Stony Brook University

(I) Synthesis and Application of Chiral Biphenol-Based Phosphorus Ligands to Catalytic Asymmetric Synthesis; (II) Rhodium-Catalyzed Cycloaddition Reactions for Rapid Construction of Polycyclic Skeletons of Biological Interest

A Dissertation Presented

by

Chih-Wei Chien

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Abstract of the Dissertation

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Chiral ligand design is crucial for the asymmetric transformations. In our laboratory, libraries of fine-tunable phosphorus ligands based on axially chiral biphenol have been well developed. These ligands exhibit excellent enantioselectivity in various transition-metal catalyzed asymmetric reactions. We present here the application of the monodentate phosphoramidite (MPN) ligand library to the Pd-catalyzed intramolecular asymmetric allylic amination (AAA) for the formation of chiral 1-vinyltetrahydroiso-quinoline skeleton, a versatile key intermediate in the synthesis of natural products such as isopyruthaline and (–)-*O*-methylthaicanine. We also studied the Pd-catalyzed inter-molecular AAA reaction using our bidentate diphosphonite (BOP) ligands. The BOP ligands exhibit excellent efficacy in this reaction, which provides a key intermediate for the total synthesis of *Strychnos* indole alkaloids.

The non-benzenoid aromatics, tropones and tropolones, are found in various natural products such as colchicine and hinokitol, which possess significant biological activities. The traditional methods to construct the tropone skeletons include oxidation of cycloheptatriene and [4+3] cycloadditions. In addition, the total synthesis of colchicine and its analogues requires laborious organic transformations in the formation of 6-7-7 fused rings systems. Transition metal-catalyzed carbocyclization and cycloaddition reactions have proven to be among the most

efficient methods for constructing complex polycyclic systems. Rh-catalyzed carbocyclizations (i.e. SiCaC, SiCaT, CO-SiCaT) and higher order cycloaddition reactions can give novel fused-cyclic products. We present here the application of Rh-catalyzed [2+2+2+1] cycloaddition to the one-step formation of the 6-7-7-5 fused-tetracyclic scaffold of colchicinoids. Furthermore, a microwave-mediated Rh-catalyzed [2+2+2] cycloaddition to synthesize the allocolchicinoids was developed as well.

Dedicated to my family

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List of Abbreviations

Ac	-	acetyl
AChE	-	acetylcholine esterase
atm	-	atmosphere
BINAP	-	2,2'-bis(diphenylphosphino)-1-1'-binapthyl
BINOL	-	1,1'-bi-2-naphthol
Bn	-	benzyl
Boc	-	*tert*-butyl carbonate
BOP	-	biphenol-based diphosphonite
Bu	-	butyl
*t*Bu	-	*tert*-butyl
bp	-	boiling point
br	-	broad
calcd	-	calculated
CAMP	-	methylcyclohexyl-o-anisylphosphine
Celite®	-	diatomaceous earth filter reagent, ® Celite Corp.
*c*Hex	-	cyclohexyl
COD	-	1,5-cyclooctadiene
CO	-	carbon monoxide
d	-	doublet
DCE	-	1,2-dichloroethane
DCM	-	dichloromethane
de	-	diastereomeric excess
DIOP	-	(+)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
dd	-	doublet of doublets
DMAP	-	4-dimethylaminopyridine
DME	-	ethylene glycol dimethyl ether
DMF	-	dimethylformamide
DMSO	-	dimethylsulfoxide
DPPP	-	diphenylphosphino propane
DuPHOS	-	(+)-1,2-Bis[(2S,5S)-2,5-dimethylphospholano]benzene
ee	-	enantiomeric excess
EI	-	electron impact (MS)
ESI	-	electrospray ionization
Et	-	ethyl
Et_2O	-	ethyl ether
EtOAc	-	ethyl acetate
EtOH	-	ethanol
FIA	-	flow-injection analysis
g	-	gram
GC-MS	-	gas chromatography mass spectrometry
h	-	hour
HFIPA	-	hexafluoroisopropanol
HMPA	-	hexamethylphosphoramide

HMPT	-	hexamethylphosphorus triamide
HPLC	-	high performance liquid chromatography
HRMS	-	high resolution mass spectrometry
Hz	-	hertz
J	-	coupling constant
K	-	Kelvin
kcal	-	kilo calorie
L	-	liter
LAH	-	lithium aluminum hydride
LiHMDS	-	lithium hexamethyldisilizane
m	-	multiplet
Me	-	methyl
MeCN	-	acetonitrile
MeOH	-	methanol
min	-	minute
mmol	-	millimole
mol	-	mole
M	-	molarity
mg	-	milligram
MHz	-	mega hertz
mL	-	milliliters
mp	-	melting point
MPN	-	biphenol-based phosphoramidite
MS	-	mass spectrometry
MW	-	molecular weight
μW	-	microwave
NBS	-	*N*-bromosuccinimide
NIS	-	*N*-iodosuccinimide
NMR	-	nuclear magnetic resonance
NP	-	naphthalenyl
on	-	overnight
PCC	-	pyridinium chlorochromate
Ph	-	phenyl
PHEN	-	phenanthrenyl
ppm	-	parts per million
Pr	-	propyl
q	-	quartet
quint.	-	quintet
Red-Al®	-	sodium bis(2-methoxyethoxy)aluminumhydride
rt	-	room temperature
s	-	singlet
t	-	triplet
td	-	triplet of doublets
TADDOL	-	α,α,α’,α’-tetraphenyl-2,2’-dimethyl-1,3-dioxolane-4,5-dimethanol
TBAF	-	tetrabutylammonium fluoride
TEA	-	triethylamine

TFA	-	trifluroacetic acid
TFE	-	2,2,2-trifluoroethanol
THF	-	tetrahydrofuran
TLC	-	thin layer chromatography
TMS	-	trimethylsilyl
Ts	-	tosylate
p-TSA	-	*p*-toluenesulfonic acid

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Chapter 1

Synthesis of Chiral Biphenol-Based Phosphorus Ligands for Catalytic Asymmetric Reactions

1.1. Introduction

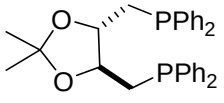
1.1.1. History of asymmetric catalysis

From the 1960s, chemical research has thrown new light on asymmetric catalysis. In 1961, an optically active polymer was obtained by Natta and co-workers by polymerizing benzofuran using $AlCl_3$/phenylalanine catalyst.[1] In 1966, Nozaki, Noyori et al. reported the employment of a chiral salen-copper complex catalyst in cyclopropanation of alkene as the first organometallic asymmetric catalysis.[2] Also in 1966, Wilkinson described the homogenous hydrogenation of alkenes catalyzed by a rhodium complex $[RhCl(PPh_3)_3]$.[3-5] In 1968, Knowles and Hornor illustrated a way to transform an achiral catalyst to a chiral catalyst. Simply by ligand exchange, they modified Wilkinson's catalyst by introducing a chiral monodentate phosphine **1-1** (**Figure 1-1**).[6,7] Even though the initial catalytic hydrogenation reaction only afforded low enantioselectivity (15% *ee*), this result has demonstrated their chirality transformation concept to be correct. According to this important achievement, a more efficient ligand, methylcyclohexyl-*o*-anisylphosphine (**CAMP**, **Figure 1-1**), was synthesized by modification of chiral monodentate phosphine **1-1**, improving the enantioselectivity to 88%. CAMP was the first reported man-made catalyst which provides an enzyme-like selectivity, and it was used as the first chiral ligand in the industrial production of L-DOPA, an drug for treating Parkinson's disease.[8]

1-1 **CAMP**

Figure 1-1. Chiral monodentate phosphine ligands.

In 1971, Kagan developed a chiral bidentate phosphine ligand, diphenylphosphino(dimethyl)dioxolane (**DIOP**, **Figure 1-2**) for the asymmetric hydrogenation of α-acetoamidocinnamic acids in high enantiopurities.[9] Kagan's work demonstrated that the chirality of a chiral catalyst does not need to be on the chelating atom (e.g. phosphorus) to give the product in good enantiomeric excess.



(*R*,*R*)-**DIOP**

Figure 1-2. (*R*,*R*)-DIOP.

In 1980, two spectacular breakthroughs in asymmetric catalysis were published by Sharpless and Noyori, respectively.[10,11] In Sharpless's paper, the asymmetric epoxidation of allylic alcohols was reported using diethyl tartrate-titanium complex. On the other hand, Noyori described the asymmetric hydrogenation induced by **BINAP**−rhodium complex. As a result of their extensive application and high enantioselectivity, these two catalytic reactions are very practical in organic synthesis. Due to their outstanding contribution to stereoselective reactions, the Nobel Prize in chemistry for 2001 was awarded to Knowles, Noyori, and Sharpless.

1.1.2. Development of monodentate phosphorus ligands

Chiral catalysts, such as chiral Lewis acids or combinations of chiral ligands with metals, are widely developed in organic chemistry. Among the chiral ligands, phosphorous ligands have been heavily studied. Even though the chiral monodentate phosphines were the first chiral phosphorus ligands used in asymmetric synthesis,[6,7] this area was long dominated by bidentate ligands. Numerous chiral bidentate ligands were designed for application to asymmetric synthesis, e.g. **DIPAMP**,[12] **BINAP**,[11] and **DuPHOS**[13] (**Figure 1-3**). However, most of these bidentate ligands are difficult to synthesize and lack fine-tuning capabilities. In order to achieve the goal of making efficient chiral catalysts for asymmetric synthesis, creating a catalyst library with fine-tuning capability and ease of synthesis is expeditious and practical. According to afore-cited requirements, monodentate phosphorus ligands can be considered as highly advantageous and have drawn much attention these days. For instance, a series of monodentate phosphorus ligands derived from **TADDOL** (**Figure 1-4**) were synthesized by Alexakis *et al.* in 1998.[14] These ligands were used with copper (II) triflate for the asymmetric conjugate addition of diethyl zinc to enones and gave up to 96% *ee*.

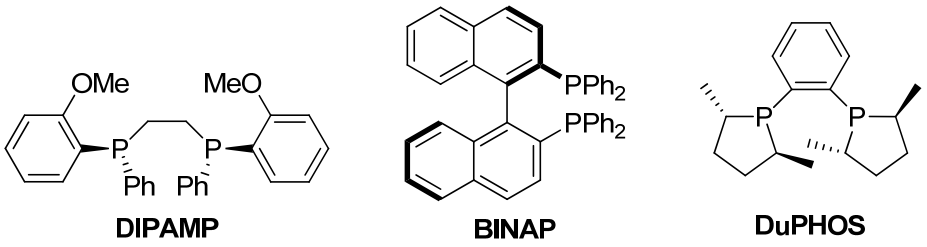


Figure 1-3. Chiral bidentate phosphine ligands.

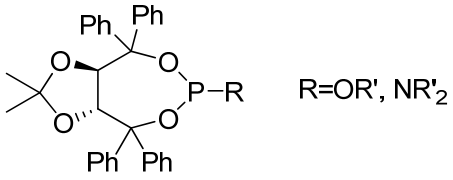


Figure 1-4. Monodentate phosphorus ligands based on (−)-TADDOL.

In 2000, Reetz and Feringa reported, respectively, the discovery of high enantionselective hydrogenation of methyl 2-acetamidoacrylate catalyzed by rhodium(I) complex accompanying with **BINOL**-based ligand family (**Figure 1-5**).[15,16]

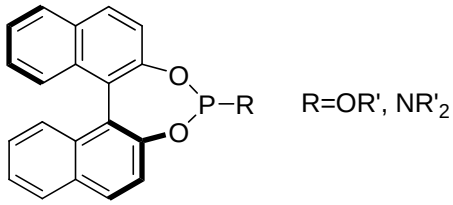


Figure 1-5. Monodentate phosphorus ligands based on (*S*)-BINOL.

In 2003, a new class of chiral monodentate phosphorus ligands derived from a readily accessible enantiopure axially chiral biphenol backbone was developed by the Ojima group (**Figure 1-6**).[17] In the light of the structures of the biphenol-based ligands, the 6 and 6'-dimethyl groups provide the axial chirality of the biphenols and make them more configurationally stable compared to the corresponding chiral BINOLs due to the restricted sterically rotation. The salient feature of these ligands is their fine-tuning capability which comes from the three modifiable substituents R^1, R^2, and R^3. The R^1 at the 5 and 5' positions of the biphenol-based ligands can be modified for recovery and recycling of catalyst.[18,19] Of decisive importance, the R^2 substituents at the 3 and 3' positions may substantially affect the catalytic activity as well as enantioselectivity of reactions, depending on their steric or electronic properties.[17,20-26] Finally,

the R^3 (also $R^{3'}$ of phosphoramidites) groups may also have influence on catalytic activity and enantioselectivity. This fine-tuning capability serves a crucial role in the applications to a variety of catalytic asymmetric transformations.

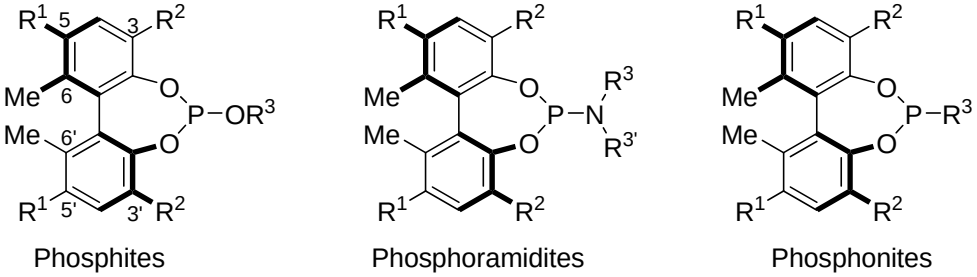
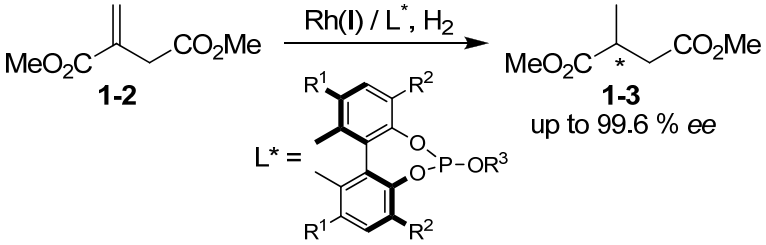


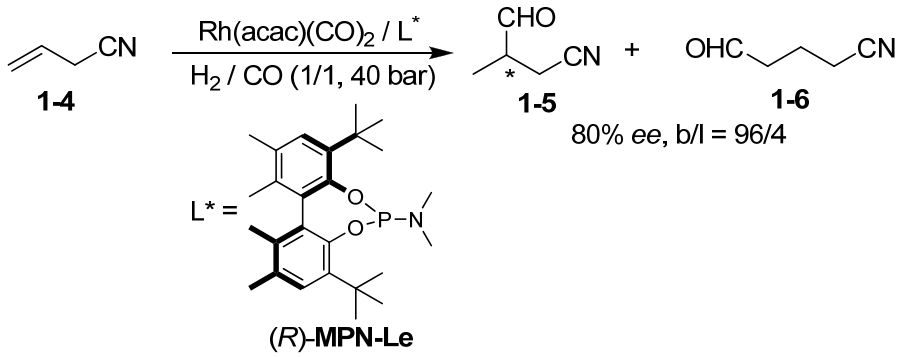
Figure 1-6. Biphenol-based monodentate phosphorus ligand libraries.

In 2003, Ojima and coworkers described excellent enantioselectivity (up to 99.6% *ee*) provided from the biphenol-based monophosphite ligands in the Rh(I)-catalyzed hydrogenation of dimethyl itaconate (**Scheme 1-1**).[17]

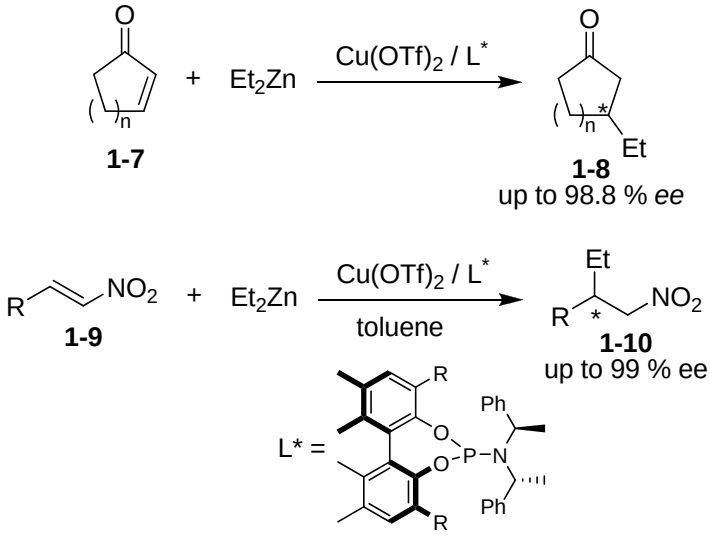


Scheme 1-1. Rh(I)-catalyzed asymmetric hydrogenation of **1-2**.

In 2004, the Ojima group's study showed that the phosphoramidite ligands (**MPN**) can be successfully applied to Rh-catalyzed hydroformylation of allyl cyanides (**Scheme 1-2**) and Cu-catalyzed conjugate addition of diethylzinc to cycloalkenones and nitroalkenes (**Scheme 1-3**).[20,21]

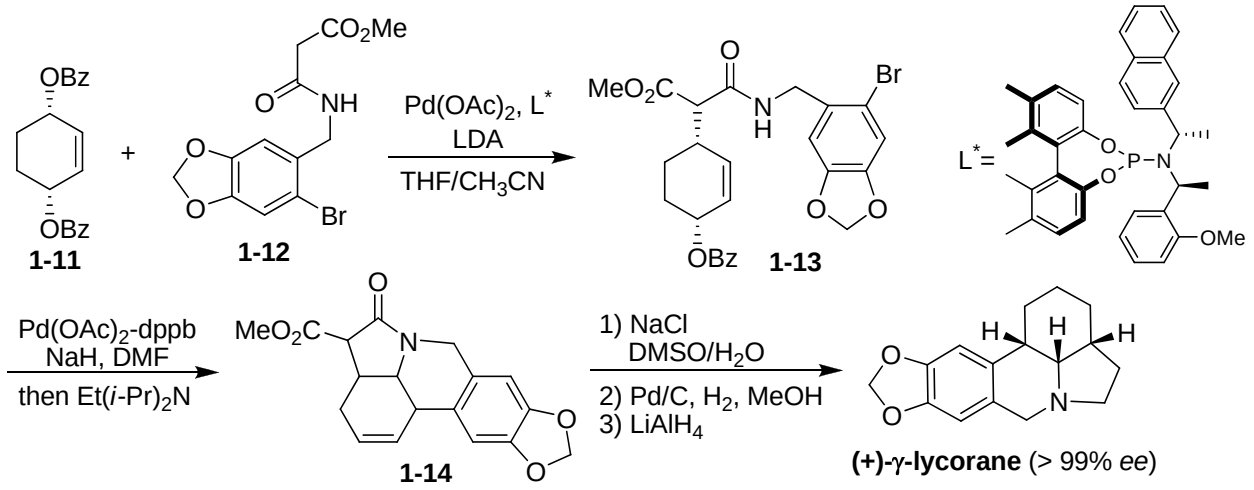


Scheme 1-2. Asymmetric hydroformylation of **1-4**.

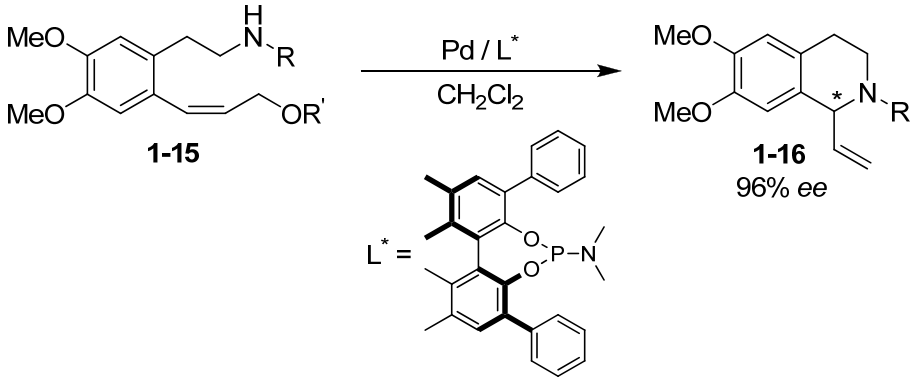


Scheme 1-3. Asymmetric conjugate addition of diethyl zinc to **1-7** and **1-9**.

The further expansion of this biphenol-based ligands library was demonstrated by Ojima *et al.* in 2006 and 2007.[22,23] They found that employing the chiral phosphoramidite ligands, (+)-γ-lycorane can be obtained with more than 99% *ee* and 41% overall yield through a short total synthesis which has Pd-catalyzed asymmetric allylic alkylation as a key step (**Scheme 1-4**). The asymmetric synthesis of 6,7-dimethoxy-1-vinyltetrahydroisoquinoline can also be achieved with excellent enantiopurity (up to 96% *ee*) *via* Pd-catalyzed intramolecular allylic amination (**Scheme 1-5**).



Scheme 1-4. Total synthesis of (+)-γ-lycorane *via* asymmetric allylic alkylation.

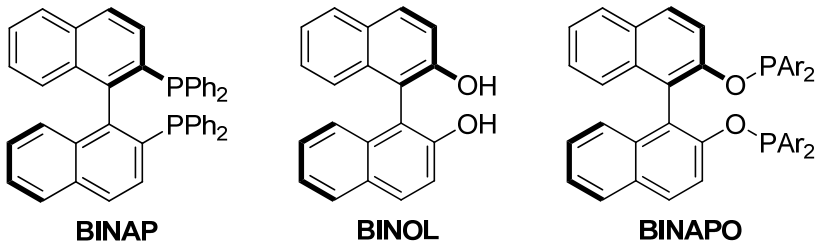


Scheme 1-5. Pd-catatalyzed intramolecular asymmetric allylic amination.

1.1.3. Development of bidentate phosphorus ligands

Although the chiral monodentae phosphines were the first chiral phosphorus ligands used in asymmetric synthesis, the development of monodentate phosphorus ligands almost ceased at the time of their beginning. After the impressive success with the DIOP ligand, chemists put their attention to bidentate ligands, especially C_2−symmetrical diphosphorus ligands. In the following years, numerous chiral bidentate phosphorus ligands were designed and proven to be effective in various asymmetric reactions.[27] Among the bidentate phosphorus ligands explored, BINAP (**Figure 1-7**) possessing an atropisomeric binaphthalene skeleton is one of the most useful ligands and agitated a wave of atropisomeric biaryl scaffolds. In 1977, with the intention to offer an alternative choice of ligands for asymmetric hydrogenation, Grubbs et al. reported the design

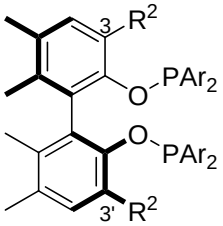
and synthesis of chiral BINOL-based diphosphonite ligands **BINAPO**.[28] Unlike the 7-membered chelating ring provided by the metal−BINAP complex, BINAPO forms a 9-membered ring with a transition metal. The conformational flexibility coming from the larger chelating ring makes BINAPO less effective than BINAP for certain asymmetric hydrogenation reactions. The larger chelating ring, nonetheless, renders BINAPO a larger bite angle (P−M−P) and increases the influence of sterically hindering moieties. Thus, BINAPO was found effective in Pd-catalyzed allylic substitution reactions.[29-32]



BINAP **BINOL** **BINAPO**

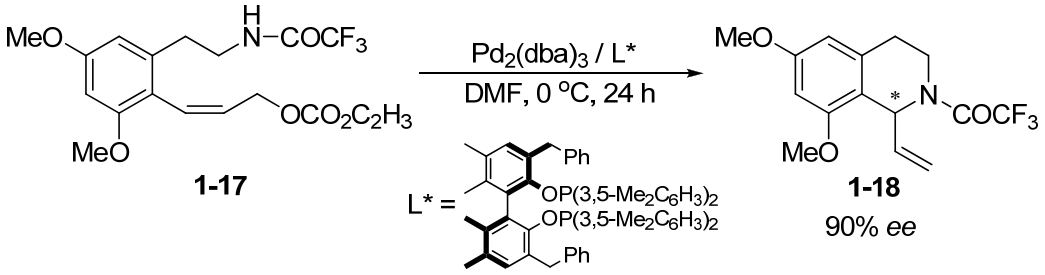
Figure 1-7. Atropisomeric biaryl-based ligands.

Based on the concept of the BINAPO ligands, a new class of novel chiral biphenol-based diphosphonite ligands (**BOP**) (**Figure 1-8**) was developed in Ojima group in 2008.[33] By easily modification of the substituents at 3 and 3' positions and Ar groups of biphenol-based ligands, this readily accessible BOP ligand library gave 90% *ee* in the synthesis of 6,7-dimethoxy-1-vinyltetrahydroisoquinoline through Pd-catalyzed intramolecular asymmetric allylic amination (**Scheme 1-6**).[34] Further ligand optimization and substrate scope studies were accomplished, introducing 96% *ee* for this intramolecular asymmetric allylic amination, a key reaction of the formal enantioselective total synthesis of Schulzeines A−C (**Scheme 1-7**).[25]

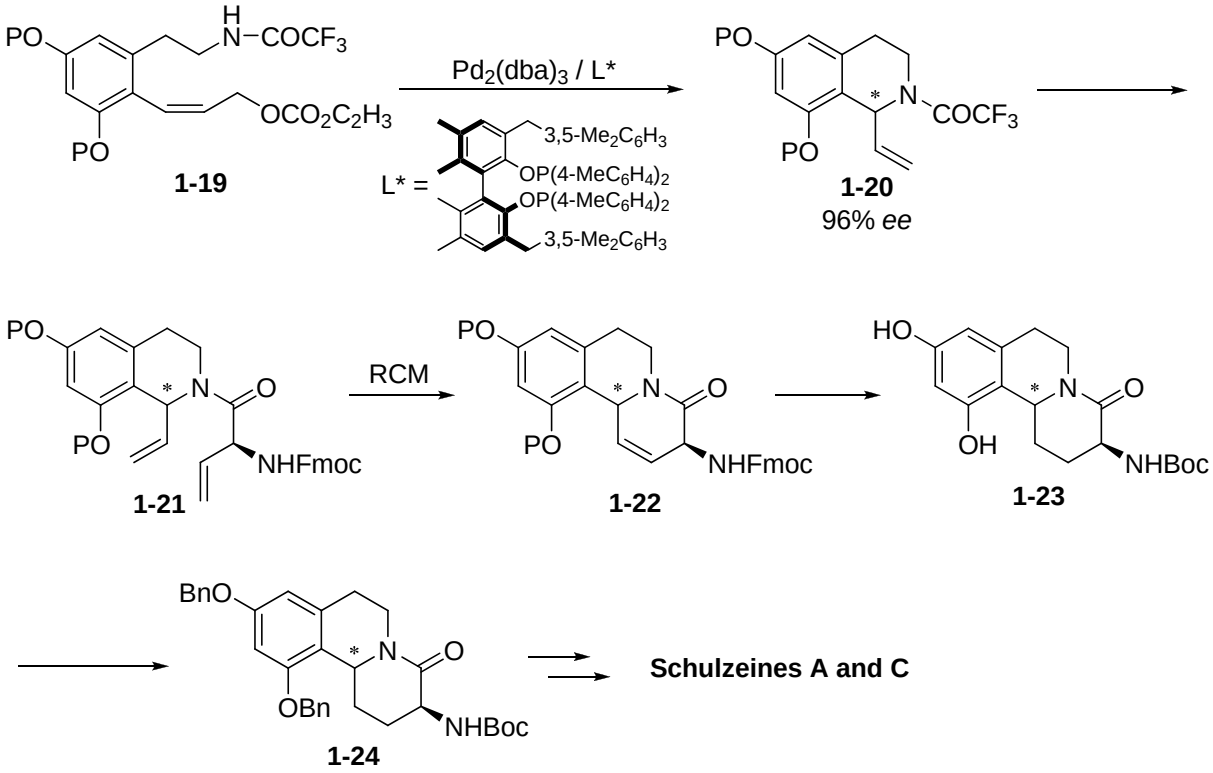


BOP

Figure 1-8. Biphenol-based diphosphonite ligand library.

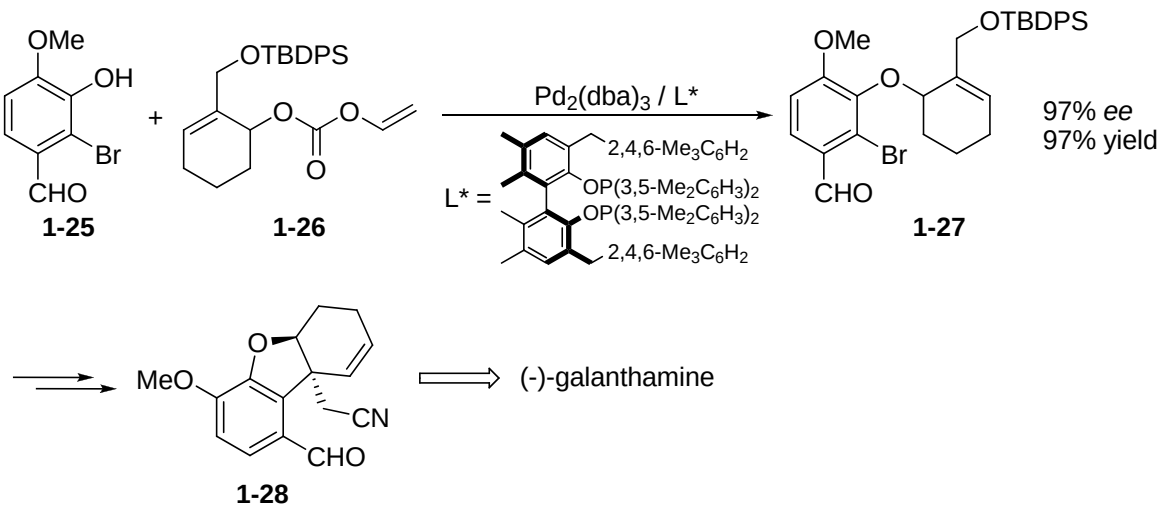


Scheme 1-6. Intramolecular asymmetric allylic amination of **1-17**.



Scheme 1-7. Formal total synthesis of Schulzeines A−C.

In addition to the asymmetric allylic amination reactions described above, the BOP ligands were applied to the intermolecular Pd-catalyzed allylic etherification reaction, which provided a key intermediate for the formal total synthesis of (−)-galanthamine with 97% *ee* in 97% yield (**Scheme 1-8**).[26]



Scheme 1-8. Formal total synthesis of (−)-galanthamine.

The goal of this project is to establish the monodentate phosphoramidite (MPN) ligand and bidentate diphosphonite (BOP) ligand libraries for catalytic asymmetric reactions. A series of phosphoramidites and diphosphonites (**Figure 1-9**, only (*S*)-isomers are shown), which have the capability for fine-tuning in catalytic activity and enantioselectivity, was prepared from enantiopure axially chiral biphenols.

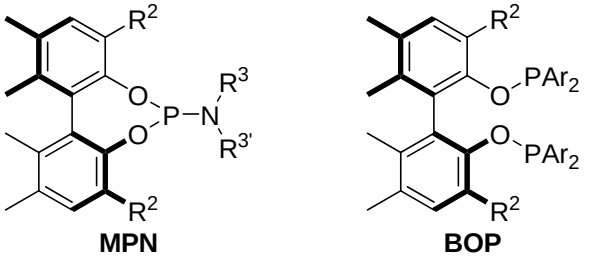
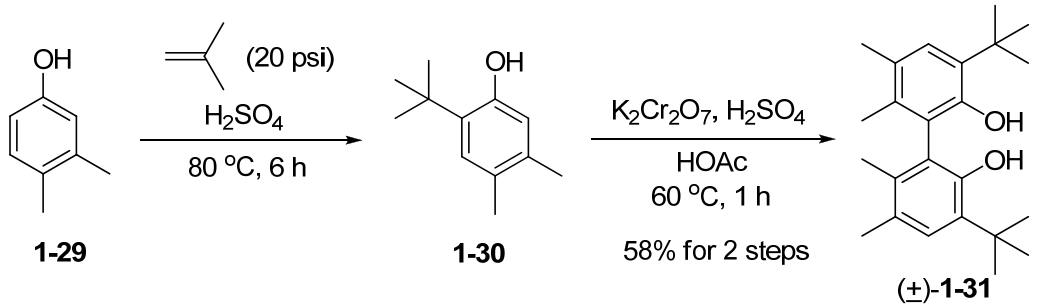


Figure 1-9. Axially chiral MPN and BOP ligands.

1.2. Results and Discussion

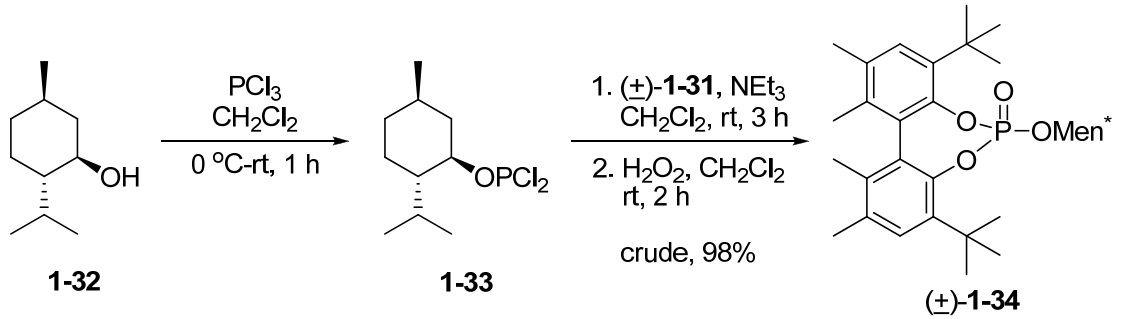
1.2.1. Synthesis of Enantiopure 3,3'-Di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol

To establish the enantiopure biphenol-based phosphorus ligand libraries with fine-tunable capability, we started by synthesizing racemic 3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl-2,2'-biphenol ((±)-**1-31**), which was obtained using literature procedures with slight modification.[35] In the presence of a catalytic amount of sulfuric acid, the Friedel-Crafts alkylation of 3,4-dimethylphenol (**1-29**) was carried out by treating with 20 psi of 2-methylpropene at 80 ^{o}C to afford crude 2-*tert*-butyl-4,5-dimethylphenol (**1-30**). By oxidative coupling using potassium dichromate, the crude **1-30** was further converted to the racemic biphenol with methyl and *tert*-butyl substituents (±)-**1-31** in 58% isolated yield for two steps (**Scheme 1-9**).



Scheme 1-9. Synthesis of racemic biphenol (±)-**1-31**.

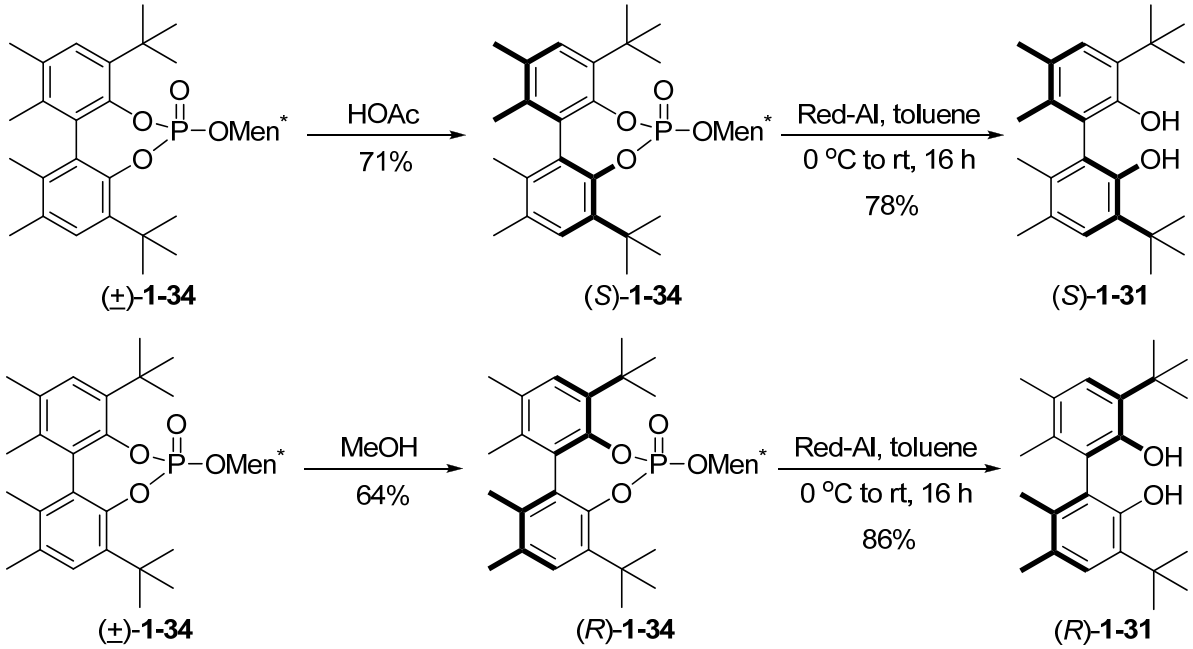
Enantiopure biphenols were prepared *via* optical resolution through the readily prepared phosphate with (−)-menthol **1-32**. (−)-Menthyl dichlorophosphite **1-33** was prepared by addition of **1-32** to a dichloromethane solution of excess phosphorous trichloride. Addition of (±)-**1-31** and triethylamine to the dichloromethane solution of crude **1-33** followed by treatment with hydrogen peroxide afforded a diastereomeric mixture of phosphates (±)-**1-34** (**Scheme 1-10**).



Scheme 1-10. Synthesis of diastereomeric phosphate (±)-**1-34**.

(*S*)-**1-34** was selectively crystallized from acetic acid. The acetic acid mother liquor was evaporated to give a solid enriched with (*R*)-**1-34**. The solid residue was then recrystallized from methanol to give phosphate (*R*)-**1-34**. By ^{31}P NMR, the diastereomeric purity was determined. The only single peak shown in each spectrum (δ −4.38 ppm for (*S*)-**1-34** and −4.86 ppm for (*R*)-**1-34**) turned out that each diastereomer has >99% *de*.[35]

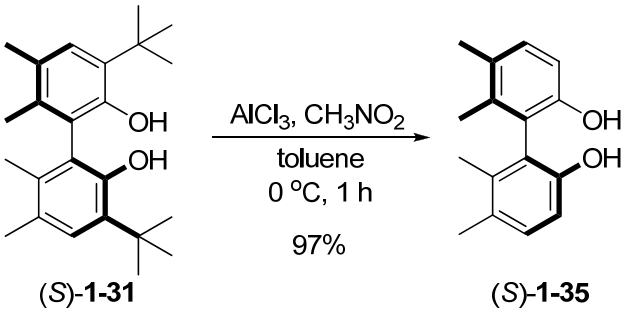
With the diastereomerically pure phosphates (*S*)-**1-34** and (*R*)-**1-34** in hand, Red-Al® was applied to reduce the phosphates to provide enantiopure biphenols (*S*)-**1-31** and (*R*)-**1-31** in 78% and 86% yield respectively (**Scheme 1-11**).[17]



Scheme 1-11. Synthesis of enantiopure bipphenols (*S*)- and (*R*)-**1-31**.

1.2.2. Synthesis of Enantiopure 5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diol

Applying the Friedel-Crafts transfer reaction, the *tert*-butyl group at the 3 and 3' positions of (*S*)- and (*R*)-**1-31** could be removed by treatment with aluminum trichloride in nitromethane-toluene at 0 ^{o}C (**Scheme 1-12**).[17] Without any loss of enantiopurity, the resulting products (*S*)- and (*R*)-**1-35** were used as the common intermediates to prepare a series of enantiopure biphenols having different groups at the 3 and 3' positions.

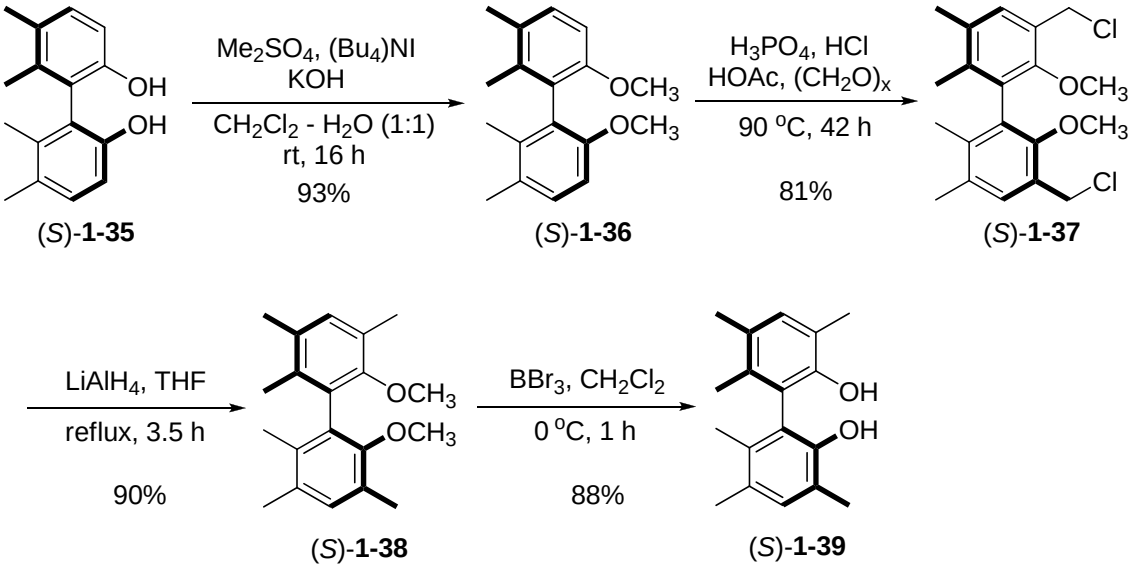


(*S*)-**1-31** (*S*)-**1-35**

Scheme 1-12. Synthesis of biphenol (*S*)-**1-35**.

1.2.3. Synthesis of Enantiopure 3,3',5,5',6,6'-Hexamethyl-1,1'-biphenyl-2,2'-diol

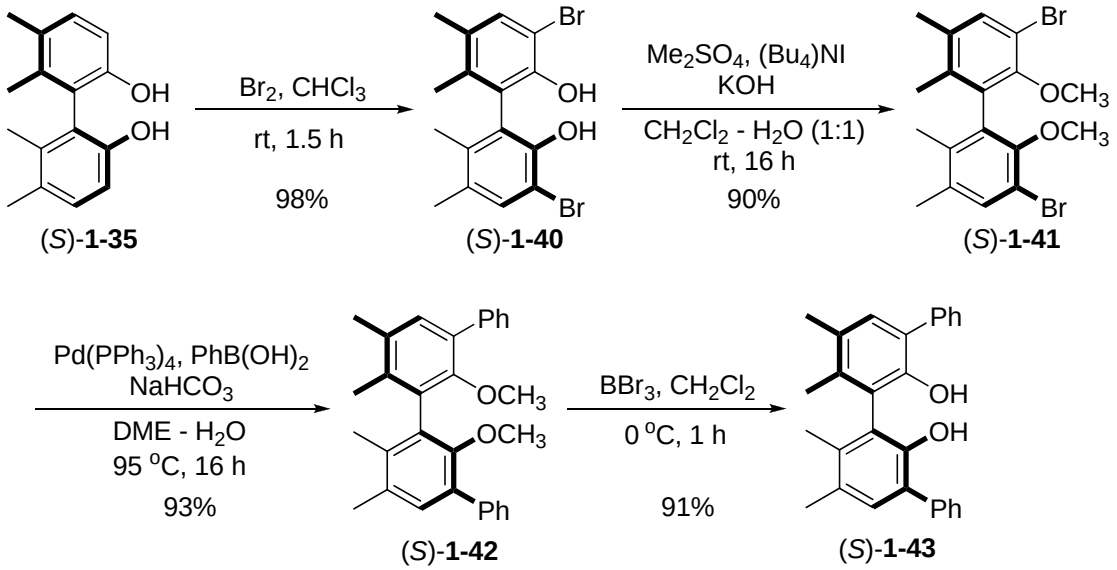
The synthesis of enantiopure hexamethyl-substituted biphenol (*S*)-**1-39** was demonstrated as **Scheme 1-13**.[17] Biphenol (*S*)-**1-35** was first protected *via* methylation with dimethyl sulfate in the presence of potassium hydroxide and tetrabutylammonium iodide to give (*S*)-**1-36** in over 90% yield. Followed by chloromethylation and $LiAlH_4$ reduction, the methyl substituents were constructed at the 3 and 3' positions of the biphenol. The deprotection of (*S*)-**1-38** using boron tribromide gave the desired enantiopure biphenol (*S*)-**1-39** in 87% yield. (*R*)-**1-39** was prepared from (*R*)-**1-35** using the same protocols.



Scheme 1-13. Synthesis of biphenol (*S*)-**1-39**.

1.2.4. Synthesis of Enantiopure 3,3'-Dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl -2,2'-diol and 3,3'-Diphenyl-5,5',6,6'-tetramethyl -1,1'-bi phenyl-2,2'-diol

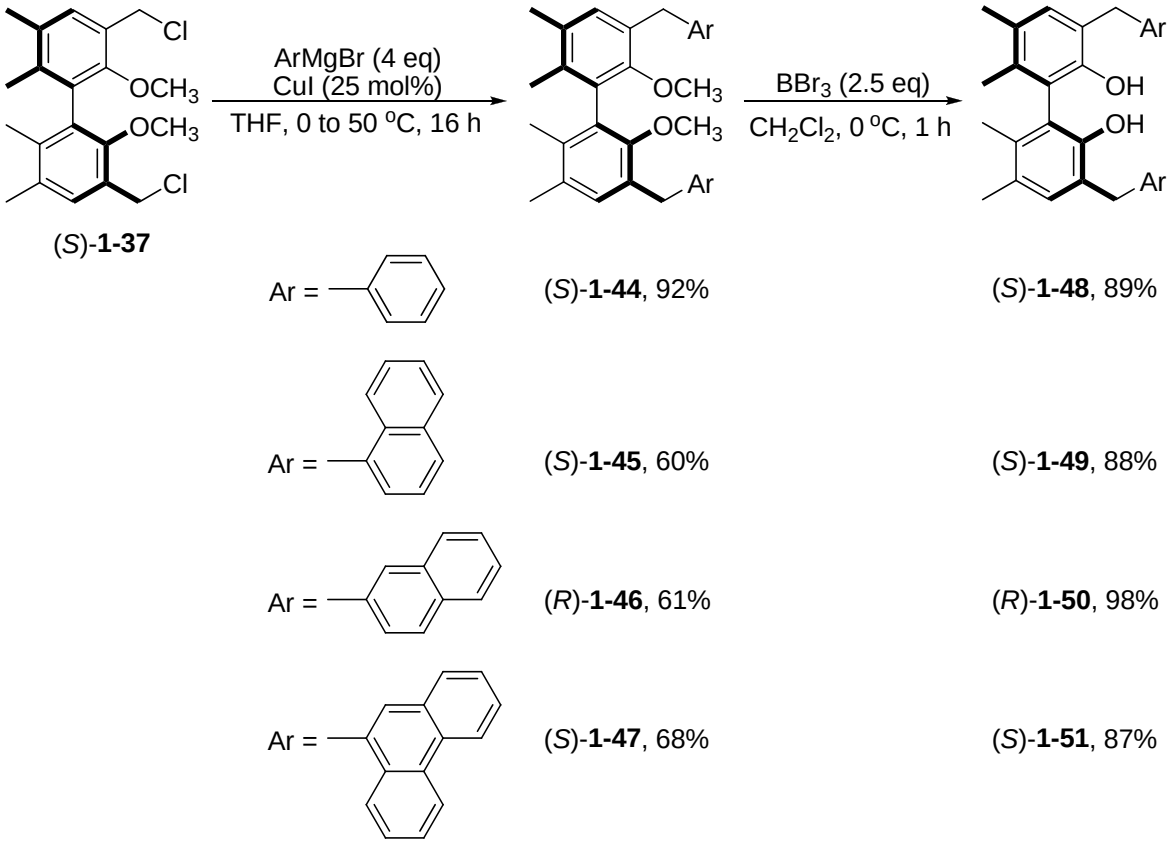
Started from (*S*)-**1-35**, bromination afforded dibromo-substituted biphenol (*S*)-**1-40** in excellent yield. Based on the previous unpublished result of our laboratory, direct Suzuki coupling of (*S*)-**1-40** would provide the desired diphenyl-substituted biphenol (*S*)-**1-43**. However, the yield was only 42%, which was definitely much lower than the three-steps process described below (overall 76% in three steps). The biphenol (*S*)-**1-40** was first protected by methylation with dimethyl sulfate to afford (*S*)-**1-41**, which was then submitted to a Suzuki coupling with phenylboronic acid catalyzed by $Pd(PPh_3)_4$ to give (*S*)-**1-42** in 93% yield. Subsequent removal of the methyl group using boron tribromide gave biphenol (*S*)-**1-43** in 91% yield (**Scheme 1-14**). In the same manner, biphenols (*R*)-**1-40** and (*R*)-**1-43** were prepared using these procedures.[17]



Scheme 1-14. Synthesis of biphenols (*S*)-**1-40** and (*S*)-**1-43**.

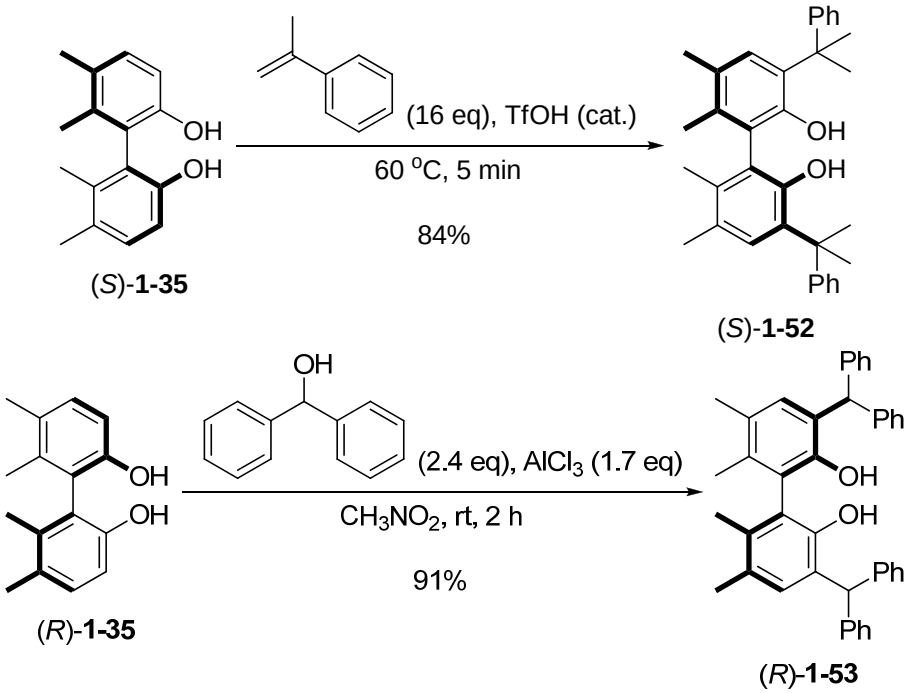
1.2.5. Synthesis of Enantiopure 3,3'-Bis(arylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diols

Biphenols (*S*)-**1-48**–**51** bearing benzyl, naphthyl, or phenanthrenyl groups were synthesized through a copper(I)-mediated cross-coupling reaction[36] using chloromethylated intermediate (*S*)-**1-37** and the corresponding aryl Grignard reagents generated *in situ*, giving the intermediates **1-44**–**47** in good to excellent yields. Subsequent removal of the methyl groups with boron tribromide afforded the desired biphenols (*S*)-**1-48**–**51** in excellent yields (**Scheme 1-15**).



Scheme 1-15. Synthesis of biphenols (*S*)-**1-48**–**51**.

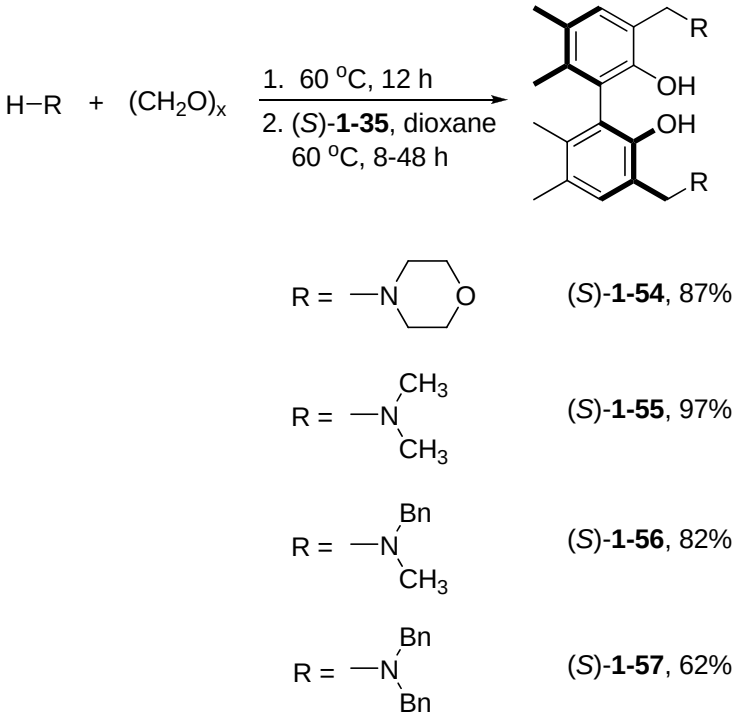
Biphenols (*S*)-**1-52** and (*R*)-**1-53**, which have bulky substituents at the 3,3'-positions, were synthesized from biphenol (*S*)-**1-35** ((*R*)-**1-35** for (*R*)-**1-53**). The Friedel-Crafts alkylation of (*S*)-**1-30** with α-methylstyrene or diphenylmethanol, in the presence of trifluoromethanesulfonic acid or aluminum chloride, went smoothly to affort (*S*)-**1-52** or (*R*)-**1-53** in excellent yields (**Scheme 1-16**).



Scheme 1-16. Synthesis of biphenols (*S*)-**1-52** and (*R*)-**1-53**.

1.2.6. Synthesis of Enantiopure 3,3'-Bis(aminomethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diols

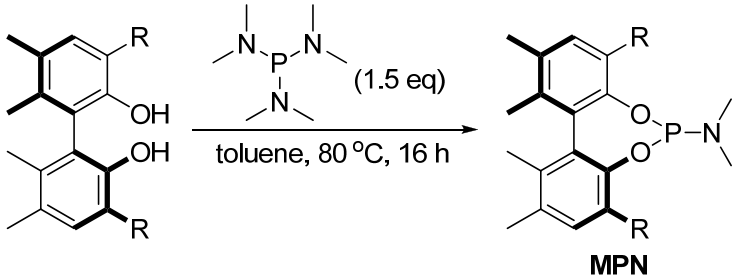
In order to construct the amino-substituents at the 3,3'-positions, the Mannich reaction was employed.[37] At first, the iminium ions were prepared by reacting amines with paraformaldehyde. The desired amino-substituted biphenols were successfully synthesized by addition of (*S*)-**1-35** to the corresponding iminium ions, giving (*S*)-**1-54** (87%), (*S*)-**1-55** (97%), (*S*)-**1-56** (82%), and (*S*)-**1-57** (62%) (**Scheme 1-17**).



Scheme 1-17. Synthesis of biphenols (*S*)-**1-54**–**57**.

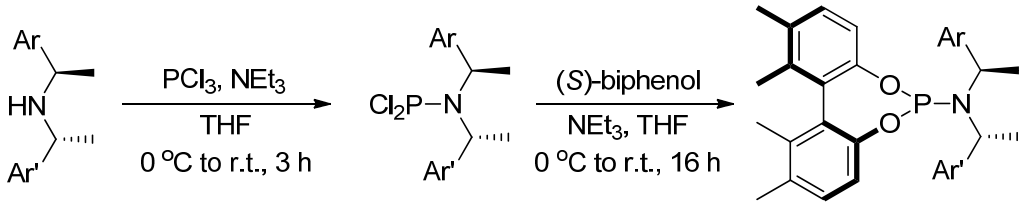
1.2.7. Synthesis of enantiopure biphenol-based monophosphoramidite ligands

Two different methods were employed to prepare the monodentate phosphoramidite (MPN) ligands. The selection of a synthetic method for a certain ligand is mainly dependent on the steric size of the 3,3'-substituted groups and amine moieties, as well as the availability of reagents. While the amine moiety of the phosphoramidite ligands was a dimethyl amino group, the enantiopure biphenols were directly reacted with the commercially available hexamethyl-phosphorustriamide (HMPT) at 80 °C (**Scheme 1-18**).[21]



Scheme 1-18. Synthesis of monodentate phosphoramidites.

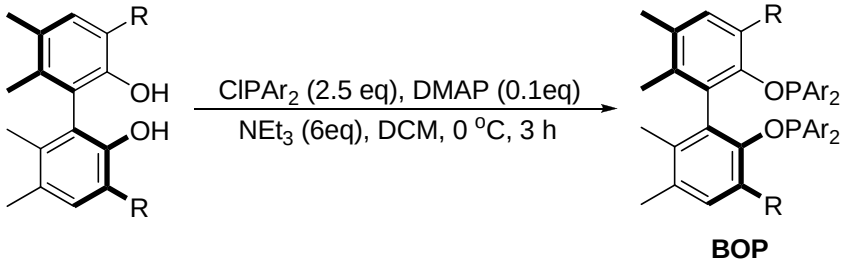
Another strategy involved the coupling of enantiopure biphenol with dialkylaminophosphorus dichloride in the presence of triethylamine at room temperature (**Scheme 1-19**).[20,21] For the purpose of constructing the desired amine moiety of the phosphoramidite, a secondary amine was reacted with phosphorous trichloride to generate a dialkylaminophosphorus dichloride, which was used *in situ* with enantiopure biphenol to give the phosphoramidite. When using the dialkylaminophosphorus dichloride generated *in situ*, ^{31}P NMR has to be monitored carefully to ensure the complete consumption of PCl_3 to avoid unnecessary side reactions in the following coupling with the biphenol.



Scheme 1-19. Synthesis of monodentate phosphoramidites.

1.2.8. Synthesis of enantiopure biphenol-based diphosphonite ligands

The 3,3'-substituted-biphenol-based diphosphonite (BOP) ligands were synthesized according to the synthetic protocol described for the binapo ligand (**Scheme 1-20**).[30] The coupling reaction between enantiopure biphenols and chlorodiarylphosphines ($ClPAr_2$) proceeded smoothly, affording the corresponding diphosphonites in good to excellent yields. By using this protocol, a small BOP ligand library was created.



Scheme 1-20. Synthesis of bidentate diphosphonites..

1.3. Conclusion

A variety of enantiopure biphenols were successfully synthesized. These biphenols were converted to the corresponding phosphoramidite MPN or diphosphonite BOP ligands, which were screened for their capability in catalyzing asymmetric reactions such as intermolecular and intramolecular asymmetric amination reactions.

1.4. Experimental Section

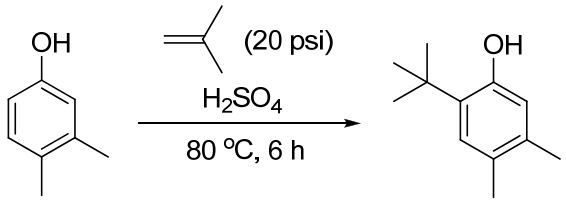
General Method

^{1}H, ^{13}C, and ^{31}P NMR spectra were measured on a Bruker Avance III HD-Nanobay 400 (400 MHz ^{1}H; 100 MHz ^{13}C; 121.5 MHz ^{31}P), Varian Inova-400 (400 MHz ^{1}H; 100 MHz ^{13}C; 121.5 MHz ^{31}P), or Varian Gemini-2300 (300 MHz ^{1}H; 75 MHz ^{13}C; 121.5 MHz ^{31}P) spectrometer in a deuterated solvent using residual proton ($CHCl_3$: ^{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 was performed on Merck DC-Alufolien Kieselgel 60F 254 and flash column chromatography was carried out on Silicyle Silia*Flash*P60®. Low-Resolution Mass Spectrometry was performed on Agilent 6890GC/5973 Mass Selective Detector. High-resolution mass spectrometric analyses were carried out at Mass Spectrometry Laboratories, University of Illinois Urbana-Champaign, Urbana, IL or ICB&DD at Stony Brook University. Unless otherwise noted, all reactions were carried out under nitrogen atmosphere in oven-dried glassware using standard Schlenck technique.

Materials

All solvents used as reaction media were purified using the Solvent Purification System 400-4 from Innovative Technology, Inc. or distilled under nitrogen immediately before use. Ether and THF were distilled from Na/benzophenone ketyl. Toluene and CH_2Cl_2 were distilled from CaH_2. Solvents for extraction and chromatography were reagent grade and used as received. All chemicals were purchased from Aldrich or Acros Chemical Co., and were used without further purification unless otherwise noted.

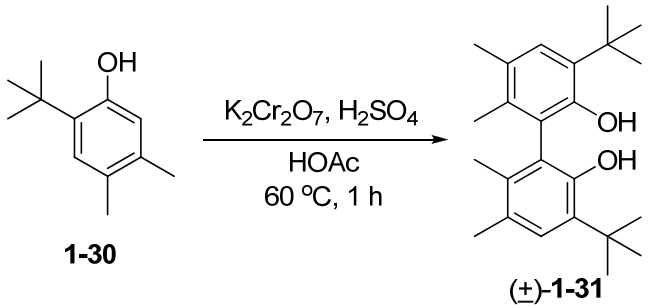
2-*tert*-Butyl-4,5-dimethylphenol (1-30)[35]



1-29 **1-30**

To a 300 mL autoclave with a glass liner and a stirring bar, 3,4-dimethylphenol (**1-29**) (100 g, 0.82 mol) and concentrated sulfuric acid (1.0 mL) were added. Then the autoclave was pressurized with 2-methylpropene (20 psi) and heated to 80 °C with stirring. After heating for 6 h, the autoclave was opened and the mixture was analyzed by GC-MS (m/z = 178). Without further purification, the crude **1-30** was used directly in next step.

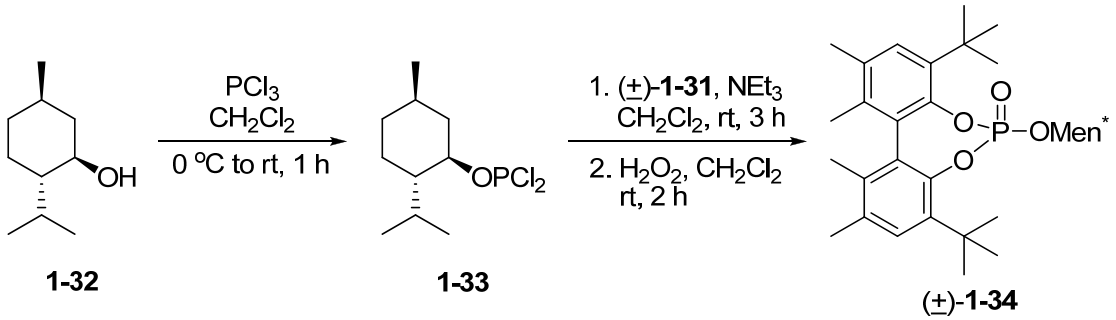
3,3'-Di-*tert*-butyl-5,5'-6,6'-tetramethyl-1,1'-diphenyl-2,2'-diol ((±)-1-31)[35]



1-30 (±)-**1-31**

A potassium dichromate solution was prepared by dissolving potassium dichromate (75.0 g, 0.255 mol) in sulfuric acid (150 mL) and water (400 mL). This potassium dichromate solution was carefully added to another acetic acid (650 mL) solution of crude 2-*tert*-Butyl-4,5-dimethyl-phenol (**1-30**) obtained from previous step. An exothermic phenomenon was observed as well as precipitation. After stirring at 60 °C for 1 h, the reaction mixture was allowed to cool to room temperature. The brown precipitate was filtered and washed with water (250 mL × 2) and methanol (200 mL × 3). Then the precipitate was stirred with methanol at 0 °C for 15 min and filtrated again. The refined solid diol (±)-**1-31** was dried *in vacuo* to give pure diol (±)-**1-31** (84.8 g, 58% yield for two steps) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 18H), 1.82 (s, 6H), 2.25 (s, 6H), 4.79 (s, 2H), 7.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 20.0, 29.6, 34.5, 121.0, 128.0, 128.7, 133.4, 134.1, 150.4. All data are in agreement with the literature values.[35]

Preparation and Resolution of (*S*)- and (*R*)-1-34[35]



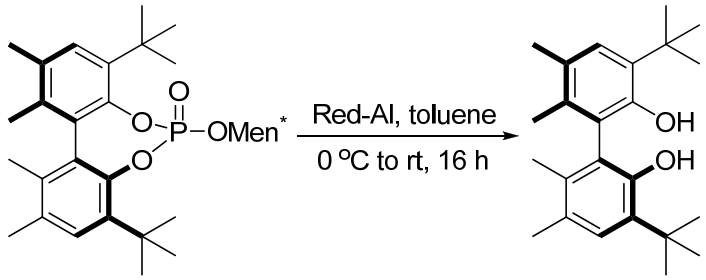
1-32 **1-33** (±)-**1-34**

(*S*)-**1-34** was crystallized from AcOH
(*R*)-**1-34** was crystallized from MeOH

To a solution of phosphorus trichloride (48.9 g, 356 mmol) in CH_2Cl_2 (200 mL) at 0 °C, the solution of (1*R*,2*S*,5*R*)-(−)-menthol (**1-32**) (37.0 g, 237 mmol) in CH_2Cl_2 (100 mL) was slowly added over 30 min. After addition of **1-32**, the ice bath was removed and the reaction mixture was kept at room temperature for another hour. The solvent and other volatile liquids were removed *in vacuo* to give the remaining oil **1-33**. The oil **1-33** was then redissolved in CH_2Cl_2 (150 mL) and a CH_2Cl_2 (300 mL) solution of triethylamine (99.4 mL, 713 mmol) and (±)-**1-31** (84.2 g, 237 mmol) was slowly added over 30 min. After additional 2 h, the solution was filtrated and H_2O_2 (35%, 145 mL) was added slowly with stirring. The resulting biphasic mixture was stirred rapidly for 2 h. The organic layer was further separated, washed with water (200 mL × 2) and brine (200 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a white solid (±)-**1-34**: ^{31}P NMR (121.5 MHz, $CDCl_3$) δ −4.86 for (*R*)-**1-34**, −4.38 for (*S*)-**1-34**.

By crystallization, the diastereomeric mixture (±)-**1-34** can be divided into two isolated isomers. First, the solid (±)-**1-34** was dissolved in a minimum amount of hot acetic acid (~300 mL). After 24 h storage at room temperature, white crystals were formed. These crystals were collected by filtration and washed with cold acetic acid (50 mL × 2). The crystals were further purified through recrstallization from hot acetic acid to give pure (*S*)-**1-34** (46.2 g, >99% *de*, corresponding to 71% of (*S*)-diastereomer). On the other hand, the crude (*R*)-**1-34** was obtained from concentrating the mother liquor of the first crystallization *in vacuo*. The remaining solid was dissolved in hot MeOH (~260 mL), and the solution was allowed to be cooled to 0 °C to form (*R*)-**1-34** crystals. The resulting (*R*)-**1-34** was refined by recrystallization procedure from hot MeOH to afford pure (*R*)-**1-34** (41.6 g, >99% *de*, corresponding to 64% of (*R*)-diastereomer). All data are in agreement with the literature values.[35]

(*S*)-3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-31)[35]



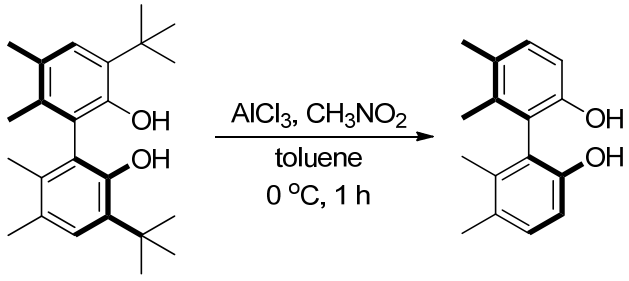
(*S*)-**1-34** (*S*)-**1-31**

(*S*)-**1-34** (40.0 g, 72.1 mmol) was dissolved in toluene (340 mL) in a 2 L round bottomed flask equipped with an addition funnel. Red-Al® (54.6 mL, 70 wt. % in toluene) was loaded into the addition funnel and then added dropwise to (*S*)-**1-34** solution with continuous gas evolution at 0 °C. After addition, the reaction mixture was stirred at room temperature for 16 h and then quenched with water (80 mL), followed by bleach (6%, 80 mL). The resulting slurry was filtered through a Celite® pad and washed with toluene (250 mL). The filtrate was extracted and the organic layer was collected. The organic layer was further washed with bleach (6%, 200 mL) and brine (200 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a white solid. The side product menthol was expelled by washing the given solid with cold MeOH several times until no minty odor remained. After filtration and driying *in vacuo*, biphenol (*S*)-**1-31** (20.2 g, 78% yield, >99% *ee*) was collected as a white solid. The optical purity of (*S*)-**1-31** was examined on the basis of ^{31}P NMR spectra of phosphite derivative of (*S*)-**1-31** with (−)-menthol: mp 165.0-167.0 °C (lit.[35] mp 165.0-167.0 °C); $[\alpha]_D^{20}$ −79.8 (*c* 0.89, CH_2Cl_2) (lit.[35] $[\alpha]_D^{22}$ −72.8 (*c* 1.25, CH_2Cl_2)); ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 18H), 1.82 (s, 6H), 2.25 (s, 6H), 4.79 (s, 2H), 7.13 (s, 2H). All data are in agreement with the literature values.[35] The reduction of (*R*)-**1-34** to (*R*)-**1-31** followed the same procedure.

(*R*)-3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-31)[35]

(*R*)-**1-31** (20.3 g, 86% yield) was obtained as a white solid: mp 165.0-167.0 °C; $[\alpha]_D^{20}$ +66.7 (*c* 0.90, CH_2Cl_2) (lit.[35] $[\alpha]_D^{22}$ +74.0 (*c* 1.69, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 18H), 1.82 (s, 6H), 2.25 (s, 6H), 4.79 (s, 2H), 7.13 (s, 2H). All data are in agreement with the literature values.[35]

(*S*)-5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-35)[17]



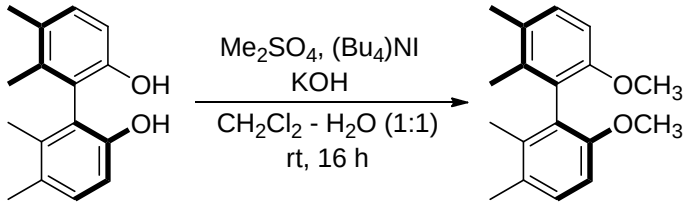
(*S*)-**1-31** (*S*)-**1-35**

To a solution of (*S*)-**1-31** (10.63 g, 30.0 mmol) in toluene (120 mL) at 0 °C, a toluene (40 mL) solution consisting of $AlCl_3$ (6.67 g, 50.0 mmol) and nitromethane was added dropwise over 30 min. After stirring for additional 30 min at 0 °C, the reaction was quenched with water (50 mL) and extracted with Et_2O (30 mL × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The solid residue was purified by recrystallization from hexanes−CH_2Cl_2 to give (*S*)-**1-35** (7.06 g, 97% yield) as a cotton-like white solid: mp 199.0−201.0 °C (lit.[17] mp 198.5−200.0 °C); $[\alpha]_D^{20}$ −56.2 (*c* 0.89, CH_2Cl_2) (lit.[17] $[\alpha]_D^{22}$ −53.3 (*c* 0.90, CH_2Cl_2)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (s, 6H), 2.26 (s, 6H), 4.49 (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 16.3, 19.8, 112.6, 120.2, 129.1, 131.2, 136.9, 151.8. All data are in agreement with the literature values.[17] The reduction of (*R*)-**1-31** to (*R*)-**1-35** followed the same procedure.

(*R*)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-35)[17]

(*R*)-**1-35** (6.91 g, 95% yield) was obtained as a white solid: mp 200.0-201.5 °C; $[\alpha]_D^{20}$ +53.2 (*c* 0.94, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (s, 6H), 2.26 (s, 6H), 4.50 (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 16.3, 19.8, 112.6, 120.2, 129.1, 131.2, 136.9, 151.8. All data are in agreement with the literature values.[17]

(*S*)-6,6'-Dimethoxy-2,2',3,3'-tetramethylbiphenyl ((*S*)-1-36)[17]



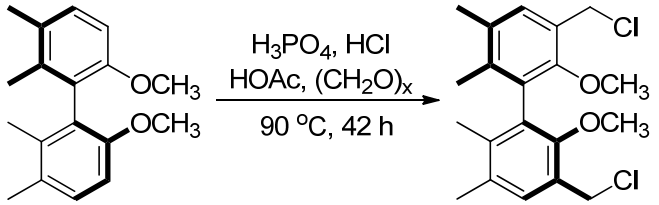
(*S*)-**1-35** (*S*)-**1-36**

Dimethyl sulfate (2.60 mL, 27.75 mmol) was added to a biphasic mixture of (*S*)-**1-35** (2.24 g, 9.25 mmol), $(Bu_4N)I$ (0.34 g, 0.75 mmol), and KOH (1.59 g, 27.75 mmol) in CH_2Cl_2−H_2O (1:1) (75 mL). After stirring overnight at room temperature, the organic and aqueous layers were separated by a separation funnel. The aqueous layer was further extracted with CH_2Cl_2 (25 mL × 3). The combined organic layers were washed with water (30 mL), NH_4OH (30 mL), and brine (30 mL). The organic layers were further dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 9:1) to give (*S*)-**1-36** (2.60 g, 93% yield) as a white solid: mp 110.5−112.0 °C (lit.[17] mp 111.0−112.0 °C); $[\alpha]_D^{20}$ −61.1 (*c* 0.90, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (s, 6H), 2.26 (s, 6H), 3.66 (s, 6H), 6.74 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.9, 55.9, 108.1, 126.8, 128.5, 128.9, 136.5, 155.3. All data are in agreement with the literature values.[17] The protection of (*R*)-**1-35** to (*R*)-**1-36** followed the same procedure.

(*R*)-6,6'-Dimethoxy-2,2',3,3'-tetramethylbiphenyl ((*R*)-1-36)[17]

(*R*)-**1-36** (2.45 g, 88% yield) was obtained as a white solid: mp 110.0−112.0 °C; $[\alpha]_D^{20}$ +48.3 (*c* 0.89, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (s, 6H), 2.26 (s, 6H), 3.66 (s, 6H), 6.74 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H). All data are in agreement with the literature values.[17]

(*S*)-3,3'-Bis(chloromethyl)-2,2'-dimethoxy-5,5',6,6'-tetramethylbiphenyl ((*S*)-1-37)[17]



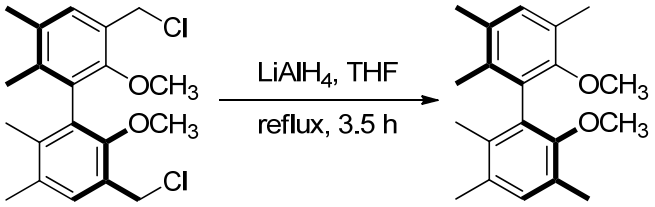
(*S*)-**1-36** (*S*)-**1-37**

(*S*)-**1-36** (1.50 g, 5.49 mmol) was dissolved in H_3PO_4 (85%, 15 mL). Then, to the above solution, concentrated HCl (15 mL), AcOH (15 mL) and paraformaldehyde (4.25 g) were added. The reaction mixture was allowed to stir at 90 °C for 42 h. After cooling down to room temperature, the mixture was extracted with benzene (50 mL × 3). The combined organic layers were washed with water (50 mL), saturated Na_2CO_3 solution (50 mL), and brine (50 mL). The organic layers were further dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 9:1) to give (*S*)-**1-37** (1.66 g, 81% yield) as a white solid: mp 104.5−106.0 °C (lit.[17] mp 98.0−101.0 °C); $[\alpha]_D^{21}$ +60.7 (*c* 0.89, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (s, 6H), 2.29 (s, 6H), 3.37 (s, 6H), 4.56 (d, J = 11.1 Hz, 2H), 4.80 (d, J = 10.8 Hz, 2H), 7.24 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 20.2, 41.7, 60.9, 127.9, 128.2, 131.2, 131.4, 132.7, 137.4, 154.0. All data are in agreement with the literature values.[17] The chloro-methylation of (*R*)-**1-36** to (*R*)-**1-37** followed the same procedure.

(*R*)-3,3'-Bis(chloromethyl)-2,2'-dimethoxy-5,5',6,6'-tetramethylbiphenyl ((*R*)-1-37)[17]

(*R*)-**1-37** (1.63 g, 80% yield) was obtained as a white solid: mp 104.0−105.5 °C; $[\alpha]_D^{21}$ −55.6 (*c* 0.90, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (s, 6H), 2.29 (s, 6H), 3.37 (s, 6H), 4.56 (d, J = 11.1 Hz, 2H,), 4.79 (d, J = 11.1 Hz, 2H), 7.24 (s, 2H). All data are in agreement with the literature values.[17]

(*S*)-2,2'-Dimethoxy-3,3',5,5',6,6'-hexamethylbiphenyl ((*S*)-1-38)[17]



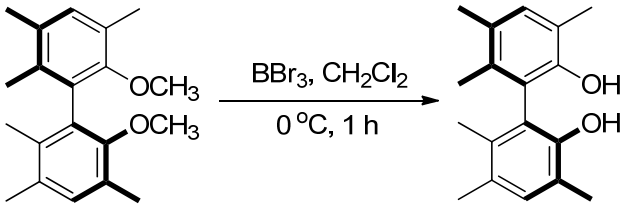
(*S*)-**1-37** (*S*)-**1-38**

To a suspension of $LiAlH_4$ (0.37 g, 9.74 mmol) in THF (8 mL), the solution of (*S*)-**1-37** (1.02 g, 2.78 mmol) in THF (15 mL) was added dropwise. After addition, the reaction mixture was refluxed for 3.5 h. The reaction was then slowly quenched with THF/water (3:1, 6 mL) at 0 ^{o}C and extracted with Et_2O (20 mL × 3). 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:EtOAc = 15:1) to give (*S*)-**1-38** (0.75 g, 90% yield) as a white solid: mp 73.5−75.0 ^{o}C (lit.[17] mp 74.0−75.0 ^{o}C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 6H), 2.24 (s, 6H), 2.27 (s, 6H), 3.33 (s, 6H), 6.99 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 16.6, 20.1, 59.5, 127.4, 131.3, 131.5, 131.7, 133.4, 154.1. All data are in agreement with the literature values.[17] The reduction of (*R*)-**1-37** to (*R*)-**1-38** followed the same procedure.

(*R*)-2,2'-Dimethoxy-3,3',5,5',6,6'-hexamethylbiphenyl ((*R*)-1-38)[17]

(*R*)-**1-38** (0.78 g, 94% yield) was obtained as a white solid: mp 74.0−76.0 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 6H), 2.24 (s, 6H), 2.27 (s, 6H), 3.33 (s, 6H), 6.99 (s, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 16.6, 20.1, 59.5, 127.4, 131.3, 131.5, 131.7, 133.4, 154.1. All data were in agreement with the reported values.[17]

(*S*)-3,3'-dimethyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-39)[17]



(*S*)-**1-38** (*S*)-**1-39**

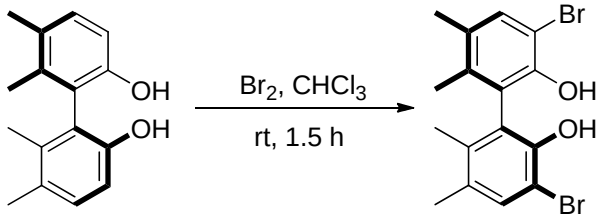
BBr_3 solution (6.2 mL, 1 M in CH_2Cl_2) was added dropwise to a stirred solution of (*S*)-**1-38** (0.74 g, 2.48 mmol) in CH_2Cl_2 (15 mL) at 0 ^{o}C. After addition, the reaction mixture was stirred

at 0 °C for 1 h. The reaction was then quenched with water (40 mL) and extracted with CH_2Cl_2 (30 mL × 2). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 19:1) to give (*S*)-**1-39** (0.59 g, 88% yield) as a white solid: mp 135.5−137 °C (lit.[17] mp 136.0−137.5 °C); $[\alpha]_D^{21}$ −54.5 (*c* 0.91, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (s, 6H), 2.22 (s, 12H), 4.53 (s, 2H), 7.00 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 16.2, 19.7, 119.9, 121.3, 128.4, 132.6, 133.8, 149.8. All data are in agreement with the literature values.[17] The deprotection of (*R*)-**1-38** to (*R*)-**1-39** followed the same procedure.

(*R*)-3,3'-dimethyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-39)[17]

(*R*)-**1-39** (0.67 g, 94% yield) was obtained as a white solid: mp 136.0−137.5 °C; $[\alpha]_D^{21}$ +37.9 (*c* 0.87, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (s, 6H), 2.22 (s, 12H), 4.53 (s, 2H), 7.00 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 16.2, 19.7, 119.9, 121.3, 128.4, 132.6, 133.8, 149.8. All data are in agreement with the literature values.[17]

(*S*)-3,3'-dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-40)[17]



(*S*)-**1-35** (*S*)-**1-40**

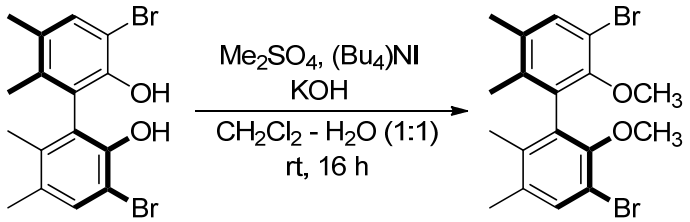
To a solution of (*S*)-**1-35** (4.85 g, 20.0 mmol) in $CHCl_3$ (120 mL), a solution of Br_2 (2.64 mL, 50.0 mmol) in $CHCl_3$ (20 mL) was slowly added over 30 min. After stirring for 1 h at room temperature, the reaction was quenched with saturated Na_2SO_3 aqueous solution (20 mL) extracted with Et_2O (30 mL × 3). The combined organic layers were washed with water (20 mL × 2) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give (*S*)-**1-40** (7.84 g, 98% yield) as an off-white solid: mp 169.5−171.0 °C (lit.[17] mp 171.0−172.5 °C); $[\alpha]_D^{20}$ +12.2 (*c* 0.90, CH_2Cl_2) (lit.[17] $[\alpha]_D^{22}$ +11.7 (*c* 0.77, CH_2Cl_2)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (s, 6H), 2.25 (s, 6H), 5.11 (s, 2H), 7.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 19.6, 106.6, 123.5, 130.5, 132.7, 136.6, 147.7. All data are in agreement with the literature values.[17]

The bromination of (*R*)-**1-35** to (*R*)-**1-40** followed the same procedure.

(*R*)-3,3'-dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-40)[17]

(*R*)-**1-40** (7.92 g, 99%) was obtained as a white solid: mp 169.0−171.0 °C; $[\alpha]_D^{20}$ −12.2 (*c* 0.90, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (s, 6H), 2.25 (s, 6H), 5.11 (s, 2H), 7.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 19.6, 106.6, 123.5, 130.5, 132.7, 136.6, 147.7. All data are in agreement with the literature values.[17]

(*S*)-3,3'-Dibromo-2,2'-dimethoxy-5,5',6,6'-tetramethylbiphenyl ((*S*)-1-41)[17]



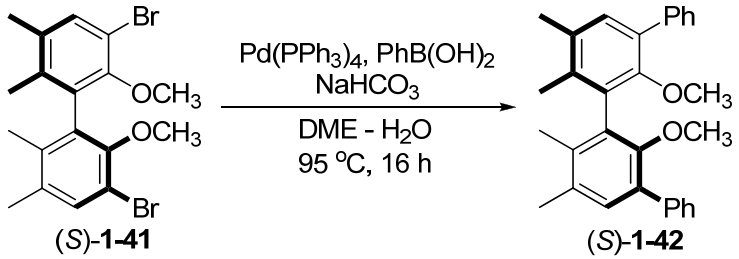
(*S*)-**1-40** (*S*)-**1-41**

Dimethyl sulfate (2.1 mL, 22.5 mmol) was added to a biphasic mixture which contains (*S*)-**1-40** (3.00 g, 7.50 mmol), $(Bu_4N)I$ (0.28 g, 0.75 mmol), and KOH (1.29 g, 22.5 mmol) in CH_2Cl_2−H_2O (1:1) (50 mL). After stirring 16 h at room temperature, the organic and aqueous layers were separated by a separation funnel. The aqueous layer was further extracted with CH_2Cl_2 (25 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The solid residue was further washed with cold MeOH to give (*S*)-**1-41** (2.90 g, 90% yield) as a white solid: mp 150.0−151.5 °C (lit.[17] mp 150.0−151.5 °C); $[\alpha]_D^{20}$ +41.6 (*c* 0.94, CH_2Cl_2) (lit.[17] $[\alpha]_D^{22}$ +38.3 (*c* 0.60, 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 16.8, 20.0, 60.4, 113.8, 133.2, 133.6, 134.2, 113.60, 152.7. All data are in agreement with the literature values.[17] The protection of (*R*)-**1-40** to (*R*)-**1-41** followed the same procedure.

(*R*)-3,3'-Dibromo-2,2'-dimethoxy-5,5',6,6'-tetramethylbiphenyl ((*R*)-1-41)[17]

(*R*)-**1-41** (2.92 g, 88 % yield) was obtained as a white solid: mp 150.0−152.0 °C; $[\alpha]_D^{20}$ −39.3 (CH_2Cl_2, *c* 0.89); ^{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 16.8, 20.0, 60.4, 113.8, 133.2, 133.6, 134.2, 113.60, 152.7. All data are in agreement with the literature values.[17]

(*S*)-2,2'-Dimethoxy-5,5',6,6'-tetramethyl-3,3'-diphenylbiphenyl ((*S*)-1-42)[17]



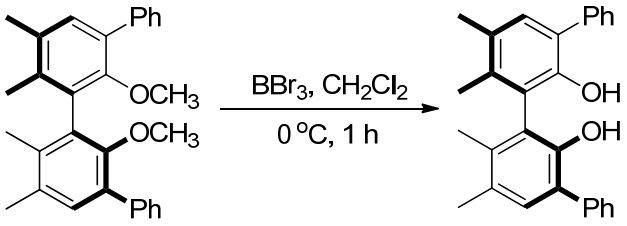
(*S*)-**1-41** (*S*)-**1-42**

A suspension of (*S*)-**1-41** (1.00 g, 2.34 mmol) and $Pd(PPh_3)_4$ (135 mg, 0.12 mmol) in DME (25 mL) was stirred for 30 min at room temperature. Slight color change was observed. Then, a solution of $PhB(OH)_2$ (630 mg, 5.17 mmol) and $NaHCO_3$ (1.18 g, 14.04 mmol) in water (15 mL) was added to the above suspension. The reaction mixture was refluxed for 16 h. The reaction mixture was cooled to room temperature and diluted with Et_2O (40 mL). The organic layer was washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 19:1) to give (*S*)-**1-42** (0.92 g, 93% yield) as a white solid: mp 56.5−58.5 °C (lit.[17] mp 56.5-58.5 °C); $[\alpha]_D^{21}$ +156.7 (*c* 0.90, CH_2Cl_2) (lit.[17] $[\alpha]_D^{22}$ +143.6 (*c* 0.55, CH_2Cl_2)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (s, 6H), 2.33 (s, 6H), 3.19 (s, 6H), 7.18−7.63 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 19.8, 121.6, 125.6, 127.0, 128.4, 129.1, 129.2, 132.1, 136.3, 137.9, 148.4. All data are in agreement with the literature values.[17] The Suzuki coupling of (*R*)-**1-41** to (*R*)-**1-42** followed the same procedure.

(*R*)-2,2'-Dimethoxy-5,5',6,6'-tetramethyl-3,3'-diphenylbiphenyl ((*R*)-1-42)[17]

(*R*)-**1-42** (0.92 g, 93% yield) was obtained as a white solid: mp 56−58 °C; $[\alpha]_D^{21}$ −139.8 (*c* 0.93, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.97 (s, 6H), 2.33 (s, 6H), 3.19 (s, 6H), 7.17−7.63 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 19.8, 121.6, 125.6, 127.0, 128.4, 129.1, 129.2, 132.1, 136.3, 137.9, 148.4. All data were in agreement with the reported values.[17]

(*S*)-3,3'-Diphenyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-43)[17]



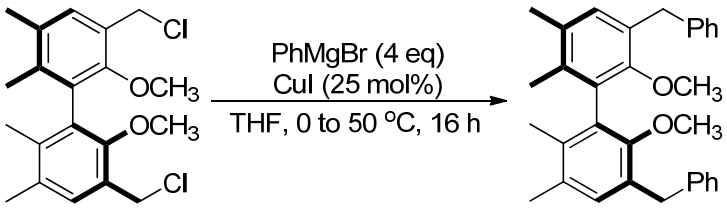
(*S*)-**1-42** (*S*)-**1-43**

BBr_3 solution (4.50 mL, 1 M in CH_2Cl_2) was added dropwise to a stirred solution of (*S*)-**1-42** (0.85 g, 2.00 mmol) in CH_2Cl_2 (15 mL) at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 1 h. The reaction was then quenched with water (40 mL) and extracted with CH_2Cl_2 (30 mL × 2). The combined organic layer was washed with brine (25 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 19:1) to give (*S*)-**1-43** (0.72 g, 91% yield) as a white solid: mp 152.0−154.0 °C (lit.[17] mp 153.0−154.0 °C); $[\alpha]_D^{21}$ +90.7 (*c* 0.86, CH_2Cl_2) (lit.[17] $[\alpha]_D^{22}$ +86.3 (CH_2Cl_2, *c* 0.53)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (s, 6H), 2.31 (s, 6H), 4.88 (s, 2H), 7.22−7.60 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 19.8, 121.6, 125.6, 126.3, 127.1, 128.4, 129.2, 132.1, 136.4, 137.9, 148.4. All data are in agreement with the literature values.[17] The deprotection of (*R*)-**1-42** to (*R*)-**1-43** followed the same procedure.

(*R*)-3,3'-Diphenyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-43)

(*R*)-**1-43** (0.75 g, 92% yield) was obtained as a white solid: mp 153.0−154.5 °C; $[\alpha]_D^{21}$ −90.9 (*c* 0.88, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (s, 6H), 2.31 (s, 6H), 4.88 (s, 2H), 7.22−7.60 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 19.8, 121.6, 125.6, 126.3, 127.1, 128.4, 129.2, 132.1, 136.4, 137.9, 148.4. All data are in agreement with the literature values.[17]

(*S*)-3,3'-Dibenzyl-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-1-44)



(*S*)-**1-37** (*S*)-**1-44**

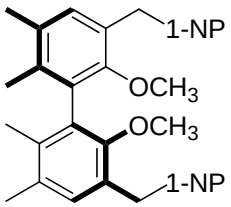
A solution of phenylmagnesium bromide in THF (1 M, 2.0 mL) was added at 0 °C to a

solution of 3,3'-bis(chloromethyl)biphenyl (*S*)-**1-37** (183 mg, 0.5 mmol) in THF (5 mL) containing CuI (24 mg, 0.125 mmol) under nitrogen over 30 min. The reaction mixture was warmed up to room temperature and stirred for an additional 30 min and then at 50 °C for 16 h. The reaction mixture was cooled to room temperature, quenched with saturated $NH_4Cl_{(aq)}$ (10 mL), and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 30:1 to 10:1) to give (*S*)-**1-44** (207 mg, 92% yield) as a colorless oil: $[\alpha]_D^{20}$ −14.0 (*c* 0.93, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (s, 6H), 2.21 (s, 6H), 3.20 (s, 6H), 3.99 (d, *J* = 15.6 Hz, 2H), 4.05 (d, *J* = 15.6 Hz, 2H), 6.91 (s, 2H), 7.15–7.30 (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; HRMS (ESI+) calcd for $C_{40}H_{34}O_2$ $[M]^+$ 450.2559, found 450.2560 (Δ = +0.1 ppm). (*R*)-**1-44** and (*S*)-**1-46**–**47** were prepared in the same manner.

(*R*)-3,3'-Dibenzyl-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-1-44)

(*R*)-**1-44** (209 mg, 93% yield) was obtained as a colorless oil: $[\alpha]_D^{22}$ +14.0 (*c* 0.86, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (s, 6H), 2.21 (s, 6H), 3.20 (s, 6H), 3.99 (d, *J* = 15.6 Hz, 2H), 4.05 (d, *J* = 15.6 Hz, 2H), 6.91 (s, 2H), 7.15–7.30 (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.

(*S*)-3,3'-Bis(naphthalene-1-ylmethyl)-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-1-45)

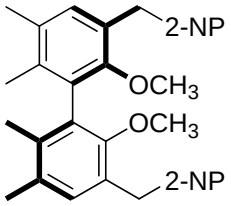


(*S*)-**1-45**

(*S*)-**1-45** was (165 mg, 60% yield) obtained as a colorless oil: $[\alpha]_D^{22}$ −24.6 (*c* 0.80, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (s, 6H), 2.13 (s, 6H), 3.40 (s, 6H), 4.45 (d, *J* = 15.6 Hz, 2H), 4.52 (d, *J* = 15.6 Hz, 2H), 6.80 (s, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.40–7.45 (m, 6H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.83–7.87 (m, 2H), 8.09–8.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 20.1,

32.6, 60.3, 124.5, 125.3, 125.5, 125.8, 126.8, 126.9, 128.5, 130.2, 130.8, 131.8, 132.0, 132.3, 133.8, 134.4, 137.5, 153.7; HRMS (ESI+) calcd for $C_{40}H_{39}O_2$ $[M]^+$ 551.2950, found 551.2943 (Δ = –1.3 ppm)

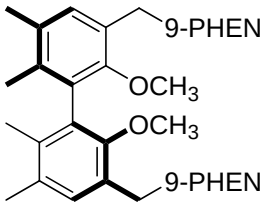
(*R*)-3,3'-Bis(naphthalene-2-ylmethyl)-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-1-46)



(*R*)-**1-46**

(*R*)-**1-46** (168 mg, 61% yield) was obtained as a pale yellow oil: $[\alpha]_D^{22}$ +25.0 (*c* 0.52, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (s, 6H), 2.28 (s, 6H), 3.34 (s, 6H), 4.22–4.30 (m, 4H), 7.02 (s, 2H), 7.45–7.53 (m, 6H), 7.72–7.86 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 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; HRMS (ESI+) calcd for $C_{40}H_{42}NO_2$ $[M+NH_4]^+$ 568.3216, found 568.3215 (Δ = –0.2 ppm).

(*S*)-3,3'-Bis(phenanthrene-9-ylmethyl)-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-1-47)

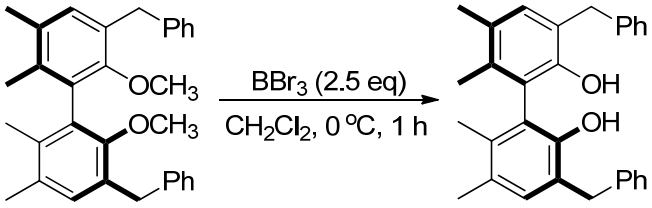


(*S*)-**1-47**

(*S*)-**1-47** (221 mg, 68% yield) was obtained as a white foam: mp 134.0–136.0 °C; $[\alpha]_D^{20}$ –39.1 (*c* 0.35, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, 6H), 2.16 (s, 6H), 3.50 (s, 6H), 4.52 (d, *J* = 15.9 Hz, 2H), 4.59 (d, *J* = 15.9 Hz, 2H), 6.90 (s, 2H), 7.57–7.67 (m, 10H), 7.85 (d, *J* = 7.4 Hz, 2H), 8.19 (d, *J* = 7.8 Hz, 2H), 8.69 (d, *J* = 8.0 Hz, 2H), 8.74 (d, *J* = 7.8 Hz, 2H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 20.1, 33.1, 60.3, 122.4, 122.9, 125.1, 126.0, 126.1, 126.5, 126.6, 127.3, 128.1, 129.8, 130.6, 130.7, 131.5, 131.8, 131.9, 132.1, 134.5, 135.7, 153.7; HRMS

(ESI+) calcd for $C_{48}H_{46}NO_2$ $[M+NH_4]^+$ 668.3529, found 668.3529 (Δ = 0.0 ppm).

(*S*)-3,3'-Dibenzyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-48)



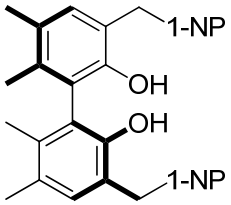
(*S*)-**1-44** (*S*)-**1-48**

BBr_3 solution (1.25 mL, 1 M in CH_2Cl_2) was added dropwise over 20 min to a stirred solution of (*S*)-**1-44** (225 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 1.5 h. The reaction was then quenched with water (20 mL) and extracted with Et_2O (10 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 15:1 to 5:1) to give (*S*)-**1-48** (189 mg, 89% yield) as a white solid: mp 105.0–106.5 °C; $[\alpha]_D^{20}$ –8.9 (*c* 1.13, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 6H), 2.23 (s, 6H), 3.99 (d, *J* = 15.2 Hz, 2H), 4.04 (d, *J* = 15.2 Hz, 2H), 4.65 (s, 2H), 6.98 (s, 2H), 7.20–7.24 (m, 2H), 7.26–7.33 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 19.7, 35.7, 120.3, 124.6, 125.8, 128.3, 128.7, 128.8, 132.3, 134.6, 141.0, 149.4; HRMS (EI+) calcd for $C_{30}H_{30}O_2$ $[M]^+$ 422.2246, found 422.2248 (Δ = +0.2 ppm). (*R*)-**1-48** and (*S*)-**1-49**–**51** were prepared in the same manner.

(*R*)-3,3'-Dibenzyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-48)

(*R*)-**1-48** (186 mg, 88% yield) was obtained as a white solid: mp 105.0–107.0 °C; $[\alpha]_D^{22}$ +9.0 (*c* 0.75, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 6H), 2.23 (s, 6H), 3.99 (d, *J* = 15.2 Hz, 2H), 4.04 (d, *J* = 15.2 Hz, 2H), 4.65 (s, 2H), 6.98 (s, 2H), 7.20–7.24 (m, 2H), 7.26–7.33 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 19.7, 35.7, 120.3, 124.6, 125.8, 128.3, 128.7, 128.8, 132.3, 134.6, 141.0, 149.4.

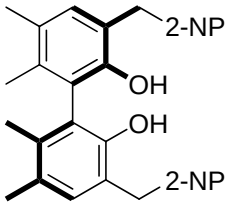
(*S*)-3,3'-Bis(naphthalene-1-ylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-49)



(*S*)-**1-49**

(*S*)-**1-49** (230 mg, 88% yield) was obtained as a white foam: mp 151.0–152.0 °C; $[\alpha]_D^{22}$ +26.8 (*c* 1.30, CH_2Cl_2); ^{1}H NMR (400 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), 7.41–7.49 (m, 6H), 7.76 (d, *J*= 8.4 Hz, 2H), 7.85–7.88 (m, 2H), 8.09–8.13 (m, 2H); ^{13}C NMR (100 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; HRMS (ESI+) calcd for $C_{38}H_{35}O_2$ $[M+H]^+$ 523.2637, found 523.2619 (Δ = –2.0 ppm).

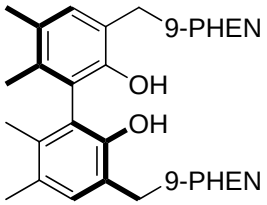
(*R*)-3,3'-Bis(naphthalene-2-ylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-50)



(*R*)-**1-50**

(*R*)-**1-50** (255 mg, 98% yield) was obtained as a white foam: mp 86.0–88.0 °C; $[\alpha]_D^{21}$ –19.6 (*c* 1.02, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (s, 6H), 2.19 (s, 6H), 4.11 (d, *J* = 15.2 Hz, 2H), 4.16 (d, *J* = 15.2 Hz, 2H), 4.66 (s, 2H), 6.97 (s, 2H), 7.39–7.45 (m, 6H), 7.66 (s, 2H), 7.74–7.80 (m, 6H); ^{13}C NMR (100 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; HRMS (ESI+) calcd for $C_{38}H_{38}NO_2$ $[M+NH_4]^+$ 540.2903, found 540.2903 (Δ = 0.0 ppm).

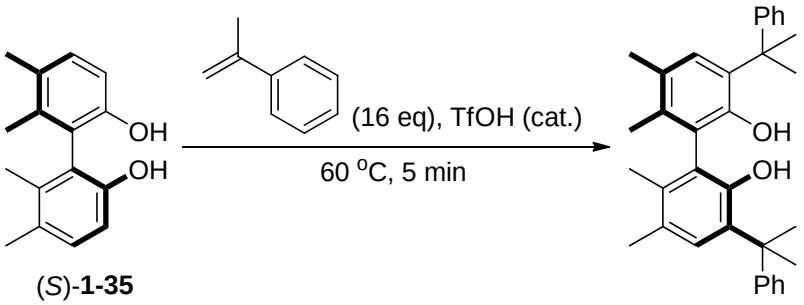
(*S*)-3,3'-Bis(phenanthrene-9-ylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-51)



(*S*)-**1-51**

(*R*)-**1-51** (271 mg, 87% yield) was obtained as a pale yellow foam: mp 178.0–180.0 °C; $[\alpha]_D^{20}$ +50.0 (*c* 0.38, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (s, 6H), 2.14 (s, 6H), 4.47 (d, *J* = 16.0 Hz, 2H), 4.58 (d, *J* = 16.0 Hz, 2H), 4.94 (s, 2H), 6.92 (s, 2H), 7.59–7.68 (m, 10H), 7.87 (d, *J* = 7.4 Hz, 2H), 8.20 (d, *J* = 7.6 Hz, 2H), 8.71 (d, *J* = 7.9 Hz, 2H), 8.76 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 19.7, 32.9, 122.2, 122.4, 123.0, 123.7, 125.0, 126.0, 126.1, 126.5, 126.5, 127.3, 128.1, 129.1, 129.9, 130.7, 131.5, 131.9, 132.0, 134.7, 135.0, 149.2; HRMS (ESI+) calcd for $C_{46}H_{42}NO_2$ $[M+NH_4]^+$ 640.3216, found 640.3217 (Δ = +0.2 ppm).

(*S*)-3,3'-Bis(2-phenylpropan-2-yl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-52)

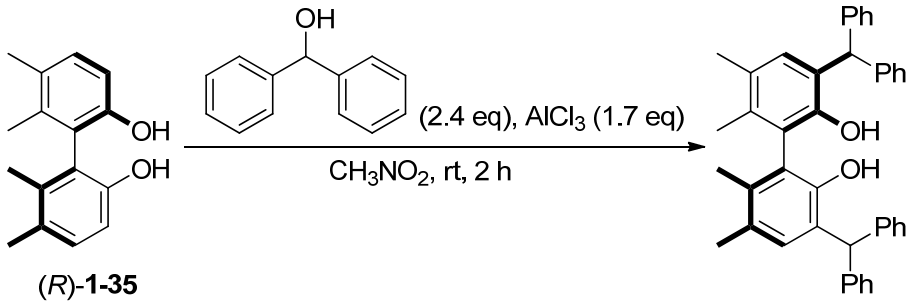


(*S*)-**1-35** (*S*)-**1-52**

A mixture of (*S*)-**1-35** (242 mg, 1.00 mmol) and α-methylstyrene (2.0 mL, 16.0 mmol) was stirred at 60 °C for 5 min. Then, the mixture was cooled down to room temperature and 2 drops of trifluoromethanesulfonic acid (TfOH) were added. The reaction mixture was stirred at 60 °C for 5 min and cooled to room temperature. The reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with 5% $NaHCO_3$ (20 mL) and brine (20 mL). The organic layers were further dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 19:1) to give (*S*)-**1-52** (403 mg, 84% yield) as a white solid: mp

205.0–207.0 °C; $[\alpha]_D^{22}$ +24.5 (*c* 1.06, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68 (s, 6H), 1.69 (s, 6H), 1.78 (s, 6H), 2.28 (s, 6H), 4.39 (s, 2H), 7.15–7.26 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 20.0, 28.7, 30.3, 41.6, 122.3, 125.4, 125.4, 127.8, 127.9, 128.3, 132.5, 134.6, 149.4, 150.5; HRMS (ESI+) calcd for $C_{34}H_{42}NO_2$ $[M+NH_4]^+$ 496.3216, found 496.3215 (Δ = –0.2 ppm).

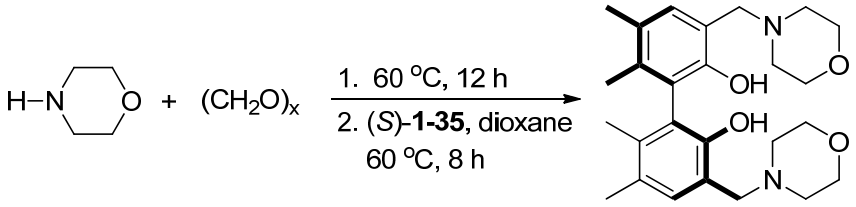
(*R*)-3,3'-Bis(diphenylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-53)



(*R*)-**1-35** (*R*)-**1-53**

Aluminum chloride (227 mg, 1.70 mmol) was added to a solution of (*R*)-**1-35** (242 mg, 1.00 mmol) and diphenylmethanol (442 mg, 2.40 mmol) in CH_3NO_2 (10 mL). After stirring for 2 h at room temperature, the reaction was quenched with H_2O (10 mL) and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 9:1) to give (*R*)-**1-53** (524 mg, 91% yield) as a white solid: mp 116.0–118.0 °C; $[\alpha]_D^{22}$ +54.5 (*c* 0.56, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 6H), 2.11 (s, 6H), 4.60 (s, 2H), 5.81 (s, 2H), 6.65 (s, 2H), 7.10–7.12 (m, 8H), 7.18–7.23 (m, 4H), 7.25–7.30 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 19.9, 50.1, 120.3, 126.1, 127.6, 128.2, 128.5, 129.1, 129.4, 132.0, 134.8, 143.4, 143.7, 149.2; HRMS (ESI+) calcd for $C_{42}H_{42}NO_2$ $[M+NH_4]^+$ 592.3216, found 592.3214 (Δ = –0.3 ppm).

(*S*)-3,3'-dimorpholinomethyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-54)



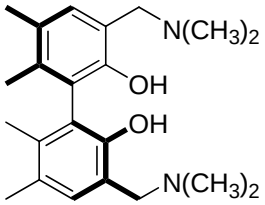
(*S*)-**1-54**

Morpholine (1.45 g, 16.5 mmol) was added dropwise to the round bottomed flask containing paraformaldehyde (0.50 g, 16.5 mmol). After addition, the reaction mixture was stirred at 60 °C for 12 h. A solution of dioxane (2 mL) and (*S*)-**1-35** (0.20 g, 0.82 mmol) was added to the round bottomed flask and the reaction mixture was stirred at 60 °C for additional 8 h. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL), washed with water (10 mL), and dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 2:1) to give (*S*)-**1-54** (0.31 g, 87% yield) as a white solid: mp 184.0–186.0 °C; $[\alpha]_D^{23}$ +17.0 (*c* 0.94, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 6H), 2.22 (s, 6H), 2.54 (br s, 8H), 3.55 (d, *J* = 13.5 Hz, 2H), 3.68 (br s, 8H), 3.85 (d, *J* = 13.8 Hz, 2H), 6.79 (s, 2H), 10.41 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 19.7, 52.8, 61.8, 66.6, 117.0, 125.2, 126.7, 129.2, 135.6, 152.5; HRMS (ESI+) calcd for $C_{26}H_{37}N_2O_4$ $[M+H]^+$ 441.2753, found 441.2752 (Δ = –0.2 ppm). (*R*)-**1-54** and (*S*)-**1-55**–**57** were obtained followed the same procedure.

(*R*)-3,3'-dimorpholinomethyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-54)

(*R*)-**1-54** (0.29 g, 82% yield) was obtained as a white solid: mp 184.5–186.5 °C; $[\alpha]_D^{23}$ –20.9 (*c* 0.86, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 6H), 2.22 (s, 6H), 2.54 (br s, 8H), 3.55 (d, *J* = 13.5 Hz, 2H), 3.68 (br s, 8H), 3.85 (d, *J* = 13.8 Hz, 2H), 6.79 (s, 2H), 10.42 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 19.7, 52.8, 61.8, 66.6, 117.0, 125.2, 126.7, 129.2, 135.6, 152.5.

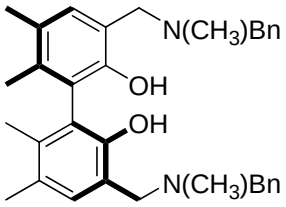
(*S*)-3,3'-bis((dimethylamino)methyl)-5,5',6,6'-tetramethylbiphenyl-2,2'-diol ((*S*)-1-55)



(*S*)-**1-55**

(*S*)-**1-55** (0.29 g, 97% yield) was obtained as a white solid: mp 158.0–160.0 °C; $[\alpha]_D^{23}$ +9.78 (*c* 0.92, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (s, 6H), 2.22 (s, 6H), 2.29 (s, 12H), 3.44 (d, *J* = 13.5 Hz, 2H), 3.85 (d, *J* = 13.2 Hz, 2H), 6.77 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 20.0, 44.3, 62.7, 118.4, 125.4, 126.6, 128.8, 135.6, 153.2; HRMS (ESI+) calcd for $C_{22}H_{33}N_2O_2$ $[M+H]^+$ 357.2542, found 357.2541 (Δ = –0.3 ppm).

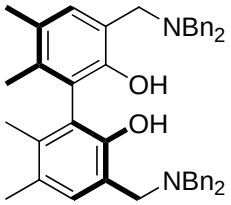
(*S*)-3,3'-bis((benzyl(methyl)amino)methyl)-5,5',6,6'-tetramethylbiphenyl-2,2'-diol ((*S*)-1-56)



(*S*)-**1-56**

(*S*)-**1-56** (0.34 g, 82% yield) was obtained as a white solid: mp 110.0–112.0 °C; $[\alpha]_D^{21}$ +29.5 (*c* 0.78, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (s, 6H), 2.18 (s, 6H), 2.24 (s, 6H), 3.52–3.63 (m, 6H), 3.93 (d, *J* = 13.8 Hz, 2H), 6.83 (s, 2H), 10.62 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 20.0, 41.0, 61.5, 61.6, 118.6, 125.6, 126.6, 127.5, 128.5, 129.1, 129.7, 135.7, 137.3, 153.1; HRMS (ESI+) calcd for $C_{34}H_{41}N_2O_2$ $[M+H]^+$ 509.3168, found 509.3168 (Δ = 0.0 ppm).

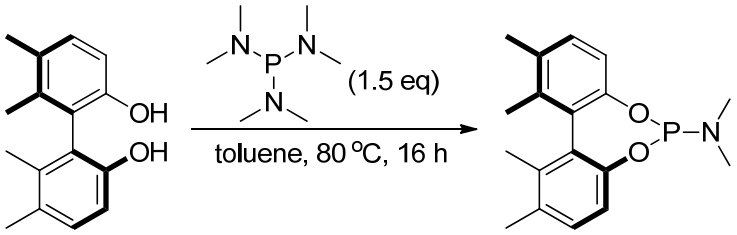
(*S*)-3,3'-bis((dibenzylamino)methyl)-5,5',6,6'-tetramethylbiphenyl-2,2'-diol ((*S*)-1-57)



(*S*)-**1-57**

(*S*)-**1-57** (0.34 g, 62% yield) was obtained as a white solid: mp 159.0–161.0 °C; $[\alpha]_D^{23}$ +26.4 (*c* 0.91, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (s, 6H), 2.23 (s, 6H), 3.46 (d, *J* = 12.9 Hz, 4H), 3.55 (d, *J* = 13.8 Hz, 2H), 3.70 (d, *J* = 13.2 Hz, 4H), 3.91 (d, *J* = 13.8 Hz, 2H), 6.83 (s, 2H), 7.21–7.26 (m, 20H), 10.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 20.0, 57.5, 57.9, 118.6, 125.4, 126.8, 127.5, 128.6, 129.8, 129.8, 135.9, 137.2, 152.8; HRMS (ESI+) calcd for $C_{46}H_{49}N_2O_2$ $[M+H]^+$ 661.3794, found 661.3792 (Δ = –0.3 ppm).

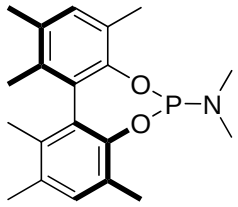
***O,O′*-(*S*)-(5,5′,6,6′-Tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-dimethylphosphoramidite ((*S*)-MPN-La)**[21]



(*S*)-**1-35** (*S*)-**MPN-La**

To a mixture of (*S*)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-**1-35**) (242 mg, 1.00 mmol) in toluene (5 ml), hexamethylphosphorous triamide (HMPT) (248 mg, 1.50 mmol) was added under nitrogen. The reaction mixture was stirred at 80 °C for 16 h and then cooled to room temperature. The solvent was removed *in vacuo* to afford a gel-like liquid, which was further purified by column chromatography on silica gel (neutralized by 1 % NEt_3 in hexanes) (hexanes:EtOAc = 19:1) to give (*S*)-**MPN-La** (300 mg, 95% yield) as a white solid: mp 159.0–161.5 °C; $[\alpha]_D^{22}$ +159.6 (*c* 0.89, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.03 (s, 3H), 2.28 (s, 3H), 2.29 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 143.0. All data are in agreement with the literature values.[21]

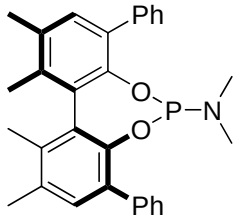
***O,O′*-(*S*)-(3,3',5,5′,6,6′-Hexamethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-dimethylphosphoramidite ((*S*)-MPN-Lb)**[21]



(*S*)-**MPN-Lb**

(*S*)-**MPN-Lb** (302 mg, 88% yield) was obtained as a white solid: mp 119.0–120.0 °C (lit.[21] mp 121.0–121.5 °C); $[\alpha]_D^{22}$ +417.3 (*c* 0.30, CH_2Cl_2) (lit.[21] $[\alpha]_D^{22}$ +488.0 (*c* 0.30, CH_2Cl_2)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (s, 3H), 1.99 (s, 3H), 2.21 (s, 3H), 2.24 (s, 3H), 2.25 (s, 3H), 2.32 (s, 3H), 2.45 (s, 3H), 2.48 (s, 3H), 6.95 (s, 1H), 7.01 (s, 1H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 138.8. All data are in agreement with the literature values.[21]

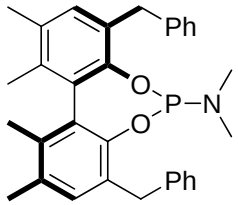
***O,O′*-(*S*)-(3,3'-Diphenyl-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-dimethylphospho ramidite ((*S*)-MPN-Ld)**[21]



(*S*)-**MPN-Ld**

(*S*)-**MPN-Ld** (458 mg, 98% yield) was obtained as a white foam: mp 107.0–109.0 °C (lit.[21] mp 109.5–112.5 °C); $[\alpha]_D^{22}$ +502.1 (*c* 0.48, CH_2Cl_2) (lit.[21] $[\alpha]_D^{22}$ +466.7 (*c* 0.45, CH_2Cl_2)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 3H), 1.90 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.35 (s, 3H), 2.36 (s, 3H), 7.21–7.66 (m, 12H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 140.5. All data are in agreement with the literature values.[21]

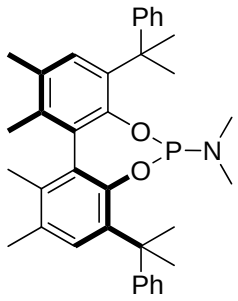
***O,O′*-(*R*)-(3,3'-Dibenzyl-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-dimethylphospho ramidite ((*R*)-MPN-Lf)**



(*R*)-**MPN-Lf**

(*R*)-**MPN-Lf** (320 mg, 65% yield) was obtained as a white solid: mp 110.0–112.0 °C; $[\alpha]_D^{22}$ –176.2 (*c* 0.56, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (s, 3H), 2.01 (s, 3H), 2.22 (s, 3H), 2.23 (s, 3H), 2.52 (s, 3H), 2.55 (s, 3H), 3.70 (d, J = 15.2 Hz, 1H), 4.17 (m, 1H), 6.86 (s, 1H), 6.91 (s, 1H), 7.28 (m, 10H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 140.8; HRMS (EI+) calcd for $C_{24}H_{26}NO_2P$ $[M]^+$ 391.1701, found 391.1703 (Δ = +0.5 ppm).

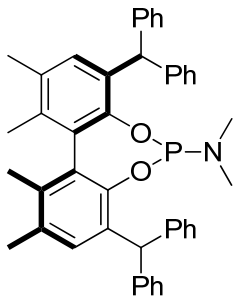
***O,O′*-(*S*)-(3,3'-Bis(dimethylphenylmethyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N* -dimethylphosphoramidite ((*S*)-MPN-Lg)**



(*S*)-**MPN-Lg**

(*S*)-**MPN-Lg** (381 mg, 69% yield) was obtained as a white solid: mp 157.0–159.0 °C; $[\alpha]_D^{20}$ +225.4 (*c* 0.59, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 3H), 1.66 (s, 3H), 1.67 (s, 3H), 1.72 (s, 3H), 1.81 (s, 3H), 1.86 (s, 3H), 2.13 (br s, 6H), 2.17 (s, 3H), 2.30 (s, 3H), 6.84 (s, 1H), 7.05–7.24 (m, 10H), 7.29 (s, 1H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 141.3; HRMS (EI+) calcd for $C_{36}H_{42}NO_2P$ $[M]^+$ 551.2953, found 551.2934 (Δ = –1.9 ppm).

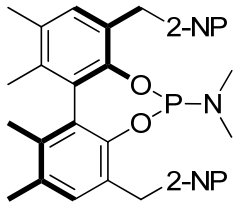
***O,O′*-(*R*)-(3,3'-Bis(diphenylmethyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-dimethylphosphoramidite ((*R*)-MPN-Lh)**



(*R*)-**MPN-Lh**

(*R*)-**MPN-Lh** (422 mg, 65% yield) was obtained as a white foam: mp 134.0–136.0 °C; $[\alpha]_D^{20}$ –177.8 (*c* 0.53, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3H), 2.00 (s, 3H), 2.16 (s, 3H), 2.19 (s, 3H), 2.33 (s, 3H), 2.35 (s, 3H), 5.75 (s, 1H), 5.94 (s, 1H), 6.73 (s, 1H), 6.76 (s, 1H), 6.98 (dd, *J* = 1.2, 8.0 Hz, 2H), 7.13–7.33 (m, 18H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 140.7; HRMS (EI+) calcd for $C_{44}H_{42}NO_2P$ $[M]^+$ 647.2953, found 647.2969 (Δ = +1.7 ppm).

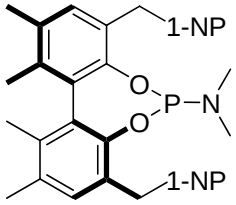
***O,O′*-(*R*)-(3,3'-Bis(naphthalen-2-ylmethyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-dimethylphosphoramidite ((*R*)-MPN-Li)**



(*R*)-**MPN-Li**

(*R*)-**MPN-Li** (375 mg, 63% yield) was obtained as a white foam: mp 158.0–160.0 °C; $[\alpha]_D^{20}$ –490.9 (*c* 0.51, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 3H), 2.00 (s, 3H), 2.18 (s, 3H), 2.19 (s, 3H), 2.54 (s, 3H), 2.56 (s, 3H), 3.84 (d, *J* = 15.0 Hz, 1H), 4.22 (d, *J* = 15.4 Hz, 1H), 4.29 (d, *J* = 15.2 Hz, 1H), 4.36 (d, *J* = 15.0 Hz, 1H), 6.86 (s, 1H), 6.91 (s, 1H), 7.39–7.48 (m, 6H), 7.68–7.83 (m, 8H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 139.1; HRMS (EI+) calcd for $C_{40}H_{38}NO_2P$ $[M]^+$ 595.2640, found 595.2659 (Δ = +1.9 ppm).

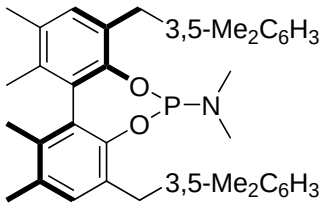
***O,O′*-(*S*)-(3,3'-Bis(naphthalen-1-ylmethyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-dimethylphosphoramidite ((*S*)-MPN-Lj)**



(*S*)-**MPN-Lj**

(*S*)-**MPN-Lj** (546 mg, 92% yield) was obtained as a white foam: mp 147.0–149.0 °C; $[\alpha]_D^{20}$ +389.5 (*c* 0.58, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.00 (s, 3H), 2.11 (s, 3H), 2.12 (s, 3H), 2.58 (s, 3H), 2.60 (s, 3H), 4.04 (d, J = 15.8 Hz, 1H), 4.53 (d, J = 16.4 Hz, 1H), 4.59 (d, J = 16.4 Hz, 1H), 4.76 (d, J = 15.8 Hz, 1H), 6.70 (s, 1H), 6.72 (s, 1H), 7.33–7.51 (m, 8H), 7.75–7.79 (m, 2H), 7.82–7.93 (m, 2H), 8.01–8.17 (m, 2H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 139.0; HRMS (EI+) calcd for $C_{40}H_{38}NO_2P$ $[M]^+$ 595.2640, found 595.2623 (Δ = –1.7 ppm).

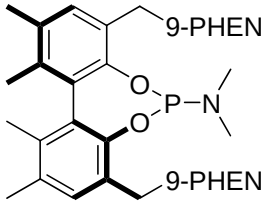
***O,O′*-(*R*)-(3,3'-Bis(3,5-dimethylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-dimethylphosphoramidite ((*R*)-MPN-Lk)**



(*R*)-**MPN-Lk**

(*R*)-**MPN-Lk** (356 mg, 65% yield) was obtained as a white foam: mp 106.0–108.0 °C; $[\alpha]_D^{22}$ –300.0 (*c* 0.62, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (s, 3H), 2.03 (s, 3H), 2.24 (s, 3H), 2.25 (s, 3H), 2.32 (s, 6H), 2.33 (s, 6H), 2.55 (s, 3H), 2.57 (s, 3H), 3.63 (d, J = 14.9 Hz, 1H), 4.01 (d, J = 15.3 Hz, 1H), 4.08 (d, J = 15.3 Hz, 1H), 4.18 (d, J = 14.9 Hz, 1H), 6.86–6.96 (m, 8H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 139.0; HRMS (ESI+) calcd for $C_{36}H_{43}NO_2P$ $[M+H]^+$ 552.3031, found 552.3031 (Δ = 0.0 ppm).

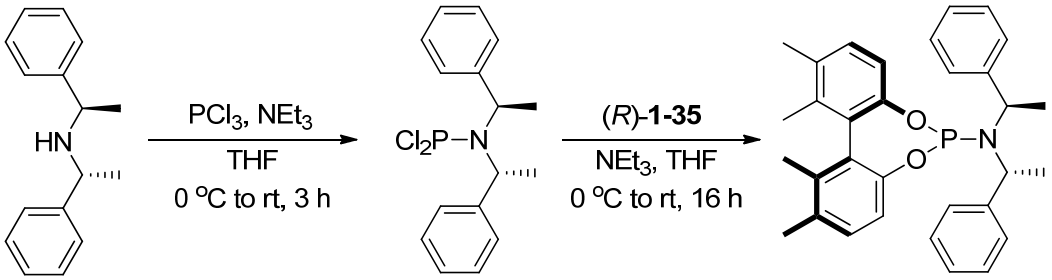
***O,O′*-(*S*)-(3,3'-Bis(phenanthrene-9-ylmethyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-dimethylphosphoramidite ((*S*)-MPN-Ll)**



(*S*)-**MPN-Ll**

(*S*)-**MPN-Ll** (692 mg, 99% yield) was obtained as a white foam: mp over 200.0 °C; $[\alpha]_D^{22}$ +308.6 (*c* 0.70, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (s, 3H), 2.03 (s, 3H), 2.10 (s, 3H), 2.11 (s, 3H), 2.63 (s, 3H), 2.65 (s, 3H), 4.06 (d, *J* = 15.9 Hz, 1H), 4.59 (d, *J* = 16.5 Hz, 1H), 4.66 (d, *J* = 16.5 Hz, 1H), 4.85 (d, *J* = 15.9 Hz, 1H), 6.77 (s, 1H), 6.79 (s, 1H), 7.51–7.71 (m, 10H), 7.86 (dt, *J* = 1.5, 7.4 Hz, 2H), 8.10 (dd, *J* = 1.3, 8.2 Hz, 1H), 8.17 (dd, *J* = 1.5, 8.1 Hz, 1H), 8.71 (td, *J* = 1.3, 7.5 Hz, 2H), 8.76 (td, *J* = 1.3, 8.3 Hz, 1H),; ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 139.0; HRMS (ESI+) calcd for $C_{48}H_{43}NO_2P$ $[M+H]^+$ 696.3031, found 696.3032 (Δ = +0.1 ppm).

***O,O′*-(*R*)-(5,5′,6,6′-Tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-bis[(*R*)-methylbenzyl] phosphoramidite ((*R,R,R*)-MPN-Lm)**[22]

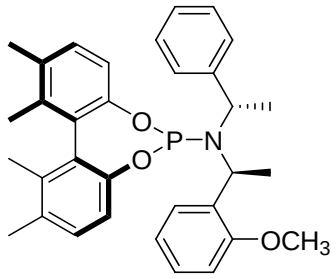


1-58 **1-59** (*R,R,R*)-**MPN-Lm**

The solution of bis((*R*)-1-phenylethyl)amine (0.14 mL, 1.00 mmol) in THF (2 mL) was added to a mixture of PCl_3 (0.17 mL, 2.00 mmol), NEt_3 (0.70 mL, 5.00 mmol), and THF (5 mL) at 0 °C. After addition, the reaction mixture was warmed to room temperature and stirred for 3 h. Then, the reaction mixture was cooled to 0 °C again, and to this cool mixture, a solution of (*R*)-**1-35** (242 mg, 1.00 mmol) in THF (3 mL) was slowly added. After addition, the reaction mixture was stirred at room temperature for 16 h. Then, the resulting mixture was diluted with toluene (10 mL) and filtered through neutral alumina. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel (neutralized by 1 % NEt_3 in

hexanes) (hexanes:EtOAc = 30:1) to give (*R,R,R*)-**MPN-Lk** (0.33 g, 67% yield) as a white foam: mp 60.0–62.5 °C; $[\alpha]_D^{22}$ +171.4 (*c* 0.88, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 3H), 1.64 (s, 3H), 1.94 (s, 3H), 2.00 (s, 3H), 2.19 (s, 3H), 2.27 (s, 3H), 3.30 (m, 2H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 148.2. All data are in agreement with the literature values.[22]

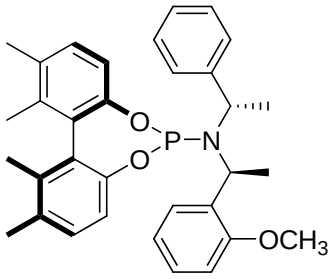
***O,O'*-(*S*)-(5,5',6,6'-Tetramethylbiphenyl-2,2'-diyl) -*N,N*-[(*S*)-1-phenylethyl][(*S*)-1-(2-methoxyphenyl)ethyl]phosphoramidite ((*S,S,S*)-MPN-Ln)**[22]



(*S,S,S*)-**MPN-Ln**

(*S,S,S*)-**MPN-Ln** (278 mg, 53% yield) was obtained as a white solid: mp 77.0–79.0 °C (lit.[22] mp 77.0–78.5 °C); $[\alpha]_D^{20}$ –100.2 (*c* 0.58, CH_2Cl_2) (lit.[22] $[\alpha]_D^{22}$ –102.4 (*c* 1.25, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (d, *J* = 6.8 Hz, 6H), 1.82 (s, 3H), 1.85 (dd, *J* = 2.0, 7.6 Hz, 3H), 1.87 (s, 3H), 1.91 (s, 3H), 2.02 (s, 3H), 3.06 (s, 3H), 5.04 (m, 2H), 6.31 (dd, *J* = 1.2, 7.6 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.90–7.04 (m, 6H), 7.26 (t, *J* = 6.8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H), 8.06 (dt, *J* = 1.6, 7.6 Hz, 1H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 147.3. All data are in agreement with the literature values.[22]

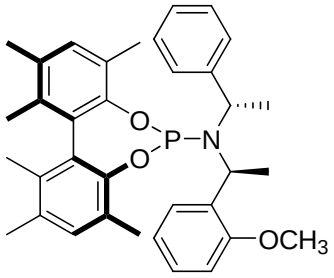
***O,O'*-(*R*)-(5,5',6,6'-Tetramethylbiphenyl-2,2'-diyl) -*N,N*-[(*S*)-1-phenylethyl][(*S*)-1-(2-methoxyphenyl)ethyl]phosphoramidite ((*R,S,S*)-MPN-Lo)**



(*R*,*S*,*S*)-**MPN-Lo**

(*R,S,S*)-**MPN-Lo** (189 mg, 36% yield) was obtained as a white solid: mp 139.0–140.0 °C ; $[\alpha]_D^{22}$ –178.0 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, *J* = 6.9 Hz, 3H), 1.66 (dd, *J* = 1.6, 7.5 Hz, 3H), 2.01 (s, 3H), 2.03 (s, 3H), 2.26 (s, 3H), 2.31 (s, 3H), 3.53 (s, 3H), 4.53–4.59 (m, 1H), 4.83–4.93 (m, 1H), 6.46 (dd, *J* = 1.1, 8.2 Hz, 1H), 6.77 (td, *J* = 1.1, 7.5 Hz, 1H), 6.83–6.92 (m, 3H), 6.98 (ddd, *J* = 1.7, 7.3, 8.1 Hz, 1H), 7.04–7.23 (m, 6H) 7.44 (dt, *J* = 1.5, 7.7 Hz, 1H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 139.0; HRMS (ESI+) calcd for $C_{33}H_{37}NO_3P$ $[M+H]^+$ 526.2511, found 526.2509 (Δ = –0.4 ppm).

***O,O'*-(*S*)-(3,3',5,5',6,6'-Hexamethylbiphenyl-2,2'-diyl) -*N,N*-[(*S*)-1-phenylethyl][(*S*)-1-(2-methoxyphenyl)ethyl]phosphoramidite ((*S,S,S*)-MPN-Lp)**

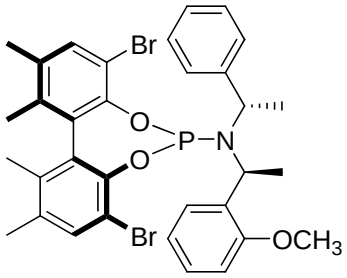


(*S*,*S*,*S*)-**MPN-Lp**

(*S,S,S*)-**MPN-Lp** (372 mg, 67% yield) was obtained as a white solid: mp 121.0–123.0 °C ; $[\alpha]_D^{22}$ +63.9 (*c* 0.72, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, *J* = 7.0 Hz, 3H), 1.57 (dd, *J* = 1.3, 7.2 Hz, 3H), 1.85 (s, 3H), 1.89 (s, 3H), 1.98 (s, 3H), 2.21 (s, 3H), 2.25 (s, 3H), 2.43 (d, *J* = 0.9 Hz, 3H), 3.61 (s, 3H), 4.47–4.54 (m, 1H), 4.87–4.95 (m, 1H), 6.63–6.69 (m, 1H), 6.81–6.87 (m, 2H), 7.05–7.19 (m, 7H), 7.64 (dd, *J* = 1.7, 7.6 Hz, 1H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 142.2; HRMS (ESI+) calcd for $C_{35}H_{41}NO_3P$ $[M+H]^+$ 554.2824, found 554.2822 (Δ

= –0.4 ppm).

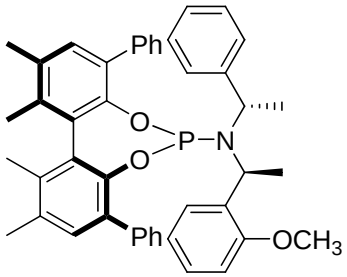
***O,O'*-(*S*)-(3,3'-Dibromo-5,5',6,6'-tetramethylbiphenyl-2,2'-diyl)-*N,N*-[(*S*)-1-phenylethyl][(*S*)-1-(2-methoxyphenyl)ethyl]phosphoramidite ((*S,S,S*)-MPN-Lq)**



(*S*,*S*,*S*)-**MPN-Lq**

(*S,S,S*)-**MPN-Lq** (537 mg, 79% yield) was obtained as a white solid: mp 134.0–136.0 °C ; $[\alpha]_D^{22}$ +171.2 (*c* 0.73, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, *J* = 7.0 Hz, 3H), 1.55 (d, *J* = 7.0 Hz, 3H), 1.88 (s, 3H), 1.94 (s, 3H), 2.21 (s, 3H), 2.21 (s, 3H), 2.28 (s, 3H), 3.66 (s, 3H), 4.40–4.47 (m, 1H), 4.82–4.90 (m, 1H), 6.61 (dd, *J* = 1.1, 8.2 Hz, 1H), 6.85 (td, *J* = 1.2, 7.5 Hz, 1H), 7.03–7.13 (m, 4H), 7.28–7.35 (m, 3H), 7.47 (s, 1H), 7.73 (dd, *J* = 1.7, 7.7 Hz, 1H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 146.4; HRMS (ESI+) calcd for $C_{33}H_{35}Br_2NO_3P$ $[M+H]^+$ 682.0721, found 682.0719 (Δ = –0.3 ppm).

***O,O'*-(*S*)-(3,3'-Diphenyl-5,5',6,6'-tetramethylbiphenyl-2,2'-diyl)-*N,N*-[(*S*)-1-phenylethyl][(*S*)-1-(2-methoxyphenyl)ethyl]phosphoramidite ((*S,S,S*)-MPN-Lr)**

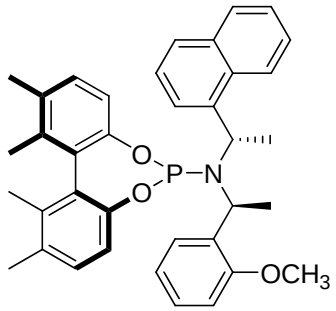


(*S*,*S*,*S*)-**MPN-Lr**

(*S,S,S*)-**MPN-Lr** (550 mg, 81% yield) was obtained as a white solid: mp 125.0–127.0 °C ; $[\alpha]_D^{22}$ +178.4 (*c* 1.11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (dd, *J* = 1.5, 7.4 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 2.05 (s, 3H), 2.15 (s, 3H), 2.34 (s, 3H), 2.36–2.39 (m, 3H), 3.32 (s, 3H), 4.27–4.34 (m, 1H), 4.36–4.44 (m, 1H), 6.42 (dd, *J* = 1.1, 8.2 Hz, 1H), 6.50 (td, *J* = 1.1, 7.5 Hz,

1H), 6.56 (dd, *J* = 1.7, 7.4 Hz, 1H), 6.78–6.83 (m, 2H), 6.86–6.92 (m, 1H), 6.94 (ddd, *J* = 1.7, 7.4, 8.1 Hz, 1H), 6.98–7.04 (m, 1H), 7.20 (s, 1H), 7.27–7.42 (m, 7H), 7.52–7.56 (m, 2H), 7.59–7.65 (m, 2H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 146.0; HRMS (ESI+) calcd for $C_{45}H_{44}NO_3P$ $[M+H]^+$ 678.3137, found 678.3133 (Δ = –0.6 ppm).

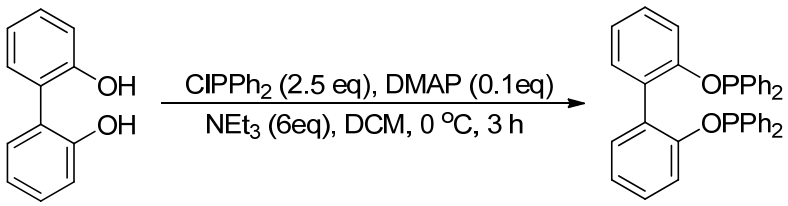
_O,O'_-(_S_)-(5,5',6,6'-Tetramethylbiphenyl-2,2'-diyl)-_N,N_-[(_S_)-1-(napthalen-2-yl)ethyl][(_S_)-1-(2-methoxy-phenyl)ethyl]phosphoramidite ((_S,S,S_)-MPN-Ls)[22]



(*S*,*S*,*S*)-**MPN-Ls**

(*S,S,S*)-**MPN-Ls** (401 mg, 70% yield) was obtained as a white solid: mp 91.0–93.0 °C (lit.[22] mp 92.0–94.0 °C); $[\alpha]_D^{22}$ +96.3 (*c* 1.02, CH_2Cl_2) (lit.[22] $[\alpha]_D^{22}$ +96.7 (*c* 1.23, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (d, *J* = 7.2 Hz, 3H), 1.60 (d, *J* = 7.2 Hz, 3H), 1.98 (s, 6H), 2.12 (s, 3H), 2.32 (s, 3H), 3.58 (s, 3H), 3.75 (m, 1H), 5.37 (m, 1H), 6.49–6.67 (m, 4H), 6.89 (td, *J* = 0.8, 7.2 Hz, 1H), 7.10 (d, *J* = 8 Hz, 1H), 7.22 (d, *J* = 8 Hz, 1H), 7.29 (t, *J* = 8 Hz, 1H), 7.37 (m, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.71 (m, 1H), 7.81 (m, 1H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 151.1. All data are in agreement with the literature values.[22]

2,2'-Bis[(diphenylphosphino)oxy]-1,1'-biphenyl (1-61)[38]

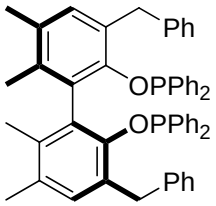


1-60 **1-61**

To a mixture of a 2,2'-biphenol **1-60** (186 mg, 1.00 mmol), 4-*N*,*N*-dimethylaminopyridine (DMAP) (12 mg, 0.10 mmol) and triethylamine (0.80 mL, 6 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added a solution of a chlorodiphenylphosphine (0.46 mL, 2.50 mmol) in CH_2Cl_2 (5 mL) over the

period of 20 min *via* a syringe. After addition, the reaction mixture was stirred at 0 °C for 3 h, and concentrated *in vacuo*. The residue was dissolved in dry Et_2O (20 mL) and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (neutralized by 1 % NEt_3 in hexanes) (hexanes:EtOAc = 9:1) to give **1-61** (399 mg, 72% yield) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02–7.26 (m, 28H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 112.8. All data are in agreement with the literature values.[38]

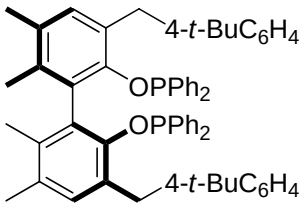
(*S*)-2,2'-Bis(diphenylphosphinyloxy)-3,3'-dibenzyl-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-BOP-Lg)



(*S*)-**BOP-Lg**

(*S*)-**BOP-Lg** (580 mg, 73% yield) was obtained as a white foam: mp 75.0–77.0 °C; $[\alpha]_D^{20}$ +101.0 (*c* 1.03, 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), 6.94–6.98 (m, 4H), 7.05–7.40 (m, 26H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 109.1; HRMS (EI+) calcd for $C_{54}H_{48}O_2P_2$ $[M]^+$ 790.3130, found 790.3136 (Δ = +0.8 ppm).

(*S*)-2,2'-Bis(diphenylphosphinyloxy)-3,3'-bis(4-*tert*-butylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-BOP-Lj)

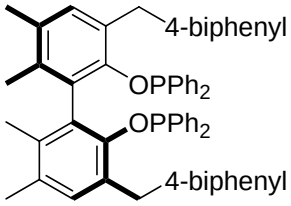


(*S*)-**BOP-Lj**

(*S*)-**BOP-Lj** (632 mg, 70% yield) was obtained as a white foam: mp 71.0–73.0 °C; $[\alpha]_D^{22}$ +93.9 (*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),

7.03–7.38 (m, 24H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 109.1; HRMS (EI+) calcd for $C_{62}H_{64}O_2P_2$ $[M]^+$ 902.4382, found 902.4388 (Δ = +0.7 ppm).

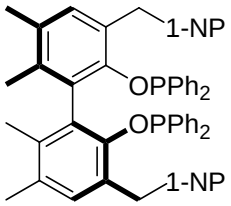
(*S*)-2,2'-Bis(diphenylphosphinyloxy)-3,3'-bis(4-phenylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-BOP-Lk)[26]



(*S*)-**BOP-Lk**

(*S*)-**BOP-Lk** (534 mg, 57% yield) was obtained as a white foam: mp 84.5–87.0 °C (lit.[26] mp 85.0–87.0 °C); $[\alpha]_D^{21}$ +111.2 (*c* 1.01, CH_2Cl_2) (lit.[26] $[\alpha]_D^{21}$ +130.0 (*c* 0.29, CH_2Cl_2)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (s, 6H), 1.88 (s, 6H), 3.52 (d, *J* = 16.2 Hz, 2H), 3.69 (d, *J* = 16.2 Hz, 2H), 6.44 (s, 2H), 7.00 (d, *J* = 8.1 Hz, 4H), 7.07–7.45 (m, 30H), 7.56 (d, *J* = 7.5 Hz, 4H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 110.62. All data are in agreement with the literature values.[26]

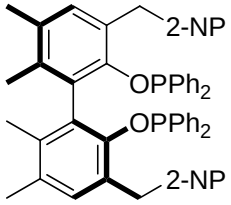
(*S*)-2,2'-Bis(diphenylphosphinyloxy)-3,3'-bis(naphthalene-1-ylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-BOP-Ll)



(*S*)-**BOP-Ll**

(*S*)-**BOP-Ll** (653 mg, 73% yield) was obtained as a white foam: mp 114.5–116.5 °C; $[\alpha]_D^{20}$ +143.9 (*c* 1.07, CH_2Cl_2); ^{1}H 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), 6.97–7.17 (m, 14H), 7.30–7.46 (m, 14H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.80–7.84 (m, 4H); ^{31}P NMR (161.9 Hz, $CDCl_3$) δ 108.7; HRMS (EI+) calcd for $C_{62}H_{52}O_2P_2$ $[M]^+$ 890.3443, found 890.3436 (Δ = –0.8 ppm).

(*S*)-2,2'-Bis(diphenylphosphinyloxy)-3,3'-bis(naphthalene-2-ylmethyl)-5,5',6,6'-tetramethyl -1,1'-biphenyl ((*S*)-BOP-Lm)



(*S*)-**BOP-Lm**

(*S*)-**BOP-Lm** (493 mg, 55% yield) was obtained as a white foam: mp 119.0–121.0 ^{o}C; $[\alpha]_D^{20}$ +137.3 (*c* 1.02, 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), 7.06–7.19 (m, 12H), 7.29–7.50 (m, 15H), 7.63–7.82 (m, 7H); ^{31}P NMR (161.9 Hz, $CDCl_3$) δ 109.0; HRMS (ESI+) calcd for $C_{62}H_{52}NO_2P_2$ $[M+H]^+$ 891.3521, found 891.3520 (Δ = –0.1 ppm).

1.5. References

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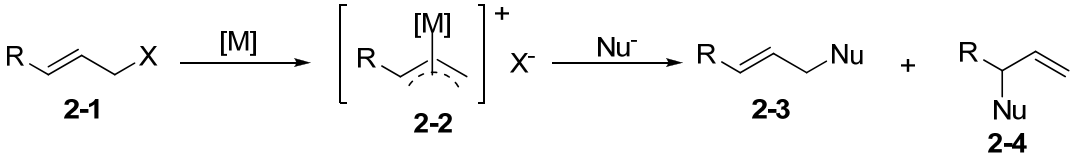
Chapter 2

Palladium-Catalyzed Intermolecular Asymmetric Allylic Amination with Bidentate Diphosphonite Ligands

2.1. Introduction

2.1.1. Allylic substitution reaction

Metal-catalyzed asymmetric reactions have played an important role in the synthesis of biologically active substances.[1,2] Among various transformations, the transition metal-catalyzed allylic substitution reactions provide unique and powerful methods for the regio- and stereocontrolled formation of carbon–carbon bonds and carbon–heteroatom bonds.[3] As illustrated in **Scheme 2-1**, these reactions involve the formation of a π-allyl metal species **2-2** which can be attacked by the nucleophile to form new chemical bonds with different chemo-, regio- and stereoselectivities. Whilst most enantioselective versions of these reactions use palladium complexes as the metal catalysts,[4] the use of molybdenum,[5-8] tungsten,[9] ruthenium,[10-14] rhodium,[15-18] and iridium catalysts[19-22] has been steadily increasing, albeit their efficiencies are not as high as that of palladium catalysts. Thus, chiral palladium catalysts have been used almost exclusively for applications of asymmetric allylic substitutions in the total synthesis of complex natural products and their congeners.[3,23]

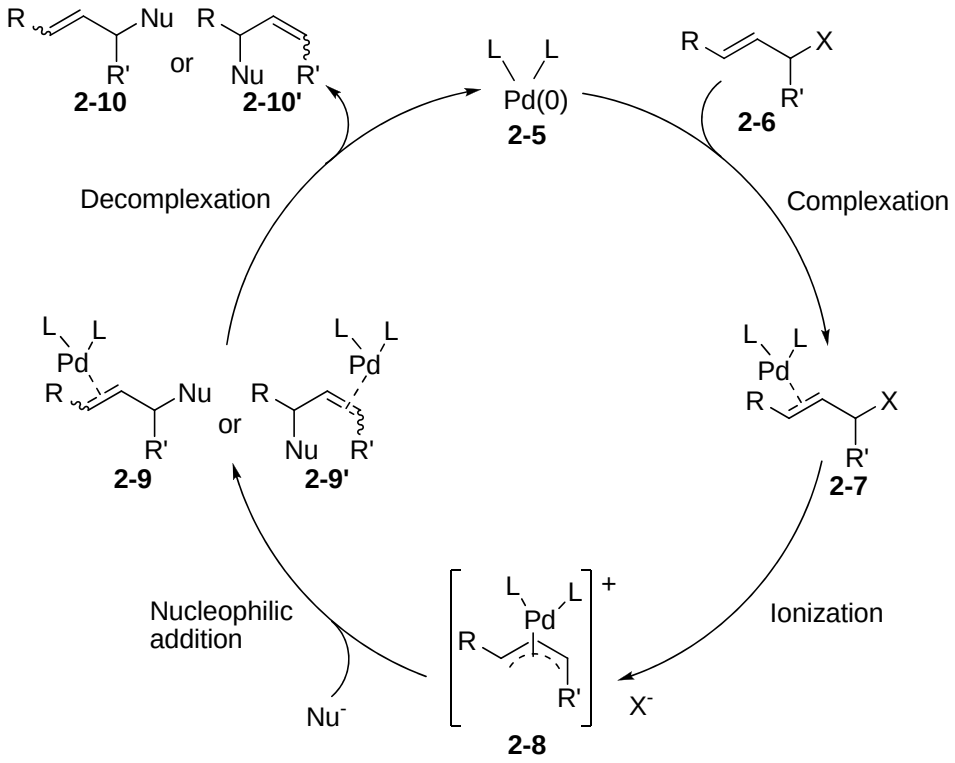


Scheme 2-1. Allylic substitution reaction.

The first example of an enantioselective palladium-catalyzed allylic substitution reaction with a nucleophile was reported by Trost and his coworker in 1977.[24] Since then, efforts have been made to harness the asymmetric potential of allylic alkylations. Understanding the origins of enantioselectivity is essential to the design and utilization of this process in applications. In this process, to fulfill the stereochemical requirement, the chiral ligands must somehow reach across the plane of the allyl fragment to transfer their chirality to the event responsible for the enantiodiscrimination.

The generally accepted mechanism for the palladium-catalyzed allylic substitution is illustrated in **Scheme 2-2**.[25] The catalytic cycle launches from the complexation step, in which the olefin coordinates to the precatalyst $Pd(0)L_2$ **2-5**. In the second step, ionization, X^- is detached from the allyl moiety leading to the formation of a Pd(II)-allyl intermediate **2-8**. In this

step, it is generally observed that the ionization occurs with the leaving group at a position *anti* to the metal. Followed by the ionization, the third step is the nucleophilic addition of the nucleophile to the Pd(II)-allyl complex **2-8** to give the corresponding Pd(0)-olefin complex (**2-9** or **2-9'**). Hard nucleophiles (pKa>25), such as alkylmetals, bind to the palladium metal first, thus resulting in a *syn*-attack on the allylic substrate. On the other hand, soft nucleophiles which generally refer to stabilized nucleophiles, give rise to attack on the π-allyl group *anti* to the metal. The last step of the catalytic cycle is the decomplexation where the newly formed products are released and $Pd(0)L_2$ **2-5** is regenerated for the next cycle. Based on the mechanism, except for the final decomplexation step, every step in the catalytic cycle could play a key role in enantiomeric discrimination.



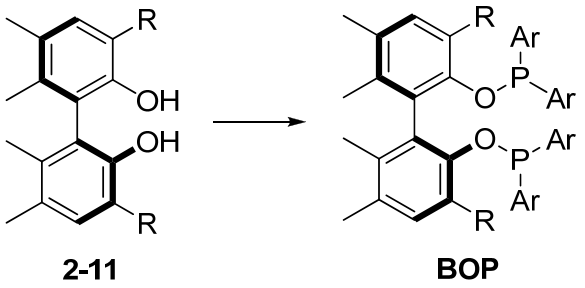
Scheme 2-2. Mechanism of the Pd(0)-catalyzed allylic substitution.

Extensive efforts have been made for the development of efficient chiral ligands for palladium-catalyzed asymmetric allylic substitution reactions.[3] Among the most successful ligands, "modular" diphosphine ligands developed by Trost *et al.*[3,23] and a series of P–N ligands developed by Pfaltz, Helmchen, and Williams independently[26-29] have been widely used. However, these chiral ligands do not always achieve high enantioselectivity or catalyst efficiency

in different various systems.[25,30] Thus, there is a continuous need for new and efficacious chiral ligands for asymmetric allylic substitution reactions. A diphosphonite ligand 2,2'-bis(diphenylphosphinoyloxy)-1,1'-binaphthyl (**BINAPO**), originally developed by Grubbs and DeVries for asymmetric hydrogenation,[31] was found to be effective and better than 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (**BINAP**) in palladium-catalyzed allylic substitution reactions.[32] The efficacy of BINAPO has been demonstrated in several total syntheses of natural products by Mori and co-workers[33-35] However, the highest enantioselectivity reported for the palladium/(*S*)-BINAPO catalyst is 84% *ee* and no systematic modifications of BINAPO had been reported. Thus, the usage of BINAPO and chiral diphosphonite ligands has been limited.

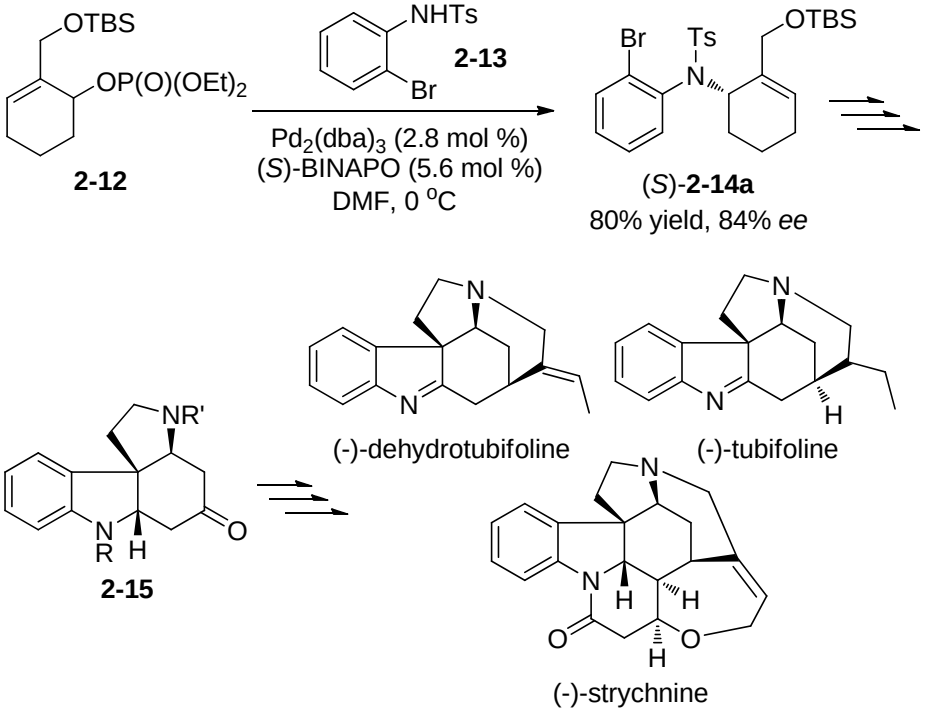
2.1.2. Asymmetric allylic amination using bidentate phosphorus ligands

We have designed and synthesized a series of new chiral biphenol compounds **2-11** (**Scheme 2-3**) that contain various substituents at the 3,3'-positions,[36] and used them to create the libraries of novel monodentate phosphite and phosphoramidite ligands with fine-tuning capabilities.[36-41] These novel monodentate phosphorus ligands have demonstrated excellent efficiency in various transition-metal-catalyzed asymmetric transformations.[36-41] We recognized that the enantiopure C_2–symmetric biphenols **2-11** would also serve as the axial chirality component of BINAPO-type novel diphosphonite (**BOP**) ligands with wide bite angles (**Scheme 2-3**). We hypothesized that a judicious choice of substituents at the 3,3'-positions of the BOP ligand would influence the conformational rigidity of the BOP/metal complex by controlling the orientation of the aryl groups on the phosphorus atoms. The development of chiral ligands bearing fine-tuning capability based on easily modifiable core structures is crucial for a practical combinatorial approach to the selection of the most-suitable ligand for a specific catalytic asymmetric process. Thus, we set out to develop a series of novel BOP ligands with a variety of substituents at the 3,3'-positions.



Scheme 2-3. Biphenol-based diphosphonite ligands (BOPs).

In 2003, Mori and co-workers reported the total synthesis of *Strychnos* indole alkaloids using a palladium/BINAPO complex to catalyze the key intermolecular asymmetric allylic amination (AAA) reaction to construct the critical chiral center (**Scheme 2-4**).[35] The product (*S*)-**2-14a** from this key reaction was converted into versatile key intermediate **2-15** through several steps, which was used as a common intermediate in the total syntheses of (−)-tubifoline, (−)-dehydrotubifoline, and (−)-strychnine (**Scheme 2-4**).[35]



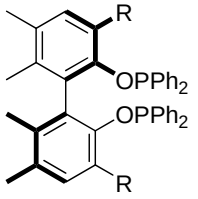
Scheme 2-4. Total synthesis of *Strychnos* indole alkaloids *via* key intermediate **2-14**.

As shown in Scheme **2-4**, the best result for the key step, that is, the intermolecular AAA reaction, was 84% *ee* and 80% yield, when the reaction was performed at 0 °C. Recrystallization

was required in the subsequent steps to obtain enantiomerically pure key intermediate **2-15**.[35] Accordingly, this very useful process still needs substantial improvement in its enantioselectivity and chemical yield. Thus, we selected this process as a showcase to examine the validity of our combinatorial approach to the optimization of the process through fine-tuning of the novel BOP ligands.

2.2. Preliminary Results

The study of the application of BOP ligands (**Figure 2-1**) to intermolecular AAA reaction was first carried out by Ce Shi in the Ojima group.[42] For initial BOP ligand screening, 2-TBSO-methylcyclohex-2-en-1-yl vinyl carbonate (**2-16a**) was used as the allylic component, because it was the best substrate in Mori's reactions with Pd-BINAPO catalyst, and *N*-(2-bromophenyl)-4-methylbenzenesulfonamide (**2-13**) as the amine component. As solvent, THF and DMF were used with the concentration of **2-16a** at 0.05 M and the Pd/ligand ratio of 1:1.5. Ligands (*R*)-**BOP-La**−**d** were screened first under those conditions.

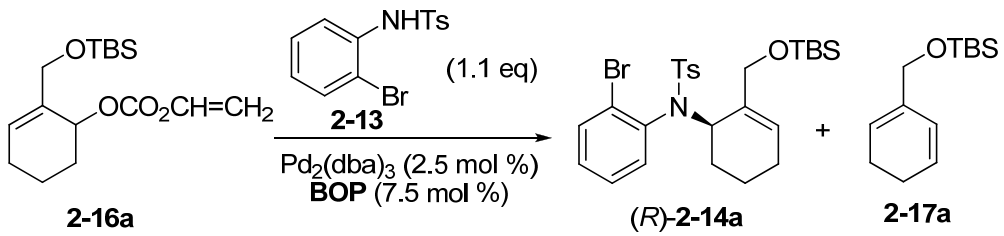


(*R*)-**BOP-La**: R= H
(*R*)-**BOP-Lb**: R= Br
(*R*)-**BOP-Lc**: R= Me
(*R*)-**BOP-Ld**: R= Ph

Figure 2-1. BOPs used for initial screening.

As Table 1 shows, all reactions gave the desired product **2-14a**, but with different conversion and enantioselectivity as the substituents at the 3,3'-positions of the biphenol moieties of BOP ligands varied. The formation of elimination product **2-17a**, which was not reported previously, was also observed.[35] It is highly likely that the ceiling of the chemical yield (64−80%) reported for the formation of **2-14a** by Mori *et al.* is attributed to the considerable formation of **2-17a**. The ratio of **2-14a** to **2-17a** was determined by ^{1}H NMR analysis. Results on the reactions in THF indicate that the reaction is slowed down as the size of the 3,3'-substituents increases (Entry 1−4). As the 3,3'-substituents change from H to Me, the enantioselectivity increases from 65% *ee* to 89% *ee* (Entries 1 and 3). The use of larger 3,3'-substituents leads to a decrease in enantioselectivity and poor catalytic activity (Entries 2 and 4). When DMF is used as the solvent, a clear acceleration of reaction rate, as well as a substantial increase in the **2-14a**:**2-17a** ratio (up to 95:5), is observed (Entries 5 and 6). Accordingly, the combination of **BOP-Lc** (R = Me) as the chiral ligand and DMF as the solvent afforded the best result in this first screening.

Table 2-1. Initial screening of BOP ligands.

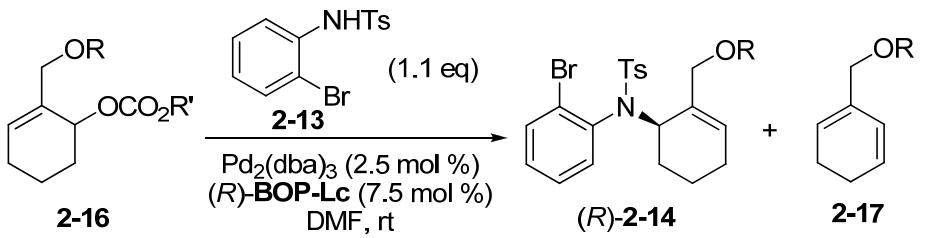


Entry	Ligand	Solvent	Time (h)	Conv.[a] (%)	**2-14a**:**2-17a**[a]	**2-14a** *ee*[b] (%)
1	(*R*)-**BOP-La**	THF	48	>95	70:30	65
2	(*R*)-**BOP-Lb**	THF	72	30	50:50	74
3	(*R*)-**BOP-Lc**	THF	60	>95	65:35	89
4	(*R*)-**BOP-Ld**	THF	72	<5	nd	nd
5	(*R*)-**BOP-La**	DMF	12	>95	95:5	67
6	(*R*)-**BOP-Lc**	DMF	20	>95	95:5	88

[a] The conversion and product yield were determined by ^{1}H NMR.
[b] Determined by chiral HPLC (Chiralpak AD-RH column, eluent: CH_3CN/H_2O = 80/20).

Next, different allylic substrates were examined using (*R*)-**BOP-Lc** as the chiral ligand in DMF. The results are summarized in **Table 2-2**. As **Table 2-2** shows, the use of TBS or TIPS as the bulky silicon protecting group for the allylic alcohol moiety does not make a large difference in the reaction rate, enantioselectivity or product selectivity. There are recognizable differences in the enantioselectivity when vinyl, trichloroethyl and diethylphosphonyl groups are used as the substituents of the carbonate moiety (Entries 1−3). Thus, **2-16d** (R = TIPS; R' = vinyl) appears to be the best allylic substrate among the ones examined, and the reaction of **2-16d** has achieved 91% *ee* at room temperature. This substrate was selected for further investigation of the intermolecular AAA reaction.

Table 2-2. Screening of allylic substrates using (*R*)-**BOP-Lc**.



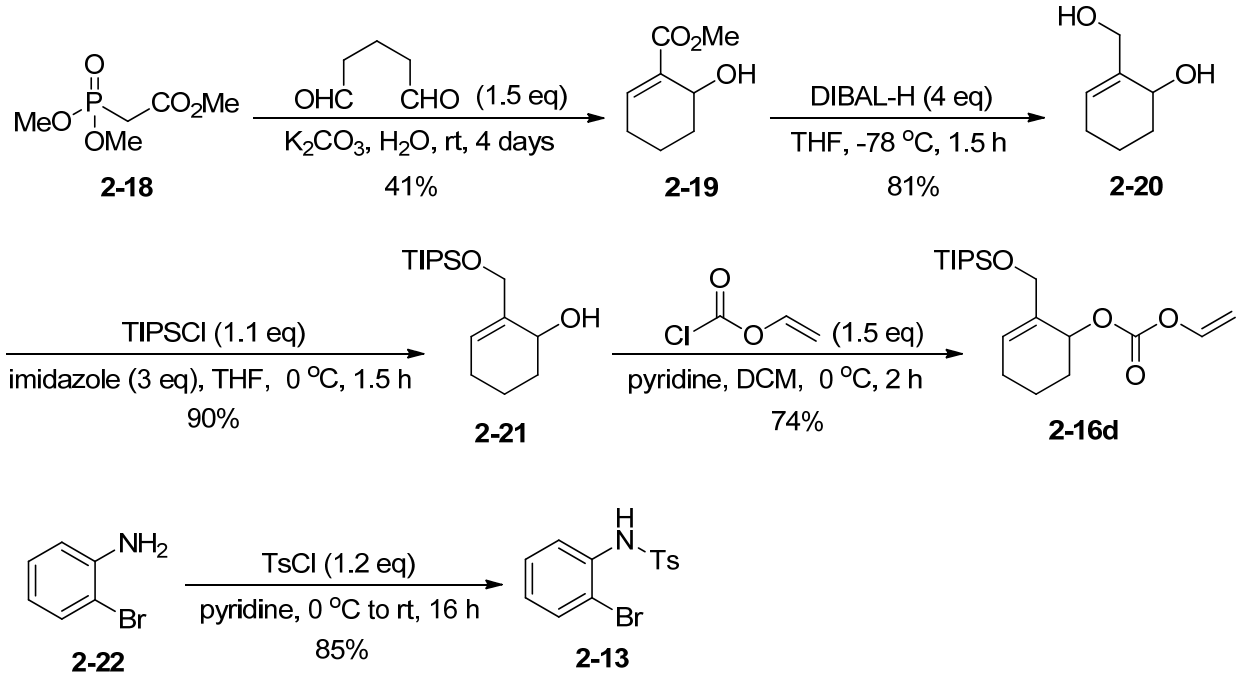
Entry	Allylic substrate	Time (h)	Conv.[a] (%)	**2-14**:**2-17**[a]	**2-14** *ee*[b,c] (%)
1	**2-16a** R = TBS ; R' = vinyl	20	>95	95:5	89
2	**2-16b** R = TBS ; R' = CH_2CCl_3	24	>95	90:10	85
3	**2-16c** R = TBS ; R' = $P(O)(OEt)_2$	16	>95	97:3	83
4	**2-16d** R = TIPS ; R' = vinyl	24	>95	95:5	91
5	**2-16e** R = TIPS ; R' = CH_2CCl_3	30	>95	90:10	88

[a] The conversion and product yield were determined by ^{1}H NMR.
[b] Determined by chiral HPLC (Chiralpak AD-RH column, eluent: CH_3CN/H_2O = 80/20) for OTBS products **2-14a**.
[c] Determined by chiral HPLC (Chiralcel OD-H column, eluent: hexanes/*i*-PrOH = 98/2) for OTIPS products **2-14b** after desilylation with 4 M $HCl_{(aq)}$.

2.3. Results and Discussion

2.3.1. Synthesis of substrate 2-16d and nucleophile 2-13

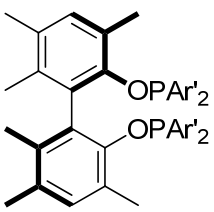
The desired carbonate **2-16d** was prepared based on the reported procedure.[35] As **Scheme 2-5** shows, trimethyl phosphonoacetate (**2-18**) was first reacted with glutaraldehyde under basic conditions. The Horner-Wadsworth-Emmons reaction and aldol condensation product **2-19** was then subjected to reduction conditions using DIBAL-H to give diol intermediate **2-20**. The primary alcohol moiety of diol intermediate **2-20** was protected by TIPS, followed by the reaction of the secondary alcohol **2-21** with vinylchloroformate, to obtain the desired substrate **2-16d**. For the nucleophile synthesis, 2-bromoaniline (**2-22**) was reacted with tosyl chloride to afford **2-13**.



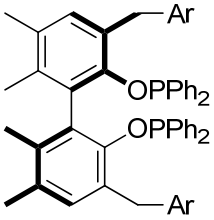
Scheme 2-5. Synthesis of the carbonate substrate and the nucleophile.

2.3.2. Pd-catalyzed intermolecular asymmetric allylic amination

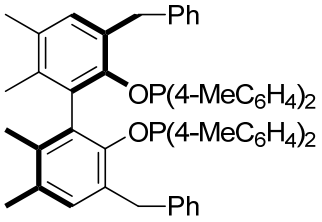
With the selected allylic substrate, **2-16d** (R = TIPS; R' = vinyl), we carry out the optimization of the BOP ligands for this particular reaction under the standard conditions using the small library of BOP ligands created in our laboratory (**Figure 2-2**). Results are summarized in **Table 2-3**.



(*R*)-**BOP-Le**: Ar' = 4-MeC_6H_4
(*R*)-**BOP-Lf**: Ar' = 3,5-$Me_2C_6H_3$



(*R*)-**BOP-Lg**: Ar = Ph
(*R*)-**BOP-Lh**: Ar = 4-MeC_6H_4
(*R*)-**BOP-Li**: Ar = 3,5-$Me_2C_6H_3$
(*S*)-**BOP-Lj**: Ar = 4-*t*-BuC_6H_4
(*S*)-**BOP-Lk**: Ar = 4-$(C_6H_5)C_6H_4$
(*S*)-**BOP-Ll**: Ar = 1-NP
(*S*)-**BOP-Lm**: Ar = 2-NP

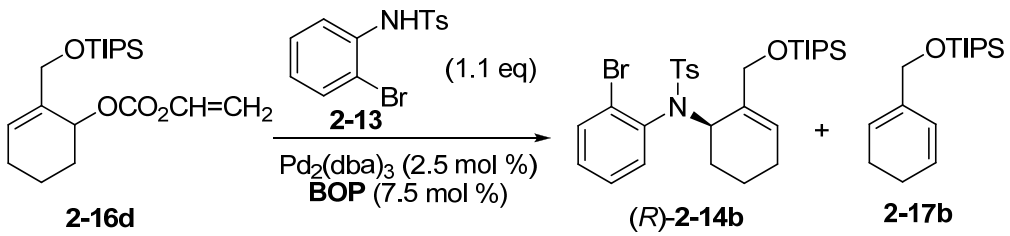


(*R*)-**BOP-Ln**

Figure 2-2. BOP ligand library.

As **Table 2-3** shows, The introduction of substituted phenyls to the diarylphosphorus moieties, i.e., (*R*)-**BOP-Le** (Ar' = 4-MeC_6H_4) (*R*)-**BOP-Lf** (Ar' = 3,5-$Me_2C_6H_3$), slows down the reaction, and also lowers the enantioselectivity as well as the product selectivity (Entries 1 and 2). Ligand (*R*)-**BOP-Lg** (Ar = Ar' = Ph) achieved 96% *ee* (**2-14b**:**2-17b** = 93:7) with complete conversion in 24 h, which is an excellent result. Introduction of substituted phenyls to the 3,3'-position, i.e., (*R*)-**BOP-Lh** (Ar = 4-MeC_6H_4; Ar' = Ph), (*R*)-**BOP-Li** (Ar = 3,5-$Me_2C_6H_3$; Ar' = Ph), (*S*)-**BOP-Lj** (Ar = 4-*t*-BuC_6H_4; Ar' = Ph), and (*S*)-**BOP-Lk** (Ar = 4-$(C_6H_5)C_6H_4$; Ar' = Ph), does not improve the enantioselectivity and product selectivity (Entries 4−7 vs. Entry 3). The 1-naphthylmethyl substituted diphosphonite (*S*)-**BOP-Ll** (Ar = 1-NP) provided 93% *ee* (Entry 8), while the ligand was changed to 2-naphthylmethyl substituted diphosphonite (*S*)-**BOP-Lm** (Ar = 2-NP), the induced *ee* dropped to 76% (Entry 9). Again, another dramatic decrease in both enantioselectivity and product selectivity was observed when introducing substituted phenyls to the diarylphosphorus moieties. (*R*)-**BOP-Ln** (Ar = Ph; Ar' = 4-MeC_6H_4) only afforded 43% *ee* and 65:35 product selectivity (Entry 10). Although it was reported that the best results (84% *ee*, 64% yield or 84% *ee*, 80% yield) with the use of BINAPO were obtained at 0 ^oC,[35] no advantage is observed in our reaction. By using (*R*)-**BOP-Lg** at 0 ^oC, the same enantioselectivity but slightly lower product selectivity were obtained (Entry 11).

Table 2-3. Optimization of chiral ligand for reaction of substrate **2-16d**.



Entry	Ligand	Time (h)	Conv.[a] (%)	**2-14b**:**2-17b**[a]	**2-14b** *ee*[b] (%)
1	(*R*)-**BOP-Le**	50	>95	85:15	89
2	(*R*)-**BOP-Lf**	50	>95	80:20	89
3	(*R*)-**BOP-Lg**	24	>95	93:7	96
4	(*R*)-**BOP-Lh**	24	>95	89:11	94
5	(*R*)-**BOP-Li**	24	>95	90:10	91
6	(*S*)-**BOP-Lj**	36	>95	75:25	73 (*S*)
7	(*S*)-**BOP-Lk**	36	>95	71:29	79 (*S*)
8	(*S*)-**BOP-Ll**	24	>95	73:27	93 (*S*)
9	(*S*)-**BOP-Lm**	24	>95	72:28	76 (*S*)
10	(*R*)-**BOP-Ln**	50	>95	65:35	43
11[c]	(*R*)-**BOP-Lg**	48	>95	90:10	96

[a] The conversion and product yield were determined by ^{1}H NMR.
[b] Determined by chiral HPLC (Chiralcel OD-H column, eluent: hexanes/*i*-PrOH = 98/2) after desilylation with 4 M $HCl_{(aq)}$.
[c] The reaction was carried out at 0 ^oC.

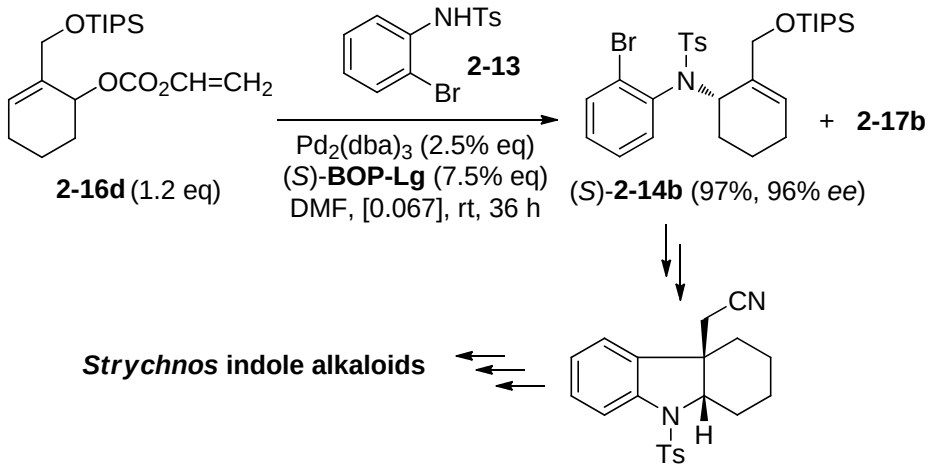
The reaction conditions were again investigated using carbonate **2-16d** and (*R*)-**BOP-Ll** as the chiral ligand. As **Table 2-4** shows, the induced enantioselectivity and product selectivity rarely changed at different reaction concentrations (Entries 1−4). Increasing the chiral ligand amount did not affect the result either. As entry 5 shows, when the ligand-to-metal ratio was increased to 2 to 1 from 1.5 to 1 (Entry 2), the results obtained are identical.

Table 2-4. Optimization of reaction conditions.

Entry	**BOP-Ll**/Pd	Conc. (M)	Time (h)	Conv.[a] (%)	**2-14b**:**2-17b**[a]	**2-14b** *ee*[b] (%)
1	1.5/1	0.05	48	>95	73:27	93
2	1.5/1	0.067	24	>95	73:27	93
3	1.5/1	0.2	16	>95	74:26	92
4	1.5/1	0.5	8	>95	75:25	92
5	2/1	0.067	24	>95	73:27	93

[a] The conversion and product yield were determined by ^{1}H NMR.
[b] Determined by chiral HPLC (Chiralcel OD-H column, eluent: hexanes/*i*-PrOH = 98/2) after desilylation with 4 M $HCl_{(aq)}$.

Finally, we carried out the synthesis of tosylamine (*S*)-**2-14b**, which is the correct enantiomer for the naturally occurring *Strychnos* indole alkaloids, using (*S*)-**BOP-Lg** ligand under the optimized reaction conditions mentioned above, except for 36 h reaction time (**Scheme 2-6**). The reaction of carbonate **2-16d** with tosylamine **2-13** (1.0 mmol) was run using a slight excess of compound **2-16d** (1.2 equiv.) to maximize the product yield. Product (*S*)-**2-14b**, with 96% *ee*, was obtained in 97% isolated yield.

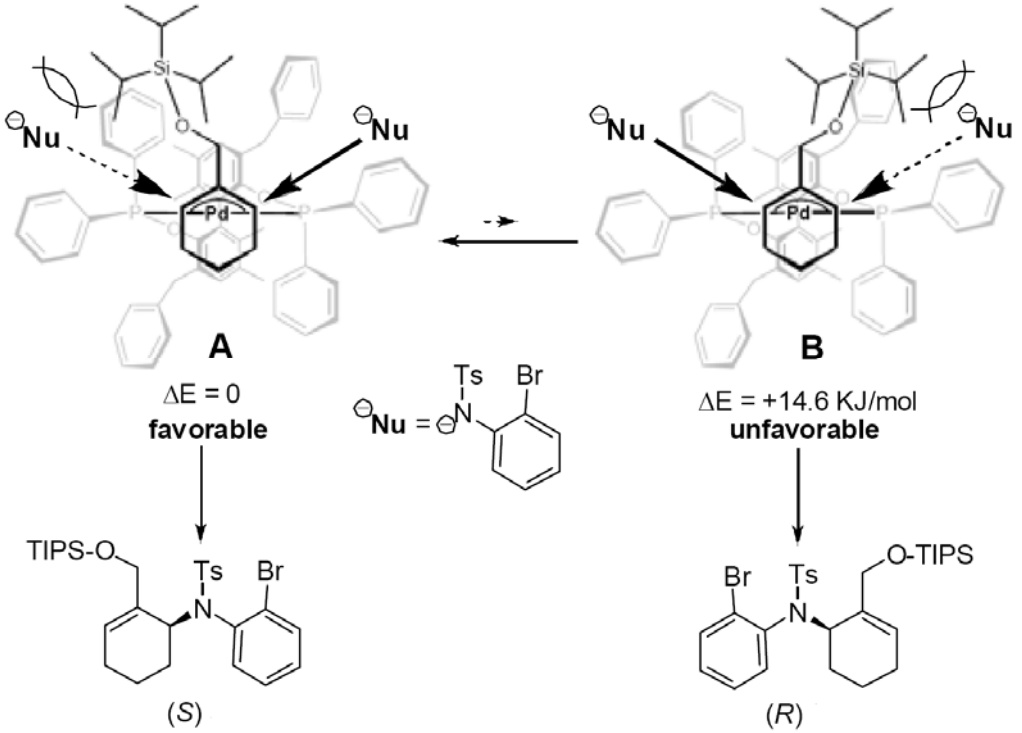


Scheme 2-6. Synthesis of (*S*)-**2-14b**, a key intermediate for *Synchonus* indole alkaloids.

It is reasonable to assume that the Pd:BOP ratio is 1:1 in the active catalyst species. Thus, we carried out molecular modeling of a simplified active catalyst species $[Pd(II)L^*(\pi\text{-allyl})]^+$ (L* = (*R*)-**BOP-Lg**) using the Spartan program (MM2/PM3 for energy minimization). The result after energy minimization clearly indicated a pseudo C_2−symmetrical structure, in which the Ph groups on the PPh_2 moieties form a C_2−symmetrical environment surrounding the allyl moiety. As

anticipated, this complex has a large bite angle (P*−Pd−P*) of 125°, which should be beneficial in achieving high enantioselectivity in the asymmetric allylic amination reaction.

Next, we examined a cationic Pd-(*S*)-**BOP-Lg** complex with a π-allylic *O*-TIPS-2-methylcyclohexenyl group, which is the most likely intermediate in the first step of the asymmetric allylic amination process using **2-16d** as the substrate, i.e., formation of the π-allylic Pd(II)L* species. The molecular modeling study of the complex has revealed that there are two possible conformational isomers, arising from the two possible orientations of the bulky TIPS-O-methyl group. Both orientations led to the local energy-minimized structures, **A** and **B**, illustrated in **Scheme 2-7**. The energy difference between **A** and **B** was calculated to be 14.6 KJ/mol, and **A** is the favorable conformer. The observed energy difference can be attributed to the steric repulsion between the TIPS group and one of the phenyl moieties of the benzyl group at the 3,3'-positions of the backbone chiral biphenyl (**Scheme 2-7**). Accordingly, the predominant pathway for the nucleophilic attack of the anion of TsNH(bromophenyl) (**2-13**) should be through the **A** complex. In the **A** complex, nucleophilic attack from the left side obviously suffers from the steric hindrance of the bulky TIPS group. Thus, the reaction should proceed through the right-side attack, leading to the formation of (*S*)-**2-14b**.



Scheme 2-7. Proposed mechanism for enantioselection.

2.4. Conclusion

A highly efficient Pd-BOP catalyst system has been developed for the intermolecular asymmetric allylic amination reaction of **2-13** and **2-16**, giving the desired product **2-14** with up to 96% *ee*, through systematic optimization of the chiral ligand, allylic substrate and reaction variables. The results clearly show the highly beneficial feature of BOP ligands bearing fine-tuning capability with various substituents on the chiral biphenyl core, especially those at the 3,3'-positions.

2.5. Experimental Section

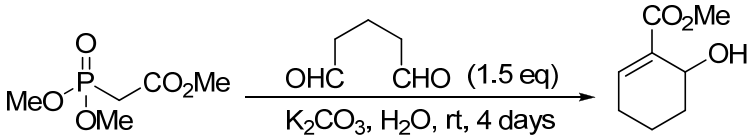
General Method

^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance III HD-Nanobay 400 (400 MHz ^{1}H; 100 MHz ^{13}C), Varian Inova-400 (400 MHz ^{1}H; 100 MHz ^{13}C), or Varian Gemini-2300 (300 MHz ^{1}H; 75 MHz ^{13}C) spectrometer in a deuterated solvent using residual proton ($CHCl_3$: ^{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-Elmer Model 241 polarimeter. TLC was performed on Merck DC-Alufolien Kieselgel 60F 254 and flash column chromatography was carried out on Silicyle Silia*Flash*P60®. Analytical HPLC was carried out with a Shimadzu LC-2010A HPLC system. Low-Resolution Mass Spectrometry was performed on Agilent 6890GC/5973 Mass Selective Detector. High-resolution mass spectrometric analyses were carried out at Mass Spectrometry Laboratories, University of Illinois Urbana-Champaign, Urbana, IL. Unless otherwise noted, all reactions were carried out under nitrogen atmosphere in oven-dried glassware using standard Schlenck technique.

Materials

All solvents used as reaction media were purified using the Solvent Purification System 400-4 from Innovative Technology, Inc. or distilled under nitrogen immediately before use. Ether and THF were distilled from Na/benzophenone ketyl. Toluene and CH_2Cl_2 were distilled from CaH_2. Solvents for extraction and chromatography were reagent grade and used as received. All chemicals were purchased from Aldrich or Acros Chemical Co., and were used without further purification unless otherwise noted.

Methyl 6-hydroxycyclohex-1-enecarboxylate (2-19)[43]

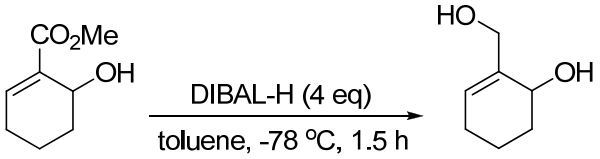


2-18 **2-19**

To a 50% aqueous solution of gluteraldehyde (60.1 g, 150 mmol) was added dropwise trimethyl phosphonoacetate (**2-18**) (14.4 mL, 100 mmol) through an addition funnel over 2 h. At

the same time, 2.5 mL of an aqueous solution of potassium carbonate (31.0 g, 225 mmol in 38 mL H_2O) was added dropwise through a second addition funnel. After the addition of **2-18** was complete, the remainder of the potassium carbonate solution was added dropwise over 2 h. The resulting turbid yellow solution was stirred at room temperature for 4 days. 1 M $HCl_{(aq)}$ (250 mL) was then added to the solution and extracted with Et_2O (50 mL × 4). 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:EtOAc = 7:3) to give **2-19** (6.33 g, 41% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60−1.65 (m, 1H), 1.75−1.86 (m, 3H), 2.14−2.19 (m, 1H), 2.28 (ddt, J = 4.9, 4.9, 20 Hz, 1H), 2.73 (br s, 1H), 3.76 (s, 3H), 4.53 (t, J = 5 Hz, 1H), 7.09 (t, J = 4.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 26.0, 29.8, 51.7, 63.2, 132.0, 143.5, 167.7. All data are in agreement with the literature values.[43]

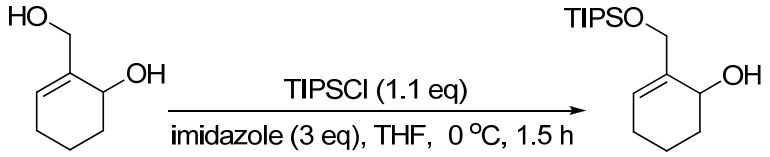
2-(Hydroxymethyl)cyclohex-2-enol (2-20)[35]



2-19 **2-20**

Diisobutylaluminium hydride (DIBAL-H) (25 wt. % in toluene, 53.0 mL, 78.8 mmol) was added to a solution of **2-19** (3.07 g, 19.7 mmol) in toluene (100 mL) at −78 °C over 20 min. After addition, the solution was stirred at −78 °C for 1.5 h. To this solution was added MeOH (1.0 mL) and saturated potassium sodium tartrate solution (50 mL). Then, EtOAc (50 mL) was added and the organic layer was separated by a separation funnel. The organic layer was further washed with water (50 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 1:2) to give **2-20** (2.28 g, 91% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55−2.17 (m, 7H), 2.32 (br s, 1H), 4.21 (br s, 2H), 4.33 (br s, 1H), 5.83 (t, J = 3.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 25.0, 31.4, 65.5, 65.8, 127.7. All data are in agreement with the literature values.[35]

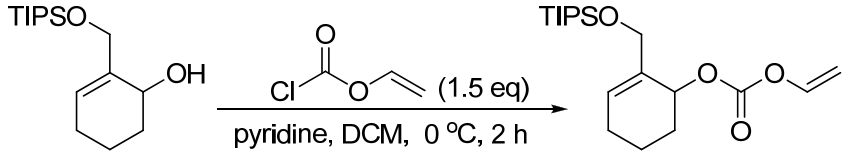
2-{[(Triisopropylsilyl)oxy]methyl}cyclohex-2-enol (2-21)



2-20 **2-21**

A solution of **2-20** (0.77 g, 6.00 mmol), triisopropylchlorosilane (TIPSCl) (1.27g, 6.60 mmol) and imidazole (1.23 g, 18.0 mmol) in THF (60 mL) was stirred at 0 °C for 1.5 h. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ (30 mL) and extracted with Et_2O (30 mL × 3). The combined organic layers were washed with water (30 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 6:1) to give **2-21** (1.42 g, 83% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04−1.10 (m, 21H), 1.53−1.60 (m, 1H), 1.71−1.83 (m, 3H), 1.93−2.01 (m, 1H), 2.05−2.13 (m, 1H), 3.03 (br s, 1H), 4.21−4.28 (m, 2H), 4.34−4.39 (m, 1H), 5.75 (br t, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 18.0, 25.2, 30.9, 66.5, 68.4, 126.8, 137.5; HRMS (EI+) calcd For $C_{13}H_{25}O_2Si$ $[M-i\text{Pr}]^+$ 241.1624, found 241.1622 (Δ = +0.2 ppm).

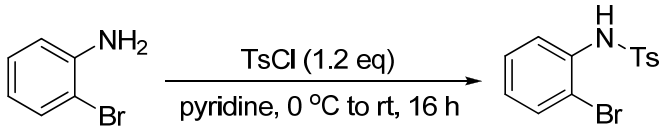
2-(Siloxymethyl)-cyclohex-2-en-1-yl ethenyl carbonate (2-16d)



2-21 **2-16d**

To a solution of **2-21** (0.96 g, 3.39 mmol) and pyridine (3 mL) in CH_2Cl_2 (10 mL) was added vinyl chloroformate (0.31 mL, 3.41 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. After removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel (hexanes) to give **2-16d** (0.89 g, 74% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01−1.08 (m, 21H), 1.61−1.84 (m, 3H), 1.95−2.23 (m, 3H), 4.14 (dd, J = 1.6, 12.9 Hz, 1H), 4.24 (dd, J = 2.1, 12.9 Hz, 1H), 4.54 (dd, J = 1.9, 6.2 Hz, 1H), 4.89 (dd, J = 1.9, 13.9 Hz, 1H), 5.29 (br t, J = 3.9, 1H), 6.02 (br td, J = 1.6, 3.1, 1H), 7.09 (dd, J = 6.2, 13.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 18.0, 24.7, 28.3, 64.4, 72.0, 97.4, 128.6, 134.1, 142.7, 152.4; HRMS (EI+) calcd for $C_{16}H_{27}O_4Si$ $[M-i\text{Pr}]^+$ 311.1679, found 311.1675 (Δ = −1.3 ppm).

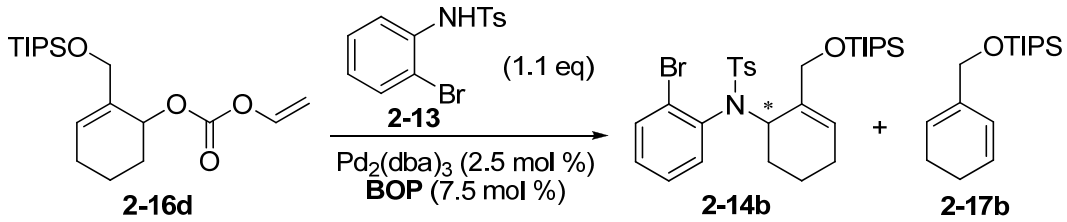
***N*-(2-bromophenyl)-4-methylbenzenesulfonamide (2-13)**[44]



2-22 **2-13**

2-Bromoaniline (**2-22**) (3.44 g, 20.0 mmol) and *p*-toluenesulfonyl chloride (3.82 g, 20.0 mmol) were cooled to 0 °C. Pyridine (30 mL) was added to the mixture under nitrogen. The reaction was stirred for 16 h at room temperature. After removal of solvent *in vacuo*, the residue was added water (30 mL) and extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The solid residue was purified by recrystallization from methanol to give **2-13** (5.56 g, 85% yield) as a white solid: mp 93.0−95.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 6.94−7.25 (m, 4H), 7.27−7.68 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 127.8, 129.0, 129.1, 131.4, 133.7, 134.1. All data are in agreement with the literature values.[44]

General procedure for asymmetric allylic substitution



2-16d **2-14b** **2-17b**

The solution of **2-16d** (35 mg, 0.1 mmol) in DMF (1.0 mL) was added to a solution of $Pd_2(dba)_3$ (2 mg, 2.5 μmol) and (*S*)-**BOP** (7.5 μmol) in DMF (0.5 mL), which was pre-incubated for 15 min before the addition. To this solution was added sulfonamide **2-13** (0.11 mmol) in DMF (0.5 mL) and the solution was stirred at appropriate temperature. Then, EtOAc (10 mL) was added to the reaction mixture. The reaction mixture was washed with water (10 mL) and brine (10mL), and dried over anhydrous Na_2SO_4. Crude product was obtained after filtration and evaporation of the solvent. The conversion and product selectivity of the reaction were checked by ^{1}H NMR. The crude product was then subjected to chiral HPLC analysis, using a Chiralcel OD-H column (isopropanol:hexanes = 2:98, 1 mL/min). The corresponding product *N*-(2-bromophenyl)-*N*-[2-(triisopropylsilyloxy)methylcyclohex-2-en-1-yl]-(4-methylbenzene)sulfonamide (**2-14b**) was isolated by column chromatography on silica gel (hexanes:EtOAc = 19:1)

by combining crude products from several runs. A small amount of 2-siloxymethylcyclo-hexa-1,3-diene (**2-17b**) was also isolated as the sole by product.

_N_-(2-Bromophenyl)-_N_-[2-(triisopropylsilyloxy)methylcyclohex-2-en-1-yl]-(4-methylbenzene)sulfonamide (2-14b)

2-14b was obtained as a colorless oil: 96% *ee* (HPLC); $[\alpha]_D^{23}$ −2.4 for *R* and +2.4 for *S* (*c* 0.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (m, 0.2H), 1.11 (m, 21H), 1.72 (m, 4.3H), 2.22 (m, 1.5H), 3.12 (s, 0.75H), 3.21 (s, 2.25H), 4.62 (m, 2H), 5.92 (br s, 0.2H), 6.07 (br s, 0.8H), 7.17 (m, 4H), 7.64 (m, 2H); 13C NMR (100 MHz, $CDCl_3$) (a mixture of two rotational isomers) δ 12.0 (major), 12.6 (minor), 18.0 (major), 18.8 (minor), 24.3, 28.6 (minor), 29.4 (major), 41.1 (major), 41.9 (minor), 55.2 (major), 57.1 (minor), 65.1 (major), 65.7 (minor), 127.8 (m), 129.7 (m), 134.3 (m), 135.6 (minor), 136.9 (major); HRMS (EI+) calcd for $C_{26}H_{35}O_3NBrSSi$ $[M-i\text{Pr}]^+$ 548.1290, found 548.1288 (Δ = −0.2 ppm).

2-Triisopropylsiloxymethylcyclo-hexa-1,3-diene (2-17b)

2-17b was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (m, 21H), 2.15 (m, 4H), 4.18 (s, 2H), 5.72 (br s, 1H), 5.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 18.2, 22.2, 22.8, 65.6, 119.8, 124.5, 127.0, 135.7; HRMS (ESI+) calcd for $C_{16}H_{31}OSi$ $[M+H]^+$ 267.2144, found 267.2148 (Δ = +1.5 ppm).

2.6. References

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Chapter 3

Palladium-Catalyzed Intramolecular Asymmetric Allylic Amination with Monodentate phosphoramidite Ligands

3.1. Introduction

Development of efficient methods for the synthesis of C1-substituted tetrahydroisoquinolines has attracted much interest among synthetic organic chemists, mainly due to the interesting pharmacological properties these alkaloids possess.[1] Members of this family (**Figure 3-1**) have shown diverse activities,[2] e.g., anti-inflammatory properties,[3,4] neuromuscular transmission blocking,[5] anti-platelet aggregation activity,[6] enzyme inhibitory activities for acetylcholinesterase (AChE),[7] and α-glucosidase.[8] Thus, in order to study the biological and pharmacological activities of this class of compounds, the efficient synthesis of these alkaloids in enantiomerically pure form is of great importance.

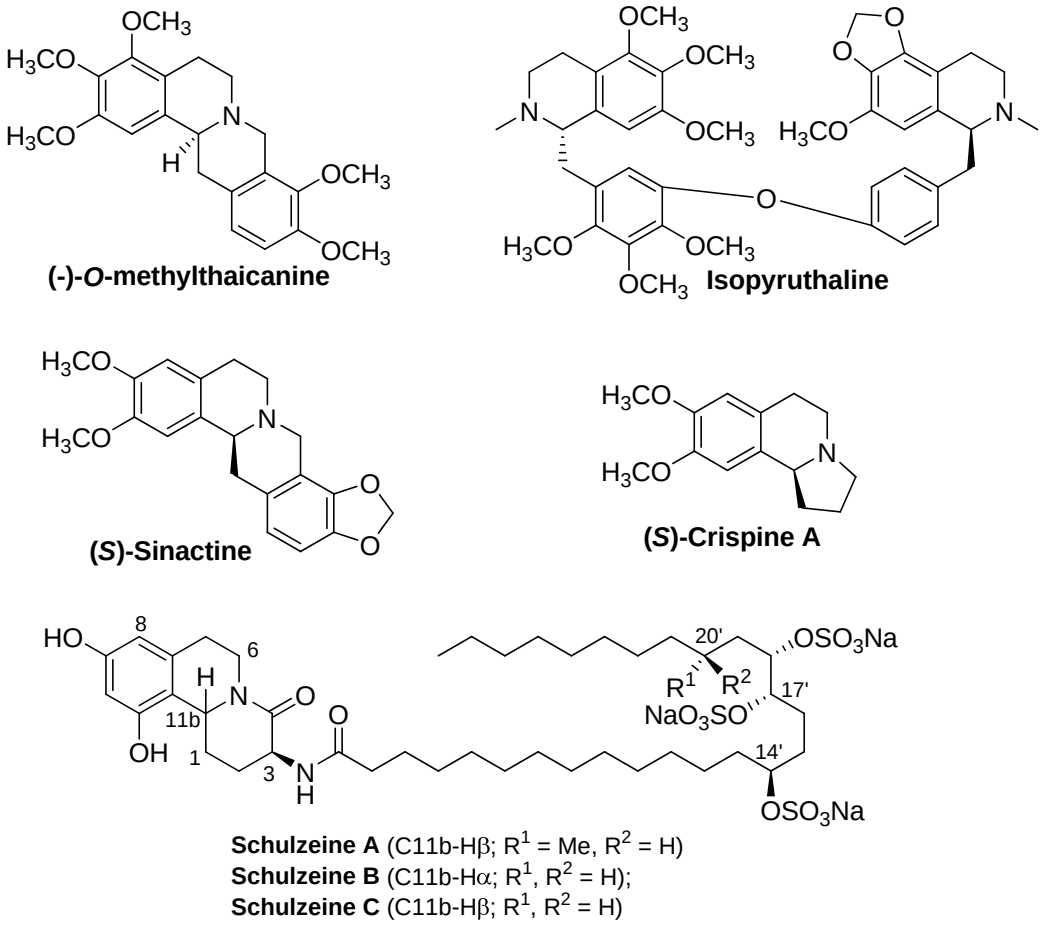


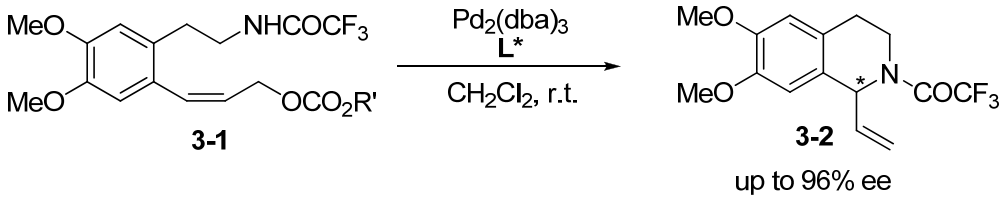
Figure 3-1. Selected naturally occurring C1-substituted tetrahydroisoquinolines.

Optically active C1-substituted tetrahydroisoquinolines have been prepared through diastereoselective reactions for the introduction of chirality at the C1 position. Other methods utilizing enantioselective reactions to introduce the chirality at the C1 position have been

developed in the past decade, e.g., enantioselective Pictete-Spengler reaction,[9] alkylation, vinylation or cyanation of 3,4-dihydroisoquinolines,[10-12] asymmetric hydrogenation of 3,4-dihydroisoquinolines[13,14] as well as 1-alkylidenetetrahydroisoquinolines,[15] and other transformations.[16] In 2003, a Pd-catalyzed intramolecular asymmetric allylic amination (AAA) catalyzed by a Pd catalyst with a chiral P,N-ligand in the presence of a strong base was reported, which gave 6,7-dimethoxy-1-vinyltetrahydroisoquinoline in a single step, introducing chirality at the C1 position.[17] Although high enantioselectivity (82−88% *ee*) was realized under optimized conditions, the catalytic activity of this system was insufficient since it required 12−23 days to reach synthetically meaningful conversions.

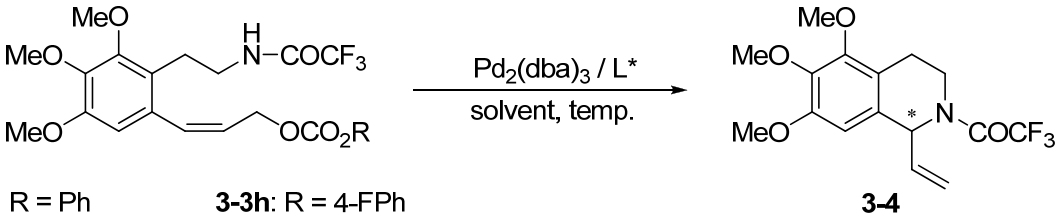
In order to achieve excellent efficiency and enantioselectivity, the selection of suitable chiral ligands for this process is essential. A library of novel enantiopure monodentate phosphite,[18] and phosphoramidite (**MPN**)[19-22] ligands based on axially chiral biphenols has been developed in the Ojima group. These ligands can be readily prepared and are fine-tunable for a variety of catalytic asymmetric reactions, e.g., asymmetric hydrogenation,[18] asymmetric hydroformylation,[20] asymmetric conjugate additions to cycloalkenones and nitroalkenes,[19,20] and asymmetric allylic alkylation as well as its application to the total synthesis of (+)- γ -lycorane.[21,22]

Since a couple of these chiral MPN ligands were found to be extremely effective (up to 99.7% *ee*) in the Pd-catalyzed asymmetric allylic alkylation mentioned above,[21,22] it is anticipated that this type of ligand would be effective for this AAA process. Thus, the employment of the chiral MPN ligands in the intramolecular AAA reaction of carbonate **3-1** was examined, which indeed gave 6,7-dimethoxy-1-vinyltetrahydroisoquinoline **3-2** with excellent enantioselectivity (up to 96% *ee*) and high catalyst activity under neutral conditions (**Scheme 3-1**).[23]



Scheme 3-1. Highly efficient AAA reaction of carbonate **3-1**.

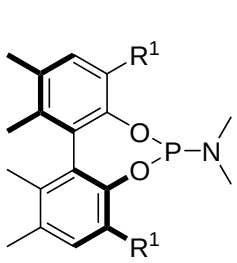
Building upon the successful application of the MPN ligands to the enantioselective synthesis of 6,7-dimethoxy-1-vinyltetrahydroisoquinoline **3-2** through Pd-catalyzed AAA reaction (**Scheme 3-1**), we have expanded the scope of the AAA reaction using MPN ligands (**Figure 3-2**) to the enantioselective synthesis of 5,6,7-trimethoxy-1-vinyltetrahydroisoquinoline **3-4** (**Scheme 3-2**), which servea as a versatile intermediate for the synthesis of the naturally occurring alkaloids exemplified in **Figure 3-1**. We describe here unexpected substituent effects of methoxy groups on the AAA reaction and interesting mechanistic implications, as well as the synthetic utility of the process.



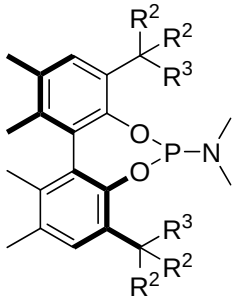
3-4

3-3a: R = Ph
3-3b: R = CH_2CCl_3
3-3c: R = CH_2CF_3
3-3d: R = C_2H_3
3-3e: R = C(Me)CH_2
3-3f: R = 4-MeOPh
3-3g: R = 4-MePh
3-3h: R = 4-FPh
3-3i: R = 4-ClPh
3-3j: R = 3-FPh
3-3k: R = F_5Ph
3-3l: R = 4-NO_2Ph
3-3m: R = 2,6-Me_2Ph
3-3n: R = 2,6-*i*Pr_2Ph

Scheme 3-2. AAA reactions of carbonates **3-3a**−**n**.



(*S*)-**MPN-La**: R^1 = H
(*S*)-**MPN-Lb**: R^1 = Me
(*S*)-**MPN-Lc**: R^1 = Br
(*S*)-**MPN-Ld**: R^1 = Ph
(*S*)-**MPN-Le**: R^1 = *t*-Bu



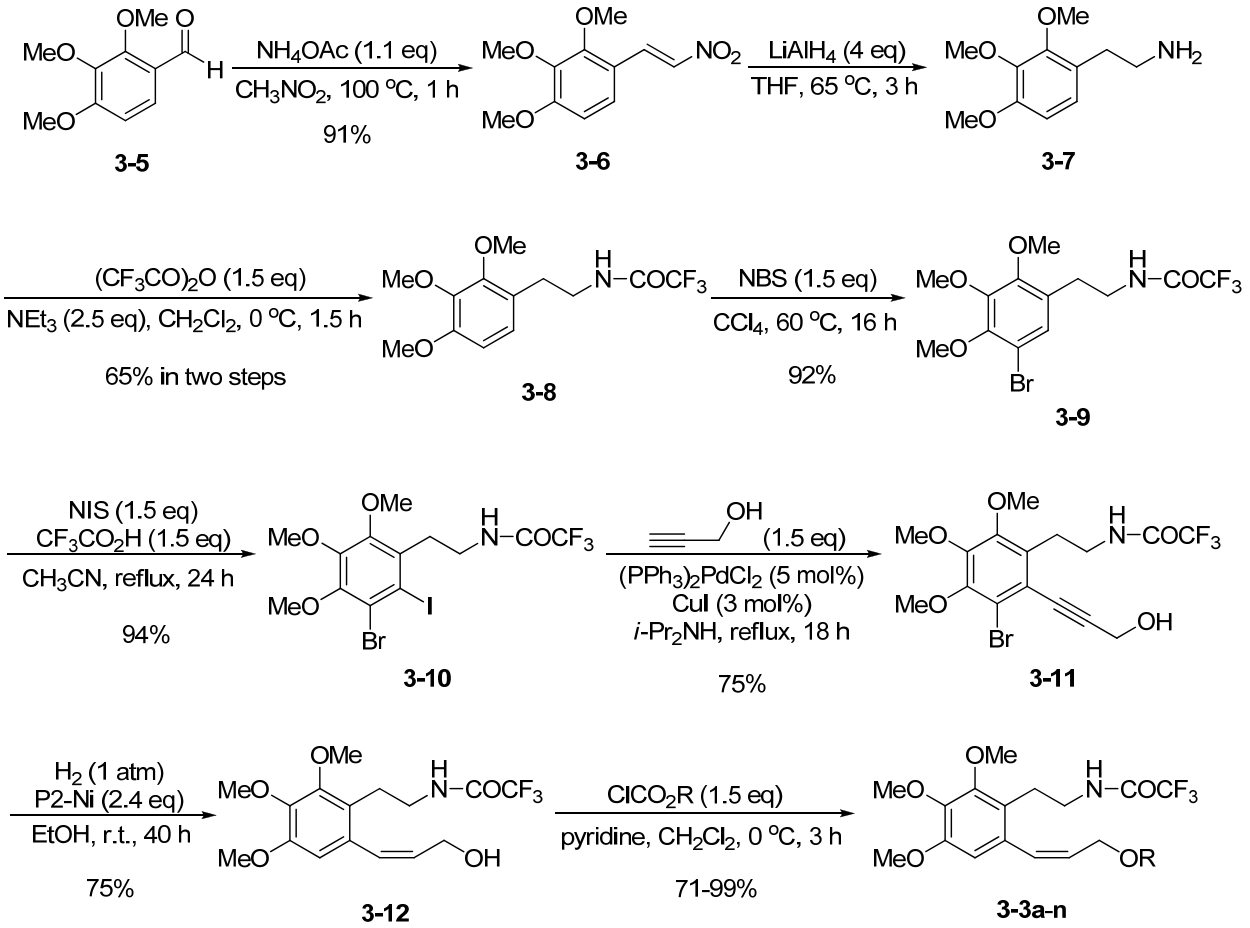
(*R*)-**MPN-Lf**: R^2 = H, R^3 = Ph
(*S*)-**MPN-Lg**: R^2 = Me, R^3 = Ph
(*R*)-**MPN-Lh**: R^2 = Ph, R^3 = H
(*R*)-**MPN-Li**: R^2 = H, R^3 = 2-Np
(*S*)-**MPN-Lj**: R^2 = H, R^3 = 1-Np

Figure 3-2. Phosphoramidite (MPN) ligands.

3.2. Results and Discussion

3.2.1. Preparation of allylic carbonate substrates

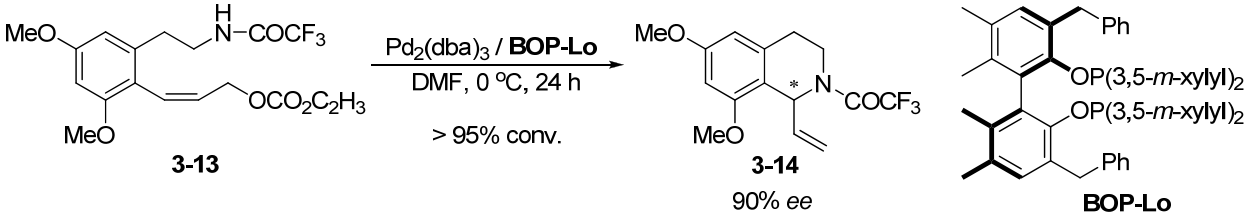
3,4,5-trimethoxy-2-(2-trifluoroacetamidoethyl) phenylallyl carbonates **3-3a**−**n** were prepared as illustrated in **Scheme 3-3**. The nitro-aldol reaction of commercially available 2,3,4-trimethoxybezaldehyde (**3-5**) gave (*E*)-nitroalkene **3-6** exclusively. Nitroalkene **3-6** was reduced to amine **3-7** by $LiAlH_4$, followed by reaction with trifluoroacetic anhydride to give trifluoroacetamide **3-8**. In order to introduce iodine at *ortho* to the trifluoroacetamidoethyl group, bromination of **3-8** with NBS was used to block the *meta* position, giving **3-9**. The iodination of **3-9** by *N*-iodosuccinimide (NIS) afforded **3-10** in 94% yield. The Sonogashira coupling of **3-10** with propargyl alcohol took place selectively with the iodide to give **3-11**. Subsequent hydrogenation of **3-11** over P2−Ni not only reduced the triple bond, but also removed the bromine to afford the corresponding (*Z*)-allylic alcohol **3-12**. Finally, the (*Z*)-allylic alcohol **3-12** was acylated with different chloroformates to give the corresponding allylic carbonates **3-3a**−**n**.



Scheme 3-3. Preparation of carbonates **3-3a**−**n**.

3.2.2. AAA reactions of allylic carbonates 3-3a−n

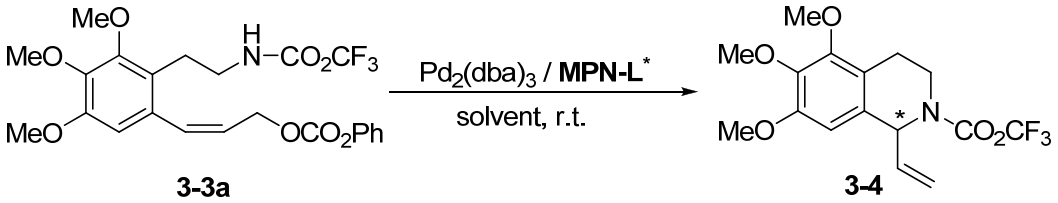
The Pd-catalyzed AAA reaction of 3,4,5-trimethoxylphenylallyl carbonate **3-3d** was first carried out in DMF at room temperature, using the (*R*)-**BOP-Lg** ligand since this ligand gave the best result (90% *ee*), so far, in the reaction of **3-13** (**Scheme 3-4**). However, to our surprise, the reaction gave (*S*)-(+)-tetrahydroisoquinoline **3-4** with only 42% *ee* although the reaction was very fast, clean and completed in 2 h. We also tried one of Trost's representative modular 'DPPBA ligand', (1*R*,2*R*)-*N*,*N'*-bis(2'-diphenylphosphinobenzoyl)-1,2-diaminocyclohexane,[24] under the same conditions, but the conversion was only 18% after 120 h and enantioselectivity was 13% *ee*.



Scheme 3-4. AAA reactions of carbonate **3-13**.

Accordingly, we screened MPN ligands as well as solvents for the reaction of **3-3a** (R=Ph), which achieved excellent results in the reaction of **3-1** (**Scheme 3-1**). Results are summarized in **Table 3-1**. When the AAA reaction was run in DMF, using (*S*)-**MPN-La**−**e**, it proceeded fast and completed in 4−7 h to give compound **3-4** in excellent yield (entries 1−3 and 6), except for (*S*)-**MPN-Ld** (entry 4). The best result in DMF (64% *ee*) was obtained with (*S*)-**MPN-Le** (entry 6). Since the reaction in DMF using (*S*)-**MPN-Ld**, was slow, for some reason, we ran the reaction in CH_2Cl_2 with all other reaction variables intact. Then, the reaction was very fast and gave compound **3-4** with 78% *ee* (entry 5). However, the yield of **3-4** was reduced to 58% with the unexpected formation of allyl phenyl ether **3-18a** (R=Ph) as the side product. This side product **3-18a** should have been formed by the attack of a phenoxide ion, which was generated upon formation of π-allylic Pd intermediate **3-16a**, on the π-allyl system (**Scheme 3-5**). The formation of side product **3-18a** is conceptually possible if the intramolecular attack of the trifluoroamide is slow. Nevertheless, we never observed such a side product in the reactions of carbonates **3-1** and **3-13**. Therefore, this result strongly suggests that there must be some unique reason for the slow nucleophilic cyclization for intermediate **3-16a**, which allows the phenoxide ion to compete.

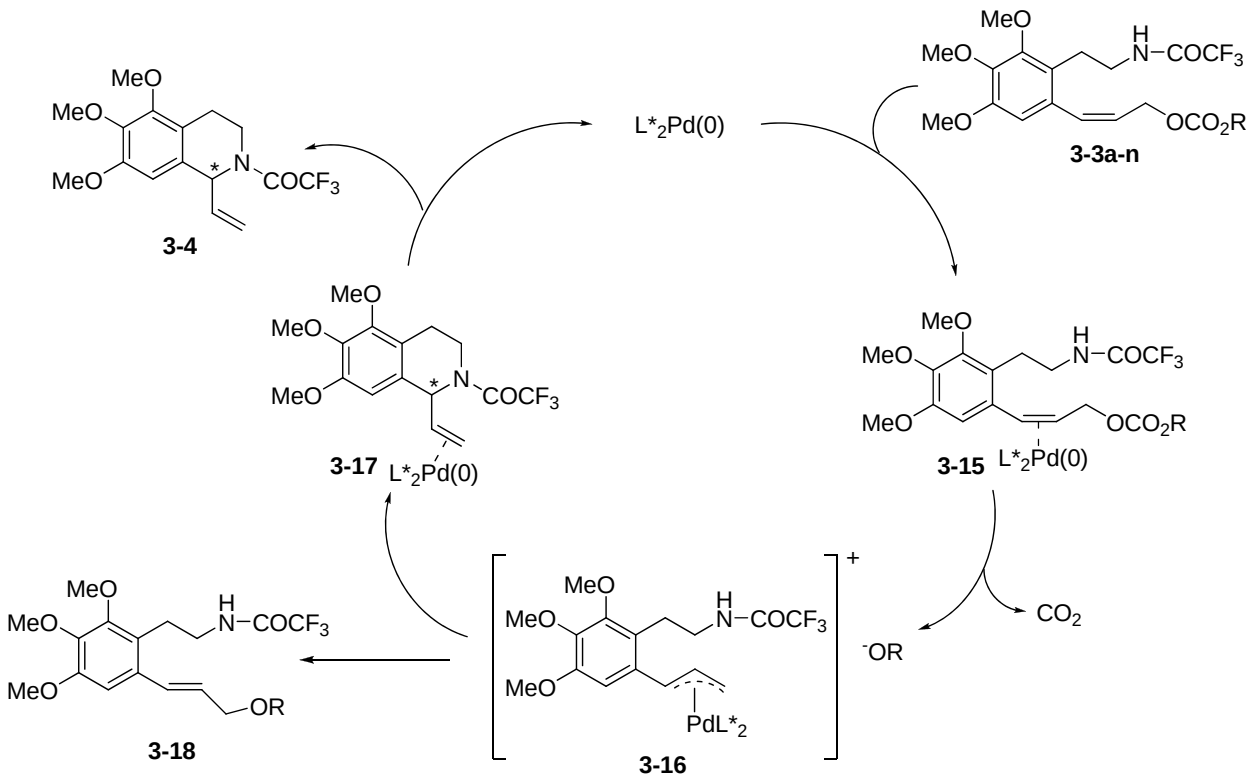
Table 3-1. Screening of MPN ligands for the AAA reaction of carbonate **3-3a**.



3-3a **3-4**

Entry[a]	Ligand	Solvent	Time (h)	Conv.[b] (%)	**3-4**[b] (%)	**3-4** (*S*) *ee*[c] (%)
1	(*S*)-**MPN-La**	DMF	7	>95	98	24 (+)
2	(*S*)-**MPN-Lb**	DMF	7	>95	98	23 (+)
3	(*S*)-**MPN-Lc**	DMF	4	>95	94	46 (+)
4	(*S*)-**MPN-Ld**	DMF	70	>95	97	68 (+)
5	(*S*)-**MPN-Ld**	CH_2Cl_2	3	>95	58	78 (+)
6	(*S*)-**MPN-Le**	DMF	7	>95	93	64 (+)
7	(*S*)-**MPN-Le**	NMP	4	>95	90	64 (+)
8	(*S*)-**MPN-Le**	CH_3CN	70	91	77	17 (−) (*R*)
9	(*S*)-**MPN-Le**	THF	4	>95	55	62 (+)
10	(*S*)-**MPN-Le**	$(CH_2Cl)_2$	4	>95	31	40 (+)
11	(*S*)-**MPN-Le**	CH_2Cl_2	4	>95	29	15 (+)
12	(*S*)-**MPN-Le**	Toluene	4	>95	24	29 (+)

[a] Reaction was run with **3-3a** (0.05 mmol), $Pd_2(dba)_3$ (1.25 μmol), and **MPN-L** (7.50 μmol) in DMF (1.0 mL).
[b] The conversion and product yield were determined by ^1H NMR.
[c] Determined by chiral HPLC (OD-H column, eluent: isopropanol/hexanes = 1.2/ 98.8), flow rate: 1 mL/min.



Scheme 3-5. Proposed mechanism for the intramolecular AAA reaction of carbonate **3-3**.

Since the choice of solvent showed marked effects on the reaction process and enantioselectivity, several different solvents were employed to assess their effects on the AAA reaction, using (*S*)-**MPN-Le**. As **Table 3-1** shows (entries 6−12), there is a remarkable solvent effect on this reaction. The reaction in acetonitrile gave the opposite enantiomer, compound (*R*)-(−)-**3-4**, with low enantiopurity (entry 8). Also, the formation of side product **3-18a** is enhanced in less polar or non-polar solvents (entries 9−12). The results may imply a possible involvement of hydrogen bonding somewhere in the mechanism.

Next, we examined the efficacy of newer MPN ligands, bearing benzyl-type substituents, i.e., $PhCH_2$, $PhCMe_2$, Ph_2CH, 2-$NpCH_2$, and 1-$NpCH_2$, at the 3,3' positions, **MPN-Lf–j** in this reaction. Results are summarized in **Table 3-2**. Reaction using (*R*)-**MPN-Lf** in CH_2Cl_2 at room temperature gave compound **3-4** with 85% *ee* in 57% yield (entry 1). Introduction of bulkier substituents, $PhCMe_2$ (**MPN-Lg**) and Ph_2CH (**MPN-Lh**), did not improve the enantioselectivity (entries 2 and 3). However, the use of 2-$NpCH_2$ (**MPN-Lh**) or 1-$NpCH_2$ (**MPN-Lh**) group in place of the benzyl group was beneficial to improve the yield of compound **3-4** (entries 4 and 5), and the reaction using (*S*)-**MPN-Lj** induced 85% *ee*, which was the same as that by **MPN-Lf**,

but the yield of compound **3-4** was better (65%) (entry 5). The reaction using (*S*)-**MPN-Lj** at 0 ^{o}C improved enantioselectivity to 88% *ee*, but the side product formation increased as well (entry 6). In a manner similar to the solvent effect observed for the reactions using (*S*)-**MPN-Le** (see **Table 3-1**), the use of polar solvent, such as DMF clearly improves the product selectivity to form compound **3-4**, but enantioselectivity was lowered (entry 8).

Table 3-2. Pd-catalyzed AAA reaction of carbonate **3-3a** with **MPN-Lf−j**.

Entry[a]	Ligand	Solvent	Time (h)	Conv.[b] (%)	**3-4**[b] (%)	**3-4** (*S*) *ee*[c] (%)
1	(*R*)-**MPN-Lf**	CH_2Cl_2	4	>95	57	85 (−)
2	(*S*)-**MPN-Lg**	CH_2Cl_2	2	>95	76	35 (+)
3	(*R*)-**MPN-Lh**	CH_2Cl_2	96	>95	71	35 (−)
4	(*R*)-**MPN-Li**	CH_2Cl_2	2	>95	67	78 (−)
5	(*S*)-**MPN-Lj**	CH_2Cl_2	2	>95	65	85 (+)
6[d]	(*S*)-**MPN-Lj**	CH_2Cl_2	2	>95	59	88 (+)
7	(*S*)-**MPN-Lj**	$CHCl_3$	2	>95	67	83 (+)
8	(*S*)-**MPN-Lj**	DMF	7	>95	98	69 (+)

[a] Reaction was run with **3-3a** (0.05 mmol), $Pd_2(dba)_3$ (1.25 μmol), and **MPN-L** (7.50 μmol) in DMF (1.0 mL).
[b] The conversion and product yield were determined by ^{1}H NMR.
[c] Determined by chiral HPLC (OD-H column, eluent: isopropanol/hexanes = 1.2/ 98.8), flow rate: 1 mL/min.
[d] Reaction was run at 0 ^{o}C.

In the hope of minimizing the formation of side product **3-18**, we prepared various allylic carbonates **3-3b−n** and examined the effects of the substituents on the product selectivity, using (*S*)-**MPN-Lj** as the chiral ligand. Results are summarized in **Table 3-3**. When electron-withdrawing substituents, i.e., CH_2CCl_3 (**3-3b**) and CH_2CF_3 (**3-3c**), were used, no or minimum amount of side product **3-18** was formed (entries 1 and 2). The use of vinyl ethers, CH=CH_2 (**3-3d**) and C(Me)=CH_2 (**3-3e**), also eliminated the formation of **3-18** (entries 3 and 4). In these four substrates, however, enantioselectivity was 66−79% *ee*. Introduction of strongly electron-withdrawing or very bulky substituents, i.e., C_6F_5 (**3-3k**), 4-$NO_2C_6H_4$ (**3-3l**), 2,6-$Me_2C_6H_3$ (**3-3m**) and 2,6-*i*-$Pr_2C_6H_3$ (**3-3n**), effectively blocks the formation of **3-18** as well (entries 10−13). It is noteworthy that allyl carbonates with strongly electron-withdrawing groups on the phenyl moiety almost shut down the reaction (entries 10 and 11). The results imply that the basicity of the leaving group, i.e., aryloxide ion, has a significant role in the formation of π-allylic Pd complex **3-16** (see **Scheme 3-5**). Other allyl carbonates, bearing 4-MeO (**3-3f**), 4-Me

(**3-3g**), 4-F (**3-3h**), 4-Cl (**3-3i**) and 3-F (**3-3j**) on the phenyl moiety, led to 83−89% *ee*, but with modest to substantial formation of **3-18** (entries 5−9).

Table 3-3. Pd-catalyzed AAA reaction of carbonates **3-3b**−**n** using (*S*)-**MPN-Lj**.

Entry[a]	Carbonate	Time (h)	Conv.[b] (%)	**3-4**[b] (%)	**3-4** (*S*) *ee*[c] (%)
1	**3-3b**, R = CH_2CCl_3	2	>95	100	66 (+)
2	**3-3c**, R = CH_2CF_3	2	>95	98	69 (+)
3	**3-3d**, R = C_2H_3	2	>95	100	76 (+)
4	**3-3e**, R = $C(Me)CH_2$	2	>95	100	79 (+)
5	**3-3f**, R = 4-MeOPh	2	>95	57	85 (+)
6	**3-3g**, R = 4-MePh	2	>95	60	83 (+)
7	**3-3h**, R = 4-FPh	2	>95	46	87 (+)
8	**3-3i**, R = 4-ClPh	2	>95	33	87 (+)
9	**3-3j**, R = 3-FPh	2	>95	28	89 (+)
10	**3-3k**, R = F_5Ph	120	<5	100	nd
11	**3-3l**, R = 4-NO_2Ph	120	<5	100	nd
12	**3-3m**, R = 2,6-Me_2Ph	2	>95	98	70 (+)
13	**3-3n**, R = 2,6-*i*Pr_2Ph	2	>95	100	71 (+)

[a] Reaction was run with **3-3** (0.05 mmol), $Pd_2(dba)_3$ (1.25 μmol), and (*S*)-**MPN-Lj** (7.50 μmol) in CH_2Cl_2 (1.0 mL) at room temperature.
[b] The conversion and product yield were determined by ^1H NMR.
[c] Determined by chiral HPLC (OD-H column, eluent: isopropanol/hexanes = 1.2/ 98.8), flow rate: 1 mL/min.

We examined the effects of additives on the product selectivity and enantioselectivity in the AAA reactions of several allylic carbonate substrates in CH_2Cl_2. As mentioned above, there seemed to be a possible involvement of hydrogen bonding when the reaction was run in non-polar solvents. Accordingly, we added *tert*-butanol, trifluoroethanol (TFE), and hexafluoroisopropanol (HFIPA). Results are shown in **Table 3-4**.

The reaction of **3-3a** in CH_2Cl_2 with 1% (v/v) *t*-BuOH did not improve the selectivities (entry 1). In contrast, the addition of 1% (v/v) TFE to the reaction of carbonate **3-3a** increased the enantioselectivity to 91% *ee* (from 85% *ee* in pure CH_2Cl_2: see **Table 3-2**), giving compound **3-4** in 66% yield (entry 2), where in the only side product was **3-18a**. However, when 5% (v/v) TFE was used, the yield of compound **3-4** was dramatically reduced to only 13% (94% *ee*) and two side products, i.e., **3-18a** (39%) and **3-18c** (R=CF_3CH_2, 48%), were formed (entry 3). When 1% (v/v) HFIPA was added, the formation of a mixture of **3-18a** (33%) and **3-18o** (R=$(CF_3)_2CH$,

67%) was observed (entry 4).

Table 3-4. Effects of additives on the AAA reaction of **3-3** using (*S*)-**MPN-Lj** in CH_2Cl_2.

Entry[a]	Carbonate	Additive	Time (h)	Conv.[b] (%)	**3-4**[b] (%)	**3-4** (*S*) ee[c] (%)
1	**3-3a**	1% *t*-BuOH	2	>95	66[d]	82 (+)
2	**3-3a**	1% TFE	2	>95	66[d]	91 (+)
3	**3-3a**	5% TFE	24	>95	13[e]	94 (+)
4	**3-3a**	1% HFIPA	2	>95	0[f]	nd
5	**3-3d**	0.5% TFE	2	>95	97[g]	76 (+)
6	**3-3d**	1% TFE	2	>95	88[g]	85 (+)
7	**3-3d**	1% HFIPA	48	>95	0[h]	nd
8	**3-3d**	1% *t*-BuOH	2	>95	100	79 (+)
9	**3-3e**	1% *t*-BuOH	2	>95	100	74 (+)
10	**3-3e**	1% TFE	2	>95	91[g]	87 (+)
11	**3-3e**	1.5% TFE	2	>95	81[g]	91 (+)
12	**3-3m**	1% TFE	2	>95	88[g]	86 (+)

[a] Reaction was run with **3-3** (0.05 mmol), $Pd_2(dba)_3$ (1.25 μmol), and (*S*)-**MPN-Lj** (7.50 μmol) in CH_2Cl_2 (1.0 mL) at room temperature. The amount of an additive (%) is by volume.
[b] The conversion and product yield were determined by ^1H NMR.
[c] Determined by chiral HPLC (OD-H column, eluent: isopropanol/hexanes = 1.2/ 98.8), flow rate: 1 mL/min.
[d] Compound **3-18a** was formed as the side product.
[e] A mixure of **3-18a** (39%) and **3-18c** (R=CF_3CH_2, 48%) was formed as side products.
[f] A mixture of **3-18a** (33%) and **3-18o** (R=$(CF_3)_2CH$, 67%) was formed.
[g] Compound **3-18c** was formed as the side product.
[h] Compound **3-18o** was formed exclusively.

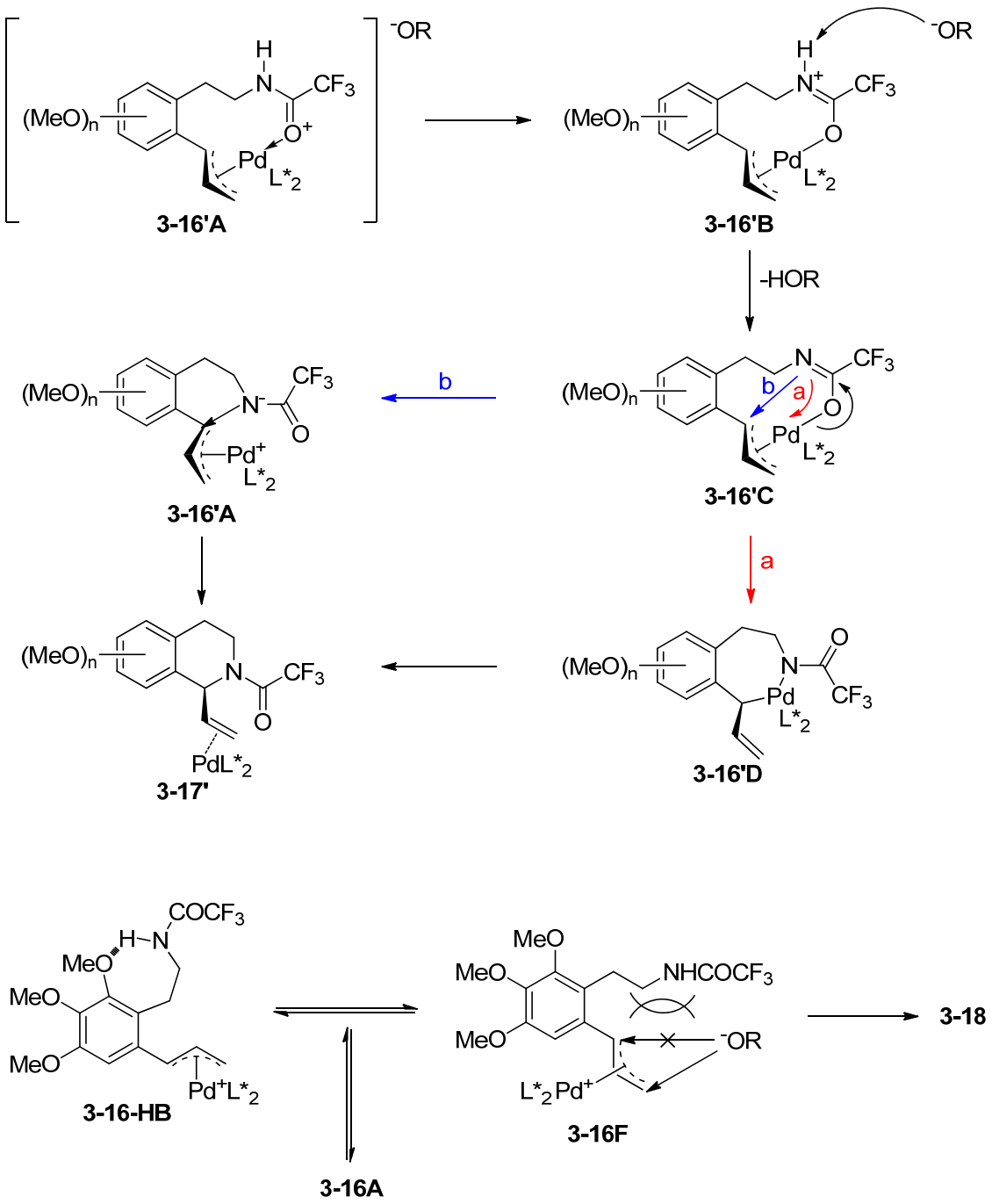
In the reaction of carbonate **3-3d**, the addition of 1% (v/v) TFE improved the enantiopurity of **3-4** to 85% *ee* (from 76% *ee* in pure CH_2Cl_2: see **Table 3-2**) with 88% product selectivity (entry 6). The addition of 0.5% (v/v) TFE, however, did not have appreciable effects (entry 5). With 1% (v/v) HFIPA, the reaction was slowed down and the exclusive formation of side product **3-18o** was observed (entry 7). The addition of *tert*-butanol slightly improved the enantioselectivity to 79% *ee* without affecting reaction rate and product selectivity (entry 8). The addition of 1% (v/v) TFE to the reactions of carbonates **3-3e** and **3-3m** was beneficial, giving compound **3-4** with 87% *ee* (entry 10) and 86% *ee* (entry 12), respectively, with only a little decrease in the product selectivity (see **Table 3-3**, entries 4 and 12 for comparison). The reaction of carbonate **3-3e** with 1.5% (v/v) TFE gave compound **3-4** in 81% yield and 91% *ee* (entry 11), which is practically the best result so far.

3.2.3. Mechanism of intramolecular AAA reaction

The findings obtained from the solvent effects, allylic carbonate structures, and effects of protic additives, provide the following mechanistic implications (**Scheme 3-6**): (i) The $CF_3CONHCH_2$ moiety in π-allylic intermediate **3-16** (**3-16'** for substrates **3-1**, **3-3**, and **3-13** in general) needs to be ionized without an extra base to undergo nucleophilic allylic substitution reaction; (ii) The RO^- counter anion in **3-16'** acts as the base to deprotonate the $CF_3CONHCH_2$ moiety, but the basicity of RO^- anion is not sufficient to do the task without the activation of the amide moiety; (iii) The Pd^{2+} acts as a Lewis acid to activate the $CF_3CONHCH_2$ moiety so that RO^- anion can abstract a proton from this moiety, and produce a neutral ROH (or its tautomer), which is an inert nucleophile under the reaction conditions; (iv) The C−N bond formation can take place through either reductive elimination (path a) or nucleophilic attack of the amide anion (path b); (v) In a non-polar solvent, there is a plausible hydrogen bonding between the oxygen of the MeO group at C5 and amide hydrogen (see **3-16-HB**), which is counterproductive for the activation of the amide group through coordination to Pd^{2+} metal center; (vi) While the ionization of the amide group is slowed down, RO^- counter anion exclusively attacks the less hindered terminal carbon of the π-allylic Pd complex (**3-16F**) to form side product **3-18**.

These mechanistic implications nicely explain the unique feature of the AAA reaction of carbonate **3-3** as compared to those of carbonates **3-1** and **3-13**, wherein the formation of side product **3-18** was observed only in the reaction of carbonate **3-3** that bears a MeO group at the C5 position.

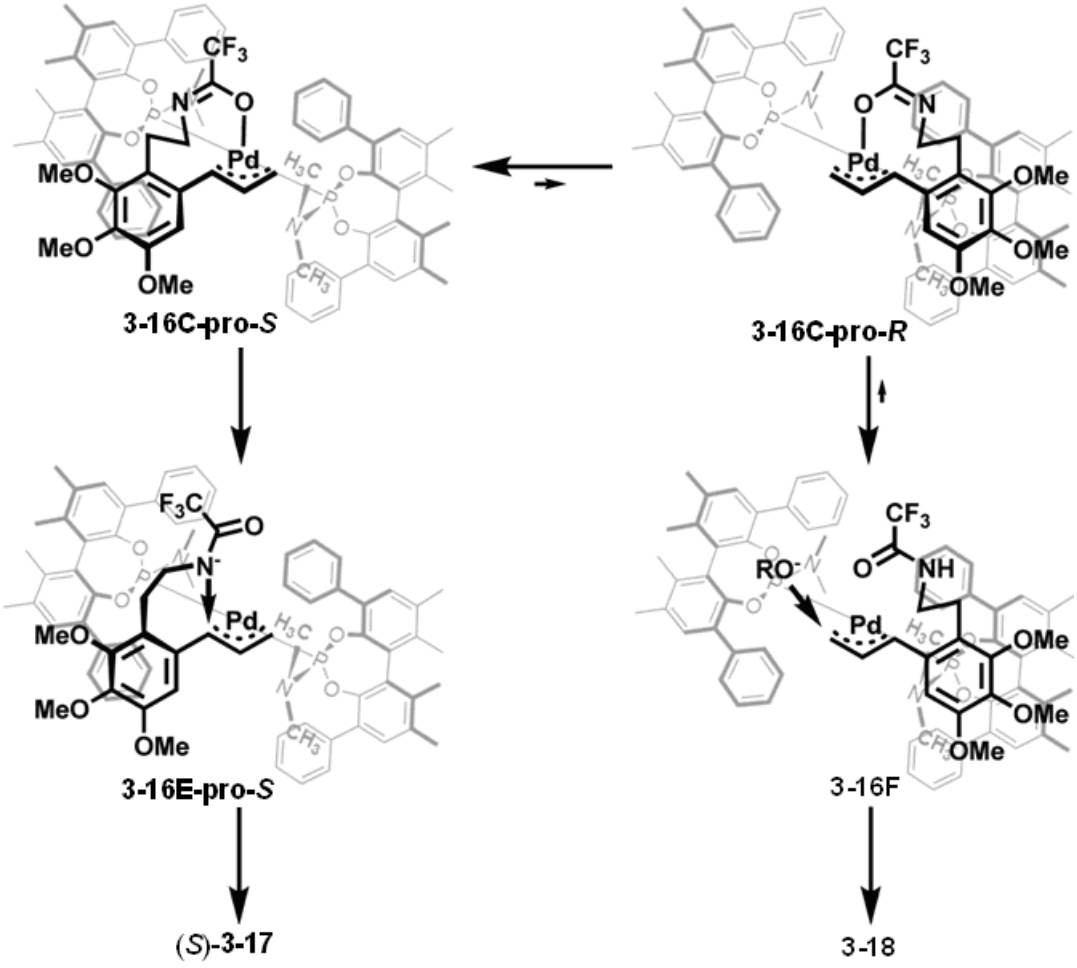
There is another intriguing mechanistic implication from the observed inverse correlation between enantioselectivity and product selectivity, including the effect of 1% (v/v) TFE as an additive. The results strongly imply that there is a kinetic resolution in the transformation of **3-16** to **3-17** and/or **3-18** (**Scheme 3-5**), and the minor diastereomer of **3-16** reacts preferentially with RO^- anion to enrich the major diastereomer of **3-16**, which leads to higher enantioselectivity in the formation of desirable product **3-4**.



Scheme 3-6. Proposed mechanism for the formation of **3-17'** and **3-18**.

To obtain insights into the implied kinetic resolution, we carried out molecular modeling of the two diastereomeric key intermediates, **3-16C-pro-*S*** and **3-16C-pro-*R***, bearing (*S*)-**MNP-Ld** as the chiral ligand, using the Spartan Program. For simplicity, we used π-allylic Pd complexes bearing a covalent O–Pd^{2+} bond with an imidate structure (**3-16C**) for this modeling study

(**Scheme 3-7**). The semi-empirical energy calculation (PM3) using the Spartan Program indicated that **3-16C-pro-*S*** is more favorable than **3-16C-pro-*R*** by 31 kJ/mol, which is consistent with the observed formation of compound (*S*)-(+)-**3-4**, and also explains the selective elimination of **3-16F** arising from **3-16C-pro-*R*** through reaction with RO^- anion to form side product **3-18**. However, it should be noted that this molecular mechanics calculation has revealed that (*S*)-**3-17** (i.e., (*S*)-**3-4** as well) is formed through either reductive elimination of **3-16D** (n = 3) or the nucleophilic attack of the amide nitrogen anion from the Pd metal side in accordance with the principle of least motion, i.e., not through normal antiperiplanar trajectory. This makes a lot of sense since this is an intramolecular process and the activation of the amide moiety through its coordination to the Lewis acidic Pd^{2+} metal center to generate amide nitrogen anion as the nucleophile (see **Scheme 3-6**).



Scheme 3-7. Proposed mechanism for the kinetic resolution.

3.3. Conclusions

As described above, we have successfully synthesized 1-vinyl-5,6,7-trimethoxytetrahydroisoquinoline **3-4** with >90% *ee* by means of Pd-catalyzed intramolecular AAA reactions, using MPN ligands developed in our laboratory. The 1-vinlyltetrahydroisoquinolines thus obtained serve as versatile intermediates for the synthesis of a variety of naturally occurring isoquinoline alkaloids. For the optimization of enantioselectivity, the fine-tuning capability of the MPN ligands has played a significant role. Plausible mechanisms of the reactions that can accommodate the results obtained have been proposed. The solvent effects have revealed the critical importance of the activation of the trifluoroamide moiety through its coordination to the Lewis acidic Pd^{2+} metal center. In the AAA reaction of carbonate **3-3**, a kinetic resolution appears to have taken place to enrich enantioselectivity. The facts that BOP ligands gave the best results in the AAA reaction of carbonate **3-13**, while MPN ligands served best in the reaction of carbonate **3-3**, may indicate the need for more flexibility to accommodate the coordination of trifluoroamide moiety of carbonate **3-3** bearing a sterically demanding methoxy group at the C3 position, which can easily be achieved by non-chelating MPN ligands.

3.4. Experimental Section

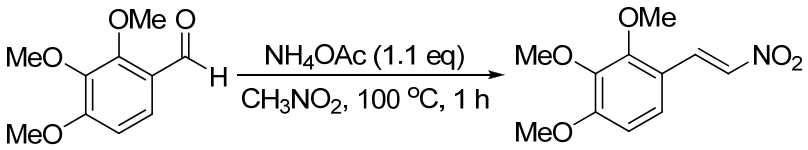
General Method

^{1}H and ^{13}C NMR spectra were measured on Varian Inova-400 (400 MHz ^{1}H; 100 MHz ^{13}C) or Varian Gemini-2300 (300 MHz ^{1}H; 75 MHz ^{13}C) spectrometer in a deuterated solvent using residual proton ($CHCl_3$: ^{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-Elmer Model 241 polarimeter. TLC was performed on Merck DC-Alufolien Kieselgel 60F 254 and flash column chromatography was carried out on Silicyle Silia*Flash*P60®. Analytical HPLC was carried out with a Shimadzu LC-2010A HPLC system. Low-Resolution Mass Spectrometry was performed on Agilent 6890GC/5973 Mass Selective Detector. High-resolution mass spectrometric analyses were carried out at Mass Spectrometry Laboratories, University of Illinois Urbana-Champaign, Urbana, IL. Unless otherwise noted, all reactions were carried out under nitrogen atmosphere in oven-dried glassware using standard Schlenck technique.

Materials

All solvents used as reaction media were purified using the Solvent Purification System 400-4 from Innovative Technology, Inc. or distilled under nitrogen immediately before use. Ether and THF were distilled from Na/benzophenone ketyl. Toluene and CH_2Cl_2 were distilled from CaH_2. Solvents for extraction and chromatography were reagent grade and used as received. All chemicals were purchased from Aldrich or Acros Chemical Co., and were used without further purification unless otherwise noted.

1-((*E*)-2-Nitroethenyl)-2,3,4-trimethoxybenzene (3-6)[25]

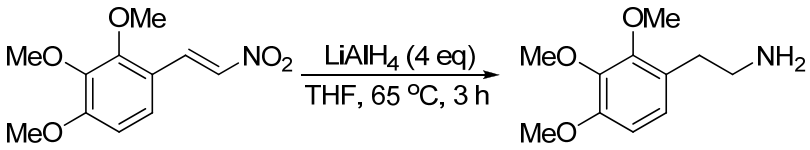


3-5 **3-6**

A mixture of 2,3,4-trimethoxybezaldehyde (**3-5**) (2.55 g, 13.0 mmol), ammonium acetate (1.10 g, 14.3 mmol) in nitromethane (65 mL) was stirred at 100 °C for 1 h. The reaction mixture was cooled to room temperature, quenched with water (50 mL), and extracted with Et_2O (60 mL

× 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was recrystallized from EtOH to give **3-6** (2.82 g, 91% yield) as a pale yellow solid: mp 77.0−77.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.92 (s, 3H), 3.99 (s, 3H), 6.72 (d, J = 8.8 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 13.6 Hz, 1H), 8.08 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 60.9, 61.2, 107.7, 117.1, 126.5, 135.2, 142.5, 154.3, 157.3. All data are in agreement with the literature values.[25]

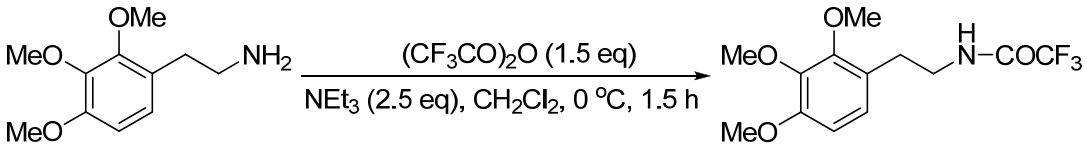
2-(2,3,4-Trimethoxyphenyl)ethylamine (3-7)[25]



3-6 **3-7**

To a suspension of $LiAlH_4$ (3.23 g, 85.1 mmol) in THF (25 mL) was added dropwise a solution of **3-6** (5.09 g, 21.3 mmol) in THF (175 mL) at 0 °C. The reaction mixture was heated to 65 °C and stirred for 3 h. The reaction was then quenched by 20% $KOH_{(aq)}$ (50 mL). The resulting slurry was filtered through Celite® pad and the filtrate was concentrated *in vacuo*. The residue was extracted with Et_2O (30 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give **3-7** (3.44 g, 16.3 mmol) as a yellow liquid, which was directly used in the next amidation step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72 (t, J = 6.9 Hz, 2H), 2.92 (d, J = 6.9 Hz, 2H), 3.83−3.88 (m, 9H), 6.61 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H). All data are in agreement with the literature values.[25]

***N*-[2-(2,3,4-Trimethoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (3-8)**

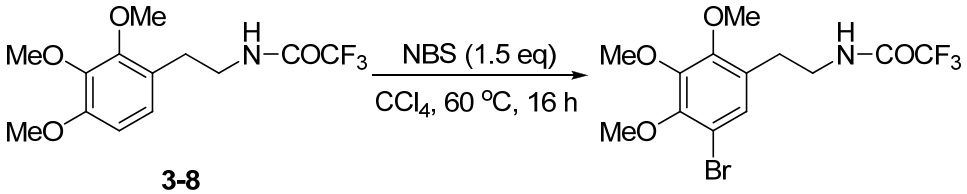


3-7 **3-8**

To a stirred solution of **3-7** (3.44 g, 16.3 mmol) and NEt_3 (4.12 g, 40.7 mmol) in CH_2Cl_2 (96 mL) was added dropwise trifluoroacetic anhydride (3.45 mL, 24.4 mmol) at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with water (30 mL) at

0 °C, and the organic and aqueous layers were separated by a separation funnel. The aqueous layer was further extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 4:1) to give **3-8** (4.24 g, 65% yield for two steps) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (t, J = 6.8 Hz, 2H), 3.45 (q, J = 6.4 Hz, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 6.58 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 7.49 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.8, 41.2, 55.7, 60.4, 60.7, 107.6, 115.7 (q, J = 286 Hz), 123.7, 124.3, 142.0, 151.4, 152.7, 157.1 (q, J = 36 Hz); HRMS (ESI+) calcd for $C_{13}H_{17}F_3NO_4$ $[M+H]^+$ 308.1110, found 308.1103 (Δ = −2.3 ppm).

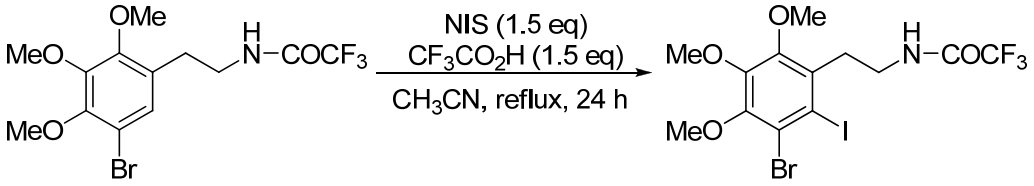
***N*-[2-(5-Bromo-2,3,4-trimethoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (3-9)**



3-8 **3-9**

N-Bromosuccinimide (NBS) (5.15 g, 28.93 mmol) was added to a solution of **3-8** (5.93 g, 19.29 mmol) in CCl_4 (50 mL). The reaction mixture was stirred at 60 °C for 16 h and then cooled to room temperature. Water (50 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (60 mL × 3). The combined organic layers were washed with saturated Na_2SO_3 (50 mL), water (50 mL), and brine (50 mL). The organic layers were further dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 4:1) to give **3-9** (6.86 g, 92% yield) as a white solid: mp 62.5−64.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (t, J = 6.8 Hz, 2H), 3.49 (q, J = 6.4 Hz, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 7.07 (s, 1H), 7.19 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.9, 41.1, 60.8, 60.9, 61.0, 111.7, 115.8 (q, J = 287 Hz), 127.9, 128.3, 147.4, 150.4, 151.2, 157.2 (q, J = 37 Hz); HRMS (ESI+) calcd for $C_{13}H_{16}BrF_3NO_4$ $[M+H]^+$ 386.0215, found 386.0215 (Δ = 0.0 ppm).

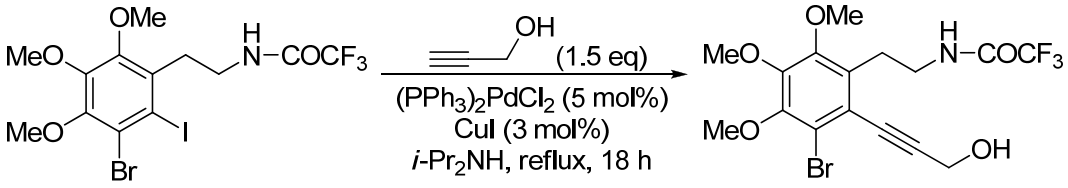
***N*-[2-(5-Bromo-6-iodo-2,3,4-trimethoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (3-10)**



3-9 **3-10**

N-Iodosuccinimide (NIS) (6.41 g, 28.50 mmol) was added to a solution of **3-9** (7.34 g, 19.00 mmol) in CH_3CN (75 mL). To the mixture was added trifluoroacetic acid (2.12 mL, 28.50 mmol) dropwise. The reaction mixture was refluxed for 24 h and then cooled to room temperature. Water (50 mL) was added to the reaction mixture, and CH_3CN was removed *in vacuo*. The residue was extracted with CH_2Cl_2 (60 mL × 3). The combined organic layers were washed with saturated $Na_2SO_{3(aq)}$ (50 mL), water (50 mL), and brine (50 mL). The organic layers were further dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 4:1) to give **3-10** (9.11 g, 94% yield) as a off-white solid: mp 75.0−77.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23 (t, J = 6.4 Hz, 2H), 3.54 (q, J = 6.8 Hz, 2H), 3.88 (m, 6H), 3.92 (s, 3H), 6.96 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.8, 38.7, 60.8, 61.0, 61.2, 101.7, 115.8 (q, J = 286 Hz), 121.9, 132.4, 147.3, 150.9, 151.0, 157.3 (q, J = 37 Hz); HRMS (ESI+) calcd for $C_{13}H_{15}BrF_3INO_4$ $[M+H]^+$ 511.9181, found 511.9185 (Δ = +0.8 ppm).

3-{2-Bromo-3,4,5-trimethoxy-6-[2-(trifluoroacetylamino)-ethyl]phenyl}prop-2-ynol (3-11)

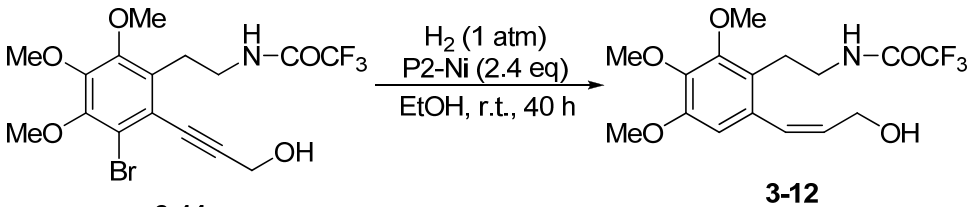


3-10 **3-11**

A mixture of **3-10** (8.63 g, 16.85 mmol), $Pd(PPh_3)_2Cl_2$ (0.59 g, 0.84 mmol), and CuI (0.10 g, 0.51 mmol) was placed in a 250 mL round bottomed flask. After purging the flask with nitrogen, diisopropylamine (84 mL) was added to the mixture, and the solution was stirred for 20 min. Propargyl alcohol (1.49 mL, 25.28 mmol) was added dropwise to the reaction mixture *via* a syringe. The reaction mixture was refluxed for 18 h and then cooled to room temperature. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ (50 mL) and extracted with Et_2O (50 mL × 3).

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:EtOAc = 3:2) to give **3-11** (5.55 g, 75% yield) as a brown solid: mp 88.5−90.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (t, J = 7.2 Hz, 2H), 3.53 (q, J = 6.4 Hz, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 4.55 (s, 2H), 7.12 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 40.1, 51.5 60.9, 61.0, 61.2, 81.8, 96.0, 115.8 (q, J = 286 Hz), 116.0, 120.7, 130.6, 147.8, 150.6, 151.2, 157.6 (q, J = 36 Hz); HRMS (ESI+) calcd for $C_{16}H_{18}BrF_3NO_5$ $[M+H]^+$ 440.0320, found 440.0316 (Δ = −0.9 ppm).

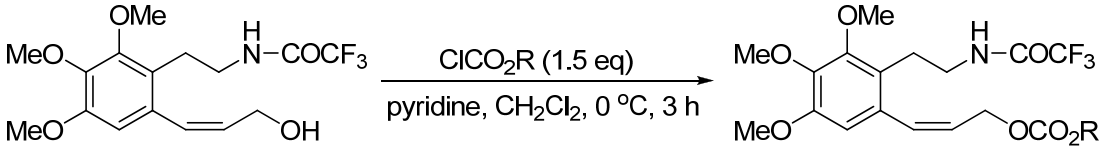
(*Z*)-3-{3,4,5-Trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enol (3-12)



3-11 **3-12**

P2–Ni catalyst was generated *in situ* following the standard procedure[26] by adding $NaBH_4$ (1.18 g, 31.21 mmol) to a suspension of $Ni(OAc)_2$ (3.89 g, 15.60 mmol) in EtOH (46 mL) at room temperature under nitrogen. After 30 min, neat ethylenediamine (2.2 mL, 0.03 mmol) was introduced to the reaction mixture. After stirring the catalyst solution for 10 min, **3-11** (2.86 g, 6.50 mmol) in ethanol (59 mL) was added. The nitrogen atmosphere was then replaced by hydrogen. The reaction mixture was stirred at room temperature for 40 h. The reaction was quenched with water (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with saturated $NaHCO_{3(aq)}$ (50 mL) and brine (50 mL). The organic layers were further dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 3:2) to give **3-12** (1.77 g, 75% yield) as a yellow solid: mp 83.0−85.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (br s, 1H), 2.83 (t, J = 6.4 Hz, 2H), 3.43 (q, J = 6.0 Hz, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 4.18 (d, J = 6.8 Hz, 2H), 5.94 (dt, J = 6.8, 11.6 Hz, 1H), 6.46 (s, 1H), 6.56 (d, J = 11.6 Hz, 1H), 7.24 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.3, 56.0 59.0, 60.6, 60.9, 109.5, 115.8 (q, J = 286 Hz), 121.7, 129.1, 131.5, 132.4, 141.3, 151.6, 151.9, 157.4 (q, J = 36 Hz); HRMS (ESI+) calcd for $C_{16}H_{20}F_3NO_5Na$ $[M+Na]^+$ 386.1191, found 386.1192 (Δ = +0.3 ppm).

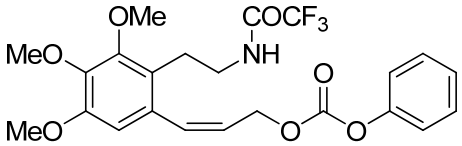
General procedure of synthesis of carbonates 3-3a−n



3-12 **3-3a-n**

To a solution of **3-12** (0.36 g, 1.00 mmol) and pyridine (2.0 mL) in CH_2Cl_2 (20 mL) was added slowly the corresponding chloroformate (1.50 mmol) in 6 mL CH_2Cl_2 at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched with saturated $CuSO_{4(aq)}$ (20 mL), and extracted with Et_2O (20 mL × 4). The combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layers were further dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give the desired carbonate.

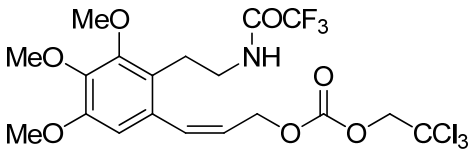
Phenyl (*Z*)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (3-3a)



3-3a

3-3a (435 mg, 90% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (t, J = 6.4 Hz, 2H), 3.43 (q, J = 6.0 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 4.84 (d, J = 7.2 Hz, 2H), 6.00 (dt, J = 7.2, 11.6 Hz, 1H), 6.54 (s, 1H), 6.79 (d, J = 11.6 Hz, 1H), 7.14−7.55 (m, 4H), 7.35−7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.4, 56.0, 60.6, 61.0, 65.0, 109.2, 115.8 (q, J = 286 Hz), 120.9, 122.2, 125.9, 126.0, 129.4, 129.5, 130.5, 133.0, 141.8, 151.0, 151.8, 152.1,153.6,157.3 (q, J = 37 Hz); HRMS (ESI+) calcd for $C_{23}H_{24}F_3NO_7Na$ $[M+Na]^+$ 506.1403, found 506.1402 (Δ = −0.2 ppm).

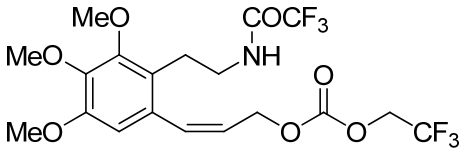
2,2,2-Trichloroethyl (*Z*)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (3-3b)



3-3b

3-3b (383 mg, 71% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (t, J = 6.0 Hz, 2H), 3.43 (q, J = 6.4 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H), 4.76 (s, 2H), 4.81 (d, J = 7.2 Hz, 2H), 5.96 (dt, J = 7.2, 11.6 Hz, 1H), 6.54 (s, 1H), 6.78 (d, J = 11.6 Hz, 1H), 7.12 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.4, 56.0, 60.6, 60.9, 65.3, 76.7, 94.3, 109.1, 115.8 (q, J = 286 Hz), 122.1, 125.6, 130.4, 133.2, 141.7, 151.7, 152.1, 153.8, 157.2 (q, J = 36 Hz); HRMS (ESI+) calcd for $C_{19}H_{21}Cl_3F_3NO_7Na$ $[M+Na]^+$ 560.0233, found 560.0237 (Δ = +0.7 ppm).

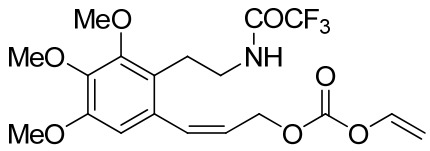
2,2,2-Trifluoroethyl (*Z*)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (3-3c)



3-3c

3-3c (363 mg, 74% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84 (t, J = 6.0 Hz, 2H), 3.42 (q, J = 6.8 Hz, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H), 4.50 (q, J = 8.4 Hz, 2H), 4.79 (dd, J = 1.2, 6.8 Hz, 2H), 5.94 (dt, J = 6.8 Hz, 11.6 Hz, 1H), 6.51 (s, 1H), 6.78 (d, J = 11.6 Hz, 1H), 7.11 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.6, 56.1, 60.7, 61.0, 63.5 (q, J = 37 Hz), 65.5, 109.2, 115.8 (q, J = 286 Hz), 122.2, 122.5 (q, J = 276 Hz), 125.6, 130.4, 133.4, 141.9, 151.8, 152.2, 153.9, 157.3 (q, J = 36 Hz); HRMS (ESI+) calcd for $C_{19}H_{21}F_6NO_7Na$ $[M+Na]^+$ 512.1120, found 512.1122 (Δ = +0.4 ppm).

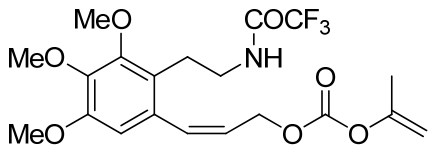
Ethenyl (*Z*)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (3-3d)



3-3d

3-3d (389 mg, 90% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84 (t, J = 6.4 Hz, 2H), 3.43 (q, J = 6.4 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H), 4.59 (dd, J = 2.0, 6.4 Hz, 1H), 4.78 (dd, J = 1.6, 7.2 Hz, 2H), 4.92 (dd, J = 2.4, 14.0 Hz, 1H), 5.94 (dt, J = 7.2, 11.2 Hz, 1H), 6.53 (s, 1H), 6.76 (dd, J = 0.4, 7.2 Hz, 1H), 7.04 (dd, J = 6.0, 13.6 Hz, 1H), 7.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.5, 56.1, 60.7, 61.0, 64.9, 98.0, 109.2, 115.8 (q, J = 286 Hz), 122.2, 125.8, 130.5, 133.0, 141.8, 142.6, 151.8, 152.2, 152.6, 157.3 (q, J = 37 Hz); HRMS (ESI+) calcd for $C_{19}H_{22}F_3NO_7Na$ $[M+Na]^+$ 456.1246, found 456.1249 (Δ = +0.7 ppm).

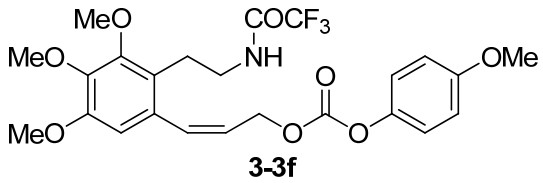
1-Methylethenyl (*Z*)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (3-3e)



3-3e

3-3e (407 mg, 91% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (s, 3H), 2.85 (t, J = 6.0 Hz, 2H), 3.43 (q, J = 6.8 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.69−4.79 (m, 4H), 5.95 (dt, J = 6.8, 11.6 Hz, 1H), 6.52 (s, 1H), 6.75 (d, J = 11.6 Hz, 1H), 7.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 25.3, 40.5, 56.1, 60.7, 61.0, 64.6, 101.9, 109.2, 115.9 (q, J = 287 Hz), 122.2, 126.2, 130.6, 132.7, 141.8, 151.8, 152.1, 152.8, 152.9, 157.3 (q, J = 37 Hz); HRMS (ESI) calcd for $C_{20}H_{24}F_3NO_7Na$ $[M+Na]^+$ 470.1403, found 470.1398 (Δ = −1.1 ppm).

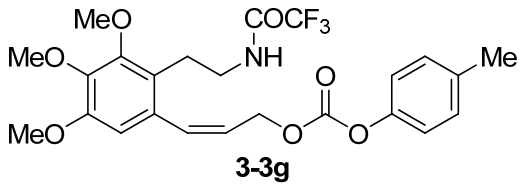
4-Methoxyphenyl (*Z*)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (3-3f)



3-3f

3-3d (487 mg, 95% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (t, J = 6.4 Hz, 2H), 3.43 (q, J = 6.8 Hz, 2H), 3.79 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.83 (dd, J = 1.2, 7.2 Hz, 2H), 6.00 (dt, J = 7.2, 11.6 Hz, 1H), 6.54 (s, 1H), 6.78 (d, J = 11.6 Hz, 1H), 6.87 (d, J = 9.2 Hz, 2H), 7.06 (d, J = 9.2 Hz, 2H), 7.11 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.5, 55.6, 56.1, 60.7, 61.0, 64.9, 109.3, 114.5, 115.9 (q, J = 281 Hz), 121.8, 122.2, 126.1, 130.6, 132.9, 141.8, 144.7, 151.8, 152.2, 154.0, 157.3 (q, J = 34 Hz), 157.5; HRMS (ESI+) calcd for $C_{24}H_{26}F_3NO_8Na$ $[M+Na]^+$ 536.1508, found 536.1509 (Δ = +0.2 ppm).

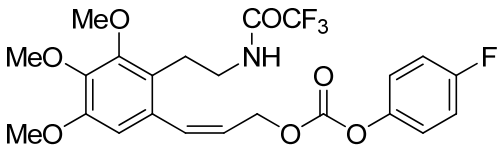
4-Methylphenyl (*Z*)-3-{3,4,5-trimethoxy-2-[2-(trifluoro-acetylamino)ethyl]phenyl}prop-2-enyl carbonate (3-3g)



3-3g

3-3d (458 mg, 92% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.85 (t, J = 6.4 Hz, 2H), 3.43 (q, J = 6.0 Hz, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.83 (d, J = 6.8 Hz, 2H), 6.00 (dt, J = 6.8, 11.6 Hz, 1H), 6.54 (s, 1H), 6.78 (d, J = 11.6 Hz, 1H), 7.02 (d, J = 8.4 Hz, 2H), 7.15−7.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 25.3, 40.5, 56.0, 60.6, 61.0, 64.9, 109.2, 115.8 (q, J = 287 Hz), 120.6, 122.2, 126.0, 129.9, 130.6, 132.9, 135.8, 141.8, 148.9, 151.8, 152.1, 153.8, 157.3 (q, J = 36 Hz); HRMS (ESI+) calcd for $C_{24}H_{26}F_3NO_7Na$ $[M+Na]^+$ 520.1559, found 520.1564 (Δ = +1.0 ppm).

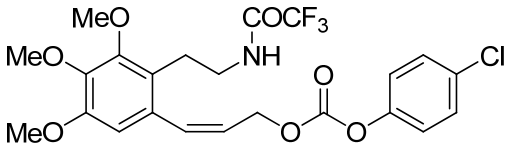
4-Fluorophenyl (*Z*)-3-{3,4,5-trimethoxy-2-[2-(trifluoro-acetylamino)ethyl]phenyl}prop-2-enyl carbonate (3-3h)



3-3h

3-3h (455 mg, 91% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (t, J = 6.4 Hz, 2H), 3.42 (q, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 4.83 (dd, J = 1.2, 6.8 Hz, 2H), 5.98 (dt, J = 6.8, 11.6 Hz, 1H), 6.53 (s, 1H), 6.79 (d, J = 11.6 Hz, 1H), 7.02−7.06 (m, 2H), 7.09−7.13 (m, 2H), 7.17 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.4, 56.0, 60.6, 61.0, 65.1, 109.2, 115.8 (q, J = 286 Hz), 116.1 (d, J = 24 Hz), 122.2, 122.4 (d, J = 8 Hz), 125.8, 130.5, 133.0, 141.8, 146.9 (d, J = 3 Hz), 151.8, 152.1, 153.6, 157.3 (q, J = 37 Hz), 160.3 (d, J = 244 Hz); HRMS (ESI+) calcd for $C_{23}H_{23}F_4NO_7Na$ $[M+Na]^+$ 524.1308, found 524.1311 (Δ = +0.6 ppm).

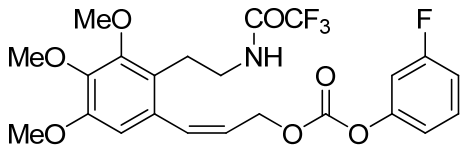
4-Chlorophenyl (*Z*)-3-{3,4,5-trimethoxy-2-[2-(trifluoro-acetylamino)ethyl]phenyl}prop-2-enyl carbonate (3-3i)



3-3i

3-3i (487 mg, 94% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (t, J = 6.0 Hz, 2H), 3.42 (q, J = 6.4 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 3.92 (s, 3H), 4.83 (dd, J = 1.2, 7.2 Hz, 2H), 5.98 (dt, J = 7.2, 11.6 Hz, 1H), 6.53 (s, 1H), 6.79 (d, J = 11.6 Hz, 1H), 7.10 (d, J = 8.8 Hz, 2H), 7.16 (br s, 1H), 7.33 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.5, 56.1, 60.6, 61.0, 65.2, 109.2, 115.8 (q, J = 286 Hz), 122.2, 122.3, 125.7, 129.5, 130.5, 131.5, 133.1, 141.8, 149.5, 151.8, 152.1, 153.3, 157.3 (q, J = 36 Hz); HRMS (ESI+) calcd for $C_{23}H_{23}ClF_3NO_7Na$ $[M+Na]^+$ 540.1013, found 540.1012 (Δ = −0.2 ppm).

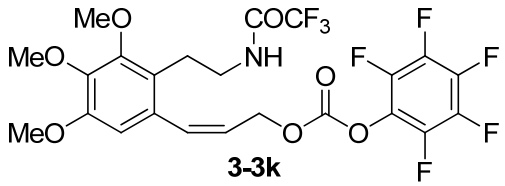
3-Fluorophenyl (*Z*)-3-{3,4,5-trimethoxy-2-[2-(trifluoro-acetylamino)ethyl]phenyl}prop-2-enyl carbonate (3-3j)



3-3j

3-3j (410 mg, 82% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84 (t, J = 6.4 Hz, 2H), 3.41 (q, J = 6.0 Hz, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 4.83 (dd, J = 0.8, 7.2 Hz, 2H), 5.97 (dt, J = 7.2, 11.6 Hz, 1H), 6.53 (s, 1H), 6.79 (d, J = 11.6 Hz, 1H), 6.91−6.96 (m, 3H), 7.21 (br s, 1H), 7.28−7.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.4, 56.0, 60.6, 60.9, 65.2, 109.0 (d, J = 23 Hz), 109.1, 113.0 (d, J = 21 Hz), 115.8 (q, J = 287 Hz), 116.6 (q, J = 3 Hz), 122.2, 125.6, 130.2 (d, J = 9 Hz), 130.4, 133.1, 141.8, 151.7 (d, J = 11 Hz), 151.8, 152.1, 153.0, 157.2 (q, J = 36 Hz), 162.7 (d, J = 247 Hz); HRMS (ESI+) calcd for $C_{23}H_{23}F_4NO_7Na$ $[M+Na]^+$ 524.1308, found 524.1305 (Δ = −0.6 ppm).

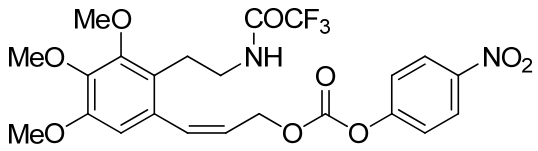
Pentafluorophenyl (*Z*)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (3-3k)



3-3k

3-3k (509 mg, 89% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (t, J = 6.4 Hz, 2H), 3.42 (q, J = 6.4 Hz, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.90 (dd, J = 1.2, 7.2 Hz, 2H), 5.99 (dt, J = 7.2, 11.6 Hz, 1H), 6.52 (s, 1H), 6.85 (d, J = 11.6 Hz, 1H), 7.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 40.4, 56.0, 60.7, 61.0, 66.8, 109.0, 115.8 (q, J = 286 Hz), 122.3, 124.7, 125.6 (m), 130.2, 134.2, 136.6 (m), 138.5 (m), 139.1 (m), 140.0 (m), 141.1 (m), 141.9, 142.5 (m), 151.2, 151.9, 152.2, 157.3 (q, J = 36 Hz); HRMS (ESI+) calcd for $C_{23}H_{19}F_8NO_7Na$ $[M+Na]^+$ 596.0931, found 596.0932 (Δ = +0.2 ppm).

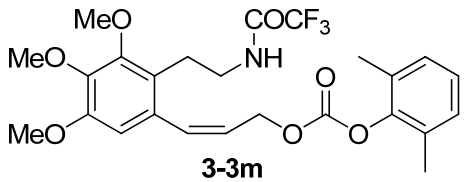
4-Nitrophenyl (*Z*)-3-{3,4,5-trimethoxy-2-[2-(trifluoro-acetylamino)ethyl]phenyl}prop-2-enyl carbonate (3-3l)



3-3l

3-3l (424 mg, 80% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (t, J = 6.4 Hz, 2H), 3.43 (q, J = 6.4 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 3.92 (s, 3H), 4.87 (dd, J = 1.2, 6.8 Hz, 2H), 5.99 (dt, J = 6.8, 11.2 Hz, 1H), 6.52 (s, 1H), 6.82 (d, J = 11.2 Hz, 1H), 7.15 (br s, 1H), 7.36 (d, J = 9.2 Hz, 2H), 8.25 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.5, 56.1, 60.7, 61.0, 65.6, 109.4, 115.8 (q, J = 287 Hz), 121.7, 122.2, 125.3, 125.4, 130.4, 133.4, 141.8, 145.4, 151.8, 152.2, 152.4, 155.4, 157.3 (q, J = 36 Hz); HRMS (ESI+) calcd for $C_{23}H_{23}F_3N_2O_9Na$ $[M+Na]^+$ 551.1253, found 551.1248 (Δ = −0.9 ppm).

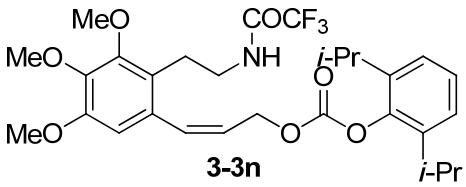
2,6-Dimethylphenyl (*Z*)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (3-3m)



3-3m

3-3m (505 mg, 99% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 6H), 2.86 (t, J = 6.4 Hz, 2H), 3.43 (q, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.85 (dd, J = 1.2, 6.8 Hz, 2H), 6.00 (dt, J = 6.8, 11.2 Hz, 1H), 6.53 (s, 1H), 6.79 (d, J = 11.2 Hz, 1H), 7.05−7.07 (m, 3H), 7.10 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 25.2, 40.3, 55.9, 60.5, 60.8, 65.0, 109.1, 115.7 (q, J = 286 Hz), 122.2, 125.9, 126.0, 128.6, 129.9, 130.4, 132.9, 141.7, 148.2, 151.7, 152.0, 152.8, 157.2 (q, J = 36 Hz); HRMS (ESI+) calcd for $C_{25}H_{28}F_3NO_7Na$ $[M+Na]^+$ 534.1716, found 534.1718 (Δ = +0.4 ppm).

2,6-Diisopropylphenyl (*Z*)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl} prop-2-enyl carbonate (3-3n)

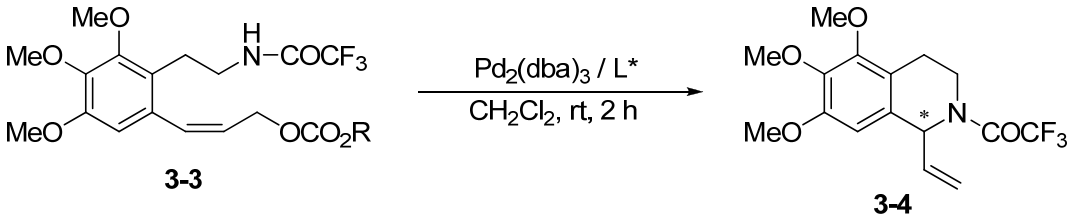


3-3n

3-3n (409 mg, 72% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.8 Hz, 12H), 2.86 (t, J = 6.4 Hz, 2H), 3.01 (septet, J = 6.8 Hz, 2H) 3.43 (q, J = 6.0 Hz, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.86 (dd, J = 1.2, 7.2 Hz, 2H), 6.00 (dt, J = 7.2, 11.2 Hz, 1H), 6.57 (s, 1H), 6.80 (d, J = 11.2 Hz, 1H), 7.14−7.24 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 25.3, 27.3, 40.4, 56.0, 60.6, 60.9, 65.1, 109.1, 115.8 (q, J = 287 Hz), 122.2, 124.0, 126.1, 126.8, 130.5, 132.8, 140.3, 141.7, 145.7, 151.8, 152.1, 153.7, 157.3 (q, J = 36 Hz); HRMS (ESI+) calcd for $C_{29}H_{36}F_3NO_7Na$ $[M+Na]^+$ 590.2342, found 590.2346 (Δ = +0.7 ppm).

General procedure for intramolecular asymmetric allylic amination

(*S*)-(+)-1-Ethenyl-2-trifluoroacetyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (3-4)

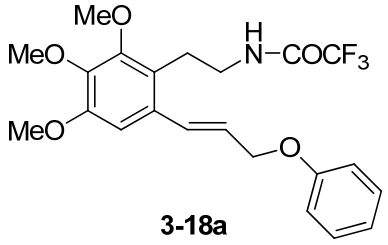


3-3 **3-4**

A solution of ligand (*S*)-**MPN-Lj** (4.5 mg, 0.0075 mmol) and $Pd_2(dba)_3$ (1.2 mg, 0.00125 mmol) in CH_2Cl_2 with 1.5% (v/v) TFE (0.5 mL) was added to a reaction tube with a stirring bar under nitrogen. The solution was stirred at room temperature until the color of the solution turned to light yellow from purple. Then, **3-3e** (22 mg, 0.05 mmol) in CH_2Cl_2 with 1.5% (v/v) TFE (0.5 mL) was added to the catalyst solution *via* a syringe. The mixture was stirred at room temperature for 2 h. The resulting solution was diluted with water (5 mL). The aqueous layer was separated and extracted with Et_2O (10 mL × 3). The combined organic layers were washed with water (20 mL), brine (20 mL), and dried over anhydrous $MgSO_4$. Crude product was obtained after filtration and evaporation of the solvent. The conversion of the reaction was checked by ^{1}H NMR, which indicated over 95% conversion and 81% product selectivity. The crude product was then subjected to chiral HPLC analysis, using a Chiralcel OD-H column (isopropanol:hexanes =

1.2:98.8, 1 mL/min), which indicated that the enantiopurity of the crude product was 91% *ee*. Further purification of the crude product by column chromatography on silica gel (hexanes:EtOAc = 9:1) to give (*S*)-(+)-1-Ethenyl-2-trifluoroacetyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**3-4**) (14 mg, 80%) as a yellow oil: 91% *ee*; $[\alpha]_D^{23}$ +134.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) (a 79:21 mixture of two rotamers) δ 2.69−2.87 (m, 2H), [3.16 (td, *J* = 4.8, 14.0 Hz, 0.21H), 3.45 (td, *J* = 4.8, 14.0 Hz, 0.79H)], 3.80 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), [3.99−4.04 (m, 0.79H), 4.45−4.50 (m, 0.21H)], 5.02−5.15 (m, 1H), 5.26−5.29 (m, 1H), [5.40−5.41 (m, 0.21H), 5.88−6.02 (m, 1.79H)], [6.38 (s, 0.21H), 6.41 (s, 0.79H)]; ^{13}C NMR (100 MHz, $CDCl_3$) (a 79:21 mixture of two rotamers) (major) δ 23.3, 39.6, 55.5, 55.9, 60.4, 60.7, 106.5, 116.4 (q, *J* = 286 Hz), 118.4, 119.6, 128.2, 135.3, 141.0, 150.8, 152.3, 155.5 (q, *J* = 36 Hz) (minor) δ 21.7, 37.3, 55.5, 55.9, 57.8, 60.3, 106.2, 116.5 (q, *J* = 286 Hz), 118.3, 120.3, 128.0, 136.3, 141.3, 151.1, 152.1, 155.5 (q, *J* = 36 Hz); HRMS (ESI+) calcd for $C_{16}H_{18}F_3NO_4$ $[M]^+$ 345.1188, found 346.1264 (Δ = −0.6 ppm).

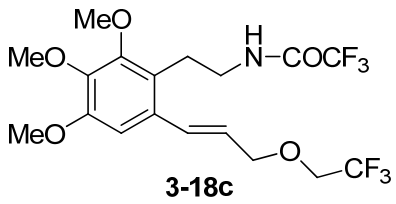
1-[(*Z*)-3-Phenoxyprop-1-enyl]-2-[2-(trifluoroacetylamino)-ethyl]-2,3,4-trimethoxybenzene (3-18a)



3-18a

3-18a was obtained as a white solid: mp 100.0−102.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (t, *J* = 6.0 Hz, 2H), 3.40 (q, *J* = 6.0 Hz, 2H), 3.85 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 4.73 (dd, *J* = 1.2, 5.6 Hz, 2H), 6.24 (dt, *J* = 5.6, 15.6 Hz, 1H), 6.83 (s, 1H), 6.87 (d, *J* = 15.6 Hz, 1H), 6.96−6.99 (m, 3H), 7.06 (br s, 1H), 7.29−7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 41.0, 56.0, 60.7, 61.0, 68.2, 105.9, 106.0, 114.8, 115.8 (q, *J* = 286 Hz), 121.0, 121.7, 127.2, 129.5, 131.7, 141.9, 151.5, 152.5, 157.3 (q, *J* = 36 Hz), 158.4; HRMS (ESI+) calcd for $C_{22}H_{24}F_3NO_5$ $[M]^+$ 439.1607, found 462.1498 (Δ = −1.3 ppm).

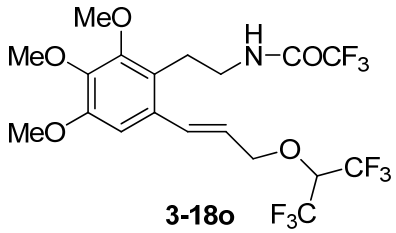
1-[(*Z*)-3-(2,2,2-Trifluoroethoxy)prop-1-enyl]-2-[2-(trifluoroacetylamino)ethyl]-2,3,4-trimethoxybenzene (3-18c)



3-18c

3-18c was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (t, J = 6.4 Hz, 2H), 3.45 (q, J = 6.0 Hz, 2H), 3.85−3.92 (m, 11H), 4.31 (dd, J = 0.8, 6.4 Hz, 2H), 6.10 (dt, J = 6.4, 15.6 Hz, 1H), 6.81 (s, 1H), 6.81 (d, J = 15.6 Hz, 1H), 7.08 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 41.0, 56.0, 60.7, 61.0, 67.4 (q, J = 34 Hz), 72.7, 105.9, 115.8 (q, J = 286 Hz), 121.8, 124.0 (q, J = 278 Hz), 126.9, 130.2, 131.4, 142.1, 151.5, 152.6, 157.3 (q, J = 36 Hz); HRMS (ESI+) calcd for $C_{18}H_{21}F_6NO_5Na$ $[M+Na]^+$ 468.1222, found 468.1226 (Δ = +0.9 ppm).

1-[(*Z*)-3-(1,1,1,3,3,3-Hexafluoroprop-2-yloxy)prop-1-enyl]-2-[2-(trifluoroacetylamino)ethyl]-2,3,4-trimethoxybenzene (3-18o)



3-18o

3-18o was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (t, J = 6.4 Hz, 2H), 3.44 (q, J = 6.4 Hz, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 4.22 (septet, J = 6.0 Hz, 1H), 4.51 (d, J = 6.6 Hz, 2H), 6.10 (dt, J = 6.6, 15.6 Hz, 1H), 6.80 (s, 1H), 6.87 (d, J = 15.6 Hz, 1H), 7.04 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 40.9, 56.0, 60.7, 61.0, 70.7, 74.9−75.9 (m), 106.0, 115.8 (q, J = 287 Hz), 121.6 (q, J = 282 Hz), 122.0, 125.4, 130.9, 132.4, 142.4, 151.6, 152.6, 157.4 (q, J = 36 Hz); HRMS (ESI+) calcd for $C_{19}H_{20}F_9NO_5Na$ $[M+Na]^+$ 536.1095, found 536.1098 (Δ = +0.6 ppm).

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Chapter 4

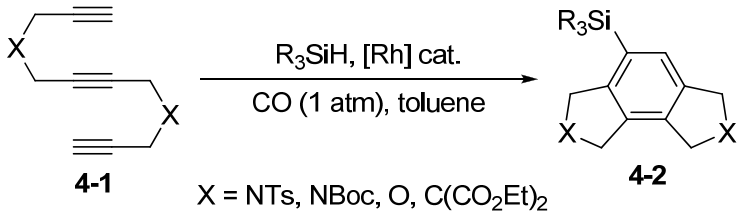
Rapid Access to Novel Colchicinoids through Rh-catalyzed [2+2+2+1] Cycloaddition of ortho-Phenylenetriynes

4.1. Introduction

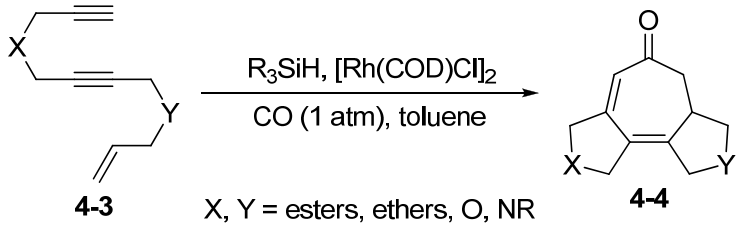
4.1.1. Rh-catalyzed [2+2+2+1] cycloaddition

The quick, quantitative, and selective synthesis of complex target molecules by a simple operation has been an important goal of organic synthesis. For rapidly increasing molecular complexity from readily available starting materials, the transition metal-catalyzed carbocyclization and cycloaddition reactions are recognized as synthetically very important processes.[1-4] Considerable advances have been made recently in the development of higher order cycloaddition reactions such as [2+2+2+1],[5-7] [3+3+1],[8] [2+2+2+2],[9,10] [4+2+2],[11,12] [5+2+1],[13-15] and [5+1+2+1][16] processes. Because many bioactive compounds contain fused-ring systems in their structures,[17] various polycyclization reactions have been employed for the construction of natural and unnatural fused-ring systems that can be further elaborated into specific targets. Accordingly, these step-economical polycyclization reactions provide powerful synthetic methods which not only construct complex structures in a single operation but also eliminate isolation and purification steps of the intermediates.

In the Ojima laboratory, part of our research has been focusing on the exploration and development of new cascade carbocyclizations and higher order cycloadditions, which provide the basis for the efficient synthesis of biologically active substances of medicinal interest. In the course of our investigation into the development of silicon-initiated cyclization processes, silylcarbotricyclization (SiCaT)[18] and carbonylative silylcarbotricyclization (CO-SiCaT)[6,19] have been discovered. The SiCaT reaction of triynes has allowed for the rapid construction of 5-6-5, 6-6-5, and 6-6-6 fused tricyclic skeletons (**Scheme 4-1**). And the CO-SiCaT reaction of enediynes affords a very efficient formation of 5-7-5 tricyclic ring systems with incorporation of the carbonyl moiety (**Scheme 4-2**).

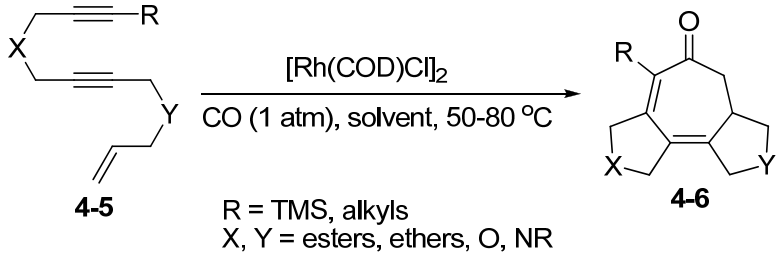


Scheme 4-1. SiCaT reaction of triynes.



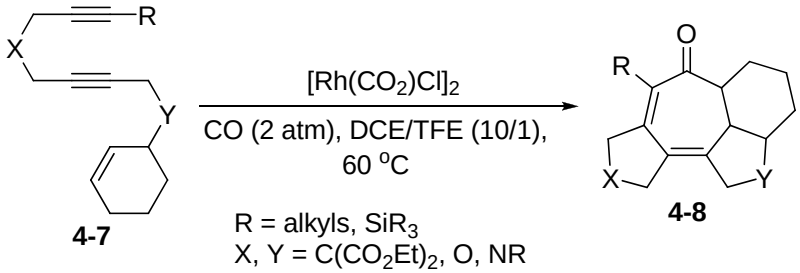
Scheme 4-2. CO-SiCaT reaction of enediynes.

During the course of the investigation, the first intramolecular [2+2+2+1] carbonylative cycloaddition reaction of enediynes catalyzed by rhodium complex was serendipitously discovered.[5,6] In the absence of the hydrosilane, this [2+2+2+1] process has proven to be efficient for the construction of 5-7-5 fused tricyclic compounds from substrates bearing substituents on the terminal acetylene moiety (**Scheme 4-3**). It is worthy of note that these substrates usually failed to form the desired 5-7-5 tricyclic products under the CO-SiCaT conditions.



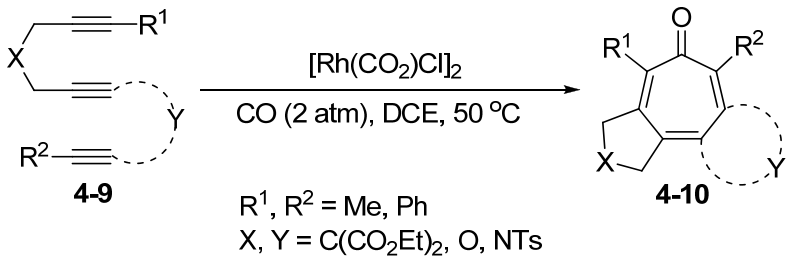
Scheme 4-3. [2+2+2+1] cycloaddition of enediynes.

In 2009, the scope of the novel [2+2+2+1] carbonylative cycloaddition reaction was expanded to the enediyne substrates having a cyclohexenyl group as the olefin moiety.[7] Through this highly efficient process, the 5-7-6-5 fused tetracyclic structures were successfully obtained from the cyclohexene-diynes (**Scheme 4-4**).



Scheme 4-4. [2+2+2+1] cycloaddition of cyclohexene-diynes.

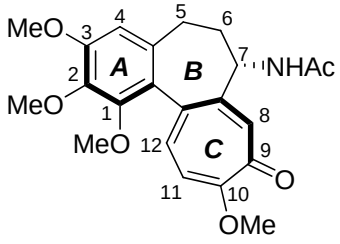
The success in the Rh-catalyzed [2+2+2+1] cycloaddition of enediynes has directed our attention toward the application of this reaction to triynes. The reaction of certain triynes in the presence of $[Rh(CO)_2Cl]_2$ and CO (2 atm) gave novel 5-7-*n* fused tricyclic products with tropone skeleton (**Scheme 4-5**).[20]



Scheme 4-5. [2+2+2+1] cycloaddition of triynes.

4.1.2. Introduction of colchicine

Colchicine (**Figure 4-1**), a toxic natural product and secondary metabolite of autumn crocus, is originally extracted from the poisonous plant meadow saffron (*Colchicum autumnale* L.). The first isolation of colchicine was achieved by the French chemists Pelletier and Caventou in 1820.[21] Despite considerable efforts, the chemical structure of colchicine remained uncertain for many years. Investigations by Zeisel[22-24] and Windaus[25] determined the methoxy groups and made more specific structural proposals. Significant progress in the structure elucidation was made by Dewar in 1945, who assumed that ring C of the tricyclic skeleton was a cycloheptatrienolone with aromatic character (**Figure 4-2**).[26] In 1952, the correct structure of colchicine was confirmed by means of X-ray crystal-structure analysis.[27]



(-)-(a*R,7S*)-*Colchicine*

Figure 4-1. Colchicine.

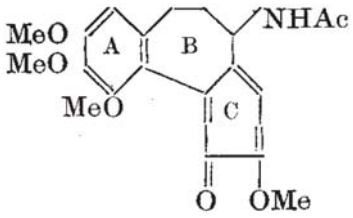
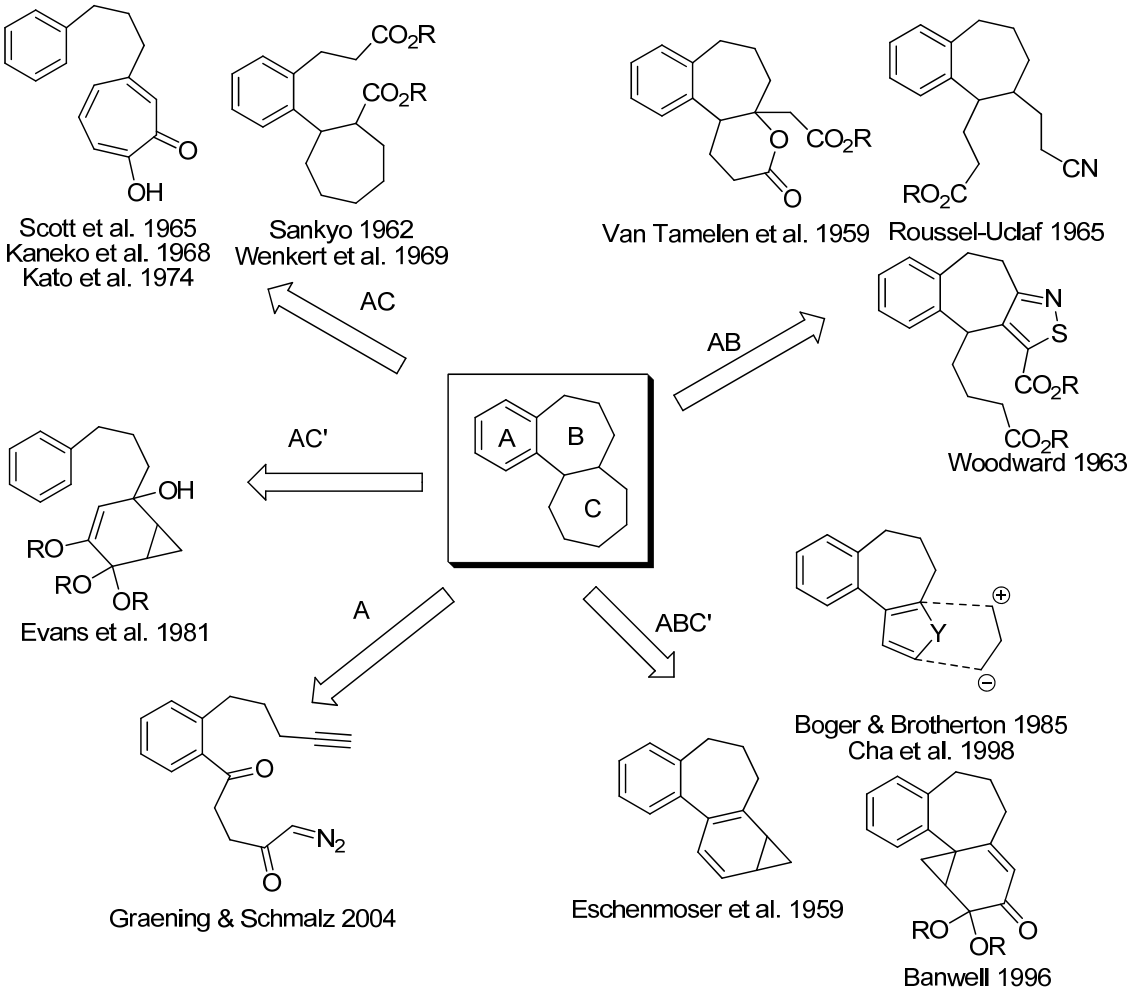


Figure 4-2. Colchicine structure proposed by Dewar in 1945.

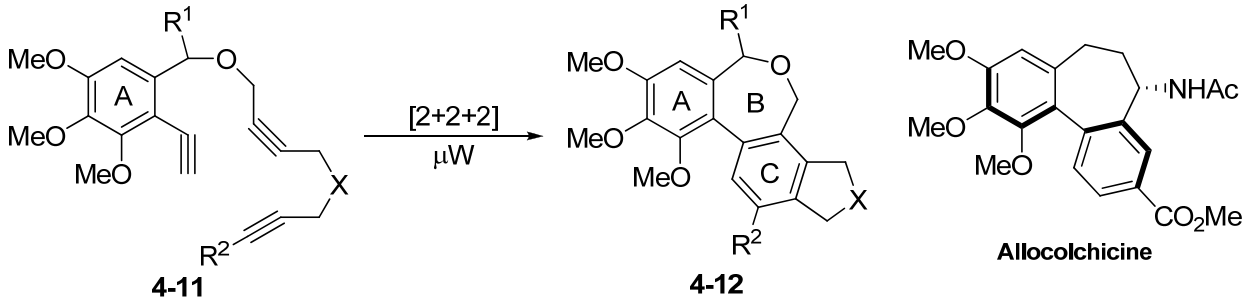
Owing to the capability in suppressing inflammation, colchicine is one of the oldest known drugs and has been used for treatment of rheumatic complaints, especially gout, for thousands of years. In the Ebers Papyrus (ca. 1500 B.C.), the plant source of colchicine was documented for treatment of rheumatism and swelling. Today, colchicine is still being used for acute gout, despite dosing issues concerning its toxicity.[21] In addition to gout, colchicine has also been used for the therapy of familial Mediterranean fever, pericarditis, and Behçet's disease, due to its anti-inflammatory effect. In recent years, colchicine and its analogues have received high interest for cancer chemotherapy. Colchicine can inhibit microtubule polymerization and act as an antimitotic agent. By binding to tubulin dimer, colchicine distorts the tubulin/microtubule equilibrium, and mitosis is arrested in the metaphase.[28,29] Accordingly, this compound can be employed to selectively damage rapidly proliferating cancer cells.[30]

After the structural confirmation in 1952, the first total synthesis of colchicine was accomplished in 1959,[31] and taken as a milestone in natural product synthesis of the 1950s. Over the past 60 years, a number of synthetic approaches have been elaborated following fundamentally different strategies towards colchicine (**Scheme 4-6**).[21] In spite of all the modern methodology available, a synthetic method with satisfying efficiency towards colchicine and its derivatives still remains a challenge. The difficulties inherent to the target structure lie in the regioselective construction of the highly oxidized ring C within the unusual 6,7,7-membered ring system.[32]



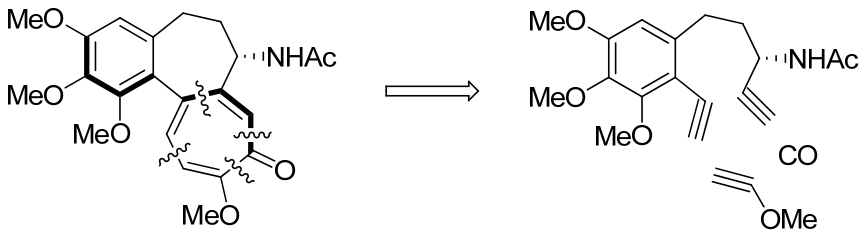
Scheme 4-6. Retrosynthetic classification of colchicine syntheses.

In 2009, Schmalz *et al.* reported a 6-oxa-allocolchicinoids synthesis based on a microwave-promoted Co- or Rh-catalyzed intramolecular [2+2+2] cycloaddition (**Scheme 4-7**).[33] This approach opens a short and efficient route towards a variety of novel allocolchinoids, some of which were found to exhibit apoptosis-inducing activities against BJAB tumor cells (Burkitt-like lymphoma cells).

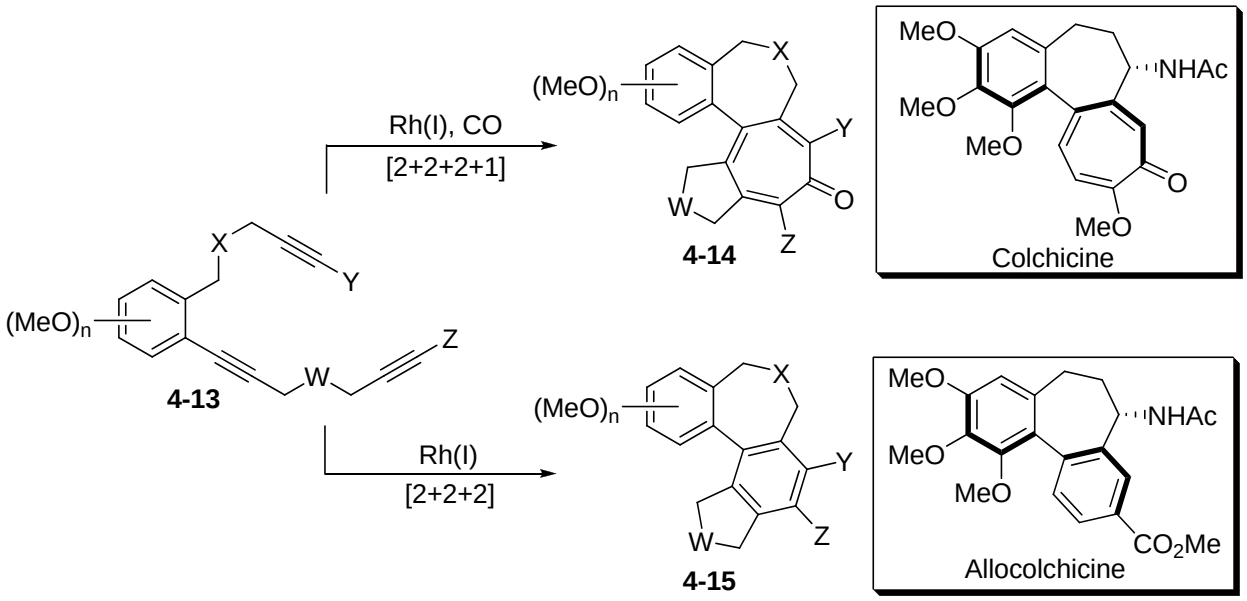


Scheme 4-7. [2+2+2] Cycloaddition approach towards 6-oxa-allocolchicinoids.

According to the National Cancer Institute, molecules interacting with the colchicine-binding site of tubulin are considered as important lead structures for developing new antitumor agents.[34] The major obstacle in discovery of more active colchicine analogues is the synthetic difficulty in accessing the target compounds. Thus, in order to further explore the pharmaceutical potential and study the structure activity relationship, it is of great importance to develop a synthetic method which enables an efficient construction of colchicine derivatives. As **Scheme 4-8** shows, the synthetically challenging ring B and tropolone ring C of colchicine can be retrosynthesized as a combination of three alkynes and a molecule of carbon monoxide, through the [2+2+2+1] cycloaddition. Based on the successful examples from [2+2+2+1] cycloaddition in the formation of 5-7-7 fused tropones (**Scheme 4-5**),[20] we investigated the possibility of [2+2+2+1] cycloaddition approach towards the synthesis of novel colchicinoids. Likewise, the formation of novel allocolchicinoid *via* [2+2+2] cycloaddition was examined (**Scheme 4-9**).



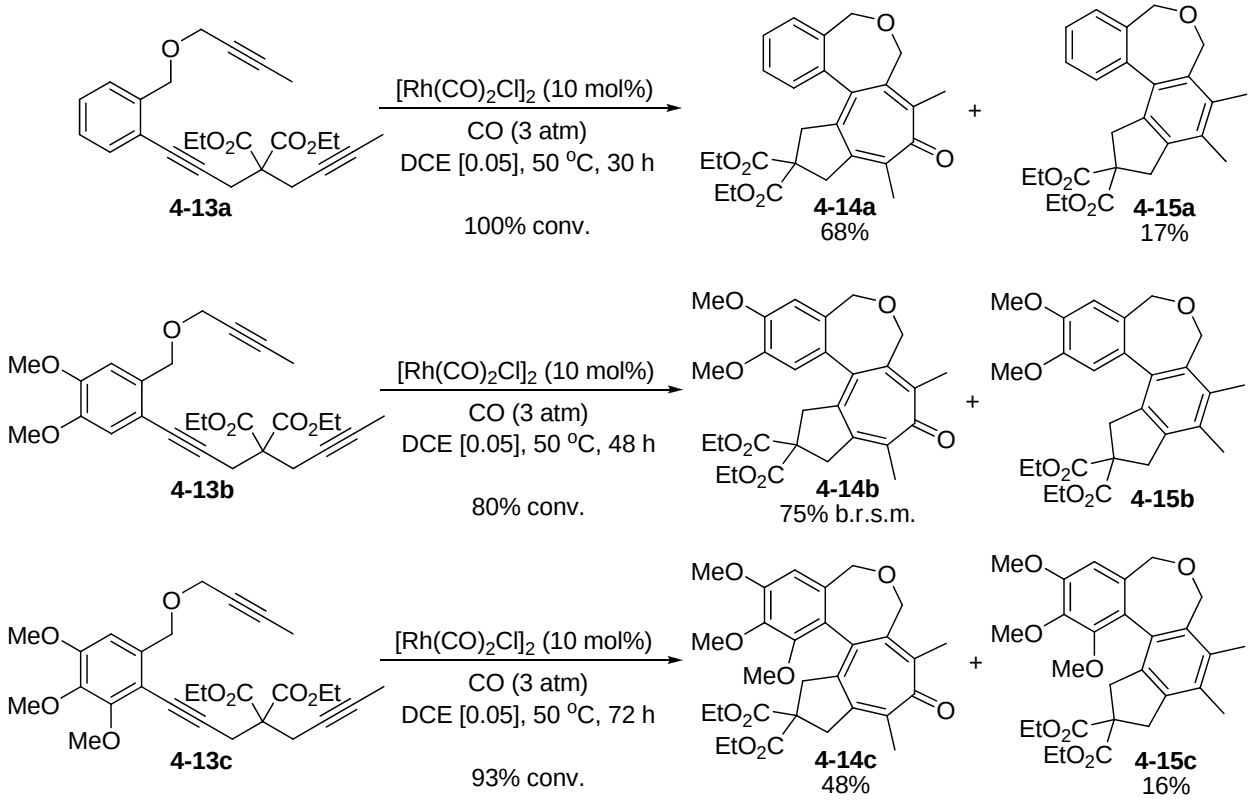
Scheme 4-8. Retrosynthetic analysis of colchicine based on [2+2+2+1] cycloaddition approach.



Scheme 4-9. Tetracycle formation from cycloadditions of triynes.

4.2. Preliminary Results

The investigation of the possibility of the [2+2+2+1] cycloaddition approach towards the synthesis of novel colchicinoids was first carried out by Gary Teng in the Ojima group.[20] As **Scheme 4-10** shows, three different triyne substrates were subjected to the [2+2+2+1] cycloaddition and the successful formation of the desired carbonylative products **4-14** was observed. Using 10 mol% of $[Rh(CO)_2Cl]_2$, 3 atm of CO in DCE at 50 ^oC, triyne **4-13a** gave carbonylative tetracyclic product **4-14a** in good yield, along with a small amount of non-carbonylative tetracyclic product **4-15a**. Compared to triyne **4-13a**, triynes **4-13b** and **4-13c** required longer reaction time to reach good conversion. Triyne **4-13b** afforded carbonylative product **4-14b** in 75% conversion yield, with no trace of non-carbonylative product **4-15b**. Triyne **4-13c** showed the slowest reaction rate and only gave moderate product selectivity.

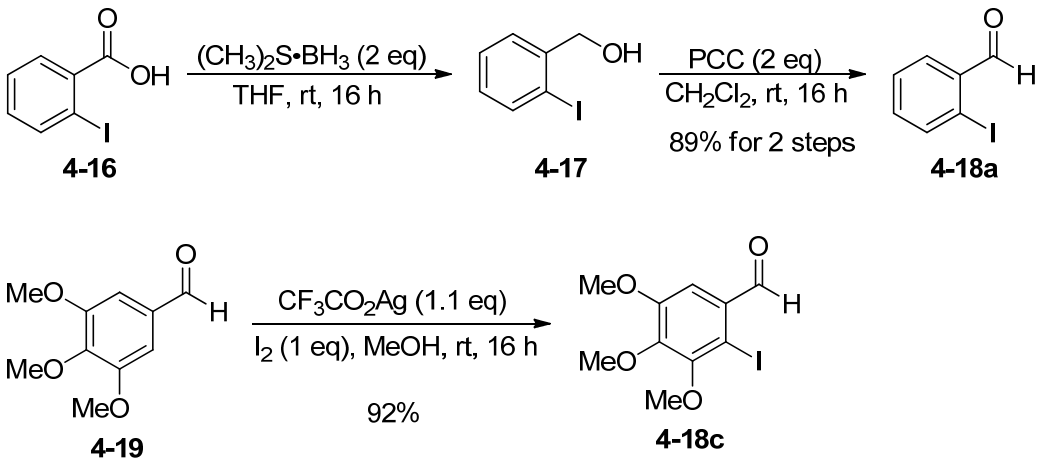


Scheme 4-10. [2+2+2+1] Cycloaddition of triynes **4-13a**–**c**.

4.3. Results and Discussions

4.3.1. Substrate synthesis

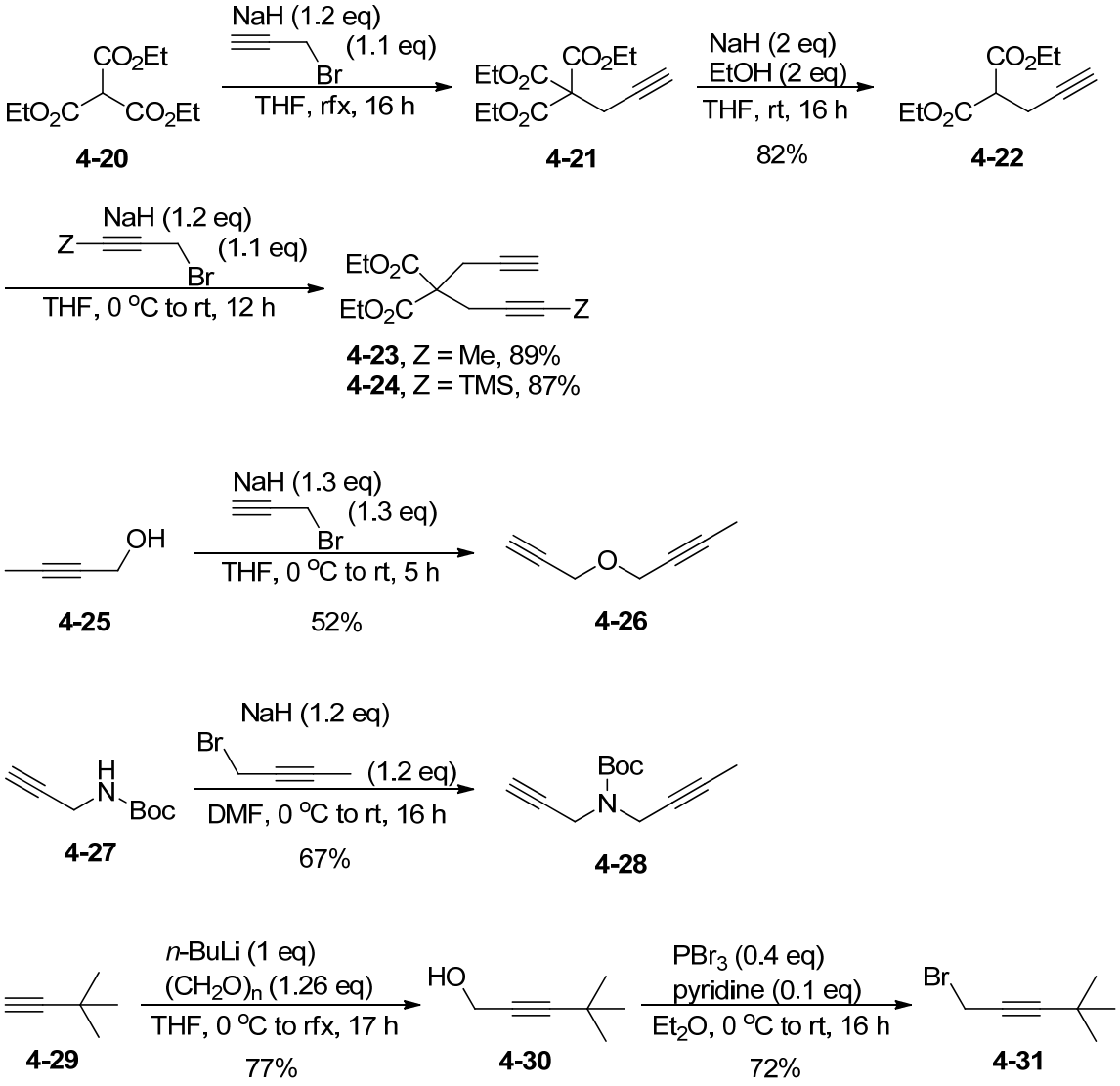
The synthesis of iodobenzaldehydes **4-18a** and **4-18c** is depicted in **Scheme 4-11**. 2-Iodobenzaldehyde (**4-18a**) was obtained in 89% yield in two steps through the reduction of 2-iodobenzoic acid (**4-16**) using borane dimethylsulfide followed by PCC (pyridinium chlorochromate) oxidation of the resulting 2-iodobenzyl alcohol (**4-17**). On the other hand, trimethoxy substituted iodobenzaldehyde **4-18c** was synthesized by the iodination of 3,4,5-trimethoxybenzaldehyde (**4-19**) in 92% yield.



Scheme 4-11. Synthesis of iodobenzaldehydes.

Scheme 4-12 illustrates the preparation of the alkyne chains. Diethyl malonate diynes **4-23** and **4-24** were synthesized from triethyl mathanetricarboxylate (**4-20**) by modification of literature procedures.[35,36] Compound **4-20** was first allowed to react with propargyl bromide in the presence of NaH as the base to give alkyne **4-21**, followed by decarboxylation using sodium ethoxide generated *in situ*, 2-(2-propynyl)malonic acid diethyl ester (**4-22**) was obtained in high yield. Compound **4-22** was then used to react with 1-bromo-2-butyne or 3-bromo-1-(trimethylsilyl)-1-propyne in the presence of NaH, to afford diethyl malonate diynes **4-23** and **4-24** respectively. 1-(Prop-2-yn-1-yloxy)but-2-yne (**4-26**) was prepared by etherification of 2-butyn-1-ol (**4-25**) with propargyl bromide and NaH.[37] In a similar manner, *tert*-butyl but-2-yn-1-yl(prop-2-yn-1-yl)carbamate (**4-28**) was successfully obtained by coupling of *N*-Boc-propargylamine (**4-27**) and 1-bromo-2-butyne. Following the literature procedures,[38] 1-bromo-4,4-dimethyl-2-pentyne (**4-31**) was synthesized. Lithiation of 3,3-dimethyl-1-butyne

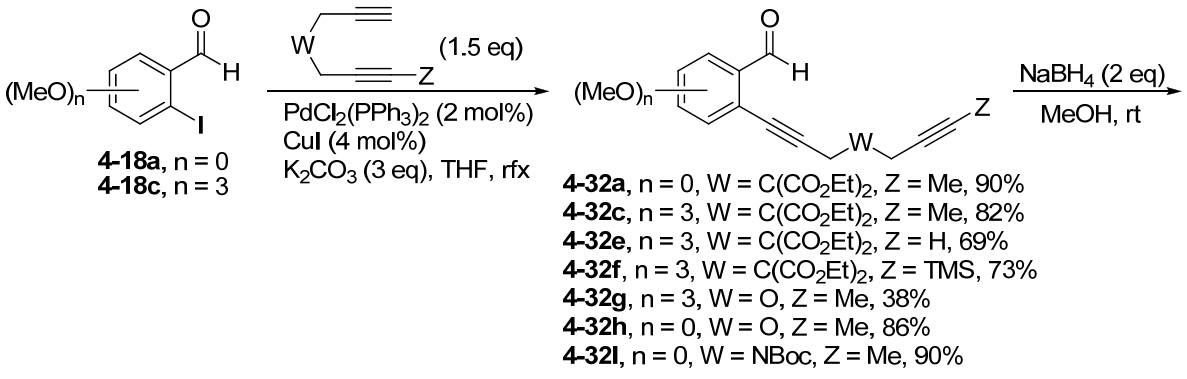
(**4-29**) and the subsequent reaction with paraformaldehyde gave 4,4-dimethyl-2-pentyn-1-ol (**4-30**). The bromination reaction of **4-30** utilizing phosphorus tribromide (PBr_3) gave the desired alkyne **4-31** in good yield.



Scheme 4-12. Synthesis of alkyne chains.

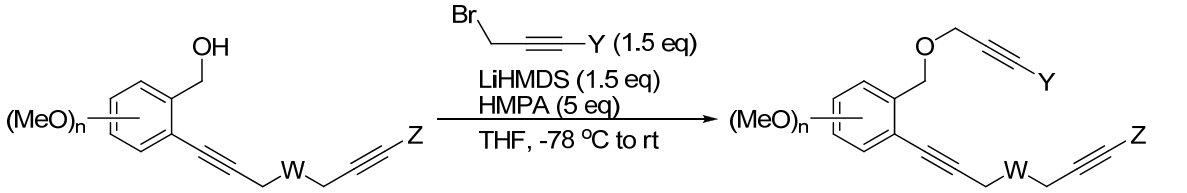
The following synthesis is illustrated in **Scheme 4-13**. With the iodobenzaldehydes and diynes in hand, the attachment of the synthesized diynes was performed under Sonogashira coupling conditions. After reduction of the diyne-aldehydes **4-32** by $NaBH_4$, diyne-alcohols **4-33** were alkylated with bromoalkynes using LiHMDS as the base to give desired *ortho*-phenylenetriynes **4-13**. It is noteworthy that the employment of LiHMDS as the base in the final etherification step provided better yields compared with the usage of NaH (38% for triyne

4-13a; 35% for triyne **4-13c**).[20] During the synthesis of triyne **4-13f**, a product with removal of TMS group, triyne **4-13e** (n = 3, W = $C(CO_2Et)_2$, Y = Me, Z = H), was also isolated in 38% yield.



4-18a, n = 0
4-18c, n = 3

4-32a, n = 0, W = $C(CO_2Et)_2$, Z = Me, 90%
4-32c, n = 3, W = $C(CO_2Et)_2$, Z = Me, 82%
4-32e, n = 3, W = $C(CO_2Et)_2$, Z = H, 69%
4-32f, n = 3, W = $C(CO_2Et)_2$, Z = TMS, 73%
4-32g, n = 3, W = O, Z = Me, 38%
4-32h, n = 0, W = O, Z = Me, 86%
4-32l, n = 0, W = NBoc, Z = Me, 90%

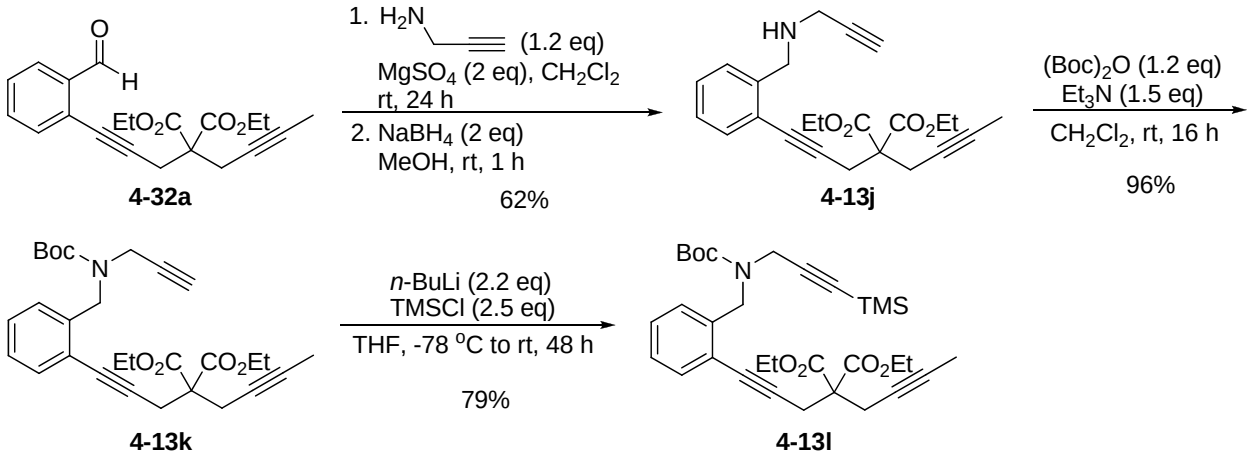


4-33a, n = 0, W = $C(CO_2Et)_2$, Z = Me, 92%
4-33c, n = 3, W = $C(CO_2Et)_2$, Z = Me, 96%
4-33e, n = 3, W = $C(CO_2Et)_2$, Z = H, 95%
4-33f, n = 3, W = $C(CO_2Et)_2$, Z = TMS, 87%
4-33g, n = 3, W = O, Z = Me, 81%
4-33h, n = 0, W = O, Z = Me, 87%

4-13a, n = 0, W = $C(CO_2Et)_2$, Y = Z = Me, 73%
4-13c, n = 3, W = $C(CO_2Et)_2$, Y = Z = Me, 78%
4-13d, n = 3, W = $C(CO_2Et)_2$, Y = *t*Bu, Z = Me, 62%
4-13e, n = 3, W = $C(CO_2Et)_2$, Y = Me, Z = H, 66%
4-13f, n = 3, W = $C(CO_2Et)_2$, Y = Me, Z = TMS, 37%
4-13g, n = 3, W = O, Y = Z = Me, 77%
4-13h, n = 0, W = O, Y = Z = Me, 55%

Scheme 4-13. Synthesis of triyne substrates **4-13**.

Scheme 4-14 shows the preparation of triynes **4-13j**–**l** which have a nitrogen atom on the top chain. The diyne-aldehyde **4-32a** was subjected to the reductive amination conditions with propargyl amine and $NaBH_4$ to give triyne **4-13j**. The free amine of triyne **4-13j** was further protected by *t*-Boc group using di-*tert*-butyl dicarbonate to afford triyne **4-13k**. Having a terminal TMS group on the acetylene moiety, triyne **4-13l** was formed by reacting triyne **4-13k** with TMSCl in the presence of *n*-BuLi.

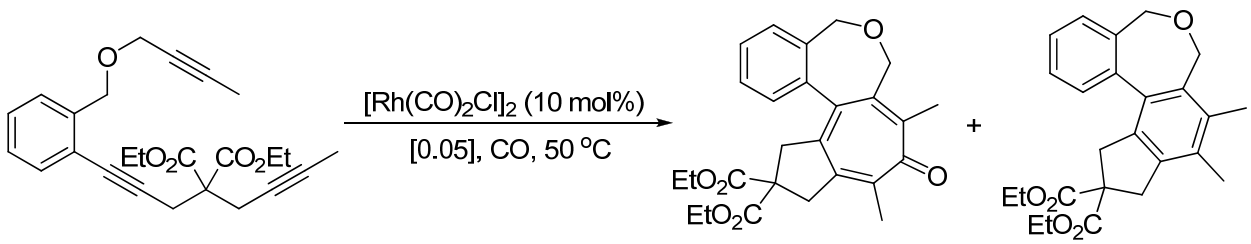


Scheme 4-14. Synthesis of triynes **4-13j**−**l**.

4.3.2. Optimization of the Rh-catalyzed [2+2+2+1] cycloaddition

Triyne **4-13a** was first employed to optimize the reaction conditions; the results are summarized in **Table 4-1**. As entries 1−10 show, the Rh-catalyzed [2+2+2+1] cycloaddition was carried out in different solvents. After 48 h, the reaction can occur in all solvent trials except DMF and EtOH. In entry 8, the DCE/TFE mixed solvents system gave the lowest product selectivity, while the highest product selectivity (96:4) was obtained with the solvent decane (entry 1), toluene (entry 3), or 1,4-dioxane (entry 7). Since toluene provided the highest conversion among these three solvents, we took it as the solvent choice for the following study. Next, reactions were carried out under different CO pressures, as shown by entries 11−13. Interestingly, the CO pressure did not have any influence on the product selectivity; but it affected the reaction rates. The highest reaction rate was obtained when the cycloaddition was performed under 1 atm CO (entry 13). Microwave was then used instead of conventional heating; after 3 h irradiation, 70% conversion and 96:4 product selectivity was achieved.

Table 4-1. Solvent and CO pressure studies.



4-13a **4-14a** **4-15a**

Entry[a]	Solvent	CO pressure (atm)	Time (h)	Conv.[b] (%)	Product selectivity[b] **4-14a** : **4-15a**
1	decane	3	48	43	96 : 4
2	*p*-xylene	3	48	71	95 : 5
3	toluene	3	48	64	96 : 4
4	THF	3	48	8	87 : 13
5	DME	3	48	15	92 : 8
6	DCE	3	48	47	93 : 7
7	1,4-dioxane	3	48	58	96 : 4
8	DCE/TFE (1/1)	3	48	96	86 : 14
9	DMF	3	48	0	nd
10	EtOH	3	48	0	nd
11	toluene	6	48	77	96 : 4
12	toluene	2	48	100	96 : 4
13	toluene	1	36	100	96 : 4
14[c]	toluene	1	3	70	96 : 4

[a] 0.05 mmol of starting material was used for each entry.
[b] The conversion and product selectivity were determined by HPLC.
[c] The reaction was carried out under microwave heating.

Based on the results described above, we carried out further optimization of reaction conditions using toluene as the solvent at 1 atm CO pressure. As entries 1−5 of **Table 4-2** show, when the reaction temperature increased, the induced product selectivity decreased. However, reaction performed at 20 °C did not improve the product selectivity further. After 5 days reaction, a lower product selectivity was found compared to 35 °C and 50 °C (entry 5 vs. 3 and 4). Therefore, 50 °C was taken as the best reaction temperature so far, considering the reaction rate and product selectivity. Next, the reaction concentration was examined (entries 6 and 7). When the reaction was performed at higher concentration, a slightly increased product selectivity was

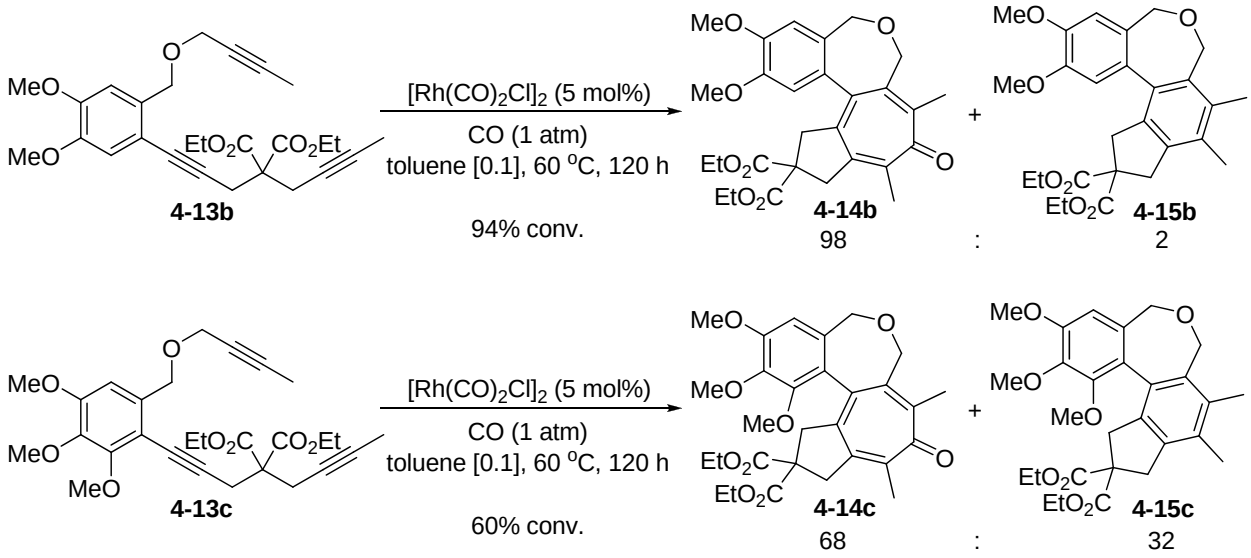
observed. Lowering the catalyst amount indeed retarded the progress of the reaction but did not make an apparent change in product selectivity (entries 8−10). Pursuing better reaction economy, 5 mol% $[Rh(CO)_2Cl_2]_2$ was used, and some reaction conditions were investigated (entries 11−14). Higher concentration (entry 11) and using bubbling CO (entry 12) gave very little acceleration in the reaction rate. Fortunately, a 10 ^oC elevation in reaction temperature improved the reaction to a decent rate without sacrificing the product selectivity (entry 13). When adding 10 mol% DPPP as additional ligand to the reaction, the whole reaction was halted (entry 14). In this case, we hypothesize that the phosphine and the carbon monoxide molecules occupy all the coordination sites of rhodium and thus inhibit the coordination of triyne substrate. The [2+2+2+1] cycloaddition was also carried out by applying $[Rh(COD)Cl]_2$ as the catalyst; similar product selectivity but lower conversion was obtained (entry 15) comparing the result using $[Rh(CO)_2Cl_2]_2$ (entry 6). We also examined several catalyst systems for this cycloaddition, including $Rh(acac)(CO)_2$, $Rh(PPh_3)_2(CO)Cl$, $Rh(PPh_3)_3Cl$, $Rh_4(CO)_{12}$, $Rh_2Co_2(CO)_{12}$, $[Rh(COD)_2]SbF_6$, $[Co(CO)_4]_2$, $Ru_3(CO)_{12}$, and $Ir(PPh_3)_2(CO)Cl$. However, none of them showed efficacy to catalyze the [2+2+2+1] or [2+2+2] cycloaddition.

Table 4-2. Reaction conditions studies.

Entry[a]	Temp. (^{o}C)	Conc. (M)	$[Rh(CO)_2Cl_2]_2$ (mol%)	Time (h)	Conv.[b] (%)	Product selectivity[b] **4-14a** : **4-15a**
1	110	0.05	10	6	100	71 : 29
2	80	0.05	10	16	100	93 : 7
3	50	0.05	10	36	100	96 : 4
4	35	0.05	10	72	62	96 : 4
5	20	0.05	10	120	58	91 : 9
6	50	0.1	10	24	100	97 : 3
7	50	0.025	10	72	96	96 : 4
8	50	0.1	7.5	48	82	97 : 3
9	50	0.1	5	48	50	97 : 3
10	50	0.1	2.5	48	26	96 : 4
11	50	0.2	5	24	31	96 : 4
12[c]	50	0.1	5	48	49	97 : 3
13	60	0.1	5	48	94	96 : 4
14	50	0.1	5 (w/ 10 mol% DPPP)	48	0	nd
15	50	0.1	10 ($[Rh(COD)Cl]_2$)	24	46	96 : 4

[a] 0.05 mmol of starting material was used for each entry.
[b] The conversion and product selectivity were determined by HPLC.
[c] The reaction was carried out using bubbling CO.

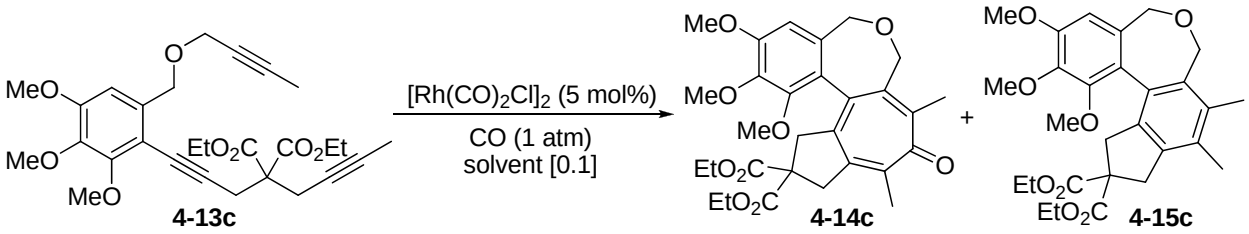
To summarize the above optimization of reaction conditions using triyne **4-13a**, the best reaction condition found so far entails using 5 mol% of the catalyst, 1 atm of CO in toluene at 60 ^{o}C, which gave good conversion and the best product selectivity in 48 h. Similarly, triynes **4-13b** and **4-13c** were also subjected to the optimized reaction conditions found so far (**Scheme 4-15**). The reaction rate was slower than that of triyne **4-13a** for both substrates. Like triyne **4-13a**, triyne **4-13b** afforded carbonylative tetracyclic product **4-14b** in excellent product selectivity. Triyne **4-13c**, nevertheless, showed sluggish rate and only moderate product selectivity.



Scheme 4-15. [2+2+2+1] Cycloaddition of triynes **4-13b** and **4-13c**.

Due to the lower reaction rate and the only moderate product selectivity of triyne **4-13c**, we conducted the screening of the reaction conditions for this substrate. As **Table 4-3** shows, when the reaction temperature was increased to 80 °C, a remarkable enhancement of the reaction rate was observed. One hundred percent conversion was reached after 60 h without a distinct loss of product selectivity (entry 2). Other solvents were examined using triyne **4-13c** as the substrate in the hope of improving the selectivity (entries 3–6). However, among those examined to date, toluene is still the best solvent, providing the highest product selectivity and suitable reaction rate for the formation of carbonylative product **4-14c**.

Table 4-3. Solvent studies of [2+2+2+1] cycloaddition of triyne **4-13c**.



Entry[a]	Solvent	Temp. (°C)	Time (h)	Conv.[b] (%)	Product selectivity[b] **4-14c** : **4-15c**
1	toluene	60	120	60	68 : 32
2	toluene	80	60	100	66 : 34
3	*p*-xylene	80	48	100	65 : 35
4	1,4-dioxane	80	72	98	61 : 39
5	DCE	80	40	100	52 : 48
6	cyclohexane	80	24	100	51 : 49

[a] 0.05 mmol of starting material was used for each entry.
[b] The conversion and product selectivity were determined by HPLC.

Next, we examined the effect of additives to the reaction using triyne **4-13c** as the substrate, and the results are summarized as **Table 4-4**. In the presence of 4Å molecular sieves, a slightly slower reaction rate but similar product selectivity was found (entry 1). A substantial increase of the reaction rate was observed when applying acidic additives, which afforded 100% conversion after 24 h (entries 2–7). Both Brønsted acids and Lewis acids gave product selectivity in more or less the same range except for $BF_3{\cdot}OEt_2$ which only afforded 61:39 product selectivity (entry 6). When montmorillonite K10 was used as the additive, the highest product selectivity (69:31) was obtained (entry 7). The acceleration of reaction rate by acidic additive becomes even remarkable at lower temperature. Comparing to the result obtained at 60 °C (entry 1 of **Table 4-3**), the addition of K10 dramatically improves the reaction rate and makes the reaction complete in 32 h (entry 8).

Table 4-4. Reaction additive studies of [2+2+2+1] cycloaddition of triyne **4-13c**.

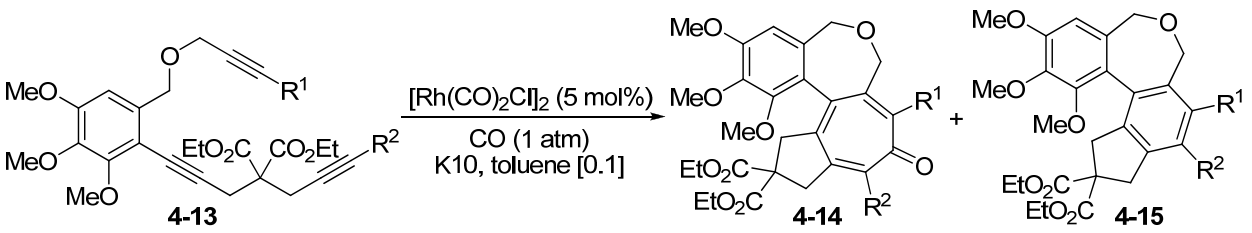
Entry[a]	Solvent	Temp. (°C)	Time (h)	Conv.[b] (%)	Product selectivity[b] **4-14c** : **4-15c**
1	4Å MS	80	72	100	65 : 35
2	CSA (20 mol%)	80	24	100	66 : 34
3	HOAc (20 mol%)	80	24	100	68 : 32
4	TFE (20 mol%)	80	24	100	68 : 32
5	$LiClO_4$ (20 mol%)	80	24	100	65 : 35
6	$BF_3{\cdot}OEt_2$ (20 mol%)	80	24	100	61 : 39
7	K10	80	24	100	69 : 31
8	K10	60	32	100	70 : 30

[a] 0.05 mmol of starting material was used for each entry.
[b] The conversion and product selectivity were determined by HPLC.
[c] The reaction was carried out under microwave heating.

To examine the effect of the terminal groups on the reactivity and mode of the reaction, we also investigated the reactions of other substrates which bear different substituents of the terminal acetylene moiety. As **Table 4-5** shows, triyne **4-13d** having *t*-Bu group at the top terminal gave, to our delight, almost exclusively carbonylative product **4-14d**, but a longer reaction time was required (entry 1). Thus, we performed the reaction at 80 °C, and a completed conversion was achieved with excellent product selectivity after 24 h (entry 2). Without the substituent at the bottom terminal, triyne **4-13e** gave the corresponding carbonylative product **4-14e** only in 56% selectivity, albeit a faster reaction rate was observed (entry 3). While the substituent at the bottom terminal was changed to trimethylsilyl (TMS) group, triyne **4-13f** was sluggish to give the full conversion after 5 days (entry 4). Triyne **4-13f** provided excellent product selectivity as triyne **4-13d** did, however, the major cycloadduct isolated was desilyl carbonylative product **4-14e** and we did not find the trace of carbonylative product **4-14f**. To our very surprise, a small amount of carbonylative product **4-14c** was formed along with the reaction. Due to the serendipitous formation of carbonylative product **4-14c**, we conducted another trial using triyne **4-13f** under the same reaction conditions otherwise the addition of montmorillonite K10 (entry 5). As we expected, a rather slow reaction was found without the acidic additive. The reaction gave similar overall carbonylative products selectivity (carbonylative product **4-14e** and carbonylative product **4-14c**) as the trial with K10 additive, but a slightly more favorable to the

formation of carbonylative product **4-14c**. Conceptually, during the course of forming carbonylative product **4-14c** from triyne **4-13f**, the only plausible methyl group source is the migration of methyl group from the TMS substituent. To our best knowledge, there is no such transformation reported in the literature, therefore, we will study this novel migration in the future. Another noteworthy finding regarding to the [2+2+2+1] cycloaddition of **4-13f** is that the predominant formation of the desilyl cycloadduct **4-14e**, whereas, the TMS group of the [2+2+2] side product **4-15f** remains intact. We believe the desilylation does not occur before the cycloaddition process since triynes **4-13e** (entry 3) and **4-13f** (entry 4) result in markedly different product selectivity. In other words, the desilylation should take place during or after the formation of the theoretical product **4-14f**. In the future, we will focus on this differential desilylation process as well. Based on the results of entries 2–4, it is essential to have substituents at the acetylenes' terminals in order to obtain better product selectivity of the [2+2+2+1] cycloaddition. This observation is consistent with our previous study of [2+2+2+1] cycloaddition of enediynes and triynes.

Table 4-5. [2+2+2+1] cycloaddition of triynes **4-13d–f**.

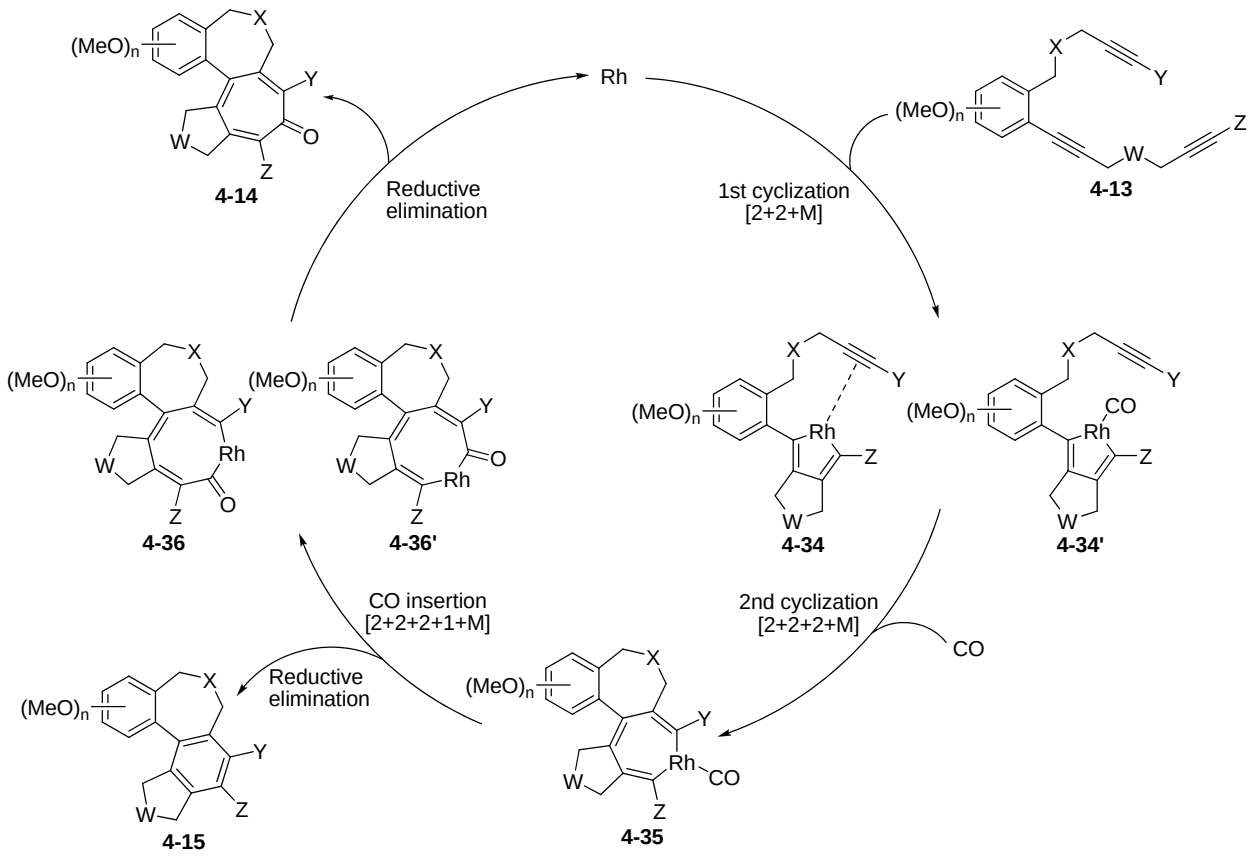


Entry[a]	Substrate	Temp. (°C)	Time (h)	Conv.[b] (%)	Product selectivity[b] **4-14** : **4-15**
1	**4-13d** R^1 = *t*-Bu, R^2 = Me	60	72	100	99 : 1
2	**4-13d** R^1 = *t*-Bu, R^2 = Me	80	24	100	99 : 1
3	**4-13e** R^1 = Me, R^2 = H	80	16	100	56 : 44
4	**4-13f** R^1 = Me, R^2 = TMS	80	120	100	90 (**4-14e**) : 6 (**4-14c**) : 4
5[c]	**4-13f** R^1 = Me, R^2 = TMS	80	120	94	81 (**4-14e**) : 13 (**4-14c**) : 6

[a] 0.05 mmol of starting material was used for each entry.
[b] The conversion and product selectivity were determined by HPLC.
[c] The reaction was carried out without K10.

4.3.3. Mechanism of the Rh-catalyzed [2+2+2+1] cycloaddition

The key to the successful rapid construction of the 6-7-7-6 fused tetracyclic skeleton in one step from *ortho*-phenylenetriynes and CO lies in the mechanism of the [2+2+2+1] cycloaddition process. **Scheme 4-16** illustrates the proposed mechanism of this [2+2+2+1] cycloaddition reaction. The reaction proceeds through (i) selective coordination of the bottom diyne moiety of triyne **4-13** to the active Rh-catalyst species to give metallacycle **4-34** or **4-34'** ([2+2+M]); (ii) insertion of the top alkyne moiety of metallacycle **4-34** into the Rh–C bond to yield 6-7-7-5 fused-tetracyclic rhodacycle **4-35** ([2+2+2+M]); (iii) coordination of CO to the [Rh] metal followed by migratory insertion of CO into the Rh–C bond to form 6-7-8-5 rhodacycle **4-36** or **4-36'** ([2+2+2+1+M]); and (iv) reductive elimination to give [2+2+2+1] cycloadduct **4-14** and regenerate the active Rh-catalyst species. Reductive elimination from rhodacycle **4-35** prior to CO insertion gives [2+2+2] cycloadduct **4-15**.



Scheme 4-16. Proposed mechanism for Rh-catalyzed [2+2+2+1] cycloaddition.

Comparing the results obtained from triynes **4-13a**–**c** (**Table 4-2** and **Scheme 4-15**), the additional methoxy group on the 1-position of triyne **4-13c** significantly affects the formation of the carbonylative cycloadduct **4-14c** and results in a lower product selectivity. The electronic effect of the methoxy group has been ruled out for this phenomenon since there is no apparent difference in product selectivity between the outcomes of triynes **4-13a** and **4-13b**. In order to have better insights into the resulting discrepancy, we carried out molecular modeling of the carbonylative cycloadducts **4-14a**–**c**. Calculations were performed using DFT at the B3LYP/6-31G* level with Spartan '08 package. As illustrated in **Figure 4-3**, the computational study shows a continuous distance decrease between A and D rings from carbonylative cycloadducts **4-14a** to **4-14c**. This implication nicely explains the lower product selectivity obtained by the trimethoxy-substituted triyne **4-13c**. Because of the crowded space for the D ring, the formation of carbonylative cycloadduct **4-14c** from triyne **4-13c** would encounter a larger steric hindrance than those of carbonylative cycloadducts **4-14a** and **4-14b**, thus, the [2+2+2] cycloaddition can compete and lead to a reduction in production selectivity. The same

observation was found in the cases of carbonylative cycloadducts **4-14d–f** (**Figure 4-3**) and is consistent with the experimental results (**Table 4-5**). It was also found that the terminal substituents at the acetylene moieties have influence on the A–D ring distance of the resulting carbonylative cycloadduct. As **Figure 4-4** shows, bearing the bulky substituents, such as *t*-Bu or TMS, yields a more twisted tropone ring C, which in turn lifts the D ring away from the plane of A ring and produces a longer A–D ring distance. Therefore, the obtained product selectivity arranges as **4-13d** > **4-13f** > **4-13c** > **4-13e** (**Table 4-5**). In agreement with the molecular modeling results, an X-ray crystallographic study of carbonylative cycloadducts **4-14c** and **4-14d** shows the same phenomenon as described above.

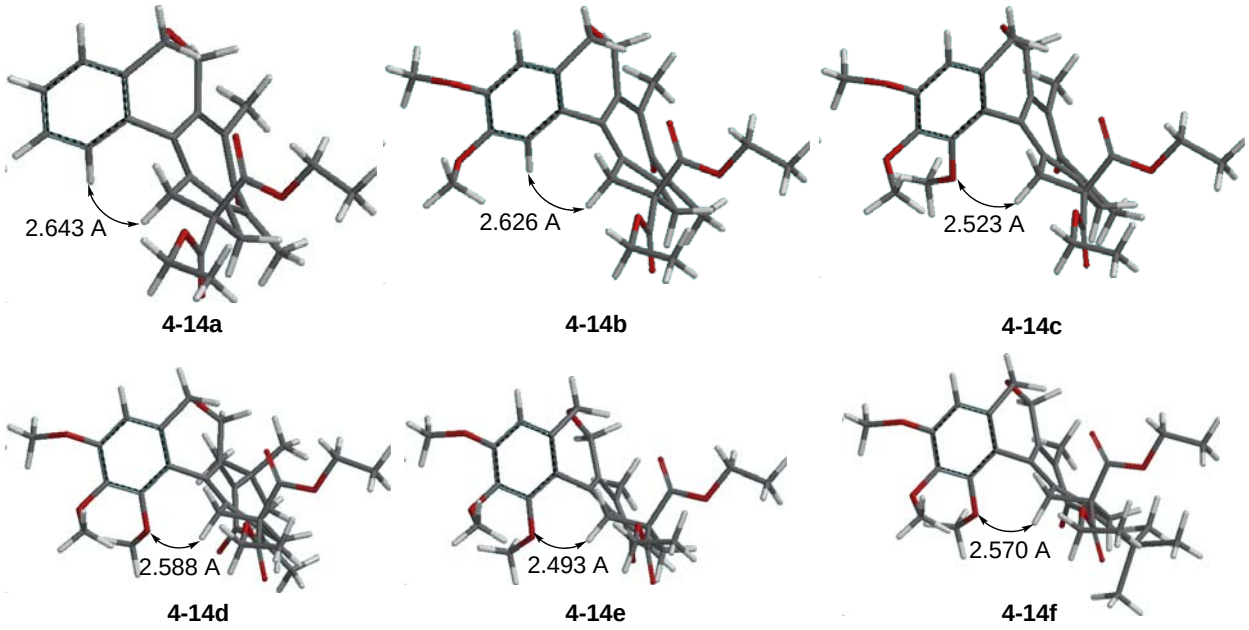


Figure 4-3. Molecular modeling of carbonylative cycloadducts **4-14a–f**.

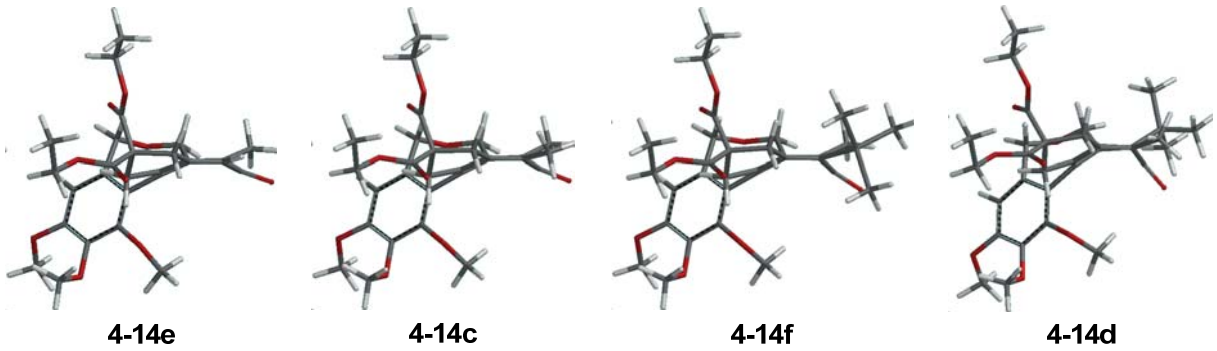
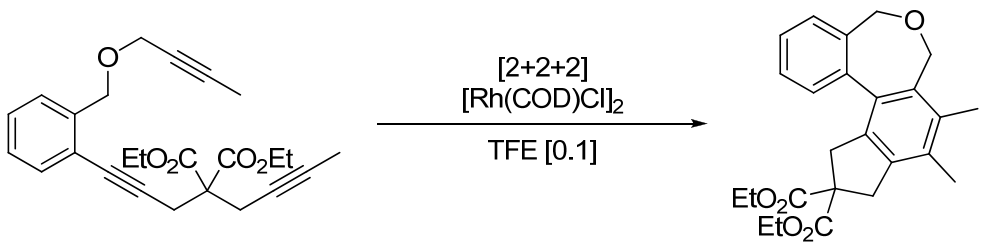


Figure 4-4. Molecular modeling of carbonylative cycloadducts **4-14c–f**.

4.3.4. Rh-catalyzed [2+2+2] cycloaddition

In addition to the development of Rh-catalyzed [2+2+2+1] cycloaddition to synthesize the colchicinoids, we also investigated the synthetic approach towards the novel allocolchicinoids *via* the Rh-catalyzed [2+2+2] cycloaddition. Triyne **4-13a** was taken as the substrate for the initial reaction optimization study, and the results are summarized in **Table 4-6**. Based on the study of [2+2+2+1] cycloaddition, only $[Rh(CO)_2Cl]_2$ or $[Rh(COD)Cl]_2$ can catalyze the cycloaddition of triyne **4-13a** (**Table 4-2**, entries 9 and 15) and the addition of TFE as co-solvent substantially increases the amount of the resulting [2+2+2] adduct (**Table 4-1**, entry 8). Therefore, $[Rh(COD)Cl]_2$ and TFE were chosen as the catalytic partners for the [2+2+2] cycloaddition. As **Table 4-6** shows, when the reaction was carried out in the presence of $[Rh(COD)Cl]_2$ (5 mol%) in TFE at 80 ^oC for 48 h, only 62% of the starting material **4-13a** was consumed, affording the desired cycloadduct **4-15a** in 51% yield (entry 1). Addition of 1,3-bis(diphenylphosphino)propane (DPPP) (10 mol%) drastically improved the efficacy of the rhodium catalyst and accelerated the cycloaddition, 100% conversion of triyne **4-13a** was achieved after 16 h and gave cycloadduct **4-15a** in 86% yield (entry 2). In addition to the conventional thermal conditions, the [2+2+2] cycloaddition proceeded well under microwave conditions. Applying microwave radiation at 80 ^oC for 1 h, cycloadduct **4-15a** was obtained in 92% yield. By lowering the catalyst and ligand amount to 2.5 and 5 mol% respectively, a longer radiation time (2 h) was needed for the reaction to reach completion (entry 4). Raising the reaction temperature as the complement to the lowered reaction rate by reducing catalyst/ligand amount, cycloadduct **4-15a** was obtained in 92% yield within 30 min (entry 5). Accordingly, the optimal reaction conditions found for the Rh-catalyzed [2+2+2] cycloaddition reaction include the use of $[Rh(COD)Cl]_2$ catalyst along with the DPPP ligand in TFE at 100 ^oC under microwave radiation. To examine the scope and limitations of this reaction for functional group tolerance, a variety of substrates containing ether, ester, silyl, and carbamate groups have been subjected to the optimal conditions for the Rh-catalyzed [2+2+2] cycloaddition process. Results are summarized in **Table 4-7**.

Table 4-6. Reaction optimization of [2+2+2] cycloaddition.



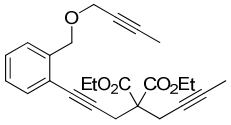
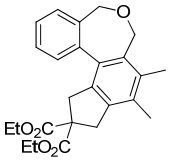
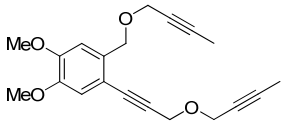
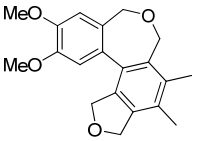
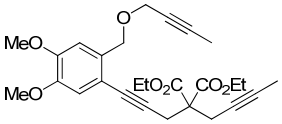
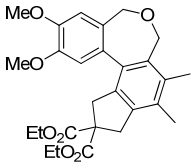
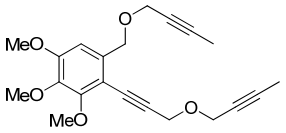
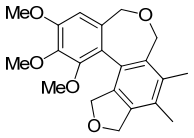
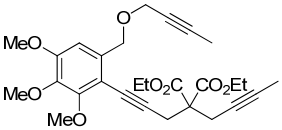
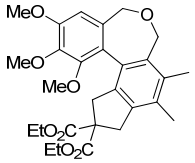
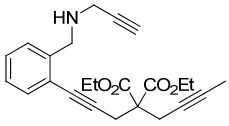
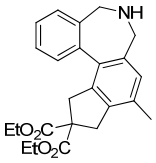
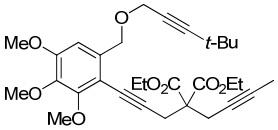
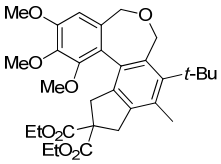
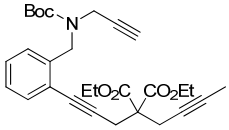
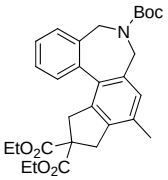
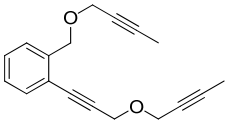
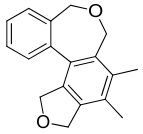
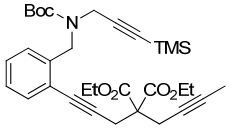
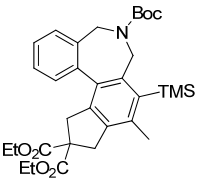
4-13a **4-15a**

Entry[a]	$[Rh(COD)Cl]_2$	Ligand	Temp. (°C)	Time (h)	Conv. (%)	Yield (%)
1	5 mol%	none	80	48	62	51
2	5 mol%	DPPP (10 mol%)	80	16	100	86
3	5 mol%	DPPP (10 mol%)	80 (μw)	1	100	92
4	2.5 mol%	DPPP (5 mol%)	80 (μw)	2	100	94
5	2.5 mol%	DPPP (5 mol%)	100 (μw)	0.5	100	92

[a] 0.05 mmol of starting material was used for each entry.
[b] The conversion was determined by HPLC.

As **Table 4-7** shows, various functional groups and heteroatoms are well tolerated in this microwave-mediated Rh-catalyzed [2+2+2] cycloaddition to give the corresponding fused 6-7-6-5 tetracyclic compounds **4-15** in good to excellent yields. All reactions went to completion within 30 min, except with substrate triyne **4-13d**, which took 1 h radiation to achieve full conversion (entry 4). It was found that free amine functionality is a limitation in this reaction. In the case of triyne **4-13j**, bearing a secondary amine, a very messy mixture was obtained, with no trace of desired cycloadduct **4-15j** (entry 8). The protected amine, on the other hand, is well tolerated in this reaction. Triynes **4-13k** and **4-13l**, bearing *tert*-butyl carbamates, proceeded well and gave the corresponding products **4-15k** and **4-15l** in good to excellent yields (entries 9 and 10).

Table 4-7. [2+2+2] cycloaddition of triynes **4-13a**–**k**.

Entry[a]	Substrate	Product (yield)	Entry[a]	Substrate	Product (yield)
1	 **4-13a**	 **4-15a** (92%)	6	 **4-13h**	 **4-15h** (87%)
2	 **4-13b**	 **4-15b** (82%)	7	 **4-13g**	 **4-15g** (79%)
3	 **4-13c**	 **4-15c** (83%)	8	 **4-13i**	 **4-15i** (-)
4	 **4-13d**	 **4-15d** (73%)	9	 **4-13j**	 **4-15j** (91%)
5	 **4-13h**	 **4-15h** (58%)	10	 **4-13k**	 **4-15k** (93%)

[a] Reaction was run with 4-13 (0.15 mmol), $[Rh(COD)Cl]_2$ (3.75 μmol), and DPPP (7.5 μmol) in TFE at 100 °C under microwave radiation (250 W).
[b] The conversion was determined by HPLC.

4.4. Conclusion

A high-order [2+2+2+1] carbonylative cycloaddition of *ortho*-phenylenetriynes with CO catalyzed by rhodium complexes was developed. This reaction allows a rapid access to the novel colchicinoids. The designed triyne derivatives were synthesized and subjected to the carbonylative cycloaddition and were found to afford the desired tetracyclic fused tropone products in good to excellent selectivities and yields. Moreover, a microwave-mediated Rh-catalyzed [2+2+2] cycloaddition to synthesize the allocolchicinoids was developed as well. These two processes have high synthetic potential to provide innovative routes for the synthesis of polycyclic skeletons of biological interest. Further studies of substrate scope and functionality limitation of these cycloaddition reactions, as well as bioactivity tests on the synthesized colchicinoids and allocolchicinoids, are actively in progress.

4.5. Experimental Section

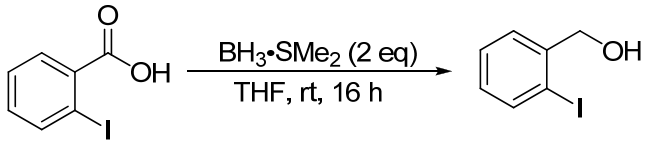
General Method

Microwave-assisted reactions were carried out with CEM Discover S series microwave reactor. ^{1}H and ^{13}C NMR spectra were measured on Bruker Avance III HD-Nanobay 400 (400 MHz ^{1}H; 100 MHz ^{13}C), Varian Inova-400 (400 MHz ^{1}H; 100 MHz ^{13}C), or Varian Gemini-2300 (300 MHz ^{1}H; 75 MHz ^{13}C) spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm. CD_3COCHD_2: ^{1}H, 2.05 ppm; ^{13}C, 29.9 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-Elmer Model 241 polarimeter. TLC was performed on Merck DC-Alufolien Kieselgel 60F 254 and flash column chromatography was carried out on Silicyle Silia*Flash*P60®. Analytical HPLC was carried out with a Shimadzu LC-2010A HPLC system. Low-Resolution Mass Spectrometry was performed on Agilent 6890GC/5973 Mass Selective Detector. High-resolution mass spectrometric analyses were carried out at Mass Spectrometry Laboratories, University of Illinois Urbana-Champaign, Urbana, IL or ICB&DD at Stony Brook University. The X-ray crystallographic structures were obtained on Oxford Gemini A diffractometer. Unless otherwise noted, all reactions were carried out under nitrogen atmosphere in oven-dried glassware using standard Schlenck technique.

Materials

All solvents used as reaction media were purified using the Solvent Purification System 400-4 from Innovative Technology, Inc. or distilled under nitrogen immediately before use. Ether and THF were distilled from Na/benzophenone ketyl. Toluene and CH_2Cl_2 were distilled from CaH_2. Solvents for extraction and chromatography were reagent grade and used as received. All chemicals were purchased from Aldrich or Acros Chemical Co., and were used without further purification unless otherwise noted.

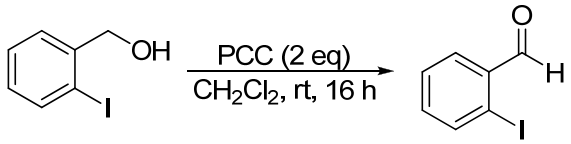
2-Iodobenzyl alcohol (4-17)



4-16 **4-17**

2-Iodobenzoic acid (**4-16**) (12.0 g, 48.4 mmol) in THF (200 mL) was added $BH_3 \cdot SMe_2$ solution (2 M in THF, 50 mL) slowly, and the mixture was stirred at room temperature under for 16 h. The reaction was quenched with water (100 mL), and the solvent was removed *in vacuo*. The aqueous layer was extracted with Et_2O (50 mL × 3), and the combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford **4-17** as a light yellow oil. The crude **4-17** was directly used to the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (s, 2H), 7.00 (dt, J = 1.5, 7.8 Hz, 1H), 7.37 (dt, J = 1.5, 7.8 Hz, 1H,), 7.46 (dd, J = 1.5, 7.8 Hz, 1H), 7.82 (dd, J = 1.5, 7.8 Hz, 1H). All data are in agreement with the literature values.[39]

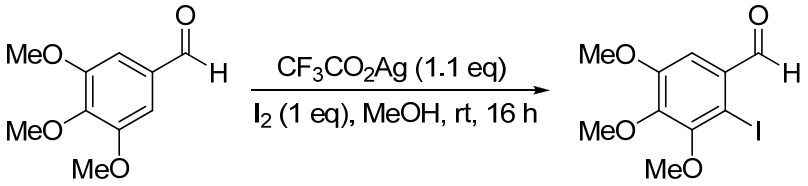
2-Iodobenzaldehyde (4-18a)[40]



4-17 **4-18a**

To a suspension of pyridinium chlorochromate (PCC) (31.2 g, 145 mmol) in CH_2Cl_2 (160 mL) was added dropwise a solution of 2-iodobenzyl alcohol (**4-17**) (11.2 g, 48.4 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred at room temperature for 16 h. The mixture was filtered through Celite® and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 9:1) to give **4-18a** (10.0 g, 89% yield for 2 steps) as a light yellow solid: mp 37.0–39.0 ^{o}C (lit.[41] 40.0–41.0 ^{o}C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.50 (m, 2H), 7.87–7.97 (m, 2H), 10.07 (d, J = 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.7, 128.6, 130.1, 135.0, 135.4, 140.5, 195.6. All data are in agreement with the literature values.[40]

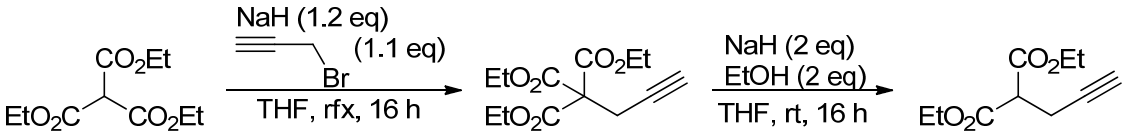
2-Iodo-3,4,5-trimethoxybenzaldehyde (4-18c)[33]



4-19 **4-18c**

To a solution of 3,4,5-trimethoxybenzaldehyde (**4-19**) (2.00 g, 10.2 mmol) in MeOH (70 mL) was added silver trifluoroacetate (2.48 g, 11.2 mmol). A solution of iodine (2.59 g, 10.2 mmol) in MeOH (30 mL) was added dropwise to the reaction mixture, and the reaction was stirred at room temperature for 16 h. The reaction mixture was filtered through Celite®, and the excess iodine was quenched with saturated $Na_2SO_{3(aq)}$ (50 mL), and the solvent was removed *in vacuo*. The aqueous layer was extracted with Et_2O (50 mL × 3), and the combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by recrystallization from cyclohexane to give **4-18c** (3.01 g, 92% yield) as a pale yellow solid: mp 65–67 °C (lit.[33] mp 67 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H), 3.92 (s, 3H), 3.97 (s, 3H), 7.35 (s, 1H), 10.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.2, 61.0, 61.1, 91.5, 108.6, 130.5, 147.7, 153.0, 154.0, 195.2. All data are in agreement with the literature values.[33]

Diethyl 2-(prop-2-yn-1-yl)malonate (4-22)[35]



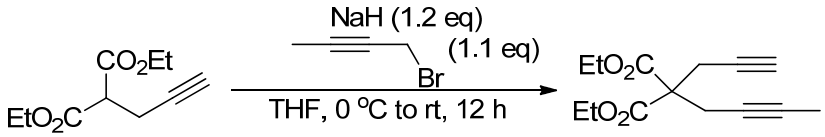
4-20 **4-21** **4-22**

Triethyl mathanetricarboxylate (**4-20**) (15.0 g, 64.6 mmol) was added dropwise to a suspension of NaH (60% dispersion in mineral oil) (3.10 g, 77.5 mmol) in THF (200 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. To the reaction mixture, propargyl bromide (80 wt. % in toluene) (7.94 mL, 71.3 mmol) was then added dropwise. After addition, the reaction mixture was refluxed for 16 h and then cooled to room temperature. The reaction was quenched with water (100 mL) and the solvent was removed *in vacuo*. The aqueous layer was extracted with Et_2O (50 mL × 3), and the combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to

afford crude **4-21**. The crude **4-21** was directly used to the next step without further purification.

EtOH (7.43 mL, 129.2 mmol) was added to a suspension of NaH (60% dispersion in mineral oil) (5.17 g, 129.2 mmol) in THF (150 mL) at 0 °C. The reaction mixture was stirred at room temperature for 20 min. To the reaction mixture, a solution of crude **4-21** in THF (20 mL) was then added dropwise. After addition, the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ (100 mL) and the solvent was removed *in vacuo*. The aqueous layer was extracted with Et_2O (50 mL × 3), and the combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by vacuum distillation to give **4-22** (10.5 g, 82% yield) as a colorless liquid: bp 83.0 °C/1.2 Torr (lit.[35] bp 71.0–72.0 °C/0.2 Torr); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 6H), 2.01 (t, J = 2.7 Hz, 1H), 2.78 (dd, J = 2.7, 7.8 Hz, 2H), 3.56 (t, J = 7.9 Hz, 1H), 4.23 (q, J = 7.2 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.5, 51.3, 61.7, 70.6, 80.1, 167.8. All data are in agreement with the literature values.[35]

Diethyl 2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (4-23)

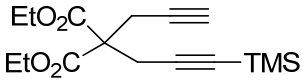


4-22 **4-23**

A solution of diethyl 2-(prop-2-yn-1-yl)malonate (**4-22**) (5.00 g, 25.2 mmol) in THF (10 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil) (1.21 g, 30.2 mmol) in THF (80 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. To the reaction mixture, a solution of 1-bromo-2-butyne (3.69 g, 27.7 mmol) in THF (10 mL) was then added dropwise at 0 °C. After addition, the reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with water (50 mL) and the solvent was removed *in vacuo*. The aqueous layer was extracted with Et_2O (30 mL × 3), and the combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 9:1) to give **4-23** (5.63 g, 89% yield) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 6H), 1.75 (t, J = 2.6 Hz, 1H), 2.00 (t, J = 2.7 Hz, 1H), 2.92 (q, J = 2.6 Hz, 2H), 4.22 (d, J = 7.1 Hz, 2H), 2.92 (q, J = 2.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.5, 14.0, 22.5, 22.9, 56.6,

61.9, 71.4, 73.0, 78.8, 79.1, 169.0.

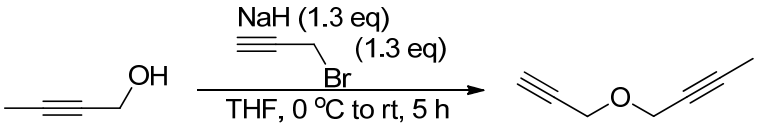
Diethyl 2-(prop-2-yn-1-yl)-2-[3-(trimethylsilyl)prop-2-yn-1-yl]malonate (4-24)[36]



4-24

4-24 (5.34 g, 87% yield) was obtained as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 9H), 1.25 (t, J = 7.1 Hz, 6H), 2.00 (t, J = 2.7 Hz, 1H), 2.95 (d, J = 2.6 Hz, 2H), 2.98 (s, 2H), 4.15–4.23 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –0.1, 14.0, 22.4, 23.8, 56.5, 61.9, 71.4, 78.6, 88.3, 100.7, 168.5. All data are in agreement with the literature values.[36]

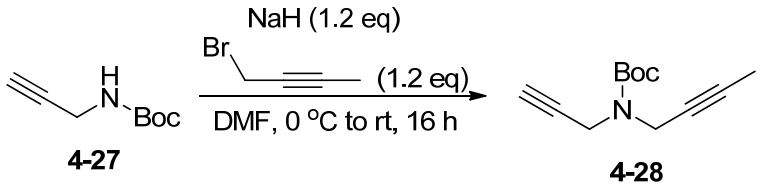
1-(Prop-2-yn-1-yloxy)but-2-yne (4-26)[42]



4-25 **4-26**

A solution of 2-butyn-1-ol (**4-25**) (3.50 g, 50.0 mmol) in THF (20 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil) (2.60 g, 65.0 mmol) in THF (80 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. To the reaction mixture, propargyl bromide (80 wt. % in toluene) (7.24 mL, 65.0 mmol) was then added dropwise at 0 °C. After addition, the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ (50 mL) and the solvent was removed *in vacuo*. The aqueous layer was extracted with Et_2O (30 mL × 3), and the combined organic layers were washed with water (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by vacuum distillation to give **4-26** (2.81 g, 52% yield) as a colorless liquid: bp 73.0–76.0 °C/15.0 Torr (lit.[42] bp 90.0 °C/70.0 Torr); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (t, J = 2.7 Hz, 3H), 2.43 (t, J = 2.4 Hz, 1H), 4.21 (q, J = 2.7 Hz, 2H), 4.24 (d, J = 2.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.3, 56.0, 56.8, 74.0, 74.5, 78.9, 83.0. All data are in agreement with the literature values.[42]

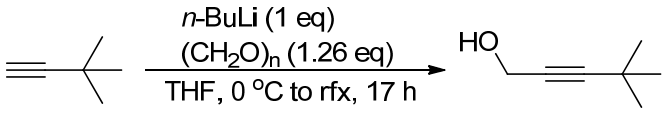
***tert*-Butyl but-2-yn-1-yl(prop-2-yn-1-yl)carbamate (4-28)**



4-27 **4-28**

NaH (60% dispersion in mineral oil) (1.44 g, 36.0 mmol) was added in small portions to a solution of *N*-Boc-propargylamine (**4-27**) (4.66 g, 30.0 mmol) in DMF (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. To the reaction mixture, 1-bromo-2-butyne (4.79 g, 36.0 mmol) was then added dropwise. After addition, the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with water (20 mL) and extracted with Et_2O (30 mL × 3). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 19:1) to give **4-28** (4.19 g, 67% yield) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.86 (t, J = 2.4 Hz, 3H), 2.19 (t, J = 2.4 Hz, 1H), 4.11 (br s, 2H), 4.14 (br s, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 3.4, 28.2, 35.4, 71.4, 73.8, 79.1, 80.5, 80.7, 154.3.

4,4-Dimethylpent-2-yn-1-ol (4-30)[43]

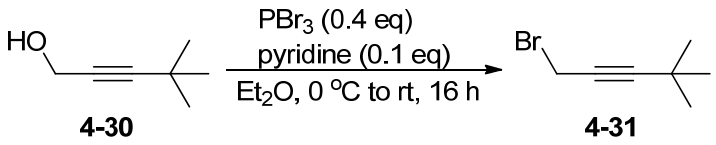


4-29 **4-30**

n-BuLi (1.6 M in hexanes) (45.0 mL, 72.1 mmol) was added slowly to a solution of 3,3-dimethyl-1-butyne (**4-29**) in THF (100 mL) at 0 °C. After addition, the reaction mixture was allowed to warm up to room temperature slowly and stirred at room temperature for 20 min. To the reaction mixture, paraformaldehyde (2.65 g, 88.3 mmol) was then added in portions. After addition, the reaction mixture was refluxed for 17 h and then cooled to room temperature. The reaction was quenched with water (50 mL) and extracted with Et_2O (30 mL × 3). The combined organic layers were washed with saturated $NH_4Cl_{(aq)}$ (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by distillation to give **4-30** (6.25 g, 77% yield) as a colorless liquid: bp 160.0–162.0 °C (lit. bp 160.4–163.4 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 1.46 (t, J = 6.0 Hz, 1H), 4.25 (d, J = 5.9 Hz, 2H); ^{13}C

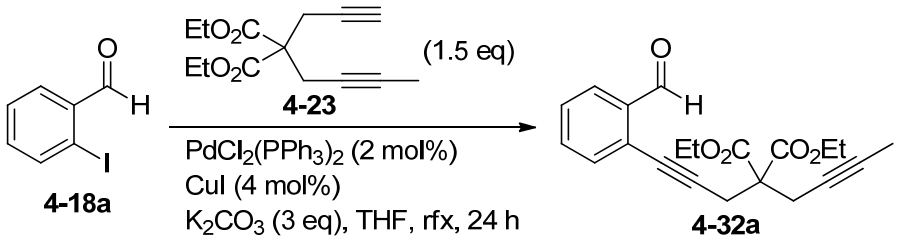
NMR (100 MHz, $CDCl_3$) δ 27.3, 30.9, 51.4, 77.0, 94.7. All data are in agreement with the literature values.[43]

1-Bromo-4,4-dimethylpent-2-yne (4-31)[38]



A solution of PBr_3 (6.03 g, 22.3 mmol) in Et_2O (7 mL) was slowly added to a mixture of pyridine (0.45 mL, 5.57 mmol) and 4,4-dimethylpent-2-yn-1-ol (**4-30**) in Et_2O (13 mL) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 16 h. The reaction was diluted with Et_2O (100 mL) and washed with water (50 mL × 2) and brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by distillation to give **4-31** (7.06 g, 72% yield) as a colorless liquid: bp 152.0–154.0 °C (lit.[44] bp 50.0–52.5 °C/18–20 Torr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 3.92 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 27.5, 30.7, 74.0, 96.0. All data are in agreement with the literature values.[38]

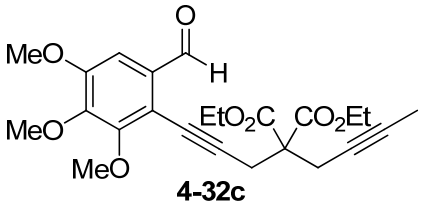
Diethyl 2-(but-2-ynyl)-2-[3-(2-formylphenyl)prop-2-ynyl]malonate (4-32a)



A solution of To a mixture of 2-iodobenzaldehyde (**4-18a**) (2.32 g, 10.0 mmol) and diethyl 2-(but-2-ynyl)-2-(prop-2-ynyl)malonate (**4-23**) (3.75 g, 15.0 mmol) in THF (40 mL) was added to a mixture of $Pd(PPh_3)_2Cl_2$ (0.14 g, 0.20 mmol), CuI (76 mg, 0.40 mmol), and K_2CO_3 (4.15 g, 30.0 mmol) in THF (40 mL). After addition, the reaction mixture was refluxed for 24 h and then cooled to room temperature. The reaction was filtered through Celite®, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 9:1) to give **4-32a** (3.18 g, 90% yield) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 6H), 1.77 (t, J = 2.4 Hz, 3H), 2.97 (q, J = 2.4 Hz, 2H), 3.27 (s, 2H), 4.24 (q, J = 7.2 Hz, 4H), 7.38–7.55 (m, 3H), 7.87–7.90 (m, 1H), 10.45 (d, J = 0.9 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 3.7, 14.3, 23.6, 24.0, 57.1, 62.2, 73.1, 79.4, 79.6, 92.2, 127.1, 127.2, 128.6, 133.8, 133.9, 136.4, 169.2, 192.1; HRMS (ESI+) calcd for $C_{21}H_{23}O_5$ $[M+H]^+$ 355.1545, found 355.1545 (Δ = 0.0 ppm). **4-32c**, **4-32e**–**h** and **4-32l** were prepared in the same manner.

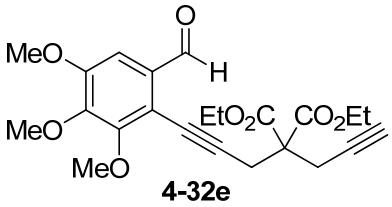
Diethyl 2-(but-2-ynyl)-2-[3-(6-formyl-2,3,4-trimethoxyphenyl)prop-2-ynyl]malonate (4-32c)



4-32c

4-32c (2.56 g, 82% yield) was obtained as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 6H), 1.77 (t, J = 2.4 Hz, 3H), 2.99 (q, J = 2.4 Hz, 2H), 3.30 (s, 2H), 3.91 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 4.23 (q, J = 7.2 Hz, 4H), 7.21 (s, 1H), 10.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.7, 14.3, 23.5, 24.3, 56.4, 57.0, 61.4, 61.6, 62.2, 73.2, 74.8, 79.5, 94.8, 105.2, 116.0, 132.5, 147.8, 154.0, 155.2, 169.2, 191.1; HRMS (ESI+) calcd for $C_{24}H_{29}O_8$ $[M+H]^+$ 445.1862, found 445.1861 (Δ = –0.2 ppm).

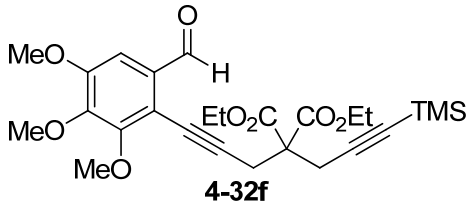
Diethyl 2-[3-(6-formyl-2,3,4-trimethoxyphenyl)prop-2-ynyl]-2-(prop-2-ynyl)malonate (4-32e)



4-32e

4-32e (1.30 g, 69% yield) was obtained a pale yellow solid: mp 95.0–96.5 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 6H), 2.05 (t, J = 2.7 Hz, 1H), 3.06 (d, J = 2.7 Hz, 2H), 3.32 (s, 2H), 3.89 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 4.21–4.26 (m, 4H), 7.20 (s, 1H), 10.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.8, 23.9, 56.1, 56.4, 61.1, 61.3, 62.1, 71.8, 74.8, 78.4, 94.0, 105.0, 115.5, 132.2, 147.5, 153.8, 154.9, 168.6, 190.6; HRMS (ESI+) calcd for $C_{23}H_{27}O_8$ $[M+H]^+$ 431.1706, found 431.1706 (Δ = 0.0 ppm).

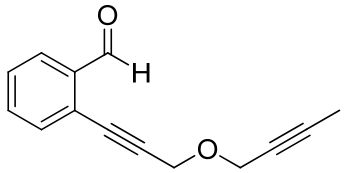
Diethyl 2-[3-(6-formyl-2,3,4-trimethoxyphenyl)prop-2-ynyl]-2-[3-(trimethylsilyl)prop-2-ynyl]malonate (4-32f)



4-32f

4-32f (1.84 g, 73% yield) was obtained as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 9H), 1.24 (t, J = 7.1 Hz, 6H), 3.05 (s, 2H), 3.28 (s, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 4.14–4.28 (m, 4H), 7.18 (s, 1H), 10.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –0.2, 14.0, 23.9, 24.2, 56.1, 56.6, 61.1, 61.3, 61.9, 74.6, 88.5, 94.2, 100.7, 104.9, 115.6, 132.1, 147.5, 153.7, 154.9, 168.5, 190.6; HRMS (ESI+) calcd for $C_{26}H_{35}O_8Si$ $[M+H]^+$ 503.2101, found 503.2100 (Δ = –0.2 ppm).

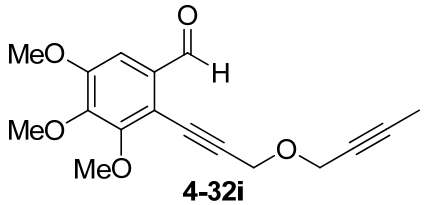
2-[3-(but-2-ynyloxy)prop-1-ynyl]benzaldehyde (4-32g)



4-32g

4-32g (0.91 g, 86% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (t, J = 2.3 Hz, 3H), 4.29 (q, J = 2.3 Hz, 2H), 4.53 (s, 2H), 7.43–7.47 (m, 1H), 7.53–7.58 (m, 2H), 7.91–7.93 (m, 1H), 10.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.6, 57.0, 57.5, 74.1, 82.1, 83.6, 91.8, 126.0, 127.2, 128.9, 133.5, 133.7, 136.1, 191.5; HRMS (ESI+) calcd for $C_{14}H_{13}O_2$ $[M+H]^+$ 213.0916, found 213.0913 (Δ = –1.4 ppm).

2-[3-(But-2-ynyloxy)prop-1-ynyl]-3,4,5-trimethoxybenzaldehyde (4-32i)

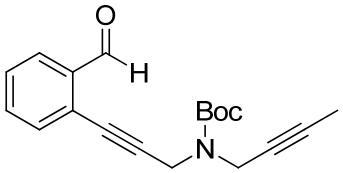


4-32i

4-32i (0.50 g, 38% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (t, J = 2.3 Hz, 3H), 3.92 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 4.31 (q, J = 2.3 Hz, 2H), 4.56 (s, 2H),

7.25 (s, 1H), 10.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.6, 56.2, 57.1, 57.3, 61.2, 61.5, 74.2, 77.8, 83.5, 94.5, 105.2, 114.9, 132.2, 147.5, 154.2, 154.9, 190.5; HRMS (ESI+) calcd for $C_{17}H_{19}O_5$ $[M+H]^+$ 303.1232, found 303.1232 (Δ = 0.0 ppm).

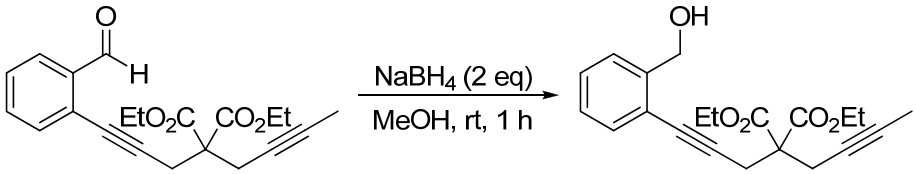
***tert*-Butyl but-2-ynyl[3-(2-formylphenyl)prop-2-ynyl]carbamate (4-32m)**



4-32m

4-32m (1.41 g, 90% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.81 (t, J = 2.4 Hz, 3H), 4.16 (br s, 2H), 4.42 (br s, 2H), 7.40–7.45 (m, 1H), 7.51–7.54 (m, 2H), 7.88–7.90 (m, 1H), 10.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.5, 28.3, 36.0, 73.8, 79.0, 80.0, 81.0, 92.2, 126.4, 127.1, 128.6, 133.4, 133.7, 136.1, 154.4, 191.6; HRMS (ESI+) calcd for $C_{19}H_{21}NNaO_3$ $[M+Na]^+$ 334.1419, found 334.1419 (Δ = 0.0 ppm).

Diethyl 2-(but-2-ynyl)-2-{3-[2-(hydroxymethyl)phenyl]prop-2-ynyl}malonate (4-33a)

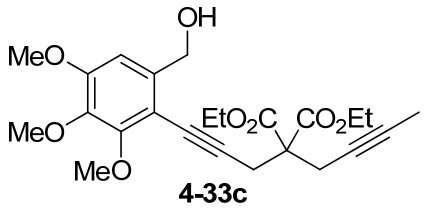


4-32a **4-33a**

To a solution of diethyl 2-(but-2-ynyl)-2-[3-(2-formylphenyl)prop-2-ynyl]malonate (**4-32a**) (3.00 g, 8.47 mmol) in MeOH (85 mL) was added sodium borohydride (0.64 g, 16.9 mmol) in one portion, and the reaction was stirred for 1 h until gas evolution stopped. The reaction was quenched with 1 M $HCl_{(aq)}$ (50 mL), and the solvent was removed *in vacuo*. The residue was extracted with Et_2O (50 mL × 3). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 7:3) to give **4-33a** (2.77 g, 92% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 6H), 1.77 (t, J = 2.4 Hz, 3H), 2.97 (q, J = 2.4 Hz, 2H), 3.22 (s, 2H), 4.24 (q, J = 7.2 Hz, 4H), 4.73 (s, 2H), 7.19–7.41 (m, 4H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.7, 14.3, 23.5, 24.1, 57.2, 62.2, 64.2, 73.2, 79.5, 81.5, 89.2, 121.9, 127.6, 128.0, 128.6, 132.7, 142.9, 169.6; HRMS (ESI+) calcd for

$C_{21}H_{25}O_5$ $[M+H]^+$ 357.1702, found 357.1702 (Δ = 0.0 ppm). **4-33c** and **4-33e**–**h** were prepared in the same manner.

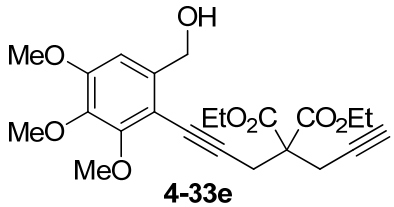
Diethyl 2-(but-2-ynyl)-2-{3-[6-(hydroxymethyl)-2,3,4-trimethoxyphenyl]prop-2-ynyl}malonate (4-33c)



4-33c

4-33c (2.48 g, 96% yield) was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 6H), 1.74 (t, J = 2.6 Hz, 3H), 2.97 (q, J = 2.5 Hz, 2H), 3.24 (s, 2H), 3.82 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 4.16–4.28 (m, 4H), 4.64 (s, 2H), 6.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.4, 14.0, 23.2, 24.0, 56.0, 56.9, 61.0, 61.2, 61.9, 63.9, 72.9, 79.2, 91.5, 107.0, 108.7, 139.3, 141.2, 153.6, 155.0, 169.3; HRMS (ESI+) calcd for $C_{24}H_{34}NO_8$ $[M+NH_4]^+$ 464.2284, found 464.2280 (Δ = –0.9 ppm).

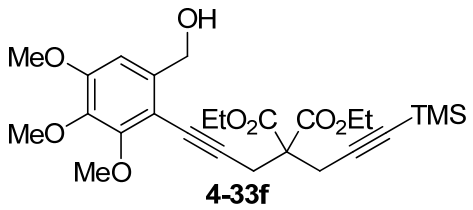
Diethyl 2-{3-[6-(hydroxymethyl)-2,3,4-trimethoxyphenyl]prop-2-ynyl}-2-(prop-2-ynyl)malonate (4-33e)



4-33e

4-33e (1.20 g, 95% yield) was obtained a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 6H), 2.05 (t, J = 2.6 Hz, 1H), 2.50 (t, J = 6.5 Hz, 1H), 3.06 (d, J = 2.6 Hz, 2H), 3.28 (s, 2H), 3.83 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 4.21–4.27 (m, 4H), 4.65 (d, J = 6.5 Hz, 2H), 6.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.8, 24.0, 56.0, 56.5, 61.0, 61.2, 62.1, 63.9, 71.8, 76.7, 78.4, 91.1, 107.0, 108.5, 139.3, 141.3, 153.7, 155.1, 169.0; HRMS (ESI+) calcd for $C_{23}H_{32}NO_8$ $[M+NH_4]^+$ 450.2128, found 450.2128 (Δ = 0.0 ppm).

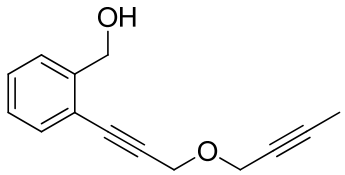
Diethyl 2-{3-[6-(hydroxymethyl)-2,3,4-trimethoxyphenyl]prop-2-ynyl}-2-[3-(trimethylsilyl)prop-2-ynyl]malonate (4-33f)



4-33f

4-33f (1.90 g, 87% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.26 (t, J = 7.1 Hz, 6H), 2.54 (t, J = 6.5 Hz, 1H), 3.06 (s, 2H), 3.26 (s, 2H), 3.83 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 4.16–4.30 (m, 4H), 4.65 (d, J = 6.4 Hz, 2H), 6.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –0.1, 14.0, 24.1, 24.2, 56.0, 56.8, 61.0, 61.2, 62.0, 63.9, 88.5, 91.3, 100.7, 107.1, 108.6, 139.3, 141.3, 153.6, 155.8, 169.0; HRMS (ESI+) calcd for $C_{26}H_{37}O_8Si$ $[M+H]^+$ 505.2258, found 505.2258 (Δ = 0.0 ppm).

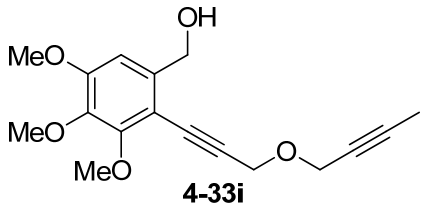
{2-[3-(But-2-ynyloxy)prop-1-ynyl]phenyl}methanol (4-33g)



4-33g

4-33g (0.77 g, 87% yield) was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (t, J = 2.3 Hz, 3H), 1.90 (br s, 1H), 4.28 (q, J = 2.3 Hz, 2H), 4.50 (s, 2H), 4.83 (s, 2H), 7.23–7.27 (m, 1H), 7.33–7.77 (m, 1H), 7.44–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.6, 57.1, 57.3, 63.9, 74.3, 83.4, 84.0, 89.3, 120.7, 127.3, 127.4, 128.9, 132.5, 142.7; HRMS (ESI+) calcd for $C_{14}H_{18}NO_2$ $[M+NH_4]^+$ 232.1338, found 232.1335 (Δ = –1.3 ppm).

{2-[3-(But-2-ynyloxy)prop-1-ynyl]-3,4,5-trimethoxyphenyl}methanol (4-33i)

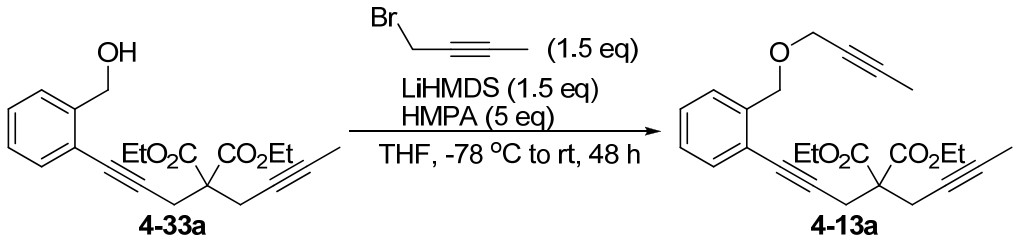


4-33i

4-33i (0.39 g, 81% yield) was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (t, J = 2.2 Hz, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.95 (s, 3H), 4.29 (q, J = 2.3 Hz, 2H), 4.52 (s,

2H), 4.75 (s, 2H), 6.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.6, 56.0, 57.0, 57.3, 61.1, 61.3, 63.8, 74.4, 80.1, 83.2, 92.0, 106.5, 107.6, 139.5, 141.2, 154.2, 155.1; HRMS (ESI+) calcd for $C_{17}H_{24}NO_5$ $[M+NH_4]^+$ 322.1654, found 322.1653 (Δ = –0.3 ppm).

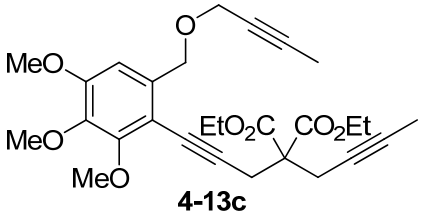
Diethyl 2-(but-2-ynyl)-2-(3-{2-[(but-2-ynyloxy)methyl]phenyl}prop-2-ynyl)malonate (4-13a)



4-33a **4-13a**

A solution of diethyl 2-(but-2-ynyl)-2-{3-[2-(hydroxymethyl)phenyl]prop-2-ynyl}malonate (**4-33a**) (0.71 g, 2.00 mmol) in THF (20 mL) was cooled to –78 °C. To the solution, LiHMDS (1 M in hexanes) (2.20 mL, 2.20 mmol) was added dropwise. Then, hexamethylphosphoramide (HMPA) (1.79 g, 10.0 mmol) was added dropwise to the reaction mixture. After addition, the reaction was stirred at –78 °C for 1 h. 1-Bromo-2-butyne (0.40 g, 6.4 mmol) was added dropwise to the reaction mixture. The reaction was stirred at –78 °C for 2 h and warmed to room temperature and stirred for 48 h. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ (20 mL) and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 9:1) to give **4-13a** (0.60 g, 73% yield) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 6H), 1.75 (t, J = 2.5 Hz, 3H), 1.86 (t, J = 2.3 Hz, 3H), 2.97 (q, J = 2.5 Hz, 2H), 3.21 (s, 2H), 4.15–4.27 (m, 6H), 4.66 (s, 2H), 7.17 (td, J = 1.4, 7.5 Hz, 1H), 7.27 (td, J = 1.4, 7.5 Hz, 1H), 7.34 (dd, J = 1.4, 7.7 Hz, 1H), 7.41–7.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.4, 3.5, 14.0, 23.0, 23.6, 56.8, 58.2, 61.7, 69.5, 73.1, 75.1, 79.0, 80.9, 82.4, 88.8, 121.6, 127.0, 127.3, 128.1, 132.1, 139.5, 168.9; HRMS (ESI+) calcd for $C_{25}H_{29}O_5$ $[M+H]^+$ 409.2015, found 409.2018 (Δ = +0.7 ppm). **4-13c**–**h** were prepared in the same manner.

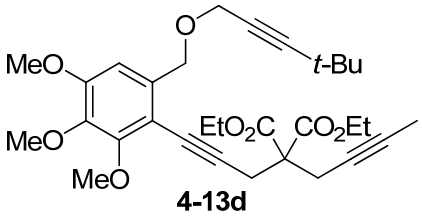
Diethyl 2-(but-2-ynyl)-2-(3-{6-[(but-2-ynyloxy)methyl]-2,3,4-trimethoxyphenyl}prop-2-ynyl)malonate (4-13c)



4-13c

4-13c (0.87 g, 78% yield) was obtained as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.1 Hz, 6H), 1.74 (t, J = 2.6 Hz, 3H), 1.86 (t, J = 2.3 Hz, 3H), 2.99 (q, J = 2.6 Hz, 2H), 3.25 (s, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.17–4.25 (m, 6H), 4.59 (s, 2H), 6.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.4, 3.6, 14.0, 23.0, 23.9, 56.0, 56.8, 58.4, 61.0, 61.1, 61.7, 69.5, 73.1, 75.1, 76.6, 78.9, 82.6, 91.5, 106.4, 108.9, 136.3, 141.1, 153.6, 154.7, 169.0; HRMS (ESI+) calcd for $C_{28}H_{35}O_8$ $[M+H]^+$ 499.2332, found 499.2334 (Δ = +0.4 ppm).

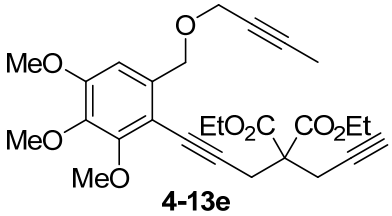
Diethyl 2-(but-2-ynyl)-2-(3-{6-[(4,4-dimethylpent-2-ynyloxy)methyl]-2,3,4-trimethoxyphenyl)}prop-2-ynyl)malonate (4-13d)



4-13d

4-13d (0.34 g, 62% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 1.23 (t, J = 7.1 Hz, 6H), 1.73 (t, J = 2.5 Hz, 3H), 2.98 (q, J = 2.5 Hz, 2H), 3.24 (s, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.15–4.26 (m, 6H), 4.59 (s, 2H), 6.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.4, 14.0, 23.0, 23.9, 27.4, 30.9, 55.9, 56.8, 58.3, 60.9, 61.1, 61.7, 69.4, 73.2, 74.3, 76.6, 78.9, 91.4, 95.3, 106.6, 108.9, 136.3, 141.1, 153.5, 154.7, 169.0; HRMS (ESI+) calcd for $C_{31}H_{44}NO_8$ $[M+NH_4]^+$ 558.3067, found 558.3067 (Δ = 0.0 ppm).

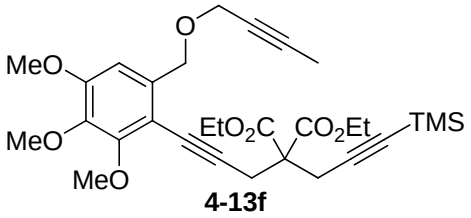
Diethyl 2-(3-{6-[(but-2-ynyloxy)methyl]-2,3,4-trimethoxyphenyl}prop-2-ynyl)-2-(prop-2-ynyl)malonate (4-13e)



4-13e

4-13e (0.77 g, 66% yield) was obtained as a white solid: mp 65.0–67.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 6H), 1.88 (t, J = 2.3 Hz, 3H), 2.04 (t, J = 2.7 Hz, 1H), 3.08 (d, J = 2.7 Hz, 2H), 3.29 (s, 2H), 3.83 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 4.17–4.29 (m, 6H), 4.60 (s, 2H), 6.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.7, 14.0, 22.7, 56.0, 56.5, 58.4, 61.0, 61.2, 62.0, 69.6, 71.6, 75.1, 77.0, 78.7, 82.6, 91.1, 106.5, 108.8, 136.3, 141.1, 153.7, 154.8, 168.7; HRMS (ESI+) calcd for $C_{27}H_{36}NO_8$ $[M+NH_4]^+$ 502.2441, found 502.2435 (Δ = –1.2 ppm).

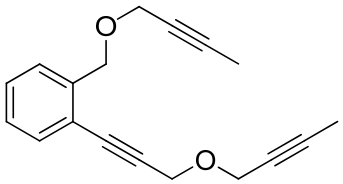
Diethyl 2-(3-{6-[(but-2-ynyloxy)methyl]-2,3,4-trimethoxyphenyl}prop-2-ynyl)-2-[3-(trimethylsilyl)prop-2-ynyl]malonate (4-13f)



4-13f

4-13f (0.20 g, 37% yield) was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.26 (t, J = 7.1 Hz, 6H), 1.88 (t, J = 2.3 Hz, 3H), 3.09 (s, 2H), 3.27 (s, 2H), 3.83 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 4.15–4.30 (m, 6H), 4.60 (s, 2H), 6.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –0.1, 3.7, 14.0, 23.9, 24.1, 56.0, 56.8, 58.4, 61.0, 61.2, 61.9, 69.6, 75.1, 76.8, 82.6, 88.2, 91.4, 101.1, 106.5, 108.9, 136.3, 141.2, 153.6, 154.8, 168.7; HRMS (ESI+) calcd for $C_{30}H_{44}NO_8Si$ $[M+NH_4]^+$ 574.2836, found 574.2836 (Δ = 0.0 ppm).

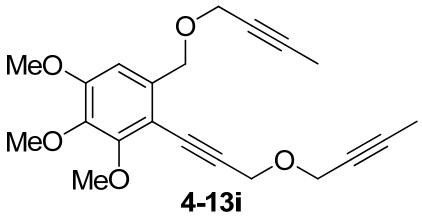
1-[(But-2-ynyloxy)methyl]-2-[3-(but-2-ynyloxy)prop-1-ynyl]benzene (4-13g)



4-13g

4-13g (0.15 g, 55% yield) was obtained as a pale yellow oil: (400 MHz, $CDCl_3$) δ 1.88 (t, J = 2.4 Hz, 6H), 4.20 (q, J = 2.3 Hz, 3H), 4.29 (q, J = 2.4 Hz, 2H), 4.50 (s, 2H), 4.73 (s, 2H), 7.21–7.25 (m, 1H), 7.31–7.35 (m, 1H), 7.43–7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.6, 3.6, 57.1, 57.2, 58.4, 69.6, 74.4, 75.1, 82.7, 83.2, 84.2, 89.1, 121.3, 127.4, 127.8, 128.7, 132.3, 139.8; HRMS (ESI+) calcd for $C_{18}H_{22}NO_2$ $[M+NH_4]^+$ 284.1651, found 284.1646 (Δ = –1.8 ppm).

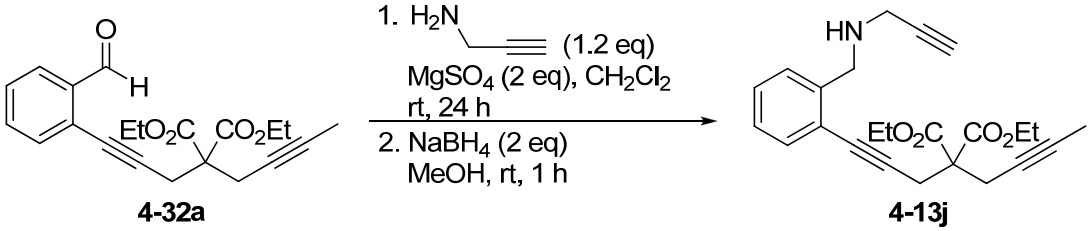
1-[(But-2-ynyloxy)methyl]-2-[3-(but-2-ynyloxy)prop-1-ynyl]-3,4,5-trimethoxybenzene (4-13i)



4-13i

4-13i (0.28 g, 77% yield) was obtained as a pale yellow oil: (400 MHz, $CDCl_3$) δ 1.87 (t, J = 2.4 Hz, 3H), 1.88 (t, J = 2.4 Hz, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 4.20 (q, J = 2.3 Hz, 2H), 4.31 (q, J = 2.3 Hz, 2H), 4.53 (s, 2H), 4.66 (s, 2H), 6.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.6, 3.6, 56.1, 56.9, 57.3, 58.5, 61.1, 61.3, 69.6, 74.5, 75.0, 80.1, 82.8, 83.0, 91.8, 106.8, 108.4, 136.5, 141.2, 154.1, 154.9; HRMS (ESI+) calcd for $C_{21}H_{25}O_5$ $[M+H]^+$ 357.1702, found 357.1702 (Δ = 0.0 ppm).

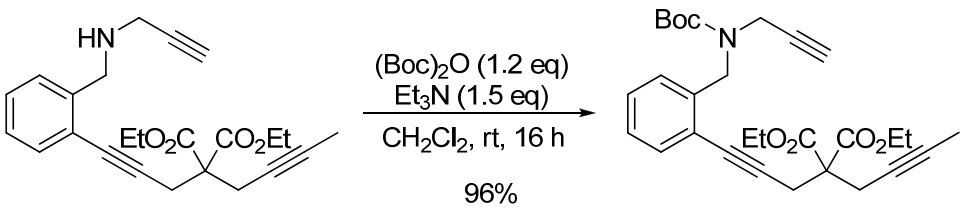
Diethyl 2-(but-2-ynyl)-2-(3-{2-[(prop-2-ynylamino)methyl]phenyl}prop-2-ynyl)malonate (4-13j)



4-32a **4-13j**

To a solution of diethyl 2-(but-2-ynyl)-2-[3-(2-formylphenyl)prop-2-ynyl]malonate (**4-32a**) (0.35 g, 1.00 mmol) and anhydrous $MgSO_4$ (0.24 g, 2.00 mmol) in CH_2Cl_2 (10 mL) was added propargylamine (0.64 g, 16.9 mmol) dropwise, and the reaction was stirred at room temperature for 24 h. The reaction was filtered through Celite®, and the filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH (10 mL), and $NaBH_4$ (76 mg, 2.00 mmol) was added in one portion. The reaction was stirred at room temperature for 1 h. The reaction was quenched with water (10 mL) and extracted with Et_2O (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 6:4) to give **4-13j** (0.24 g, 62% yield) as a pale yellow oil: (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 6H), 1.76 (t, J = 2.6 Hz, 3H), 1.81 (s, 1H), 2.26 (t, J = 2.4 Hz, 1H), 2.98 (d, J = 2.6 Hz, 2H), 3.23 (s, 2H), 3.43 (d, J = 2.4 Hz, 2H), 3.95 (s, 2H), 4.23 (q, J = 7.1 Hz, 4H), 7.15–7.19 (m, 1H), 7.23–7.27 (m, 1H), 7.33–7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.5, 14.1, 23.2, 23.8, 37.5, 50.9, 56.9, 61.9, 71.5, 73.1, 79.2, 81.5, 82.1, 88.7, 122.6, 126.9, 128.2, 128.7, 132.7, 141.2, 169.1; HRMS (ESI+) calcd for $C_{24}H_{28}NO_4$ $[M+H]^+$ 394.2018, found 394.2017 (Δ = –0.3 ppm).

Diethyl 2-(but-2-ynyl)-2-[3-(2-{[tert-butoxycarbonyl(prop-2-ynyl)amino]methyl}phenyl)prop-2-ynyl]malonate (4-13k)

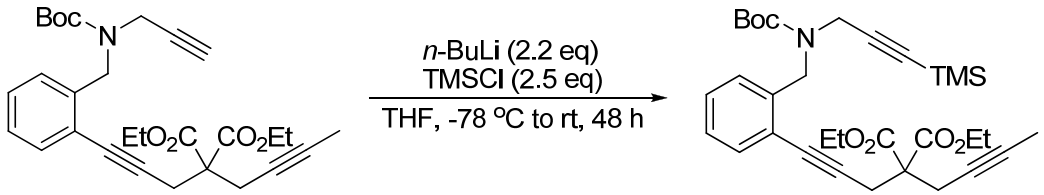


4-13j **4-13k**

Di-*tert*-butyl dicarbonate (0.13 mL, 0.55 mmol) was added dropwise to a mixture of diethyl 2-(but-2-ynyl)-2-(3-{2-[(prop-2-ynylamino)methyl]phenyl}prop-2-ynyl)malonate (**4-13j**) (0.18 g,

0.46 mmol) and triethylamine (0.10 mL, 0.69 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated $NaHCO_{3(aq)}$ (5 mL) and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 8:2) to give **4-13k** (0.22 g, 96% yield) as a colorless oil: (400 MHz, acetone-d_6) δ 1.25 (t, J = 7.1 Hz, 6H), 1.34–1.55 (m, 9H), 1.75 (t, J = 2.6 Hz, 3H), 2.72 (t, J = 2.5 Hz, 1H), 2.96 (q, J = 2.6 Hz, 2H), 3.22 (s, 2H), 3.97–4.19 (m, 2H), 4.24 (q, J = 7.1 Hz, 4H), 4.67 (s, 2H), 7.23–7.27 (m, 2H), 7.30–7.43 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 3.8, 14.9, 24.3, 24.8, 29.0, 37.5, 49.6, 58.1, 63.1, 73.8, 74.4, 80.5, 81.0, 81.2, 82.3, 91.0, 123.0, 127.5, 128.3, 129.8, 133.7, 141.4, 156.1, 170.0; HRMS (ESI+) calcd for $C_{29}H_{36}NO_6$ $[M+H]^+$ 494.2543, found 494.2543 (Δ = 0.0 ppm).

Diethyl 2-(but-2-ynyl)-2-{3-[2-({tert-butoxycarbonyl[3-(trimethylsilyl)prop-2-ynyl]amino}methyl)phenyl]prop-2-ynyl}malonate (4-13l)

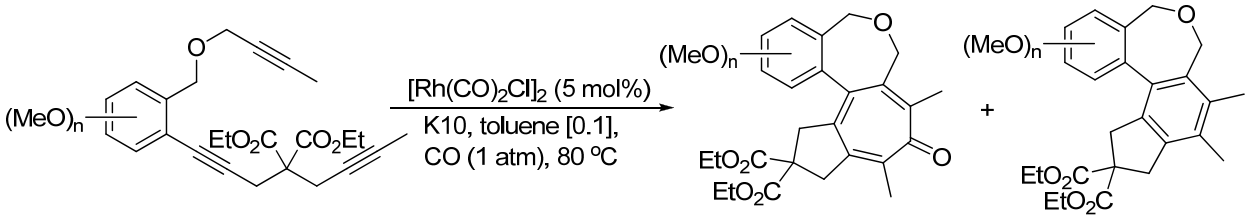


4-13k **4-13l**

A solution of diethyl 2-(but-2-ynyl)-2-[3-(2-{[tert-butoxycarbonyl(prop-2-ynyl)amino]-methyl}phenyl)prop-2-ynyl]malonate (**4-13k**) (0.38 g, 0.78 mmol) in THF (5 mL) was cooled to –78 °C. To the solution, *n*-BuLi (1.6 M in hexanes) (1.07 mL, 1.71 mmol) was added dropwise. After addition, the reaction was stirred at –78 °C for 2 h. Chlorotrimethylsilane (0.25 mL, 1.94 mmol) was added dropwise to the reaction mixture. The reaction was warmed to room temperature and stirred for 48 h. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ (5 mL) and extracted with Et_2O (10 mL × 3). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 9:1) to give **4-13l** (0.35 g, 79% yield) as a pale yellow oil: (400 MHz, acetone-d_6) δ 0.12 (s, 9H), 1.25 (t, J = 7.1 Hz, 6H), 1.30–1.59 (m, 9H), 1.75 (t, J = 2.6 Hz, 3H), 2.96 (q, J = 2.6 Hz, 2H), 3.22 (s, 2H), 4.04–4.26 (m, 6H), 4.65 (s, 2H), 7.18–7.45 (m, 4H); ^{13}C NMR (100 MHz, acetone-d_6) δ 0.1, 3.3, 14.5, 23.9,

24.4, 28.5, 38.1, 49.3, 57.7, 62.6, 73.9, 80.0, 80.7, 82.0, 90.4, 102.8, 122.3, 127.2, 127.8, 129.3, 133.1, 141.3, 155.7, 169.5; HRMS (ESI+) calcd for $C_{32}H_{43}NO_6Si$ $[M+H]^+$ 566.2938, found 566.2938 (Δ = 0.0 ppm).

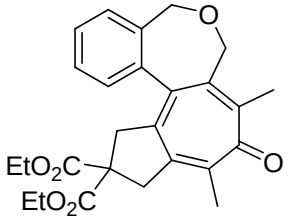
Rh-catalyzed [2+2+2+1] cycloaddition of triynes



4-13 **4-14** **4-15**

Triyne **4-13** (0.05 mmol), montmorillonite K10 (equal weight to **4-13**), and $[Rh(CO)_2Cl]_2$ (1.0 mg, 2.5 μmol) were introduced to a 5 mL round-bottomed flask. The reaction flask was evacuated and refilled with carbon monoxide three times and placed under a carbon monoxide atmosphere (**Caution!! must be done in a well-ventilated fume hood**). Toluene (0.5 mL) was added to the reaction flask and the reaction mixture was stirred at 80 °C for 48 h and then cooled to room temperature. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. To check the conversion and product selectivity, the crude product was then subjected to HPLC analysis using a C-18 column (MeOH:H_2O = 7:3, 0.2 mL/min). The corresponding product **4-14** was isolated by column chromatography on silica gel (hexanes:EtOAc = 7:3) by combining crude products from several runs. Other substrates were run with similar procedure.

8,8-Di(carbethoxy)-4,6-dimethyl-5-oxo-2,3,7,9-tetrahydro-1*H*-azuleno[5,4-*c*]benzo[*e*]oxepine (4-14a)

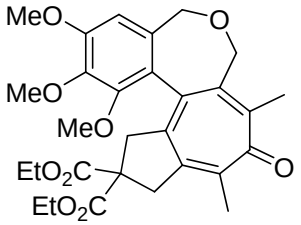


4-14a

4-14a was obtained as an off-white solid: mp 142.5–143.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08–1.28 (m, 6H), 2.26 (s, 3H), 2.37 (s, 3H), 2.93 (br s, 1H), 3.37 (br s, 1H), 3.49 (d, J = 1.4 Hz, 2H), 3.88 (br s, 1H), 4.00–4.26 (m, 4H), 4.55 (s, 2H), 4.71 (br s, 1H), 7.10–7.15 (m, 1H),

7.35–7.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 18.2, 19.4, 42.0, 44.4, 57.5, 61.7, 64.9, 67.7, 128.4, 128.5, 128.7, 128.8, 132.3, 137.7, 139.6, 139.9, 140.8, 141.6, 141.6, 145.3, 170.4, 190.4;HRMS (ESI+) calcd for $C_{26}H_{29}O_6$ $[M+H]^+$ 437.1964, found 437.1966 (Δ = +0.5 ppm).

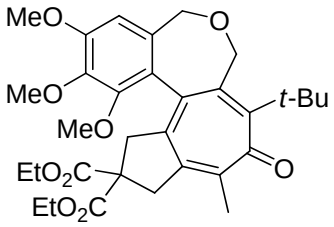
8,8-Di(carbethoxy)-4,6-dimethyl-10,11,12-trimethoxy-5-oxo-2,3,7,9-tetrahydro-1*H*-azuleno[5,4-*c*]benzo[*e*]oxepine (4-14c)



4-14c

4-14c was obtained as an off-white foam: mp 123.0–125.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 2.26 (s, 3H), 2.39 (s, 3H), 2.93 (d, J = 16.6 Hz, 1H), 3.36 (d, J = 10.5 Hz, 1H), 3.41 (d, J = 10.7 Hz, 1H), 3.44 (s, 3H), 3.62 (dd, J = 1.6, 17.8 Hz, 1H), 3.89 (s, 3H), 3.92 (s, 3H), 3.95 (d, J = 13.9 Hz, 1H), 3.98–4.26 (m, 4H), 4.41 (d, J = 11.2 Hz, 1H), 4.47 (d, J = 11.3 Hz, 1H), 4.76 (d, J = 12.8 Hz, 1H), 6.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.0, 18.3, 19.9, 42.3, 43.6, 56.1, 57.4, 61.2, 61.3, 61.7, 61.8, 65.3, 67.9, 107.9, 127.4, 127.9, 134.8, 137.5, 140.1, 141.8, 142.3, 145.5, 150.7, 153.7, 170.5, 171.0, 190.4; HRMS (ESI+) calcd for $C_{29}H_{35}O_9$ $[M+H]^+$ 527.2881, found 527.2885 (Δ = +0.8 ppm).

4-*tert*-Butyl-8,8-di(carbethoxy)-6-methyl-10,11,12-trimethoxy-5-oxo-2,3,7,9-tetrahydro-1*H*-azuleno[5,4-*c*]benzo[*e*]oxepine (4-14d)

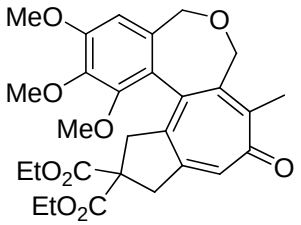


4-14d

4-14d was obtained as an off-white solid: mp 144.0–146.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H), 1.39 (s, 9H), 2.19 (s, 3H), 2.77 (dd, J = 1.4, 16.4 Hz, 1H), 3.19 (d, J = 16.5 Hz, 1H), 3.24 (d, J = 17.6 Hz, 1H), 3.34 (s, 3H), 3.45 (dd, J = 1.6, 17.7 Hz, 1H), 3.85 (s, 3H), 3.89 (d, J = 13.3 Hz, 1H), 3.90 (s, 3H), 3.99–4.22 (m, 4H), 4.42 (d, J

= 11.2 Hz, 1H), 4.46 (d, *J* = 11.1 Hz, 1H), 4.93 (d, *J* = 13.3 Hz, 1H), 6.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 13.9, 16.2, 32.9, 37.0, 39.8, 42.8, 56.0, 57.7, 61.2, 61.2, 61.6, 61.7, 63.8, 67.7, 107.6, 127.4, 127.7, 132.2, 133.3, 134.4, 140.3, 140.4, 142.1, 147.6, 151.0, 153.3, 170.6, 171.2, 197.1; HRMS (ESI+) calcd for $C_{32}H_{41}O_9$ $[M+H]^+$ 569.2751, found 569.2749 (Δ = –0.4 ppm).

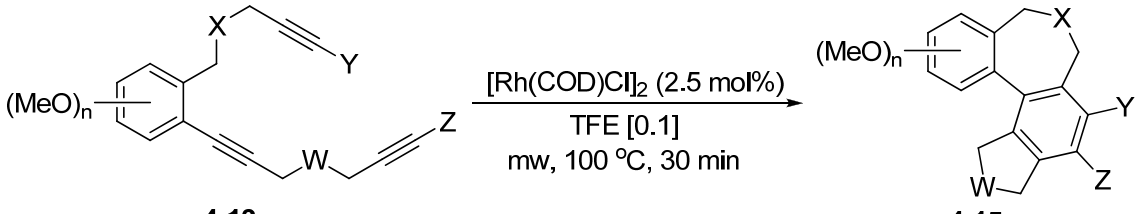
8,8-Di(carbethoxy)-4-methyl-10,11,12-trimethoxy-5-oxo-2,3,7,9-tetrahydro-1*H*-azuleno[5,4-*c*]benzo[*e*]oxepine (4-14e)



4-14e

4-14e was obtained as an off-white solid: mp 136.0–138.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 2.42 (s, 3H), 2.92 (d, *J* = 17.4 Hz, 1H), 3.36 (d, *J* = 17.1 Hz, 1H), 3.45 (d, *J* = 16.9 Hz, 1H), 3.49 (s, 3H), 3.69 (dd, *J* = 2.0, 17.2 Hz, 1H), 3.89 (s, 3H), 3.92 (d, *J* = 13.3 Hz, 1H), 3.93 (s, 3H), 4.00–4.25 (m, 4H), 4.37 (d, *J* = 11.3 Hz, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.80 (d, *J* = 12.4 Hz, 1H), 6.69 (s, 1H), 6.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 13.9, 19.4, 43.3, 43.9, 56.1, 58.4, 61.2, 61.4, 61.8, 66.0, 67.8, 108.0, 127.1, 127.8, 131.7, 137.9, 139.4, 142.4, 144.5, 147.3, 149.2, 150.5, 154.0, 170.1, 187.5; HRMS (ESI+) calcd for $C_{28}H_{32}O_9$ $[M+H]^+$ 513.2125, found 513.2123 (Δ = –0.4 ppm).

Microwave-mediated Rh-catalyzed [2+2+2] cycloaddition of triynes

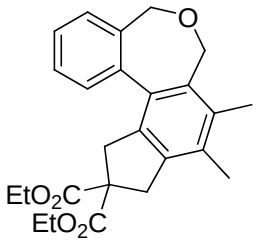


4-13 **4-15**

Triyne **4-13** (0.15 mmol), 1,3-bis(diphenylphosphino)propane (DPPP) (3.1 mg, 7.5 μmol) and $[Rh(COD)Cl]_2$ (1.8 mg, 3.75 μmol) were introduced to a 10 mL microwave reaction vessel. The reaction vessel was evacuated and refilled with nitrogen three times and placed under a

nitrogen atmosphere. 2,2,2-Trifluoroethanol (TFE) (1.5 mL) was added to the reaction vessel and the reaction mixture was stirred at 80 °C for 30 min under microwave radiation (250 W). The reaction mixture was concentrated *in vacuo*. To check the conversion, the crude product was then subjected to HPLC analysis using a C-18 column (MeOH:H_2O = 7:3, 0.2 mL/min). The corresponding product **4-15** was isolated by column chromatography on silica gel (hexanes:EtOAc = 9:1).

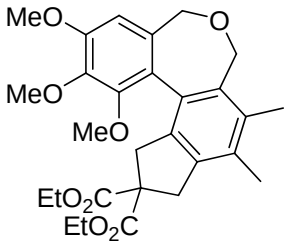
11,11-Di(carbethoxy)-8,9-dimethyl-7,10,11,12-tetrahydro-5*H*-benzo[*e*]indeno[5,4-*c*]oxepine, (4-15a)



4-15a

4-15a (56 mg, 92% yield) was obtained as a white solid: mp 125.0–126.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.31 (s, 3H), 2.39 (s, 3H), 3.35 (d, J = 16.5 Hz, 1H), 3.60 (d, J = 16.5 Hz, 1H), 3.73 (d, J = 16.5 Hz, 1H), 3.85 (d, J = 12.0 Hz, 1H), 4.03–4.21 (m, 4H), 4.22–4.34 (m, 2H), 4.47 (d, J = 11.1 Hz, 1H), 4.83 (d, J = 11.9 Hz, 1H), 7.36–7.51 (m, 3H), 7.60–7.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.0, 15.4, 16.8, 40.2, 40.4, 59.8, 61.5, 61.7, 62.6, 67.2, 127.8, 127.9, 128.0, 129.4, 132.4, 134.0, 134.1, 134.5, 135.1, 139.7, 139.9, 171.4, 171.7; HRMS (ESI+) calcd for $C_{25}H_{29}O_5$ $[M+H]^+$ 409.2015, found 409.2015 (Δ = 0.0 ppm).

1,2,3-Trimethoxy-11,11-di(carbethoxy)-8,9-dimethyl-7,10,11,12-tetrahydro-5*H*-benzo[*e*]indeno[5,4-*c*]oxepine (4-15c)

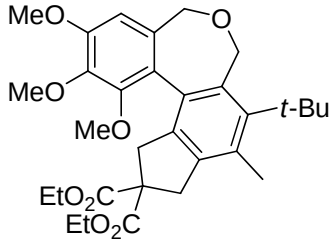


4-15c

4-15c (62 mg, 83% yield) was obtained as a white solid: mp 153.5–155.5 °C; ^{1}H NMR (400

MHz, $CDCl_3$) δ 1.17 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 2.28 (s, 3H), 2.36 (s, 3H), 3.22 (d, J = 16.9 Hz, 1H), 3.47 (s, 3H), 3.51 (d, J = 16.5 Hz, 1H), 3.71 (d, J = 16.8 Hz, 1H), 3.84–3.94 (m, 6H), 3.96 (s, 3H), 4.07–4.15 (m, 2H), 4.20–4.28 (m, 2H), 4.31 (d, J = 11.2 Hz, 1H), 4.84 (d, J = 11.7 Hz, 1H), 6.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.0, 15.4, 16.9, 40.3, 40.7, 56.0, 59.5, 60.7, 61.3, 61.4, 61.5, 62.9, 67.3, 108.1, 125.6, 130.9, 131.2, 131.9, 132.1, 133.1, 136.3, 139.2, 142.2, 150.5, 152.9, 171.9, 172.0; HRMS (ESI+) calcd for $C_{28}H_{35}O_8$ $[M+H]^+$ 499.2332, found 499.2328 (Δ = +0.8 ppm).

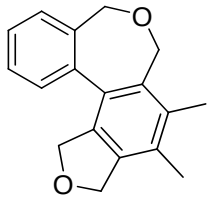
8-*tert*-Butyl-1,2,3-Trimethoxy-11,11-di(carbethoxy)-9-methyl-7,10,11,12-tetrahydro-5*H*-ben zo[*e*]indeno[5,4-*c*]oxepine (4-15d)



4-15d

4-15d (59 mg, 73% yield) was obtained as a white solid: mp 128.0–130.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.60 (s, 9H), 2.45 (s, 3H), 3.20 (d, J = 16.9 Hz, 1H), 3.38 (s, 3H), 3.42 (d, J = 16.5 Hz, 1H), 3.71 (d, J = 16.5 Hz, 1H), 3.79–3.87 (m, 2H), 3.91 (s, 3H), 3.93 (s, 3H), 4.04–4.16 (m, 3H), 4.19–4.27 (m, 2H), 4.34 (d, J = 11.2 Hz, 1H), 5.14 (d, J = 12.2 Hz, 1H), 6.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.0, 21.6, 34.5, 38.4, 40.5, 41.1, 56.0, 59.1, 60.7, 61.3, 61.4, 61.4, 64.5, 67.1, 107.5, 125.4, 130.5, 132.3, 132.7, 132.8, 136.1, 140.8, 142.2, 147.1, 150.5, 153.0, 171.9, 172.0; HRMS (ESI+) calcd for $C_{31}H_{44}NO_8$ $[M+NH_4]^+$ 558.3067, found 558.3066 (Δ = –0.2 ppm).

4,5-Dimethyl-1,3,6,8-tetrahydrobenzo[*e*]isobenzofuro[5,4-*c*]oxepine (4-15g)

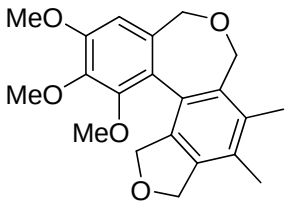


4-15g

4-15g (23 mg, 58% yield) was obtained as a white solid: mp 125.0–127.0 °C; ^{1}H NMR (400

MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.45 (s, 3H), 3.84–4.59 (m, 3H), 4.79–5.69 (m, 5H), 7.38–7.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 17.0, 62.5, 67.3, 73.8, 74.2, 126.8, 128.2, 128.4, 129.8, 129.9, 132.7, 132.9, 133.6, 134.7, 135.0, 139.1, 139.8; HRMS (ESI+) calcd for $C_{18}H_{19}O_2$ $[M+H]^+$ 267.1385, found 267.1362 (Δ = –8.6 ppm).

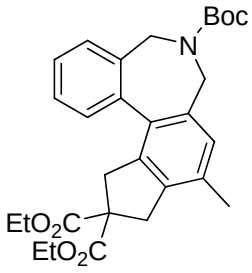
10,11,12-Trimethoxy-4,5-dimethyl-1,3,6,8-tetrahydrobenzo[*e*]isobenzofuro[5,4-*c*]oxepine (4-15i)



4-15i

4-15i (42 mg, 79% yield) was obtained as a white solid: mp 159.5–161.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.40 (s, 3H), 3.52 (s, 3H), 3.89 (d, J = 11.2 Hz, 1H), 3.92 (s, 3H), 3.94 (d, J = 11.7 Hz, 1H), 3.94 (s, 3H), 4.34 (d, J = 11.2 Hz, 1H), 4.71 (d, J = 12.5 Hz, 1H), 4.88 (d, J = 11.7 Hz, 1H), 5.12 (d, J = 12.0 Hz, 1H), 5.19 (d, J = 12.1 Hz, 1H), 5.42 (d, J = 12.5 Hz, 1H), 6.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 16.9, 56.0, 60.8, 61.3, 62.8, 67.3, 73.6, 74.9, 108.4, 125.1, 128.9, 129.5, 130.9, 132.4, 133.7, 135.5, 138.7, 142.3, 150.5, 153.1; HRMS (ESI+) calcd for $C_{21}H_{25}O_5$ $[M+H]^+$ 357.1702, found 357.1699 (Δ = –0.8 ppm).

6-*tert*-Butyl 11,11-diethyl 9-methyl-10,12-dihydrobenzo[*e*]indeno[5,4-*c*]azepine-6,11,11(5*H*,7*H*)-tricarboxylate (4-15k)

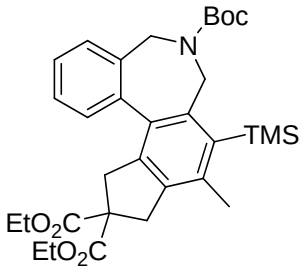


4-15k

4-15k (67 mg, 91% yield) was obtained as an off-white solid: mp 102.0–104.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.50 (s, 9H), 2.31 (s, 3H), 3.33 (d, J = 16.7 Hz, 1H), 3.43–3.70 (m, 4H), 4.02 (d, J = 16.7 Hz, 1H), 4.06–4.20 (m, 2H), 4.22–4.30 (m, 2H), 4.66 (d, J = 13.4 Hz, 1H), 4.81 (d, J = 13.4 Hz, 1H), 6.95–7.16 (m, 1H),

7.31–7.44 (m, 3H), 7.50–7.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.0, 18.8, 28.5, 39.3, 40.3, 46.8, 47.2, 47.6, 47.9, 60.2, 61.6, 61.8, 79.7, 127.8, 127.8, 128.4, 129.5, 129.8, 133.5, 133.7, 134.8, 137.5, 138.7, 139.5, 154.1, 17134, 171.7; HRMS (ESI+) calcd for $C_{29}H_{36}NO_6$ $[M+H]^+$ 494.2543, found 494.2541 (Δ = –0.4 ppm).

6-*tert*-Butyl 11,11-diethyl 9-methyl-8-(trimethylsilyl)-10,12-dihydrobenzo[*e*]indeno[5,4-*c*]azepine-6,11,11(5*H*,7*H*)-tricarboxylate (4-15l)



4-15l

4-15l (79 mg, 93% yield) was obtained as a white solid: mp 157.5–158.5 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.46 (s, 9H), 1.18 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.49 (br s, 9H), 2.43 (s, 3H), 3.24 (d, J = 16.9 Hz, 1H), 3.32–3.71 (m, 4H), 4.02 (d, J = 16.9 Hz, 1H), 4.05–4.20 (m, 2H), 4.21–4.32 (m, 2H), 4.68–5.16 (m, 2H), 7.28–7.47 (m, 3H), 7.50–7.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.4, 3.7, 13.9, 14.0, 21.3, 28.4, 40.5, 40.9, 46.1, 46.4, 46.7, 47.3, 59.5, 61.6, 61.8, 79.7, 80.0, 127.5, 127.5, 128.1, 128.3, 128.7, 134.9, 135.3, 137.9, 138.4, 138.8, 139.0, 139.6, 154.0, 171.5, 171.8; HRMS (ESI+) calcd for $C_{32}H_{44}NO_6Si$ $[M+H]^+$ 566.2938, found 566.2939 (Δ = +0.2 ppm).

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Chapter 1

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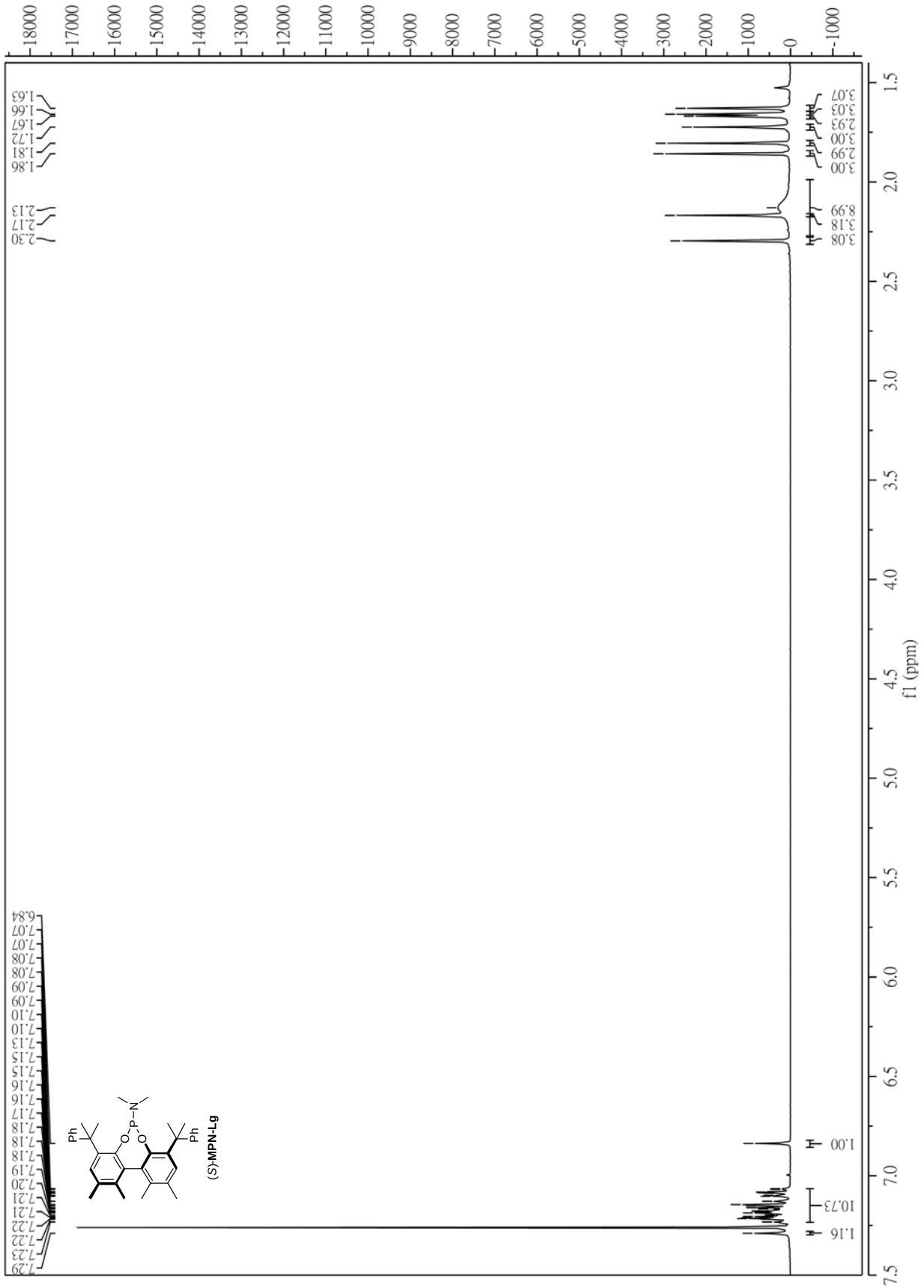
Appendices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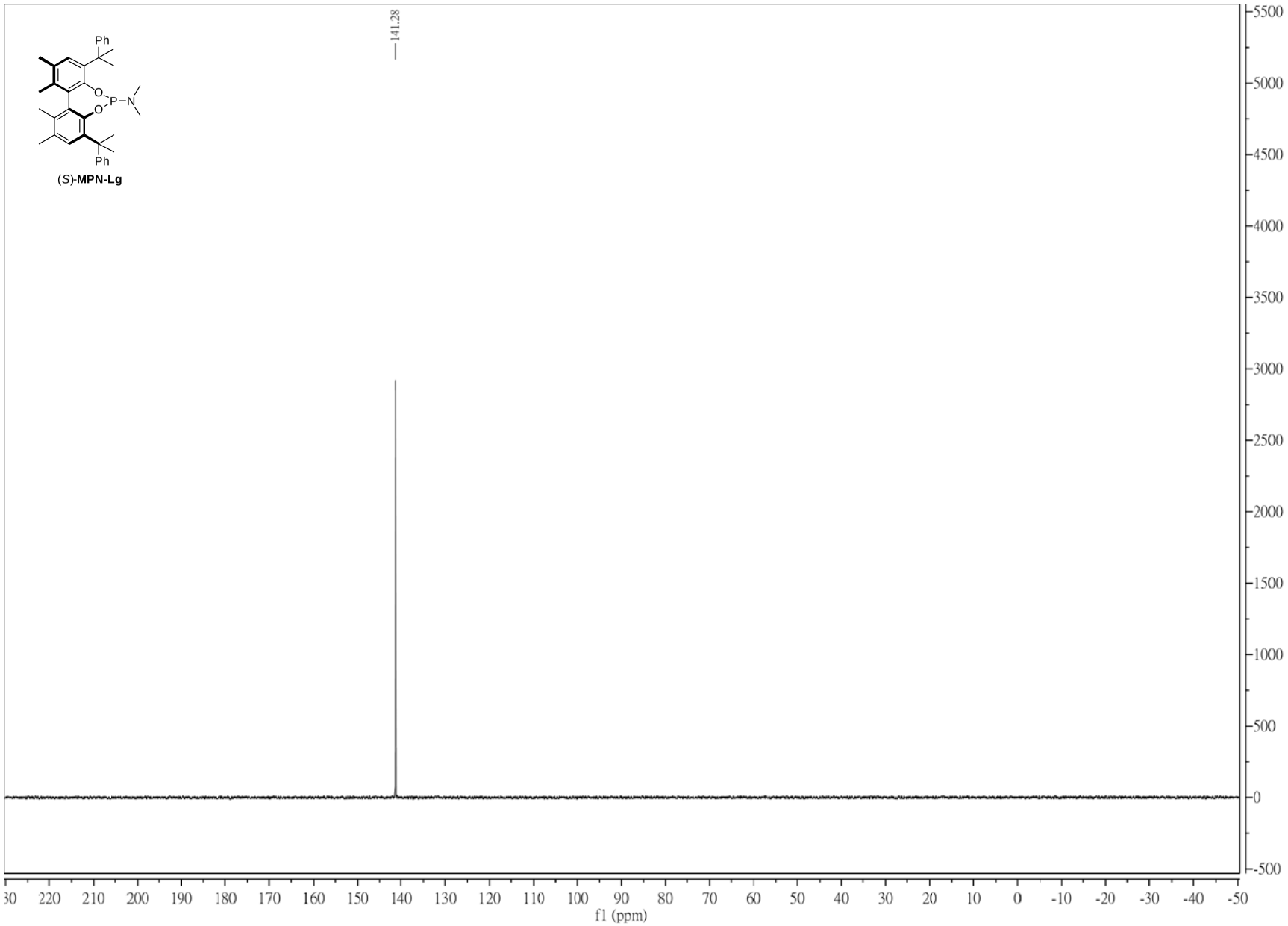
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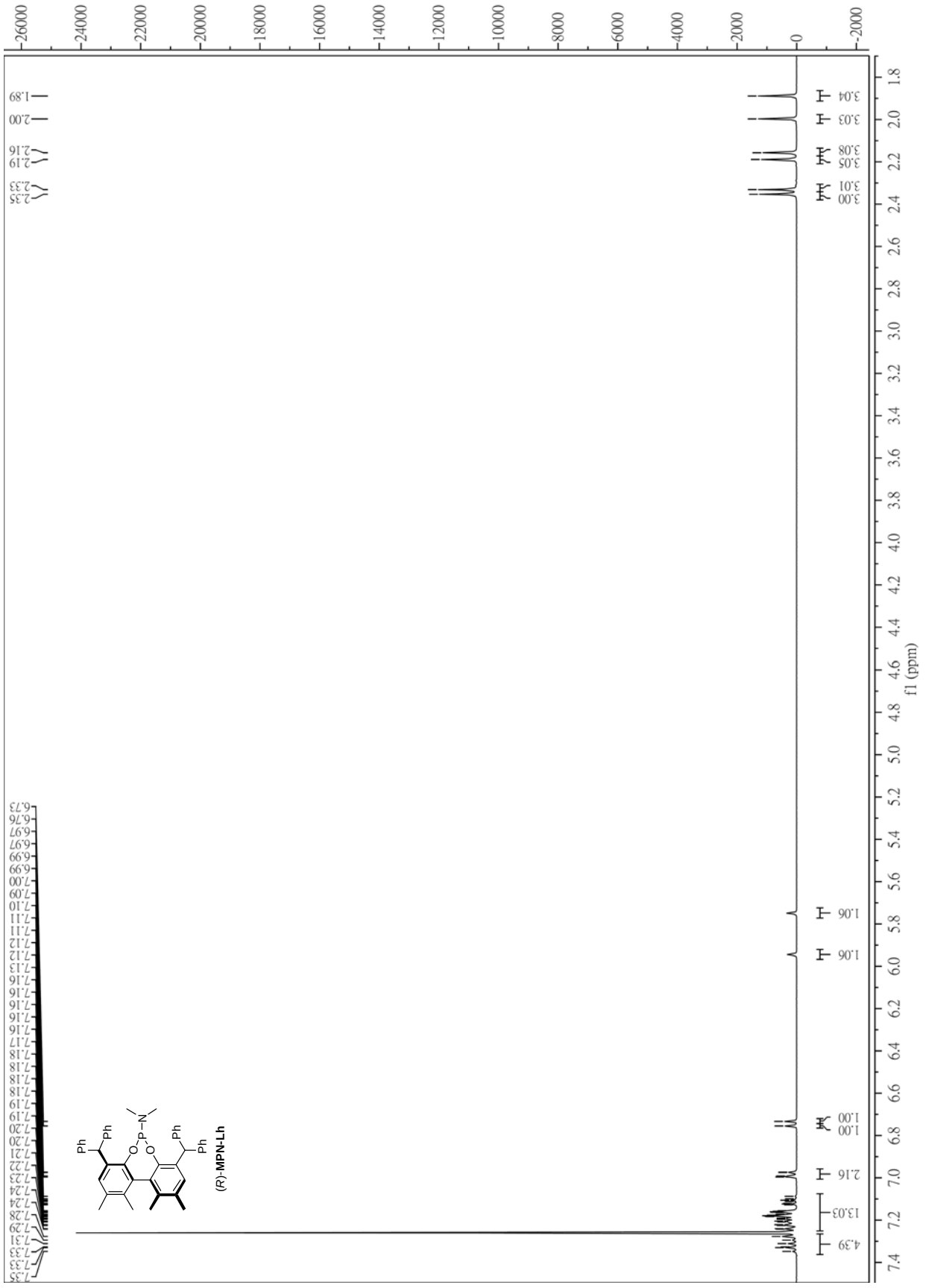
P
N
O
Ph
(S)-MPN-Lg
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50
f1 (ppm)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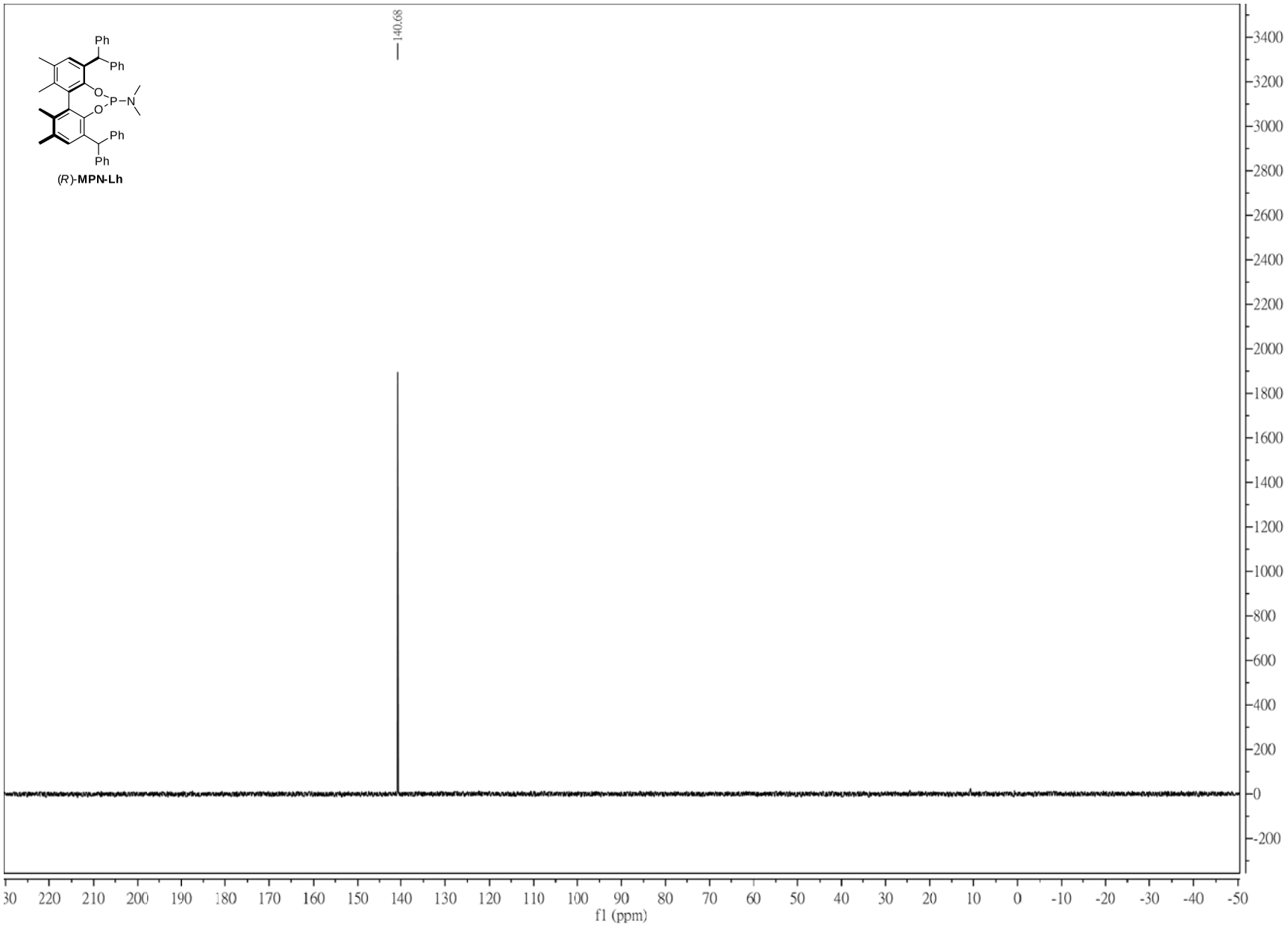
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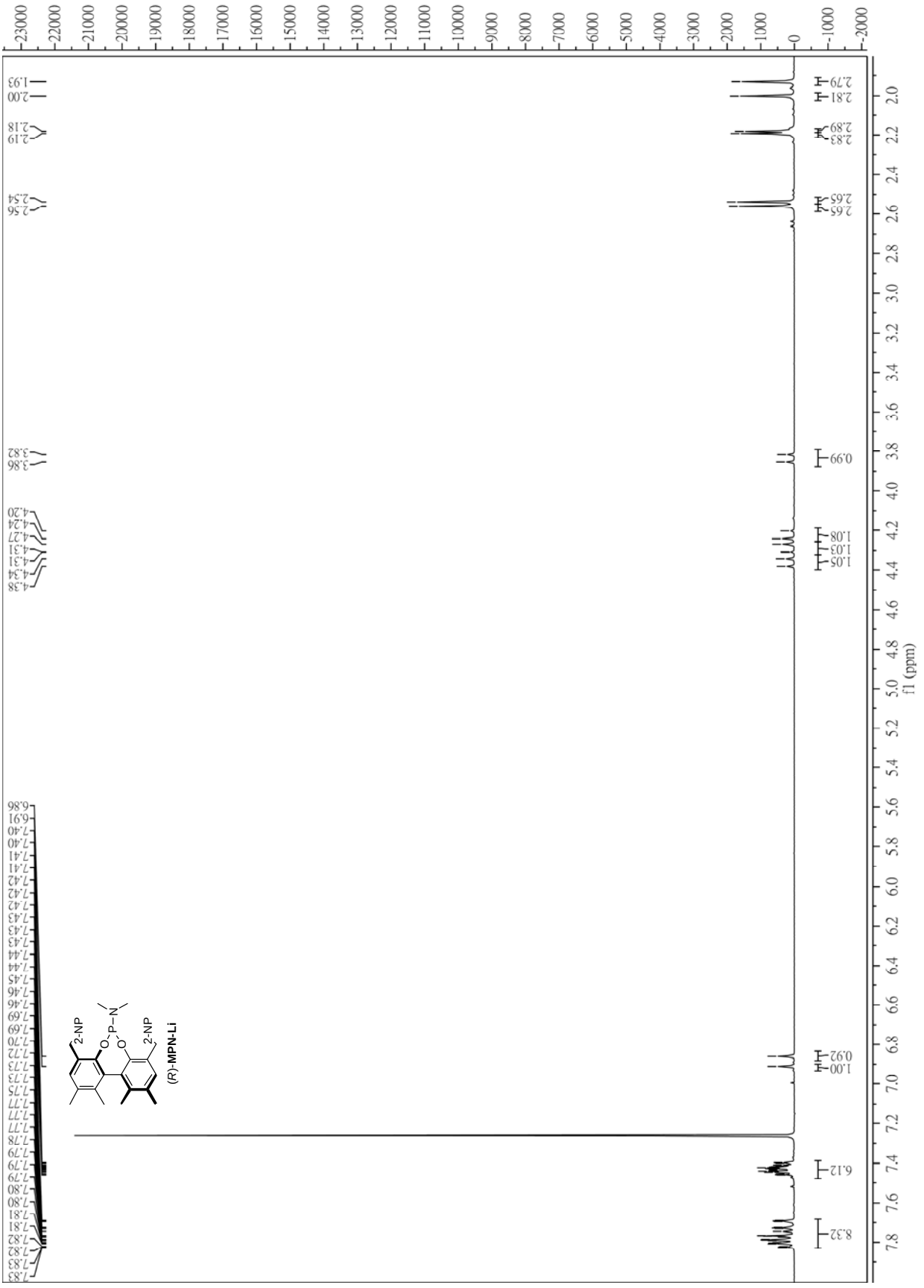
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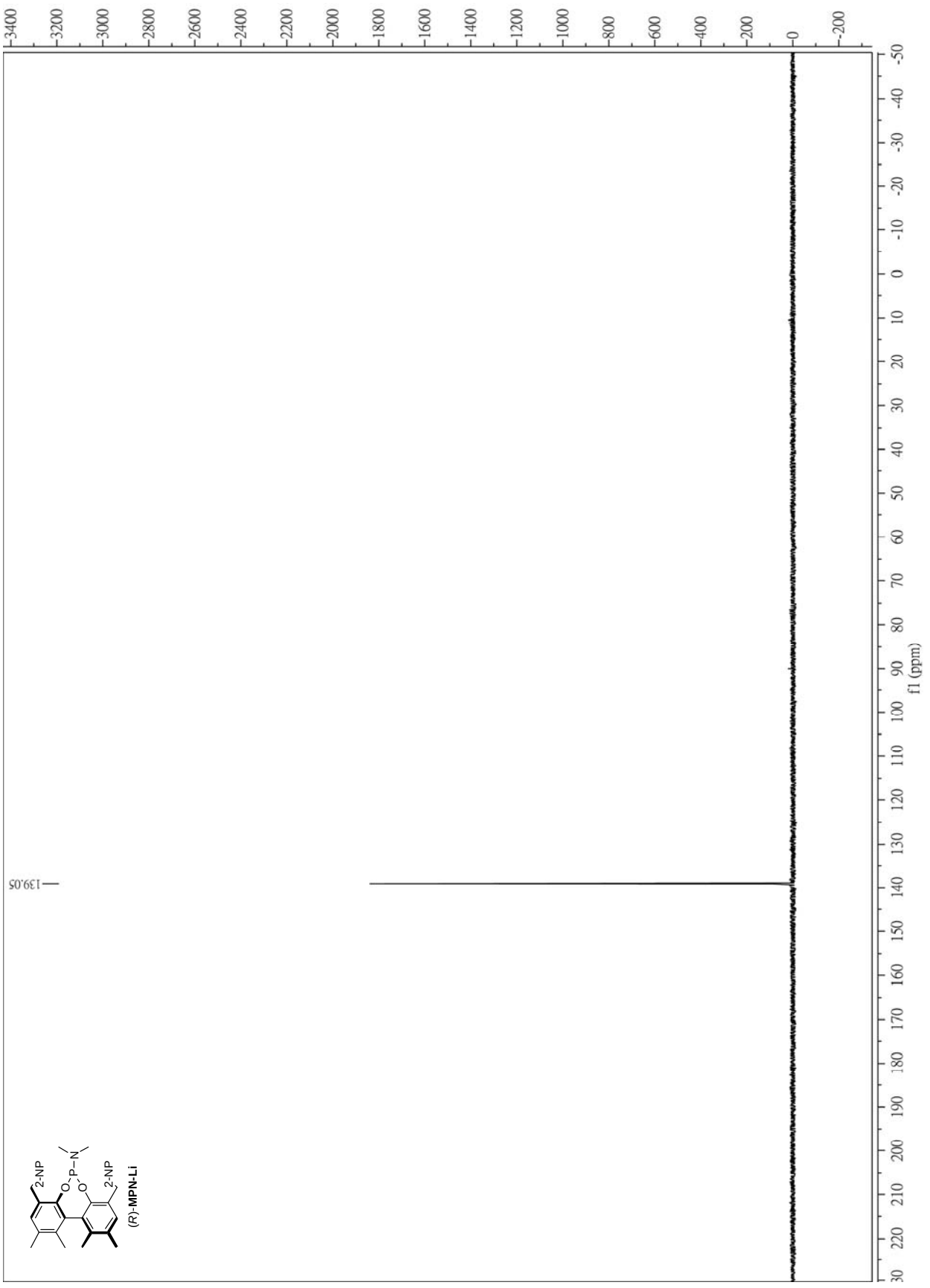
O
P
N
O
2-NP
(R)-MPN-Li
f1 (ppm)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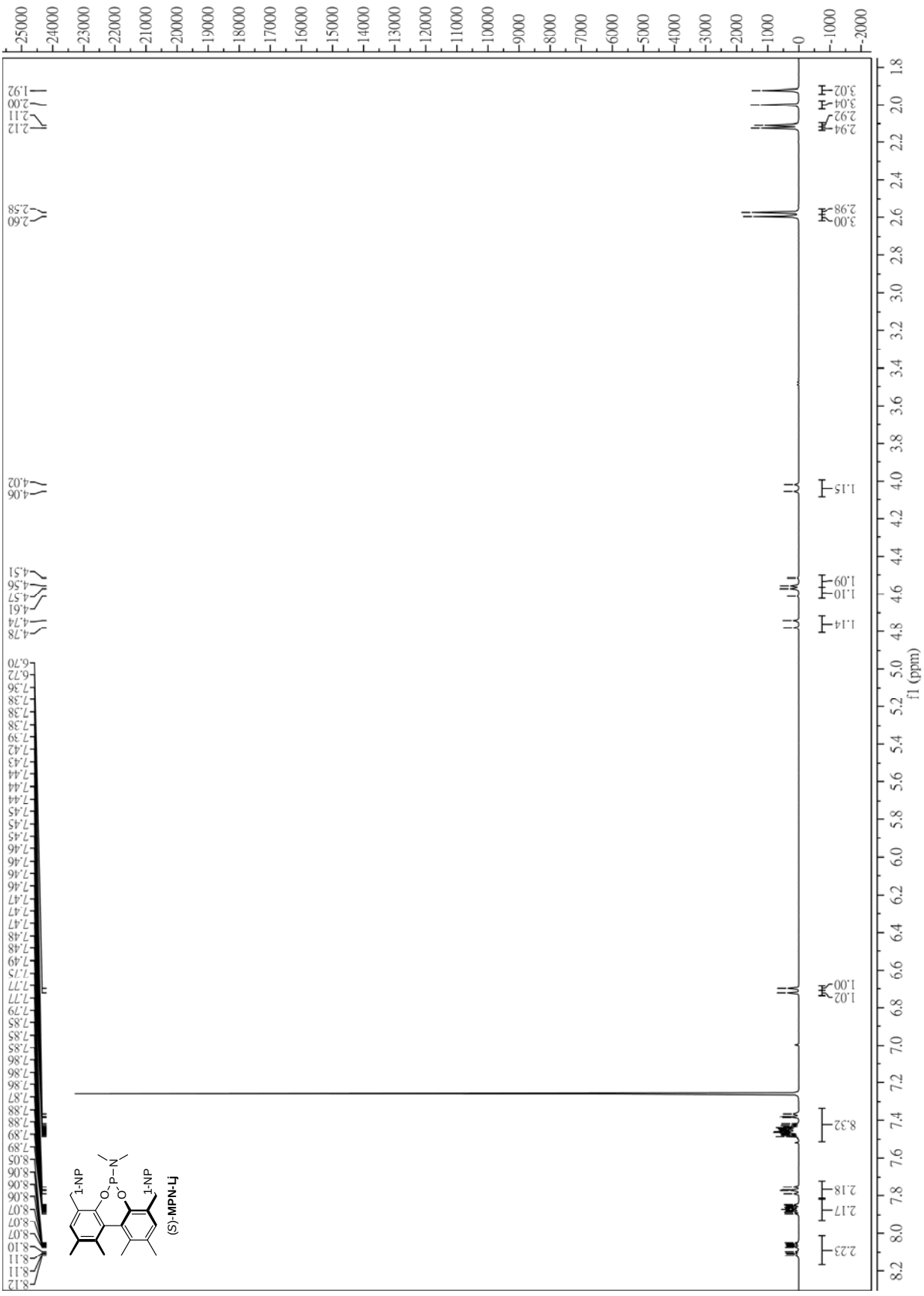
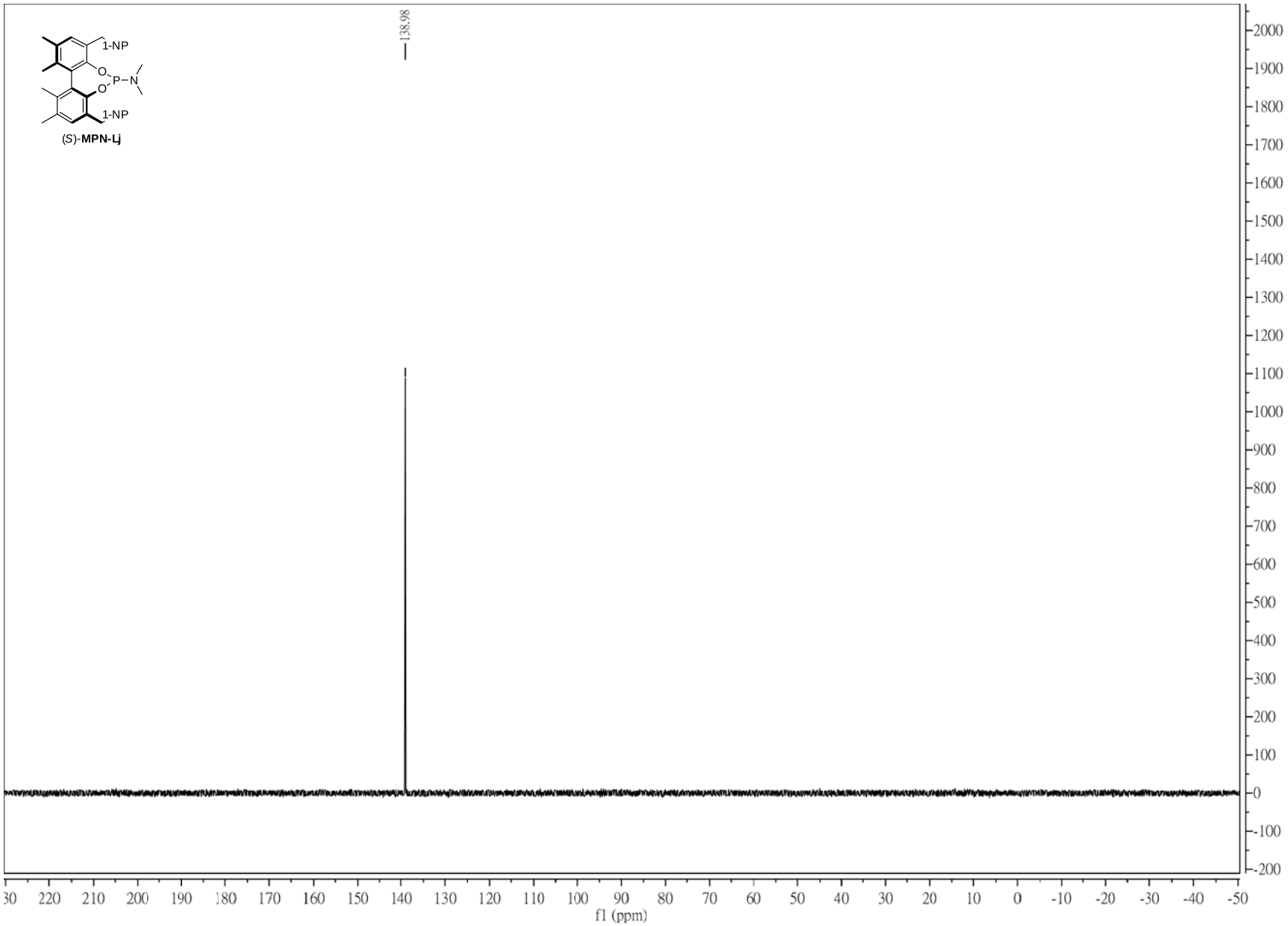
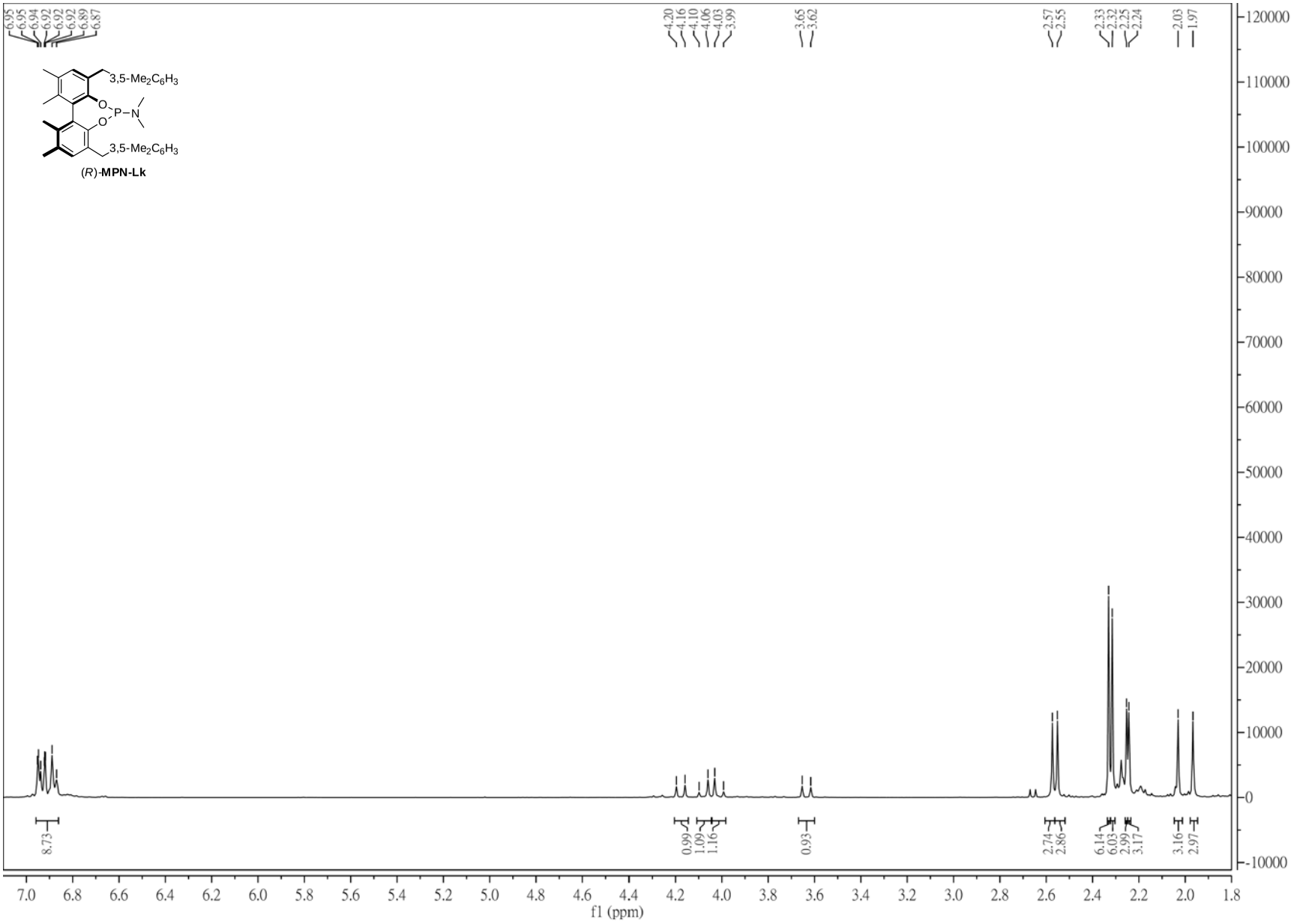
f1 (ppm)
2-NP
2-NP
(R)-MPN-Li


1-NP
1-NP
(S)-MPN-Lj
f1 (ppm)


1-NP
O
P–N
O
1-NP
(S)-MPN-Lj
138.98
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50
f1 (ppm)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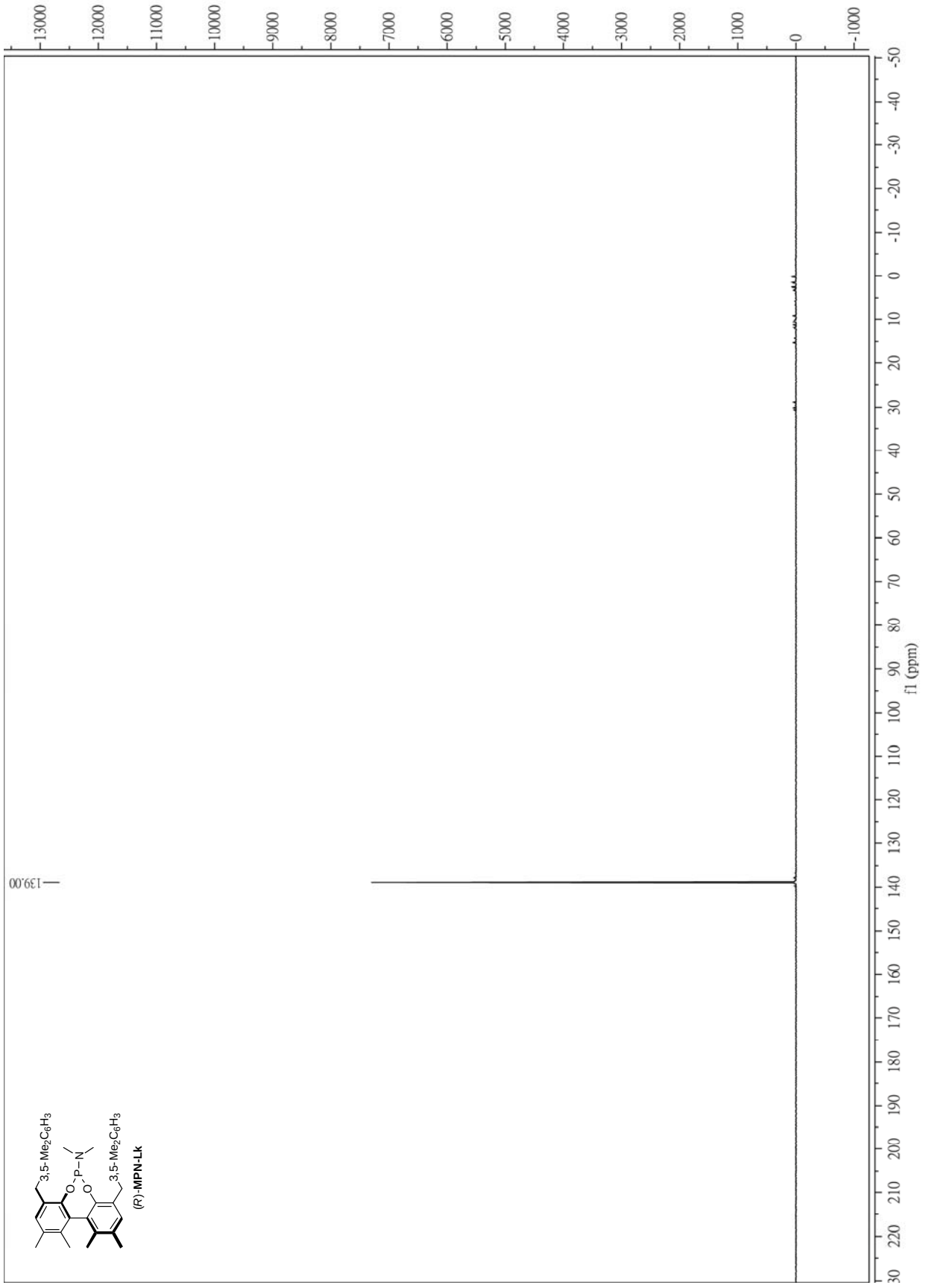
6.95
6.94
6.92
6.92
6.92
6.89
6.87
4.20
4.16
4.10
4.06
4.03
3.99
3.65
3.62
2.57
2.55
2.33
2.32
2.25
2.24
2.03
1.97
3,5-Me2C6H3
O
P–N
O
3,5-Me2C6H3
(R)-MPN-Lk
8.73
0.99
1.09
1.16
0.93
2.74
2.86
6.14
6.03
2.99
3.17
3.16
2.97
f1 (ppm)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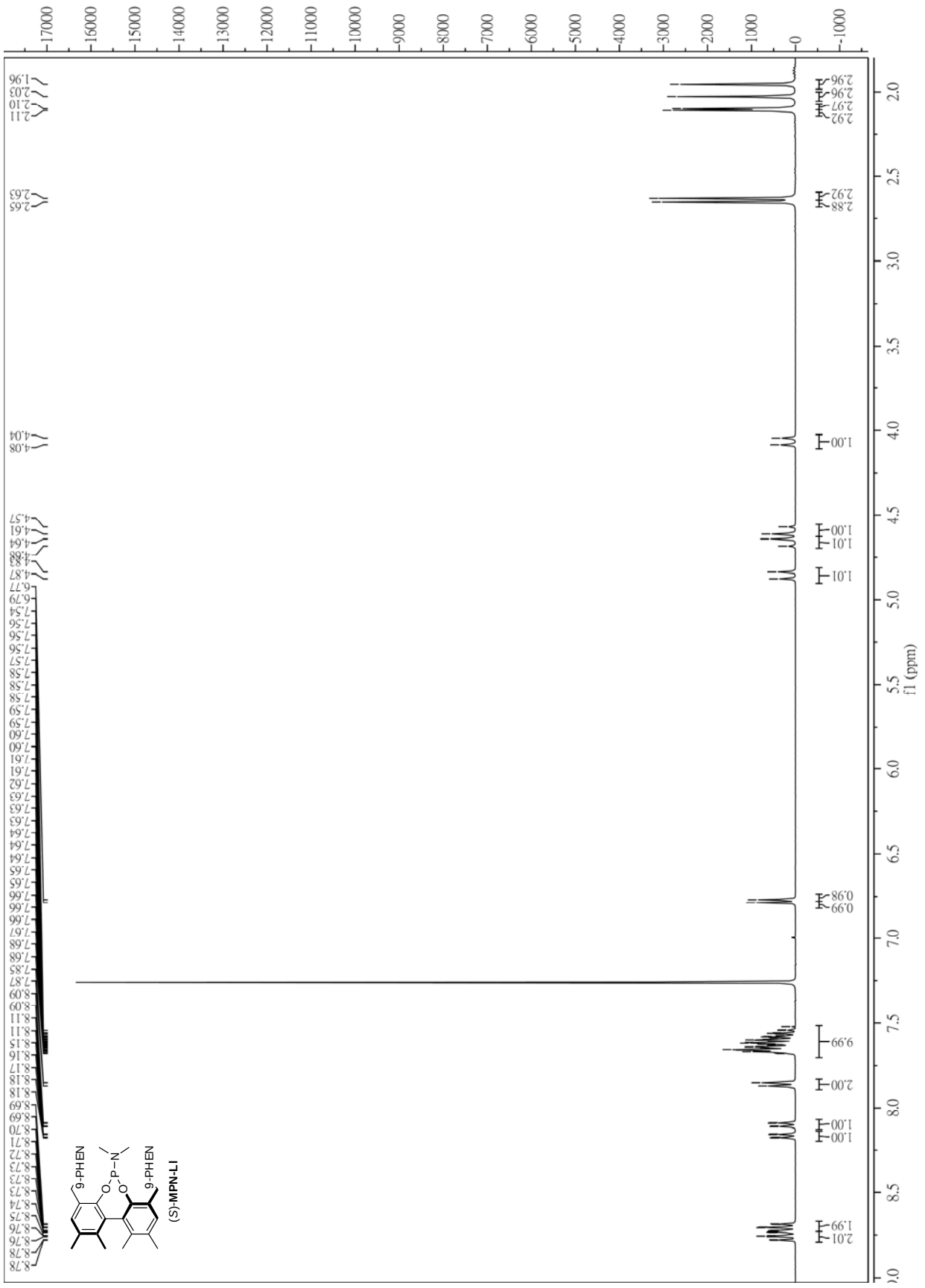
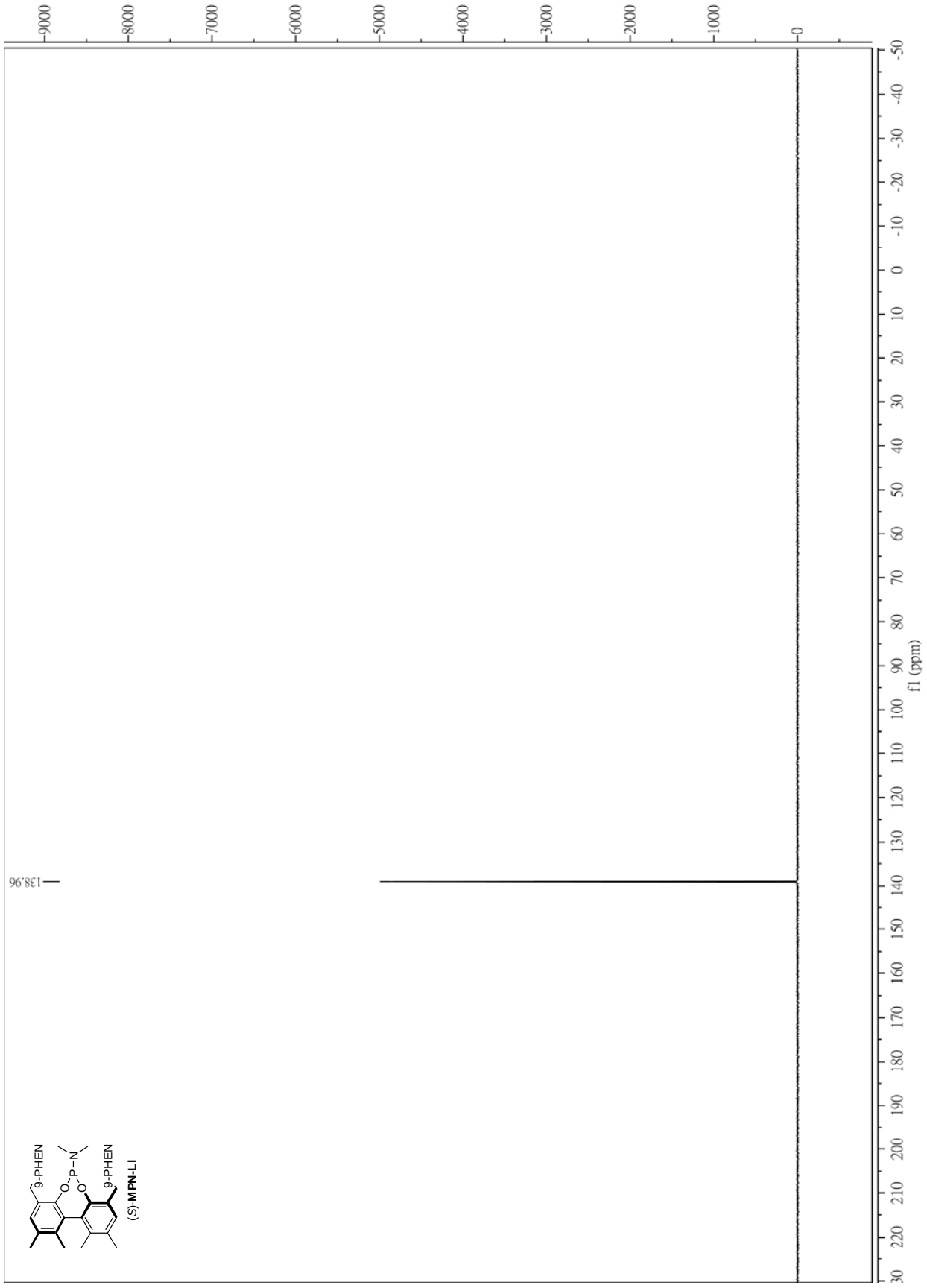
f1 (ppm)
(R)-MPN-Lk


9-PHEN
9-PHEN
(S)-MPN-LI
f1 (ppm)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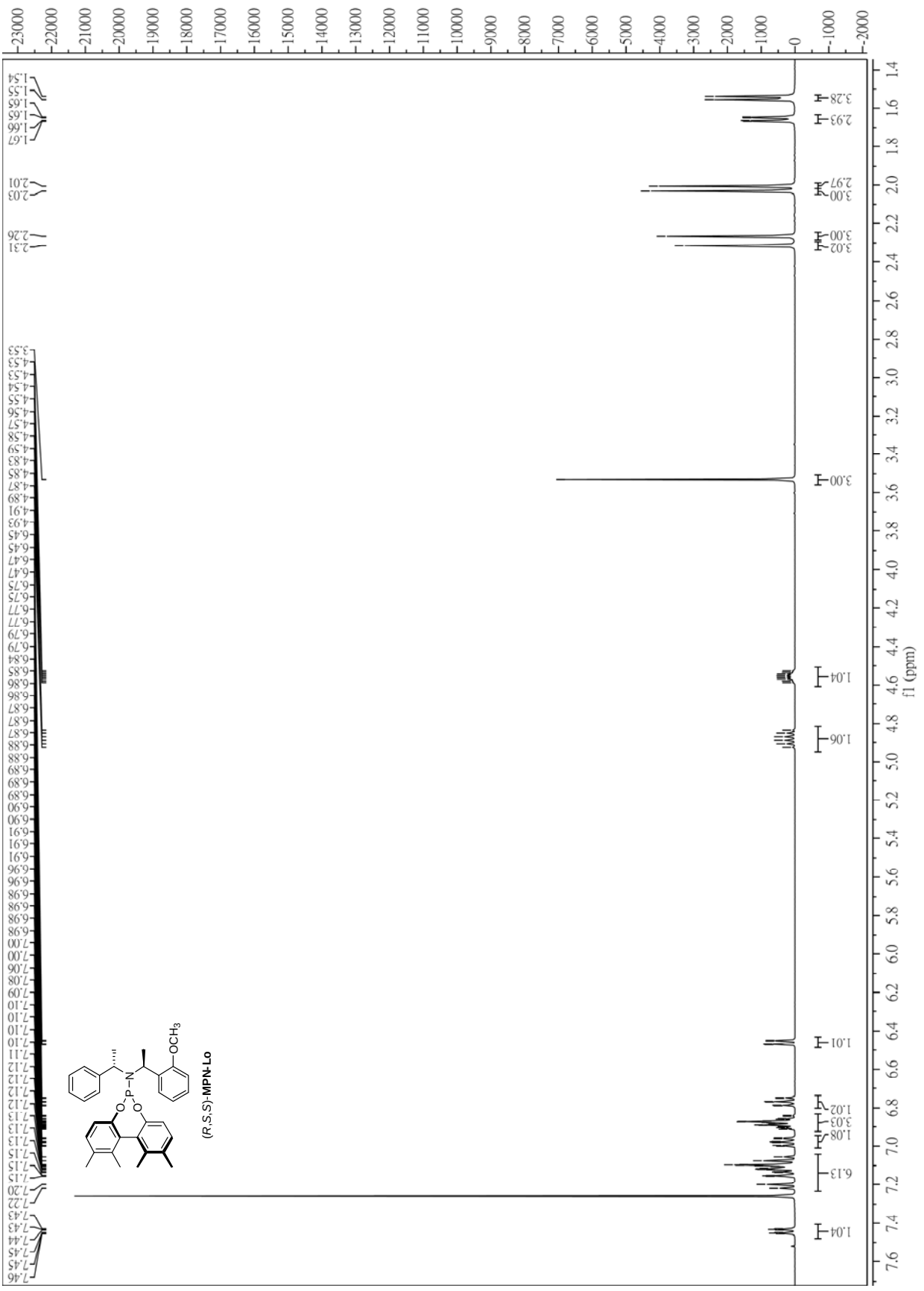
9-PHEN
9-PHEN
(S)-MPN-LI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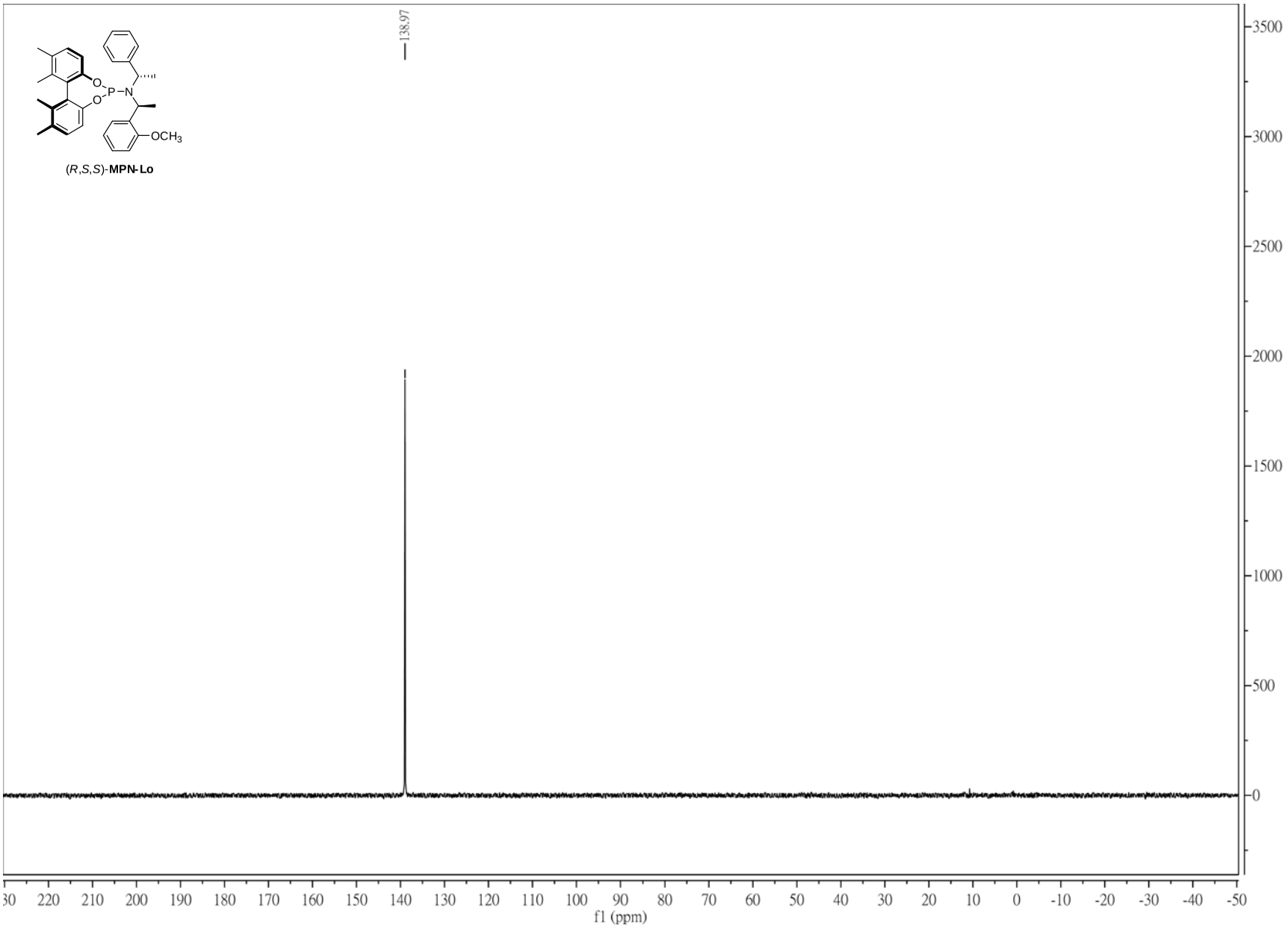
138.97
OCH3
(R,S,S)-MPN-Lo
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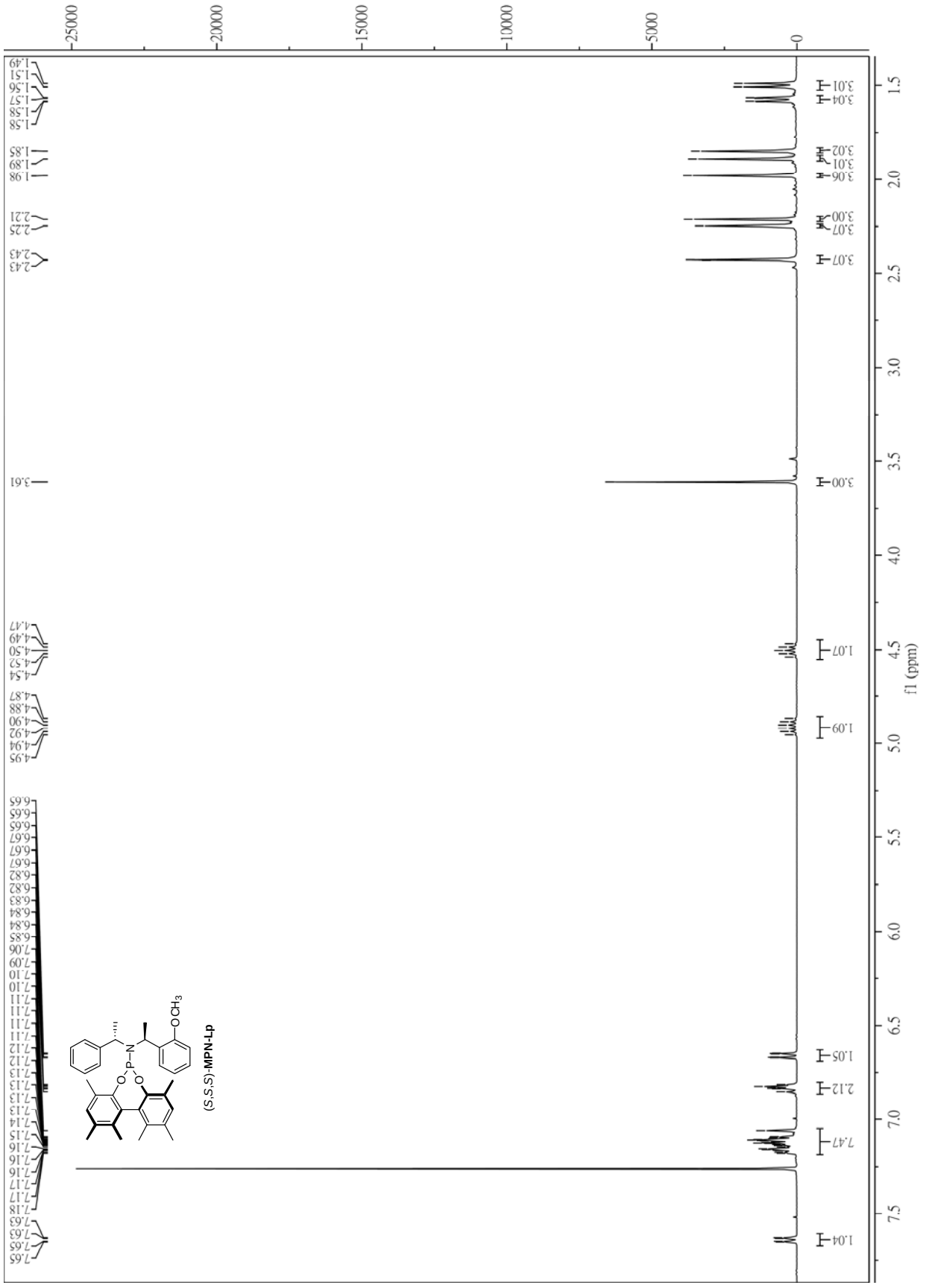
3000
2500
2000
1500
1000
500
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50
f1 (ppm)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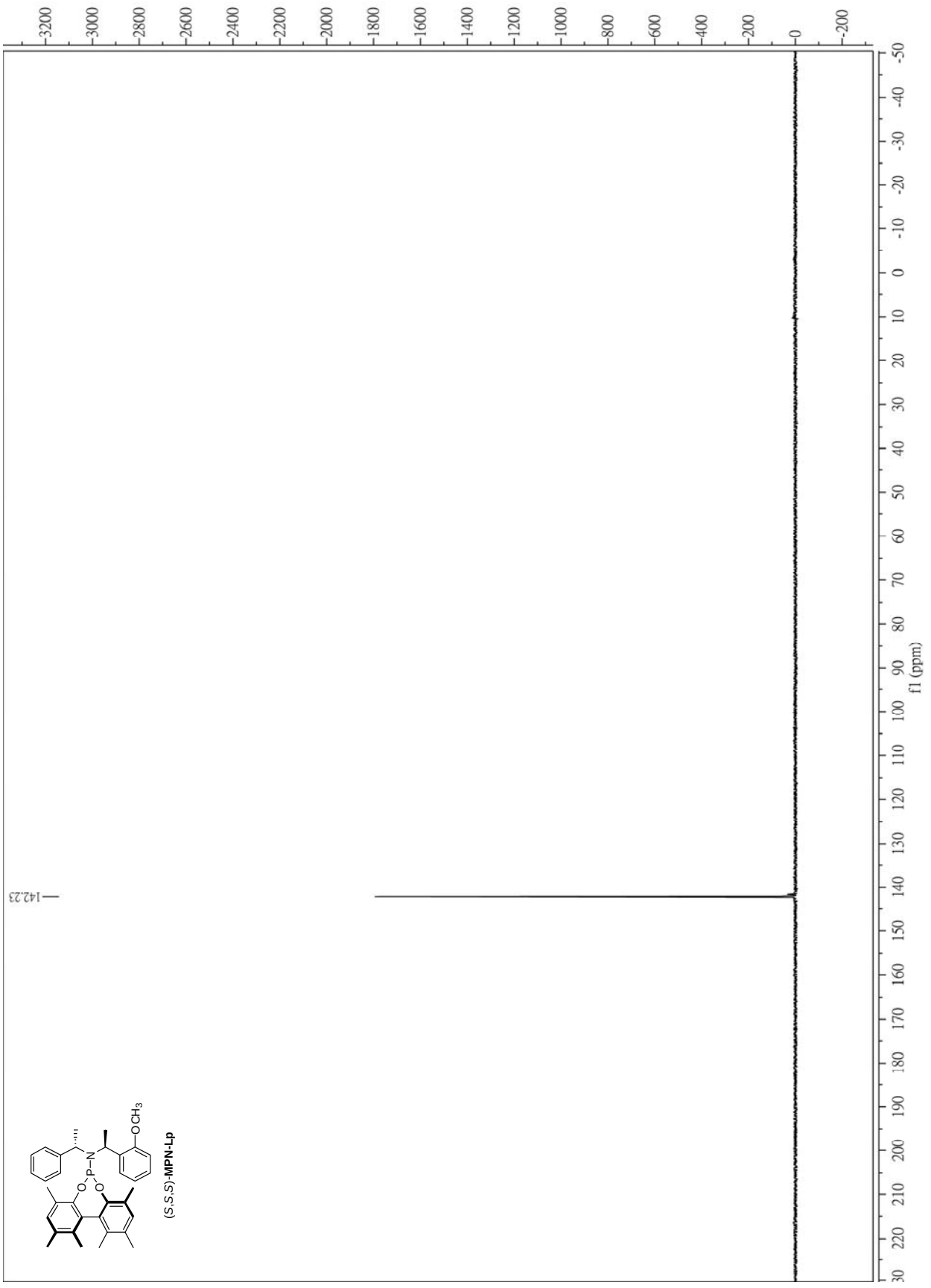
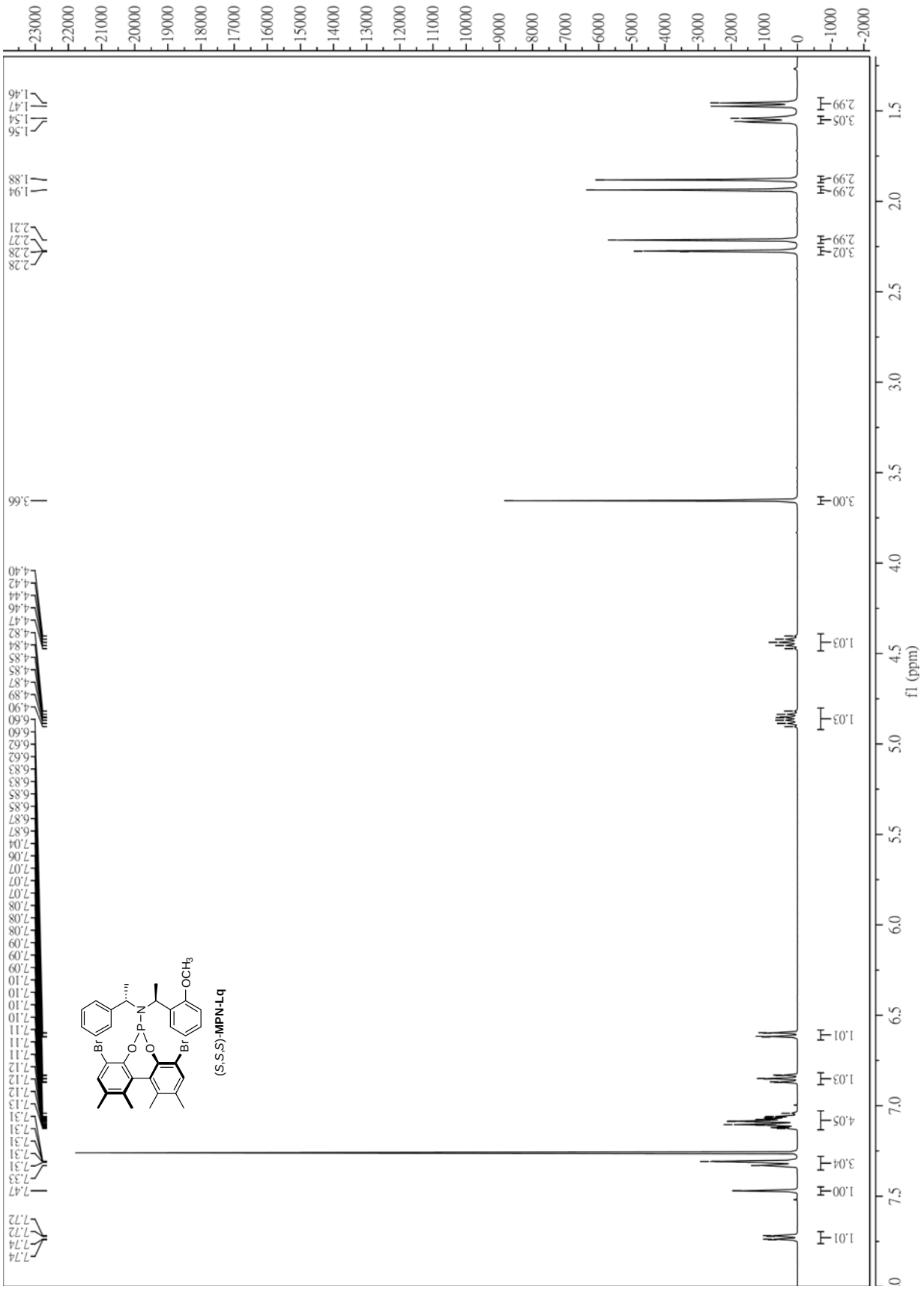
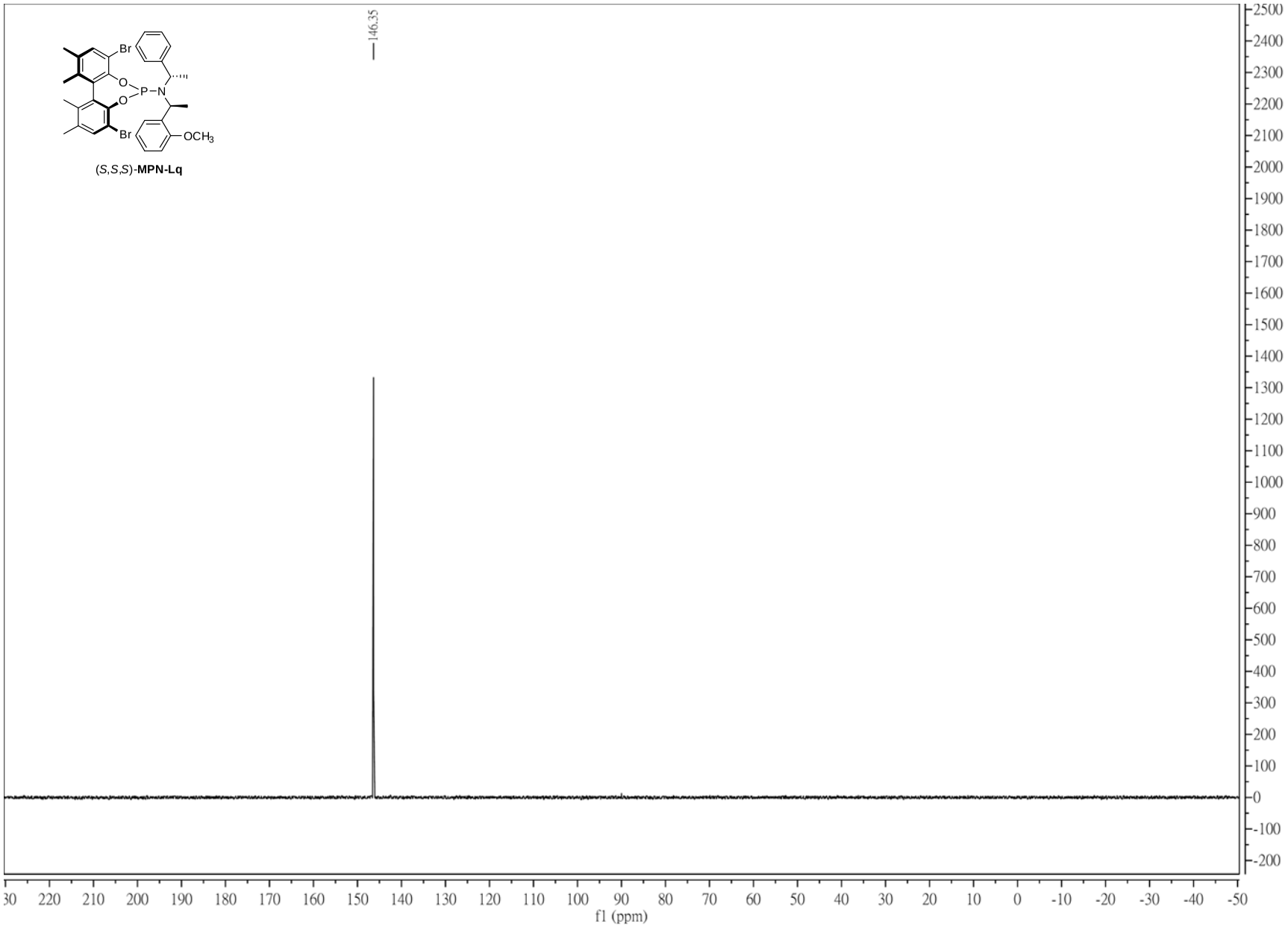

142.23
f1 (ppm)
(S,S,S)-MPN-Lp


(S,S,S)-MPN-Lq
f1 (ppm)


146.35
Br
O
P
N
O
Br
OCH3
(S,S,S)-MPN-Lq
2500
2400
2300
2200
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2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
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100
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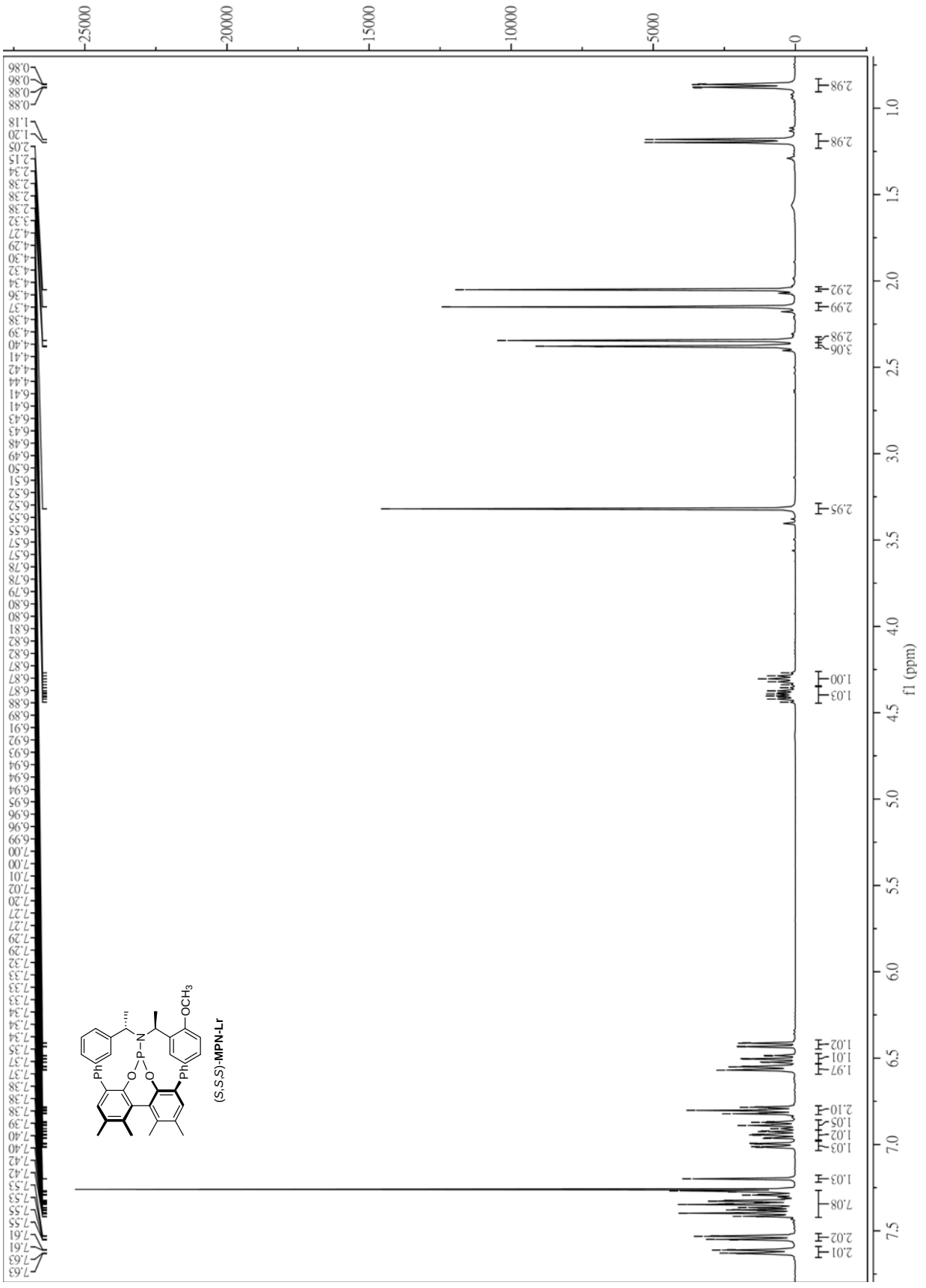
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50
f1 (ppm)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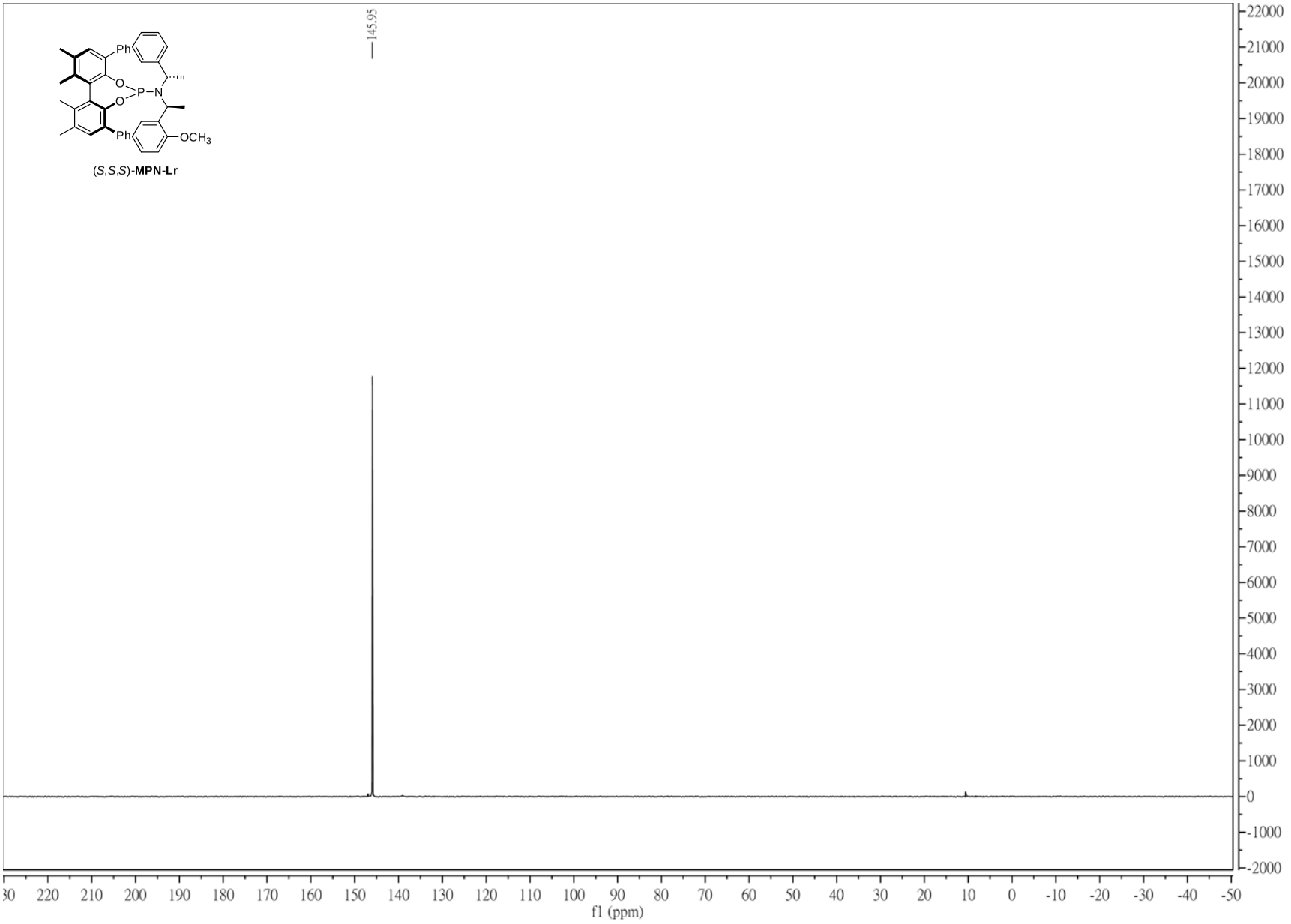
145.95
Ph
O
P
N
O
Ph
OCH3
(S,S,S)-MPN-Lr
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
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-2000
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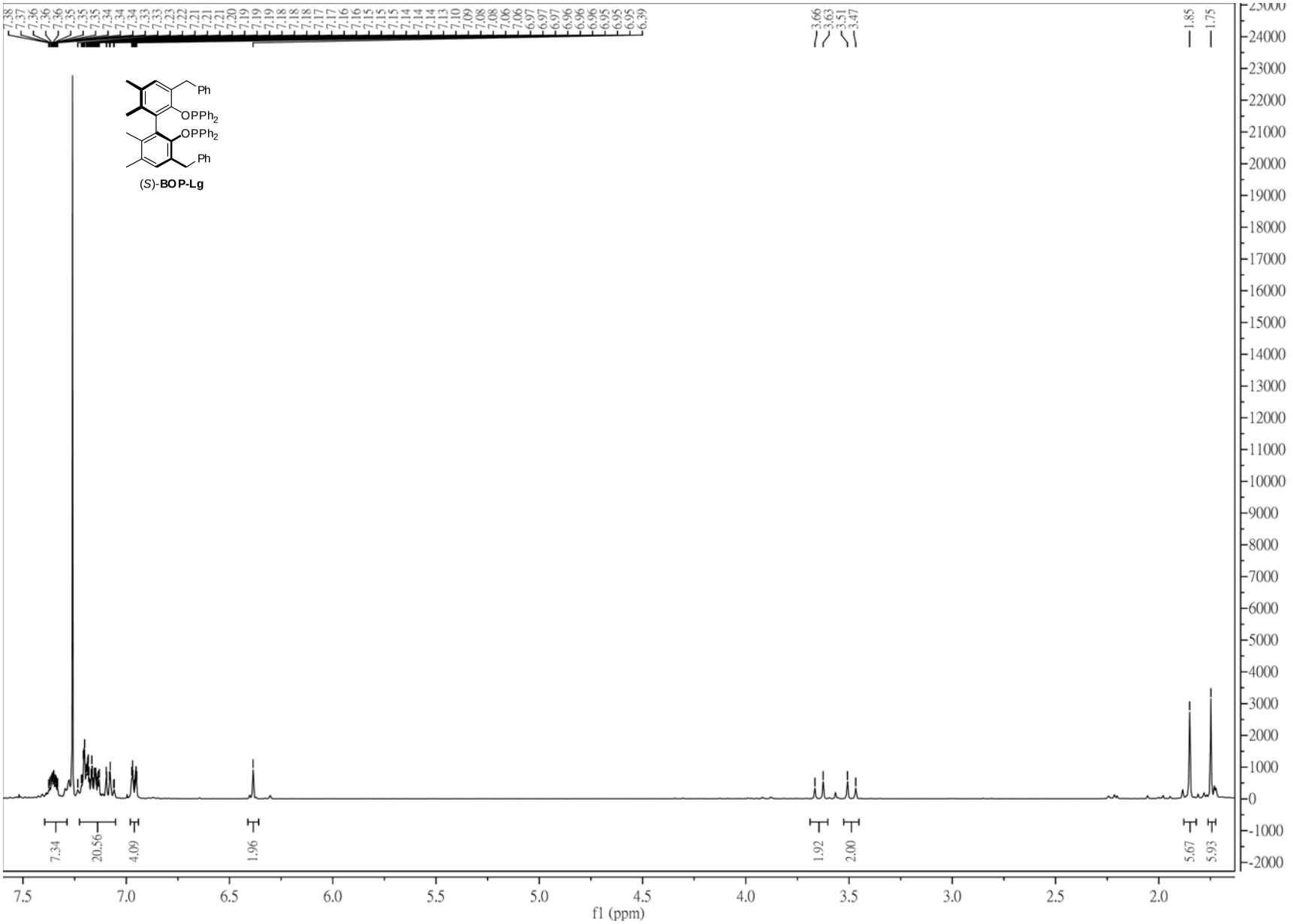
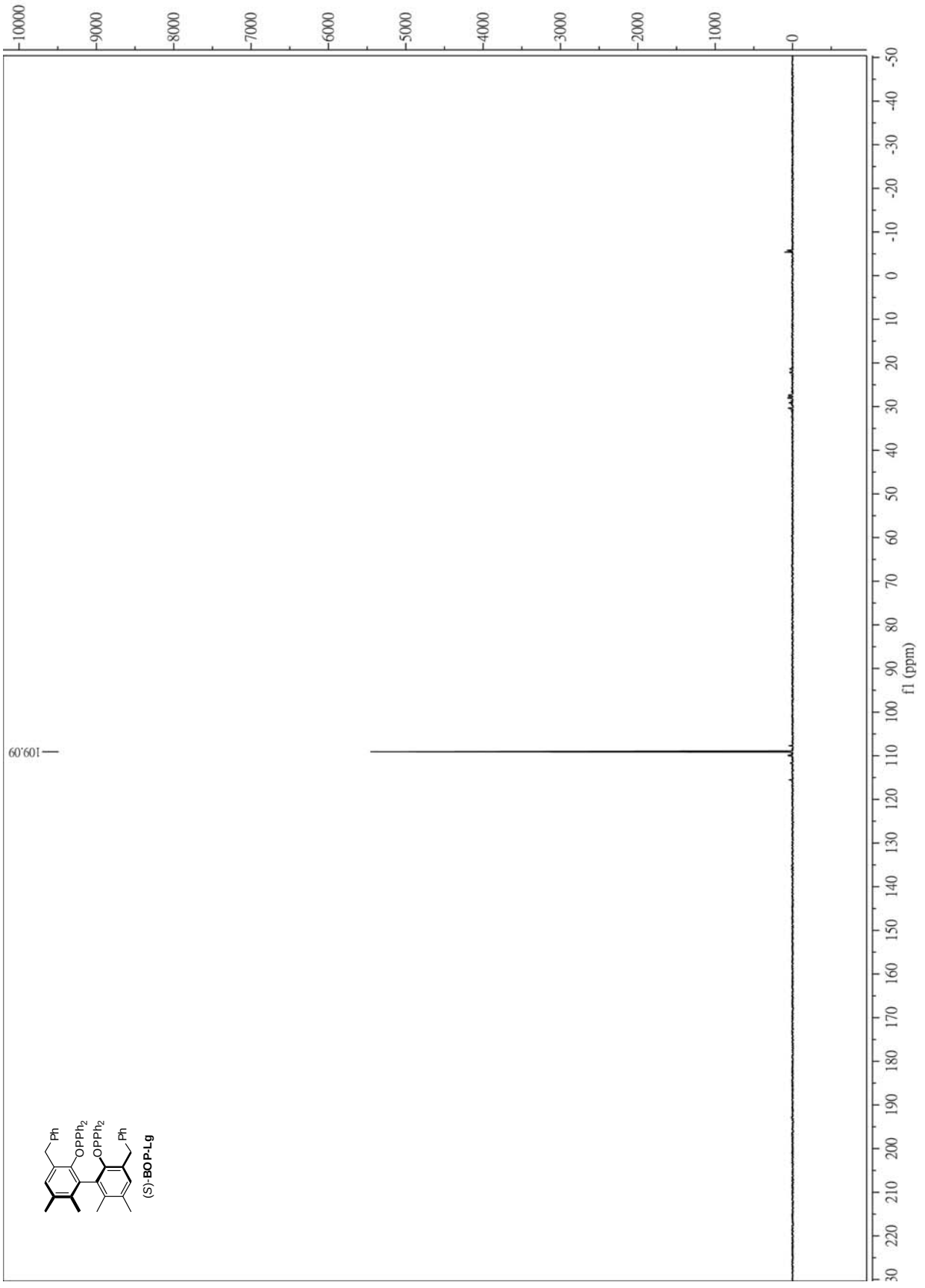
f1 (ppm)


Ph
OPPh2
OPPh2
Ph
(S)-BOP-Lg
f1 (ppm)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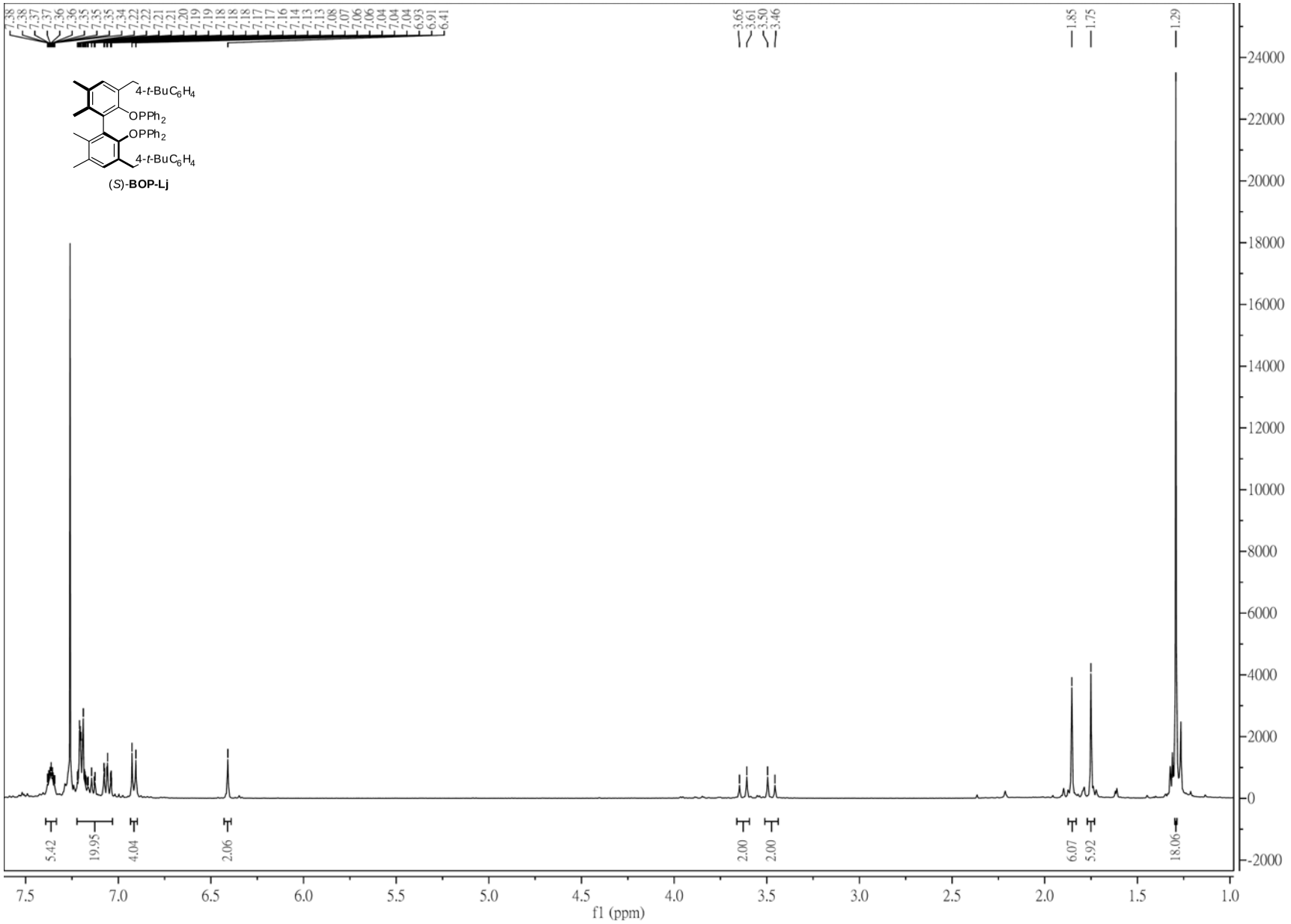
(S)-BOP-Lg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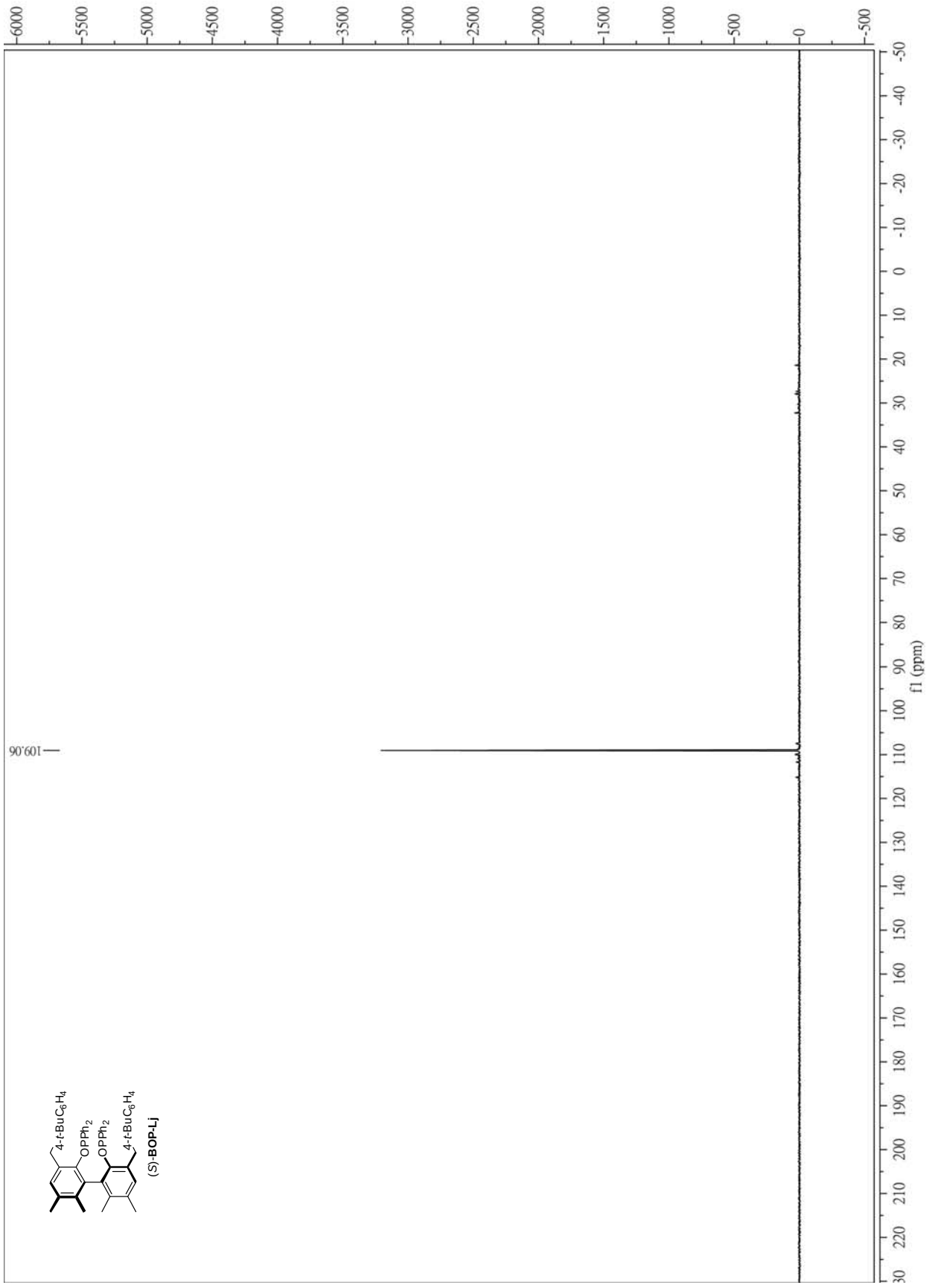
OPPh2
OPPh2
4-t-BuC6H4
(S)-BOP-Lj
f1 (ppm)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OPPh2
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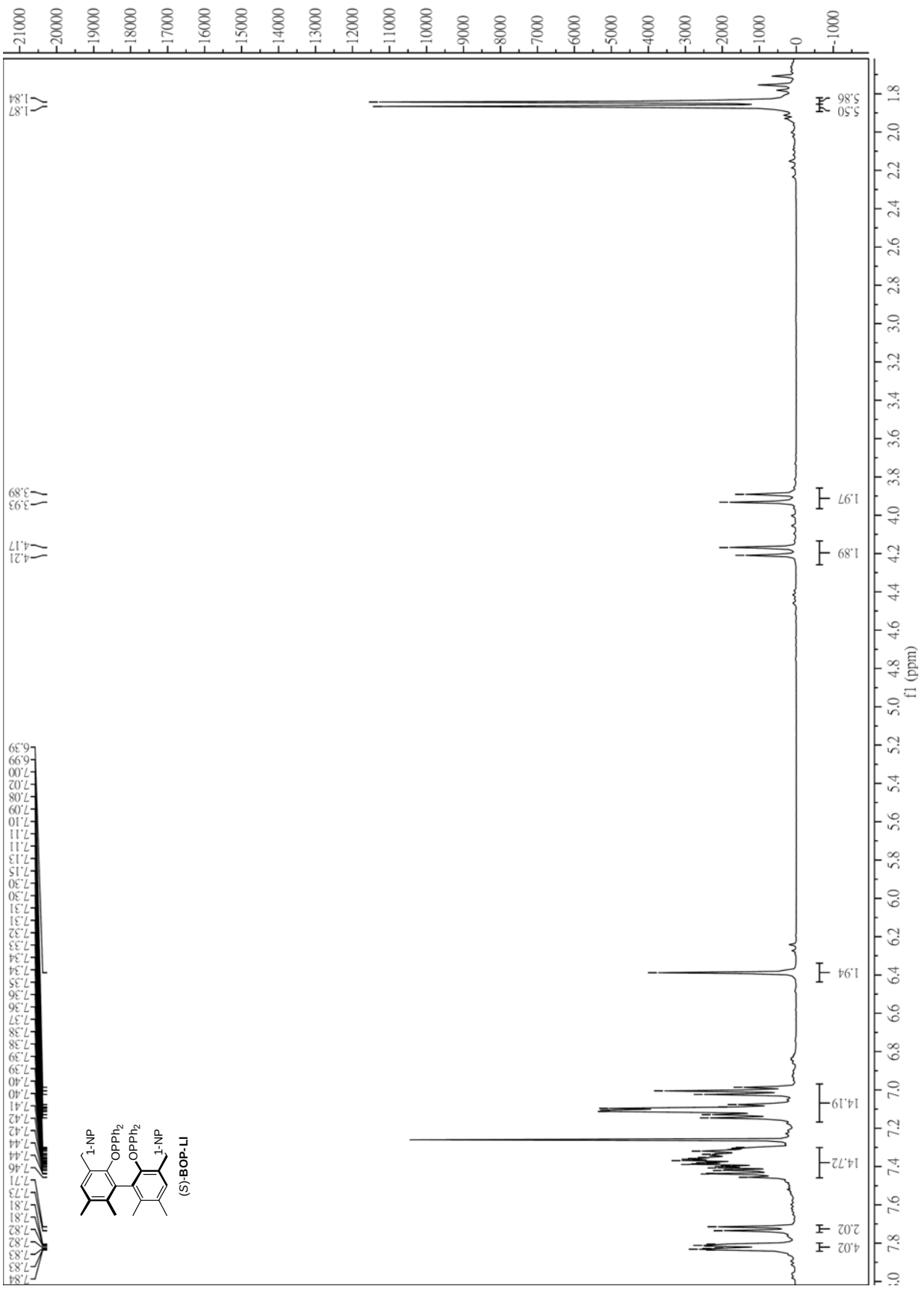
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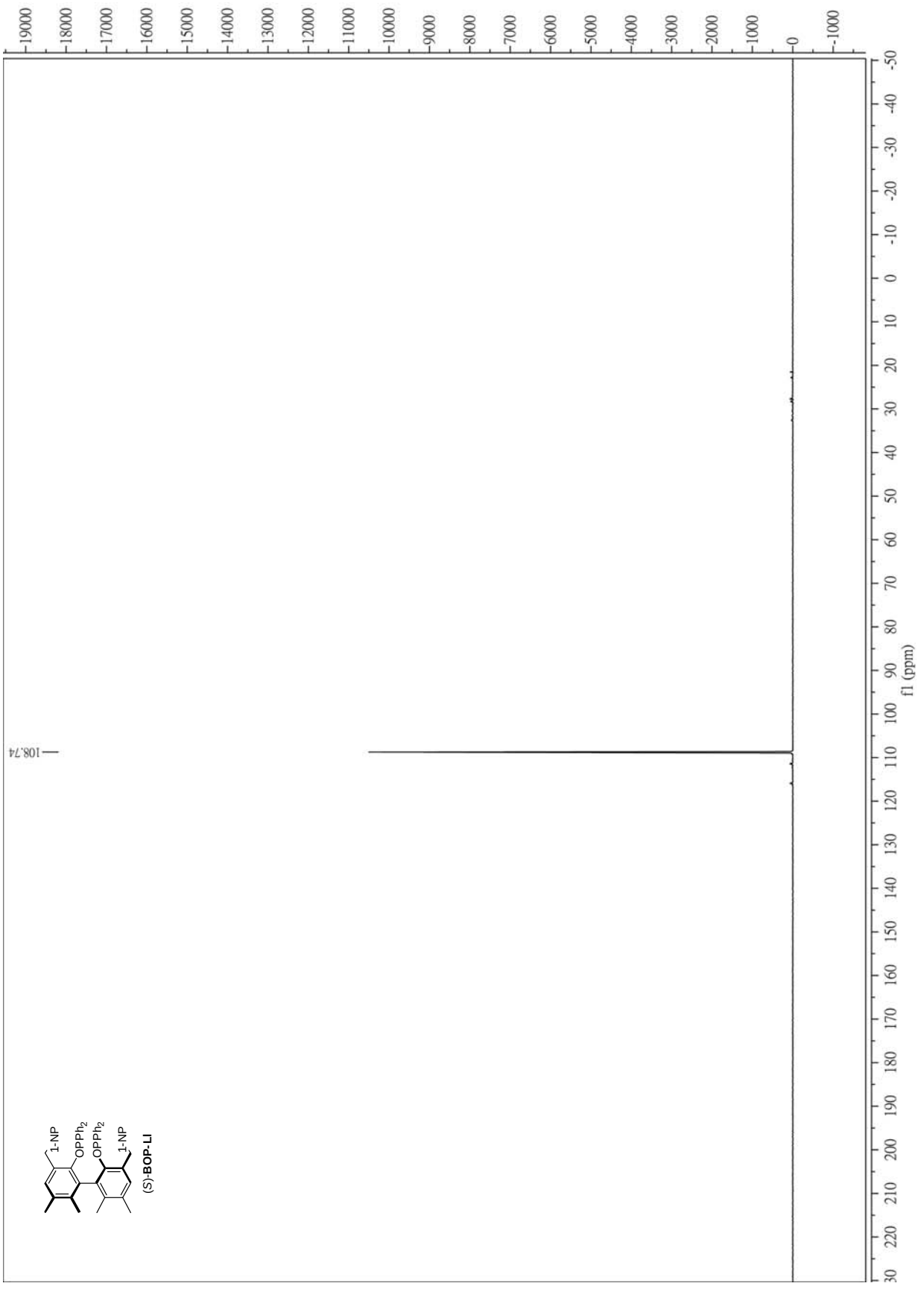
OPPh2
OPPh2
1-NP
f1 (ppm)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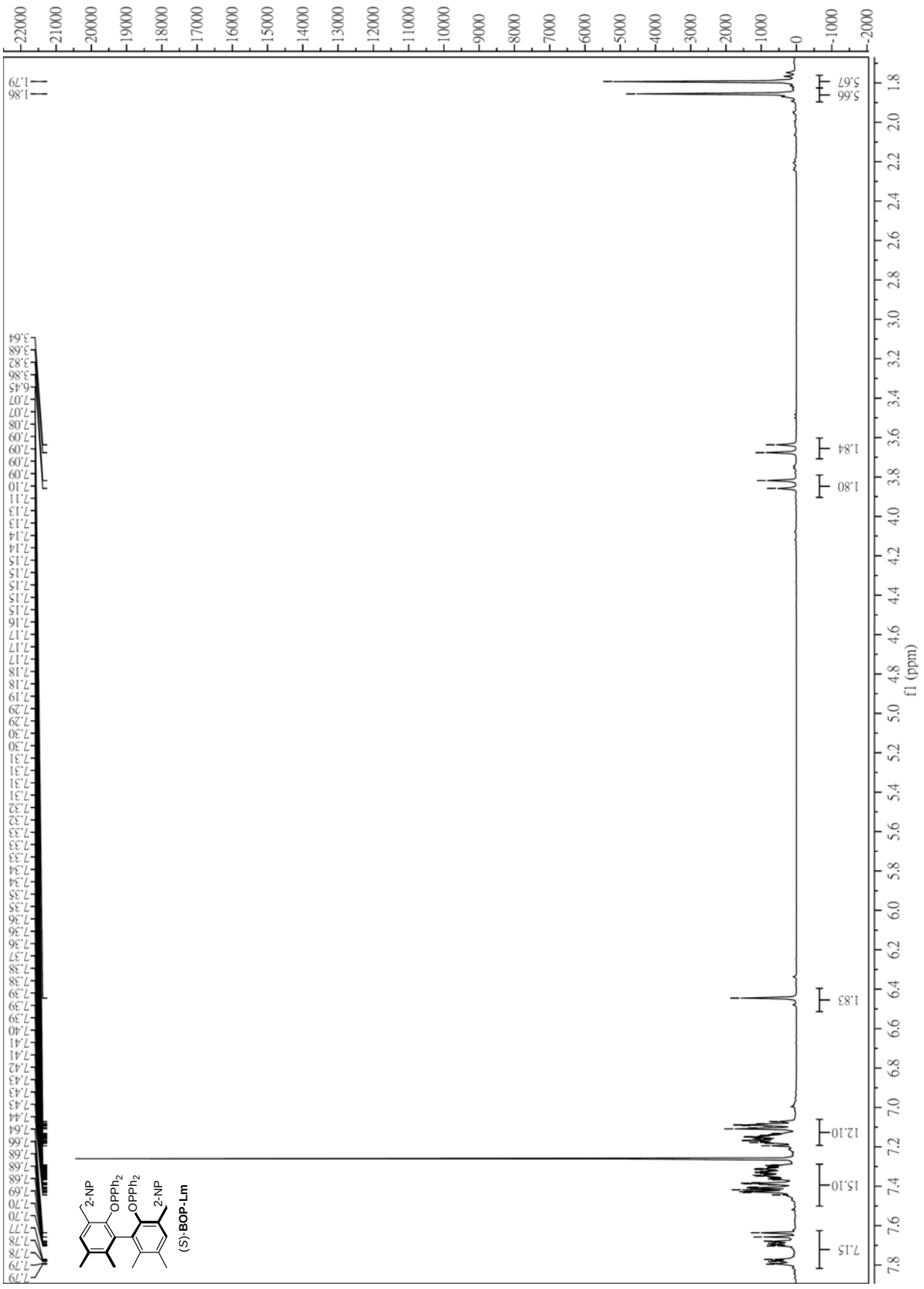
2-NP
OPPh2
OPPh2
2-NP
(S)-BOP-Lm
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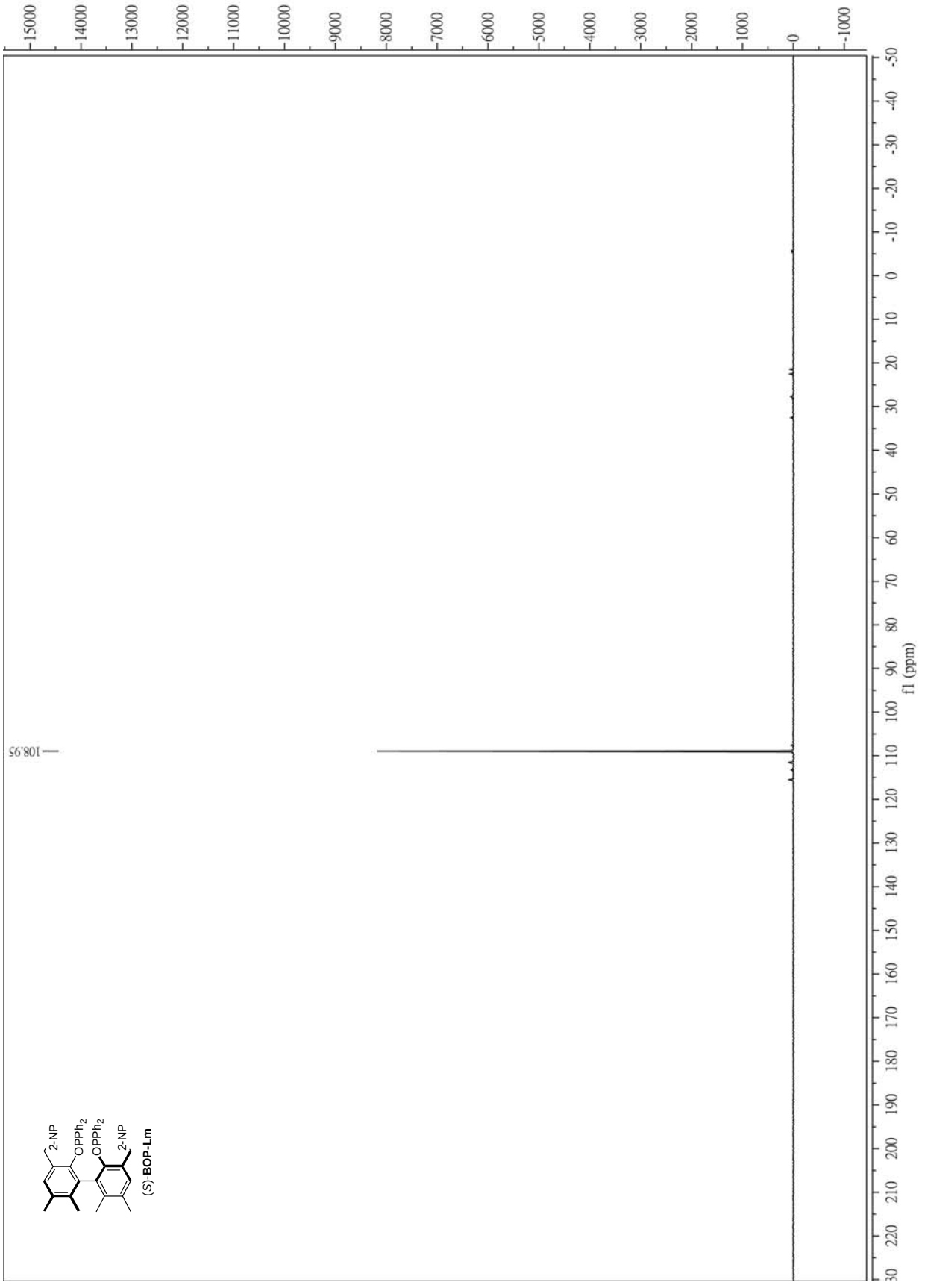
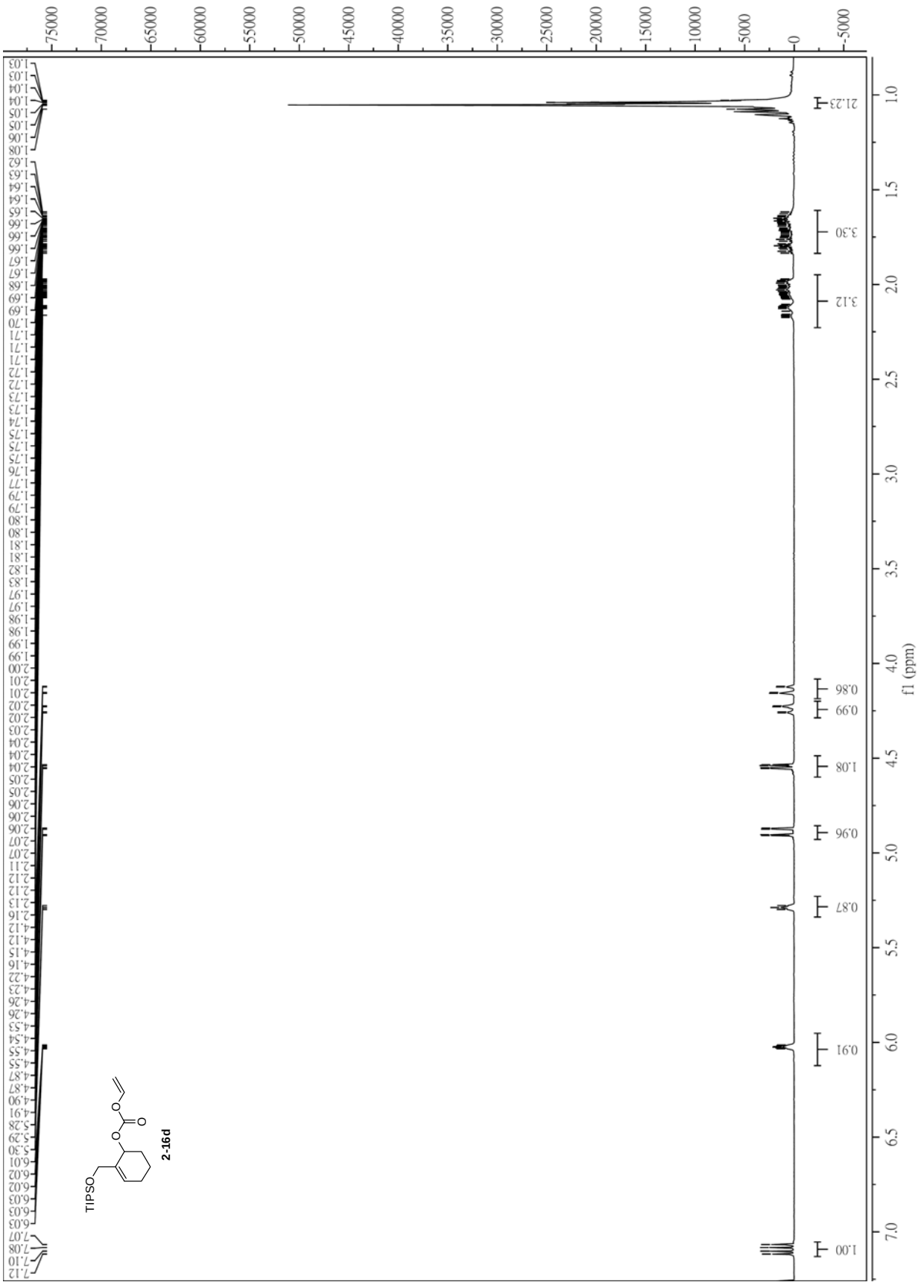
15.10
12.10
1.83
1.80
1.84
5.66
5.67
f1 (ppm)


15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-50
-40
-30
-20
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
f1 (ppm)
108.95
2-NP
OPPh2
OPPh2
2-NP
(S)-BOP-Lm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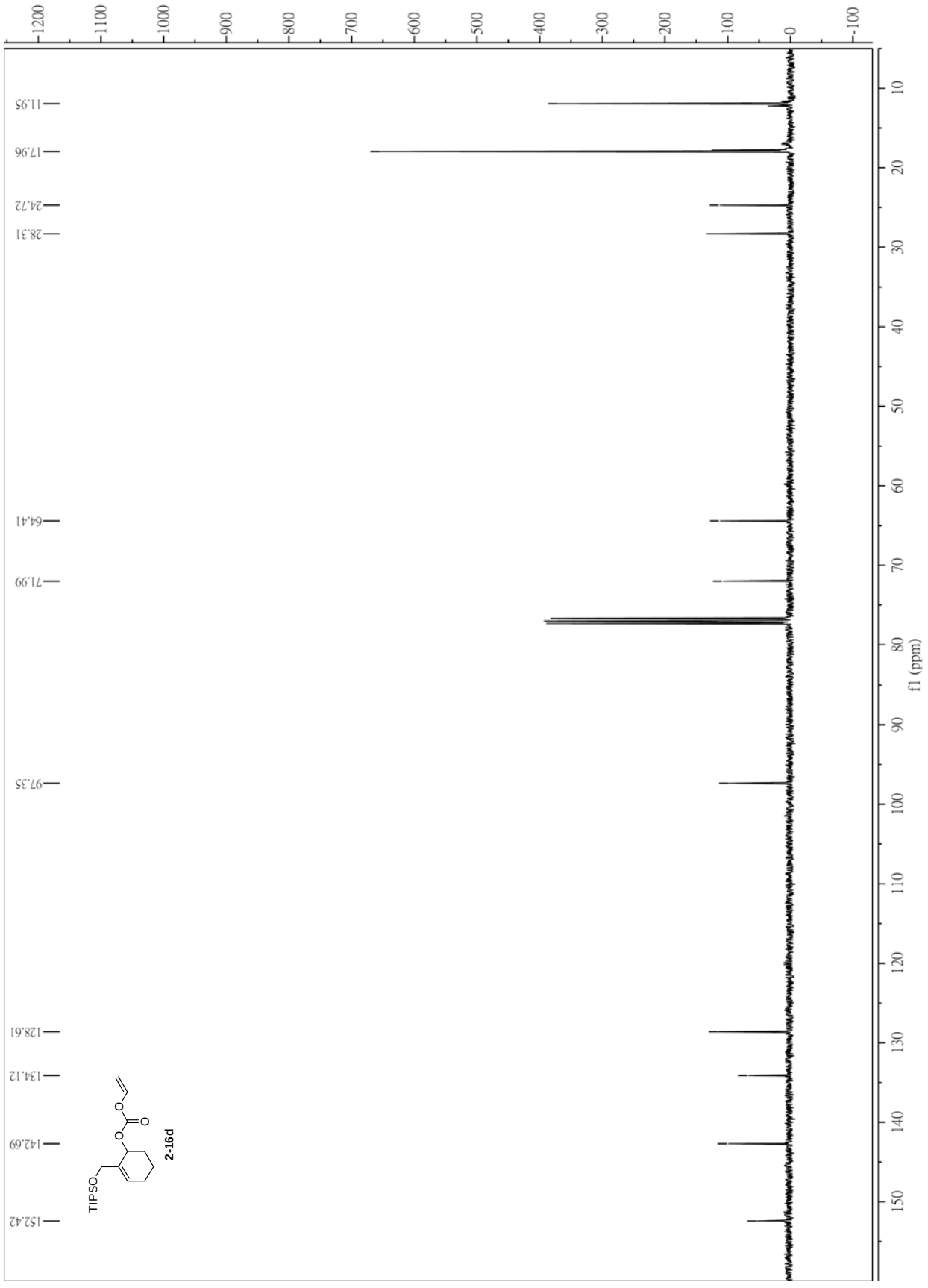
2-16d
f1 (ppm)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17.96
24.72
28.31
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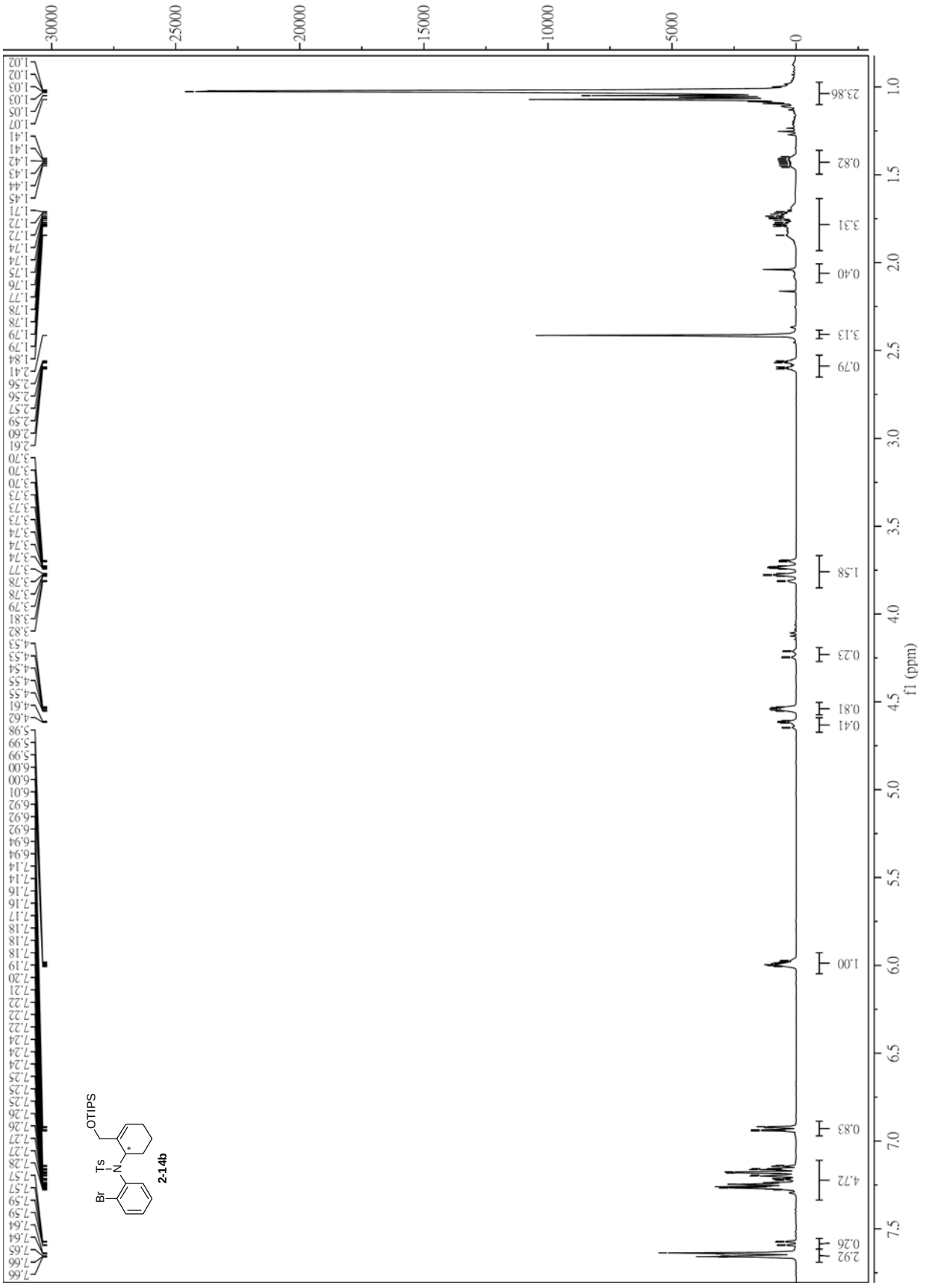
71.99
97.35
128.61
134.12
142.69
152.42
TIPSO
2-16d
f1 (ppm)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Br
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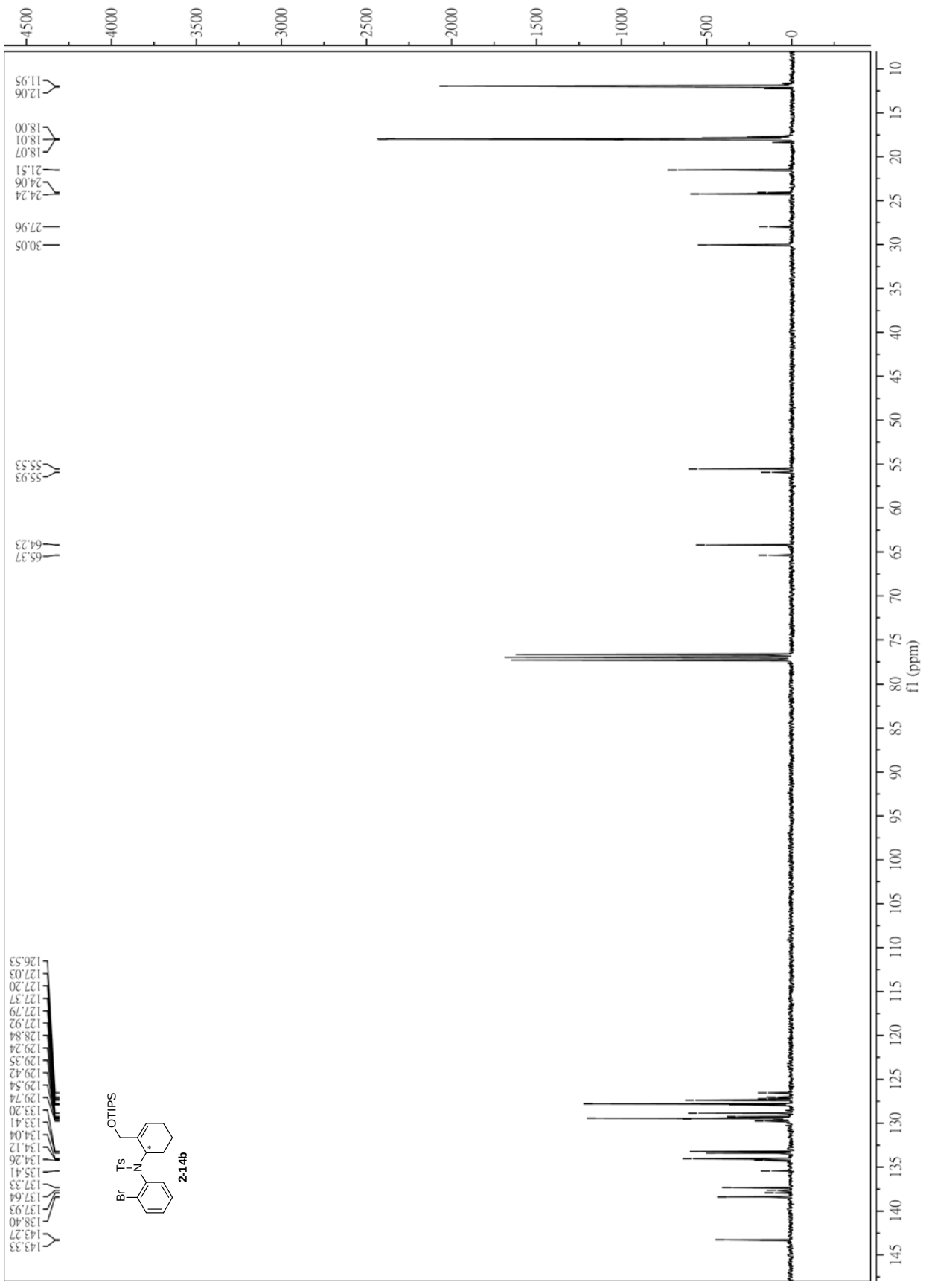
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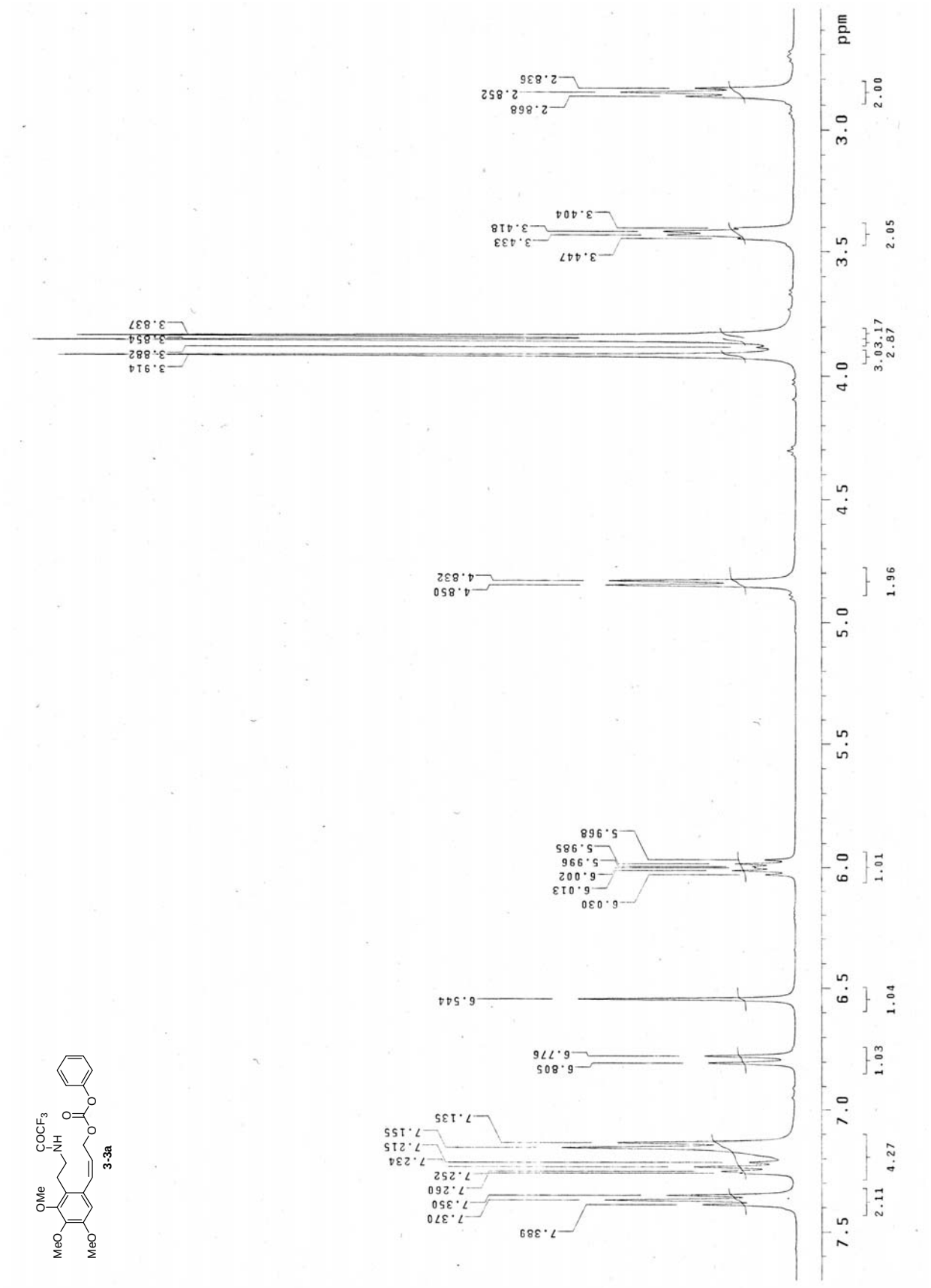
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OMe
MeO
MeO
COCF3
NH
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O
O
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7.350
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7.234
7.215
7.155
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5.996
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2.868
2.852
2.836
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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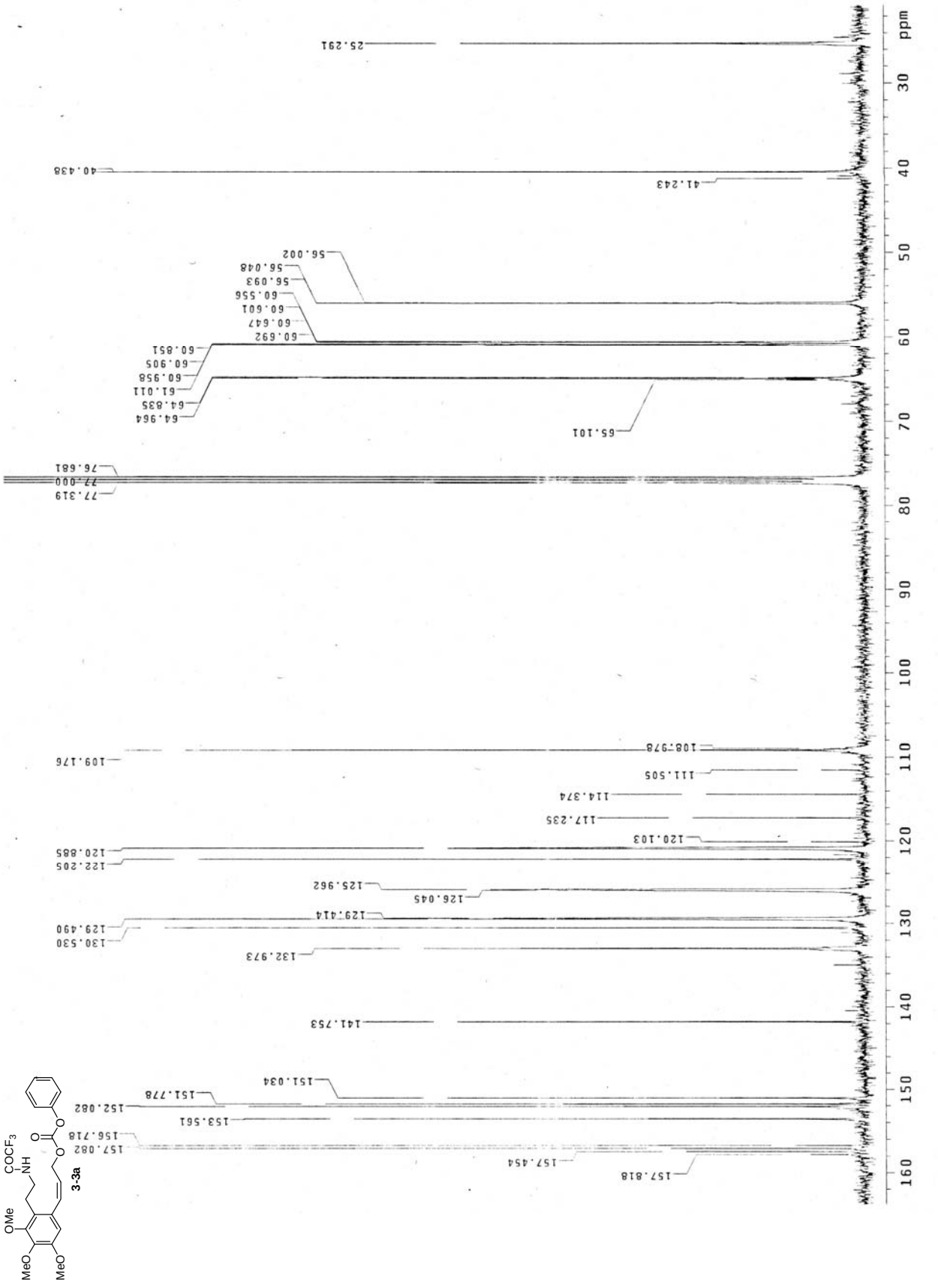
3.03.17
2.87
2.05
2.00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129.490
130.530
132.973
141.753
151.034
151.778
152.082
153.561
156.718
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157.454
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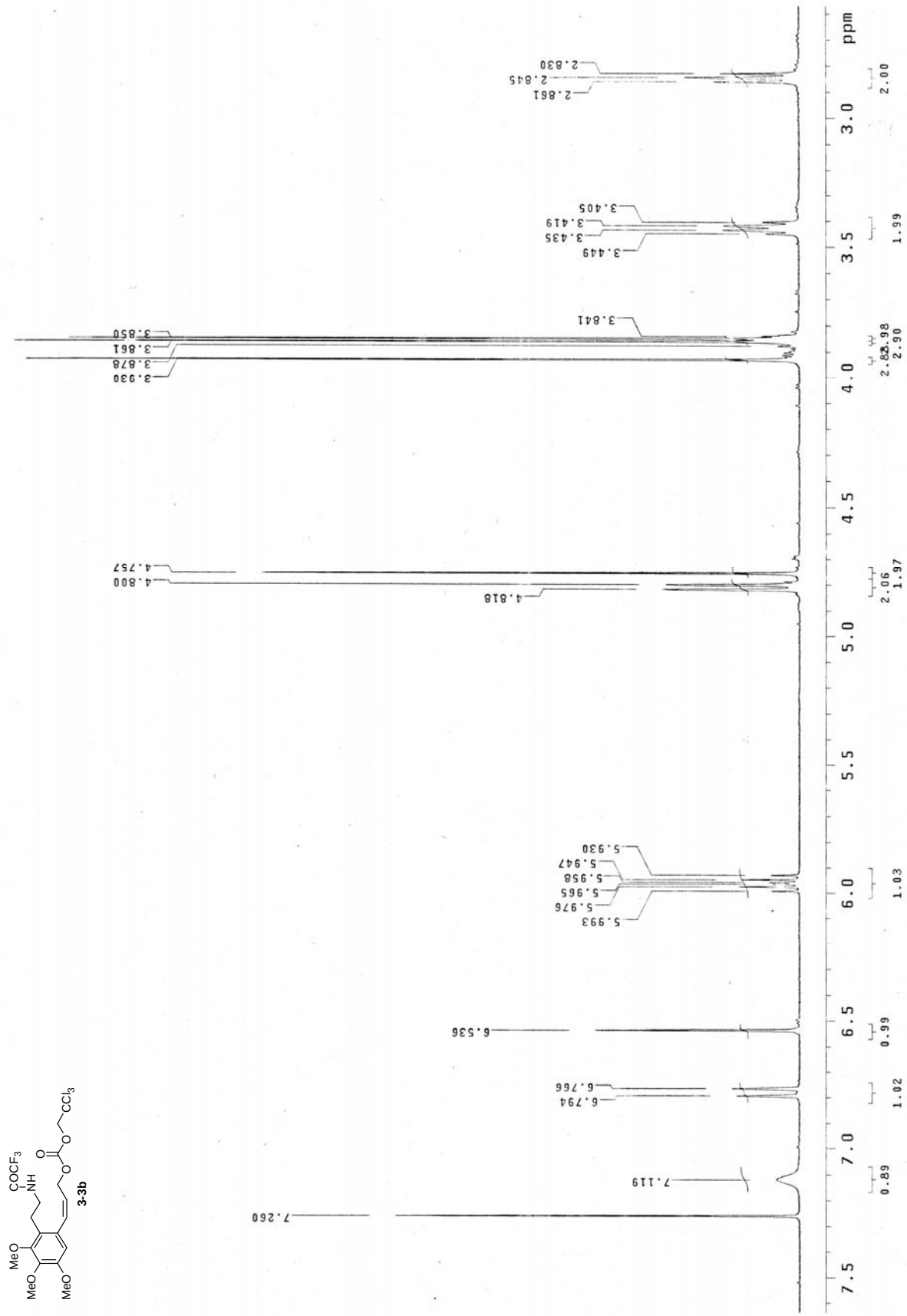
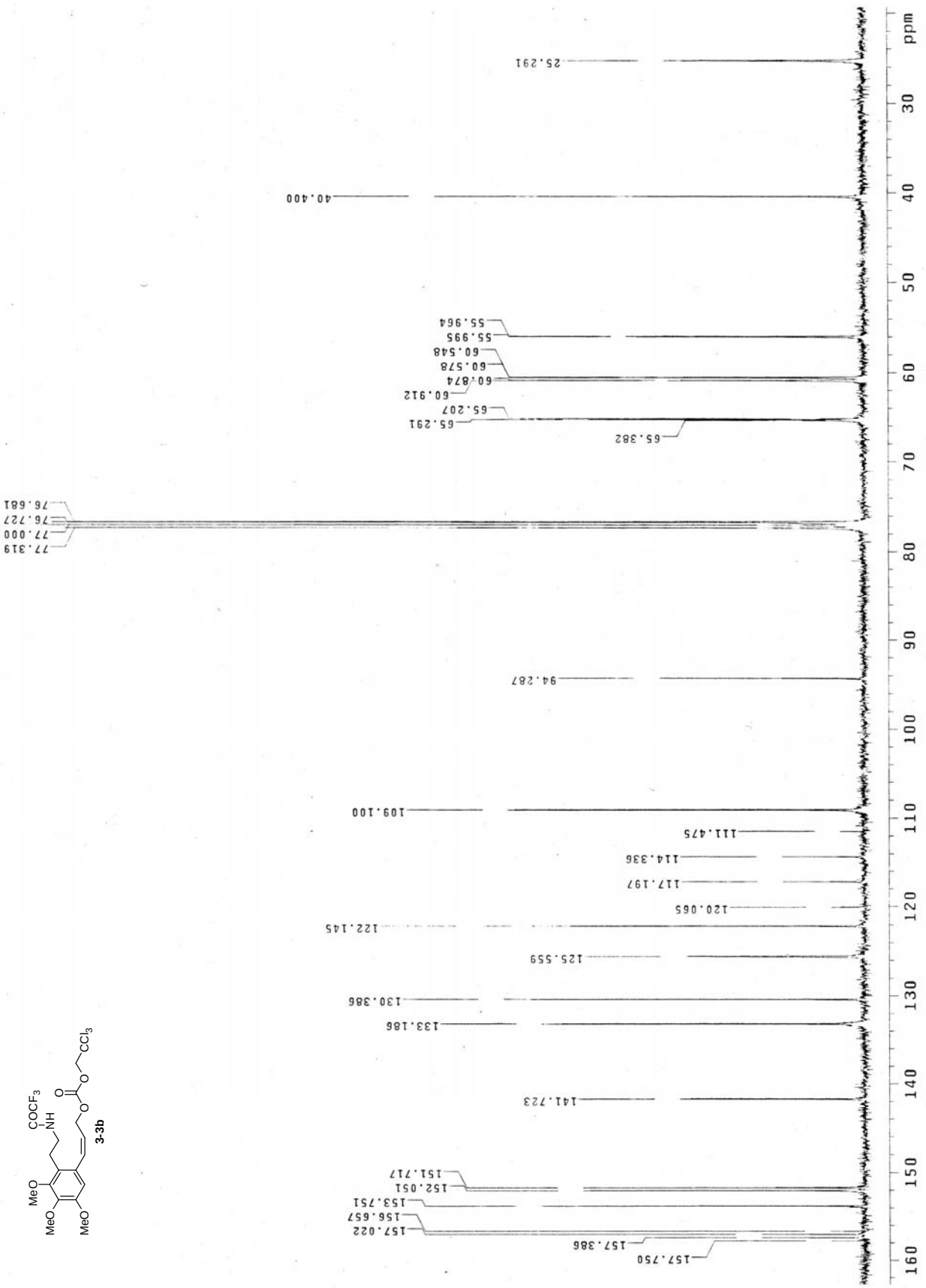
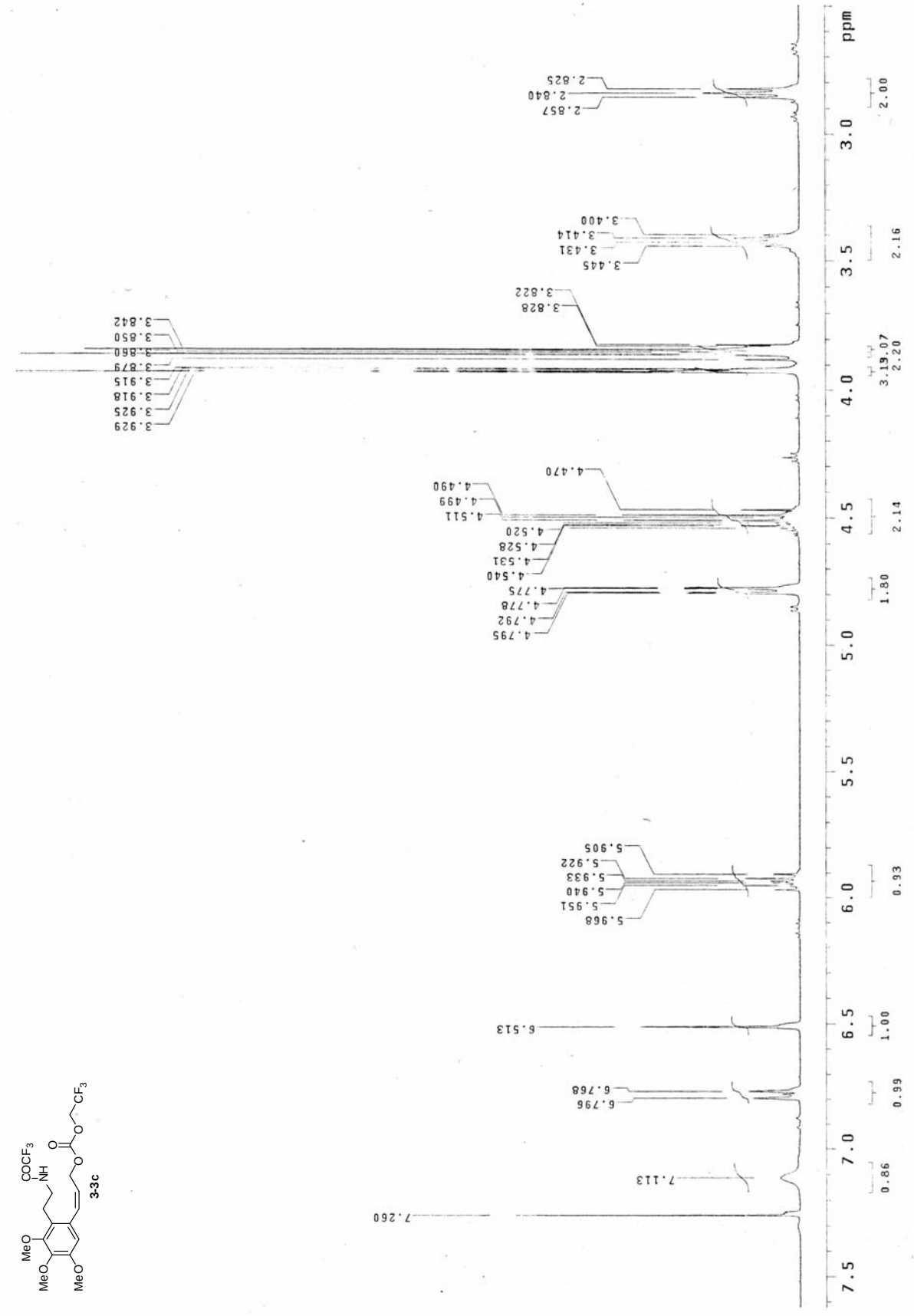
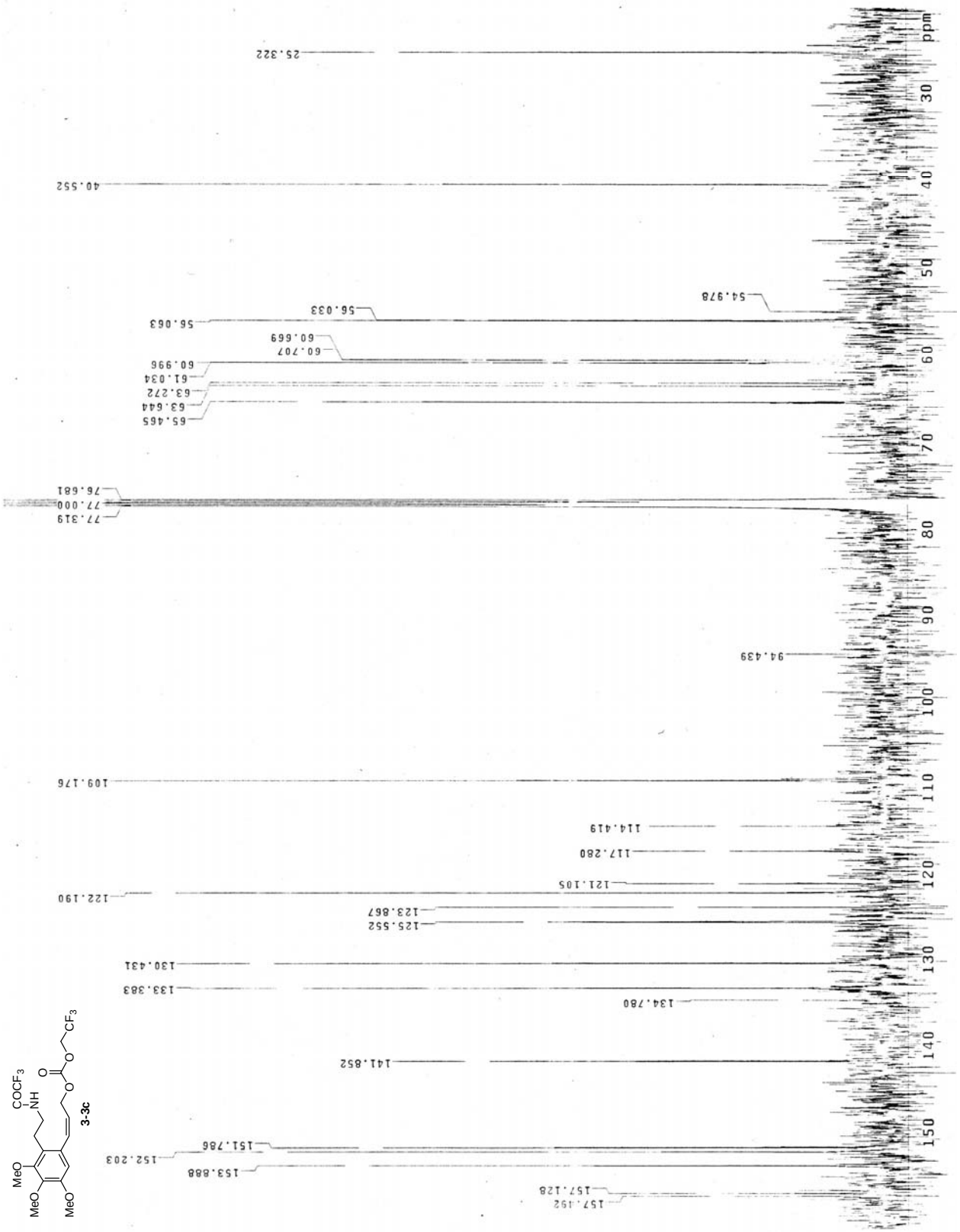
ppm
COCF3
NH
OMe
MeO
MeO
3-3a


3-3b
MeO
MeO
MeO
NH
COCF3
CCl3
7.260
7.119
6.794
6.766
6.536
5.993
5.976
5.965
5.958
5.947
5.930
4.818
4.800
4.757
3.930
3.878
3.861
3.850
3.841
3.449
3.435
3.419
3.405
2.861
2.845
2.830
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
0.89
1.02
0.99
1.03
2.06
1.97
2.98
2.90
1.99
2.00


25.291
40.400
55.964
55.995
60.548
60.578
60.874
60.912
65.207
65.291
65.382
76.681
76.727
77.000
77.319
94.287
109.100
111.475
114.336
117.197
120.065
122.145
125.559
130.386
133.186
141.723
151.717
152.051
153.751
156.657
157.022
157.386
157.750
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
MeO
MeO
MeO
COCF3
NH
O
O
O
O
CCl3
3-3b


3-3c
MeO
MeO
MeO
COCF3
NH
CF3
7.260
7.113
6.796
6.768
6.513
5.968
5.951
5.940
5.933
5.922
5.905
4.795
4.792
4.778
4.775
4.540
4.531
4.528
4.520
4.511
4.499
4.490
4.470
3.929
3.925
3.918
3.915
3.879
3.860
3.850
3.842
3.828
3.822
3.445
3.431
3.414
3.400
2.857
2.840
2.825
ppm
3.19.07
2.20
2.00
2.16
2.14
1.80
0.93
1.00
0.99
0.86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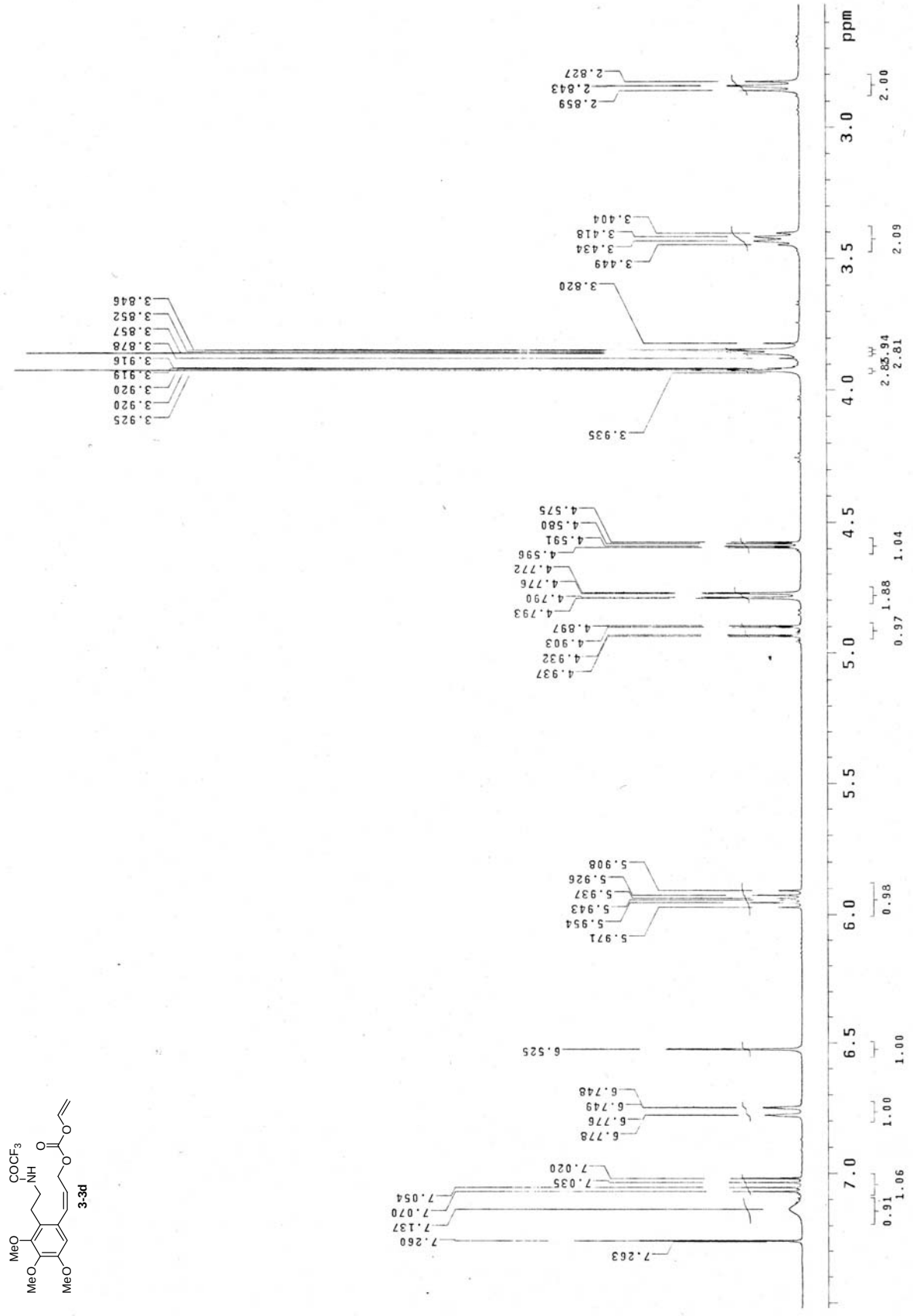
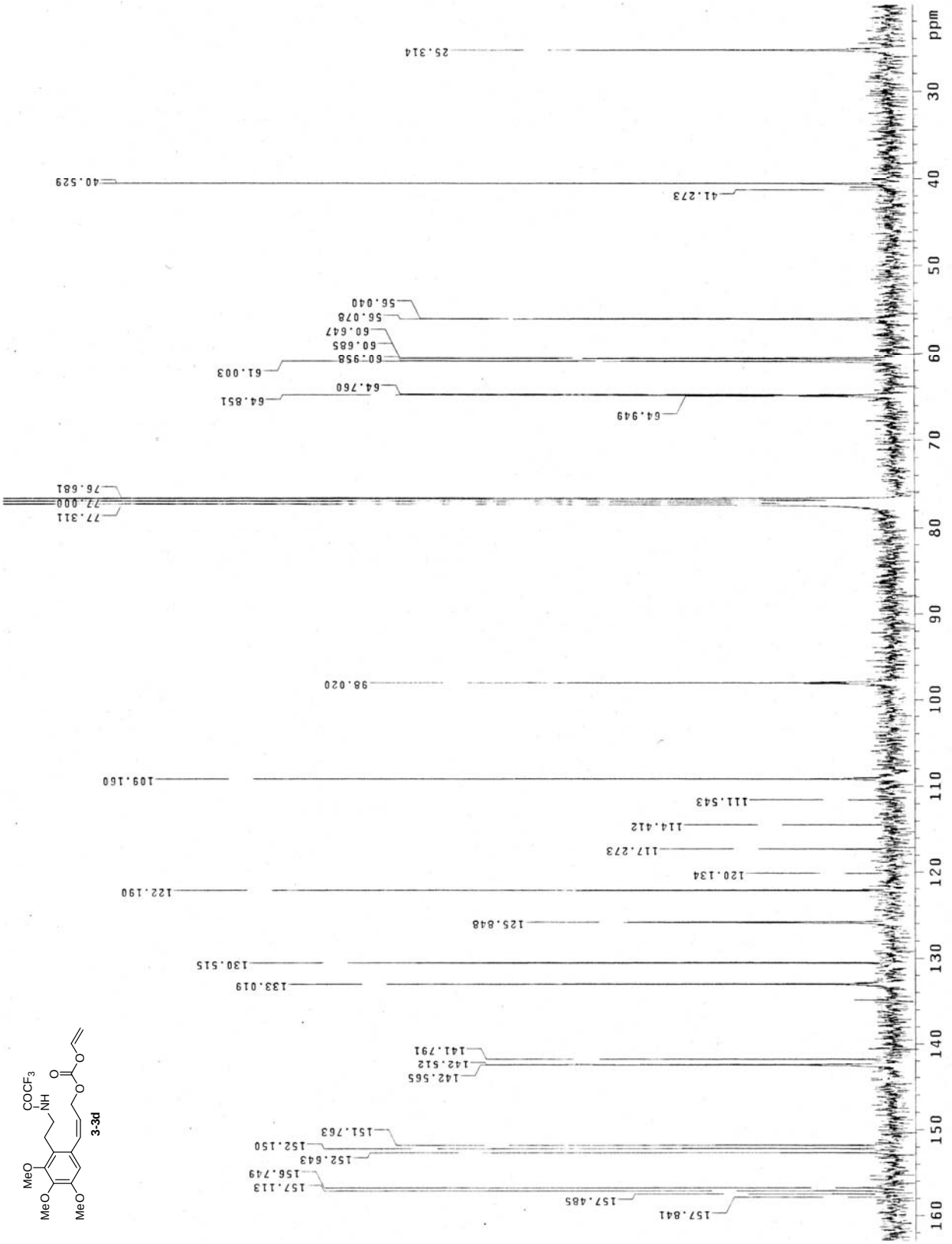
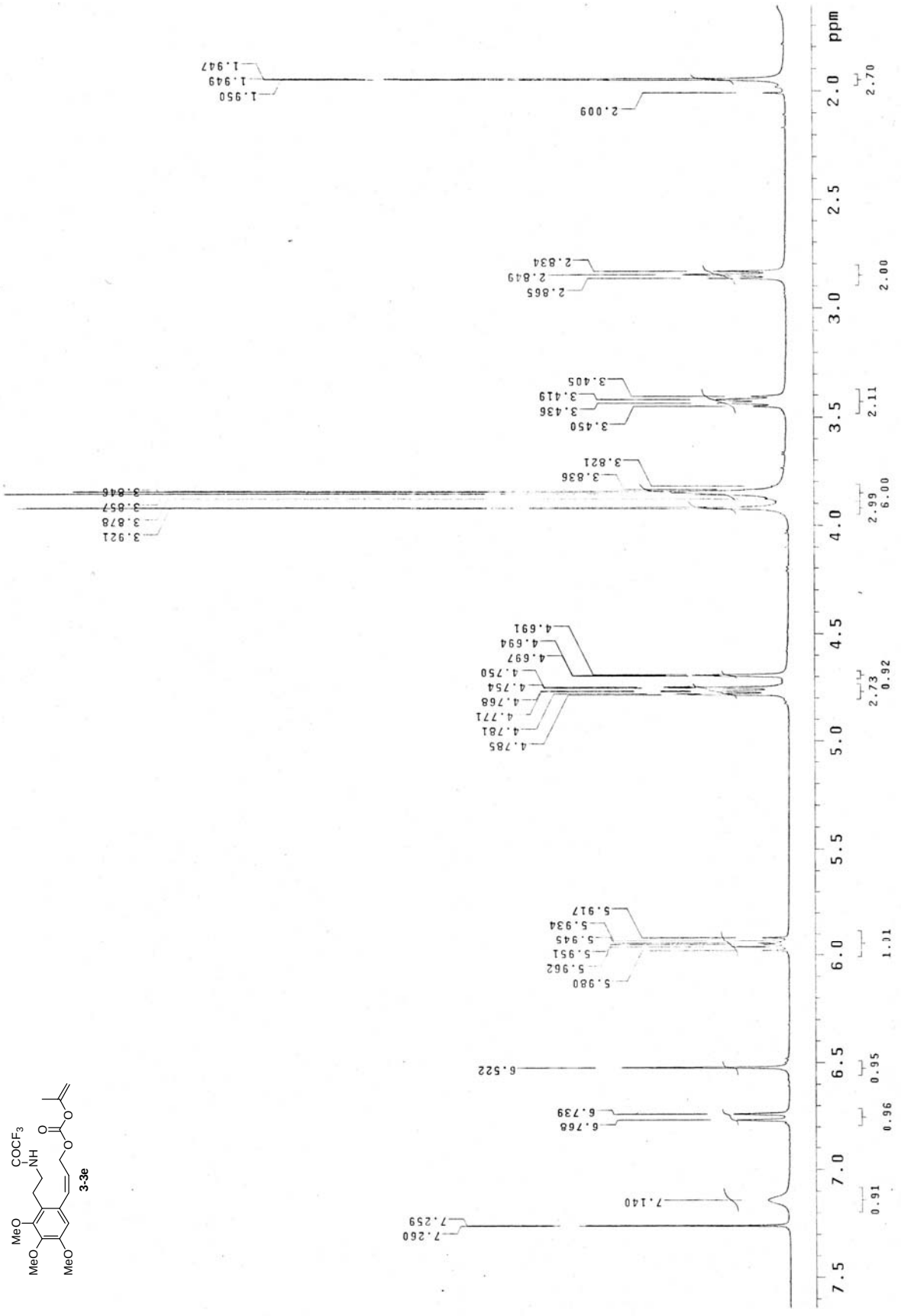
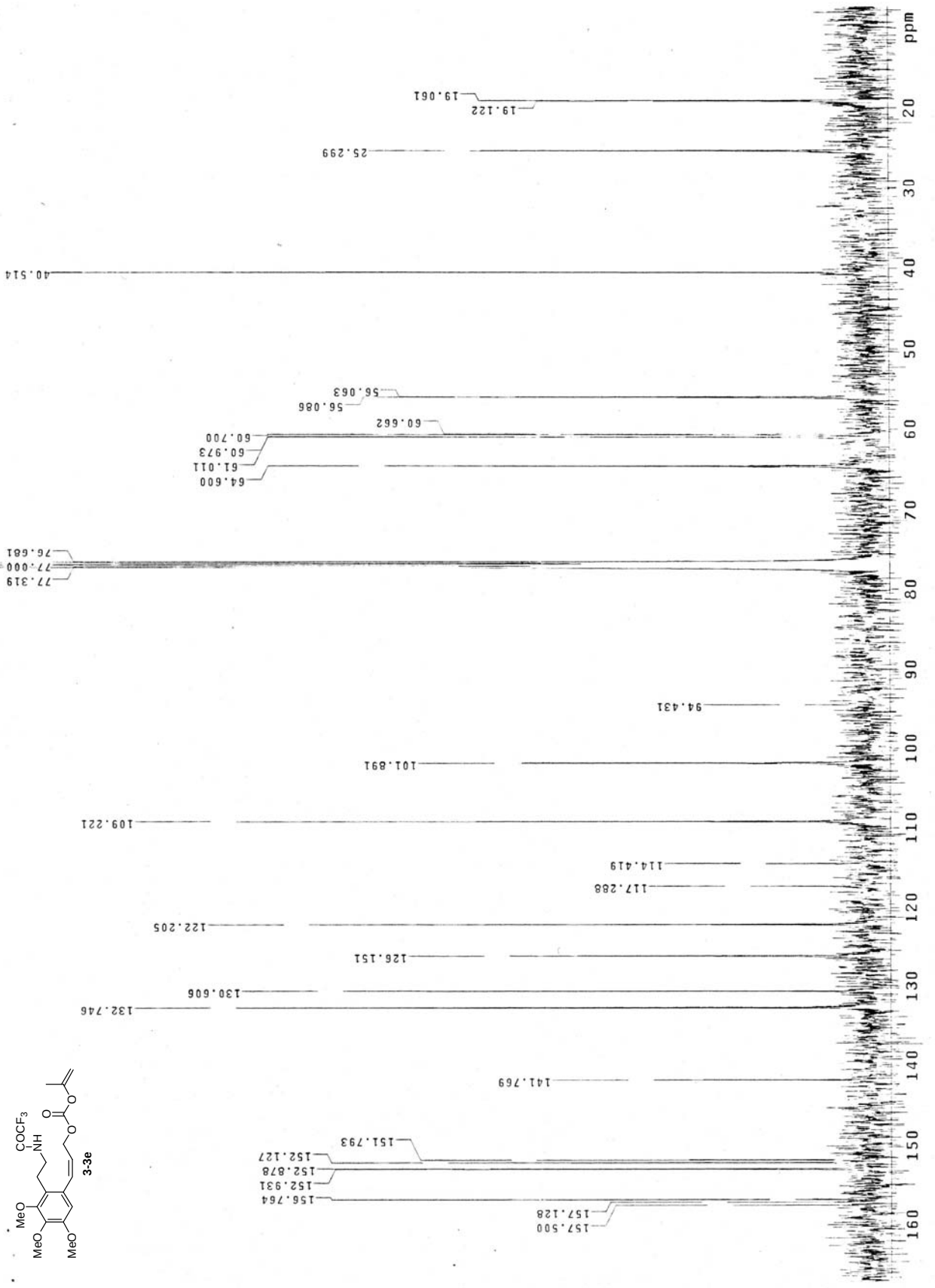
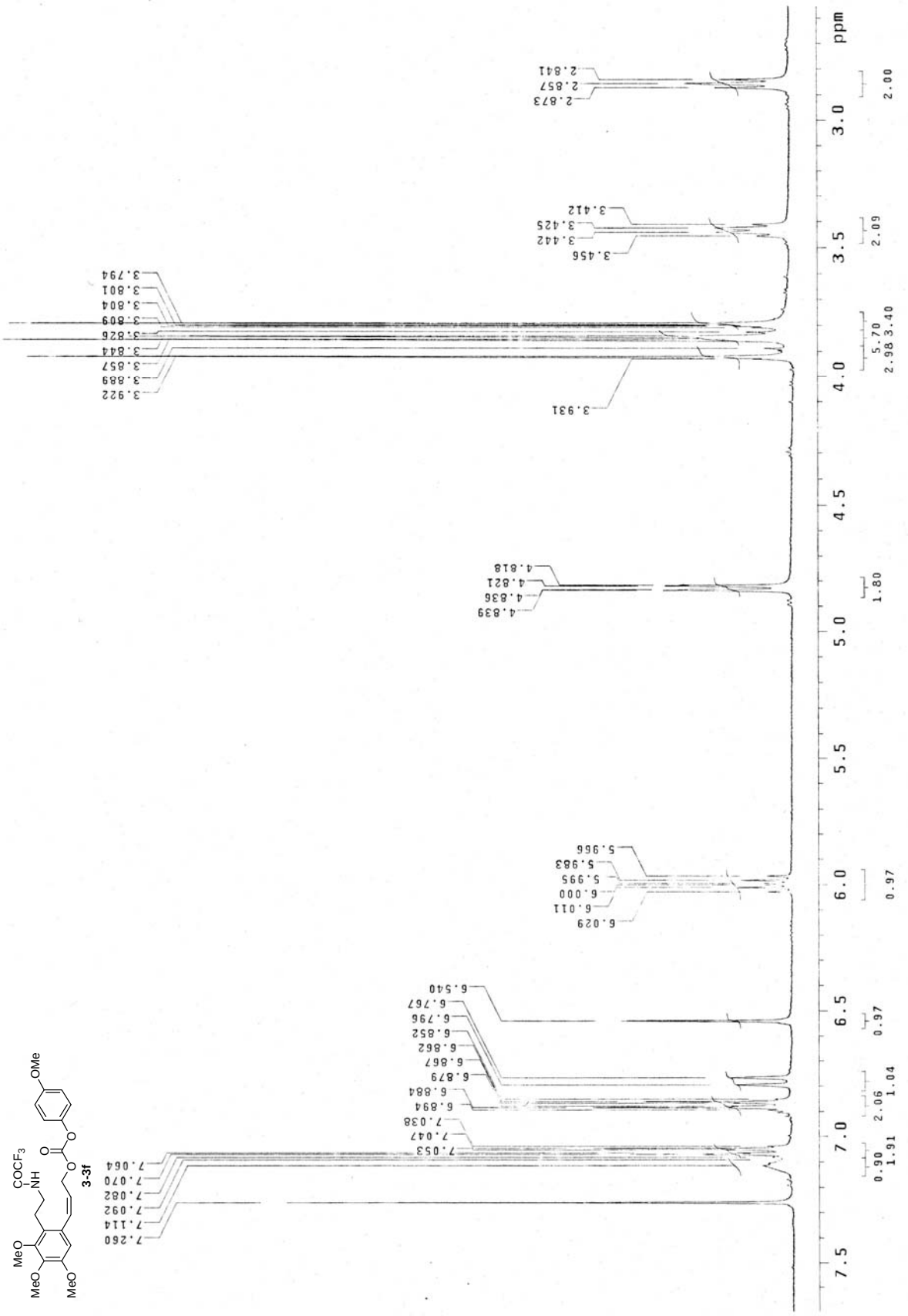
40.552
54.978
56.033
56.063
60.669
60.707
60.996
61.034
63.272
63.644
65.465
76.681
77.000
77.319
94.439
109.176
114.419
117.280
121.105
122.190
123.867
125.552
130.431
133.383
134.780
141.852
151.786
152.203
153.888
157.128
157.192
ppm
3-3c

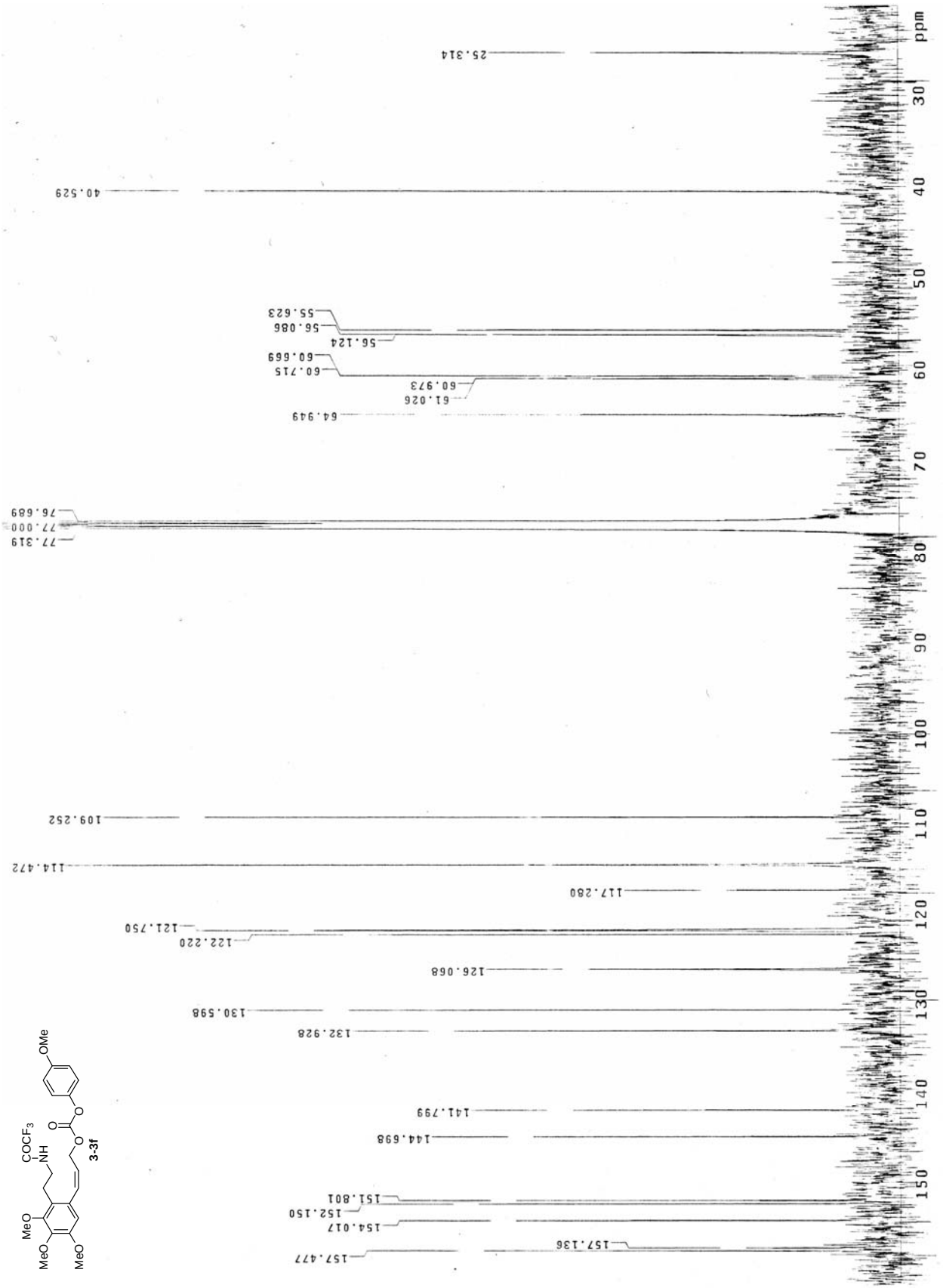

3-3d
MeO
MeO
MeO
COCF3
NH
O
O
O
ppm
7.263
7.260
7.137
7.070
7.054
7.035
7.020
6.778
6.776
6.749
6.748
6.525
5.971
5.954
5.943
5.937
5.926
5.908
4.937
4.932
4.903
4.897
4.793
4.790
4.776
4.772
4.596
4.591
4.580
4.575
3.935
3.925
3.920
3.920
3.919
3.916
3.878
3.857
3.852
3.846
3.820
3.449
3.434
3.418
3.404
2.859
2.843
2.827

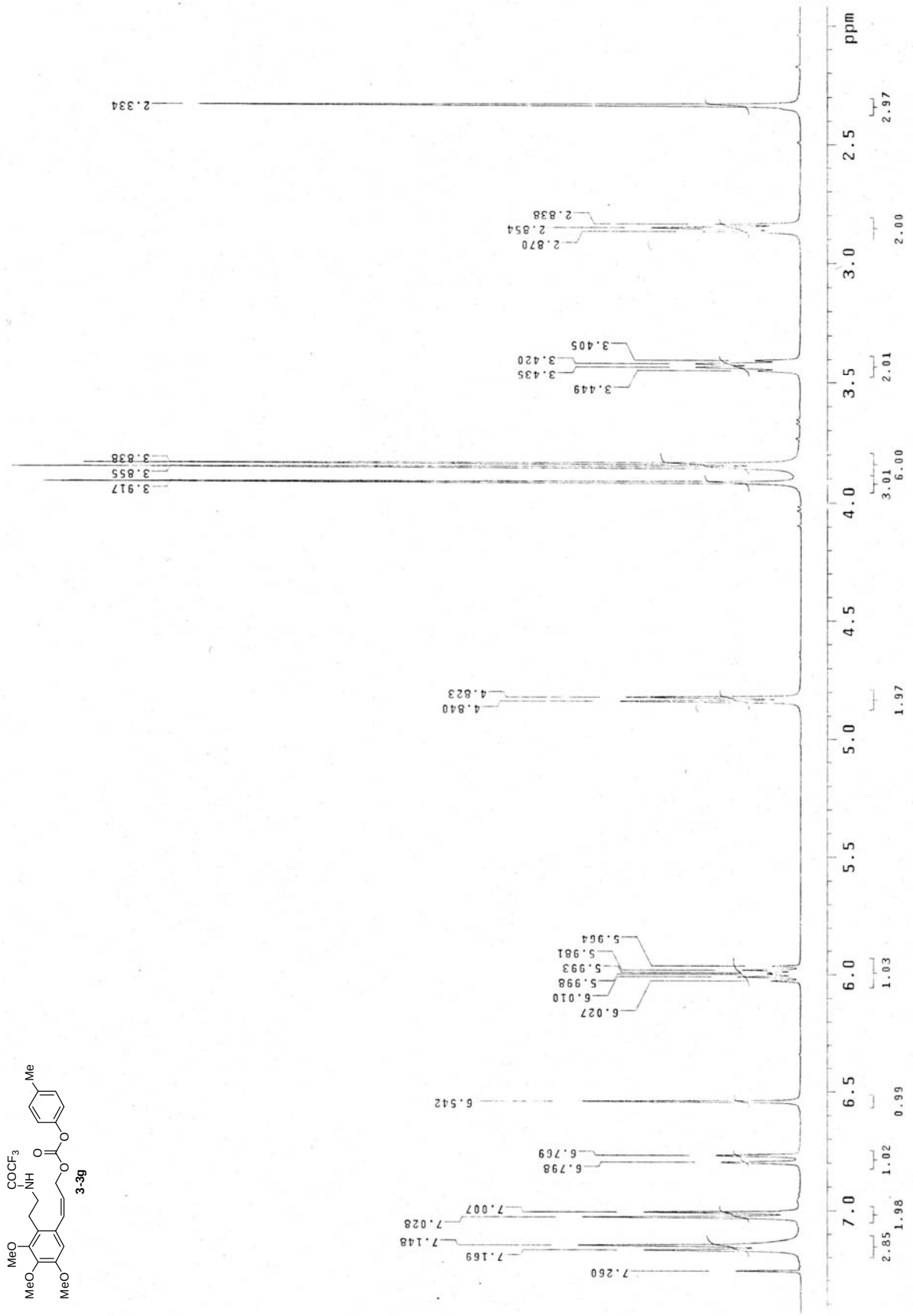

25.314
40.529
41.273
56.040
56.078
60.647
60.685
60.958
61.003
64.760
64.851
64.949
76.681
77.000
77.311
98.020
109.160
111.543
114.412
117.273
120.134
122.190
125.848
130.515
133.019
141.791
142.512
142.565
151.763
152.150
152.643
156.749
157.113
157.485
157.841
ppm
3-3d
MeO
MeO
MeO
NH
COCF3

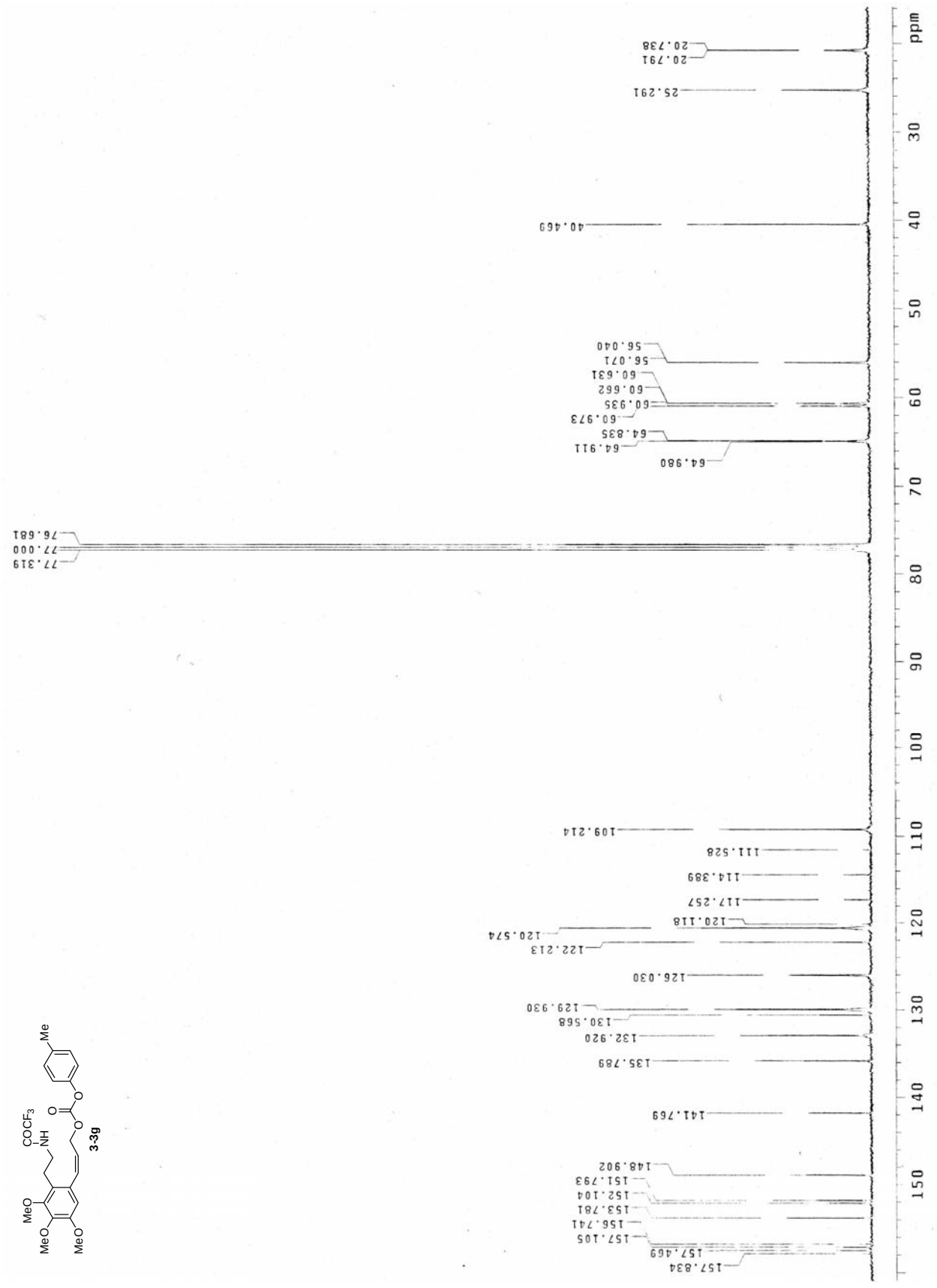

3-3e
MeO
MeO
MeO
COCF3
NH
O
O
O
7.260
7.259
7.140
6.765
6.739
6.522
5.980
5.962
5.951
5.945
5.934
5.917
4.785
4.781
4.771
4.768
4.754
4.750
4.697
4.694
4.691
3.921
3.878
3.857
3.846
3.836
3.821
3.450
3.436
3.419
3.405
2.865
2.849
2.834
2.009
1.950
1.949
1.947
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
0.91
0.96
0.95
1.01
0.92
2.73
6.00
2.99
2.11
2.00
2.70

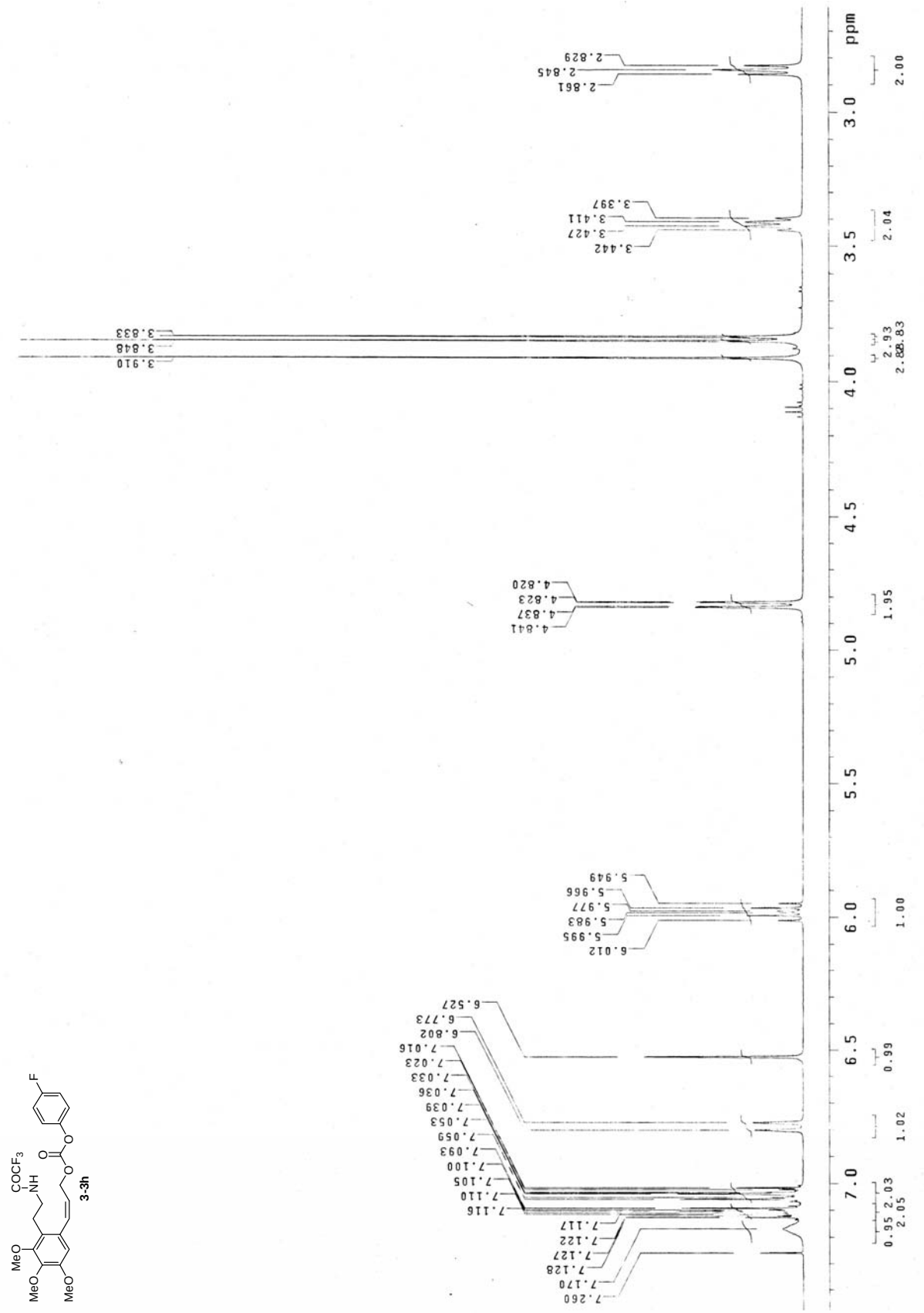

19.061
19.122
25.299
40.514
56.063
56.086
60.662
60.700
60.973
61.011
64.600
76.661
77.000
77.319
94.431
101.891
109.221
114.419
117.288
122.205
126.151
130.606
132.746
141.769
151.793
152.127
152.878
152.931
156.764
157.128
157.500
ppm
MeO
MeO
MeO
NH
COCF3
3-3e

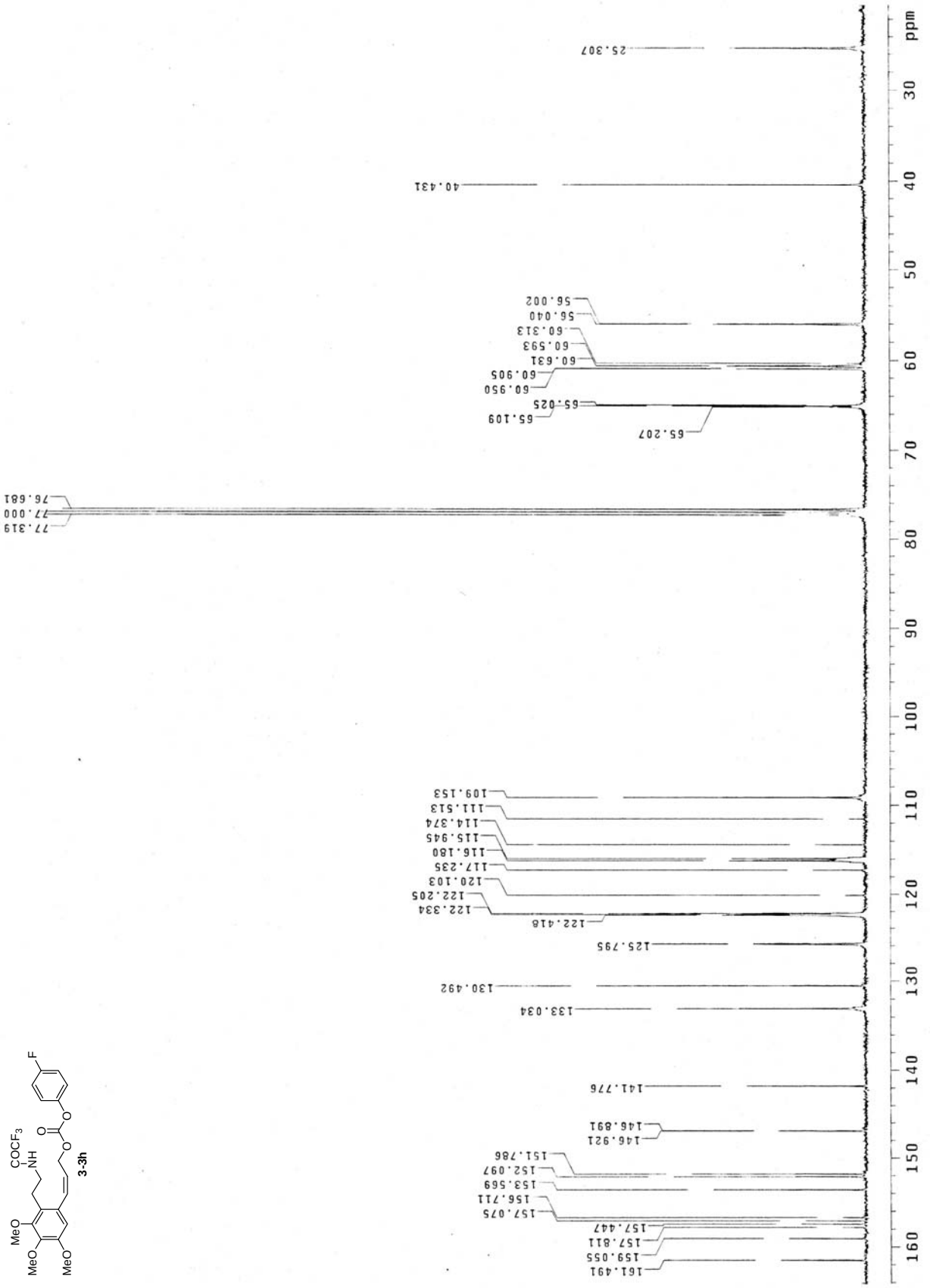

3-31f
MeO
MeO
MeO
COCF3
NH
O
O
OMe
7.260
7.114
7.092
7.082
7.070
7.064
7.053
7.047
7.038
6.894
6.884
6.879
6.867
6.862
6.852
6.796
6.767
6.540
6.029
6.011
6.000
5.995
5.983
5.966
4.839
4.836
4.821
4.818
3.931
3.922
3.889
3.857
3.844
3.826
3.809
3.804
3.801
3.794
3.456
3.442
3.425
3.412
2.873
2.857
2.841
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
0.90
1.91
2.06
1.04
0.97
0.97
1.80
5.70
2.98
3.40
2.09
2.00


25.314
40.529
55.623
56.086
56.124
60.669
60.715
60.973
61.026
64.949
76.689
77.000
77.319
109.252
114.472
117.280
121.750
122.220
126.068
130.598
132.928
141.799
144.698
151.801
152.150
154.017
157.136
157.477
ppm
30
40
50
60
70
80
90
100
110
120
130
140
150
OMe
COCF3
NH
MeO
MeO
MeO
3-3f


Me
COCF3
NH
O
O
O
MeO
MeO
MeO
3-3g
2.334
2.838
2.854
2.870
3.405
3.420
3.435
3.449
3.838
3.855
3.917
4.823
4.840
5.964
5.981
5.993
5.998
6.010
6.027
6.542
6.769
6.798
7.007
7.028
7.148
7.169
7.260
ppm
2.97
2.00
2.01
6.00
1.97
1.03
0.99
1.02
1.98
2.85


20.738
20.791
25.291
40.469
56.040
56.071
60.631
60.662
60.935
60.973
64.835
64.911
64.980
76.681
77.000
77.319
109.214
111.528
114.389
117.257
120.118
120.574
122.213
126.030
129.930
130.568
132.920
135.789
141.769
148.902
151.793
152.104
153.781
156.741
157.105
157.469
157.834
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
Me
COCF3
NH
O
MeO
MeO
MeO
3-3g


3-3h
MeO
MeO
MeO
COCF3
NH
O
O
O
F
7.260
7.170
7.128
7.127
7.122
7.117
7.116
7.110
7.105
7.100
7.093
7.059
7.053
7.039
7.036
7.033
7.023
7.016
6.802
6.773
6.527
6.012
5.995
5.983
5.977
5.966
5.949
4.841
4.837
4.823
4.820
3.910
3.848
3.833
3.442
3.427
3.411
3.397
2.861
2.845
2.829
ppm
0.95 2.03
2.05
1.02
0.99
1.00
1.95
2.93
2.83
2.04
2.00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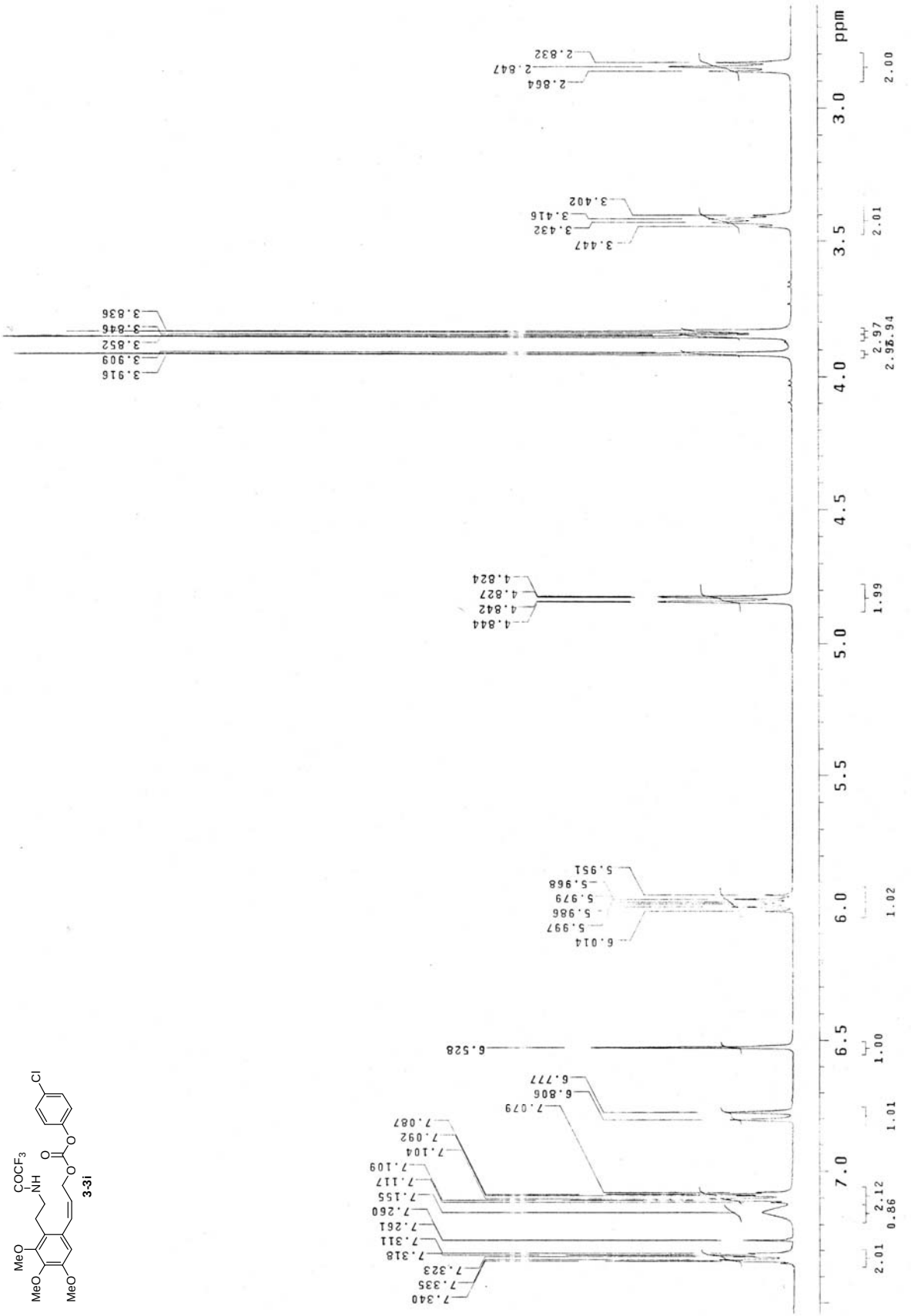
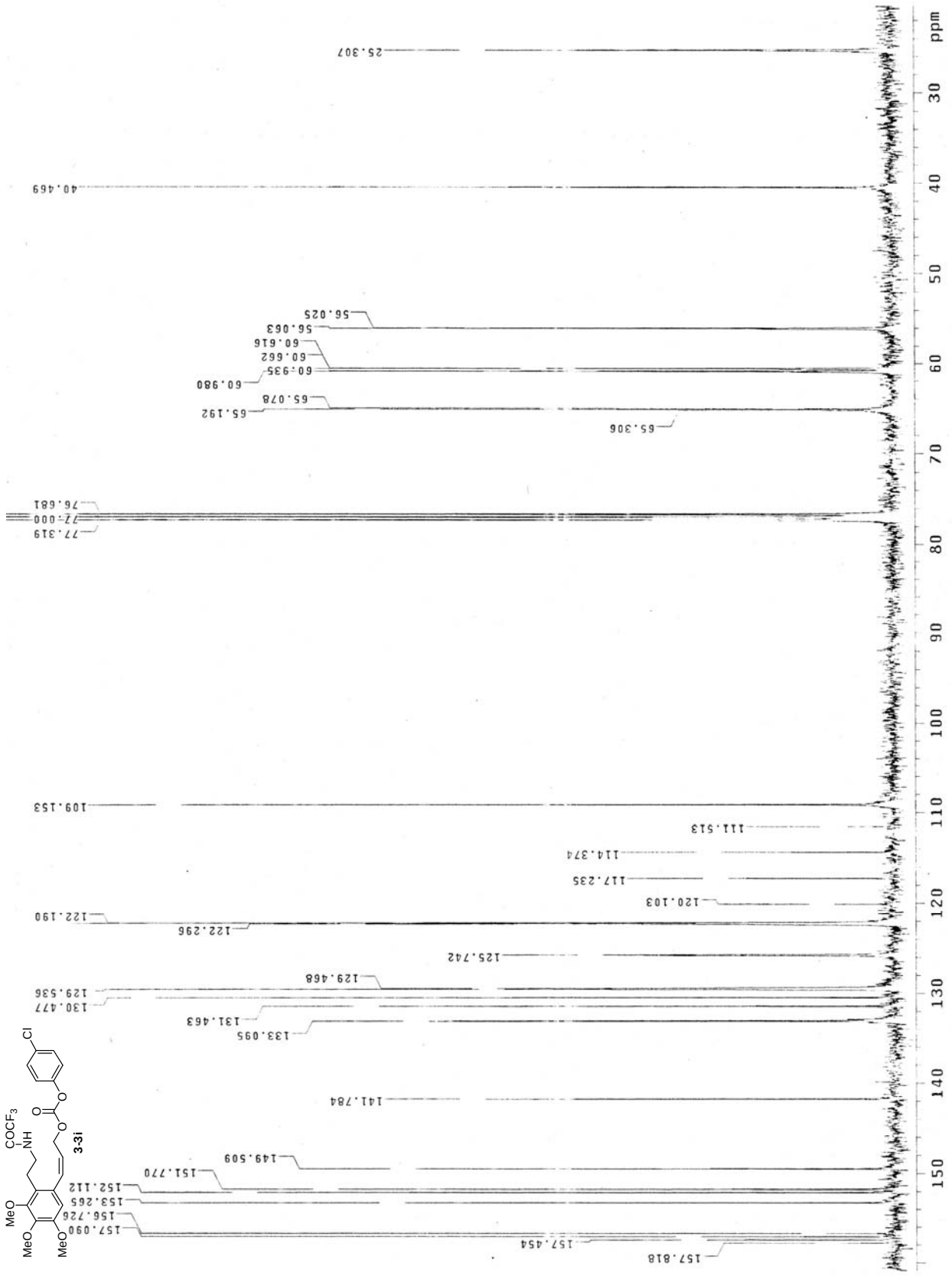
40.431
56.002
56.040
60.313
60.593
60.631
60.905
60.950
65.025
65.109
65.207
76.681
77.000
77.319
109.153
111.513
114.374
115.945
116.180
117.235
120.103
122.205
122.334
122.418
125.795
130.492
133.034
141.776
146.891
146.921
151.786
152.097
153.569
156.711
157.075
157.447
157.811
159.055
161.491
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
F
O
O
O
COCF3
NH
MeO
MeO
MeO
3-3h


MeO
MeO
MeO
COCF3
NH
O
O
O
Cl
3-3i
7.340
7.335
7.323
7.318
7.311
7.261
7.260
7.155
7.117
7.109
7.104
7.092
7.087
7.079
6.806
6.777
6.528
6.014
5.997
5.986
5.979
5.968
5.951
4.844
4.842
4.827
4.824
3.916
3.909
3.852
3.846
3.836
3.447
3.432
3.416
3.402
2.864
2.847
2.832
ppm
2.01
2.12
0.86
1.01
1.00
1.02
1.99
2.97
2.98
2.94
2.01
2.00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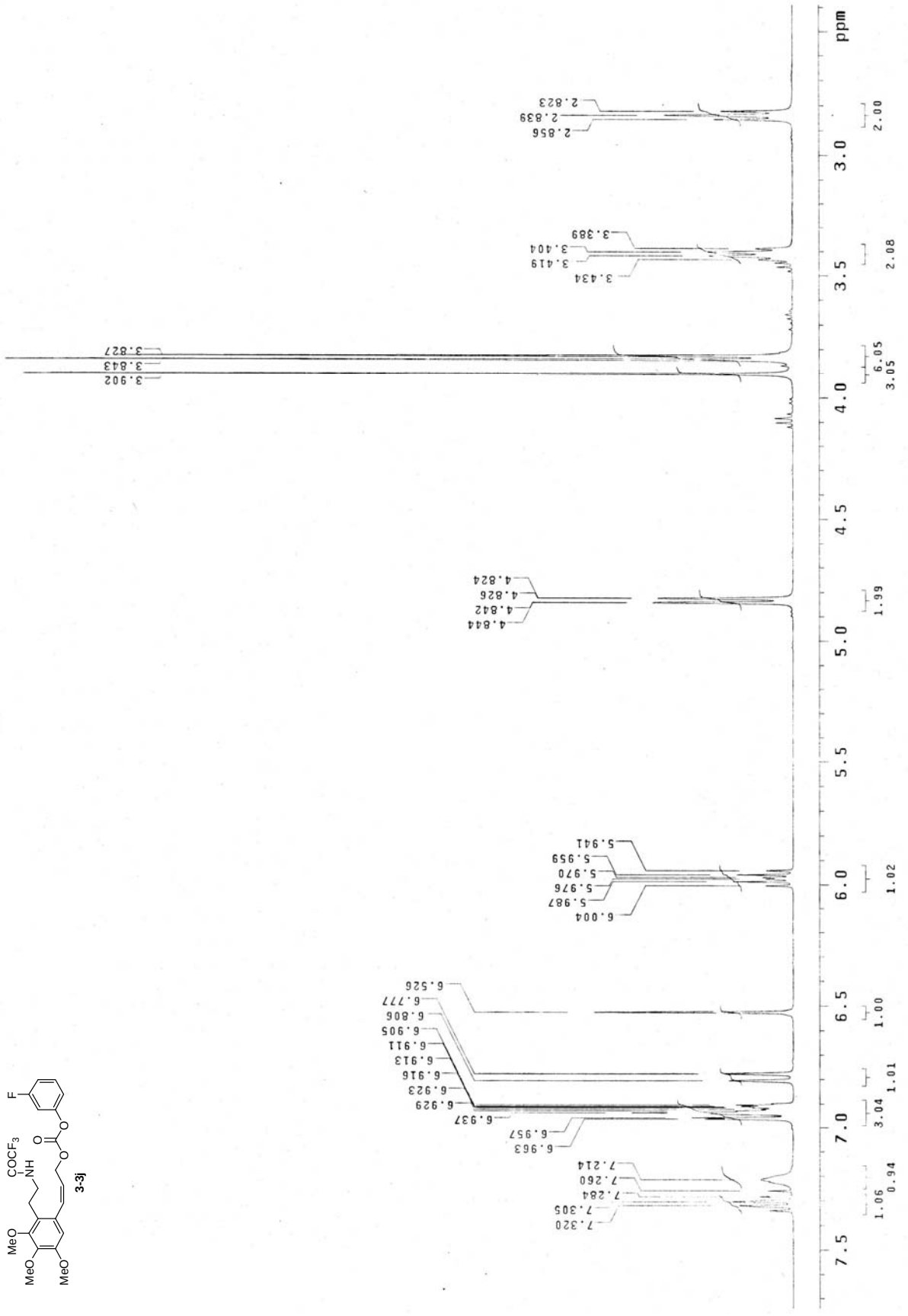
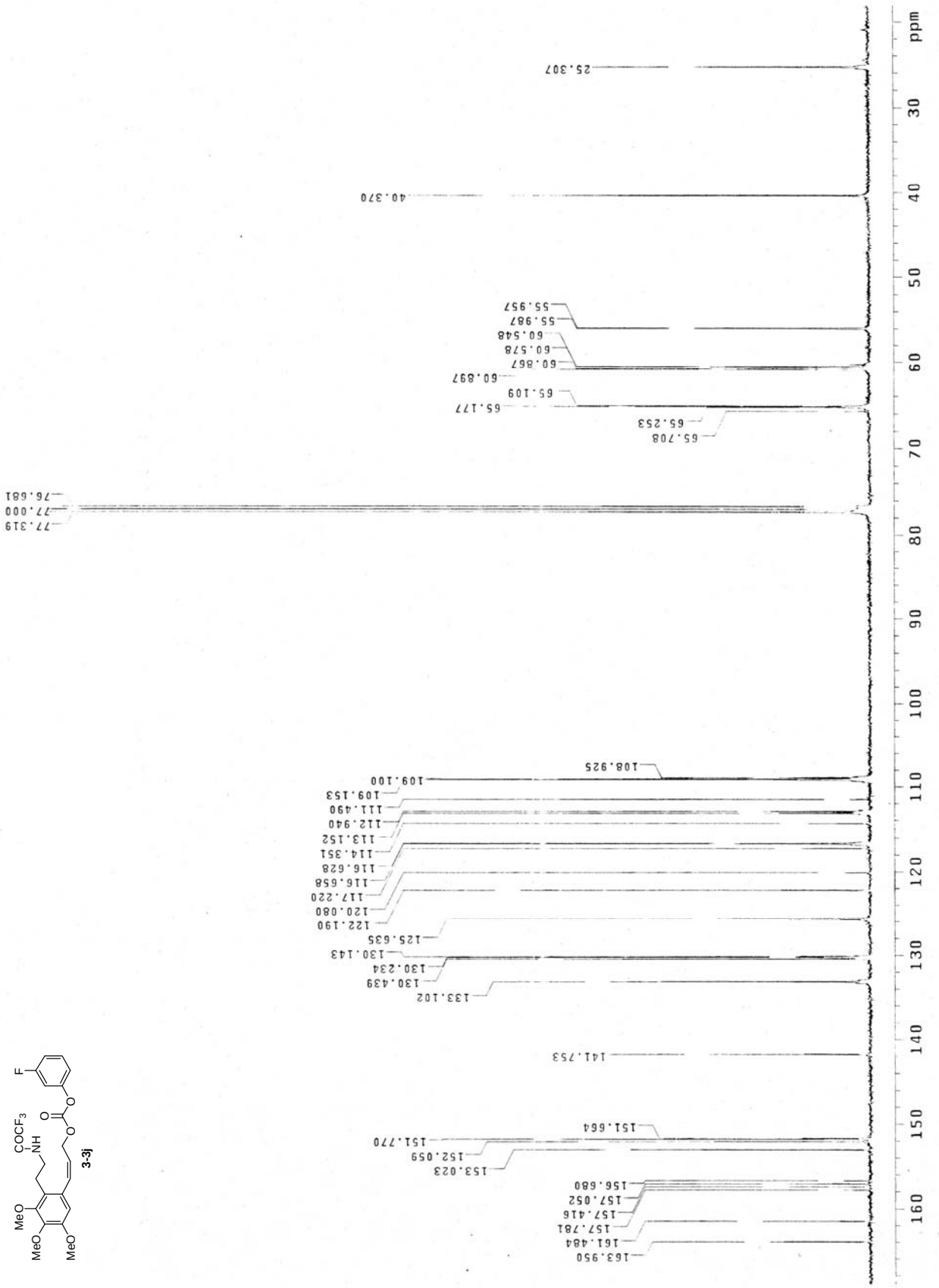
56.025
56.063
60.616
60.662
60.935
60.980
65.078
65.192
65.306
76.681
77.000
77.319
109.153
111.513
114.374
117.235
120.103
122.190
122.296
125.742
129.468
129.536
130.477
131.463
133.095
141.784
149.509
151.770
152.112
153.265
156.726
157.090
157.454
157.818
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
MeO
MeO
MeO
NH
COCF3
O
O
O
Cl
3-3i


F
COCF3
NH
O
O
O
MeO
MeO
MeO
3-3j
7.320
7.305
7.284
7.260
7.214
6.963
6.957
6.937
6.929
6.923
6.916
6.913
6.911
6.905
6.806
6.777
6.526
6.004
5.987
5.976
5.970
5.959
5.941
4.844
4.842
4.826
4.824
3.902
3.843
3.827
3.434
3.419
3.404
3.389
2.856
2.839
2.823
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
1.06
0.94
3.04
1.01
1.00
1.02
1.99
6.05
3.05
2.08
2.00


F
COCF3
NH
O
O
O
MeO
MeO
MeO
3-3j
ppm
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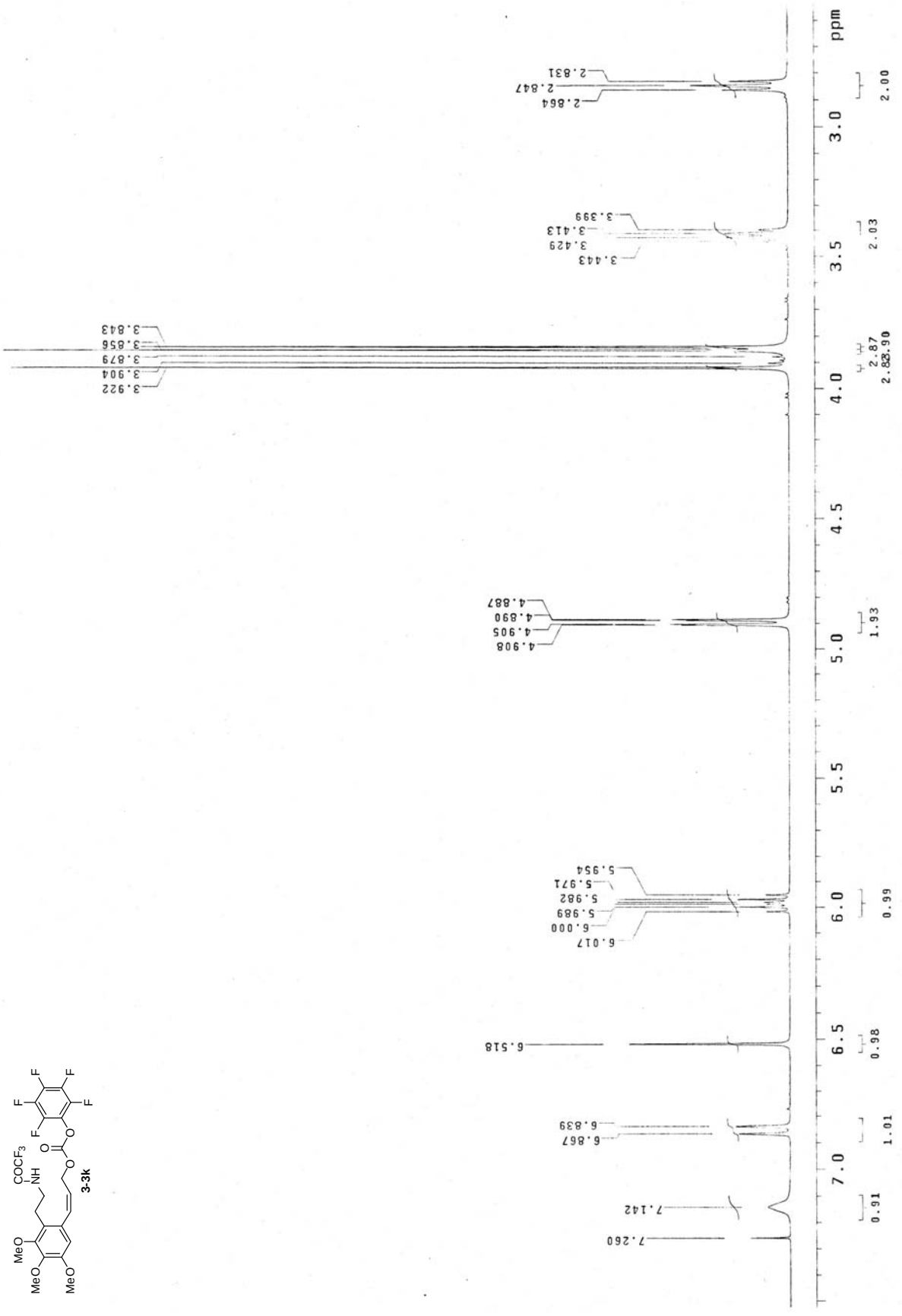
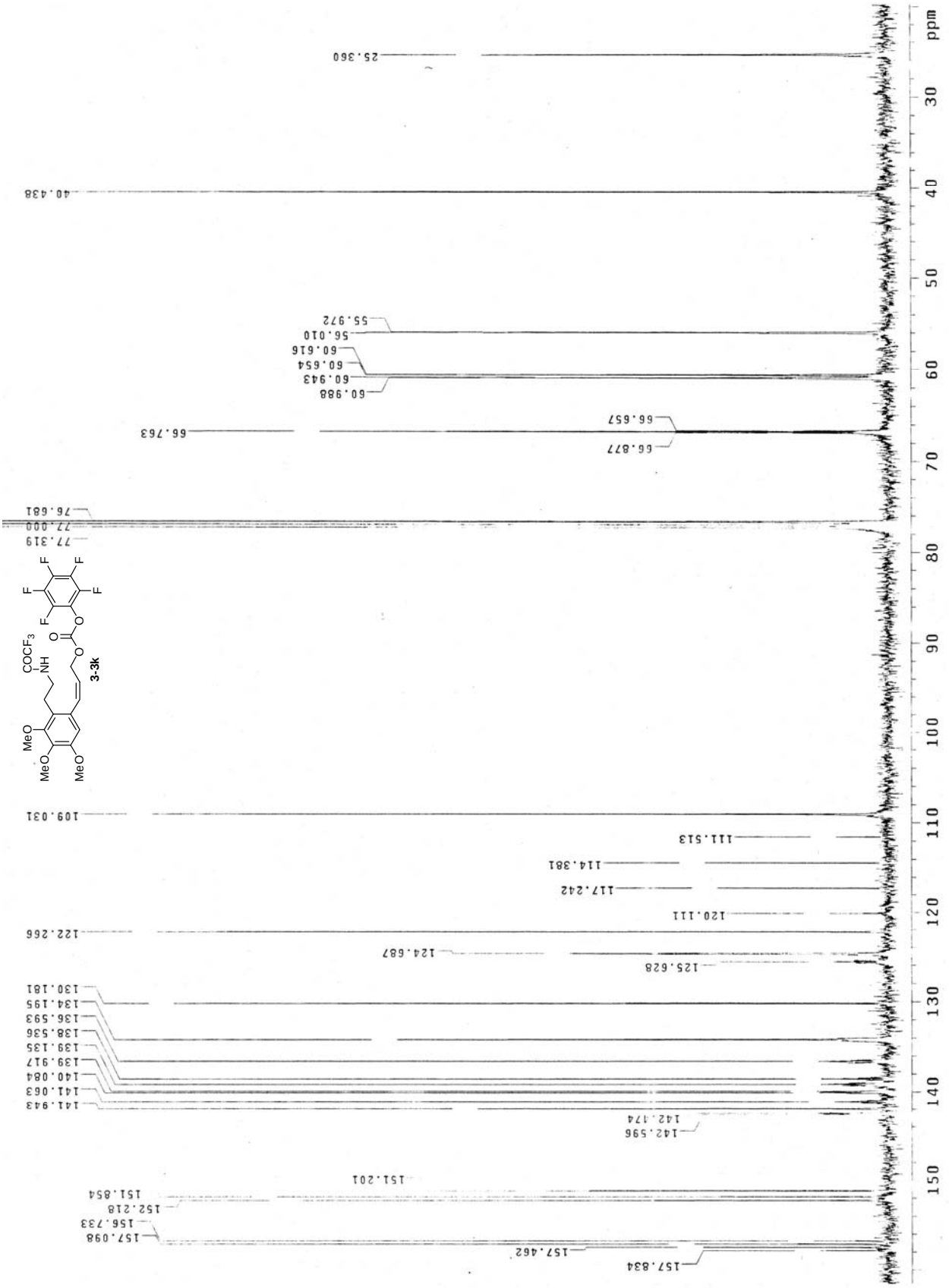
40.370
55.957
55.987
60.548
60.578
60.867
60.897
65.109
65.177
65.253
65.708
76.681
77.000
77.319
108.925
109.100
109.153
111.490
112.940
113.152
114.351
116.628
116.658
117.220
120.080
122.190
125.635
130.143
130.234
130.439
133.102
141.753
151.664
151.770
152.059
153.023
156.680
157.052
157.416
157.781
161.484
163.950


7.260
7.142
6.867
6.839
6.518
6.017
6.000
5.989
5.982
5.971
5.954
4.908
4.905
4.890
4.887
3.922
3.904
3.879
3.856
3.843
3.443
3.429
3.413
3.399
2.864
2.847
2.831
ppm
0.91
1.01
0.98
0.99
1.93
2.87
2.90
2.03
2.00
3-3k
COCF3
NH
MeO
MeO
MeO
F
F
F
F
F
O
O
O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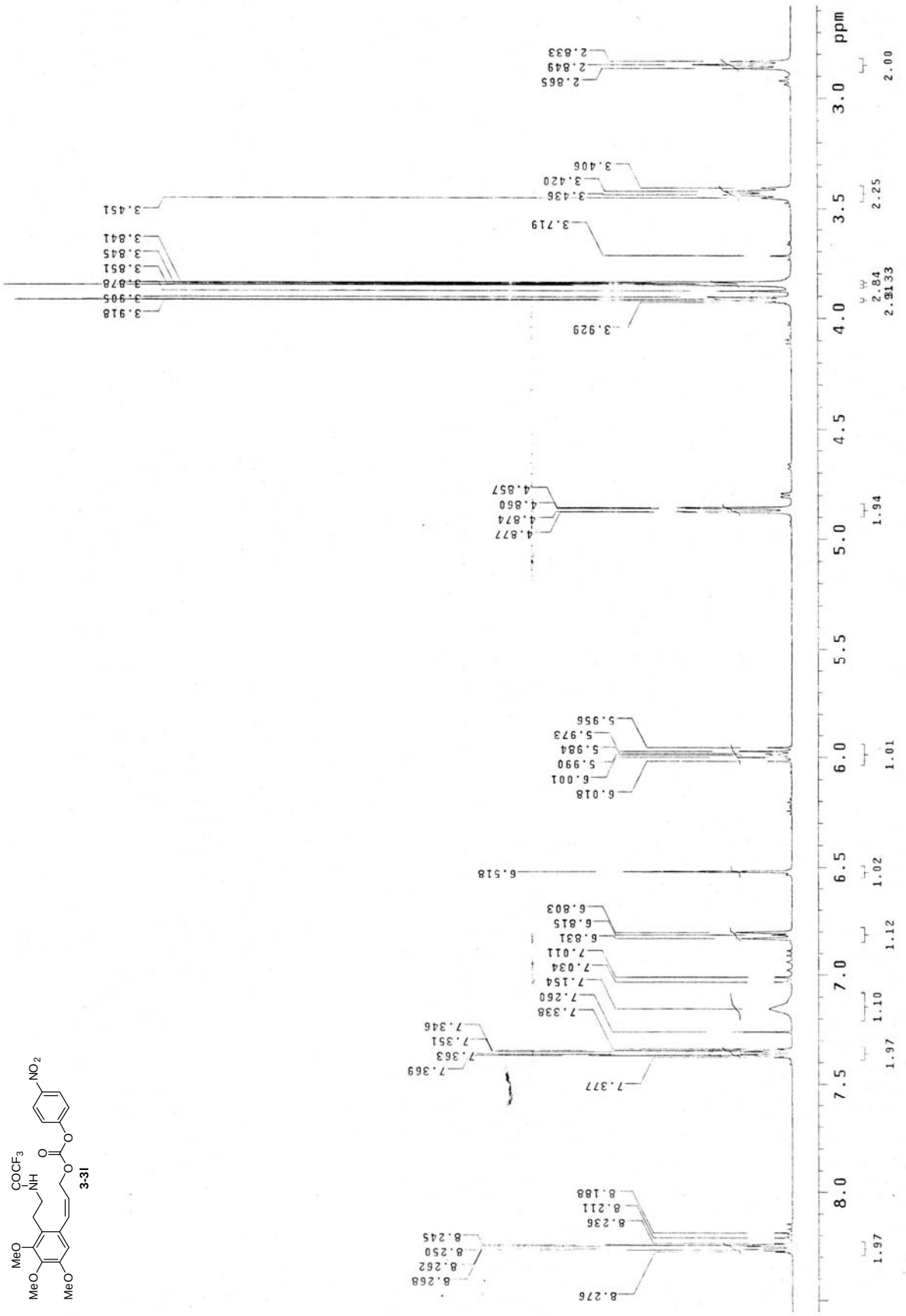
77.000
77.319
109.031
111.513
114.381
117.242
120.111
122.266
124.687
125.628
130.181
134.195
136.593
138.536
139.135
139.917
140.084
141.063
141.943
142.174
142.596
151.201
151.854
152.218
156.733
157.098
157.462
157.834
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
F
F
F
F
F
O
O
O
COCF3
NH
MeO
MeO
MeO
3-3k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MeO
MeO
COCF3
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O
O
O
NO2
3-3l
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8.245
8.236
8.211
8.188
7.377
7.369
7.363
7.351
7.346
7.338
7.260
7.154
7.034
7.011
6.831
6.815
6.803
6.518
6.018
6.001
5.990
5.984
5.973
5.956
4.877
4.874
4.860
4.857
3.929
3.918
3.905
3.878
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3.406
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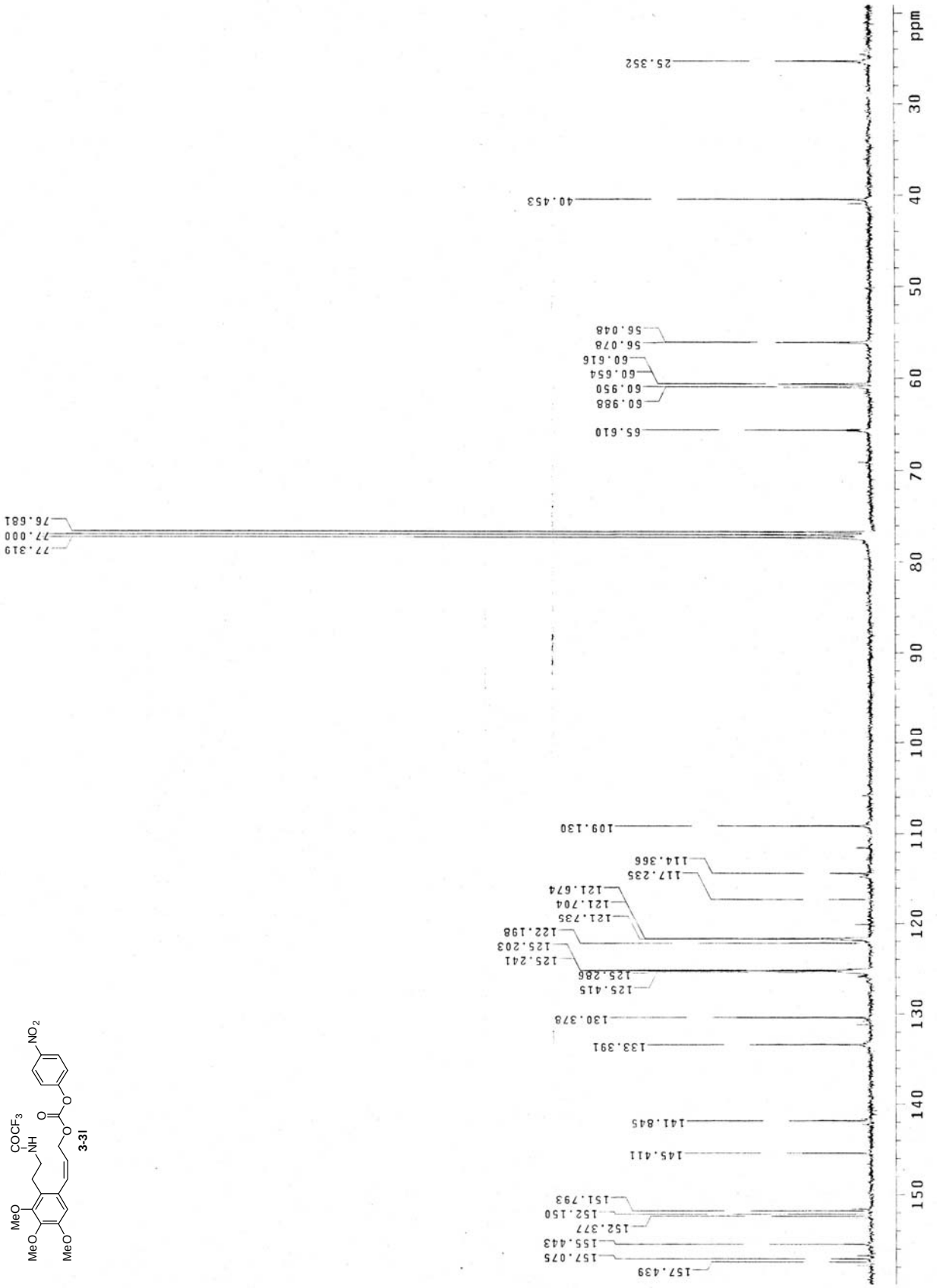
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77.000
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114.366
117.235
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121.704
121.735
122.198
125.203
125.241
125.286
125.415
130.378
133.391
141.845
145.411
151.793
152.150
152.377
155.443
157.075
157.439
ppm
10
20
30
40
50
60
70
80
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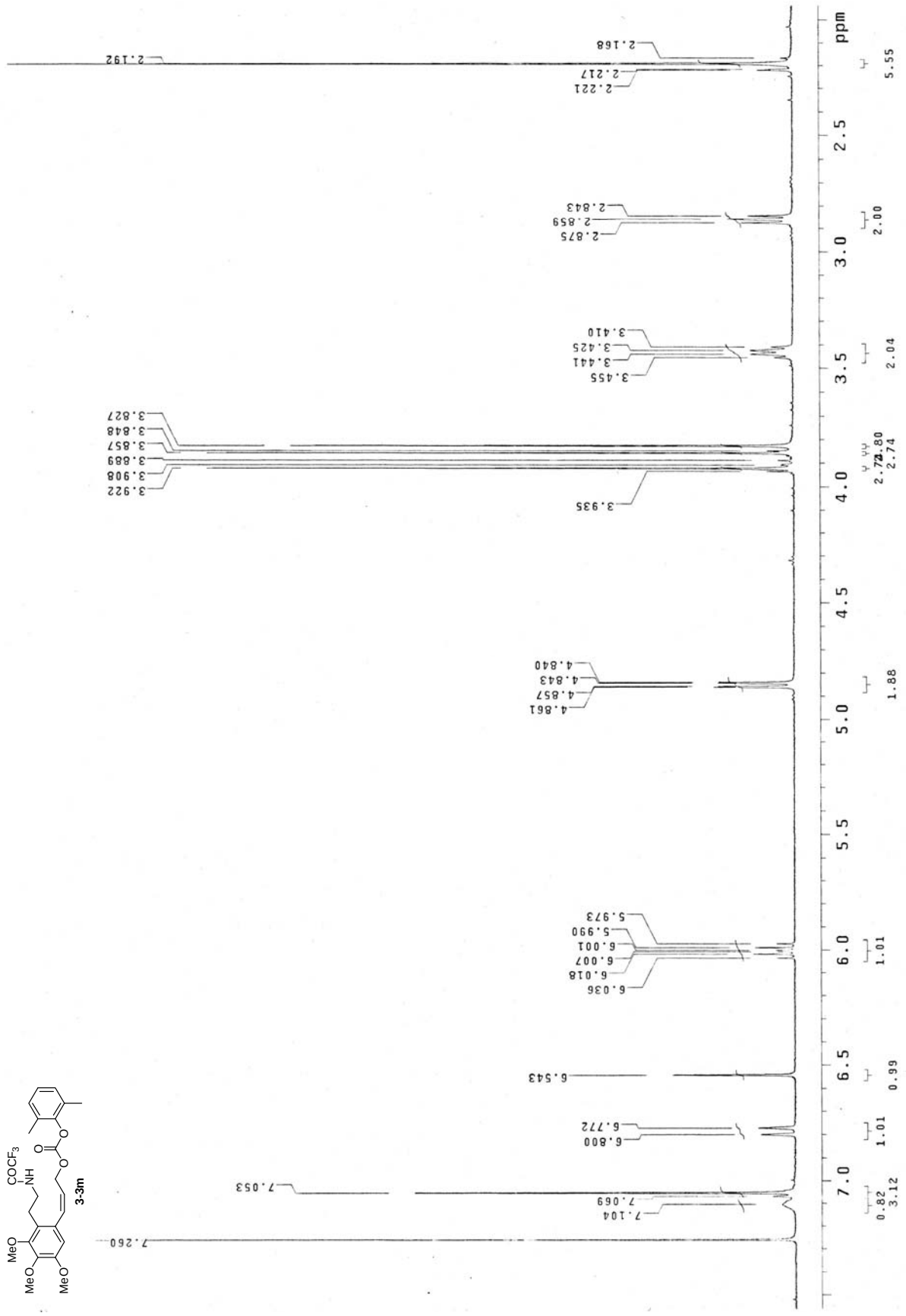
110
120
130
140
150
NO2
COCF3
NH
MeO
MeO
MeO
3-3l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COCF3
NH
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MeO
MeO
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6.036
6.018
6.007
6.001
5.990
5.973
4.861
4.857
4.843
4.840
3.935
3.922
3.908
3.889
3.857
3.848
3.827
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3.425
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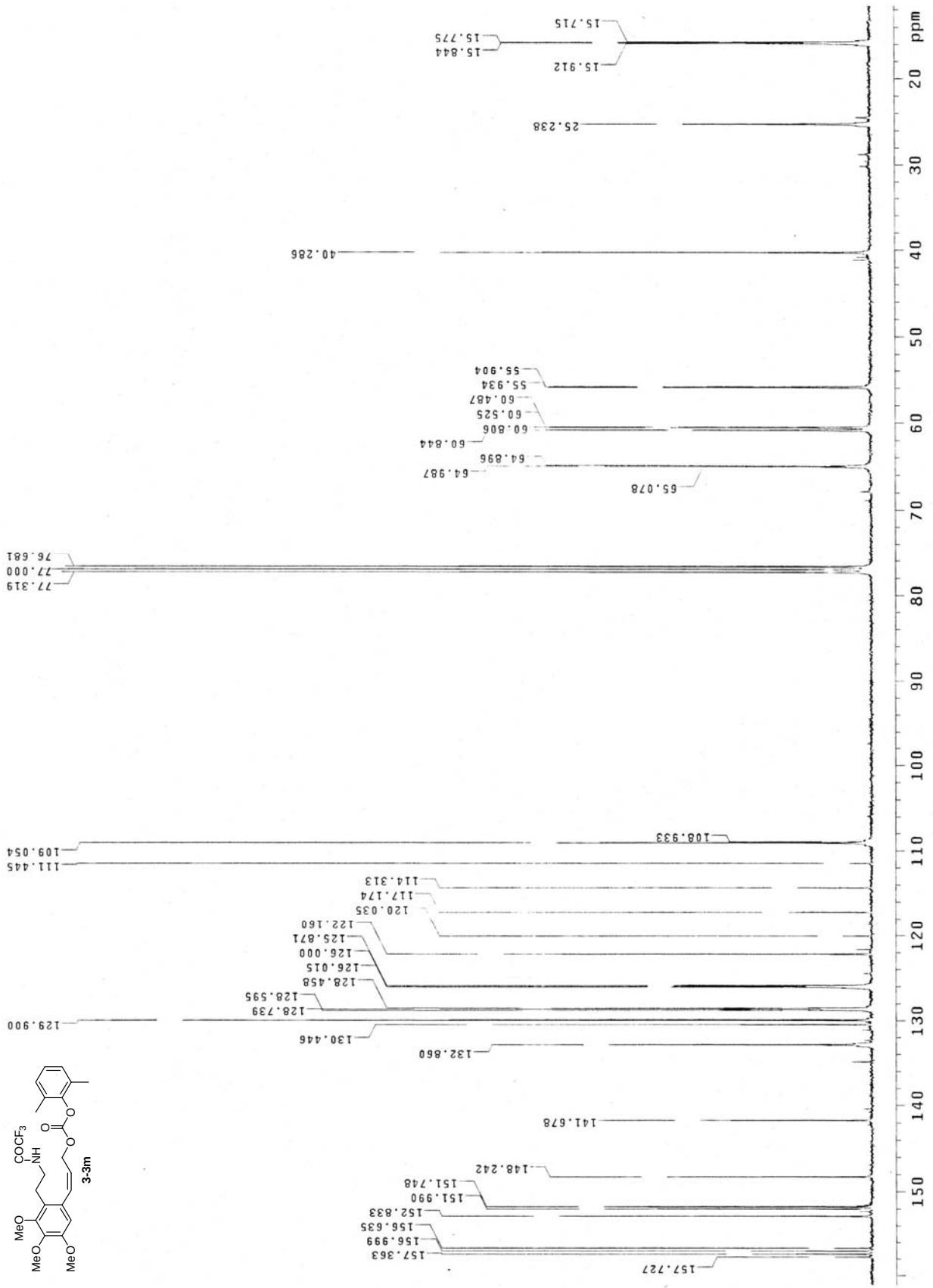
ppm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64.896
64.987
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77.000
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108.933
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111.445
114.313
117.174
120.035
122.160
125.871
126.000
126.015
128.458
128.595
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129.900
130.446
132.860
141.678
148.242
151.748
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156.635
156.999
157.363
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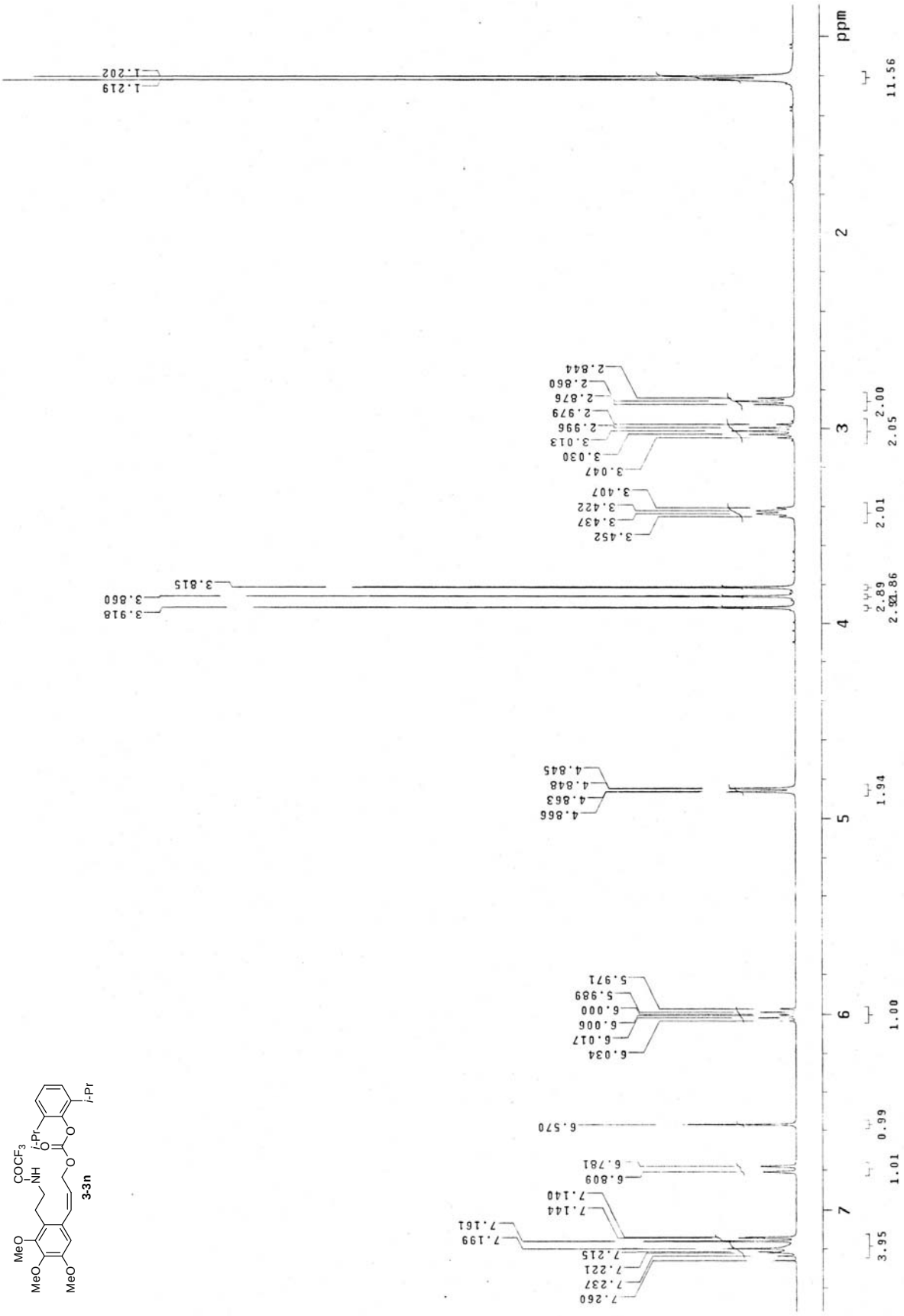
ppm
COCF3
NH
MeO
MeO
MeO
3-3m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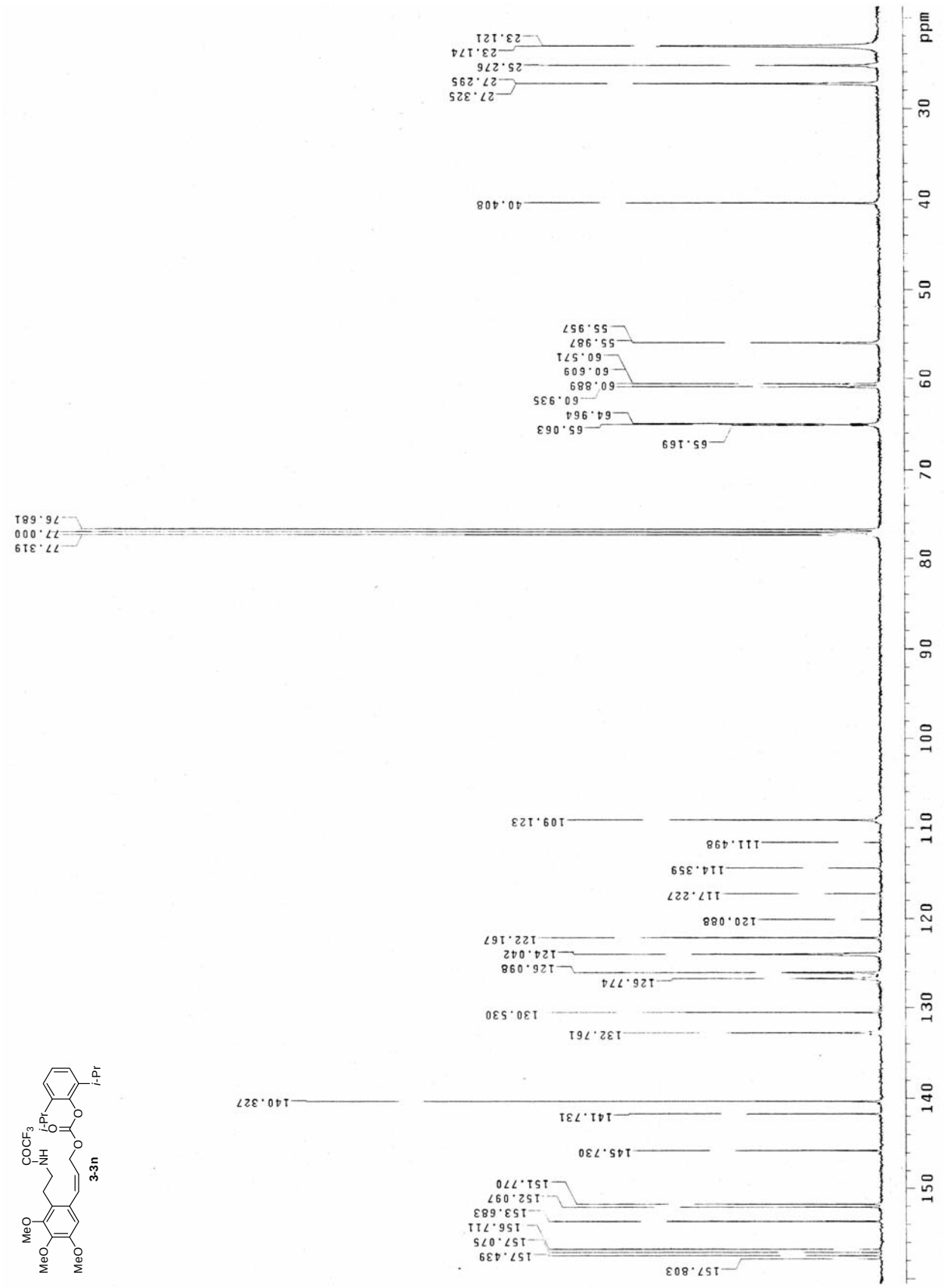
3.013
3.030
3.047
3.407
3.422
3.437
3.452
3.815
3.860
3.918
4.845
4.848
4.863
4.866
5.971
5.989
6.000
6.006
6.017
6.034
6.570
6.781
6.809
7.140
7.144
7.161
7.199
7.215
7.221
7.237
7.260
ppm
11.56
2.00
2.05
2.01
2.89
2.92
1.86
1.94
1.00
0.99
1.01
3.95
MeO
MeO
MeO
COCF3
NH
i-Pr
i-Pr
O
O
O
3-3n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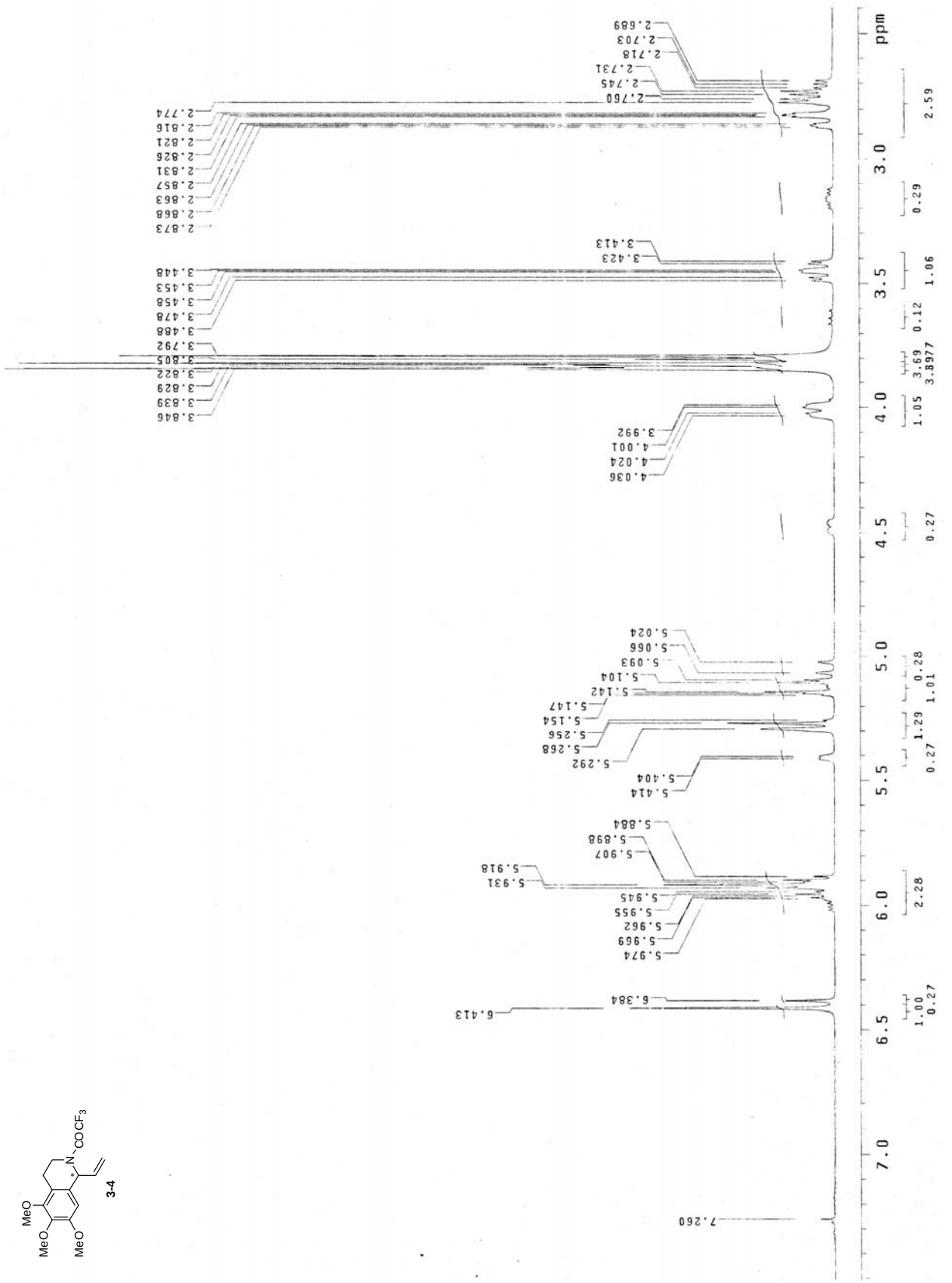
55.987
60.571
60.609
60.889
60.935
64.964
65.063
65.169
76.681
77.000
77.319
109.123
111.498
114.359
117.227
120.088
122.167
124.042
126.098
126.774
130.530
132.761
140.327
141.731
145.730
151.770
152.097
153.683
156.711
157.075
157.439
157.803
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
MeO
MeO
MeO
NH
COCF3
i-Pr
i-Pr
O
O
O
O
3-3n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2.760
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2.816
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2.826
2.831
2.857
2.863
2.868
2.873
3.413
3.423
3.448
3.453
3.458
3.478
3.488
3.792
3.805
3.822
3.829
3.839
3.846
3.992
4.001
4.024
4.036
5.024
5.066
5.093
5.104
5.142
5.147
5.154
5.256
5.268
5.292
5.404
5.414
5.884
5.898
5.907
5.918
5.931
5.945
5.955
5.962
5.969
5.974
6.384
6.413
7.260
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
1.00
0.27
2.28
0.27
1.29
0.27
1.01
0.28
0.27
1.05
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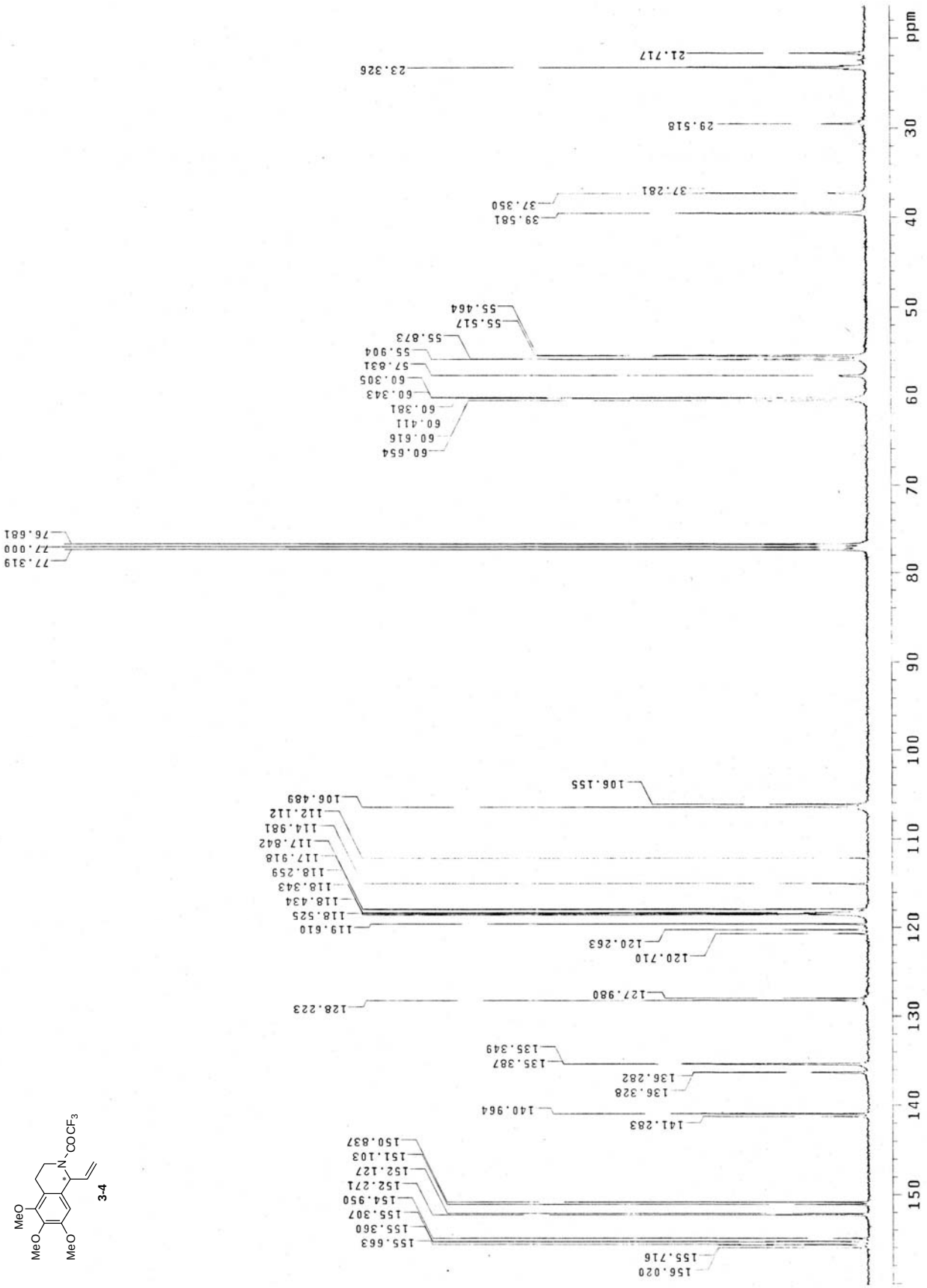
0.12
1.06
0.29
2.59
MeO
MeO
MeO
COCF3
N
3-4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55.517
55.873
55.904
57.631
60.305
60.343
60.381
60.411
60.616
60.654
76.681
77.000
77.319
106.155
106.489
112.112
114.981
117.842
117.918
118.259
118.343
118.434
118.525
119.610
120.263
120.710
127.980
128.223
135.349
135.387
136.282
136.328
140.964
141.283
150.837
151.103
152.127
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155.360
155.663
155.716
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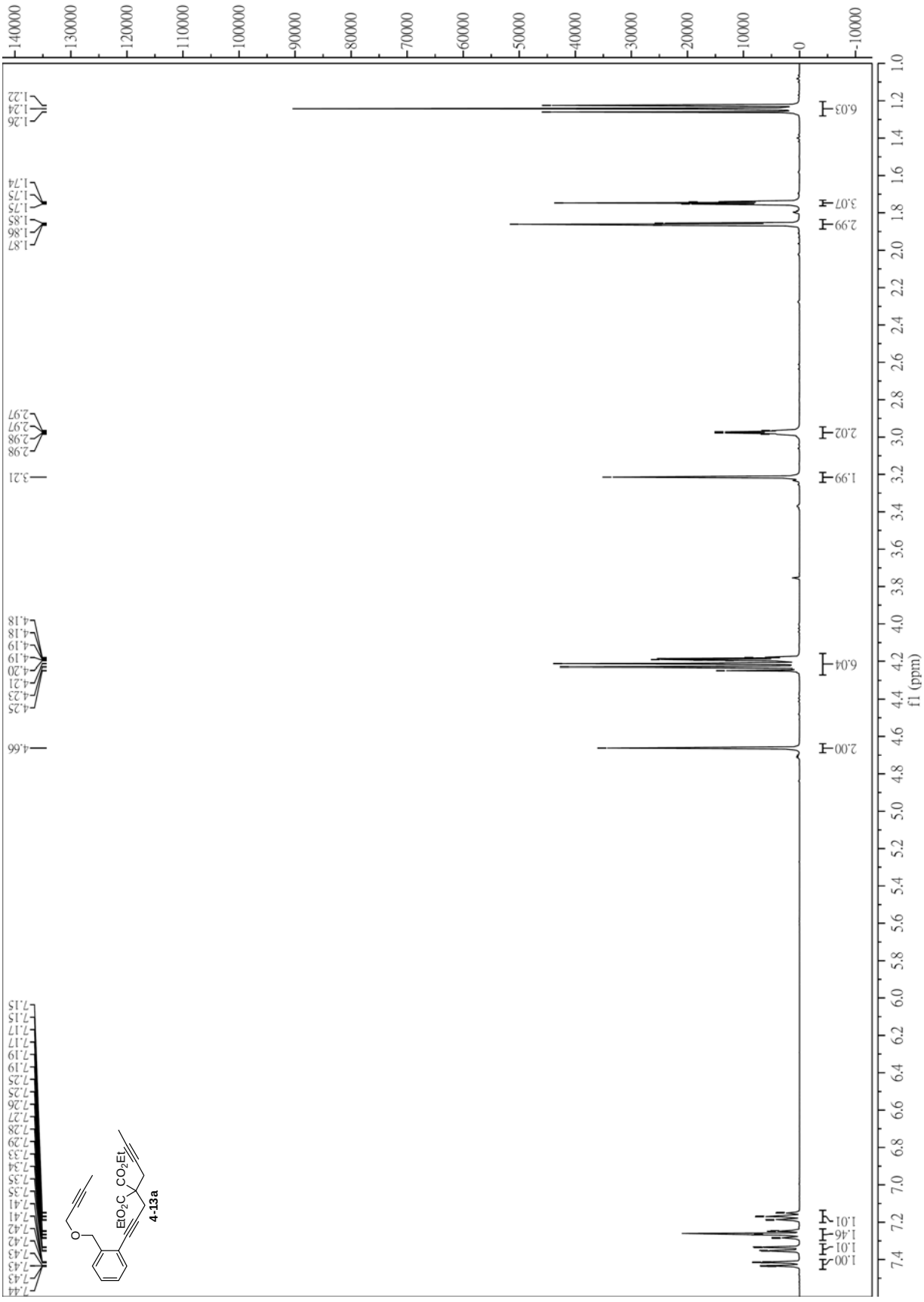
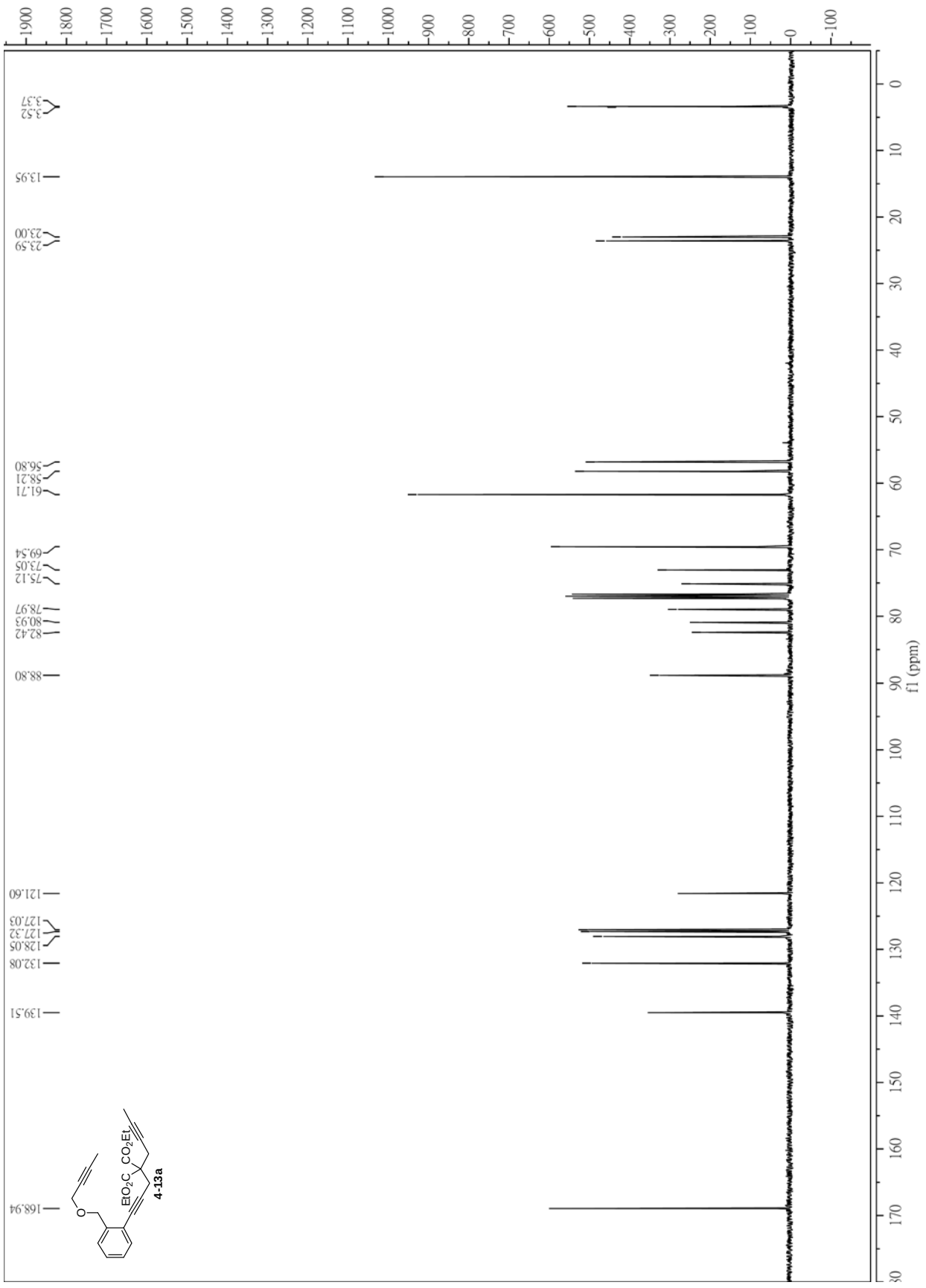
ppm
MeO
MeO
MeO
COCF3
3-4


EtO2C
CO2Et
4-13a
f1 (ppm)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23.00
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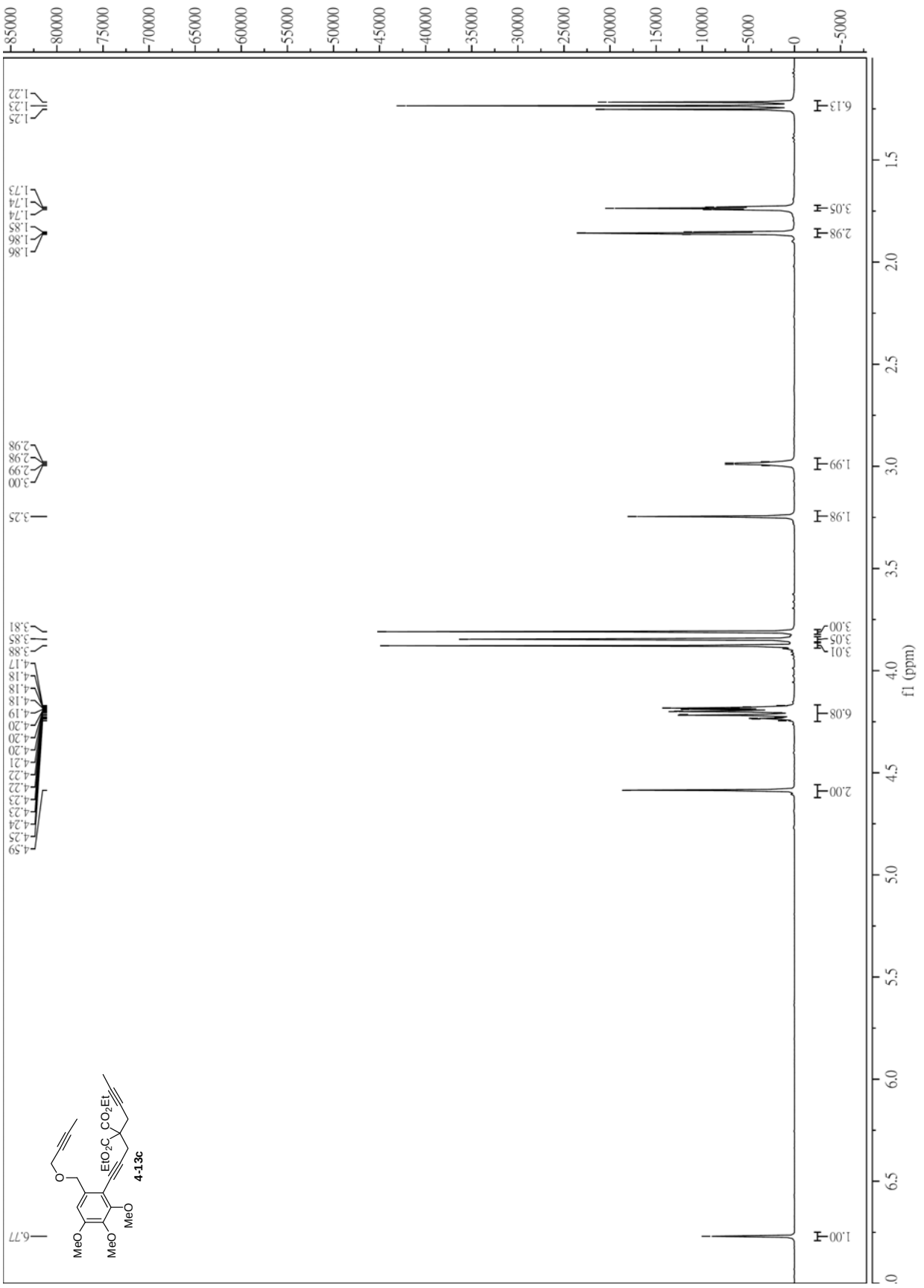
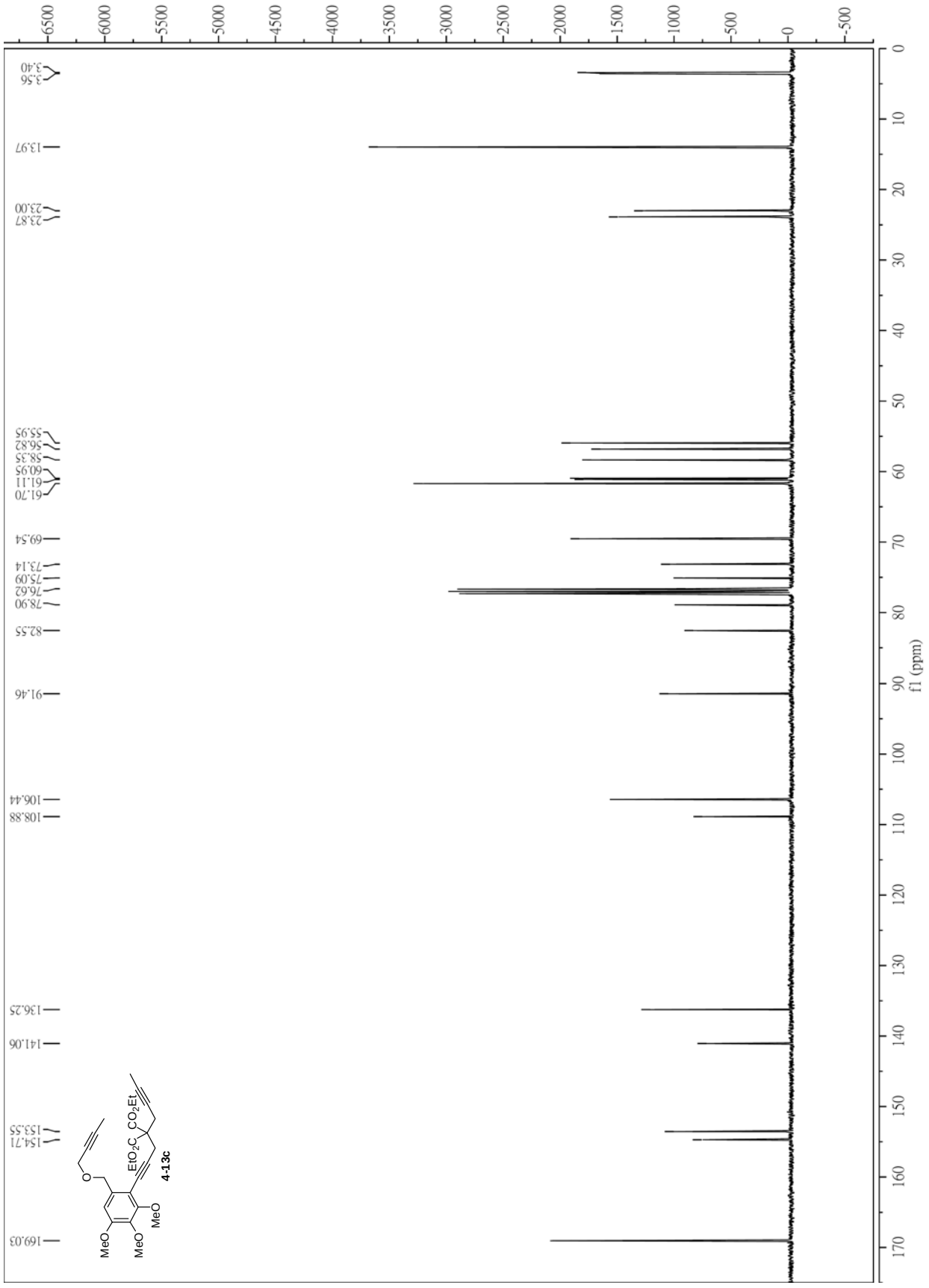
56.80
58.21
61.71
69.54
73.05
75.12
78.97
80.93
82.42
88.80
121.60
127.03
127.32
128.05
132.08
139.51
168.94
EtO2C
CO2Et
4-13a
f1 (ppm)


f1 (ppm)
4-13c
MeO
MeO
MeO
EtO2C
CO2Et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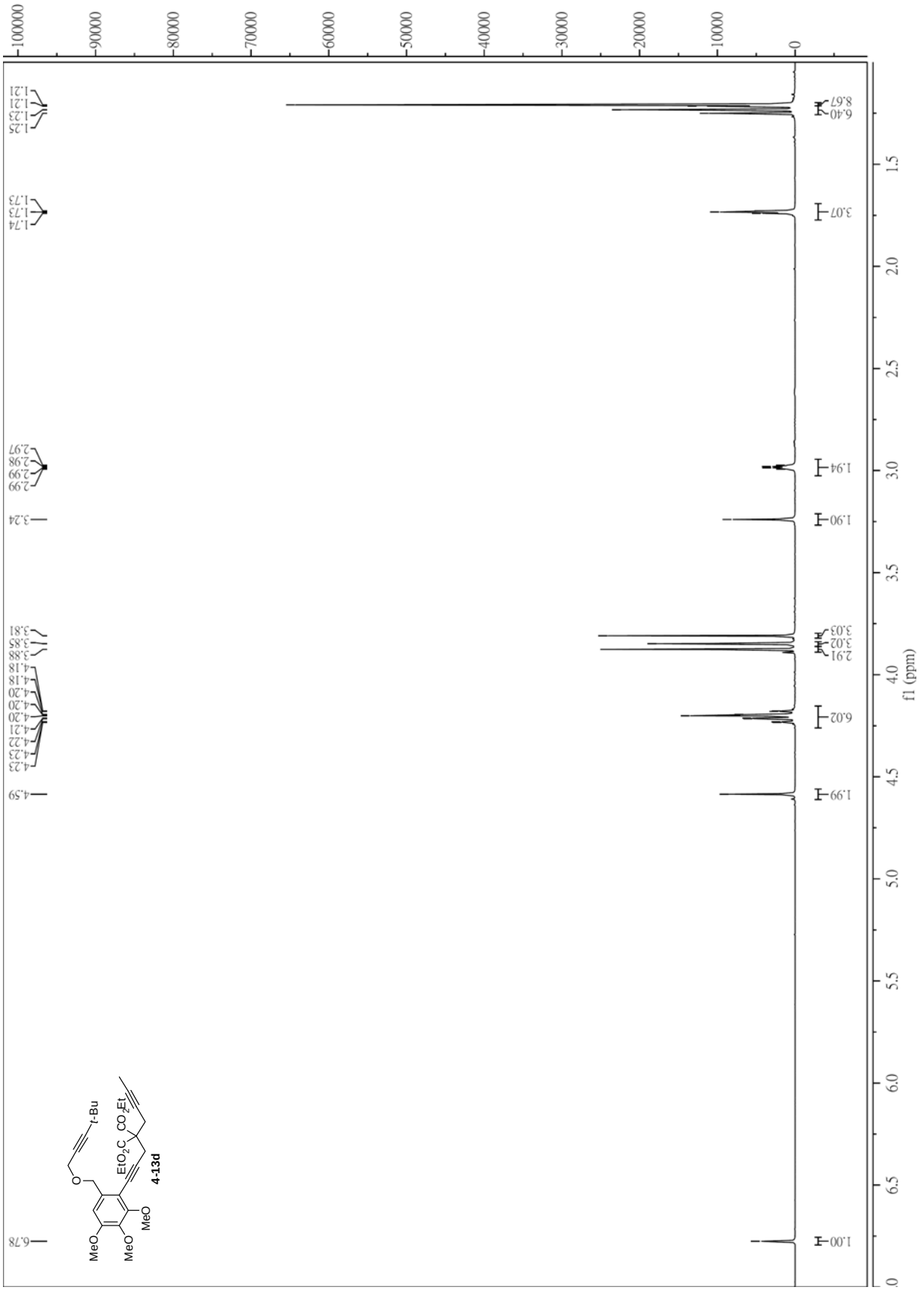
58.35
60.95
61.11
61.70
69.54
73.14
75.09
76.62
78.90
82.55
91.46
106.44
108.88
136.25
141.06
153.55
154.71
169.03
MeO
MeO
MeO
EtO2C
CO2Et
4-13c
f1 (ppm)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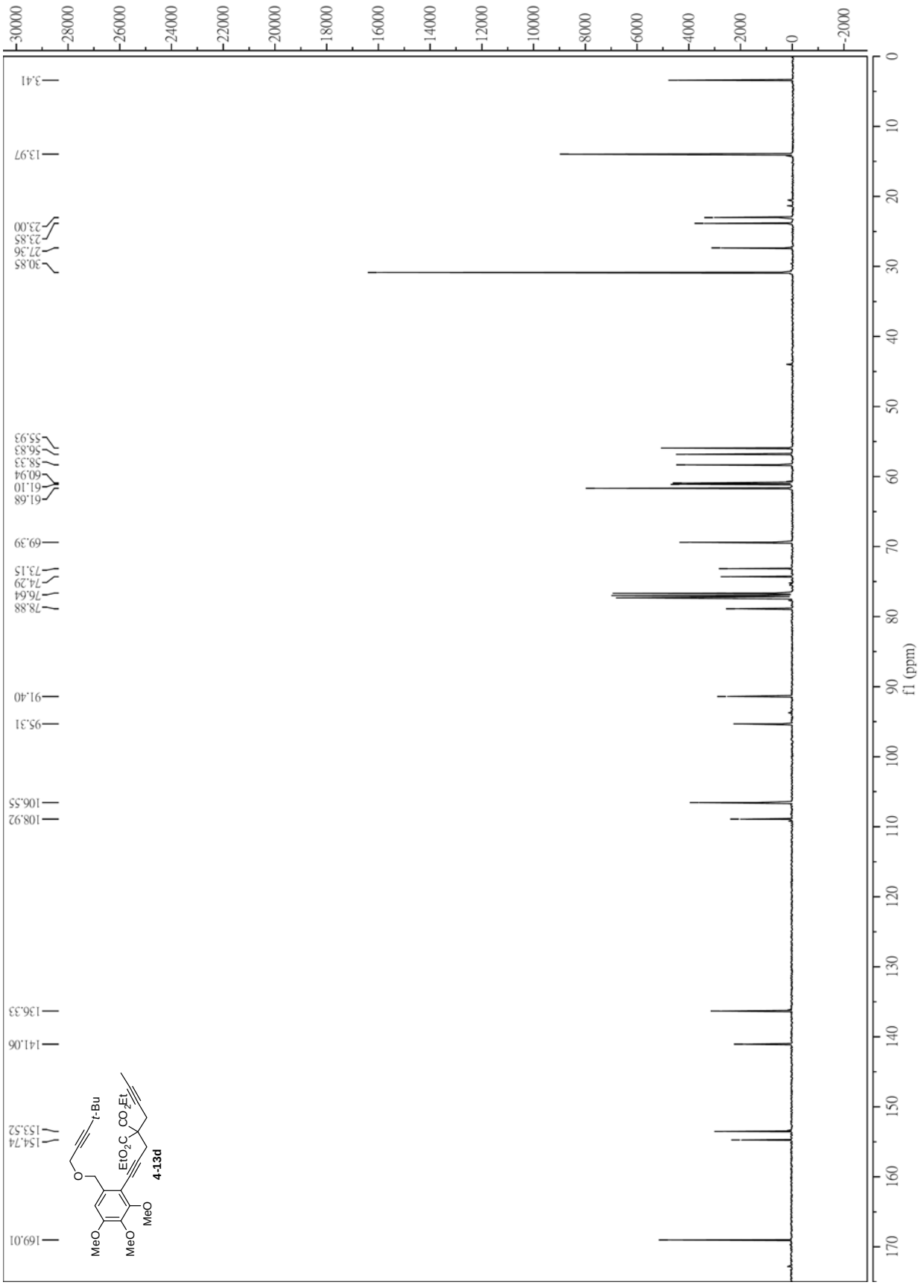
MeO
MeO
MeO
t-Bu
EtO2C
CO2Et
f1 (ppm)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30.85
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56.83
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60.94
61.10
61.68
69.39
73.15
74.29
76.64
78.88
91.40
95.31
106.55
108.92
136.33
141.06
153.52
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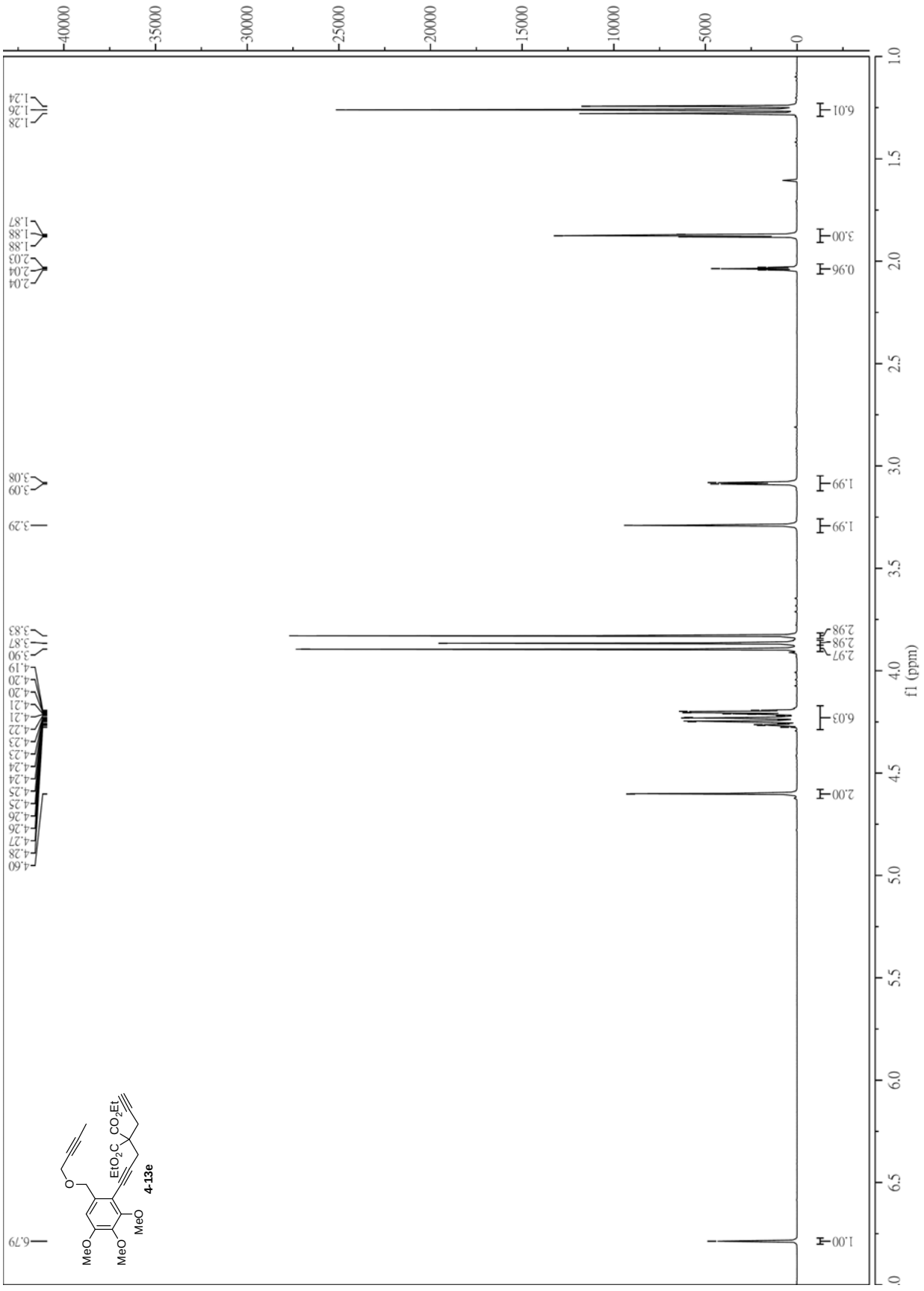
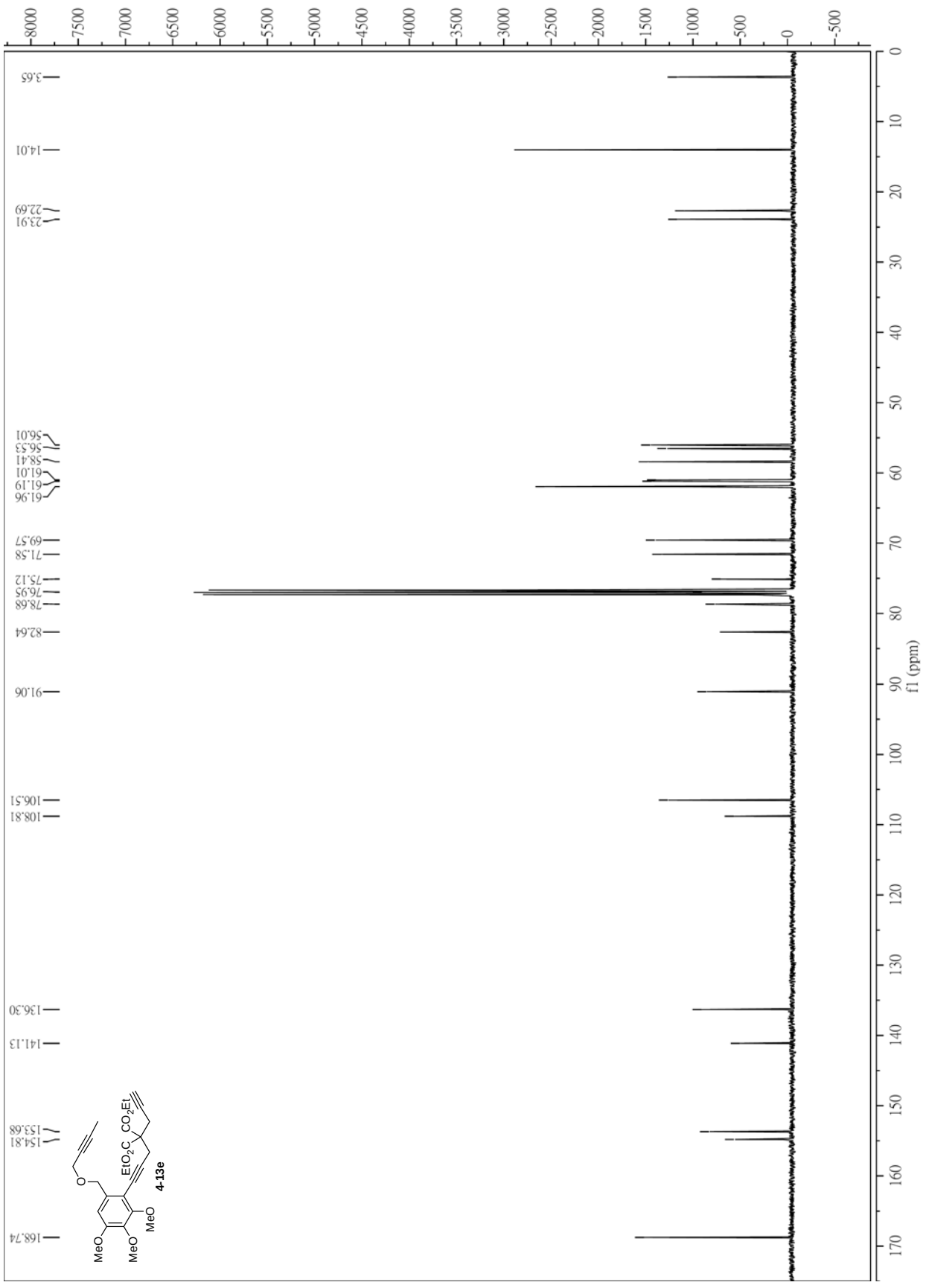
169.01
MeO
MeO
MeO
EtO2C
CO2Et
t-Bu
4-13d
f1 (ppm)


4-13e
f1 (ppm)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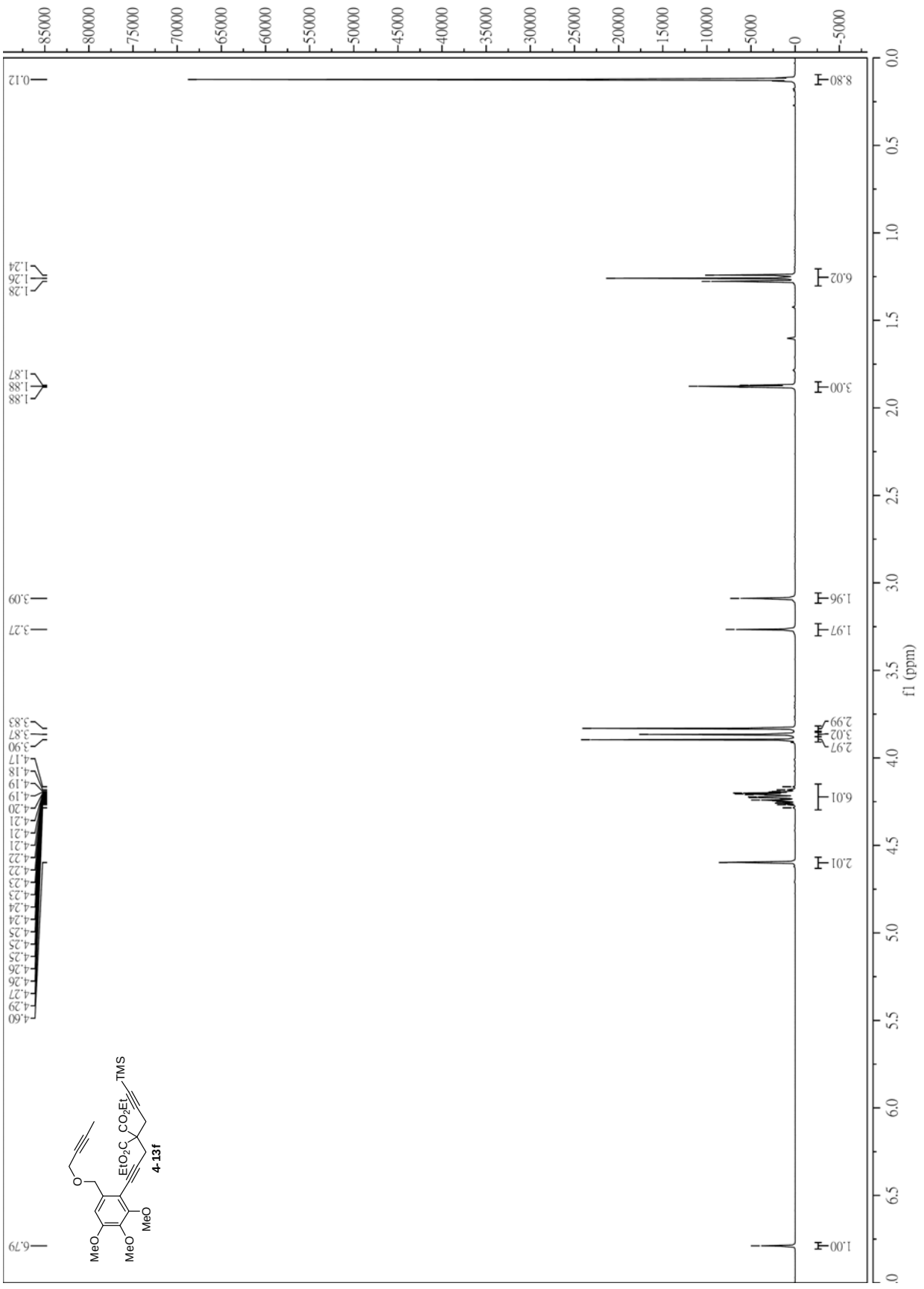
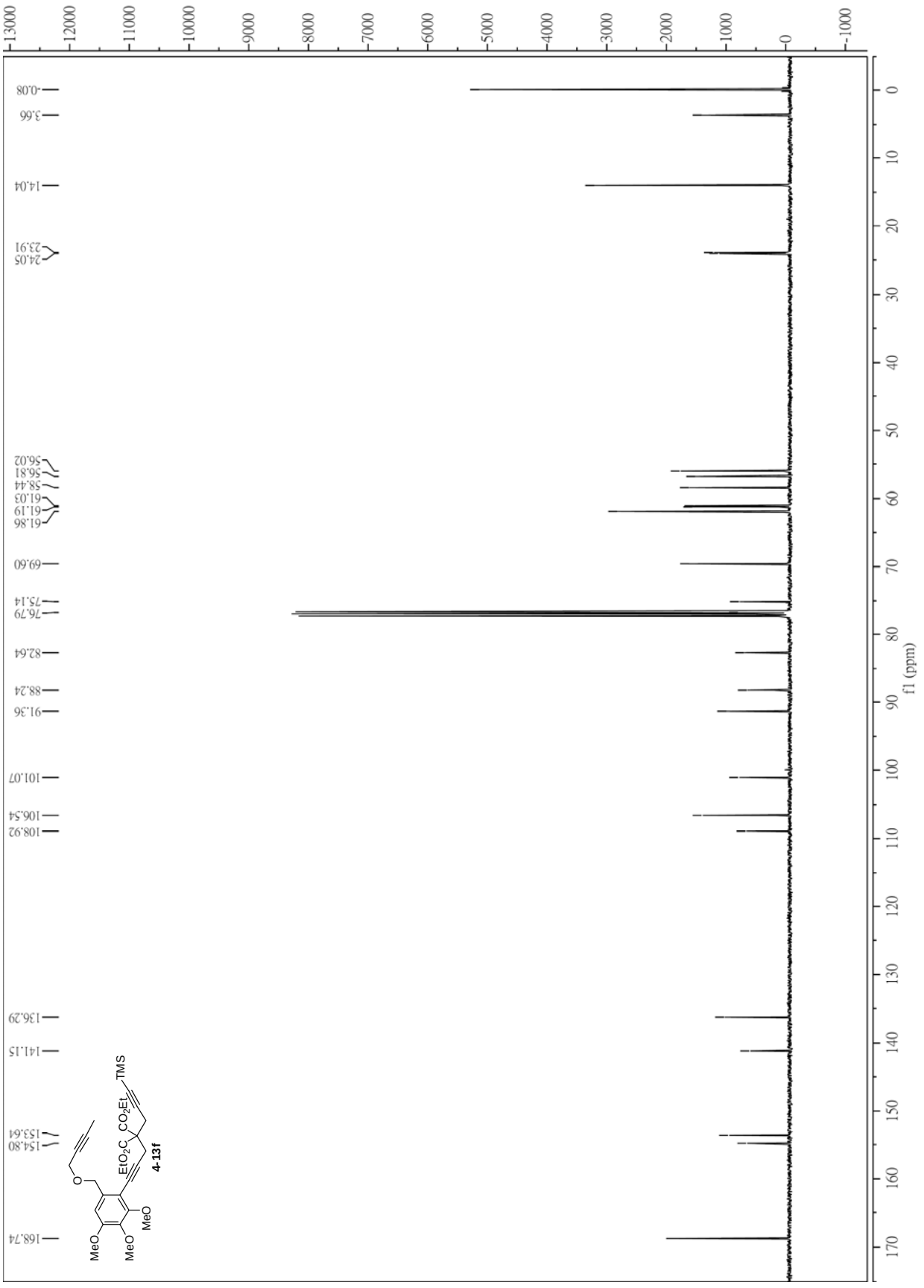
61.01
61.19
61.96
69.57
71.58
75.12
76.95
78.68
82.64
91.06
106.51
108.81
136.30
141.13
153.68
154.81
168.74
MeO
MeO
MeO
EtO2C
CO2Et
4-13e
f1 (ppm)


f1 (ppm)
4-13f
MeO
MeO
MeO
EtO2C
CO2Et
TMS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56.81
58.44
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61.19
61.86
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76.79
82.64
88.24
91.36
101.07
106.54
108.92
136.29
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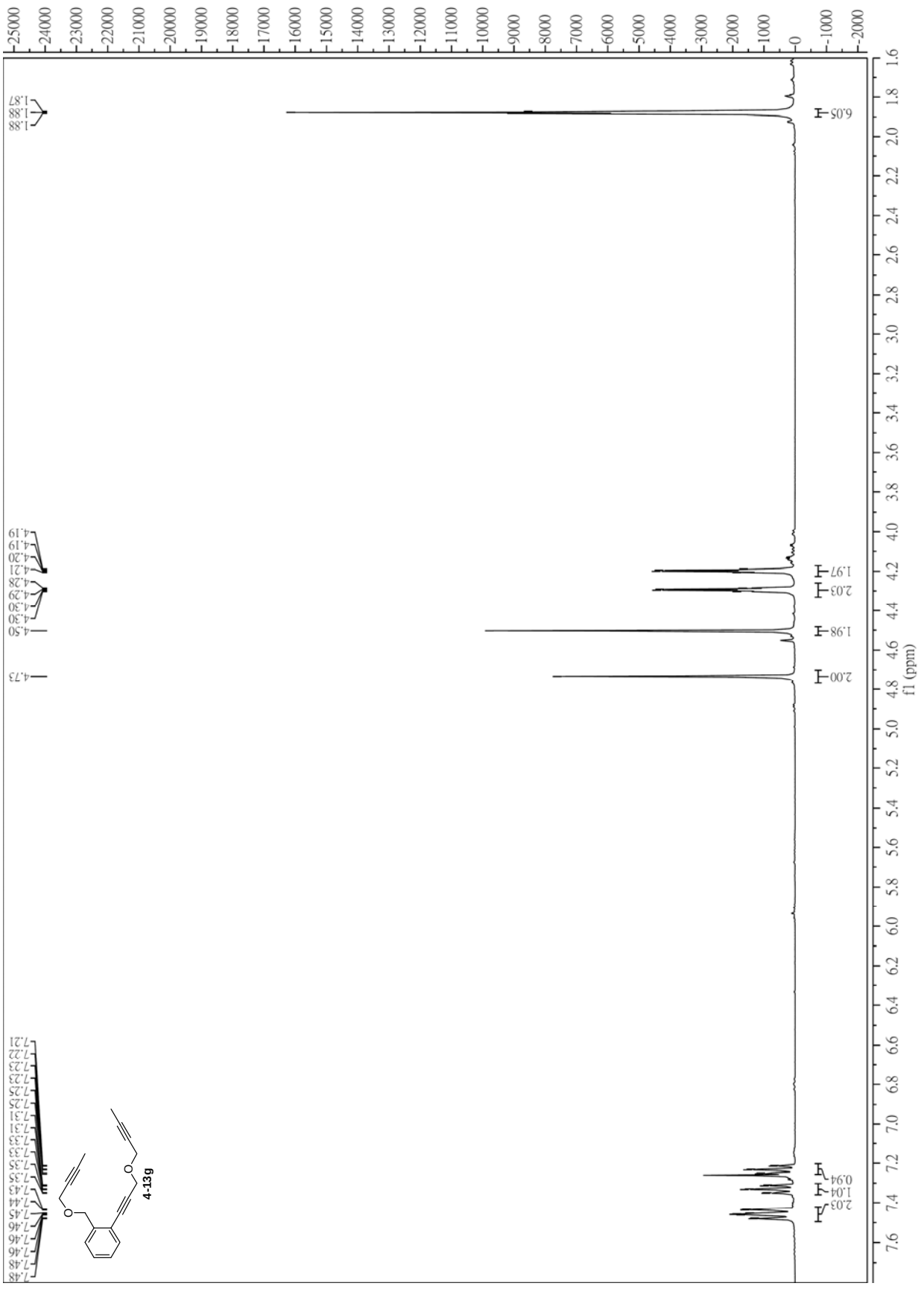
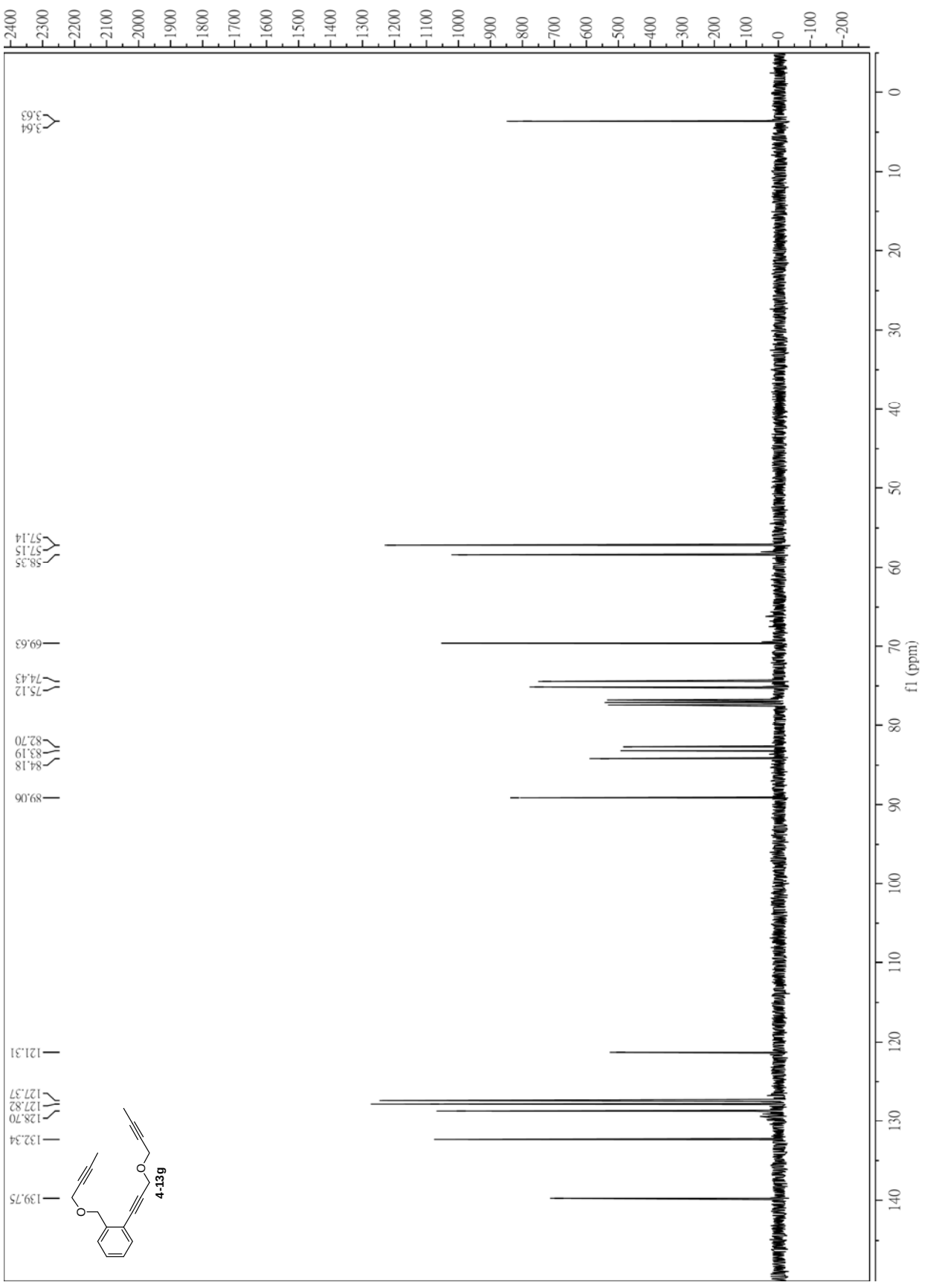
153.64
154.80
168.74
MeO
MeO
MeO
EtO2C
CO2Et
TMS
4-13f
f1 (ppm)


4-13g
f1 (ppm)


4-13g
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127.82
127.37
121.31
89.06
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83.19
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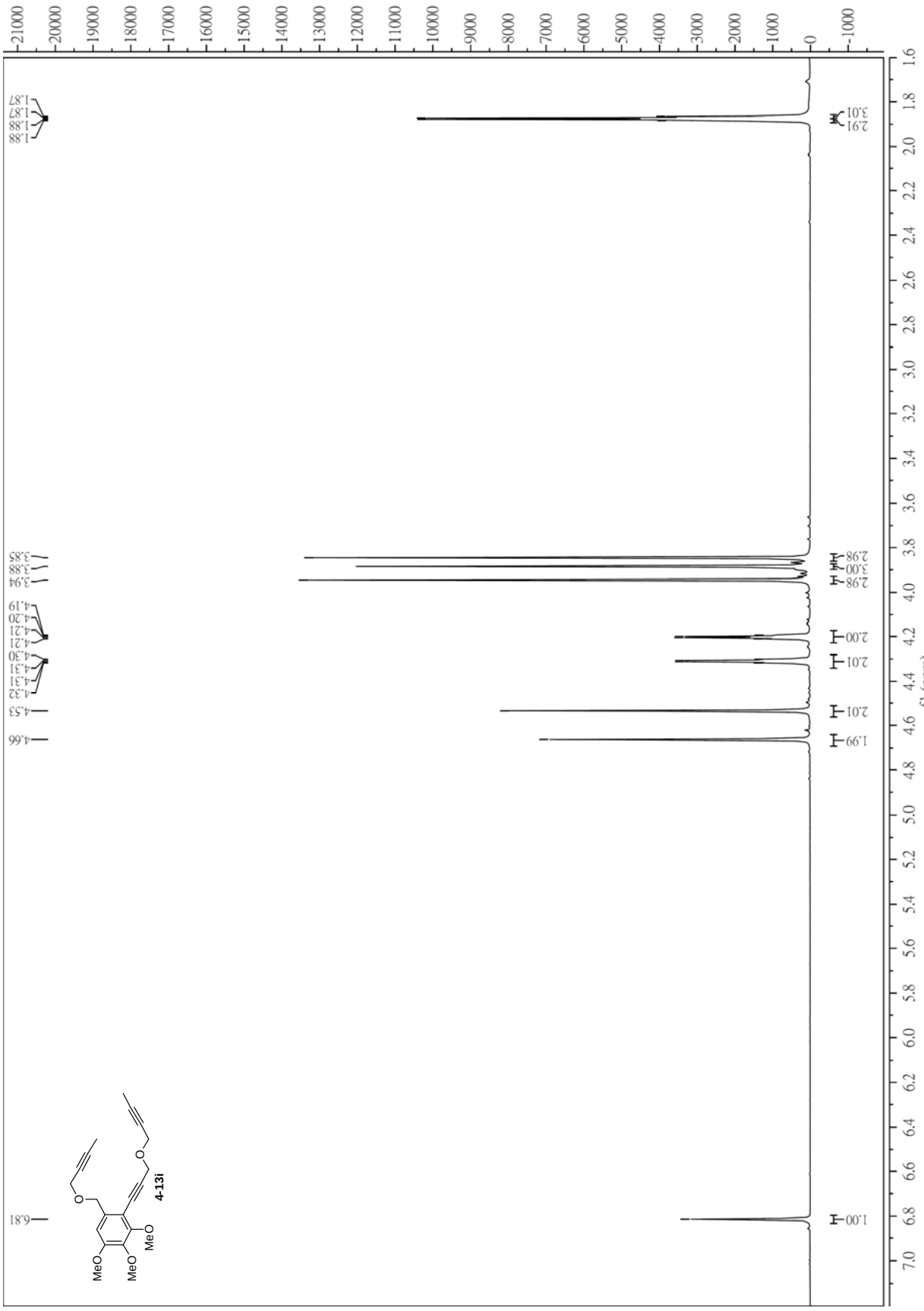
57.15
57.14
3.64
3.63
f1 (ppm)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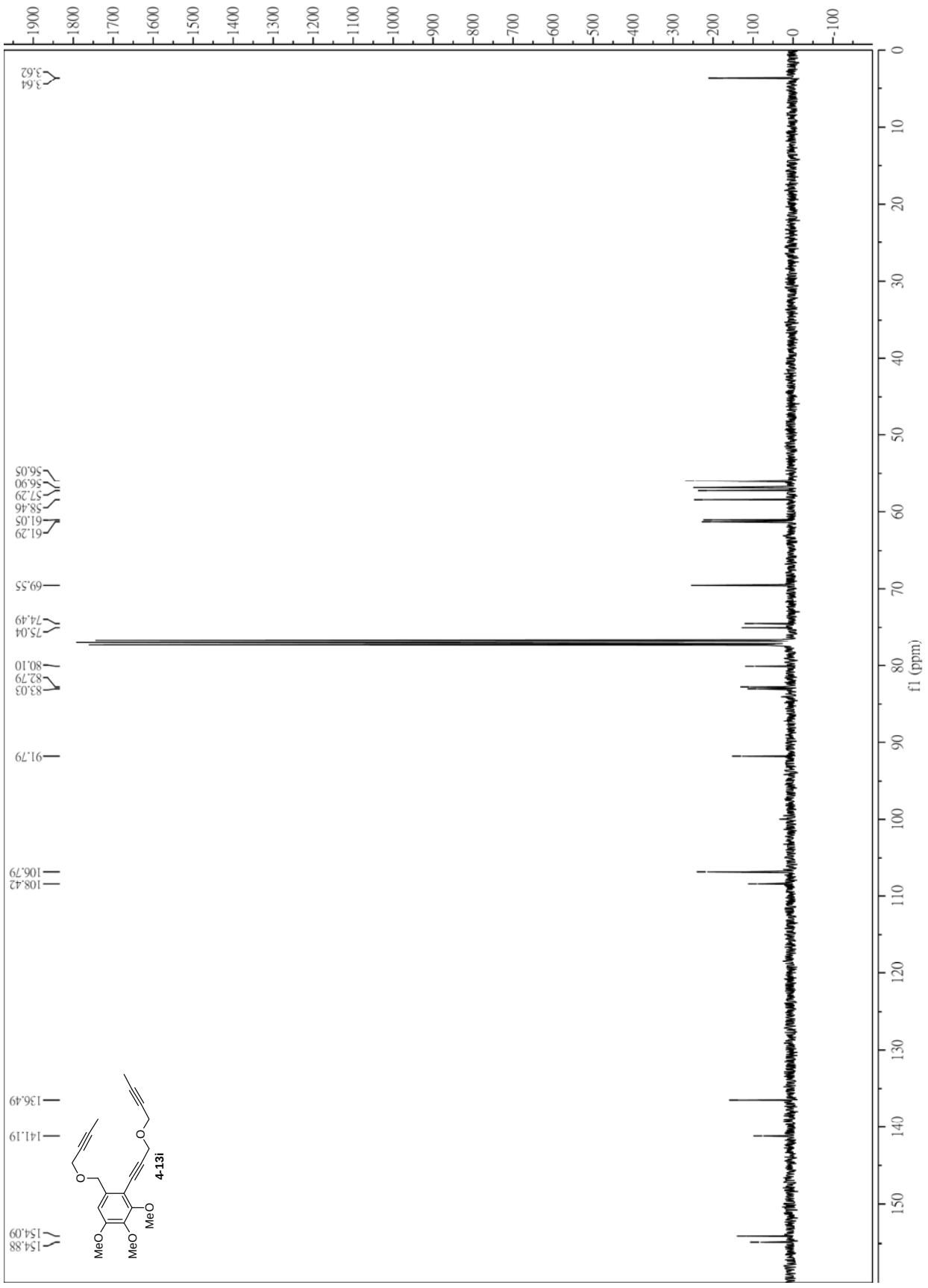
MeO
MeO
MeO
f1 (ppm)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58.46
61.05
61.29
69.55
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75.04
80.10
82.79
83.03
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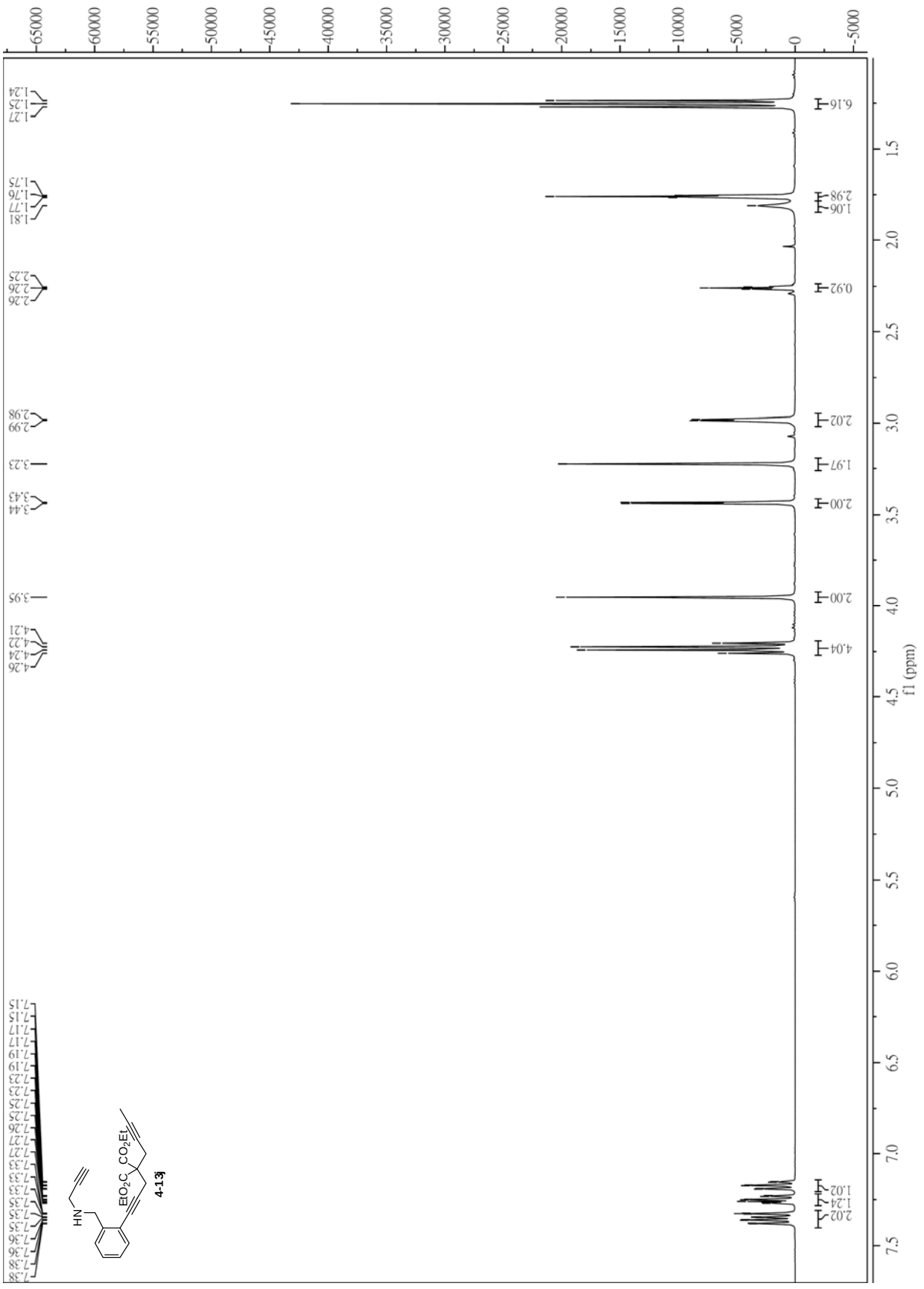
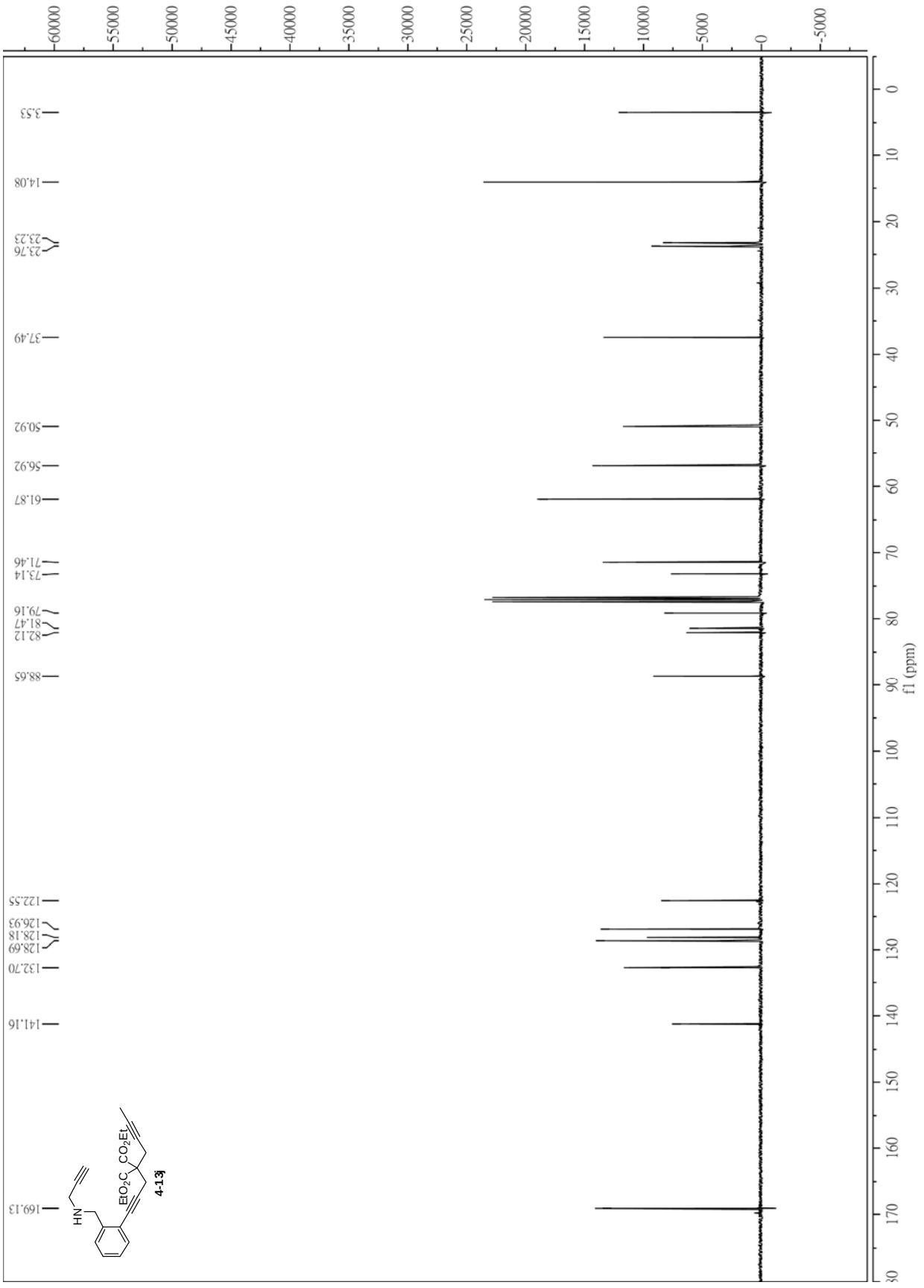
141.19
154.09
154.88
MeO
MeO
MeO
4-13i
f1 (ppm)


4-13j
f1 (ppm)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128.69
128.18
126.93
122.55
88.65
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79.16
73.14
71.46
61.87
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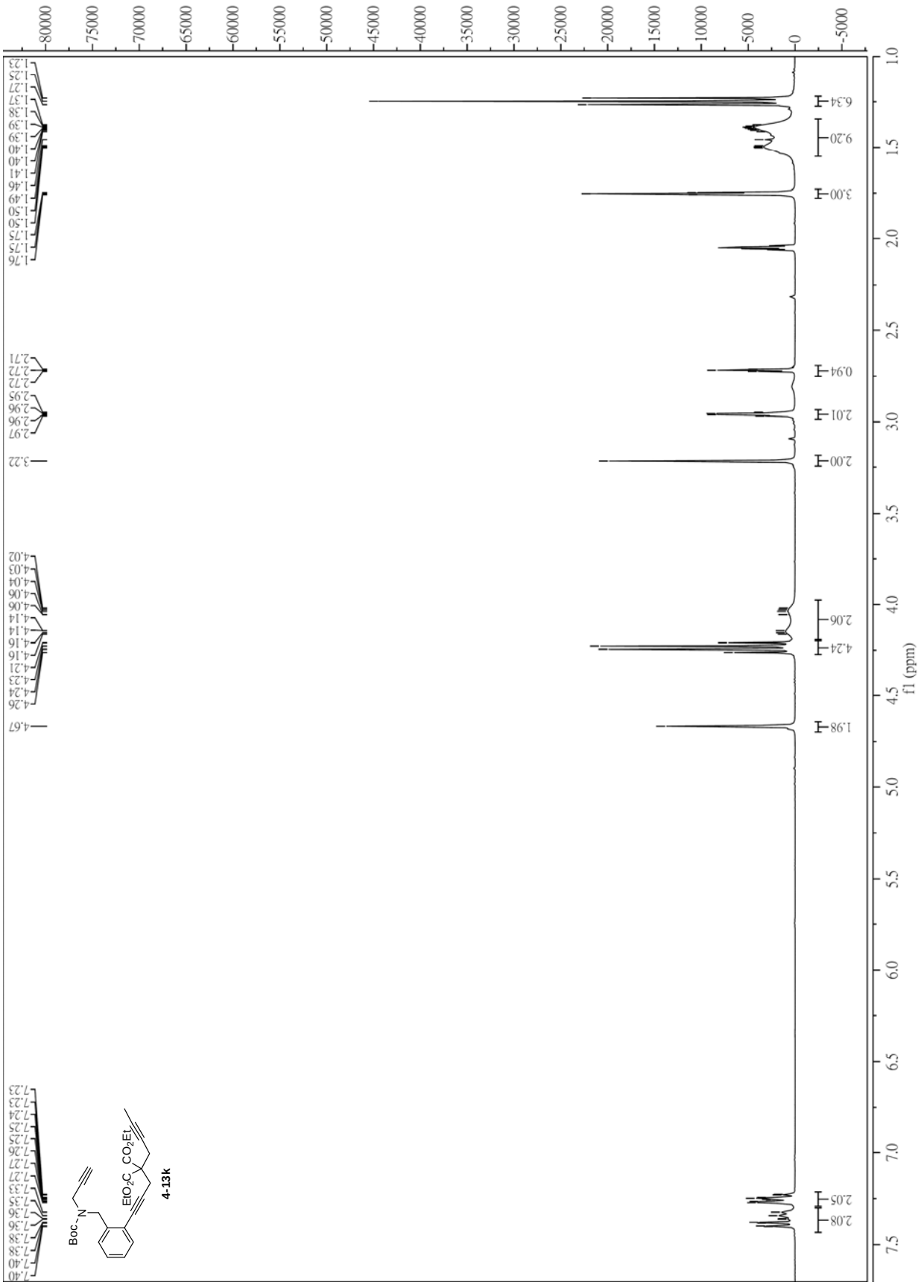
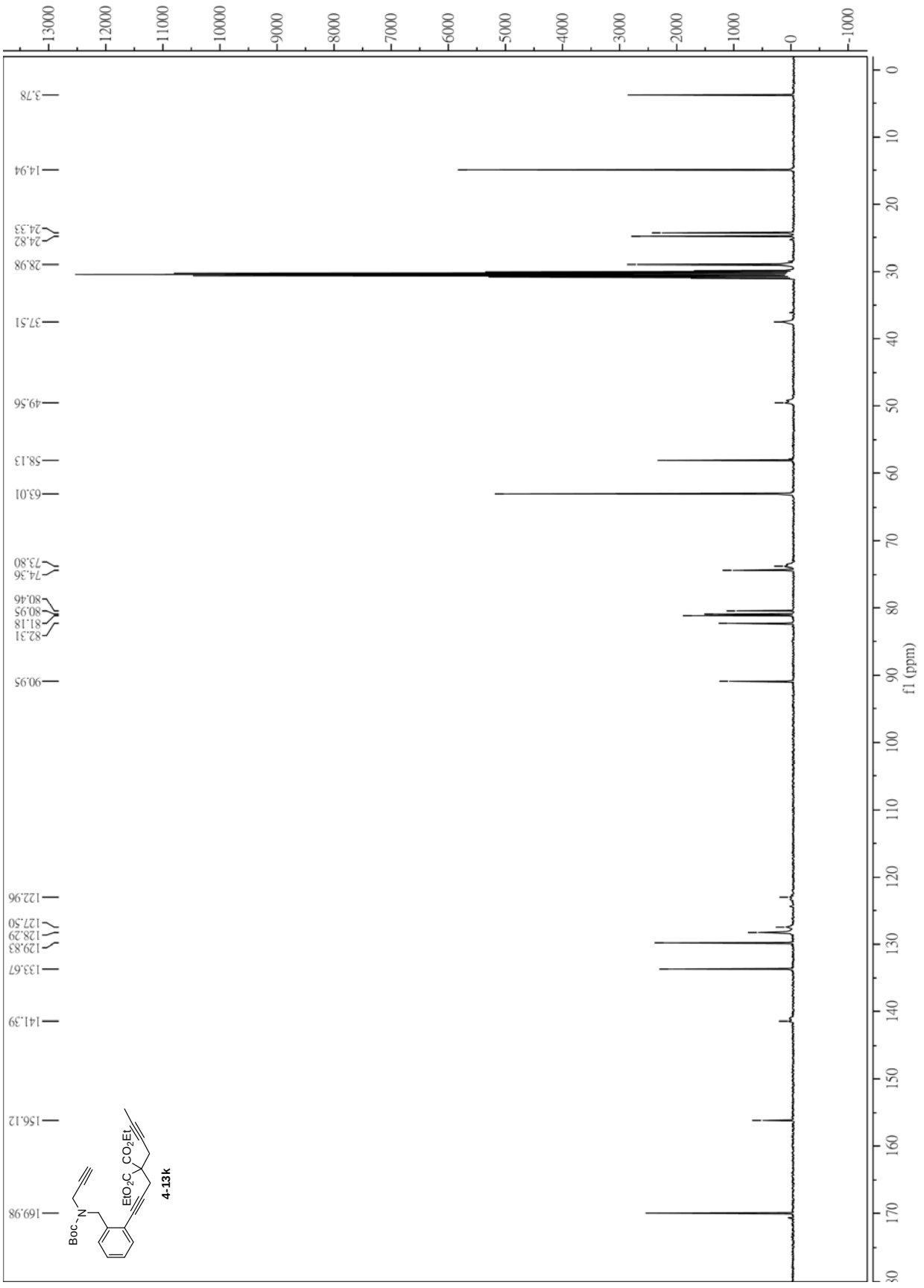
23.76
23.23
14.08
3.53
HN
EtO2C
CO2Et
4-13j
f1 (ppm)


Boc
N
EtO2C
CO2Et
4-13k
f1 (ppm)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82.31
90.95
122.96
127.50
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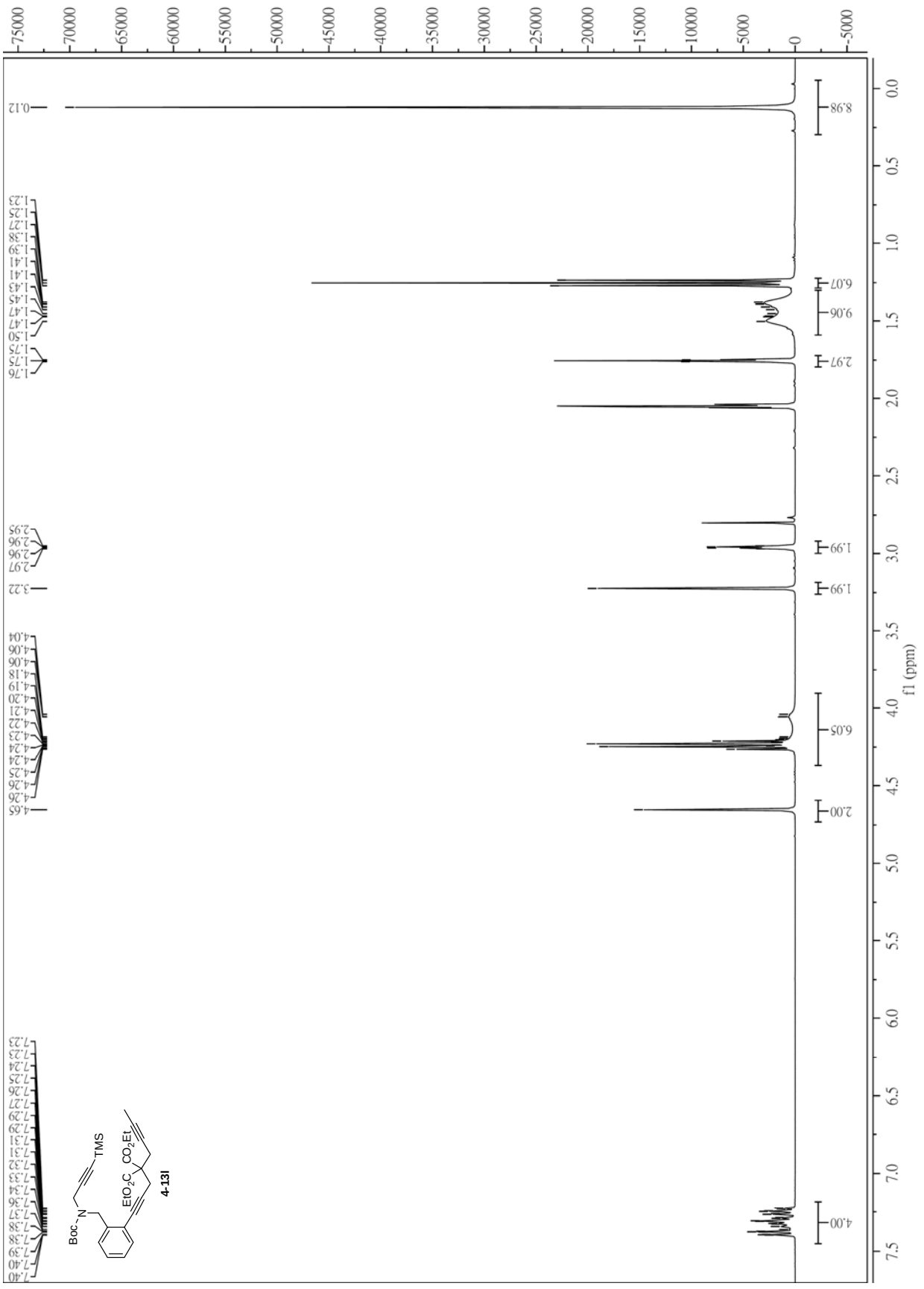
EtO2C
CO2Et
4-13k
f1 (ppm)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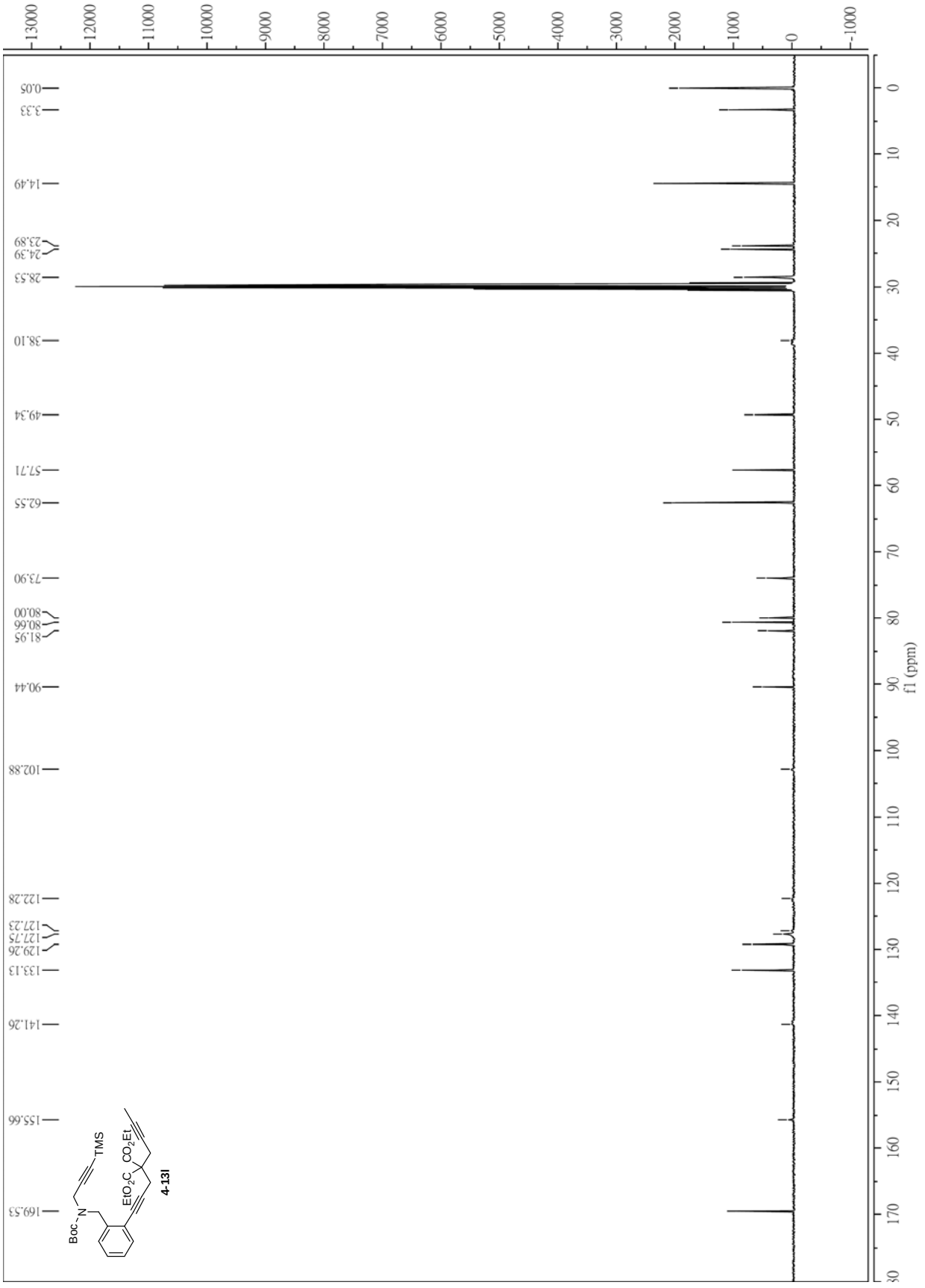
f1 (ppm)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127.75
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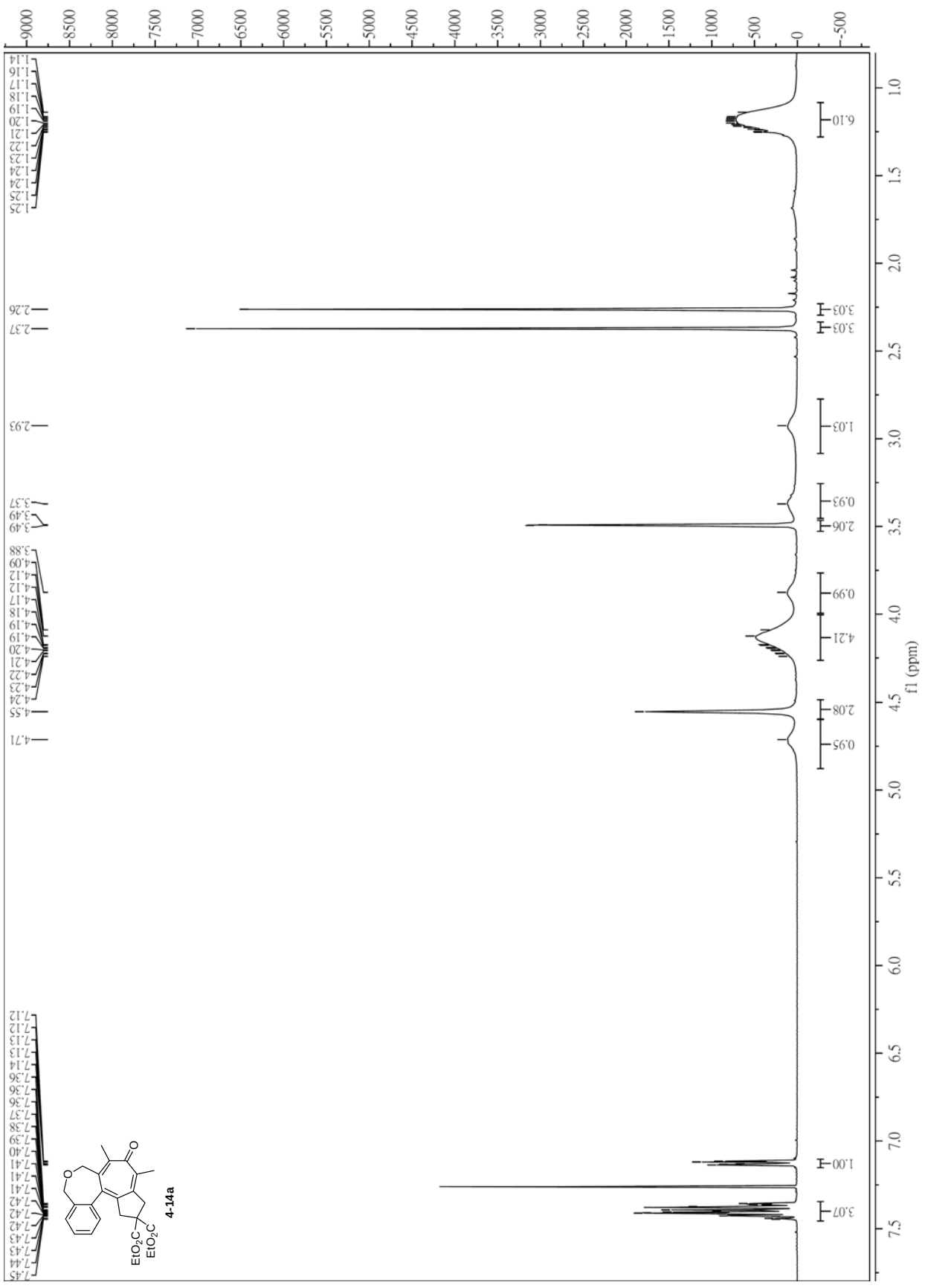
EtO2C
CO2Et
4-13l
f1 (ppm)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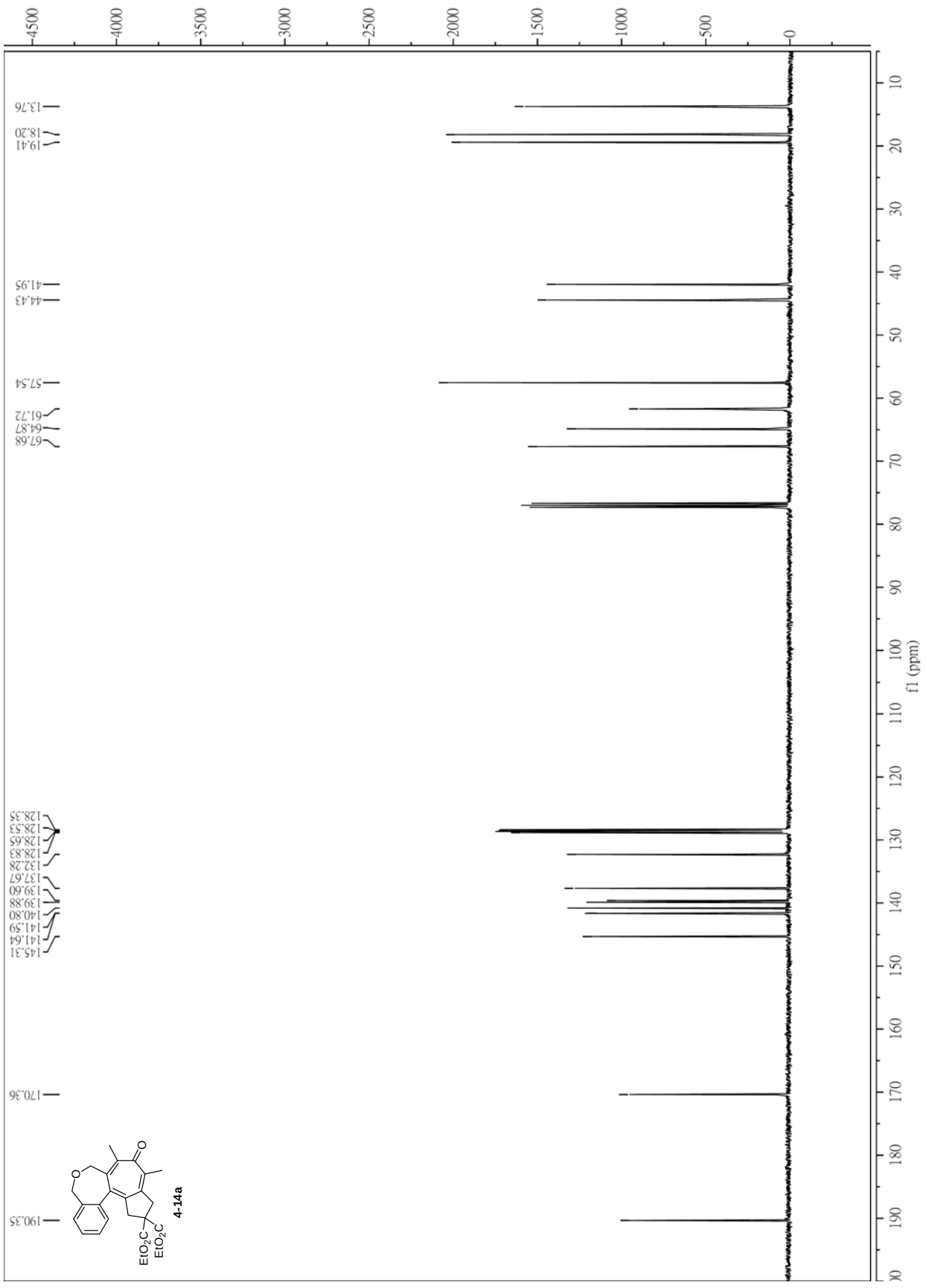
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128.83
132.28
137.67
139.60
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141.64
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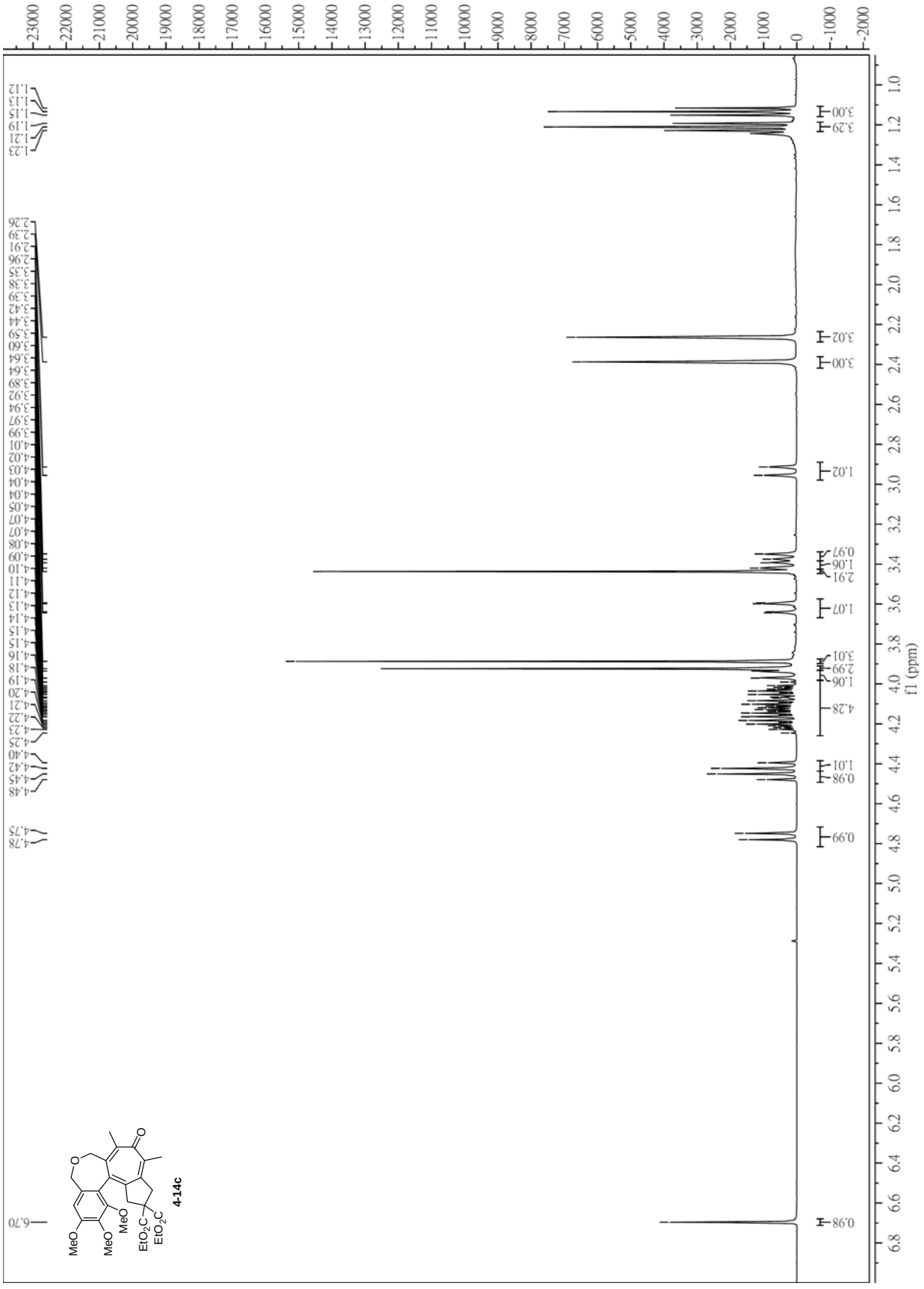
190.35
EtO2C
EtO2C
4-14a
f1 (ppm)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EtO2C
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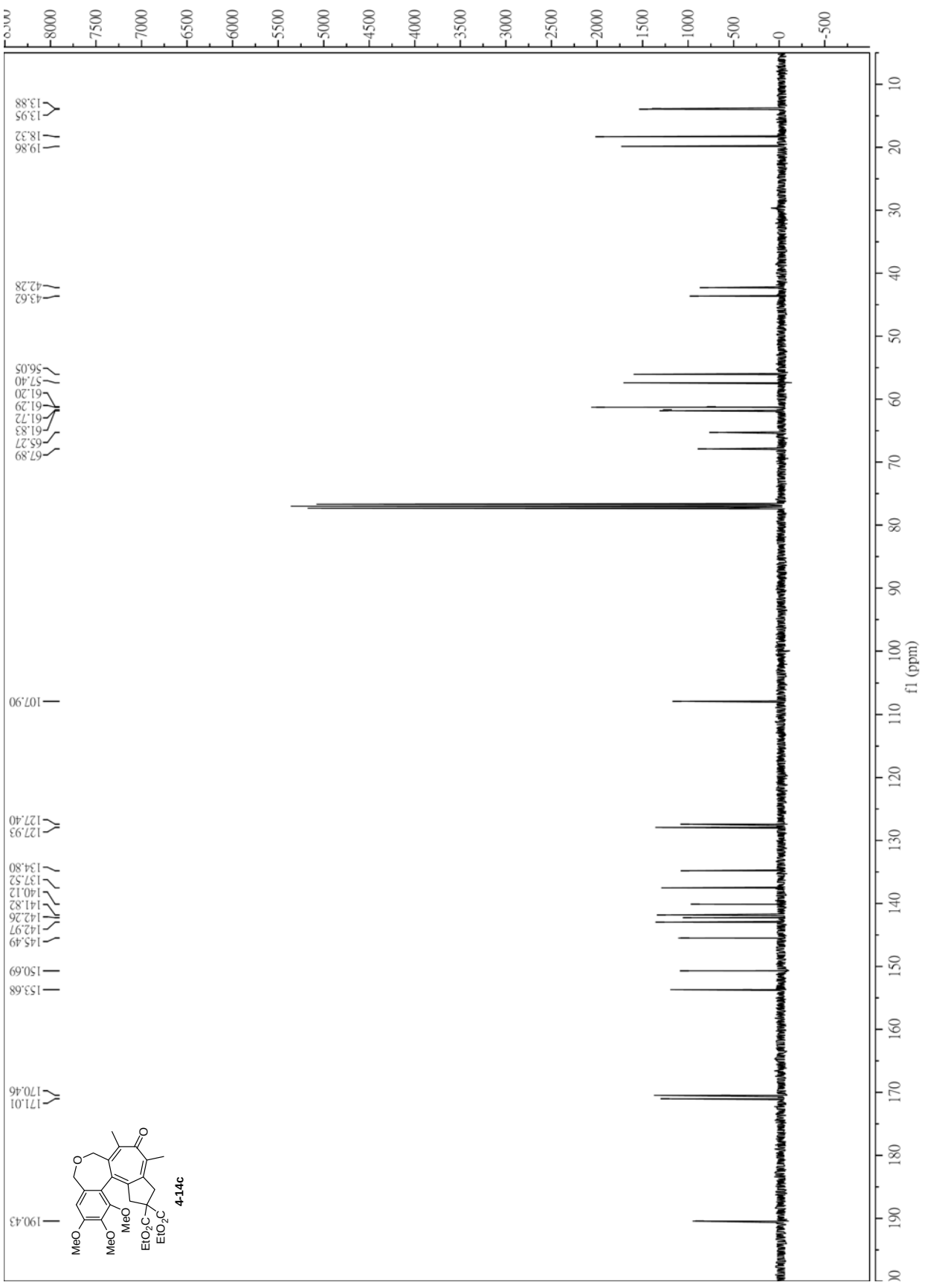
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137.52
140.12
141.82
142.26
142.97
145.49
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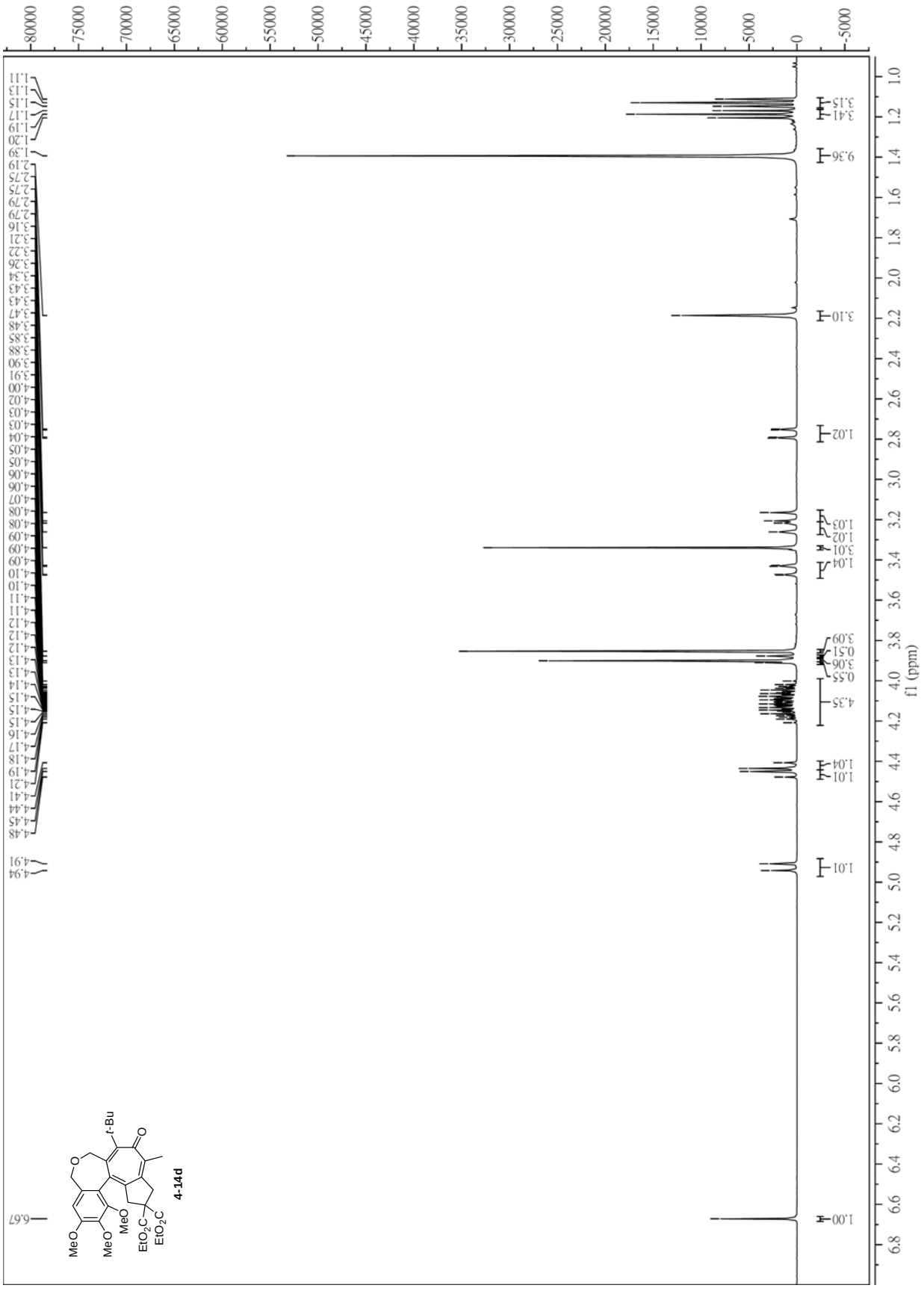
EtO2C
EtO2C
4-14c
f1 (ppm)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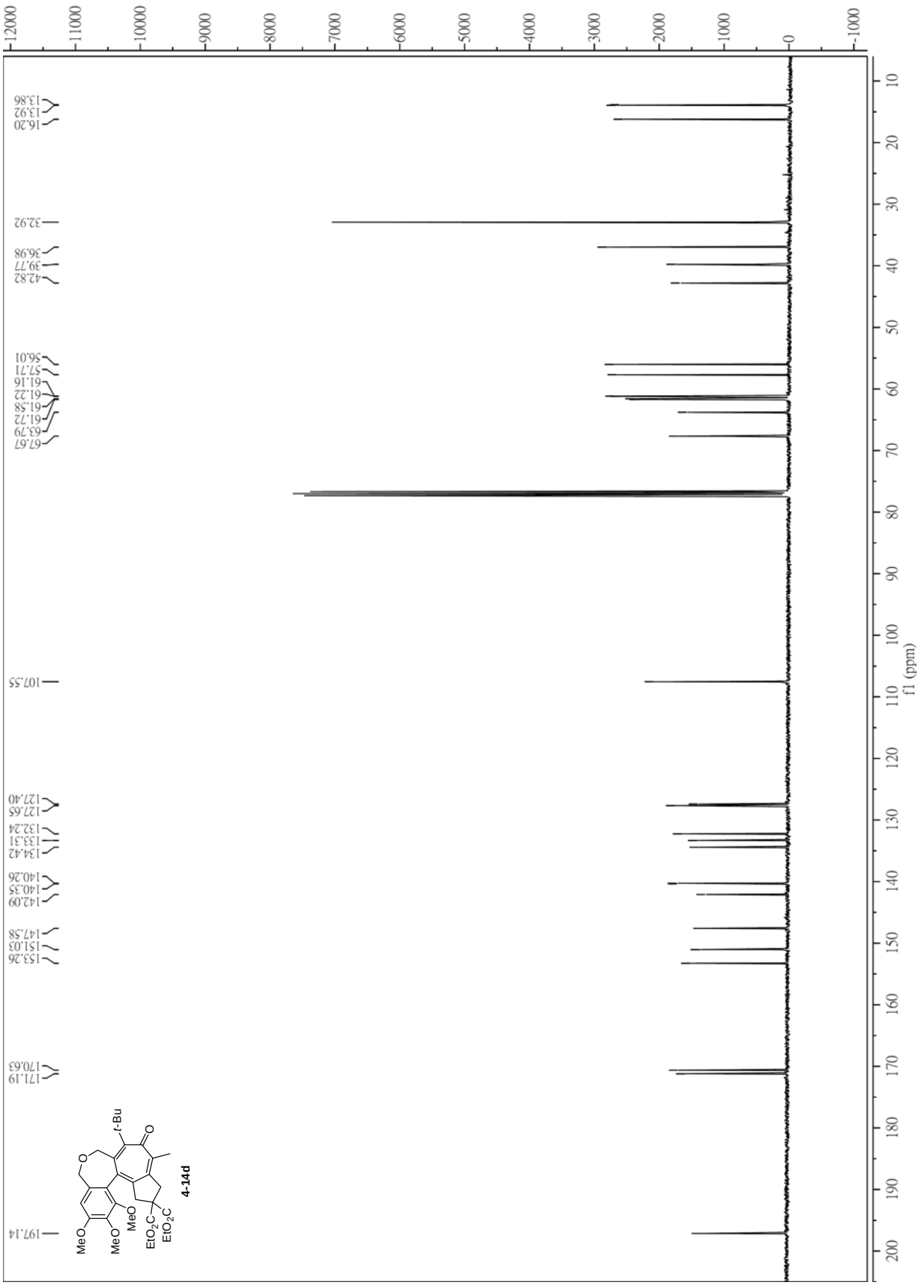
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127.40
107.55
67.67
63.79
61.72
61.58
61.22
61.16
57.71
56.01
42.82
39.77
36.98
32.92
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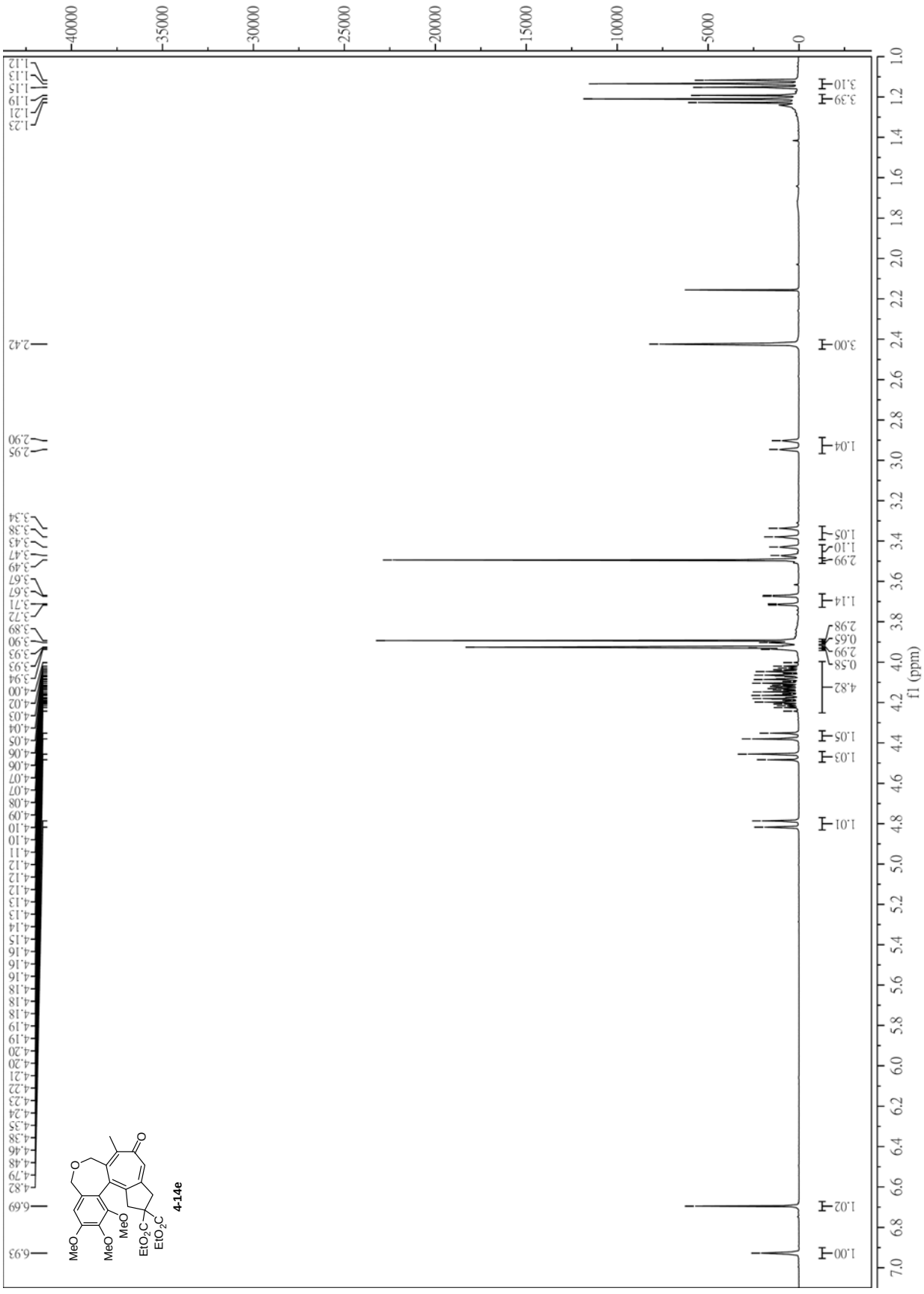
EtO2C
t-Bu
O
O
4-14d
f1 (ppm)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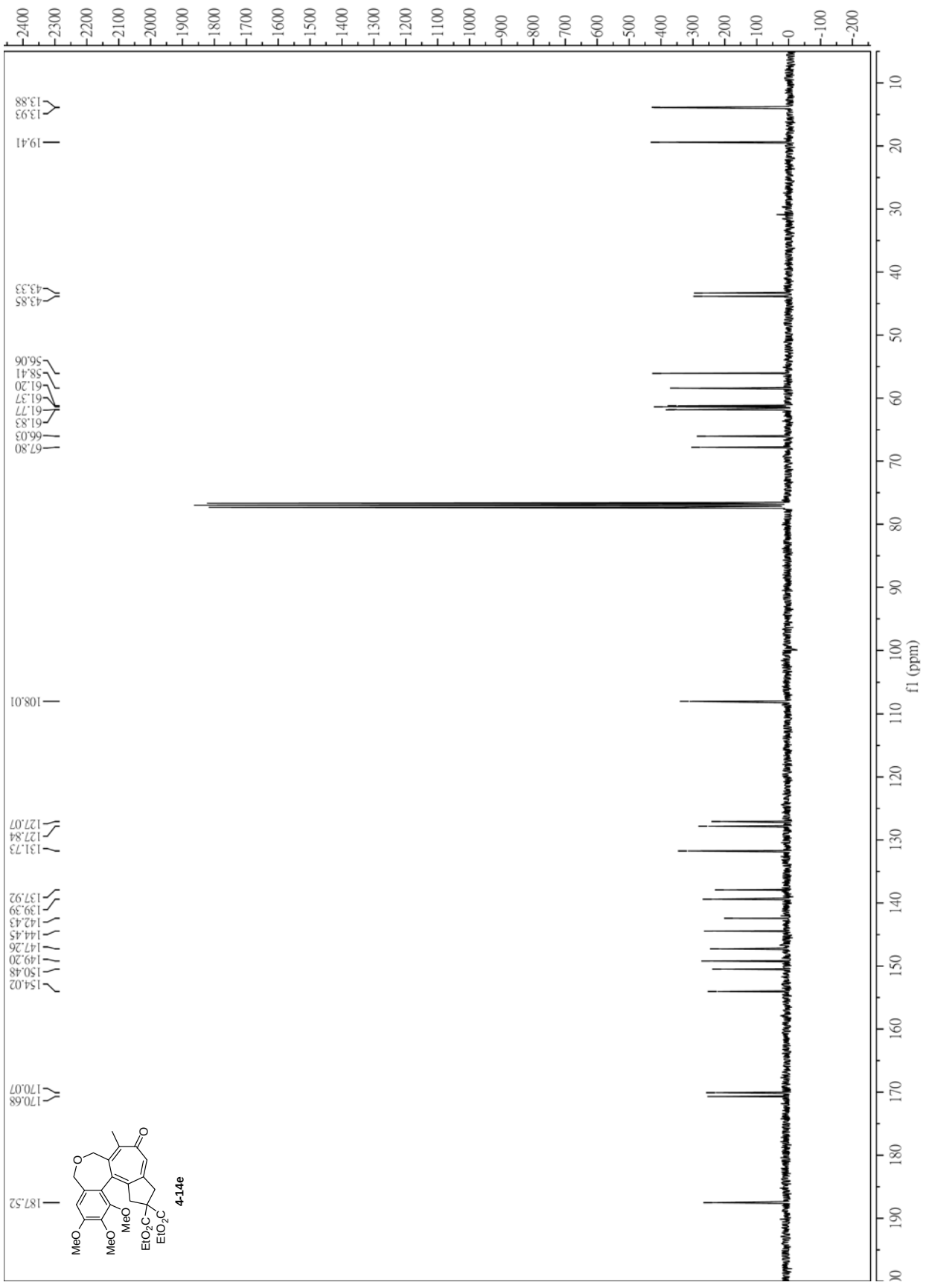
4-14e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139.39
142.43
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147.26
149.20
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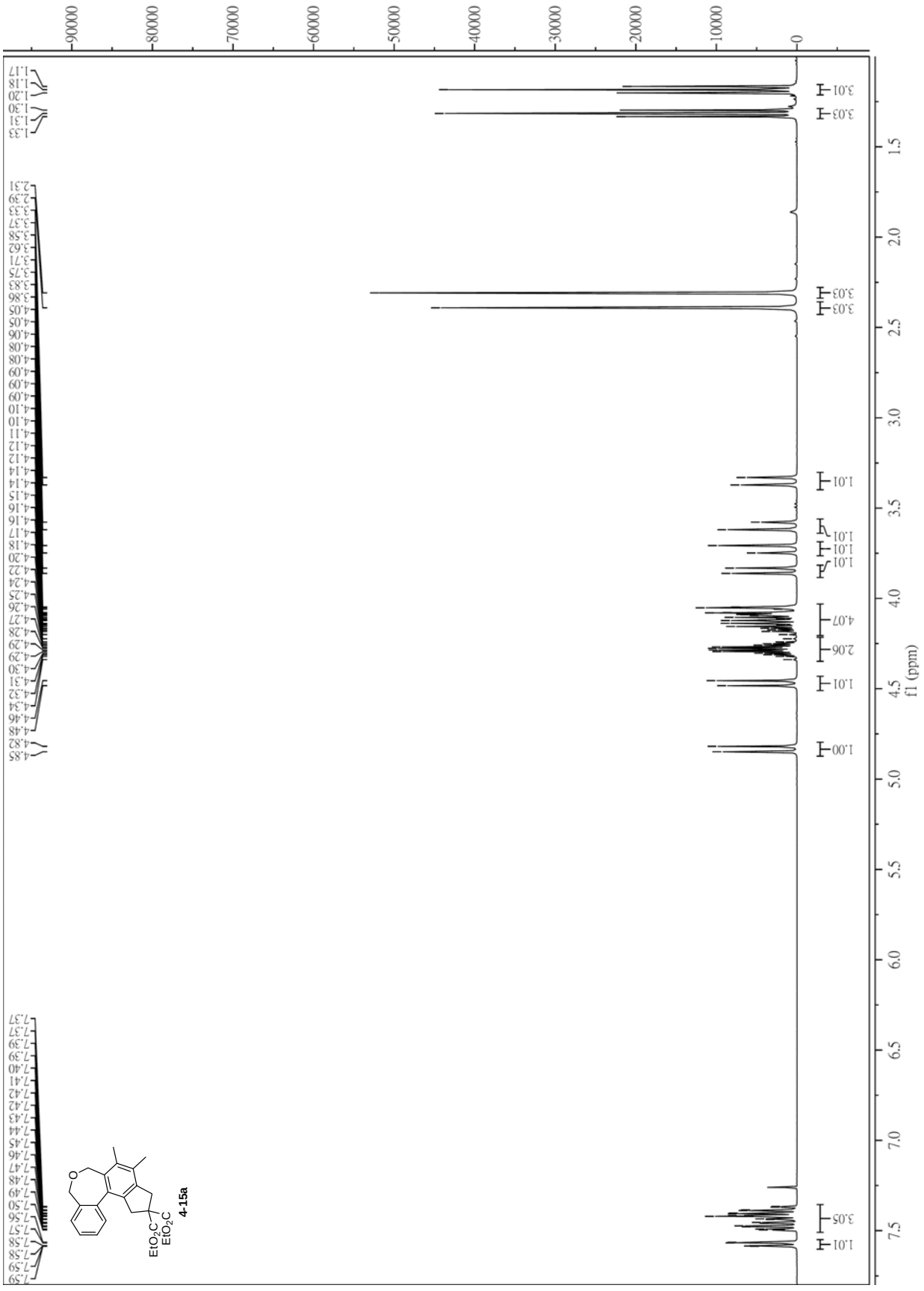
MeO
MeO
EtO2C
EtO2C
4-14e
f1 (ppm)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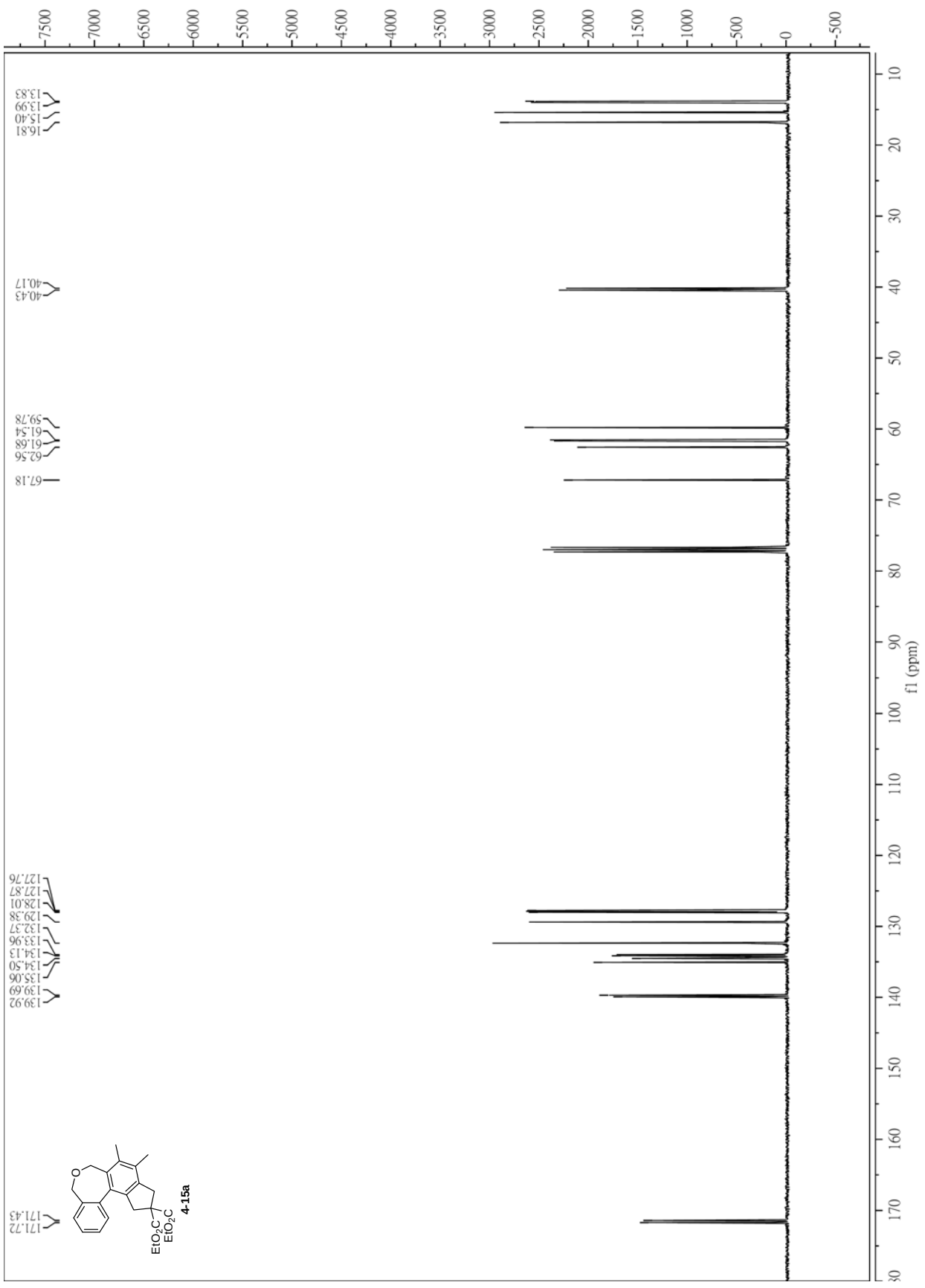
f1 (ppm)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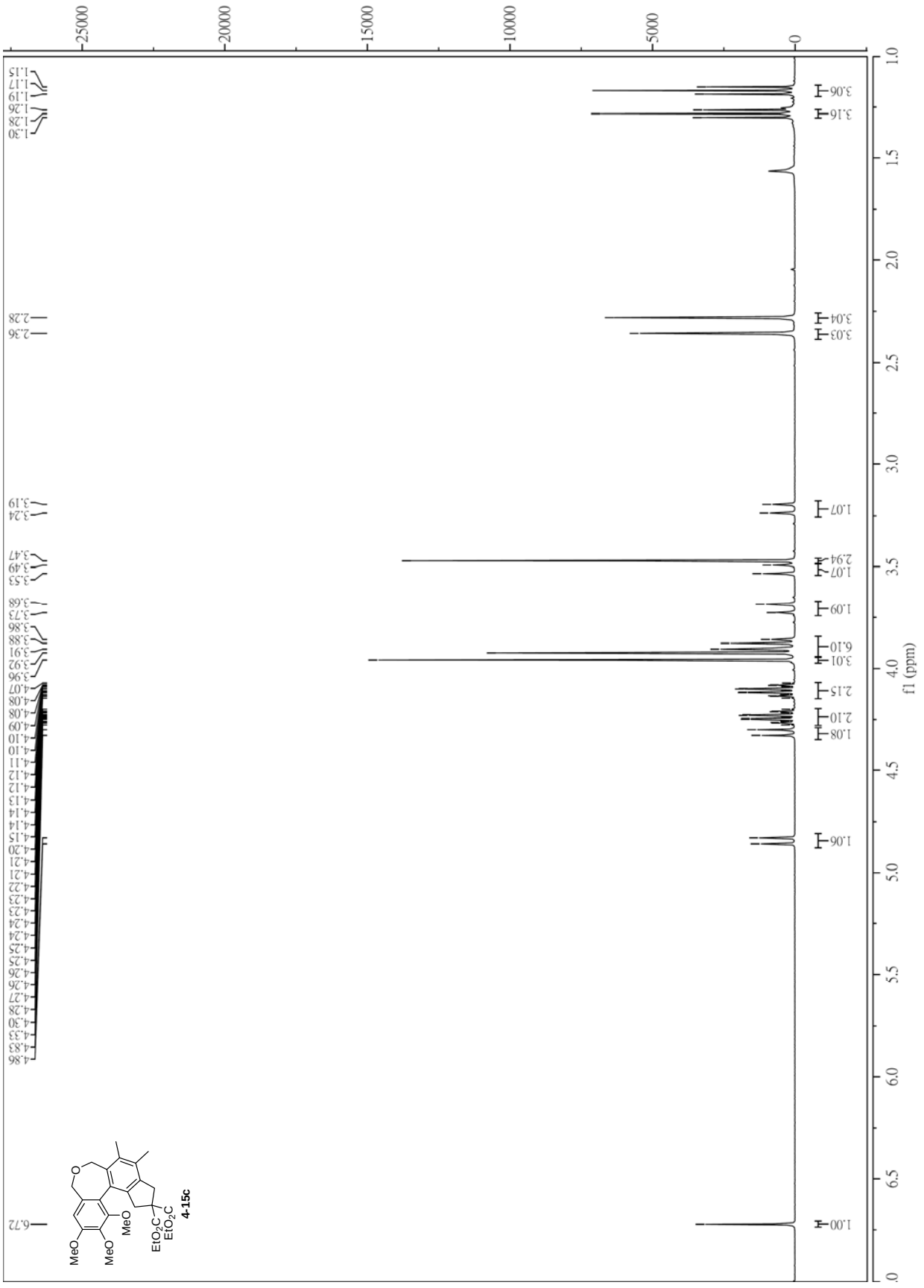
EtO2C
EtO2C
4-15a
f1 (ppm)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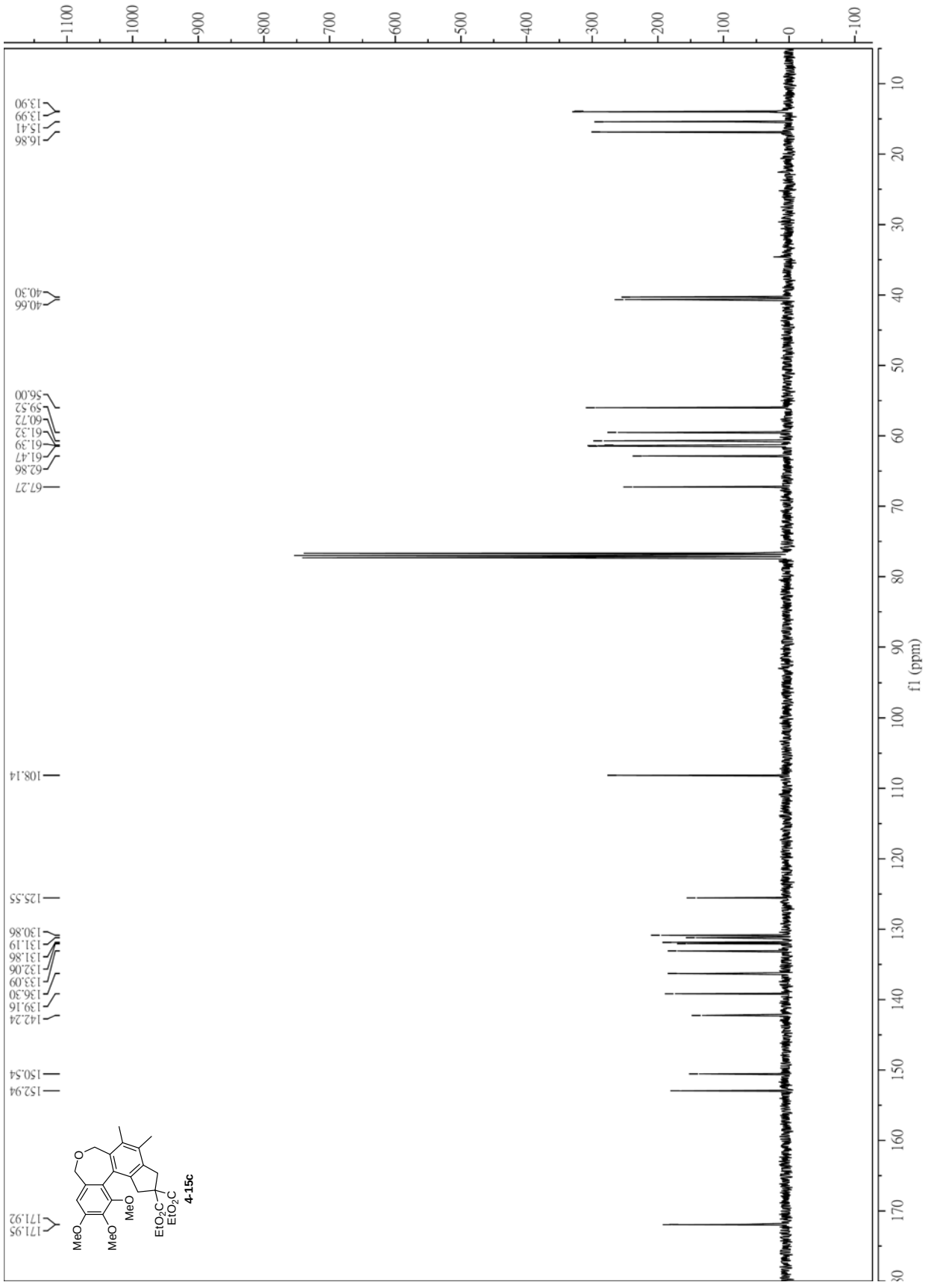
4-15c
f1 (ppm)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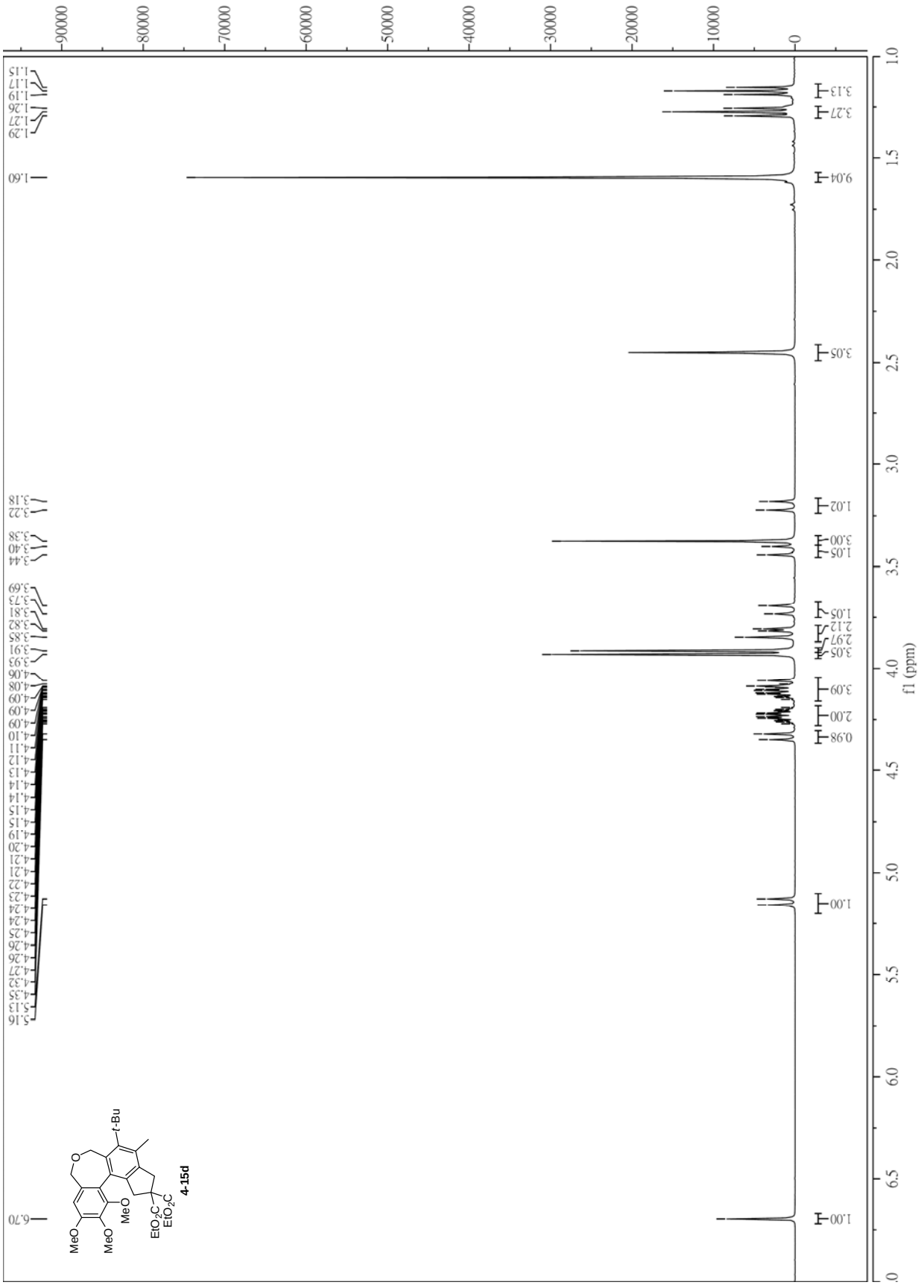
MeO
EtO2C
EtO2C
4-15c
f1 (ppm)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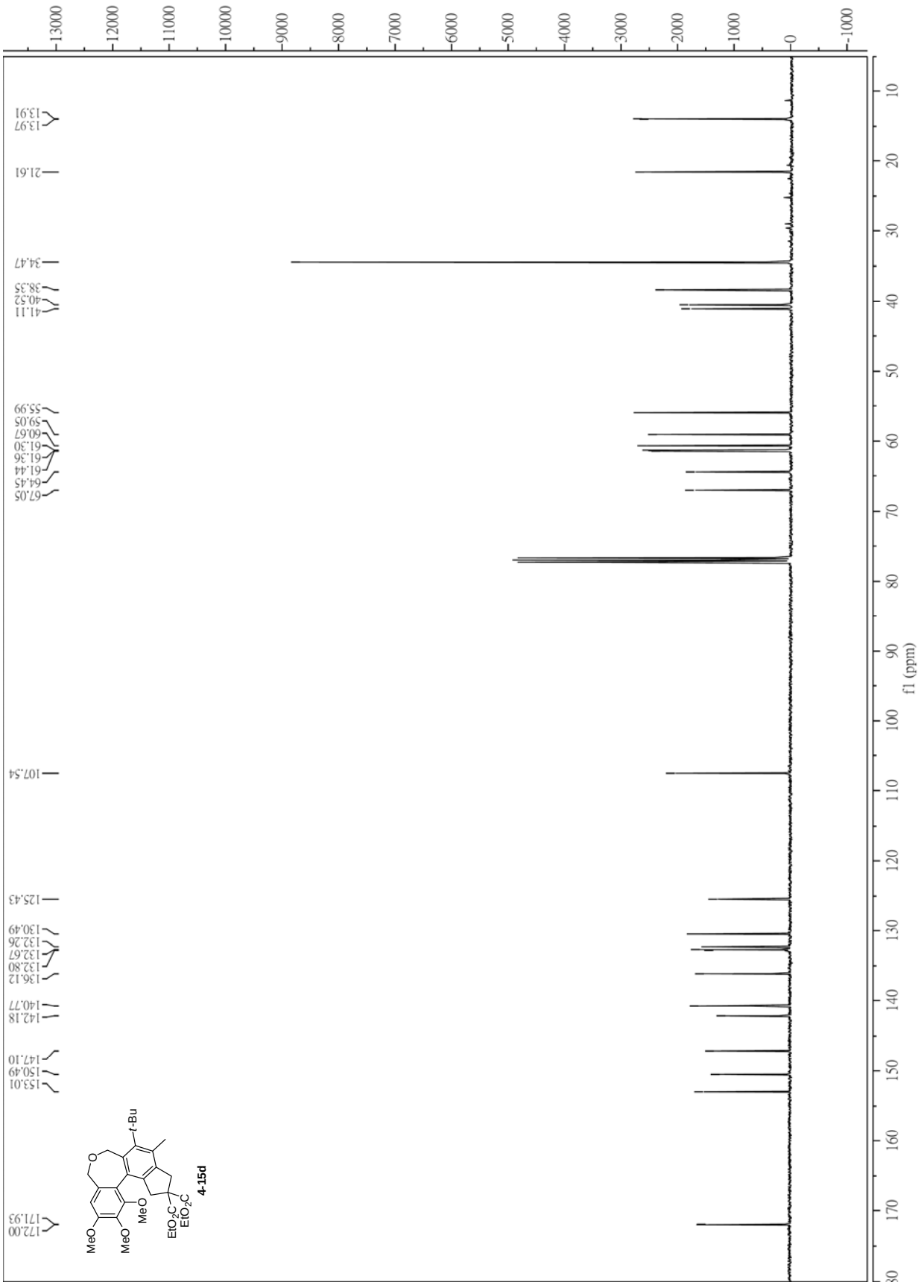
EtO2C
EtO2C
t-Bu
4-15d
f1 (ppm)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61.36
61.30
60.67
59.05
55.99
41.11
40.52
38.35
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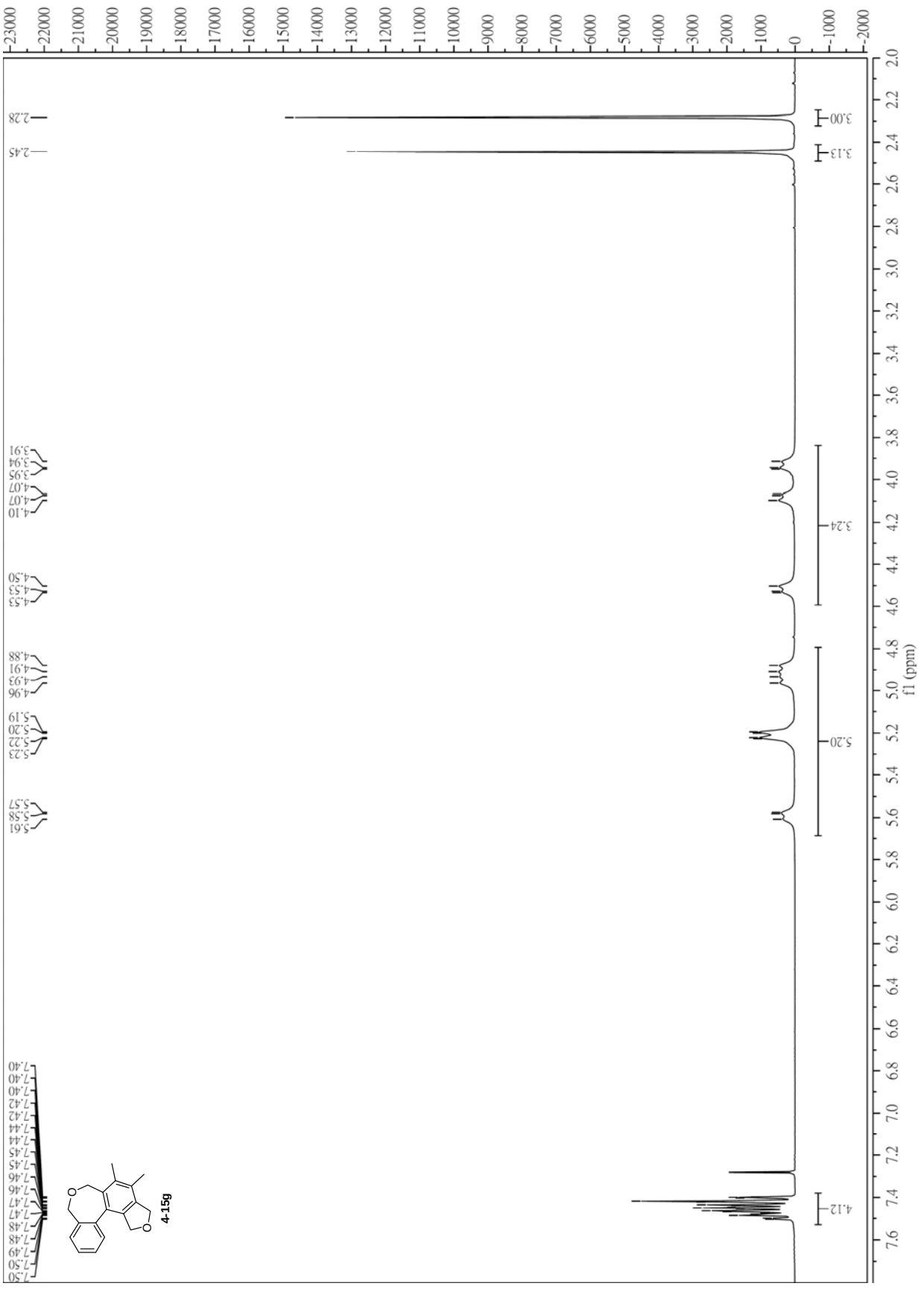
13.91
MeO
MeO
MeO
t-Bu
EtO2C
EtO2C
4-15d
f1 (ppm)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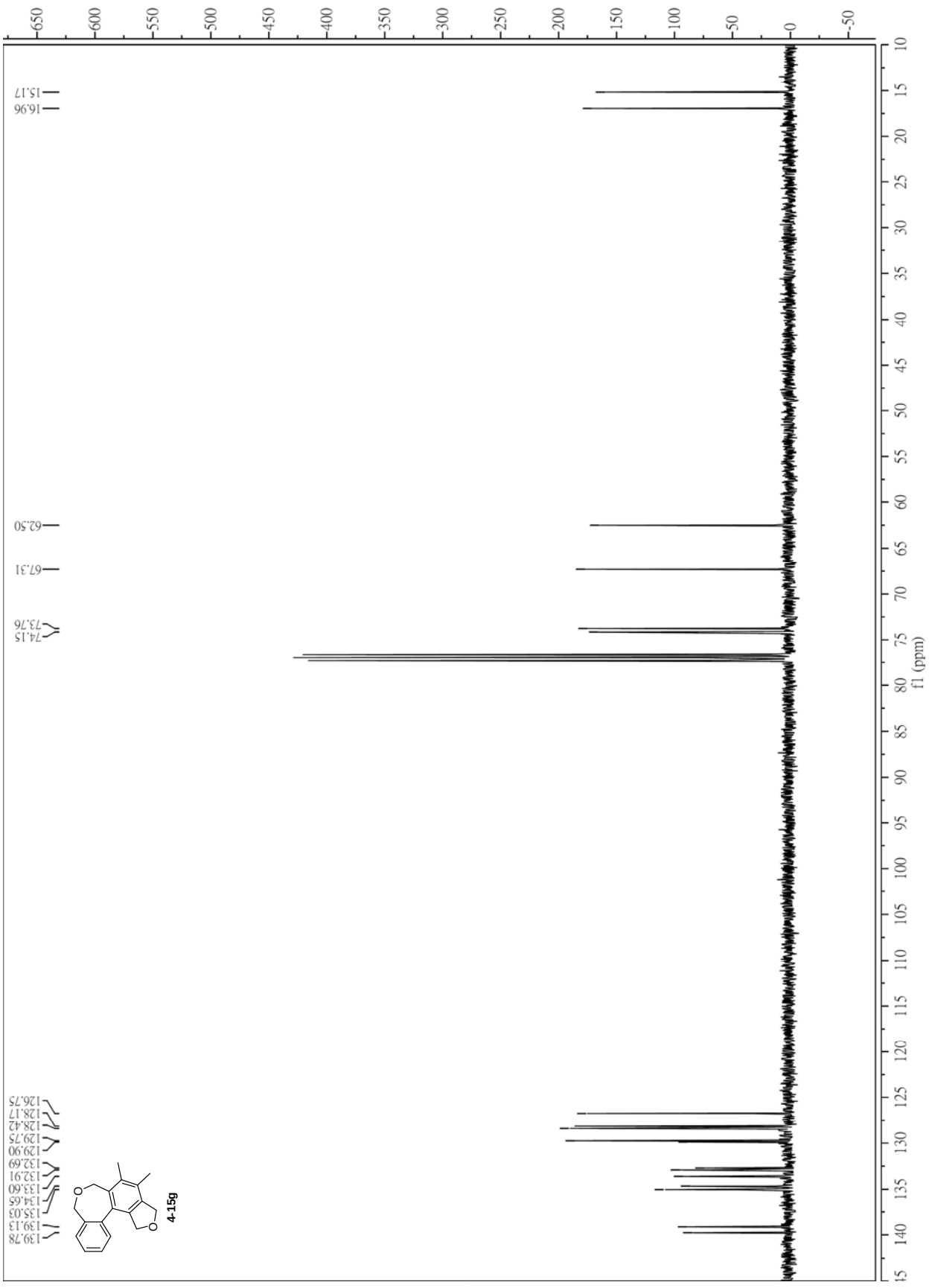
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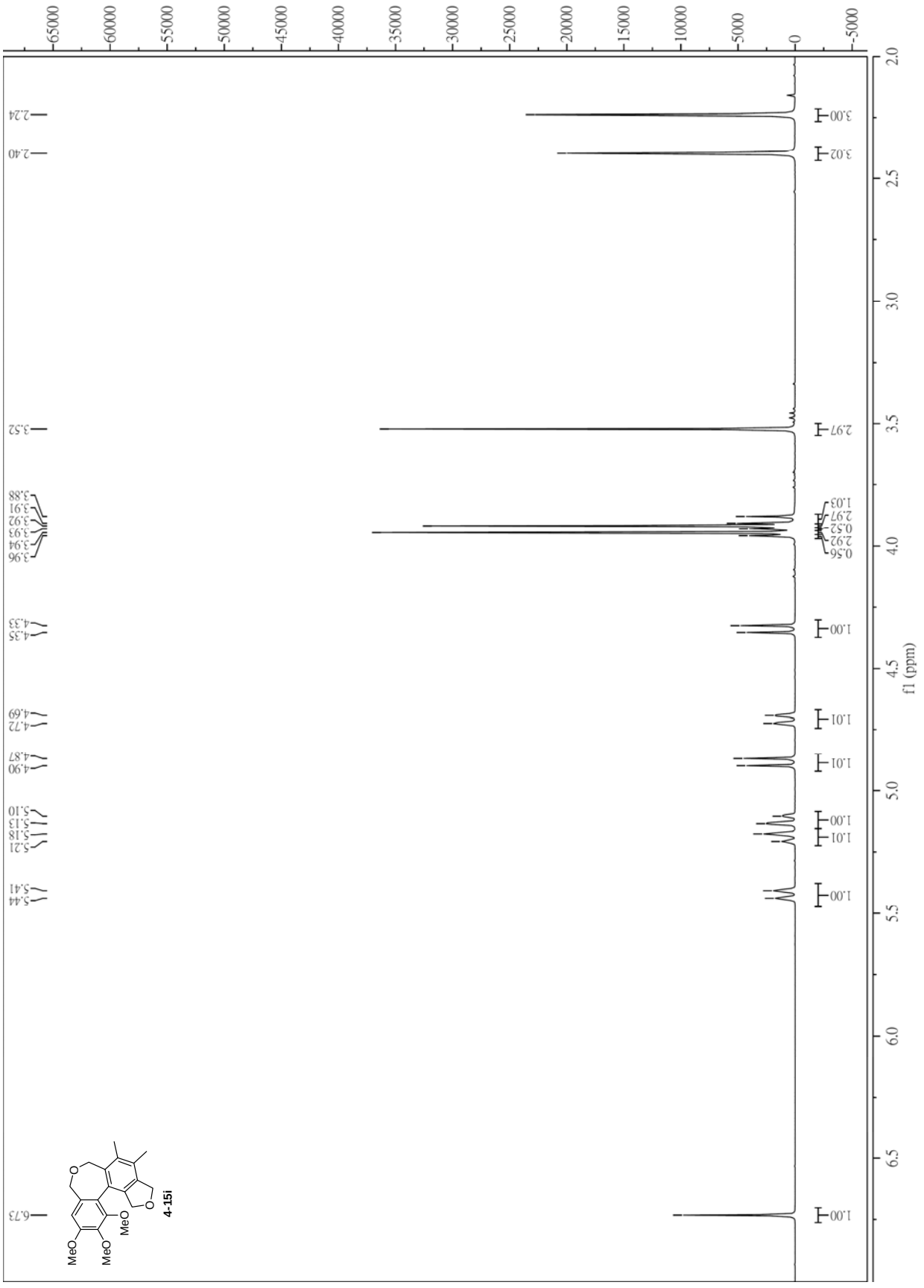
4-15g
f1 (ppm)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3.93
3.92
3.91
3.88
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0.56
2.92
0.52
2.97
1.03
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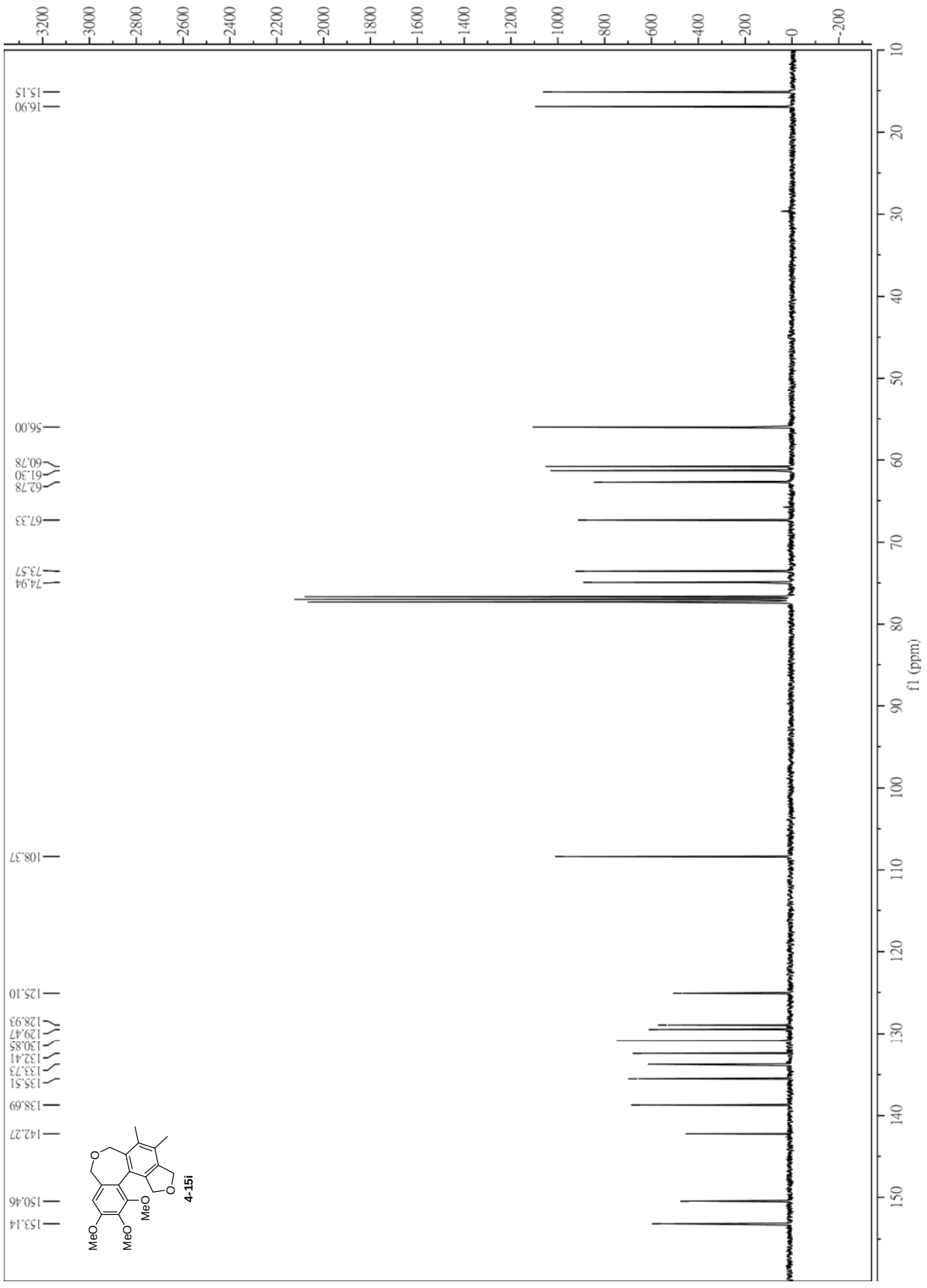
f1 (ppm)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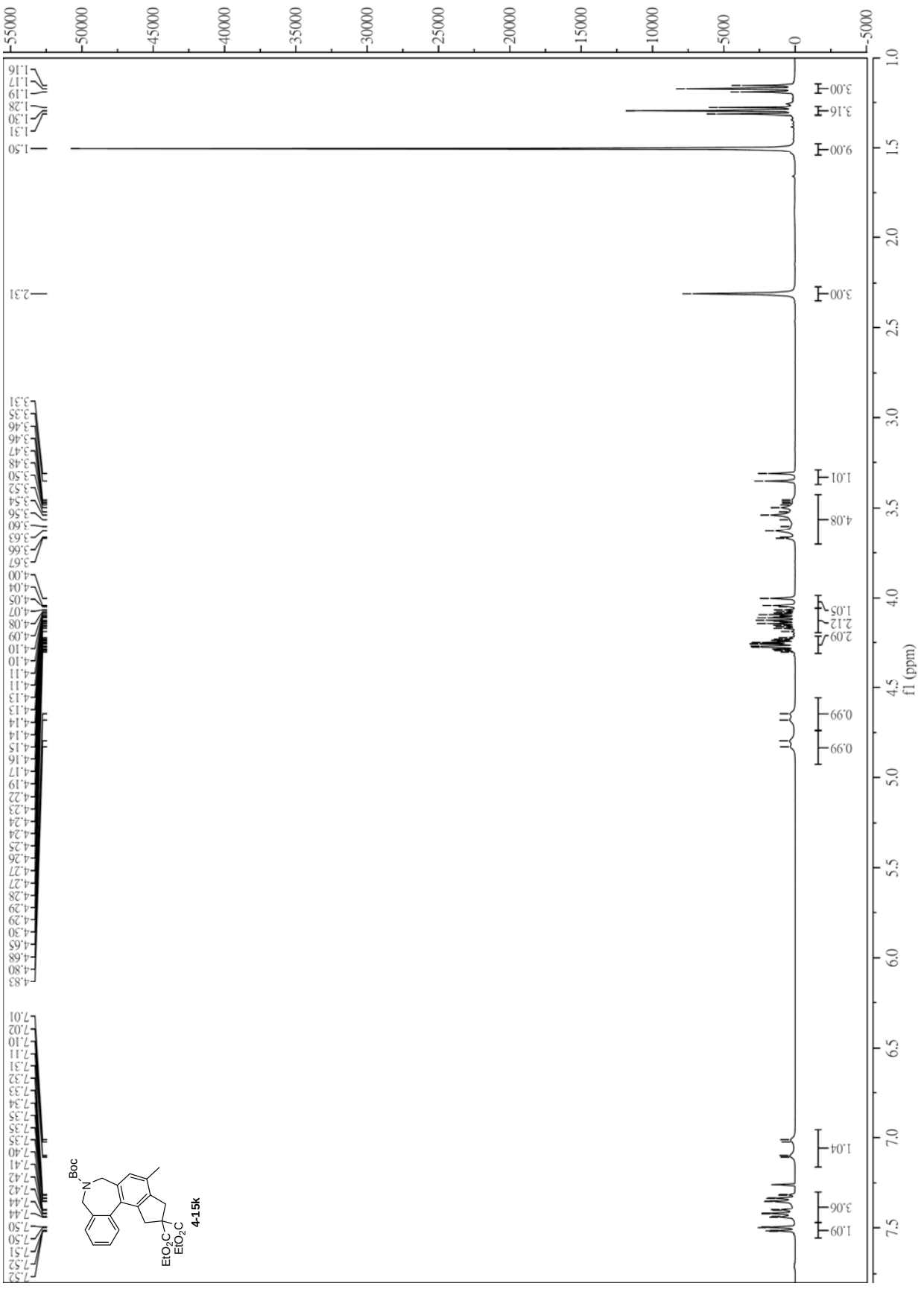
f1 (ppm)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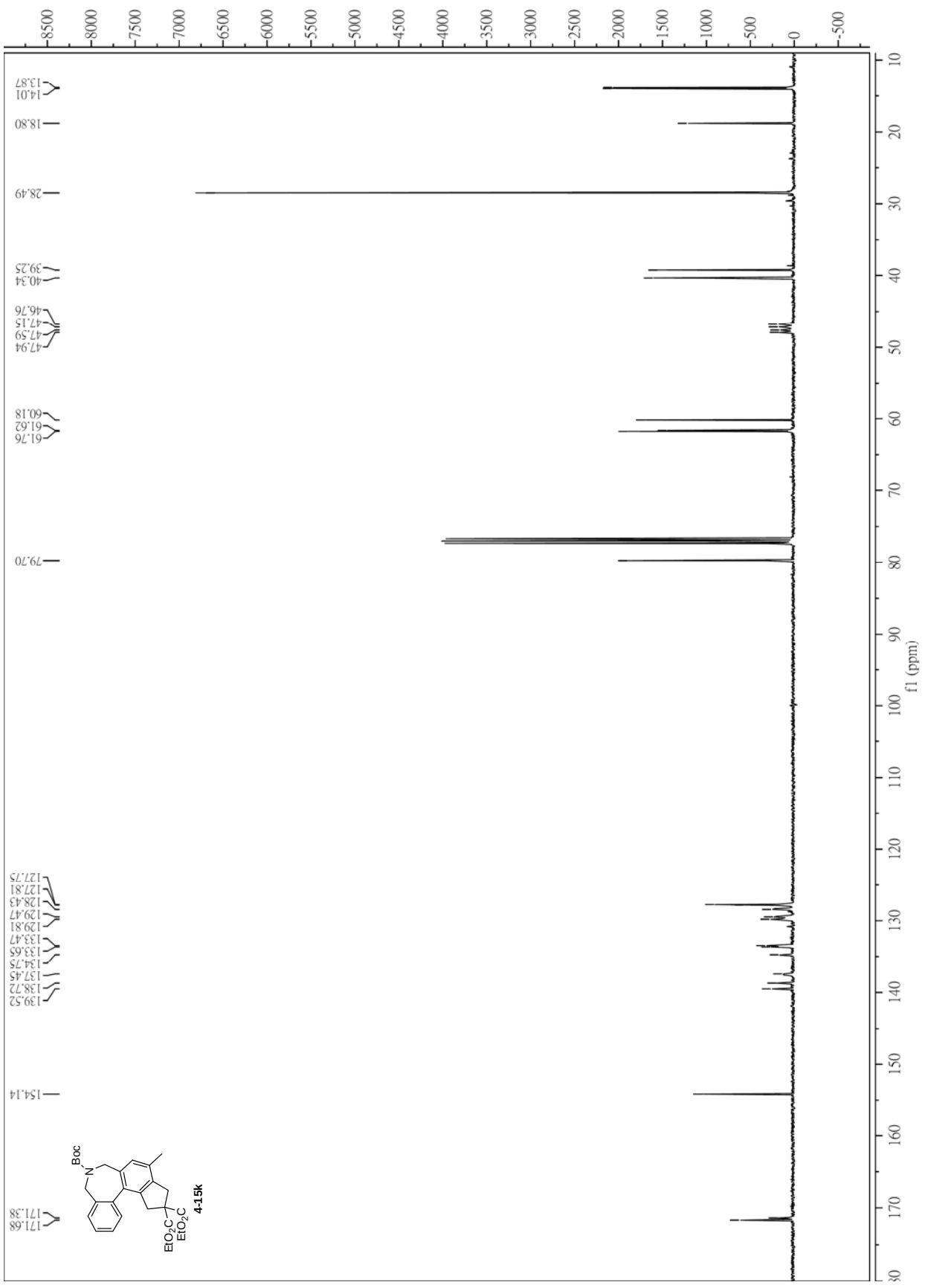
EtO2C
4-15k
f1 (ppm)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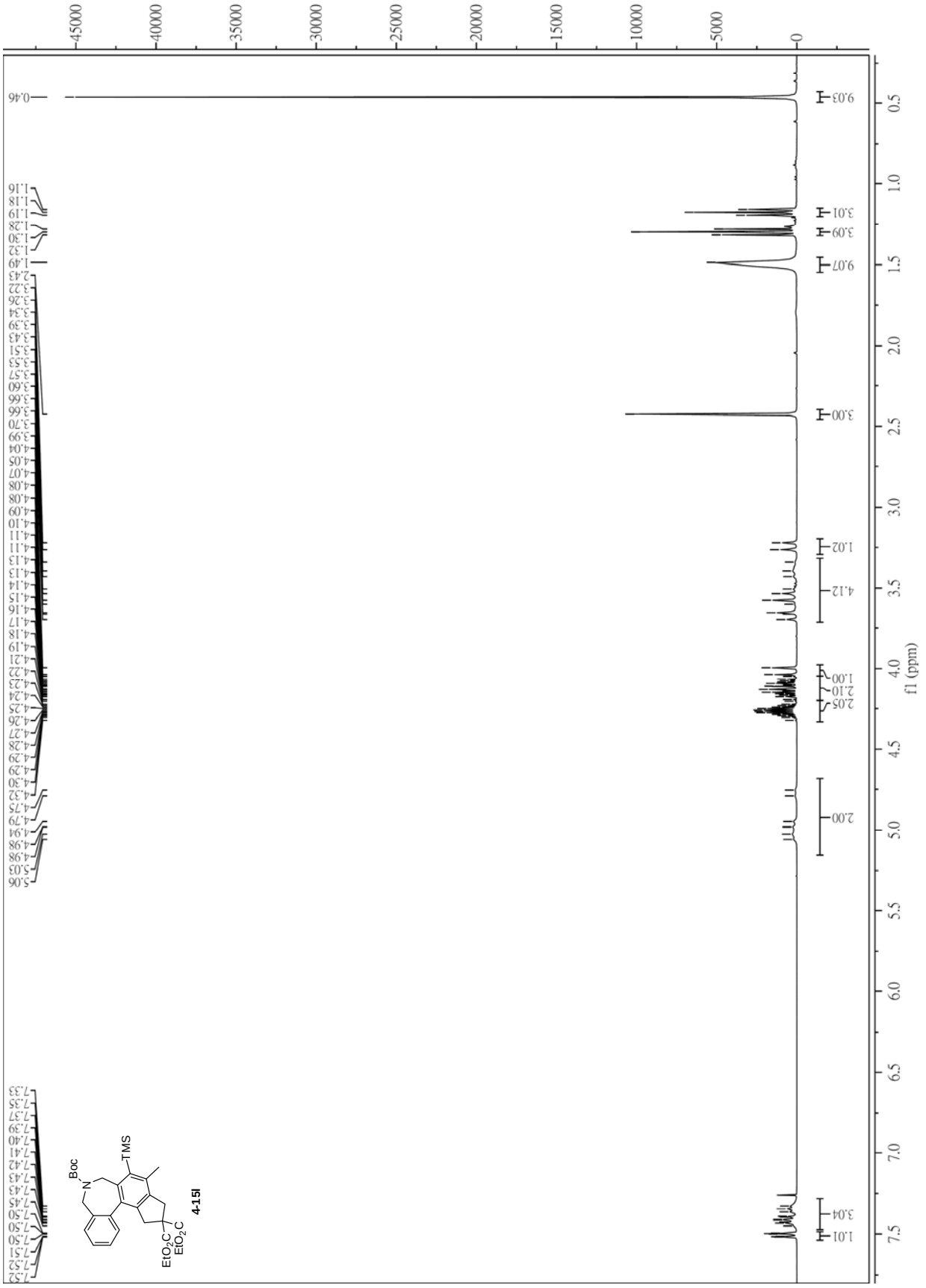
f1 (ppm)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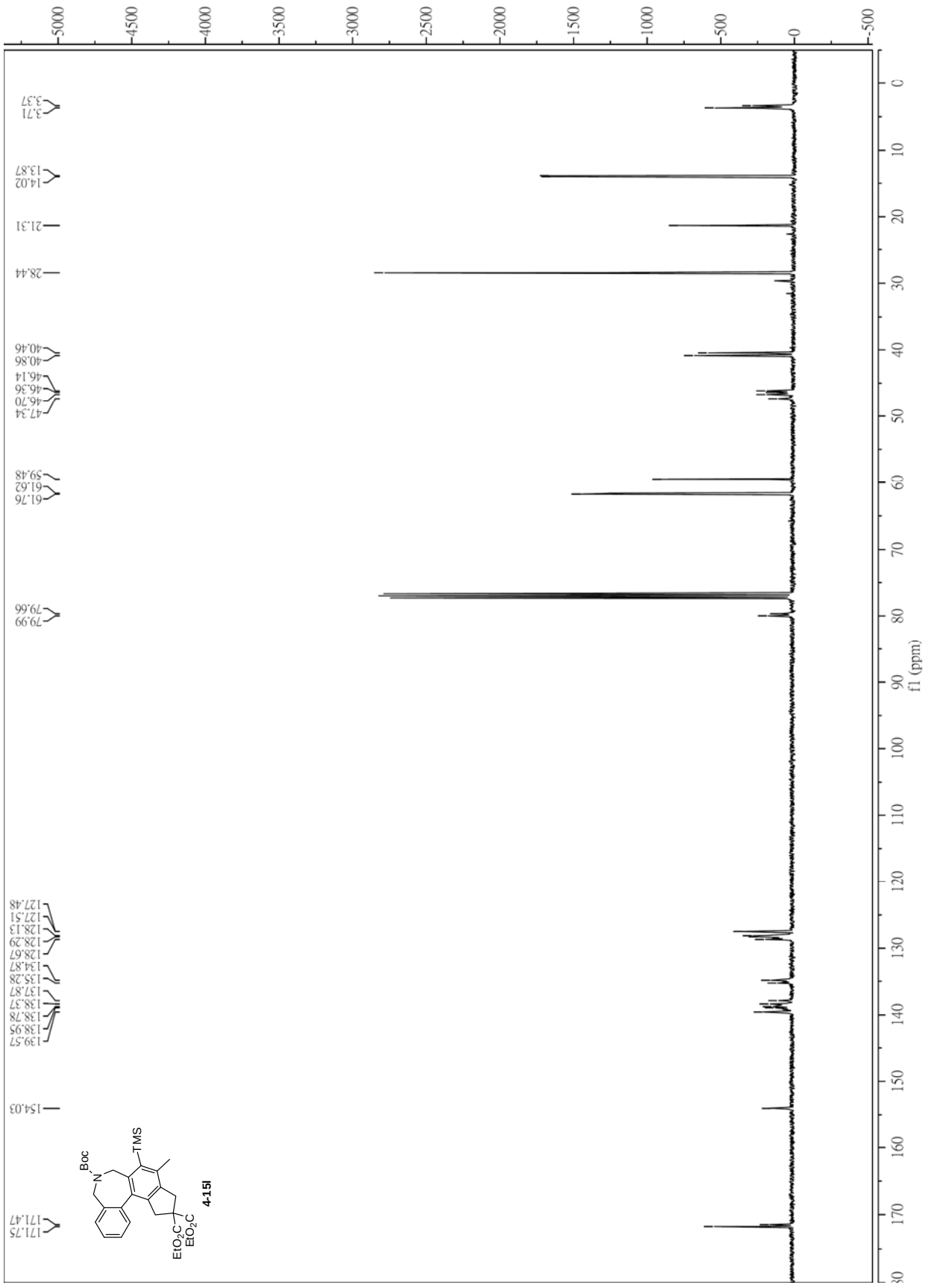
4-15l
f1 (ppm)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154.03
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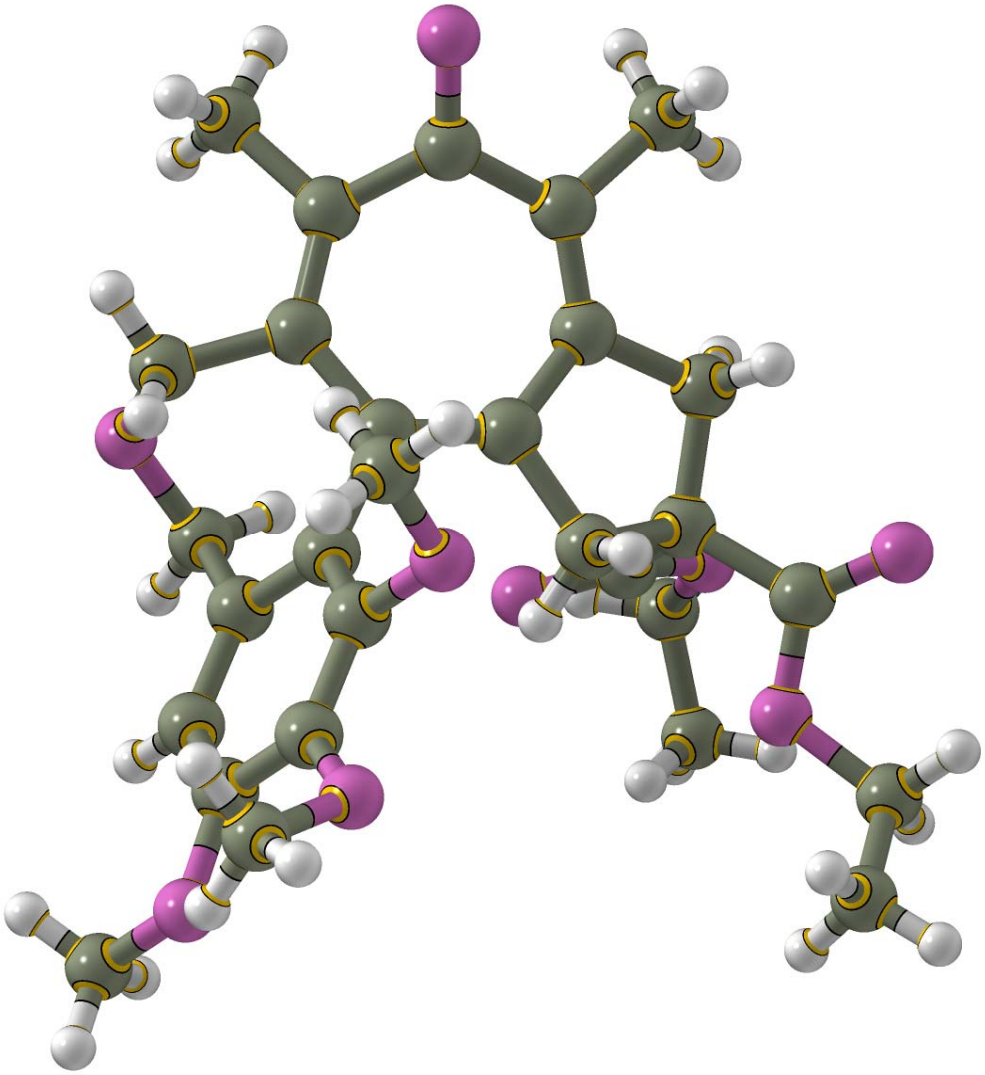
N
TMS
EtO2C
EtO2C
4-15l
f1 (ppm)

Molecular Structure and Crystallography Data for Compound 4-14c



Crystal Data for 4-14c

Table 1. Crystal data and structure refinement for **4-14c**.

Identification code	cwc	
Empirical formula	C58 H68 O18	
Formula weight	1053.12	
Temperature	293(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.5272(4) Å	α= 87.567(4)°
	b = 12.5400(6) Å	β= 77.802(4)°
	c = 15.1515(7) Å	γ= 75.833(4)°
Volume	1355.30(12) $Å^3$	
Z	1	
Density (calculated)	1.290 Mg/m^3	
Absorption coefficient	0.792 mm^{-1}	
F(000)	560	
Theta range for data collection	3.64 to 73.59°.	
Index ranges	-9<=h<=9, -15<=k<=15, -17<=l<=18	
Reflections collected	19769	
Independent reflections	5339 [R(int) = 0.0406]	
Completeness to theta = 73.59	97.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5339 / 0 / 351	
Goodness-of-fit on F^2	1.022	
Final R indices [I>2sigma(I)]	R1 = 0.0574, wR2 = 0.1495	
R indices (all data)	R1 = 0.0865, wR2 = 0.1746	
Extinction coefficient	0.0077(8)	
Largest diff. peak and hole	0.262 and -0.203 $e.^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	-4896(4)	11017(2)	6967(2)	79(1)
C(2)	-1797(3)	9893(2)	6820(2)	50(1)
C(3)	-2415(3)	8936(2)	6961(2)	51(1)
C(4)	128(3)	9837(2)	6657(2)	46(1)
C(5)	423(5)	11446(2)	5798(2)	79(1)
C(6)	1384(3)	8819(2)	6664(1)	42(1)
C(7)	771(3)	7854(2)	6848(1)	41(1)
C(8)	-1154(3)	7922(2)	6977(2)	47(1)
C(9)	-1804(4)	6878(2)	7101(2)	61(1)
C(10)	531(4)	6197(2)	5788(2)	60(1)
C(11)	2045(3)	5891(2)	6335(2)	47(1)
C(12)	2081(3)	6761(2)	6927(1)	41(1)
C(13)	3005(3)	6631(2)	7622(1)	42(1)
C(14)	4221(3)	5655(2)	7896(2)	46(1)
C(15)	5201(3)	4737(2)	7408(2)	52(1)
C(16)	5013(4)	4480(2)	6504(2)	59(1)
C(17)	3228(4)	4866(2)	6203(2)	55(1)
C(18)	2861(6)	4014(2)	5635(2)	86(1)
C(19)	6675(4)	3892(2)	7760(2)	78(1)
C(20)	4451(3)	5840(2)	8847(2)	55(1)
C(21)	2733(3)	7528(2)	8309(2)	50(1)
C(22)	2961(3)	6890(2)	9186(2)	51(1)
C(23)	3570(4)	7526(3)	9852(2)	66(1)
C(24)	2581(9)	9093(4)	10818(3)	138(2)
C(25)	2003(10)	10182(4)	10639(4)	181(3)
C(26)	-1608(5)	6992(3)	11535(3)	103(1)
C(27)	-589(5)	6014(3)	10979(2)	83(1)
C(28)	1094(4)	6642(2)	9626(2)	55(1)
C(29)	4217(5)	8487(3)	5615(2)	93(1)
O(1)	-2945(2)	10924(1)	6835(1)	68(1)
O(2)	823(3)	10759(1)	6539(1)	63(1)

O(3)	3272(2)	8780(1)	6508(1)	50(1)
O(4)	2242(4)	8409(2)	10139(2)	101(1)
O(5)	4984(4)	7258(3)	10113(2)	116(1)
O(6)	-249(3)	6809(2)	9291(2)	85(1)
O(7)	1162(3)	6188(2)	10432(1)	69(1)
O(8)	6286(3)	3810(2)	6027(1)	93(1)
O(9)	-1307(3)	6234(2)	6299(2)	74(1)

Table 3. Bond lengths (Å) and angles (°).

C(1)-O(1)	1.416(3)
C(2)-O(1)	1.367(3)
C(2)-C(3)	1.383(3)
C(2)-C(4)	1.402(3)
C(3)-C(8)	1.390(3)
C(4)-O(2)	1.371(3)
C(4)-C(6)	1.392(3)
C(5)-O(2)	1.424(3)
C(6)-O(3)	1.380(2)
C(6)-C(7)	1.394(3)
C(7)-C(8)	1.403(3)
C(7)-C(12)	1.497(3)
C(8)-C(9)	1.497(3)
C(9)-O(9)	1.419(3)
C(10)-O(9)	1.426(3)
C(10)-C(11)	1.513(3)
C(11)-C(17)	1.368(3)
C(11)-C(12)	1.451(3)
C(12)-C(13)	1.363(3)
C(13)-C(14)	1.440(3)
C(13)-C(21)	1.513(3)
C(14)-C(15)	1.358(3)
C(14)-C(20)	1.521(3)
C(15)-C(16)	1.464(4)
C(15)-C(19)	1.505(3)
C(16)-O(8)	1.229(3)
C(16)-C(17)	1.472(4)
C(17)-C(18)	1.510(4)
C(20)-C(22)	1.532(3)
C(21)-C(22)	1.540(3)
C(22)-C(23)	1.519(4)
C(22)-C(28)	1.523(3)
C(23)-O(5)	1.180(4)
C(23)-O(4)	1.316(4)
C(24)-C(25)	1.362(6)

C(24)-O(4)	1.467(4)
C(26)-C(27)	1.469(4)
C(27)-O(7)	1.461(3)
C(28)-O(6)	1.194(3)
C(28)-O(7)	1.331(3)
C(29)-O(3)	1.407(3)

O(1)-C(2)-C(3)	124.5(2)
O(1)-C(2)-C(4)	115.8(2)
C(3)-C(2)-C(4)	119.7(2)
C(2)-C(3)-C(8)	120.7(2)
O(2)-C(4)-C(6)	118.3(2)
O(2)-C(4)-C(2)	122.3(2)
C(6)-C(4)-C(2)	119.3(2)
O(3)-C(6)-C(4)	118.48(19)
O(3)-C(6)-C(7)	119.95(18)
C(4)-C(6)-C(7)	121.5(2)
C(6)-C(7)-C(8)	118.25(19)
C(6)-C(7)-C(12)	122.58(19)
C(8)-C(7)-C(12)	119.16(19)
C(3)-C(8)-C(7)	120.4(2)
C(3)-C(8)-C(9)	121.1(2)
C(7)-C(8)-C(9)	118.4(2)
O(9)-C(9)-C(8)	112.9(2)
O(9)-C(10)-C(11)	114.0(2)
C(17)-C(11)-C(12)	127.9(2)
C(17)-C(11)-C(10)	117.9(2)
C(12)-C(11)-C(10)	114.24(19)
C(13)-C(12)-C(11)	125.57(19)
C(13)-C(12)-C(7)	117.41(18)
C(11)-C(12)-C(7)	116.40(18)
C(12)-C(13)-C(14)	129.0(2)
C(12)-C(13)-C(21)	122.90(19)
C(14)-C(13)-C(21)	107.88(19)
C(15)-C(14)-C(13)	129.3(2)
C(15)-C(14)-C(20)	121.9(2)

C(13)-C(14)-C(20)	108.53(19)
C(14)-C(15)-C(16)	125.2(2)
C(14)-C(15)-C(19)	121.2(2)
C(16)-C(15)-C(19)	113.6(2)
O(8)-C(16)-C(15)	119.3(2)
O(8)-C(16)-C(17)	118.4(2)
C(15)-C(16)-C(17)	121.6(2)
C(11)-C(17)-C(16)	126.9(2)
C(11)-C(17)-C(18)	120.8(2)
C(16)-C(17)-C(18)	112.2(2)
C(14)-C(20)-C(22)	105.07(18)
C(13)-C(21)-C(22)	103.48(18)
C(23)-C(22)-C(28)	109.0(2)
C(23)-C(22)-C(20)	111.9(2)
C(28)-C(22)-C(20)	111.7(2)
C(23)-C(22)-C(21)	112.6(2)
C(28)-C(22)-C(21)	108.5(2)
C(20)-C(22)-C(21)	102.93(18)
O(5)-C(23)-O(4)	123.9(3)
O(5)-C(23)-C(22)	126.0(3)
O(4)-C(23)-C(22)	110.0(2)
C(25)-C(24)-O(4)	111.0(4)
O(7)-C(27)-C(26)	110.5(3)
O(6)-C(28)-O(7)	124.1(3)
O(6)-C(28)-C(22)	125.0(2)
O(7)-C(28)-C(22)	110.9(2)
C(2)-O(1)-C(1)	117.8(2)
C(4)-O(2)-C(5)	117.2(2)
C(6)-O(3)-C(29)	113.6(2)
C(23)-O(4)-C(24)	116.9(3)
C(28)-O(7)-C(27)	117.1(2)
C(9)-O(9)-C(10)	114.19(18)

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	54(2)	65(2)	107(2)	-3(2)	-17(2)	11(1)
C(2)	49(1)	44(1)	54(1)	0(1)	-16(1)	-3(1)
C(3)	41(1)	53(1)	58(1)	2(1)	-13(1)	-10(1)
C(4)	50(1)	41(1)	51(1)	3(1)	-16(1)	-12(1)
C(5)	89(2)	60(2)	93(2)	24(2)	-24(2)	-25(2)
C(6)	41(1)	43(1)	43(1)	0(1)	-14(1)	-10(1)
C(7)	44(1)	40(1)	42(1)	2(1)	-13(1)	-9(1)
C(8)	45(1)	47(1)	51(1)	4(1)	-13(1)	-12(1)
C(9)	51(1)	55(1)	82(2)	9(1)	-18(1)	-19(1)
C(10)	69(2)	52(1)	66(2)	-5(1)	-31(1)	-11(1)
C(11)	57(1)	41(1)	47(1)	4(1)	-19(1)	-11(1)
C(12)	42(1)	40(1)	41(1)	6(1)	-11(1)	-11(1)
C(13)	43(1)	42(1)	40(1)	3(1)	-9(1)	-11(1)
C(14)	43(1)	51(1)	44(1)	8(1)	-12(1)	-9(1)
C(15)	49(1)	49(1)	54(1)	8(1)	-14(1)	-3(1)
C(16)	72(2)	45(1)	51(1)	4(1)	-15(1)	3(1)
C(17)	76(2)	43(1)	48(1)	2(1)	-23(1)	-11(1)
C(18)	137(3)	44(1)	85(2)	-8(1)	-51(2)	-9(2)
C(19)	78(2)	72(2)	73(2)	3(2)	-31(2)	14(2)
C(20)	51(1)	67(2)	47(1)	7(1)	-17(1)	-8(1)
C(21)	54(1)	50(1)	47(1)	1(1)	-16(1)	-11(1)
C(22)	53(1)	60(1)	43(1)	-1(1)	-16(1)	-15(1)
C(23)	76(2)	80(2)	50(2)	0(1)	-19(1)	-26(2)
C(24)	232(6)	93(3)	115(3)	-29(2)	-92(4)	-36(3)
C(25)	259(7)	103(4)	199(6)	-61(4)	-136(6)	10(4)
C(26)	89(2)	110(3)	97(3)	-24(2)	17(2)	-23(2)
C(27)	82(2)	100(2)	66(2)	-1(2)	9(2)	-40(2)
C(28)	58(2)	61(2)	48(1)	-6(1)	-12(1)	-13(1)
C(29)	68(2)	139(3)	73(2)	-29(2)	8(2)	-41(2)
O(1)	56(1)	46(1)	97(1)	-1(1)	-22(1)	3(1)
O(2)	71(1)	42(1)	87(1)	12(1)	-33(1)	-20(1)

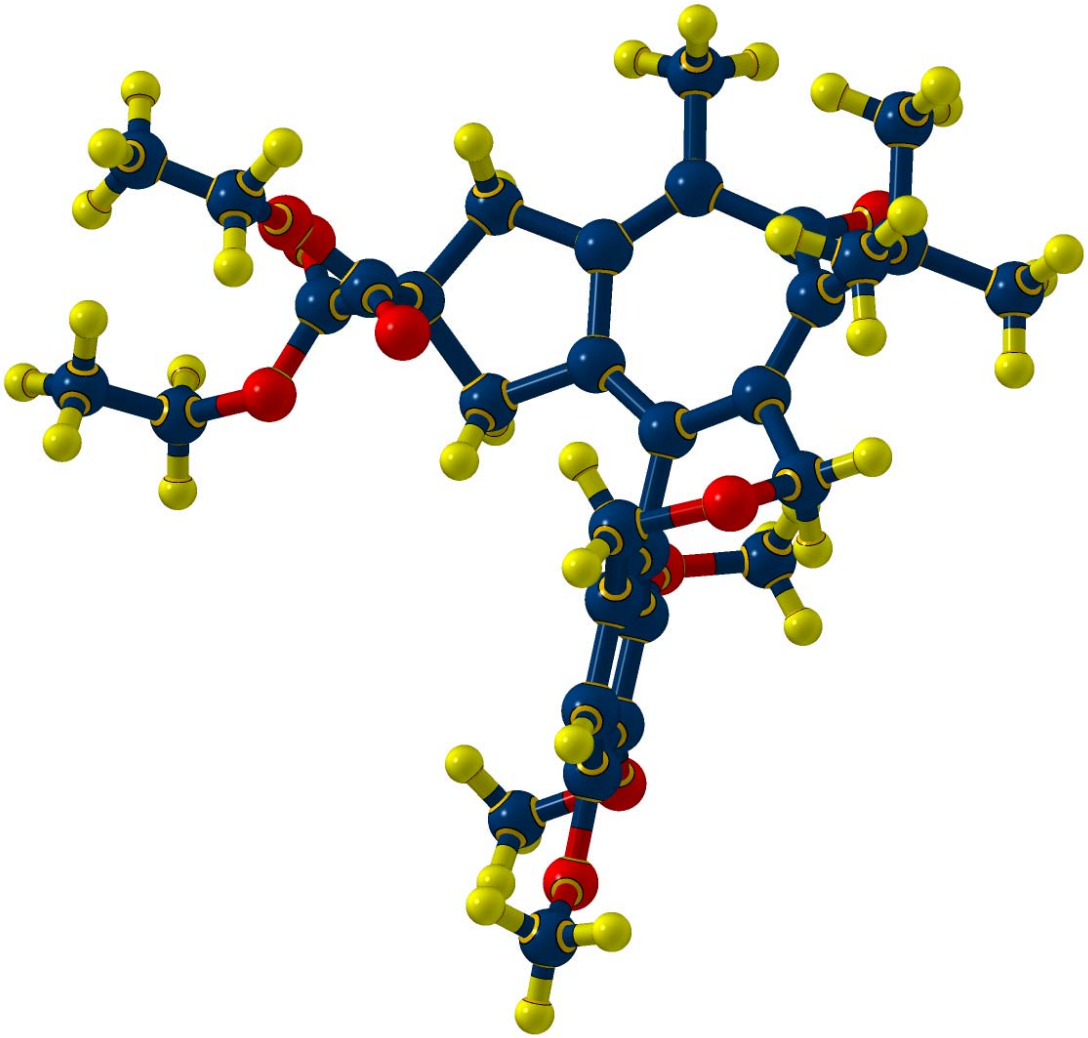
O(3)	43(1)	52(1)	58(1)	1(1)	-12(1)	-14(1)
O(4)	143(2)	76(1)	96(2)	-27(1)	-66(2)	-10(1)
O(5)	81(2)	179(3)	103(2)	-40(2)	-42(2)	-33(2)
O(6)	62(1)	126(2)	74(1)	9(1)	-22(1)	-32(1)
O(7)	69(1)	87(1)	51(1)	5(1)	-7(1)	-23(1)
O(8)	100(2)	85(1)	66(1)	-15(1)	-18(1)	35(1)
O(9)	67(1)	64(1)	102(2)	-11(1)	-32(1)	-23(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å ^{2}x 10 ^{3}).

	x	y	z	U(eq)
H(1A)	-5136	10578	6522	119
H(1B)	-5529	11772	6909	119
H(1C)	-5346	10764	7560	119
H(3)	-3689	8970	7047	61
H(5A)	524	10998	5283	119
H(5B)	1300	11901	5654	119
H(5C)	-825	11903	5956	119
H(9A)	-1262	6449	7569	73
H(9B)	-3155	7057	7303	73
H(10A)	549	6912	5521	72
H(10B)	815	5667	5299	72
H(18A)	1560	4007	5794	129
H(18B)	3611	3302	5742	129
H(18C)	3177	4192	5008	129
H(19A)	7879	4043	7536	117
H(19B)	6688	3173	7561	117
H(19C)	6397	3920	8408	117
H(20A)	5696	5933	8839	66
H(20B)	4249	5222	9230	66
H(21A)	1498	8021	8376	60
H(21B)	3671	7951	8138	60
H(24A)	1914	8937	11411	165
H(24B)	3908	8915	10823	165
H(25A)	2485	10313	10016	271
H(25B)	2456	10607	11015	271
H(25C)	659	10394	10760	271
H(26A)	-836	7150	11918	155
H(26B)	-2737	6858	11901	155
H(26C)	-1917	7609	11151	155
H(27A)	-321	5385	11366	100
H(27B)	-1363	5859	10587	100

H(29A)	3956	7819	5450	140
H(29B)	5541	8377	5571	140
H(29C)	3799	9064	5216	140

Molecular Structure and Crystallography Data for Compound 4-14d



Crystal Data for 4-14d

Table 1. Crystal data and structure refinement for **4-14d**.

Identification code	cwc-tbu2	
Empirical formula	C32 H40 O9	
Formula weight	568.64	
Temperature	293(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 20.1858(3) Å	α= 90°
	b = 20.9578(2) Å	β= 90°
	c = 14.3999(2) Å	γ= 90°
Volume	6091.88(14) $Å^3$	
Z	8	
Density (calculated)	1.240 Mg/m^3	
Absorption coefficient	0.741 mm^{-1}	
F(000)	2432	
Theta range for data collection	3.72 to 73.56°.	
Index ranges	-24<=h<=25, -25<=k<=26, -17<=l<=14	
Reflections collected	47331	
Independent reflections	10747 [R(int) = 0.0254]	
Completeness to theta = 73.56	99.2 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10747 / 1 / 757	
Goodness-of-fit on F^2	1.006	
Final R indices [I>2sigma(I)]	R1 = 0.0512, wR2 = 0.1480	
R indices (all data)	R1 = 0.0592, wR2 = 0.1611	
Absolute structure parameter	-0.01(16)	
Largest diff. peak and hole	0.309 and -0.248 $e.^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å ^{2}x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	930(1)	6829(1)	1639(2)	43(1)
O(3)	-355(1)	5286(1)	1333(2)	70(1)
O(4)	844(1)	6681(1)	3285(1)	58(1)
C(8)	366(1)	8725(1)	2446(2)	48(1)
O(11)	36(1)	5646(1)	3043(1)	61(1)
C(13)	1532(1)	8490(1)	2427(2)	46(1)
C(14)	253(1)	5978(1)	2279(2)	49(1)
C(15)	68(1)	5797(1)	1384(2)	52(1)
C(16)	302(1)	6135(1)	624(2)	50(1)
C(17)	462(1)	7997(1)	2471(2)	47(1)
C(18)	2047(1)	7318(1)	1277(2)	48(1)
O(19)	224(1)	8625(1)	776(1)	81(1)
C(21)	727(1)	6651(1)	753(2)	48(1)
C(25)	687(1)	6494(1)	2405(2)	45(1)
O(27)	1692(1)	6820(1)	-222(1)	73(1)
C(28)	1410(1)	7377(1)	1760(2)	44(1)
C(29)	1181(1)	7908(1)	2198(2)	43(1)
C(32)	2193(1)	8571(1)	2500(2)	52(1)
O(35)	52(1)	9563(1)	1449(2)	87(1)
C(36)	1043(1)	8991(1)	2734(2)	53(1)
O(37)	3124(1)	7943(1)	2838(2)	84(1)
O(39)	-138(1)	9261(1)	3756(2)	93(1)
C(43)	206(1)	8948(1)	1455(2)	54(1)
C(45)	2594(1)	7688(1)	1428(2)	51(1)
C(47)	2661(1)	8044(1)	2314(2)	55(1)
C(48)	1016(2)	7003(1)	-52(2)	63(1)
C(53)	2079(1)	6763(1)	605(2)	63(1)
C(57)	-483(2)	5026(2)	449(3)	93(1)
C(60)	3203(1)	7749(1)	773(2)	62(1)
O(61)	-757(1)	8711(2)	2801(2)	109(1)
C(62)	3001(2)	7754(2)	-252(2)	78(1)

C(64)	-194(1)	8942(1)	3087(2)	63(1)
C(65)	2498(2)	9176(1)	2875(2)	71(1)
C(67)	3541(2)	8394(2)	944(3)	105(1)
C(68)	-632(2)	5774(2)	3290(3)	79(1)
C(71)	3714(2)	7221(2)	945(3)	95(1)
C(72)	-883(2)	9923(2)	540(3)	102(1)
C(73)	-153(2)	9862(2)	582(3)	101(1)
C(75)	1333(2)	6337(2)	3727(3)	117(2)
C(78)	-1360(2)	8873(4)	3325(4)	176(3)
C(2)	3355(1)	3231(1)	1648(2)	45(1)
O(5)	2046(1)	4757(1)	1348(2)	72(1)
C(6)	2692(1)	3902(1)	641(2)	51(1)
O(7)	3309(1)	3413(1)	3292(1)	62(1)
O(9)	2487(1)	4428(1)	3052(2)	70(1)
C(10)	2683(1)	4085(1)	2289(2)	51(1)
C(12)	3125(1)	3582(1)	2409(2)	47(1)
C(20)	3839(1)	2691(1)	1757(2)	45(1)
C(22)	3982(1)	1575(1)	2416(2)	50(1)
C(23)	3128(1)	3395(1)	764(2)	48(1)
C(24)	2911(1)	2061(1)	2499(2)	50(1)
O(26)	2321(1)	726(1)	3698(2)	87(1)
O(30)	4068(1)	3191(1)	-251(1)	77(1)
C(31)	2475(1)	4251(1)	1404(2)	53(1)
C(33)	3621(1)	2153(1)	2201(2)	45(1)
C(34)	4466(1)	2751(1)	1258(2)	49(1)
C(38)	4642(1)	1511(1)	2492(2)	55(1)
O(40)	2750(2)	1450(1)	776(2)	94(1)
C(41)	3497(1)	1059(1)	2702(2)	58(1)
C(42)	4471(1)	3285(1)	555(2)	62(1)
C(44)	2811(1)	1328(1)	2445(2)	54(1)
C(46)	3393(2)	3029(1)	-44(2)	62(1)
O(49)	2398(2)	566(1)	1396(2)	106(1)
C(50)	2658(1)	1135(1)	1441(2)	60(1)
C(51)	1834(2)	4951(1)	455(3)	85(1)
C(52)	2260(2)	1103(1)	3092(2)	62(1)
O(54)	5539(1)	2180(1)	2852(2)	91(1)

C(55)	5639(1)	2346(1)	779(2)	66(1)
C(56)	5093(1)	2055(1)	2320(2)	58(1)
C(58)	5026(1)	2401(1)	1427(2)	53(1)
C(59)	5441(2)	2301(2)	-245(3)	88(1)
O(63)	1712(1)	1417(1)	2918(2)	104(1)
C(66)	4967(2)	919(1)	2865(2)	75(1)
C(69)	6010(2)	1727(2)	987(4)	127(2)
C(70)	1808(2)	4344(2)	3305(3)	89(1)
C(74)	6125(2)	2896(2)	910(3)	105(1)
C(76)	3916(2)	3675(2)	3589(3)	96(1)
C(77)	698(3)	858(2)	2946(5)	146(2)
C(80)	2258(4)	313(3)	459(3)	142(2)
C(90)	1116(2)	1282(2)	3471(4)	118(2)
C(91)	1848(4)	-160(3)	461(4)	211(5)
C(01)	-1833(3)	9094(4)	2800(6)	213(4)

Table 3. Bond lengths (Å) and angles (°).

C(1)-C(21)	1.390(3)
C(1)-C(25)	1.395(3)
C(1)-C(28)	1.513(3)
O(3)-C(15)	1.370(3)
O(3)-C(57)	1.408(4)
O(4)-C(25)	1.363(3)
O(4)-C(75)	1.379(4)
C(8)-C(64)	1.528(3)
C(8)-C(36)	1.534(3)
C(8)-C(43)	1.536(3)
C(8)-C(17)	1.538(3)
O(11)-C(14)	1.374(3)
O(11)-C(68)	1.419(4)
C(13)-C(32)	1.349(3)
C(13)-C(29)	1.449(3)
C(13)-C(36)	1.508(3)
C(14)-C(15)	1.395(4)
C(14)-C(25)	1.404(3)
C(15)-C(16)	1.387(4)
C(16)-C(21)	1.392(3)
C(17)-C(29)	1.515(3)
C(18)-C(45)	1.366(3)
C(18)-C(28)	1.467(3)
C(18)-C(53)	1.515(3)
O(19)-C(43)	1.190(3)
C(21)-C(48)	1.493(4)
O(27)-C(53)	1.429(4)
O(27)-C(48)	1.439(4)
C(28)-C(29)	1.361(3)
C(32)-C(47)	1.478(3)
C(32)-C(65)	1.509(3)
O(35)-C(43)	1.327(3)
O(35)-C(73)	1.456(4)
O(37)-C(47)	1.221(3)

O(39)-C(64)	1.178(3)
C(45)-C(47)	1.484(4)
C(45)-C(60)	1.556(3)
C(60)-C(62)	1.531(5)
C(60)-C(71)	1.531(4)
C(60)-C(67)	1.535(4)
O(61)-C(64)	1.302(4)
O(61)-C(78)	1.472(4)
C(72)-C(73)	1.479(7)
C(78)-C(01)	1.302(9)
C(2)-C(23)	1.396(3)
C(2)-C(12)	1.400(3)
C(2)-C(20)	1.504(3)
O(5)-C(31)	1.372(3)
O(5)-C(51)	1.415(4)
C(6)-C(31)	1.391(4)
C(6)-C(23)	1.391(3)
O(7)-C(12)	1.371(3)
O(7)-C(76)	1.410(4)
O(9)-C(10)	1.371(3)
O(9)-C(70)	1.430(4)
C(10)-C(31)	1.386(4)
C(10)-C(12)	1.392(3)
C(20)-C(33)	1.368(3)
C(20)-C(34)	1.461(3)
C(22)-C(38)	1.344(3)
C(22)-C(33)	1.447(3)
C(22)-C(41)	1.516(3)
C(23)-C(46)	1.493(4)
C(24)-C(33)	1.508(3)
C(24)-C(44)	1.550(3)
O(26)-C(52)	1.184(3)
O(30)-C(42)	1.431(4)
O(30)-C(46)	1.436(4)
C(34)-C(58)	1.369(3)
C(34)-C(42)	1.509(3)

C(38)-C(56)	1.479(4)
C(38)-C(66)	1.502(3)
O(40)-C(50)	1.179(3)
C(41)-C(44)	1.540(4)
C(44)-C(52)	1.527(4)
C(44)-C(50)	1.533(4)
O(49)-C(50)	1.304(3)
O(49)-C(80)	1.477(5)
C(52)-O(63)	1.311(4)
O(54)-C(56)	1.211(3)
C(55)-C(69)	1.527(5)
C(55)-C(74)	1.525(4)
C(55)-C(59)	1.531(5)
C(55)-C(58)	1.555(4)
C(56)-C(58)	1.483(4)
O(63)-C(90)	1.470(4)
C(77)-C(90)	1.440(7)
C(80)-C(91)	1.291(7)

C(21)-C(1)-C(25)	119.11(19)
C(21)-C(1)-C(28)	119.9(2)
C(25)-C(1)-C(28)	121.0(2)
C(15)-O(3)-C(57)	117.7(2)
C(25)-O(4)-C(75)	116.5(2)
C(64)-C(8)-C(36)	112.8(2)
C(64)-C(8)-C(43)	108.35(18)
C(36)-C(8)-C(43)	109.1(2)
C(64)-C(8)-C(17)	112.0(2)
C(36)-C(8)-C(17)	104.01(17)
C(43)-C(8)-C(17)	110.51(19)
C(14)-O(11)-C(68)	114.1(2)
C(32)-C(13)-C(29)	127.5(2)
C(32)-C(13)-C(36)	122.47(19)
C(29)-C(13)-C(36)	109.37(18)
O(11)-C(14)-C(15)	121.10(19)
O(11)-C(14)-C(25)	119.1(2)

C(15)-C(14)-C(25)	119.7(2)
O(3)-C(15)-C(16)	124.7(2)
O(3)-C(15)-C(14)	115.4(2)
C(16)-C(15)-C(14)	119.9(2)
C(15)-C(16)-C(21)	120.1(2)
C(29)-C(17)-C(8)	103.67(17)
C(45)-C(18)-C(28)	125.7(2)
C(45)-C(18)-C(53)	120.2(2)
C(28)-C(18)-C(53)	113.92(19)
C(1)-C(21)-C(16)	120.8(2)
C(1)-C(21)-C(48)	117.7(2)
C(16)-C(21)-C(48)	121.4(2)
O(4)-C(25)-C(1)	120.61(18)
O(4)-C(25)-C(14)	119.0(2)
C(1)-C(25)-C(14)	120.3(2)
C(53)-O(27)-C(48)	113.47(19)
C(29)-C(28)-C(18)	125.98(18)
C(29)-C(28)-C(1)	117.13(18)
C(18)-C(28)-C(1)	116.26(18)
C(28)-C(29)-C(13)	128.8(2)
C(28)-C(29)-C(17)	123.17(18)
C(13)-C(29)-C(17)	107.87(17)
C(13)-C(32)-C(47)	121.5(2)
C(13)-C(32)-C(65)	122.5(2)
C(47)-C(32)-C(65)	115.6(2)
C(43)-O(35)-C(73)	119.3(3)
C(13)-C(36)-C(8)	104.56(17)
O(19)-C(43)-O(35)	123.6(3)
O(19)-C(43)-C(8)	125.8(2)
O(35)-C(43)-C(8)	110.6(2)
C(18)-C(45)-C(47)	119.7(2)
C(18)-C(45)-C(60)	126.1(2)
C(47)-C(45)-C(60)	114.1(2)
O(37)-C(47)-C(32)	120.5(2)
O(37)-C(47)-C(45)	120.9(2)
C(32)-C(47)-C(45)	118.3(2)

O(27)-C(48)-C(21)	111.8(2)
O(27)-C(53)-C(18)	116.4(2)
C(62)-C(60)-C(71)	109.9(3)
C(62)-C(60)-C(67)	105.5(3)
C(71)-C(60)-C(67)	108.1(3)
C(62)-C(60)-C(45)	112.0(2)
C(71)-C(60)-C(45)	112.0(2)
C(67)-C(60)-C(45)	109.0(2)
C(64)-O(61)-C(78)	118.3(3)
O(39)-C(64)-O(61)	123.6(3)
O(39)-C(64)-C(8)	126.3(3)
O(61)-C(64)-C(8)	110.1(2)
O(35)-C(73)-C(72)	110.8(4)
C(01)-C(78)-O(61)	113.0(6)
C(23)-C(2)-C(12)	118.39(19)
C(23)-C(2)-C(20)	119.6(2)
C(12)-C(2)-C(20)	122.0(2)
C(31)-O(5)-C(51)	117.7(2)
C(31)-C(6)-C(23)	120.0(2)
C(12)-O(7)-C(76)	114.6(2)
C(10)-O(9)-C(70)	114.5(2)
O(9)-C(10)-C(31)	121.2(2)
O(9)-C(10)-C(12)	118.8(2)
C(31)-C(10)-C(12)	119.8(2)
O(7)-C(12)-C(10)	119.0(2)
O(7)-C(12)-C(2)	120.02(19)
C(10)-C(12)-C(2)	120.9(2)
C(33)-C(20)-C(34)	125.52(18)
C(33)-C(20)-C(2)	117.32(19)
C(34)-C(20)-C(2)	116.50(18)
C(38)-C(22)-C(33)	126.9(2)
C(38)-C(22)-C(41)	123.2(2)
C(33)-C(22)-C(41)	109.3(2)
C(6)-C(23)-C(2)	120.8(2)
C(6)-C(23)-C(46)	121.3(2)
C(2)-C(23)-C(46)	117.8(2)

C(33)-C(24)-C(44)	103.70(18)
C(42)-O(30)-C(46)	113.8(2)
O(5)-C(31)-C(10)	116.0(2)
O(5)-C(31)-C(6)	124.0(2)
C(10)-C(31)-C(6)	120.0(2)
C(20)-C(33)-C(22)	128.8(2)
C(20)-C(33)-C(24)	123.05(18)
C(22)-C(33)-C(24)	108.04(18)
C(58)-C(34)-C(20)	125.5(2)
C(58)-C(34)-C(42)	120.8(2)
C(20)-C(34)-C(42)	113.56(19)
C(22)-C(38)-C(56)	121.3(2)
C(22)-C(38)-C(66)	123.0(2)
C(56)-C(38)-C(66)	115.3(2)
C(22)-C(41)-C(44)	104.66(18)
O(30)-C(42)-C(34)	116.0(2)
C(52)-C(44)-C(50)	110.2(2)
C(52)-C(44)-C(41)	113.3(2)
C(50)-C(44)-C(41)	108.1(2)
C(52)-C(44)-C(24)	111.8(2)
C(50)-C(44)-C(24)	109.66(19)
C(41)-C(44)-C(24)	103.55(18)
O(30)-C(46)-C(23)	112.3(2)
C(50)-O(49)-C(80)	116.8(3)
O(40)-C(50)-O(49)	122.4(3)
O(40)-C(50)-C(44)	125.8(2)
O(49)-C(50)-C(44)	111.8(2)
O(26)-C(52)-O(63)	124.3(3)
O(26)-C(52)-C(44)	125.5(3)
O(63)-C(52)-C(44)	110.1(2)
C(69)-C(55)-C(74)	107.6(3)
C(69)-C(55)-C(59)	105.3(3)
C(74)-C(55)-C(59)	109.5(3)
C(69)-C(55)-C(58)	109.7(3)
C(74)-C(55)-C(58)	112.4(2)
C(59)-C(55)-C(58)	111.9(2)

O(54)-C(56)-C(58)	120.7(2)
O(54)-C(56)-C(38)	121.3(3)
C(58)-C(56)-C(38)	117.7(2)
C(34)-C(58)-C(56)	119.4(2)
C(34)-C(58)-C(55)	126.2(2)
C(56)-C(58)-C(55)	114.3(2)
C(52)-O(63)-C(90)	119.3(3)
C(91)-C(80)-O(49)	113.3(5)
C(77)-C(90)-O(63)	108.3(4)

Table 4. Anisotropic displacement parameters (^{2}x 10^3) for cwc-tbu2. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	46(1)	38(1)	45(1)	-5(1)	-1(1)	2(1)
O(3)	81(1)	62(1)	68(1)	-6(1)	-4(1)	-24(1)
O(4)	75(1)	57(1)	42(1)	-2(1)	-5(1)	-4(1)
C(8)	57(1)	48(1)	38(1)	-4(1)	-2(1)	9(1)
O(11)	65(1)	55(1)	62(1)	14(1)	-1(1)	-9(1)
C(13)	60(1)	41(1)	38(1)	-1(1)	-4(1)	-1(1)
C(14)	53(1)	43(1)	52(1)	4(1)	-1(1)	1(1)
C(15)	48(1)	47(1)	60(2)	-5(1)	-5(1)	-2(1)
C(16)	53(1)	53(1)	46(1)	-8(1)	-5(1)	4(1)
C(17)	51(1)	45(1)	45(1)	-4(1)	3(1)	1(1)
C(18)	51(1)	46(1)	47(1)	3(1)	4(1)	3(1)
O(19)	123(2)	77(1)	43(1)	-9(1)	2(1)	11(1)
C(21)	52(1)	49(1)	43(1)	-4(1)	2(1)	3(1)
C(25)	49(1)	41(1)	46(1)	-2(1)	-2(1)	3(1)
O(27)	71(1)	97(1)	52(1)	-23(1)	15(1)	-15(1)
C(28)	49(1)	41(1)	40(1)	1(1)	-1(1)	-1(1)
C(29)	49(1)	41(1)	39(1)	0(1)	-1(1)	0(1)
C(32)	59(1)	50(1)	46(1)	0(1)	-6(1)	-5(1)
O(35)	129(2)	68(1)	62(1)	3(1)	-15(1)	40(1)
C(36)	67(1)	41(1)	50(1)	-6(1)	-6(1)	2(1)
O(37)	70(1)	103(2)	78(1)	-11(1)	-28(1)	15(1)
O(39)	98(2)	112(2)	69(2)	-41(1)	2(1)	29(1)
C(43)	58(1)	57(1)	46(1)	-3(1)	3(1)	7(1)
C(45)	48(1)	53(1)	52(1)	5(1)	-1(1)	4(1)
C(47)	49(1)	59(1)	57(1)	1(1)	-6(1)	-5(1)
C(48)	77(2)	67(1)	44(1)	-3(1)	0(1)	-5(1)
C(53)	58(1)	61(1)	70(2)	-16(1)	14(1)	0(1)
C(57)	105(2)	86(2)	89(3)	-25(2)	-7(2)	-32(2)
C(60)	47(1)	77(2)	60(2)	2(1)	4(1)	-4(1)
O(61)	60(1)	170(3)	98(2)	-61(2)	20(1)	1(1)
C(62)	65(2)	106(2)	63(2)	15(2)	9(1)	-2(2)

C(64)	72(2)	72(2)	46(2)	-7(1)	2(1)	20(1)
C(65)	80(2)	62(1)	71(2)	-10(1)	-11(2)	-19(1)
C(67)	87(2)	124(3)	105(3)	-13(3)	22(2)	-48(2)
C(68)	81(2)	80(2)	75(2)	4(2)	22(2)	0(2)
C(71)	58(2)	135(3)	92(3)	16(2)	11(2)	32(2)
C(72)	127(3)	84(2)	96(3)	8(2)	-34(2)	17(2)
C(73)	134(3)	94(2)	73(2)	28(2)	-6(2)	35(2)
C(75)	140(4)	114(3)	97(3)	-13(2)	-68(3)	25(3)
C(78)	74(2)	324(10)	131(4)	-74(5)	35(3)	38(4)
C(2)	47(1)	41(1)	47(1)	5(1)	4(1)	5(1)
O(5)	74(1)	59(1)	85(2)	2(1)	-1(1)	26(1)
C(6)	52(1)	51(1)	50(1)	7(1)	-1(1)	2(1)
O(7)	68(1)	72(1)	46(1)	0(1)	0(1)	6(1)
O(9)	67(1)	67(1)	75(1)	-23(1)	3(1)	11(1)
C(10)	49(1)	45(1)	60(2)	-5(1)	4(1)	2(1)
C(12)	49(1)	47(1)	45(1)	2(1)	2(1)	-2(1)
C(20)	51(1)	43(1)	41(1)	1(1)	-1(1)	6(1)
C(22)	67(1)	42(1)	40(1)	1(1)	-7(1)	6(1)
C(23)	52(1)	47(1)	45(1)	7(1)	4(1)	1(1)
C(24)	56(1)	46(1)	47(1)	9(1)	3(1)	0(1)
O(26)	106(2)	85(1)	70(1)	31(1)	0(1)	-19(1)
O(30)	75(1)	103(2)	52(1)	19(1)	17(1)	26(1)
C(31)	48(1)	46(1)	67(2)	8(1)	1(1)	5(1)
C(33)	54(1)	43(1)	39(1)	1(1)	-3(1)	5(1)
C(34)	53(1)	43(1)	50(1)	-3(1)	3(1)	2(1)
C(38)	67(1)	49(1)	50(1)	-4(1)	-10(1)	11(1)
O(40)	140(2)	95(2)	47(1)	10(1)	2(1)	-29(2)
C(41)	78(2)	42(1)	53(2)	7(1)	-12(1)	-2(1)
C(42)	59(1)	63(1)	64(2)	13(1)	15(1)	8(1)
C(44)	70(1)	52(1)	41(1)	7(1)	-5(1)	-7(1)
C(46)	79(2)	64(1)	43(1)	3(1)	2(1)	12(1)
O(49)	177(3)	86(2)	55(1)	5(1)	-27(2)	-55(2)
C(50)	69(1)	67(1)	43(1)	7(1)	-1(1)	-6(1)
C(51)	89(2)	60(2)	105(3)	12(2)	-23(2)	25(2)
C(52)	82(2)	62(1)	43(1)	11(1)	-5(1)	-18(1)
O(54)	87(1)	97(2)	88(2)	11(1)	-42(1)	-17(1)

C(55)	47(1)	81(2)	71(2)	-10(2)	2(1)	9(1)
C(56)	57(1)	57(1)	59(2)	-5(1)	-10(1)	9(1)
C(58)	52(1)	52(1)	56(1)	-6(1)	-4(1)	5(1)
C(59)	69(2)	121(3)	72(2)	-33(2)	7(2)	9(2)
O(63)	69(1)	139(2)	103(2)	59(2)	15(1)	-6(1)
C(66)	86(2)	61(1)	79(2)	6(2)	-17(2)	22(1)
C(69)	99(3)	143(4)	137(4)	13(3)	29(3)	70(3)
C(70)	80(2)	102(2)	84(2)	-11(2)	23(2)	16(2)
C(74)	69(2)	155(4)	89(3)	-34(3)	13(2)	-33(2)
C(76)	106(3)	95(2)	87(3)	-7(2)	-34(2)	-2(2)
C(77)	130(4)	117(3)	191(6)	-21(4)	52(4)	-40(3)
C(80)	221(6)	142(4)	64(2)	-9(3)	-30(3)	-70(4)
C(90)	96(3)	140(4)	118(4)	27(3)	28(2)	-22(3)
C(91)	322(11)	232(8)	78(3)	-5(4)	-40(5)	-164(8)
C(01)	137(5)	305(10)	197(7)	0(7)	54(5)	121(6)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å ^{2}x 10 ^{3}).

	x	y	z	U(eq)
H(16)	175	6017	27	60
H(17A)	379	7830	3089	57
H(17B)	169	7786	2034	57
H(36A)	1130	9395	2427	63
H(36B)	1064	9054	3400	63
H(48A)	753	6918	-602	75
H(48B)	997	7458	70	75
H(53A)	2538	6701	427	75
H(53B)	1938	6381	931	75
H(57A)	-761	5313	104	140
H(57B)	-704	4623	518	140
H(57C)	-73	4966	124	140
H(62A)	2669	8075	-350	117
H(62B)	2825	7344	-418	117
H(62C)	3381	7846	-629	117
H(65A)	2672	9424	2370	106
H(65B)	2850	9070	3297	106
H(65C)	2166	9419	3196	106
H(67A)	3211	8724	975	158
H(67B)	3842	8484	445	158
H(67C)	3781	8379	1520	158
H(68A)	-701	6227	3314	118
H(68B)	-724	5591	3887	118
H(68C)	-922	5590	2835	118
H(71A)	4077	7270	519	142
H(71B)	3510	6812	852	142
H(71C)	3875	7251	1570	142
H(72A)	-1075	9514	401	154
H(72B)	-1001	10222	63	154
H(72C)	-1046	10071	1128	154
H(73A)	0	9606	63	121

H(73B)	47	10281	532	121
H(75A)	1279	5891	3594	175
H(75B)	1303	6405	4385	175
H(75C)	1759	6476	3511	175
H(78A)	-1518	8494	3643	211
H(78B)	-1251	9189	3792	211
H(6)	2546	4008	48	61
H(24A)	2610	2281	2084	60
H(24B)	2842	2215	3127	60
H(41A)	3526	976	3363	69
H(41B)	3584	665	2368	69
H(42A)	4326	3673	862	74
H(42B)	4924	3352	354	74
H(46A)	3365	2576	89	74
H(46B)	3120	3114	-585	74
H(51A)	2212	5074	91	127
H(51B)	1537	5307	512	127
H(51C)	1610	4603	156	127
H(59A)	5823	2197	-612	131
H(59B)	5263	2702	-446	131
H(59C)	5112	1974	-320	131
H(66A)	4648	675	3209	113
H(66B)	5327	1037	3266	113
H(66C)	5133	668	2359	113
H(69A)	6242	1768	1566	190
H(69B)	6322	1643	498	190
H(69C)	5700	1381	1026	190
H(70A)	1534	4608	2919	134
H(70B)	1747	4461	3944	134
H(70C)	1685	3905	3221	134
H(74A)	6266	2910	1547	157
H(74B)	5912	3290	752	157
H(74C)	6503	2833	516	157
H(76A)	4274	3472	3265	144
H(76B)	3967	3608	4245	144
H(76C)	3922	4125	3460	144

H(77A)	480	1093	2462	219
H(77B)	372	673	3350	219
H(77C)	963	526	2677	219
H(80A)	2078	653	78	170
H(80B)	2671	175	177	170
H(90A)	1239	1084	4055	142
H(90B)	882	1675	3605	142
H(91A)	2034	-508	807	316
H(91B)	1765	-294	-166	316
H(91C)	1439	-29	744	316
H(01A)	-1694	9489	2524	320
H(01B)	-2222	9165	3169	320
H(01C)	-1931	8790	2320	320