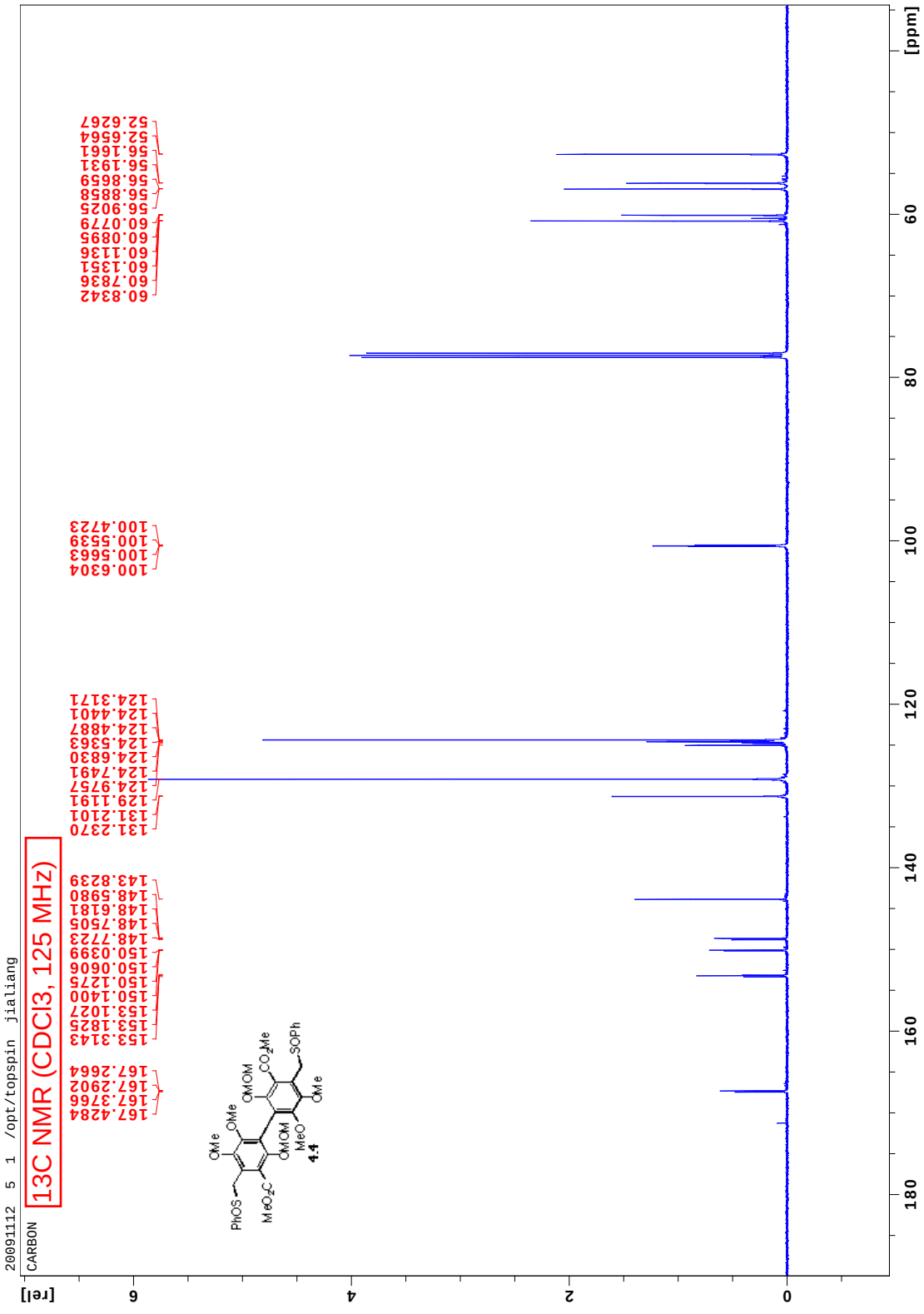
5.7988
6.0924
5.9881
1.9908
2.0000
4.0626
4.2513
6.5009


13C NMR (CDCl3, 125 MHz)
20091112 5 1 /opt/topspin jialiang
CARBON
[rel]
[ppm]
167.4284
167.3766
167.2902
167.2664
153.3143
153.1825
153.1027
150.1400
150.1275
150.0606
150.0399
148.7723
148.7505
148.6181
148.5980
143.8239
131.2370
131.2101
129.1191
124.9757
124.7491
124.6830
124.5363
124.4887
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124.3171
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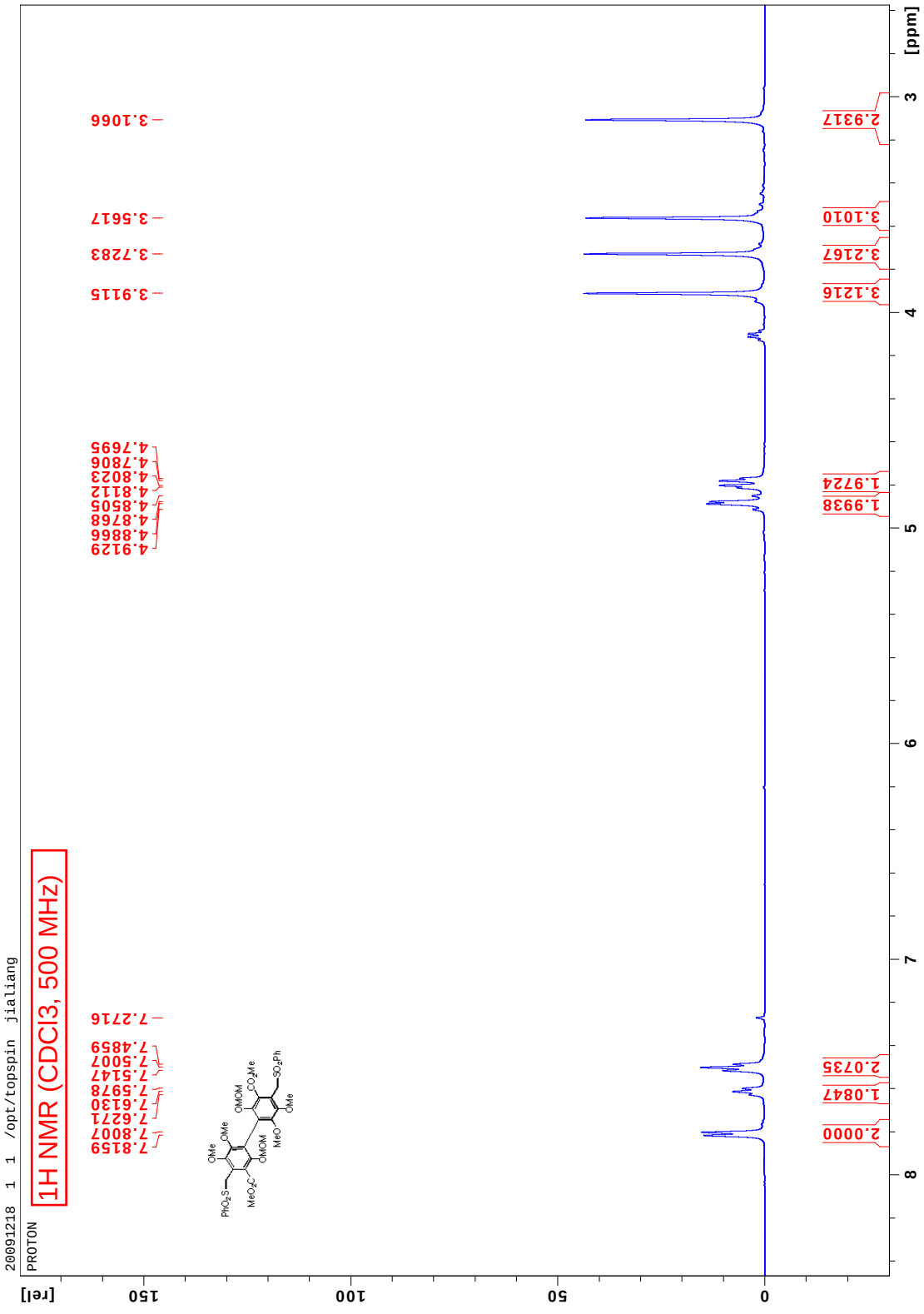
100.5663
100.5539
100.4723
60.8342
60.7836
60.1351
60.1136
60.0895
60.0779
56.9025
56.8858
56.8659
56.1931
56.1661
52.6564
52.6267
PhOS
MeO2C
OMe
OMe
OMOM
OMOM
CO2Me
MeO
SOPh
OMe
4.4


20091218 1 1 /opt/topspin jialiang
PROTON
1H NMR (CDCl3, 500 MHz)
7.8159
7.8007
7.6271
7.6130
7.5978
7.5147
7.5007
7.4859
7.2716
4.9129
4.8866
4.8768
4.8505
4.8112
4.8023
4.7806
4.7695
3.9115
3.7283
3.5617
3.1066
2.0000
1.0847
2.0735
1.9724
1.9938
3.1216
3.2167
3.1010
2.9317
[rel]
150
100
50
0
[ppm]
3
4
5
6
7
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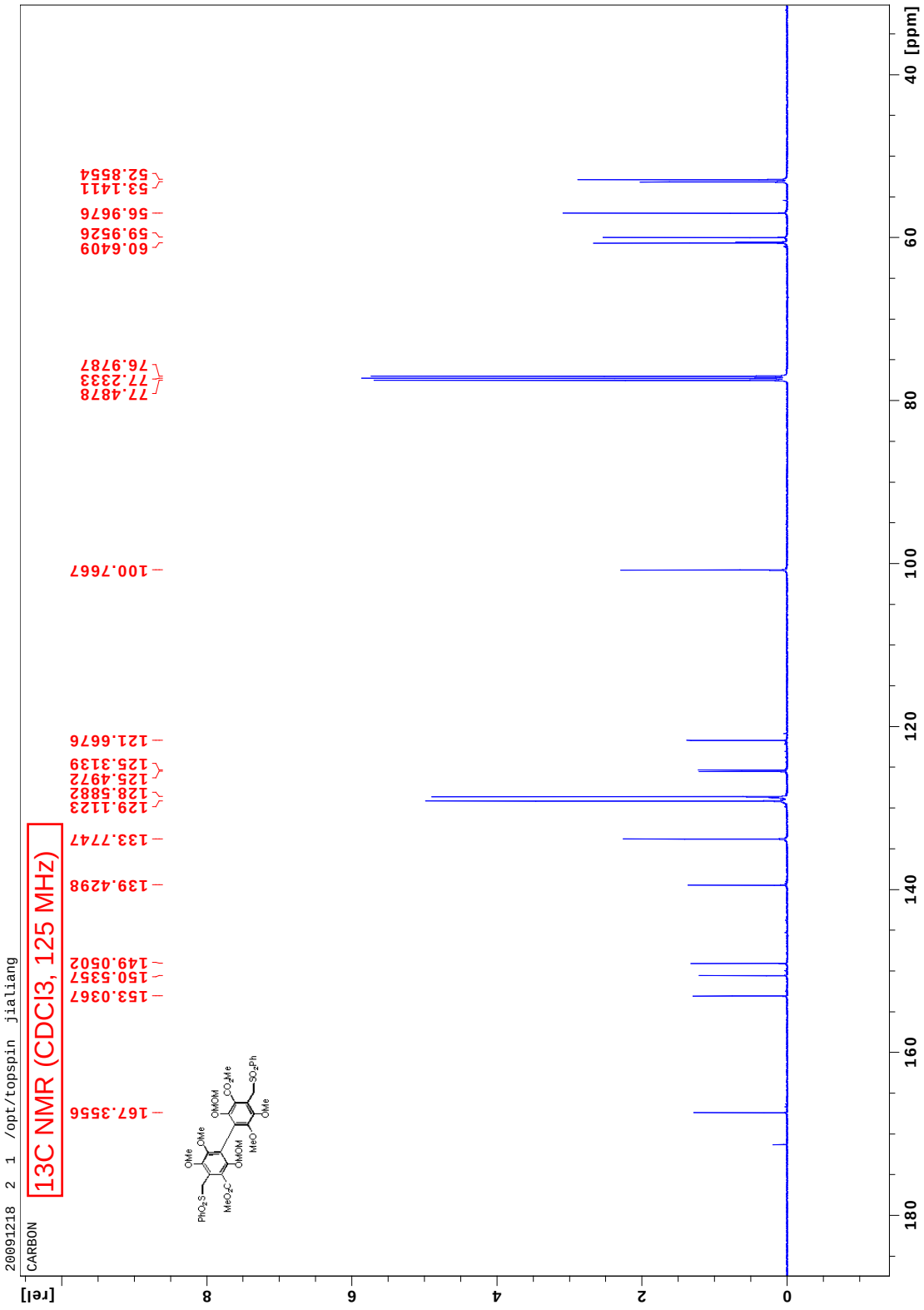
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20091218 2 1 /opt/topspin jialiang
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153.0367
150.5357
149.0502
139.4298
133.7747
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128.5882
125.4972
125.3139
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77.4878
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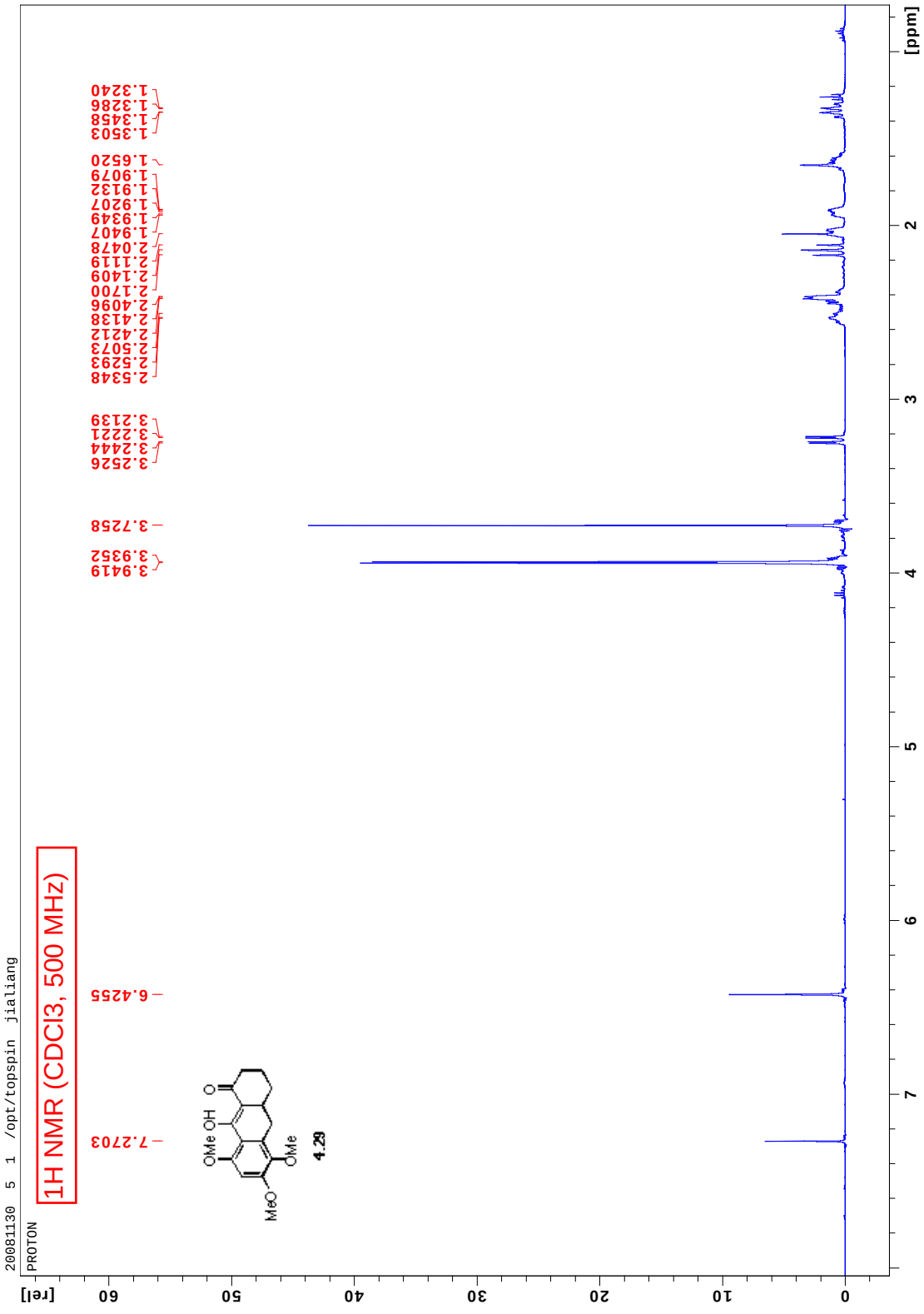
53.1411
52.8554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3.9419
3.9352
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3.2526
3.2444
3.2221
3.2139
2.5348
2.5293
2.5073
2.4212
2.4138
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2.0478
1.9407
1.9349
1.9207
1.9132
1.9079
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OH
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MeO
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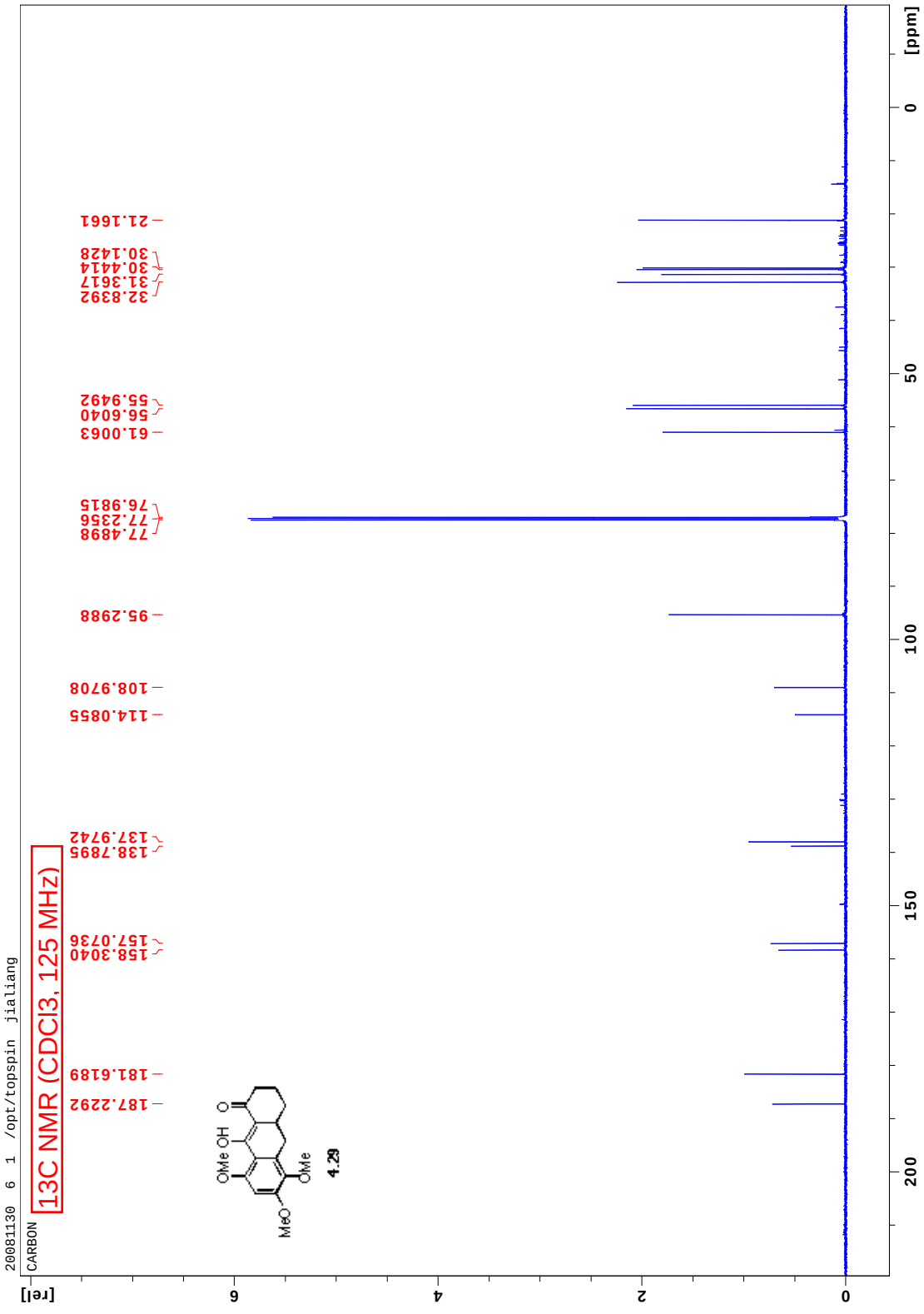
[ppm]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MeO
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157.0736
138.7895
137.9742
114.0855
108.9708
95.2988
77.4898
77.2356
76.9815
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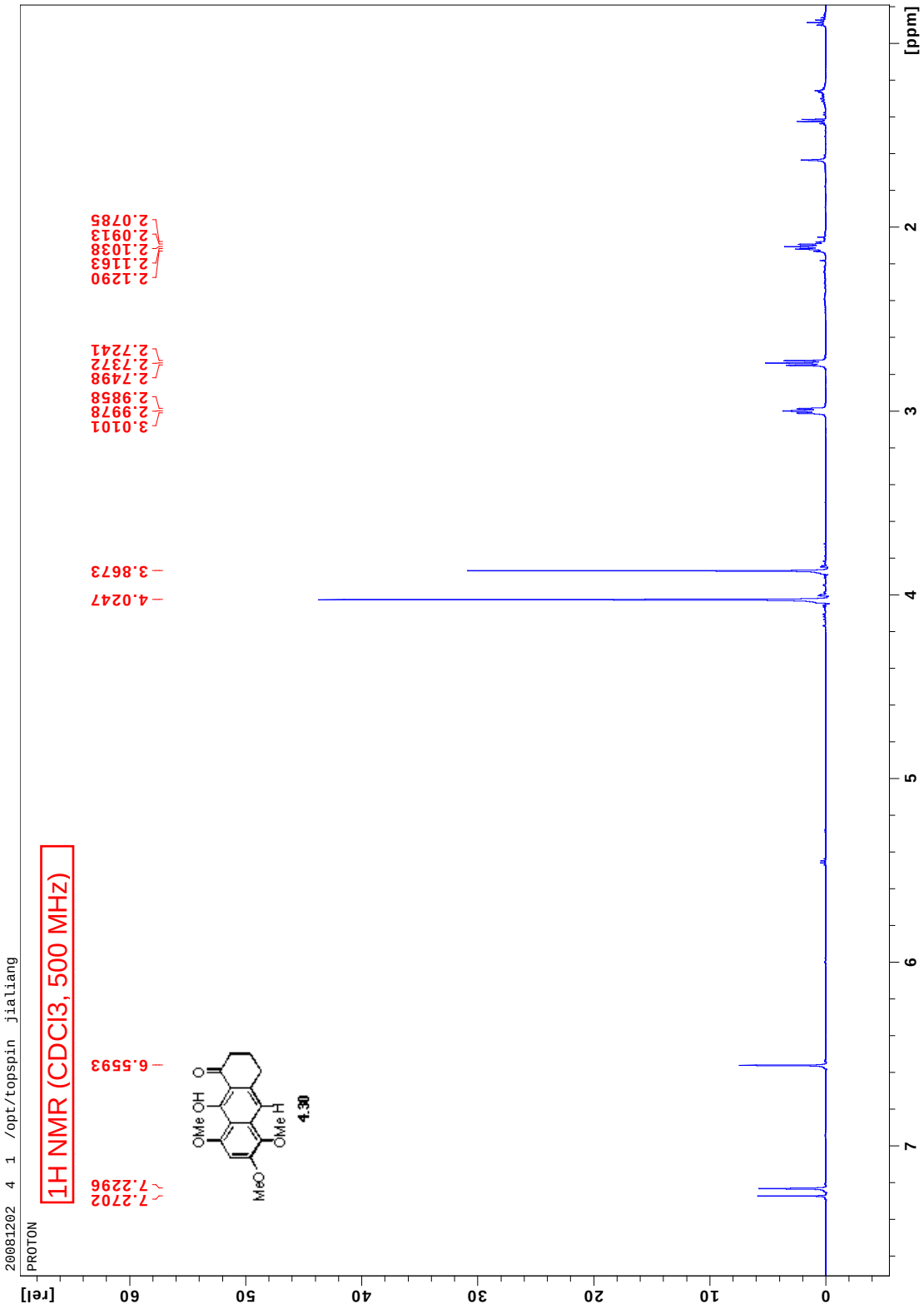
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3.8673
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3.0101
2.9978
2.9858
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2.1290
2.1163
2.1038
2.0913
2.0785
4.30
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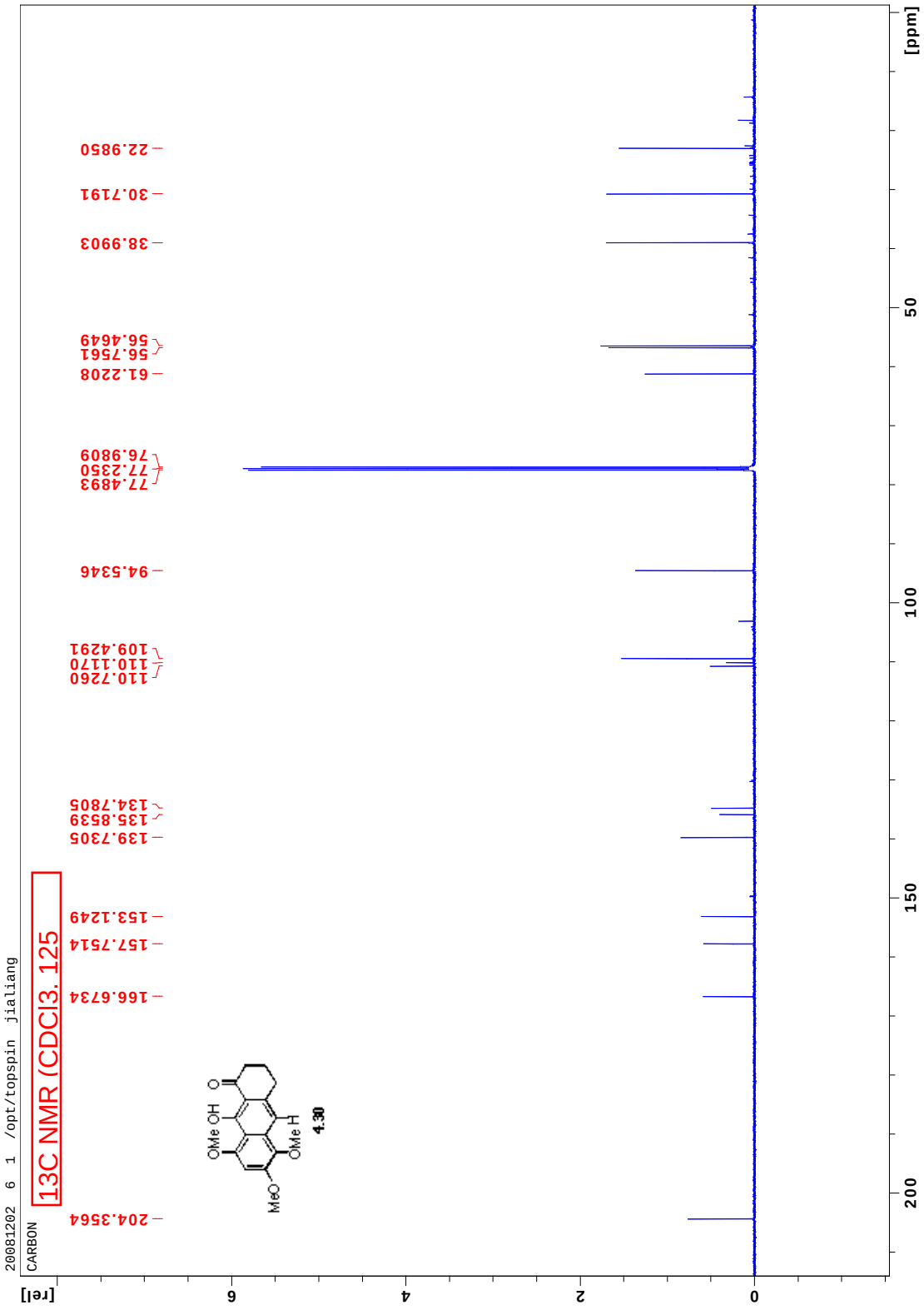
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139.7305
135.8539
134.7805
110.7260
110.1170
109.4291
94.5346
77.4893
77.2350
76.9809
61.2208
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OMe H
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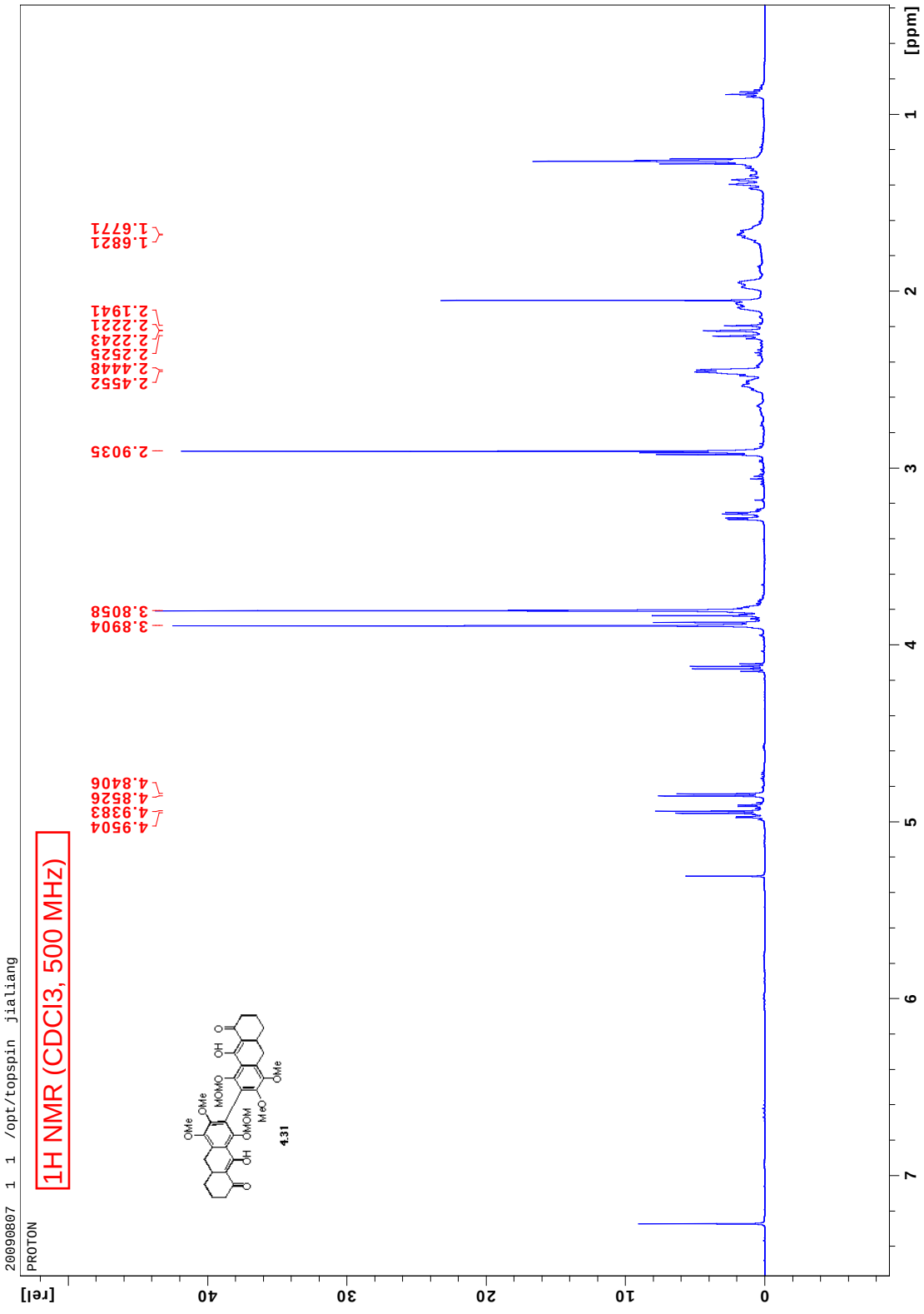
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4.8526
4.8406
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2.9035
2.4552
2.4448
2.2525
2.2243
2.2221
2.1941
1.6821
1.6771
OMe
OMe
MOMO
OH
O
OH
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20
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1
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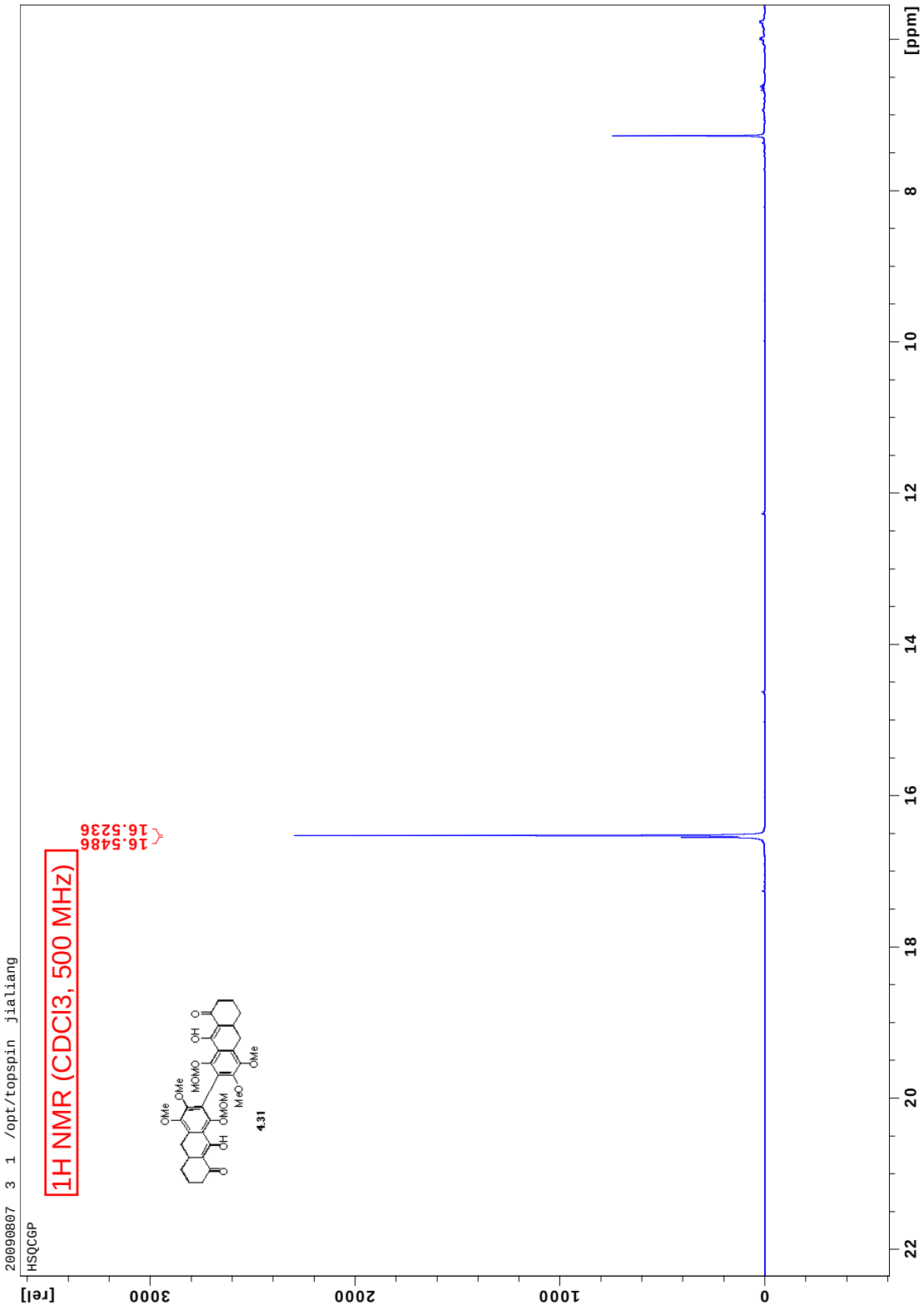
6
7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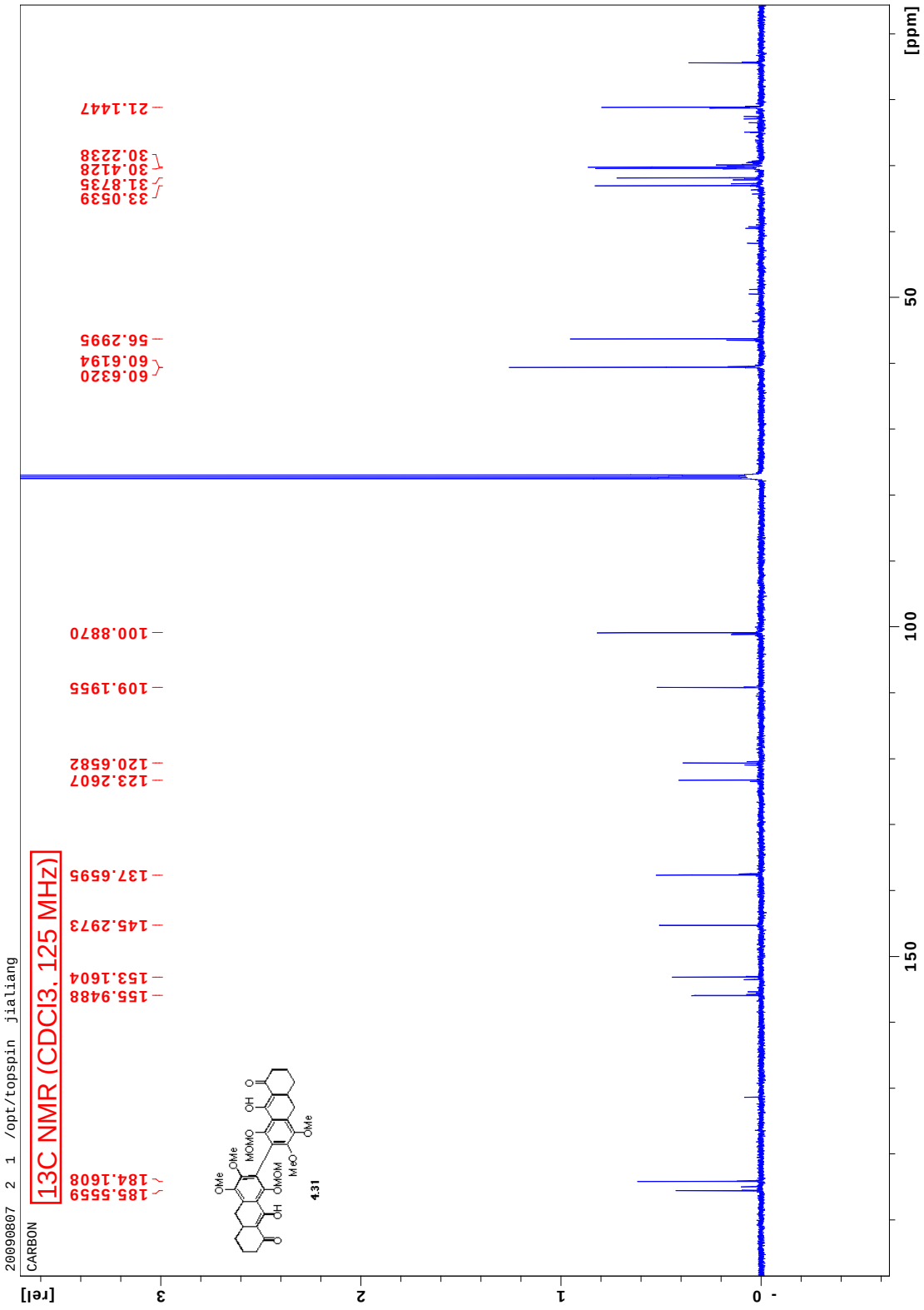
3000
2000
1000
0
[ppm]
22
20
18
16
14
12
10
8


20090807 2 1 /opt/topspin jialiang
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155.9488
153.1604
145.2973
137.6595
123.2607
120.6582
109.1955
100.8870
60.6320
60.6194
56.2995
33.0539
31.8735
30.4128
30.2238
21.1447
OMe
OMe
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OH
O
OMe
4.31
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3
2
1
0
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150
100
50

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