Stony Brook University

Development and Application of Chiral Biphenol-based Diphosphinite Ligands to Pd-Catalyzed Asymmetric Allylic Substitution Reactions

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Yang Zang

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Yang Zang

We, the dissertation committee for the above candidate for the

Doctor of Philosophy degree, hereby recommend

acceptance of this dissertation.

Professor Iwao Ojima
Dissertation Advisor
Department of Chemistry

Professor Jonathan G. Rudick
Chairperson of Defense
Department of Chemistry

Professor Joseph W. Lauher
Third Member
Department of Chemistry

Professor Yu Chen
Outside Member
Department of Chemistry and Biochemistry
Queens College, City University of New York

This dissertation is accepted by the Graduate School

Charles Taber
Dean of the Graduate School

Abstract of the Dissertation

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In the past decade, libraries of chiral biphenol-based phosphite, phosphoramidite, and diphosphinite ligands have been designed and developed in our laboratory. These ligands are easy to prepare and fine-tunable through modification of the groups at the 3,3'-positions and the substituents attached to the phosphorous atoms. Therefore, our chiral ligand system is suitable for new and specific asymmetric reactions to follow the rapid progress in modern synthetic organic chemistry, e.g., the asymmetric allylic substitution reactions. As an exploration of the scope of the applications of our chiral ligands, we studied the Pd-catalyzed asymmetric allylic etherification in the most critical step to introduce the chiral centers to the key intermediates for the total synthesis of (-)-galanthamine. Galanthamine, an amaryllidaceae alkaloid, is a centrally acting reversible inhibitor of acetylcholinesterase, which has been used for the treatment of mild to moderate Alzheimer's disease.

We also applied our highly efficacious biphenol-based diphosphinite ligands to the Pd-catalyzed asymmetric allylic amination for the synthesis of chiral bicyclic and tetracyclic alkaloids, the similar intermediates to amaryllidaceae alkaloids such as crinine, montanine,

lycorine and pancratistatin. These alkaloids exhibited antitumor, antibacterial, antifungal, antiviral, antimalarial, antidepressive and anticonvulsive activities.

Additionally, cyclopentenediynes and cycloheptenediynes substrates were synthesized. One of the substrates was investigated in the Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction.

TABLE OF CONTENTS

Chapter 3

Pd-Catalyzed Asymmetric Allylic Amination Using Chiral BOP Ligands and Its Application for The Syntheses of Bicyclic and Tricyclic Alkaloids

Chapter 4

The Synthesis of Enediynes and Their Applications to Rh(I)-Catalyzed [2+2+2+1] Cycloaddition Reactions

LIST OF FIGURES

Chapter 1

Chapter 2

Chapter 3

Chapter 4

LIST OF SCHEMES

Chapter 1

Chapter 2

Chapter 3

Chapter 4

LIST OF TABLES

Chapter 2

Chapter 3

LIST OF ABBREVIATIONS

Ac	acetyl
Ache	acetylcholine esterase
AcOEt	ethyl acetate
atm	atmosphere
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binapthyl
Boc	*tert*-butyl carbonate
BOP	biphenol-based diphosphinite
bp	boiling point
brs	broad singlet
calcd.	calculated
CAMP	methylcyclohexyl-o-anisylphosphine
Celite®	diatomaceous earth filter reagent, ®Celite Corp.
COD	1,5-cyclooctadiene
CO	carbon monoxide
d	doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
DIOP	(+)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPAMP	ethane-1,2-diybis[(2-methoxyphenyl)phenylphosphane]
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
DMF	dimethylformamide
L-DOPA	(*S*)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid
DPPBA	diphenylphosphino benzoic acid
dppp	diphenylphosphino propane
Du-PHOS	(+)-1,2-bis[(2*S*, 5*S*)-2,5-dimethylphospholano]benzene
ee	enantiomeric excess
EI	electron impact
ESI	electrospray ionization
Et	ethyl
Et_2O	ethyl ether
g	gram
GC-MS	gas chromatography mass spectrometry
h	hour
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
J	coupling constant
L	liter
LC-MS	liquid chromatography mass spectrometry
Me	methyl

MeOH	methanol
min	minute
mmol	millimole
mol	mole
M	molarity
mg	milligram
MHz	mega hertz
mL	milliliters
mp	melting point
Ms	mesylate
MW	molecular weight
NMR	nuclear magnetic resonance
2-Ns	2-nitrobenzenesulfonylate
Ph	phenyl
ppm	parts per million
q	quartet
Red-Al®	sodium bis(2-methoxyethoxy)aluminumhydride
rt	room temperature
s	singlet
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TBDPMS	*tert*-butyldiphenylsilyl
TEA	triethylamine
TFA	trifluroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
Ts	tosylate

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Last but not least, I would like to give my deepest gratitude to my entire family, my grandparents, my parents, my uncles and aunts. Thank you for caring me, supporting me, inspiring me and encouraging me for all these years.

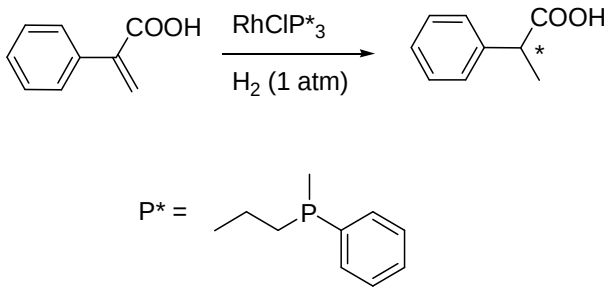
Chapter 1

Introduction and Synthesis of Bidentate Phosphorous Ligands for Asymmetric Synthesis

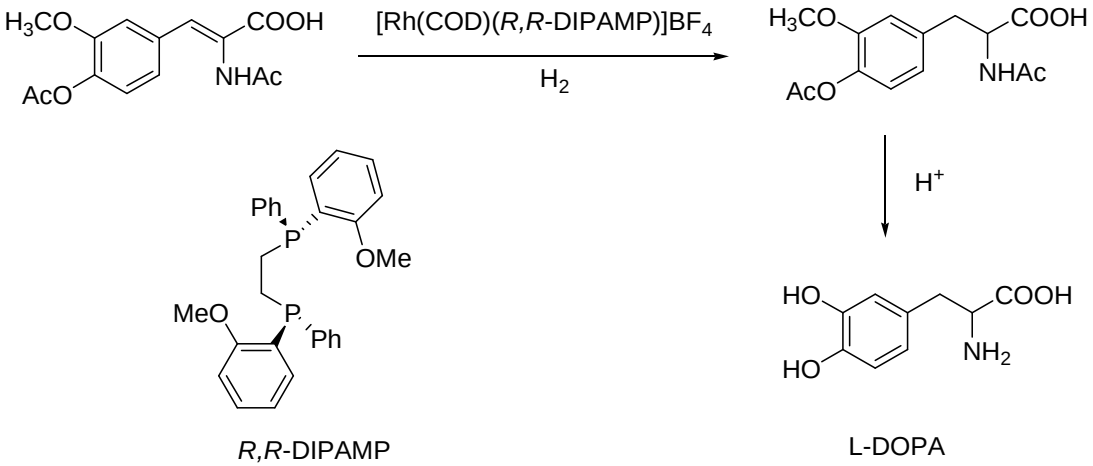
§1.1 History of phosphorous ligands for asymmetric synthesis

Asymmetric synthesis is defined by IUPAC as "a chemical reaction (or reaction sequence) in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts."[1] The recent decades have witnessed asymmetric synthesis fast development. Today, asymmetric synthesis plays an important role in the field of pharmaceuticals and agrochemicals, which is accomplished by chiral auxiliaries, chiral pool synthesis, biocatalysis, and enantioselective catalysis. Among these approaches, enantioselective catalysis is widely used in industrial-scale syntheses due to the high efficacy of chiral catalysts at low concentrations.[2-4] These catalysts are usually made of transition metals and chiral ligands which create an asymmetric environment for the transformation of prochiral compounds to chiral and non-racemic ones.

Metal-catalyzed enantioselective catalysis involving chiral ligands was pioneered by William S. Knowles in 1968. He replaced the triphenylphosphine in Wilkinson's catalyzed with chiral (-)-methylpropylphenylphosphine (69% optical purity). This modified catalyst was applied to the asymmetric hydrogenation of atropic acid, giving hydratropic acid in 15% ee (Scheme 1-1).[5] Although the enantioselectivity was moderate, his work demonstrated that asymmetric synthesis had entered the modern age. Several years later, more efficient chiral phosphine ligands, such as CAMP and DIPAMP were developed by optimization of chiral methylpropylphenylphosphine and employed in the commercial synthesis of 3,4-dihydroxyphenylalanine (L-DOPA), a drug used for treating Parkinson's disease (Scheme 1-2).[6-7] For the work on chirally catalysed hydrogenation reactions, Knowles shared the Nobel Prize in Chemistry in 2001.



Scheme 1-1. Asymmetric hydrogenation of atropic acid



Scheme 1-2. Asymmetric synthesis of L-DOPA

In the following years, a good number of chiral phosphorous ligands were designed and prepared, e.g. DIOP,[8] BINAP,[9] Du-PHOS,[10] DPPBA[11] (Figure 1-1). All of them are bidentate with C_2-symmetry. Compared to monodentate phosphorous ligands, bidentate ones are able to form more rigid complexes with center metals by chelation, leading to the good performance on the asymmetric hydrogenation of various prochiral substrates bearing carbon-carbon and carbon-heteroatom double bonds. Therefore, bidentate ligands dominate the field of asymmetric synthesis to date.

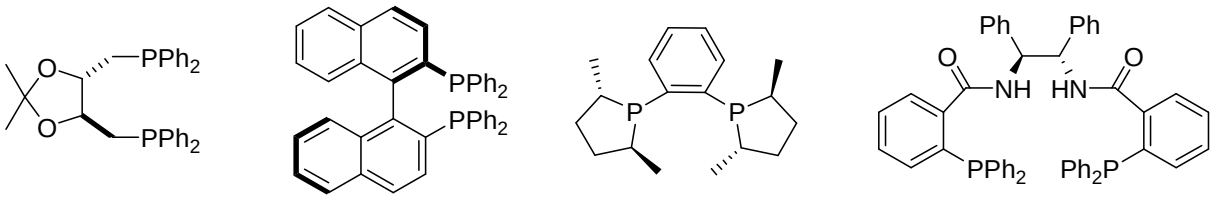
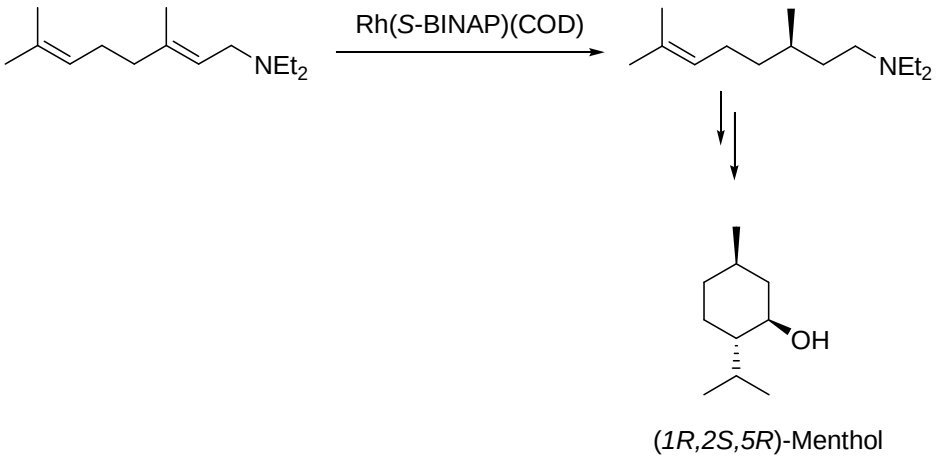


Figure 1-1. Bidentate phosphorous ligands

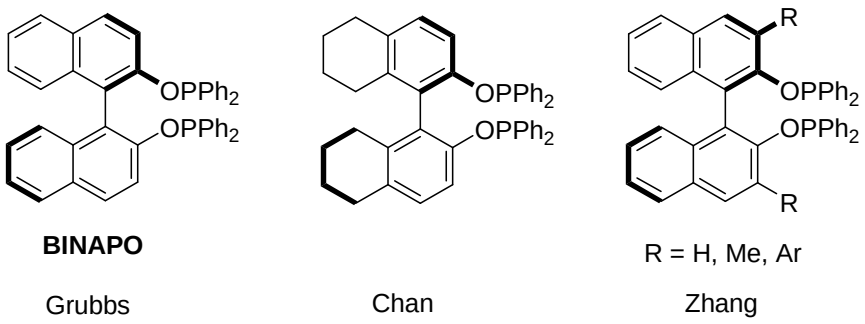
Among these C_2-symmetrical diphosphorous ligands, BINAP which has a binapthalene skeleton turned out to be well suited for the demand of industrial synthesis. Each year 3000 tons of enantiomerically pure menthol are produced by Takasago International Corporation using

((*S*)-BINAP)Rh(COD) catalyst (Scheme 1-3).[12] Due to the development of the feasible BINAP ligands, Ryoji Noyori shared half of the Nobel Prize in Chemistry in 2001 with William S. Knowels.



Scheme 1-3. Asymmetric synthesis of enantiomerically pure menthol

Because of the great efficacy of BINAP ligands, many chiral bidentate phosphorous ligands were designed and developed based on the scaffolds of astropisomeric biaryls.[13] A good example is BINAPO (Figure 1-2), reported by Grubbs in 1977.[14] At the beginning, it was supposed to be an alternative to BINAP for transition metal-catalyzed asymmetric hydrogenation. However, BINAPO did not demonstrate the same efficacy as BINAP. A plausible reason is that the chelating ring (9-membered ring) of metal-BINAPO complex is larger than that of the metal-BINAP complex making the conformation more flexible. To make it more rigid, Chan modified the biaryl skeleton by using H_8-binapthol (Figure 1-2).[15,16] Meanwhile, Zhang introduced substituents on the 3,3'-positions of the binapthol moiety (Figure 1-2).[17,18] These modifications result in higher enantioselectivity in certain asymmetric hydrogenation reactions. Interestingly, BINAPO was found to be more effective in Pd-catalyzed asymmetric allylic substitution reactions.[19-22] The large chelating ring renders not only a flexible conformation but also a large bite angle (P-M-P) which makes the PAr_2 moiety moving towards the palladium π-allyl complex (Figure 1-3).



BINAPO

Grubbs Chan Zhang

Figure 1-2. BINAPO-type ligands

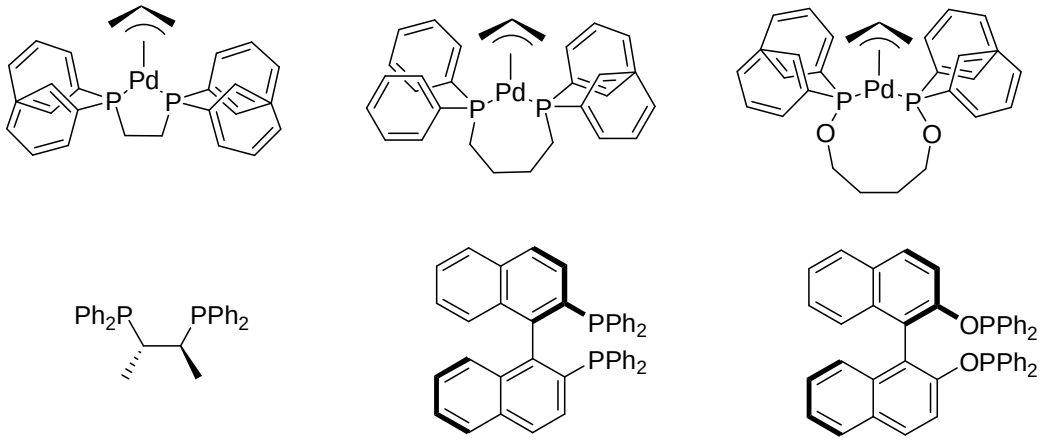


Figure 1-3. Palladium π-allyl complexes

§1.2 Development of chiral biphenol-based diphosphinite ligands

Discovery of simple and fine-tunable chiral ligands to a specific reaction is more popular in the asymmetric synthesis than a super ligand for all organic reactions. Based on this concept, we have been developing a new class of chiral biphenol-based diphosphinite ligands (BOP ligands) since 2008 (Figure 1-4). One of the salient features of BOP ligands is their fine-tuning capability through modification of the substituents at the 3,3'-positions of the biphenyl moiety as well as the aromatic groups attached to the phosphorus atoms (Figure 1-4). Different substituents have different steric and electronic effects. Additionally, The methyl groups at the 5,5',6,6'-positions "acting as a lock" freeze the rotation of the biphenol backbone (Figure 1-4). Indeed,

these novel BOP ligands have exhibited excellent efficacy in intramolecular and intermolecular palladium-catalyzed asymmetric allylic amination (Pd-AAA) reaction.[23,24] For example, 96% ee was achieved in the synthesis of 6,7-dimethoxy-1-vinyltetrahydroisoquinoline which is a key intermediate for the total synthesis of marine natural products, Schulzeines A-C (Scheme 1-4).[23] The same enantioselectivity was obtained in the crucial step for the synthesis of Strychnos indole alkaloids compared to only 84% ee when BINAPO ligands were used (Scheme 1-5).[22,24]

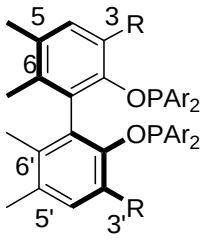
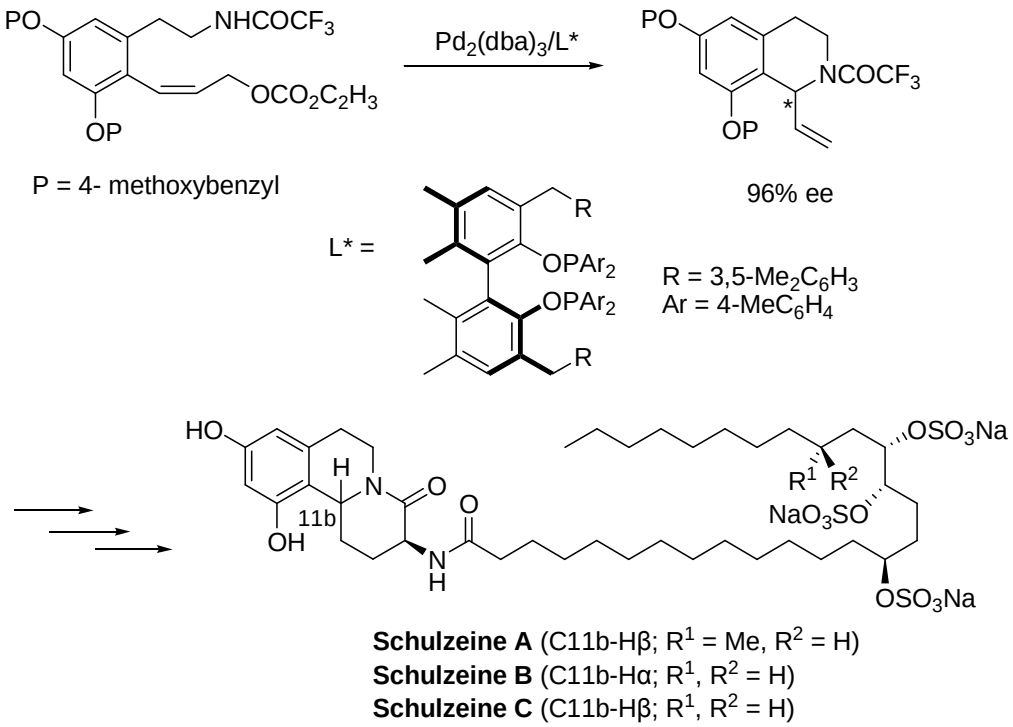
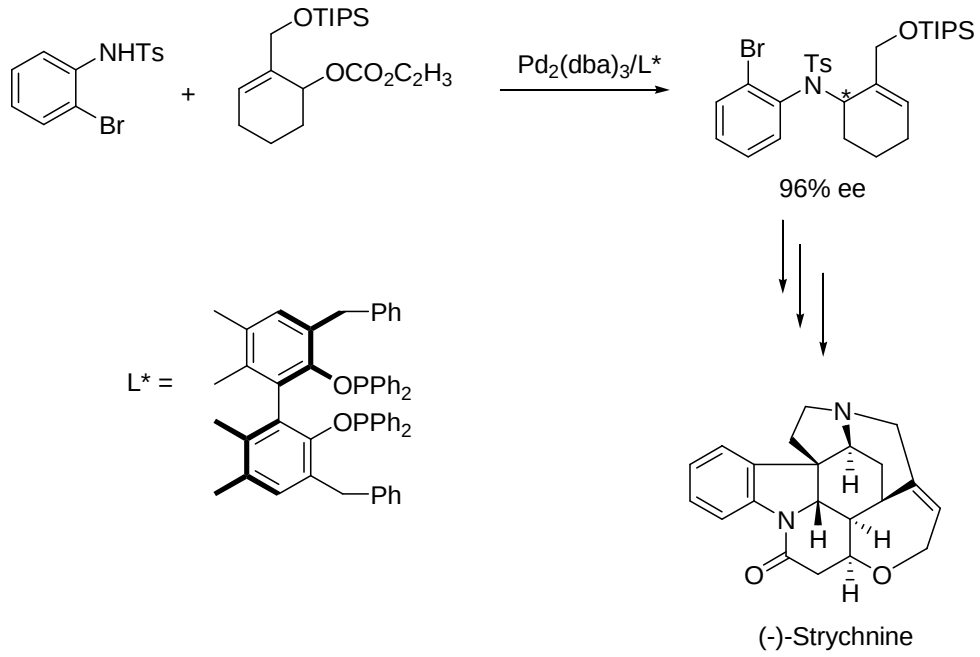


Figure 1-4. Fine-tunable BOP Ligands



Scheme 1-4. Enantioselective synthesis of 1-vinyltetrahydroisoquinoline

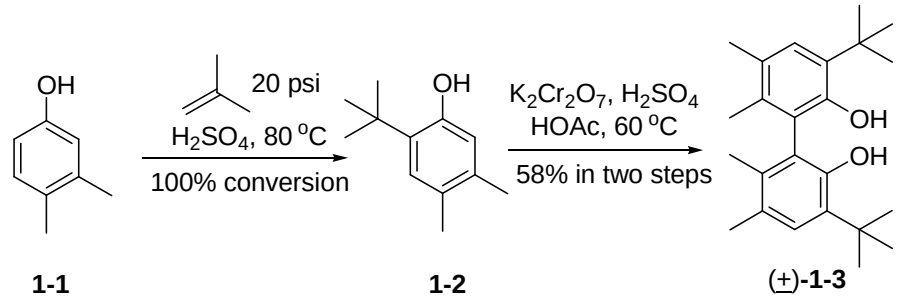


Scheme 1-5. Enantioselective synthesis of cyclohexenyl amine

§1.3 Results and discussion

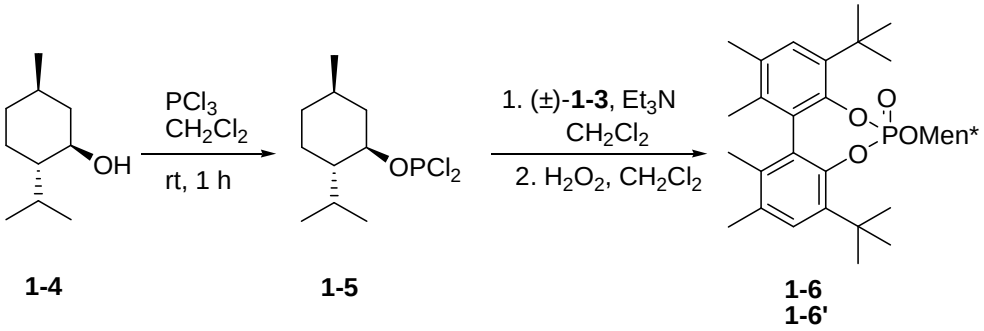
§1.3.1 Synthesis of enantiopure 5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol

Starting from 3,4-dimethylphenol **1-1,** racemic 3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl 1,1'-biphenyl-2,2'-diol (±)-**1-3** was prepared in 58% isolated yield for two steps.[26] First, Friedel-Crafts alkylation was carried out at 80 ^{o}C under 20 psi of 2-methylpropene in the presence of a catalytic amount of sulfuric acid to give 2-*tert*-butyl-4,5-dimethylphenol **1-2.** Without further purification, crude **1-2** was directly used in the oxidative coupling steps to afford (±)-**1-3**. The pure product was obtained by washing with water and prepared for the following optical resolution (Scheme 1-6).



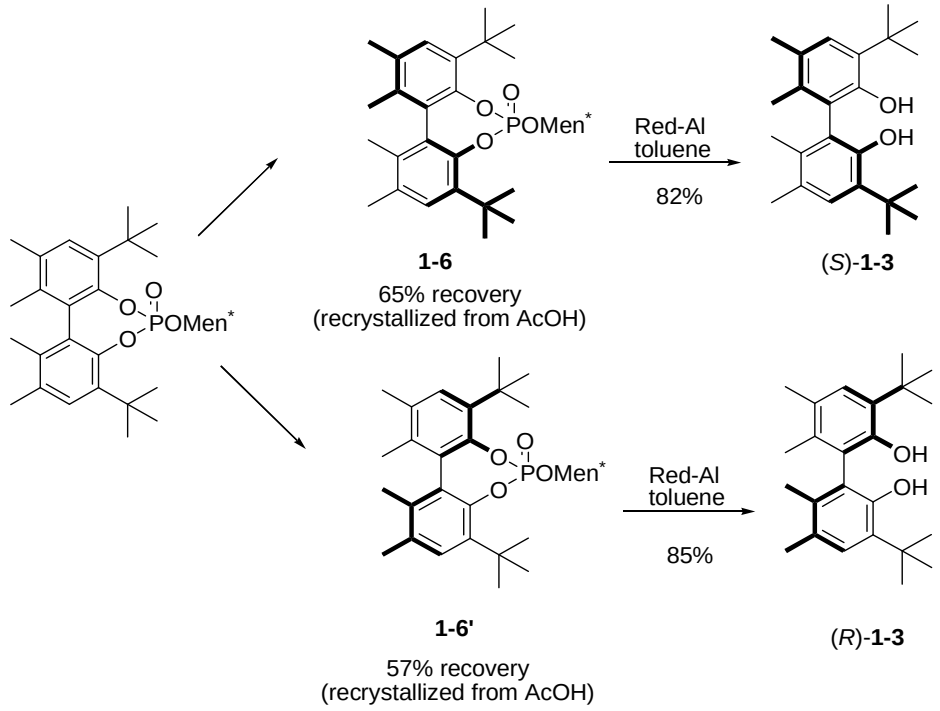
Scheme 1-6. Synthesis of racemic biphenol (±)-**1-3**

The chiral auxiliary, (-)-menthyl dichlorophosphite **1-5** was synthesized by treatment of (-)-menthol with phosphorus trichloride. Addition of (±)-**1-3** to **1-5** in a dichloromethane solution followed by oxidation gave two diastereomeric phosphates, **1-6** and **1-6'** (Scheme 1-7).



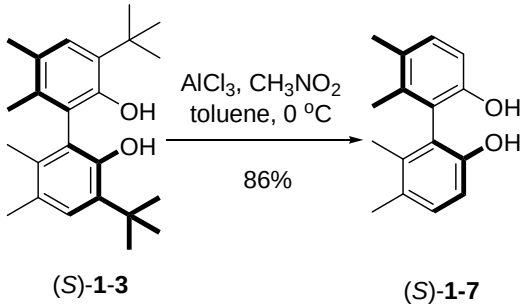
Scheme 1-7. Synthesis of diastereomeric phosphates

Phosphate **1-6** was collected first by recrystallization in acetic acid. After the mother liquor was removed, the solid residue enriched with the other diastereomer was recrystallized in methanol to give phosphate **1-6'**. Their diastereomeric purities were determined by ^{31}P NMR. Only one signal was found in each spectrum indicating that they are diastereomerically pure. Subsequently, the menthol chiral auxiliaries in resolved phosphates were removed through Red-Al® reduction. The enantiopure biphenols (*S*)-**1-3** and (*R*)-**1-3** were obtained in good yields (Scheme 1-8).



Scheme 1-8. Synthesis of enantiopure biphenols (*S*)-**1-3** and (*R*)-**1-3**

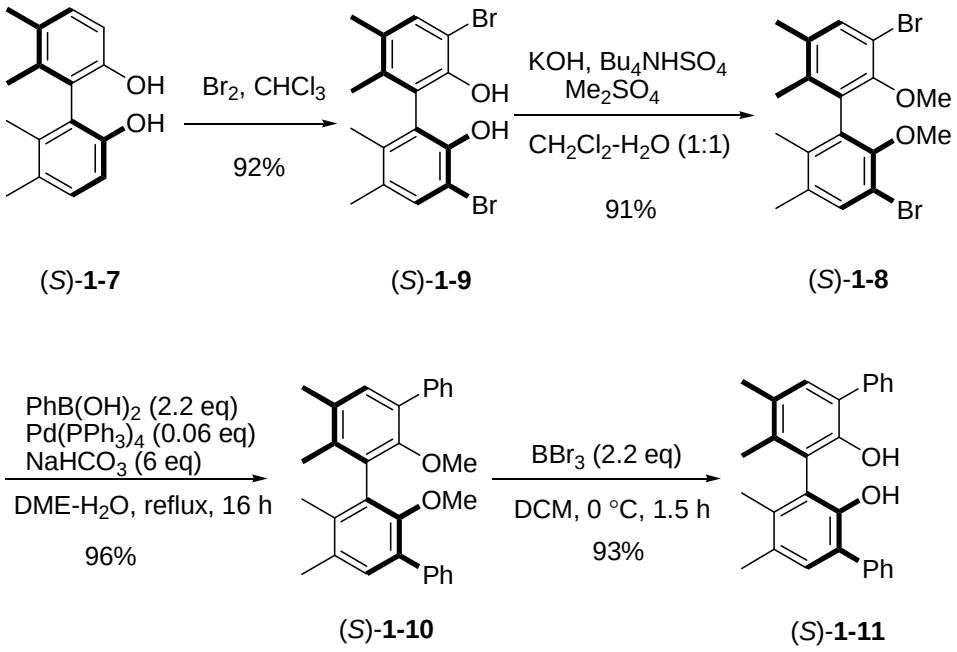
The *tert*-butyl groups at the 3,3'-positions of (*S*)-**1-3** and (*R*)-**1-3** were removed in the presence of aluminum chloride via a Friedel-Crafts transfer reaction. With the common intermediates (*S*)-**1-7** and (*R*)-**1-7** in hand, various chemical modifications were made by introduce of different groups at the 3,3'-positions**.** It was noteworthy that toluene acted as a scavenger of *t*-butyl carbocation in the reaction (Scheme 1-9).



Scheme 1-9. Synthesis of enantiopure biphenols (*S*)-**1-7** and (*R*)-**1-7** (only *S* configuration is shown for simplicity)

§1.3.2 Synthesis of enantiopure 3,3'-diphenyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol

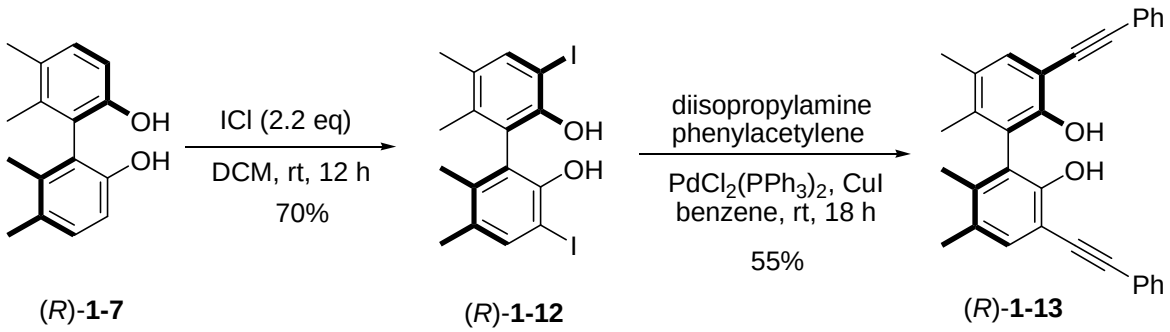
Bromination of (*S*)-**1-7** afforded (*S*)-3,3'-dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-**1-9**) in 92% yield. Because the direct Suzuki coupling of unprotected (*S*)-**1-9** with phenylboronic acid gave 3,3-diphenyl biphenol (*S*)-**1-11** in a relative low yield, (*S*)-**1-9** was first methylated by dimethyl sulfate and then coupled with phenylboronic acid. The desired product (*S*)-**1-11** was obtained by removal of protecting groups with BBr_3. All the steps gave excellent yields (Scheme 1-10). In the same manner, (*R*)-**1-11** was prepared.[26]



Scheme 1-10. Synthesis of enantiopure diphenyl biphenols

§1.3.3 Synthesis of (*R*)-5,5',6,6'-tetramethyl-3,3'-bis(phenylethynyl)biphenyl-2,2'-diol

The enantiopure (*R*)-5,5',6,6'-tetramethyl-3,3'-bis(phenylethynyl)biphenyl-2,2'-diol ((*R*)-**1-13**) was synthesized from (*R*)-**1-7** as shown in Scheme 1-11. Iodination of (*R*)-**1-7**, followed by Sonogashira coupling of unprotected (*R*)-**1-12** with phenyl acetylene gave the desired product (*R*)-**1-13** in moderate yield (Scheme 1-11).

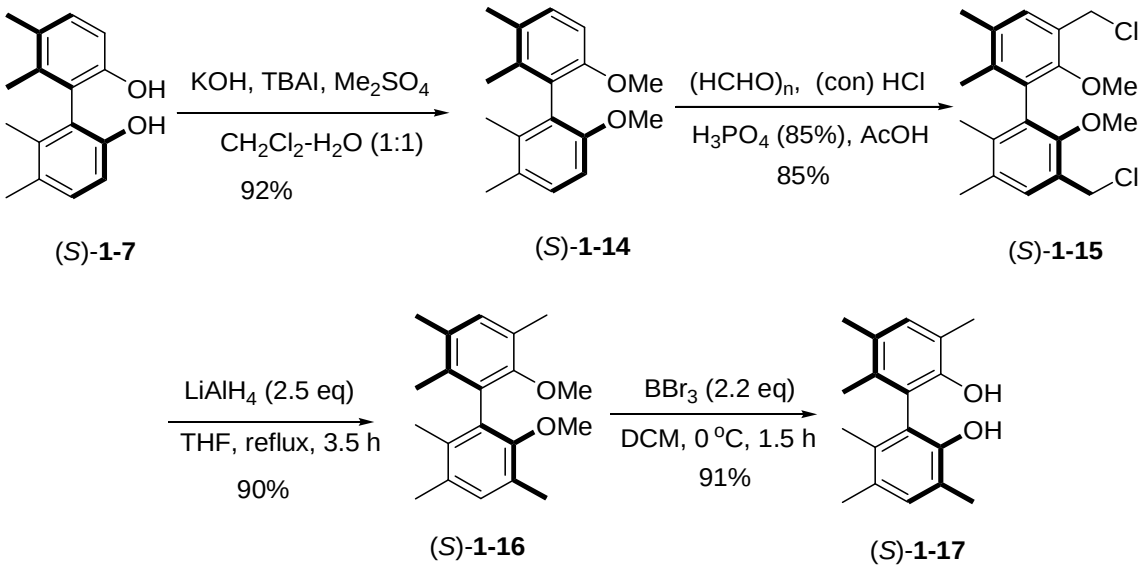


(*R*)-**1-7** (*R*)-**1-12** (*R*)-**1-13**

Scheme 1-11. Synthesis of (*R*)-**1-13**

§1.3.4 Synthesis of enantiopure 3,3',5,5',6,6'-hexamethyl-1,1'-biphenyl-2,2'-diol

Protection of (*S*)-**1-7** was carried out in a water/dichloromethane system using tetrabutylammonium iodide as a phase-transfer catalyst. Subsequently, introduction of chloromethyl groups at 3,3-positions gave another common intermediate (*S*)-**1-15** in 85% yield. (*S*)-**1-15** was subjected to $LiAlH_4$ reduction, followed by deprotection using BBr_3 to afford the hexamethyl biphenol (*S*)-**1-17** in 91% yield (Scheme 1-12). In the same manner, (*R*)-**1-17** was prepared.[26]



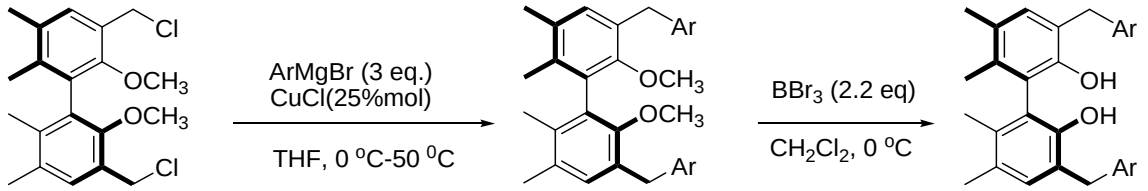
(*S*)-**1-7** (*S*)-**1-14** (*S*)-**1-15**

(*S*)-**1-16** (*S*)-**1-17**

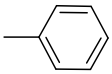
Scheme 1-12. Synthesis of enantiopure hexamethyl biphenols

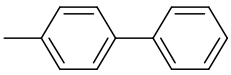
§1.3.5 Synthesis of enantiopure 3,3'-bis(substituted-benzyl)-5,5',6,6'-hexamethyl-1,1'-biphenyl-2,2'-diol

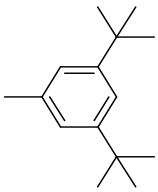
The chloromethylated biphenols (*S*)-**1-7** and (*R*)-**1-7** reacted with a series of aryl magnesium bromide reagents generated *in situ*, through a copper(I)-mediated cross-coupling, to give the corresponding methylated intermediates (*S*)-**1-18a,** (*R*)-**1-18f** and (*R*)-**1-18i-l** in good to excellent yields.[24] Subsequent removal of the methyl groups in **1-18** with BBr_3 gave final products, bis(substituted-benzyl) biphenols in good to excellent yields. Because the considerable self coupling of the excess Grignard reagents occurred, it was difficult to separate the byproducts and the desired products ((*S*)-**1-18b-e**, (*S*)-**1-18g** and (*S*)-**1-18h**) through column chromatography. Thus, methylated intermediates (*S*)-**1-18b-e**, (*S*)-**1-18g** and (*S*)-**1-18h** were washed with water and the resulting oils were directly used for the next steps (Scheme 1-13).

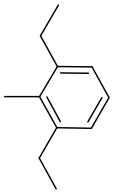


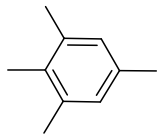
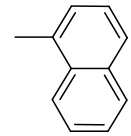
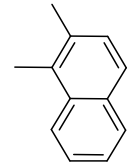
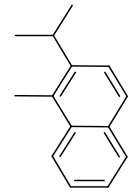
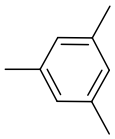
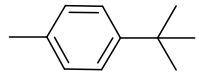
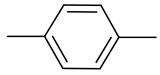
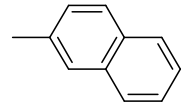
(*S*)-**1-7** (*S*)-**1-18** (*S*)-**1-19**

Ar =  (*S*)-**1-18a** 95% (*S*)-**1-19a** 90%

Ar =  (*S*)-**1-18b** crude (*S*)-**1-19b** 93% (two steps)

Ar =  (*S*)-**1-18c** crude (*S*)-**1-19c** 89% (two steps)

Ar =  (*S*)-**1-18d** crude (*S*)-**1-19d** 84% (two steps)

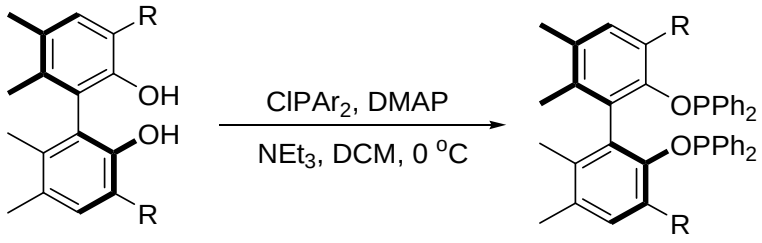
Ar = 	(*S*)-**1-18e** crude	(*S*)-**1-19e** 94% (two steps)
Ar = 	(*R*)-**1-18f** 80%	(*R*)-**1-19f** 93%
Ar = 	(*S*)-**1-18g** crude	(*S*)-**1-19g** 88% (two steps)
Ar = 	(*S*)-**1-18h** crude	(*S*)-**1-19h** 87% (two steps)
Ar = 	(*R*)-**1-18i** 98%	(*R*)-**1-19i** 91%
Ar = 	(*R*)-**1-18j** 85%	(*R*)-**1-19j** 89%
Ar = 	(*R*)-**1-18k** 93%	(*R*)-**1-19k** 94%
Ar = 	(*R*)-**1-18l** 82%	(*R*)-**1-19l** 98%

Scheme 1-13. Synthesis of enantiopure bis(substituted-benzyl) biphenols (only *S* configuration is shown for simplicity)

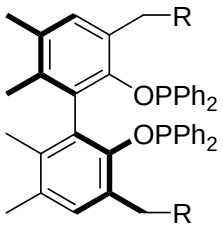
§1.3.6 Synthesis of enantiopure biphenol-based diphosphinite ligands

With the above enantiopure biphenols in hand, we were in a position to create a library of BOP ligands. They were prepared following the protocol for the synthesis of BINAPO ligands described by Miwako Mori,[20] as illustrated in Scheme 1-14. The coupling of enantiopure

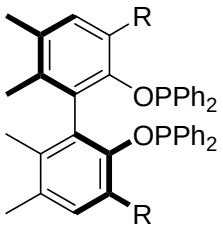
biphenols with chlorodiarylphosphine proceeded smoothly. Finally, the pure BOP ligands were successfully obtained through column chromatography on silica gel pretreated with triethylamine. The library of ligands is shown in Figure 1-5. Among them, (*S*)-L**1b-e,** (*S*)-L**1g,** (*S*)-L**1h,** (*S*)-L**2e** (*S*)-L**3e**, and (*R*)-L**3e** are newly developed by the author.



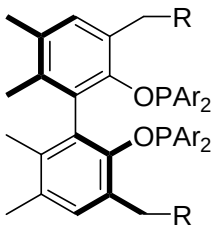
Scheme 1-14. General procedure for BOP ligand synthesis



(*S*)-L**1a** R = Ph
(*R*)-L**1a** R = Ph
(*S*)-L**1b** R = 4-biphenyl
(*S*)-L**1c** R = 3,5-*t*-$Bu_2C_6H_3$
(*S*)-L**1d** R = 2,6-$Et_2C_6H_3$
(*S*)-L**1e** R = 2,4,6-$Me_3C_6H_2$
(*R*)-L**1f** R = 1-Np
(*S*)-L**1g** R = 1-(2-MeNp)
(*S*)-L**1h** R = 1-(2-*i*-PrNp)
(*R*)-L**1i** R = 3,5-$Me_2C_6H_3$
(*R*)-L**1j** R = 4-*t*-BuC_6H_4
(*R*)-L**1k** R = 4-MeC_6H_4
(*R*)-L**1l** R = 2-Np

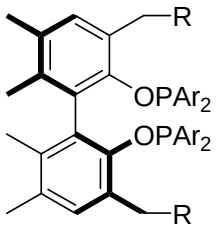


(*S*)-L**1m** R = H
(*R*)-L**1m** R = H
(*S*)-L**1n** R = Me
(*R*)-L**1o** R = Br
(*R*)-L**1p** R = Ph
(*R*)-L**1q** R = C≡CPh



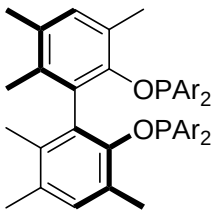
(*S*)-L**2e** Ar = tolyl
(*S*)-L**3e** Ar = *m*-xylyl
(*R*)-L**3e** Ar = *m*-xylyl

R = 2,4,6-$Me_3C_6H_2$



(*S*)-L**2i** Ar = 4-MeC_6H_4
(*R*)-L**2i** Ar = 4-MeC_6H_4
(*R*)-L**3i** Ar = 4-$MeOC_6H_4$
(*R*)-L**4i** Ar = 4-$CF_3C_6H_4$

R = 3,5-$Me_2C_6H_3$



(*R*)-L**2n** Ar = tolyl
(*R*)-L**3n** Ar = *m*-xylyl

Figure 1-5. BOP ligand library (only *S* configuration is shown for simplicity)

§1.4 Conclusions

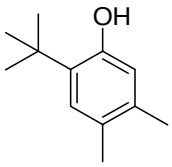
A library of fine-tunable BOP ligands was designed and developed in our lab. The newly synthesized BOP ligands have been studied for intermolecular asymmetric allylic substitution reactions. Some of them give promising results and will be discussed in later chapters.

§1.5 Experimental section

General Methods. ^{1}H, ^{13}C, and ^{31}P NMR spectra were measured on a Bruker Avance 500 (500 MHz for ^{1}H; 125 MHz for ^{13}C), a Bruker Avance 400 (400 MHz for ^{1}H; 100 MHz for ^{13}C; 162 MHz for ^{31}P), or a Varian Gemini-2300 300 MHz (300 MHz for ^{1}H; 75 MHz for ^{13}C; 121.5 MHz for ^{31}P) NMR spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm) as the internal standard or phosphoric acid as the external reference (^{31}P 0.00 ppm). Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. TLC analyses were performed using Merck DC Alufolien $60F_{254}$ aluminum pre-coated silica gel plates. Flash column chromatography was carried out using Silicyle Silia*Flash*P60® silica gel (particle size 40_63 μm). Low-resolution mass spectrometry was performed on Agilent 6890GC/5973 mass selective detector. High-resolution mass spectrometric analyses were carried out at the Mass Spectrometry Laboratory, University of Illinois Urbana-Champaign, Urbana, IL or by ICB&DD at Stony Brook University. Unless otherwise noted all reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques.

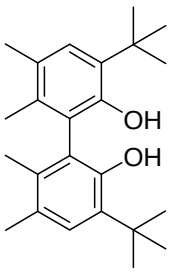
Material. Solvents were reagents grade and freshly dried, degassed and distilled before use. Anhydrous *N*,*N*-dimethylformamide (DMF) and acetonitrile were purchased from Acros Organic and used without further purification. Chemicals and reagents were purchased from VWR, Fisher Scientific or Sigma-Aldrich and used without further purification unless otherwise noted.

2-*tert*-Butyl-4,5-dimethylphenol (1-2)



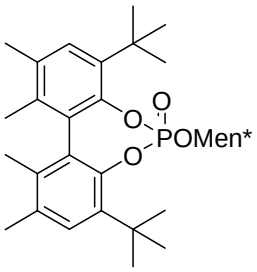
In an autoclave with a glass liner and stirring bar, 3, 4-dimethylphenol **1-1** (100.5 g, 0.82 mol) and concentrated sulfuric acid (0.5 mL) were added. The autoclave was pressurized with 2-methylpropene (20 psi) and heated to 80 ^{o}C with stirring for 6 h. The autoclave was cooled to room temperature and then opened. The crude product was pure enough to be used for the next step. GC-MS: 100% conversion, M.W.: 178 m/z

(±)-3,3'–Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((±)-1-3)



Potassium dichromate (75.0 g, 0.246 mol) dissolved in a solution of sulfuric acid (150 mL) and water was carefully added to an acetic acid (800 mL) solution of 2-*tert*-butyl-4,5-dimethyl-phenol **1-2** (crude product from the previous step). The reaction was stirred at 60 ^{o}C for 30 min and then cooled to room temperature. The mixture was filtered, and the brown solid was washed with water and methanol. The resulting solid was stirred in methanol at 0 ^{o}C for 15 min, and isolated by filtration to give a colorless solid (84.3 g, 58% in two steps). mp 160.0-162.0 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 18H), 1.80 (s, 6H), 2.24 (s, 6H), 4.79 (s, 2H), 7.12 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 20.1, 29.7, 34.7, 121.1, 128.1, 128.7, 133.4, 134.1, 150.4. All data were consistent with literature values.[25]

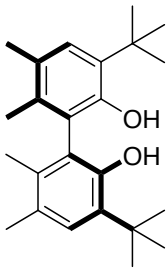
Preparation and resolution of 1-6 and 1-6'



A solution of (1*R*,2*S*,5*R*)-(-)-menthol **1-4** (37.1 g, 238 mmol) in CH_2Cl_2 (67 mL) was added to a solution of phosphorous trichloride (48.9 g, 357 mmol) in CH_2Cl_2 (134 mL) over 30 min at 0 ^oC. Then the solution was stirred at room temperature for another hour. After the volatiles were removed *in vacuo*, the resulting oil was redissolved in CH_2Cl_2 (126 mL), to which a CH_2Cl_2 (253 mL) solution of Et_3N (99 mL, 714 mmol) and **1-3** (84.3 g, 238 mmol) was added over 30 min. The mixture was stirred at room temperature for 2 h and then filtered. The remaining solution was cooled to 0 ^oC. H_2O_2 (35% in water, 145 mL) was added slowly. The biphasic mixture was stirred for 2 h. The organic layer was washed with water (150 mL), brine (150 mL), and dried over anhydrous $MgSO_4$. The solution was filtered and concentrated by rotary evaporation to afford an off-white solid **6** (111 g, 90%). ^{31}P NMR (121 MHz, $CDCl_3$) **1-6**: -4.98; **1-6'**: -4.46.

The diastereomeric mixture of compounds **1-6** and **1-6'** (111 g, 203 mmol) was dissolved in a minimum amount of hot acetic acid. White crystals were obtained after standing at room temperature overnight. The crystals were washed with cold acetic acid and dried *in vacuo*. They were recrystallized in refluxing acetic acid again to give pure **1-6** (43.1 g, 65%, >99% de). ^{31}P NMR (121 MHz, $CDCl_3$) δ -4.98. The mother liquor from the first crystallization was concentrated *in vacuo* to afford **1-6'**. The solid residue was recrystallized from hot MeOH to give pure **1-6'** (37.5 g, 57%, >99% de). ^{31}P NMR (121 MHz, $CDCl_3$) δ -4.46. All data were consistent with literature values.[25]

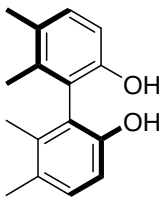
(*S*)-3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-3)



Resolved (*S*)-**1-6** (32.5 g, 58.6 mmol) was dissolved in toluene in a round bottom flask equipped with an addition funnel. Red-Al® (70% wt. in toluene, 45 mL) was added into the addition funnel and then added dropwise to the phosphate solution at 0 °C. The reaction was stirred at room temperature for 16 h and quenched with water (60 mL) and sodium hypochlorite (5% in water, 60 mL). The mixture was filtered through Celite®, and was washed with toluene. The separated organic layer was washed with sodium hypochlorite (5% in water, 160 mL) and brine (160 mL) and then dried over $MgSO_4$. The drying agent was removed by filtration, and the solvent was evaporated. The menthol was removed by repeated washing with cold MeOH until the minty odor disappeared. The (*S*)-**1-3** was collected by filtration and dried *in vacuo* (16.9 g, 82%). White solid; mp 160.5-162.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 18H), 1.81 (s, 6H), 2.25 (s, 6H), 4.80 (s, 2H), 7.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 20.1, 29.7, 34.7, 121.1, 128.1, 128.7, 133.4, 134.1, 150.4. All data were consistent with literature values.[25]

The synthesis of (*R*)-**1-3** followed the same procedure (11.7 g, 85% yield). White solid; mp 160.0-162.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 18H), 1.81 (s, 6H), 2.25 (s, 6H), 4.80 (s, 2H), 7.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 20.1, 29.7, 34.7, 121.1, 128.1, 128.7, 133.4, 134.1, 150.4. All data were consistent with literature values.[25]

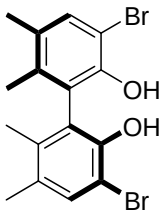
(*S*)-5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-7)



To a solution of (*S*)-**1-3** (3.98 g 11.4 mmol) in toluene (57 mL) at 0 ^{o}C, a solution of $AlCl_3$ (2.40 g, 18.3 mmol) in toluene (10 mL) and nitromethane (22 mL) was added dropwise by addition funnel over 30 min. The mixture was stirred at 0 ^{o}C for another 30 min. The reaction was quenched by slowly addition of water (30 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (50 mL) and then dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure to give crude (*S*)-**1-7**. The crude product was recrystallized from hexanes-CH_2Cl_2 to afford pure (*S*)-**1-7** as a white solid (2.32 g, 86%). mp 197.0-198.0 ^{o}C; $[\alpha]_D^{21}$ -54.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (s, 6H), 2.26 (s, 6H), 4.53 (s, 2H), 6.82 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 19.8, 112.6, 120.2, 129.2, 131.2, 136.9, 151.9. All data were consistent with literature values.[26]

The synthesis of (*R*)-**1-7** followed the same procedure (3.19 g 83% yield). White solid; mp 196.0-197.0 ^{o}C; $[\alpha]_D^{21}$ +48.0 (CH_2Cl_2, *c* 1.00); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (s, 6H), 2.26 (s, 6H), 4.53 (s, 2H), 6.82 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 19.8, 112.6, 120.2, 129.2, 131.2, 136.9, 151.9. All data were consistent with literature values.[26]

(*S*)-3,3'-Dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-9)

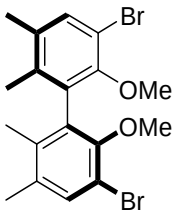


To a solution of (*S*)-**1-7** (0.708 g, 3.0 mmol) in $CHCl_3$ (21 mL), a solution of Br_2 (0.36 mL, 7 mmol) in $CHCl_3$ (4 mL) was added dropwise over 20 min. The solution was stirred at room temperature for 1.5 h. The reaction was quenched with saturated sodium sulfite solution (20 mL). The aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL) and then dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure to afford an off-white solid (*S*)-**1-9** (1.11 g,

93%). mp 172.0-173.0 ^{o}C; $[\alpha]_D^{21}$ +12.0 (CH_2Cl_2, *c* 1.00); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 6H), 2.25 (s, 6H), 5.12 (s, 2H), 7.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.8, 106.7, 123.6, 130.7, 132.7, 136.8, 147.7. All data were consistent with literature values.[26]

The synthesis of (*R*)-**1-9** followed the same procedure (1.83 g, 85% yield). Off-white solid; mp 171.5-173.0 ^{o}C; $[\alpha]_D^{21}$ -11.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 6H), 2.25 (s, 6H), 5.12 (s, 2H), 7.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.8, 106.7, 123.6, 130.7, 132.7, 136.8, 147.7. All data were consistent with literature values.[26]

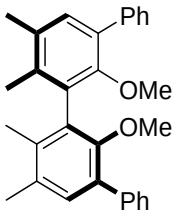
(*S*)-3,3'-Dibromo-5,5',6,6'-tetramethyl-2,2'-dimethoxy-1,1'-biphenyl ((*S*)-1-8)



To a biphasic mixture of (*S*)-**1-9** (1.12 g, 2.80 mmol), potassium hydroxide (0.470 g, 8.4 mmol) and Bu_4NHSO_4 (95 mg, 0.28 mmol) in CH_2Cl_2-H_2O (1:1, 20 mL), dimethyl sulfate (0.78 mL, 8.4 mmol) was added dropwise. The mixture was stirred at room temperature overnight and then separated by a separation funnel. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration, the remain solution was concentrated under reduced pressure and the crude product was triturated with methanol to give (*S*)-**1-8** (1.09 g, 91%) as a white solid. mp 150.5-152.5 ^{o}C; $[\alpha]_D^{21}$ +38.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (s, 6H), 2.26 (s, 6H), 3.50 (s, 6H), 7.39 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 20.0, 60.2, 113.8, 133.0, 133.5, 134.2, 113.60, 152.6. All data were consistent with literature values.[26]

The synthesis of (*R*)-**1-8** followed the same procedure (0.95 g, 93% yield). White solid; mp 151.0-152.0 ^{o}C; $[\alpha]_D^{21}$ -39.1 (CH_2Cl_2, *c* 1.00); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (s, 6H), 2.26 (s, 6H), 3.50 (s, 6H), 7.39 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 20.0, 60.2, 113.8, 133.0, 133.5, 134.2, 113.60, 152.6. All data were consistent with literature values.[26]

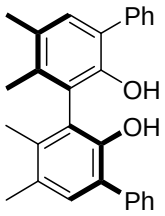
(*S*)-3,3'-Diphenyl-5,5',6,6'-tetramethyl-2,2'-dimethoxy-1,1'-biphenyl ((*S*)-1-10)



A suspension of (*S*)-**1-9** (1.11 g, 2.60 mmol) and $Pd(PPh_3)$ (185 mg, 0.156 mmol) in DME (25 mL) was stirred at room temperature for 30 min. To this solution, a mixture of phenylboronic acid (698 mg, 5.72 mmol) and sodium bicarbonate (1.30 g, 15.6 mmol) in water (15 mL) was added at the same temperature. The mixture was refluxed for 16 h with stirring. The mixture was then cooled to room temperature and diluted with ether. The organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EA= 20:1) to give (*S*)-**1-10** (1.06 g, 96%) as a white solid. mp 57.0-58.0 ^oC; $[\alpha]_D^{21}$ +148.4 (*c* 1.00, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.98 (s, 6H), 2.34 (s, 6H), 3.20 (s, 6H), 7.19 (s, 2H), 7.36 (m, 6H), 7.62 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1, 20.4, 60.5, 126.8, 128.6, 129.4, 131.5, 131.6, 132.4, 132.9, 135.8, 139.7, 153.5. All data were consistent with literature values.[26]

The synthesis of (*R*)-**1-10** followed the same procedure (0.771 g, 95% yield). White solid; mp 55.5-56.5 ^oC; $[\alpha]_D^{21}$ -141.7 (CH_2Cl_2, *c* 1.00);^1H NMR (300 MHz, $CDCl_3$) δ 1.98 (s, 6H), 2.34 (s, 6H), 3.20 (s, 6H), 7.19 (s, 2H), 7.36 (m, 6H), 7.62 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1, 20.4, 60.5, 126.8, 128.6, 129.4, 131.5, 131.6, 132.4, 132.9, 135.8, 139.7, 153.5. All data were consistent with literature values.[26]

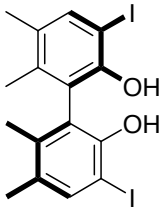
(*S*)-3,3'-Diphenyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-11)



To a solution of (*S*)-**1-10** (1.062 g, 2.50 mmol) in CH_2Cl_2 (20 mL), BBr_3 (1.0 M solution in CH_2Cl_2, 5.5 mL) was added dropwise at 0 ^oC over 20 min. The mixture was stirred at the same temperature for 1.5 h, and then quenched by slowly adding water (20 mL). The mixture was separated and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel (hexanes/AcOEt = 60:1) to give (*S*)-**1-11** (0.915 g, 93%) as a white solid. mp 155.0-156.5 ^oC; $[\alpha]_D^{21}$ +77.0 (*c* 1.00, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 6H), 2.32 (s, 6H), 4.88 (s, 2H), 7.23 (s, 2H), 7.33 (m, 2H), 7.43 (m, 4H), 7.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 19.8, 121.6, 125.8, 127.1, 128.4, 129.1, 129.4, 132.1, 136.4, 137.9, 148.5. All data were consistent with literature values.[26]

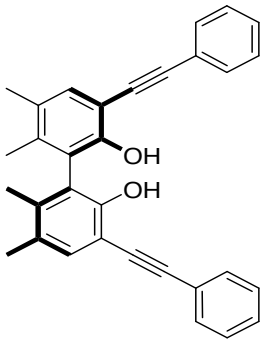
The synthesis of (*R*)**-1-11** followed the same procedure (0.694 g, 96% yield). White solid; mp 153.5-155.0 ^oC; $[\alpha]_D^{21}$ -87.3 (CH_2Cl_2, *c* 1.10); ^1H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 6H), 2.32 (s, 6H), 4.90 (s, 2H), 7.23 (s, 2H), 7.33 (m, 2H), 7.43 (m, 4H), 7.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 19.8, 121.6, 125.8, 127.1, 128.4, 129.1, 129.4, 132.1, 136.4, 137.9, 148.5. All data were consistent with literature values.[26]

(*R*)-3,3'-Diiodo-5,5',6,6'-tetramethylbiphenyl-2,2'-diol ((*R*)-1-12)



To a solution of (*R*)-**1-7** (236 mg, 1.0 mmol) in 10 mL CH_2Cl_2, a solution of ICl (1.1 mL, 1M in CH_2Cl_2, 2.2 eq.) was added dropwise at room temperature over 20 min. The solution was stirred at the same temperature for 12 h. The solution was quenched by adding saturated Na_2SO_3 water solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (30 mL x 3). The combined organic layers were washed with water (30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. The solution was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (hexanes/AcOEt = 20:1) to give (*R*)-**1-12** (338 mg, 70%) as a white solid. mp 213.5-214.0 ^oC; $[\alpha]_D^{21}$ +52.6 (*c* 0.95, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 6H), 2.23 (s, 6H), 4.96 (s, 2H), 7.56 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.5, 80.6, 122.2, 131.5, 137.8, 139.3, 150.6. All data were consistent with literature values.[24]

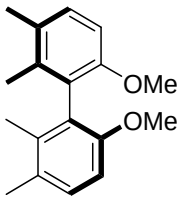
(*R*)-5,5',6,6'-Tetramethyl-3,3'-bis(phenylethynyl)-1,1'-biphenyl-2,2'-diols ((*R*)-1-13)



Phenylacetylene (0.17 mL, 1.5 mmol) was added to a suspension of $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), CuI (17 mg, 0.09 mmol), and (*R*)-**1-12** (247 mg, 0.5 mmol) in benzene (5 mL) at room temperature. Diisopropylamine (0.14 mL, 1.0 mmol) was then added to the mixture and stirred at the same temperature for 18 h. The aqueous layer was separated and extracted with Et_2O (15 mL x 3). The combined organic layers were washed with water (20 mL), brine (20 mL), and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated under reduced pressure to give the crude product as a light yellow solid. Further purification by flash column chromatography on silica gel (hexanes/AcOEt = 10:1) afforded pure (*R*)-**1-13** as a light yellow solid (121 mg, 55% yield): mp 73.5-75.0 ^oC; $[\alpha]_D^{21}$ +130.5 (*c* 1.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 6H), 2.29 (s, 6H), 5.54 (s, 2H),

7.36 (m, 8H), 7.53 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 19.8, 20.9, 84.1, 95.2, 106.8, 122.5, 123.1, 128.5, 129.0, 131.5, 132.3, 138.6, 152.3. All data are in agreement with the literature values.[24]

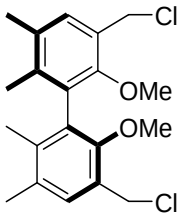
(*S*)-5,5',6,6'-Tetramethyl-2,2'-dimethoxy-1,1'-biphenyl ((*S*)-1-14)



To a mixture of (*S*)-**1-14** (2.47 g, 10.0 mmol), potassium hydroxide (1.65 g, 29.5 mmol) and tetrabutyl ammonium iodide (0.2 g, 1.0 mmol) in CH_2Cl_2-water (1:1, 130 mL) was added dimethyl sulfate (2.85 mL, 30 mmol) and the biphasic mixture was stirred at room temperature overnight. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with water (150 mL), ammonium hydroxide (150 mL) and brine (150 mL), and dried over anhydrous $MgSO_4$. The solution was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (hexanes/ AcOEt = 15:1) to give (*S*)-**1-14** as a white solid (2.28 g, 84%). mp 112.0-113.0 ^{o}C; $[\alpha]_D^{21}$ -56.5 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (s, 6H), 2.27 (s, 6H), 3.67 (s, 6H), 6.75 (d, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.9, 55.9, 108.4, 126.8, 128.5, 128.9, 136.6, 155.5. All data were consistent with literature values.[26]

The synthesis of (*R*)-**1-14** followed the same procedure (2.53 g, 92% yield). White solid; mp 110.5.5-111.0 ^{o}C; $[\alpha]_D^{21}$+51.1 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (s, 6H), 2.27 (s, 6H), 3.67 (s, 6H), 6.75 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.9, 55.9, 108.4, 126.8, 128.5, 128.9, 136.6, 155.5. All data were consistent with literature values.[26]

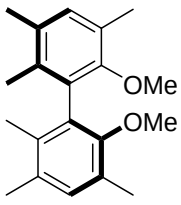
(*S*)-3,3'-Dichloromethyl-5,5',6,6'-tetramethyl-2,2'-dimethoxy-1,1'-biphenyl ((*S*)-1-15)



To a solution of concentrated HCl (18.5 mL), 85% H_3PO_4(18.5 mL), glacial acetic acid (18.5 mL) and (*S*)-**1-14** (2.01 g, 7.44 mmol) was added paraformaldehyde (4.9 g, 163 mmol). The solution was stirred at 90 ^{0}C for 48 h. The solution was cooled to room temperature and then extracted with toluene (3 x 50 mL). The combined organic layers were washed with water (100 mL), saturated Na_2CO_3 (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$. The drying agent was filtered and the solution was concentrated under reduced pressure to give crude (*S*)-**1-15**. The crude (*S*)-**1-15** is purified by column chromatography on silica gel (hexanes/AcOEt = 30:1) to afford a white solid (2.32 g, 85%). mp 107.0-109.0 ^{o}C; $[\alpha]_D^{21}$ +68.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (s, 6H), 2.29 (s, 6H), 3.36 (s, 6H), 4.56 (d, *J* = 10.8Hz, 2H), 4.81 (d, *J* = 11.1 Hz, 2H), 7.27 (s, 1H), 7.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 20.3, 41.7, 60.9, 127.9, 128.3, 131.2, 131.5, 132.7, 137.6, 154.1. All data were consistent with literature values.[26]

The synthesis of (*R*)-**1-15** followed the same procedure (2.92 g, 85% yield). White solid; mp 106.0-108.0 ^{o}C; $[\alpha]_D^{21}$ -66.0 (CH_2Cl_2, *c* 1.00); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (s, 6H), 2.30 (s, 6H), 3.38 (s, 6H), 4.57 (d, *J* = 10.8Hz, 2H), 4.82 (d, *J* = 11.1 Hz, 2H), 7.27 (s, 1H), 7.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 20.3, 41.7, 60.9, 127.9, 128.3, 131.2, 131.5, 132.7, 137.6, 154.1. All data were consistent with literature values.[26]

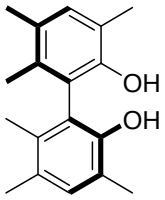
(*S*)-3,3',5,5',6,6'-Hexamethyl-2,2'-dimethoxy-1,1'-biphenyl ((*S*)-1-16)



To a suspension of $LiAlH_4$ (0.19 g, 5 mmol) in THF (5 mL), a solution of (*S*)-**1-15** (0.734 g, 2.0 mmol) in THF (2.5 mL) was added dropwise at room temperature. The mixture was refluxed for 3.5 h with stirring and then quenched with THF/water (3:1) at 0 ^oC. To the biphasic mixture, H_2SO_4/H_2O (1:1, 4 mL) was added and stirred for 30 min at room temperature. The aqueous layer was extracted with ether (3 x 15 mL). The combined organic layers were washed with water (30 mL), and dried over anhydrous $MgSO_4$. The drying agent was filtered and the solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/AcOEt = 20:1) to give (*S*)-**1-16** (0.535 g, 90%) as a white solid. mp 72.5-74.0 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 6H), 2.25 (s, 6H), 2.28 (s, 6H), 3.33 (s, 6H), 7.00 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 16.8, 20.3, 59.7, 127.6, 131.4, 131.5, 131.9, 133.6, 154.2. All data were consistent with literature values.[26]

The synthesis of (*R*)-**1-16** followed the same procedure (0.407 g, 81% yield). White solid; mp 73.0-75.0 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 6H), 2.25 (s, 6H), 2.28 (s, 6H), 3.33 (s, 6H), 7.00 (s, 2H)' ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 16.8, 20.3, 59.7, 127.6, 131.4, 131.5, 131.9, 133.6, 154.2. All data were consistent with literature values.[26]

(*S*) -3,3',5,5',6,6'-Hexamethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-17)

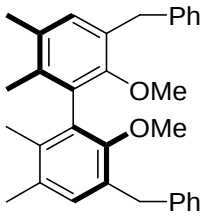


To a stirred solution of (*S*)-**1-16** (0.535 g, 1.8 mmol) in CH_2Cl_2 (20 mL), BBr_3 (1.0 M solution in DCM, 4 mL) was added dropwise over 20 min at 0 ^0C. The mixture was stirred at the same temperature for 1.5 h, and then quenched by the slow addition of water (20 mL). The mixture was separated and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/AcOEt = 60:1) to give (*S*)-**1-17** (0.444 g, 91%) as a white solid. mp 137.0-138.0 ^oC; $[\alpha]_D^{21}$ -48.0 (*c* 1.00, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ

1.85 (s, 6H), 2.23 (s, 6H), 4.53 (s, 2H), 7.00 (s, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 15.9, 16.2, 19.8, 119.9, 121.4, 128.4, 132.8, 133.8, 149.8. All data were consistent with literature values.[26]

The synthesis of (*R*)-**1-17** followed the same procedure (0.311 g, 82% yield). White solid; mp 136.0-137.5 ^{o}C; $[\alpha]_D^{21}$ +41.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (s, 6H), 2.23 (s, 6H), 4.54 (s, 2H), 7.00 (s, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 15.9, 16.2, 19.8, 119.9, 121.4, 128.4, 132.8, 133.8, 149.8. All data were consistent with literature values.[26]

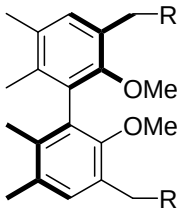
(*S*)-3,3'-Dibenzyl-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-1-18a)



To a solution of (*S*)-**1-17** (0.367 g, 1.0 mmol) in THF (10 mL) containing CuI (48 mg, 0.25 mmol), a solution of phenyl bromide in THF (1M, 4.0 eq) was added at 0 ^{o}C. The solution was stirred over 30 min and then warmed to room temperature with stirring for another 30 min. The solution was heated to 50 ^{o}C for 10 h. The mixture was quenched with aqueous NH_4Cl solution (40 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with water (80 mL) and brine (80 mL), dried over $MgSO_4$. The drying agent was filtered and the solution was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexanes/AcOEt = 80:1) to give (*S*)-**1-18a** (0.413 g, 95%) as a white foam. $[\alpha]_D^{21}$ -20.6 (*c* 1.00, CH_2Cl_2).^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (s, 6H), 2.22 (s, 6H), 3.20 (s, 6H), 3.99 (d, *J* = 15.3 Hz, 2H), 4.06 (d, *J* = 15.0 Hz, 2H), 6.92 (s, 2H), 7.23 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 19.8, 35.7, 60.0, 121.6, 125.6, 127.1, 128.4, 129.2, 129.3, 132.1, 136.4, 137.9, 148.4; All data were consistent with literature values.[24]

In the same manner, (*R*)-**1-18f** and (*R*)-**1-18i-l** were synthesized.

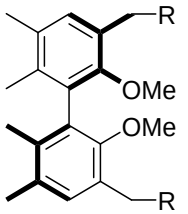
(*R*)-3,3'-Bis(naphthalene-1-ylmethyl)-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-1-18f)



R = 1-Np

White foam; 80% yield; $[\alpha]_D^{21}$ +26.0 (*c* 1.00, CH_2Cl_2).^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (s, 6H), 2.13 (s, 6H), 3.40 (s, 6H), 4.48 (d, *J* = 15.6 Hz, 2H), 4.55 (d, *J* = 15.6 Hz, 2H), 6.80 (s, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.46 (m, 6H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.85 (m, 2H), 8.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 20.1, 32.6, 60.3, 124.5, 125.3, 125.7, 125.8, 126.8, 126.9, 128.8, 130.2, 130.8, 131.8, 132.0, 132.5, 133.8, 134.4, 137.7 153.9. All data were consistent with literature values.[24]

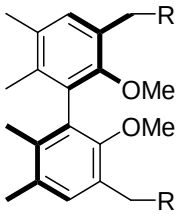
(*R*)-3,3'-Bis(3,5-dimethylbenzyl)-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-1-18i)



R = 3,5-$Me_2C_6H_3$

White foam; 98% yield; $[\alpha]_D^{21}$ +14.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (s, 6H), 2.21 (s, 6H), 2.27 (s, 12H), 3.26 (s, 6H), 3.97 (d, *J* = 15.0 Hz, 2H), 3.90 (d, *J* = 15.0 Hz, 2H), 6.82 (s, 2H), 6.84 (s, 4H), 6.90 (s, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 20.1, 21.4, 35.7, 60.0, 126.8, 127.3, 130.9, 131.1, 131.8, 131.9, 134.3, 137.5, 141.5, 154.0. All data were consistent with literature values.[23]

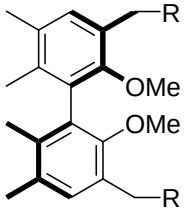
(*R*)-3,3'-Bis(4-*tert*-butylbenzyl)-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-1-18j)



R = 4-*t*-BuC_6H_4

White foam; 85% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 18H), 1.90 (s, 6H), 2.22 (s, 6H), 3.24 (s, 6H), 3.96 (d, J = 15.6 Hz, 2H), 4.02 (d, J = 15.0 Hz, 2H), 6.93 (s, 2H), 7.15 (d, J = 7.8 Hz, 4H), 7.29 (d, J = 8.4 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 20.1, 31.4, 34.3, 35.2, 60.3, 125.2, 128.5, 130.9, 131.2, 131.8 134.3, 138.5, 148.4, 154.3. All data were consistent with literature values.[24]

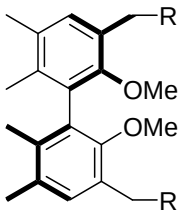
(*R*)-3,3'-Bis(4-methylbenzyl)-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-1-18k)



R = 4-MeC_6H_4

White foam; 93% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88 (s, 6H), 2.21 (s, 6H), 2.31 (s, 6H), 3.23 (s, 6H), 3.95 (d, J = 15.3 Hz, 2H), 4.01 (d, J = 15.6 Hz, 2H), 6.91 (s, 2H), 7.08 (d, J = 8.4 Hz, 4H), 7.12 (d, J = 8.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 20.2, 21.0, 35.3, 60.1, 128.9, 129.1, 129.3, 131.0, 131.1, 131.8, 134.5, 135.2, 138.7, 153.9. All data were consistent with literature values.[24]

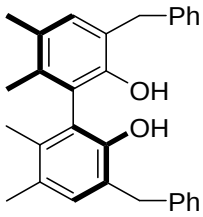
(*R*)-3,3'-Bis(naphthalene-2-ylmethyl)-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-1-18l)



R = 2-Np

White foam; 82% yield; $[\alpha]_D^{21}$ +24.3 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (s, 6H), 2.21 (s, 6H), 3.26 (s, 6H), 4.17 (d, *J* = 15.0 Hz, 2H), 4.23 (d, *J* = 15.0 Hz, 2H), 6.95 (s, 2H), 7.42 (m, 6H), 7.66 (s, 2H), 7.78 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ16.6, 20.1, 35.9, 60.1, 125.1, 125.7, 126.9, 127.0, 127.4, 127.6, 127.7, 127.8, 130.6, 131.3, 131.8, 131.9, 133.6, 134.5, 139.2, 154.1. All data were consistent with literature values.[24]

(*S*)-3,3'-Dibenzyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-19a)

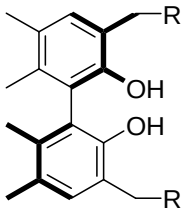


To a solution of (*S*)-**1-18a** (0.458 g, 1.0 mmol) in CH_2Cl_2 (20 mL), BBr_3 (1.0 M solution in DCM, 2.2 mL) was added dropwise at 0 ^{o}C over 20 min. The mixture was stirred at the same temperature for 1.5 h, and then quenched by the slow addition of water (20 mL). The mixture was separated and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/AcOEt = 80:1) to give (*S*)-**1-19a** (0.379 g, 90%) as a white solid. Mp 105.0-106.5 ^{o}C; $[\alpha]_D^{21}$ -11.2 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (s, 6H), 2.20 (s, 6H), 3.94 (d, *J* = 15.3 Hz, 2H), 4.01 (d, *J* = 15.0 Hz, 2H), 4.69 (s, 2H), 6.94 (s, 2H), 7.23 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.9, 35.7, 120.3, 124.8, 125.8, 128.3,

128.9, 128.8, 132.5, 134.8, 141.0, 149.4. All data were consistent with literature values.[24]

In the same manner, (*R*)-**1-19f** and (*R*)-**1-19i-l** were synthesized.

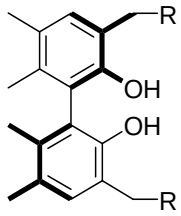
(*R*)-3,3'-Bis(naphthalene-1-ylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-19f)



R = 1-Np

White solid; 93% yield; mp 151.5–153.0 ^{o}C; $[\alpha]_D^{21}$ -28.5 (*c* 1.30, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (s, 6H), 2.11 (s, 6H), 4.39 (d, *J* = 15.6 Hz, 2H), 4.48 (d, *J* = 15.6 Hz, 2H), 4.79 (s, 2H), 6.81 (s, 2H), 7.33 (d, *J* = 6.9 Hz, 2H), 7.45 (m, 6H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.87 (m, 2H), 8.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 19.7, 32.4, 120.2, 124.1, 124.3, 125.5, 125.6, 125.8, 126.8, 126.9, 129.0, 132.1, 132.3, 133.9, 134.6, 136.9, 149.2. All data were consistent with literature values.[24]

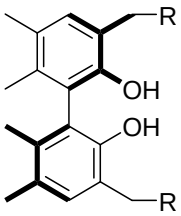
(*R*)-3,3'-Bis(3,5-dimethylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-19i)



R = 3,5-$Me_2C_6H_3$

White solid; 91% yield; mp 49.5-50.0 ^{o}C; $[\alpha]_D^{21}$ -10.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 6H), 2.20 (s, 6H), 2.26 (s, 12H), 3.86 (d, *J* = 15.3 Hz, 2H), 3.93 (d, *J* = 14.7 Hz, 2H), 4.69 (s, 2H), 6.82 (s, 2H), 6.85 (s, 4H), 6.94 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 19.7, 21.3, 35.6, 120.4, 124.8, 126.5, 127.5, 128.8, 132.4, 134.5, 137.7, 140.9, 149.5. All data were consistent with literature values.[24]

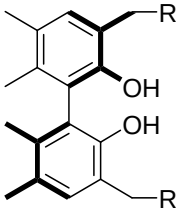
(*R*)-3,3'-Bis(4-*tert*-butylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-19j)



R = 4-*t*-BuC_6H_4

White foam; 89% yield; $[\alpha]_D^{21}$ +12.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 18H), 1.86 (s, 6H), 2.20 (s, 6H), 3.92 (d, *J* = 15.0 Hz, 2H), 3.98 (d, *J* = 15.0 Hz, 2H), 4.69 (s, 2H), 6.97 (s, 2H), 7.17 (d, *J* = 8.4 Hz, 4H), 7.30 (d, *J* = 8.4 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 19.7, 31.4, 34.3, 35.2, 120.4, 124.7, 125.3, 128.3, 128.9, 132.5, 134.6, 137.9, 149.5. All data were consistent with literature values.[24]

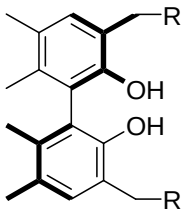
(*R*)-3,3'-Bis(4-methylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-19k)



R = 4-MeC_6H_4

White foam; 94% yield; $[\alpha]_D^{21}$ -18.5 (*c* 0.40, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (s, 6H), 2.20 (s, 6H), 2.32 (s, 6H), 3.91 (d, *J* = 15.0 Hz, 2H), 3.97 (d, *J* = 15.3 Hz, 2H), 4.63 (s, 2H), 6.94 (s, 2H), 7.09 (d, *J* = 8.4 Hz, 4H), 7.14 (d, *J* = 8.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 19.7, 21.2, 35.5, 120.6, 125.1, 128.9, 129.2, 129.4, 132.5, 134.7, 135.3, 138.1, 149.6. All data were consistent with literature values.[24]

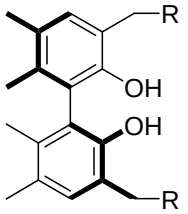
(*R*)-3,3'-Bis(naphthalene-2-ylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-19l)



R = 2-Np

White solid; 98% yield; mp 86.5-88.0 ^{o}C; $[\alpha]_D^{21}$ -16.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88 (s, 6H), 2.20 (s, 6H), 4.11 (d, *J* = 15.0 Hz, 2H), 4.17 (d, *J* = 15.3 Hz, 2H), 4.69 (s, 2H), 6.98 (s, 2H), 7.43 (m, 6H), 7.67 (s, 2H), 7.78 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 19.7, 35.9, 120.4, 124.6, 125.1, 125.8, 126.7, 126.8, 127.6, 127.8, 127.9, 128.9, 132.0, 132.5, 133.6, 134.7, 138.5, 149.5. All data were consistent with literature values.[24]

(*S*)-3,3'-Bis(2,4,6-tri-methylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-19e)



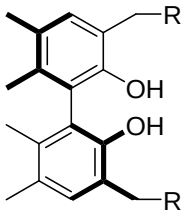
R = 2,4,6-$Me_3C_6H_2$

A solution of mesitylmagnesium bromide in tetrahydrofuran (THF, 1 M, 3 mL) was added at 0 ^{o}C to a solution of (*S*)-3,3'-bis(chloromethyl)-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl (366 mg, 1 mmol) in THF (10 mL) containing CuI (48 mg, 0.125 mmol) over 30 min. The mixture was warmed up to room temperature and stirred for an additional 30 min and then at 50 ^{o}C for 10 h. The reaction was quenched with aqueous NH_4Cl solution (20 mL) and the reaction mixture was extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were washed with water (40 mL) and brine (40 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting oil was directly used for the next step without further purification.

BBr_3 (2.2 mL, 1 M solution in CH_2Cl_2) was added dropwise over 20 min to a stirred solution of the previous crude product in CH_2Cl_2 (20 mL) at 0 ^oC. The mixture was stirred at 0 ^oC for 1.5 h. The reaction was quenched by the slow addition of water. The aqueous layer was extracted with Et_2O (20 mL x 3). The combined organic layers were washed with water (40 mL) and brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/AcOEt = 50:1 to 30:1) to afford (*S*)-**1-19e** (476 mg, 94% over two steps) as a white solid. mp 185-186 ^oC; $[\alpha]_D^{21}$ -20.0 (*c* 0.30, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.87 (s, 6H), 2.12 (s, 6H), 2.25 (s, 12H), 2.33 (s, 6H), 3.95 (d, *J* = 17 Hz, 2H), 4.00 (d, *J* = 17 Hz, 2H), 4.76 (s, 2H), 6.45 (s, 2H), 6.93 (s, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.0, 19.9, 20.0, 20.9, 28.2, 119.7, 123.5, 128.8, 128.8, 129.8, 133.6, 133.9, 135.4, 137.2, 149.5; HRMS (EI+) calcd for $C_{36}H_{42}O_2$ $[M]^+$ 506.3185, found 506.3193 (Δ = 1.6 ppm).

In the same manner, chiral biphenols, (*S*)-**1-19b-d** and (*S*)-**1-19g-h** were synthesized.

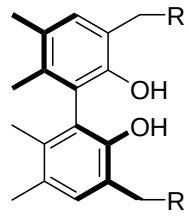
(*S*)-3,3'-Bis(4-phenylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-19b)



R = 4-biphenyl

White solid; yield 93%; mp 141-142 ^oC; $[\alpha]_D^{21}$ +10.8 (*c* 0.65, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.94 (s, 6H), 2.28 (s, 6H), 4.06 (d, *J* = 15.2 Hz, 2H), 4.11 (d, *J* = 15.2 Hz, 2H), 4.72 (s, 2H), 7.06 (s, 2H), 7.38 (m, 6H), 7.46 (m, 4H), 7.57 (d, *J* = 7.8 Hz, 4H), 7.63 (d, *J* = 7.8 Hz, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.3, 19.9, 35.6, 120.5, 124.7, 127.1, 127.1, 127.2, 128.8, 129.1, 129.2, 132.6, 134.9, 138.9, 140.3, 141.2, 149.7; HRMS (EI+) calcd for $C_{42}H_{38}O_2$ $[M]^+$ 574.2872, found 574.2869 (Δ = -0.5 ppm).

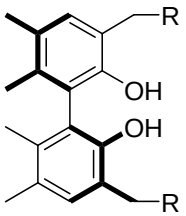
(*S*)-3,3'-Bis(3,5-di-*tert*-butylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-19c)



R = 3,5-*t*-$Bu_2C_6H_3$

White solid; yield 89%; mp 80-81 ^oC; $[\alpha]_D^{21}$ +40.0 (*c* 0.45, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 36H), 1.88 (s, 6H), 2.21 (s, 6H), 3.92 (d, *J* = 15.2 Hz, 2H), 4.04 (d, *J* = 15.2 Hz, 2H), 4.62 (s, 2H), 6.97 (s, 2H), 7.10 (s, 4H), 7.26 (s, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.2, 19.8, 31.5, 34.8, 36.2, 119.9, 120.6, 122.9, 124.8, 128.8, 132.5, 134.4, 140.0, 149.5, 150.6; HRMS (EI+) calcd for $C_{46}H_{62}O_2$ $[M]^+$ 646.4750, found 646.4743 (Δ = -1.1 ppm).

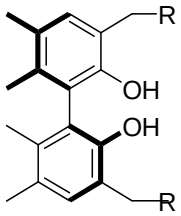
(*S*)-3,3'-Bis(2,6-diethylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-19d)



R = 2,6-$Et_2C_6H_3$

White solid; yield 84%; mp 170-171 ^oC; $[\alpha]_D^{21}$ -14.9 (*c* 0.47, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.5 Hz, 12H), 1.90 (s, 6H), 2.12 (s, 6H), 2.65 (q, *J* = 7.5 Hz, 8H), 4.05 (d, *J* = 17.2 Hz, 2H), 4.12 (d, *J* = 17.2 Hz, 2H), 4.81 (s, 2H), 6.45 (s, 2H), 7.17 (d, *J* = 7.5 Hz, 4H), 7.26 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 15.4, 16.0, 19.8, 26.4, 27.1, 119.6, 124.4, 126.2, 126.6, 128.8, 130.3, 133.9, 135.2, 143.4, 149.2; HRMS (EI+) calcd for $C_{38}H_{46}O_2$ $[M]^+$ 534.3498, found 534.3491 (Δ = -1.3 ppm).

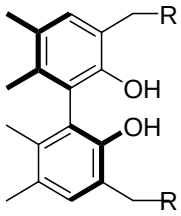
(*S*)-3,3'-Bis(2-methylnaphthalen-1-ylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-19g)



R = 1-(2-MeNp)

White solid; yield 88%; mp 127-128 ^{o}C; $[\alpha]_D^{21}$ -12.2 (*c* 0.74, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 6H), 2.02 (s, 6H), 2.54 (s, 6H), 4.47 (s, 4H), 4.94 (s, 2H), 6.42 (s, 2H), 7.43 (m, 6H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 6.9 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.1, 19.8, 20.5, 27.4, 119.8, 123.8, 124.3, 124.6, 126.0, 126.6, 128.4, 129.0, 129.2, 130.5, 132.6, 133.1, 133.4, 134.2, 134.5, 149.2; HRMS (EI+) calcd for $C_{40}H_{38}O_2$ $[M]^+$ 550.2872, found 550.2863 (Δ = -1.6 ppm).

(*S*)-3,3'-Bis(2-isopropylnaphthalen-1-ylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)- 1-19h)

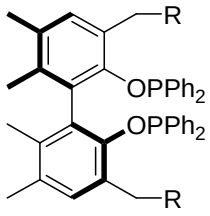


R = 1-(2-*i*-PrNp)

White solid; yield 87%; mp 125-126 ^{o}C; $[\alpha]_D^{21}$ -12.9 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.7 Hz, 12H), 1.89 (s, 6H), 2.02 (s, 6H), 3.46 (m, 2H), 4.49 (d, *J* = 18.6 Hz, 2H), 4.54 (d, *J* = 18.6 Hz, 2H), 4.94 (s, 2H), 6.45 (s, 2H), 7.43 (m, 4H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.82 (m 4H), 7.99 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.1, 19.8, 23.9, 23.9, 26.6, 29.8, 119.7, 123.9, 124.5, 124.7, 124.9, 126.1, 127.3, 128.3, 128.9, 130.8, 131.8, 132.4, 133.1, 134.1, 144.8, 149.0; HRMS (EI+) calcd for $C_{44}H_{46}O_2$ $[M]^+$ 606.3498, found 606.3507 (Δ

= 1.5 ppm).

(*S*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(2,4,6-tri-methylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-L1e)

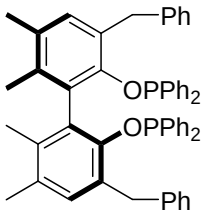


R = 2,4,6-$Me_3C_6H_2$

A solution of chlorodiphenylphosphine (221 mg, 1 mmol) in CH_2Cl_2 (2 mL) was added slowly over 20 min to a solution of an enantiopure biphenol (*S*)-**1-19e** (202 mg, 0.4 mmol), 4-*N*,*N*-dimethylaminopyridine (DMAP) (5 mg, 0.04 mmol), and triethylamine (TEA) (0.3 ml, 2.5 mmol) in CH_2Cl_2 (4 mL) at 0 ^oC. The mixture was stirred at the same temperature for additional 2 h. The reaction mixture was then concentrated in vacuo. The residue was dissolved in ether (4 mL) and filtered through a pad of Celite®. The filtrate was concentrated again and the crude product was purified on a silical gel column pretreated with TEA by using hexanes/AcOEt (50:1) as the eluent to afford (*S*)-L**1e** (248 mg, 71%), as a white foam. mp 95-97 ^oC; $[\alpha]_D^{21}$ +127.6 (*c* 0.29, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.79 (s, 6H), 1.83 (s, 6H), 2.03 (s, 12H), 2.28 (s, 6H), 3.49 (d, *J* = 16.8 Hz, 2H), 3.66 (d, *J* = 16.8 Hz, 2H), 6.06 (s, 2H), 6.82 (s, 4H), 7.18 (m, 12H), 7.38 (m, 8H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.7, 20.0, 20.9, 29.9, 127.7, 127.9, 128.2, 128.5, 129.0, 129.2, 130.2, 130.3, 131.4, 134.1, 134.2, 135.1, 137.2, 151.9; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 108.75; HRMS (ESI+) calcd for $C_{60}H_{61}O_2P_2$ $[M + H]^+$ 875.4147, found 875.4165 (Δ = 1.8 ppm).

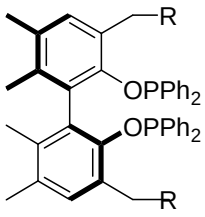
In the same manner, BOP ligands, (*S*)-L**1a-d,** (*S*)-L**1g-h,** (*R*)-L**1f,** (*R*)-L**1i-m,** (*S*)-L**1n,** (*R*)-L**1o-p** and (*S*)-L**2-3e** were synthesized.

(*S*)-2,2'-Bisdiphenylphosphinoxy-3,3'-dibenzyl-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-L1a)



White Solid; 70% yield; mp 75.0–77.0 ^{o}C; $[\alpha]_D^{21}$ +101.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 6H), 1.85 (s, 6H), 3.49 (d, *J* = 15.9 Hz, 2H), 3.65 (d, *J* = 15.8 Hz, 2H), 6.39 (s, 2H), 6.96 (m, 4H), 7.28 (m, 26H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 109.1. All data were consistent with literature values.[24]

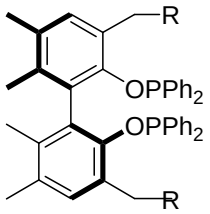
(*S*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(4-phenylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-L1b)



R = 4-biphenyl

White solid; yield 70%; mp 85-87 ^{o}C; $[\alpha]_D^{21}$ +130.0 (*c* 0.29, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (s, 6H), 1.90 (s, 6H), 3.55 (d, *J* = 15.9 Hz, 2H), 3.72 (d, *J* = 15.9 Hz, 2H), 6.48 (s, 2H), 7.02 (d, *J* = 8.0 Hz, 4H), 7.16 (m, 12H), 7.39 (m, 18H), 7.58 (d, *J* = 8.0 Hz, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 17.0, 19.9, 36.0, 126.7, 126.9, 127.7, 127.8, 128.7, 128.7, 128.8, 128.9, 129.5, 129.8, 130.6, 131.1, 131.6, 134.9, 138.3, 140.3, 141.2, 151.8; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 110.63; HRMS (ESI+) calcd for $C_{66}H_{57}O_2P_2$ $[M + H]^+$ 943.3834, found 943.3858 (Δ = 2.5 ppm).

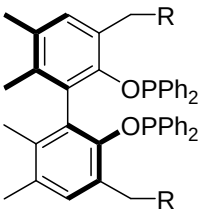
(*S*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(3,5-di-*tert*-butylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-L1c)



R = 3,5-*t*-$Bu_2C_6H_3$

White solid; yield 81%; mp 81-83 °C; $[\alpha]_D^{21}$ +77.1 (*c* 0.48, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 36H), 1.75 (s, 6H), 1.82 (s, 6H), 3.57 (d, *J* = 15.4 Hz, 2H), 3.69 (d, *J* = 15.4 Hz, 2H), 6.48 (s, 2H), 6.94 (m, 4H), 6.99 (s, 4H), 7.10 (m, 2H), 7.21 (m, 6H), 7.29 (m, 6H), 7.42 (m, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.9, 19.8, 31.5, 34.7, 36.8, 119.4, 123.4, 127.5, 127.7, 128.2, 128.7, 129.1, 129.8, 130.4, 130.9, 131.3, 134.3, 140.2, 150.1; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 109.45; HRMS (ESI+) calcd for $C_{70}H_{81}O_2P_2$ $[M + H]^+$ 1015.5712, found 1015.5728 (Δ = 1.6 ppm).

(*S*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(2,6-diethylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-L1d)

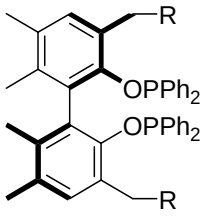


R = 2,6-$Et_2C_6H_3$

White solid; yield 74%; mp 80-82 °C; $[\alpha]_D^{21}$ +125.8 (*c* 0.31, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, *J* = 7.5 Hz, 12H), 1.81 (s, 6H), 1.84 (s, 6H), 2.45 (q, *J* = 7.5 Hz, 8H), 3.58 (d, *J* = 16.9 Hz, 2H), 3.81 (d, *J* = 16.9 Hz, 2H), 6.08 (s, 2H), 7.07 (d, *J* = 7.6 Hz, 4H), 7.21 (s, 14H), 7.41 (m, 8H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 15.3, 16.6, 20.0, 26.3, 29.0, 126.0, 126.3, 127.7, 127.9, 128.4, 128.7, 129.0, 130.2, 130.3, 131.4, 134.0, 135.8, 143.2, 151.6; ^{13}P NMR

(121.5 Hz, $CDCl_3$) δ 108.84; HRMS (ESI+) calcd for $C_{62}H_{65}O_2P_2$ $[M + H]^+$ 903.4460, found 903.4478 (Δ = 2.0 ppm).

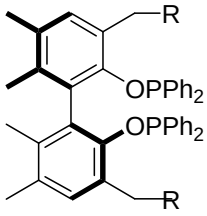
(*R*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(naphthalen-1-ylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-L1f)



R = 1-Np

White solid; yield 81%; mp 114.0–116.0 ^oC; $[\alpha]_D^{21}$ +148.1 (*c* 1.00, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.84 (s, 6H), 1.87 (s, 6H), 3.91 (d, *J* = 16.4 Hz, 2H), 4.19 (d, *J* = 16.4 Hz, 2H), 6.39 (s, 2H), 7.07 (m, 14H), 7.38 (m, 14H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.82 (m, 4H); ^{31}P NMR (161.9 Hz, CDCl3) δ 108.7. All data were consistent with literature values.[24]

(*S*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(2-methylnaphthalen-1-ylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-L1g)

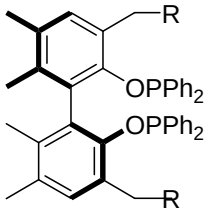


R = 1-(2-MeNp)

White solid; yield 78%; mp 109-111 ^oC; $[\alpha]_D^{21}$ +106.2 (*c* 0.65, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.68 (s, 6H), 1.75 (s, 6H), 2.31 (s, 6H), 4.06 (d, *J* = 16.8 Hz, 2H), 4.17 (d, *J* = 16.8 Hz, 2H), 6.04 (s, 2H), 7.06 (m, 4H), 7.13 (m, 2H), 7.35 (m, 16H), 7.52 (m, 4H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.82 (m, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.8, 19.9, 20.5, 29.4, 124.5, 124.7, 125.9, 126.4, 127.9, 128.2, 128.8, 129.0, 129.7, 129.8, 130.3, 130.4, 131.6, 132.4, 133.0, 133.8, 134.4, 134.5, 143.2, 151.5; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 110.15; HRMS (ESI+) calcd for

$C_{64}H_{57}O_2P_2$ $[M + H]^+$ 919.3834, found 919.3842 (Δ = 0.9 ppm).

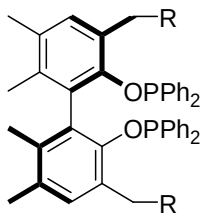
(*S*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(2-isopropylnaphthalen-1-ylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-L1h)



R = 1-(2-*i*-PrNp)

White solid; yield 71%; mp 106-108 °C; $[\alpha]_D^{21}$ +162.2 (*c* 0.37, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.8 Hz, 6H), 1.27 (d, *J* = 6.8 Hz, 6H), 1.73 (s, 6H), 1.78 (s, 6H), 3.26 (m, 2H), 4.12 (d, *J* = 17.1 Hz, 2H), 4.26 (d, *J* = 17.1 Hz, 2H), 6.13 (s, 2H), 7.09 (m, 4H), 7.16 (m, 2H), 7.29 (m, 6H), 7.39 (m, 4H), 7.52 (m, 10H), 7.81 (m, 4 H), 7.88 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.7, 19.9, 23.8, 23.9, 28.6, 29.6, 123.8, 124.6, 125.3, 125.9, 127.0, 127.9, 128.1, 128.7, 129.0, 129.4, 129.7, 130.3, 131.5, 131.9, 132.2, 133.0, 134.4, 143.2, 144.5, 151.2; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 109.95; HRMS (ESI+) calcd for $C_{68}H_{65}O_2P_2$ $[M + H]^+$ 975.4460, found 975.4490 (Δ = 3.1 ppm).

(*R*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(3,5-dimethylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-L1i)

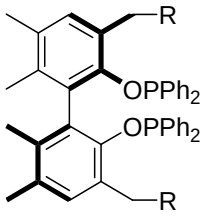


R = 3,5-$Me_2C_6H_3$

White foam; yield 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (s, 6H), 1.87 (s, 6H), 2.25 (s, 12H), 3.49 (d, *J* = 15.6 Hz, 2H), 3.66 (d, *J* = 15.6 Hz, 2H), 6.46 (s, 2H), 6.68 (s, 4H), 6.80 (s,

2H), 7.23 (m, 20H); ^{31}P NMR (161.9 Hz, $CDCl_3$) δ 110.5. All data were consistent with literature values.[23]

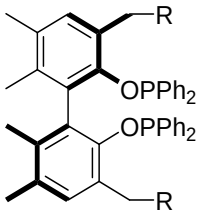
(*R*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(4-*tert*-butylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-L1j)



R = 4-*t*-BuC_6H_4

White solid; yield 80%; mp 71.0–73.0 ^{o}C; $[\alpha]_D^{22}$ -100.5 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 18H), 1.75 (s, 6H), 1.85 (s, 6H), 3.48 (d, *J* = 15.7 Hz, 2H), 3.63 (d, *J* = 15.8 Hz, 2H), 6.41 (s, 2H), 6.92 (d, *J* = 8.2 Hz, 4H), 7.15 (m, 24H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 110.2. All data were consistent with literature values.[24]

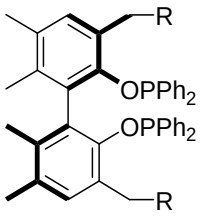
(*R*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(4-methylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-L1k)



R = 4-MeC_6H_4

White foam; yield 73%;^{1}H NMR (400 MHz, $CDCl_3$) δ1.75 (s, 6H), 1.85 (s, 6H), 2.32 (s, 6H), 3.48 (d, *J* = 16.0 Hz, 2H), 3.63 (d, *J* = 16.0 Hz, 2H), 6.44 (s, 2H), 6.90 (d, *J* = 8.0 Hz, 4H), 7.03 (d, *J* = 8.0 Hz, 4H), 7.22 (m, 20H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 110.7. All data were consistent with literature values.[24]

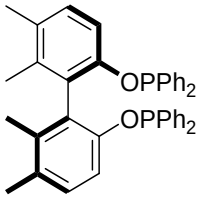
(*R*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(naphthalen-2-ylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-L1l)



R = 2-Np

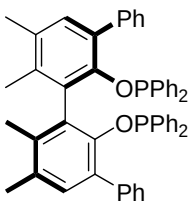
White solid: yield 71%; mp 119.0–121.0 ^{o}C; $[\alpha]_D^{22}$ -145.3 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (s, 6H), 1.86 (s, 6H), 3.66 (d, *J* = 15.9 Hz, 2H), 3.84 (d, *J* = 15.9 Hz, 2H), 6.45 (s, 2H), 7.11 (m, 12H), 7.41 (m, 15H), 7.69 (m, 7H); ^{31}P NMR (161.9 Hz, $CDCl_3$) δ 109.4; All data were consistent with literature values.[24]

(*R*)-2,2'-Bisdiphenylphosphinoxy-5,5',6,6'-tetramenthyl-1,1'-biphenyl ((*R*)-L1m)



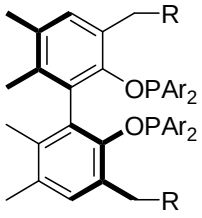
White foam; yield 77%; $[\alpha]_D^{22}$ +38.2 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81 (s, 6H), 2.15 (s, 6H), 6.87 (d, *J* = 7.8 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 7.18 (m, 20H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 109.5. All data were consistent with literature values.[24]

(*R*)-2,2'-Bisdiphenylphosphinoxy-3,3'-diphenyl-5,5',6,6'-tetramenthyl-1,1'-biphenyl ((*R*)-L1p)



White solid; yield 71%; mp 69.0-71.0 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (s, 6H), 1.99 (s, 6H), 6.87 (s, 2H), 7.18 (m, 30H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 109.5. All data were consistent with literature values.[24]

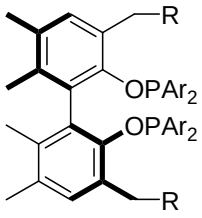
(*S*)-2,2'-Bis[bis(*p*-tolyl)phosphinoxy]-3,3'-bis(2,4,6-tri-methylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-L2e)



R = 2,4,6-$Me_3C_6H_2$
Ar = tolyl

White solid; yield 78%; mp 110-112 ^{o}C; $[\alpha]_D^{21}$ +119.4 (*c* 0.31, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 6H), 1.87 (s, 6H), 2.07 (s, 12H), 2.28 (s, 6H), 2.32 (s, 6H), 2.33 (s, 6H), 3.54 (d, *J* = 16.8 Hz, 2H), 3.70 (d, *J* = 16.8 Hz, 2H), 6.12 (s, 2H), 6.87 (s, 4H), 7.01 (d, *J* = 7.8 Hz, 4H), 7.06 (d, *J* = 7.8 Hz, 4H), 7.32 (m, 8H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.7, 19.9, 20.9, 21.3, 21.3, 29.9, 128.0, 128.5, 128.6, 129.4, 130.3, 130.5, 131.2, 134.1, 134.5, 135.0, 137.2, 138.2, 138.6, 152.0; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 110.40; HRMS (ESI+) calcd for $C_{64}H_{69}O_2P_2$ $[M + H]^+$ 931.4773, found 931.4798 (Δ = 2.7 ppm).

(*S*)-2,2'-Bis[bis(*m*-xylyl)phosphinoxy]-3,3'-bis(2,4,6-tri-methylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-L3e)



R = 2,4,6-$Me_3C_6H_2$
Ar = *m*-xylyl

White solid; yield 75%; mp 114-116 ^{o}C; $[\alpha]_D^{21}$ +104.8 (*c* 0.21, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (s, 6H), 1.83 (s, 6H), 2.03 (s, 12H), 2.20 (s, 12H), 2.22 (s, 12H), 2.27 (s, 6H), 3.43 (d, *J* = 16.6 Hz, 2H), 3.71 (d, *J* = 16.4 Hz, 2H), 6.10 (s, 2H), 6.82 (s, 4H), 6.83 (s, 4H), 7.04 (s, 4H), 7.08 (s, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.6, 19.9, 20.8, 21.3, 21.4, 29.6, 126.8, 127.8, 128.2, 128.5, 130.3, 130.5, 130.9, 133.9, 134.8, 135.0, 136.8, 136.9, 137.1, 151.9; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 111.25; HRMS (ESI+) calcd for $C_{68}H_{77}O_2P_2$ $[M + H]^+$ 987.5399, found 987.5406 (Δ = 0.7 ppm).

§1.6 References

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Chapter 2

Pd-Catalyzed Asymmetric Allylic Etherification Using Chiral BOP Ligands and Its Application for The Formal Total Synthesis of (-)-Galanthamine

§2.1 Introduction of galanthamine

Galanthamine (Figure 2-1), an amaryllidaceae alkaloid,[1,2] has been used for the treatment of mild to moderate Alzheimer's disease and other memory impairments.[3] It is a reversible inhibitor of acetylcholinesterase (Ache)[4,5] and less toxic than other Ache inhibitors, such as physostigmine and tarcine.[6-9] Because the isolation from natural sources is tedious, expensive, and insufficient for clinical use, many chemical syntheses have been reported.[10-18] In addition, a biomimetic synthesis through phenol coupling followed by dynamic resolution has been performed on a pilot scale (Scheme 2-1).[19] Although the *para-para* oxidative coupling of **2-3** was blocked by introduction of a bromine protecting group, moderate yields of **2-4** were obtained. The bromine was removed by $LiAlH_4$ later. Interestingly, enantiopure (-)-narwedine (>99% ee) was transformed from racemic narwedine using 2.5% of (-)-narwedine as a crystal seed. This successful process is based on two phenomena-(i) narwedine crystallizes as a conglomerate and (ii) an equilibrium between (-)-narwedine and (+)-narwedine through a retro-Michael reaction.

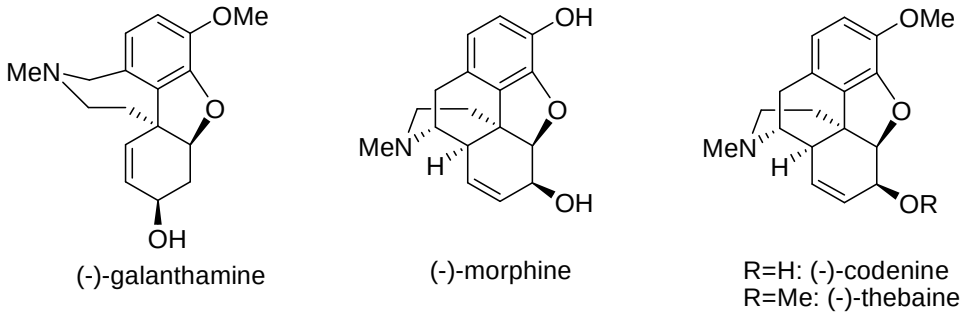
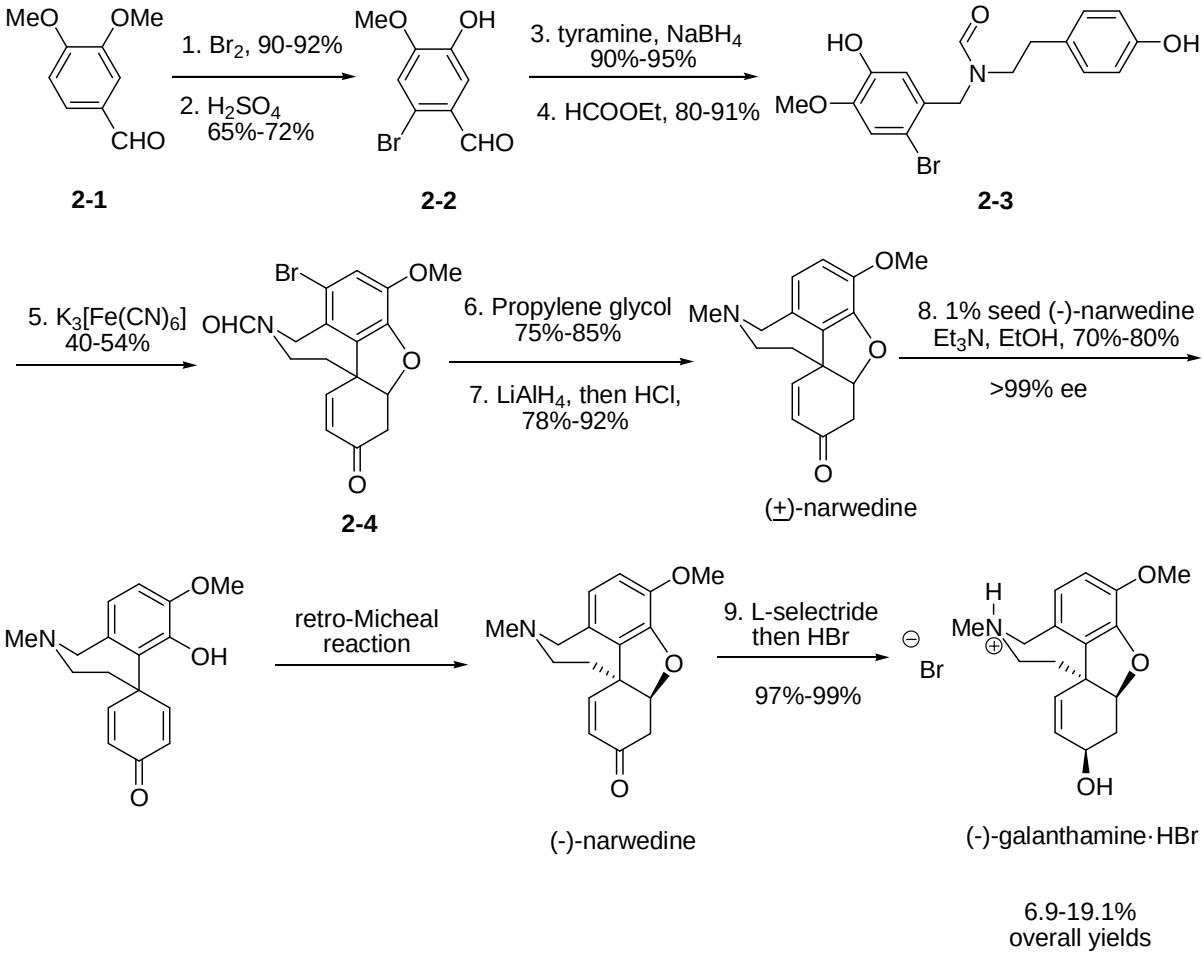


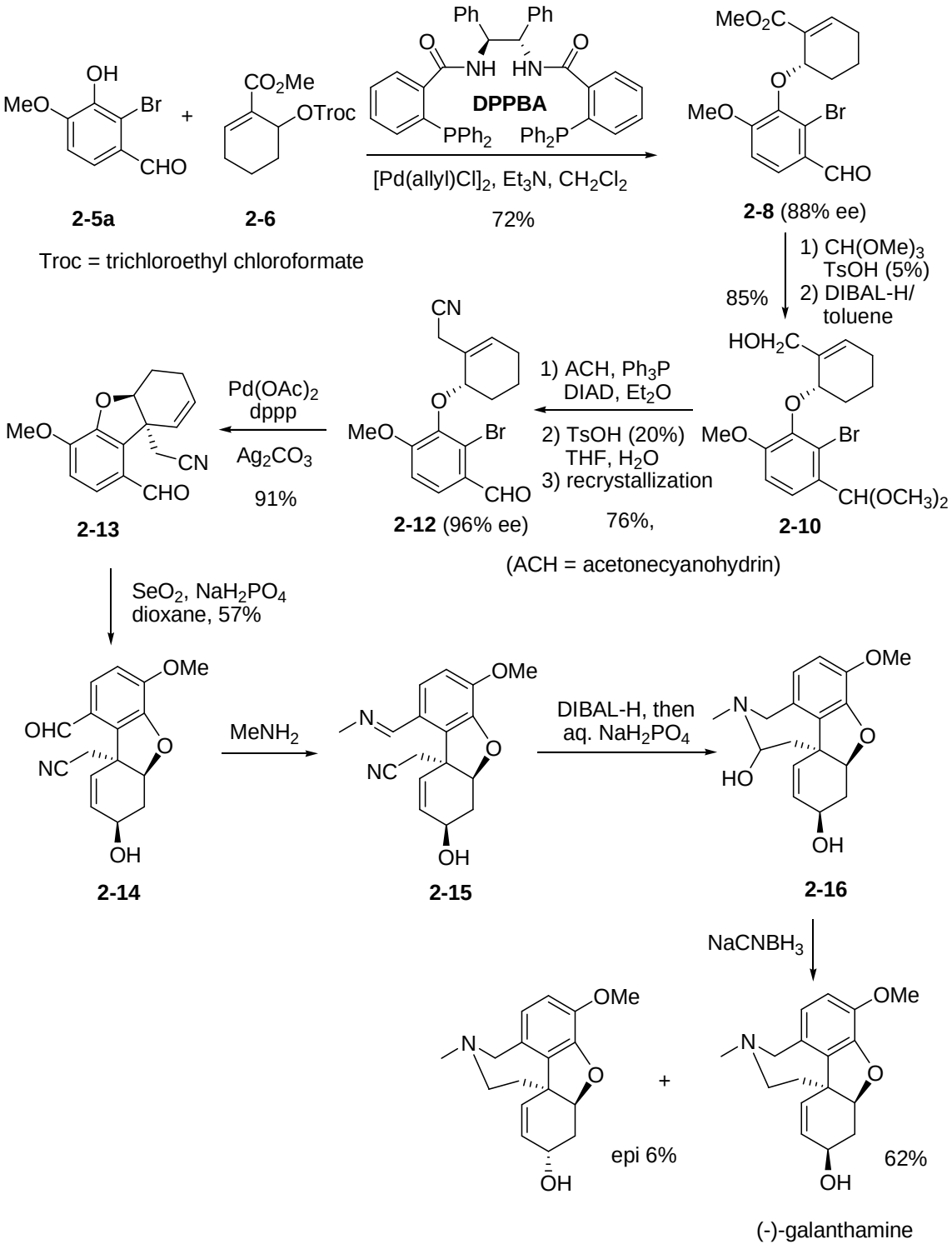
Figure 2-1. (-)-Galanthamine, (-)-morphine and its derivatives

In the 21st century, some approaches to the asymmetric total synthesis of (-)-galanthamine have been reported.[20-24] One of the most efficient methods was reported by Trost *et al.*, wherein the critical chiral centers were created by Pd-catalyzed intermolecular asymmetric allylic etherification (Pd-catalyzed AAE).[20-22] The best result achieved so far in the key step using his "modular" diphosphine ligand, DPPBA, was 88% ee and 72% yield, and recrystallization was required in the subsequent step to afford the key intermediate **2-13** (96% ee), bearing a tricyclic benzofuran skeleton with a chiral quaternary carbon (Scheme 2-2).[20] Allylic

oxidation by selenium dioxide provided alcohol **2-14** with the desired stereochemistry. The one pot reductive amination constructed the final hydrobenzazepine ring to give (-)-galanthamine with 6% epimerization. In addition, **2-13** is a versatile intermediate for the syntheses of (-)-morphine and its derivatives, (-)-codeine and (-)-thebaine (Figure 2-1).[20] Accordingly, this useful process to provide **2-13** still needs substantial improvement in its enantioselectivity and chemical yield to be more practical.



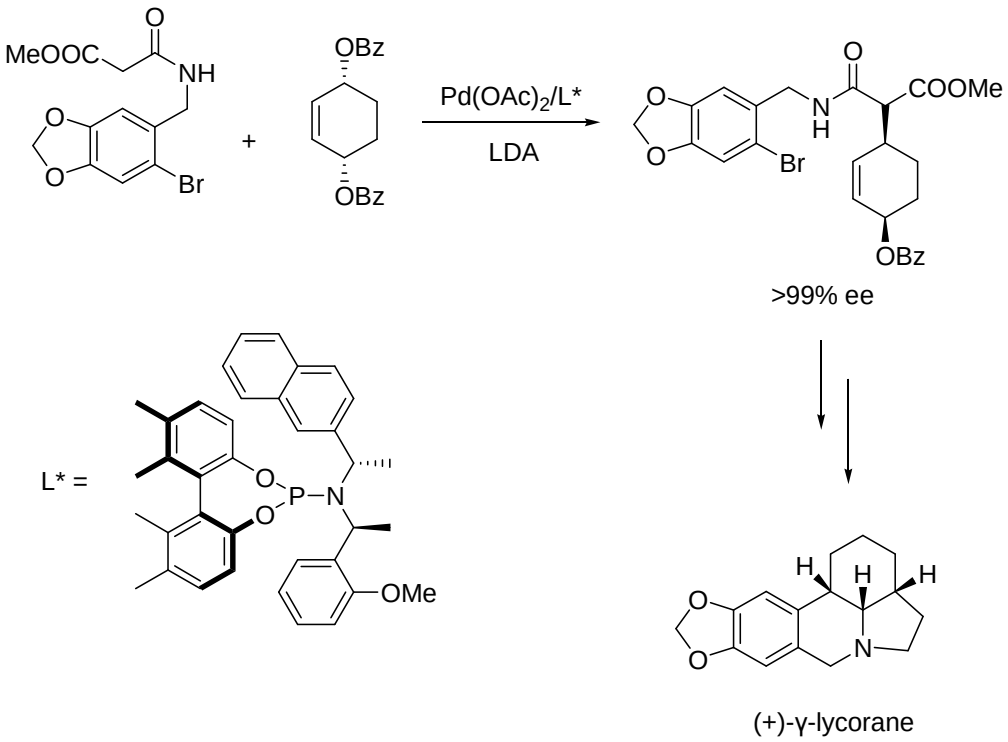
Scheme 2-1. Sanochemia's synthesis of (-)-galanthamine



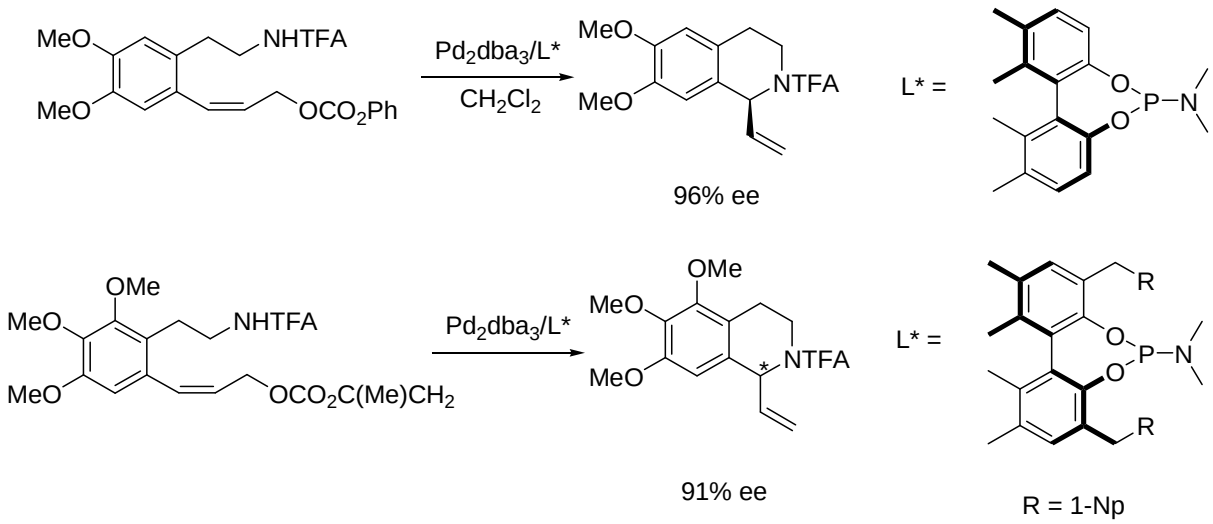
Scheme 2-2. Trost's synthesis of (-)-galanthamine

§2.2 Pd-catalyzed asymmetric allylic substitution reactions

Pd-catalyzed allylic substitution reactions were first pioneered by Tsuji in 1965.[25] The scope of the reaction was expanded gradually until triphenyl phosphine was introduced by Trost in 1973.[26] His work led to a good number of asymmetric allylic substitution strategies which were fulfilled by using chiral phosphine ligands. As mentioned in Chapter 1, our BOP ligands were successfully applied to the asymmetric synthesis of Schulzeine A-C and (-)-strychnine.[27,28] Additionally, a library of monodentate phosphoramidite ligands was developed in our lab. They have proven to be very effective in many catalytic asymmetric transformations,[29-33] especially Pd-catalyzed asymmetric allylic substitution reactions,[31-33] as illustrated in Scheme 2-3 and Scheme 2-4.



Scheme 2-3. Total synthesis of (+)-γ-lycorane



Scheme 2-4. Pd-catalyzed intramolecular asymmetric allylic amination

The catalytic cycle of asymmetric allylic substitution reactions is outlined in Scheme 2-5. First, a Pd(0) catalyst approaches and coordinates to the olefin. Second, oxidative addition (ionization) occurs and the leaving group is expelled to form a π-allyl Pd(II) complex. In this step, palladium is at an anti position to the leaving group. The nucleophile then adds to the π-allyl Pd(II) complex and followed by decomplexation releasing the desired product and regenerates the Pd(0) catalyst. It is noteworthy that the nucleophiles are divided into hard and soft types based on the pKas of their conjugate acids. Hard nucleophiles with pKas greater than 25, bind to the palladium first, leading to a syn-attack on the allylic substrate. On the other hand, soft nucleophiles with pKas less than 25, attack the allylic substrate directly from the back of the palladium.[35]

For most of the allylic substrates, each step except the final one affects enantioselectivity. However, the allylic substrate **2-6** in the Pd-AAE reaction for the total synthesis of (-)-galanthamine, formed a symmetric π-allyl complex. Therefore the nucleophilic addition step determined the enantioselectivity.

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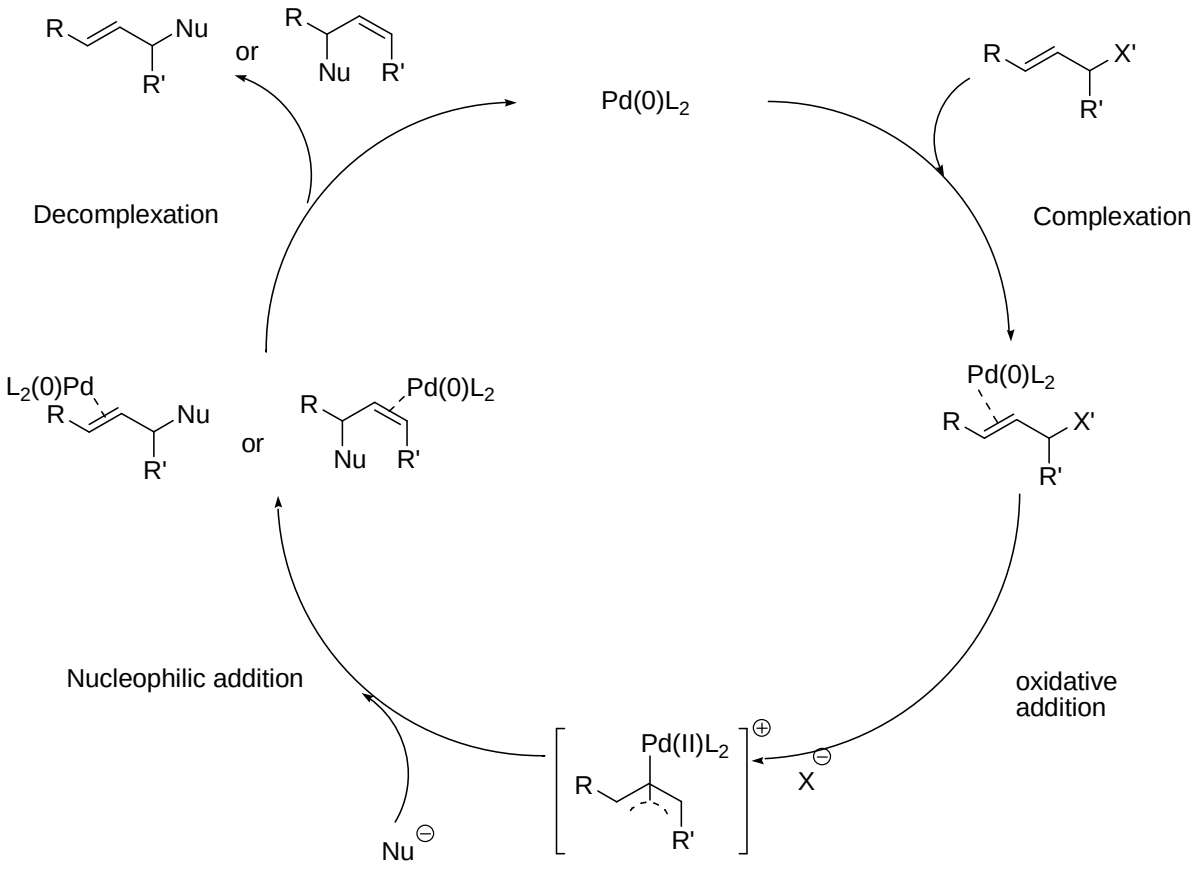
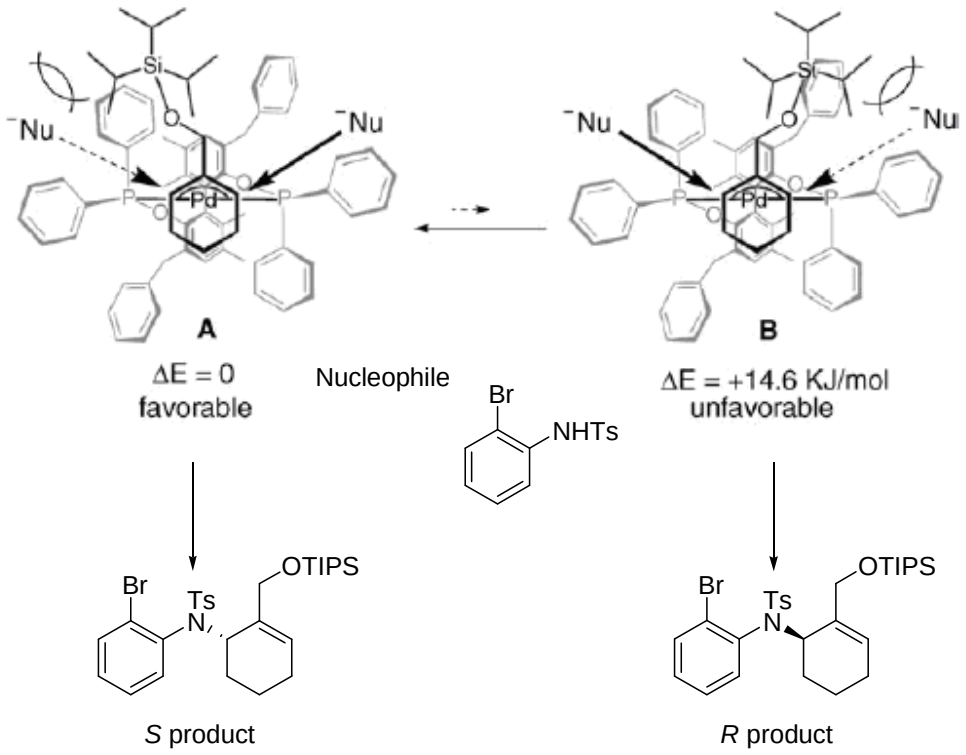


Scheme 2-5. Mechanism of Pd-catalyzed allylic substitution reactions

A similar allylic substrate **2-7a** was used in the Pd-AAA reaction for the total synthesis of (-)-strychnine.[28] A molecular modeling study of a cationic Pd(II)/(*S*)-L**1a** complex with the π-allyllic 2-TIPS-*O*-methylcyclohexenyl was made in our lab (MM2/PM3 for energy minimization).[28] The result indicated that the bulky TIPS group was crucial for the enantioselectivity (Scheme 2-6). The steric repulsion between the TIPS group and the benzyl group at the 3-position of the biphenyl moiety, led to an unfavorable conformer B. Thus the nucleophiles preferred to attack from the right side of complex A to give *S* product



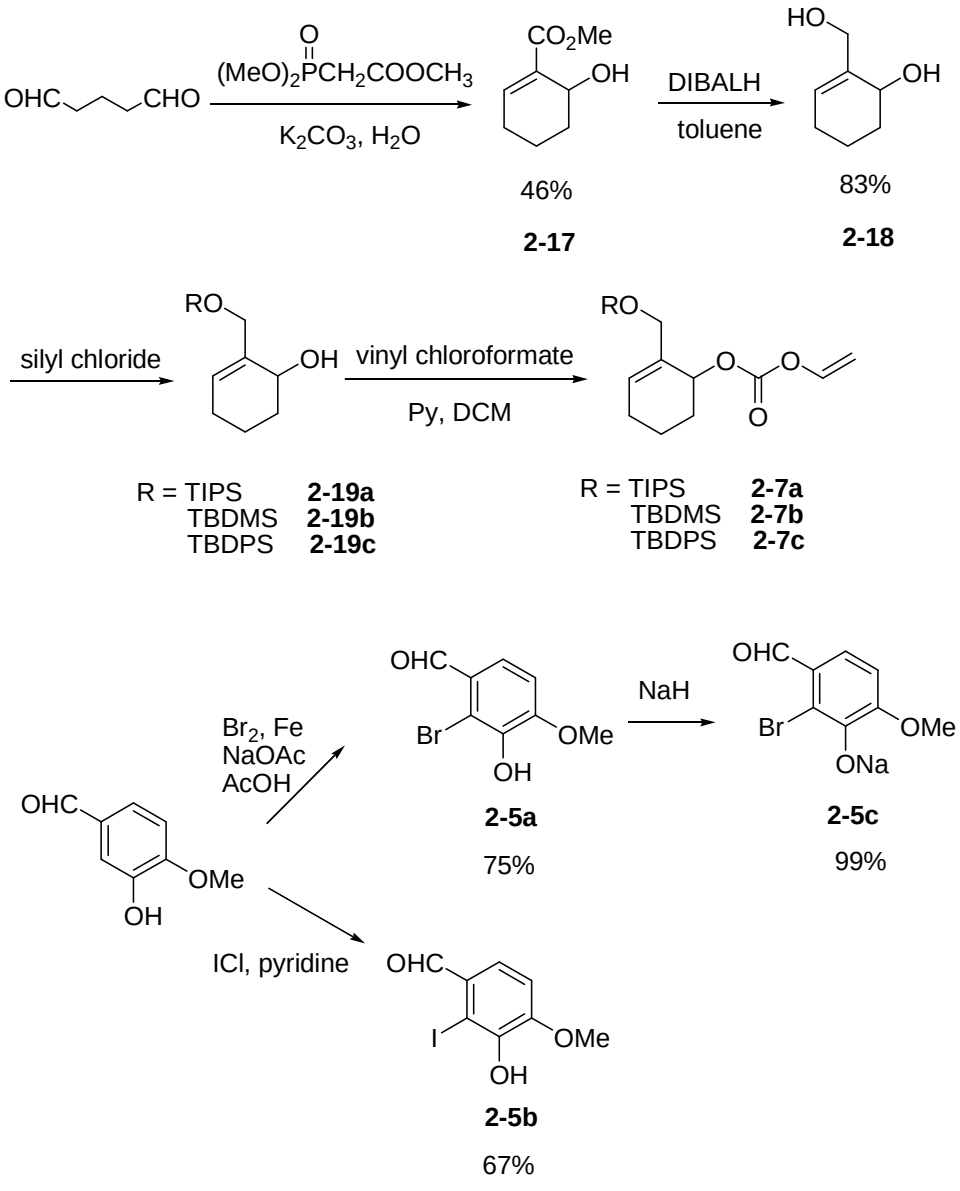
Scheme 2-6. A molecular modeling study of the π-allyl Pd(II)/(S)-L**1a** complex.

§2.3 Results and discussion

§2.3.1 Synthesis of substrates

We investigated the AAE reaction of phenol **2-5** and allylic carbonates **2-7** instead of **2-6** in Trost's synthesis. Since the ester moiety of **2-6** was reduced to a hyroxymethyl group later in Trost's synthesis, we decided to use a protected hydroxymethyl group in the allylic carbonates **2-7** from the beginning. It was reported that the methyl ester moiety at the 2-position of **2-6** was essential for the reaction to take place under Trost's conditions, and no reactions took place when other substrates bearing nonester moieties were at the 2-position.[22] We have recently used **2-7a** and **2-7b** for the successful intermolecular AAA reaction.[28] Thus the carbonates **2-7a-c** were prepared according to the reported procedure (Scheme 2-7). Glutaraldehyde was reacted with trimethyl phosphonoacetate through Horner-Wadsworth-Emmons reaction and aldol condensation to give the cyclic alcohol **2-17**. It was then subjected to DIBAL-H reduction to

afford the diol **2-18**. The hydroxymethyl group of **2-8** was protected by TIPS, TBDMS or TBDPS, followed by the coupling of the secondary hydroxyl group with vinyl chloroformate to give the corresponding carbonates **2-7a-c**. Bromination and Iodination of isovaniline afforded **2-5a** and **2-5b** respectively (Scheme 2-7). The phenolate **2-5c** was prepared by simple treatment of **2-5a** with NaH.

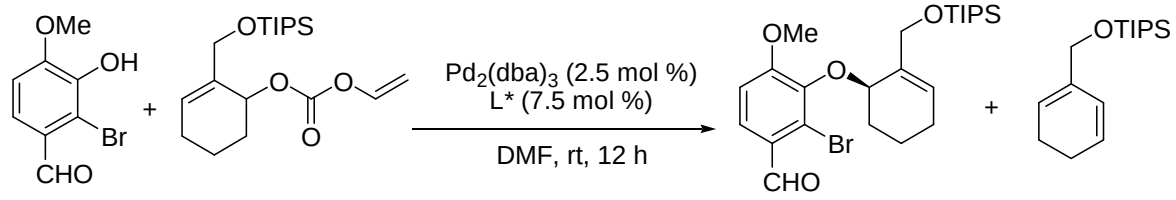


Scheme 2-7. Synthesis of substrates

§2.3.2 Pd-catalyzed asymmetric allylic etherification

Preliminary study of BOP ligands was performed using carbonate **2-7a** under conditions nearly identical to those used for the previously reported intermolecular Pd-catalyzed AAA reaction.[28] Thus, the reactions were carried out in DMF at a substrate concentration of 0.025 M with a $Pd_2(dba)_3$/ligand ratio of 1:3. Results are summarized in Table 2-1.

Table 2-1. Preliminary study of BOP ligands



2-5a (1.1 eq.) **2-7a** (+)-**2-9a** **2-20a**

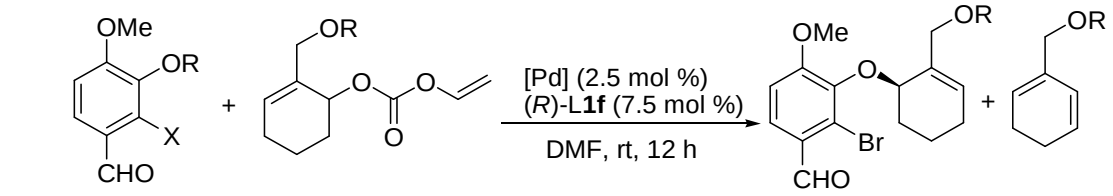
entry	ligand	conv (%)[a]	(+)-**2-9a** (% ee)[b]	**2-9a:2-20a**[a]
1	(*R*)-L**1q**	>95	8 (+)	64:36
2	(*R*)-L**1p**	>95	32 (+)	88:12
3	(*R*)-L**1a**	>95	53 (+)	84:16
4	(*R*)-L**1f**	>95	54 (+)	80:20

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC using Chiralcel OJ after desilylation with TBAF.

As Table 2-1 shows, the aryl ethers **2-9a** were obtained in good yields in all reactions, but together with byproduct **2-20a**. It is interesting to note that the formation of this type of byproduct was not reported by Trost, who used **2-6** instead of **2-7**.[20-22] The phenylethynyl and phenyl groups at the 3,3-positions, e.g. (*R*)-L**1q** and (*R*)-L**1p**, stretched out, leading to a weak steric repulsion with the bulky silyl group of carbonates. Accordingly, (*R*)-L**1q** and (*R*)-L**1p** gave lower enantioseletivities than (*R*)-L**1a** and (*R*)-L**1f**.

Since (*R*)-L**1f** had the best performance in the preliminary study, it was used for the initial screening of the allylic substrates **2-7a-c** and nucleophiles **2-5a-c** (Table 2-2). Palladium-catalyzed reaction of iodophenol **2-5b** and carbonate **2-7a** failed to produce any of the desired cyclohexenyl ether (Table 2-2, entry 1). Using phenolate **2-5c** as the nucleophile accelerated the reaction significantly, but enantioselectivity decreased to 42% ee (Table 2-2, entry 2). An increase in enantioselectivity for the formation of (+)-**2-9a** was observed as the size of the silyl group increased (Table 2-2, entries 3-5). Switching the Pd-catalyst precursor Pd(0) ($Pd_2(dba)_3$) to Pd(II) ($[Pd(allyl)Cl]_2$) increased the enantioselectivity to 80% ee (Table 2-2, entry 6). All reactions except the first two completed within 12 h at room temperature. Lowering the reaction temperature to 0 ^oC slightly increased the enantioselectivity to 82% ee (Table 2-3, entry1), but the reaction was naturally slowed down.

Table 2-2. Initial screening of substrates



2-5a R = H, X = Br
2-5b R = H, X = I
2-5c R = Na, X = Br
(1.1 eq.)

2-7a R = TIPS
2-7b R = TBDMS
2-7c R = TBDPS

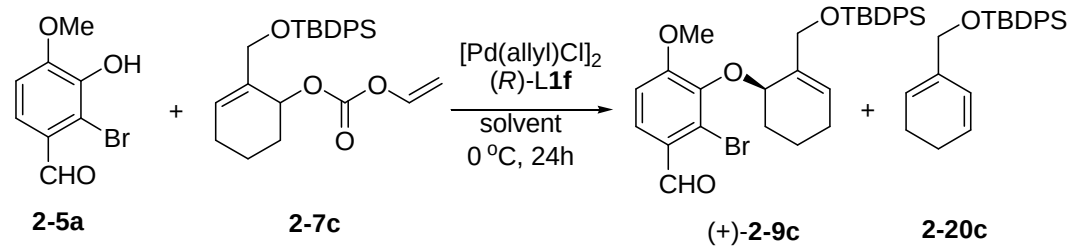
(+)-**2-9a** R = TIPS **2-20a**
(+)-**2-9b** R = TBDMS **2-20b**
(+)-**2-9c** R = TBDPS **2-20c**

entry	substrates	catalyst	conv (%)[a]	(+)-**2-9** (% ee)[b]	**2-9:2-20**[a]
1	**2-5b, 2-7a**	$Pd_2(dba)_3$	no reaction	--	--
2[c]	**2-5c, 2-7a**	$Pd_2(dba)_3$	>95	42 (+)	75:25
3	**2-5a, 2-7a**	$Pd_2(dba)_3$	>95	54 (+)	80:20
4	**2-5a, 2-7b**	$Pd_2(dba)_3$	>95	62 (+)	79:21
5	**2-5a, 2-7c**	$Pd_2(dba)_3$	>95	72 (+)	82:18
6	**2-5a, 2-7c**	$[Pd(allyl)Cl]_2$	>95	80 (+)	85:15

[a,b]See the footnotes of Table 2-1. [c]The reaction was completed within 5 h.

The effect of solvents on this reaction was also examined, using **2-7c** as the allylic substrate and $[Pd(allyl)Cl]_2$ as the catalyst precursor, at 0 ºC for 24 h. As Table 2 shows, the reactions run in CH_3CN and CH_2Cl_2 gave (+)-**2-9c** with 86% ee, but with only 46-65% conversion (Table 2-3, entries 2 and 3). It was found that phenol **2-5a** precipitated out in these solvents at 0 ^oC. Then, the addition of 1.1 equivalents of triethylamine (TEA) was found to solve or improve this problem and the reactions proceeded much more smoothly, especially in CH_3CN (Table 2-3, entries 4 and 5).

Table 2-3. Effect of solvents



2-5a (1.1 equiv) **2-7c** (+)-**2-9c** **2-20c**

entry	solvent	conv (%)[a]	(+)-**2-9c** (% ee)[b]	**2-9c:2-20c**[a]
1	DMF	>95	82 (+)	90:10
2	CH_3CN	65	86 (+)	92:8
3	CH_2Cl_2	46	86 (+)	93:7
4[c]	CH_3CN	>95	84 (+)	89:11
5[c]	CH_2Cl_2	76	84 (+)	91:9

[a,b] See the footnote of Table 2-1. [c] 1.1 equiv of TEA was added.

Next, BOP ligands were screened using **2-7c** as the allylic substrate, CH_3CN as the solvent and TEA (1.1 equiv) as the additive at 0 ^oC for 24 h. The results are summarized in Table 2-4 (The result when (*R*)-L**1f** from Table 2-3 was used is included for comparison). It should be noted that, at this point, we screened (*S*)-BOP ligands since the intermediate **2-12** for (-)-galanthamine should have the (-)-(*S*) configuration, and thus **2-9** should also have the (-)-(*S*)

configuration, which was found to be achieved by using (*S*)-BOP ligands based on the results shown above.

As Table 2-4 shows, (*S*)-L**1b** bearing a 4-phenylbenzyl group at the 3,3'-positions afforded **2-9c** with 78% ee (Table 2-4, entry 2), which was close to the results using 3,3'-unsubustitued ligand (*S*)-L**1a** (Table 2-4, entry 1). However, the introduction of a bulky substituent at the *meta* position, i.e., 3,5-di-*tert*-butylbenzyl group at the 3,3'-positions, i.e., (*S*)-L**1c**, resulted in a substantial decrease in enantioselectivity as well as conversion (Table 2-4, entry 3). In contrast to the *para* and *meta* substitutions, a significant increase in enantioselectivity was observed when ligands bearing an *ortho*-substituted benzyl group, including 2,6-disubstituted and 2,4,6-trisubsituted benzyl groups, were used at the 3,3'-positions, i.e., (*S*)-L**1d-h** (Table 2-4, entries 4-8). It should be noted that the introduction of very bulky benzyl groups, such as 2-methylnaphth-1-ylmethyl [(*S*)-L**1g**], and 2-isopropylnaphth-1-ylmethyl [(*S*)-L**1h**], slightly reduced the reaction rate and product selectivity, but enantioselectivity was not affected (Table 2-4, entries 7 and 8). Among the BOP ligands screened, (*S*)-L**1e** gave the best result (Table 2-4, entry 5). Thus, (*S*)-L**1e** was selected for further optimization. At this point, we also ran the reaction with (*S*)-L**1e** in DMF and found that the same enantioselectivity (91% ee) was obtained without addition of TEA, and the product selectivity was improved to 94:6 (see Table 2-5, entry 1).

Table 2-4. Screening of BOP ligands[a]

entry	ligand	conv (%)[b,c]	**2-9c** (% ee)[b,c]	**2-9c:2-20c**[b,c]
1	(*S*)-L**1a**	>95	79 (-)	92:8
2	(*S*)-L**1b**	>95	78 (-)	92:8
3	(*S*)-L**1c**	78	69 (-)	87:13
4	(*S*)-L**1d**	90	90 (-)	90:10
5	(*S*)-L**1e**	>95	91 (-)	92:8
6	(*R*)-L**1f**	>95	84 (+)	89:11

7	(*S*)-L**1g**	89	90 (-)	89:11
8	(*S*)-L**1h**	83	90 (-)	88:12

[a]Reactions were run using **2-7c** (0.025 M), [Pd(allyl)Cl_2] (2.5 mol %) with a BOP ligand (7.5 mol %) and 1.1 equiv of TEA in CH_3CN at 0 °C for 24 h.
[b,c]See the footnote of Table 2-1.

For further optimization of (*S*)-L**1e**, two new BOP ligands bearing *p*-tolyl [(*S*)-L**2e**] and *m*-xylyl [(*S*)-L**3e**] groups in the diarylphosphorus moieties were designed and prepared. Their efficacy was evaluated under the same conditions as those employed for ligand (*S*)-L**1e**. As Table 4 shows, the introduction of a *p*-tolyl group [(*S*)-L**2e**] slightly decreased the enantioselectivity (88% ee) and reaction rate (Table 2-5, entry 2), while that of a *m*-xylyl group [(*S*)-L**3e**] considerably increased the enantioselectivity to 97% ee with very good product selectivity (93:7), but slowed down the reaction (Table 2-5, entry 3). Accordingly, the reaction was run at higher concentration of **2-7c** (0.1 M), which gave a moderate increase in conversion (Table 2-5, entry 4). Thus, this substrate concentration was used in the subsequent reactions as well. To our delight, 97% ee with full conversion (>95% by ^{1}H NMR analysis wherein no **2-7c** was observed) after 36 h was achieved by increasing the Pd catalyst precursor loading to 5 mol % (Table 2-5, entry 5). When the reaction was run at room temperature, the reaction was completed within 12 h and **2-9c** was obtained with 94% ee (Table 2-5, entry 6). Addition of TEA at 0 °C accelerated the reaction, but enantioselectivity was 94% ee (Table 2-5, entry 7).

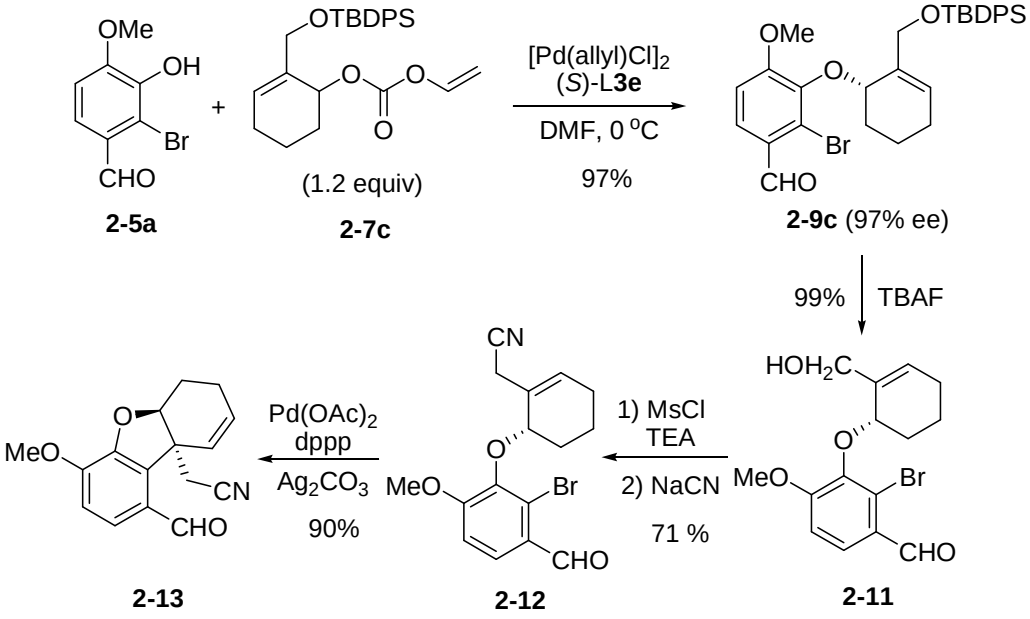
Table 2-5. Optimization of BOP ligands and conditions [a]

entry	ligand	time (h)	conv (%)[b,c]	(-)-**2-9c** (% ee)[b,c]	**2-9c:2-20c**[b,c]
1	(*S*)-L**1e**	24	>95	91 (-)	94:6
2	(*S*)-L**2e**	24	85	88 (-)	95:5
3	(*S*)-L**3e**	24	41	97 (-)	93:7
4[d]	(*S*)-L**3e**	24	51	97 (-)	89:11
5[d,e]	(*S*)-L**3e**	36	>95	97 (-)	91:9

6[d,f]	(*S*)-L**3e**	12	>95	94 (-)	83:17
7[d,g]	(*S*)-L**3e**	12	>95	94 (-)	83:17

[a] Reactions were run using **2-7c** (0.025 M), [Pd(allyl)Cl_2] (2.5 mol %) with a BOP ligand (7.5 mol %) in DMF at 0 ^oC. [b, c] See the footnote of Table 1. [d] At 0.1 M concentration of **2-7c**. [e] 5 mol % [Pd(allyl)Cl]$_2$ and 15 mol % (*S*)-L**3e**. [f] At room temperature. [g] 1.1 equiv TEA was added.

§2.3.3 Synthesis of the benzofuran intermediate



Scheme 2-8. Synthesis of the benzofuran intermediate

With the optimized conditions for the asymmetric allylic etherification, we prepared (-)-**2-9c** with 97% ee and 97% isolated yield using a slight excess of **2-7c** (1.2 equiv) to increase the product yield; i.e., phenol **2-5a** became the limiting reactant under these conditions (Scheme 2-8). Deprotection of (-)-**2-9c** with TBAF afforded allylic alcohol **2-11** in 99% yield. The nitrile **2-12**, was prepared in good yield (71% for two steps) by treatment of **2-11** with MsCl/TEA and then NaCN in DMSO. The crucial tricyclic key intermediate **2-13** for the total synthesis of (-)-galanthamine was obtained in 90% yield through intramolecular Heck reaction. Thus, the critical

intermediate **2-13** was obtained via 5 steps in 61% overall yield from **2-5a**. As compared to Trost's original work (42 % yield for 6 steps from **2-5a**), our synthesis of **2-13** has made significant improvement in that substantial enhancement of enantioselectivity (97% ee vs 88% ee) was achieved in the AAE step so that recrystallization of **2-12** was not necessary and the protection and deprotection of aldehyde (-)-**2-9c** is not required.

§2.4 Conclusions

A new series of BOP ligands have been developed that exhibit excellent efficacy when applied to the Pd-catalyzed AAE reaction, leading to the formal total synthesis of (-)-galanthamine. The results presented here further demonstrate the advantages of readily fine-tuning capability of our BOP ligands for a specific process in a variety of catalytic asymmetric reactions, including the AAE reaction. Further applications of BOP ligands as well as other biphenol-based chiral phosphorus ligands are described in the next chapter.

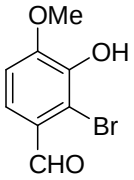
§2.5 Experimental section

General Methods. ^{1}H, ^{13}C, and ^{31}P NMR were measured on a Bruker Avance 500 (500 MHz for ^{1}H; 125 MHz for ^{13}C), a Bruker Avance 400 (400 MHz for ^{1}H; 100 MHz for ^{13}C), or a Varian Gemini-2300 300 MHz (300 MHz for ^{1}H; 75 MHz for ^{13}C) NMR spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm) as the internal standard. Analytical HPLC in normal phase was carried out with a Shimadzu LC-2010A HPLC system using a Chiralcel OJ, or Chiralcel ODH analytical column. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Helmer Model 241 polarimeter. TLC analyses were performed using Merck DC Alufolien $60F_{254}$ aluminum pre-coated silica gel plates. Flash column chromatography was carried out using Silicyle Silia*Flash*P60® silica gel (particle size 40_63 μm). High-resolution mass spectrometric analyses were carried out at the Mass Spectrometry Laboratory, University of Illinois Urbana-Champaign, Urbana, IL or by ICB&DD at Stony

Brook University. Unless otherwise noted all reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques.

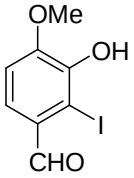
Material. Solvents were reagents grade and freshly dried, degassed and distilled before use. Anhydrous *N*,*N*-dimethylformamide (DMF) and acetonitrile were purchased from Acros Organic and used without further purification. Chemicals and reagents were purchased from VWR, Fisher Scientific or Sigma-Aldrich and used without further purification unless otherwise noted.

2-Bromoisovanillin (**2-5a**)



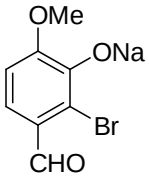
To a suspension of isovanillin (5.0 g, 32.9 mmol), anhydrous sodium acetate (5.45 g, 66.4 mmol), and iron powder (0.15 g) in glacial acetic acid (30 mL), a solution of bromine (1.8 mL, 35.1 mmol) in acetic acid (6 mL) was added dropwise at room temperature over 15 min. After the addition was completed, the reaction mixture was stirred at the same for 1 h, and then poured into ice water (200 mL). The white precipitate was collected, washed with cold water (50 mL), and dried in the air to give **2-5a** (5.38 g, 71%) as a off-white solid. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 3.45 (brs, 1H), 3.97 (s, 3H), 7.19 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 10.15 (s, 1H). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 56.8, 110.6, 113.7, 122.3, 125.4, 144.4, 153.6, 191.3. All data were consistent with literature results.[22]

2-Iodoisovanillin (**2-5b**)



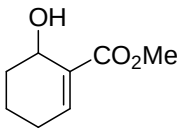
Isovanillin (3.04 g, 20.0 mmol) was dissolved in pyridine (12 mL) and cool to 0 ^{o}C. A solution of ICl (1.03 mL, 20.0 mmol) in 1,4-dioxane (20 mL) was added dropwise, and the resulting solution was protected for light and allowed to warm to room temperature. The solution was stirred at the same temperature for 6 d. After removal of the solvent in vacuo, water (60 mL) was added. The mixture was acidified to pH 1 with aq. HCl (6 M, 3 mL). The aqueous layer was extracted with ethyl acetate (3 x 60 mL). The organic layer was washed with saturated aqueous Na_2SO_4 (2 x 40 mL), water (2 x 60 mL) and brine (60 mL). The solution was dried over $MgSO_4$. After the solution was concentrated in vacuo, the crude product was recrystallized with MeOH to afford **2-5b** (3.65 g, 67%) as a off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (s, 3H), 6.30 (s, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 10.03 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.9, 88.5, 110.3, 124.2, 129.0, 145.9, 150.9, 195.1. All data were consistent with literature results.[22]

Sodium 2-bromo-3-formyl-6-methoxyphenolate (2-5c)



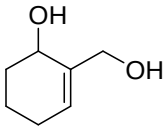
To a solution of 2-bromoisovanillin (1.16 g, 5 mmol) in THF was added NaH (0.12 g) at room temperature. The solution was stirred at the same temperature for 1 h. The solvent was removed *in vacuo* to afford **2-5c** (1.26 g, 99%) as a yellow solid. ^{l}H NMR (300 MHz, D_2O) δ 3.73 (s, 3H), 6.79 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 9.91 (s, 1H).

Methyl 6-hydroxycyclohex-1-enecarboxylate (2-17)



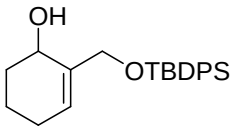
To a solution of 50% aqueous glutaraldehyde (20 mL, 100 mmol), trimethyl phosphonoacetate (16.2 mL, 100 mmol) was added dropwise at the room temperature over 2h. After the addition was completed, 6.4 M aqueous K_2CO_3 (40 mL, 250 mmol) was added dropwise at the same temperature over another 2 h. The reaction mixture was stirred at the same temperature for 2 d, and then was diluted with H_2O and extracted with Et_2O twice. The combined organic layer was washed with brine, dried over $MgSO_4$. After the drying agent was removed by filtration, the resulting solution was concentrated under reduced pressure to give crude **2-17**. The pure compound was obtained as a colorless oil (7.05 g, 46%) by distillation at 4 mmHg, 82 ^oC. ^1H NMR (300 MHz, $CDCl_3$) δ 1.63 (m, 1H), 1.81 (m, 3H), 2.16 (m, 1H), 2.28 (ddt, J = 20 Hz, 4.9 Hz, 4.9 Hz, 1H), 2.73 (broad s, 1H), 3.76 (s, 3H), 4.53 (t, J = 5.0 Hz, 1H), 7.09 (t, J = 4.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 26.2, 30.1, 52.0, 63.4, 132.2, 143.7, 167.9. All data were consistent with literature results.[22]

2-(Hydroxymethyl)cyclohex-2-enol (2-18)



A solution of DIBAL-H (1.0 M, 84 mL) in toluene was added to a solution of **2-17** (4.59 g, 28 mmol) in toluene at -78 ^oC. The solution was stirred at the same temperature for 3 h. To this solution was added MeOH (1.1 mL) and saturated Rochelle's salt (150 mL). Then AcOEt was added and the organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (hexanes/AcOEt = 1:2) to give **2-18** (0.83 g, 83%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.55-1.81 (m, 4H), 1.98-2.13 (m, 2H), 2.33 (broad s, 2H), 4.16 (d, J = 12.0 Hz, 1H), 4.21 (d, J = 12.0 Hz, 1H), 4.31 (t, J = 4.4 Hz, 1H), 5.82 (t, J = 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 25.0, 31.4, 65.5, 65.8, 127.7. All data were consistent with literature results.[28]

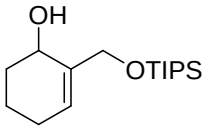
2-*tert*-Butyldiphenylsiloxymethyl-2-cyclohexenol (2-19c)



A solution of 2-hydroxymethyl-2-cyclohexenol **2-18** (1.3 g, 10 mmol), *tert*-butyl-diphenylsilyl-chloride (2.8 g, 10 mmol) and imidazole (2 g, 30 mmol) in THF (16 mL) was stirred at 0 ^{o}C for 1.5 h. Then AcOEt (50 mL) was added and the organic layer was washed with water (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes/AcOEt = 6:1) to afford **2-19c** (3.3 g, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.58 (m, 1H), 1.78 (m, 4H), 2.08 (m, 1H), 2.86 (s, 1H), 4.20 (d, J = 11.9 Hz, 1H), 4.31 (m, 2H), 5.70 (brs, 1H), 7.42 (m, 6H), 7.73 (d, J = 7.4 Hz, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 17.8, 19.1, 25.2, 26.8, 31.0, 66.0, 68.3, 127.2, 127.7, 127.7, 129.7, 129.7, 133.0, 133.0, 135.6, 135.6, 137.2; HRMS (ESI+) calcd for $C_{23}H_{31}O_2Si$ $[M + H]^+$ 367.2093, found 367.2103 (Δ = 2.7 ppm).

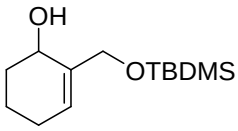
In the same manner, **2-19a** and **2-19b** were synthesized.

2-Triisopropylsiloxymethyl-2-cyclohexenol (2-19a)



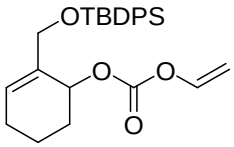
Colorless oil; 87% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (m, 21H), 1.53 (m, 1H), 1.80 (m, 3H), 1.95 (m, 1H), 2.01 (m, 1H), 2.92 (broad s, 1H), 4.25 (m, 3H), 5.72 (broad t, J = 4.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 17.9, 25.1, 30.9, 66.3, 68.2, 126.5, 137.5. All data were consistent with literature results.[28]

2-*tert*-Butyldimethylsiloxymethyl-2-cyclohexenol (2-19b)



Colorless oil; 89% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.85 (s, 9H), 1.45 (m, 1H), 1.67 (m, 3H), 2.01 (m, 1H), 3.06 (s, 1H), 4.16 (m, 3H), 5.69 (broad t, J = 3.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.6, 17.7, 25.1, 30.9, 35.8, 57.4, 126.5, 137.5. All data were consistent with literature results.[28]

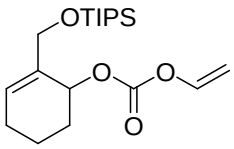
2-*tert*-Butyldiphenylsiloxymethylcyclohex-2-enyl ethenyl carbonate (2-7c)



To a solution of **2-19c** (2.9 g, 8 mmol) and pyridine (7 mL) in CH_2Cl_2 (24 mL) was added vinyl chloroformate (0.7 mL, 8 mmol) at 0 ^{o}C. The resulting solution was stirred at 0 ^{o}C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexanes/AcOEt = 30:1) to afford **2-7c** (3.2 g, 91%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.74 (m, 3H), 2.08 (m, 3H), 4.10 (d, J=12.8 Hz, 1H), 4.23 (d, J=12.8 Hz, 1H), 4.56 (dd, J = 1.9, 6.2 Hz, 1H), 4.90 (dd, J = 1.9, 13.9 Hz, 1H), 5.37 (brs, 1H), 5.97 (brs, 1H), 7.10 (dd, J = 6.2, 13.9 Hz, 1H), 7.40 (m, 6H), 7.67 (d, J = 7.0 Hz, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 17.58, 19.10, 24.69, 26.69, 28.18, 64.91, 71.74, 97.25, 127.53, 127.56, 129.47, 129.50, 129.53, 133.30, 133.41, 133.54, 135.44, 135.46, 142.62, 154.25; HRMS (ESI+) calcd for $C_{26}H_{32}O_4SiNa$ $[M + Na]^+$ 459.1968, found 459.1971 (Δ = 0.7 ppm)

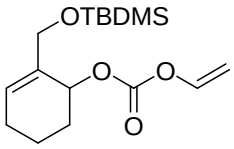
In the same manner, **2-7a** and **2-7b** were synthesized.

2-Triisopropylsiloxymethylcyclohex-2-enyl ethenyl carbonate (2-7a)



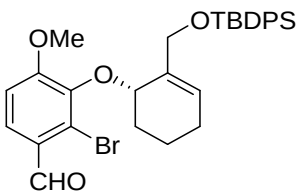
Colorless oil; 91% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (m, 21H), 1.72 (m, 3H), 2.05 (m, 3H), 4.14 (d, J = 13.8 Hz, 1H), 4.25 (d, J = 13.8 Hz, 1H), 4.55 (dd, J = 2.1, 6.3 Hz, 1H), 4.90 (dd, J = 2.1, 12.0 Hz, 1H), 5.29 (broad t, J = 4 Hz, 1H), 6.03 (broad m, 1H), 7.10 (dd, J = 6.3, 13.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 17.9, 24.7, 28.3, 64.4, 71.9, 97.3, 128.5, 134.2, 142.7, 152.4. All data were consistent with literature results.[28]

2-*tert*-Butyldimethylsiloxymethylcyclohex-2-enyl ethenyl carbonate (2-7b)



Colorless oil; 88% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.73 (m, 3H), 2.05 (m, 3H), 4.06 (d, J = 17.2 Hz, 1H), 4.17 (d, J = 17.2 Hz, 1H), 4.56 (dd, J = 2, 6.4 Hz, 1H), 4.90 (dd, J = 2, 14 Hz, 1H), 5.27 (broad t, J = 4 Hz, 1H), 6.00 (m, 1H), 7.10 (dd, J = 6, 14 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.5, 17.7, 24.7, 25.9, 28.3, 64.3, 71.2, 97.3, 129.2, 134.0, 142.7, 152.4. All data were consistent with literature results.[28]

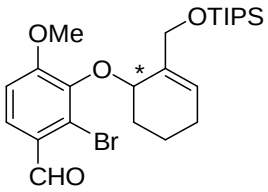
(-)-2-Bromo-3-(2-((*tert*-butyldiphenylsiloxy)methyl)cyclohex-2-enyloxy)-4-methoxy benzaldehyde ((-)-2-9c)



A solution of **2-7c** (105 mg, 0.24 mmol) in DMF (1 mL) was added to a solution of **1** (46 mg, 0.20 mmol)**,** $[Pd(allyl)Cl]_2$ (3.6 mg 5 mol%) and (*S*)-**3e** (30 mg, 15 mol%) in DMF (1 mL) at 0 ^oC, which was preincubated for 15 min. The solution was kept stirred at the same temperature for 36 h. The reaction mixture was diluted with diethyl ether and washed with water (3 x 10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexanes/AcOEt = 20: 1) to afford (-)-**2-9c** (112 mg, 97%) as a colorless oil. $[\alpha]_D^{21}$ -59.8 (*c* 0.28, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.56 (m, 2H), 2.12 (m, 4H), 3.66 (s, 3H), 4.35 (d, *J* = 13.8 Hz, 1H), 4.43 (d, *J* = 13.8 Hz, 1H), 4.81 (brs, 1H), 6.10 (brs, 1H), 6.85 (d, *J* = 8.4, 1H), 7.37 (m, 6H), 7.67 (m, 5H), 10.25 (s, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 18.1, 19.3, 25.1, 26.9, 28.3, 55.7, 65.4, 75.7, 110.7, 123.5, 125.7, 127.3, 127.5, 127.6, 127.6, 129.5, 129.5, 133.7, 133.9, 135.5, 135.6, 135.6, 144.8, 158.4, 191.4; HRMS (ESI+) calcd for $C_{31}H_{36}O_4SiBr$ $[M + H]^+$ 579.1566, found 579.1561 (Δ = -0.9 ppm).

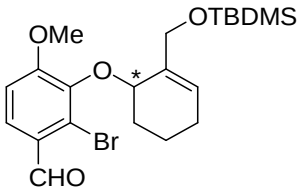
In a similar manner, allylic etherification products, (+)-**2-9a** and (+)-**2-9b**, were obtained using (*R*)-L**1f** as the chiral ligand.

(+)-2-Bromo-4-methoxy-3-(2-(triisopropylsiloxymethyl)-cyclohex-2-enyloxy)benzaldehyde ((+)-2-9a)



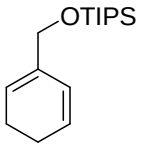
Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (d, *J* = 7.6 Hz, 18H), 1.10 (m, 3H), 1.59 (m, 2H), 2.02 (m, 3H), 2.22 (m, 1H), 3.92 (s, 3H), 4.38 (d, *J* = 13.9 Hz, 1H), 4.48 (d, *J* = 13.9 Hz, 1H), 4.85 (brs, 1H), 6.09 (brs, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 1H), 10.28 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 17.7, 18.0, 25.1, 28.3, 55.9, 64.6, 75.8, 110.7, 123.7, 125.7, 126.4, 127.6, 136.1, 144.7, 158.5, 191.5; HRMS (ESI+) calcd for $C_{24}H_{37}O_4SiBr$ [M]+ 496.1644, found 496.1645 (Δ = 0.2 ppm).

(+)-2-Bromo-3-(2-(*tert*-butyldimethylsiloxymethyl)cyclohex-2-enyloxy)-4-methoxy benzaldehyde ((+)-2-9b)



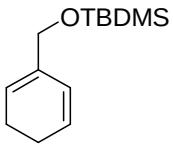
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.90 (s, 9H), 1.55 (m, 2H), 2.08 (m, 4H), 3.92 (s, 3H), 4.35 (brs, 2H), 4.88 (brs, 1H), 6.03 (brs, 1H), 6.93 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 10.27 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4, −5.2, 18.1, 18.4, 25.1, 25.9, 28.2, 56.0, 64.5, 75.6, 110.7, 123.6, 125.7, 127.1, 127.5, 136.2, 144.7, 158.5, 191.5; HRMS (ESI+) calcd for $C_{21}H_{31}O_4SiBr$ $[M]^+$ 454.1175, found 454.1179 (Δ = 0.8 ppm).

2-Triisopropylsiloxymethylcyclo-hexa-1,3-diene (2-20a)



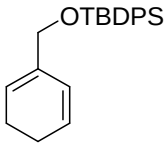
Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (m, 21H), 2.15 (m, 4H), 4.18 (s, 2H), 5.72 (brs, 1H), 5.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2, 18.2, 22.2, 22.8, 65.6, 119.8, 124.5, 127.0, 135.7. All data were consistent with literature results.[28]

2-*tert*-Butyldimethylsiloxymethylcyclo-hexa-1,3-diene (2-20b)



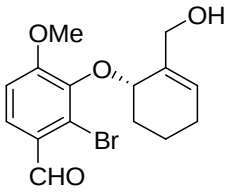
Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.90 (s, 9H), 2.14 (m, 4H), 4.10 (s, 2H), 5.68 (brs, 1H), 5.86 (m, 2H). All data were consistent with literature results.[28]

2-*tert*-Butyldiphenylsiloxymethylcyclo-hexa-1,3-diene (2-20c)



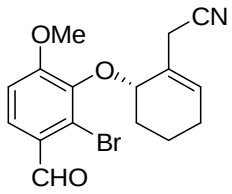
Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 1.03 (s, 9H), 2.13 (m, 4H), 4.12 (s, 2H), 5.68 (s, 1H), 5.83 (m, 2H), 7.38 (m, 6H), 7.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 22.0, 22.4, 26.8, 65.9, 120.0, 124.4, 126.8, 127.6, 129.6, 133.8, 135.0, 135.6. All data were consistent with literature results.[34]

(-)-2-Bromo-3-(2-(hydroxymethyl)cyclohex-2-enyloxy)-4-methoxybenzaldehyde ((-)-2-11)



To a solution of (-)-**2-9c** (90 mg, 0.16 mmol) in THF (1.6 mL) was added tetra-*n*-butylammonium fluoride (1 M in THF, 0.2 mL) dropwise at room temperature. The mixture was stirred at the same temperature for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexanes/AcOEt = 2:1) to afford (-)-**2-11** (54 mg, 99%) as a white solid. $[\alpha]_D^{21}$ -106.5 (*c* 0.40, CH_2Cl_2); ^{1}H NMR (400MHz, $CDCl_3$): δ 1.50 (m, 2H), 2.03 (m, 3H), 2.24 (m, 1H), 3.98 (s, 3H), 4.27 (d, *J* = 12.4 Hz, 1H), 4.38 (d, *J* = 12.4 Hz, 1H), 4.95 (t, *J* = 4.1 Hz, 1H), 6.04 (brs, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 10.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 25.2, 28.2, 56.3, 65.9, 77.3, 110.9, 124.0, 126.2, 127.8, 130.5, 136.3, 144.2, 158.1, 191.2. Enantiomers were separated by HPLC using Chiralcel OJ column eluting with 95:5 hexanes/isopropanol at 0.8 mL/min. Retention times: major enantiomer 55.1 min. and minor 66.8 min.^{1}H NMR and ^{31}C NMR data are in agreement with the literature values.[22]

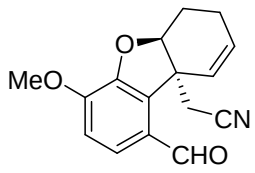
(-)-[6-(2-Bromo-3-dimethoxymethyl-6-methoxy-phenoxy)-cyclohex-1-enyl]-acetonitrile ((-)-2-12)



To a solution of (-)-**2-11** (41 mg, 0.12 mmol) and TEA (0.04 mL, 0.29 mmol) in DCM (1 mL) was added methanesulfonyl chloride (0.013 mL, 0.17 mmol), and the solution was stirred at 0 ^{o}C for 15 min. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ether and filtered through a pad of Celite®. The filtrate was concentrated again. Because the crude product was unstable and prone to decomposition, it was immediately used for the next step without further purification.

To a solution of the previous crude product in DMSO (1 mL) was added NaCN (11.8 mg, 0.24 mmol), and the solution was stirred at room temperature for 1h. Then AcOEt was added and the organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silical gel (hexanes/AcOEt = 5:1) to afford (-)-**2-12** (30 mg, 71% over two steps) as a white solid. $[\alpha]_D^{21}$ -81.0 (*c* 0.30, CH_2Cl_2) (97% ee based on optical rotation); ^{1}H NMR (400MHz, $CDCl_3$): δ 1.60 (m, 2H), 2.01 (m, 3H), 2.25 (m, 1H), 3.35 (d, *J* = 18.1 Hz, 1H), 3.53 (d, *J* = 17.1 Hz, 1H), 3.99 (s, 3H), 4.82 (t, *J* = 3.5 Hz, 1H), 6.15 (brs, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 10.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 22.7, 25.4, 28.0, 56.2, 76.1, 111.0, 118.4, 123.6, 126.4, 127.0, 127.6, 132.9, 143.9, 158.2, 191.1. All data are in agreement with the literature values.[22]

(-)-(1-Formyl-4-methoxy-6,7-dihydro-5a*H*-dibenzofuran-9a-yl)-acetonitrile ((-)-2-13)



To a 10 mL of flask was added (-)-**2-12** (30 mg, 0.08 mmol), $Pd(OAc)_2$ (2.9 mg, 0.012 mmol), Ag_2CO_3 (70.9 mg, 0.24 mmol) and dppp (5.3 mg, 0.012 mmol). Degassed toluene (1 mL) was added and the resulting suspension was heated at 107 ^oC for 24h. Direct column chromatography on silical gel (hexanes/AcOEt = 5:1) afford (-)-**2-13** (19 mg, 90%) as a colorless liquid. $[\alpha]_D^{21}$ -201.0 (*c* 0.30, CH_2Cl_2); ^1H NMR (400MHz, $CDCl_3$): δ 2.00 (m, 2H), 2.22 (m, 1H), 2.38 (m, 1H), 3.13 (d, *J* = 17.0 Hz, 1H), 3.45 (d, *J* = 17.0 Hz, 1H), 3.97 (s, 3H), 4.97 (t, *J* = 3.4 Hz, 1H), 5.98 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 9.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 23.5, 26.1, 48.2, 56.2, 86.3, 111.0, 117.4, 126.0, 126.5, 130.5, 130.6, 132.0, 148.9, 150.3, 191.6. All data are in agreement with the literature values.[22]

§2.6 References

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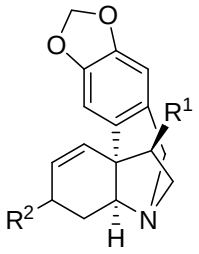
Chapter 3

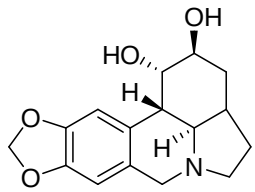
Pd-Catalyzed Asymmetric Allylic Amination Using Chiral BOP Ligands and Its Application for The Syntheses of Polycyclic Alkaloids

§3.1 Introduction of amarylidaceae alkaloids

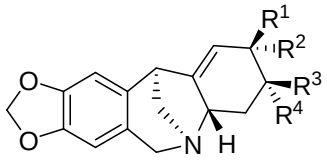
Amaryllidaceae family consists of about 85 genera and 1100 species.[1] To date, nearly 500 structurally diverse alkaloids have been isolated from these plants.[1] As mentioned in Chapter 2, (-)-galanthamine, one of the amarylidaceae alkaloids, possesses acetylcholinesterase inhibitory activities.[2,3] In addition, some representative alkaloids are shown in Figure 3-1. Most of them exhibit biological activities.[4-19] Crinine-type alkaloids have been shown to be active against rat hepatoma cells.[4] A preliminary structure-activity study revealed that a free secondary hydroxyl group at C11 and an α-5,10b-ethano bridge were essential for their biological activity.[4,5] Lycorine was found to be a potential therapeutic agent against acute promyelocytic leukemia cells.[6] Montanine and pancratistatin exhibited antiviral, anxiolytic, antidepressive, and anticonvulsive activities.[7-19]



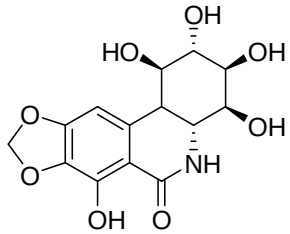
R^1 = H, R^2 = α-OH crinine
R^1 = OH, R^2 = α-OMe crinamine
R^1 = OH, R^2 = β-OMe haemanthamine



lycorine



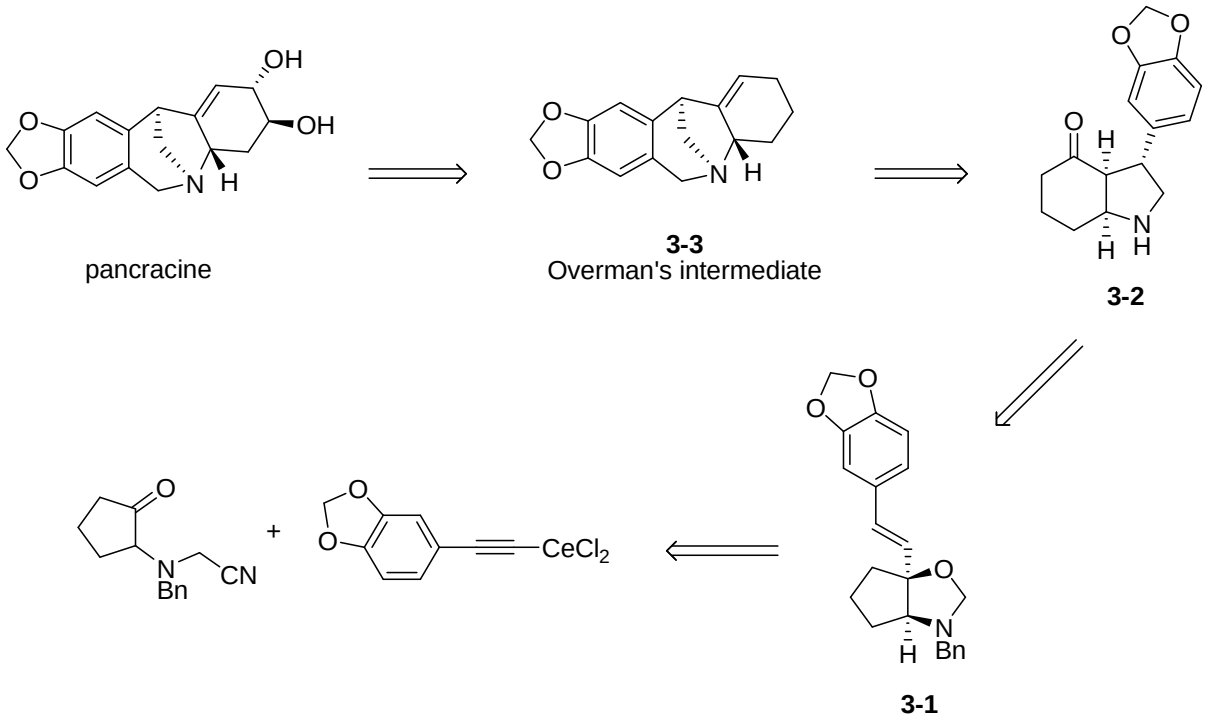
R^1 = H, R^2 = OMe, R^3 = OH, R^4 = H montanine
R^1 = OMe, R^2 = H, R^3 = OH, R^4 = H coccinine
R^1 = H, R^2 = OH, R^3 = OH, R^4 = H pancracine
R^1 = H, R^2 = OH, R^3 = H, R^4 = OH brunsvigine



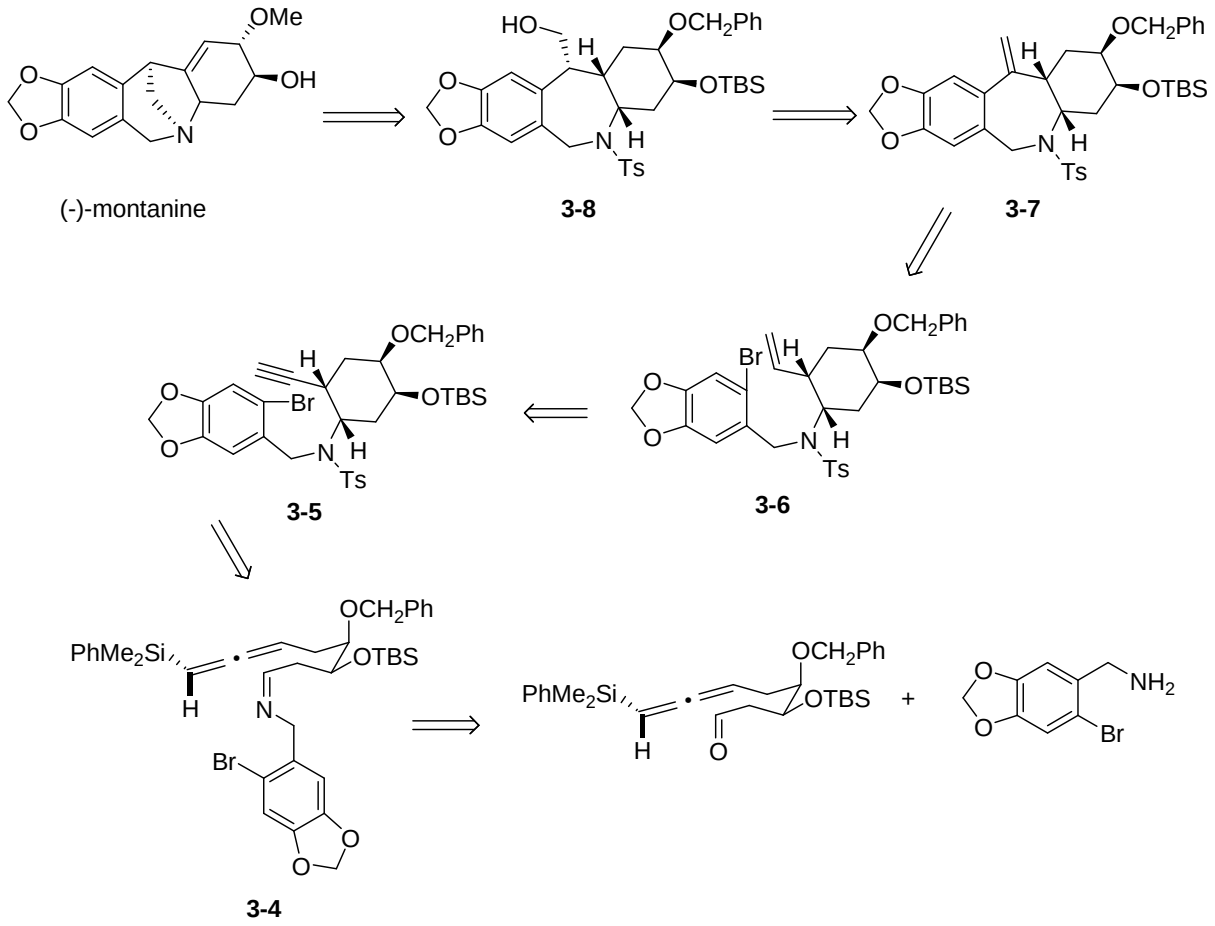
pancratistatin

Figure 3-1. Amarylidaceae alkaloids

Because of their diverse potential biological activities and intriguing structures, many chemical syntheses of these alkaloids have been reported.[20-31] The first total synthesis of racemic pancracine was accomplished by Overman (Scheme 3-1).[20] The Overman's intermediate **3-3** bearing a 5,11-methanomorphanthridine skeleton was constructed through a tandem aza-Cope rearrangement/Mannich cyclization of **3-1** and a Pictect-Spengler cyclization of **3-2**.[20] This intermediate **3-3** was also used in the asymmetric total synthesis of (-)-pancracine by Anada.[21] Weinreb achieved the first enantioselective total synthesis of (-)-montanine employing an intramolecular concerted allenylsilane imino ene cyclization of **3-4** and an intramolecular Heck reaction of **3-5** as the pivotal steps (Scheme 3-2).[22]



Scheme 3-1. Overman's total synthesis of pancracine

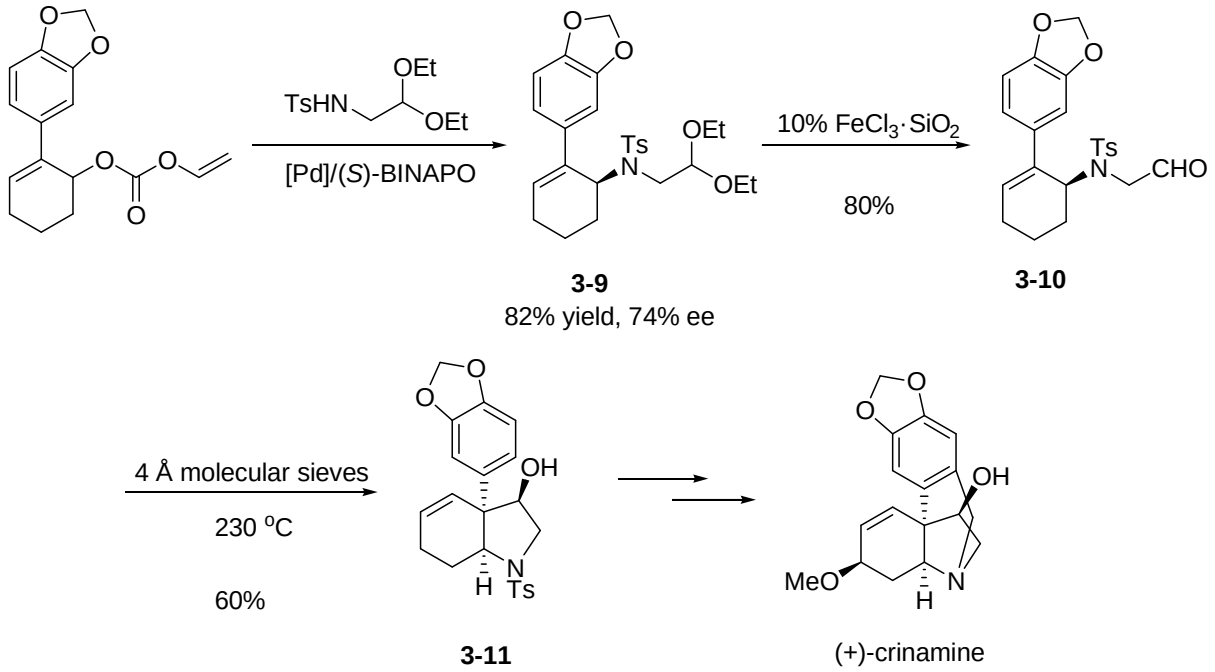


Scheme 3-2. Weinreb's enantioselective total synthesis of (-)-montanine

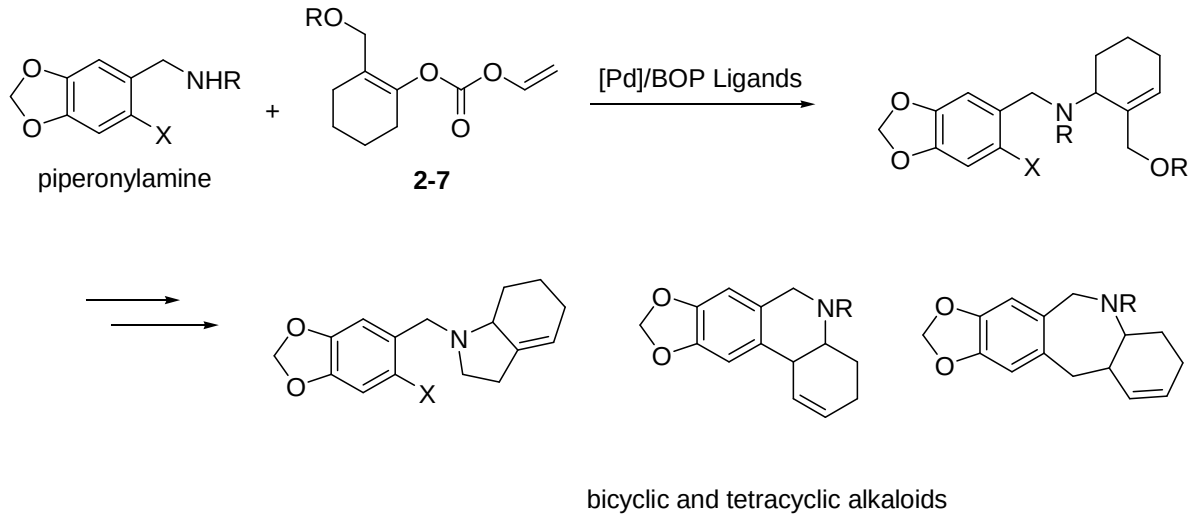
A Pd-catalyzed asymmetric allylic amination reaction was also applied in the total syntheses of crinine-type alkaloids.[23,31] One of them was reported by Mori in 2004 (Scheme 3-3).[23] The cyclohexenylamine **3-9** was obtained in 82% yield and with 74% ee, followed by carbon-ene reaction to give the key intermediate **3-11** bearing a hydroindole moiety. From **3-11**, (+)-crinamine and (-)-haemanthidine were synthesized in a short sequence of steps.

The bicyclic and tetracyclic alkaloids (**3-2**, **3-7**, **3-11**, *etc.*) serve as key intermediates for the total synthesis of the amarylidaceae alkaloids. Some similar bicyclic and tetracyclic alkaloids bearing piperonylamine skeleton (Scheme 3-4) were designed as lead compounds in our lab. To synthesize these compounds and expand the scope of our BOP ligands, we decided to apply the

ligands to the Pd-catalyzed asymmetric allylic amination between derivatives of piperonylamines and carbonates **2-7** (Scheme 3-4)**.**



Scheme 3-3. Mori's asymmetric total synthesis of (+)-crinamine

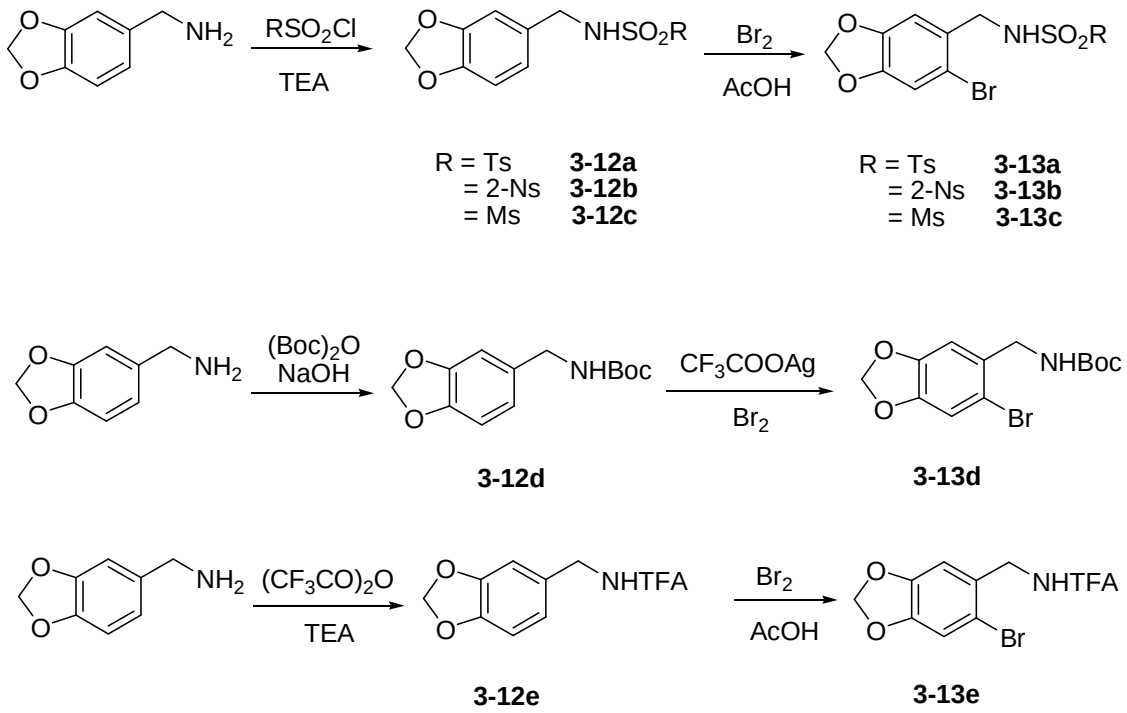


Scheme 3-4. Pd-AAA reactions for the syntheses of bicyclic and tetracyclic alkaloids

§3.2 Results and discussion

§3.2.1 Synthesis of substrates

A series of piperonylamides was prepared in our lab. Starting from commercially available piperonylamine, sulfonylamide **3-12a-c**, Boc-amide **3-12d** and trifluoroacetamide **3-12e** were obtained in good to excellent yields. Bromination of these amides afforded the corresponding 6-bromopiperonylamides **3-13a-e** (Scheme 3-5).



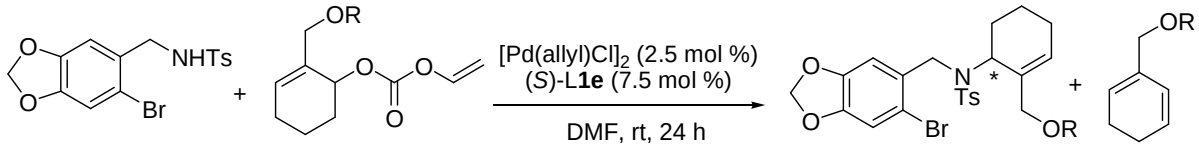
Scheme 3-5. Synthesis of substrates

§3.2.2 Pd-catalyzed asymmetric allylic amination

Initial screening of the allylic substrates **2-7a-c** was performed using the BOP ligand, (*S*)-L**1e**, and the nucleophile **3-13a**, under conditions nearly the same as those used for the successful intermolecular Pd-catalyzed AAE reaction.[32] Thus, the reactions were carried out in DMF at a substrate concentration of 0.1 M with a Pd/(*S*)-L**1e** ratio of 1:1.5. The results are shown in Table 3-1. The cyclohexenylamides **3-14a** and **3-14g** were obtained in good yields and ees (Table 3-1,

entry 1 and 2), but with the same byproducts **2-20** in Pd-catalyzed AAE reaction.[32] The size of the silyl groups affected the reaction significantly. No reaction occurred when **2-7c** was used as the substrate (Table 3-1, entry 3). We hypothesized that the nucleophilic attack suffered from the steric hindrance of the bulky TBDPS group. On the other hand, a slight increase in enantioselectivity for the formation of **3-14** was observed as the size of the silyl group increased (Table 3-1, entry 1 and 2). The cyclohexadiene was suppressed using **2-7b** as the substrate. Thus, **2-7b** was selected for the further study.

Table 3-1. Initial screening of allylic substrates



3-13a (1.1 eq.)

2-7a R = TIPS
2-7b R = TBDMS
2-7c R = TBDPS

3-14g R = TIPS
3-14a R = TBDMS

2-20a
2-20b

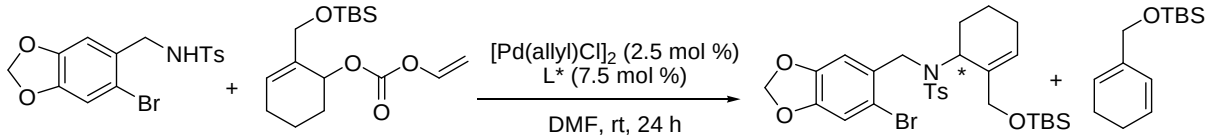
entry	substrate	conv[a] (%)	**3-14**[b] (% ee)	**3-14:2-20**
1	**2-7a**	>95%	82	72:28
2	**2-7b**	>95%	85	85:15
3	**2-7c**	No Reaction (N.R.)	--	--

[a]Determined by ^{1}H NMR. [b]Determined by HPLC using Chiralcel ODH.

Next, BOP ligands were screened using DMF as the solvent at room temperature for 24 h. The results are summarized in Table 3-2. (The result when (*S*)-L**1e** from Table 3-1 is used included for comparison). (*S*)-L**1a** bearing a benzyl group at the 3,3'-positions afforded **3-14a** with 80% ee (Table 3-2, entry 1). The introduction of a bulky substituent at the *meta* position, i.e., the 3,5-di-*tert*-butylbenzyl group at the 3,3'-positions, i.e., (*S*)-L**1c**, slightly improved the enantioselectivity but generated more byproducts (Table 3-2, entry 2). When (*S*)-L**3e**, the most efficacious ligand in Pd-AAE reaction,[32] was employed in the reaction, the enantioselectivity is

considerably increased to 93% ee but with a lower product selectivity (Table 3-2, entry 4). All reactions were completed within a day.

Table 3-2. Screening of BOP ligands



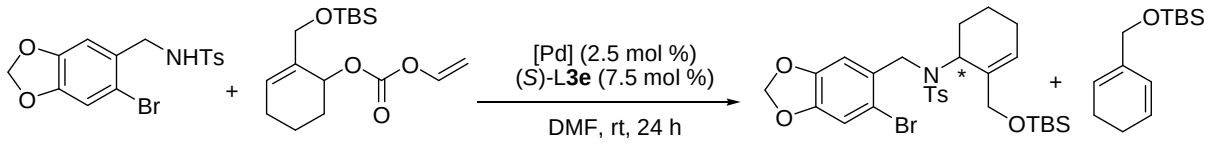
3-13a (1.1 eq.) + **2-7b** → **3-14a** + **2-20b**

entry	ligand	conv[a] (%)	**3-14a**[b] (% ee)	**3-14a:2-20b**
1	(*S*)-L**1a**	>95%	80	91:9
2	(*S*)-L**1c**	>95%	83	85:15
3	(*S*)-L**1e**	>95%	85	85:15
4	(*S*)-L**3e**	>95%	93	73:27

[a,b]See the footnotes of Table 3-1

For further optimization, we switched the Pd-catalyst precursor Pd (II) $[Pd(allyl)Cl]_2$ to Pd(0) $Pd_2(dba)_3$. The same enantioselectivity was obtained (Table 3-3, entry 1). Lowering the temperature to 0 ^oC slightly increased the enantioselectivity to 95% ee, but the reaction was naturally slowed down (Table 3-3, entry 2). Lowering the catalyst loading to 1% did not affect the enantioselectivity, but the reaction was also slowed down (Table 3-3, entry 3). To our delight, 95% ee with full conversion was achieved by running the reaction at a higher concentration of **2-7b** (0.2 M) (Table 3-3, entry 4). Thus, this substrate concentration was used in the subsequent reactions as well. We also ran the reaction with $[Pd(allyl)Cl]_2$ catalyst and found that the nearly same result was obtained (Table 3-3, entry 5). Because $Pd_2(dba)_3$ released dba which has a similar polarity as the desired product and it is difficult to separate them through column chromatography, $[Pd(allyl)Cl]_2$ was selected for further study.

Table 3-3. Optimization of Pd-catalyzed AAA reactions



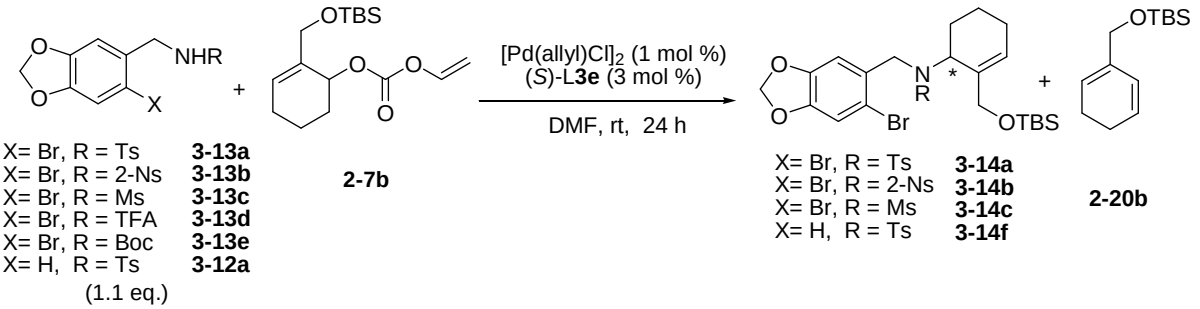
3-13a (1.1 eq.) **2-7b** **3-14a** **2-20b**

entry	catalyst	conv[a] (%)	**3-14a**[b] (% ee)	**3-14a:2-20b**
1	$Pd_2(dba)_3$	>95	93	79:21
2[c]	$Pd_2(dba)_3$	66	95	86:14
3[d]	$Pd_2(dba)_3$	68	95	75:25
4[d,e]	$Pd_2(dba)_3$	>95	95	75:25
5[d,e]	$[Pd(allyl)Cl]_2$	>95	95	73:27

[a,b]See the footnotes of Table 3-1. [c]At 0 °C. [d]1 mol% of [Pd] and 3 mol% of BOP ligands. [e]At 0.2 M concentration of **2-7b**.

The scope of the Pd-catalyzed AAA reaction was investigated using several piperonylamides under the optimized conditions (Table 3-4). The reaction employing sulfonylamide as nucleophiles proceeded smoothly to afford the corresponding products with excellent enantioseletivities (Table 3-4, entries 1-3, 6). The nucleophile **3-13c** with a small sulfonyl protecting group slightly decreased the enantioselectivity to 90% ee (Table 3-4, entry 3). The Boc protecting group is not stable in the Pd-catalyzed AAA reaction, since a considerable amount of piperonylamine was observed (Table 3-4, entry 4). Because of the strong electron withdrawing protecting group TFA, no reaction occurred when **3-13d** was used as the nucleophile (Table 3-4, entry 5).

Table 3-4. Pd-catalyzed AAA reactions



entry	substrate	conv[a] (%)	**3-14**[b] (% ee)	**3-14:2-20**
1	**3-13a**	>95%	95	73:27
2	**3-13b**	>95%	94	70:30
3	**3-13c**	>95%	90	78:22
4	**3-13d**	N.R.	--	--
5	**3-13e**	N.R.	--	--
6	**3-12a**	>95%	93	78:22

[a]See the footnotes of Table 3-1.[b]Determined by HPLC.

§3.2.3 Synthesis of polycyclic alkaloids

Because the 2-nitrobenzenesulfonyl protecting group can be removed readily by thiophenol,[39] we selected **3-13b** for the following syntheses of bicyclic and tetracyclic alkaloids. Additionally, we prepared (-)-**3-14b** with 94% ee and isolated 96% yield using a small excess of **2-7b** (1.4 equiv) to increase the product yield; i.e., piperonylamide **3-13b** became the limiting reactant under these conditions (Scheme 3-6). The absolute configuration of (+)-**3-14b** was determined by X-ray crystallography and the structure was shown in Figure 3-2. Since the nitro group is base sensitive, 4 N HCl in THF instead of TBAF was used for the deprotection of (-)-**3-14b** affording allylic alcohol **3-15b** in 99% yield. The nitrile **3-16** was prepared in excellent yield through a modified Mitsunobu protocol.[33] Next, the intramolecular Heck reaction of **3-16** was

examined under the same condition for the synthesis of the benzofuran compound **2-13**. Unfortunately, no reaction occurred. We conjectured that the 2-nitrobenzenesulfonyl group was too bulky. Thus, a nitrile **3-18** bearing a smaller protecting group TFA was prepared by the simple deprotection and protection of **3-16.** The successful intramolecular Heck reaction of **3-18** proved our hypothesis. However, **3-19** containing a small amount of isomers was difficult to purify and was directly deprotected in the presence of NaOH to give a *cis* tetracyclic alkaloid **3-20.** The relative stereochemistry of **3-20** was determined by 2D-NOESY.

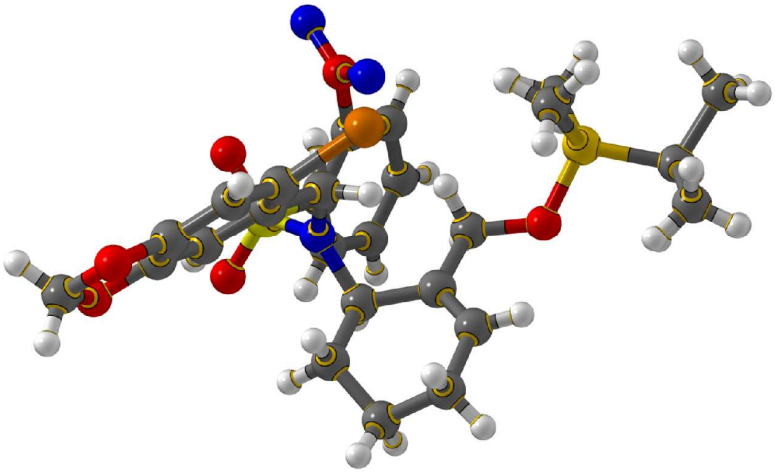
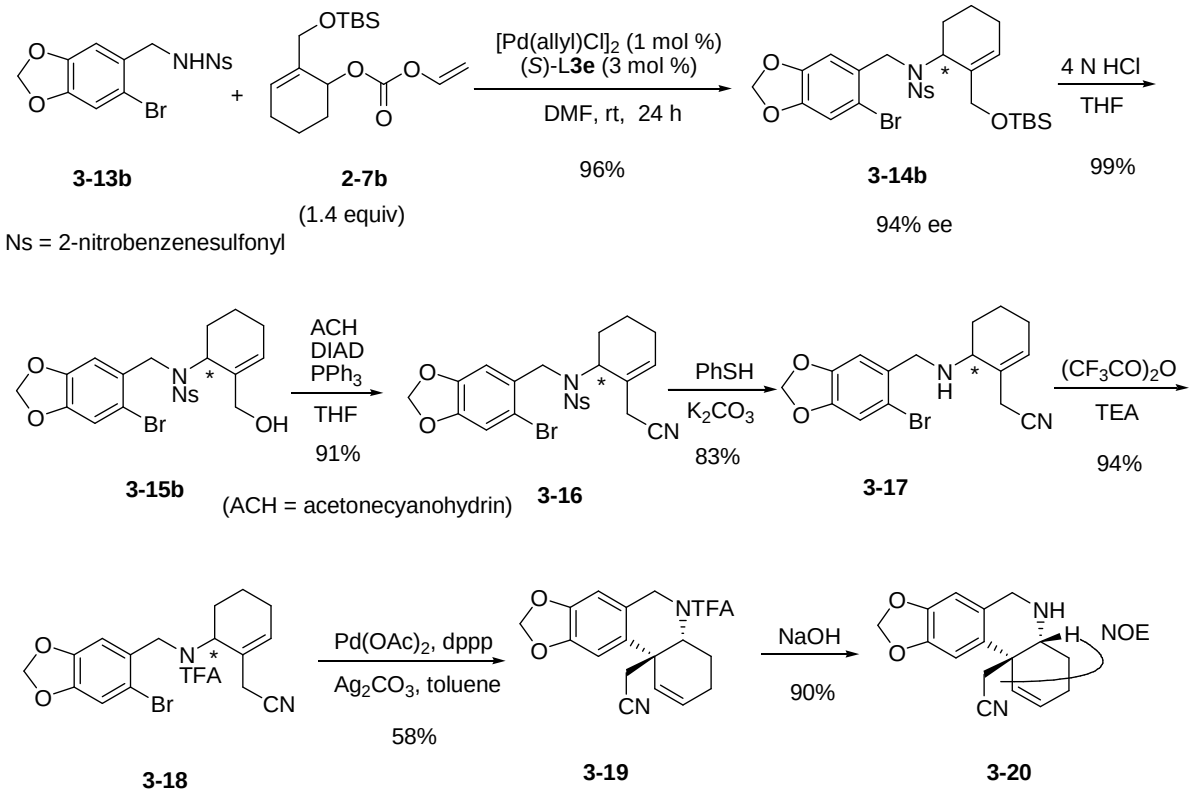


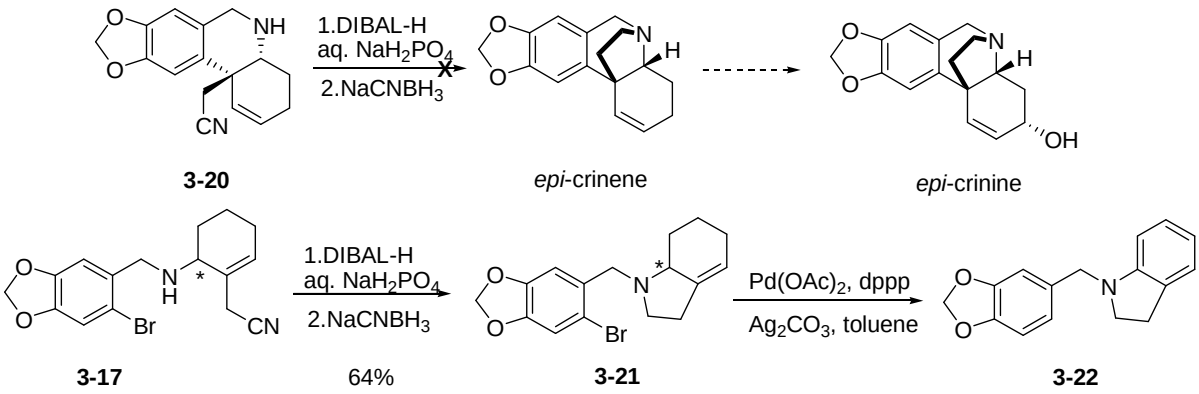
Figure 3-2. The absolute configuration of (+)-**3-14b**

With the tetracyclic alkaloid **3-20** in hand, we decided to synthesize *epi*-crinine. The direct way to accomplish this is using reductive amination to construct the five-membered ring (Scheme 3-7). This method is similar to that reported by Trost in his synthesis of (-)-glanthamine.[33] Unfortunately, it failed to give *epi*-crinene. The intermolecular reductive amination occurred and was determined by mass spectrum. At this point, we decided to construct the five-membered ring first. The reductive amination reaction preformed smoothly to give **3-21** in 64% yield (Scheme 3-7). However, a racemic indoline **3-22** instead of *epi*-crinene was obtained through the intramolecular Heck reaction. The mechanism is unclear and further study is underway. Meanwhile, another tetracyclic alkaloid **3-24** was synthesized starting from **3-14f**. Deprotection of **3-14** with TBAF gave allylic alcohol **3-15f** in 99% yield. Conversion of the alcohol **3-15f** to the allylic bromide **3-17** proceeded smoothly in the presence of phosphorus

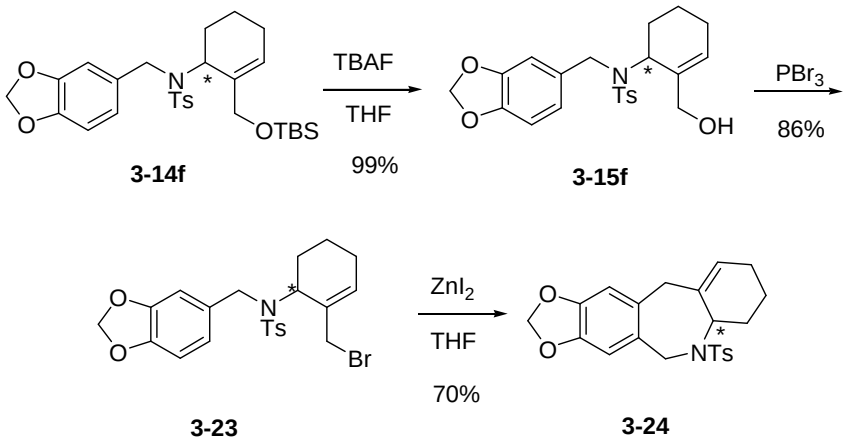
tribromide. In the final step, the tetracyclic alkaloid **3-24** was obtained in 70% yield through Friedel-Crafts alkylation.



Scheme 3-6. Synthesis of the tetracyclic alkaloid **3-20**

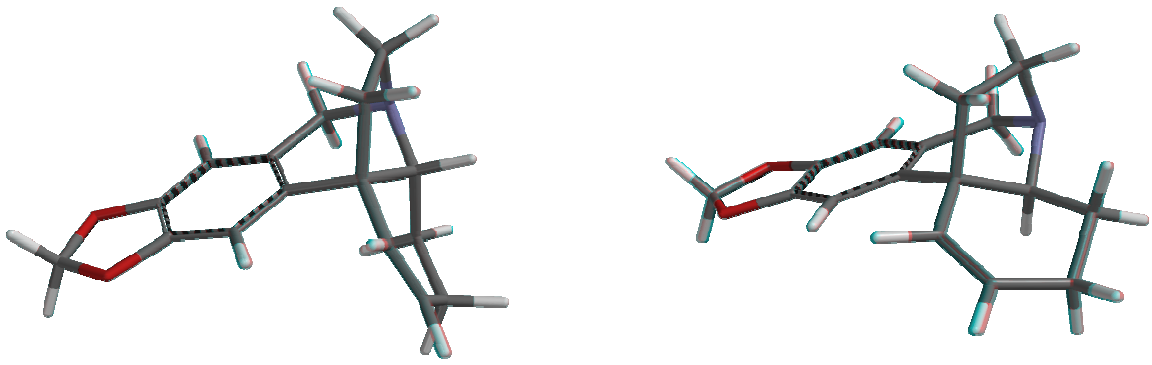


Scheme 3-7. Synthesis of *epi*-crinene



Scheme 3-8. Synthesis of the tetracyclic alkaloid **3-24**

The molecular modeling of crinene and *epi*-crinene was carried out using the Spartan program (MM2/PM3 for energy minimization) (Figure 3-3). The energy difference between crinene and *epi*-crinene was calculated to be 18.4 kJ/mol. The high ring strain energy of *epi*-crinene causes the failure of the formation of *epi*-crinene through the reductive amination and the intramolecular Heck reaction.



epi-crinene ΔE = 18.4 kJ/mol crinene ΔE = 0 kJ/mol

Figure 3-3. A molecular modeling study of crinene and *epi*-crinene

§3.3 Conclusions

The asymmetric efficacy of our novel BOP ligands were evaluated in the Pd-catalyzed asymmetric allylic amination reactions. The cyclohexenylamides **3-14a-c** and **3-14f** with excellent ees were obtained using the BOP ligand (*S*)-L**3e**. Starting from these amides, chiral polycyclic alkaloids **3-20, 3-22** and **3-24** were synthesized in a short sequence of steps. Further syntheses of the derivatives of amarylidaceae alkaloids from the bicyclic and tetracyclic alkaloids are actively underway in our laboratory.

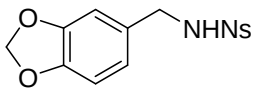
§3.4 Experimental section

General Methods. ^{1}H, ^{13}C, and ^{31}P NMR were measured on a Bruker Avance 500 (500 MHz for ^{1}H; 125 MHz for ^{13}C), a Bruker Avance 400 (400 MHz for ^{1}H; 100 MHz for ^{13}C), or a Varian Gemini-2300 300 MHz (300 MHz for ^{1}H; 75 MHz for ^{13}C) NMR spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm) as the internal standard. Analytical HPLC in normal phase was carried out with a Shimadzu LC-2010A HPLC system using a Chiralcel OJ or a Chiralcel ODH. Analytical HPLC in reverse phase was carried out with a Shimadzu LC-2010A HPLC system using Chiralpak AD-RH analytical column. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Helmer Model 241 polarimeter. TLC analyses were performed using Merck DC Alufolien $60F_{254}$ aluminum pre-coated silica gel plates. Flash column chromatography was carried out using Silicyle Silia*Flash*P60® silica gel (particle size 40_63 μm). High-resolution mass spectrometric analyses were carried out at the Mass Spectrometry Laboratory, University of Illinois Urbana-Champaign, Urbana, IL or by ICB&DD at Stony Brook University. Unless otherwise noted all reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques.

Material. Solvents were reagents grade and freshly dried, degassed and distilled before use. Anhydrous *N*,*N*-dimethylformamide (DMF) and acetonitrile were purchased from Acros Organic and used without further purification. Chemicals and reagents were purchased from

VWR, Fisher Scientific or Sigma-Aldrich and used without further purification unless otherwise noted.

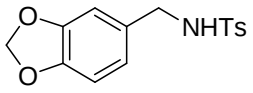
***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-nitrobenzenesulfonamide (3-12b)**



To a solution of piperonyl amine (2.57 g, 17 mmol) and triethylamine (2.32 ml, 42 mmol) in dry CH_2Cl_2 (8.5 mL), a solution of 2-nitrobenzene sulfonyl chloride (3.02 g, 20 mmol) in CH_2Cl_2 (7 ml) was slowly added at room temperature. The resulting solution was stirred at the same temperature for 2.5 h. To the mixture was added aqueous 10% HCl, and then extracted with CH_2Cl_2 (3 x 15 ml). The combined organic layers were dried over $MgSO_4$. After the drying agent was removed by filtration, the solution was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (hexanes/AcOEt = 2:1) to afford the amide **3-12b** (4.8 g, 78%) as a off-white solid. mp 159-160 ^oC; ^1H NMR (400 MHz, DMSO- *6d*) δ 3.33 (brs, 1H), 4.06 (d, J = 6.2 Hz, 2H), 5.93 (s, 2H), 6.72 (m, 3H), 7.76 (m, 2H), 7.77 (m, 2H), 7.88 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*6d*) δ 46.0, 100.9, 107.8, 108.1, 121.1, 124.2, 131.0, 132.4, 133.2, 133.8, 146.3, 147.1, 147.4. HRMS (ESI+) calcd for $C_{14}H_{16}N_3O_6$ $[M]^+$ 354.0754, found 354.0762 (Δ = 2.2 ppm).

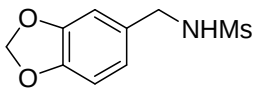
In the same manner, **3-12a** and **3-12c** were synthesized.

***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-methylbenzenesulfonamide (3-12a)**



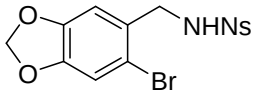
White solid; 85% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.93 (d, J = 6.0 Hz, 2H), 4.66 (brs, 1H), 5.84 (s, 2H), 6.58 (m, 3H), 7.23 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 47.6, 108.6, 108.9, 121.8, 127.6, 130.1, 130.5, 137.3, 143.9, 147.7, 148.3. All data are in agreement with the literature values.[35]

***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)methanesulfonamide (3-12c)**



White solid; 87% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (s, 3H), 4.21 (d, J = 6.0 Hz, 2H), 4.82 (brs, 1H), 5.96 (s, 2H), 6.81 (m, 3H). All data are in agreement with the literature values.[36]

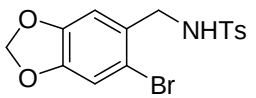
***N*-((6-Bromobenzo[*d*][1,3]dioxol-5-yl)methyl)-2-nitrobenzenesulfonamide (3-13b)**



To a solution of **3-12b** (3.05 g, 10 mmol) in AcOH (10 mL) was added bromine (0.63 mL) dropwise. The resulting solution was stirred at room temperature for 3 h. Then it was washed with 5% Na_2SO_3 solution until decolorization. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford **3-13b** (3.56 g, 92%) as a off-white solid. mp 162-163 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*6d*) δ 4.19 (s, 1H), 6.05 (s, 1H), 6.94 (s, 1H), 7.16 (s, 1H), 7.85 (m, 2H), 7.95 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 8.1 Hz, H), 8.68 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*6d*) δ 47.1, 103.0, 110.3, 113.0, 113.8, 125.3, 130.2, 130.4, 133.5, 133.8, 135.0, 148.0, 148.4, 148.5. HRMS (ESI+) calcd for $C_{14}H_{16}N_3O_6S$ $[M+NH_4]^+$ 431.9859, found 431.9864 (Δ = 1.2 ppm)

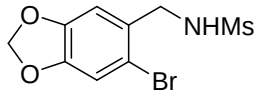
In the same manner, **3-13a** and **3-13c** were synthesized

***N*-((6-Bromobenzo[*d*][1,3]dioxol-5-yl)methyl)-4-methylbenzenesulfonamide (3-13a)**



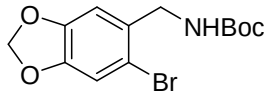
White solid; 92% yield; mp 156-157 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 3H), 4.11 (d, J = 6.5 Hz, 2H), 4.87 (brs, 1H), 5.94 (s, 2H), 6.76 (s, 1H), 6.89 (s, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 47.4, 101.9, 110.4, 112.6, 114.1, 127.1, 128.6, 129.6, 136.9, 143.4, 147.4, 148.1. HRMS (ESI+) calcd for $C_{15}H_{15}BrNO_4S$ $[M+NH_4]^+$ 383.9900, found 383.9900 (Δ = 0 ppm).

_N_-((6-Bromobenzo[_d_][1,3]dioxol-5-yl)methyl)methanesulfonamide (3-13c)



White solid; 91% yield; mp 140-141 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.86 (s, 3H), 4.30 (d, J = 6.5 Hz, 2H), 4.81 (brs, 1H), 6.00 (s, 2H), 6.94 (s, 1H), 7.02 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.2, 47.3, 101.9, 110.3, 112.8, 114.1, 128.7, 147.5, 148.3. HRMS (ESI+) calcd for $C_9H_{14}BrN_2O_4S$ $[M+NH_4]^+$ 324.9852, found 324.9850 (Δ = -0.6 ppm).

***tert*-Butyl (6-bromobenzo[*d*][1,3]dioxol-5-yl)methylcarbamate (3-13d)**

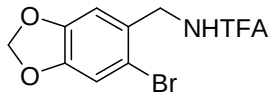


To a suspension of piperonylamine (3.02 g, 20 mmol) in water (20 mL) was added $(Boc)_2O$ (5.68 g, 26 mmol) and NaOH (1.6 g, 40 mmol) at 0 ^{o}C. The mixture was stirred at room temperature for 12 h. AcOH (40 mL) was then added. The mixture was cooled to 0 ^{o}C and pH was adjusted to 2-3 with 2N HCl. The organic layer was washed with 1 M $KHSO_4$ water solution and brine and dried over Na_2SO_4. After the drying agent was removed by filtration, the solution was concentrated *in vacuo* to give the crude **3-12d** (4.6 g, 92%) as a white solid. The crude product was directly used for the next step without any further purification.

To a suspension of **3-12d** and CF_3COOAg in CH_2Cl_2, bromine (1.2 mL, 24 mmol) was added dropwise at room temperature. The mixture was stirred at the same temperature for 3 h

and then filtered. The resulting solution was washed with 5% $NaHCO_3$ solution and dried over Na_2SO_4. After the drying agent was removed by filtration, the solution was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (hexanes/AcOEt = 6:1) to afford the **3-13d** (3.6 g, 61%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 4.28 (d, J = 6.2 Hz, 2H), 4.99 (brs, 1H), 5.97 (s, 2H), 6.95 (s, 1H), 6.99 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 44.5, 79.4, 101.6, 109.5, 112.5, 113.6, 131.1, 147.3, 147.4, 155.6. All data are in agreement with the literature values.[36]

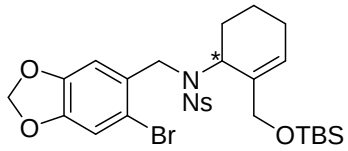
***N*-((6-Bromobenzo[*d*][1,3]dioxol-5-yl)methyl)-2,2,2-trifluoroacetamide (3-13e)**



To a solution of piperonylamine (151 mg, 1.0 mmol) in DCM was added triethylamine (0.34 mL, 2.5 mmol) and $(CF_3CO)_2O$ (0.18 mL, 1.3 mmol.) at 0 ^{o}C. The mixture was stirred at the same temperature for 1 h, and then was diluted with H_2O. The resulting mixture was extracted with AcOEt. The combined organic layers were dried over Na_2SO_4. After removal of the drying agent, the solution was concentrated in Na_2SO_4 to give **3-12e** as a white solid. The crude product was directly used for the next step without any further purification.

To a solution of **3-12e** in AcOH (1 mL) was added bromine (0.06 mL, 1.2 mmol) dropwise at room temperature. The resulting solution was stirred at the same temperature for 3 h. Then it was washed with 5% Na_2SO_3 solution until decolorization. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford **3-13e** (243 mg, 75% over two steps) as a white solid. mp 98-99 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.51 (d, J = 6.1 Hz, 2H), 5.99 (s, 2H), 6.76 (brs, 1H), 6.88 (s, 1H), 7.02 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.1, 102.1, 110.7, 113.0, 114.63, 115.8 (q, J = 286 Hz), 128.2, 147.8, 148.7, 157.1 (q, J = 37.1 Hz); HRMS (ESI+) calcd for $C_{10}H_8BrF_3NO_3$ $[M+H]^+$ 325.9634, found 325.9633 (Δ = -0.3 ppm).

(-)-*N*-(6-Bromobenzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-(2-(*tert*-butyldimethylsiloxymethyl) cyclohex-2-enyl)-2-nitrobenzenesulfonamide ((-)-3-14b)

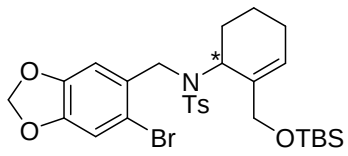


A solution of **3-13b** (1.2 g, 3.2 mmol)**,** [Pd(allyl)Cl]$_2$ (11.5 mg 1 mol%) and (*S*)-L**3e** (94.72 mg, 3 mol%) in DMF (15 mL) was preincubated for 15 min. To the solution was added a solution of carbonate **2-7b** (1.7 g, 5.3 mmol) in DMF (15 mL) dropwise at room temperature. The solution was stirred at the same temperature for 24 h. The reaction mixture was diluted with diethyl ether and washed with water (3 x 10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexanes/AcOEt = 20:1) to afford **3-14b** (1.8 g, 96%) as a white solid. Enantiomers were separated by HPLC using Chiralcel OJ column eluting with 99:1 hexanes/isopropanol at 1.0 mL/min. Retention times: major enantiomer 33.1 min. and minor 40.8 min. mp 144-145 ^{o}C; $[\alpha]_D^{21}$ -88.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.07 (s, 3H), -0.04 (s, 3H), 0.83 (s, 9H), 1.44 (m, 2H), 1.67 (m, 1H), 1.97 (m, 3H), 3.37 (d, *J* = 14.6 Hz, 1H), 3.88 (d, *J* = 14.6 Hz, 1H), 4.22 (d, *J* = 17.6 Hz, 1H), 4.51 (brs, 1H), 4.73 (d, *J* = 17.6 Hz, 1H), 5.89 (s, 1H), 5.93 (s, 1H), 6.12 (brs, 1H), 6.91 (s, 1H), 7.61 (m, 2H), 7.67 (m, 1H), 7.99 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.5, -5.4, 18.3, 20.7, 24.4, 25.9, 29.9, 48.6, 55.9, 63.0, 101.7, 109.1, 112.3, 112.5, 124.1, 128.8, 130.6, 131.6, 131.7, 133.5, 133.6, 133.7, 147.3, 147.4, 147.6; HRMS (ESI+) calcd for $C_{27}H_{35}BrN_2O_7SSi$ $[M]^+$ 638.1118, found 638.1127 (Δ = 1.4 ppm).

The synthesis of (+)-**3-14b** followed the same procedure. $[\alpha]_D^{21}$ +84.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.07 (s, 3H), -0.04 (s, 3H), 0.83 (s, 9H), 1.44 (m, 2H), 1.67 (m, 1H), 1.97 (m, 3H), 3.37 (d, *J* = 14.6 Hz, 1H), 3.88 (d, *J* = 14.6 Hz, 1H), 4.22 (d, *J* = 17.6 Hz, 1H), 4.51 (brs, 1H), 4.73 (d, *J* = 17.6 Hz, 1H), 5.89 (s, 1H), 5.93 (s, 1H), 6.12 (brs, 1H), 6.91 (s, 1H), 7.61 (m, 2H), 7.67 (m, 1H), 7.99 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.5, -5.4, 18.3, 20.7, 24.4, 25.9, 29.9, 48.6, 55.9, 63.0, 101.7, 109.1, 112.3, 112.5, 124.1, 128.8, 130.6, 131.6, 131.7, 133.5, 133.6, 133.7, 147.3, 147.4, 147.6.

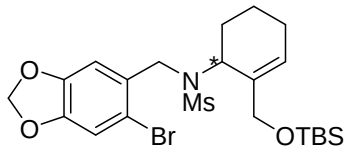
In the same manner, **3-14a, 3-14c, 3-14f** and **3-14g** were synthesized

***N*-(6-Bromobenzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-(2-(*tert*-butyldimethylsiloxymethyl) cyclohex-2-enyl)-4-methylbenzenesulfonamide (3-14a)**



White solid; Enantiomers were separated by HPLC using Chiralcel ODH column eluting with 99:1 hexanes/isopropanol at 1.0 mL/min. Retention times: major enantiomer 30.5 min. and minor 38.3 min; mp 127-128 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.03 (s, 6H), 0.89 (s, 9H), 1.41 (m, 2H), 1.79 (m, 2H), 1.94 (m, 2H), 2.44 (s, 3H), 3.41 (d, J = 14.1 Hz, 1H), 3.47 (d, J = 14.1 Hz, 1H), 3.99 (d, J = 15.8 Hz, 1H), 4.39 (s, 1H), 4.50 (d, J = 15.8 Hz, 1H), 5.96 (s, 1H), 6.06 (brs, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.93 (s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.7, -5.6, 18.2, 20.5, 21.4, 24.4, 25.8, 30.0, 48.1, 54.8, 63.4, 100.9, 107.7, 108.9, 121.6, 127.1, 127.9, 129.5, 132.3, 134.2, 138.2, 143.0, 146.7, 147.6; HRMS (ESI+) calcd for $C_{28}H_{38}BrNNaO_5SSi$ $[M+Na]^+$ 630.1316, found 630.1315 (Δ = -0.2 ppm).

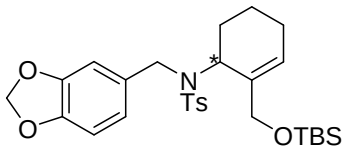
***N*-(6-Bromobenzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-(2-(*tert*-butyldimethylsiloxymethyl) cyclohex-2-enyl)methanesulfonamide (3-14c)**



Amphorus solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.42 (m, 1H), 1.47 (m, 1H), 1.90 (m, 4H), 3.08 (s, 3H), 4.02 (d, J = 12.7 Hz, 1H), 4.06 (d, J = 12.7 Hz, 1H), 4.15 (d, J = 17.3 Hz, 1H), 4.38 (d, J = 17.3 Hz, 1H), 4.58 (brs, 1H), 5.95 (d, J = 1.4 Hz, 1H), 5.98 (d, J = 1.4 Hz, 1H), 6.92 (s, 1H), 7.26 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -

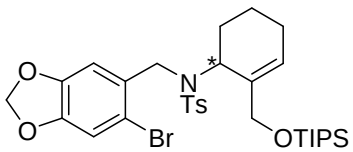
5.3, -4.8, 18.3, 19.8, 24.8, 25.9, 30.5, 38.4, 48.6, 53.8, 65.4, 101.8, 109.9, 112.1, 112.4, 131.1, 132.6, 134.5, 147.5, 147.6; HRMS (ESI+) calcd for $C_{22}H_{34}BrNNaO_5SSi$ $[M+Na]^+$ 554.1003, found 554.1007 (Δ = 0.7 ppm).

_N_-(Benzo[_d_][1,3]dioxol-5-ylmethyl)-_N_-(2-(_tert_-butyldimethylsiloxymethyl)cyclohex-2-enyl)-4-methylsulfonamide (3-14f)



White solid; 94% yield (using 1.2 equiv of **2-7b**); Enantiomers were separated by HPLC using Chiralcel OJ column eluting with 99:1 hexanes/isopropanol at 1.0 mL/min. Retention times: major enantiomer 36.3 min. and minor 44.5 min; mp 88-89 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ -0.03 (s, 6H), 0.89 (s, 9H), 1.41 (m, 2H), 1.79 (m, 2H), 1.95 (m, 2H), 2.45 (s, 3H), 3.42 (d, J = 14.1 Hz, 1H), 3.47 (d, J = 14.6 Hz, 1H), 3.99 (d, J = 15.8 Hz, 1H), 4.39 (brs, 1H), 4.51 (d, J = 15.8 Hz, 1H), 5.96 (s, 2H), 6.06 (brs, 1H), 6.72 (d, J = 8.0Hz, 1H), 6.79 (d, J = 8.0Hz, 1H), 6.93 (s, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.6, 18.2, 20.5, 21.4, 24.4, 25.8, 30.0, 48.1, 54.8, 63.4, 100.9, 107.7, 108.9, 121.6, 127.1, 127.9, 129.5, 132.3, 134.2, 138.2, 143.0, 146.7, 147.6; HRMS (ESI+) calcd for $C_{28}H_{40}NO_5SSi$ $[M+H]^+$ 530.2391, found 530.2384 (Δ = -1.3 ppm).

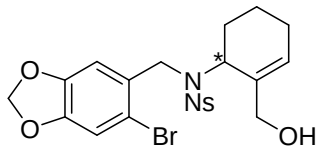
_N_-(6-Bromobenzo[_d_][1,3]dioxol-5-ylmethyl)-_N_-(2-(triisopropylsiloxymethyl)cyclohex-2-enyl)-4-methylbenzenesulfonamide (3-14g)



White solid; mp 120-121 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (s, 21H), 1.30 (m, 1H), 1.42 (m, 1H), 1.82 (m, 2H), 1.93 (m, 2H), 2.45 (s, 3H), 3.30 (d, J = 14.6 Hz, 1H), 3.44 (d, J =

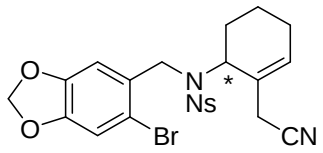
14.6 Hz, 1H), 4.14 (d, *J* = 17.4 Hz, 1H), 4.30 (brs, 1H), 4.44 (d, *J* = 17.4 Hz, 1H), 5.94 (d, *J* = 1.4 Hz, 1H), 5.97 (d, *J* = 1.5 Hz, 1H), 6.92 (s, 1H), 7.27 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 17.9, 17.9, 19.8, 21.4, 24.3, 30.6, 48.6, 54.9, 63.1, 101.6, 109.6, 112.0, 112.0, 121.6, 127.1, 127.2, 128.0, 129.6, 131.1, 133.2, 137.4, 143.4, 147.1, 147.3; HRMS (ESI+) calcd for $C_{31}H_{44}BrNaNO_5SSi$ $[M+Na]^+$ 672.1785, found 672.1787 (Δ = 0.3 ppm).

_N_-(6-Bromobenzo[_d_][1,3]dioxol-5-ylmethyl)-_N_-(2-hydroxymethylcyclohex-2-enyl)-2-nitrobenzenesulfonamide (3-15b)



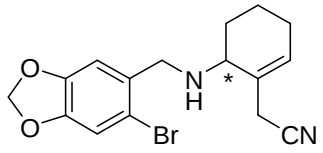
To a solution of **3-14b** (1.59 g, 2.6 mmol) in THF (30 mL) was added 4N HCl (6.5 mL) dropwise at room temperature. The mixture was stirred at the same temperature for 1 h. The aqueous layer was extracted with AcOH. The organic layer was dried over anhydrous Na_2SO_4. After removal of the drying agent, the solution was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (hexanes/AcOEt = 2:1) to afford **3-15b** (1.31 g, 99%) as a white solid. mp 78-79 ^{o}C; $[\alpha]_D^{21}$ -114.0 (*c* 0.88, CH_2Cl_2); ^{1}H NMR (400MHz, $CDCl_3$): δ 1.58 (m, 2H), 1.75 (m, 1H), 2.03 (m, 3H), 2.83 (d, *J* = 17.1 Hz, 1H), 2.94 (d, *J* = 17.1 Hz, 1H), 4.27 (d, *J* = 17.1 Hz, 1H), 4.54 (brs, 1H), 4.74 (d, *J* = 17.1 Hz, 1H), 5.89 (s, 1H), 5.93 (s, 1H), 6.21 (brs, 1H), 6.91 (s, 1H), 6.96 (s, 1H), 7.66 (m, 3H), 7.94 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 24.8, 28.7, 48.4, 55.2, 64.1, 101.8, 109.4, 112.4, 113.3, 124.2, 129.8, 131.6, 131.8, 133.5, 133.7, 133.8, 135.2, 147.4, 147.5, 147.6; HRMS (ESI+) calcd for $C_{21}H_{22}BrN_2O_7S$ $[M + H]^+$ 525.0326, found 525.0328 (Δ = 0.4 ppm).

***N*-(6-Bromobenzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-(2-cyanomethylcyclohex-2-enyl)-2-nitrobenzenesulfonamide (3-16)**



To a stirred solution of triphenylphosphine (130 mg, 0.5 mmol) in dry THF (2.5 mL) was added dropwise diisopropyl azodicarboxylate (0.1 mL, 0.5 mmol) at –20 ^{o}C. The resulting mixture was stirred for 20 min at the same temperature. Alcohol **3-15b** (124 mg, 0.25 mmol) in THF (0.5 mL) was added to the mixture and stirred for 20 min at –20 ^{o}C. To the solution was added acetone cyanohydrin (0.034 mL, 0.38 mmol) in 0.15 mL of THF. The resulting solution was stirred at –20 ^{o}C for 4h and then warmed to room temperature and stirred for additional 8 h. Methanol (0.1 mL) was added to the solution to quench the excess acetone cyanohydrin. The organic solvent was removed *in vacuo*. The residue was purified by chromatography on silical gel (hexanes/AcOEt = 5:1) to give **3-16** (115 mg, 91%) as a white solid. mp 189 ^{o}C-191 ^{o}C; $[\alpha]_D^{21}$ -91.3 (*c* 0.46, CH_2Cl_2); ^{1}H NMR (500MHz, $CDCl_3$): δ 1.55 (m, 2H), 1.75 (m, 1H), 2.02 (m, 2H), 2.84 (d, *J* = 19.1 Hz, 1H), 2.94 (d, *J* = 19.1 Hz, 1H), 4.27 (d, *J* = 17.0 Hz, 1H), 4.54 (brs, 1H), 4.74 (d, *J* = 17.0 Hz, 1H), 5.90 (s, 1H), 5.92 (s, 1H), 6.22 (brs, 1H), 6.91 (s, 1H), 6.96 (s, 1H), 7.62 (m, 1H), 7.70 (m, 2H), 7.94 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 22.0, 24.9, 28.5, 48.2, 57.1, 101.9, 109.3, 112.6, 113.5, 117.2, 124.5, 125.5, 129.1, 131.9, 132.0, 133.5, 134.1, 134.5, 147.6, 147.7, 147.8; HRMS (ESI+) calcd for $C_{22}H_{21}BrN_3O_6S$ $[M + H]^+$ 534.0329, found 534.0330 (Δ = 0.2 ppm).

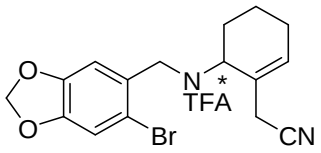
2-(6-(6-Bromobenzo[*d*][1,3]dioxol-5-ylmethylamino)cyclohex-1-enyl)acetonitrile (3-17)



To a stirred solution of **3-16** (267 mg, 0.5 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in DMF was added PhSH (93.5 mg, 0.85 mmol) dropwise at room temperature. The mixture was stirred

for 3 h at the same temperature. The resulting solution was washed with water and extracted with ethyl acetate, dried over anhydrous Na_2SO_4. After removal of the drying agent, the solution was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel pretreated with TEA (hexanes/AcOEt = 8:1) to give **3-17** as a colorless oil (140 mg, 83% yield). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.60 (brs, 1H), 1.81 (m, 2H), 1.91 (m, 2H), 2.1 (m, 2H), 3.1 (brs, 1H), 3.12 (d, J = 2.2 Hz, 1H), 3.16 (d, J = 2.2 Hz, 1H), 3.63 (d, J = 13.3 Hz, 1H), 3.89 (d, J = 13.3 Hz, 1H), 5.88 (brs, 1H), 5.89 (s, 1H), 6.96 (s, 1H), 6.98 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 23.0, 25.2, 27.6, 50.9, 53.6, 101.6, 110.1, 112.6, 114.0, 118.5, 128.4, 130.0, 132.8, 147.3, 147.4; HRMS (ESI+) calcd for $C_{16}H_{18}BrN_2O_2$ $[M + H]^+$ 349.0546, found 349.0547 (Δ = 0.3 ppm).

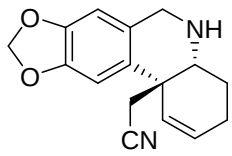
***N*-(6-Bromobenzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-(2-cyanomethylcyclohex-2-enyl)-2,2,2-trifluoroacetamide (3-18)**



To a solution of **3-17** (145 mg, 0.41 mmol) in DCM was added TEA (0.14 mL, 1.0 mmol) and $(CF_3CO)_2O$ (0.07 mL, 0.53 mmol) at 0 ^{o}C. The mixture was stirred at the same temperature for 1 h. The resulting solution was washed with water and extracted with ethyl acetate, dried over anhydrous Na_2SO_4. After removal of the drying agent, the solution was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (hexanes/AcOEt = 5:1) to give **3-18** (174 mg, 94%)as a amorphous solid. $[\alpha]_D^{21}$ -72.3 (*c* 0.39, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.66 (m, 3.3 H), 1.96 (m, 0.7 H), 2.10 (m, 2H), 2.83 (s, 0.35H), 2.86 (s, 0.35H), 2.89 (s, 1.3 H), 4.14 (d, J = 16.0 Hz, 0.65H), 4.46 (d, J = 17.0 Hz, 0.35H), 4.62 (brs, 1H), 4.68 (d, J = 17.0 Hz, 0.35H), 4.77 (d, J = 16.0 Hz, 0.65H), 5.95 (s, 0.65H), 5.97 (s, 0.65H), 6.12 (s, 0.7H), 6.12 (brs, 0.35H), 6.39 (s, 0.65H), 6.55 (s, 0.65H), 6.72 (s, 0.35H), 6.98 (s, 0.65H), 7.01 (s, 0.35H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 21.0, 21.8, 22.0, 24.7, 24.8, 26.6, 29.1, 46.9, 49.7, 56.9, 56.9, 102.0, 102.2, 107.3, 108.4, 112.7, 112.8, 112.8, 113.4, 116.0 (q, J =230 Hz), 116.4 (q, J = 229 Hz), 116.4, 117.1, 124.2, 125.0, 127.5, 127.9, 132.4, 135.1, 147.6, 147.8, 147.8, 148.3,

157.9, 158.2 (q, J = 35.7 Hz); HRMS (ESI+) calcd for $C_{18}H_{17}BrF_3N_2O_3$ $[M + H]^+$ 445.0369, found 445.0370 (Δ = 0.2 ppm).

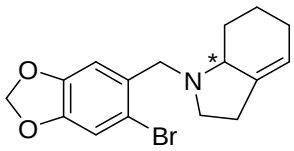
cis-2-(3,4,4a,5,6,11b-Hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridin-11b-yl)acetonitrile (3-20)



To a 10 mL of flask was added **3-18** (120 mg, 0.32 mmol), $Pd(OAc)_2$ (11.6 mg, 0.05 mmol), Ag_2CO_3 (284 mg, 1.0 mmol) and dppp (21 mg, 0.05 mmol). Degassed toluene (4 mL) was added and the resulting suspension was heated at 110 ^oC for 24h. The mixture was filtered and the resulting solution was concentrated *in vacuo*. The residue was purified by column chromatography on silical gel (hexanes/AcOEt = 6:1) afford **3-19** (49 mg, 58%) as a colorless oil, containing a small amount of isomers. $[\alpha]_D^{21}$ -80.0 (*c* 1.5, CH_2Cl_2); ^1H NMR (500MHz, $CDCl_3$): δ 1.81 (m, 2H), 2.20 (m, 1H), 2.33 (m, 1H), 2.55 (s, 0.8H), 2.59 (s, 0.6H), 2.61 (s, 0.6 H), 4.14 (d, J = 10.9 Hz, 0.6H), 4.29 (d, J = 18.2 Hz, 0.6H), 4.57 (d, J = 16.8 Hz, 0.4H), 4.82 (m, 0.8H), 5.06 (d, J = 18.2 Hz, 0.6H), 5.95 (brs, 3H), 6.11 (m, 1H), 6.54 (s, 0.4H), 6.58 (s, 0.6H), 6.82 (s, 0.6H), 6.86 (s, 0.4H); HRMS (ESI+) calcd for $C_{18}H_{16}F_3N_2O_3$ $[M + H]^+$ 365.1108, found 365.1112 (Δ = 1.1 ppm).

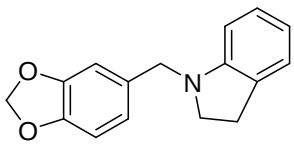
To a stirred solution of **3-19** (36 mg, 0.1 mmol) in EtOH was added 2 M NaOH (0.2 mL) at room temperature. The solution was stirred overnight at the same condition. After removal of the solvent, the residue was purified by column chromatography on silical gel pretreated with TEA (hexanes/AcOEt = 1:1) afford **3-20** (24 mg, 90%) as a colorless oil. $[\alpha]_D^{20}$ -74.7 (*c* 1.5, CH_2Cl_2); ^1H NMR (500MHz, $CDCl_3$): δ 1.84 (m, 3H), 2.17 (m, 2H), 2.69 (d, J = 21.1 Hz, 1H), 2.92 (d, J = 21.1 Hz, 1H), 3.22 (dd, J = 10.4 Hz, J = 4.0 Hz, 1H), 3.94 (d, J = 19.8 Hz, 1H), 4.02 (d, J = 19.8 Hz, 1H), 5.84 (s, 2H), 5.91 (s, 2H), 6.47 (s, 1H), 6.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 24.5, 30.8, 40.0, 45.7, 54.6, 100.9, 106.1, 106.6, 117.8, 128.0, 128.6, 130.6, 131.3, 146.3, 146.8; HRMS (ESI+) calcd for $C_{16}H_{17}N_2O_2$ $[M + H]^+$ 269.1285, found 269.1282 (Δ = -1.1 ppm).

1-(6-Bromobenzo[*d*][1,3]dioxol-5-ylmethyl)-2,3,5,6,7,7a-hexahydro-1*H*-indole (3-21)



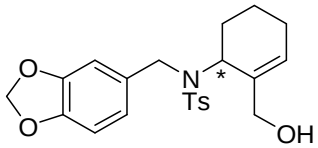
To a solution of **3-17** (33 mg, 0.1 mmol) was added toluene (1.5 mL) and DIBAL-H (0.15 mL, 1.0 M in hexane) at –78 ^{o}C. The solution was stirred at that temperature for 4 h and it was then warmed to 0 ^{o}C. The solution was stirred for additional 2 h at the same temperature. To the solution were added methanol (5 mL) and a solution of sodium monobasic hydrogen phosphate in water (2 mL) at 0 ^{o}C. The heterogeneous solution was stirred at room temperature for 2 h. The flask was cooled to 0 ^{o}C and $NaCNBH_3$ (64 mg, 1.0 mmol) was added. The solution was stirred at room temperature for 8 h. The excess $NaCNBH_3$ was destroyed by addition of 2 M HCl. Nitrogen was bubbled through the solution for 3 h. The pH was adjusted to basic (pH>12) using 50% NaOH. The resulting mixture was extracted with methylene chloride (6 x 10mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (10% to 20% MeOH in CH_2Cl_2) provided **3-21** (21 mg, 64% yield) as a white solid. Enantiomers were separated by HPLC using Chiralcel AD-RH column eluting with 30:70 water/acetonitrile at 1.0 mL/min. Retention times: major enantiomer 6.5 min. and minor 8.1 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (m, 1H), 1.48(m, 1H), 1.83 (m, 1H), 2.14 (m, 4H), 2.37 (m, 2H), 2.68 (brs, 1H), 3.03 (m, 1H), 3.35 (d, J = 13.8 Hz, 1H), 3.96 (d, J = 13.8Hz, 1H), 5.42 (brs, 1H), 5.93 (s, 2H), 6.96 (s, 1H), 7.00 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.4, 25.0, 28.0, 28.0, 52.2, 57.7, 64.4, 101.4, 110.4, 112.2, 114.1, 118.4, 131.8, 140.2, 146.9, 147.2. All data are in agreement with the literature values.[37]

1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)indoline (3-22)



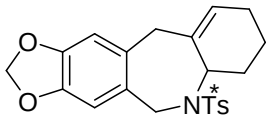
To a 10 mL of flask was added **3-21** (16 mg, 0.05 mmol), $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), Ag_2CO_3 (43 mg, 0.15 mmol) and dppp (3.4 mg, 0.008 mmol). Degassed toluene (0.5 mL) was added and the resulting suspension was heated at 110 ^oC for 24h. The mixture was filtered and the resulting solution was concentrated *in vacuo*. The residue was purified by column chromatography on silical gel (hexanes/AcOEt = 10:1) afford **3-22** (9 mg, 71%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 3.00 (t, J = 8.3 Hz, 2H), 3.33 (t, J = 8.3 Hz, 2H), 4.19 (s, 2H), 5.98 (s, 2H), 6.54 (d, J = 7.9 Hz, 1H), 6.71 (m, 1H), 6.85 (m, 2H), 6.91 (s, 1H), 7.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.5, 53.5, 53.5, 101.0, 107.1, 108.1, 108.4, 117.8, 121.0, 124.5, 127.3, 130.1, 132.4, 146.7, 147.9, 152.5. All data are in agreement with the literature values.[38]

***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-(2-hydroxymethylcyclohex-2-enyl)-4-methylbenzene sulfonamide (3-15f)**



To a solution of **3-14f** (106 mg, 0.2 mmol) in THF (2.0 mL) was added TBAF (1 M in THF, 0.25 mL) dropwise at room temperature. The mixture was stirred at the same temperature for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexanes/AcOEt = 2:1) to afford **3-15f** (82 mg, 99%) as a white solid. mp 112-113 ^oC; ^1H NMR (500MHz, $CDCl_3$): δ 1.60 (m, 4H), 1.93 (brs, 2H), 2.42 (s, 3H), 2.64 (brs, 1H), 3.60 (d, J = 12.9 Hz, 1H), 3.89 (d, J = 12.9 Hz, 1H), 4.22 (d, J = 15.6 Hz, 1H), 4.36 (d, J = 15.6 Hz, 1H), 4.60 (brs, 1H), 5.93 (m, 3H), 6.66 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.81 (s, 1H), 7.25 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.8, 21.4, 24.5, 27.9, 47.6, 53.6, 64.1, 100.9, 107.6, 109.0, 122.0, 126.8, 129.5, 130.9, 131.1, 136.1, 137.8, 143.2, 146.7, 147.4; HRMS (ESI+) calcd for $C_{22}H_{26}NO_5S$ $[M + H]^+$ 416.1526, found 416.1526 (Δ = 0 ppm).

6-(4-Methylbenzenesulfonyl)-6,6a,7,8,9,11-hexahydro-5*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*e*]benzo[*b*]azepine (3-24)



To **3-15f** (180 mg, 0.43 mmol) in THF was added PBr_3 (38 mg, 0.14 mmol) at 0 ^oC. The solution was stirred at the same temperature for 1 h. The mixture was quenched with water, and then extracted with ether. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. Flash column chromatography provided **3-23** (176 mg, 96%) as a colorless oil contaminated with a small amount of impurity. ^1H NMR (500MHz, $CDCl_3$): δ 1.46 (m, 2H), 1.80 (m, 2H), 1.96 (m, 2H), 2.43 (s, 3H), 3.61 (brs, 2H), 4.18 (d, J = 15.4 Hz, 1H), 4.30 (d, J = 15.4 Hz, 1H), 5.93 (s, 1H), 6.14 (brs, 1H), 6.67 (m, 2H), 6.81 (s, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.1, 21.4, 25.1, 28.3, 34.7, 48.4,53.6, 100.9, 107.7, 109.2, 122.2, 127.2, 129.6, 131.1, 133.7, 135.9, 138.0, 143.2, 146.9, 147.5; HRMS (ESI+) calcd for $C_{22}H_{24}BrNNaO_4S$ $[M + Na]^+$ 500.0502, found 500.0499 (Δ = -0.6 ppm).

To **3-23** (135 mg, 0.28 mmol) in THF was added ZnI_2 (89 mg, 0.28 mmol) at 0 ^oC. The solution was stirred at the same temperature for 20 min. The mixture was quenched with water, and then extracted with ether. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. Flash column chromatography provided **3-24** (78 mg, 70%) as a colorless oil. Enantiomers were separated by HPLC using Chiralcel AD-RH column eluting with 50:50 water/ acetonitrile at 1.0 mL/min. Retention times: major enantiomer 21.5 min. and minor 30.4 min; ^1H NMR ($CDCl_3$, 500MHz): δ 1.63 (m, 4H), 1.98 (brs, 2H), 2.09 (m, 1.2H), 2.32 (s, 3.3H), 2.57 (d, J = 15.8 Hz, 0.7H), 3.03 (d, J = 15.8 Hz, 0.7H), 3.25 (d, J =16.6 Hz, 0.3H), 4.32 (m, 2H), 4.59 (m, 1H), 5.70 (brs, 0.7H), 5.74 (brs, 0.3H), 5.83 (d, J = 9.0 Hz, 0.6H), 5.91 (d, J = 23.6 Hz, 1.4H), 6.30 (s, 0.6H), 6.59 (s, 1.4H), 7.01 (d, J = 8.0 Hz, 0.6H), 7.05 (d, J = 8.0 Hz, 1.4H), 7.32 (d, J = 8.3 Hz, 0.6H), 7.38 (d, J = 8.3 Hz, 1.4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.9, 21.1, 21.3, 24.8, 29.2, 30.0, 34.1, 41.2, 46.7, 46.8, 58.0, 58.2, 100.6, 100.9, 105.5, 108.2, 109.3, 119.9, 120.9, 126.8, 126.9, 128.2, 128.6, 128.8, 130.0, 130.2, 131.0, 133.3, 134.6, 137.5, 137.6, 142.4, 142.5, 145.0, 145.4, 145.8, 146.5; HRMS (ESI+) calcd for $C_{22}H_{24}NO_4S$ $[M + H]^+$ 398.1421, found 398.1426 (Δ = 1.3 ppm).

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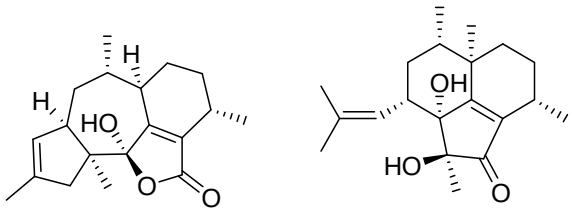
Chapter 4

The Synthesis of Enediynes and Their Applications to Rh(I)-Catalyzed [2+2+2+1] Cycloaddition Reactions

§4.1 Introduction

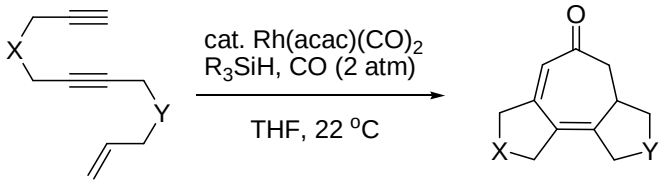
Polycyclic skeletons are widely found in a variety of bioactive compounds,[1] e.g. Caribenol A and Caribenol B (Figure 4-1).[2] The development of highly efficient methods for the synthesis of these building blocks has attracted much interest in modern organic chemistry. One of the most efficient methods is the transition metal-catalyzed cycloaddition,[3] which generates polycyclic cores from linear unsaturated starting materials often in a single step. To date, many higher order cycloaddition reactions including [2+2+2+1][4-6], [2+2+2+2][7,8], [3+3+1][9], [4+2+2][10,11], [5+2+1][12,13] and [5+1+2+1][14] processes were reported.



Caribenol A Caribenol B

Figure 4-1. Caribenol A and Caribenol B

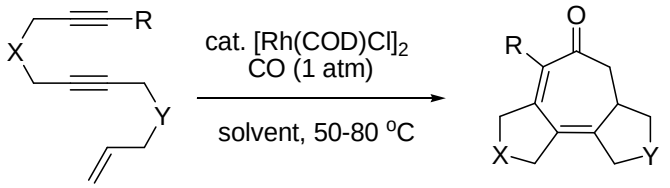
A series of Rh(I)-catalyzed [2+2+2+1] cycloadditions for the formation of fused seven-membered rings have been developed in the Ojima laboratory.[3-6,15-18] Among them, syntheses of tricyclic and tetracyclic compounds employing linear enediyne as the substrates have been the most extensively studied.[3-6,17] The carbonylative silylcarbotricyclization (CO-SiCaT) of enediynes **4-1** bearing a terminal alkyne moiety provided 5-7-5 tricyclic products **4-2** in good to excellent yields (Scheme 4-1).[17] Interestingly, CO-SiCaT reactions using enediynes with all internal alkynes failed to afford the desired products **4-4**, while they were achieved through Rh-catalyzed [2+2+2+1] cycloaddition in the absence of hydrosilane (Scheme 4-2).[4,5] Further study discovered that these two reactions underwent different process.[5] Based on the success of the formation of 5-7-5 tricyclic compounds, we decided to expand the scope of the Rh-catalyzed [2+2+2+1] cycloaddition. Thus, enediynes bearing carbocyclic rings were prepared, and some of them were subjected to the Rh-catalyzed [2+2+2+1] cycloaddition to give 5-7-n-5 fused tetracyclic compounds (Scheme 4-3).[6,19,20]



4-1 **4-2**

X,Y = $C(CO_2Et)_2$, $C(CH_2OMe)_2$, $C(CH_2OBn)_2$, NTs, O

Scheme 4-1. Rh(I)-catalyzed CO-SiCaT reaction

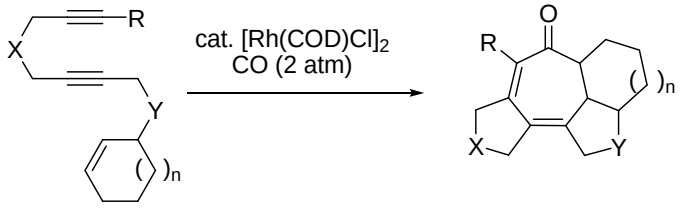


4-3 **4-4**

R = Me, Ph, TMS, $PhMe_2Si$

X,Y = $C(CO_2Et)_2$, $C(CH_2OMe)_2$, $C(CH_2OBn)_2$, NTs, O

Scheme 4-2. Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction of **4-3**



4-5 **4-6**

n = 0, 1, 2

R = Me, Ph, TMS, $PhMe_2Si$

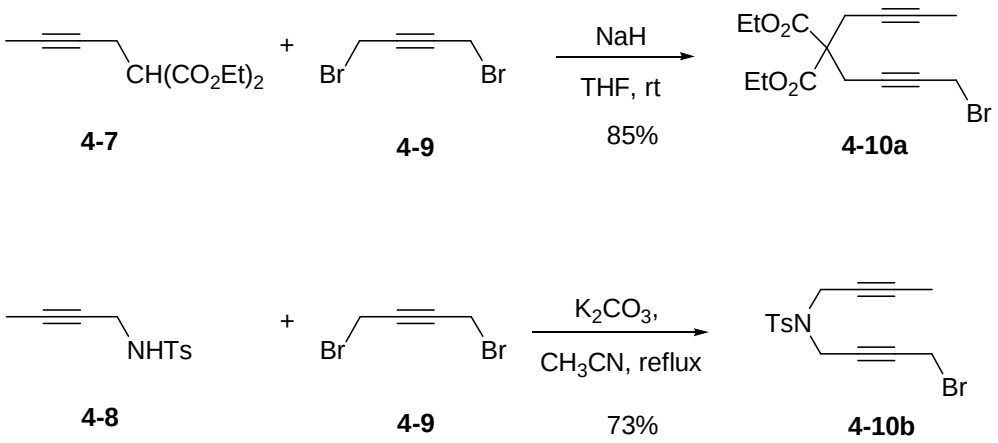
X,Y = $C(CO_2Et)_2$, NTs, O

Scheme 4-3. Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction of **4-5**

§4.2 Results and disscusion

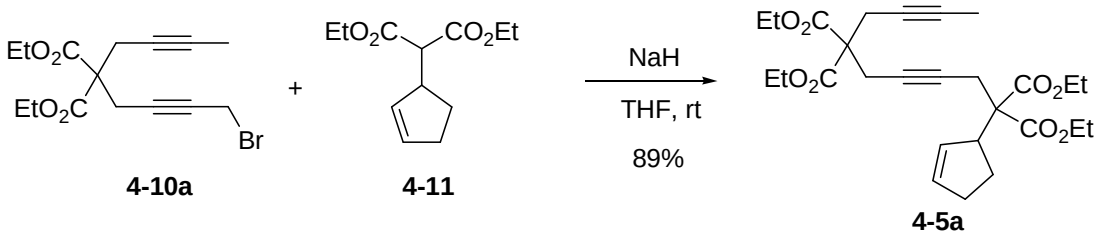
§4.2.1 Synthesis of enediynes

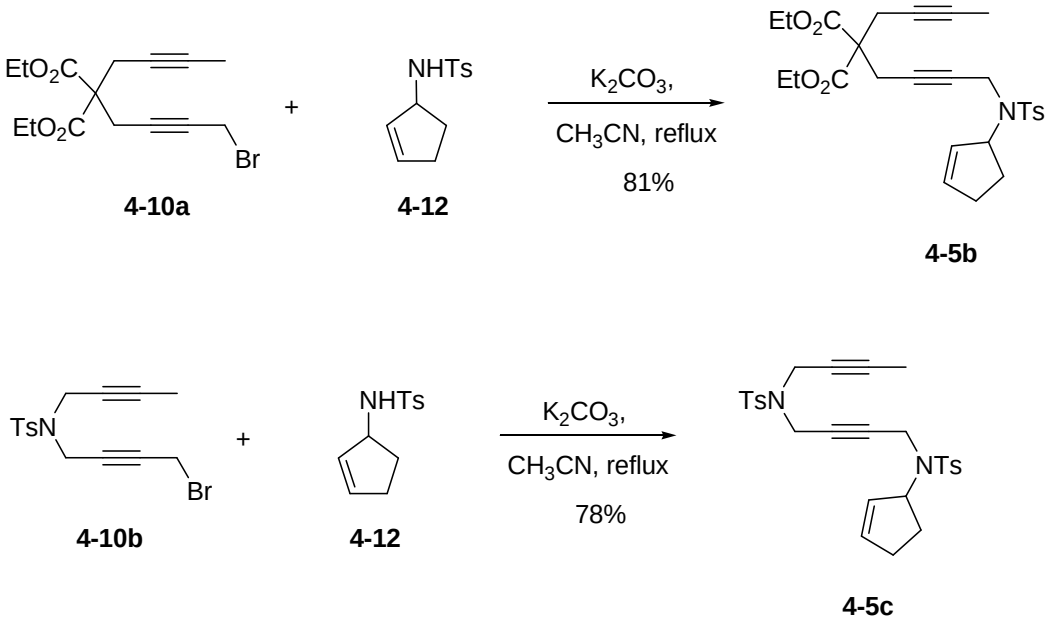
Diethyl-2-(but-2-ynyl)malonate **4-7** was coupled with 1,4-dibromobut-2-yne **4-9** in the presence of NaH to give the diyne bromide **4-10a** in good yield (Scheme 4-4). The *N*-tosyl tethered diyne bromide **4-10b** was obtained from the coupling of *N*-butynyl-*N*-tosylamide **4-8** with **4-9** using K_2CO_3 as the base (Scheme 4-4).



Scheme 4-4. Synthesis of diyne bromides

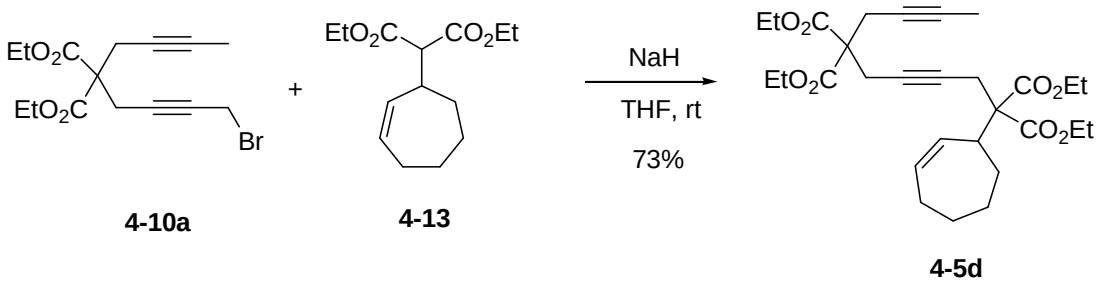
The sodium hydride mediated coupling of diyne bromide **4-10a** with diethyl 2-(cyclopent-2-enyl)malonate **4-11** afford the cyclopentenediyne **4-5a** in 89% yield. The cyclopentenediynes **4-5b** and **4-5c** were obtained from the reactions of *N*-cyclopent-2-enyl sufonamides **4-12** with diyne bromides **4-10a** and **4-10b**, respectively (Scheme 4-5).

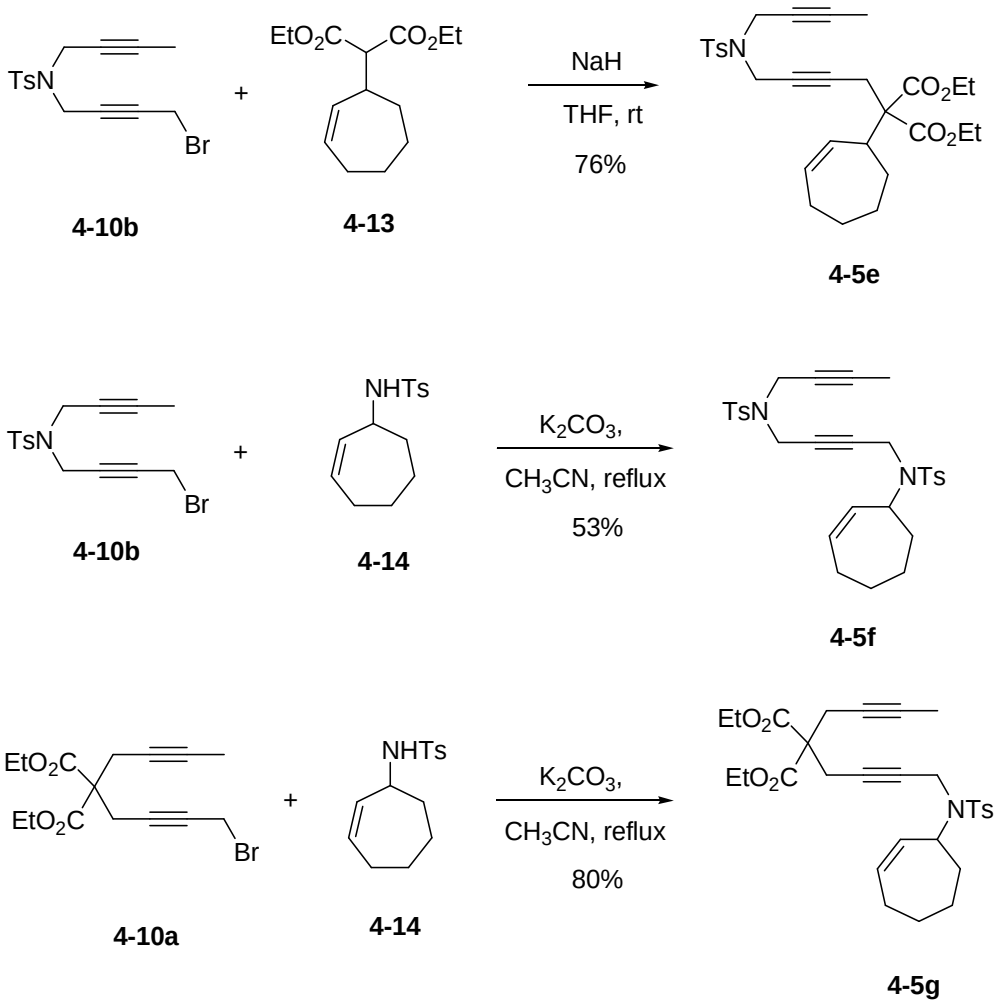




Scheme 4-5. Synthesis of cyclopentenediynes

The cycloheptenediyne **4-5d** was synthesized by the treatment of **4-10a** with diethyl 2-(cyclohept-2-enyl)malonate **4-13** in the presence of NaH. The cycloheptenediyne **4-5e** was synthesized according to the same procedure (Scheme 4-6). The K_2CO_3 mediated coupling of **4-10b** with sulfonamide **4-14** gave bis-NTs-tethered substrate **4-5f** in moderate yield. The cycloheptenediyne **4-5g** bearing a malonate and sulfonamide tether was synthesized in the same manner (Scheme 4-6).

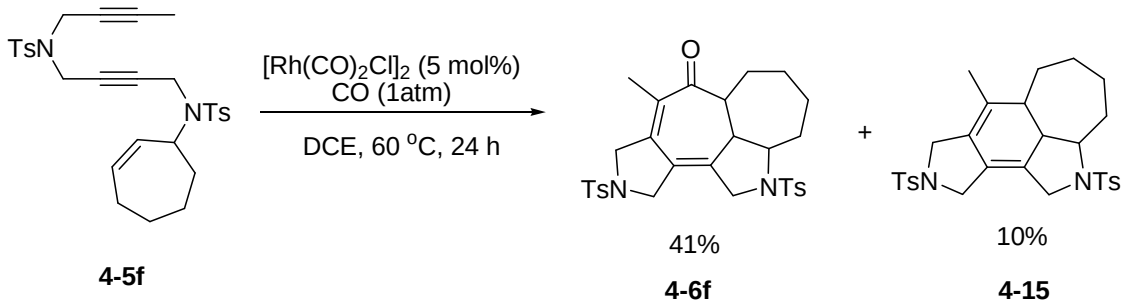




Scheme 4-7. Synthesis of cycloheptenediynes

§4.2.2 Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction

The cycloheptenediyne **4-5f** was investigated in the Rh(I)-catalyzed [2+2+2+1] cycloaddition by the author. The reaction was carried out in DCE at 60 ^{o}C under 1 atm CO. This condition was optimized by Alexandra A. Athan in the Ojima group.[19,20] The 5-7-7-5 fused tetracyclic product **4-6f** was obtained in 41% yield with a small amount of [2+2+2] side product (Scheme 4-7).



Scheme 4-8. Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction of **4-5f**

§4.3 Conclusions

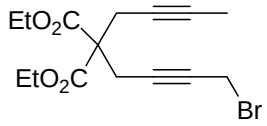
Cyclopentenediynes and cycloheptenediynes substrates were synthesized in moderate to good yields for the formation of 5-7-5-5 and 5-7-7-5 fused tetracyclic products. One of the substrates was applied to the Rh(I)-catalyzed [2+2+2+1] to give the tetracyclic product **4-6f** in moderate yield. Further optimization of the conditions is underway in our laboratory.

§4.4 Experimental section

General Methods. ^{1}H, ^{13}C, and ^{31}P NMR were measured on a Bruker Avance 500 (500 MHz for ^{1}H; 125 MHz for ^{13}C), a Bruker Avance 400 (400 MHz for ^{1}H; 100 MHz for ^{13}C), or a Varian Gemini-2300 300 MHz (300 MHz for ^{1}H; 75 MHz for ^{13}C) NMR spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm) as the internal standard. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Helmer Model 241 polarimeter. TLC analyses were performed using Merck DC Alufolien $60F_{254}$ aluminum pre-coated silica gel plates. Flash column chromatography was carried out using Silicyle Silia*Flash*P60® silica gel (particle size 40_63 μm). High-resolution mass spectrometric analyses were carried out at the Mass Spectrometry Laboratory, University of Illinois Urbana-Champaign, Urbana, IL or by ICB&DD at Stony Brook University. Unless otherwise noted all reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques.

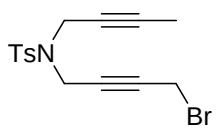
Material. Solvents were reagents grade and freshly dried, degassed and distilled before use. Anhydrous *N*,*N*-dimethylformamide (DMF) and acetonitrile were purchased from Acros Organic and used without further purification. Chemicals and reagents were purchased from VWR, Fisher Scientific or Sigma-Aldrich and used without further purification unless otherwise noted. **4-11**[19]**, 4-12**[19]**, 4-13**[20] and **4-14**[20] were prepared according to the procedure previously reported in our laboratory.

Diethyl 2-(4-bromobut-2-ynyl)-2-(prop-2-ynyl)malonate (4-10a)



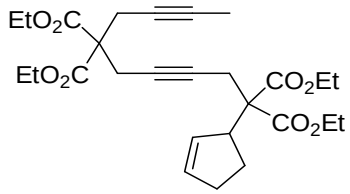
To a suspension of NaH (60% dispersion in mineral oil, 0.5 g, 12 mmol) and in THF (40 mL), diethyl 2-(but-2-ynyl)malonate **4-7a** (2.5 g, 12 mol) was added dropwise at room temperature. The mixture was stirred at the same temperature for 1 h, and then transferred to a solution of 1,4-dibromobut-2-yne **4-9** (7.5 g, 35 mmol) in THF (50 mL) over 2.5 h. The mixture was stirred at room temperature for 18 h, and then diluted with water. The aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes/AcOEt = 10:1) to afford **4-10a** (3.4 g, 85%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 6H), 1.75 (t, J = 2.7 Hz, 2H), 2.88 (q, J = 2.7 Hz, 2H), 3.02 (t, J = 2.1 Hz, 2H), 3.87 (t, J = 2.1 Hz, 2H), 4.25 (q, J = 7.2 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.5, 14.0, 14.7, 22.7, 23.0, 56.7, 61.7, 61.9, 72.9, 78.2, 79.1, 82.2, 168.9. All data are in agreement with the literature values.[4,5]

***N*-(4-Bromobut-2-ynyl)-*N*-(but-2-ynyl)-4-methylbenzenesulfonamide (4-10b)**



To a suspension of K_2CO_3 (375 mg, 2.72 mmol) and 1,4-dibromobut-2-yne **4-9** (865 mg, 4.22 mmol) in CH_3CN (7 mL), *N*-(but-2-ynyl)-4-methylbenzenesulfonamide **4-7b** (308 mg) was added dropwise at room temperature. The mixture was stirred under reflux overnight. The crude reaction mixture was filtered over Celite®, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes/AcOEt = 10:1) to afford **4-10b** (352 mg, 73%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (t, J = 2.4 Hz, 3H), 2.50 (s, 3H), 3.78 (t, J = 2.1 Hz, 2H), 4.12 (q, J = 2.4 Hz, 2H), 4.27 (d, J = 2.1 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.4, 13.7, 21.5, 36.5, 37.0, 71.3, 79.6, 80.4, 82.0, 127.9, 129.4, 135.3, 143.7. All data are in agreement with the literature values.[4,5]

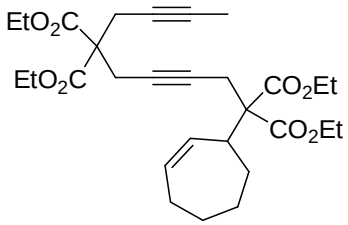
1-(Cyclopent-2-en-1-yl)-1,16,6-tetracarbethoxydeca-3,8-diyne, (4-5a)



To a suspension of NaH (60% dispersion in mineral oil, 48 mg, 1.2 mmol) in THF (6 mL) was added diethyl 2-(cyclopent-2-enyl) malonate **4-11** (363 mg, 1.60 mmol) in THF (6 mL) at room temperature. The resulting mixture was stirred for 30min at the same temperature. Diyne bromide **4-10a** (550 mg, 1.60 mmol) in THF (3 mL) was added and the mixture was then stirred at the same temperature for 18 h. The reaction mixture was diluted with water and extracted with Et_2O. The organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes/AcOEt = 10:1) to give **4-5a** as a light yellow oil (433 mg, 89%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (m, 12H), 1.70 (m, 4H), 2.00 (m, 1H), 2.25 (m, 2H), 2.78 (m, 2H), 2.90 (m, 2H), 2.90 (m, 2H), 3.57 (m, 1H), 4.20 (m, 8H), 5.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.4, 14.0, 14.0, 22.7, 22.8, 23.3, 25.1, 31.7, 48.6, 56.7, 59.9, 61.1, 61.2, 61.6, 73.2, 78.4, 78.7, 131.5, 132.1, 169.0, 169.9, 170.0. All data are in agreement with the literature values.[19]

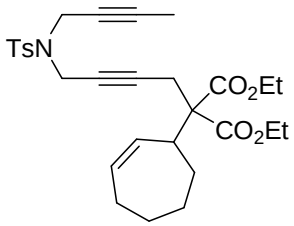
In the same manner, **4-5d** and **4-5e** were synthesized.

1-(Cyclohept-2-en-1-yl)-1,1,6,6-tetracarbethoxydeca-3,8-diyne (4-5d)



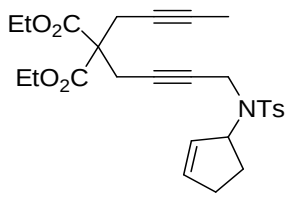
Yellow oil; 73% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (m, 14H), 1.73 (m, 5H), 1.86 (m, 1H), 2.00 (m, 1H), 2.15 (m, 1H), 2.26 (m, 1H), 2.80 (m, 2H), 2.90 (m, 4H), 3.19 (m, 1H), 4.21 (m, 8H), 5.72 (m, 1H), 5.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.6, 14.1, 22.9, 23.6, 26.3, 27.9, 29.9, 31.6, 42.6, 56.9, 60.4, 61.4, 61.4, 61.8, 73.5, 77.5, 78.6, 78.8, 131.7, 132.9, 169.2, 170.0, 170.0. All data are in agreement with the literature values.[20]

6-Aza-1-(cyclohept-2-en-1-yl)-1,1-dicarbethoxy-6-(4-methylbenzenesulfonyl)deca-3,8-diyne (4-5e)



Yellow oil; 76% yield; 1H NMR (300 MHz, $CDCl_3$) δ 1.23 (m, 8H), 1.60 (s, 3H), 1.65(m, 3H), 1.98 (m, 1H), 2.15 (m, 2H), 2.42 (s, 3H), 2.70 (s, 2H), 3.12 (m, 1H), 4.05 (m, 4H), 4.15 (m, 4H), 5.65 (m, 1H), 5.82 (m, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.5, 14.2, 14.2, 21.7, 23.5, 26.2, 28.0, 30.0, 31.6, 36.7, 36.7, 43.0, 60.4, 61.6, 61.6, 71.7, 75.8, 81.6, 81.8, 128.1, 129.4, 132.1, 132.8, 135.7, 143.6, 169.9, 170.0. All data are in agreement with the literature values.[20]

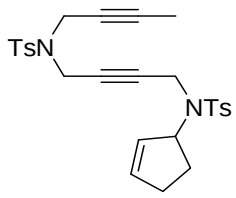
1-Aza-1-(cyclopent-2-en-1-yl)-6,6-dicarbethoxy-1-(4-methylbenzenesulfonyl)nona-3,8-diyne (4-5b)



To a suspension of *N*-(cyclopent-2-ynyl)-4-methylbenzenesulfonamide **4-12** (230 mg, 0.97 mmol) and K_2CO_3 (268 mg, 1.94 mmol) in CH_3CN (10 mL) was added a solution of the diyne-bromide **2-12** (335 mg, 0.97 mmol) in CH_3CN (10 mL) at room temperature. The mixture was refluxed overnight. The mixture was then cooled to room temperature, filtered over Celite® and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes/AcOEt = 10:1) to give **4-5b** as a yellow oil (393 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (m, 6H), 1.77 (m, 4H), 2.03 (m, 1H), 2.20 (m, 1H), 2.40 (m, 1H), 2.43 (s, 3H), 2.77 (m, 2H), 2.83 (m, 2H), 3.90 (m, 2H), 4.15 (m, 4H), 5.02 (m, 1H), 5.44 (m, 1H), 5.97 (m, 1H), 7.32 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.4, 14.0, 21.5, 22.7, 22.9, 27.3, 31.3, 32.6, 56.5, 61.7, 64.1, 73.1, 78.2, 78.9, 79.6, 127.5, 129.1, 129.4, 136.3, 137.7, 143.0, 168.9. All data are in agreement with the literature values.[19]

In the same manner, **4-5c, 4-5f** and **4-5g** were synthesized.

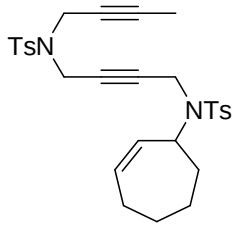
1,6-Bis(4-methylphenylsulfonyl)-1-(cyclopent-2-en-1-yl)-1,6-diazadeca-3,8-diyne (4-5c)



Yellow oil; 78% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (m, 4H), 2.06 (m, 1H), 2.35 (m, 2H), 2.48 (s, 3H), 2.53 (s, 3H), 3.99 (m, 6H), 5.12 (m, 1H), 5.40 (m, 1H), 6.03 (m, 1H),7.33 (m, 4H), 7.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.4, 21.5, 27.4, 31.4, 32.4, 36.4, 36.7, 64.1, 71.3, 76.4, 81.8, 81.9, 127.4, 127.9, 129.0, 129.4, 129.5, 135.4, 136.5, 137.5, 143.4, 143.7. All

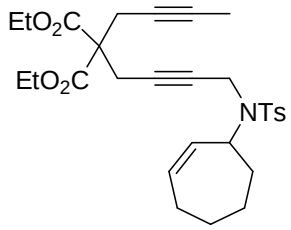
data are in agreement with the literature values.[20]

1,6-Bis(4-methylphenylsulfonyl)-1-(cyclohept-2-en-1-yl)-1,6-diazadeca-3,8-diyne (4-5f)



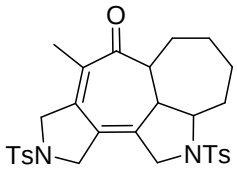
Yellow oil; 53% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (m, 2H), 1.61 (m, 6H), 1.69 (m, 1H), 2.03 (m, 1H), 2.16 (m, 1H), 2.41 (s, 6H), 4.00 (m, 6H), 4.52 (m, 1H), 5.40 (m, 1H), 5.72 (m, 1H), 7.28 (m, 4H), 7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.4, 21.6, 21.6, 26.4, 27.6, 28.3, 33.2, 33.4, 36.5, 36.8, 59.6, 71.4, 77.0, 81.8, 81.9, 127.4, 128.0, 129.6, 132.7, 133.1, 135.5, 137.9, 143.4, 143.8. All data are in agreement with the literature values.[20]

1-Aza-1-(cyclohept-2-en-1-yl)-6,6-dicarbethoxy-1-(4-methylbenzenesulfonyl)nona-3,8-diyne (4-5g)



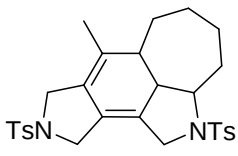
Yellow oil; 80% yield; ^{1}H NMR (300 MHz, $CDCl_3$z) δ 1.25 (m, 6H), 1.32 (m, 1H), 1.47 (m, 1H), 1.75 (m, 6H), 1.87 (m, 1H), 2.04 (m, 1H), 2.18 (m, 1H), 2.42 (s, 3H), 2.79 (m, 2H), 2.86 (m, 2H), 4.10 (m, 2H), 4.21 (m, 4H), 4.51 (m, 1H), 5.50 (m, 1H), 5.72 (m, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.4, 14.0, 21.5, 22.8, 23.0, 26.3, 27.5, 28.2, 33.1, 33.5, 56.6, 59.5, 61.8, 61.8 73.1, 78.8, 78.9, 79.4,127.4, 129.4, 129.6, 132.4, 133.3, 143.0, 169.0. All data are in agreement with the literature values.[20]

11-Methyl-2,5-bis(4-methylbenzenesulfonyl)-1,2,3,3b1,4,5,5a,6,7,8,9,9a-dodecahydro-10*H*-heptaleno[10,1-*bc*:2,3-*c*']dipyrrol-10-one (4-6f)



Cycloheptenediyne **4-5f** (105 mg, 0.2 mmol) and $[Rh(CO)Cl]_2$ (3.3 mg, 0.01 mmol) in DCE (4 mL) were combined in a 10 mL round bottom flask. The flask was transferred to an autoclave and purged with CO and released 4 times. **Caution: Purging with CO must be done in a ventilated fume hood.** The autoclave was then purged to 1 atm of CO. The reaction was stirred at 60 ^{o}C for 24 h, and then cooled to room temperature. The gas was released from the autoclave in a ventilated fume hood. The solution was removed *in vacuo* and the residue was purified by column chromatography (hexanes/AcOEt = 5:1) to afford **4-6f** (46 mg, 41% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19(m, 1H), 1.45 (m, 3H), 1.68(s, 3H), 1.75(m, 1H), 1.86 (m, 3H), 2.18 (s, 3H), 2.45 (m, 1H), 2.48 (s, 3H), 2.88 (m, 1H), 3.20 (m, 1H), 3.35 (m, 1H), 3.45 (m, 1H), 3.70(m, 4H), 6.93 (d, J = 8.0 Hz, 2H), 7.42 (m, 4H), 7.71 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.4, 21.2, 21.6, 24.4, 28.1, 28.1, 38.7, 50.7, 51.2, 51.7, 52.0, 52.3, 61.2, 125.7, 127.1, 128.0, 129.7, 130.0, 132.0, 133.3, 133.9, 134.4, 135.0, 143.4, 144.4, 202.2; HRMS (ESI+) calcd for $C_{30}H_{38}N_3O_5S_2$ $[M + NH_4]^+$ 584.2247, found 584.2235 (Δ = 1.4 ppm).

7-Methyl-2,9-bis(4-methylbenzenesulfonyl)-1,2,2a,2a1,3,4,5,6,6a,8,9,10-dodecahydro-2,9-diaza-cyclohepta[*cd*]-*as*-indacene (4-15)



Colorless oil; 10% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (m, 1H), 1.32 (m, 1H), 1.45 (s, 3H), 1.47 (m, 3H), 1.65 (m, 1H) 2.20 (m, 1H), 2.43 (s, 6H), 4.00 (m, 4H), 4.53 (m, 1H), 5.42

(m, 1H), 5.76 (m, 1H), 7.30 (m, 4H), 7.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$f) δ 3.3, 21.5, 26.2, 27.4, 28.1, 33.1, 33.2, 36.5, 36.6, 59.4, 71.2, 76.8, 81.7, 81.8, 127.2, 127.9, 129.3, 129.5, 132.6, 133.0, 135.3, 137.7, 143.3, 143.6. HRMS (ESI+) calcd for $C_{30}H_{38}N_3O_5S_2$ $[M + NH_4]^+$ 556.2298, found 584.2303 (Δ = 0.9 ppm).

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APPENDICES

^{1}H, ^{13}C, ^{31}P NMR Spectra and Crystallography Data

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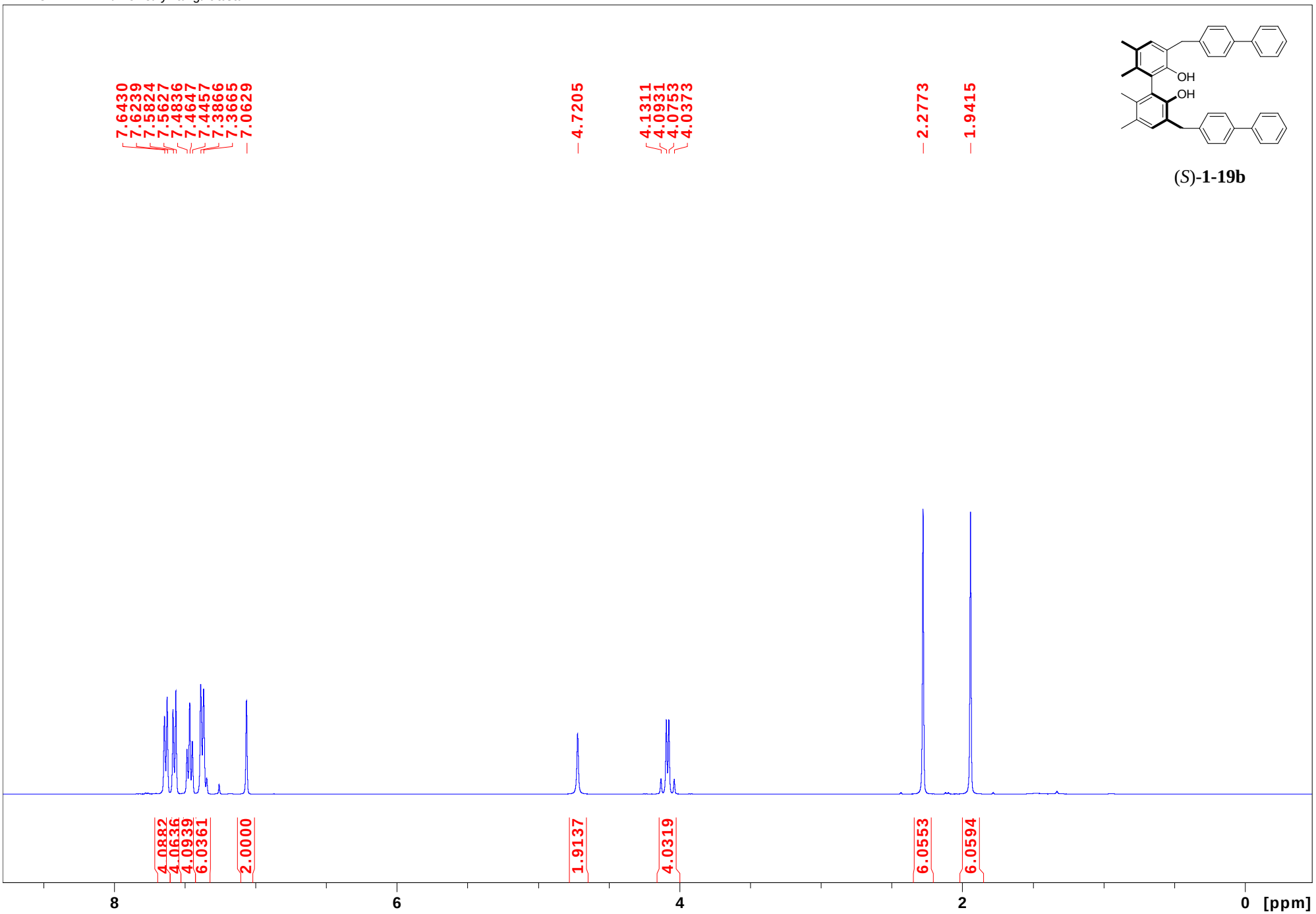

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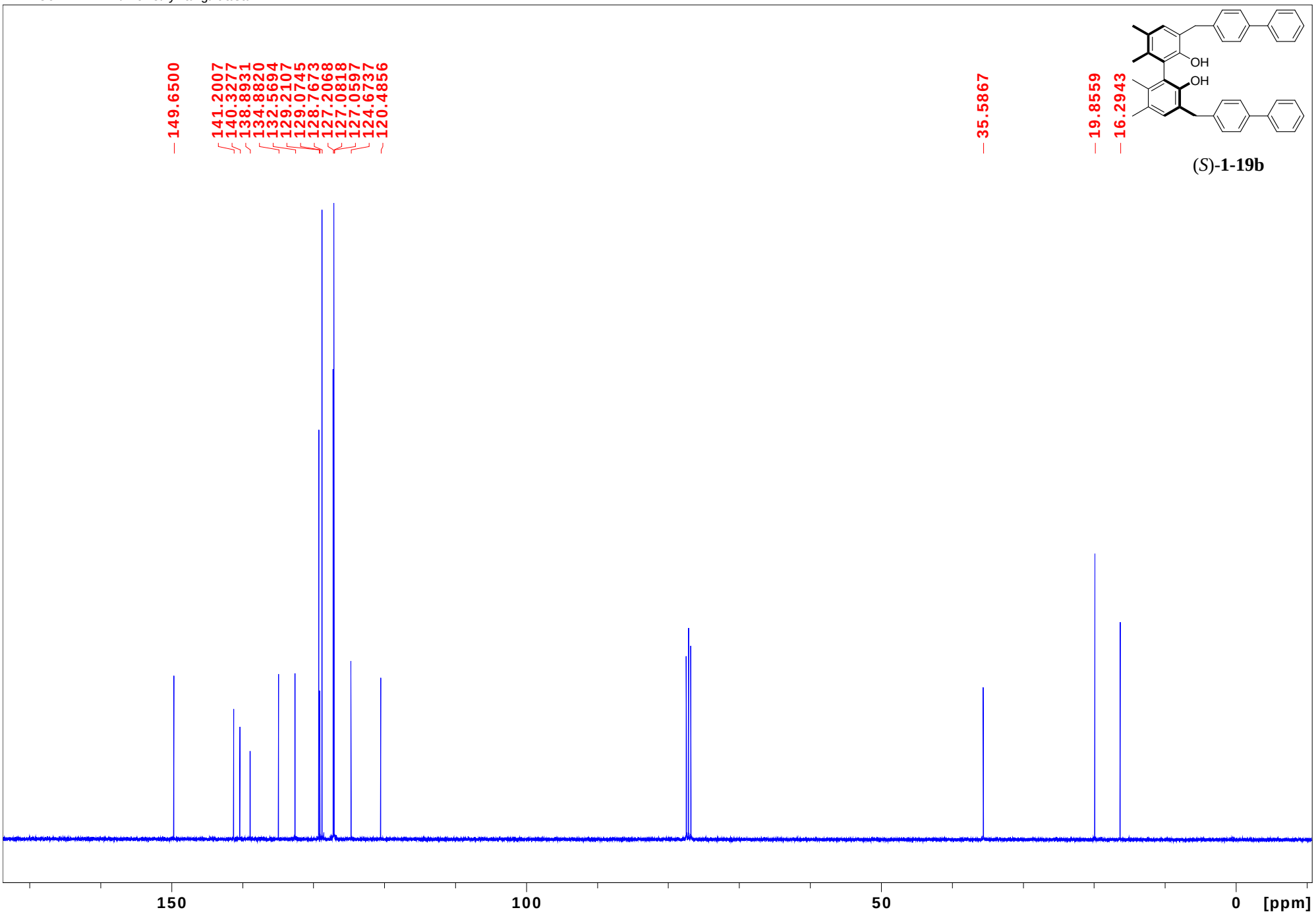

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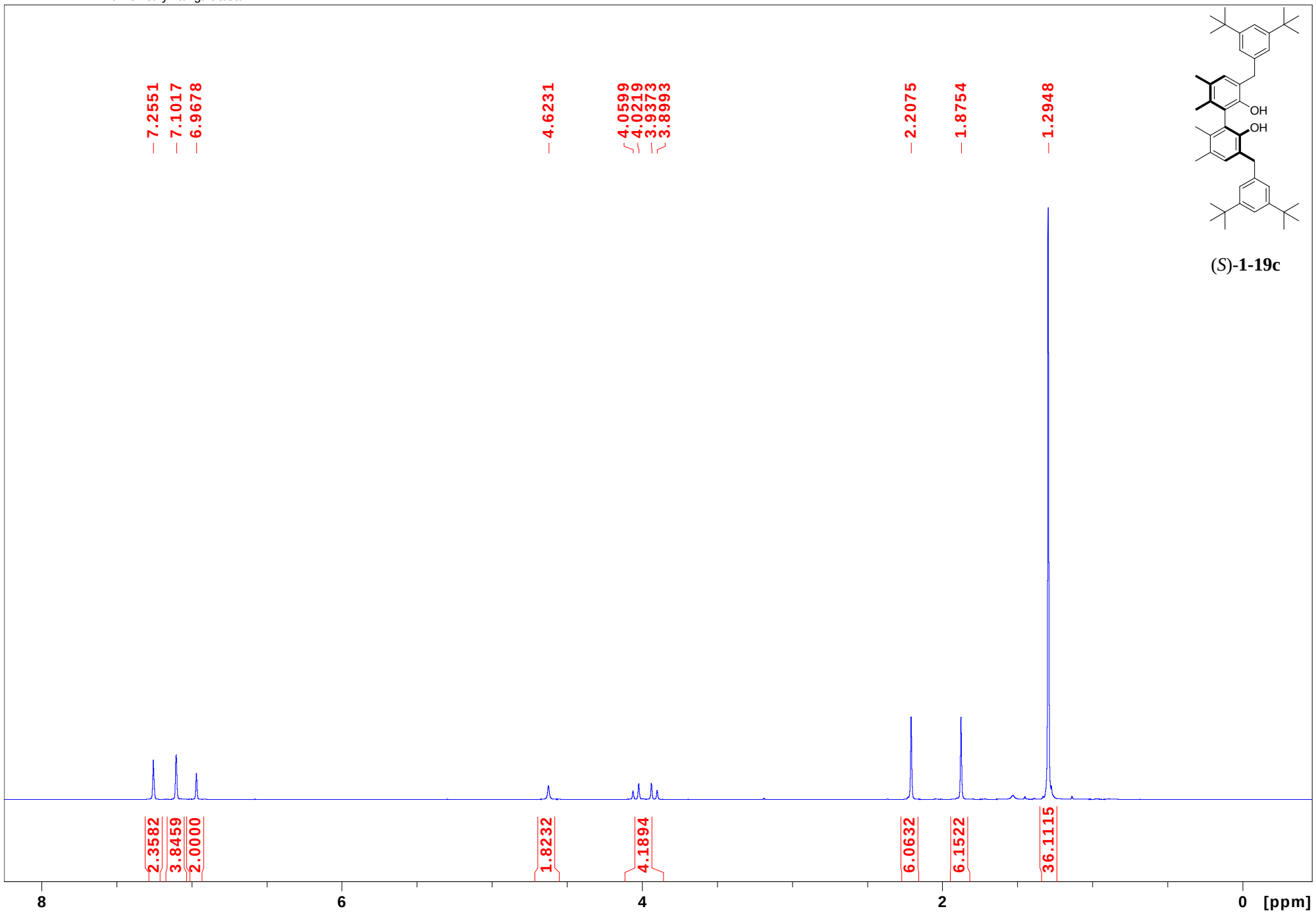

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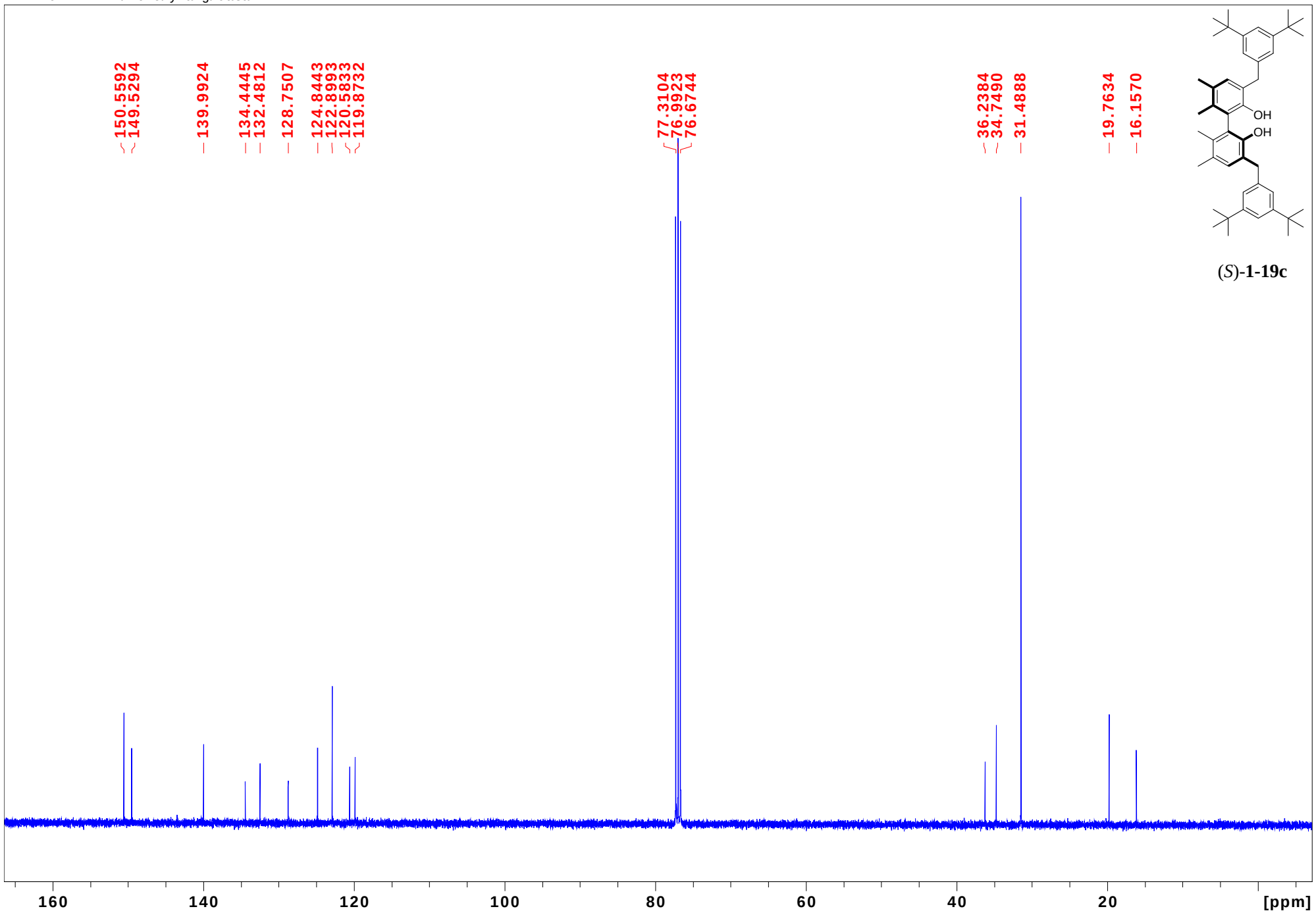

(*S*)-**1-19c**

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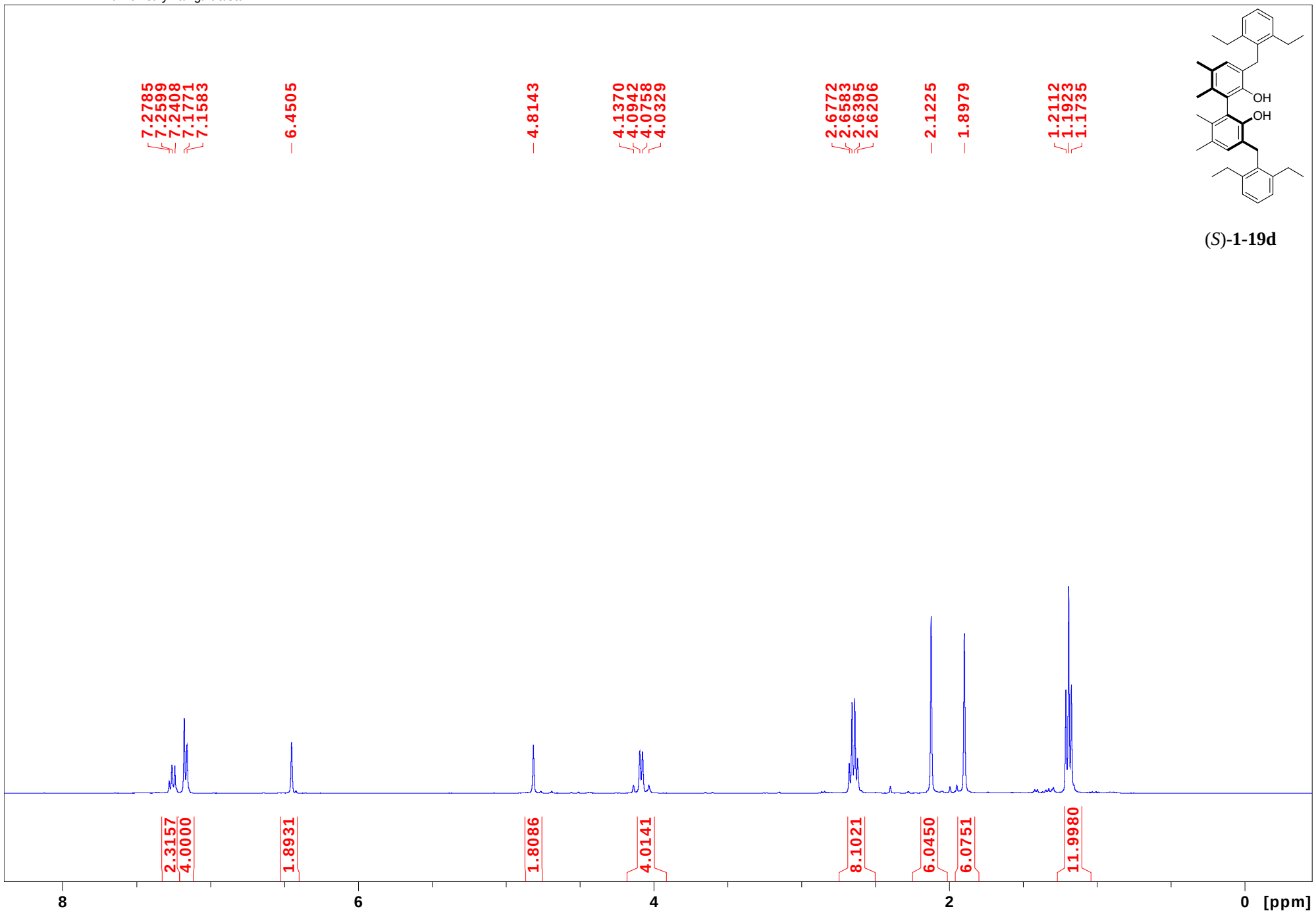

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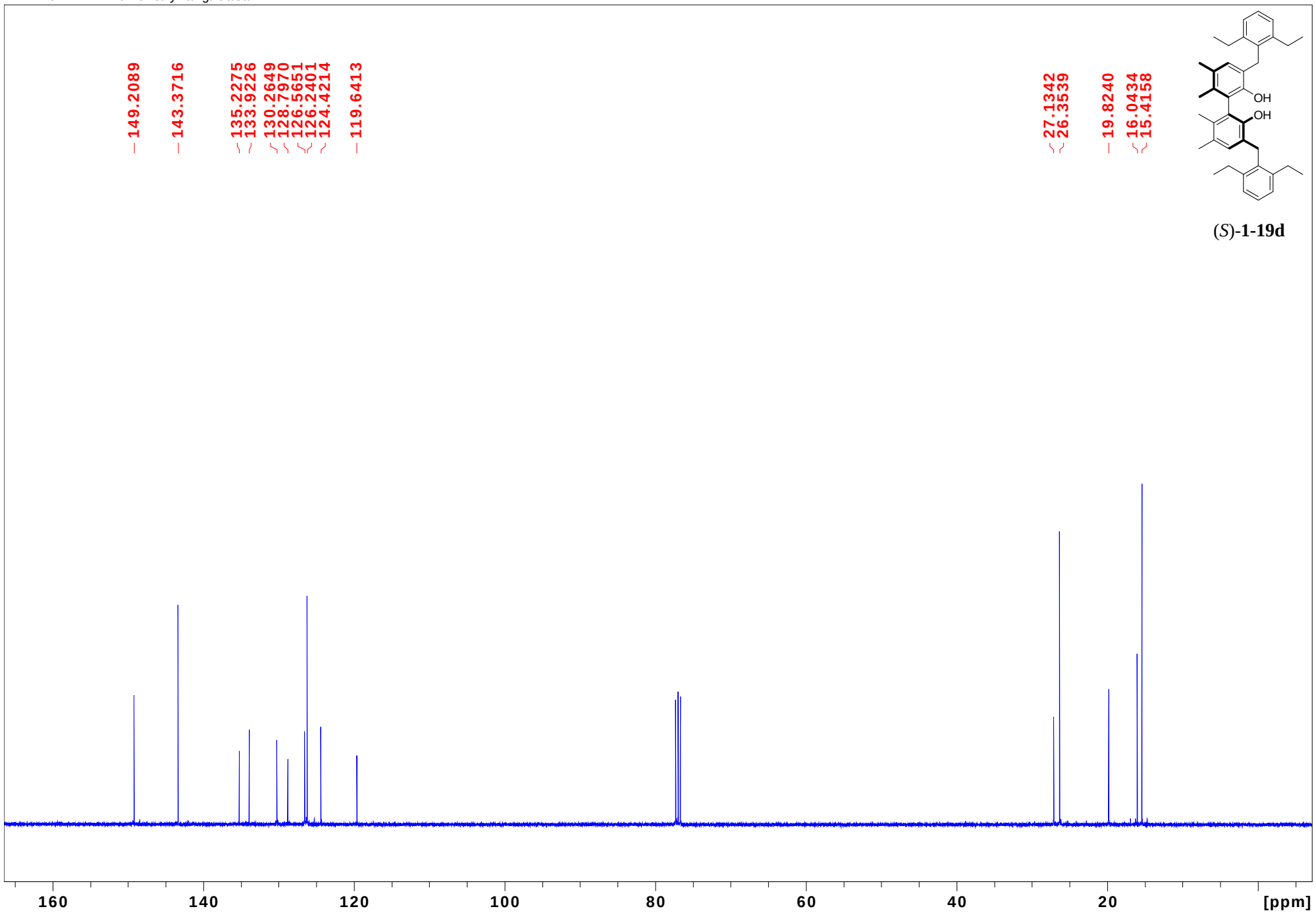

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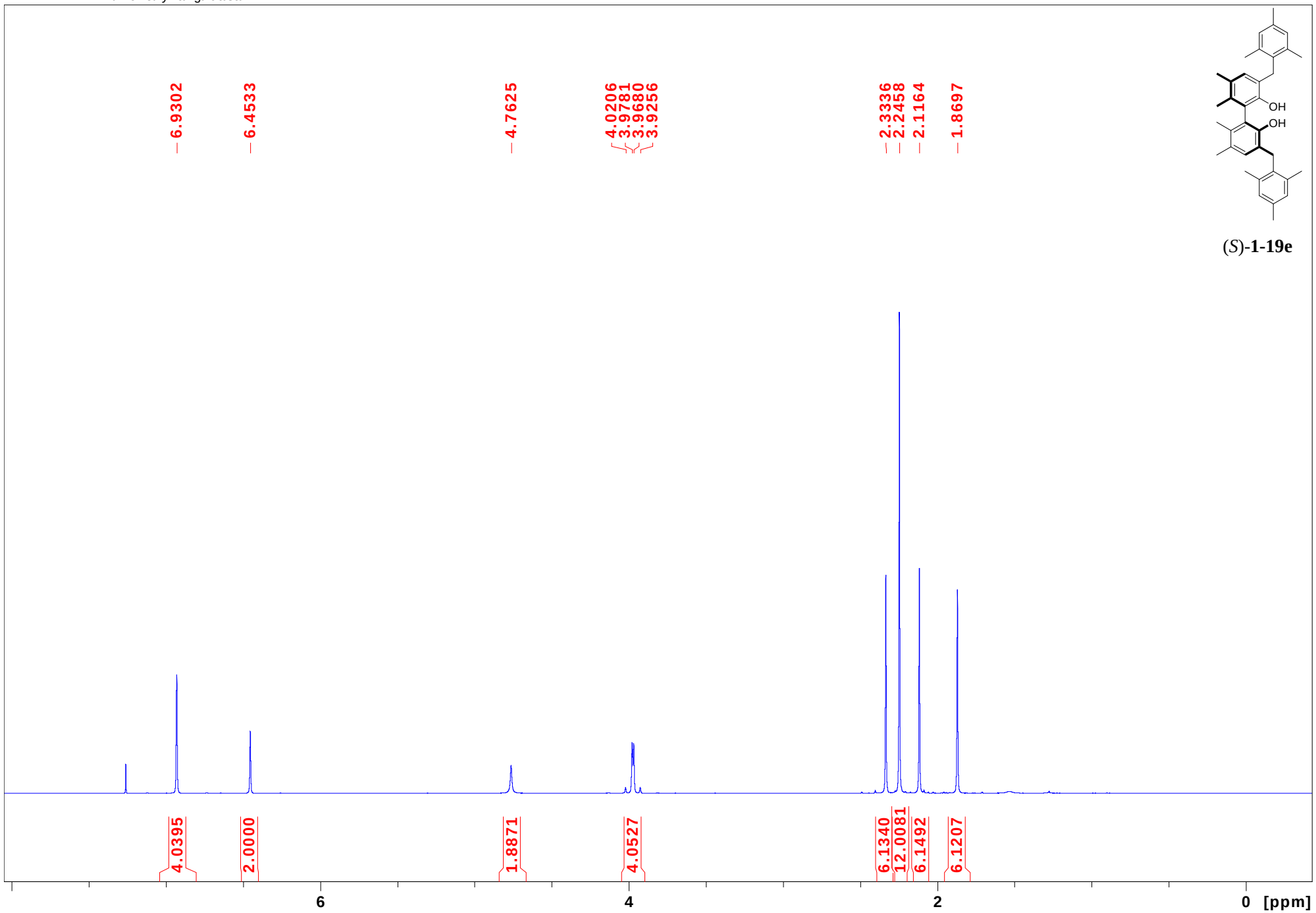

(*S*)-**1-19e**

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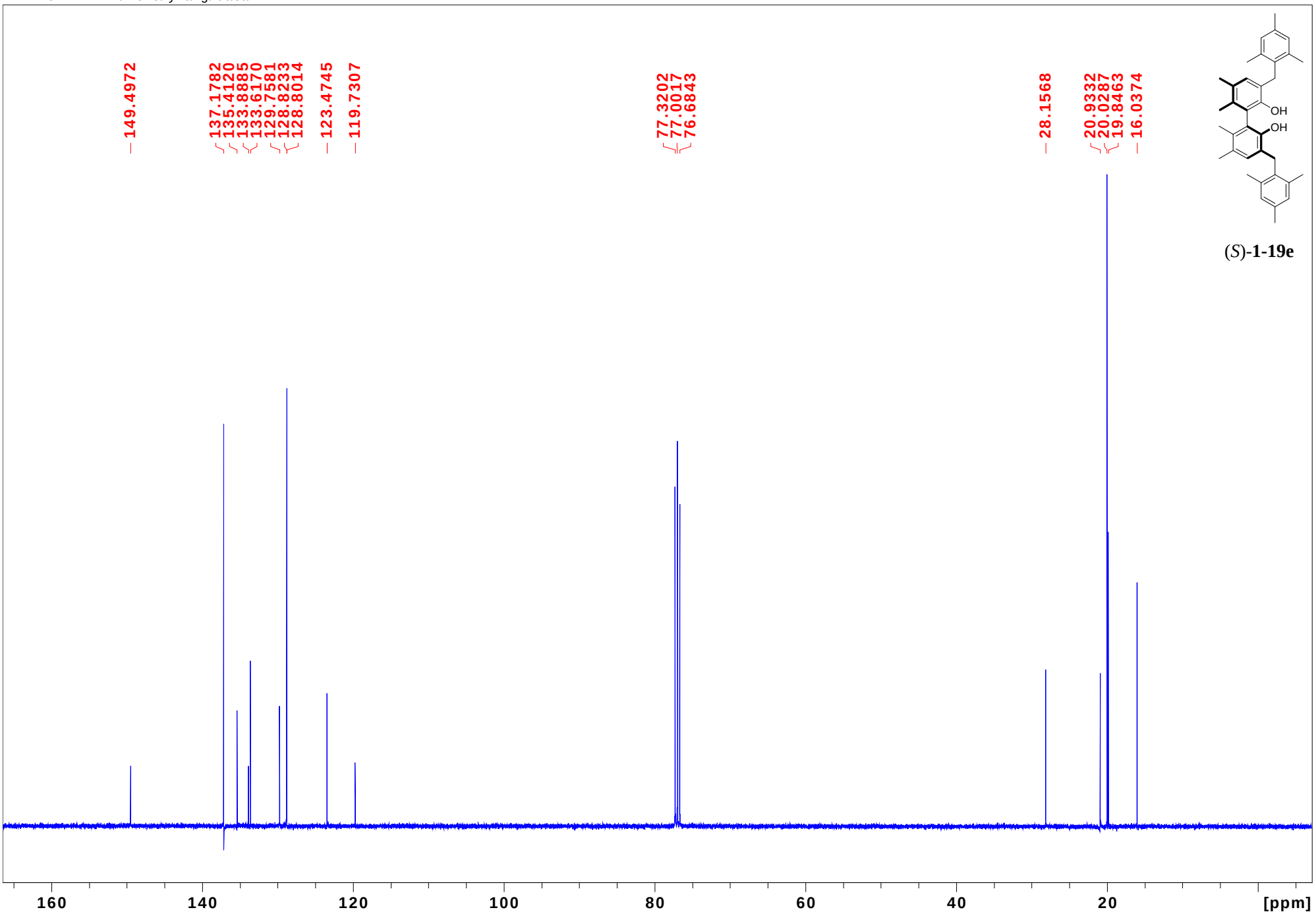

(*S*)-**1-19e**

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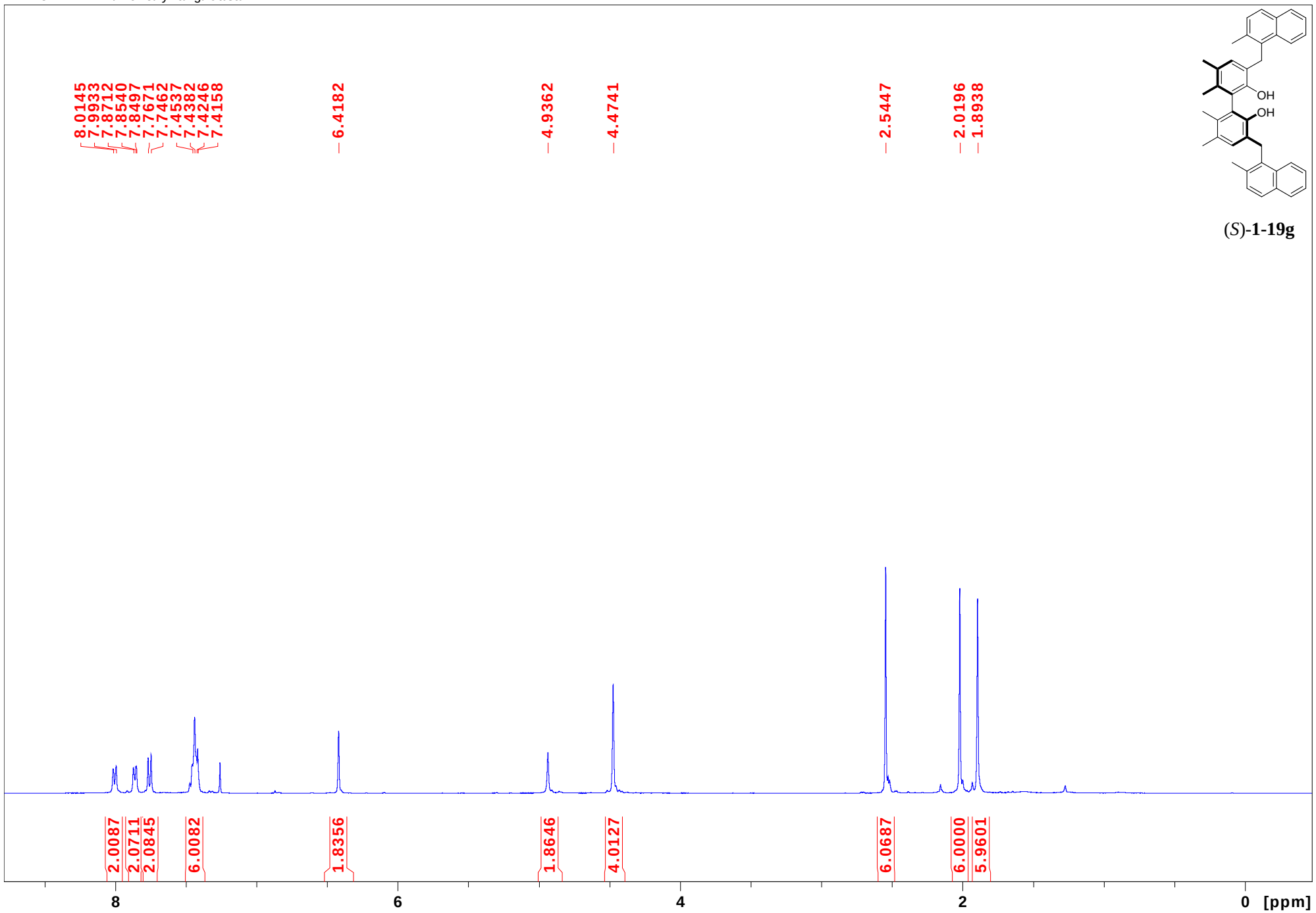
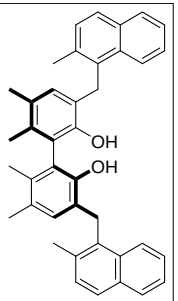


(*S*)-**1-19g**

B-178C 1 1 /home/yzang/data

149.2130
134.4651
134.1471
133.3705
133.0568
132.5736
130.4451
129.1863
128.9843
128.3795
126.6363
126.0281
124.5546
124.2863
123.8336
119.7949
27.4366
20.4900
19.7963
16.0901



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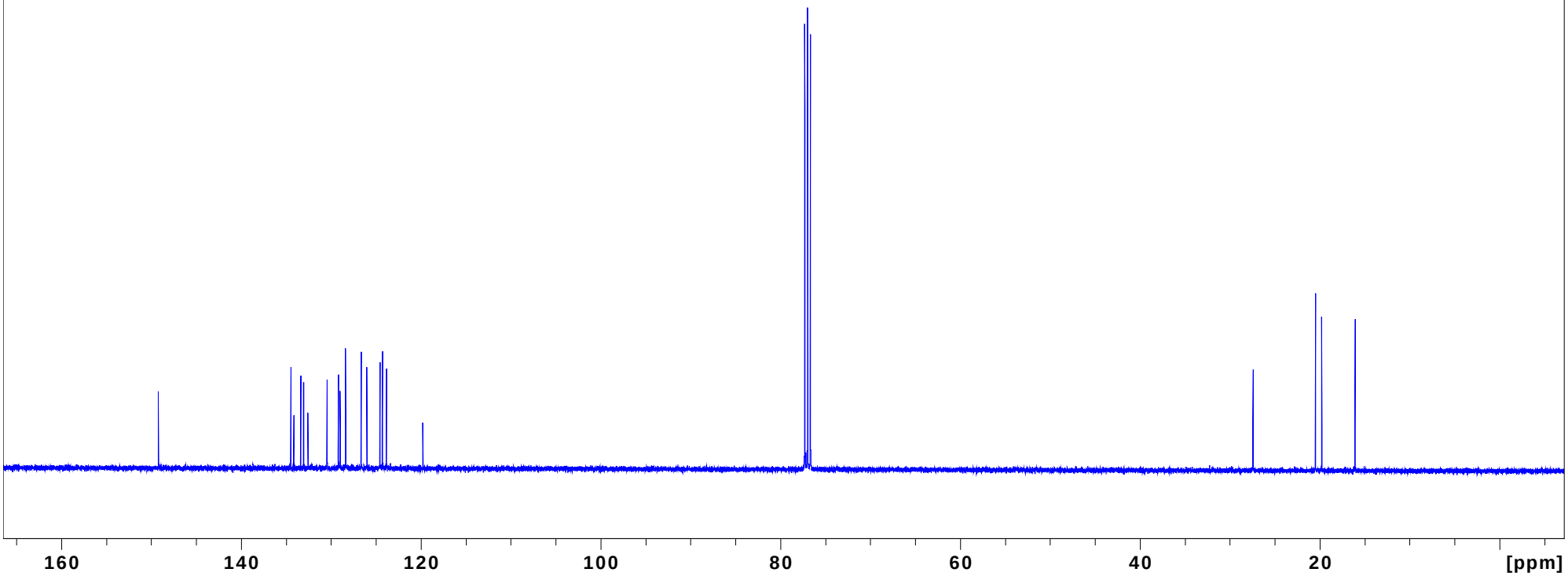

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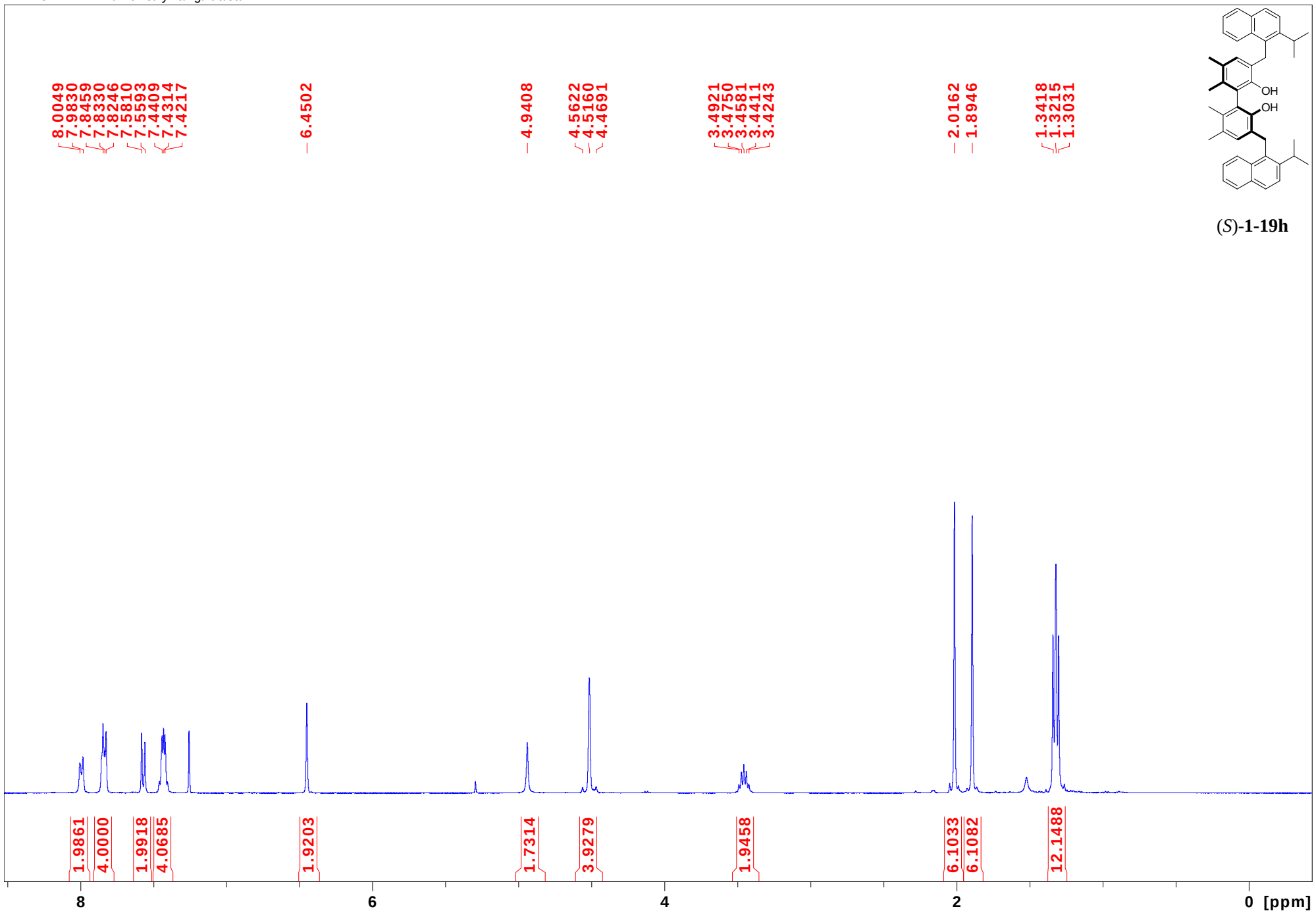
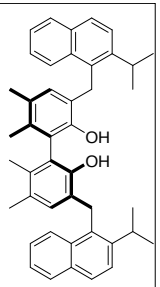


(*S*)-**1-19h**

B-173C 1 1 /home/yzang/data

148.9553
144.7664
134.1212
133.0482
132.3836
131.3842
130.7930
128.9397
128.3133
127.2837
126.0531
124.8473
124.7162
124.5158
123.9300
119.7364

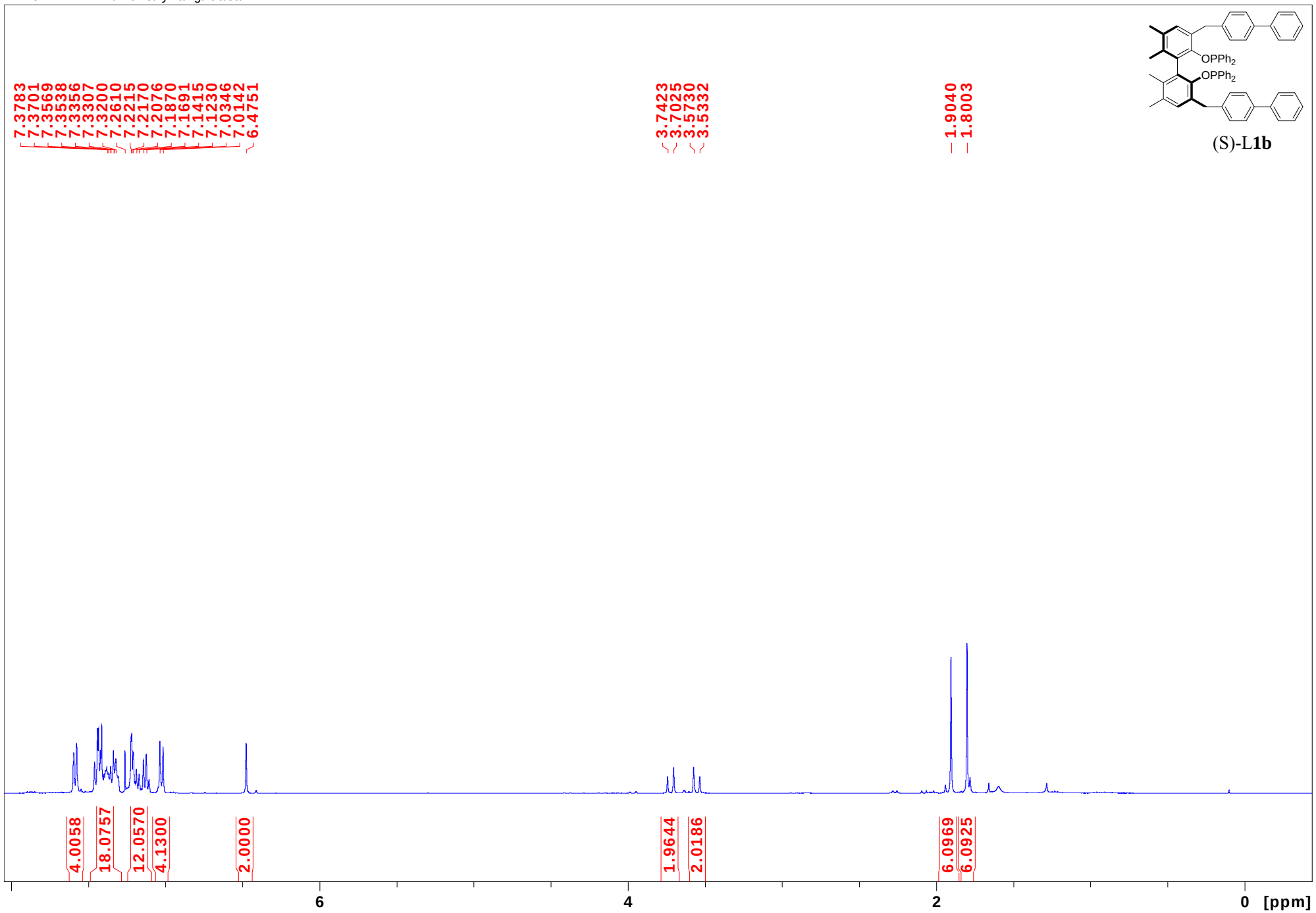
29.7460
26.6244
23.9370
23.8804
19.7820
16.1174

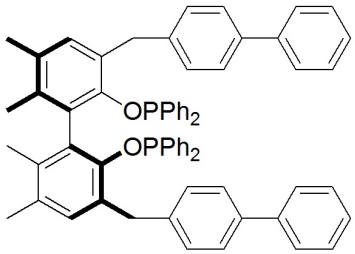


(*S*)-**1-19h**

160 140 120 100 80 60 40 20 [ppm]

B-192 1 1 /home/yzang/data




OPPh2
OPPh2

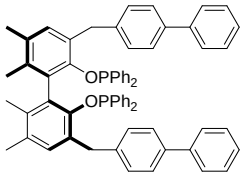
(S)-L**1b**

110.63
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

001 1 1 /home/yzang/data

151.8046
141.2254
140.2703
138.3424
134.8848
131.5518
131.1377
130.5798
129.7568
129.4971
128.8858
128.8210
128.7474
128.6615
127.8425
127.6668
126.9450
126.6926

77.3150
76.9979
76.6796

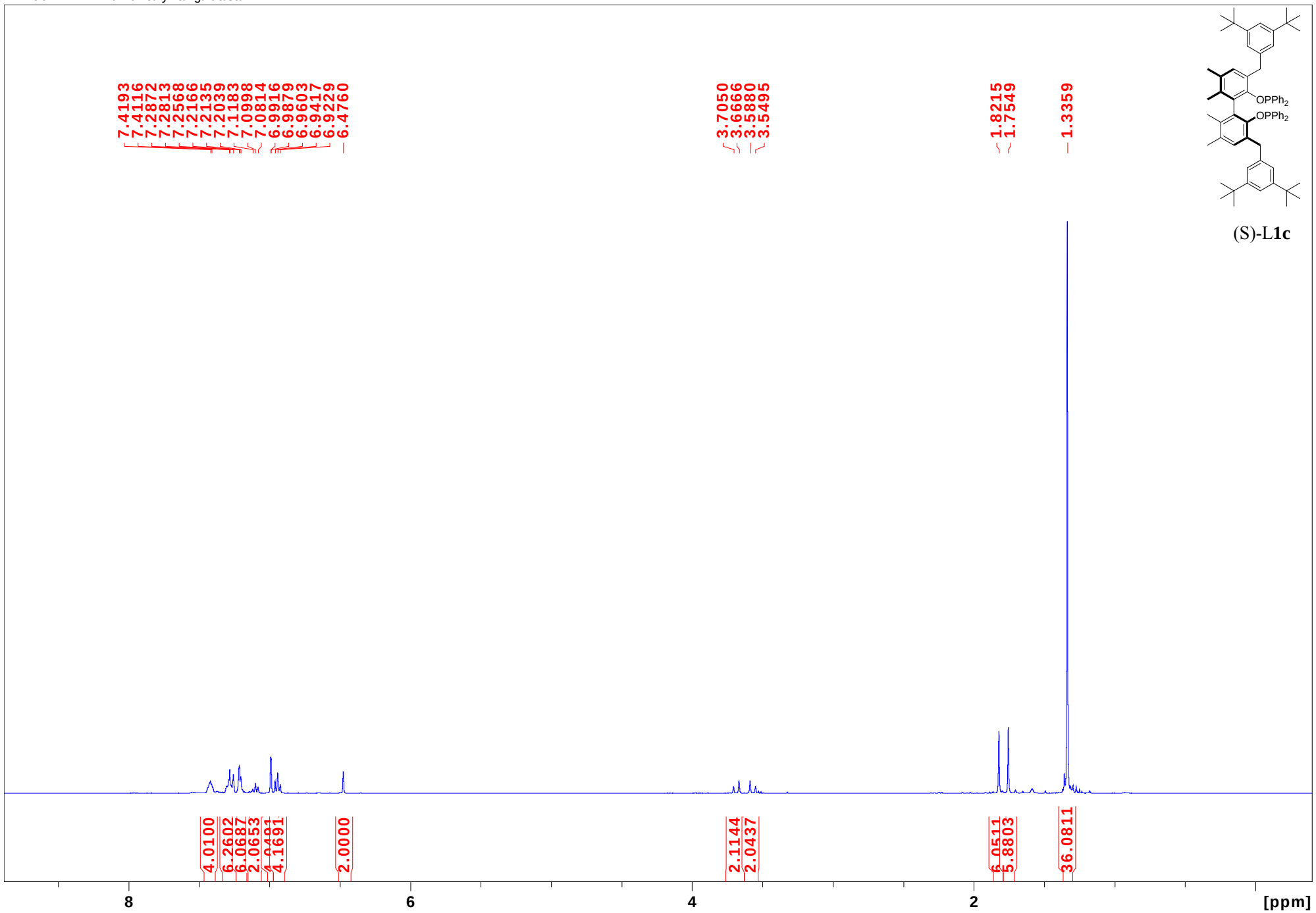


(S)-L**1b**

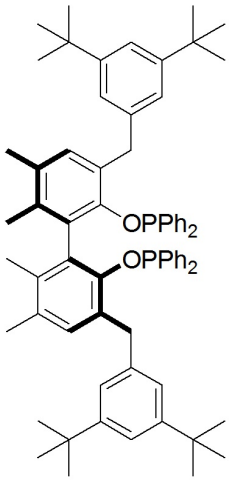
35.9860

19.8916
17.0329

B-206 1 1 /home/yzang/data



(S)-L**1c**

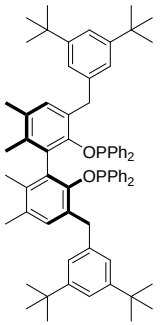

OPPh2
OPPh2

(S)-L**1c**

109.45
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

003 1 1 /home/yzang/data

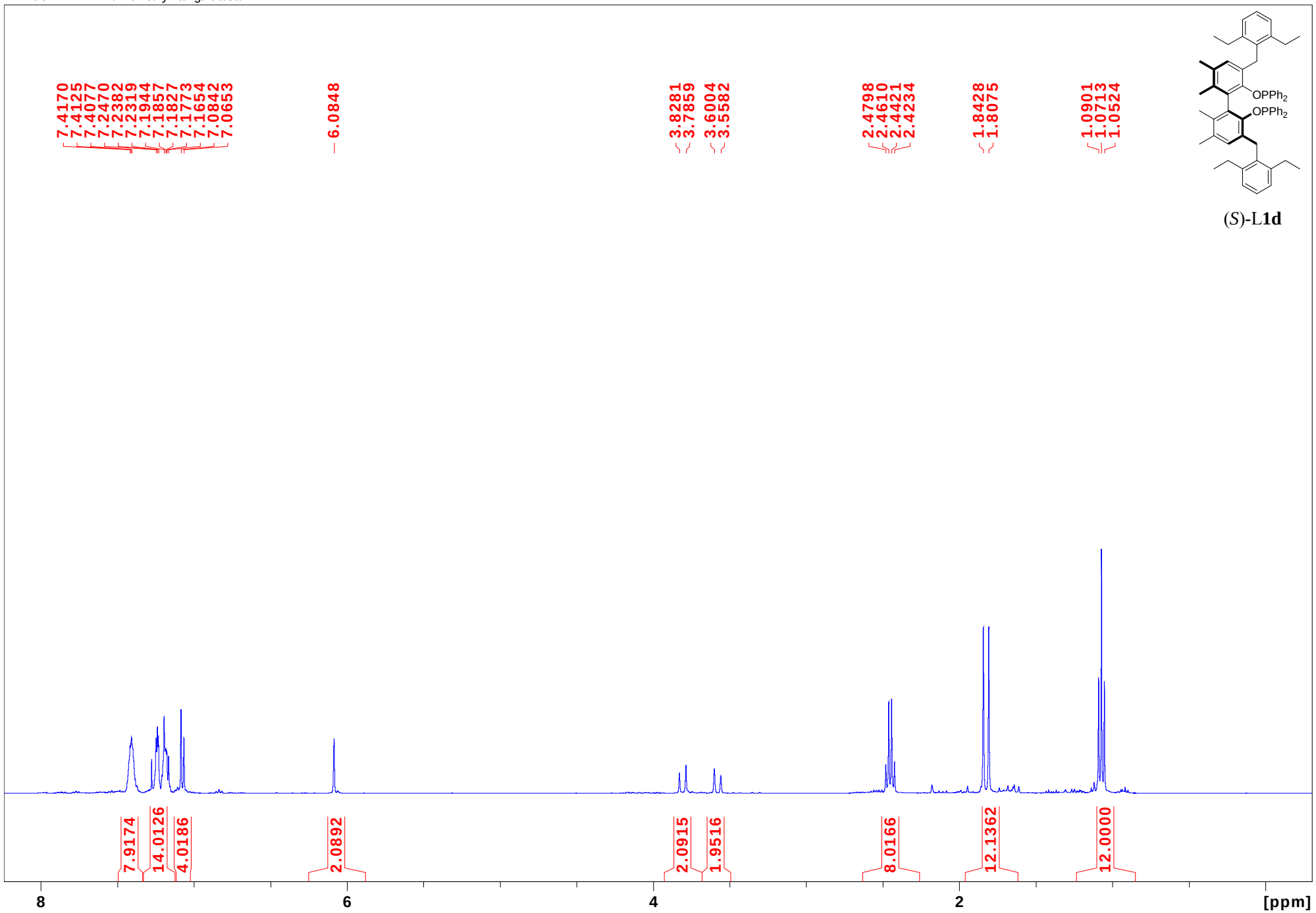
150.1119
140.1650
134.2540
131.2544
130.9384
130.4152
129.7983
129.1394
128.7212
128.2117
127.7387
127.4676
123.3968
119.4275
77.2203
76.9017
76.5845
36.8478
34.6533
31.4640
19.7705
16.9143



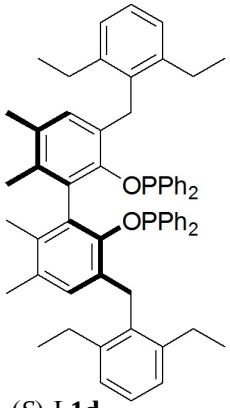
(S)-L**1c**

150 100 50 0 [ppm]

B-193 1 1 /home/yzang/data



(*S*)-L**1d**

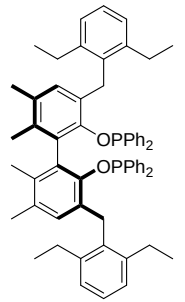

OPPh2
OPPh2

(*S*)-L**1d**

108.84
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)
150

002 1 1 /home/yzang/data

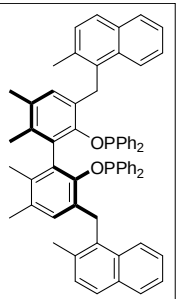
151.6175
143.2407
135.7736
134.0471
131.3971
130.2986
130.1730
129.0252
128.7126
128.4330
127.9029
127.6929
126.2772
125.9704
77.3166
76.9998
76.6808
29.0036
26.2718
19.9917
16.6420
15.3073



(*S*)-L**1d**

150 100 50 0 [ppm]

B-208 1 1 /home/yzang/data



(*S*)-L**1g**

7.8102
7.8036
7.7954
7.7868
7.6945
7.6736
7.5365
7.5318
7.5181
7.4422
7.4253
7.4164
7.4070
7.3911
7.3779
7.3725
7.3630
7.3545
7.3470
7.3375
7.3167
7.2870
7.2754
7.1363
7.1181
7.0779
7.0593
7.0409

6.0395

4.1941
4.1520
4.0900
4.0479

2.3077

1.7508
1.6818

3.9178
2.0926
4.0105
16.0962
2.0296
4.1412

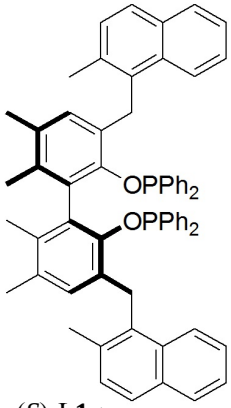
2.0000

1.9417
1.9387

5.9586

6.0842
5.8186

8
6
4
2
0 [ppm]


OPPh2
OPPh2

(*S*)-L**1g**

110.15
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

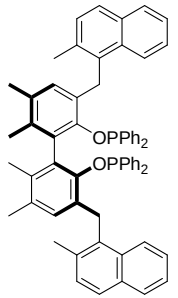
006 1 1 /home/yzang/data

151.5185
143.1752
134.4863
134.3979
133.8015
133.0212
132.3878
131.5797
130.3751
130.2512
129.7777
129.6555
129.0170
128.7952
128.1582
127.8773
126.3841
125.8740
124.7152
124.4502

77.3228
77.0055
76.6870

29.3740

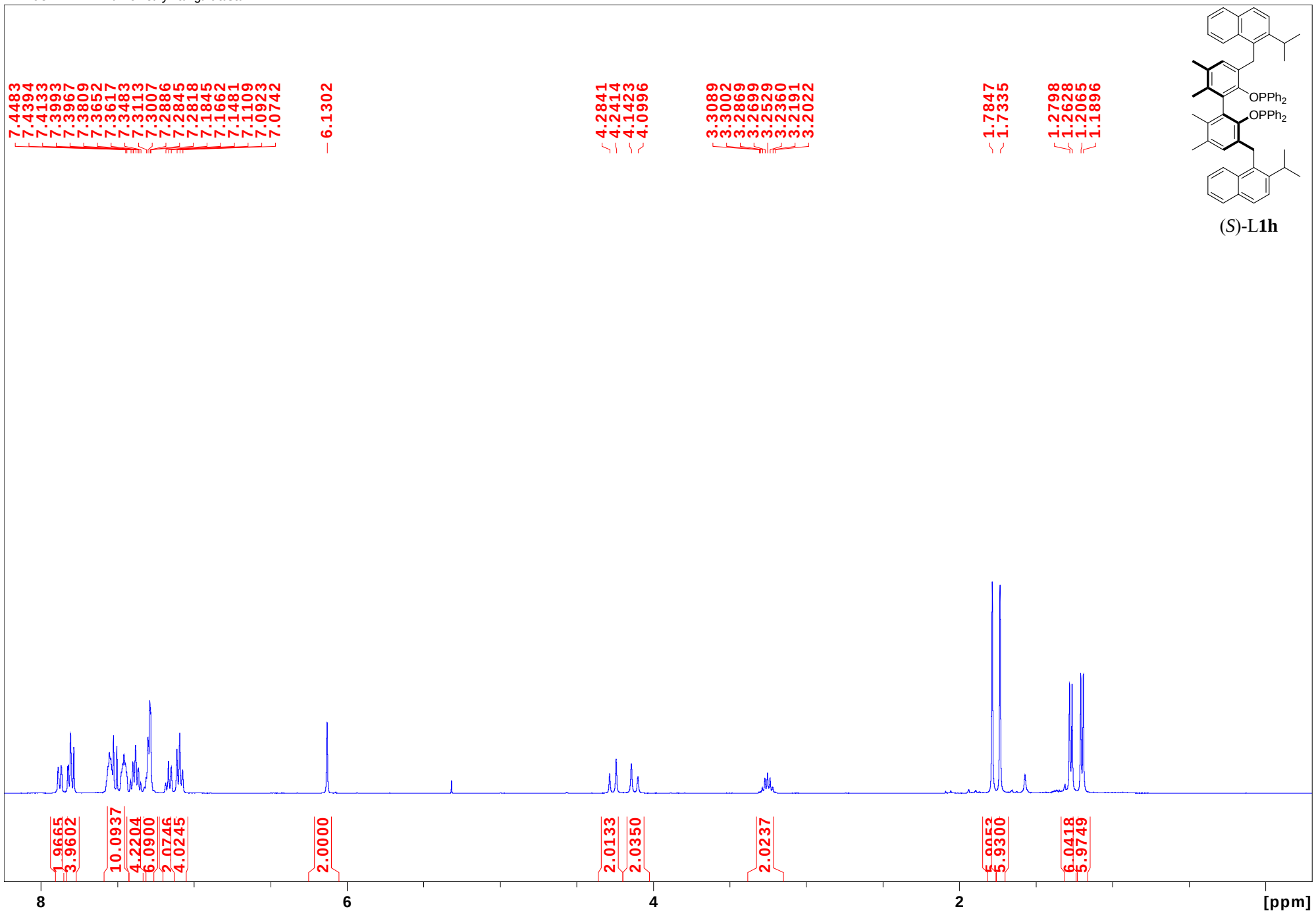
20.4804
19.9403
16.7833



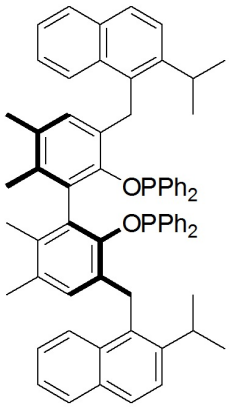
(*S*)-L**1g**

150 100 50 0 [ppm]

B-205 1 1 /home/yzang/data



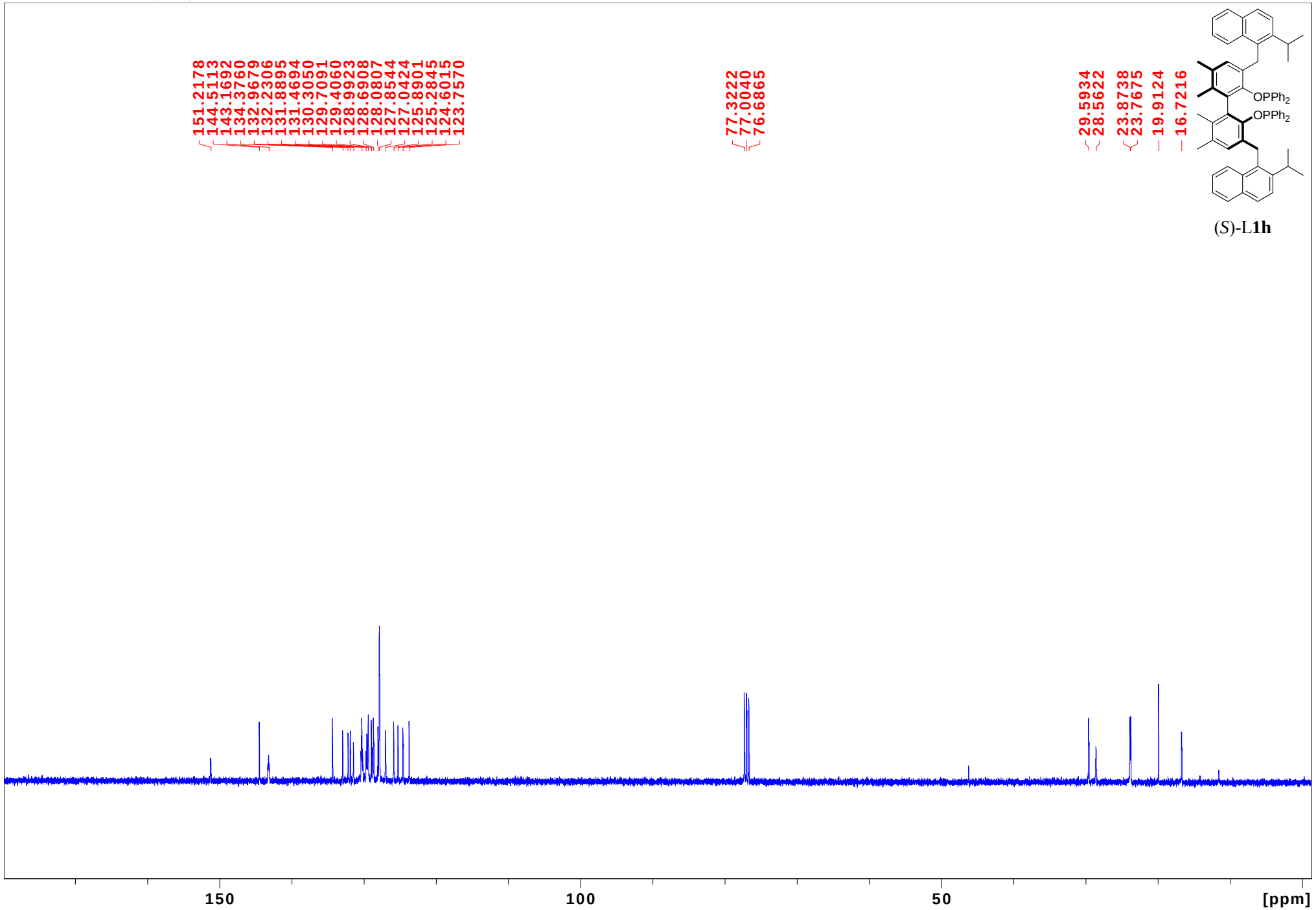
(*S*)-L**1h**


OPPh2
OPPh2

(*S*)-L**1h**

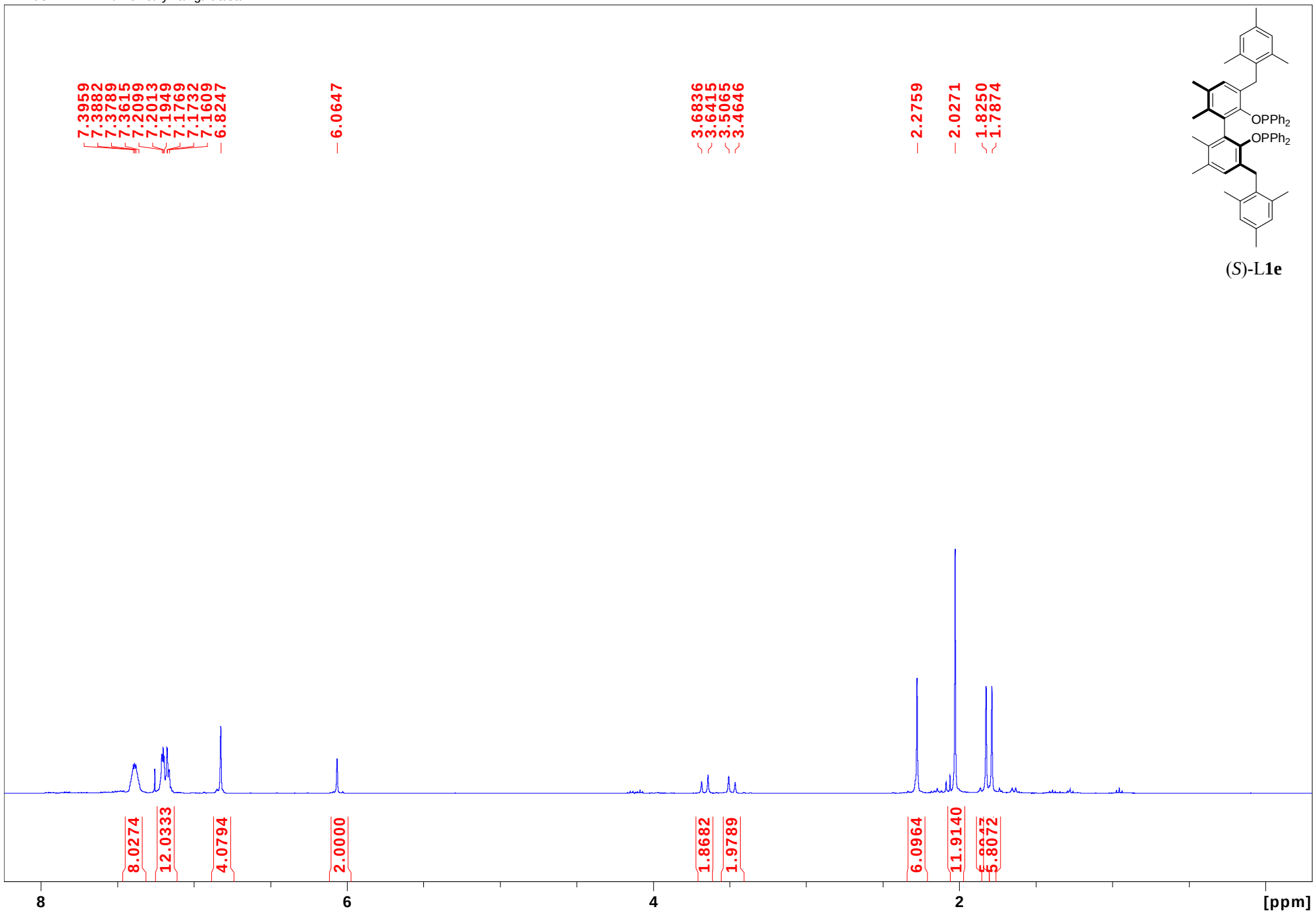
109.95
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

0051 1 1 /home/yzang/data

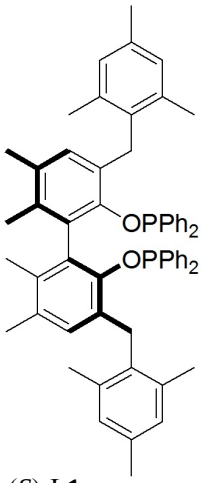


(*S*)-L**1h**

B-203 1 1 /home/yzang/data



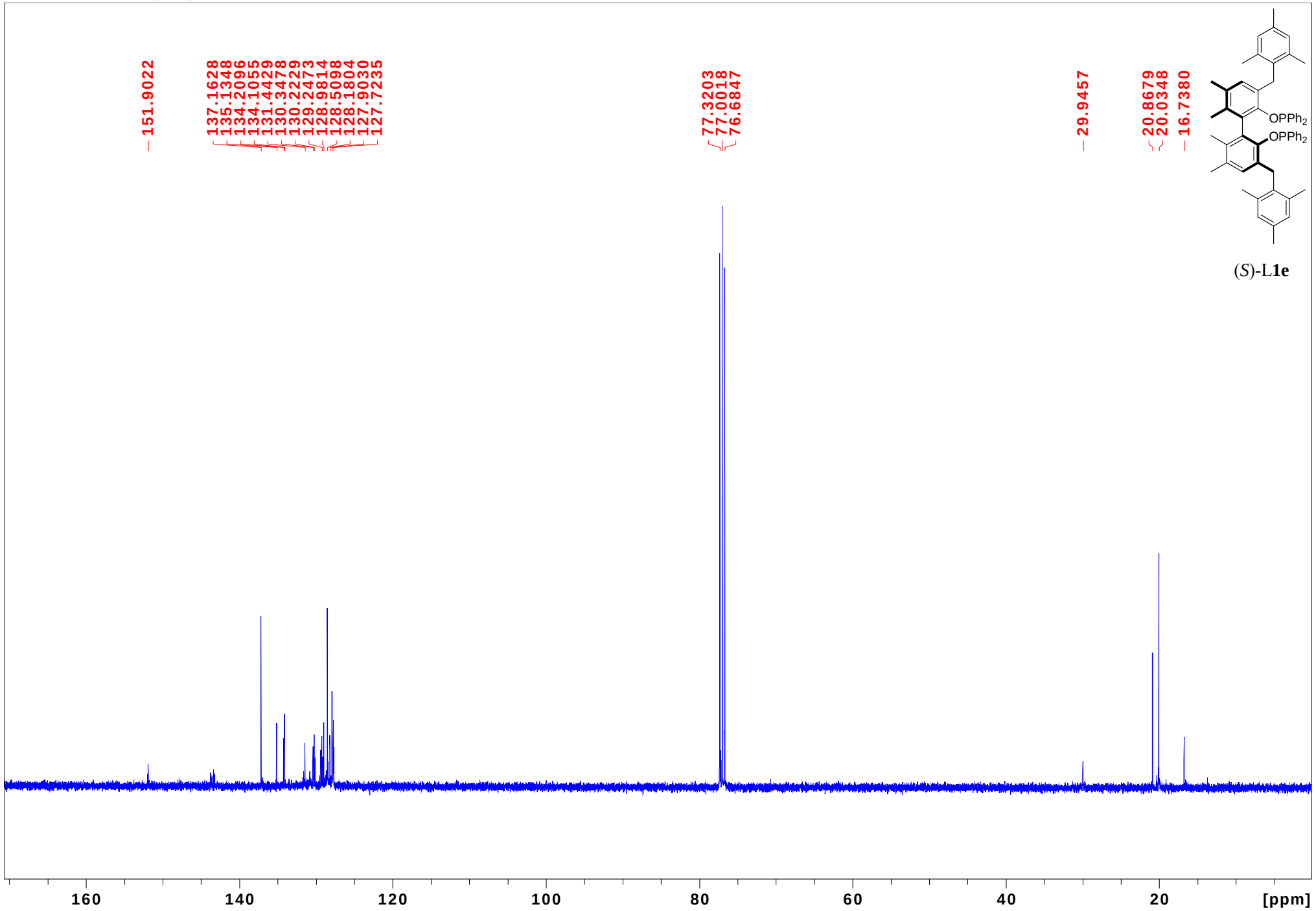
(*S*)-L**1e**


OPPh2
OPPh2

(*S*)-L**1e**

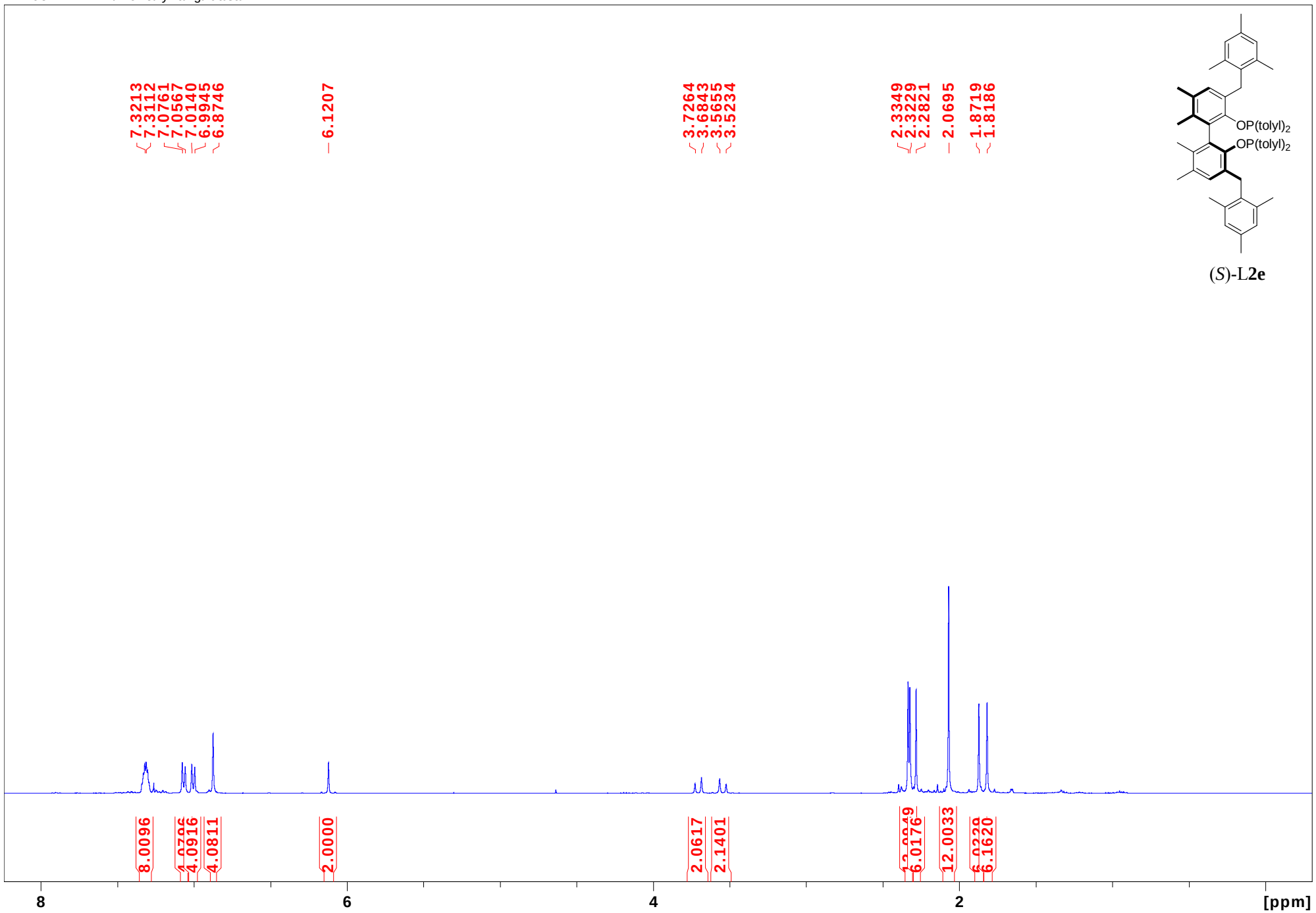
108.75
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

0082 1 1 /home/yzang/data

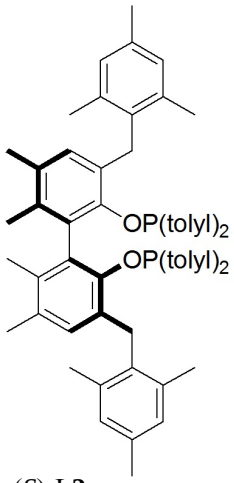


(*S*)-L**1e**

B-195 1 1 /home/yzang/data



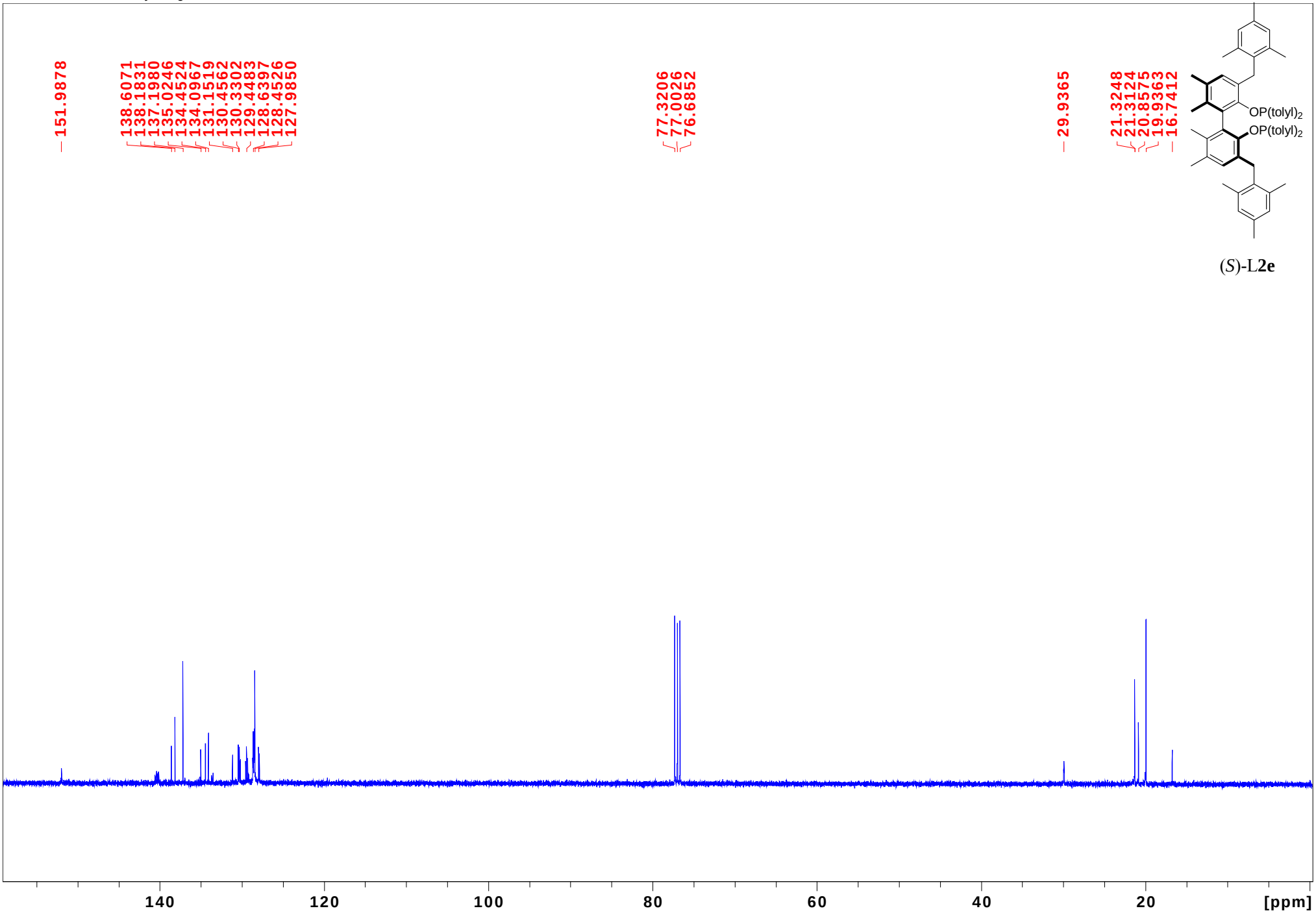
(*S*)-L**2e**


OP(tolyl)2
OP(tolyl)2

(*S*)-L**2e**

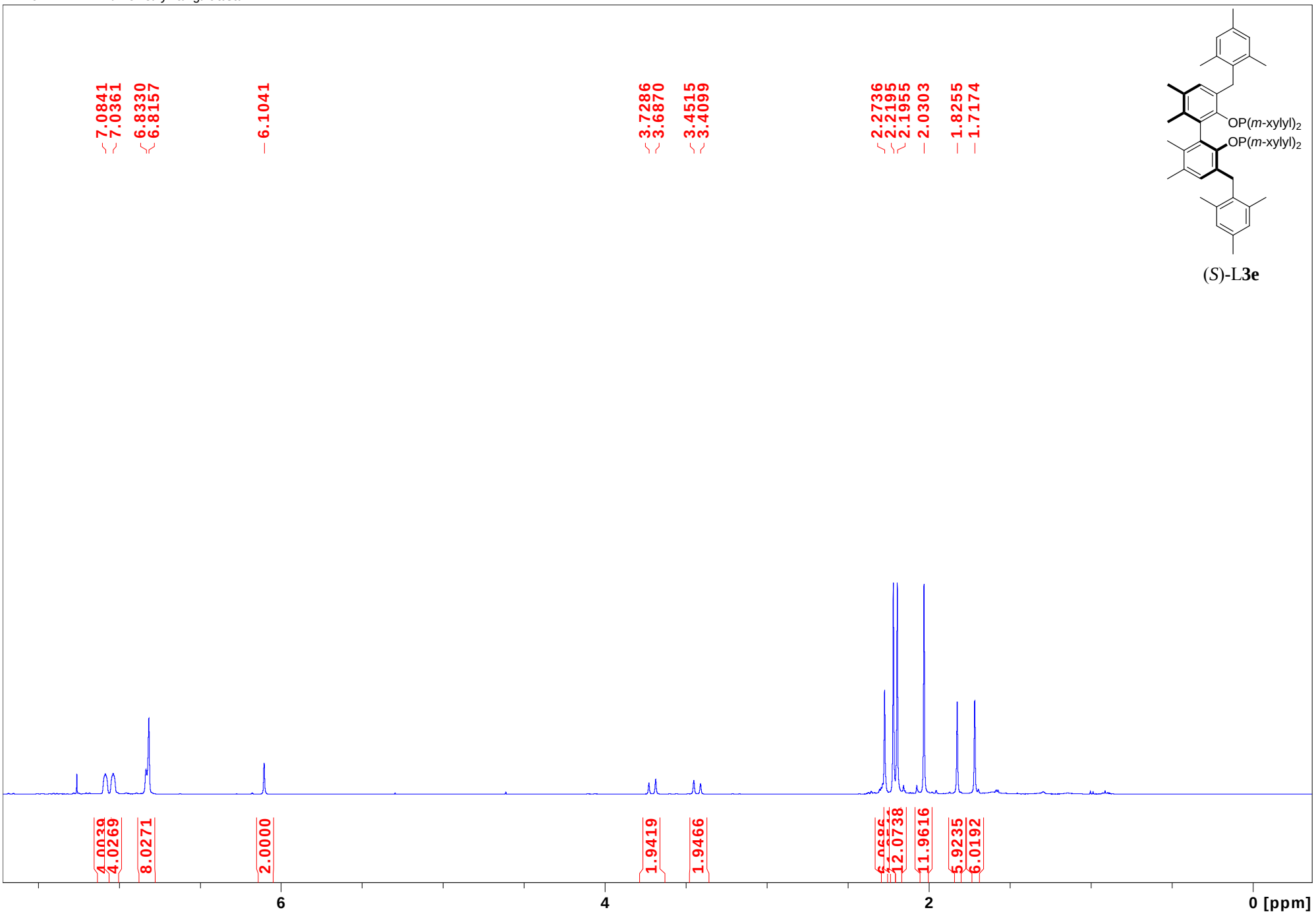
110.40
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

004 1 1 /home/yzang/data

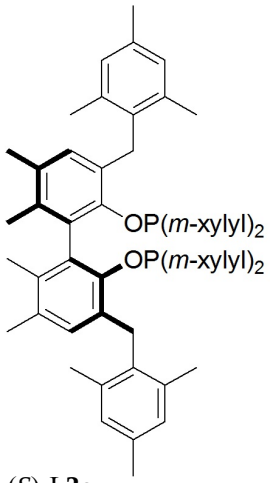


(*S*)-L**2e**

B-204 1 1 /home/yzang/data

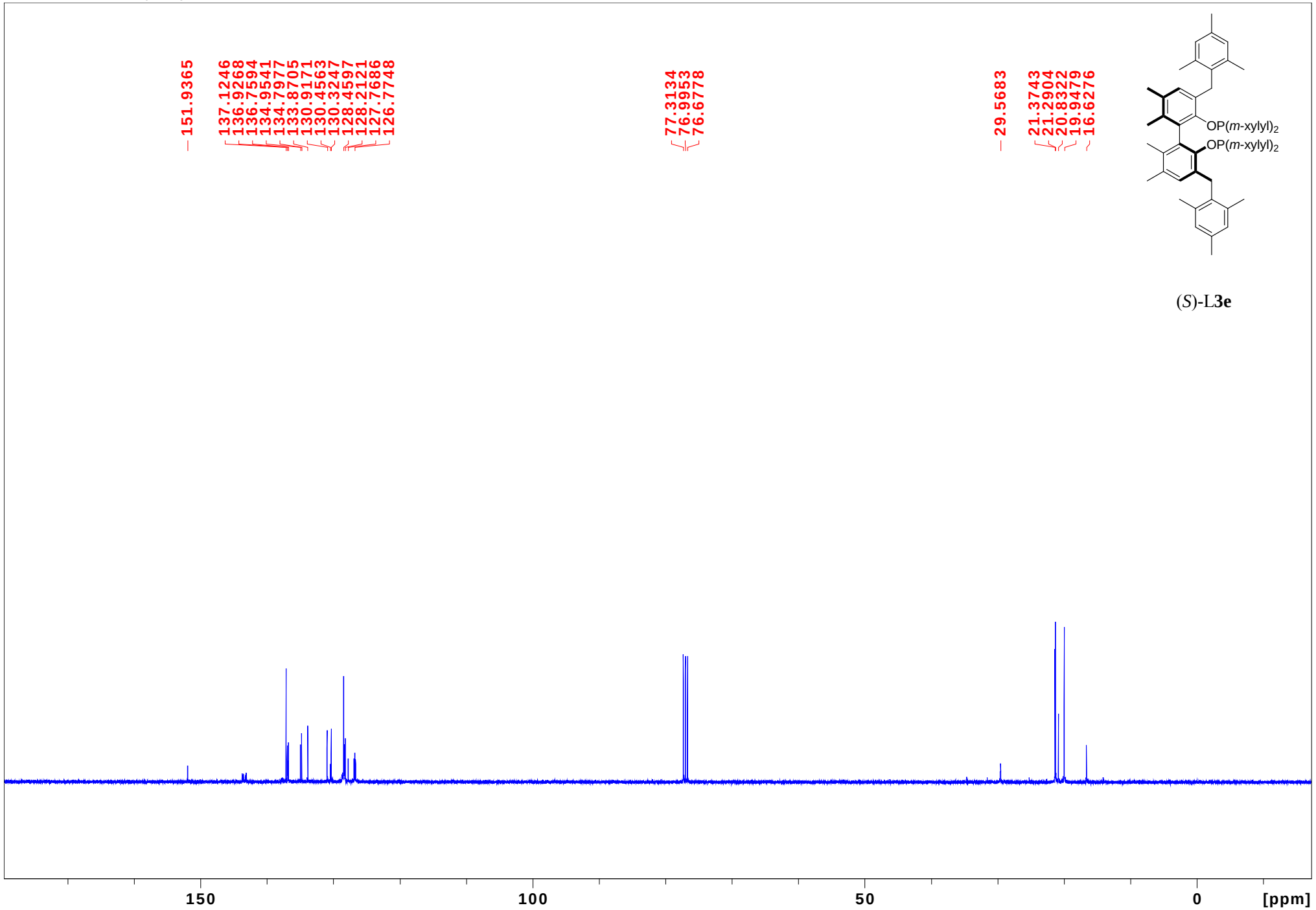


(*S*)-L**3e**


OP(m-xylyl)2
OP(m-xylyl)2

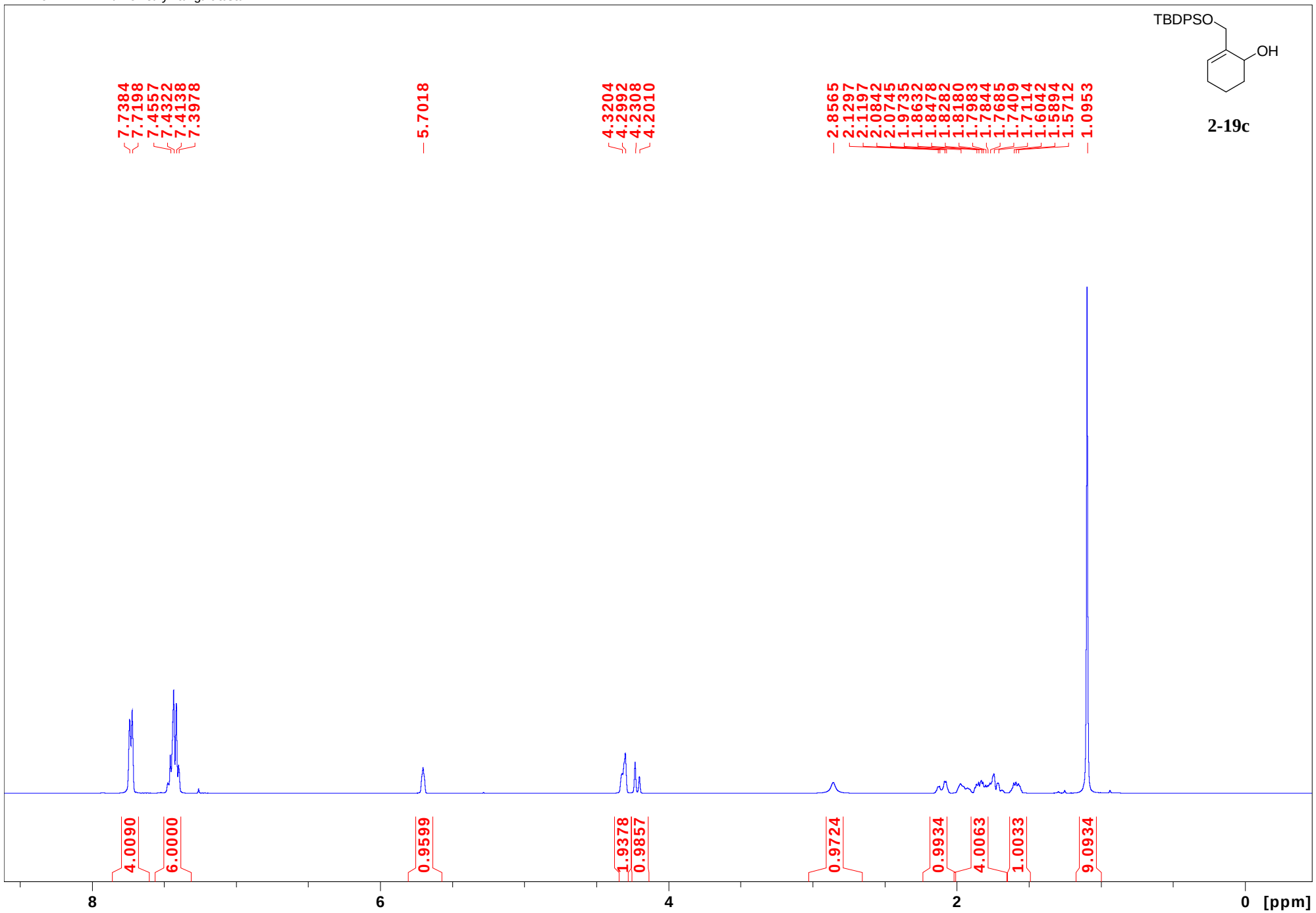
(*S*)-L**3e**

111.25
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

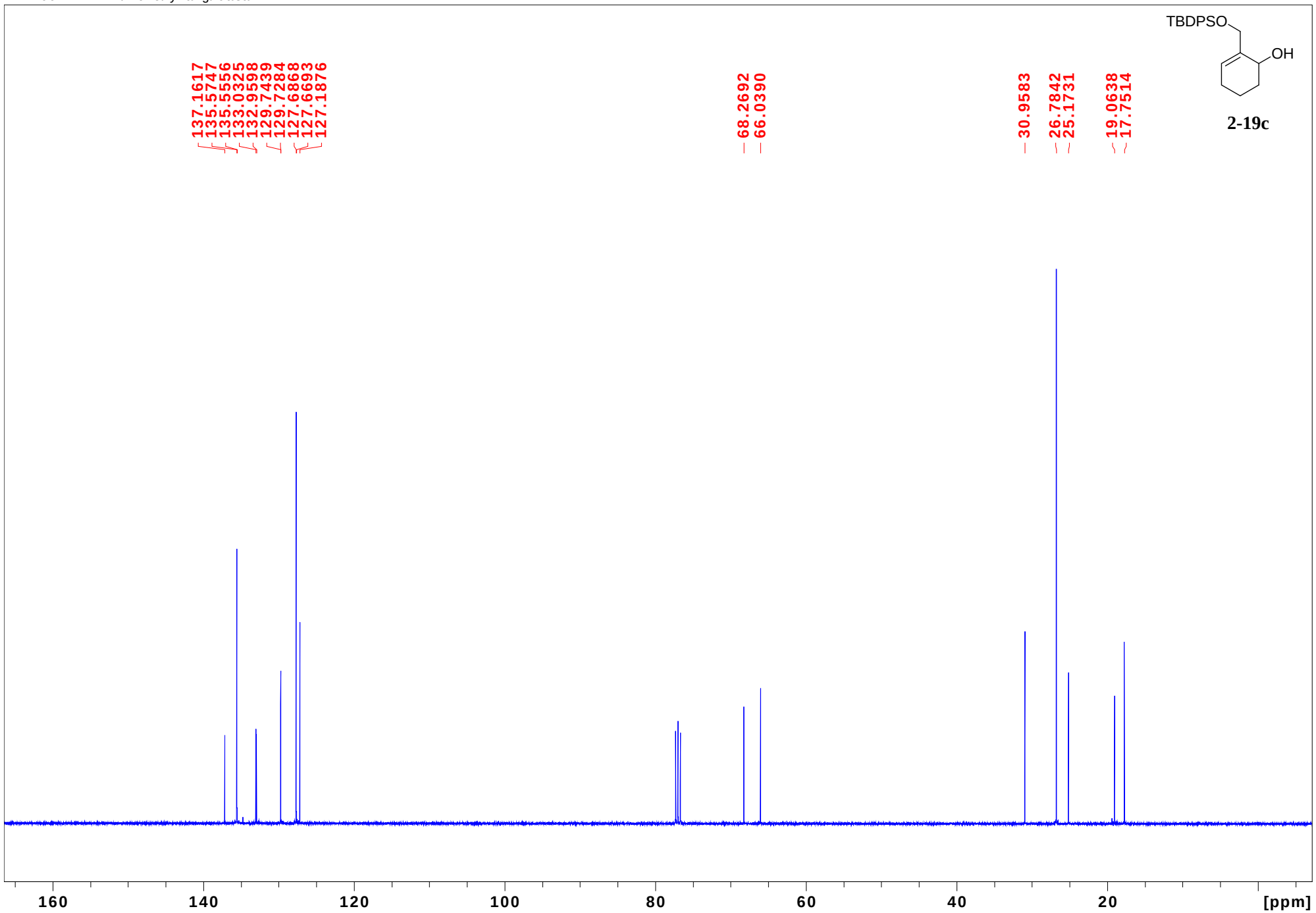

151.9365
137.1246
136.9268
136.7594
134.9541
134.7977
133.8705
130.9171
130.4563
130.3247
128.4597
128.2121
127.7686
126.7748
77.3134
76.9953
76.6778
29.5683
21.3743
21.2904
20.8322
19.9479
16.6276
OP(m-xylyl)2
OP(m-xylyl)2
150
100
50
0
[ppm]

(*S*)-L**3e**

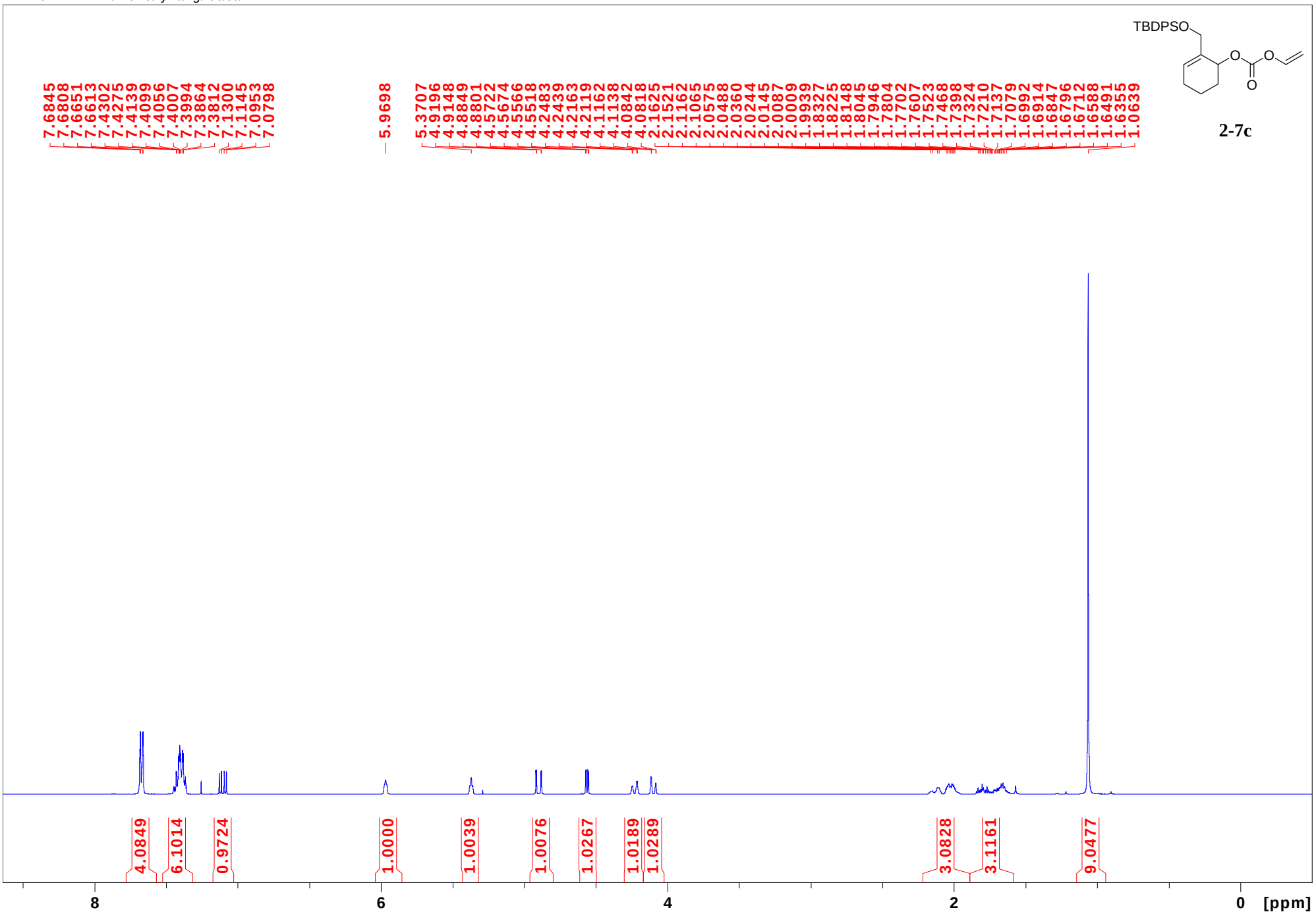
B-176 1 1 /home/yzang/data



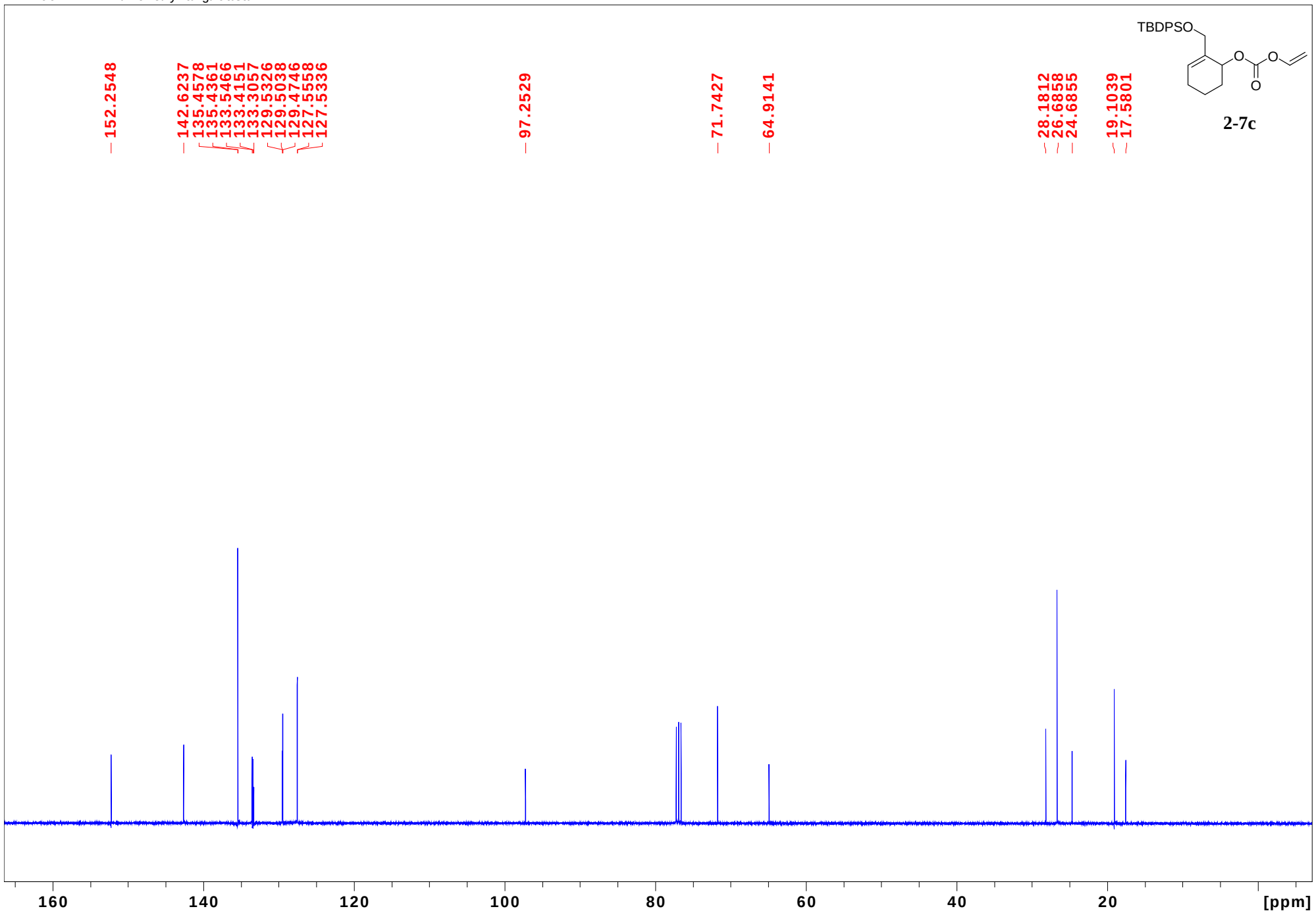
B-176C 1 1 /home/yzang/data

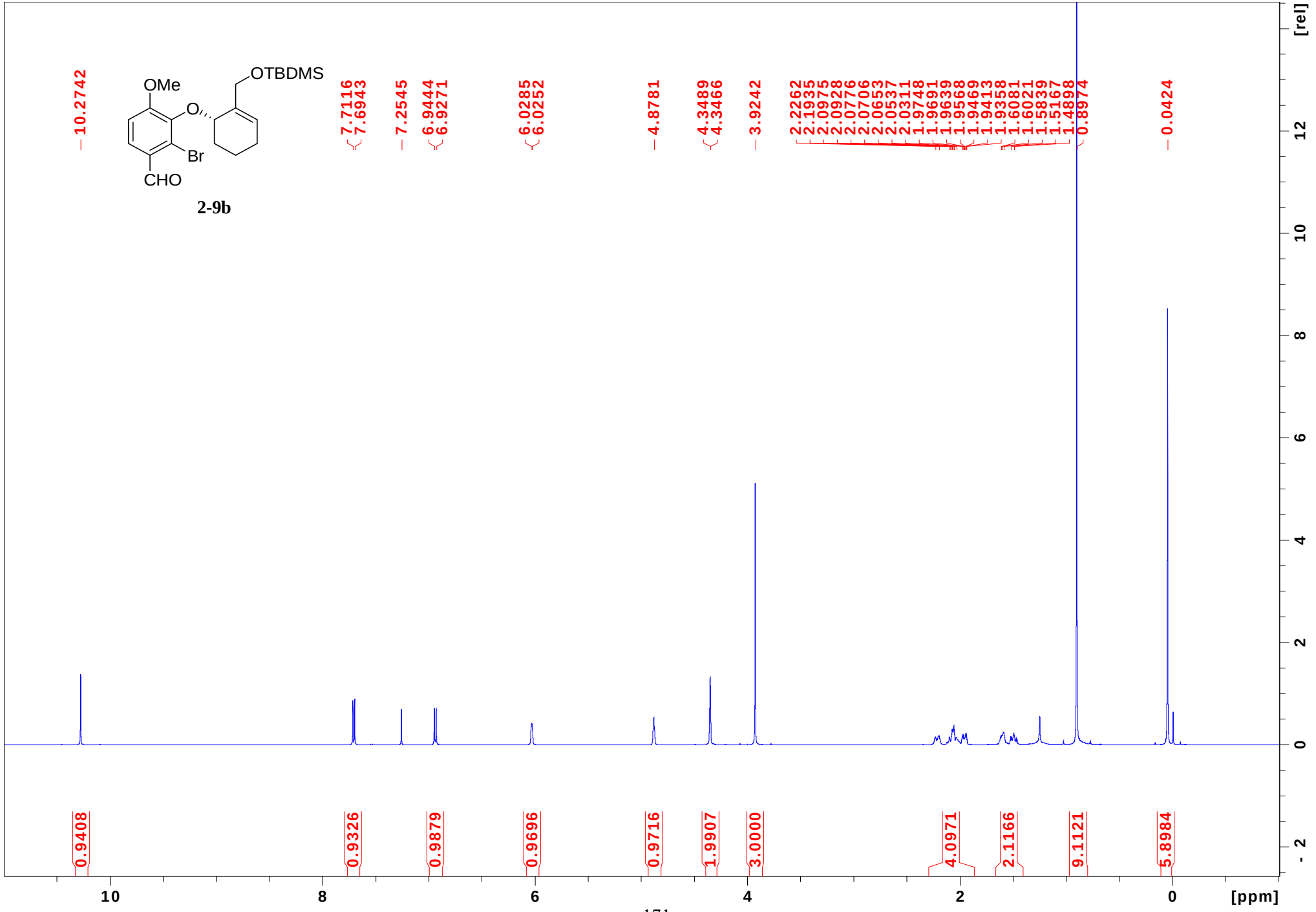


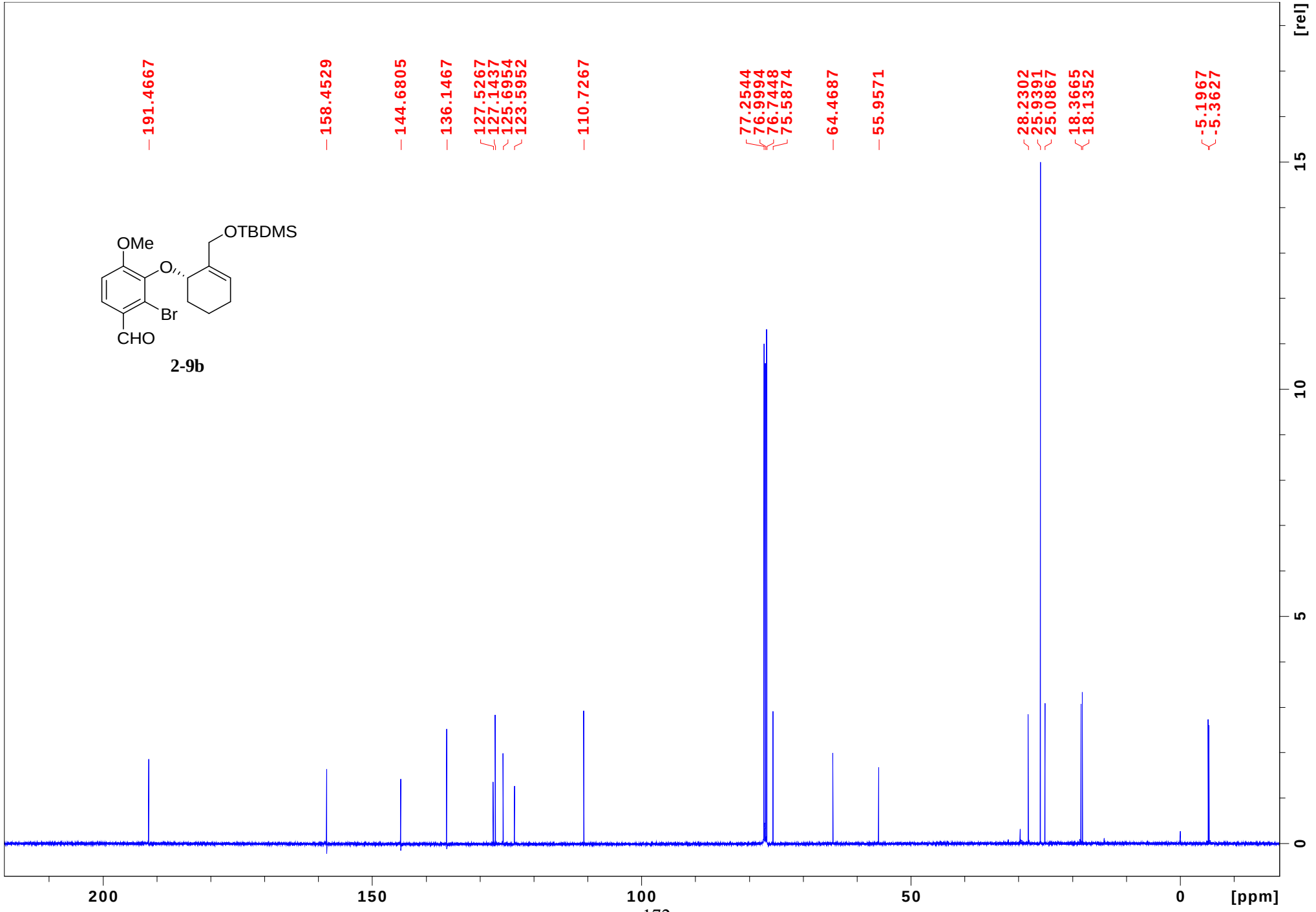
B-210 1 1 /home/yzang/data



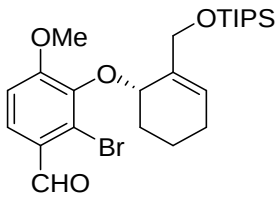
B-210C 1 1 /home/yzang/data




yz-1 1 1 /home/twang/data
OMe
OTBDMS
O
Br
CHO
2-9b
10.2742
7.7116
7.6943
7.2545
6.9444
6.9271
6.0285
6.0252
4.8781
4.3489
4.3466
3.9242
2.2262
2.1935
2.0975
2.0928
2.0776
2.0706
2.0653
2.0537
2.0311
1.9748
1.9691
1.9639
1.9568
1.9469
1.9413
1.9358
1.6081
1.6021
1.5839
1.5167
1.4898
0.8974
0.0424
0.9408
0.9326
0.9879
0.9696
0.9716
1.9907
3.0000
4.0971
2.1166
9.1121
5.8984
[rel]
[ppm]

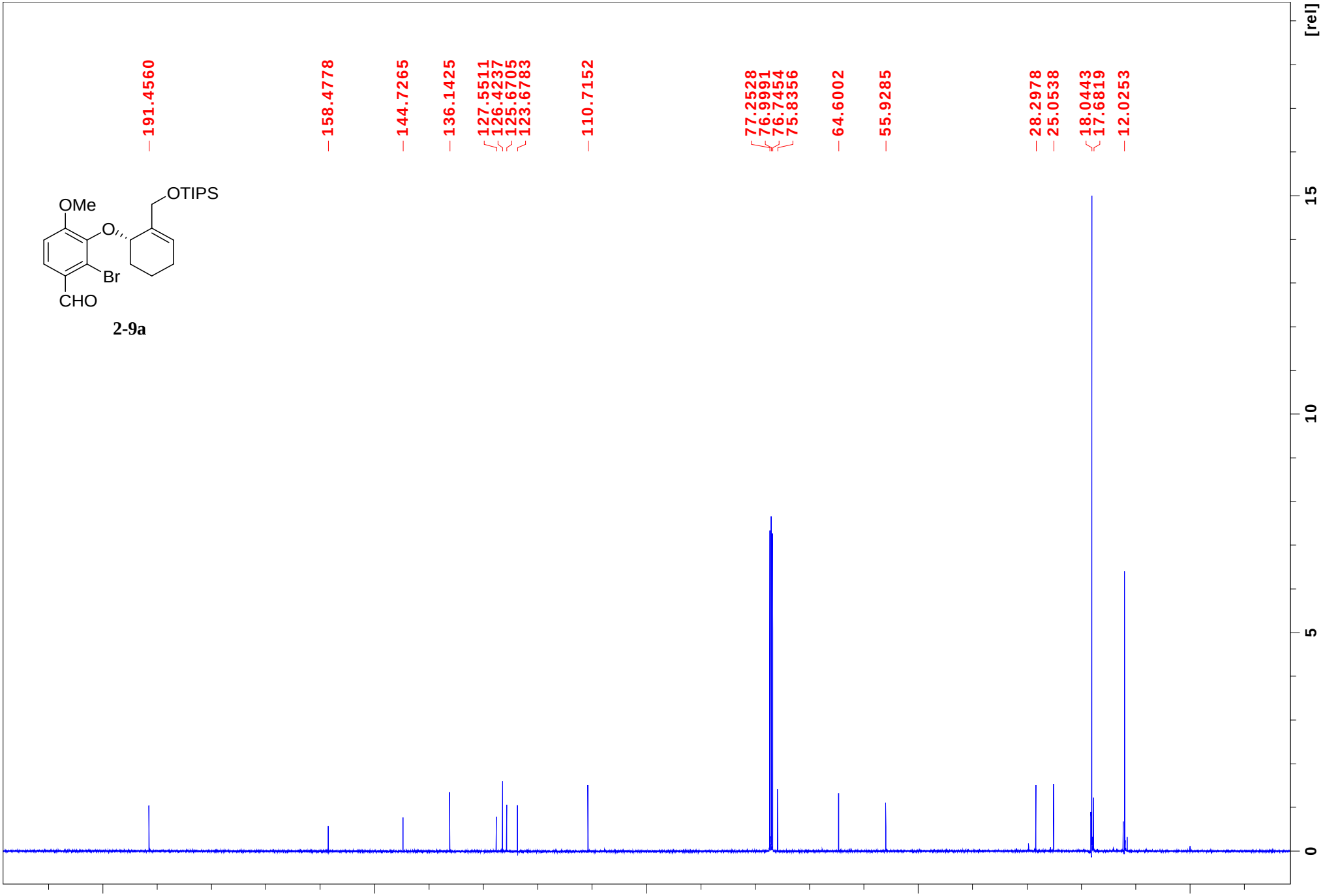

yz-1C 1 1 /home/twang/data
191.4667
158.4529
144.6805
136.1467
127.5267
127.1437
125.6954
123.5952
110.7267
77.2544
76.9994
76.7448
75.5874
64.4687
55.9571
28.2302
25.9391
25.0867
18.3665
18.1352
-5.1967
-5.3627
OMe
O
OTBDMS
Br
CHO
2-9b
[rel]
15
10
5
0
200
150
100
50
0
[ppm]

yz-2 1 1 /home/twang/data



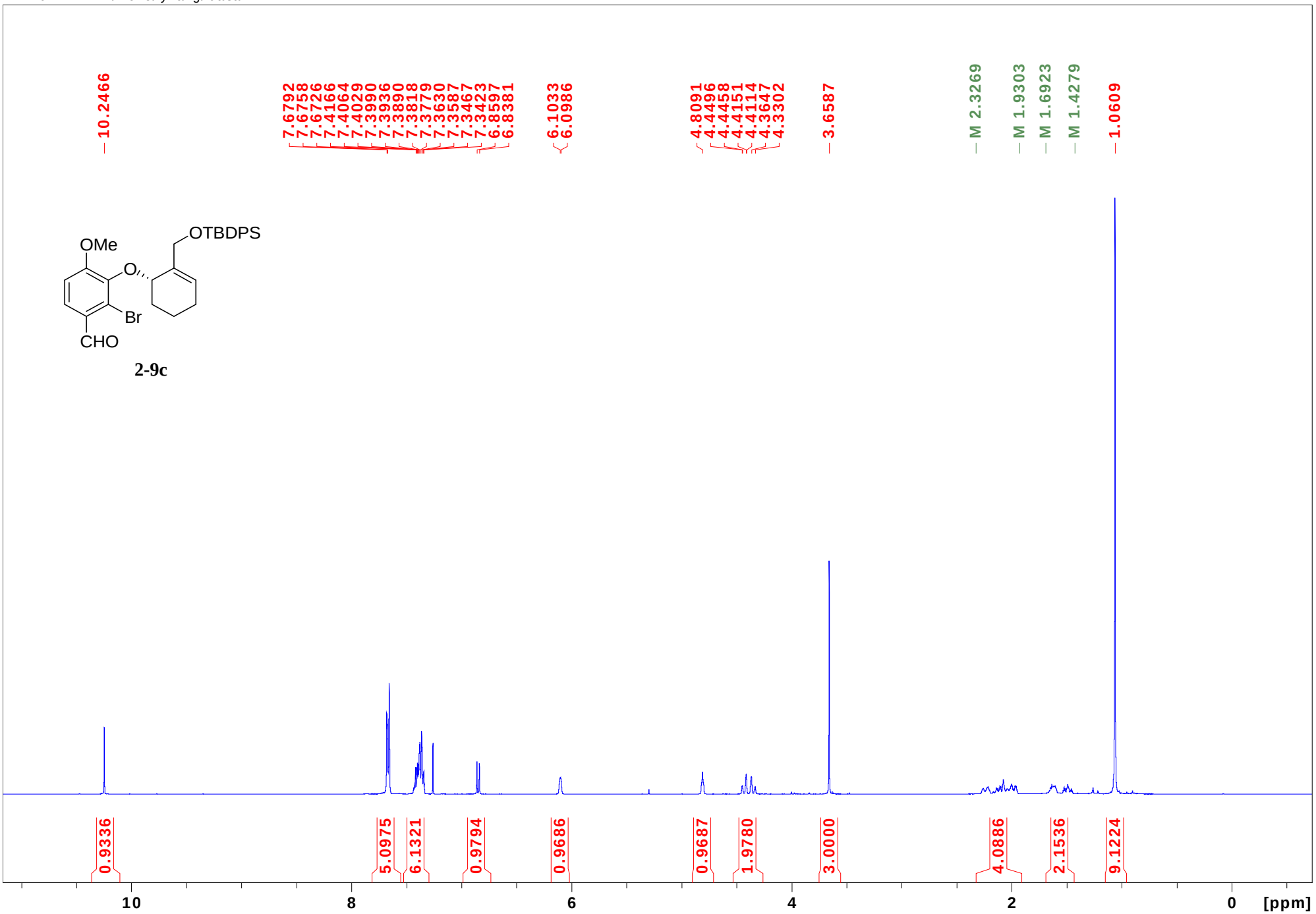
2-9a

yz-2C 1 1 /home/twang/data



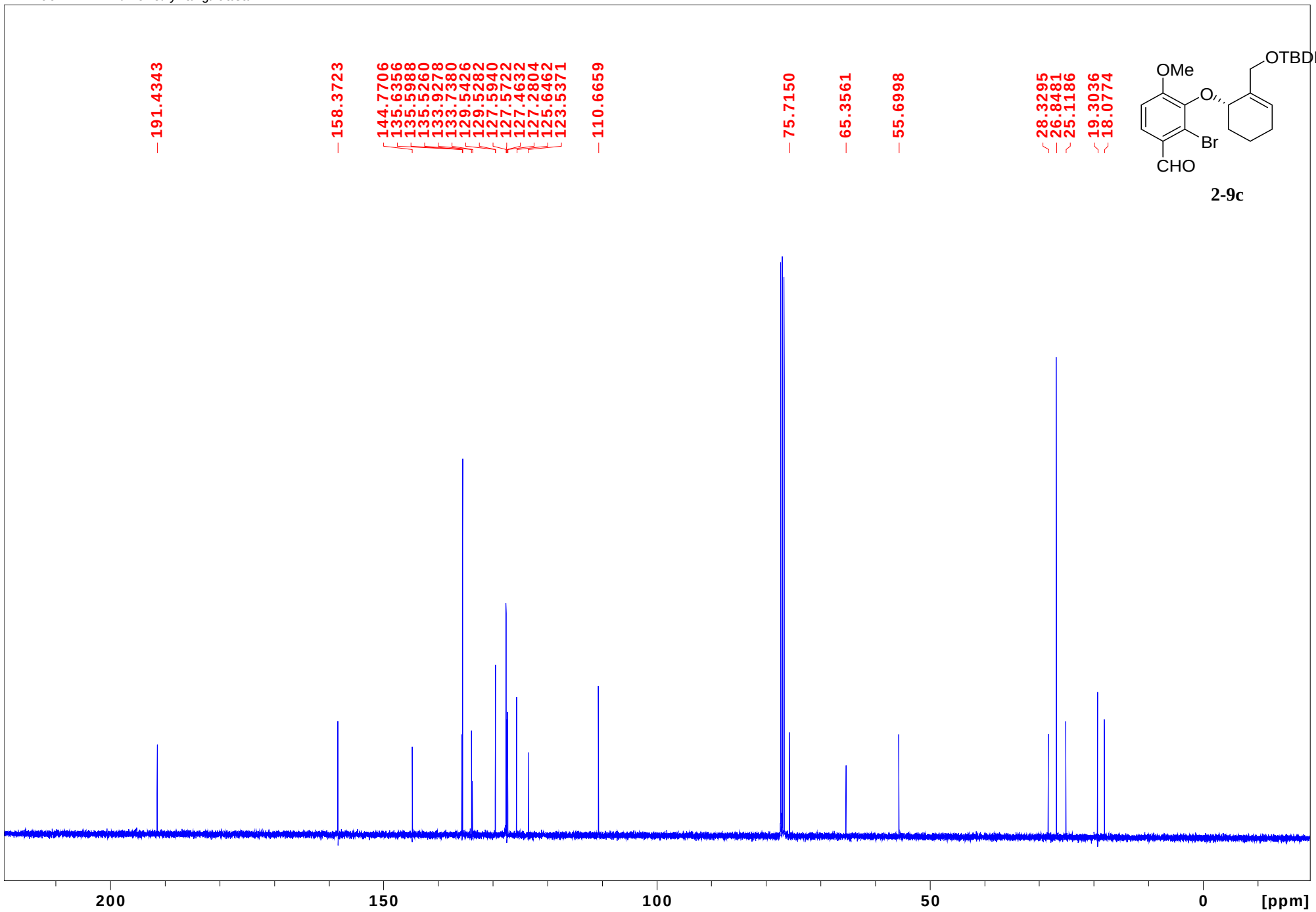
2-9a

B-170 1 1 /home/yzang/data

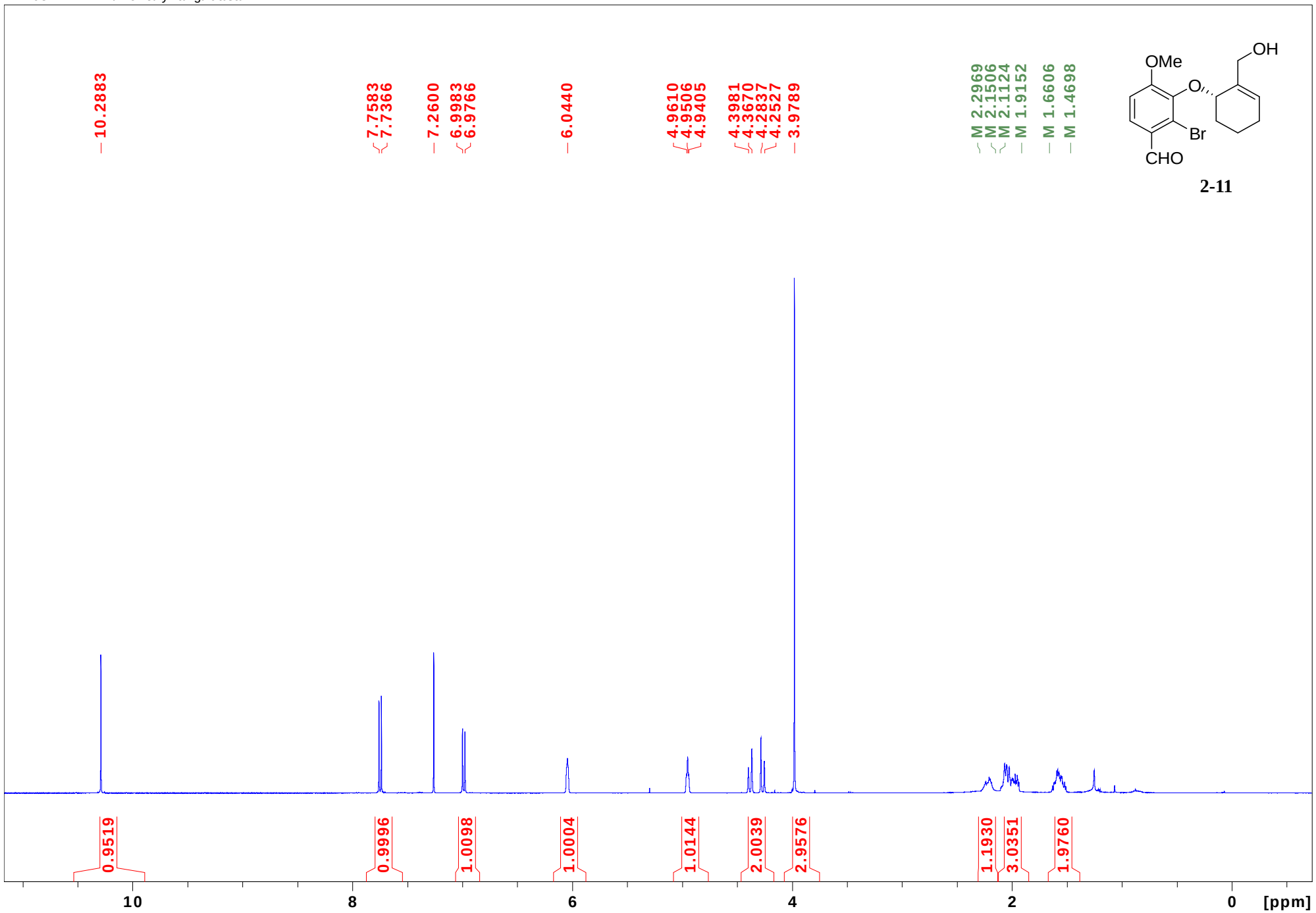


2-9c

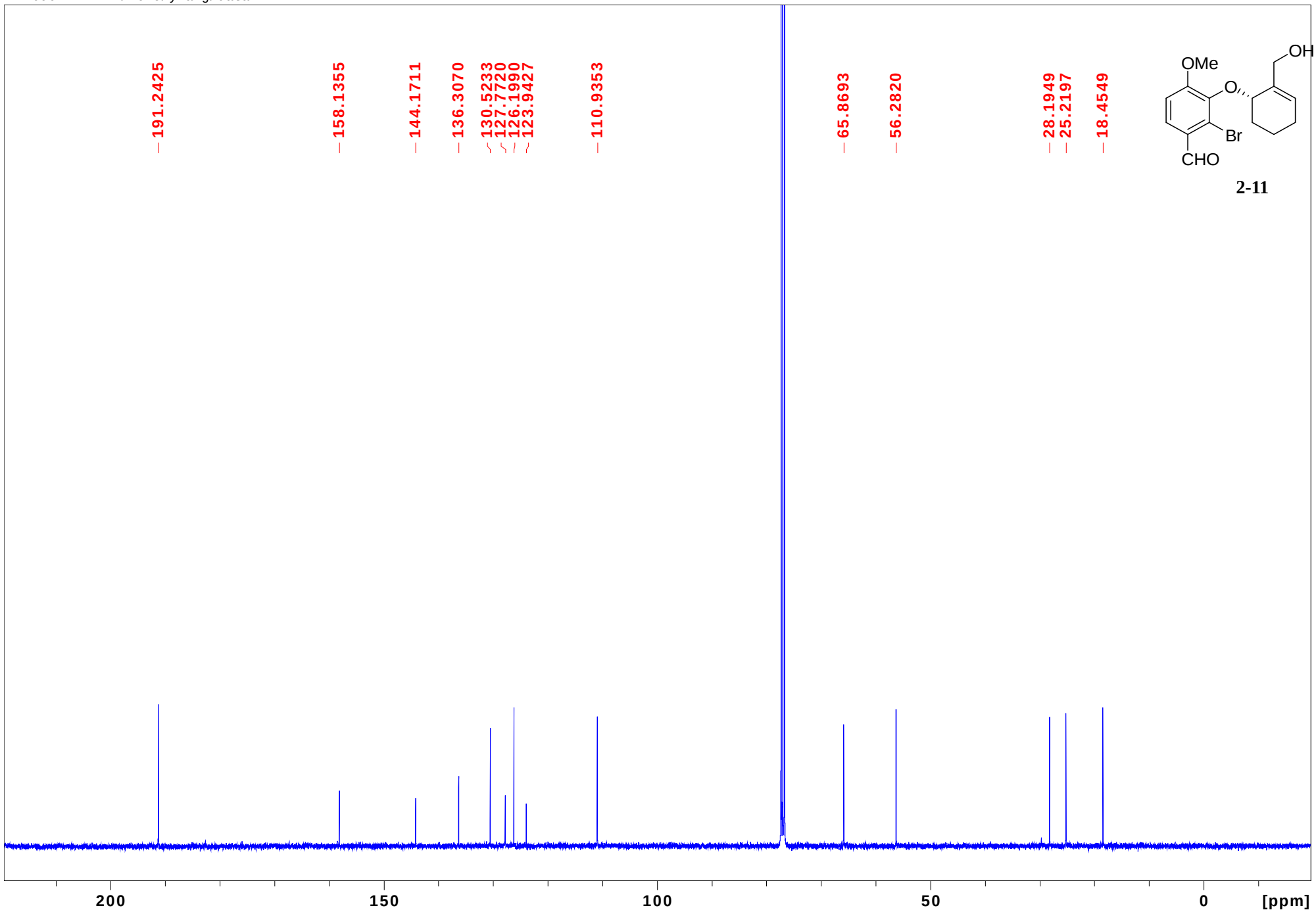
B-170C 1 1 /home/yzang/data



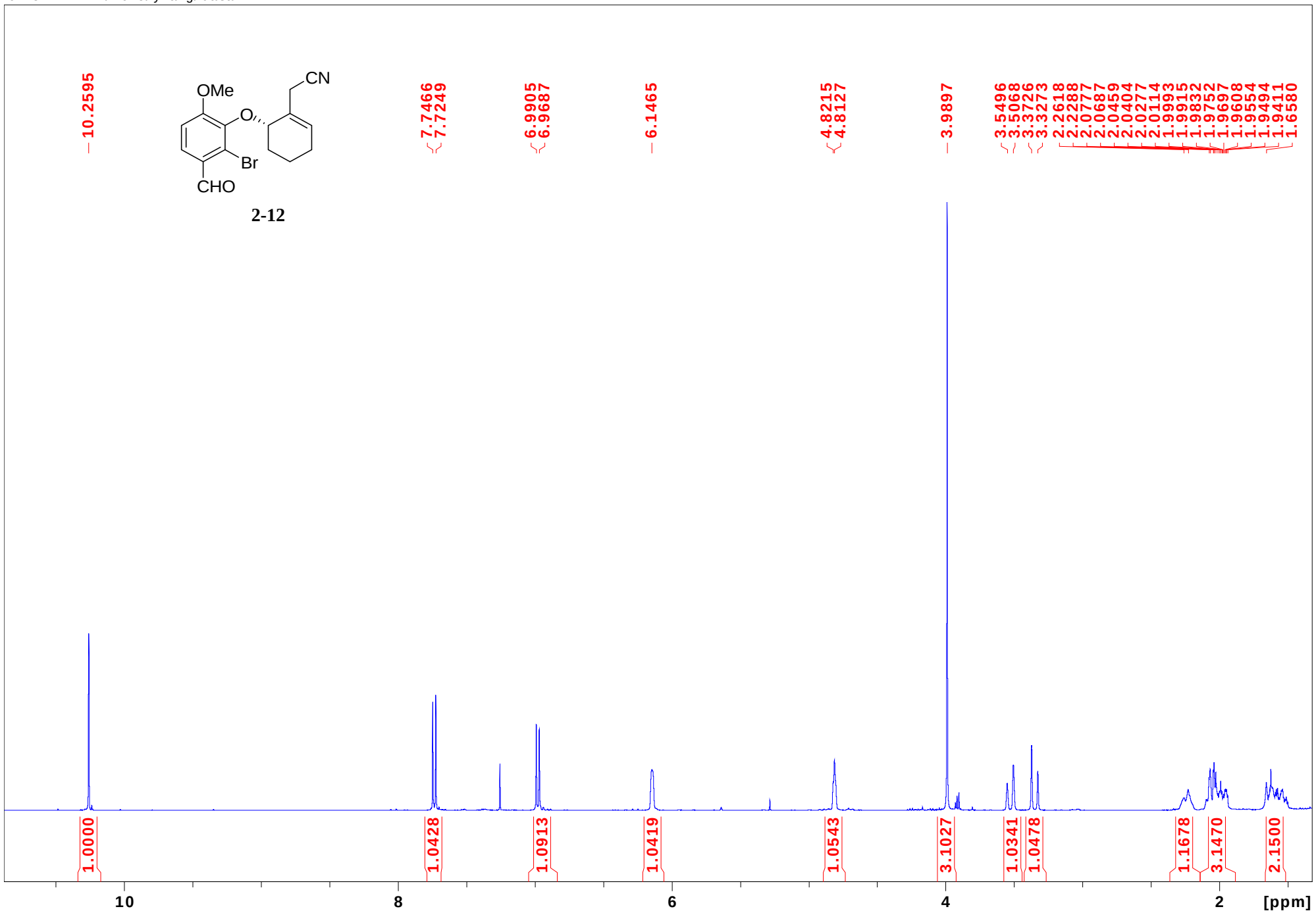
B-168 1 1 /home/yzang/data



B-169C 1 1 /home/yzang/data

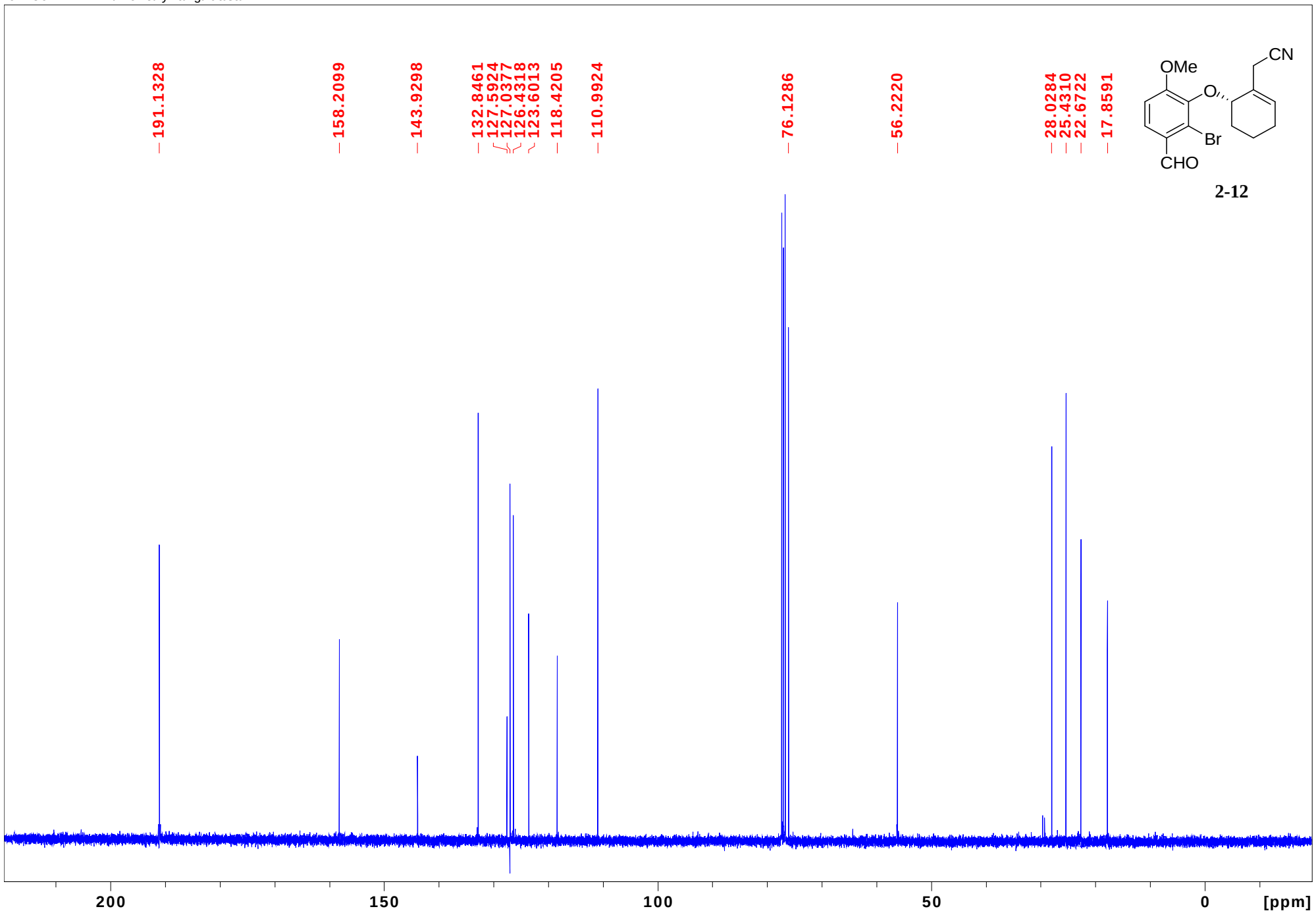


C-18 1 1 /home/yzang/data

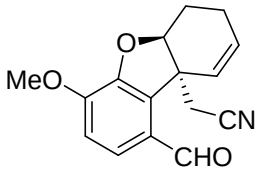


2-12

C-18C 1 1 /home/yzang/data



C-35 1 1 /home/yzang/data



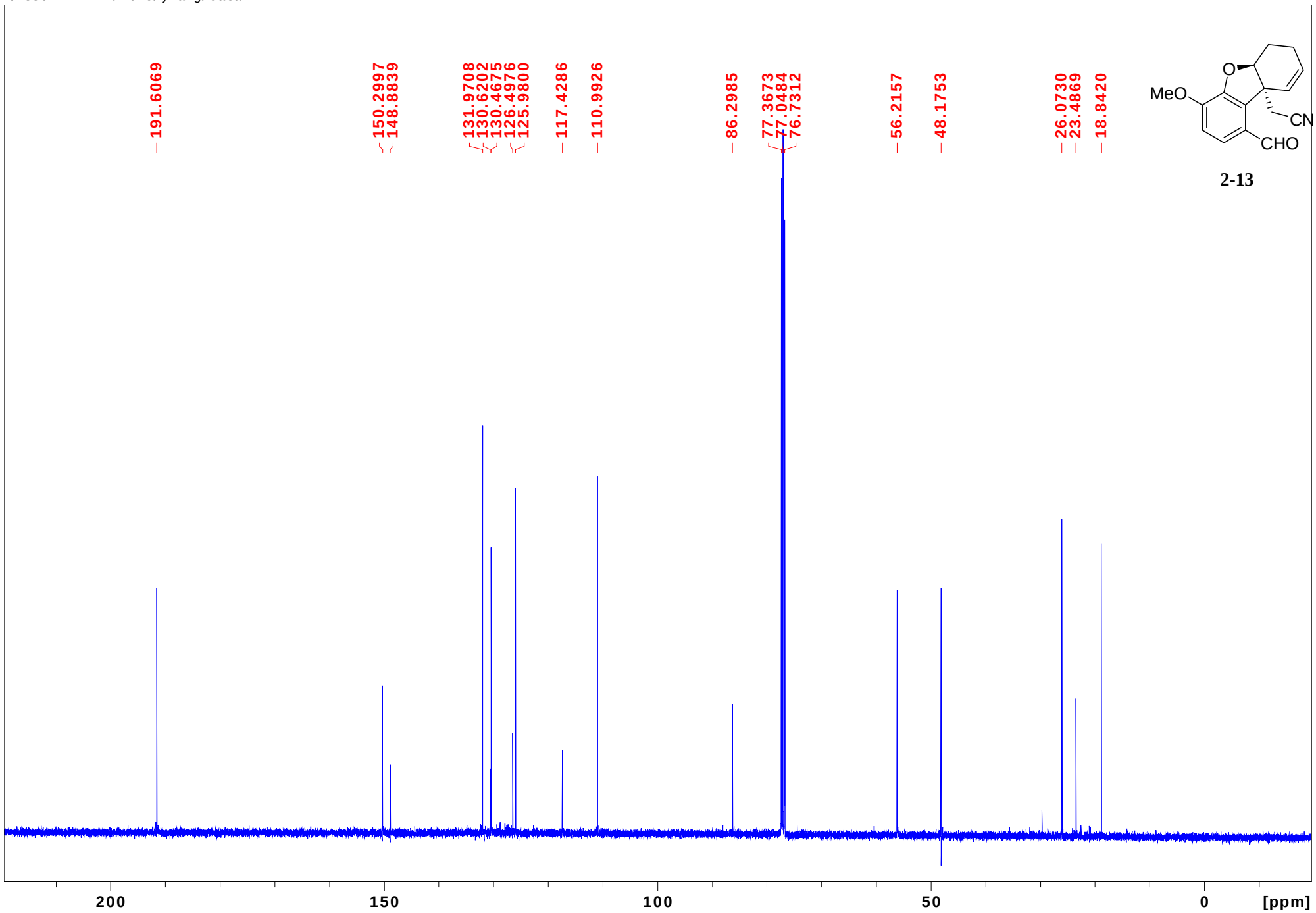
2-13

9.7876
7.3883
7.3674
6.9457
6.9247
6.0153
6.0121
6.0092
5.9899
5.9863
5.9838
5.9710
5.9678
5.9597
5.9540
4.9832
4.9750
4.9660
3.9673
3.4686
3.4261
3.1508
3.1084
2.4011
2.3655
2.3634
2.3583
2.2432
2.2147
2.0348
1.9989
1.9637

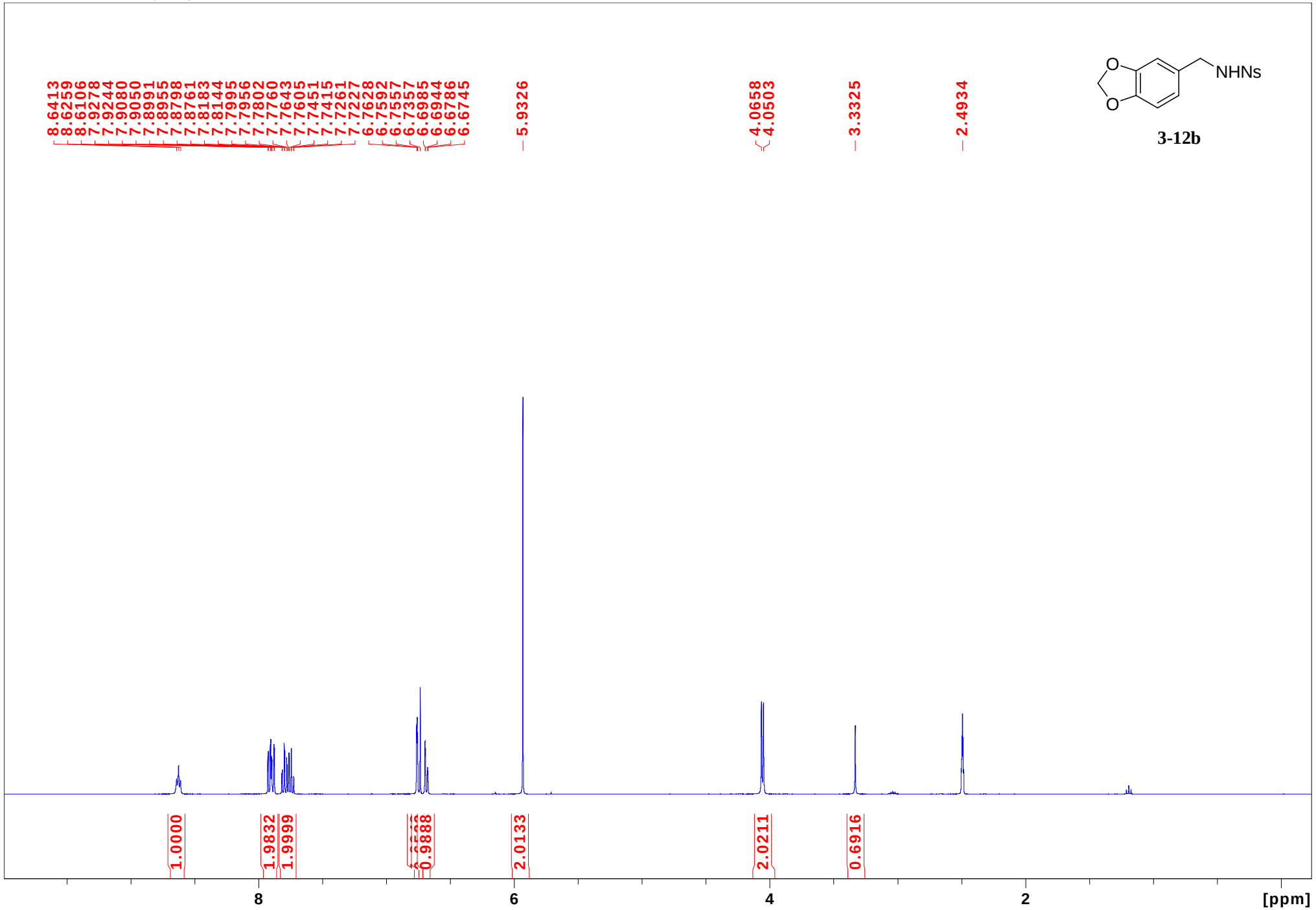
1.0000
1.0863
1.1357
1.9832
1.0527
3.2701
0.9370
0.9954
1.1482
1.0829
2.3877

10
8
6
4
2
[ppm]

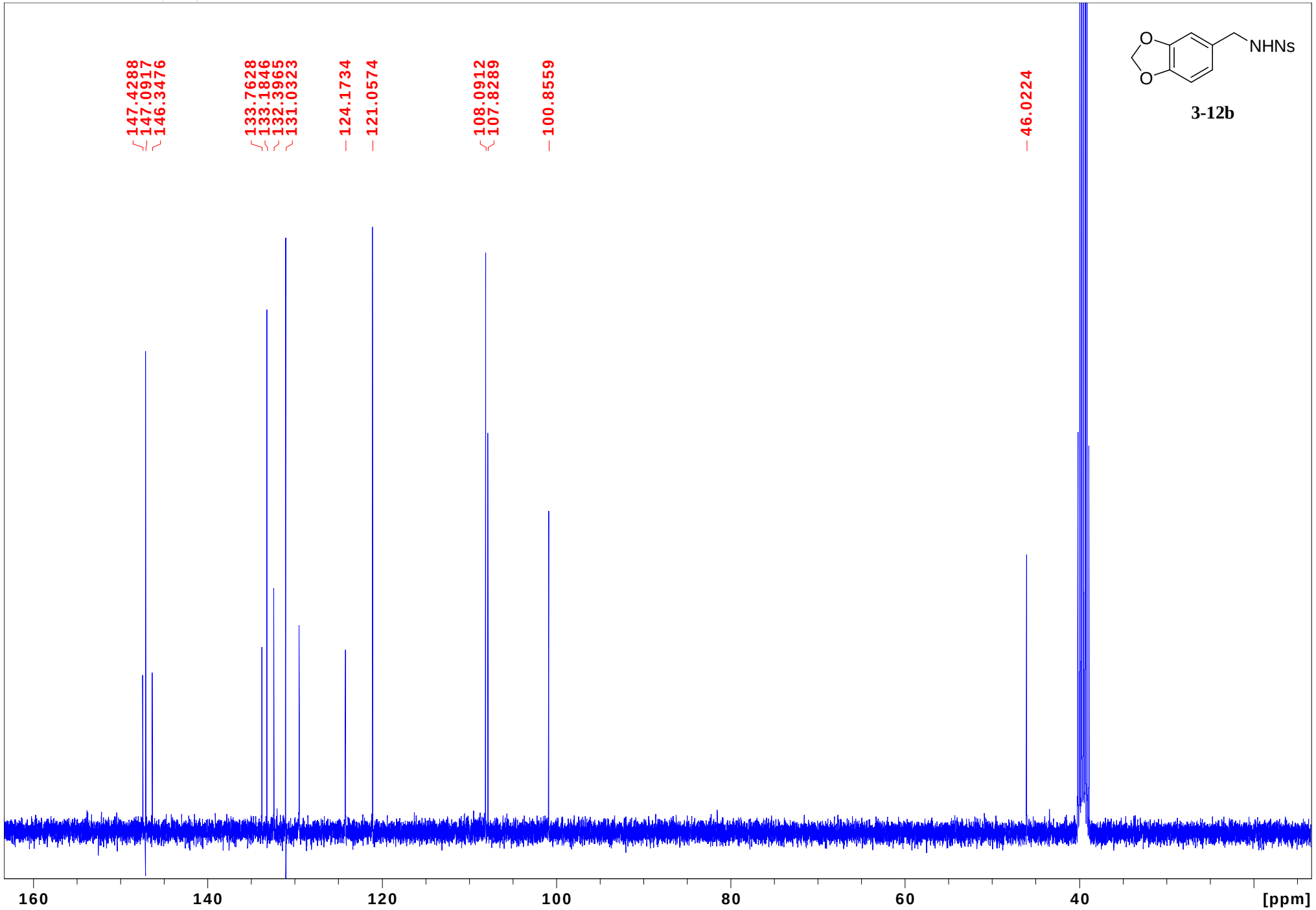
C-35C 1 1 /home/yzang/data



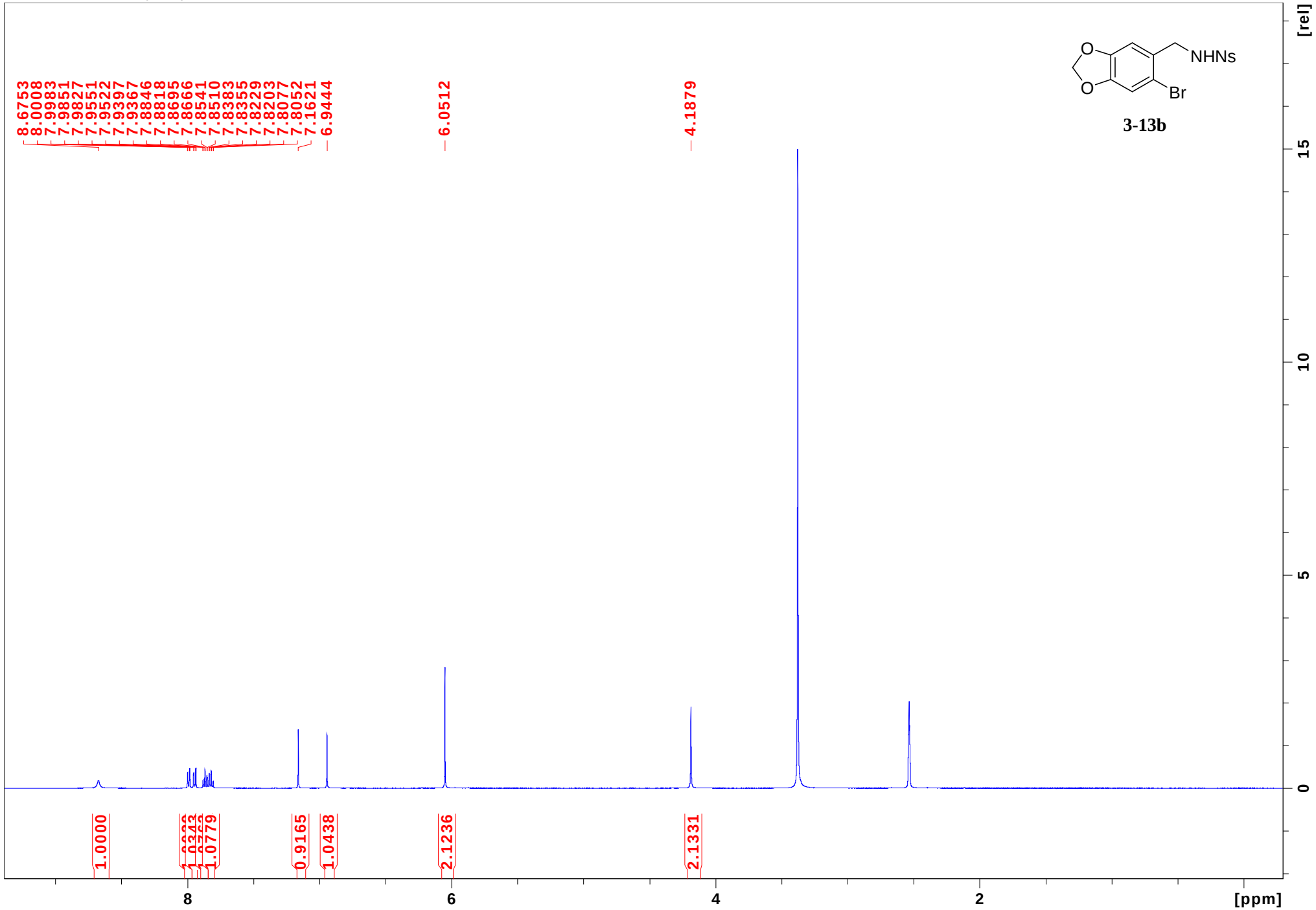
D-18 1 1 /home/yzang/data

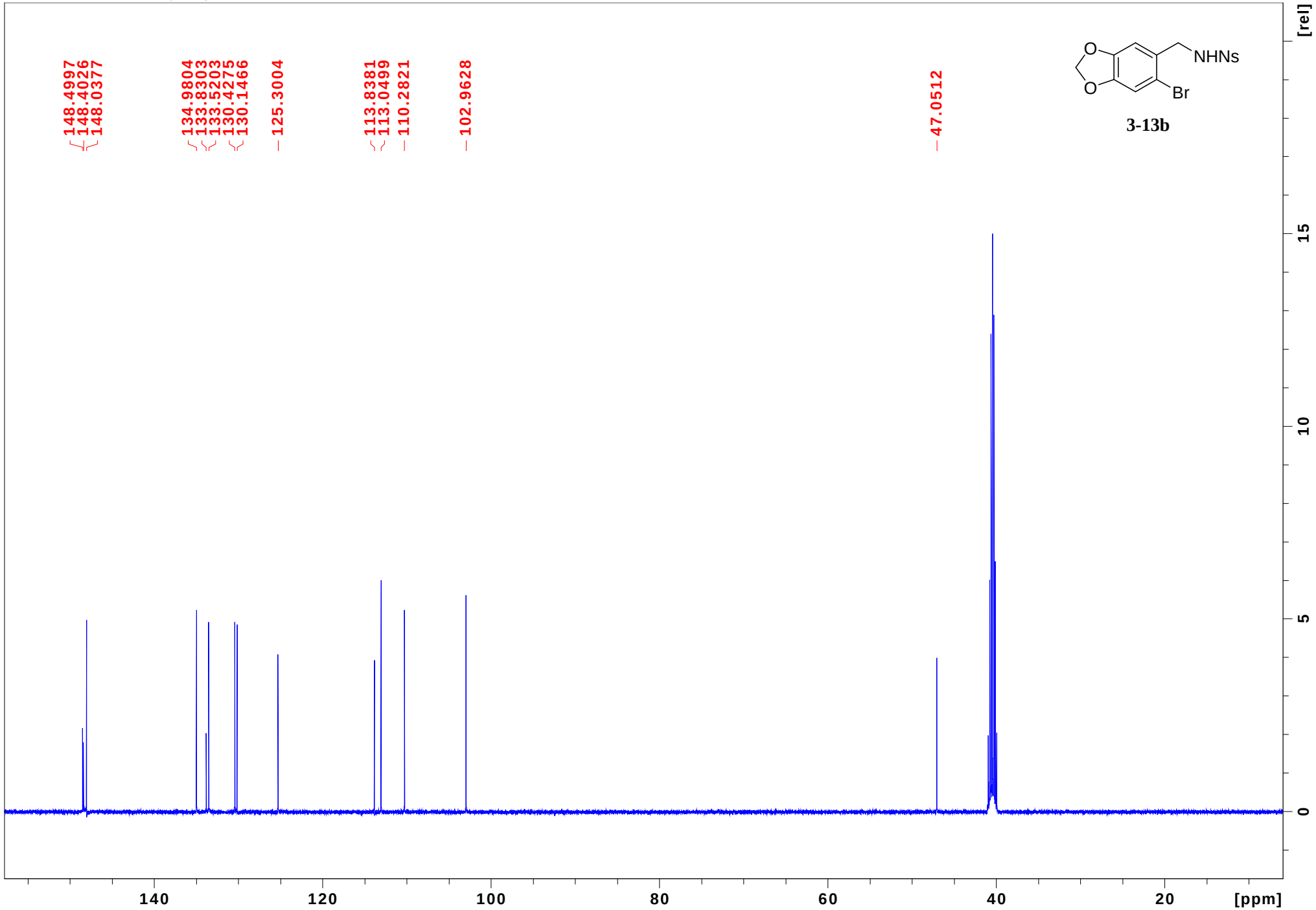


D-18C 1 1 /home/yzang/data

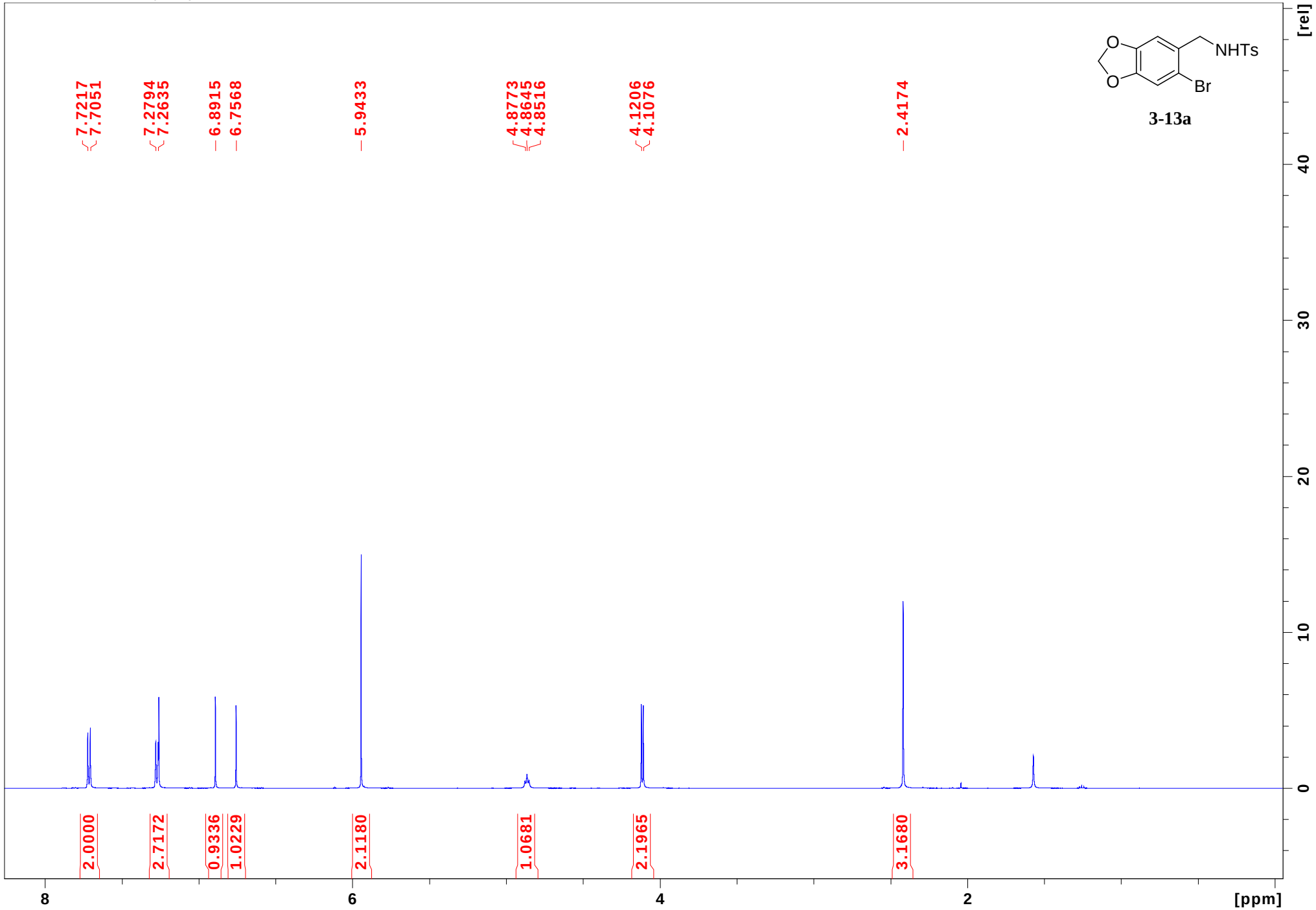


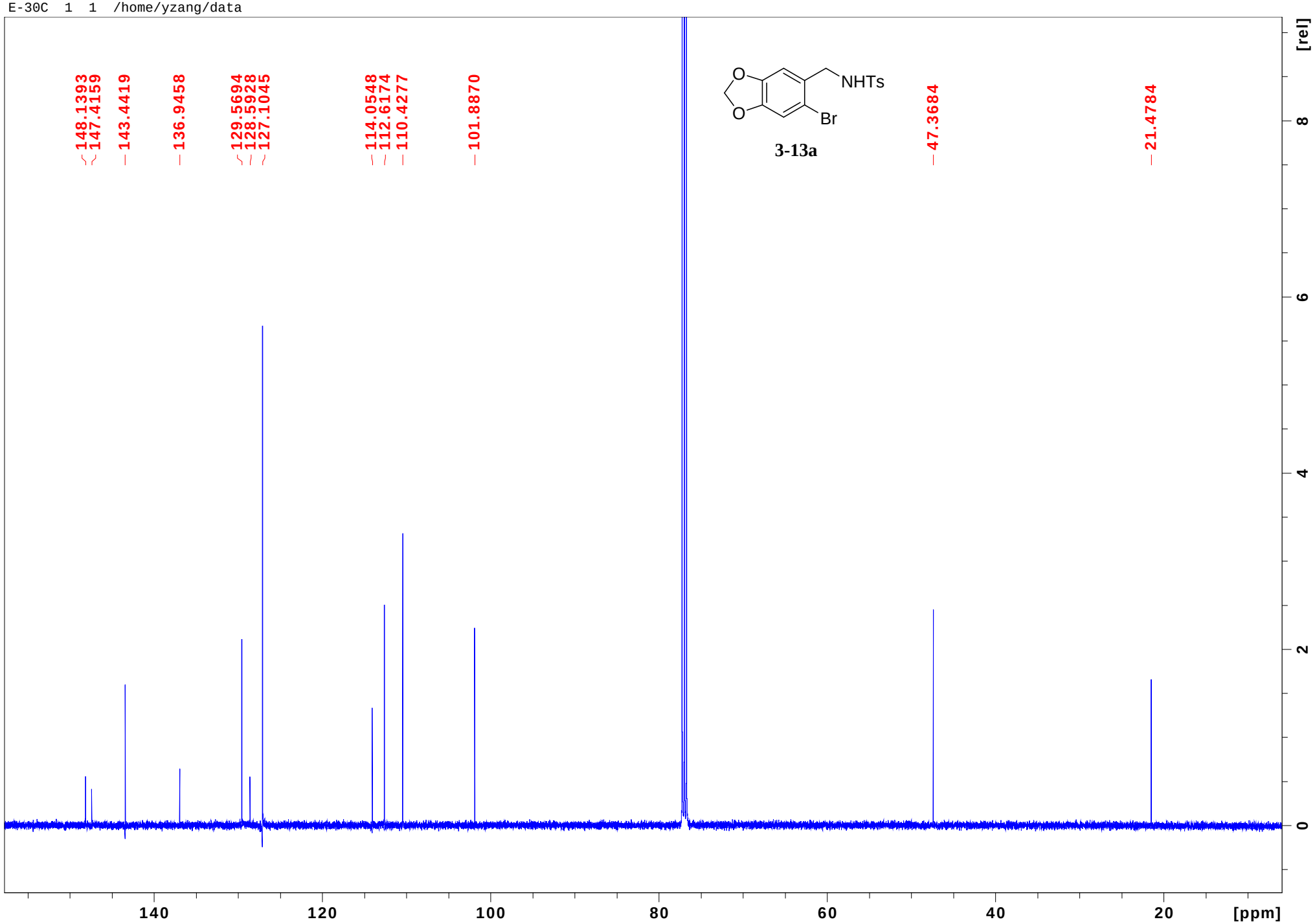
D-7 1 1 /home/yzang/data



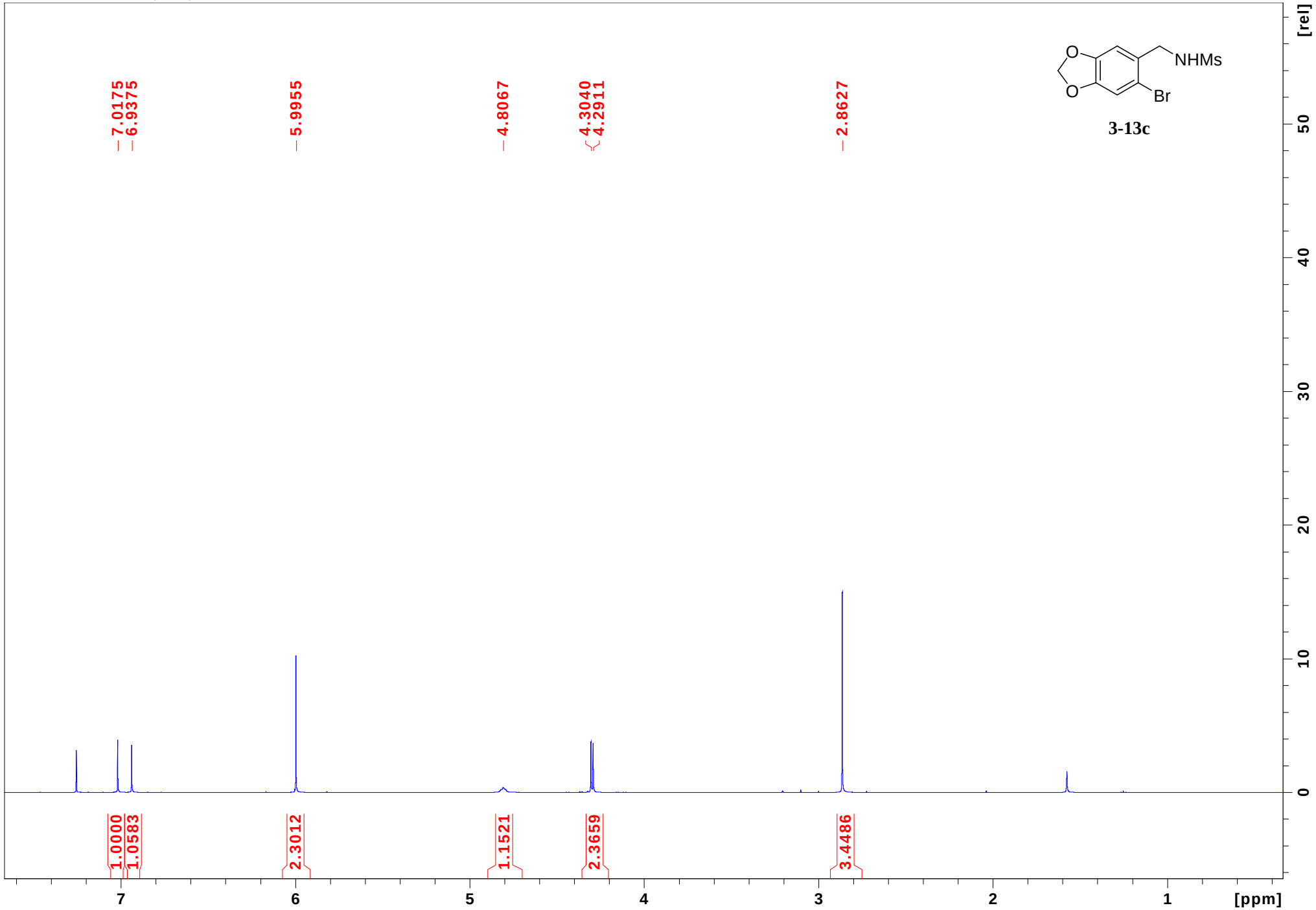

D-7C-1 1 1 /home/yzang/data
148.4997
148.4026
148.0377
134.9804
133.8303
133.5203
130.4275
130.1466
125.3004
113.8381
113.0499
110.2821
102.9628
47.0512
NHNs
Br
3-13b
[rel]
0
5
10
15
140
120
100
80
60
40
20
[ppm]

E-30 1 1 /home/yzang/data

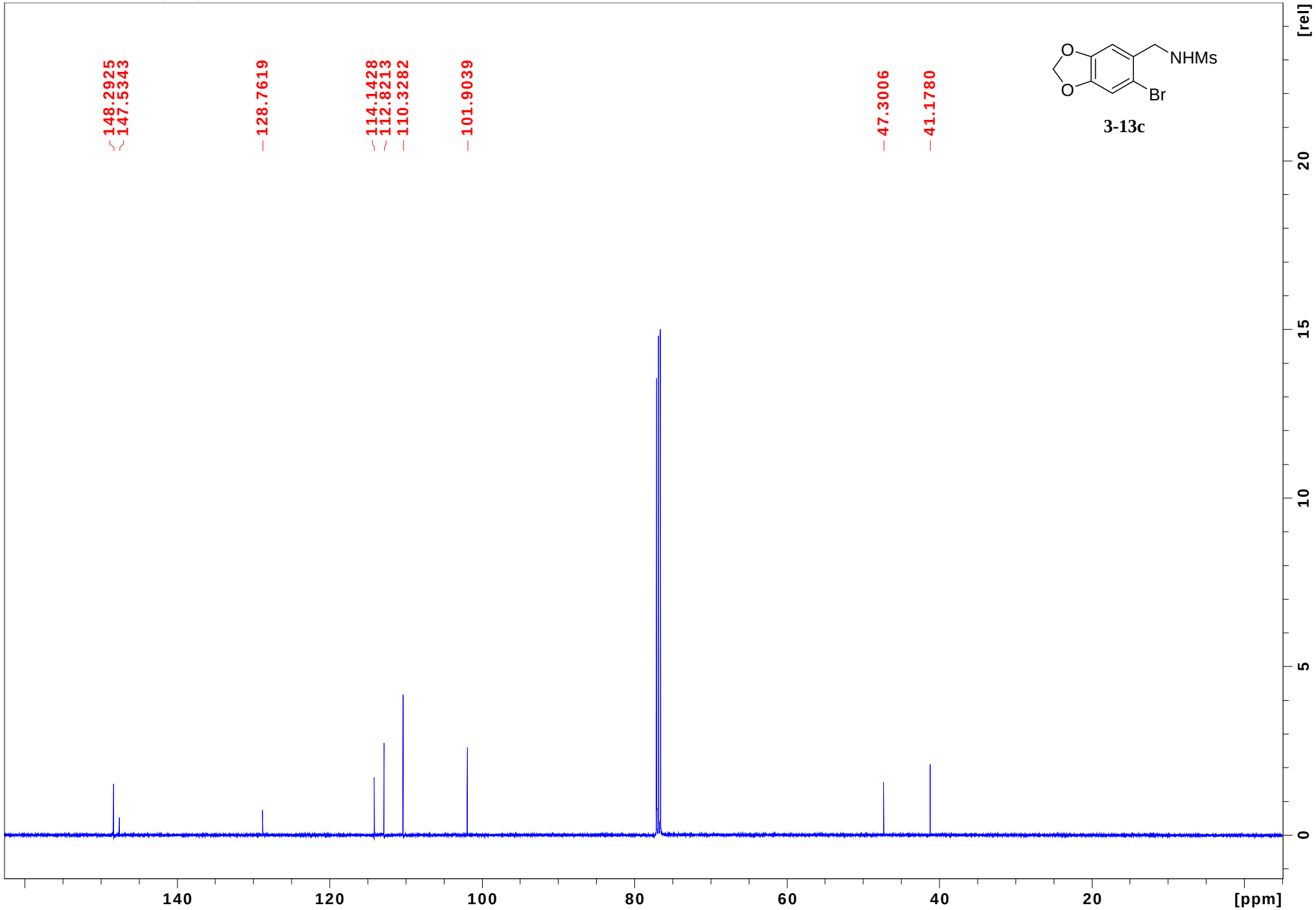



E-30C 1 1 /home/yzang/data
148.1393
147.4159
143.4419
136.9458
129.5694
128.5928
127.1045
114.0548
112.6174
110.4277
101.8870
47.3684
21.4784
NHTs
Br
3-13a
[rel]
[ppm]
140
120
100
80
60
40
20
0
2
4
6
8

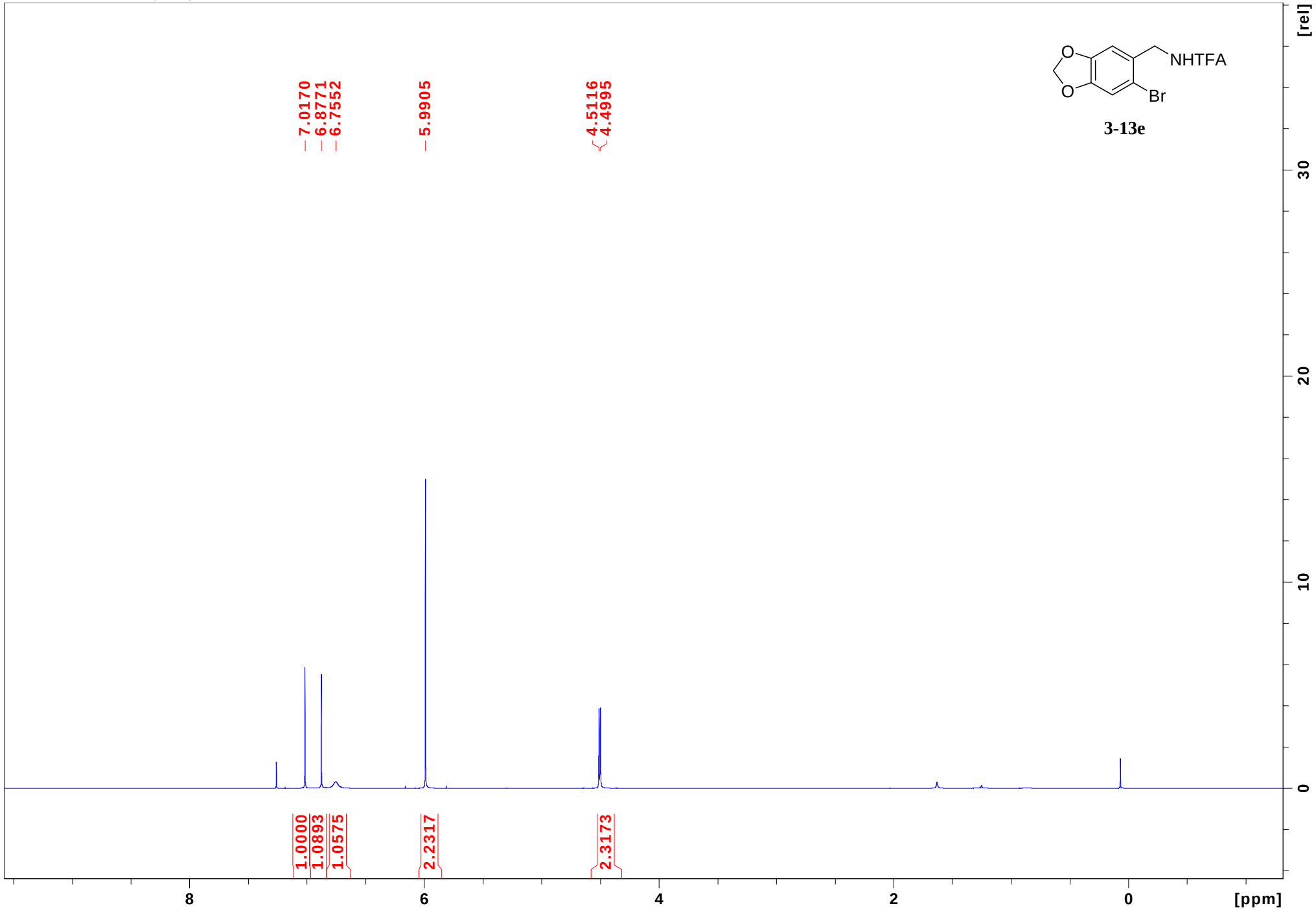
E-31 1 1 /home/yzang/data



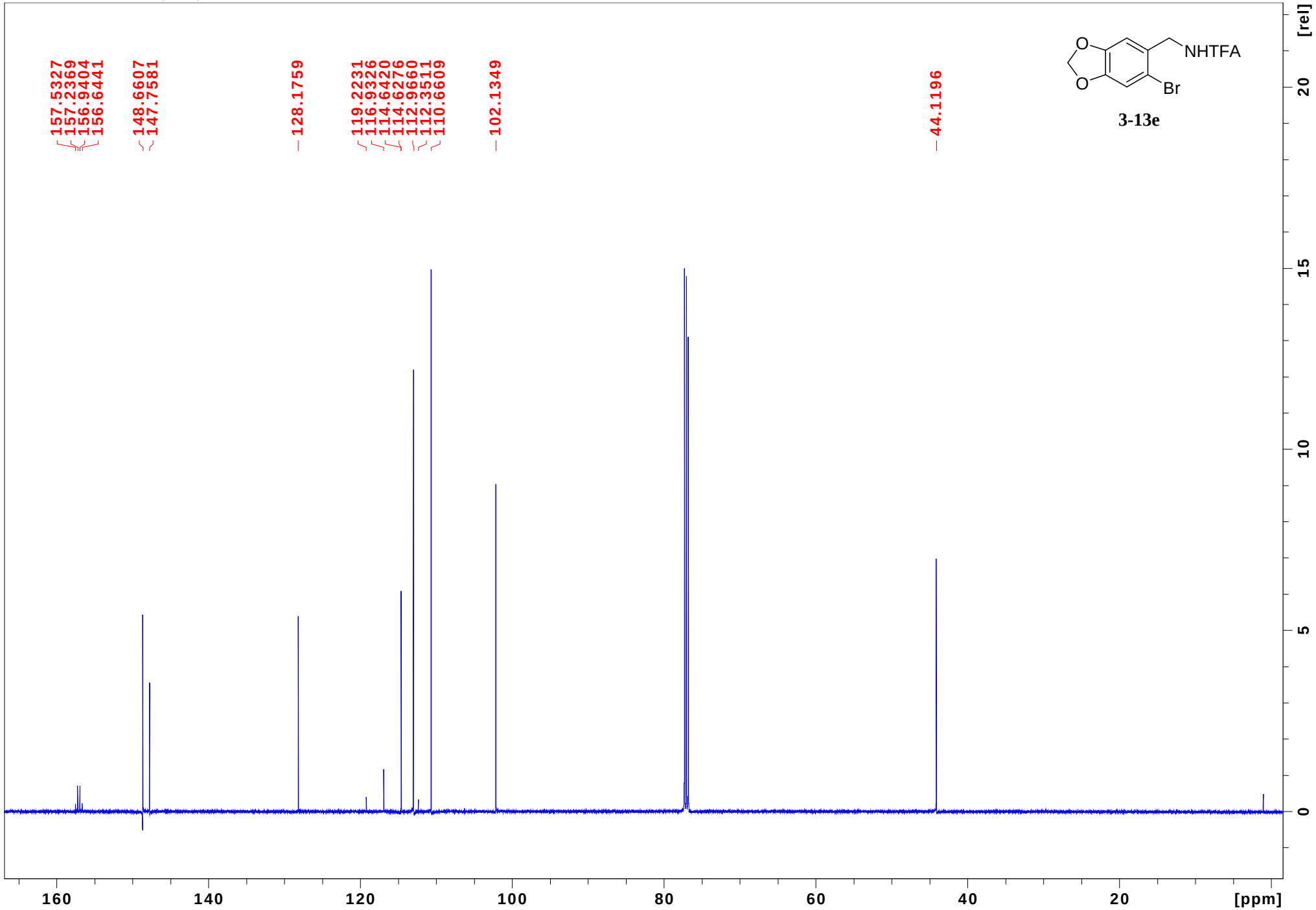
E-31C 1 1 /home/yzang/data



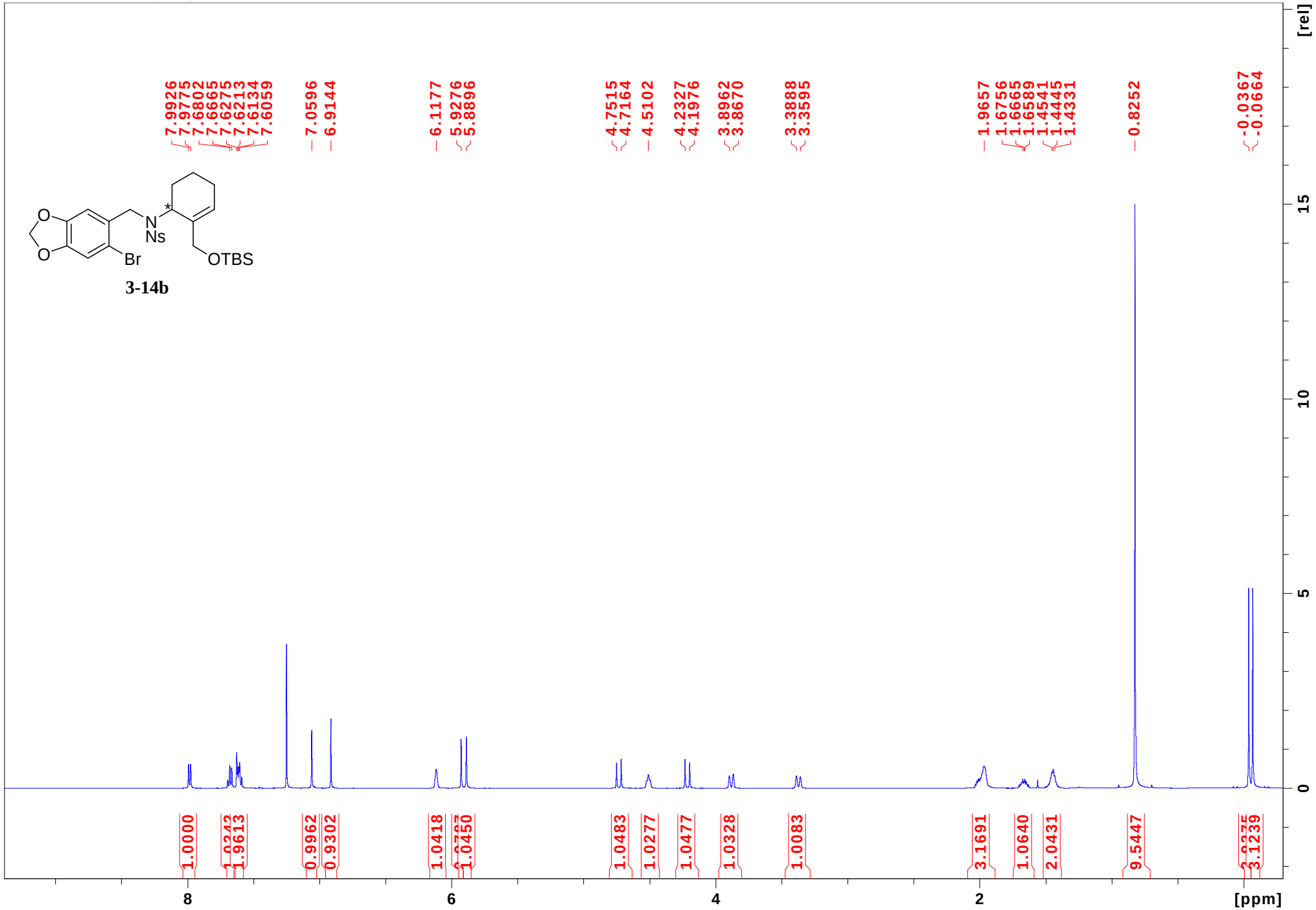
E-32 1 1 /home/yzang/data



E-32C 1 1 /home/yzang/data



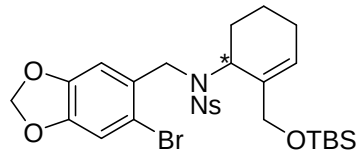
D-54 1 1 /home/yzang/data



3-14b

D-54C 1 1 /home/yzang/data

147.6155
147.4430
147.3198
133.7352
133.5625
133.4973
131.6637
131.5532
130.5778
128.8383
124.0670
112.4699
112.3054
109.1315
101.6750
77.2496
76.9948
76.7400
62.9573
55.9356
48.6373
29.9152
25.8835
24.3982
20.6926
18.3473
-5.4104
-5.4838



3-14b

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5
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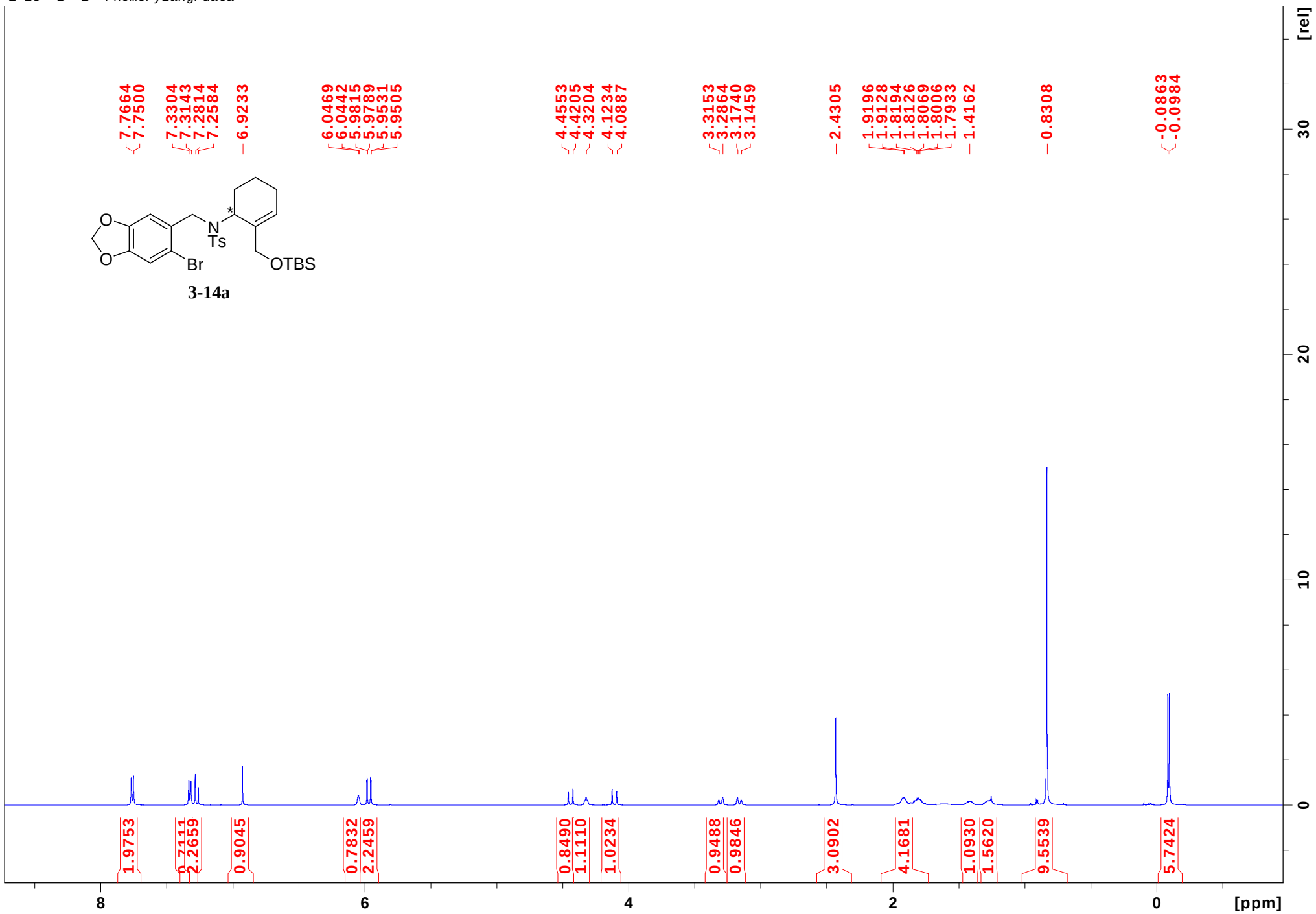
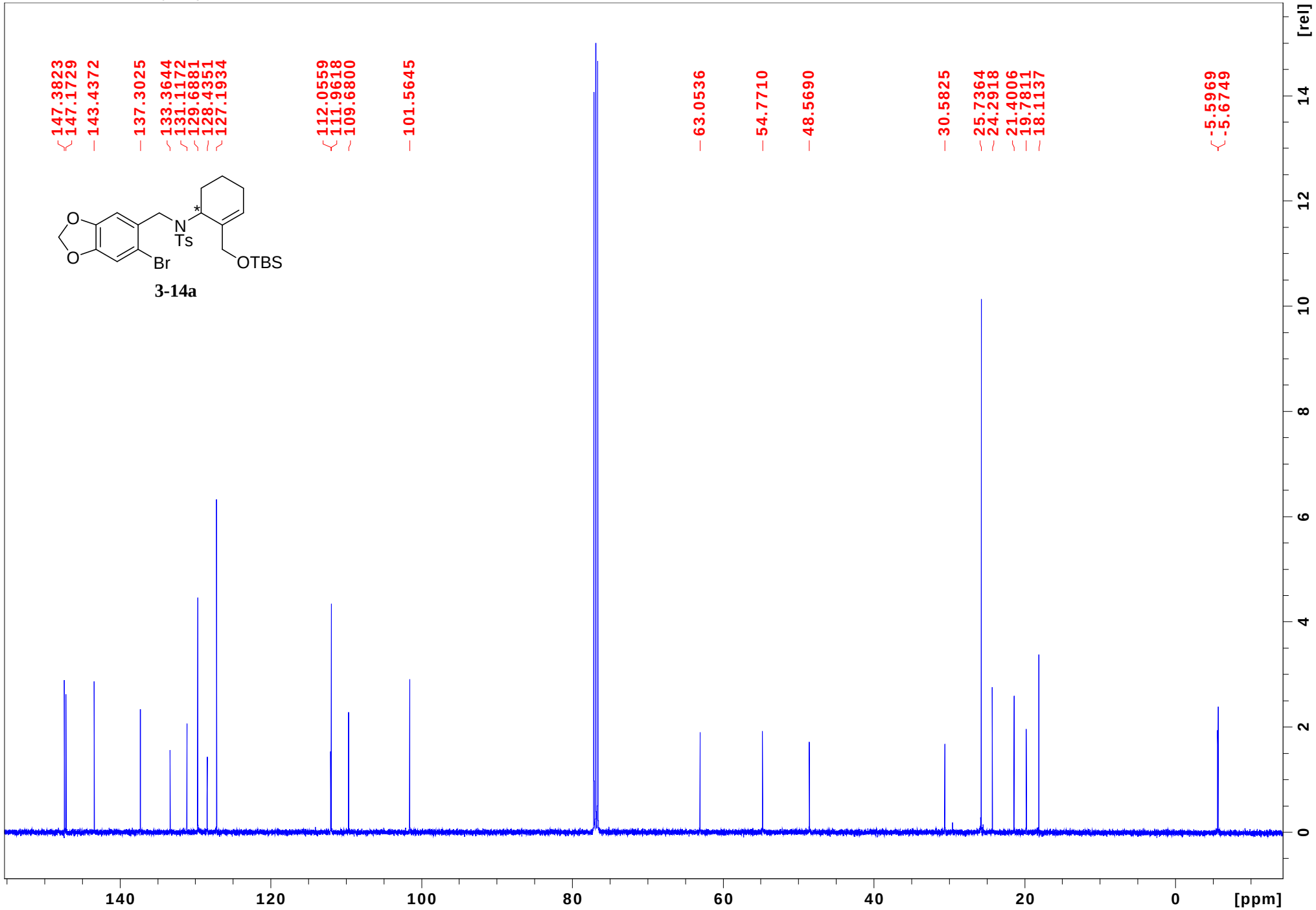
150
100
50
0
[ppm]

E-28 1 1 /home/yzang/data



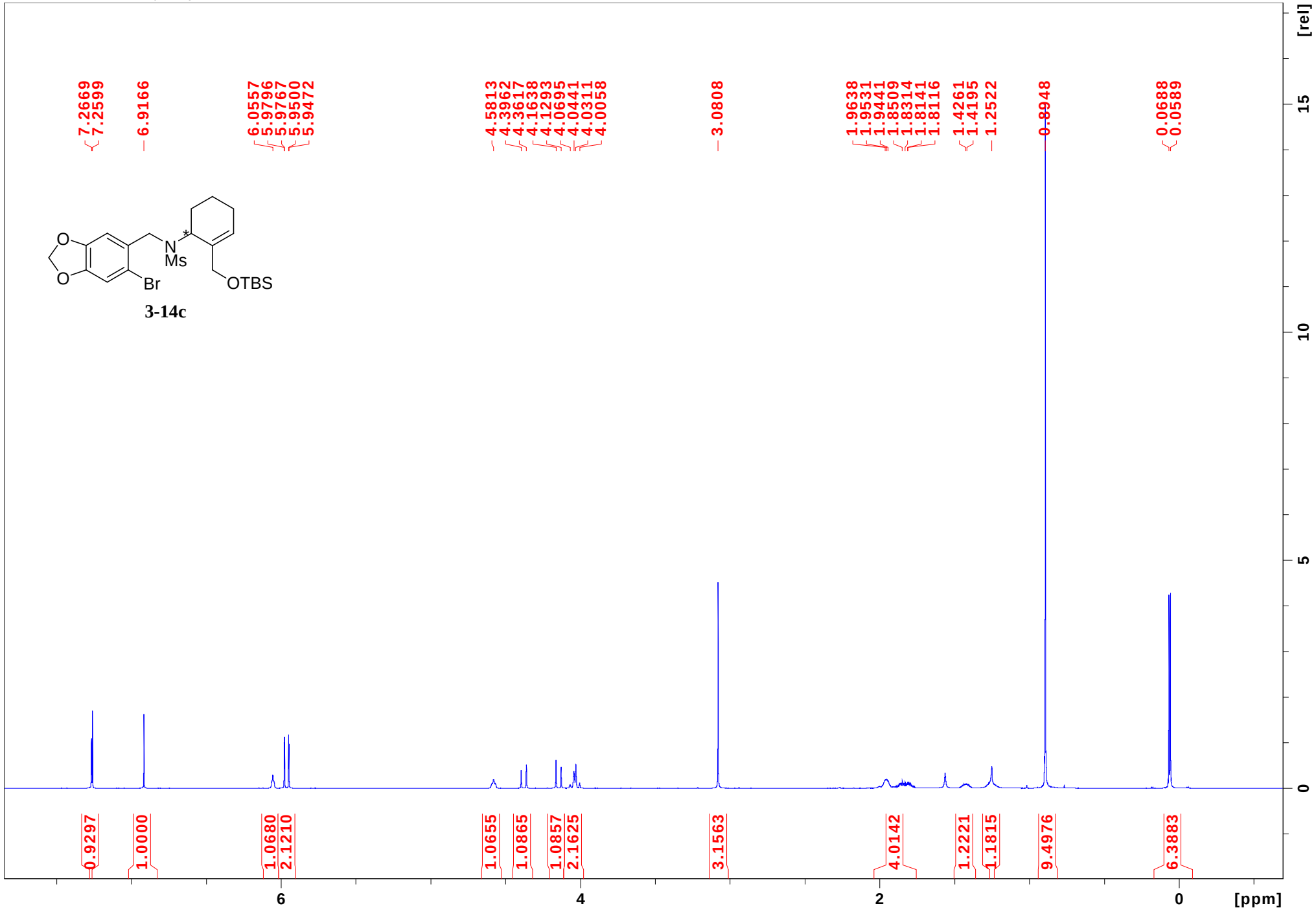
3-14a

E-28C 1 1 /home/yzang/data



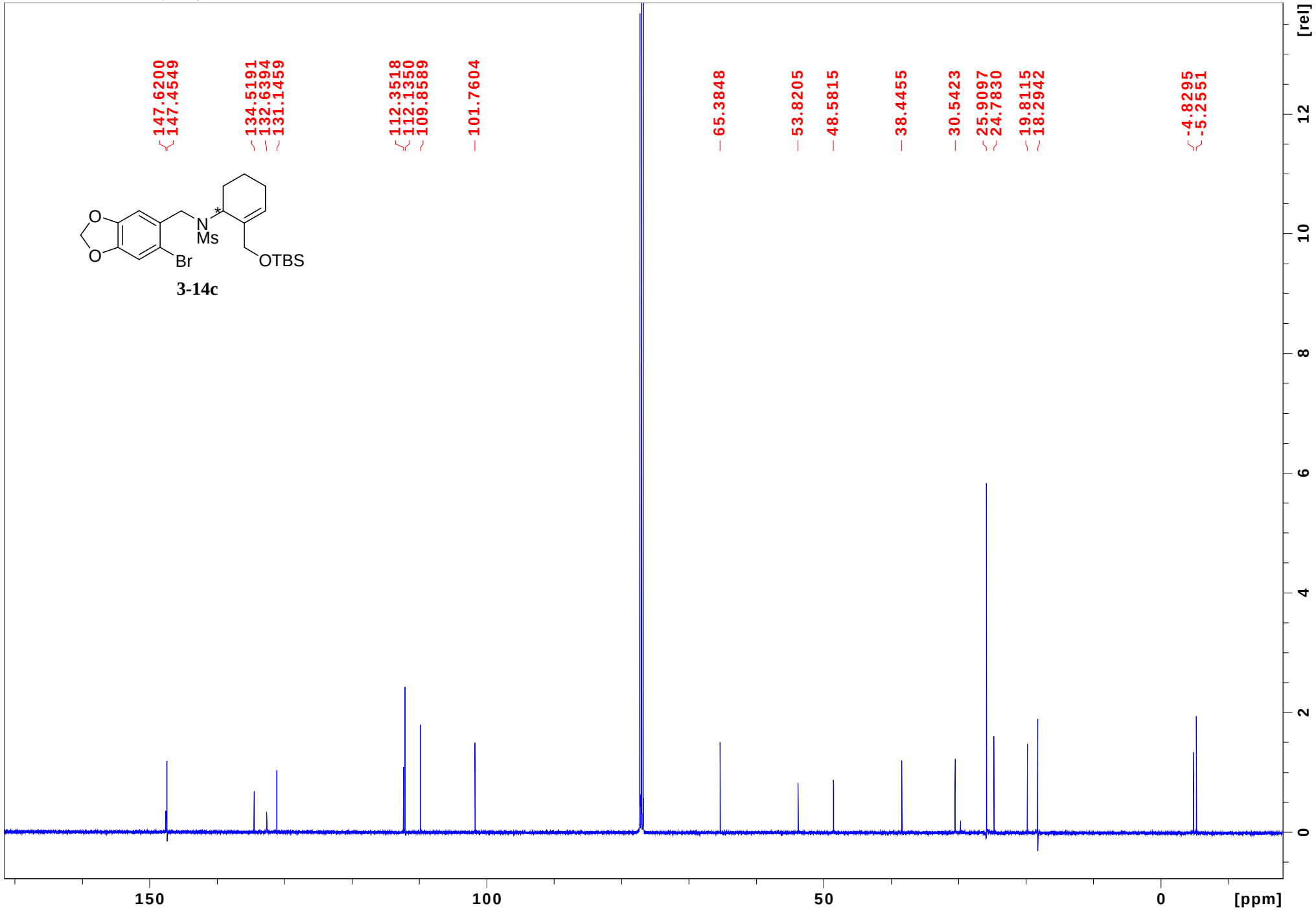
3-14a

E-11 1 1 /home/yzang/data



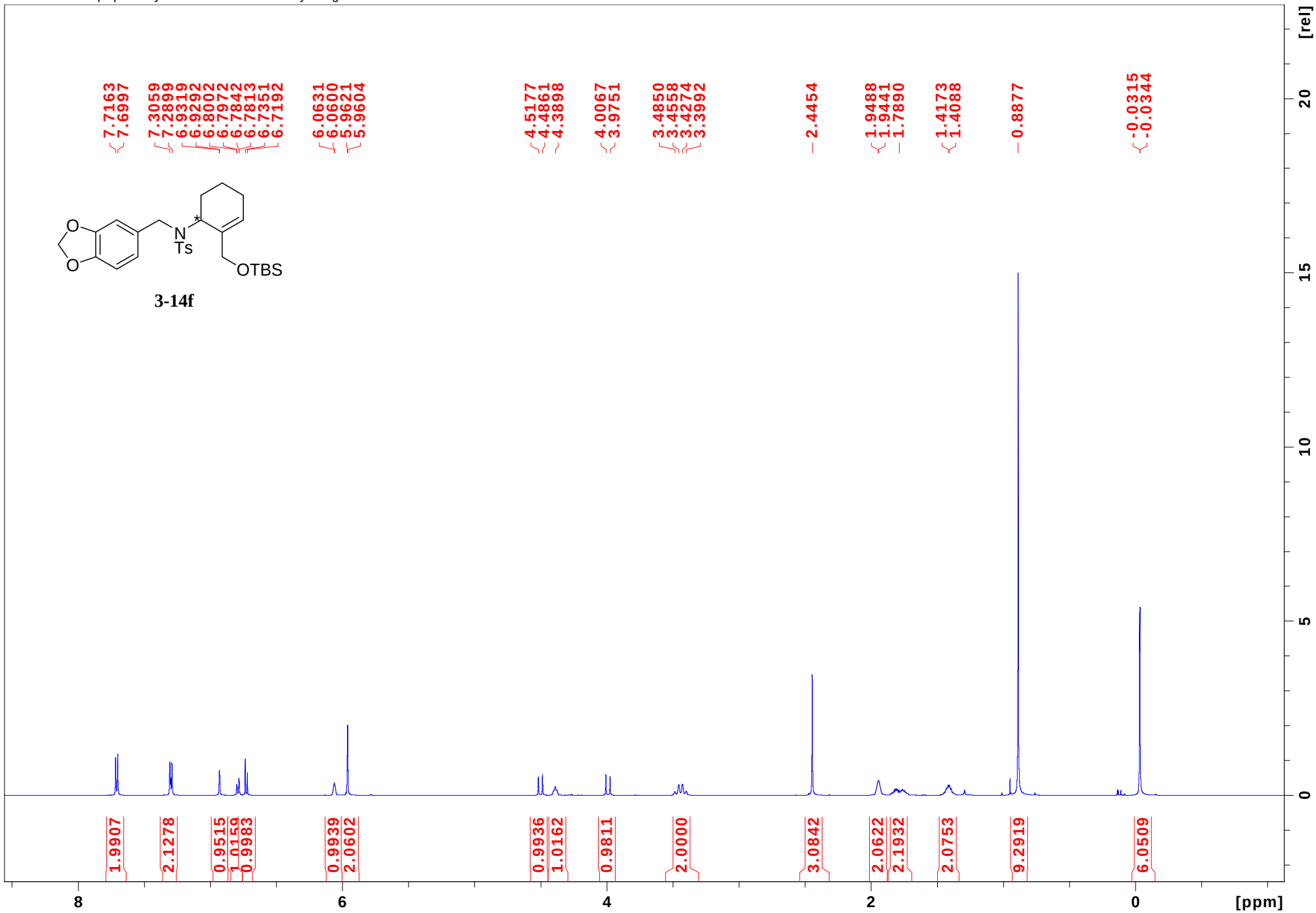
3-14c

E-11C 1 1 /home/yzang/data



3-14c

Crinine-Ts-piperonyl-H 1 1 /home/yzang/data



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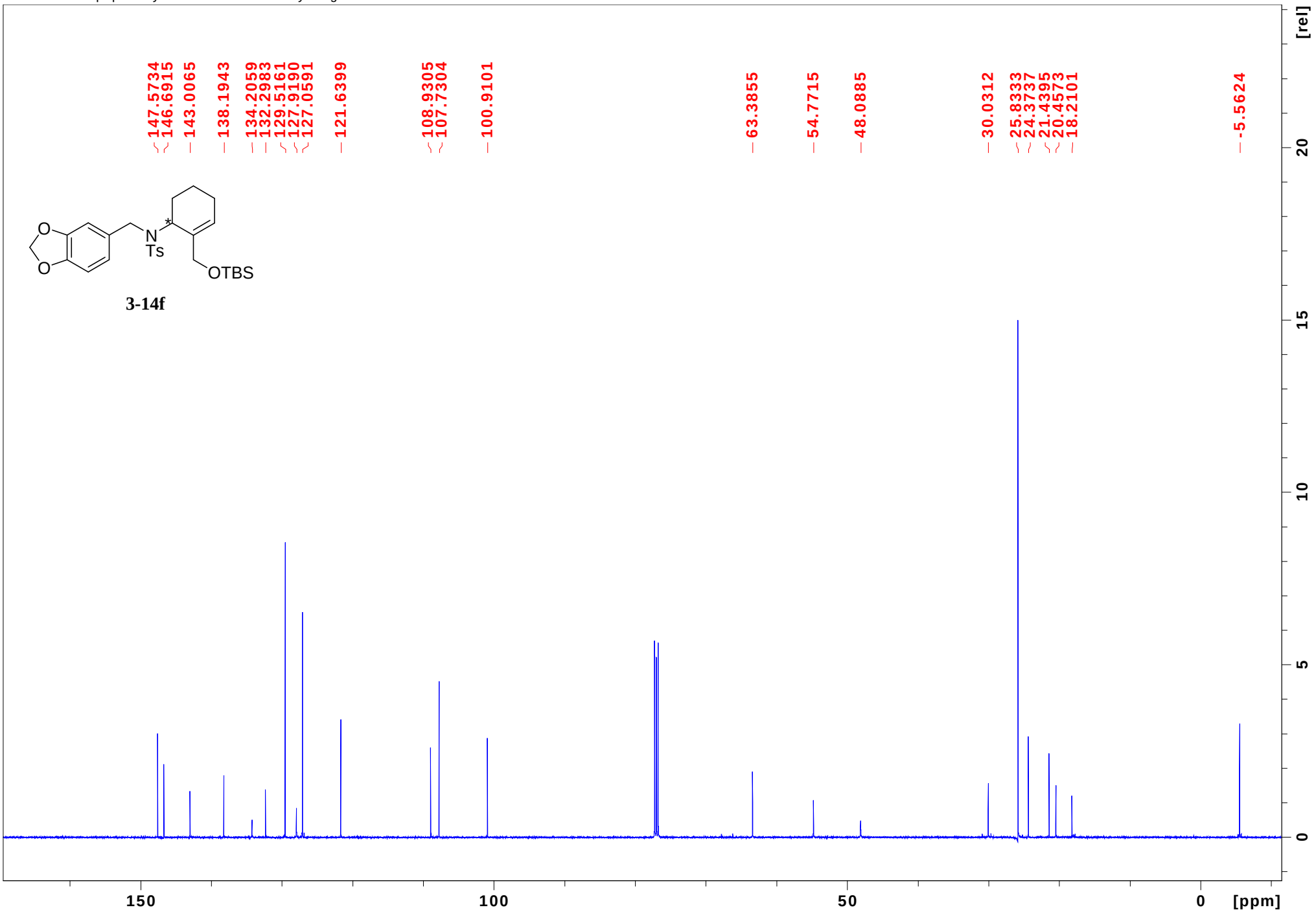
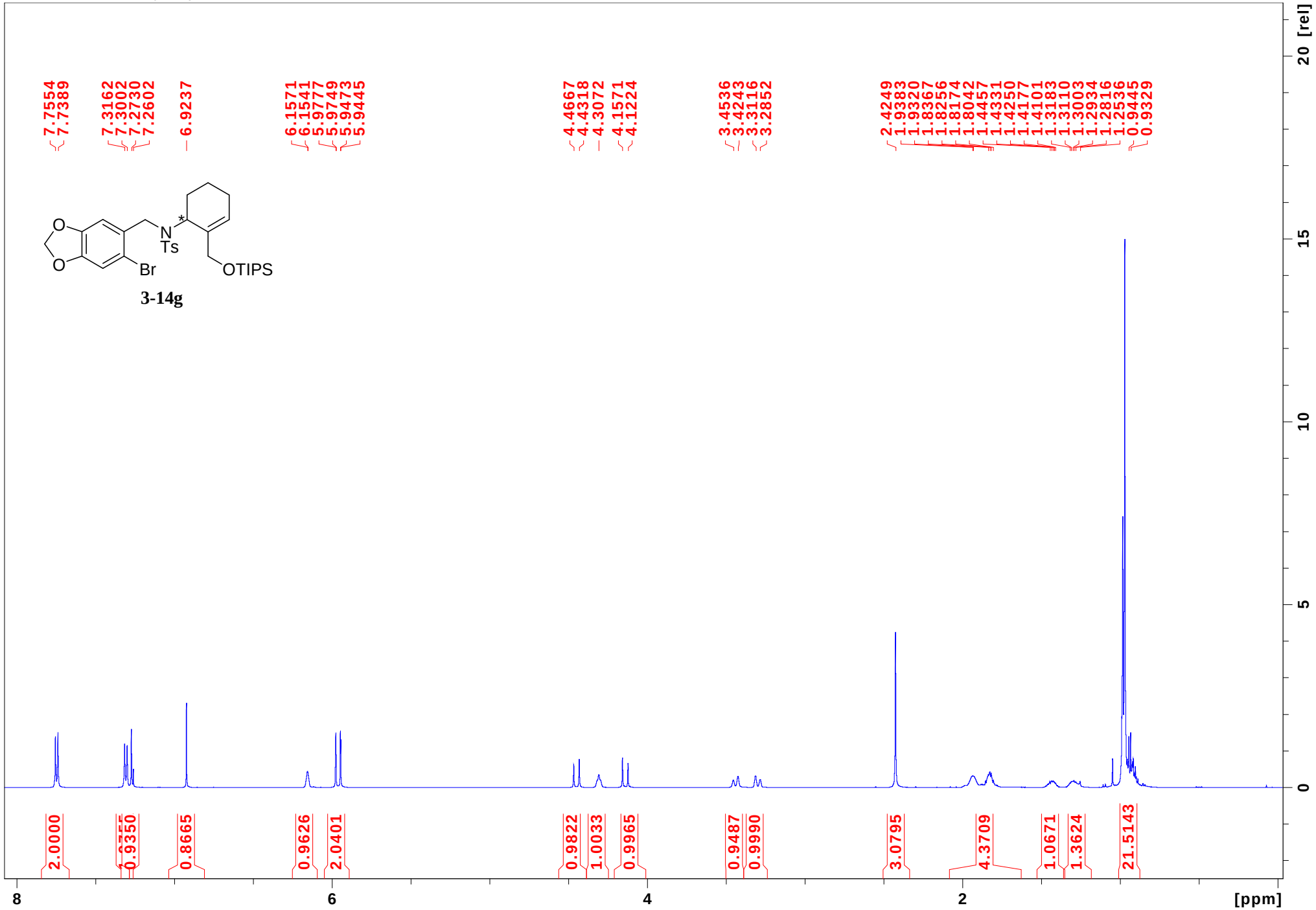


3-14f

E-29 1 1 /home/yzang/data



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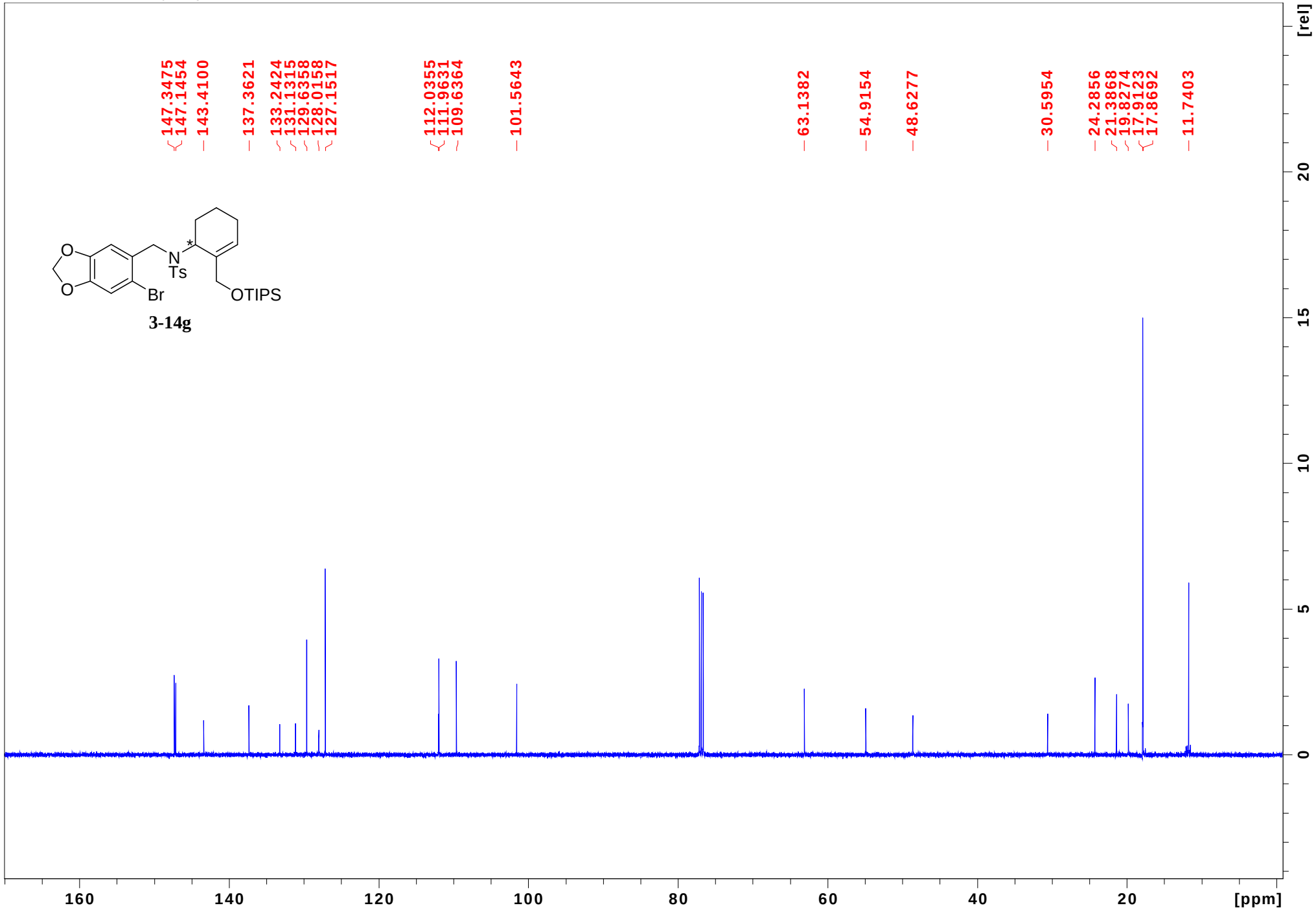

3-14g

D-19 1 1 /home/yzang/data

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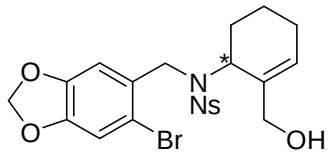
7.6723
7.6639
7.5826
7.5739
7.5692
7.5625
7.5532
7.5502
6.9342
6.9002
6.0541
5.9056
5.9025
5.8755
5.8723
4.7924
4.7734
4.7493
4.3074
4.2643
3.9107
3.8784
3.7640
3.7318
2.0107
2.0044
1.9922
1.7628
1.7412
1.5510



3-15b

1.0000
2.0071
1.0295
0.9228
1.0113
2.0138
1.9984
1.0122
1.0120
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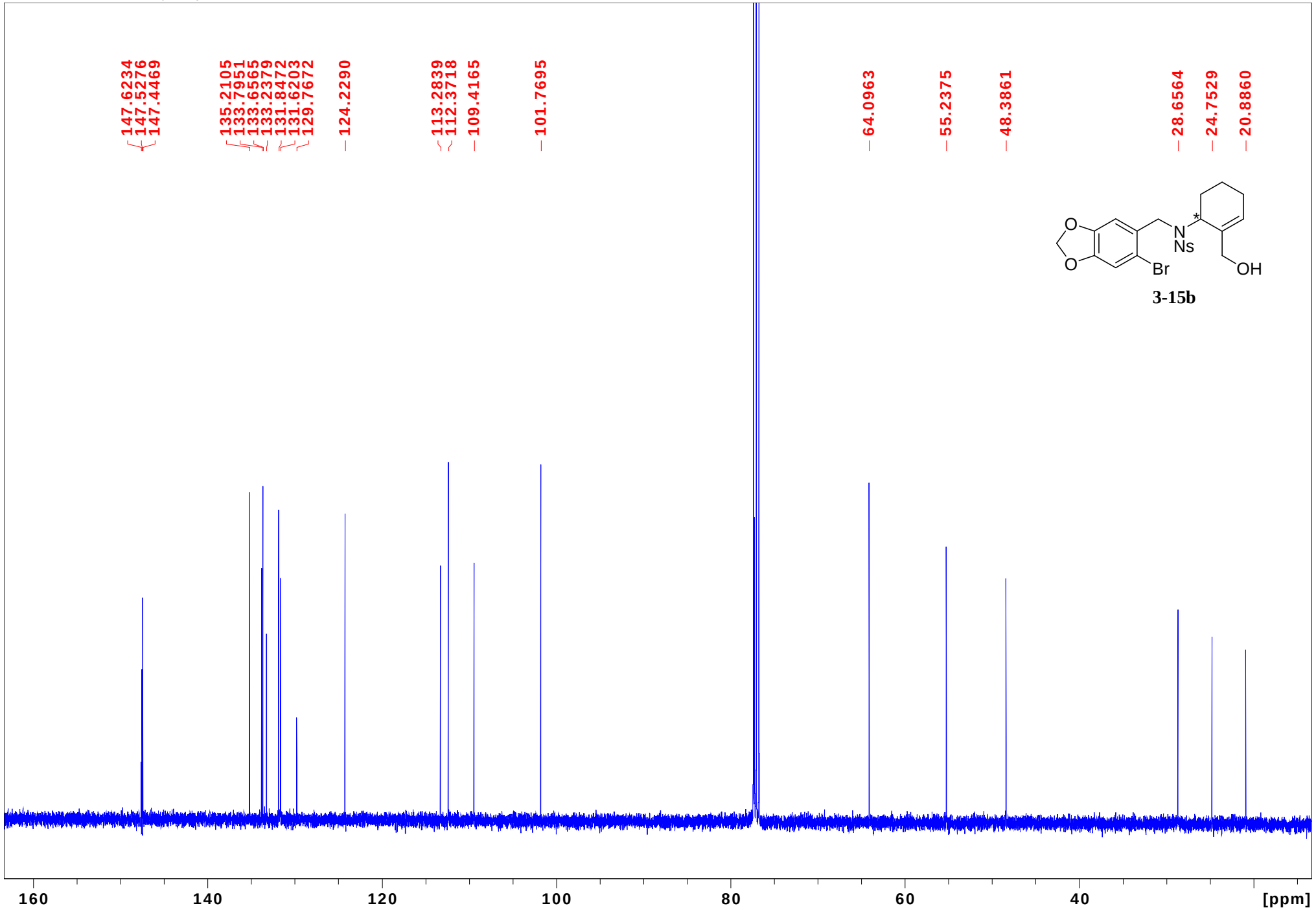
1.2987
2.2935

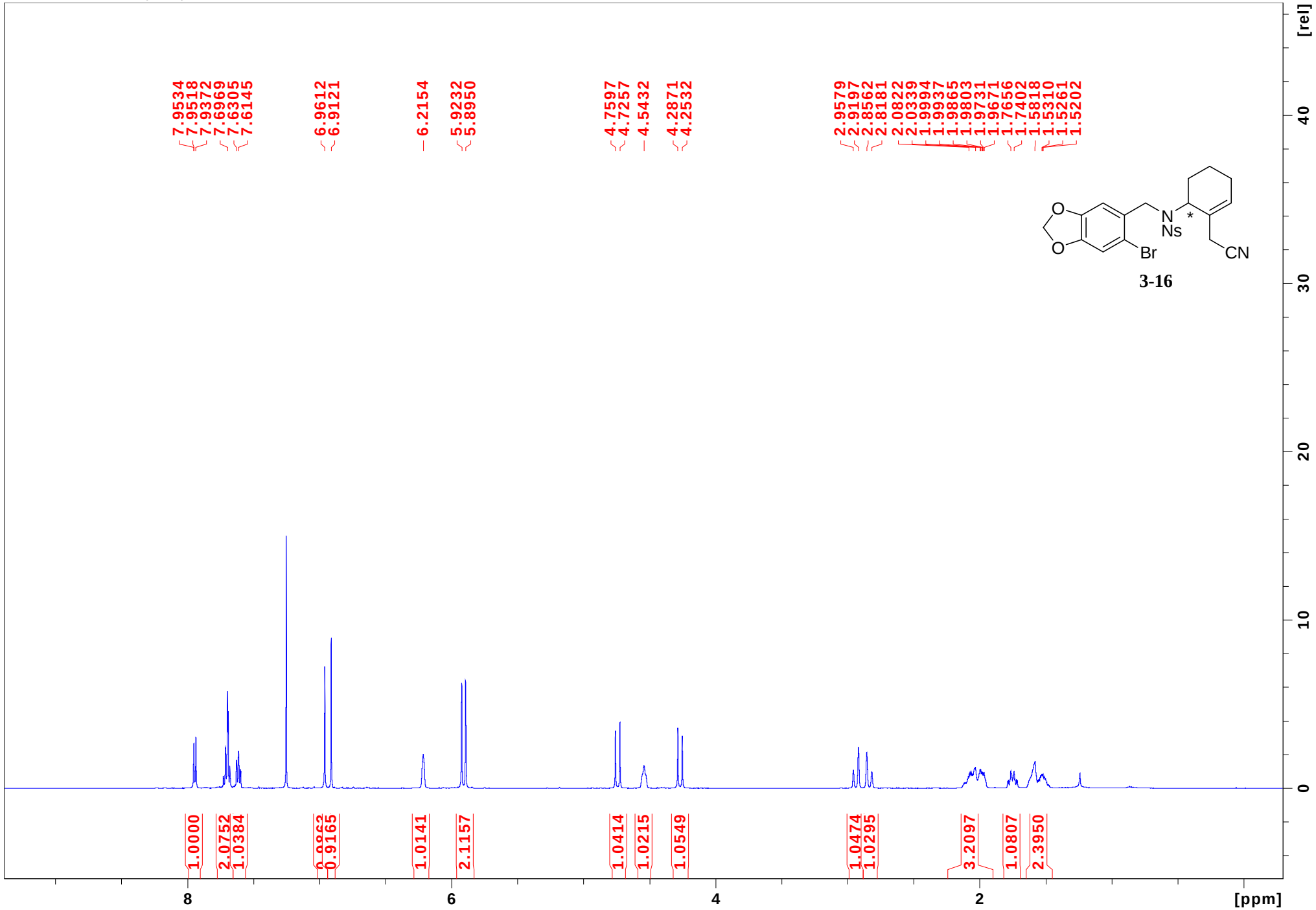
8
6
4
2
0
[ppm]

D-19C 1 1 /home/yzang/data



3-15b

D-3 1 1 /home/yzang/data



3-16

D-3C1 1 1 /home/yzang/data

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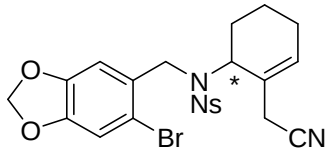
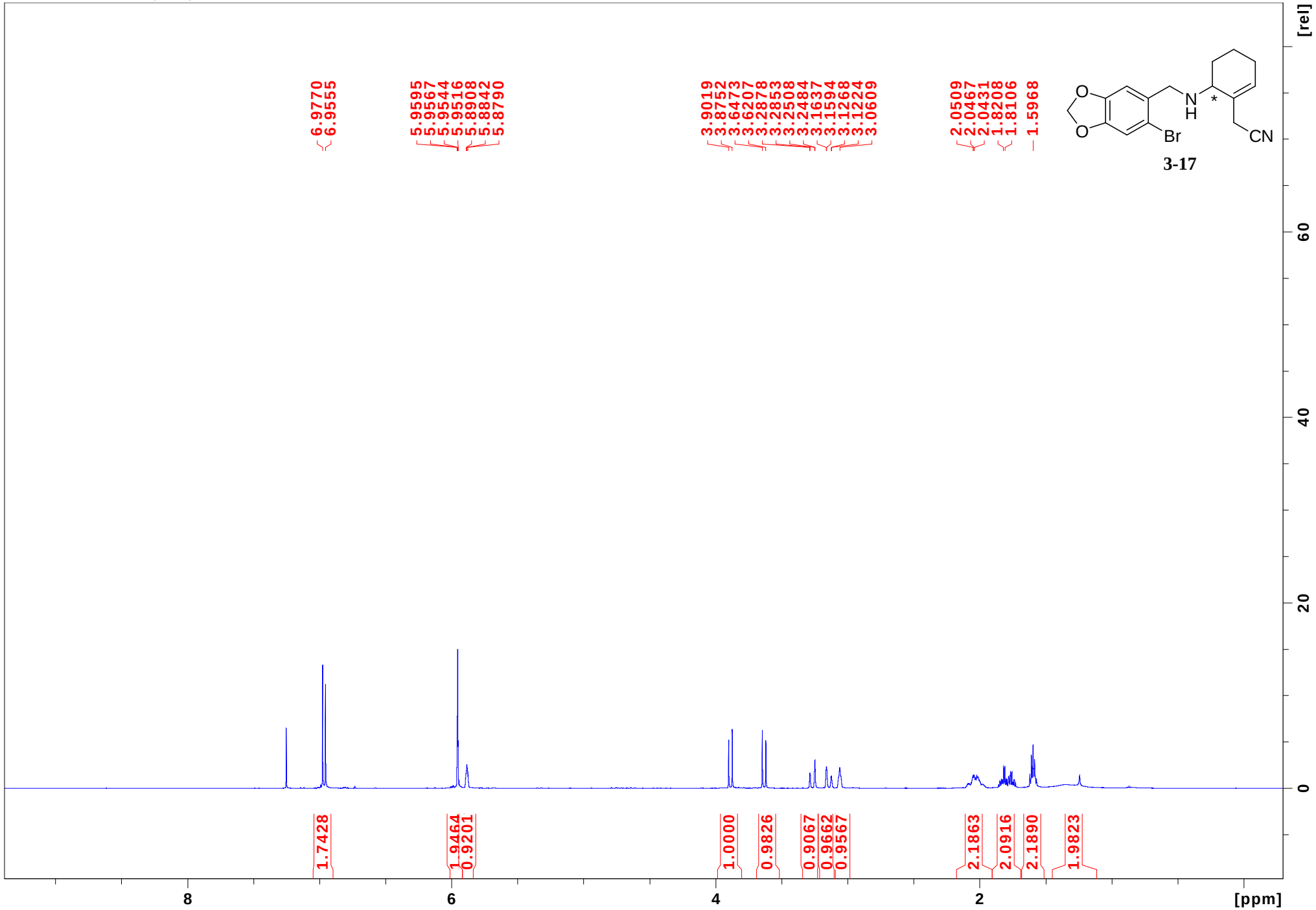
147.6712
147.5654
134.4785
134.0726
133.5086
132.0412
131.8540
129.1312
125.5303
124.4773
117.2435
113.5366
112.5546
109.3380
101.9228
57.0664
48.1548
28.4529
24.9057
21.9932
20.7875



3-16

[rel]
8
6
4
2
0
140
120
100
80
60
40
20
[ppm]

E-27 1 1 /home/yzang/data



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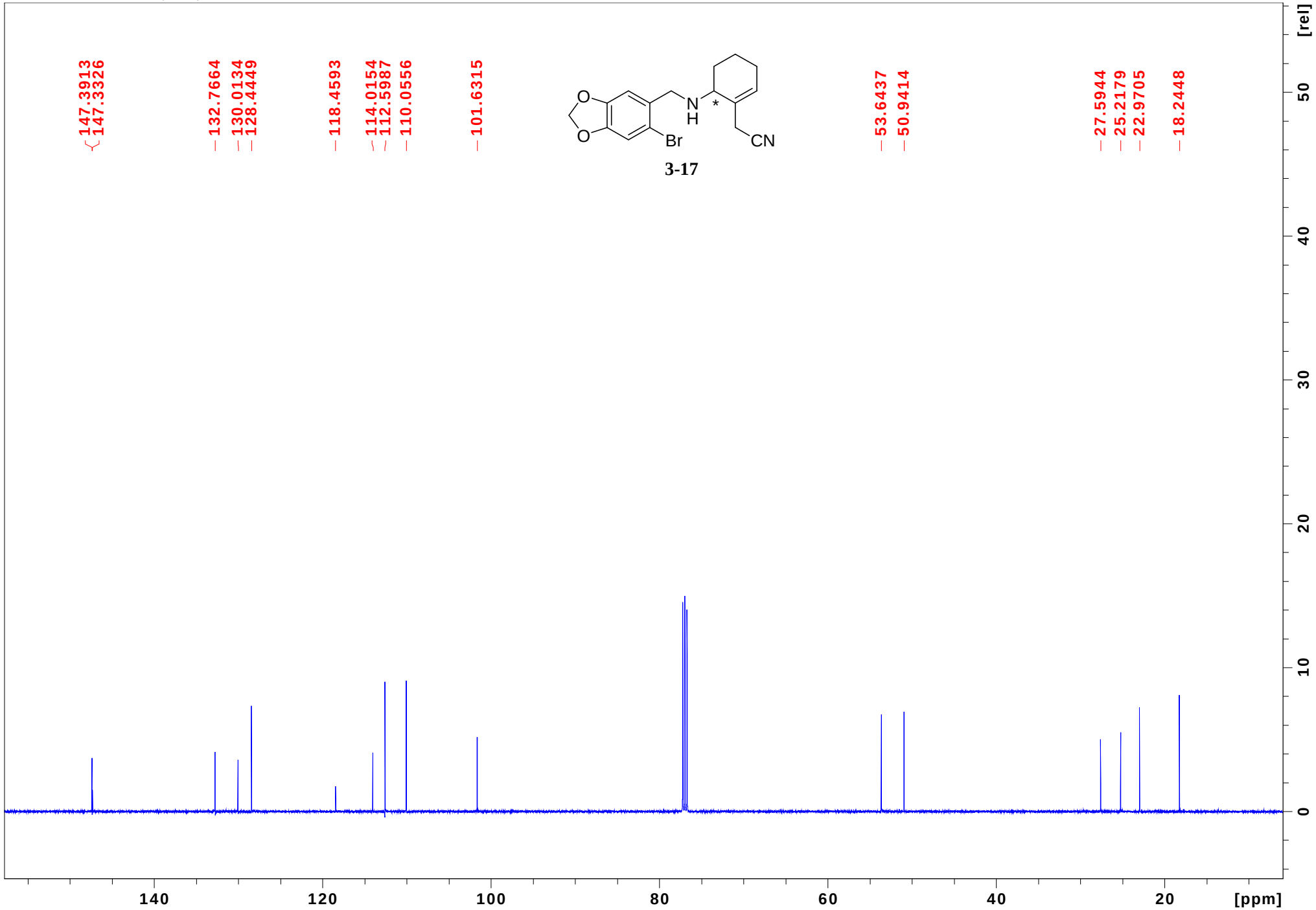

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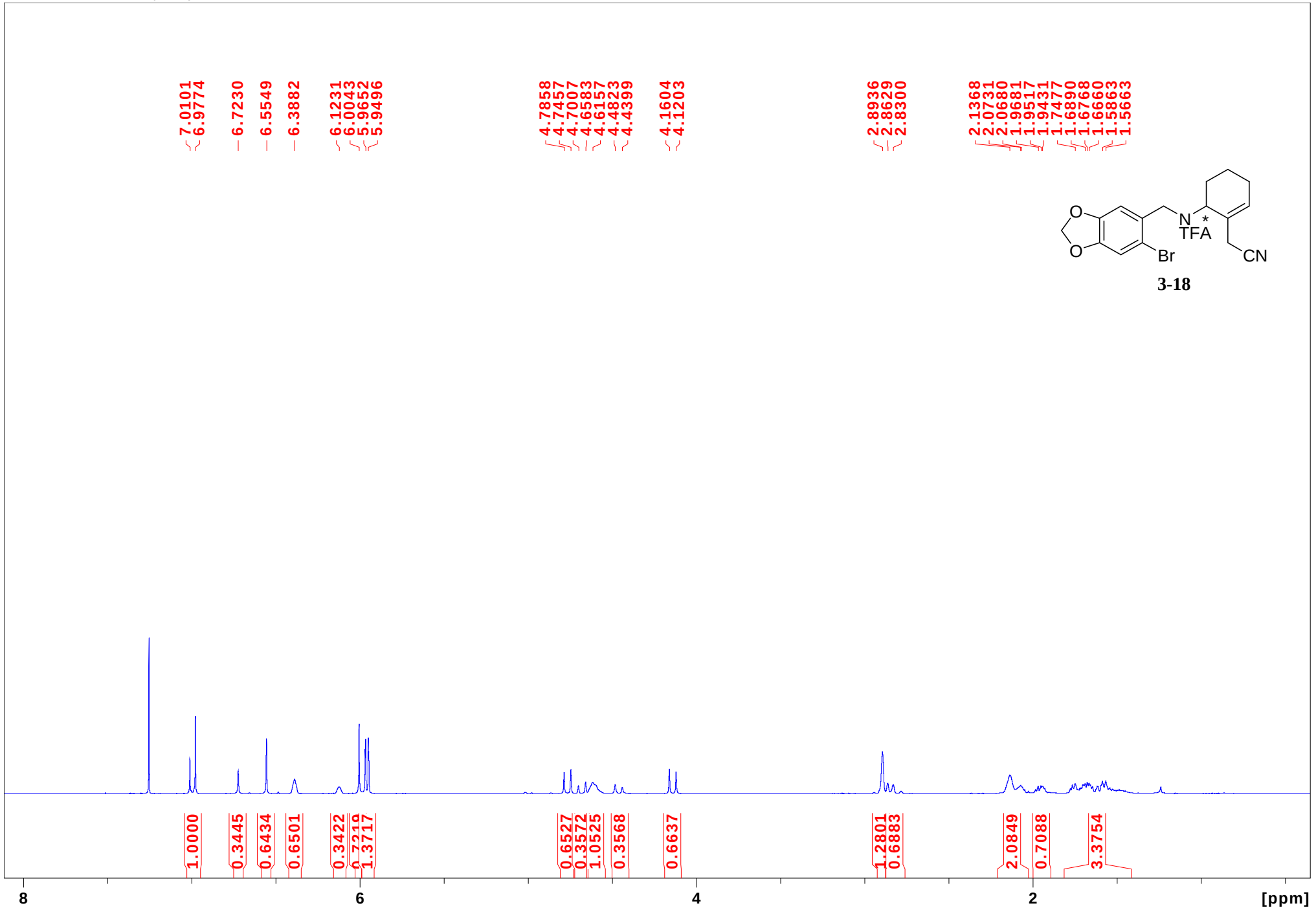

3-18

D-4C 1 1 /home/yzang/data

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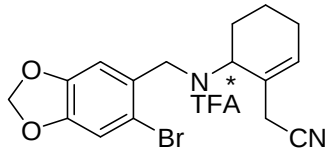
147.8926
147.8188
147.6589
135.1445
132.4726
127.9586
127.5719
125.0239
124.2651
120.7990
117.9386
117.4842
116.9049
116.4348
115.0774
114.6106
113.4691
112.8960
112.8316
112.7520
108.3068
107.2721
102.1508
101.9011
56.8659
56.8309
49.6198
46.8405
29.0064
26.5483
24.7233
24.6718
21.9404
21.7467
20.8994
20.4057

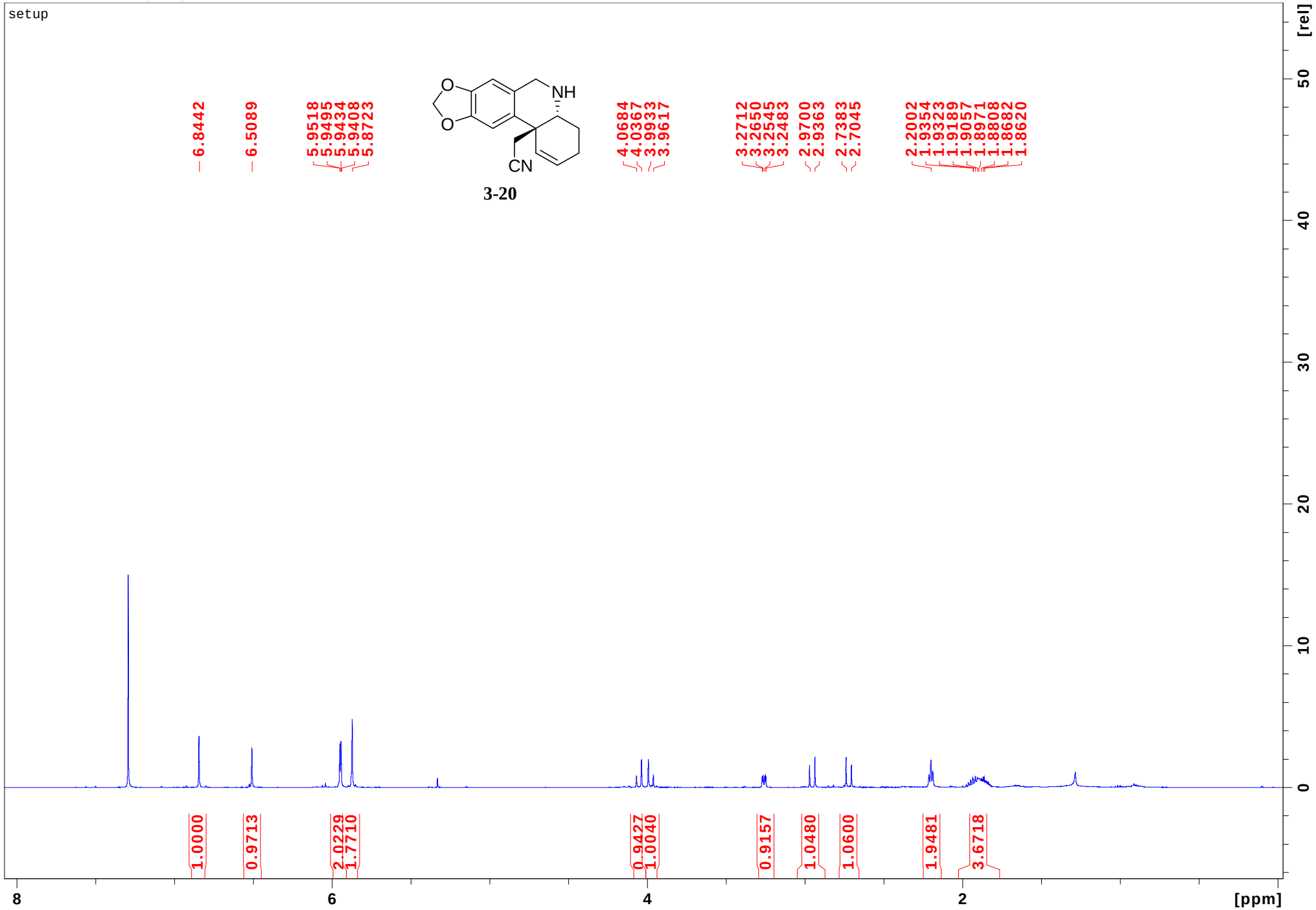


3-18

160 140 120 100 80 60 40 [ppm]

D-5 1 1 /home/yzang/data

setup



3-20

D-1C 1 1 /home/yzang/data

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146.2916
131.3115
130.5968
128.6117
128.0497
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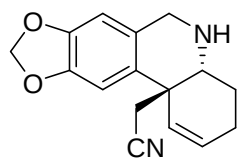
106.1230
100.9422
54.6071
45.7153
39.9705
30.8725
24.5441
22.8515



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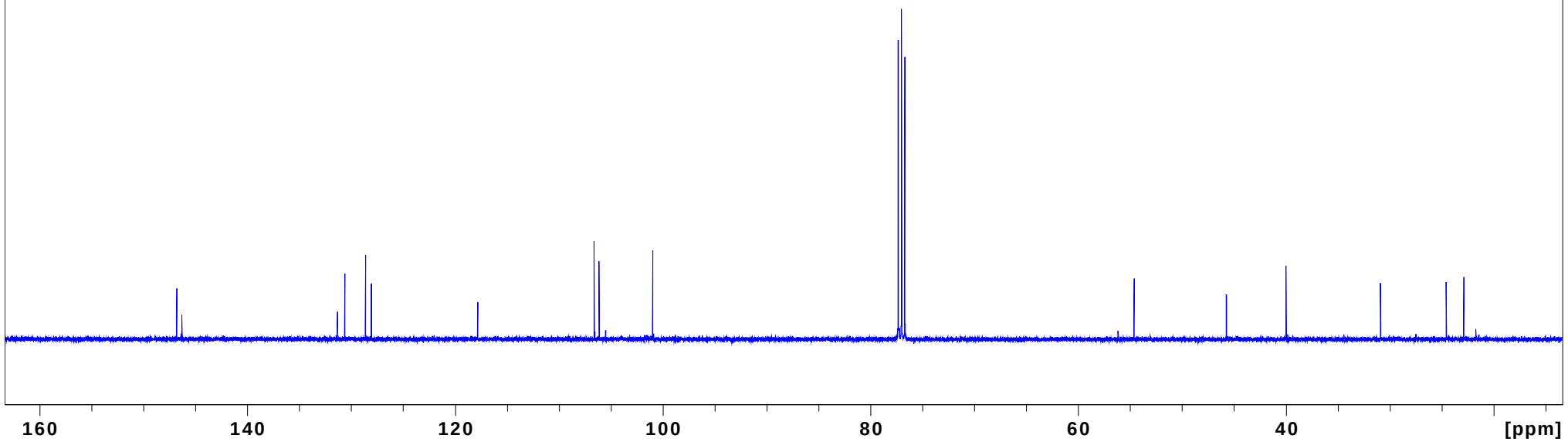

D-112 1 1 /home/yzang/data

3-21

"D-112 C" 1 1 /home/yzang/data

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140.2007
131.7540
118.4008
114.0577
112.2442
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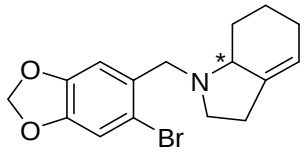
101.4349
64.3670
57.6679
52.2187
28.0497
28.0064
25.0145
20.3614



3-21

[rel]
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25
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15
10
5
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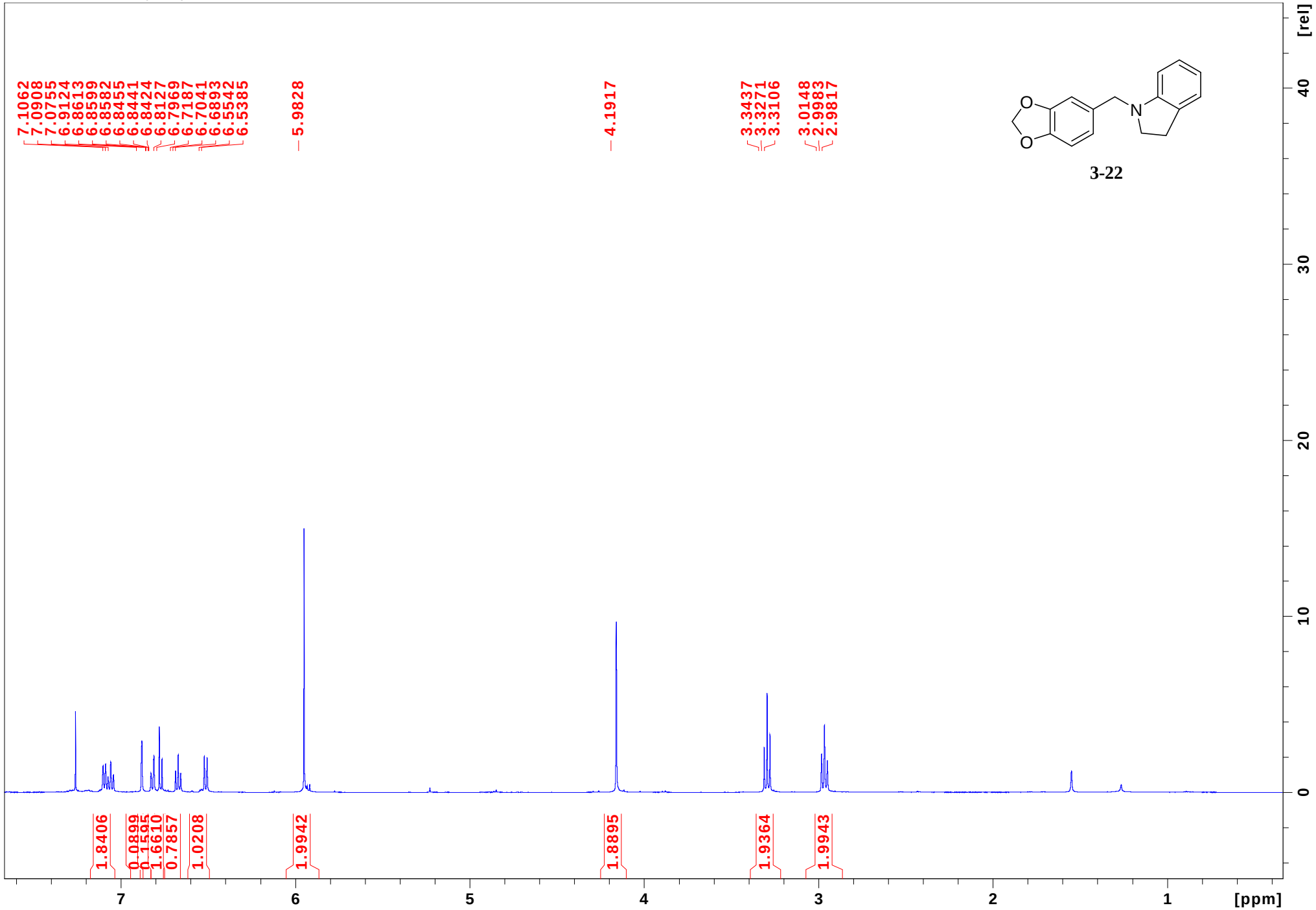
140
120
100
80
60
40
20
[ppm]

111 1 1 /home/yzang/data




111C 1 1 /home/yzang/data
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146.6745
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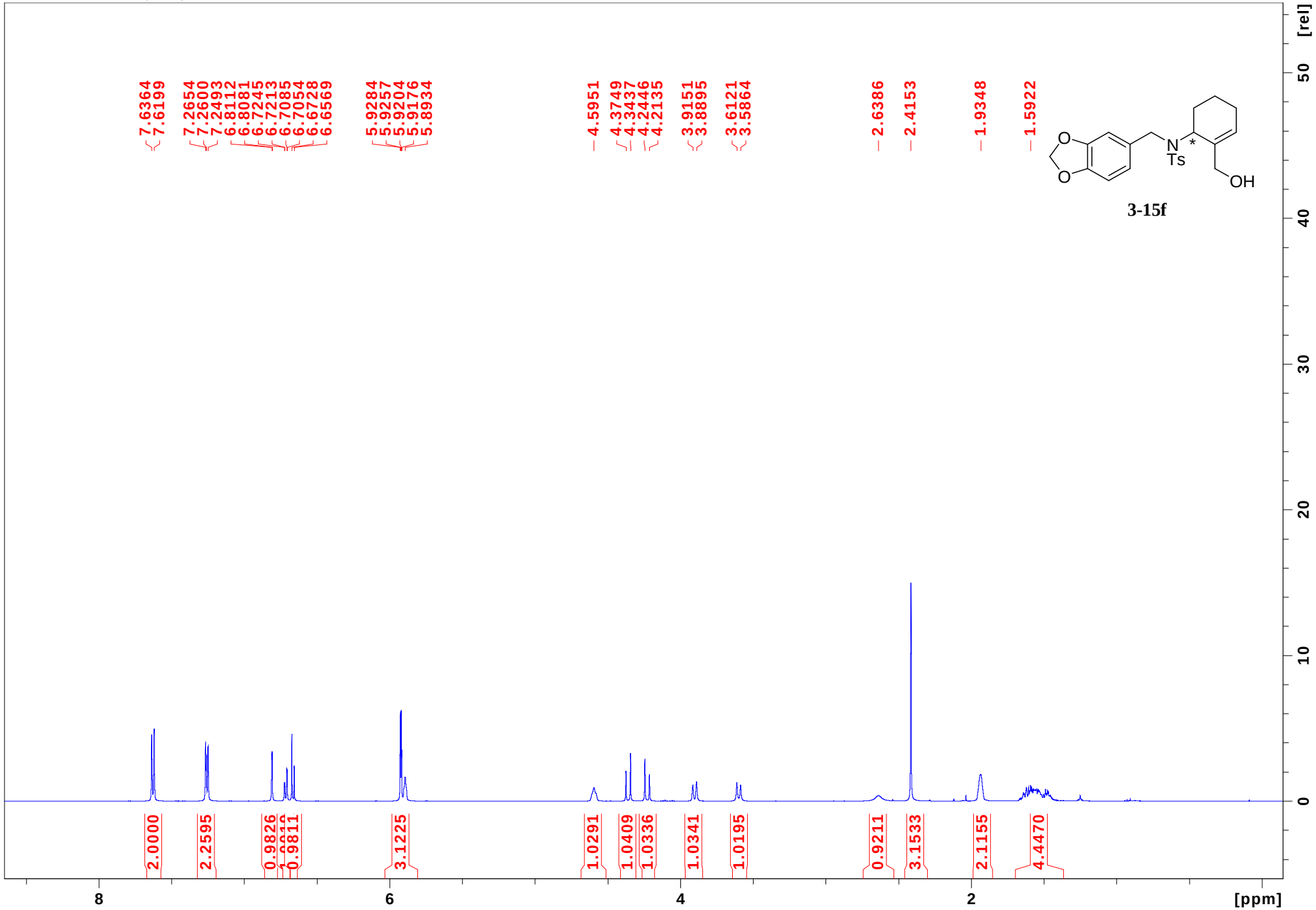
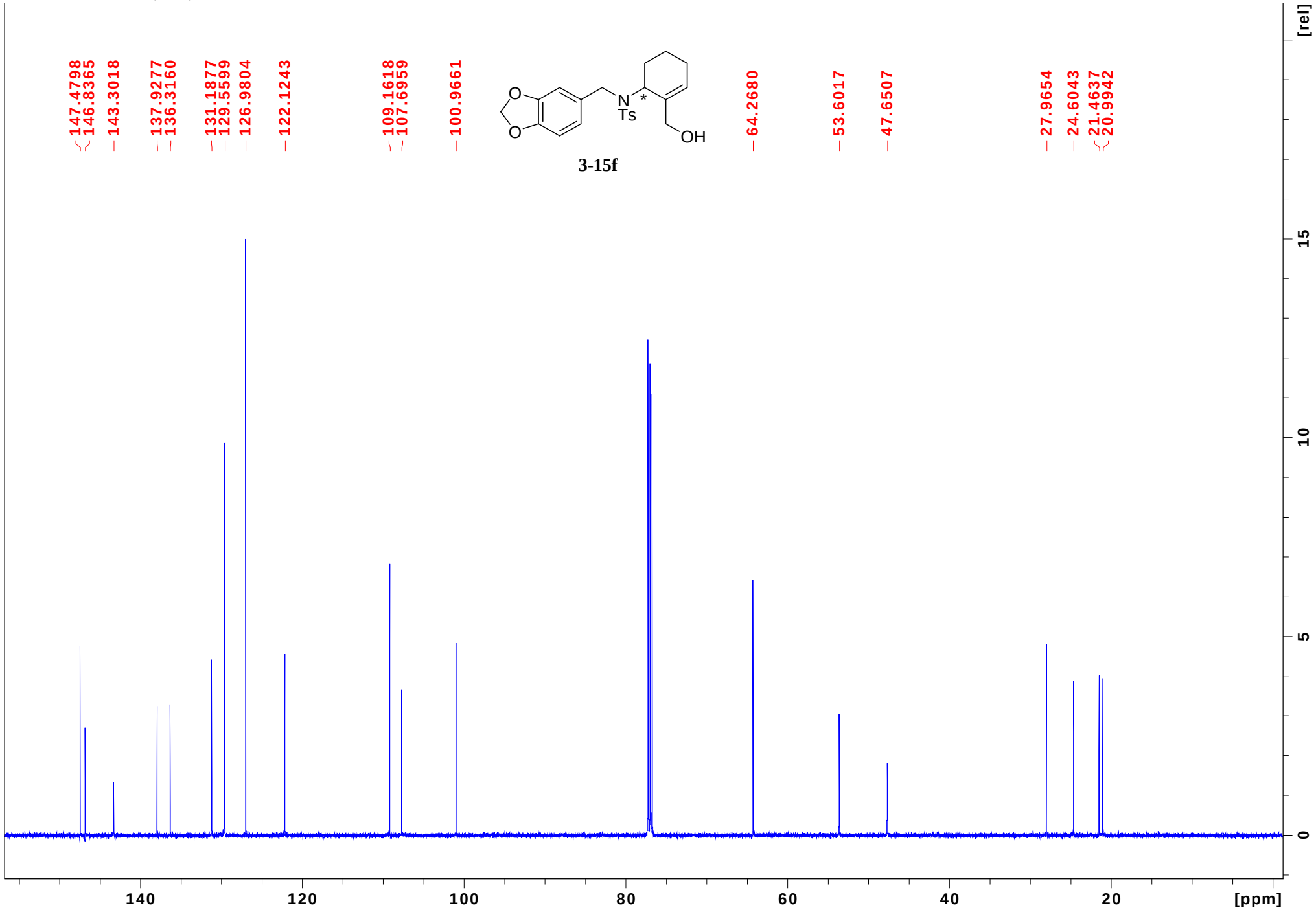
124.5413
120.9868
117.7553
108.4279
108.1379
107.0696
100.9661
53.4938
53.4703
28.5376
O
O
N
3-22
[rel]
0
5
10
15
20
140
120
100
80
60
40
20
[ppm]

E-5 1 1 /home/yzang/data



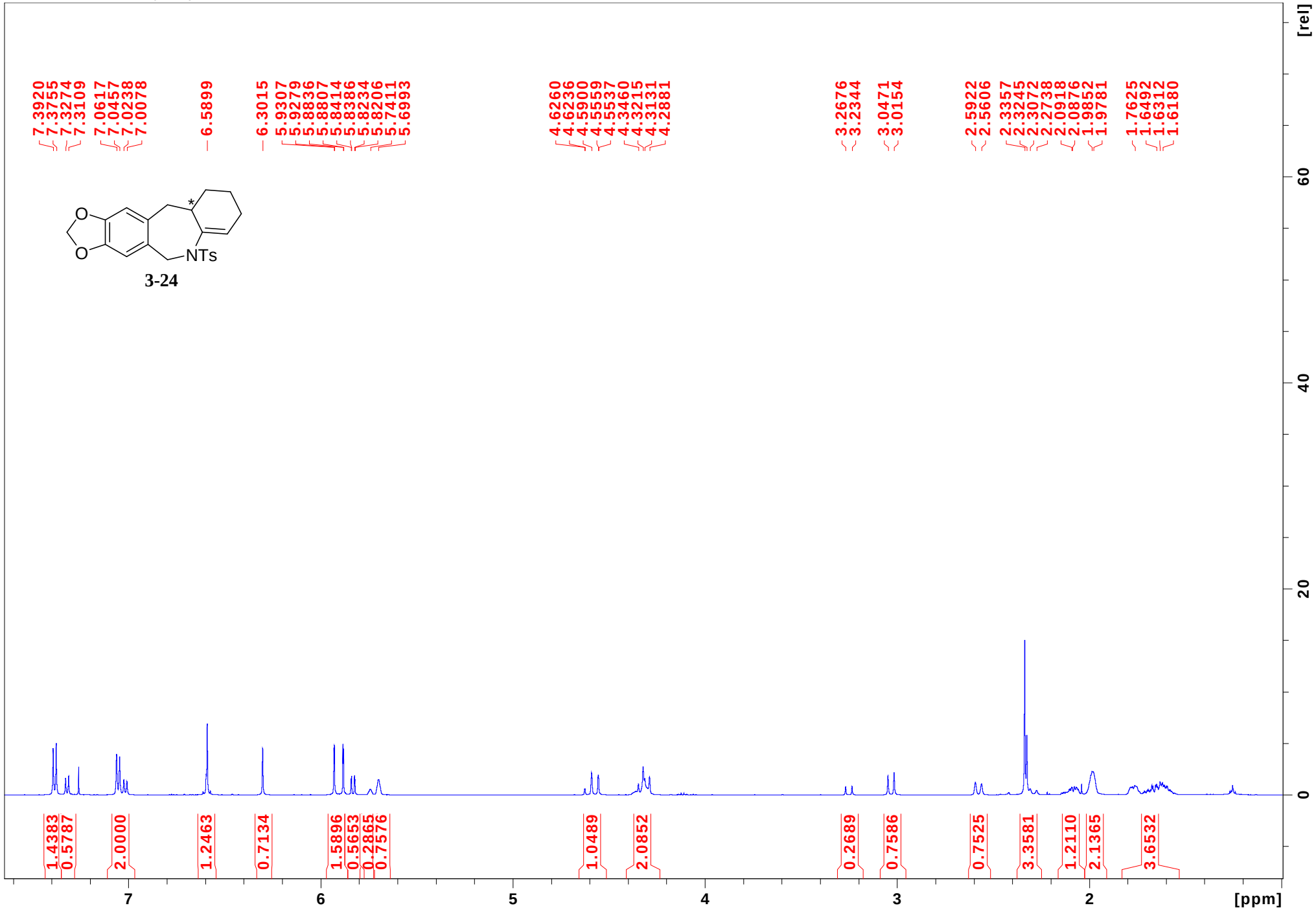
3-15f

E-5C 1 1 /home/yzang/data



3-15f

E-23 1 1 /home/yzang/data



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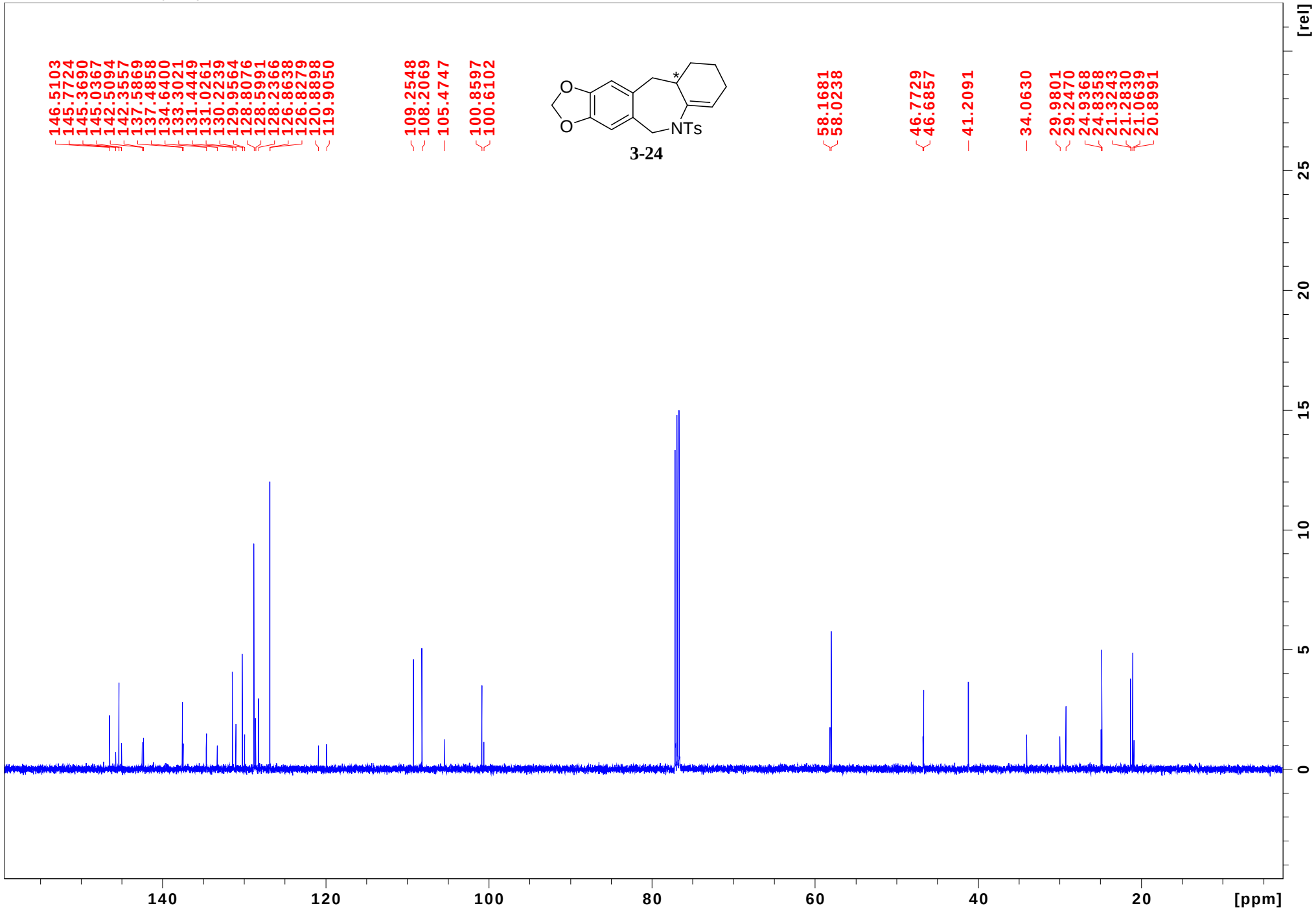

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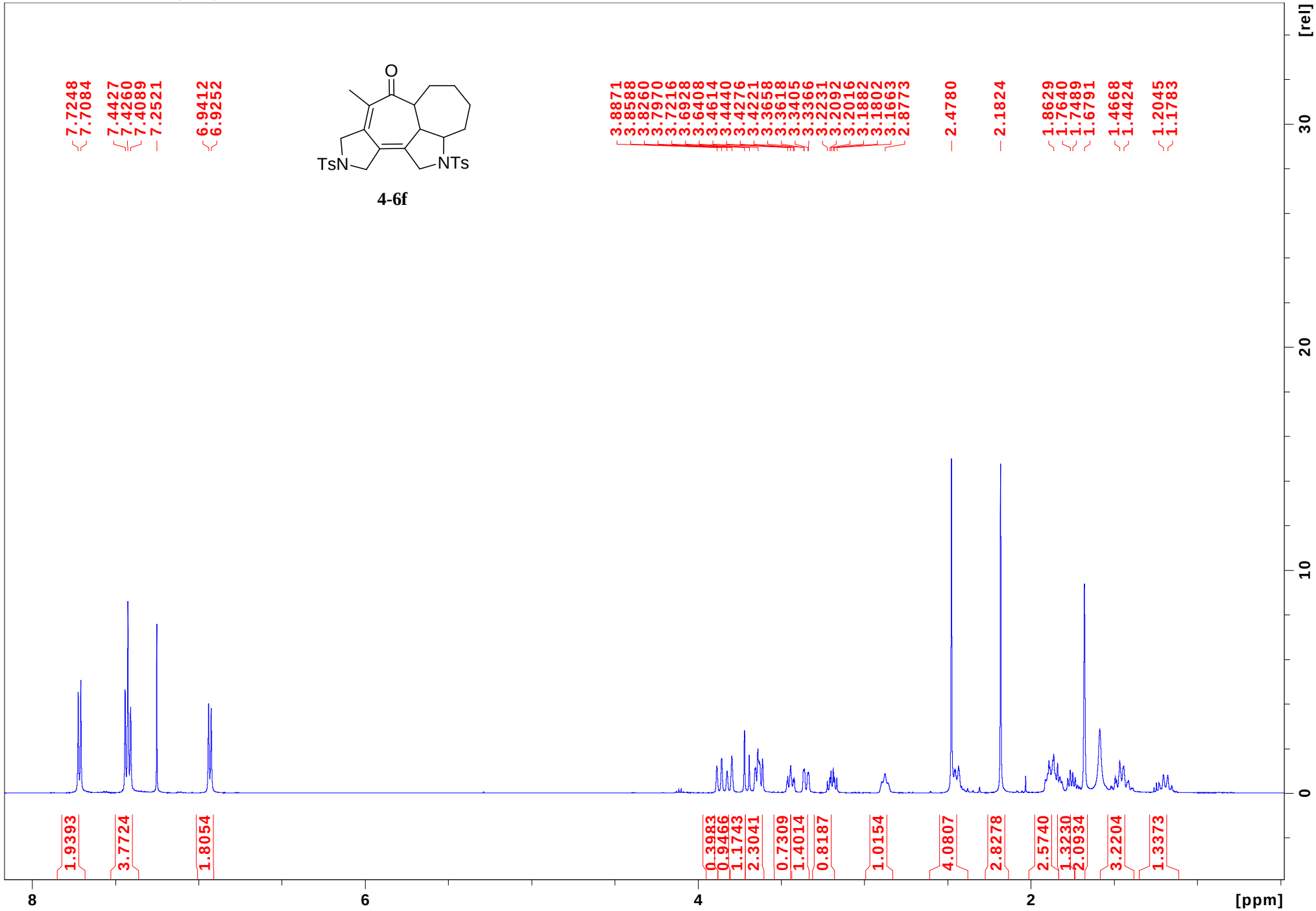
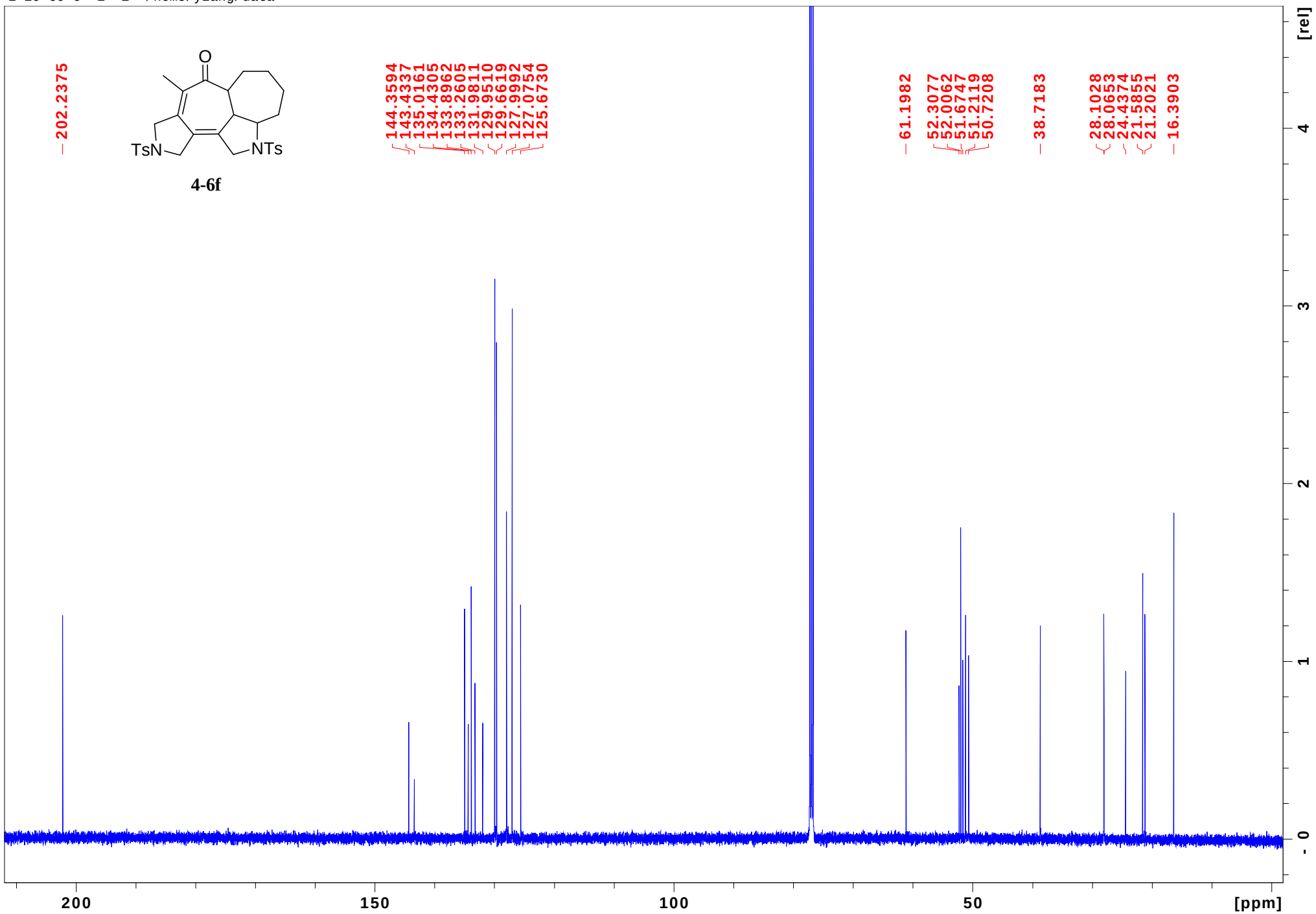


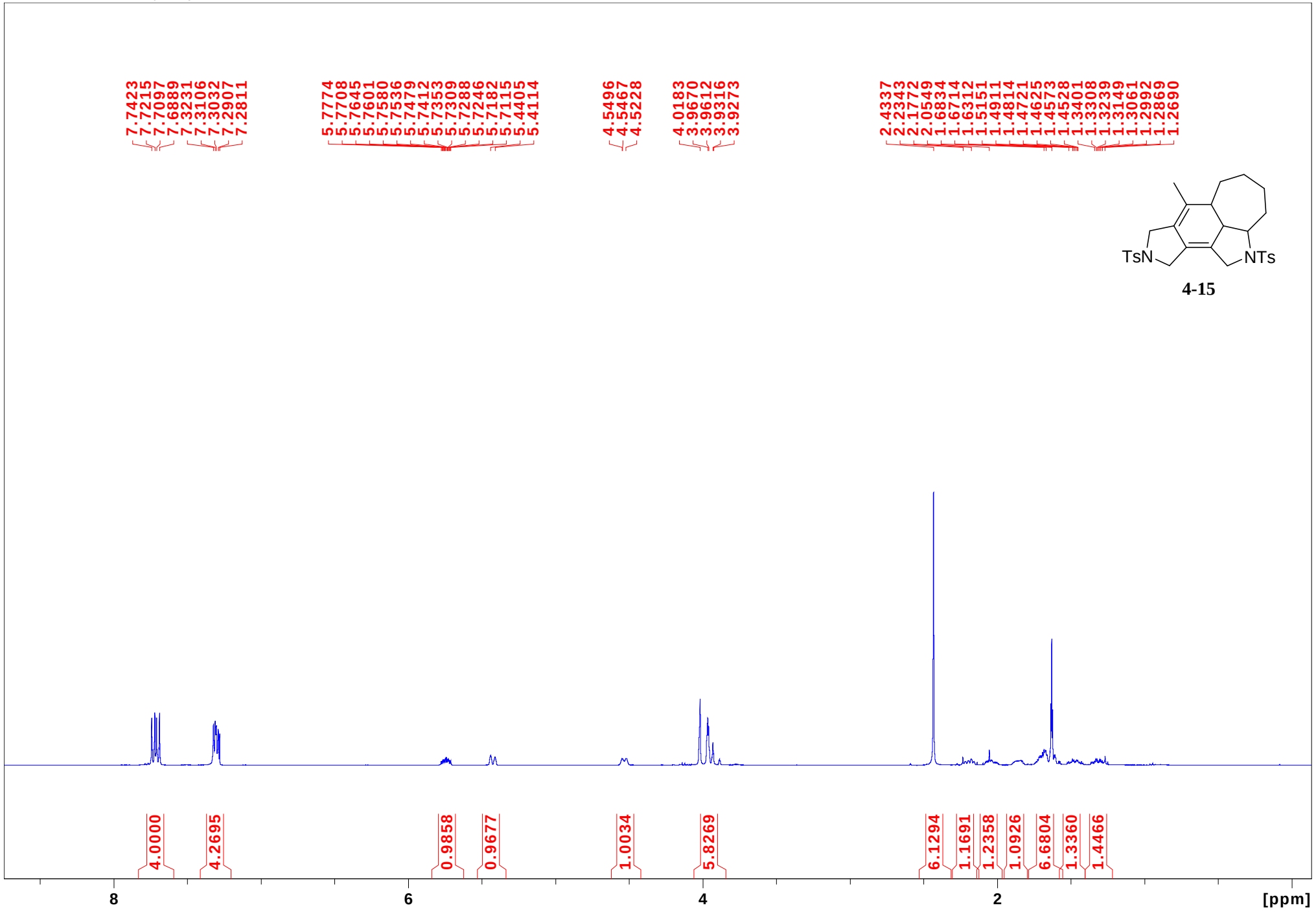
4-6f

E-29-CO-C 1 1 /home/yzang/data

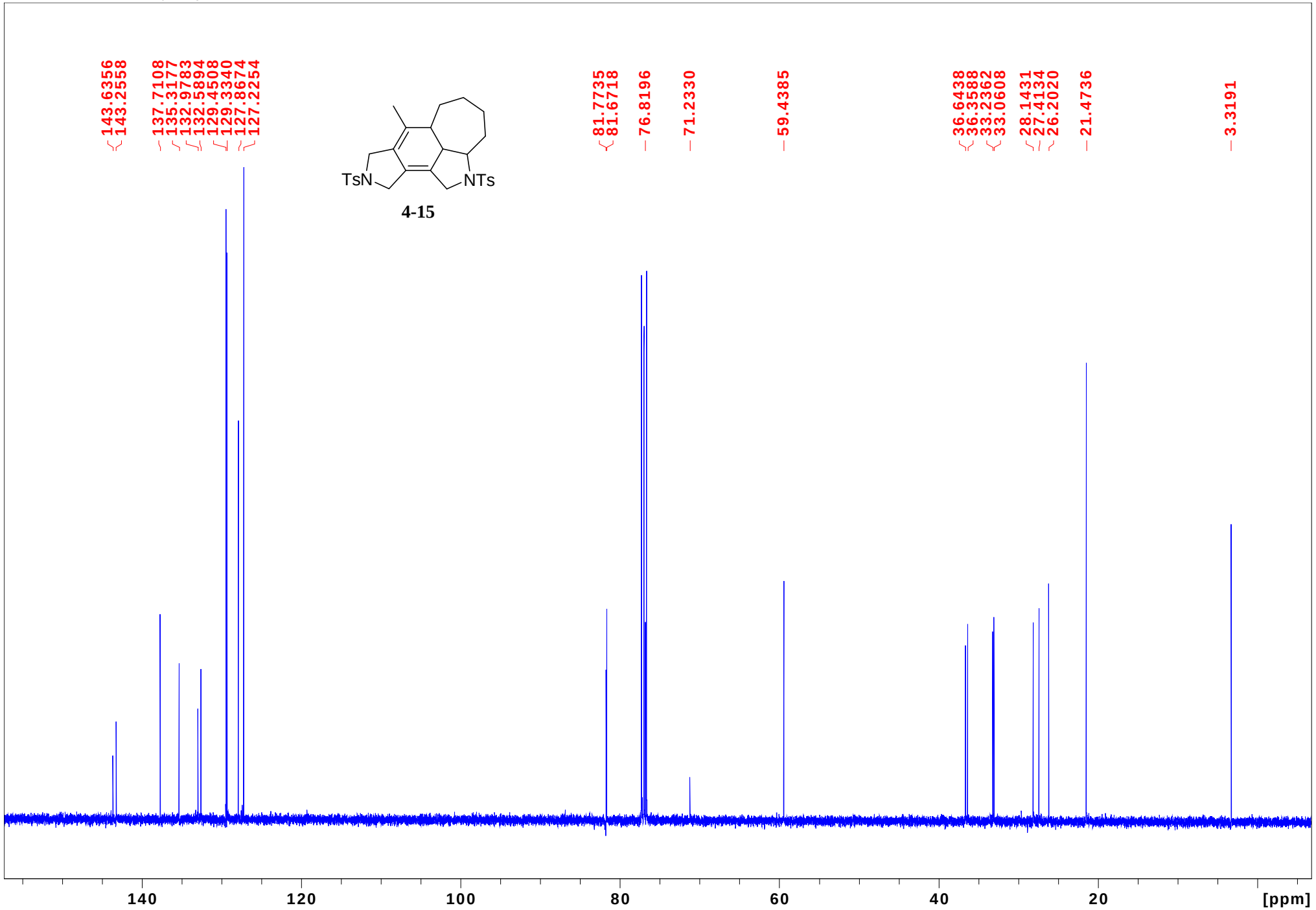


4-6f

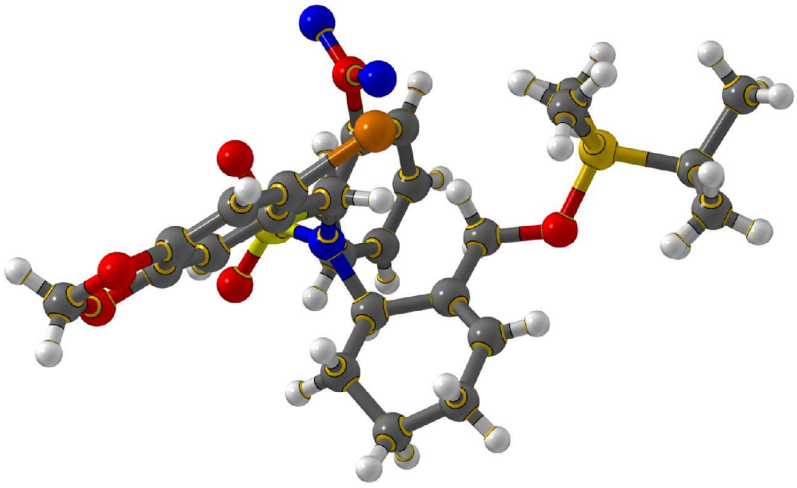
E-31 1 1 /home/yzang/data



E-31C 1 1 /home/yzang/data



Molecular Structure and Crystallography Data for Compound 3-14b



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 'Si'   'Si'     0.2541     0.3302
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'x+1/2, -y+1/2, -z'
'-x, y+1/2, -z+1/2'

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_cell_length_c 9.3304(8)
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_cell_angle_beta 90.00
_cell_angle_gamma 90.00
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_diffrn_radiation_source 'fine-focus sealed tube'
_diffrn_radiation_monochromator graphite
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_diffrn_reflns_av_R_equivalents 0.0729
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Refinement of F^2^ against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2^, conventional R-factors R are based on F, with F set to zero for negative F^2^. The threshold expression of F^2^ > 2\s(F^2^) is used only for calculating R-factors(gt) etc. and is

not relevant to the choice of reflections for refinement. R-factors based on F^2^ are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

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S5 S -0.67257(8) -0.48415(14) -0.5935(2) 0.0651(5) Uani 1 1 d . . .
O18 O -0.7250(2) -0.4379(4) -0.5440(8) 0.0811(18) Uani 1 1 d . . .
O17 O -0.6773(3) -0.5447(5) -0.7087(8) 0.094(2) Uani 1 1 d . . .
N3 N -0.6213(3) -0.4129(4) -0.6385(6) 0.0573(15) Uani 1 1 d . . .
O21 O -0.4513(2) -0.3929(5) -0.4185(9) 0.093(2) Uani 1 1 d . . .
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C18 C -0.6451(3) -0.5402(5) -0.4395(9) 0.0601(18) Uani 1 1 d . . .
O3 O -0.7044(4) -0.2488(6) -1.2319(8) 0.107(3) Uani 1 1 d . . .
C24 C -0.6193(4) -0.3741(5) -0.8985(9) 0.0632(18) Uani 1 1 d . . .
C6 C -0.6106(3) -0.3355(5) -0.5363(9) 0.0582(17) Uani 1 1 d . . .
H6 H -0.6307 -0.3493 -0.4454 0.070 Uiso 1 1 calc R . .
C27 C -0.6713(5) -0.2902(6) -1.1329(10) 0.080(3) Uani 1 1 d . . .
C25 C -0.6807(4) -0.3558(6) -0.8995(10) 0.073(2) Uani 1 1 d . . .
H25 H -0.7052 -0.3719 -0.8227 0.087 Uiso 1 1 calc R . .
C26 C -0.7046(4) -0.3137(6) -1.0163(10) 0.072(2) Uani 1 1 d . . .
C11 C -0.5438(3) -0.3248(5) -0.5069(9) 0.0609(18) Uani 1 1 d . . .
C21 C -0.6057(4) -0.6134(6) -0.4485(12) 0.077(2) Uani 1 1 d . . .
C20 C -0.6658(3) -0.5150(6) -0.3092(10) 0.067(2) Uani 1 1 d . . .
H20 H -0.6943 -0.4698 -0.3039 0.080 Uiso 1 1 calc R . .
C19 C -0.6459(4) -0.5542(7) -0.1836(12) 0.085(3) Uani 1 1 d . . .
H19 H -0.6607 -0.5351 -0.0956 0.102 Uiso 1 1 calc R . .
C28 C -0.6095(4) -0.3090(7) -1.1402(10) 0.078(3) Uani 1 1 d . . .
H28 H -0.5859 -0.2946 -1.2194 0.094 Uiso 1 1 calc R . .
C30 C -0.5162(4) -0.2512(6) -0.5216(12) 0.087(3) Uani 1 1 d . . .
H30 H -0.4746 -0.2506 -0.5078 0.104 Uiso 1 1 calc R . .
C22 C -0.5880(5) -0.6532(7) -0.3197(16) 0.099(4) Uani 1 1 d . . .
H22 H -0.5638 -0.7037 -0.3226 0.119 Uiso 1 1 calc R . .
C2 C -0.7648(5) -0.2534(8) -1.1813(13) 0.100(4) Uani 1 1 d . . .
H2A H -0.7887 -0.2915 -1.2430 0.120 Uiso 1 1 calc R . .
H2B H -0.7829 -0.1949 -1.1809 0.120 Uiso 1 1 calc R . .
C23 C -0.6054(5) -0.6197(9) -0.1894(14) 0.096(3) Uani 1 1 d . . .
H23 H -0.5891 -0.6426 -0.1053 0.115 Uiso 1 1 calc R . .
C5 C -0.5463(5) -0.1662(7) -0.5596(17) 0.112(4) Uani 1 1 d . . .
H5A H -0.5342 -0.1209 -0.4918 0.134 Uiso 1 1 calc R . .
H5B H -0.5331 -0.1477 -0.6542 0.134 Uiso 1 1 calc R . .
C1 C -0.5129(3) -0.4093(7) -0.4536(12) 0.083(3) Uani 1 1 d . . .
H1A H -0.5339 -0.4313 -0.3695 0.099 Uiso 1 1 calc R . .
H1B H -0.5151 -0.4545 -0.5273 0.099 Uiso 1 1 calc R . .
C8 C -0.6378(5) -0.2505(7) -0.5941(15) 0.100(3) Uani 1 1 d . . .
H8A H -0.6383 -0.2545 -0.6978 0.120 Uiso 1 1 calc R . .
H8B H -0.6796 -0.2477 -0.5624 0.120 Uiso 1 1 calc R . .
C29 C -0.5857(4) -0.3514(6) -1.0186(10) 0.077(2) Uani 1 1 d . . .
Si1 Si -0.39788(13) -0.4640(3) -0.4560(6) 0.1281(15) Uani 1 1 d . . .

C31 C -0.5887(4) -0.4182(7) -0.7746(10) 0.077(2) Uani 1 1 d . . .
H31A H -0.5826 -0.4802 -0.7981 0.092 Uiso 1 1 calc R . .
H31B H -0.5491 -0.3916 -0.7621 0.092 Uiso 1 1 calc R . .
C35 C -0.3294(5) -0.4227(12) -0.372(2) 0.146(6) Uani 1 1 d . . .
C36 C -0.6112(6) -0.1742(10) -0.559(4) 0.240(17) Uani 1 1 d . . .
H36A H -0.6248 -0.1591 -0.4627 0.288 Uiso 1 1 calc R . .
H36B H -0.6270 -0.1290 -0.6223 0.288 Uiso 1 1 calc R . .
C33 C -0.3893(9) -0.460(3) -0.660(2) 0.31(2) Uani 1 1 d . . .
H33A H -0.4133 -0.5062 -0.7022 0.465 Uiso 1 1 calc R . .
H33B H -0.3476 -0.4689 -0.6847 0.465 Uiso 1 1 calc R . .
H33C H -0.4026 -0.4037 -0.6946 0.465 Uiso 1 1 calc R . .
C34 C -0.4191(8) -0.5739(10) -0.386(4) 0.27(2) Uani 1 1 d . . .
H34A H -0.4323 -0.5683 -0.2885 0.409 Uiso 1 1 calc R . .
H34B H -0.3847 -0.6127 -0.3903 0.409 Uiso 1 1 calc R . .
H34C H -0.4513 -0.5980 -0.4430 0.409 Uiso 1 1 calc R . .
O22 O -0.5982(4) -0.7238(5) -0.6153(14) 0.136(4) Uani 1 1 d . . .
N4 N -0.5834(4) -0.6490(6) -0.5810(12) 0.093(3) Uani 1 1 d . . .
C37 C -0.3161(8) -0.3273(14) -0.441(3) 0.243(14) Uani 1 1 d . . .
H37A H -0.2884 -0.3337 -0.5200 0.364 Uiso 1 1 calc R . .
H37B H -0.2986 -0.2893 -0.3701 0.364 Uiso 1 1 calc R . .
H37C H -0.3532 -0.3019 -0.4752 0.364 Uiso 1 1 calc R . .
O23 O -0.5492(5) -0.6027(7) -0.6502(12) 0.131(3) Uani 1 1 d . . .
C38 C -0.2779(8) -0.4916(17) -0.395(3) 0.268(16) Uani 1 1 d . . .
H38A H -0.2670 -0.5172 -0.3045 0.401 Uiso 1 1 calc R . .
H38B H -0.2434 -0.4627 -0.4361 0.401 Uiso 1 1 calc R . .
H38C H -0.2917 -0.5374 -0.4586 0.401 Uiso 1 1 calc R . .
C7 C -0.3434(9) -0.423(3) -0.214(2) 0.27(2) Uani 1 1 d . . .
H7A H -0.3826 -0.3977 -0.1985 0.402 Uiso 1 1 calc R . .
H7B H -0.3135 -0.3892 -0.1641 0.402 Uiso 1 1 calc R . .
H7C H -0.3430 -0.4831 -0.1796 0.402 Uiso 1 1 calc R . .

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S5 0.0399(8) 0.0849(11) 0.0706(11) 0.0072(11) -0.0088(9) -0.0089(8)
O18 0.031(2) 0.100(4) 0.112(5) 0.032(4) -0.004(3) 0.004(2)
O17 0.088(4) 0.108(5) 0.087(4) -0.003(4) -0.043(4) -0.022(4)
N3 0.044(3) 0.086(4) 0.042(3) -0.003(3) -0.002(3) -0.013(3)

O21 0.038(2) 0.118(5) 0.124(6) -0.002(5) -0.012(3) 0.006(3)
O1 0.068(4) 0.140(6) 0.083(4) 0.030(5) -0.010(4) -0.011(4)
C18 0.038(3) 0.078(4) 0.064(5) 0.007(4) 0.000(3) -0.006(3)
O3 0.099(5) 0.151(7) 0.072(4) 0.043(5) -0.018(4) -0.028(5)
C24 0.062(4) 0.074(4) 0.054(4) -0.009(4) -0.001(4) -0.019(4)
C6 0.042(3) 0.076(4) 0.057(4) -0.005(4) -0.003(3) -0.001(3)
C27 0.090(6) 0.087(5) 0.063(5) 0.011(5) -0.016(5) -0.037(5)
C25 0.057(4) 0.102(6) 0.059(4) 0.008(5) -0.003(4) -0.009(4)
C26 0.063(5) 0.094(6) 0.060(5) -0.001(5) -0.004(4) -0.017(4)
C11 0.042(3) 0.081(4) 0.059(4) 0.000(4) 0.000(3) -0.006(3)
C21 0.058(4) 0.067(4) 0.106(7) -0.001(5) 0.001(5) -0.004(4)
C20 0.044(4) 0.081(5) 0.076(5) 0.006(5) -0.002(4) -0.013(4)
C19 0.056(4) 0.108(7) 0.091(7) 0.027(6) 0.000(5) -0.015(5)
C28 0.079(6) 0.098(6) 0.058(5) -0.004(5) 0.002(5) -0.030(5)
C30 0.058(4) 0.091(6) 0.111(8) 0.008(6) 0.006(5) -0.011(4)
C22 0.068(5) 0.080(6) 0.150(11) 0.039(7) -0.018(7) 0.003(5)
C2 0.096(7) 0.109(7) 0.097(8) 0.032(7) -0.049(7) -0.017(6)
C23 0.074(6) 0.122(8) 0.093(7) 0.027(8) -0.004(6) 0.002(6)
C5 0.090(7) 0.096(7) 0.150(12) 0.004(8) 0.021(8) -0.021(6)
C1 0.042(4) 0.106(6) 0.100(7) 0.012(6) -0.019(4) 0.001(4)
C8 0.087(7) 0.088(6) 0.126(9) -0.015(7) -0.038(7) 0.008(5)
C29 0.071(5) 0.088(5) 0.071(5) -0.012(5) -0.005(5) -0.031(4)
Si1 0.0560(14) 0.136(3) 0.192(4) -0.029(3) 0.001(2) 0.0135(15)
C31 0.049(4) 0.111(6) 0.069(5) -0.018(5) 0.005(4) -0.003(4)
C35 0.061(6) 0.193(14) 0.183(16) 0.061(13) 0.009(8) 0.034(8)
C36 0.081(8) 0.127(11) 0.51(5) 0.12(2) -0.016(17) -0.006(8)
C33 0.115(14) 0.65(7) 0.168(18) -0.19(3) 0.037(13) 0.03(2)
C34 0.112(11) 0.120(10) 0.59(6) 0.14(2) -0.03(2) 0.021(9)
O22 0.114(6) 0.095(5) 0.198(10) -0.046(6) -0.012(7) 0.018(4)
N4 0.076(5) 0.089(5) 0.115(7) -0.018(6) 0.005(6) 0.020(4)
C37 0.103(11) 0.199(18) 0.43(4) 0.02(3) 0.00(2) -0.064(12)
O23 0.124(7) 0.124(6) 0.144(8) -0.036(6) 0.050(7) 0.008(6)
C38 0.106(12) 0.29(3) 0.41(4) 0.01(3) 0.07(2) 0.115(16)
C7 0.129(14) 0.55(6) 0.122(13) 0.08(2) -0.033(12) 0.09(3)

_geom_special_details

All s.u.'s (except the s.u. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell s.u.'s are taken into account individually in the estimation of s.u.'s in distances, angles and torsion angles; correlations between s.u.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell s.u.'s is used for estimating s.u.'s involving l.s. planes.

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S5 C18 1.774(8) . ?
N3 C31 1.462(10) . ?
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C18 C21 1.410(11) . ?
O3 C27 1.334(11) . ?
O3 C2 1.420(14) . ?
C24 C25 1.387(11) . ?
C24 C29 1.388(13) . ?
C24 C31 1.496(13) . ?
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C6 C8 1.515(13) . ?
C27 C26 1.361(13) . ?
C27 C28 1.398(14) . ?
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C28 C29 1.404(13) . ?
C30 C5 1.488(16) . ?
C22 C23 1.373(17) . ?
C5 C36 1.441(17) . ?
C8 C36 1.33(2) . ?
Si1 C35 1.813(17) . ?
Si1 C34 1.843(17) . ?
Si1 C33 1.91(2) . ?
C35 C7 1.51(3) . ?
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C35 C38 1.56(2) . ?
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O17 S5 O18 120.1(4) . . ?
O17 S5 N3 106.5(4) . . ?
O18 S5 N3 109.1(4) . . ?
O17 S5 C18 109.4(4) . . ?
O18 S5 C18 104.4(4) . . ?
N3 S5 C18 106.7(3) . . ?
C31 N3 C6 120.6(6) . . ?
C31 N3 S5 122.3(6) . . ?
C6 N3 S5 117.0(5) . . ?
C1 O21 Si1 121.9(7) . . ?
C26 O1 C2 105.6(8) . . ?
C20 C18 C21 118.9(8) . . ?
C20 C18 S5 118.5(6) . . ?
C21 C18 S5 122.5(7) . . ?
C27 O3 C2 105.3(7) . . ?
C25 C24 C29 118.0(9) . . ?
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C29 C24 C31 119.5(8) . . ?
C11 C6 C8 111.3(7) . . ?
C11 C6 N3 110.2(6) . . ?
C8 C6 N3 111.4(7) . . ?
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O3 C2 O1 107.7(8) . . ?
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C24 C29 Br1 119.9(7) . . ?
C28 C29 Br1 115.7(7) . . ?
O21 Si1 C35 106.7(6) . . ?
O21 Si1 C34 109.4(8) . . ?
C35 Si1 C34 111.7(10) . . ?
O21 Si1 C33 105.4(10) . . ?
C35 Si1 C33 109.5(10) . . ?
C34 Si1 C33 113.8(17) . . ?
N3 C31 C24 115.0(7) . . ?
C7 C35 C38 106.2(18) . . ?
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C38 C35 Si1 108.9(16) . . ?
C37 C35 Si1 106.9(12) . . ?
C8 C36 C5 120.7(16) . . ?
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O23 N4 C21 117.2(9) . . ?
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