A Thesis for the Degree of Ph.D. in Science

Two-step Synthesis of Multi-substituted Amines and Unified Total Synthesis of Stemoamide-type Alkaloids

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Contents

Part 2. Unified Total Synthesis of Stemoamide-type Alkaloids

Abbreviations

PIFA	[bis(trifluoroacetoxy)iodo]benzene
TMDS	1,1,3,3-tetramethyldisiloxane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
CSA	10-camphorsulfonic acid
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
HOBt	1-hydroxybenzotriazole
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
IBX	2-iodoxybenzoic acid
ACE	acenaphthylene
Ac	acetyl
R	any alkyl group
M	any metal
aq.	aqueous
Bn	benzyl
Cbz	benzyloxycarbonyl
Bu	butyl
cat.	catalytic amount of
cod	cyclooctadiene
coe	cyclooctene
Cp	cyclopentadienyl
dr	diastereomeric ratio
dba	dibenzylideneacetone
DHP	dihydropyran
DIBAL-H	diisobutylalminium hydride
DIPT	diisopropyltartrate
DMF	dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
equiv	equivalent
Et	ethyl
(en)	ethylenediamine
DG	Gibbs free energy
h	hour
i	iso
K	Kelvin
LLS	longest linear sequence
mCPBA	*m*-chloroperbenzoic acid
Ms	mesyl
m	meta
MEM	methoxyethoxymethyl
Me	methyl
min	minute
MS4A	molecular sieve 4A
NMM	*N*-methylmorpholine
n	normal
N/A	not applicable
NMR	nuclear magnetic resonance
PMB	paramethoxybenzyl
p	para
Ph	phenyl
PEI	polyethylene imine
PLC	preparative layer chromatography
Pr	propyl
PPTS	*p*-toluenesulfonic acid pyridine salt
Py	pyridine
quant	quantitative yield
rt	room temperature
s	secondary
sec	secondary
Boc	*t*-butoxycarbonyl
TBS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
temp.	temperature
t	tertiary
tert	tertiary
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
Ts	tosyl (*p*-toluenesulfonyl)
TFA	trifluoroacetyl or trifluoroacetic acid
Tf	trifluoromethylsulfonyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl

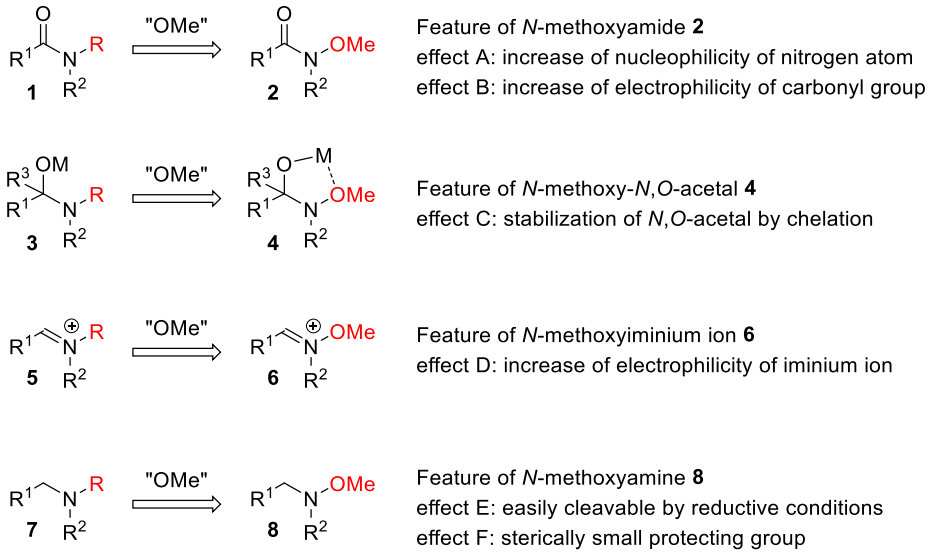
Part 1. Two-step Synthesis of Multi-substituted Amines

Chapter 1. Introduction

1-1. Features of *N*-Alkoxyamine Derivatives

Not only Weinreb amide but other *N*-alkoxyamine derivatives possess various features originated from conflicting nature of "electronegativity" and "unshared electron pair" of the oxygen atom in the *N*-alkoxy group. Herein, the important effects of *N*-alkoxy group positively assisting various type of reaction are summarized (Figure 1-1). For example, while a carbonyl oxygen atom is the most nucleophilic site in an ordinary amide **1**, a nitrogen atom becomes the most nucleophilic in *N*-methoxyamide **2** (effect A). This is because the inductive electron withdrawal of the alkoxy group and the acyl group competes within each other. In addition, the electron withdraw effect of the methoxy group also increases the electrophilicity of the carbonyl group (effect B).[1] Comparing an ordinary *N*,*O*-acetal **3**, *N*,*O*-acetal **4** can be stabilized by formation of a five-membered chelation, which plays an important role in Weinreb ketone synthesis[2] by preventing C-O or N-O bond cleavage (effect C). In addition, a chemoselective nucleophilic addition of Grignard reagent to an ester in the presence of an aldehyde or a ketone reported by Colby and co-workers also use chelation effect.[3] Compared to ordinary iminium ion **5**, the inductive electron withdrawal of the methoxy group also leads to increase in electrophilicity of oxyiminium ion **6** (effect D).[4] Furthermore, the methoxy group serves as a unique protecting group of the nitrogen atom, removable with a mild single electron reducing agent such as SmI_2, $Mo(CO)_6$, or Zn/acid (compound **7** or compound **8**, effect E).[5,6,7] Besides the characteristic conditions for cleaving N-O bond, the *N*-methoxy group is sterically the smallest protecting group, which would be advantageous for various reactions occurring around nitrogen atom (effect F).

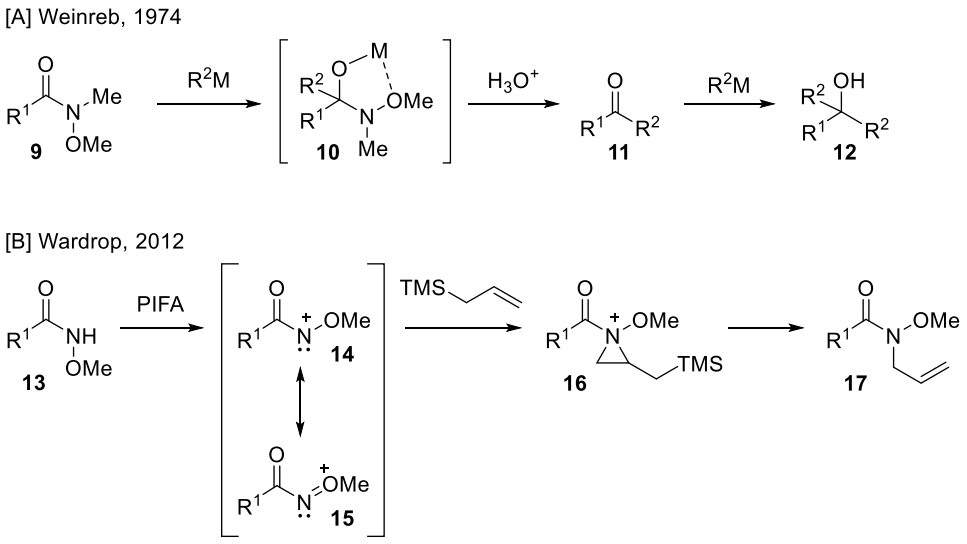
Figure 1-1. Features of *N*-alkoxyamine derivatives



1-2. *N*-Methoxyamide (Weinreb Amide)[8]

Chida-Sato research group has been exploring new synthetic strategies that take advantage of a heteroatom-heteroatom bond for the synthesis of biologically active complex natural products. The connection of a heteroatom and another heteroatom opens it up to new reactivities as represented by α-effect of hydroperoxide, [9] and chelation effect of Weinreb amide.[2] In 1981, Weinreb and co-workers reported a reliable method to access ketone from carboxylic acid derivative (Scheme 1-1A, **9**→**10**→**11**). Treatment of Weinreb amide **9** with organometallic reagent 'R^2M' leads to the formation of the five-membered chelated intermediate **10**, which prevents the addition of second nucleophile. And sequential workup gives ketone **11** without the formation of tertiary alcohol **12**. Secondary *N*-methoxyamide **13** shows a unique reactivity originated from the adjacent methoxy group (Scheme 1-1B, **13**→**14**→**16**→**17**).[10] Treatment of *N*-methoxyamide **13** with $PhI(OCOCF_3)_2$ (PIFA) results in formation of *N*-allylated methoxyamide **17** via aziridinium ion **16** generated by concerted insertion of allylsilane to acylnitrenium ion **14**. Driving forth of producing highly reactive species **14** is the resonance stabilization of nitrenium ion (**14**↔**15**).

Scheme 1-1. Unique reactivities of *N*-alkoxyamide

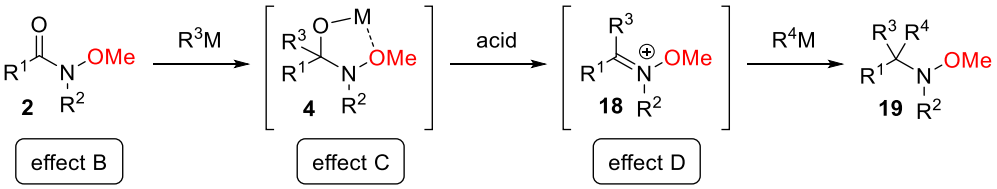


1-3. Reductive Nucleophilic Addition to *N*-Methoxyamide

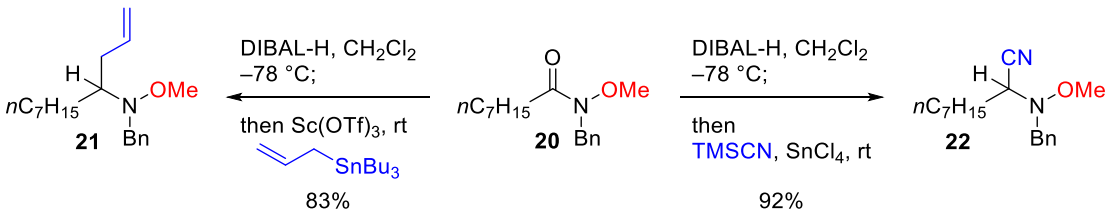
The reductive functionalization of amides is one of the greatest methods for synthesizing multi-substituted amines due to the following two reasons. First, synthetic method to form amide bonds have been established. Second, while amines cannot be handled easily due to its strong basicity, nucleophilicity, and oxophilicity, amides can be handled because of its low reactivity. Thus amides would be a useful nitrogen source for synthesis of alkaloids. However, the stability of amides has prevented the late-stage conversion of amides to functionalized amines in the presence of more reactive functional groups. Therefore, recently, development of amide-selective conversion in the late-stage of natural products and drug syntheses have been desired.

The proposed mechanism of the reductive nucleophilic addition to *N*-methoxyamide **2** is shown in Scheme 1-2. Treatment of *N*-methoxyamide **2** with an organometallic reagent (R^3M) allows the formation of the chelated intermediate **4** at moderate temperatures (Figure 1-1, effects B and C). Then, addition of acid promotes the formation of highly electrophilic *N*-oxyiminium ion **18**, and subsequent addition of second nucleophile (R^4M) would proceed smoothly due to high electrophilicity of **18** to give *N*-methoxyamine **19** in a one-pot process (Figure 1-1, effect D). In 2010, Chida-Sato group developed the novel method of the reductive nucleophilic addition to *N*-methoxyamide in using DIBAL-H (Scheme 1-3).[1,11] Addition of DIBAL-H to a solution of *N*-methoxyamide **20** in CH_2Cl_2 at –78 °C, and subsequent one-pot addition of allylstannane (3.0 equiv) and $Sc(OTf)_3$ (1.1 equiv) afforded the desired amine **21** in 92% yield. Reductive cyanation of **20** also proceeded successfully to form α-cyanoamine **22**, whose substructure is often seen in the bioactive complex alkaloids.

Scheme 1-2. Nucleophilic addition to *N*-methoxyamide

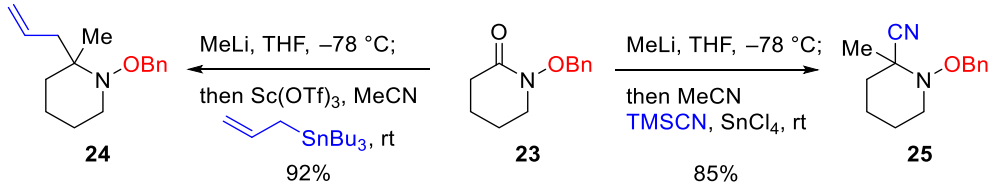


Scheme 1-3. Reductive allylation and cyanation of *N*-methoxyamide

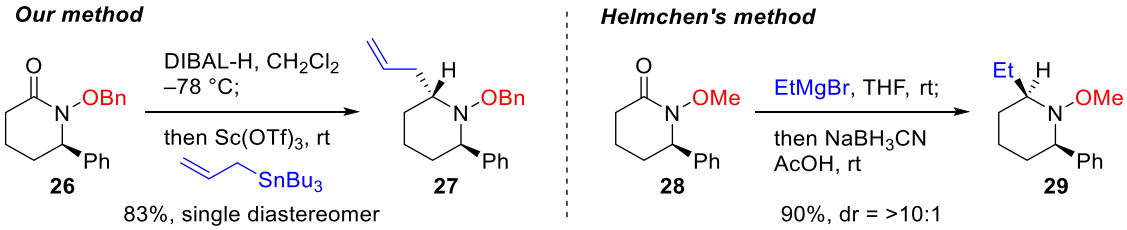


The nucleophilic addition to *N*-alkoxyamides also enabled access to *α*-tertiary amine moiety in a one-pot reaction (Scheme 1-4).[11] Treatment of *N*-benzyloxyamide **23** with MeLi at –78 °C followed by allylation or cyanation afforded tertiary amines **24** or **25** in 92% or 85% yield, respectively. The reductive allylation of *N*-benzyloxyamide **26** afforded 2,6-*trans*-substituted piperidine **27** with complete diastereoselectivity by treatment of DIBAL-H and allylstannane (Scheme 1-5-left). Helmchen and co-workers reported Grignard reagent mediated reductive nucleophilic addition of *N*-methoxyamide (Scheme 1-5-right).[12] In their method, first nucleophile is carbon nucleophile and second nucleophile is hydride reductant such as $NaBH_4$ or Raney nickel, and the inverse order of hydride and carbon source resulted in opposite diastereoselectivity. They performed the successive addition of EtMgBr and $NaBH_3CN$ to *N*-methoxyamide **28** to afford the 2,6-*cis*-substituted piperidine **29** in 90% yield and >10:1 diastereomeric ratio.

Scheme 1-4. Reductive allylation and cyanation of *N*-benzyloxyamide **23**

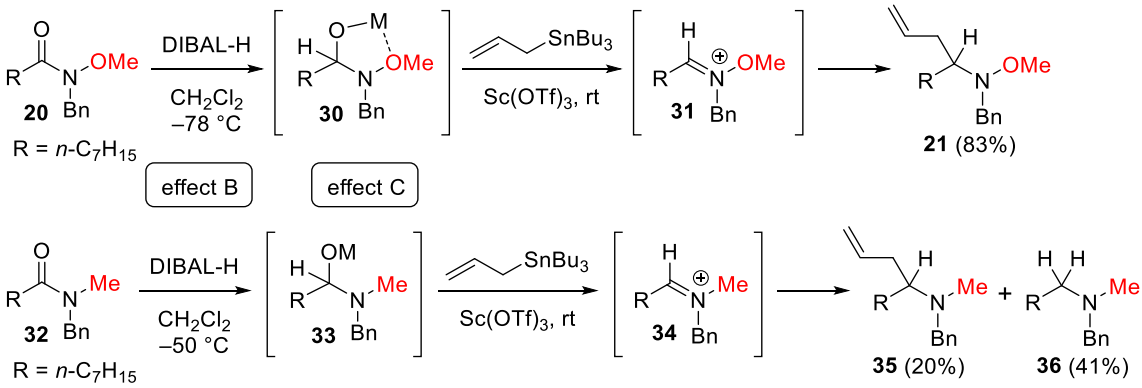


Scheme 1-5. Control of diastereoselectivity by exchanging the order of nucleophiles



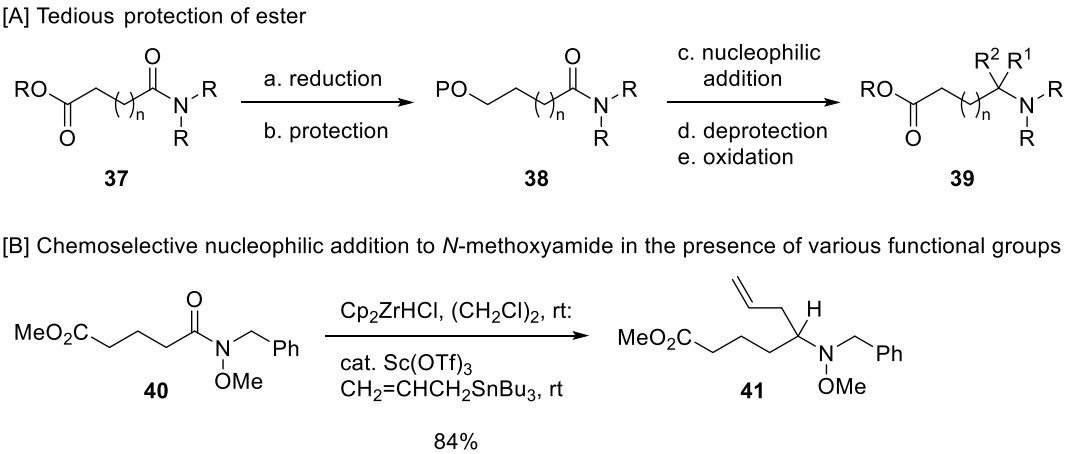
To confirm the beneficial effects of *N*-alkoxy groups, a control experiment between *N*-methoxyoctanamide **20** and *N*-methyloctanamide **32** was conducted (Scheme 1-6). *N*-Methoxyamide **20** reacted with DIBAL-H (1.3 equiv) at –78 °C, and subsequent allylation gave *N*-methoxyamine **21** as a single product. In contrast, the reduction of *N*-methylamide **32** was not complete at –78 °C, and the reaction was required to be performed at –50 °C (effect B). Furthermore, after completion of the allylation, *N*-methylamine **35** was obtained in low yield along with the undesired over reduced product **36** (**35**: 20%, **36**: 41%). These results indicates that *N*,*O*-acetal **33** would easily decompose to form iminium ion **34**, which would readily be converted to over-reduced product **36**. Moreover, the chelation effect was crucial for this one-pot process.

Scheme 1-6. Control experiment with and without *N*-methoxy group



Although various effects of the *N*-methoxy group enable addition of two different nucleophiles to an amide carbonyl group in one-pot process, these methods require the addition of highly nucleophilic organometallic reagent such as DIBAL-H, alkyllithium reagent, or Grignard reagent. Therefore, more electrophilic functional groups such as ester, nitro, or nitrile groups cannot be tolerated under these conditions. For example, ester and amide are embedded in a same molecule, the ester group of **37** should be converted to non-reactive ether **38** through reduction and protection. Next the nucleophilic addition of amide followed by reconstruction of the ester could give the desired product **39** (Scheme 1-7A). These tedious redox reactions and protecting group manipulation would decrease synthetic efficiency. However, the Schwartz reagent, which is an amide-selective reducing agent, was effective for the development of the amide-selective nucleophilic addition (Scheme 1-7B).[13] Treatment of *N*-methoxyamide **40** with the Schwartz reagent, and subsequent addition of $Sc(OTf)_3$ and allylstannane afforded *N*-methoxyamine **41** without harming more electrophilic methyl ester.

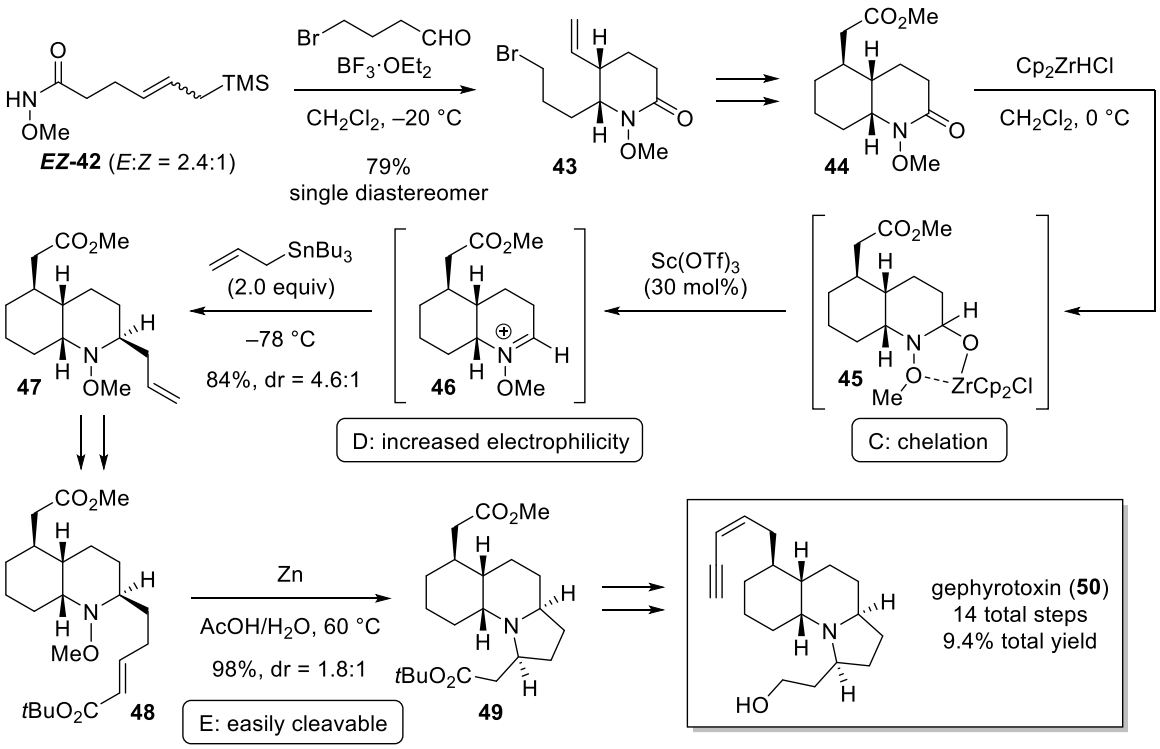
Scheme 1-7. Amide-selective nucleophilic addition by using Schwartz reagent



1-4. Total Synthesis of Gephyrotoxin (**50**)

In 2014, Chida-Sato group disclosed the total synthesis of gephyrotoxin featuring two-step construction of multi-substituted *N*-methoxypiperidines in highly chemoselective fashion (Scheme 1-8).[13] Details of the key reactions are depicted in Chapter 2. The synthesis commenced with the synthesis of the bicyclic *N*-methoxylactam **44** taking advantage of the key coupling reaction of *N*-methoxyamide ***EZ*-42** and 4-bromobutyraldehyde. A solution of an amide and an aldehyde in CH_2Cl_2 was treated with $BF_3 \cdot OEt_2$ at –20 °C to form *N*-methoxypiperidone **43**. The key bicyclic intermediate **44** was prepared by several transformations from **43**, and then the lactam-selective nucleophilic addition was performed. The reduction of **44** with 1.1 equiv of Cp_2ZrHCl led to formation of the five-membered chelated intermediate **45** (Figure 1-1, effect C). Then treatment with $Sc(OTf)_3$ (30 mol%) and allylstannane (2.0 equiv) achieved reductive allylation via oxyiminium intermediate **46** in completely lactam-selective fashion. Surprisingly, this allylation proceeded at –78 °C due to the increased electrophilicity of **46** (Figure 1-1, effect D), and favorably produced the desired compound **47** with 4.6:1 diastereoselectivity. The resulting decahydroquinoline **47** was then converted to enoate **48**. Reductive cleavage of N-O bond of **48** was achieved by addition of activated Zn powder in the presence of AcOH at 60 °C, and subsequent *aza*-Michael reaction proceeded to give **49** in 98% yield and with moderate diastereoselectivity (Figure 1-1, effect E). Finally, introduction of the enyne side-chain and reduction of *tert*-butyl ester accomplished the total synthesis of gephyrotoxin (**50**).

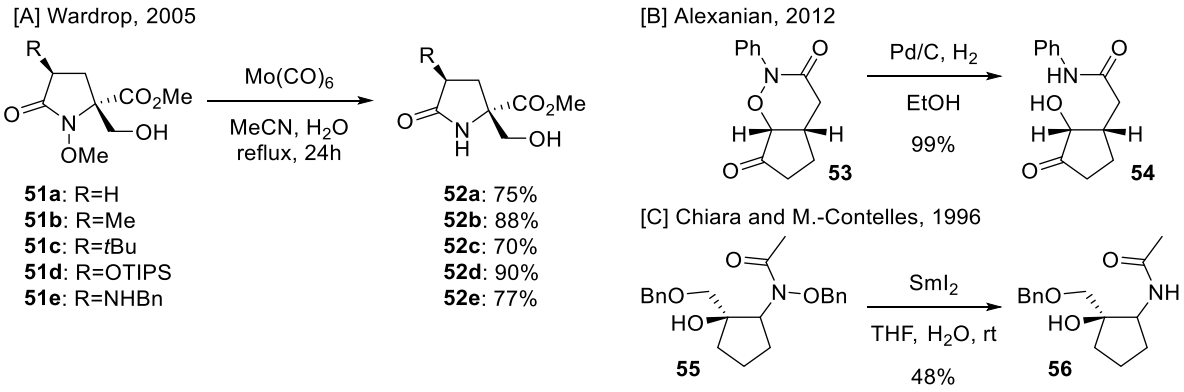
Scheme 1-8. Total Synthesis of Gephyrotoxin (**50**)



1-5. Cleavage of N-O Bond[14]

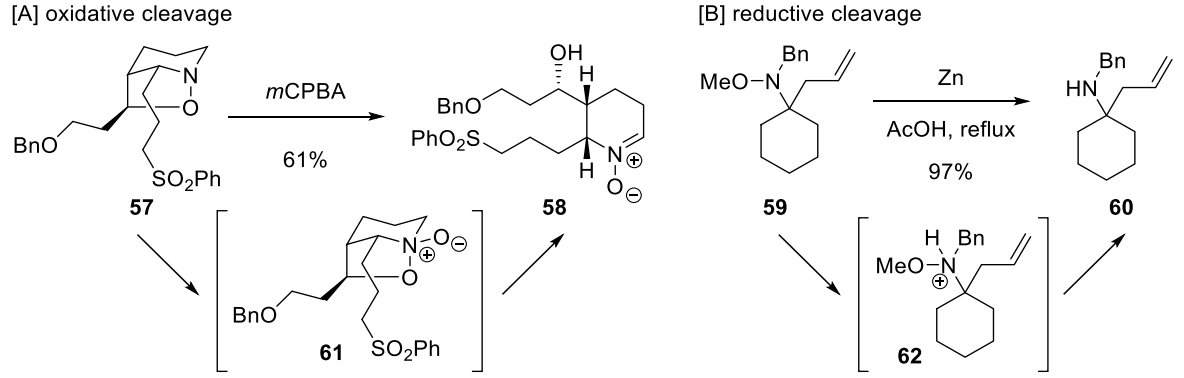
Heteroatom-heteroatom bonds, for instance N=N, N-N, N-O, O-O, are known to be cleaved under reductive-, radical-, or oxidative conditions. To cleave the N-O bond of *N*-alkoxyamides, two representative methods have been commonly used. The first method is single-electron reduction with low valent metals (Scheme 1-9A, 1-9C).[5-7,15] The other is Pd or Ni catalyzed hydrogenation (Scheme 1-9B).[16]

Scheme 1-9. Reductive cleavage of N-O bond of *N*-alkoxyamides



The required conditions to cleave the N-O bonds of amines are different from those of amides. In case to cleave the N-O bond of *N*-alkoxyamines, the basicity and electrophilicity of the amine are important. For example, treatment of bicyclic compound **57** with *m*CPBA provoked oxidative N-O bond cleavage to give nitrone **58** (Scheme 1-10A).[17] *N*-Methoxyamine **59** was converted to secondary amine **60** by treatment with Zn/AcOH (Scheme 1-9B).[4] These reactions proceeded via onium intermediates such as **61** and **62**.

Scheme 1-10. Oxidative and reductive cleavage of N-O bond of *N*-alkoxyamines



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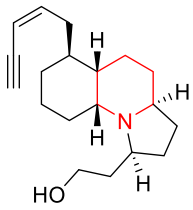
Chapter 2. Two-step Synthesis of Multi-substituted *N*-Methoxypiperidine

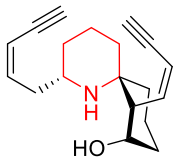
2-1. Piperidine Alkaloids

The secondary metabolites generated from plants or animals possess a variety of bioactivities. In general, most of medicinal drugs contain nitrogen atom in its structure. Therefore various scientists have been interested in the development of synthetic method for alkaloids and heterocyclic compounds including nitrogen atom. Piperidines are one of the most common and important structural motifs seen in a number of natural products. Some selected examples of piperidine alkaloids attracting a number of synthetic chemist are listed in Figure 2-1. Gephyrotoxin (**50**)[1,2] and histrionicotoxin (**63**)[3,4] possesses synthetically attractive structures including α-multi-substituted piperidine skeleton and enyne structure. Therefore a number of synthetic studies on **50** and **63** have been investigated to date. From the roots of *Rauwolfia serpentina*, several bioactive indole alkaloids were isolated including reserpine (**64**) and ajmaline (**65**). Reserpine (**64**) possesses an antihypertensive and antipsychotic activities,[5] and ajmaline (**65**) has an antiarrhythmic activity.[6] From the Chinese plant *Gelsemium* (*G. elegans*), an indole alkaloid, koumidine (**66**) was isolated, which has a structure similar to **64** and **65**.[7] In fact, the biosynthetic route of **64**, **65**, and **66** were considered through the same intermediate.[8] Morphine (**67**) and cocaine (**68**) are well known as highly addictive drugs due to the strong activity on the central nerve.[9,10] On the other hand, tiotropium bromide (**69**: also known as Spiriva®), which possesses a structure similar to **68**, is utilized as a COPD (Chronic Obstructive Pulmonary Disease) drug.[11] Synthetic studies of these natural products and drugs shown in Figure 2-1 have been contributed to the improvement of organic synthetic chemistry from many aspects.

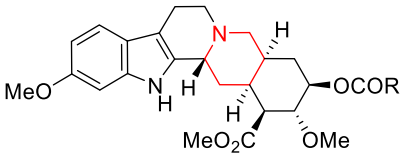
Figure 2-1. The piperidine alkaloids



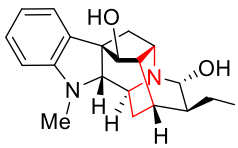
gephyrotoxin (**50**)



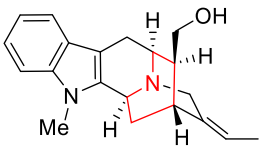
histrionicotoxin 283A (**63**)



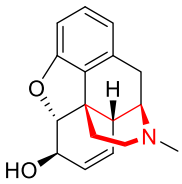
reserpine (**64**: R = 3,4,5-$(MeO)_3C_6H_2$)



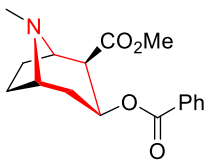
ajmaline (**65**)



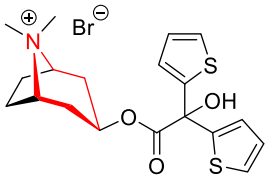
koumidine (**66**)



morphine (**67**)



cocaine (**68**)

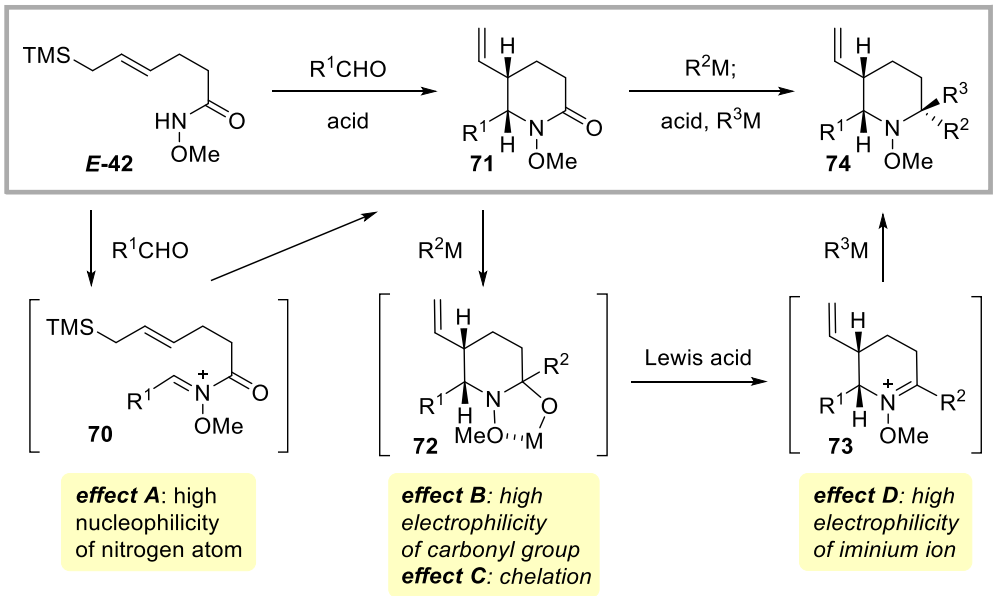


tiotropium bromide (**69**)

2-2. Synthetic Plan

We supposed that *N*-methoxy amides would be useful for synthesis of highly substituted piperidine compounds, including gephyrotoxin (**50**), ajmaline (**65**), and koumidine (**66**). These natural products possess the common structural motif; 2,3,6-trisubstituted piperidine skeleton **74**. A synthetic plan for the two-step access to highly substituted piperidine **74** from *N*-methoxyamide ***E*-42** is described in Scheme 2-1 (***E*-42→71→74**). The success of this process is highly dependent on the assistance from the *N*-methoxy group which acts as a reactivity control element. The first step is an acid-mediated direct coupling of *N*-methoxyamide ***E*-42** with an aldehyde, followed by spontaneous intramolecular allylation of the generated *N*-acyliminium ion **70** to give 2,3-disubstituted *N*-methoxy-piperidone **71**.[12] Intermolecular condensation of an ordinary amide with an aldehyde is very challenging due to the poor nucleophilicity of the amide nitrogen atom. However, incorporation of a methoxy group on the nitrogen atom results in an increase of the nucleophilicity (Figure 1-1, effect A), enabling direct coupling with an aldehyde R^1CHO. The second step of the two-step sequence is the nucleophilic addition to *N*-methoxylactam **71**, affording 2,3,6-multi-substituted *N*-methoxypiperidine **74**.[13] This nucleophilic addition takes advantage of both the increased electrophilicity of the *N*-methoxyamide and the chelation effect (Figure 1-1, effects B and C), and the increased electrophilicity of the *N*-methoxyiminium ion **73** (Figure 1-1, effect D). The addition of the first nucleophile R^2M to the *N*-methoxylactam would provide the five-membered chelated intermediate **72**. After addition of acid, the generated oxocarbenium ion **73** would then react with a mild nucleophile to provide *N*-methoxypiperidine **74** in a one-pot process.

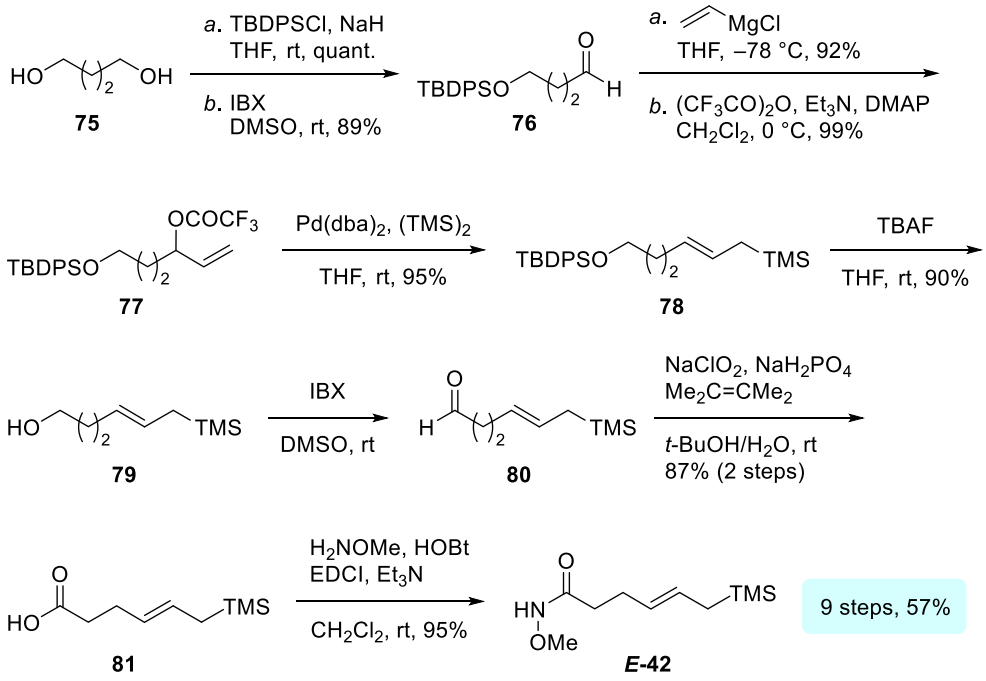
Scheme 2-1. Synthetic plan for the two-step synthesis of multi-substituted piperidine



2-3. Synthesis of Allylsilanes ***E*-42**, ***Z*-42**, and ***EZ*-42**

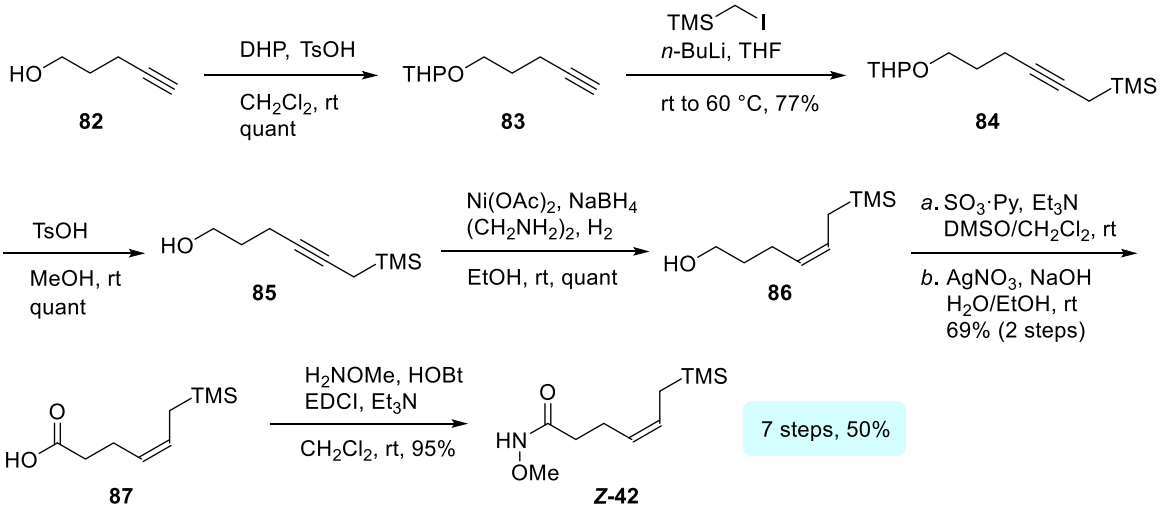
Allylsilane ***E*-42** was synthesized as shown in Scheme 2-2. Mono protection of the commercially available 1,4-butanediol (**75**) with the TBDPS group, followed by oxidation with IBX gave aldehyde **76**. Next, the resulting aldehyde **76** was converted to allylic ester **77** by Grignard reaction followed by trifluoroacetylation of the allylic alcohol. Treatment of **77** with a catalytic amount of $Pd(dba)_2$ and $(TMS)_2$ led to the formation of allylsilane **78**. Subsequently, the TBDPS group of **78** was removed with TBAF, and the resulting alcohol **79** was oxidized by IBX (**79**→**80**) and Kraus-Pinnick oxidation to afford carboxylic acid **81**. Finally, the condensation of **81** and *N*-methoxyamine hydrochloride proceeded to give ***E*-42** in 57% total yield over 9 steps.

Scheme 2-2. Synthesis of *E*-allylsilane ***E*-42**



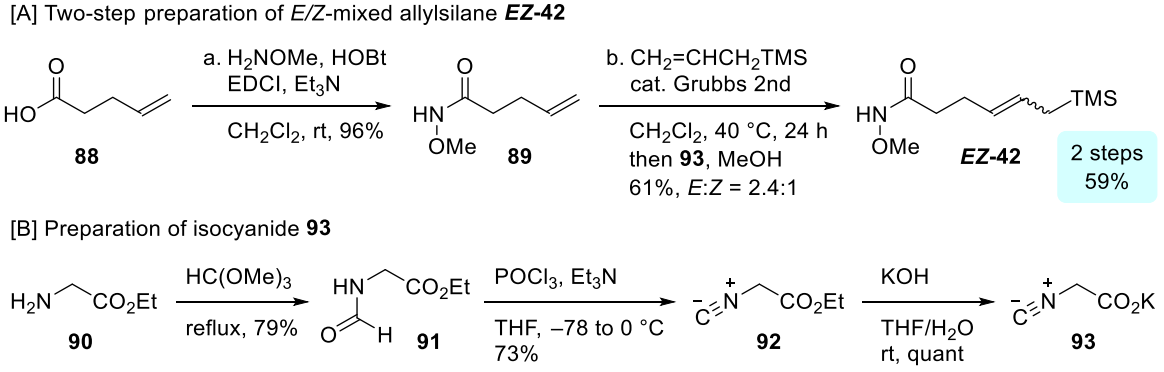
The allylsilane ***Z*-42** was prepared by using other synthetic route (Scheme 2-3). The commercially available 4-pentyn-1-ol (**82**) was protected as a THP ether, and subsequent alkylation of **83** with trimethylsilyl iodomethane gave internal alkyne **84**. Subsequently, the removal of the THP group (**84**→**85**), followed by *Z*-selective semi-reduction with nickel boride afforded the *Z*-olefin **86**. Finally, the primary hydroxy group of **86** was converted to *N*-methoxyamide by oxidation (**86**→**87**) and condensation, giving ***Z*-42** in 50% total yield over 7 steps.

Scheme 2-3. Synthesis of *Z*-allylsilane ***Z*-42**



Although both stereoisomers of allylsilanes ***E*-42** and ***Z*-42** were obtained, the sequence required a number of steps due to multiple oxidation and protection/deprotection. Thus, a two-step synthesis of *EZ*-allylsilane ***EZ*-42** was developed by utilizing cross metathesis reaction between *N*-methoxyamide **89** and allyltrimethylsilane (Scheme 2-4A). The commercially available 4-butenoic acid (**88**) was converted to *N*-methoxyamide **89** by condensation with *N*-methoxyamine in good yield. In this reaction, the workup with $NaHCO_3$ was necessary due to the removal of the side product derived from HOBt, which was inseparable from **89** by silica gel chromatography. Then, optimization of the cross metathesis reaction was conducted. The cross metathesis reaction with Grubbs 2nd generation catalyst proceeded in moderate yield, despite the presumable deactivation of catalyst caused by coordination with nitrogen atom.[14] The addition of isocyanide **93**, which was prepared from **90** by the sequence of reaction sequence depicted in Scheme 2-5B (**90**→**91**→**92**→**93**),[15] was effective in order to remove the side product derived from ruthenium catalyst.

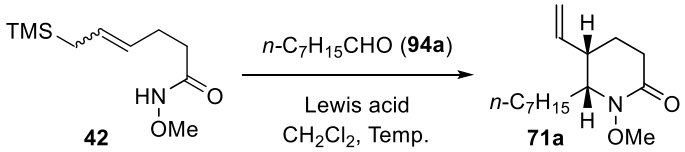
Scheme 2-4. Two-step synthesis of *EZ*-allylsilane ***EZ*-42**



2-4. The First Step: Coupling of *N*-Methoxyamide and Aldehyde

With both allylsilanes ***E*-42** and ***Z*-42** in hand, the first coupling reaction was optimized using *N*-methoxyamide ***E*-42** and octanal **94a**. No desired product **71a** was formed with $Sc(OTf)_3$, $TiCl_4$, $SnCl_4$, or TMSOTf (Table 2-1, entries 1-4). However, addition of $LiClO_4$ and a catalytic amount of $Bi(OTf)_3$[16] to a solution of ***E*-42** and octanal **94a** in CH_2Cl_2 initiated the coupling reaction, giving **71a** in 53% yield (Table 2-1, entry 5). The reaction proceeded in completely *cis*-stereoselective fashion with **71a** isolated as the single diastereomer. The yield of **71a** was improved to 85% with 2 equiv of $BF_3{\cdot}OEt_2$ at –20 °C, along with recovery of ***E*-42** in 12% yield (Table 2-1, entry 6). To consume the remaining ***E*-42**, added 1.0 equivalent of $BF_3{\cdot}OEt_2$ every 30 minutes, and found that addition of 6 equiv of $BF_3{\cdot}OEt_2$ resulted in complete consumption of ***E*-42** to give **71a** in 90% yield (Table 2-1, entry 7). Even if *Z*-allylsilane ***Z*-42** was treated with the optimized conditions, the reaction proceeded in 93% yield and completely *cis*-selective fashion (Table 2-1, entry 8). This result clearly suggested that the geometry of the double bond had no significant effect on either the yield or the diastereoselectivity.

Table 2-1. Optimization of acid and effect of the geometry of double bond

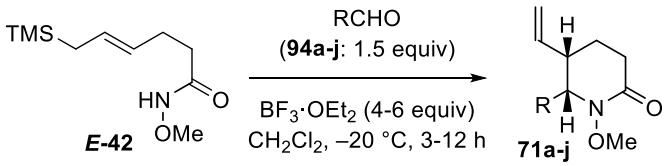


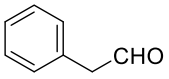
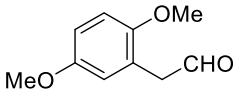
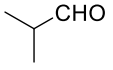
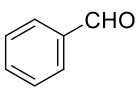
Entry	*E*/*Z*	substrate	Lewis acid (equiv)	Temp.	Yield
1	*E*	***E*-42**	$Sc(OTf)_3$ (2.0)	rt	0%
2	*E*	***E*-42**	$TiCl_4$ (2.0)	–78 °C	0%
3	*E*	***E*-42**	$SnCl_4$ (2.0)	–78 °C	0%
4	*E*	***E*-42**	TMSOTf (2.0)	–78 °C to –20 °C	trace
5	*E*	***E*-42**	$Bi(OTf)_3$ (5 mol%)/$LiClO_4$ (3.0)	0 °C to rt	53%
6	*E*	***E*-42**	$BF_3{\cdot}OEt_2$ (2.0)	–20 °C	85%
7	*E*	***E*-42**	$BF_3{\cdot}OEt_2$ (6.0)	–20 °C	90%
8	*Z*	***Z*-42**	$BF_3{\cdot}OEt_2$ (6.0)	–20 °C	93%

With optimal conditions in hand, the substrate scope of the coupling reaction with several aldehydes was surveyed (Table 2-2). Despite the strongly acidic conditions using $BF_3{\cdot}OEt_2$, the reaction smoothly proceeded in the presence of various functional groups. The coupling reaction with ***E*-42** and aldehyde **94b** with the hydroxy group protected as a TBDPS ether proceeded in 92% yield (Table 2-2, entry 2, **71b**: 92%). Methyl ester and alkyl bromide moieties did not interfere with this transformation (Table 2-2, entries 3 and 4, **71c**: 92%, **71d**: 80%). The coupling reaction of ***EZ*-42** (*E*:*Z* = 2.4:1) and aldehyde **94d** was used in the total synthesis of gephyrotoxin reported by Chida-Sato group, which afforded the desired *cis*-piperidone **71d** with complete *cis*-

selectivity (Table 2-2, entry 5, **71d**: 79%). Carbamates including acid-sensitive Boc group were compatible with these conditions (Table 2-2, entries 6 and 7, **71e**: 92%, **71f**: 75%). Although 2-arylacetoaldehyde derivatives **94g** and **94h** tend to be enolized, the coupling reactions smoothly took place, with **71g** and **71h** isolated in 78% and 92% yields, respectively (Table 2-2, entries 8 and 9). The sterically hindered *iso*-butyraldehyde **94i** required a longer reaction time (3 hour vs 2 days), but still gave the *cis*-cyclized product **71i** in 67% yield (Table 2-2, entry 10). The coupling reaction using the less electrophilic benzaldehyde **94j** resulted in moderate yield (Table2-2, entry 11, **71j**: 34%).

Table 2-2. Substrate scope of the coupling reaction of ***N*-methoxyamide *E*-42** and aldehyde **94**

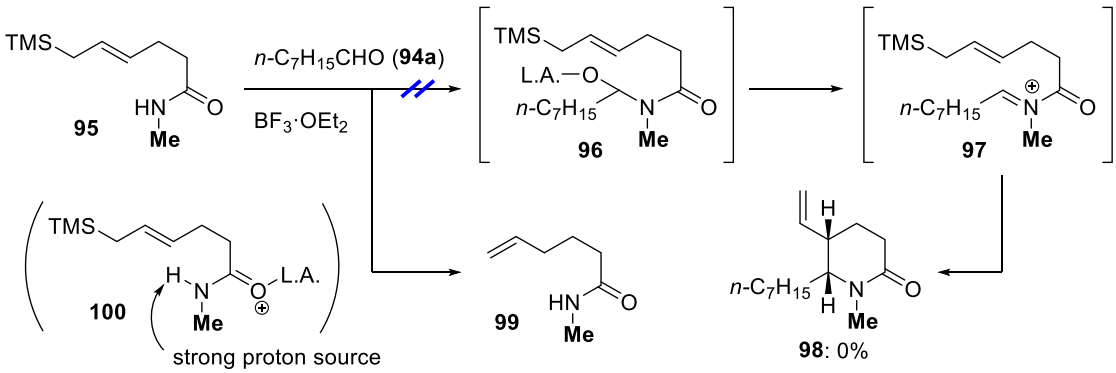


Entry	RCHO (**94a-j**)		Yield (%)[a]
1	n-$C_7H_{15}CHO$	(**94a**)	90
2	TBDPSO–CHO	(**94b**)	92
3	MeO_2C–CHO	(**94c**)	92
4	Br–CHO	(**94d**)	80
5			79[b]
6	Cbz(Bn)N–(CH2)4–CHO	(**94e**)	92
7	Boc(Bn)N–(CH2)4–CHO	(**94f**)	75
8		(**94g**)	78[c]
9		(**94h**)	92[c]
10		(**94i**)	67
11		(**94j**)	34

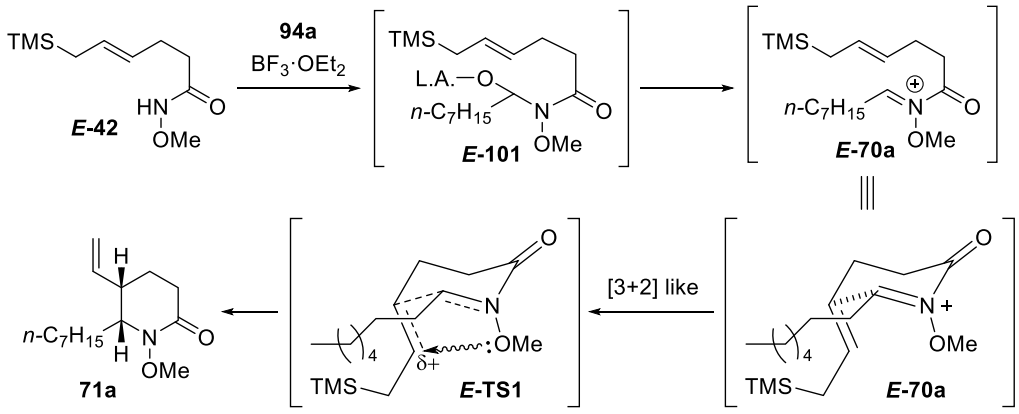
[a]Isolated yield of product **71**, [b]*E*/*Z*-mixed amide ***EZ*-42** was used instead of ***E*-42** [c]The diastereomeric ratios of **71g** and **71h** were 11:1 in favour of the cis-product.

In order to demonstrate the utility of the *N*-methoxy group, the coupling reaction of *N*-methylamide **95** with octanal **94a** was attempted. As a result, the coupling product **98** was not produced, but instead, formation of the terminal olefin **99** was observed. This can be rationalized by the intramolecular protonation via six-membered intermediate **100** (Scheme 2-5). In this coupling reaction, *N*-methoxy group would increase the nucleophilicity of the nitrogen atom of *N*-methoxyamide **42** and enable the formation of *N*,*O*-acetal ***E*-101**. The intramolecular cyclization would proceed smoothly due to higher electrophilicity of *N*-acyl-*N*-oxyiminium ion ***E*-70a** than that of ordinary *N*-acyliminium ion. In addition, stabilization of transition state ***E*-TS1** by through-space interaction between non-bonding electron of oxygen atom and *β*-cation of silyl group would affect the diastereocelectivity.[17]

Scheme 2-5. The attempt of coupling reaction with *N*-methylamide **95** and octanal **94a**



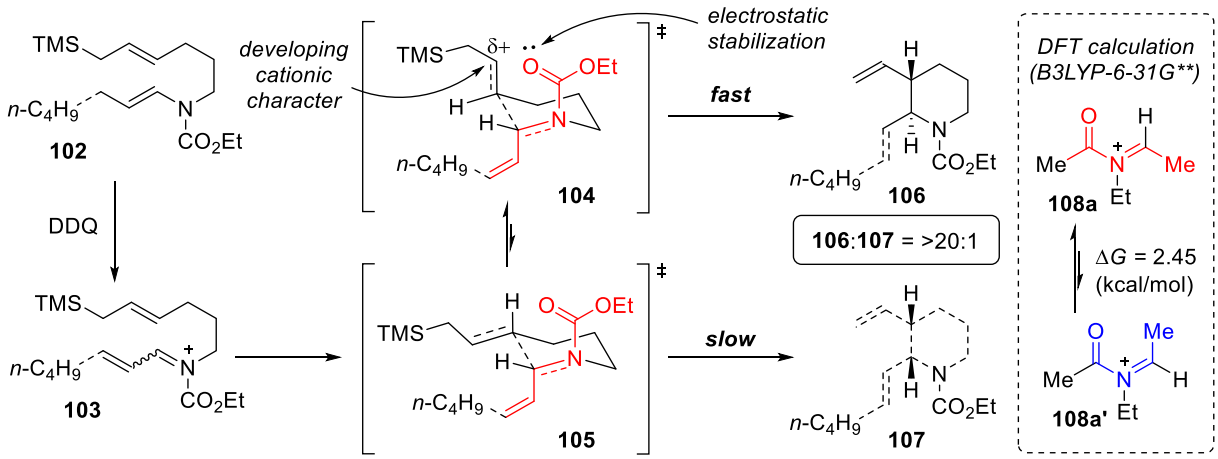
Scheme 2-6. Plausible effect of the *N*-methoxy group in the amide/aldehyde coupling reaction



Although the through space interaction of *N*-methoxy group have not been reported, Floreancig and co-workers reported a closely related chemistry (Scheme 2-7).[17] In their case, the 6-endo-cyclization of the acyliminium ion **103** gave 2,3-*trans*-piperidine **106** as a major product. They supposed that this stereoselectivity would be determined by the geometry of the iminium ion,[18]

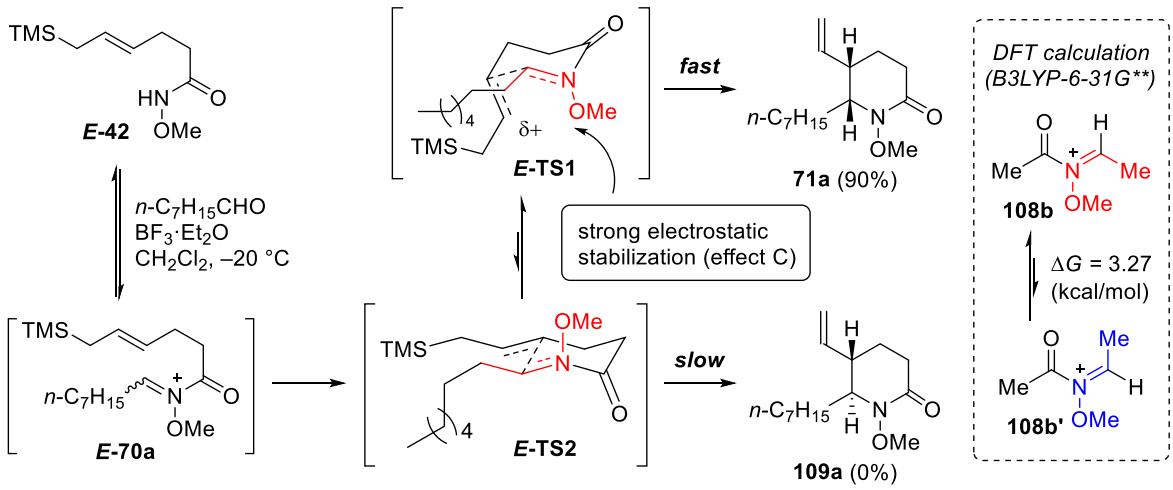
and through space interaction between acyl group and cationic β-silyl carbon. According to the calculation of a model *N*-acyliminium ion **108a** and **108a'**, the *E*-isomer **108a** was more stable than **108a'** significantly (the Boltzmann population of **108a** and **108a'** at 298 K was calculated as 98.4:1.6). Therefore, the transition states **104** and **105** would adopt *E*-acyliminium ion in the cyclization reaction. Although **104** seems to be sterically disfavored due to the 1,3-diaxial-like interaction, a through-space interaction between oxygen atom of the carbamate and the β-silyl cation is overwhelmingly stronger than the sterical effect to give *trans*-product **107** with highly stereoselective fashion.

Scheme 2-7. Example of through-space interaction (reported by Floreancig and co-workers)

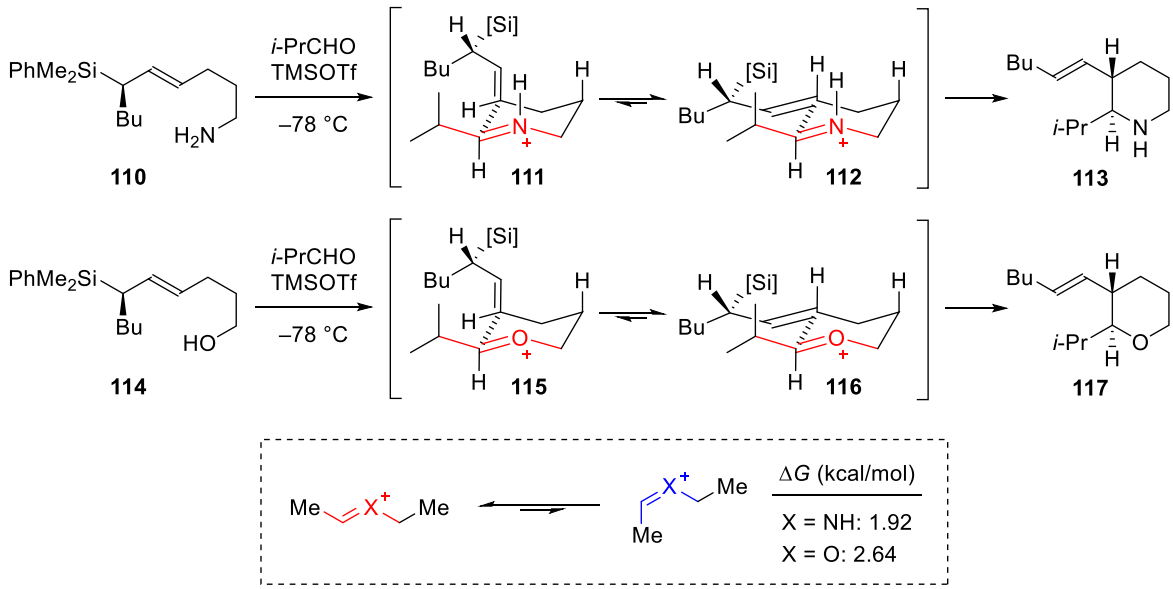


Based on these context, the stereochemical outcome of our intramolecular cyclization would be explained as shown in Scheme 2-8. DFT calculation indicated that *N*-oxy-*N*-acyliminium ion **108b** preferred the *Z*-geometry than the *E*-geometry.[19] Therefore, two possible transition state ***E*-TS1** and ***E*-TS2** adopt the *Z*-geometry in the transient iminium ions. In this occasion, while the transition state ***E*-TS1** will be transformed to *cis*-product **71a**, the competing ***E*-TS2** will be converted to *trans*-product **109a**. In general, ***E*-TS2** considered to be favorable transition state, because the alkyl side-chain and the allylsilane occupied the pseudoequatorial positions.[20] For example, Ito and co-workers reported highly *trans*-selective intramolecular allylation of **110** and **114** via favorable transition states **112** and **116** rather than unfavorable **111** and **115** affording the 2,3-*trans* product **113** and **117** (Scheme 2-9).[20c] The favorable transition states **112** and **116**, alkyl side-chain and allylsilane were placed in pseudoequatorial positions. Despite such sterical advantages in ***E*-TS2**, our experimental results showed the complete *cis*-selectivity via transition state ***E*-TS1**, probably because the strong through-space interaction as shown in Scheme 2-7 would stabilize the transition state ***E*-TS1**.

Scheme 2-8. Plausible mechanistic rational for *cis*-selective intramolecular allylation of ***E*-42**

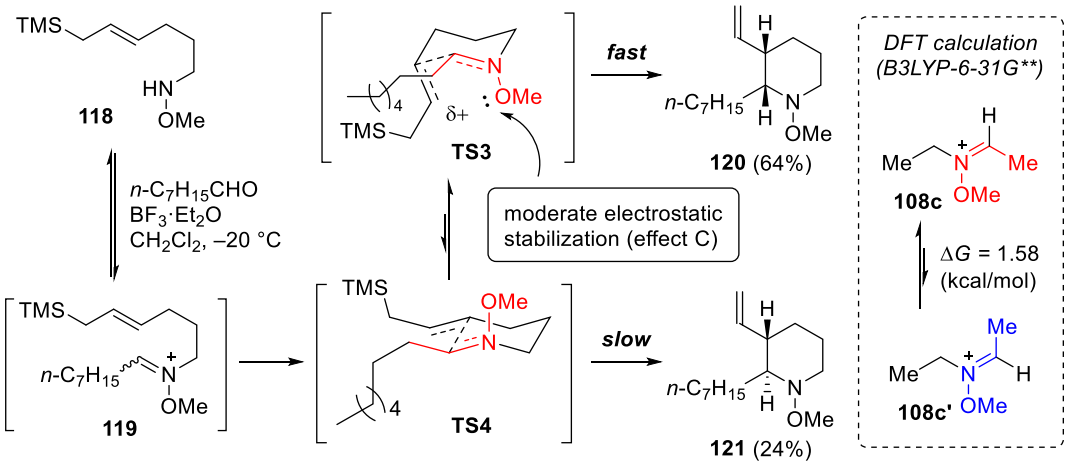


Scheme 2-9. Example of *trans*-selective cyclization (reported by Speckamp and co-workers)



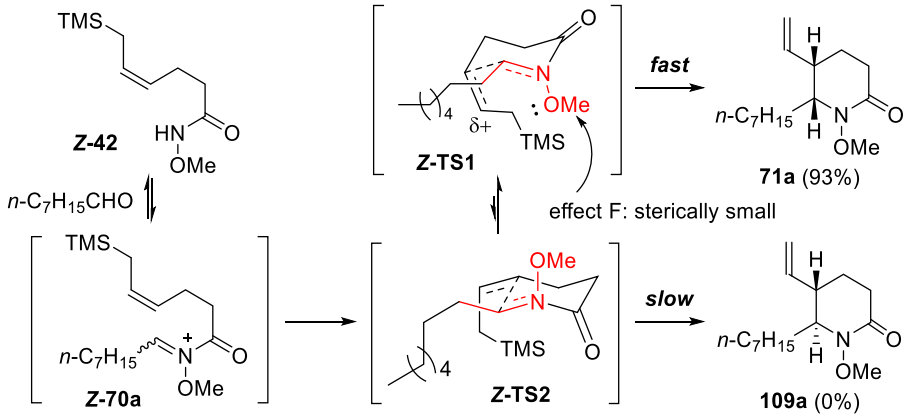
To elucidate the role of the amide carbonyl group, the coupling reaction of *N*-methoxyamine **118** was attempted instead of *N*-methoxyamide ***E*-42** (Scheme 2-10). In this case, the *Z*-geometry of iminium ion was dominant, which was supported by the calculation of model iminium ion **108c** and **108c'**. Interestingly, although the stereoselectivity was decreased, the cyclization still afforded *cis*-isomer **120** as a major product (**120**: 64%, **121**: 24%). This cyclization would also be considered to proceed through **TS3** and **TS4** derived from the favorable *Z*-geometrical iminium ion. Although the reason is not clear why *trans*-product **121** was obtained, in this case also *cis*-product **120** was generated as a major product, probably because the through-space interaction would be still dominant.

Scheme 2-10. The effect of the carbonyl group



The next control experiment was the coupling reaction using *Z*-allylsilane ***Z*-42**. As a result, the coupling reaction between ***Z*-42** and **94a** afforded *cis*-isomer **71a** with perfect stereoselectivity in 93% yield (Scheme 2-11). The reaction of ***Z*-42** would proceed via the transition state ***E*-42** shown in Scheme 2-8. Although a larger 1,3-diaxial-like repulsion in transition state ***Z*-TS1** would be expected than in ***E*-TS1**,[17] we considered that the electrostatic interaction between *β*-silyl cation and *N*-methoxy group would still be dominant, resulting in the complete *cis*-cyclization to give **71a**.

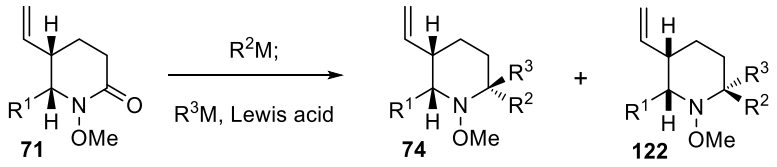
Scheme 2-11. The effect of the geometry of allylsilane

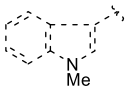


2-5. The second step: Nucleophilic Addition of *N*-Methoxylactam

With *N*-methoxylactam **71** in hand, then the nucleophilic addition of *N*-methoxylactam **71** was attempted using a variety of nucleophiles (Table 2-3). The reductive cyanation of lactam **71a** successfully proceeded upon treatment with DIBAL-H at –78 °C and subsequent addition of TMSCN and $SnCl_4$ to give *N*-methoxypiperidine **74a**, along with the diastereomer **122a** in 87% combined yield (Table 2-4, entry 1, **74a**:**122a** = 2.2:1). By changing the first and second nucleophiles, this nucleophilic addition allowed quick access to various multi-substituted piperidines from the identical *N*-methoxylactam **71a**. The reductive allylation proceeded by using a combination of DIBAL-H as a first nucleophile (R^2M) and allylstannane as a second nucleophile (R^3M) (Table 2-4, entry 2, 86%, **74b**:**122b** = 4.1:1). Reductive Pictet-Spengler reaction with *N*-methylindole at –40 °C afforded **74c** in highly diastereoselective fashion (Table 2-4, entry 3, 88%, **74c**:**122c** = 14:1). The reductive Mukaiyama Mannich reaction using silylenolether gave **74d** as a single diastereomer in 65% yield (Table 2-4, entry 4). In this reaction, when DIBAL-H was used as the first nucleophile, inseparable unknown side product was generated, and the yield of **74d** was 51%. Furthermore, if organolithium reagent was employed as a first nucleophile, *α*-tertiary amines were successfully constructed. For instance, the addition of MeLi to *N*-methoxylactam **71a** followed by the cyanation and allylation proceeded smoothly to give *α*-tri-substituted *N*-methoxypiperidines (Table 2-4, entry 5: 83%, **74e**:**122e** = 1:4.0; entry 6: 57%, **74f**:**122f** = 4.2:1). Nucleophilic addition to *N*-methoxylactam **71d** was more challenging because the methyl ester was incompatible with both DIBAL-H and organolithium reagent. However, our chemoselective variant of nucleophilic addition using the Schwartz reagent was highly effective with substrates bearing sensitive functional groups.[21] The reduction of *N*-methoxylactam **71d** with Cp_2ZrHCl at room temperature followed by the addition of TMSCN and 20 mol% $Sc(OTf)_3$ furnished a 1:4.3 diastereomeric mixture of **74g** and **122g** in 86% yield (Table 2-4, entry 7). The reaction was completely chemoselective, and proceeded without affecting the methyl ester which is more electrophilic than ordinary amide or the terminal olefin. The corresponding allylation of **71d** gave **74h** as a major diastereomer (Table 2-4, entry 8: 74%, **74h**:**122h** = 4.2:1). Thus, the two-step procedure including *N*-methoxyamide/aldehyde coupling and subsequent nucleophilic addition proved to be highly practical to afford a variety of multi-substituted piperidines.

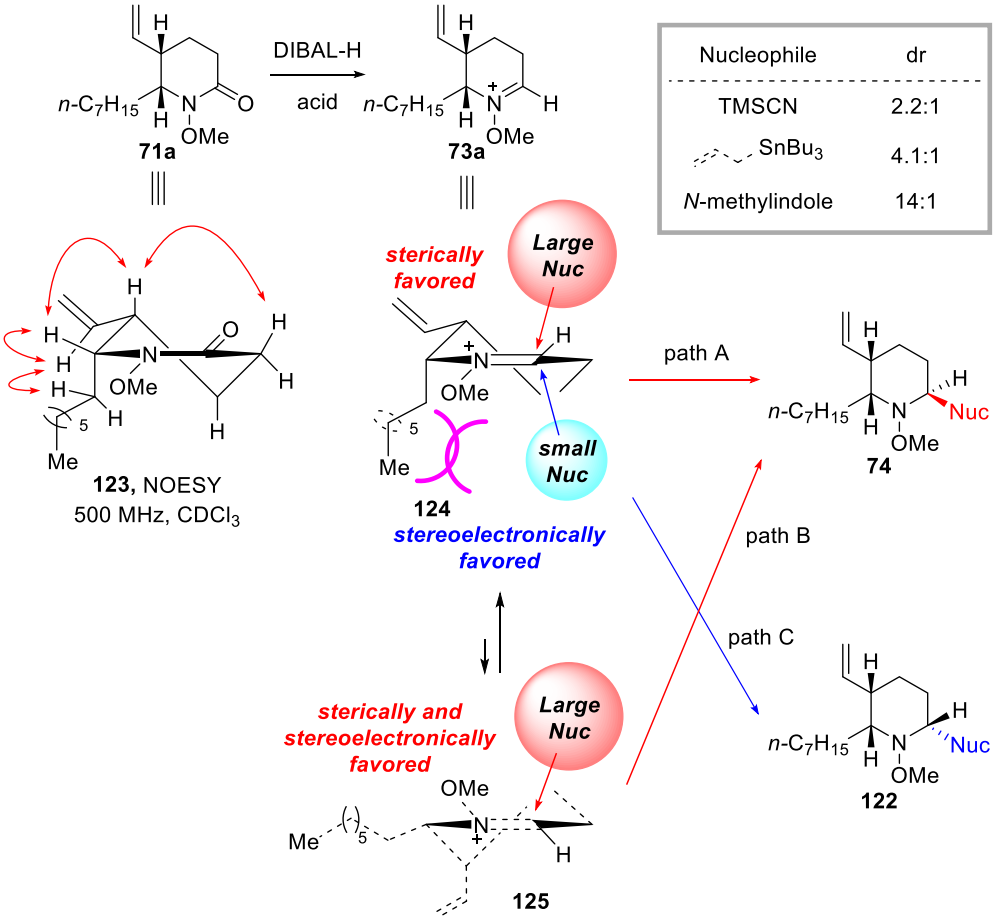
Table 2-3. Nucleophilic addition of a variety of nucleophiles to *N*-methoxypiperidine



Entry	**71** (R^1)	Conditions	R^2	R^3	Combined yield [%]	Diastereomeric ratio
1		DIBAL-H, CH_2Cl_2, –78 °C; TMSCN, $SnCl_4$, rt	H	CN	87	**74a:122a** = 2.2:1
2		DIBAL-H, CH_2Cl_2, –78 °C; CH_2=$CHCH_2SnBu_3$ $Sc(OTf)_3$, rt	H	CH_2CH=CH_2	86	**74b:122b** = 4.1:1
3	**71a** (n-C_7H_{15})	DIBAL-H, CH_2Cl_2, –78 °C; *N*-methylindole $Sc(OTf)_3$, –40 °C	H		88	**74c**:**122c** = 14:1
4		Cp_2ZrHCl, $(CH_2Cl)_2$, rt; CH_2=C(OTIPS)Ph 20 mol% $Sc(OTf)_3$, rt	H	CH_2COPh	65	**74d**: single diastereomer
5		MeLi, THF, –78 °C; TMSCN $SnCl_4$, MeCN, rt	Me	CN	83	**74e:122e** = 1:4.0
6		MeLi, THF, –78 °C; CH_2=$CHCH_2SnBu_3$ $SnCl_4$, MeCN, rt	Me	CH_2CH=CH_2	57	**74f**:**122f** = 4.2:1
7	**71d** ($MeO_2C(CH_2)_2$)	Cp_2ZrHCl, $(CH_2Cl)_2$, rt; TMSCN 10 mol% $Sc(OTf)_3$, rt	H	CN	86	**74g:122g** = 1:4.3
8		Cp_2ZrHCl, $(CH_2Cl)_2$, rt; CH_2=$CHCH_2SnBu_3$ 30 mol% $Sc(OTf)_3$, –30 °C	H	CH_2CH=CH_2	74	**74h:122h** = 4.2:1

The stereochemical rationale for the reductive nucleophilic addition to *N*-methoxylactam **71a** was shown in Scheme 2-13. NOESY experiment (500 MHz, $CDCl_3$) indicated that *N*-methoxylactam **71a** mainly existed as a half-chair conformation **123**, in which the alkyl side chain occupied the pseudoaxial position. We believed that transient *N*-oxyiminium ion **73a** might exist mainly as a half-chair conformation **124** similar to **123**, and the transition state **125** might exist as a minor conformation due to 1,2-allylic strain between the methoxy group and alkyl side-chain. The sterically large nucleophile would avoid the steric repulsion with alkyl side-chain of **124**. Considering the stereoelectronical effect,[22] a large nucleophile would be difficult to react at *β*-side of **124** (path A), and would react immediately with *β*-side of **125** to provide **74** as a major product (path B). On the other hand, in the case using sterically small nucleophile, the interaction with alkyl side-chain would be negligible. Therefore, the small nucleophile relatively favored the *α*-side attack to **124** (path C, cf. Table 2-4, entries 5 and 7).

Scheme 2-13. Plausible mechanistic rationale for reductive nucleophilic addition to **71a**



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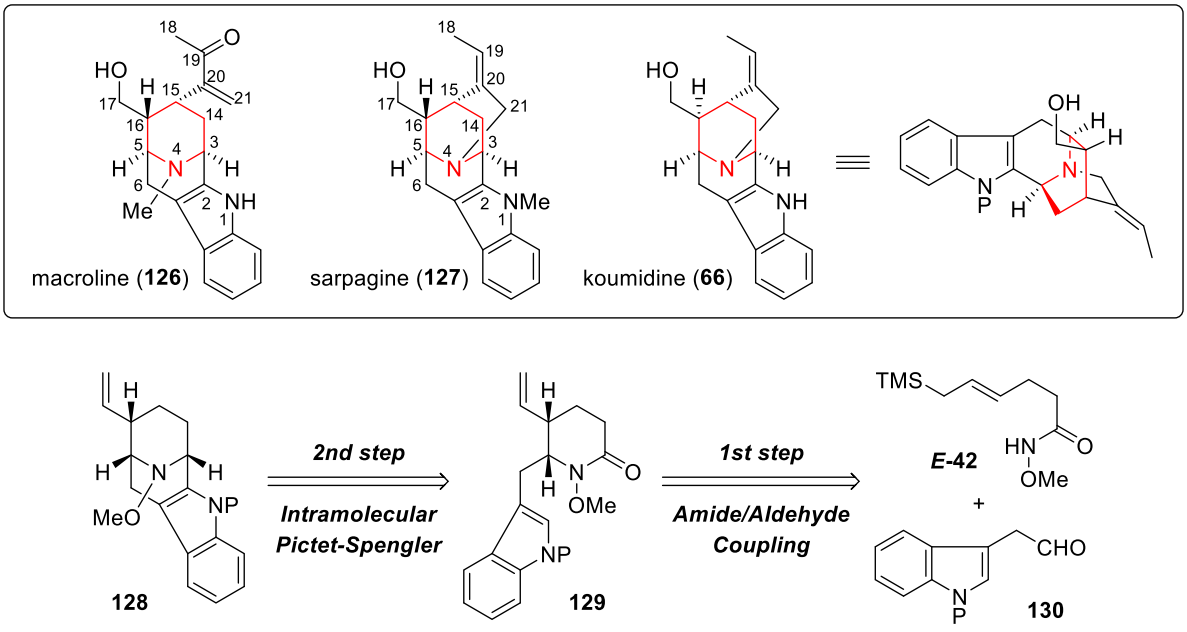
Chapter 3. Further Application of the Two-step Synthesis

3-1. Macroline- and Sarpagine-type Alkaloids

As a demonstration to show that the developed method was applicable to complex molecules relating to natural alkaloids, we took an interest in the quick synthesis of a tetracyclic structure embedded in macroline- and sarpagine-type alkaloids (Figure 3-1).[1] Macroline (**126**) and sarpagine (**127**) alkaloids possess an indole-annulated azabicyclo[3.3.1] core structure, and koumidine (**66**) contains the opposite relative stereochemistry between C5 and C16. Macroline-type alkaloids have the same skeletal connectivity, only that N4-C21 linkage does not exist. On the other hand, sarpagine-type alkaloids possesses the N4-C21 linkage and the C16-(*R*) configuration. The skeletal difference between sarpagine (**127**) and koumidine (**66**) is the configuration at C16. By taking advantage of our two-step synthesis of multi-substituted piperidine, the quick access to tetracyclic compound **128** which correspond to the core structure of koumidine (**66**) would be practical. *N*-Methoxypiperidine **128** would be synthesized by amide/aldehyde coupling reaction between ***E*-42** and indole acetaldehyde derivative **130** as the first step, followed by intramolecular reductive Pictet-Spengler reaction of *N*-methoxylactam **129** as the second step.

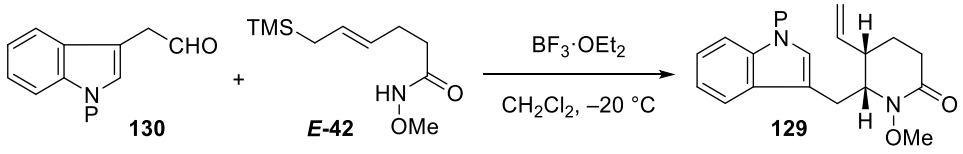
Figure 3-1. Synthetic plan of macroline- and sarpagine-type alkaloids



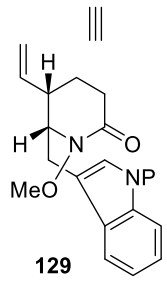
3-2. Construction of Tetracyclic Skeleton of Koumidine (**66**)

In the first step, the protecting group of the indole nitrogen atom would affect the stability of the indole unit because indoles are vulnerable to acidic conditions. In addition, indole acetaldehyde **130**[2] is likely to form benzylic enolate and decompose by dimerization or polymerization. As expected, the protecting group of the indole nitrogen atom was crucial in this reaction (Table 3-1, entry 1). The *N*-methyl indole **130b** also decomposed under the acidic conditions (Table 3-1, entry 2). However, the electron withdrawing Boc group was effective for this coupling reaction to give *N*-methoxylactam **129c** in 44% yield in *cis*-selective fashion (Table 3-1, entry 3). The Cbz protection of the indole significantly increased the yield of *N*-methoxylactam **129d** up to 68% (Table 3-1, entry 4). When the more electron withdrawing benzene sulfonyl group was used as a protecting group, the coupling reaction proceeded in 65% yield comparable to the Cbz group (Table 3-1, entry 5, **129e**: 65%).

Table 3-1. Coupling reaction of *N*-methoxyamide ***E*-42** and indole acetaldehyde **130**

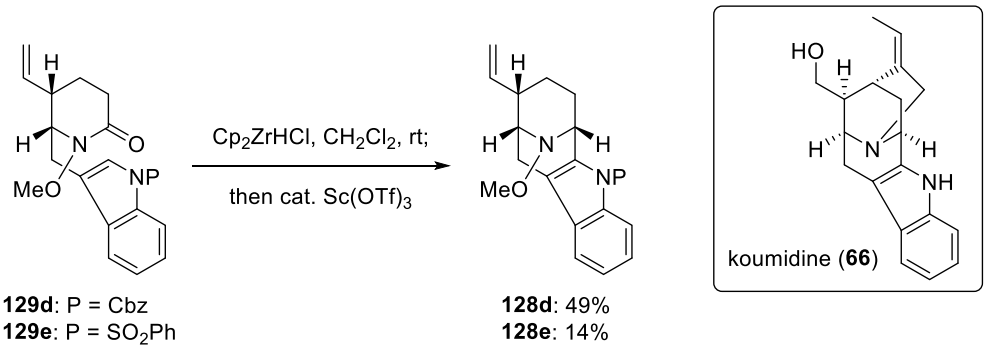


entry	protecting group	yield
1	**130a**: P = H	**129a**: 0%
2	**130b**: P = Me	**129b**: 0%
3	**130c**: P = Boc	**129c**: 44%
4	**130d**: P = Cbz	**129d**: 68%
5	**130e**: P = SO_2Ph	**129e**: 65%



Next, we attempted the intramolecular reductive Pictet-Spengler reaction (Scheme 3-1). Treatment of the Cbz-protected *N*-methoxylactam **129d** with the Schwartz reagent, followed by addition of a catalytic amount of $Sc(OTf)_3$ induced the reductive intramolecular Pictet-Spengler reaction to give the tetracyclic compound **128d** in a reasonable yield. It is noteworthy that this reductive cyclization was also highly chemoselective without touching the indole carbamate despite its similar structure to the *N*-methoxylactam. The stereochemistries of lactam **129d** and tetracyclic compound **128d** were determined by NOESY experiments (Figure 3-2, 500 MHz, $CDCl_3$). In the case using lactam **129e**, the cyclization resulted in low yield presumably due to the low nucleophilicity of indole moiety.

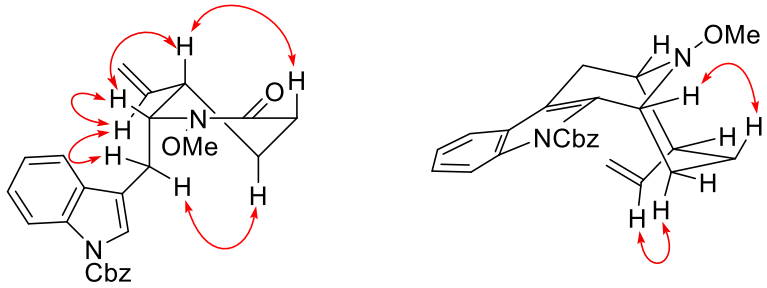
Scheme 3-1. Construction of tetracyclic compound **128**



129d: P = Cbz
129e: P = SO_2Ph

128d: 49%
128e: 14%

Figure 3-2. NOESY experiment of **129d** and **128d**



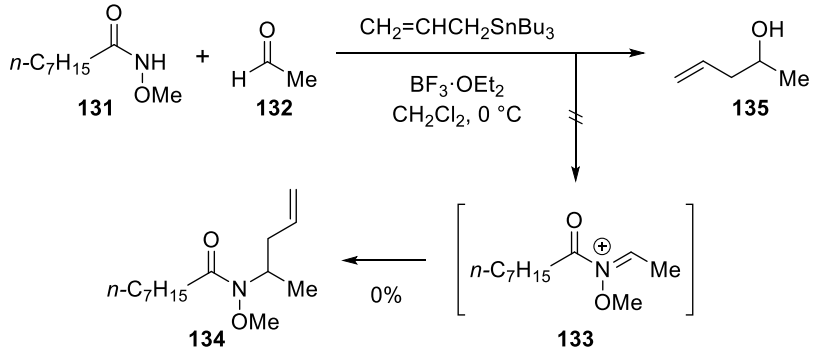
129d (500 MHz, $CDCl_3$)

128d (500 MHz, $CDCl_3$)

3-3. Three-component Coupling Reaction

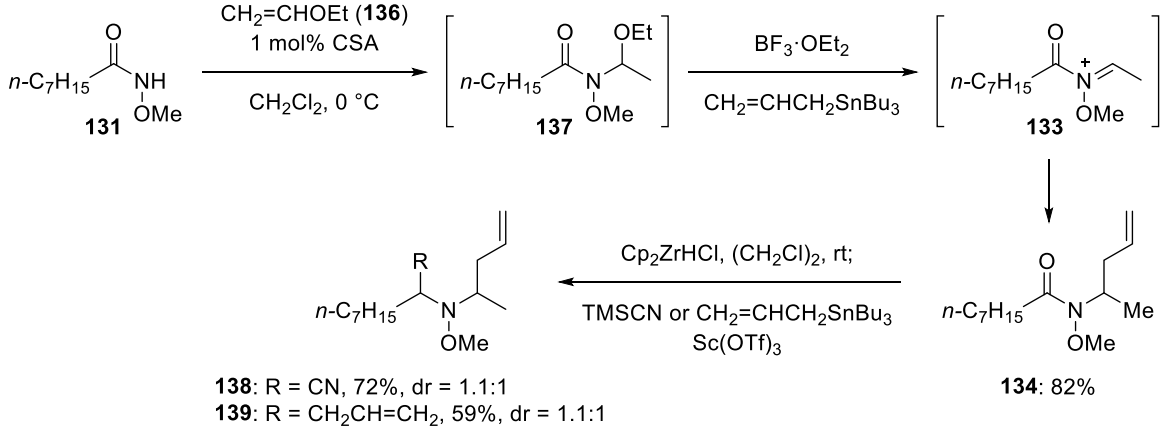
All successful examples in the first coupling reaction thus far are two-component reactions employing *N*-methoxyamide **131** that possesses the allylic silane in the same molecule as the nucleophilic moiety. In order to render the developed method more general, a three-component coupling reaction was attempted by using *N*-methoxyamide **131**, acetaldehyde **132** and allylstannane in the presence of $BF_3 \cdot OEt_2$ (Scheme 3-2). Unfortunately, initial attempts were unsuccessful due to the direct allylation of acetaldehyde by allylstannane to form homoallylic alcohol **135**.

Scheme 3-2. Unsuccessful attempt of the three component coupling reaction



The issue in the three-component coupling reaction is the unfavorable reactivity of each component; the addition of allylstannane to acetaldehyde **132** was much faster than the addition of *N*-methoxyamide **131**, and prevented the formation of the *N*-acyliminium ion **133**. In order to prevent the formation of **135**, utilization of an enol ether was attempted as the aldehyde equivalent (Scheme 3-3). First, *N*-methoxyamide **131** and ethyl vinyl ether **136** were pre-coupled in the presence of 1 mol% CSA. The subsequent treatment of resulting *N*,*O*-acetal **137** with allylstannane and $BF_3 \cdot OEt_2$ successfully promoted the allylation via iminium ion **133** to give *N*-methoxyamide**134** in 82% yield in a one-pot process. The reductive cyanation and allylation of *N*-methoxyamide **134** provided **138** and **139** in 72% and 59% yields, respectively.

Scheme 3-3. First attempt of the three component coupling reaction



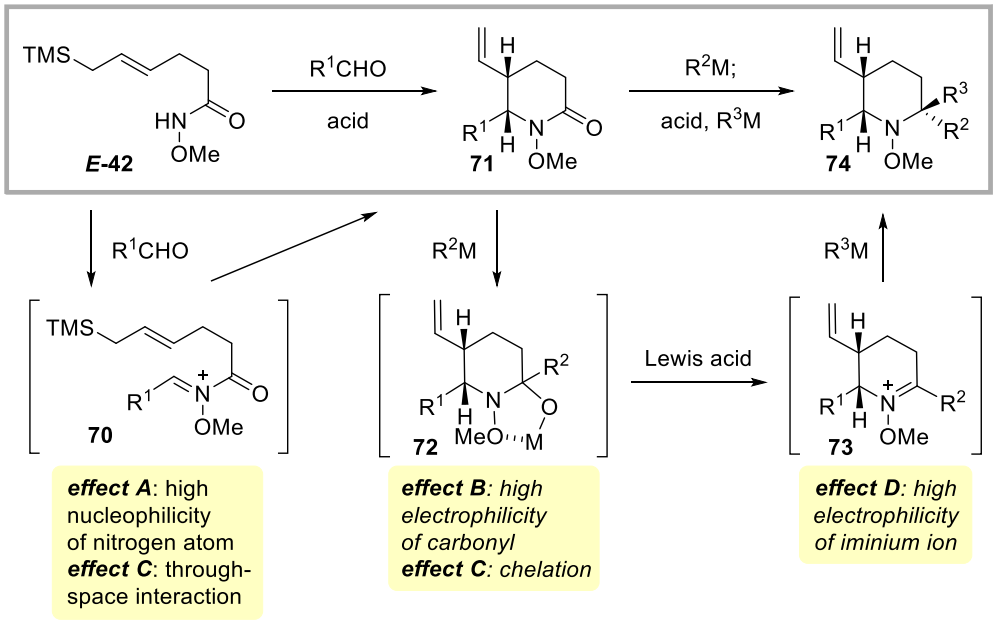
Reference in Chapter 3

1 Lewis, S. E. *Tetrahedron* **2006**, *62*, 8655.

2 For synthetic methods of indole acetaldehyde **130a-e**, see experimental section.

Chapter 4. Conclusion

We have documented a two-step synthesis of multi-substituted *N*-methoxyamines involving an *N*-methoxyamide/aldehyde coupling reaction and subsequent nucleophilic addition to amide carbonyls. The key to success was the utilization of the *N*-methoxy group as a reactivity control element. The first coupling reaction between the amide and aldehyde took place with enhancement of the nucleophilicity of the nitrogen atom by assistance of the *N*-methoxy group (effect A). The unusual *cis*-stereoselectivity was developed by the strong through-space interaction between *N*-methoxy group and transient *β*-silyl cation (effect C). The next nucleophilic addition was achieved by taking advantage of the high electrophilicity of amide carbonyls (effect B), the chelation effect of *N*-methoxyamides (effect C), and the high electrophilicity of *N*-oxyiminium ion (effect D). At every stage of this synthetic method, *N*-methoxy group played a role as sterically less hindered protecting group (effect F). The developed synthesis enabled quick supply of a set of various 2,3,6-multi-substituted *N*-methoxypiperidines including a substructure of a complex alkaloid. The method was then applied to a three-component coupling reaction, giving acyclic compounds. Thus, *N*-alkoxyamine derivatives possess a great potential to create practical chemical reactions for synthesis of complex molecules. From now on, a variety of new synthetic method using *N*-alkoxyamine derivatives will be discovered.



Part 2. Unified Total Synthesis of Stemoamide-type Alkaloids

Chapter 5. Introduction

5-1. Stemoamide-type Alkaloids

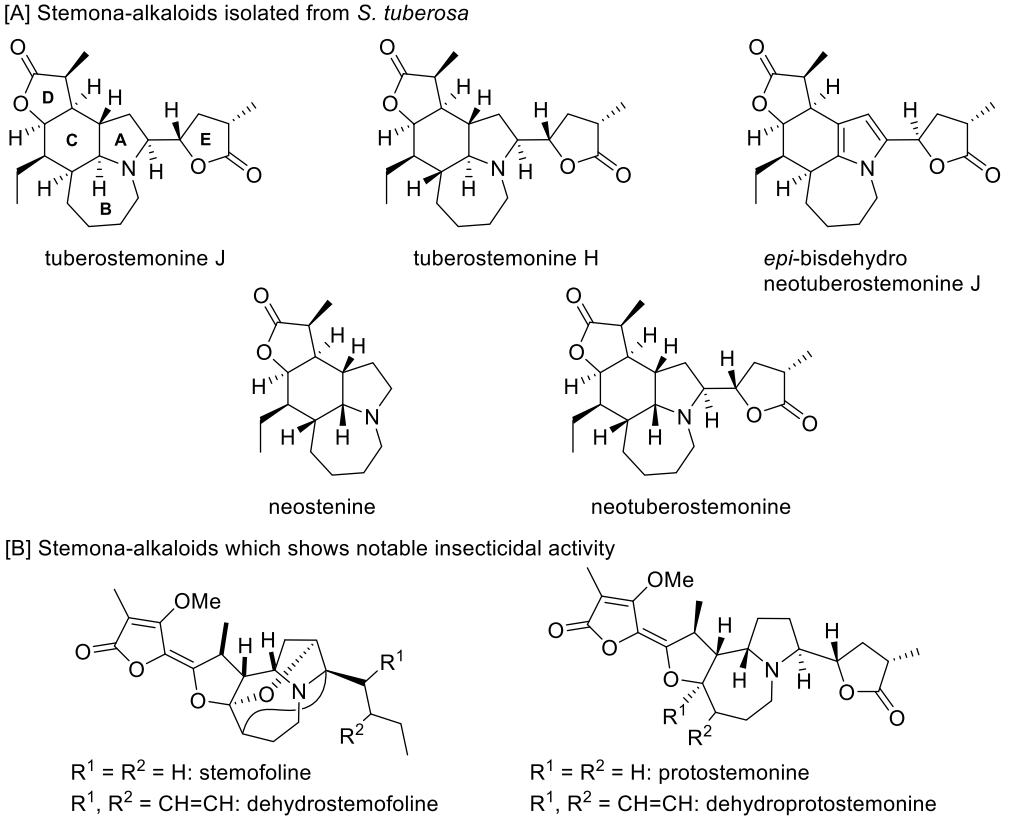
5-1-1. Isolation and Bioactivity

Stemona-alkaloids were isolated from the extracts of 'Stemonaceae', which have been used in folk medicine in East Asia from ancient years. In China, mainly three species of the *Stemona* genus (*S. tuberosa*, *S. japonica*, and *S. sessilifolia*) have been utilized as a cough medicine and an insecticide agent.[1,2]

For instance, a water extract of *S. tuberosa* mainly contains five stemona-alkaloids (Figure 5-1A) that showed anti cough activity. Especially neostenine and neotuberostemonine were revealed to possess the strongest anti-cough activity among these five alkaloids.[3]

Stemona-alkaloids also show insecticidal activity (Figure 5-1B). Stemofoline and didehydrostemofoline possess strong insecticidal and growth inhibitory activity against neonate larvae of the cotton leaf worm *Spodoptera littoralis* Boisduval.[4] Protostemonine and dehydroprotostemonine showed notable nematicidal bioactivity against panagrellus redivevus.[2c]

Figure 5-1. Alkaloids extracted from the root of *S. tuberosa*



5-1-2. Classification of the Stemona-alkaloids

More than 150 stemona-alkaloids have been reported to date and they can be classified into eight groups (Figure 5-2).[1,2,5] The alkaloids belonging to group **I** to **VI** possess five- and seven-membered ring system remarked as pyrrolo[1,2-*a*]azepine skeleton, which is regarded as the most common structure of stemona species. While the alkaloids belonging to group **VII** possess six- and seven-membered ring system remarked as pyrido[1,2-*a*]azepine skeleton. The alkaloids belonging to group **VIII** do not possess these core structures.

Among stemona-alkaloids, approximately 40 natural products belong to stemoamide group (**II**), which is the largest group of these alkaloids (Figure 5-3). Stemoamide-type alkaloids possess the tricyclic core structure of stemoamide comprised of a γ-lactone, an azepane, and a γ-lactam.

Figure 5-2. Classification of the stemona-alkaloids

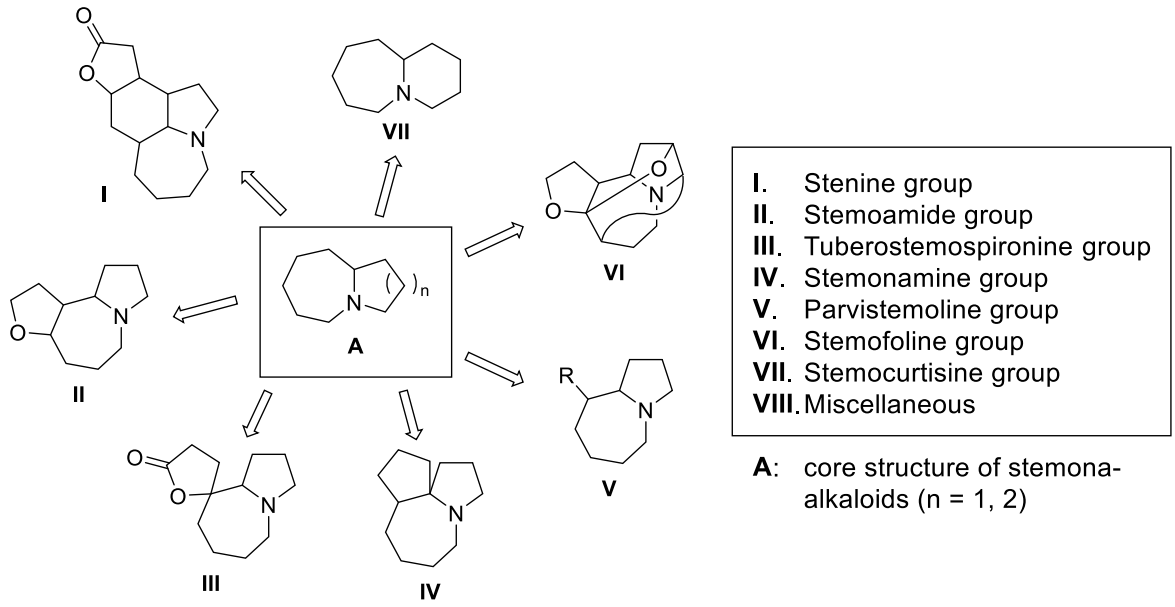
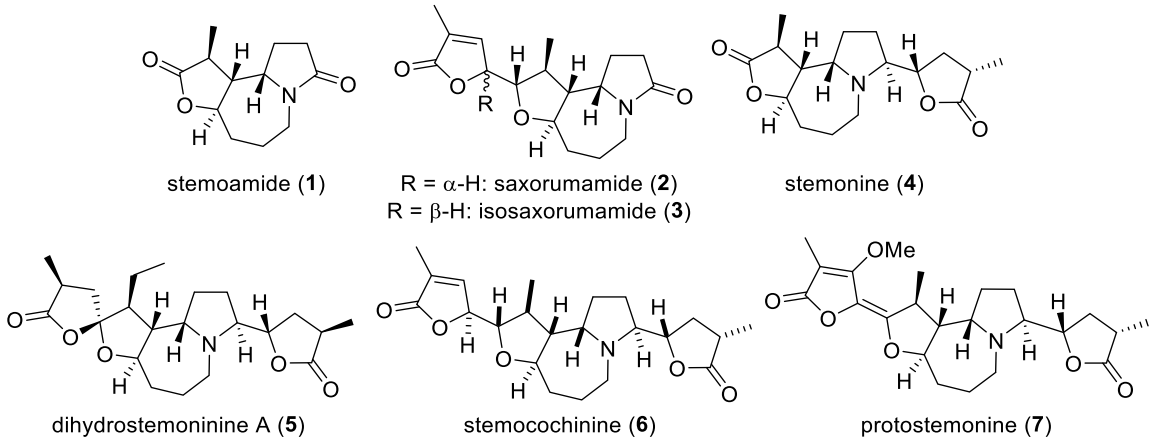


Figure 5-3. The stemoamide-type alkaloids



5-1-3. Synthetic Examples of Stemoamide (**1**)

More than 20 synthetic examples of stemoamide (**1**) have been reported to date. Examples of enantioselective and racemic total syntheses of stemoamide are listed below (Table 5-1, 5-2).[6,7]

Table 5-1. Enantioselective synthesis of stemoamide (**1**)

group	year	LLS	total yield	quantity of obtained stemoamide
Williams	1994	25 steps	5.6%	N/A
Mori	1996	13 steps	8.3%	6.3 mg
Jacobi	2000	7 steps	4.2%	18 mg
Sibi	2004	14 steps	7.0%	N/A
Olivo	2006	13 steps	<14.1%*	25 mg
Somfai	2007	12 steps	19.6%	6.8 mg
Honda	2011	9 steps	23.4%	32.2 mg
Hong	2012	12 steps	18.7%	24.7 mg
Sato/Chida	2016	22 steps	2.2%	8.9 mg

* Yields of first three steps are not reported

Table 5-2. Racemic synthesis of stemoamide (**1**)

group	year	LLS	total yield	quantity of obtained stemoamide
Narasaka	1996	14 steps	1.1%	12 mg
Jacobi	1997	7 steps	19.9%	438 mg
Bates	2009	11 steps	5.70%	N/A
Hong	2011	9 steps	30.1%**	166 mg
Zhang, Qiu	2014	7 steps	5.1%	24 mg

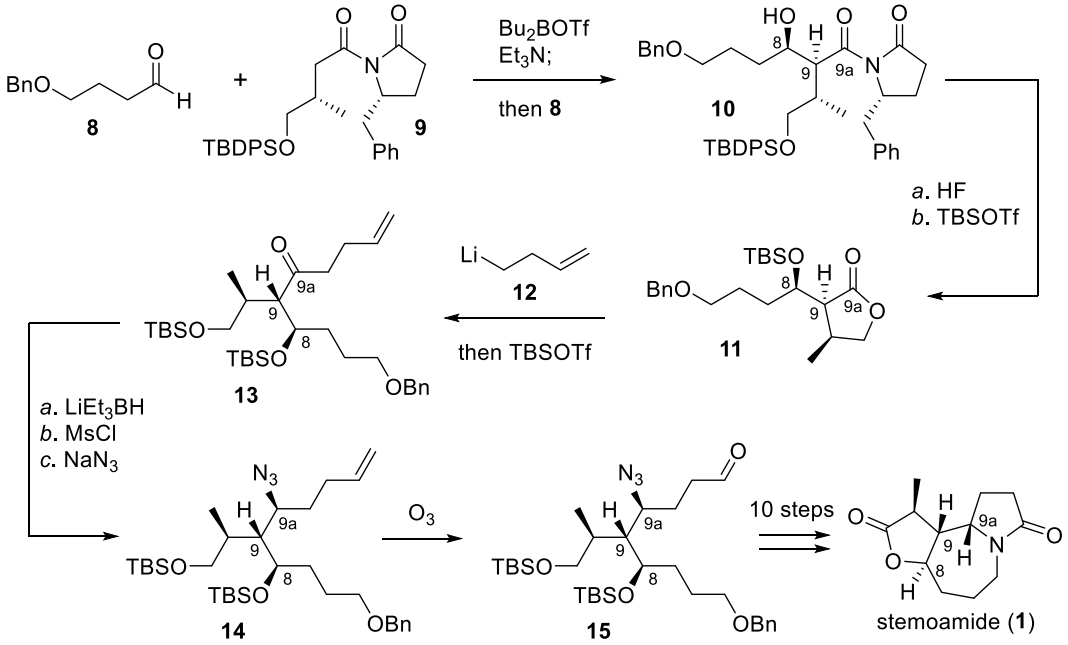
** They originally counted the steps starting from 4-bromobutyraldehyde, which is not generally commercially available.

5-1-4. Brief Outline of Representative Total Synthesis of Stemoamide (**1**)

5-1-4-1. Williams and co-workers

The first total synthesis of stemoamide (**1**) was reported by Williams and co-workers featuring Evans diastereoselective aldol reaction and late-stage construction of tricyclic structure from acyclic intermediate (**15**) (Scheme 5-1).[6a] The synthesis commenced with preparation of **15**, which contains all carbon atoms of stemoamide (**1**). A diastereoselective coupling of aldehyde **8** and amide **9** with chiral auxiliary proceeded by treatment with Bu_2BOTf and triethylamine to afford oxazolidinone **10**. After altering the protecting group of alcohol, lactone **11** was converted to ketone **13** by introducing butenyl lithium reagent **12**. Then the reduction of ketone, mesylation, and azidation were conducted to give azide **14**. Following ozonolysis of **14** completed the installation of all carbon atoms of stemoamide (**1**). In the end of this synthesis, the sequential multi-step deprotection, oxidation, and cyclization of A, B, and C rings took place to accomplish the first concise total synthesis of stemoamide (**1**).

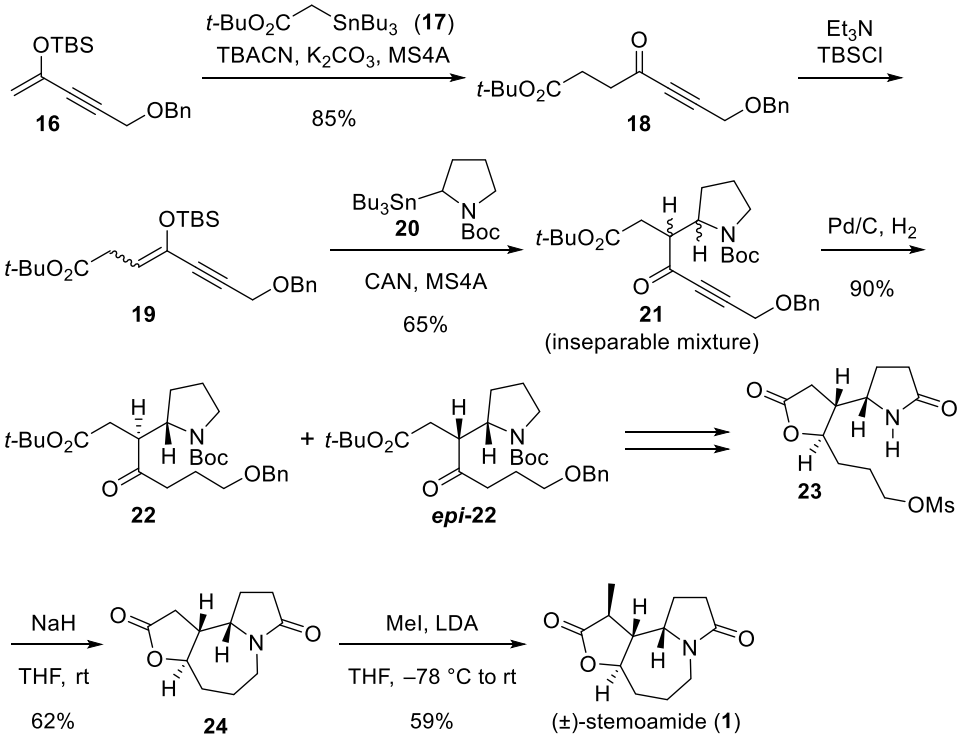
Scheme 5-1. Total Synthesis Reported by Williams



5-1-4-2. Narasaka and co-worker

Narasaka and co-worker developed oxidative coupling of silyl enol ether and stannyl compound, and it was applied to the total synthesis of stemoamide (**1**) (Scheme 5-2).[6b] The first key coupling reaction was conducted by treatment of silyl enol ether **16** and α-stannyl ester **17** with tetrabutylammonium nitratocerate (IV) (TBACN, cerium tetrabutylammonium nitrate; CTAN) to give γ-ketoester **18** in 85% yield. Second key coupling reaction was the oxidative coupling of silyl enol ether **19** and stannyl pyrrolidine **20** with cerium ammonium nitrate (CAN). Subsequent reduction of alkyne **21** afforded ketone **22** and ***epi*-22**. After construction of A and C rings, the treatment of mesylate **23** with sodium hydride led to tricyclic compound **24** in 62% yield. Finally, regio- and diastereo-selective methylation of **24** resulted in the second total synthesis of stemoamide (**1**) in 14 total steps.

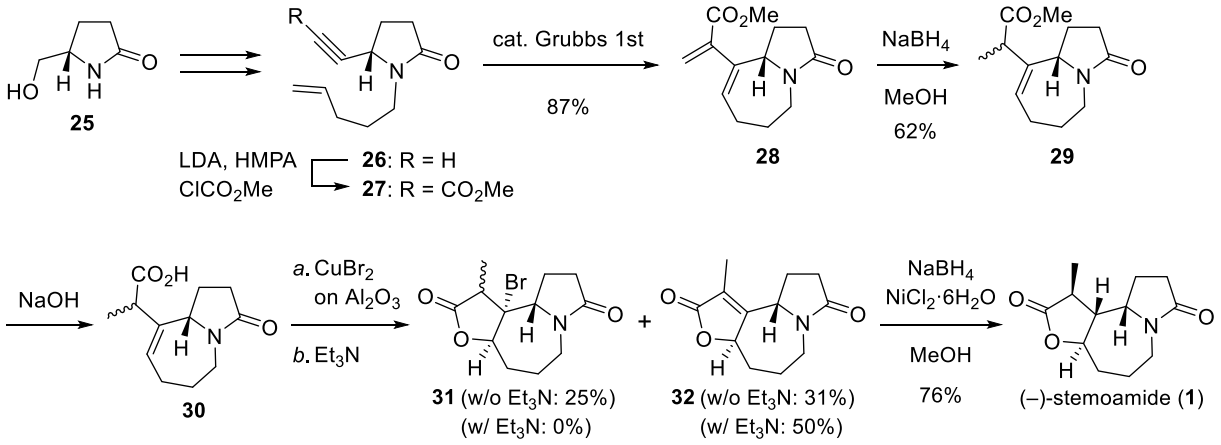
Scheme 5-2. Total Synthesis Reported by Narasaka



5-1-4-3. Mori and co-worker

Mori and co-worker reported the total synthesis of (–)-stemoamide (**1**) using a ruthenium catalyzed eneyne metathesis developed by the Grubbs group and the Mori group (Scheme 5-3).[6c,e] Eneyne **26** was prepared in 7 steps (6 pots) from **25**, and subsequent homologation of terminal alkyne provided **27** in 68% yield. The eneyne metathesis of **27** with Grubbs catalyst 1st generation proceeded to give a bicyclic compound **28** in 87% yield. 1,4-Reduction of enoate moiety in **28** followed by hydrolysis of ester and bromolactonization afforded butenolide **32** and tricyclic bromide **31**, which was successfully converted to **32** by addition of triethylamine. Eventually, the total synthesis of (–)-stemoamide (**1**) was accomplished by nickel boride catalyzed hydrogenation of **32** in total 13 total steps and in 8.3% overall yield.

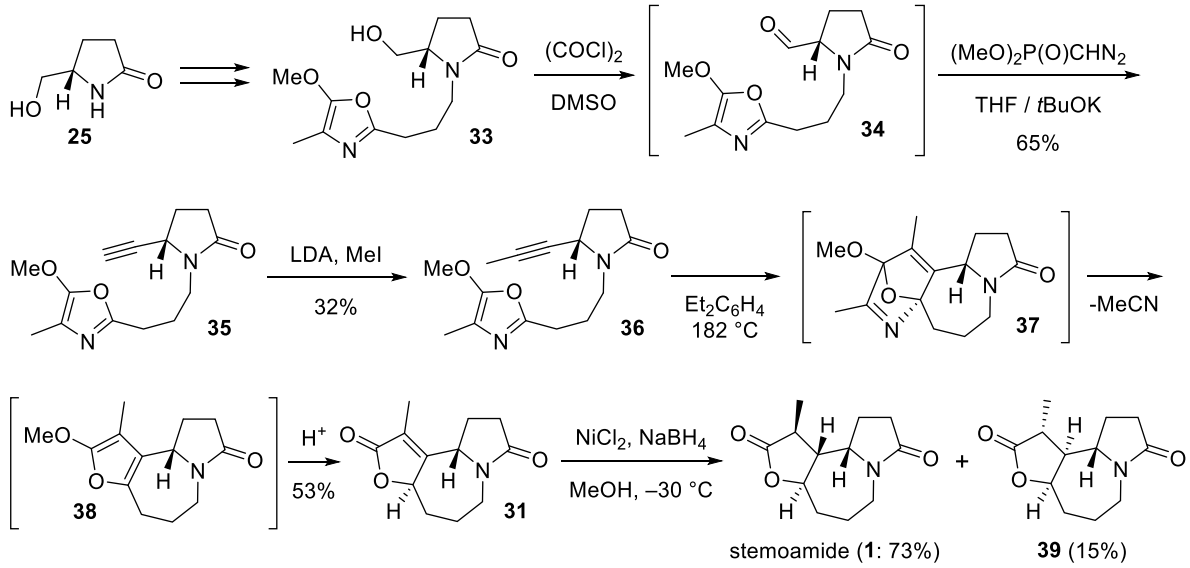
Scheme 5-3. Total Synthesis Reported by Mori



5-1-4-4. Jacobi and co-worker

In 2000, Jacobi and co-worker reported an innovative 7-step total synthesis of (–)-stemoamide (**1**) (Scheme 5-4).[6d,f] The key step of this synthesis was the intramolecular Diels-Alder/*retro*-Diels-Alder reaction of oxazole of **36**, which would directly form the tricyclic system. The Swern oxidation of alcohol **33** prepared from **25**, Seyferth-Gilbert reaction of aldehyde **34**, and methylation of terminal alkyne **35** were sequentially performed to synthesize key intermediate **36**. Then the intramolecular Diels-Alder reaction followed by *retro*-Diels-Alder reaction of **37** immediately proceeded to form 2-oxyfuran **38**. Subsequent workup gave α,β-unsaturated lactone **31**. Finally, the diastereoselective reduction of **31** with nickel boride afforded stemoamide as a major product (73%) along with undesired diastereomer **39** (15%).

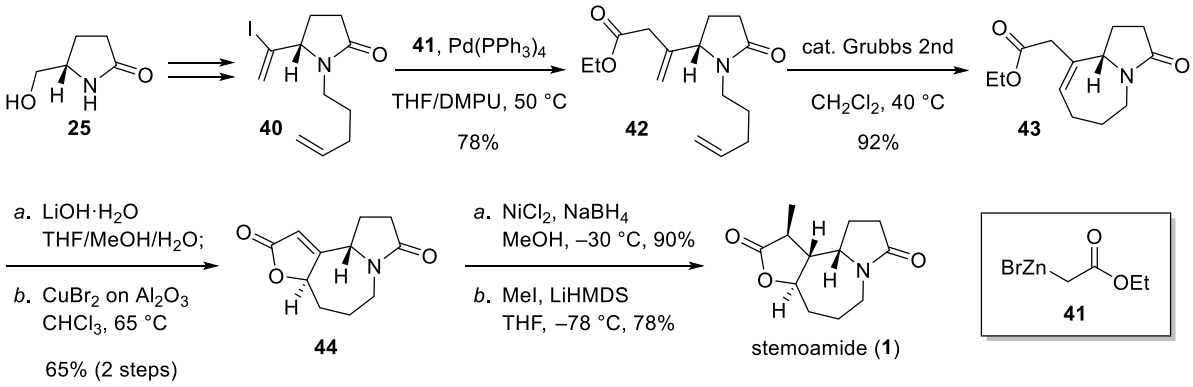
Scheme 5-4. Total Synthesis Reported by Jacobi



5-1-4-5. Somfai and co-workers

Somfai and co-workers demonstrated a highly efficient total synthesis of stemoamide featuring sp^2-sp^3 Negishi coupling (**40**+**41**→**42**) and ring closing metathesis (**42**→**43**) (Scheme 5-5).[6i] The synthesis began with the construction of iododiene **40** taking advantages of alkylation of amide and Ohira-Bestmann alkynylation. Treatment of iodide **40** with $Pd(PPh_3)_4$ and nucleophile **41** allowed C-C bond formation to afford the precursor of metathesis **42** in 78% yield. The key ring closing metathesis led to construction of the seven-membered ring in excellent yield. Resulting ester **43** was converted to tricyclic compound **44** by treatment with modifying hydrolysis and bromolactonization of the Mori's method. Hydrogenation of **44** was performed under similar conditions reported by Mori and Jacobi. Finally, the regio- and stereo-selective methylation reported by Narasaka accomplished the total synthesis of (–)-stemoamide (**1**) in 12 total steps in 19.6% overall yield.

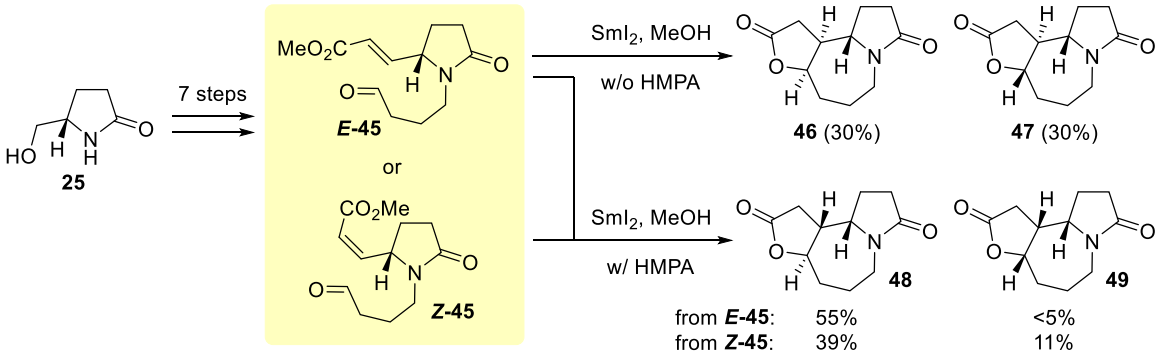
Scheme 5-5. Total Synthesis Reported by Somfai



5-1-4-6. Honda and co-workers

An efficient total synthesis of stemoamide (**1**) was reported by Honda and co-workers in 2011 (Scheme 5-6).[6k] The key step is SmI_2-mediated sequential cyclization of seven- and five-membered ring, which directly provided the tricyclic structure (***E*-45→48**). The aldehyde ***E*-45** was prepared from commercially available **25** with five-step conversion. The SmI_2 mediated cyclization had a possibility to produce four diastereomers at C8 and C9 stereocenters. While treatment of ***E*-45** with SmI_2 (5 equiv) and MeOH (5 equiv) at 0 °C showed only undesired diastereoselectivity to form C9-epimers **46** and **47** (60%, **46**:**47** = 1:1), additional treatment with HMPA (20 equiv) realized the complete opposite selectivity at C9 to give diastereomers **48** and **49** in 55% and 5%, respectively. In addition, it was revealed that the geometry of olefin would affect both the yield and diastereoselectivity, and regioisomer ***Z*-45** was converted to **48** and **49** in 39% and 11%, respectively. The efficient total synthesis of **1** was achieved by methylation of **48** in 9 total steps and in 23.4% overall yield.

Scheme 5-6. Total Synthesis Reported by Honda

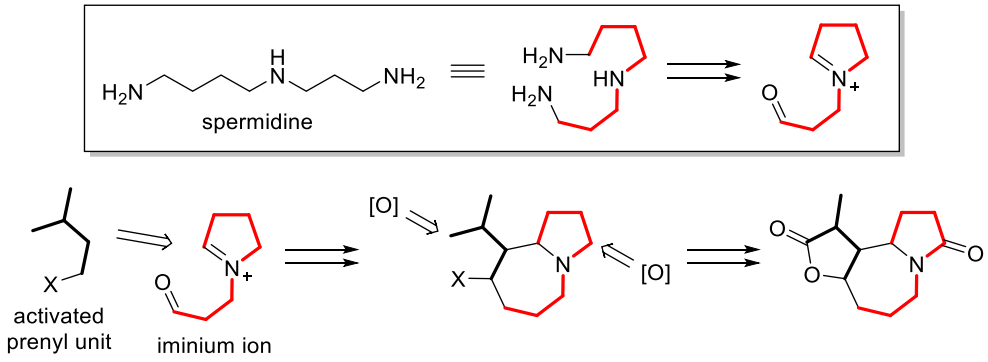


5-1-4-7. Hong and co-worker

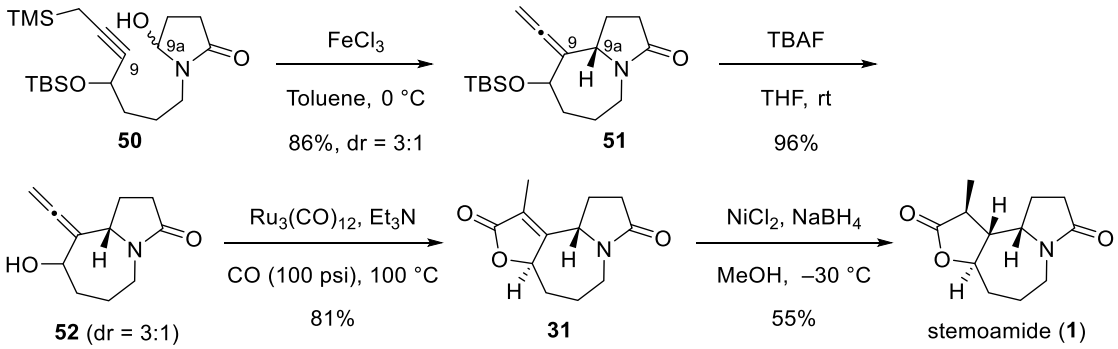
A biomimetic total synthesis of stemoamide (**1**) was reported by Hong and co-workers.[6l,m] Seger, Greger and co-workers suggested a biosynthesis of stemona-alkaloids stemming from a spermidine precursor, which couple with an isoprene unit, followed by oxidation and cyclization may afford carbon framework of stemoamide (Scheme 5-7A).[8] Therefore, Hong and co-workers planned to connect the C9-C9a bond by intramolecular allenylation of acyliminium ion (Scheme 5-7B). Treatment of *N*,*O*-acetal **50** with $FeCl_3$ led to formation of bicyclic structure, and TBS group was subsequently removed by the addition of TBAF. The late-stage construction of γ-lactone was accomplished by dynamic ruthenium-catalyzed CO-insertion, which convergently transformed the two isomers **52**/**52'** to a single isomer **31**, which was the same intermediate reported by Mori and co-workers.

Scheme 5-7. Total Synthesis Reported by Hong

[a] Biosynthesis of stemoamide



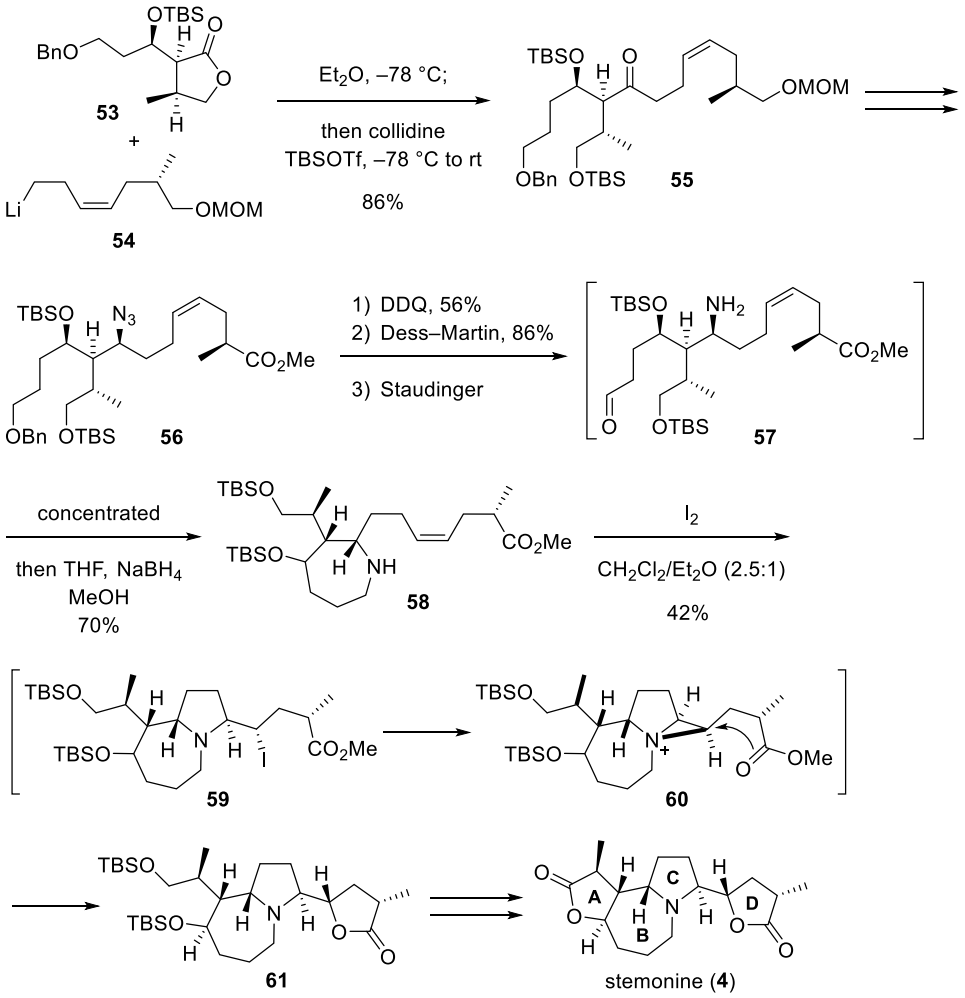
[b] Biomimetic total synthesis of stemoamide (**1**)



5-1-5. The First Total Synthesis of Stemonine

Stemonine (**4**) possesses the core-tricyclic structure of stemoamide-type alkaloids. Despite its high structural similarity to stemoamide (**1**), only one synthetic example of stemonine (**4**) was reported by Williams and co-workers (Scheme 5-8).[9] The synthetic strategy was identical as their first total synthesis of stemoamide (**1**), featuring the late-stage C and D ring construction from acyclic substrate containing all carbon, oxygen, and nitrogen atoms of **4**. Their total synthesis commenced with the synthesis of a key intermediate **56** through coupling of lactone **53** and alkyllithium **54**, followed by protection of primary alcohol with TBS group. Then the resulting **55** was transformed to the key intermediate **56** through deprotection and oxidation of the primary alcohol and azidation of the ketone. Removal of benzyl group followed by oxidation of the resulting primary alcohol and Staudinger reaction provided aminoaldehyde **57**, which was immediately converted to azepane **58** by intramolecular cyclization and reduction. Treatment of **58** with iodine promoted the key cascade cyclization of C and D rings (**58**→**59**→**60**→**61**). Finally, the total synthesis of stemonine (**4**) was accomplished by the formation of the A-ring.

Scheme 5-8. The landmark total synthesis of stemonine (**4**) reported by Williams

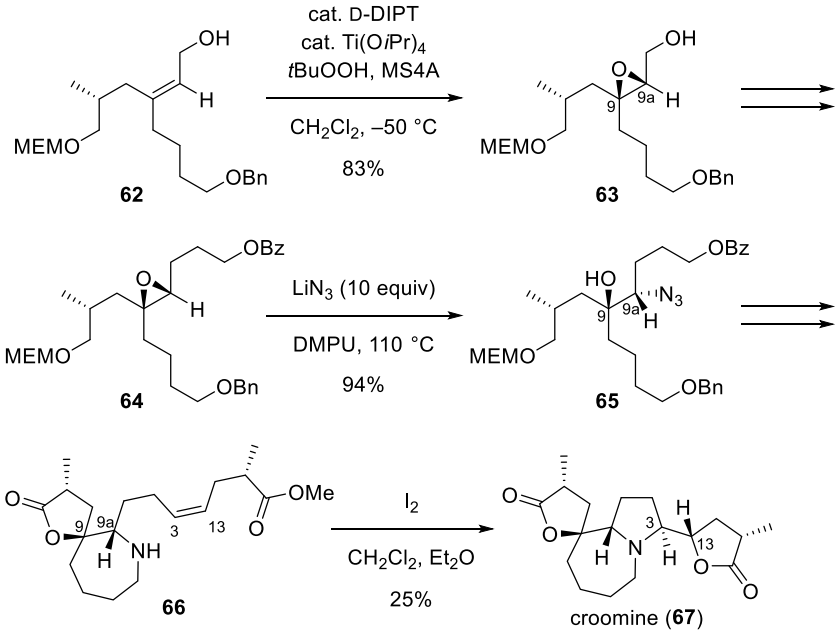


5-1-6. Synthetic Examples of Croomine

5-1-6-1. Williams and co-workers

Croomine (**67**) belonging to tuberostemospironine group partially shares the common structure corresponding to stemonine, such as pyrrolo[1,2-*a*]azepine skeleton and γ-lactone connected to the C3 position. Williams and co-workers reported the first total synthesis of (+)-croomine (**67**) featuring iodine-mediated cascade cyclization (Scheme 5-9).[10] At the early stage of the synthesis, diastereoselective epoxidation of allylic alcohol **62** led to construction of two consecutive stereocenters at C9 and C9a. Treatment of **62** with catalytic amount of D-diisopropyltartrate, Ti(O*i*-Pr)$_4$, and *t*-butyl hydroperoxide in the presence of MS4A at –50 °C successfully afforded epoxide **63** in 83% yield. After several steps, addition of excess amount of lithium azide to epoxide **64** resulted in construction of nitrogen functionality at the less hindered the C9a position in complete stereocontrol. Resulting azide **65** was converted to spirolactone **66** in multiple steps through deprotection and oxidation. In the last step of this synthesis, the key iodine-mediated cascade cyclization of **66** gave (+)-croomine (**67**) in 25% yield.

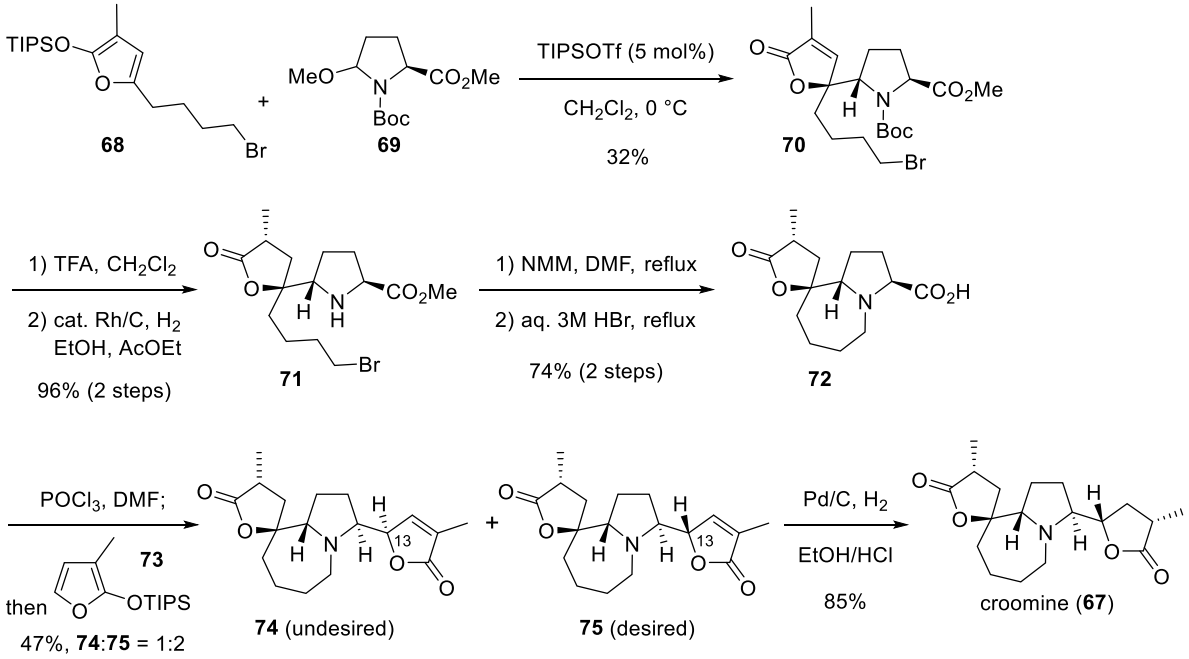
Scheme 5-9. The landmark total synthesis of croomine (**67**) reported by Williams



5-1-6-2. Martin and co-workers

In 1999, Martin and co-workers reported a convergent total synthesis of (+)-croomine by taking advantage of two vinylogous Mukaiyama Mannich reaction (Scheme 5-10).[11] The first key Mannich reaction of siloxyfuran **68** and *N*,*O*-acetal **69** proceeded by the treatment of catalytic amount of TIPSOTf (5 mol%) to give bicyclic compound **70** in 32% yield. Next, removal of the Boc group and hydrogenation of the unsaturated lactone led to the formation of secondary amine **71**, which would serve as a substrate of the seven-membered ring closure. Treatment of **71** with *N*-methylmorpholine in refluxing DMF followed by acidic hydrolysis of the methyl ester gave access to tricyclic compound **72** in 74% yield. The second key Mannich reaction of **72** was promoted by the addition of phospholic chloride and siloxyfuran **73** to afford two diastereomers **74** and **75** in combined 47% yield. The total synthesis of (+)-croomine (**67**) was achieved by a Pd/C-catalyzed diastereoselective hydrogenation of the major isomer **75** possessing the desired stereochemistry at C13.

Scheme 5-10. Total synthesis of croomine (**67**) reported by Martin

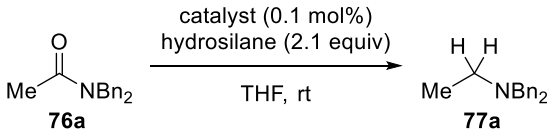


5-2. Chemoselective Reduction of Amides

5-2-1. Rhodium-catalyzed Amide-selective Hydrosilylation

To reduce the amide carbonyl group, $LiAlH_4$ has been frequently used in either the late- or early-stage of natural product synthesis. However, the hazardous reductant often tends to be avoided, and alternative methods have been extensively investigated. To the best of our knowledge, the first example of catalytic chemoselective hydrosilylation of amides was reported by Ito and co-workers in 1998.[12] Optimization of rhodium-catalyst and hydrosilane reductant revealed that the combination of rhodium(I) hydride catalyst and Ph_2SiH_2 showed quick reduction of tertiary amide **76a** to give amine **77a** (Table 5-3). A remarkable advantage of this reaction is high functional group tolerance. For instance, aliphatic and aromatic esters, an aryl bromide, and an epoxide were tolerated (Figure 5-4).

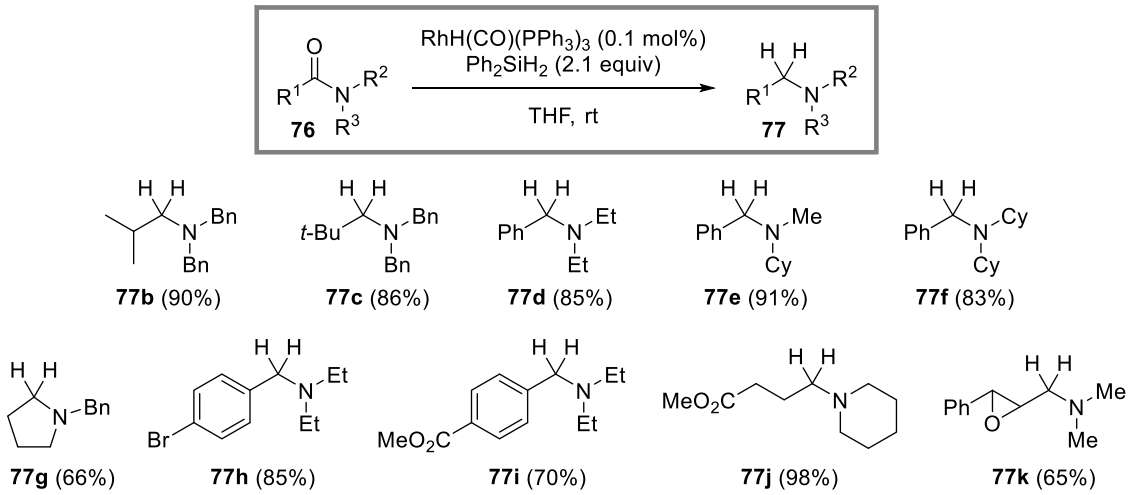
Table 5-3. Optimization of catalyst



entry	catalyst	hydrosilane	time, h	yield, %[a]
1	$RhH(CO)(PPh_3)_3$	Ph_2SiH_2	1	94
2	$RhH(PPh_3)_4$	Ph_2SiH_2	0.5	93
3	$[Rh(cod)_2]BF_4 \cdot 2PPh_3$	Ph_2SiH_2	42	86
4	$RhCl(PPh_3)_3$	Ph_2SiH_2	48	93
5	$RhCl_3 \cdot 3H_2O$	Ph_2SiH_2	48	95
6	$RhH(CO)(PPh_3)_3$	Ph_2SiH_2[b]	1	49
7	$RhH(CO)(PPh_3)_3$	$PhSiH_3$[c]	2	90
8	$RhH(CO)(PPh_3)_3$	Ph_3SiH	—	0

[a] Isolated yield, [b] 1.0 equiv of Ph_2SiH_2 was used, [c] 1.1 equiv of $PhSiH_3$ was used.

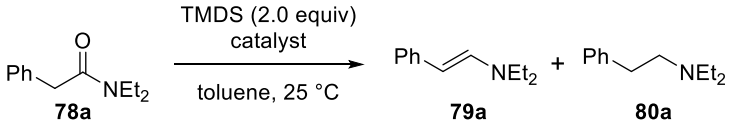
Figure 5-4. Substrate scope



5-2-2. Iridium-catalyzed Semi-reduction of *tert*-Amides

After the first discovery of the catalytic mild reduction of amides by Ito and co-wokers, double-reduction to give *α*-primary amine with a variety of organometallic complex have been reported to date.[13] In contrast to this, the less number of reports regarding a catalytic semi-reduction of amides to give enamines have been existed. However, Nagashima and co-workers invented a chemoselective semi-reduction of amides taking advantage of the Vaska's complex and $(Me_2HSi)_2O$ (tetramethyldisiloxane: TMDS) (optimization of catalyst; shown in Table 5-4, substrate scope; shown in Figure 5-5).[14]

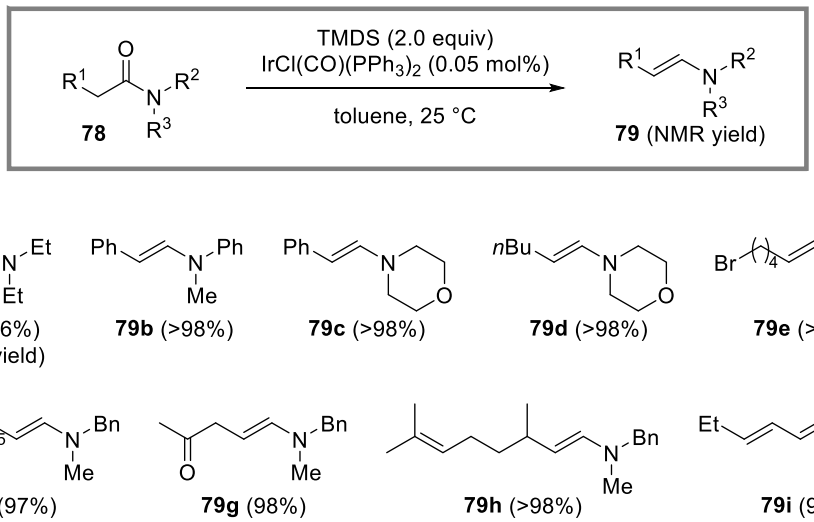
Table 5-4. Optimization of catalyst



entry	catalyst (mol%)	time, h	yield, %[a]	
			79a	**80a**
1	$(ACE)Ru_3(CO)_7$ (0.1)	4	13	4
2	$PtCl_2(cod)$ (0.1)	4	43	8
3	Karstedt's cat. (0.1)	4	41	7
4	$[RhCl(cod)]_2$ (0.05)	4	11	<2
5	$[IrCl(cod)]_2$ (0.05)	4	15	3
6	$RhCl(PPh_3)_3$ (0.1)	4	3	<1
7	$IrCl(CO)(PPh_3)_2$ (0.05)	0.5	96	<1
8	$IrCl(CO)(PPh_3)_2$ (0.01)	0.5	82	<1

[a] Determined by GLC analysis

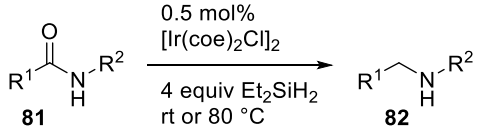
Figure 5-5. Substrate scope

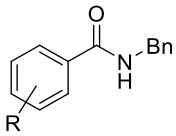
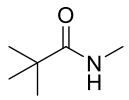
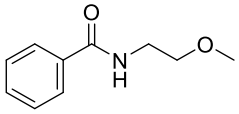
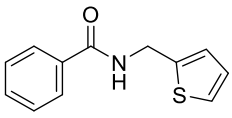
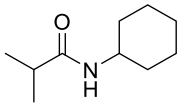


5-2-3. Iridium-catalyzed Semi-reduction of *sec*-Amides

In 2012, Brookhart and co-workers established an iridium-catalyzed hydrosilylation of secondary amides.[15] Treatment of secondary amides **81** with 0.5 mol% of $[Ir(COE)_2Cl]_2$ and 4 equiv of Et_2SiH_2 afforded the corresponding amines **82** or imines **83** with good chemoselectivity. While secondary amines **82** were produced by conducting the reduction with 0.5 mol% of $[Ir(COE)_2Cl]_2$ and 4 equiv of Et_2SiH_2 at room temperature or 80 °C (Table 5-5), imines **83** were obtained by restricting Et_2SiH_2 to 2 equiv (Table 5-6).

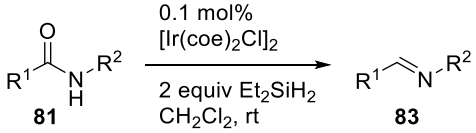
Table 5-5. Synthesis of secondary amine

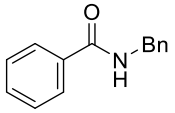
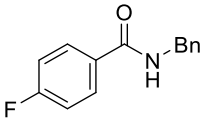
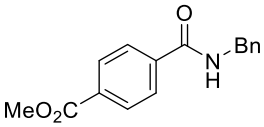
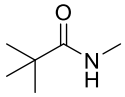
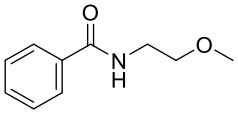
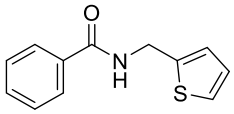
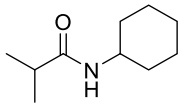


substrate		temp. (°C)	time (h)	yield (%)[a]
	**81a**: R=H	rt	2	91
	81a: R=H	rt	40	92
	81a: R=H	80	2	98[b]
	81b: R=4-F	80	1	88
	81c: R=4-Br	80	3	79
	81d: R=4-I	80	15	76
	81e: R=4-NMe_2	rt	6	68
	81f: R= 3,5-$(CF_3)_2$	rt	12	85
	81g: R=4-CN	80	50	16[b]
	81h: R=4-NO_2	rt	–	–
	**81i**	80	72	65[c]
	**81j**	rt	24	75
	**81k**	rt	5	87
	**81l**	rt	1	81[d]

[a]Isolated yields, [b]Yields determined by ^{1}H NMR, [c]Isolated as the HCl salt, [d]Product is somewhat volatile.

Table 5-6. Synthesis of imine



substrate		time (h)	yield (%)[a]
	**81a**	0.2	86
	**81b**	0.5	77
	**81m**	5	97[b]
	**81i**	1	63
	**81j**	1	79
	**81k**	0.2	71
	**81l**	0.5	95[b]

[a]Isolated yields, [b]Yields determined by ^{1}H NMR

5-2-4. Molybdenum-catalyzed Semi-reduction of *tert*-Amides

A molybdenum catalyst has been widely used for catalytic oxidation or reduction of carbonyl compounds. Adolfsson and co-workers developed a catalytic reduction of tertiary amides utilizing $Mo(CO)_6$, which is an inexpensive and a commercially available metal complex.[16] The expected products were dependent on either the substrate or the corresponding intermediate. *α,β*-Unsaturated tertiary amides **84** were converted to allylamines **85** by addition of 5 mol% of $Mo(CO)_6$ and $(Me_2HSi)_2O$ under reflux conditions (Figure 5-6). Under the same conditions, *β,γ*-unsaturated amides **86** was converted to dienamines **87** (Figure 5-7). The key of the molybdenum-catalyzed semi-reduction is the stabilization of enamines due to resonance effect derived from the adjacent aromatic ring or stylene unit. Recently, further applications of this synthetic method of enamines were reported such as [2+3] cycloaddition with azide[17] or nitrile oxide[18] (ex., **88→89→90**).

Figure 5-6. $Mo(CO)_6$ catalyzed 1,2-reduction of *α,β*-unsaturated amides to allylamines

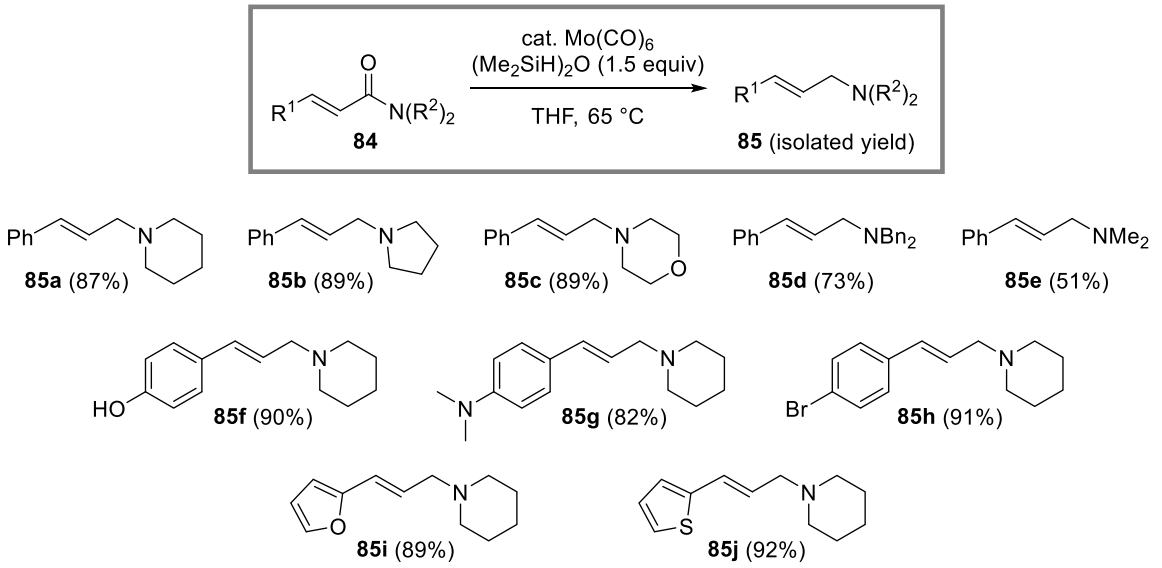
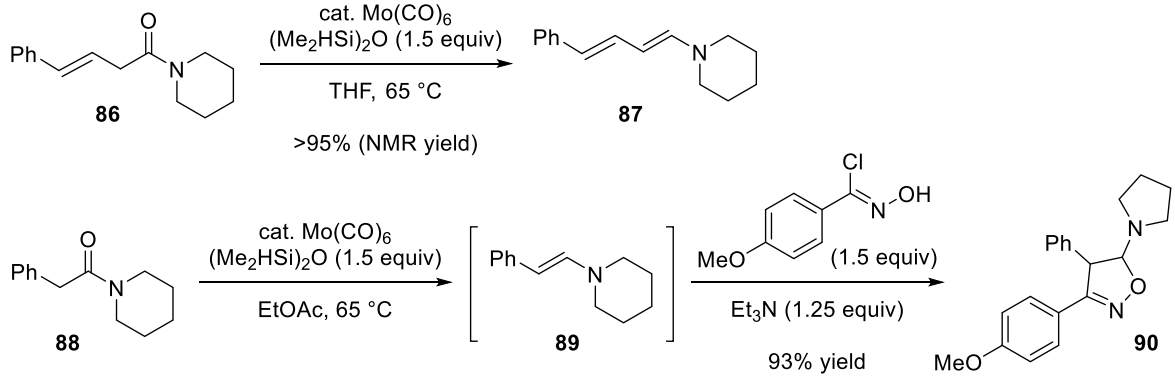


Figure 5-7. $Mo(CO)_6$ catalyzed reduction of *β,γ*-unsaturated amide

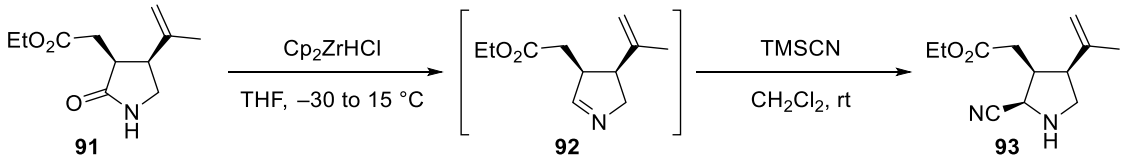


5-3. Chemoselective Nucleophilic Addition to *sec*- and *tert*-Amides

5-3-1. Amide-selective Nucleophilic Addition by Using the Schwartz Reagent

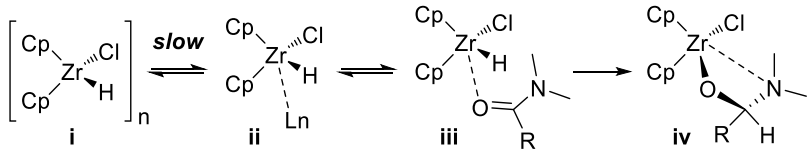
In contrast to the reduction of amides to amines, reductive nucleophilic addition to amides requires selective semi-reduction. To restrict the over reduction, various methods were developed to date. A pioneering work of chemoselective reductive nucleophilic addition to amides was reported by Ganem and co-workers (Scheme 5-11).[19] The key of chemoselective nucleophilic addition was lactam-selective reduction with the Schwartz reagent.[20] Secondary lactam **91** was treated with Cp_2ZrHCl to give imine **92** without harming ethyl ester, and subsequent addition of TMSCN led to direct access to α-cyanoamine **93** in 75% yield.

Scheme 5-11. Secondary lactam-selective reductive cyanation using the Schwartz reagent



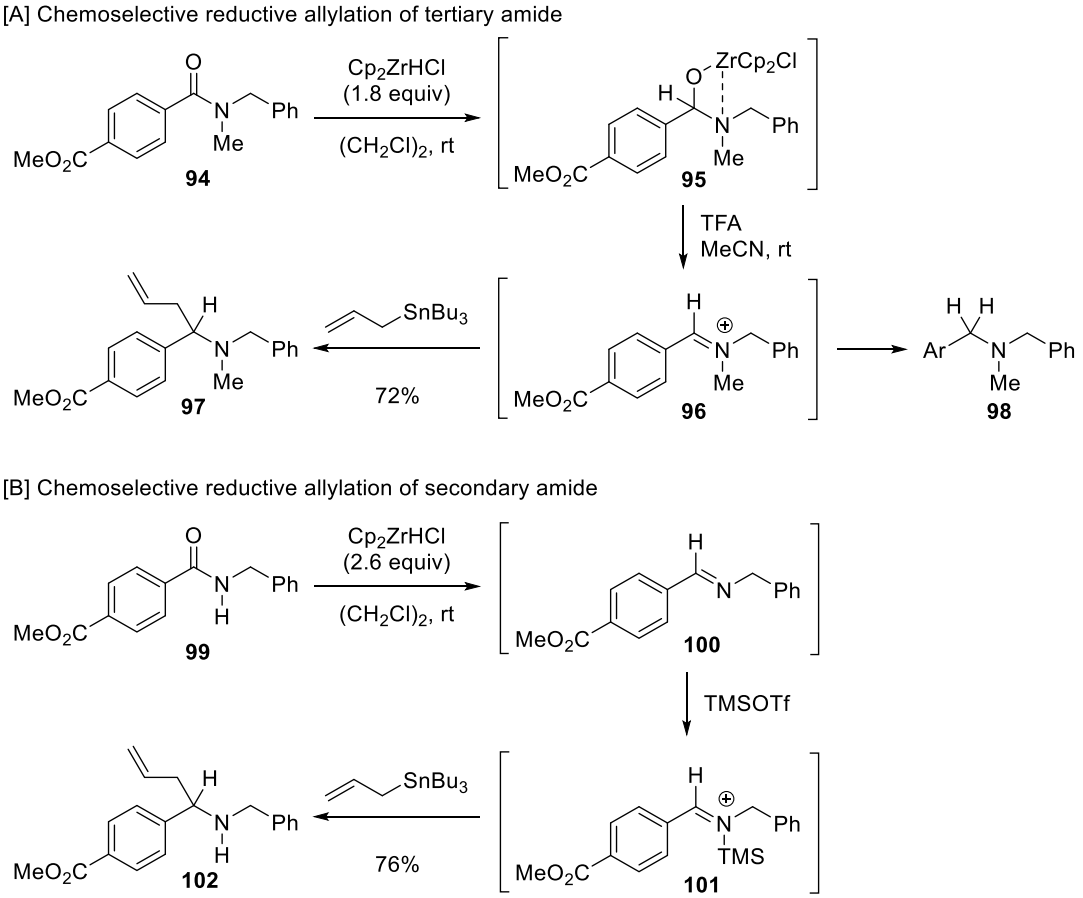
The principle of the amide-selectivity with the Schwartz reagent could be explained by the following two reasons. Firstly, the coordination of zirconium to a carbonyl oxygen atom would be important for the reduction with the Schwartz reagent, according to the mechanism reported by Georg and co-workers (Figure 5-8).[21] Secondly, esters also has a potential to react with the Schwartz reagent to give alcohols.[22] This means reduction of esters with the Schwartz reagent is not impossible but slower than reduction of amides. The reaction of amides is faster than that of esters due to higher Lewis basicity of amides than esters favorably forming amide-Zr complex **iii**. However, aldehydes and ketones were reduced by the Schwartz reagent even in the presence of amides, due to theirs relatively higher electrophilicity than that of amides.

Figure 5-8. Principle of Amide-selectivity with the Schwartz reagent



In 2012, Chida-Sato group developed a chemoselective reductive allylation of secondary- and tertiary amides using the Schwartz reagent.[23] The reduction of tertiary amide **94** with 1.8 equiv of Cp_2ZrHCl showed complete amide-selectivity to form the four-membered chelated intermediate **95** (Scheme 5-12A). Although **95** is less stable than the five-membered chelated intermediate like **4** (see p1), the stability is enough to prevent the spontaneous formation of iminium ion **96** followed by undesired over-reduction to form amine **98**. After treatment of **95** with TFA, the resulting intermediate **96** was immediately converted to allylated amine **97** by treatment of allylstannane without decomposition of the methylester. In the case of secondary amide **99** as a substrate, 2.6 equiv of Cp_2ZrHCl promoted amide-selective reduction in the presence of the ester group (Scheme 5-12B). And subsequent allylation of imine **100** was conducted by treatment with allylstannane and TMSOTf to form secondary amine **102** via iminium ion **101**.

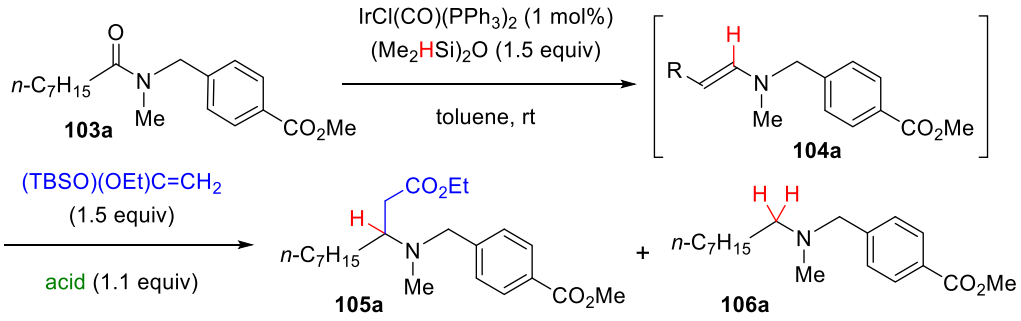
Scheme 5-12. Amide-selective reductive allylation using the Schwartz reagent



5-2-6. Iridium-catalyzed Reductive Nucleophilic Addition to *tert*-Amides

The key of our previous methods for the reductive nucleophilic addition to amide was utilization of *N*-methoxyamides whose reactivity was controlled by the *N*-methoxy group. However, it would not be applicable for more general tertiary amides due to the lack of positive supplementary effect of methoxy group. Very recently, Chida-Sato group found an iridium-catalyzed highly chemoselective nucleophilic addition to tertiary amides (Table 5-7). Considering the Nagashima's report (Table 5-4 and Figure 5-5), treatment of tertiary amide **103a** with a catalytic amount of Vaska's complex and $(Me_2HSi)_2O$ would allow the formation of enamine **104a** in a highly chemoselective fashion. Next, optimization of acid for the Mannich reaction of enamine **104a** with silylketenacetal to give α-substituted amine **105a** was conducted. After extensive investigation of acids, PPTS was revealed to be the optimal acid, which gave the desired product **105a** in 85% yield and the undesired over reduced product **106a** in merely 5% yield.

Table 5-7. Iridium-catalyzed chemoselective reductive nucleophilic addition to *tert*-amide



entry	acid	yield [a]	
		105a	**106a**
1	TFA	multispots	
2	$TsOH \cdot H_2O$	59%	15%
3	CSA	53%	31%
4 [b]	PPTS	85%	5%

[a] Yields were determined by ^1H NMR, [b] Isolated yield

Next, the tolerance of the functional groups was investigated. The optimized conditions were applicable to a variety of substrates, which contain a methyl ester, a nitrile group, a nitro group, an aryl bromide, a MOM group, a tosic amide, a carbamate, and a terminal olefin (Figure 5-9).

The nucleophiles were also investigated. As a result, silyl ketene acetal, TMSCN, allylstannane, and 2-siloxyfuran were available under the optimized conditions (Table 5-8).

Figure 5-9. Substrate scope

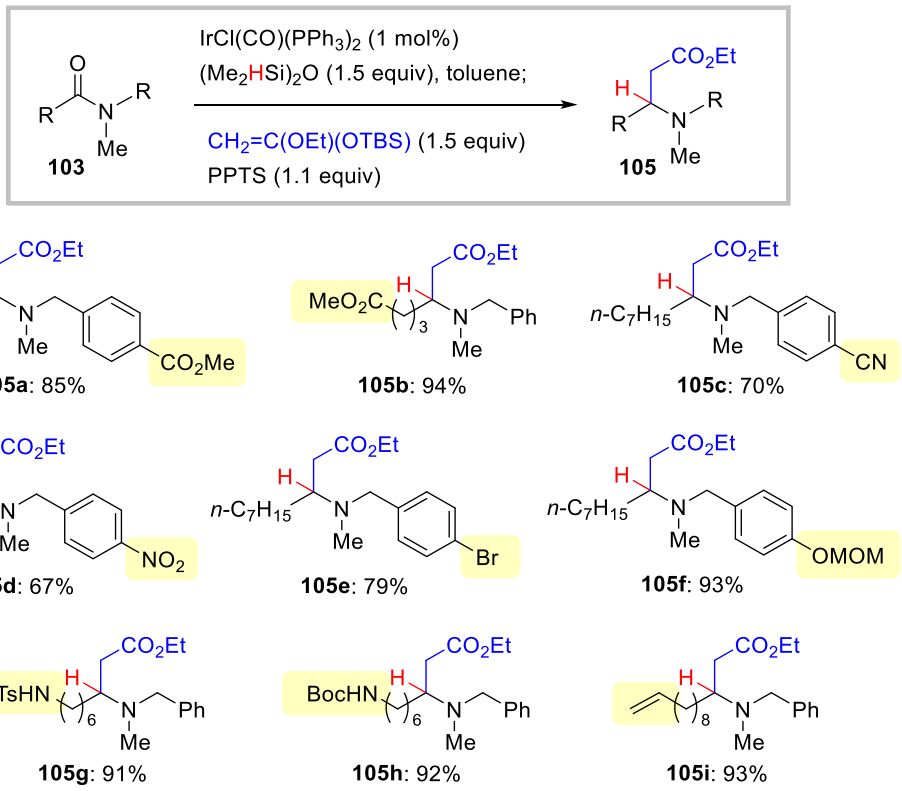
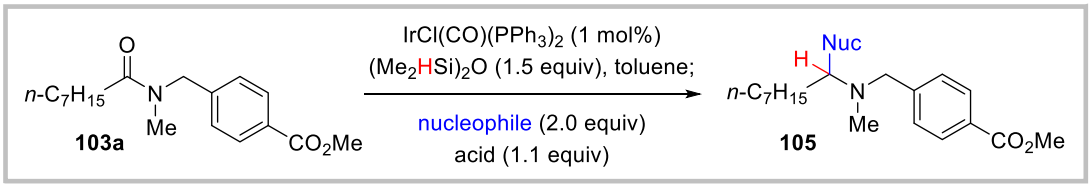


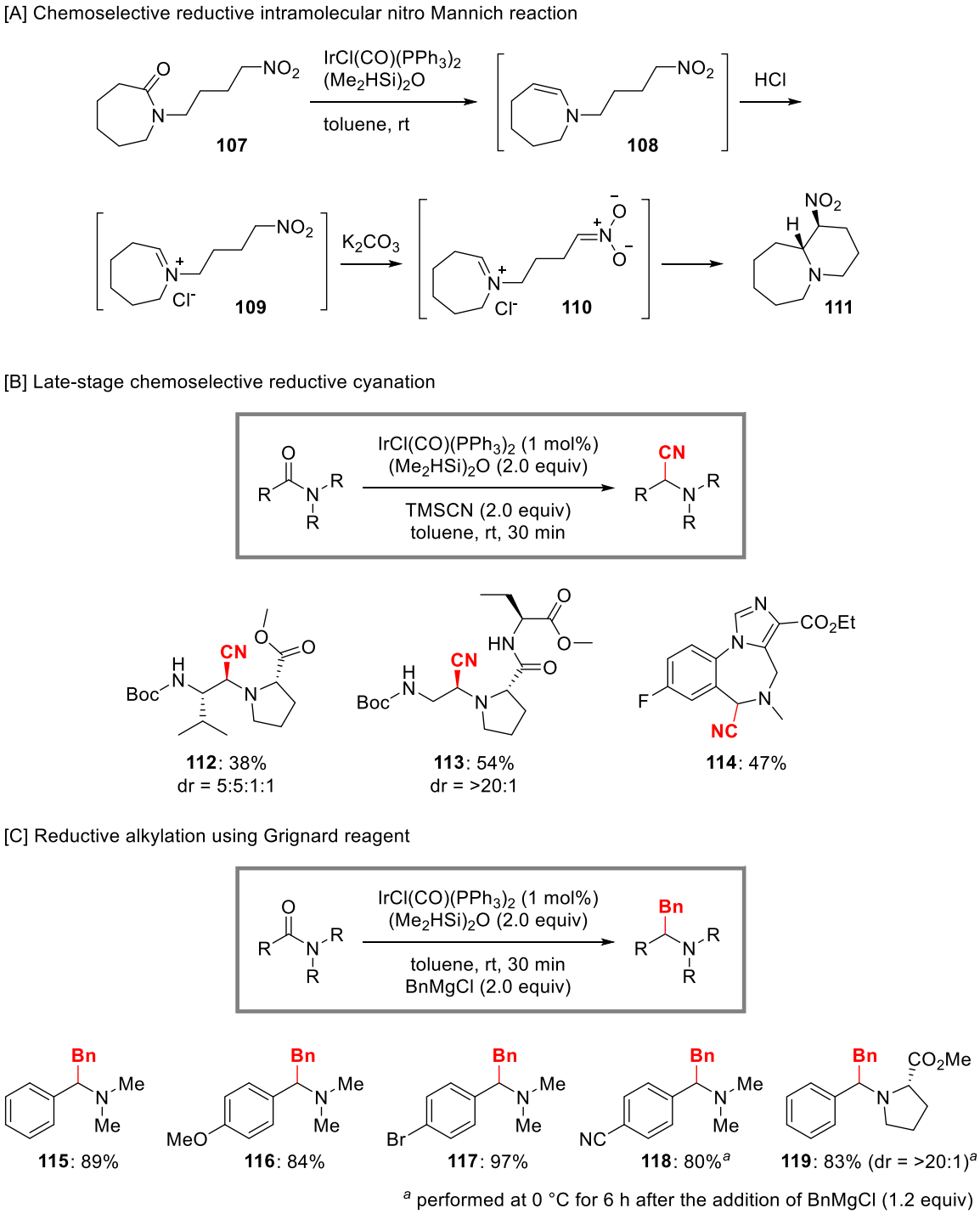
Table 5-8. Scope of nucleophiles



entry	nucleophile	acid	yield	entry	nucleophile	acid	yield
1	OTBS, OEt (1.5 equiv.)	PPTS	85%	3	TMSCN	$Sc(OTf)_3$ (10 mol%)	87%
2*	OTBS, OEt	$BF_3{\cdot}OEt_2$	79%	4*	$SnBu_3$	TFA	77%
				5	O, OTBS	PPTS	83%

Dixon and co-workers reported highly chemoselective reductive functionalization of the amide carbonyl group taking advantage of Nagashima's conditions.[24] Firstly, they reported the reductive intramolecular nitro Mannich reaction (Scheme 5-13A).[24a] Moreover, they demonstrated the reductive cyanation by using TMSCN (Scheme 5-13B),[24c] and reductive alkylation by using Grignard reagent (Scheme 5-13C).[24d]

Scheme 5-13. Amide-selective nucleophilic addition reported by Dixon and co-workers



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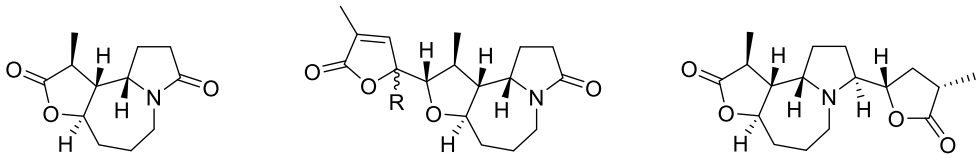
Chapter 6. Enantioselective Total Synthesis of Stemoamide

6-1. Stemoamide-type Alkaloids

We planned to synthesize a variety of stemona-alkaloids by taking advantage of the late-stage chemoselective transformation of γ-lactam and γ-lactone. Especially, we focused on the synthesis of stemoamide-type alkaloids (Figure 6-1). Stemoamide (**1**)[1] possesses a tricyclic core structure. While saxorumamide (**2**) and isosaxorumamide (**3**)[2] have an additional γ-lactone on the lactone of stemoamide (**1**), stemonine (**4**)[3] possesses an additional γ-lactone on the lactam of stemoamide (**1**). More than 20 synthetic example of **1** have been reported to date due to its relatively simple structure.[4] In contrast, the tetracyclic derivatives cannot be synthesized easily because of its complex structures. Indeed, only the Williams' group achieved the total synthesis of stemonine (**4**) by late-stage ring closure from acyclic intermediate with complete stereoselectivity (Chapter 5, Scheme 5-8).[5]

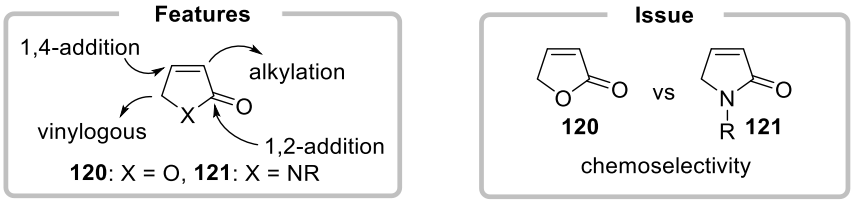
Figure 6-1. Stemoamide-type Alkaloids



6-2. Chemoselective Assembly of Hetero Five-membered Building Blocks

For the unified total synthesis of stemoamide-type alkaloids, we devised the following synthetic strategy. Stemoamide-type alkaloids possess five-membered hetero cyclic structures, and they could be introduced by utilizing *α,β*-unsaturated lactone **120** and lactam **121**. These five-membered blocks allow for carbon-carbon bond or carbon-heteroatom bond formation at any position of each building blocks such as vinylogous addition or Michael addition (Figure 6-2, Features). These features would enable an efficient and short step synthesis of natural products containing repetitive structures such as stemoamide-type alkaloids **1**-**4**. However, in order to accomplish the unified synthesis of these natural products, the precise control of chemoselectivity is required (Figure 6-2, Issue). Convergent assembly is not feasible without the differentiation between the γ-lactone **120** and the γ-lactam **121**.

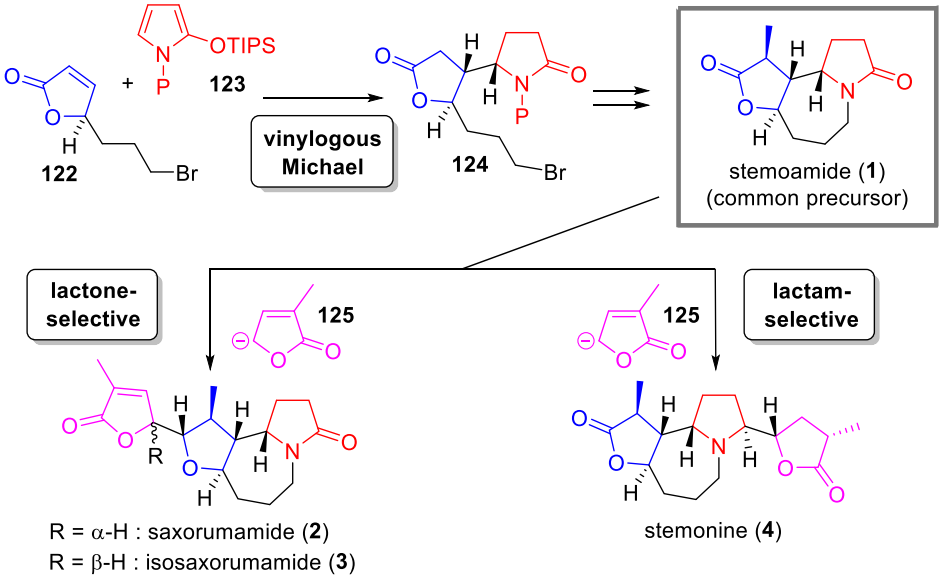
Figure 6-2. The features and issue of the building block strategy



6-3. Synthetic Plan for Unified Total Synthesis of Stemoamide-type Alkaloids

Our actual synthetic plan is outlined in Scheme 6-1. We envisioned that stemoamide (**1**) could serve as a common precursor to the tetracyclic natural products, and incorporated two successive coupling reactions of the five-membered building blocks. First coupling reaction is vinylogous Michael reaction/reduction sequence of γ-lactam derivatives **123** to α,β-unsaturated lactone **122**. The second coupling reaction is the chemoselective nucleophilic addition of lactone derivative **125** to common precursor **1**. The lactone-selective nucleophilic addition would afford saxorumamide (**2**) and isosaxorumamide (**3**), while the lactam-selective nucleophilic addition would afford stemonine (**4**).

Scheme 6-1. Synthetic plan of stemoamide-type alkaloids



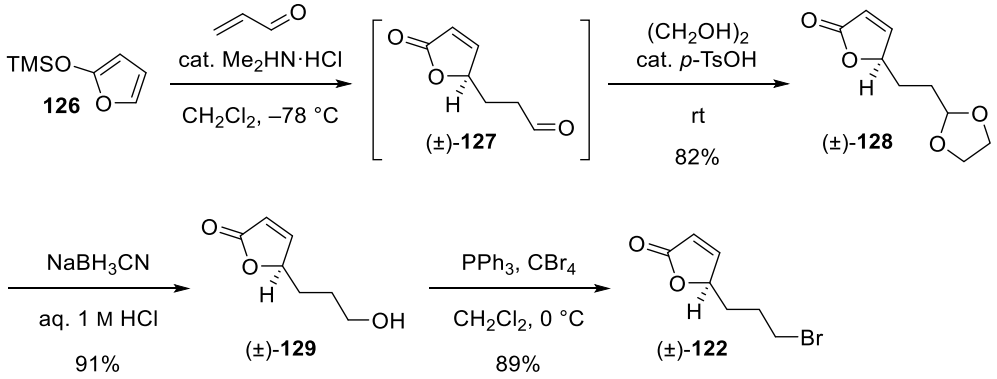
The lactone-selective nucleophilic addition would be easily accomplished than the lactam-selective nucleophilic addition because of the inherent larger electrophilicity of the lactone. In contrast, the lactam-selective nucleophilic addition would be more challenging. If successful, the method would enable the pioneering direct synthesis of stemonine (**4**) from stemoamide (**1**).

6-4. Preparation of Five-membered Building Blocks

6-4-1. Preparation of Chiral γ-Butenolide **122**

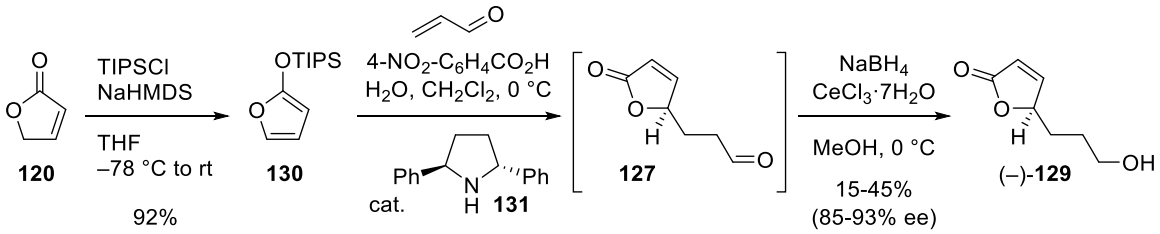
The unified total synthesis of stemoamide-type alkaloids commenced with synthesis of γ-butenolide **122**, which is the coupling fragment of vinylogous Michael reaction (Scheme 6-2). First, the Michael reaction between siloxyfuran **126** and acrolein was examined.[6] The Michael reaction successfully proceeded upon treatment of siloxyfuran **126** with a catalytic amount of dimethylamine hydrochloride. The subsequent one-pot protection of aldehyde (±)-**127** immediately gave acetal (±)-**128** in 82% yield. Acetal (±)-**128** was then converted to butenolide (±)-**122** by hydrolysis, reduction of aldehyde (**128**→**129**), and the Appel reaction in good yield.

Scheme 6-2. Synthesis of racemic butenolide (±)-**78**



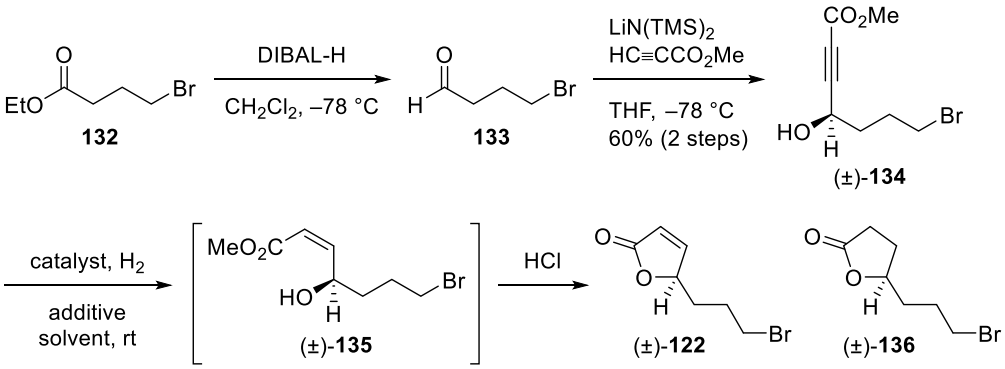
Then, the enantioselective Michael reaction of siloxyfuran **130** and acrolein to synthesize chiral butenolide (–)-**129** was investigated (Scheme 6-3). Siloxyfuran **130** was prepared from furanone **120** with TIPSCl and $NaN(TMS)_2$. According to the literature reported by Pihko and co-workers, we attempted the Michael reaction catalyzed by C_2-symmetric pyrrolidine catalyst **131** followed by Luche reduction of aldehyde **127**.[7] However, the reaction lacked both the reproducibility of yield and enantioselectivity, especially in the large scale.

Scheme 6-3. Failure to provide chiral butenolide **129**



To improve the reproducibility, an alternative route to synthesize butenolide **122** was investigated (Scheme 6-4). The reduction of commercially available ethyl 4-bromobutyrate **132** with DIBAL-H followed by the nucleophilic addition of lithium acetylide to the resulting aldehyde **133** gave propargylic alcohol **134** in 60% yield over two-steps. Next, the semi-reduction of alkyne **134** was attempted. Extensive investigation revealed semi-reduction of alkyne cannot be achieved by homogeneous palladium catalyst,[8a-d] homogeneous nickel catalyst,[8e-g] or heterogeneous palladium catalyst,[8h] and combinations of additives and solvents (entries 1-6). However, the palladium catalyst supported on polyethylene imine reported by Sajiki and co-wokers was effective for the semi-reduction.[9] Subsequent one-pot addition of aqueous hydrogen chloride afforded (±)-**122** along with over-reduced byproduct **136**. Under these conditions, the combination of solvent was very important. In fact, although the reaction in 1,4-dioxane was not effective for this semi-reduction (entry 7), use of MeOH/1,4-dioxane 1:1 resulted in highly selective formation of butenolide **122** in 73% yield along with **136** in 5% yield (entry 8).

Scheme 6-4. Alternative route for racemic butenolide **122**

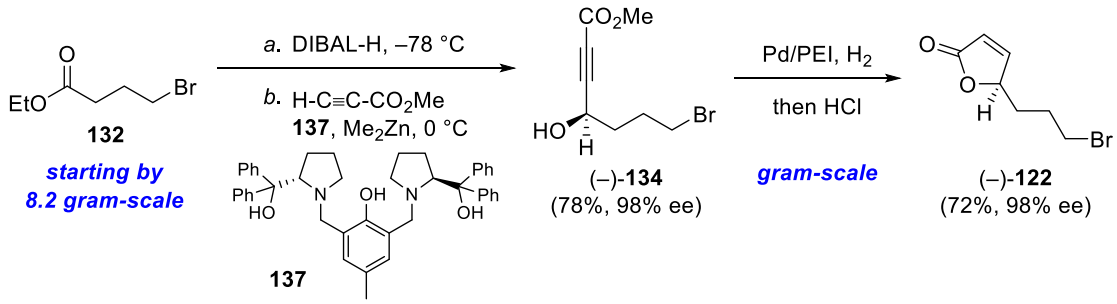


entry[a]	catalyst	solvent	additive	result
1	Lindlar catalyst	AcOEt	none	only **136**
2	Lindlar catalyst	THF	none	multi spot
3	$Pd/BaSO_4$	AcOEt	quinoline (10 mol%)	only **136**
4	Pd/(en)	AcOEt	none	only **136**
5	$Ni(OAc)_2$, $NaBH_4$	THF or EtOH	ethylenediamine	multi spot
6	Pd(TPP) (1 mol%)	pyridine	DMAP (2 mol%)	no reaction
7	Pd/PEI (5 wt%)	dioxane	none	no reaction
8	Pd/PEI (5 wt%)	MeOH/dioxane[b]	none	**122**: 73%, **136**: 5%[c]

[a]reactions were performed around 100 mmol scale, [b]MeOH:dioxane = 1:1 [c]**122** and **136** were inseparable mixture,

Once we set the appropriate conditions for the synthesis of racemic butenolide **122**, we then focused on enantioselective synthesis of butenolide **122** (Scheme 6-5). To achieve the enantioselective alkynylation, we decided to employ conditions reported by Trost and co-workers.[10] After reduction of **132** (8.16 g), treatment of resulting aldehyde with 20 mol% of (*S*,*S*)-Prophenol catalyst **137**, Me_2Zn, and methyl propiolate gave (–)-**134** in 78% yield and with 98% ee. Following semi-reduction/cyclization under optimized condition in Scheme 6-4 afforded 3.18 g of (–)-**122** in 72% yield with high reproductivity without racemization.

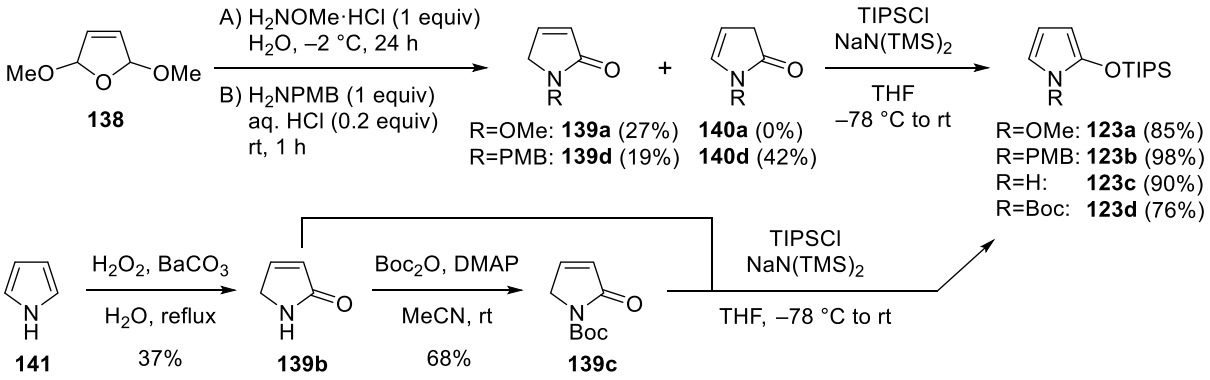
Scheme 6-5. Asymmetric synthesis of butenolide (–)-**122**



6-4-2. Synthesis of 2-Siloxypyrroles **123a-d**

2-Siloxypyrroles **123a** and **123d** were synthesized in 2 steps from commercially available 2,5-dimethoxy-2,5-dihydrofuran **138** and primary amines (Scheme 6-6).[11] The reaction between **138** and *N*-methoxyamine hydrochloride was conducted at –2 °C for 24 h to prevent the runaway reaction due to unavoidable use of excessive amount of acid as the HCl salt (1 equiv HCl, condition A). The reaction between **138** and H_2NPMB could be conducted under milder acidic conditions (0.2 equiv HCl, condition B). In order to keep the pH approximately around 4, the H_2NPMB should be added dropwise, especially in large scale. **123b** and **123c** were prepared through oxidation of pyrrole **141** followed by Boc- and TIPS-protections.[12]

Scheme 6-6. Synthesis of siloxypyrrole **123**

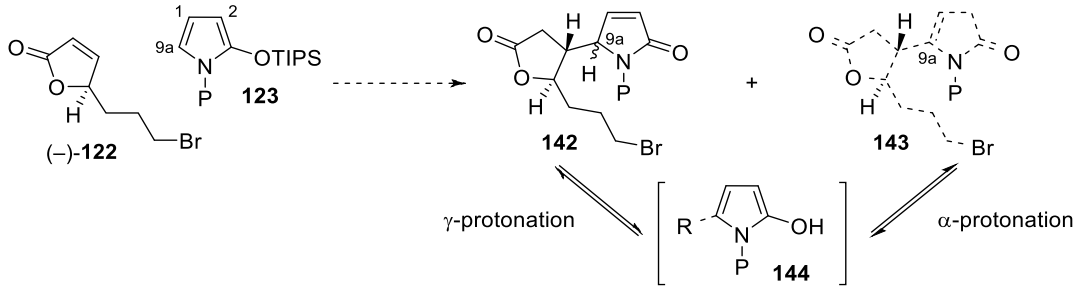


6-5. Vinylogous Michael Reaction

6-5-1. Initial Investigation of Vinylogous Michael Reaction

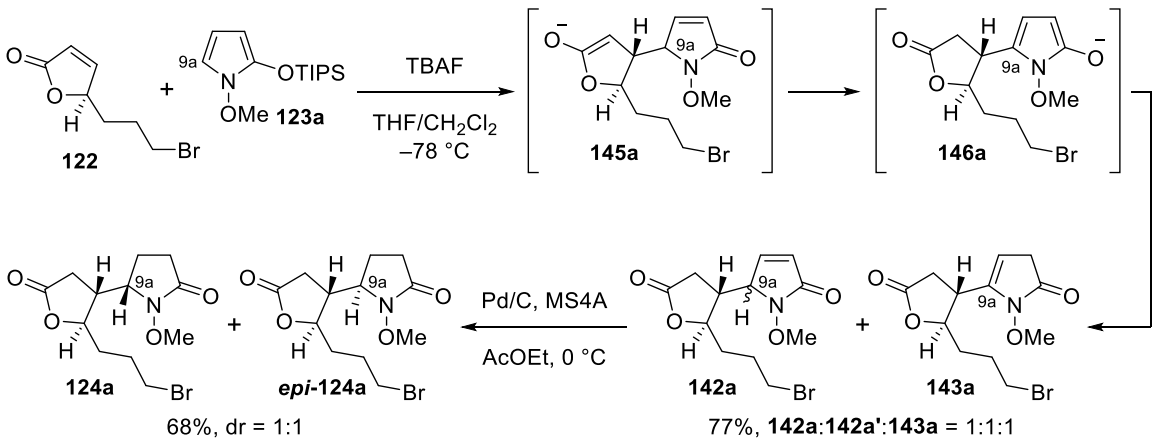
With butenolide **122** and 2-oxipyrrole **123** in hand, we then attempted the vinylogous Michael reaction. In general, *α*,*β*-unsaturated lactam **142** and enamide **143**, which are plausible product of vinylogous Michael reaction of **122** and **123**, would tautomerize respectively via 2-oxypyrrole **144** under basic conditions.[13]

Figure 6-3. Predictable issue in vinylogous Michael reaction



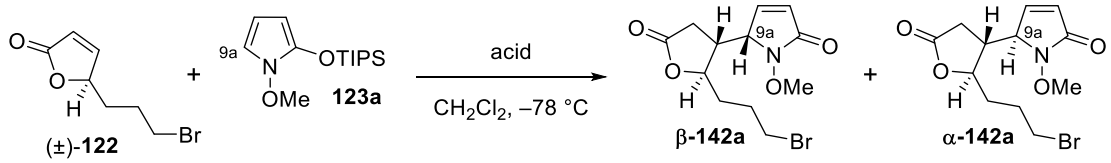
Taking the above context into account, we optimized the Mukaiyama-type vinylogous Michael reaction of butenolide **122** and 2-siloxypyrrole **123a**. First we attempted the fluoride ion mediated Michael reaction (Scheme 6-7). After investigation, we found that sufficiently dried TBAF was essential for C-C bond formation to afford bicyclic compound **145a**, which was immediately transformed to enolate **146a**. Then the protonation of **146a** afforded **142a** and **143a** (**142a**: 51%, dr = 1:1, **143a**: 26%). However the intermediate **146a** tended to undergo quick oxidation when the slight amount of oxygen was present. Therefore, the use of completely degassed solvent and careful control of temperature below –78 °C were necessary. Furthermore, hydrogenation of **142a** and **143a** resulted in poor yield and low stereoselectivity at C9a (68%, **124a**:***epi*-124a** = 1:1).

Scheme 6-7. TBAF mediated vinylogous Michael reaction

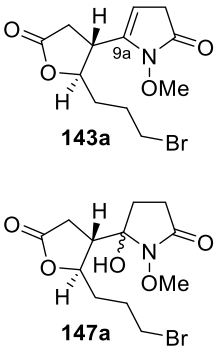


We then investigated the Lewis acid-mediated vinylogous Michael reaction (Table 6-1). Interestingly, this reaction did not proceed with acid other than $SnCl_4$ (Table 6-1, entries 1 to 5). In addition, in entry 5, hydrated product **147a** was produced in 11% yield. Further investigation revealed that excess amount of $SnCl_4$ suppressed the coupling reaction and result in significant recovery of butenolide **122** (Table 6-1, entry 6). In contrast, 0.5 equivalent of $SnCl_4$ promoted the formation of **147a**, and decrease recovery of starting material **122** (Table 6-1, entry 7). Moreover, the combined yield of coupling products **142a**, **143a**, and **147a** was largest in entry 7 (87%), and optimal acid for vinylogous Michael reaction was decided as 0.5 equiv $SnCl_4$.

Table 6-1. Acid mediated vinylogous Michael reaction



entry	acid (equiv)	result β-142a	α-142a	143a	147a	rec-122
1	$Sc(OTf)_3$ (1.0)					
2	TMSOTf (1.0)			***no reaction***		
3	$BF_3{\cdot}OEt_2$ (1.0)					
4	$TiCl_4$ (1.0)					
5	$SnCl_4$ (1.0)	18%	30%	34%	11%	10%
6	$SnCl_4$ (1.5)	6%	20%	11%	0%	64%
7	$SnCl_4$ (0.5)	12%	18%	38%	19%	7%

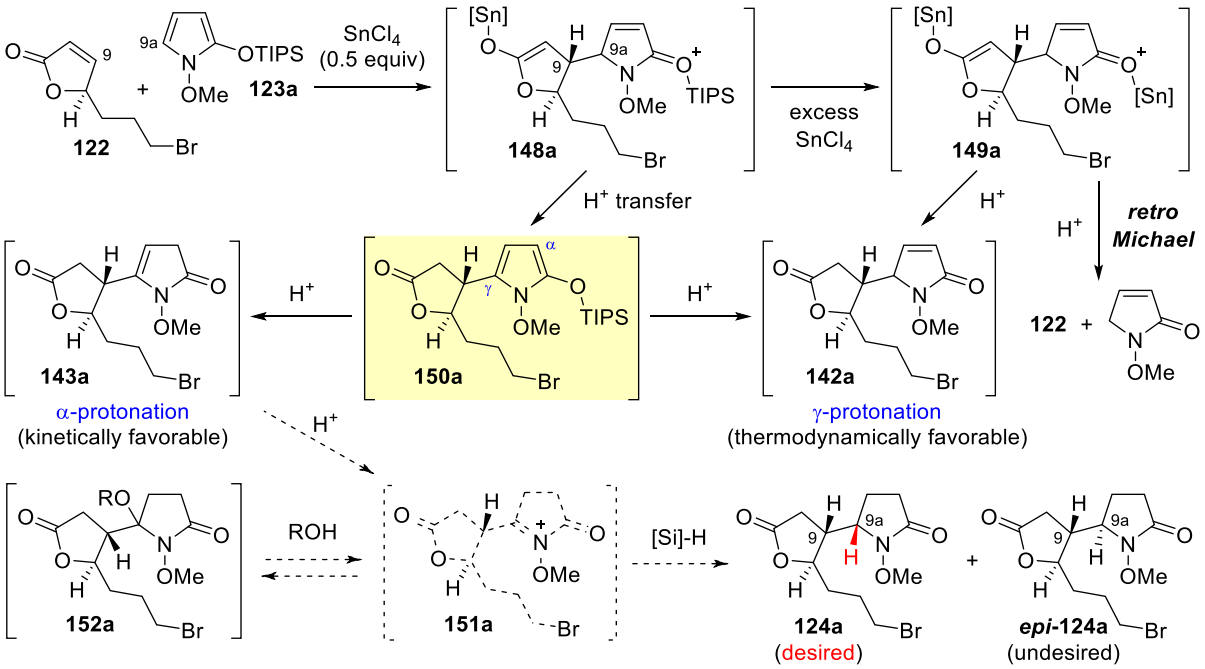


6-5-2. Plausible Mechanism and Working Hypothesis for the One-pot Reaction

Based on the results shown in Table 6-1, we postulated the reaction mechanism and proposed a working hypothesis (Scheme 6-8). Treating the mixture of butenolide **122** and 2-siloxypyrrole **123a** with $SnCl_4$ would immediately construct the carbon-carbon bond at C9 and C9a position to form ketenacetal **148a** with complete stereoselectivity at C9. The excess amount of $SnCl_4$ would cause deprotection of TIPS group of **148a** to form enolate **149a**, which would decompose by *retro*-Michael reaction or transform to *α*,*β*-unsaturated lactam **142a**. Without the excess amount of $SnCl_4$, **148a** would immediately be converted to the siloxypyrrole **150a** via proton transfer.

We predicted that **150a** would be stable under Lewis acidic conditions at low temperature, and converted to enamide **143a** via protonation at the less hindered *α*-position of **150a**. In fact, according to the TLC analysis, enamide **143a** was selectively produced at –78 °C. Then, further protonation of enamide **143a** would form acyliminium ion **151a**, which would react with hydrosilane to give the desired lactam **124a**. In case we employ an alcohol as a proton source, it may assist extending the life-span of iminium ion **151a** via the formation of *N*,*O*-acetal **152a**. One of the advantages in this strategy was the every intermediate would converge to the iminium ion **151a**. In other words, the stereoselectivity of reduction at C9a would only rely on the silane reagent and protecting group of the nitrogen. In addition this one-pot reaction would allow us to evade the isolation of the unstable intermediate **143a**.

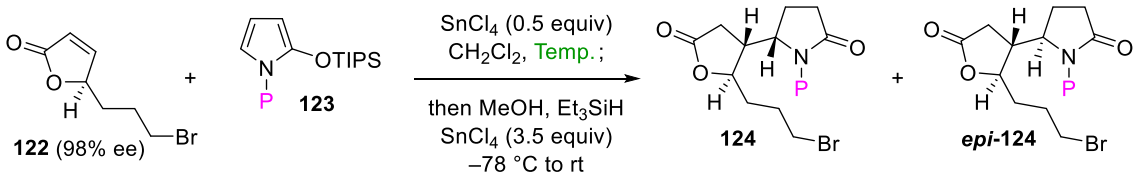
Scheme 6-8. Proposed reaction mechanism and working hypothesis



6-5-3. Acid-Mediated Vinylogous Michael Reaction

To demonstrate our working hypothesis, we optimized the reaction conditions for the one-pot vinylogous Michael reaction and reduction sequence. After optimization of the reaction between butenolide **122** and *N*-methoxypyrrole **123a**, the bicyclic lactam **124** and ***epi*-124** were produced in 77% combined yield (Table 6-2, entry 1). However, under these conditions, not only the poor stereoselectivity at C9a was observed, but also racemization was slightly observed. To solve these problems, we conducted further investigation. The protecting group of nitrogen was essential, and no coupling product was obtained with *N*-H pyrrole (Table 6-2, entry 2). The reaction with *N*-Boc pyrrole **123c** resulted in decomposition due to its instability under acidic conditions (Table 6-2, entry 3). We found that the utilization of *N*-PMB group would improve the diastereoselectivity (**124**:***epi*-124** = 2.7:1), and did not cause racemization (Table 6-2, entry 4).

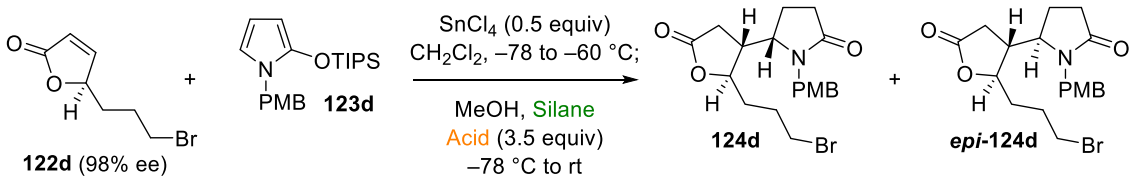
Table 6-2. Optimization of the protecting group on nitrogen



entry	P	Temp.	combined yield	**124**:***epi*-124**	ee (**124**, ***epi*-124**)
1	**123a**: OMe	–78 °C	77%	1.0:1	94%, 90%
2	**123b**: H	–78 °C	0%	—	—
3	**123c**: Boc	–60 °C	0%	—	—
4	**123d**: PMB	–60 °C	85%	2.7:1	98%, 98%

With the appropriate protecting group of the nitrogen in hand, the silane reductant and additional acid were then surveyed (Table 6-3). Use of more sterically hindered triphenylsilane and less hindered phenylsilane resulted in poor diastereoselectivity (Table 6-3, entries 2, 3). To form *N*-acyliminium ion, $TiCl_4$ was revealed as an optimal Lewis acid (Table 6-3, entries 4, 5). The optimized conditions were successfully applied to gram-scale reaction between chiral butenolide **122** (3.11 g, 98% ee) and *N*-PMB-siloxypyrrole **123d** to afford the bicyclic compound **124** and ***epi*-124** in 73% combined yield with 3.7:1 diastereoselectivity as an inseparable mixture (Table 6-3, entry 6).

Table 6-3. Optimization of silane reductant and acid

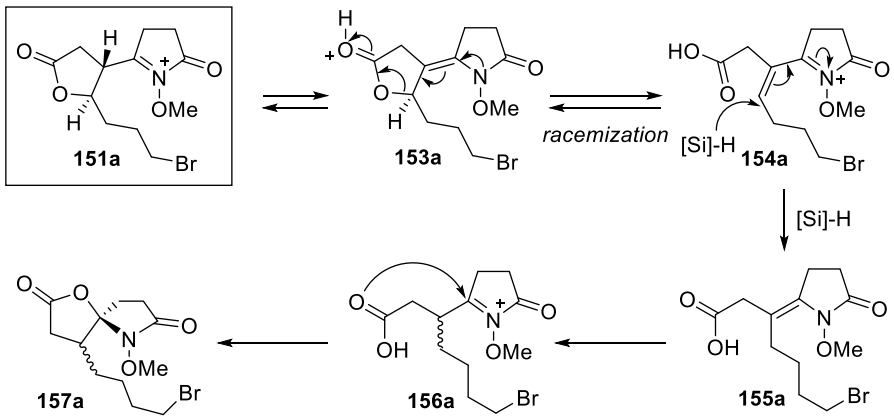


entry	Acid	Silane	combined yield	124d:*epi*-124d
1	$SnCl_4$	Et_3SiH	85%	2.7:1
2	$SnCl_4$	$PhSiH_3$	39%	1.1:1
3	$SnCl_4$	Ph_3SiH	77%	1.2:1
4	$BF_3{\cdot}OEt_2$[a]	Et_3SiH	72%	3.3:1
5	$TiCl_4$	Et_3SiH	77%	3.7:1
6[b]	$TiCl_4$	Et_3SiH	73%[c]	3.7:1

[a]10 equivalents of $BF_3{\cdot}OEt_2$ was used.
[b]Butenolide **122** (3.11 g, 15.2 mmol, 98% ee) was used.
[c]The ee of both product **124** and ***epi*-124** were both 98% ee.

The racemization of the product **124a** was rationalized when using *N*-methoxypyrrole **123a** (Scheme 6-9). First, the coupling reaction gave spiroacetal **157a** as an important side product. The deprotonation of acyliminium ion **151a** could form tetra-substituted enamide **153a**. Then, the chirality of the C8 position would disappear via the elimination of the carboxylate **154a**. While reconstruction of γ-lactone **153a** would provoke the racemization of **151a**, irreversible reduction of **154a** by silane reagent would form enamide **155a**. Protonation of **155a** and subsequent cyclization of iminium ion **156a** led to spiroacetal **157a**. The driving forth of these reactions would be the increased electrophilicity of *N*-acyl-*N*-oxyiminium ion **151a**, which enables not only the reduction but also the deprotonation to form enamide **153a**.

Scheme 6-9. Mechanism of racemization of the *N*-methoxy substrate

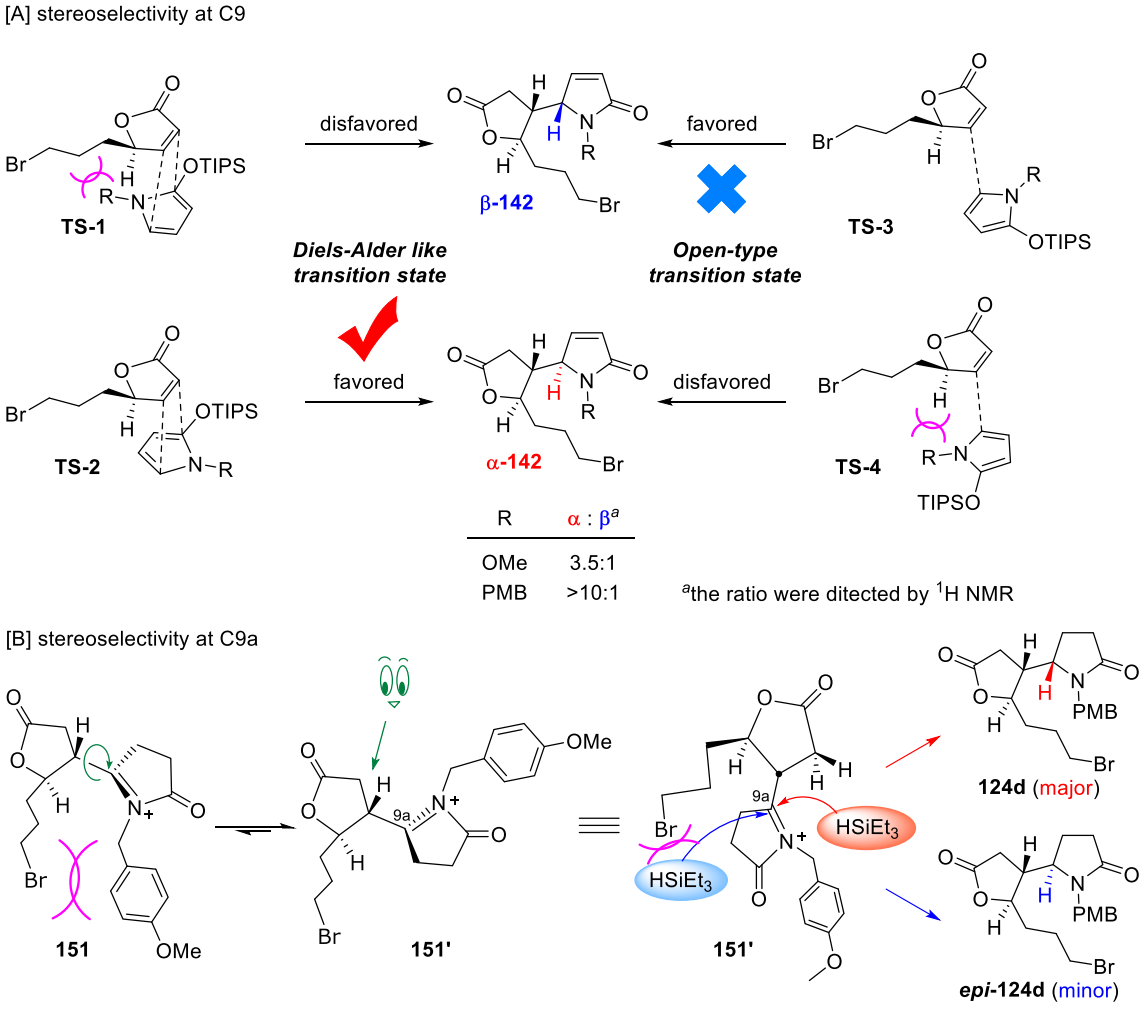


6-5-4. Proposed Mechanism of Stereoselectivity

A proposed mechanism of stereocontrol at the C9 and C9a in vinylogous Michael reaction is described in Scheme 6-10A. Firstly, the siloxyfurans would avoid a steric repulsion with bromide side chain. Therefore, the C9 stereochemistry was completely controlled, and the C9a stereochemistry would depend on the face-selectivity of siloxypyrrole. In transition states **TS-1** and **TS-4**, the steric repulsion between the substituent of the nitrogen atom and the bromoalkyl side-chain would be large. However, transition state **TS-2** (Diels-Alder-type) and **TS-3** (Open-type) seems to avoid this steric repulsion.[14] Considering the experimental results, the Diels-Alder like transition state **TS-2** which affords major product ***α*-142** seems to be the most dominant transition state.

In the one-pot reduction, the stereoselectivity at the C9a stereocenter yet to be clarified, the selectivity would be explained as shown in Scheme 6-10B. The PMB group would point out the opposite direction to the bromide side-chain. Thus, the conformer **151'** would be more dominant than **151**. The reduction of iminium ion **151'** with triethylsilane would proceed to avoid the bromide side-chain affording **124d** as a major product.

Scheme 6-10. Plausible mechanism of vinylogous Michael reaction and reduction sequence

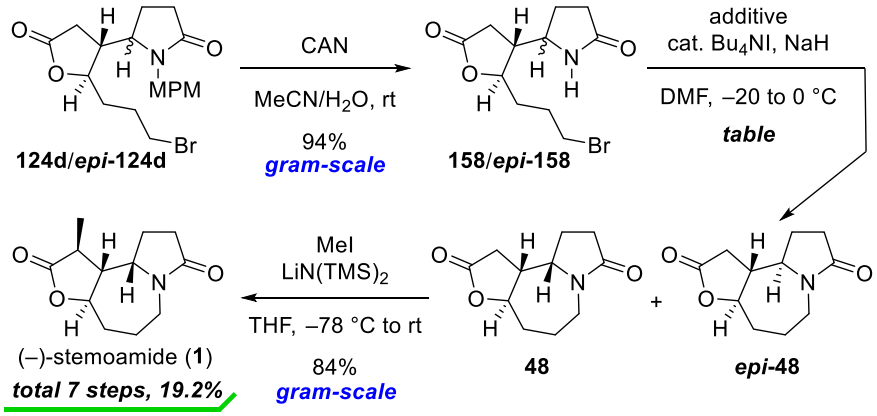


6-6. Gram-scale Total Synthesis of (–)-Stemoamide

Having a practical method for supplying bicyclic compound **124** and ***epi*-124** established on multi-gram scale, the next subject is the total synthesis of stemoamide (**1**) (Scheme 6-11). Oxidative removal of *N*-PMB group using cerium ammonium nitrate gave secondary lactam **158** and ***epi*-158** in 94% yield (**158**:***epi*-158** = 3.7:1). Then, treatment with sodium hydride in the presence of catalytic amount of TMSOTf and tetrabutylammonium iodide led to the formation of a separable mixture **48** and ***epi*-48** (**48**: 57%, ***epi*-48**: 19%). During the construction of the seven-membered ring, residual sodium hydroxide induced the hydrolysis of γ-lactone of **1** and formed undesired side product **161** (Scheme 6-12). If sodium hydride reacts with slight amount of water, sodium hydroxide would easily hydrolyze the γ-lactone **158**, giving γ-hydroxy carboxylate **48**. Then, intramolecular cyclization of the secondary alcohol with alkyl bromide would produce furan carboxylic acid **161**. Therefore, to avoid this side reaction, we treated the suspension of sodium hydride and DMF with TMSOTf to remove the residual sodium hydroxide in advance.

The total synthesis of stemoamide (**1**) was accomplished by the site- and stereo-selective methylation of tricyclic compound **48** in 84% yield.[15] Our enantioselective route enabled the gram-scale supply of stemoamide (**1**: 1.07 g) from a single path in 7 steps and 19.2% total yield, which represents one of the most efficient enantioselective synthesis to date.

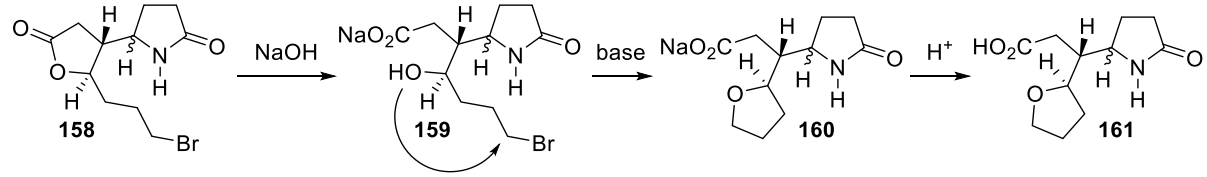
Scheme 6-11. Total Synthesis of Stemoamide (**1**)



scale	additive	yield[a,b]
35 mg	none	73%
730 mg	none	53%
290 mg	TMSOTf[c]	92%
2.3 g	TMSOTf[c]	57%[d]

[a]determined by ^{1}H NMR, [b]yields were based on only **158** (excluding ***epi*-158**), [c]20 mol% of TMSOTf was used, [d]isolated yield of **48**

Scheme 6-12. Reaction mechanism from secondary lactam **158** to side product **161**



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[4] References of total and formal synthesis of stemoamide (**1**) were listed in pp 13-14.

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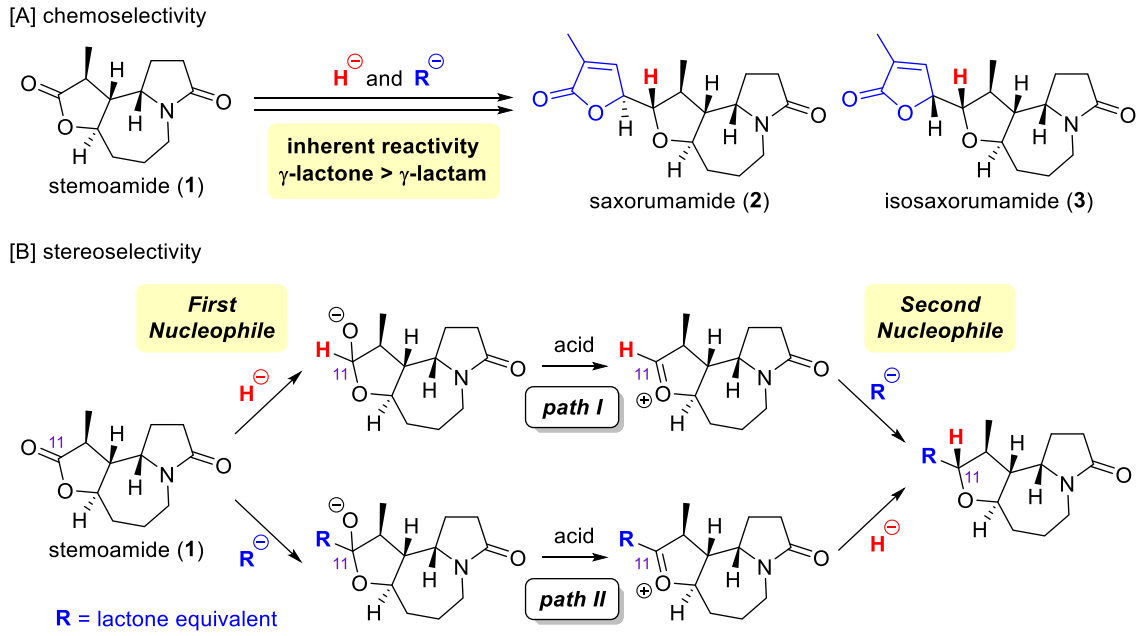
Chapter 7. Total Syntheses of Tetracyclic Natural Products

7-1. Strategies for Lactone-selective Nucleophilic Addition

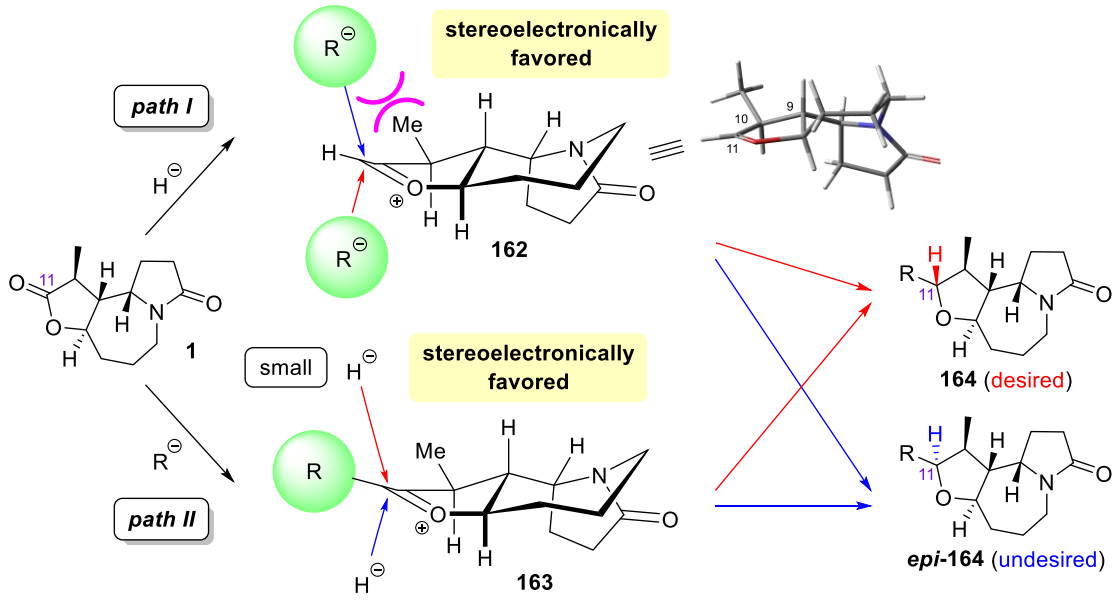
With stemoamide (**1**) in hand, we embarked on the total syntheses of saxorumamide and isosaxorumamide featuring the lactone-selective nucleophilic addition. This chemoselectivity could be achieved with classic transformations by taking advantages of the inherent electrophilicity: γ-lactone > γ-lactam (Figure 7-1A). In addition, the stereocenter at C11 could be constructed with the addition of second nucleophile to an oxocarbenium ion, which is equally important as chemoselectivity (Figure 7-1B). To construct desired stereochemistry at C11, we proposed two reaction pathway in terms of the order of introduction of reductant ($H^{\ominus}$) and lactone equivalent ($R^{\ominus}$).

Figure 7-1. Synthetic plan of saxorumamide (**2**) and isosaxorumamide (**3**)



To construct the desired stereochemistry at C11, the most stable conformation of oxocarbenium intermediate **162** and **163** were calculated and depicted in Figure 7-2.[1] Stereochemical outcome could be predictable based on both steric effect of methyl group and stereoelectronical effect proposed by Woerpel and co-workers.[2] In "path I", the sterically large lactone equivalent would attack from both faces due to the competition between steric repulsion of methyl group and stereoelectronic effect which arise from the eclipse interaction between the nucleophile and the hydrogen atom at C10. In "path II", if the sterically small reductant is employed, the steric effect of the methyl group would become negligible. In such case, the stereoselectivity may be controlled by stereoelectronic effect to produce the desired isomer **164**.

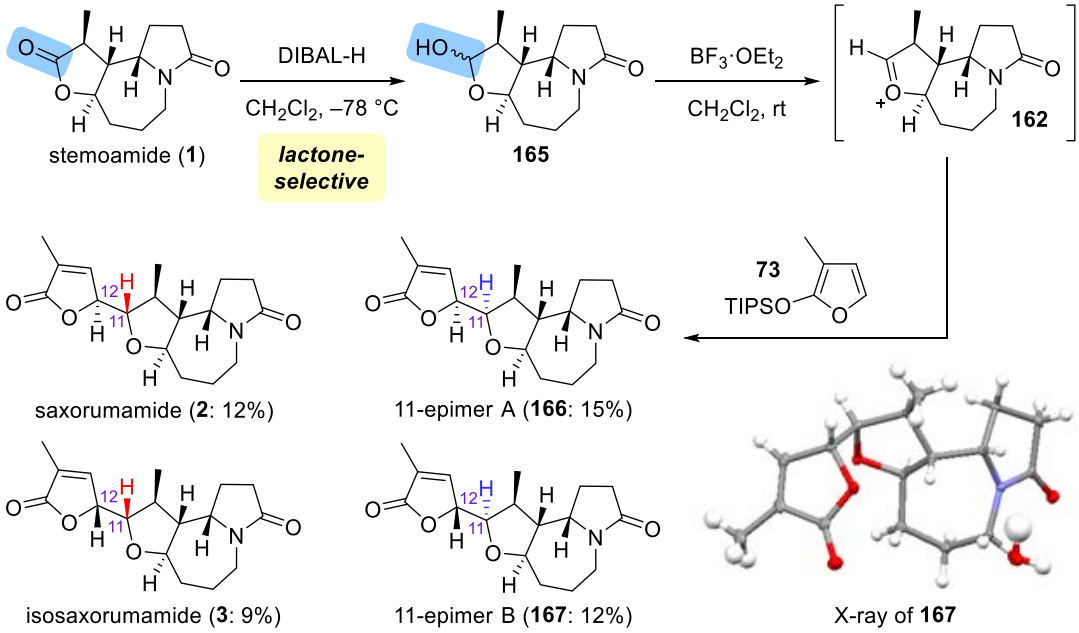
Figure 7-2. Prediction of Stereochemistry



7-2. Total Syntheses of saxorumamide and isosaxorumamide via "path I"

We investigated the "path I" shown above (Scheme 7-1). The lactone-selective reduction of stemoamide (**1**) was accomplished by treatment with DIBAL at –78 °C to form lactol **165**. The five-membered lactone was successfully introduced to **165** in the presence of $BF_3 \cdot OEt_2$ via oxocarbenium ion **162**. However, the stereoselectivity could not be controlled at all, and four diastereomers; saxorumamide **2**, isosaxorumamide **3**, and 11-epimers **166** and **167** were produced (**2**: 12%, **3**: 9%, **166**: 15%, **167**: 12%, two-step yield from **1**).

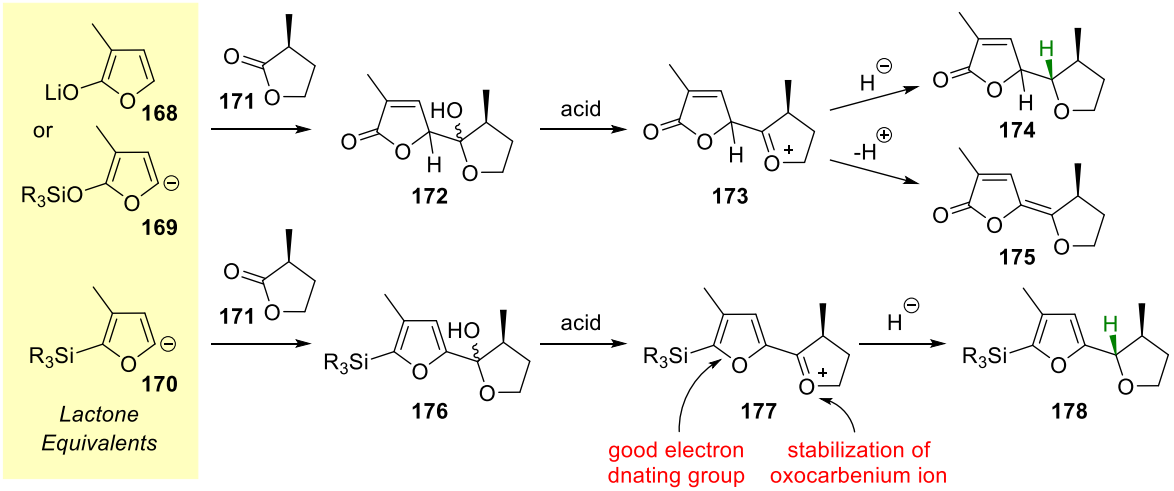
Scheme 7-1. Total Syntheses of Saxorumamide and Isosaxorumamide through "Path I"



7-3. Total Syntheses of saxorumamide and isosaxorumamide via "path II"

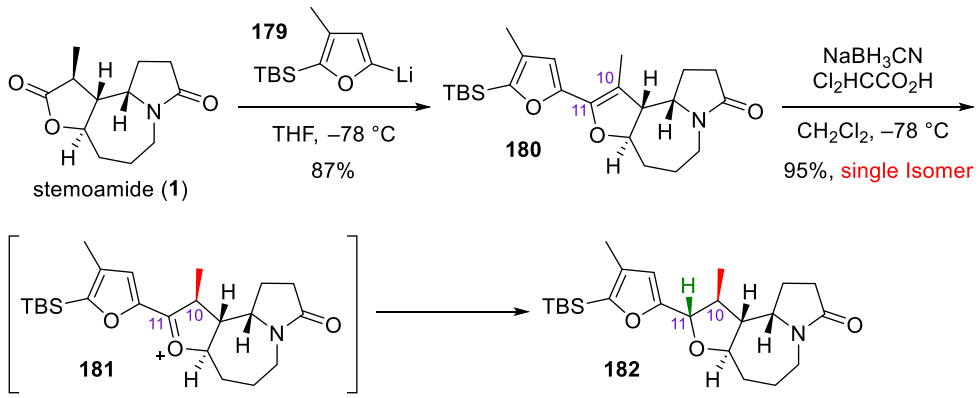
Next we investigated "path II". Firstly, success of this reaction would rely on a design of the lactone equivalent (Figure 7-3). The candidates of lactone equivalent **168** or **169** would react with lactone **171**, and subsequent reduction of lactol **172** would afford the target structure **174**. However, **173** could also be converted to dienoate **175** via undesired deprotonation, which might be difficult to transform to **174**. Therefore, furyllithium **170** would be more practical candidate, which would be converted to furan **178** through nucleophilic addition to lactone **171** followed by reduction of lactol **176**. In addition, the benzylic lactol **176** would be transformed to oxocarbenium ion **177** at low temperature, and lead to stereoselective construction of the desired structure **178**.

Figure 7-3. The candidates of lactone equivalent in "Path II"



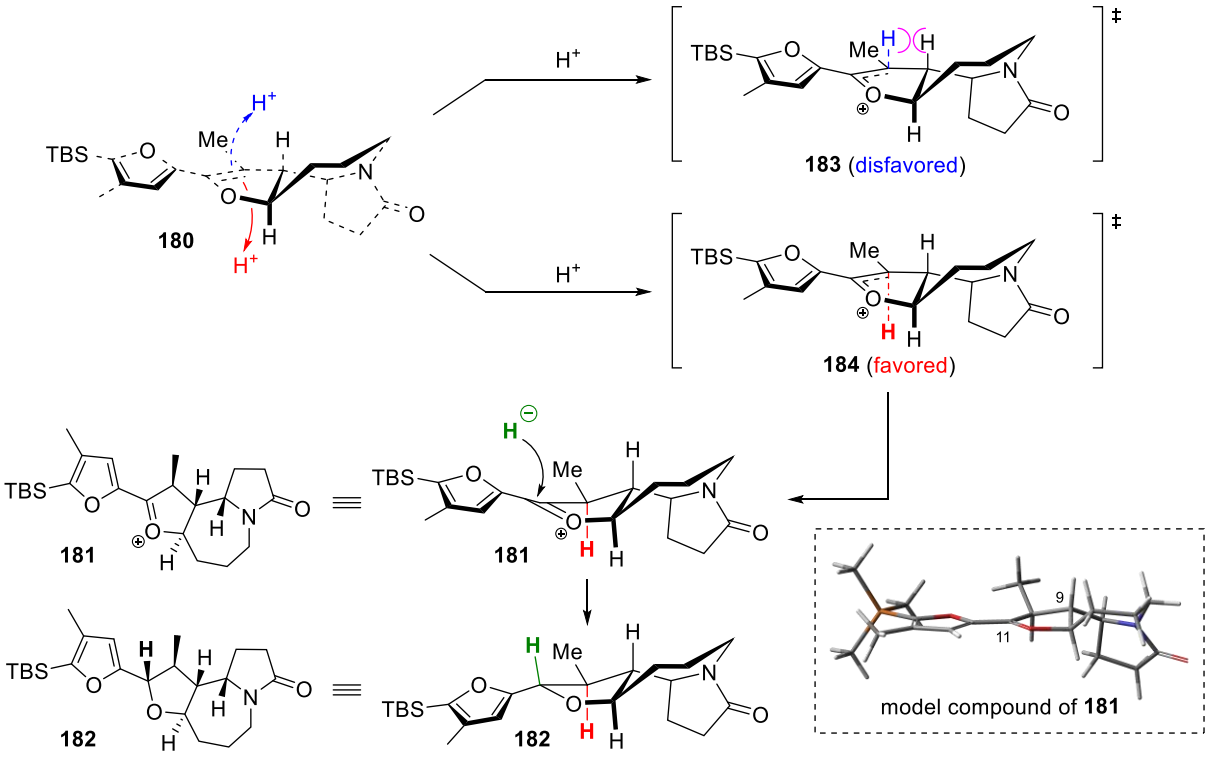
Taking these synthetic plan into considering, furyllithium nucleophile **179**[3] was selected as appropriate nucleophile for the concise and efficient synthesis of saxorumamide families (Scheme 7-2). The lactone-selective nucleophilic addition of furyllithium **179** to stemoamide (**1**) provided enol ether **180** in 87% yield through concomitant dehydration of lactol via oxocarbenium ion **181** probably with the assistance of the adjacent electron donating furan ring. Gratifyingly, stereoselective reduction of enol ether **180** was achieved with $NaBH_3CN$ in the presence of CCl_2HCO_2H at –78 °C. Two consecutive stereocenters (C10 and C11) were established by stereoselective protonation of the enol ether and subsequent reduction of the resulting oxocarbenium ion **181**,[1] giving **182** in 95% yield as a single diastereomer.

Scheme 7-2. Construction of C11 stereocenter through "Path II"



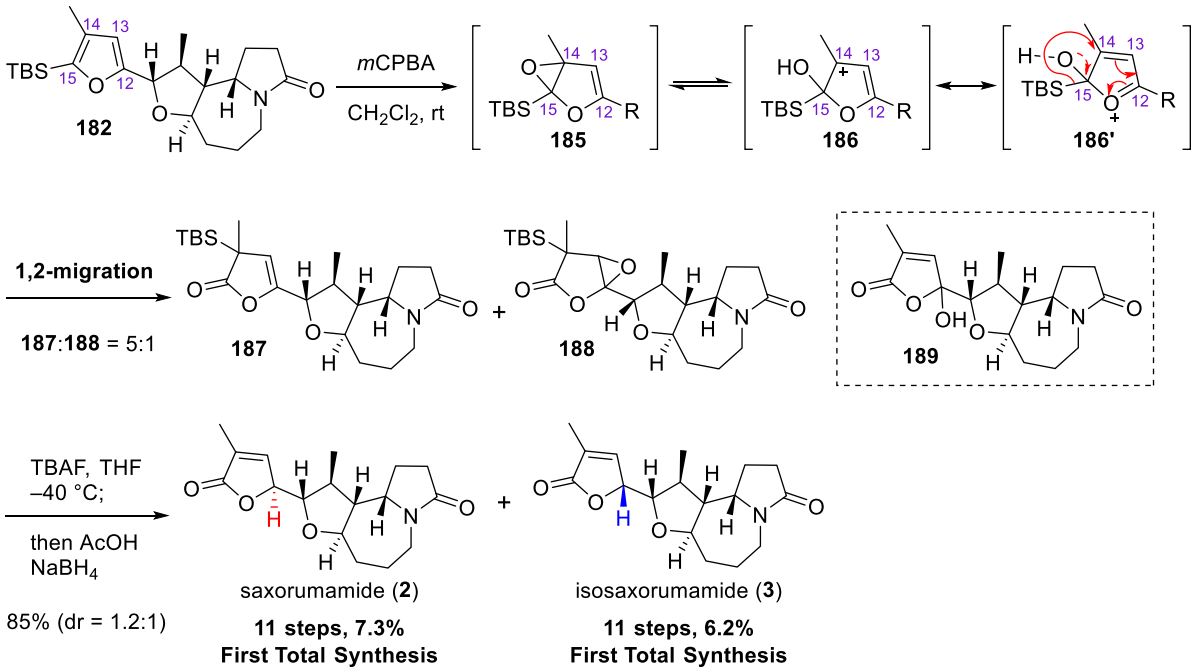
The mechanistic rational of stereoselective protonation of enol ether **180** and reduction of oxocarbenium ion **181** were described in Scheme 7-3. The protonation of enol ether **180** would proceed through transition state **183** or **184** in which **183** would be disfavored due to the steric repulsion between two hydrogen atom located eclipse relationships. Therefore, protonation at *β*-side through transient **184** would be preferable to form oxocarbenium ion **181**. As expected, the stereoselective reduction took place from *β*-side of oxocarbenium ion **181** to afford furan **182** as a single diastereomer.

Scheme 7-3. Construction of C11 stereocenter through "Path II"



The remaining task was the conversion of furan ring to *α*,*β*-unsaturated lactone (Scheme 7-4). Treatment of furan **182** with *m*CPBA (1.2 equiv) led to lactone **187** through Meinwald rearrangement of epoxy silane **185** with weak acidic condition of *m*-chlorobenzoic acid derived from *m*CPBA.[3] The driving force of the 1,2-migration was the strong cationic character at C14 due to the *β*-effect of silyl group and the mesomeric effect (**186↔186'**). In addition, the remaining *m*CPBA oxidized the resulting enol ether **187** affording **188**. Treatment a mixture of **187** and **188** with TBAF, followed by addition of AcOH and $NaBH_4$ gave saxorumamide (**2**) and isosaxorumamide (**3**).[3a] Epoxide **188** was produced by bisepoxidation of furan **182**, and converted to *γ*-hydroxy-*α*,*β*-unsaturated lactone **189**. Therefore treatment of **189** with AcOH and $NaBH_4$ led to formation of **2** and **3**. Thus, we accomplished the first total synthesis of saxorumamide (**2**) and isosaxorumamide (**3**) in 11 longest liner steps in 7.3% and 6.2% total yield, respectively.

Scheme 7-4. Total synthesis of saxorumamide (**2**) and isosaxorumamide (**3**)

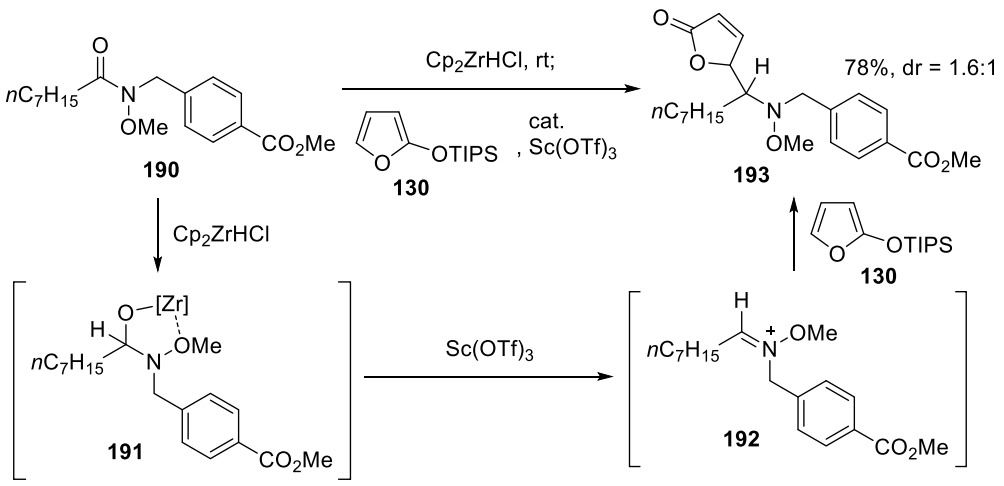


7-4. Lactam-selective Nucleophilic Addition Using Schwartz Reagent

Lactone is known to be more electrophilic than lactam. On the contrary, the lactam possesses higher Lewis basicity than lactone due to the mesomeric effect of nitrogen, which contributes to stability of carbonyl group of lactam. Therefore, the high Lewis basicity of lactam have a potential to overcome the difficulty to differentiate γ-lactam and γ-lactone.

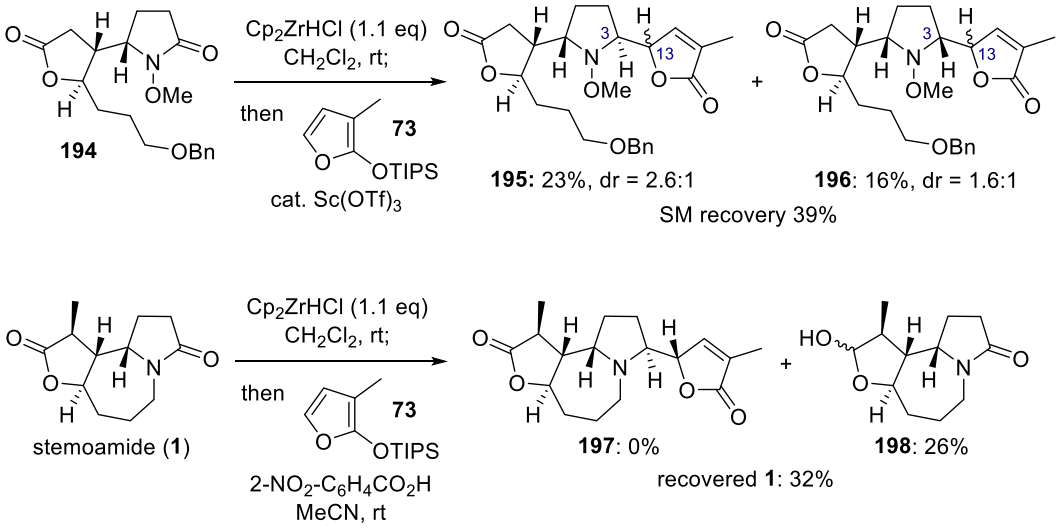
Previously, Chida-Sato group reported the amide-selective reductive functionalization by taking advantage of the Schwartz reagent [Cp_2ZrHCl], which is reliable amide-selective reducing agent even in presence of ester (Scheme 7-5).[4,5] Treatment of *N*-methoxyamide **190** with 1.1 equivalent of Cp_2ZrHCl gave five-membered chelate intermediate **191**. Subsequent addition of siloxyfuran **130** and a catalytic amount of $Sc(OTf)_3$ to the chelated intermediate **191** provided *α*-substituted *N*-methoxyamine **193** via iminium ion **192** in 78% yield.

Scheme 7-5. Amide-selective nucleophilic addition with the Schwartz reagent



Thus, this method was adopted to the *γ*-lactam-selective reductive nucleophilic addition of siloxyfuran **73** to *N*-methoxylactam **194** (Scheme 7-6). The reductive nucleophilic addition of **194** proceeded in 39% combined yield and the four diastereomers were obtained in poor diastereoselectivity at C3 and C13 stereocenters, along with recover of the starting material **194** in 39% yield. In addition, when we attempted the reductive nucleophilic addition to stemoamide (**1**) using the Schwartz reagent, the tetracyclic compound **197** was not observed, and instead lactol **198** was obtained and the starting material **1** was recovered in 26% and 32%, respectively. These results indicated that the Schwartz reagent cannot achieve the *γ*-lactam-selective reduction of the substrate that include γ-lactone moiety such as **194** or **1**.

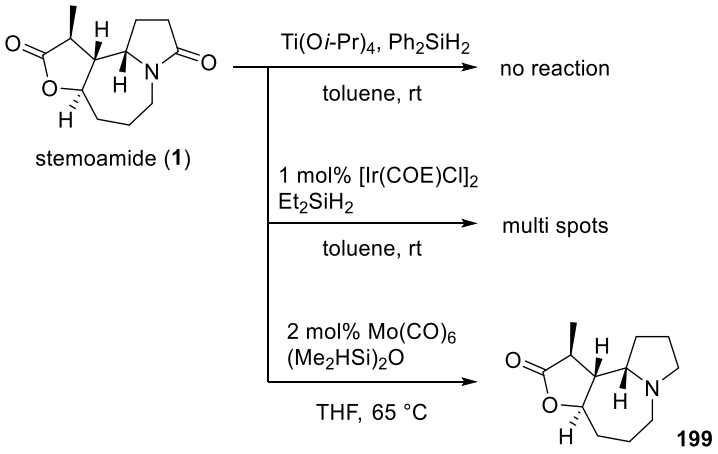
Scheme 7-6. The attempt of *γ*-lactam-selective nucleophilic addition with Schwartz reagent



7-5. Total Synthesis of Stemonine

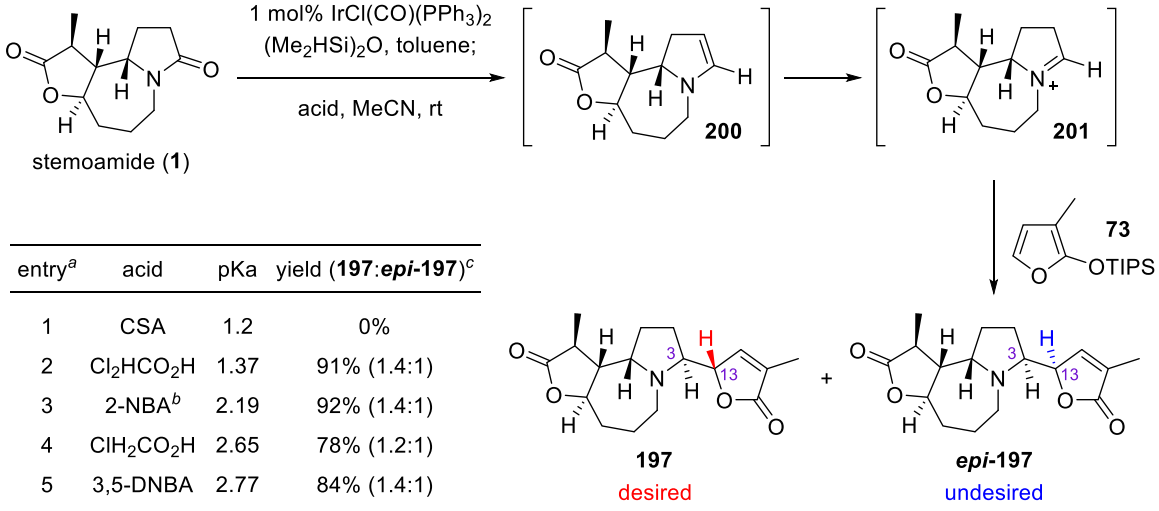
Since the Schwartz reagent was not effective for the lactam-selective functionalization of stemoamide (**1**), other *γ*-lactam-selective reducing agent was explored. Buchwald reduction with $Ti(OiPr)_4$ and Ph_2SiH_2,[6] Brookhart method with cat. $[Ir(COE)_2Cl]_2$ and Et_2SiH_2,[7] Tinnis/Adolfsson reduction with cat. $Mo(CO)_6$ and $(Me_2HSi)_2O$,[8] could not achieve the chemoselective semi-reduction of the *γ*-lactam (Scheme 7-7).

Scheme 7-7. Investigation of lactam-selective reducing agent



However, we solved this problem by utilizing Nagashima's conditions for an iridium-catalyzed hydrosilylation (Table 7-1).[9,10] Treatment of stemoamide (**1**) with the Vaska complex [IrCl(CO)(PPh_3)$_2$] (1 mol%) and (Me_2HSi)$_2$O (1.5 equiv)[11] initiated hydrosilylation of the γ-lactam carbonyl and subsequent elimination of the siloxy group to form enamine **200**. Next, the optimization of acid was conducted. Treatment of enamine **200** with 2-siloxyfuran **73**, MeCN and a Brønsted acid in a one-pot process generated the transient iminium ion **201**, which underwent the vinylogous Mannich reaction to give tetracyclic compounds **197** and ***epi*-197**. The optimal acid was proved to be 2-nitrobenzoic acid whose pK_a is 2.19 (entry 3, 92%, dr = 1.4:1). Both reduction of the γ-lactam and the subsequent addition of **73** took place in highly chemoselective fashion without affecting the reactive γ-lactone even in 20 mg scale, giving the products **197** in 43% and ***epi*-197** in 30% isolated yield, respectively (entry 9). The addition of 2-siloxyfuran **73** resulted in complete stereocontrol at the C3 carbon center. In contrast, a slight diastereoselectivity at C13 (dr = 1.4:1)[12,13] was observed favoring the desired product **197** over the undesired product ***epi*-197**, which could be isomerized to **197** with DBU in CH_2Cl_2. Thus, we achieved the first direct installation of the γ-lactone to stemoamide (**1**) at the late stage of the synthesis.

Table 7-1. Lactam-selective nucleophilic addition to stemoamide (**1**)

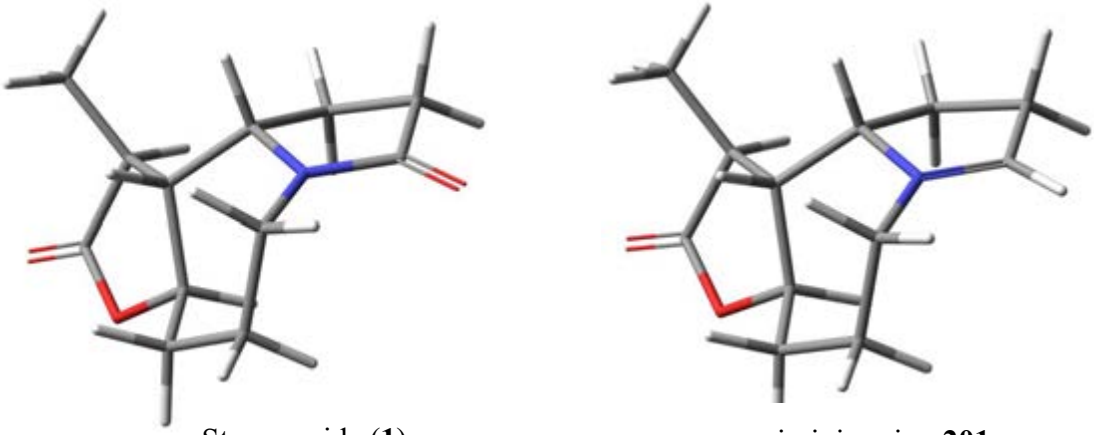


entry[a]	acid	pKa	yield (**197**:***epi*-197**)[c]
1	CSA	1.2	0%
2	Cl_2HCO_2H	1.37	91% (1.4:1)
3	2-NBA[b]	2.19	92% (1.4:1)
4	ClH_2CO_2H	2.65	78% (1.2:1)
5	3,5-DNBA	2.77	84% (1.4:1)
6	4-NBA[b]	3.42	66% (1.4:1)
7	AcOH	4.79	<67% (1.2:1)
8	PPTS	5.21	0%
9[d]	2-NBA[b]	2.19	73% (1.4:1)[e]

[a]4 mg of stemoamide (**1**) was used in entries 1~8. [b]NBA: nitrobenzoic acid. [c]Diastereomeric ratios was determined by ^{1}H NMR. [d]20 mg of stemoamide (**1**) was used. [e]Diastereomers were separated with PLC.

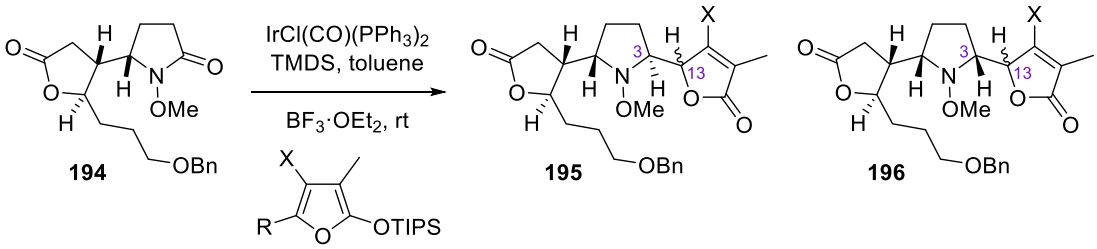
The diastereoselectivity at the C3 and C13 stereocenters would be controlled by inherent conformation of the substrate. The most stable conformation of stemoamide (**1**) and iminium intermediate **201** were calculated as shown below (Figure 7-4).[14] According to this structure, 2-siloxyfuran **73** approached from the convex side of iminium ion **201**, resulting in complete stereocontrol at the C3 carbon center. To prove the importance of the rigid tricyclic cage structure, nucleophilic addition to bicyclic compound **194** was performed with various nucleophiles (Table 7-2). As a result, we could not achieve the stereoselective introduction of siloxyfuran to the lactam carbonyl group of **194**. Therefore, the tricyclic structure of stemoamide was crucial for the construction of the desired stereochemistry at C3. In contrast, the stereoselectivity at C13 was moderate due to the planarity of the nucleophile.

Figure 7-4. Conformation of stemoamide (**1**) and iminium ion (**201**)



Stemoamide (**1**) iminium ion **201**

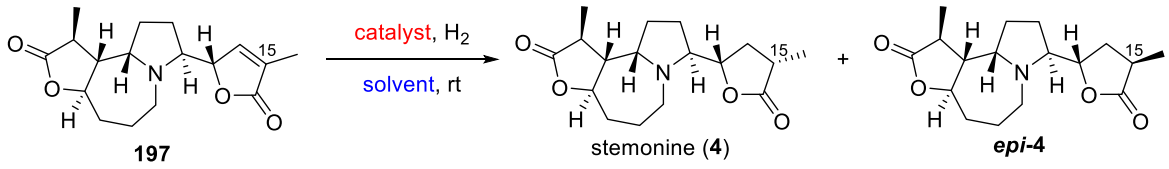
Table 7-2. Nucleophilic addition to the bicyclic substrate **194**



entry	Nucleophile	combined yield	C3 selectivity	C13 selectivity	
			195:**196**	**195**	**196**
1	**73**: R = H, X = H	71% (SM: 16%)	0.59 : 1	dr = 2.4:1	dr = 2.0:1
2	**202**: R = H, X = Br	84% (SM: 6%)	0.39 : 1	dr = 1.7:1	dr = 1.3:1
3	**203**: R = Bu_3Sn, X = H	50% (SM: trace)	0.93 : 1	dr = 2.2:1	dr = 4.8:1

The hydrogenation of α,β-unsaturated lactone **197** was investigated (Table 7-3). The Pd/C catalyzed reduction of **197** led to 5.6:1 mixture of diastereomers of stemonine (**4**) and 15-epi-stemonine (***epi*-4**) (Table 7-3, entry 2). This hydrogenation of γ-lactone using homogeneous catalyst proceeded on the opposite face to the substituent at C13 to give stemonine (**4**) as a major product. The silica gel column chromatography was attempted for the separation of two diastereomers **4** and ***epi*-4**. However, it resulted in isolation of stemonine (**4**) in merely 18% yield because either **4** or ***epi*-4** would be unstable to air and silica gel (Table 7-3, entry 3). Therefore, we had to find a heterogeneous reducing agent, which can achieve perfect chemoselectivity at C15 and can be removable by simple filtration. Finally, we revealed that Rh/Al_2O_3-catalyzed reduction could achieve this task, giving stemonine (**4**) in high yield as the sole product (Table 7-3, entry 5). Thus, we succeed in establishing the novel method for the direct access to stemonine (**4**) from stemoamide (**1**) in two steps including chemoselective nucleophilic addition and hydrogenation.

Table 7-3. Hydrogenation of α,β-unsaturated lactone **198**



entry	catalyst	solvent	yield	**4** : ***epi*-4**
1	Pd/C	THF	0%	—
2	Pd/C	EtOH	87%	5.6:1
3	Pd/C	EtOH	18%[a]	single diastereomer[b]
4	Rh/Al_2O_3	THF	0%	—
5	Rh/Al_2O_3	EtOH	98%	single diastereomer

[a]Isolated yield after purification with silica gel chromatography
[b]Compound ***epi*-4** was completely decomposed during purification.

References in Chapter 7

[1] The lowest energy conformations of oxocarbenium ions **162** and model compound of **181** were calculated by geometry optimizations using B3LYP/6-31G** implemented in Jaguar, version 9.1, Schrödinger, Inc., New York, NY, 2016.

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[11] Greene, J.; Curtis, M. D. *J. Am. Chem. Soc.* **1977**, *99*, 5176.

[12] Martin group and Williams group achieved vinylogous Mannich reaction during the total synthesis of stemonine (**4**) or croomine (**67**) with higher diastereoselectivity at C13, see Scheme 5-8, 9, 10.

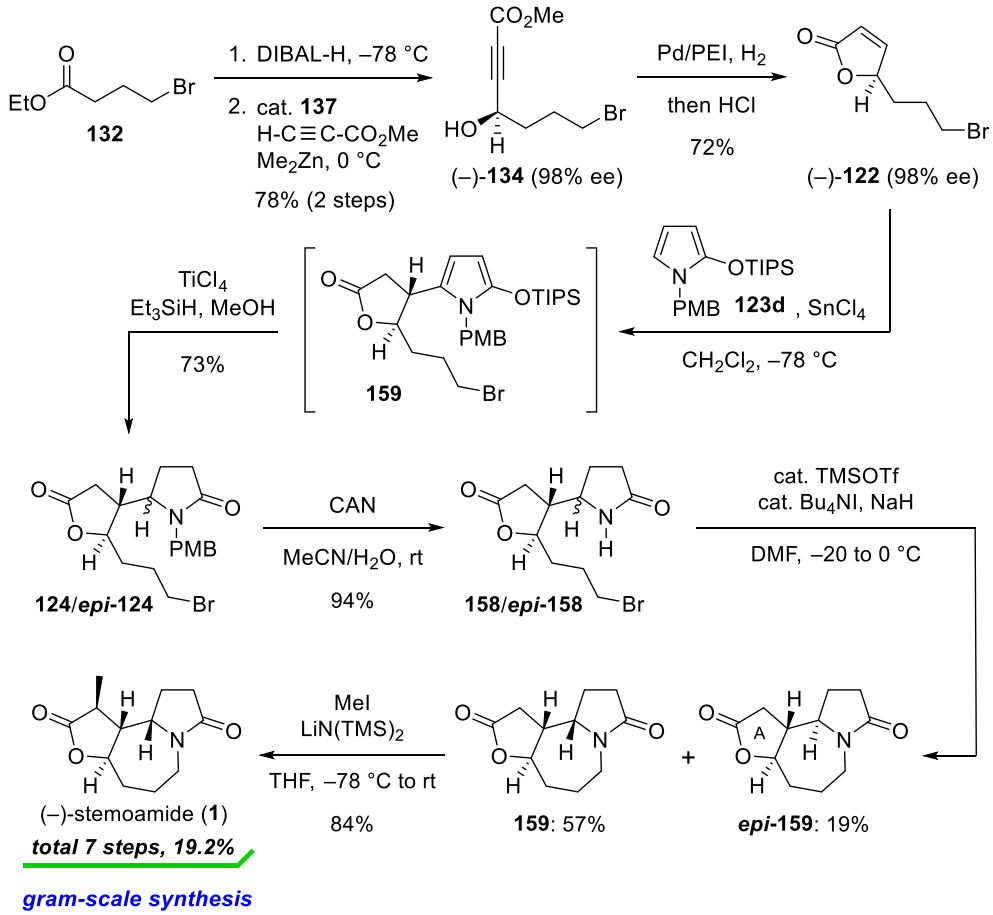
[13] For review on vinylogous Mannich reaction using the *γ*-lactone, see; Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221.

[14] The lowest energy conformations of stemoamide (**1**) and iminium ion **201** were calculated by geometry optimizations using B3LYP/6-31G** implemented in Jaguar, version 9.1, Schrödinger, Inc., New York, NY, 2016.

Chapter 8. Conclusion

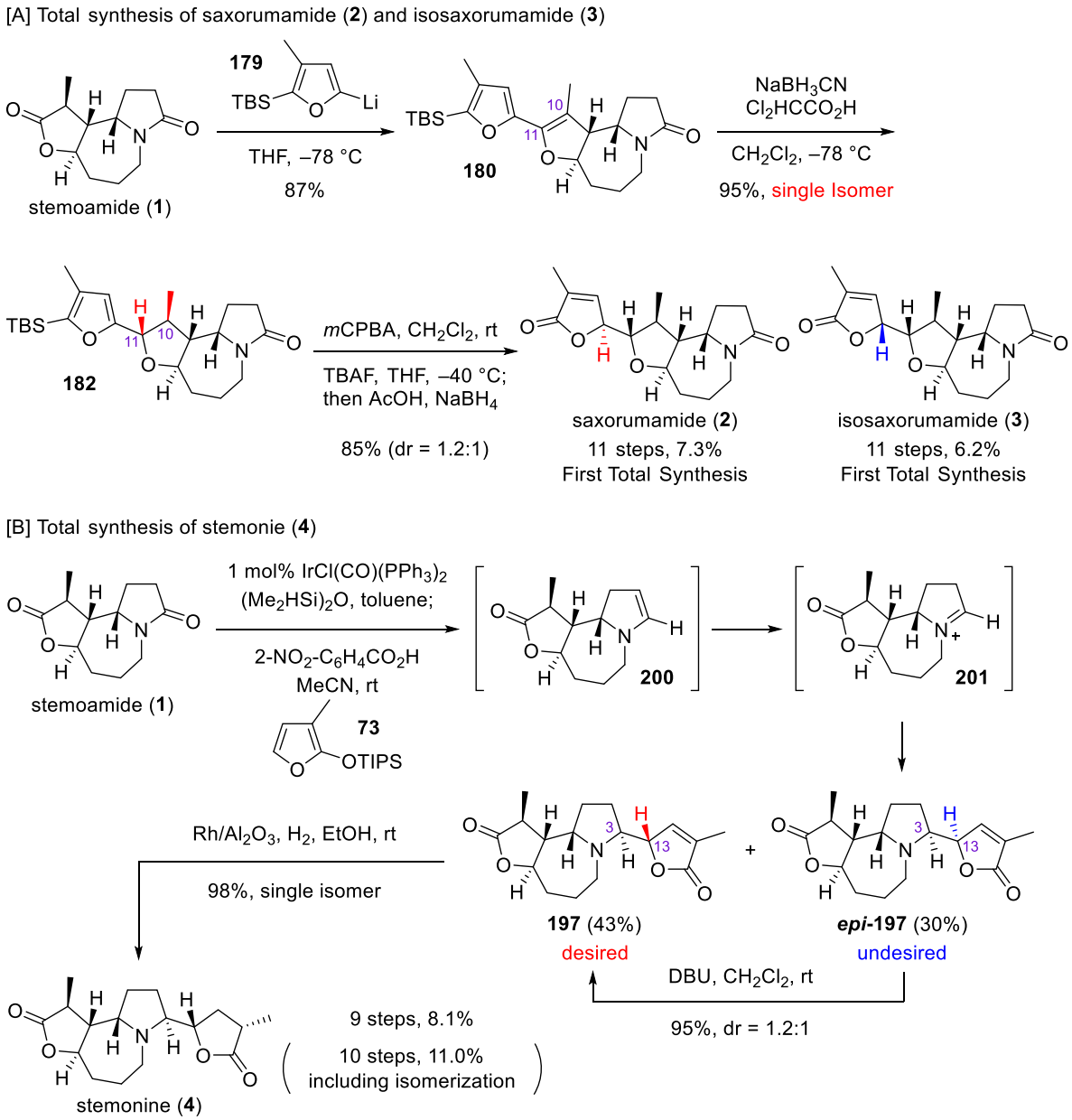
We accomplished a unified total synthesis of stemoamide-type alkaloids through convergent assembly of three five-membered building blocks. The first key reaction was the vinylogous Michael reaction/reduction of butenolide **122** and 2-siloxypyrrole **123d**. The second key reaction was the chemoselective nucleophilic addition to stemoamide (**1**) as the common precursor to the tetracyclic natural products. While the lactone-selective nucleophilic addition led to first total synthesis of saxorumamide (**2**) and isosaxorumamide (**3**), the lactam-selective reductive nucleophilic addition enabled the direct access to stemonine (**4**) in 2 steps from stemoamide (**1**). Overview of synthetic route is described below (Scheme 8-1, 8-2). The gram-scale total synthesis of stemoamide (**1**) was accomplished from commercially available ethyl 4-bromobutyrate **132** from a single path in 7 steps and 19.2% total yield.

Scheme 8-1. Overview of unified total synthesis of stemoamide-type alkaloids (Part I)

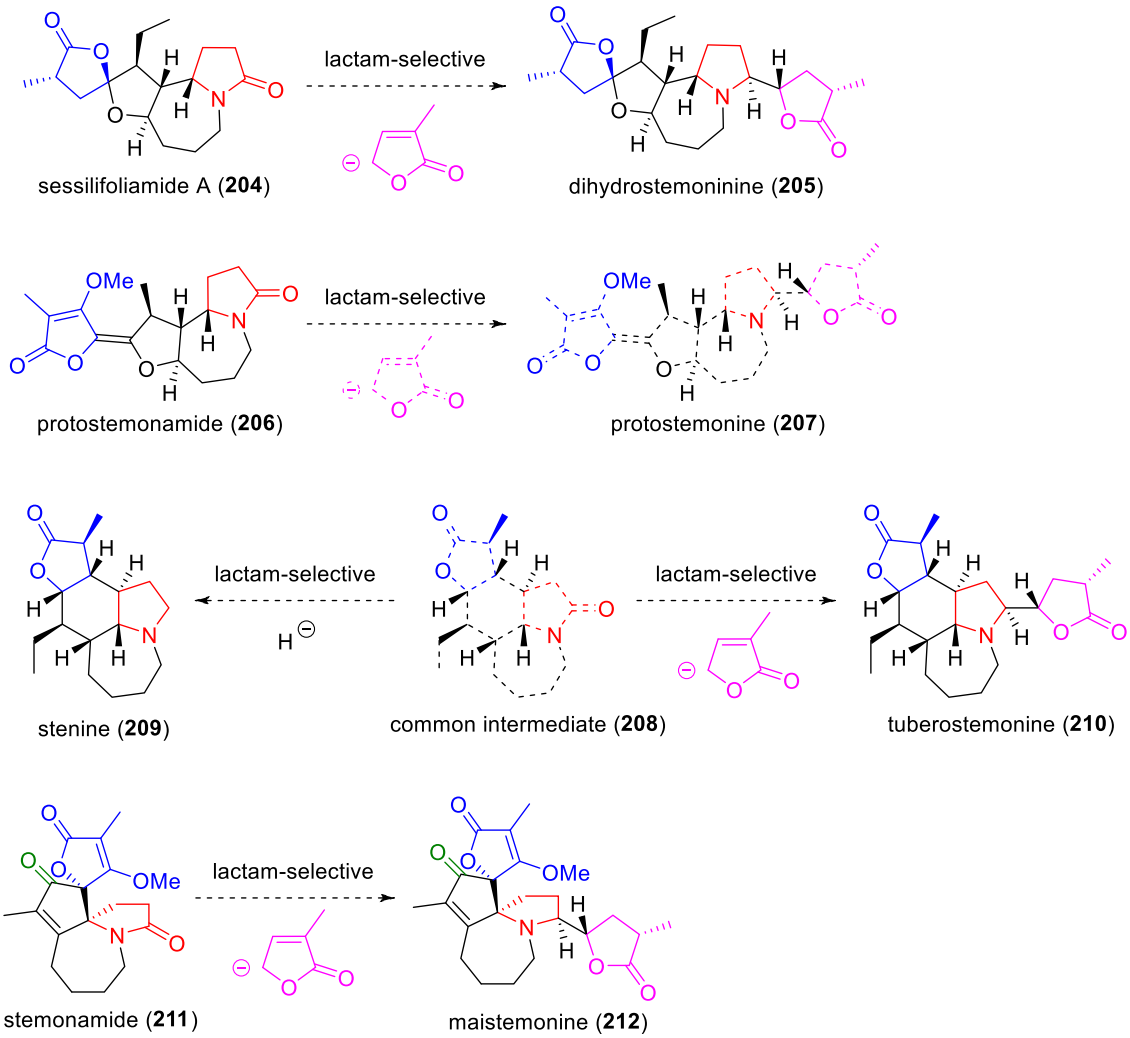


The first total synthesis of saxorumamide (**2**) and isosaxorumamide (**3**) in 11 longest liner steps in 7.3% and 6.2% total yield, respectively. A concise and efficient total synthesis of stemonine (**4**) was accomplished in 9 steps with an overall yield of 8.1% (10 steps and 11.0% total yield including isomerization of ***epi*-197**)

Scheme 8-2. Overview of unified total synthesis of stemoamide-type alkaloids (Part II)



The lactam-selective reductive nucleophilic addition in the presence of lactones could be applicable to total syntheses of other members of the Stemona-alkaloids.



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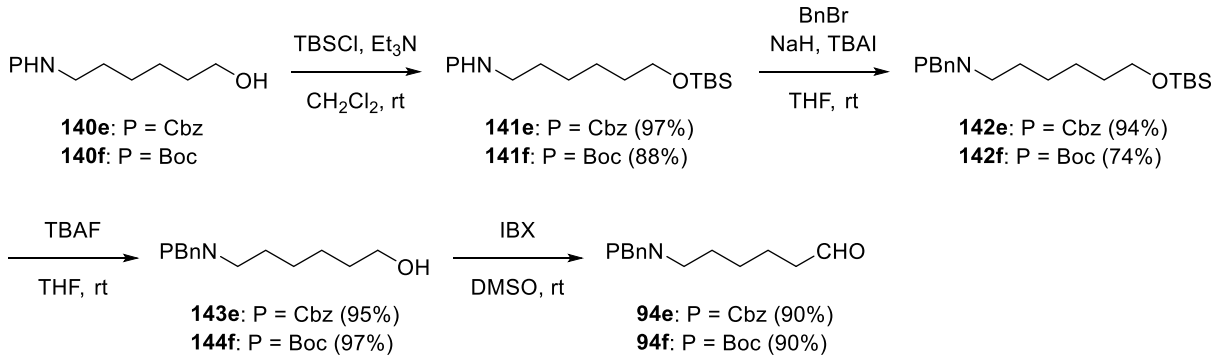
A. Experimental Procedures

General Details. Reactions were performed in oven-dried glassware fitted with rubber septa under an argon atmosphere. Toluene, DMSO and $(CH_2Cl)_2$ were distilled from CaH_2. DMF and MeOH were distilled from $CaSO_4$. Pyridine was distilled from sodium hydroxide. All distilled solvents, MeCN, CH_2Cl_2 and EtOH were dried over activated 3Å molecular sieves. THF (dehydrated, stabilizer free) was from KANTO CHEMICAL CO., INC. Commercial reagents were used without further purification. Thin-layer chromatography was performed on Merck 60 F254 precoated silica gel plates, which were visualized by exposure to UV (254 nm) or stained by submersion in aquatic cerium- ammonium molybdate, aquatic potassium manganate or ethanolic phosphomolybdic acid solution followed by heating on a hot plate. Flash column chromatography was performed on silica gel (Silica Gel 60 N; 63–210 or 40–50 mesh, KANTO CHEMICAL CO., INC.). ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra at 125 MHz with JEOL ECA-500 spectrometers. Chemical shifts are reported in ppm with reference to solvent signals [^{1}H NMR: $CDCl_3$ (7.26), CD_3OD (3.31), *d*-acetone (2.05), C_6D_6 (7.16); ^{13}C NMR: $CDCl_3$ (77.16)]. Signal patterns are indicated as brs, broad peak; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. MPLC was performed on Yamazen, YFLC AI-580. Infrared spectra were recorded using a BRUKER ALPHA FT-IR spectrometer. Mass spectra (EI and FAB) were measured with a JEOL GC-Mate spectrometer. Mass spectra (ESI-TOF) were measured with a Waters, LCT Premier XE. Melting points were measured with a Mitamura-Riken microhot stage or Yanaco MODEL MP-S3.

Two-step Synthesis of Multi-substituted Amines

A-1. Two-step Synthesis of Multi-substituted *N*-Methoxypiperidine

Preparation of aldehydes 94e, 94f



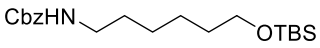
140e: P = Cbz
140f: P = Boc

141e: P = Cbz (97%)
141f: P = Boc (88%)

142e: P = Cbz (94%)
142f: P = Boc (74%)

143e: P = Cbz (95%)
144f: P = Boc (97%)

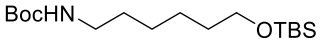
94e: P = Cbz (90%)
94f: P = Boc (90%)



141e

benzyl (6-((*tert*-butyldimethylsilyl)oxy)hexyl)carbamate (141e)

tert-Butyldimethylsilyl chloride (300 mg, 1.99 mmol) was added to a solution of alcohol **140e** (414 mg, 1.65 mmol),[1] triethylamine (280 μL, 2.0 mmol) and CH_2Cl_2 (8.2 mL) at room temperature. The solution was maintained for 24 h at room temperature, and quenched with H_2O (10 mL). The resulting mixture was extracted with chloroform (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:20 to 1:10) to give 585 mg of **141e** (97%): a colorless oil; IR (film) 3337, 2932, 2858, 1700, 1540, 1457, 1255, 1098, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5H), 5.09 (s, 2H), 4.71 (bs, 1H), 3.59 (t, *J* = 6.6 Hz, 2H), 3.19 (dt, *J* = 6.6, 6.6 Hz, 2H), 1.54–1.46 (m, 4H), 1.37–1.29 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5 (C), 136.8 (C), 128.6 (CH), 128.20 (CH), 128.15 (CH), 66.6 (CH_2), 63.2 (CH_2), 41.2 (CH_2), 32.8 (CH_2), 30.1 (CH_2), 26.7 (CH_2), 26.1 (CH_3), 25.6 (CH_2), 18.5 (C), –5.2 (CH_3); HRMS (ESI), calcd for $C_{20}H_{35}NO_3SiNa^+$ $(M+Na)^+$ 388.2284, found 388.2281.

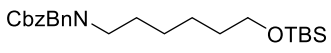


141f

***tert*-butyl (6-((tert-butyldimethylsilyl)oxy)hexyl)carbamate (141f)**

tert-Butyldimethylsilyl chloride (310 mg, 2.06 mmol) was added to a solution of alcohol **140f** (373 mg, 1.72 mmol),[2] triethylamine (290 μL, 2.1 mmol) and CH_2Cl_2 (8.6 mL) at room temperature. The solution

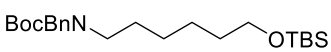
was maintained for 24 h at room temperature, and quenched with H_2O (10 mL). The resulting mixture was extracted with chloroform (2x10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:30 to 1:20) to give 505 mg of **141f** (88%): a colorless oil; IR (film) 3360, 2932, 2859, 1697, 1525, 1366, 1254, 1175, 1100, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.49 (bs, 1H), 3.59 (t, J = 6.6 Hz, 2H), 3.10 (dt, J = 7.2, 7.2 Hz, 2H), 1.54–1.42 (m, 4H), 1.44 (s, 9H), 1.36–1.29 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1 (C), 79.0 (C), 63.2 (CH_2), 40.7 (CH_2), 32.8 (CH_2), 30.2 (CH_2), 28.5 (CH_3), 26.7 (CH_2), 26.1 (CH_3), 25.6 (CH_2), 18.5 (C), –5.2 (CH_3); HRMS (ESI), calcd for $C_{17}H_{37}NO_3SiNa^+$ $(M+Na)^+$ 354.2440, found 354.2437.



142e

benzyl benzyl(6-((*tert*-butyldimethylsilyl)oxy)hexyl)carbamate (142e)

Sodium hydride (60 wt%, 71.5 mg, 4.96 mmol) was added to a solution of carbamate **141e** (362 mg, 990 μmol) and THF (2.0 mL) at room temperature. After stirring for 20 min, benzyl bromide (240 μL, 2.0 mmol) and tetrabutylammomium iodide (3.7 mg, 9.9 μmol) were added to the mixture of **141e** at room temperature. The resulting mixture was stirred for 24 h, and quenched with H_2O (5 mL). The resulting mixture was extracted with EtOAc (5 mL). The organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:40) to give 423 mg of **142e** (94%): a colorless oil; IR (film) 2932, 2858, 1703, 1472, 1422, 1248, 1097, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.44–7.12 (m, 10H), 5.18 (s, 2H), 4.50 (s, 2H), 3.59 (t, J = 6.3 Hz, 2H), 3.30–3.18 (m, 2H), 1.58–1.41 (m, 4H), 1.35–1.20 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 156.6 (C), 138.3 (C), 137.2 (C), 128.65 (CH), 128.56 (CH), 128.0 (CH), 128.0 (CH), 127.8 (CH), 127.4 (CH), 67.3 (CH_2), 63.2 (CH_2), 50.7 (CH_2), 47.2 (CH_2), 32.9 (CH_2), 28.2 (CH_2), 26.8 (CH_2), 26.1 (CH_3), 25.7 (CH_2), 18.5 (C), –5.1 (CH_3); HRMS (ESI), calcd for $C_{27}H_{42}NO_3Si^+$ $(M+H)^+$ 456.2934, found 456.2938.

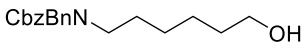


142f

***tert*-butyl benzyl(6-((*tert*-butyldimethylsilyl)oxy)hexyl)carbamate (142f)**

Sodium hydride (60 wt%, 71.5 mg, 4.96 mmol) was added to a solution of carbamate **141f** (330 mg, 995 μmol) and THF (2.0 mL) at room temperature. After stirring for 20 min, benzyl bromide (240 μL, 2.0 mmol) and tetrabutylammomium iodide (3.7 mg, 9.9 μmol) were added to the mixture of **141f** at room

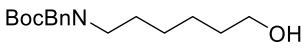
temperature. The resulting mixture was stirred for 24 h, and quenched with H_2O (5 mL), and extracted with EtOAc (5 mL). The organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:60) to give 309 mg of **142f** (74%): a colorless oil; IR (film) 2930, 2857, 1697, 1463, 1416, 1365, 1249, 1170, 1099, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.31 (t, *J* = 7.5 Hz, 2H), 7.27–7.21 (m, 3H), 4.43 (s, 2H), 3.58 (t, *J* = 6.6 Hz, 2H), 3.22–3.12 (m, 2H), 1.55–1.43 (m, 4H), 1.47 (s, 9H), 1.36–1.22 (m, 4H), 0.90 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 156.0 (C), 139.0 (C), 128.6 (CH), 127.6 (CH), 127.2 (CH), 79.6 (C), 63.3 (CH_2), 50.5 (CH_2), 46.9 (CH_2), 33.0 (CH_2), 28.7 (CH_3), 28.3 (CH_2), 26.9 (CH_2), 26.1 (CH_3), 25.8 (CH_2), 18.5 (C), –5.1 (CH_3) ; HRMS (ESI), calcd for $C_{24}H_{43}NO_3SiNa^+$ $(M+Na)^+$ 444.2910, found 444.2907.



143e

benzyl benzyl(6-hydroxyhexyl)carbamate (143e)

Tetrabutylammonium fluoride (1.0 M in THF, 760 μL, 760 μmol) was added to a solution of **142e** (288 mg, 632 μmol) and THF (3.2 mL) at room temperature. The solution was maintained for 2 h at room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:2) to give 206 mg of **143e** (95%): a colorless oil; IR (film) 3158, 2937, 2863, 1701, 1454, 1423, 1236, 733, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 7.41–7.10 (m, 10H), 5.18 (s, 1H), 5.17 (s, 1H), 4.49 (s, 2H), 3.27 (t, *J* = 7.0 Hz, 1H), 3.20 (t, *J* = 7.0 Hz, 1H), 2.32 (t, *J* = 7.0 Hz, 1H), 2.26 (t, *J* = 7.0 Hz, 1H), 1.70–1.39 (m, 4H), 1.39–1.16 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 156.7 (C), 138.2 (C), 137.1 (C), 128.65 (CH), 128.56 (CH), 128.03 (CH), 128.00 (CH), 127.7 (CH), 127.4 (CH), 67.3 (CH_2), 62.8 (CH_2), 50.7 (CH_2), 46.9 (CH_2), 32.8 (CH_2), 28.1 (CH_2), 26.6 (CH_2), 25.5 (CH_2); HRMS (ESI), calcd for $C_{21}H_{27}NO_3Na^+$ $(M+Na)^+$ 364.1889, found 364.1886.

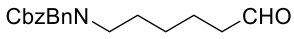


143f

***tert*-butyl benzyl(6-hydroxyhexyl)carbamate (143f)**

Tetrabutylammonium fluoride (1.0 M in THF, 680 μL, 680 μmol) was added to a solution of **142f** (219 mg, 567 μmol) and THF (2.8 mL) at room temperature. The solution was maintained for 2 h at room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:2) to give 168 mg of **143f** (97%): a colorless oil; IR (film) 3441, 2932, 2860, 1693, 1455, 1417, 1366, 1246, 1168, 879, 732, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.31 (t, *J*

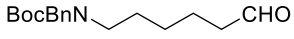
= 6.9 Hz, 2H), 7.27–7.21 (m, 3H), 4.43 (s, 2H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.19 (bs, 2H), 1.58–1.48 (m, 4H), 1.47 (s, 9H), 1.40–1.25 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 156.1 (C), 139.0 (C), 128.6 (CH), 127.6 (CH), 127.2 (CH), 79.7 (C), 62.9 (CH_2), 50.5 (CH_2), 46.7 (CH_2), 32.9 (CH_2), 28.6 (CH_3), 28.2 (CH_2), 26.7 (CH_2), 25.6 (CH_2); HRMS (ESI), calcd for $C_{18}H_{29}NO_3Na^+$ $(M+Na)^+$ 330.2045, found 330.2040.



94e

benzyl benzyl(6-oxohexyl)carbamate (94a)

2-Iodoxybenzoic acid (223 mg, 795 μmol) was added to a solution of alcohol **143e** (181 mg, 530 μmol) and DMSO (5.3 mL) at room temperature. The solution was maintained for 12 h at room temperature, and diluted with hexane (5 mL) and H_2O (20 mL). The mixture was filtered through a pad of Celite, which was washed with hexane (30 mL). The filtrate was extracted with hexane (5 mL). The combined organic extracts were washed with brine (2x 30 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:30 to 1:9) to give 162 mg of **94e** (90 %): a colorless oil; IR (film) 2936, 2861, 2720, 1698, 1454, 1421, 1235, 1125, 734, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 9.73 (s, 1/2H), 9.68 (s, 1/2H), 7.42–7.12 (m, 10H) , 5.19 (s, 1H), 5.17 (s, 1H), 4.50 (s, 1H), 4.49 (s, 1H), 3.27 (t, *J* = 6.9 Hz, 1H), 3.20 (t, *J* = 6.9 Hz, 1H), 2.40 (t, *J* = 6.6 Hz, 1H), 2.31 (t, *J* = 6.6 Hz, 1H), 1.65–1.45 (m, 4H), 1.35–1.16 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 202.7 (CH), 202.5 (CH), 156.9 (C), 156.4 (C), 138.0 (C), 138.0 (C), 136.95 (C), 136.85 (C), 128.7 (CH), 128.7 (CH), 128.61 (CH), 128.58 (CH), 128.14 (CH), 128.05 (CH), 128.00 (CH), 127.97 (CH), 127.48 (CH), 127.44 (CH), 127.3 (CH), 127.3 (CH), 67.36 (CH_2), 67.32 (CH_2), 50.7 (CH_2), 50.4 (CH_2), 47.0 (CH_2), 46.1 (CH_2), 43.84 (CH_2), 43.77 (CH_2), 28.0 (CH_2), 27.6 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 21.9 (CH_2), 21.7 (CH_2); HRMS (ESI), calcd for $C_{21}H_{26}NO_3^+$ $(M+H)^+$ 340.1913, found 340.1903.



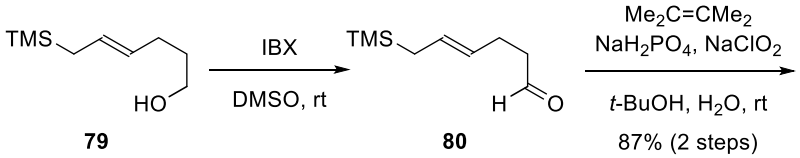
94f

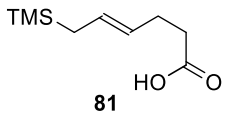
***tert*-butyl benzyl(6-oxohexyl)carbamate (94f)**

2-Iodoxybenzoic acid (179 mg, 639 μmol) was added to a solution of alcohol **143f** (131 mg, 426 μmol) and DMSO (4.3 mL) at room temperature. The solution was maintained for 12 h at room temperature, and diluted with hexane (5 mL) and H_2O (20 mL). The mixture was filtered through a pad of Celite, which was washed with hexane (30 mL). The filtrate was extracted with hexane (5 mL). The combined organic extracts were washed with brine (2x 30 mL), dried over Na_2SO_4, and concentrated. The residue was

purified by silica gel column chromatography (EtOAc/hexane 1:30 to 1:9) to give 117 mg of **94f** (90 %): a colorless oil; IR (film) 2974, 2933, 2864, 2864, 1726, 1693, 1455, 1416, 1366, 1246, 1163, 879, 734, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 9.74 (t, *J* = 1.7 Hz, 1H), 7.32 (t, *J* = 6.9 Hz, 2H), 7.28–7.18 (m, 3H), 4.43 (bs, 1H), 4.40 (bs, 1H), 3.27–3.17 (m, 1H), 3.17–3.06 (m, 1H) , 2.40 (td, *J* = 7.5, 1.7 Hz, 2H) 5, 1.66–1.56 (m, 2H), 1.56–1.38 (m, 11H), 1.34–1.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 202.8 (CH), 202.5 (CH), 156.2 (C), 155.8 (C), 138.8 (C), 138.6 (C), 128.6 (CH), 128.6 (CH), 127.8 (CH), 127.8 (CH), 127.2 (CH), 127.2 (CH), 79.8 (C), 79.8 (C), 50.6 (CH_2), 50.0 (CH_2), 46.5 (CH_2), 46.3 (CH_2), 43.9 (CH_2), 43.9 (CH_2), 28.6 (CH_3), 28.6 (CH_3), 28.0 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 26.5 (CH_2), 21.9 (CH_2), 21.9 (CH_2); HRMS (ESI), calcd for $C_{18}H_{27}NO_3Na^+$ $(M+Na)^+$ 328.1889, found 328.1883.

Preparation of *N*-methoxyamide *E*-42 and *N*-methylamide 95



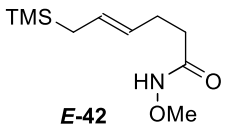


(*E*)-6-(trimethylsilyl)hex-4-enoic acid (81)

2-Iodoxybenzoic acid (924 mg, 3.30 mmol) was added to a solution of alcohol **79** (1.07 g, 6.21 mmol),[3] and DMSO (12 mL) at room temperature. The solution was maintained for 16 h at room temperature, and diluted with Et_2O (25 mL) and H_2O (20 mL). The mixture was filtered through a pad of Celite, which was washed with Et_2O (15 mL). The filtrate was extracted with Et_2O (5 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated to give (*E*)-6-(trimethylsilyl)hex-4-enal **80**, which was immediately used in the next reaction without further purification.

A mixture of sodium chlorite (2.24 g, 24.8 mmol), sodium dihydrogenphosphate (1.49 g, 12.4 mmol) and H_2O (5.2 mL) was quickly added to a mixture of aldehyde **80**, 2,3-Dimethyl-2-butene (18 mL, 160

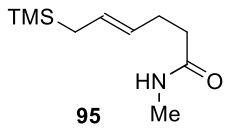
mmol) and *t*-BuOH (110 mL) at room temperature. The resulting mixture was stirred for 2 h at room temperature, and extracted with EtOAc (2x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:19 to 1:4) to give 1.01 g of **81** (87%, 2 steps): a colorless oil; IR (film) 3022, 2955, 2670, 1713, 1412, 1249, 1154, 967, 850, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.47 (dt, *J* = 15.2, 8.0 Hz, 1H), 5.24 (dt, *J* = 15.2, 7.2 Hz, 1H), 2.40 (t, *J* = 6.9 Hz, 2H), 2.31 (dt, *J* = 7.2, 6.9 Hz, 2H), 1.41 (d, *J* = 8.0 Hz, 2H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.9 (C), 128.3 (CH), 126.1 (CH), 34.7 (CH_2), 28.0 (CH_2), 22.8 (CH_2), –1.9 (CH_3); LRMS (EI) *m*/*z* 186 (M^+, 8.1%), 118 (8), 117 (74), 116 (6), 79 (6), 78 (47), 77 (13), 76 (7), 75 (52), 74 (11), 73 (100), 72 (9), 68 (15), 59 (6); HRMS (EI), calcd for $C_9H_{18}O_2$ M^+ 186.1076, found 186.1068.



***E*-42**

(*E*)-*N*-methoxy-6-(trimethylsilyl)hex-4-enamide (*E*-42)

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI, 3.53 g, 18.4 mmol) was added to a solution of carboxylic acid **81** (3.12 g, 16.8 mmol), *O*-methylhydroxylamine hydrochloride (1.54 g, 18.4 mmol), HOBt·H_2O (2.48 g, 18.4 mmol), triethylamine (5.1 mL, 37 mmol) and CH_2Cl_2 (170 mL) at room temperature. The solution was maintained for 21 h at room temperature, and quenched with saturated aqueous $NaHCO_3$ (100 mL). The resulting mixture was extracted with CH_2Cl_2 (2x 100 mL). The combined organic extracts were washed with brine (150 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4 to 1:2) to give 3.43 g of ***E*-42**[4] (95%): a colorless oil; IR (film) 3180, 2955, 1659, 1441, 1248, 1068, 967, 856 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (dt, *J* = 15.2, 8.0 Hz, 1H), 5.29–5.17 (m, 1H), 3.75 (s, 3H), 2.33 (dt, *J* = 6.9, 6.9 Hz, 2H), 2.21–2.05 (m, 2H), 1.40 (d, *J* = 8.0 Hz, 2H), –0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7 (C), 128.5 (CH), 126.3 (CH), 64.6 (CH_3), 33.9 (CH_2), 28.6 (CH_2), 22.8 (CH_2), –1.9 (CH_3); HRMS (ESI), calcd for $C_{10}H_{22}NO_2Si^+$ $(M+H)^+$ 216.1420, found 216.1419.

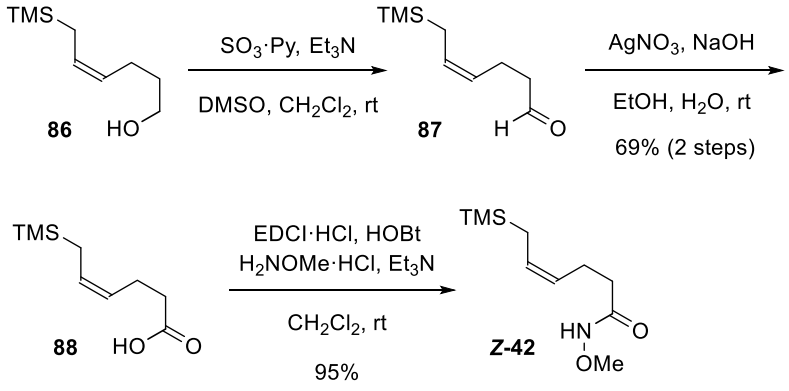


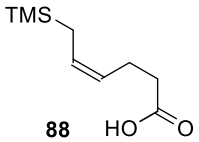
95

(*E*)-*N*-methyl-6-(trimethylsilyl)hex-4-enamide (95)

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI, 9.5 mg, 49.6 μmol) was added to a solution of carboxylic acid **81** (8.4 mg, 45.1 mmol), *N*-methylamine hydrochloride (3.4 mg, 49.6 μmol), $HOBt·H_2O$ (6.7 mg, 49.6 μmol), triethylamine (14 μL, 99 μmol) and CH_2Cl_2 (1.0 mL) at room temperature. The solution was maintained for 24 h at room temperature, and quenched with saturated aqueous $NaHCO_3$ (5 mL). The resulting mixture was extracted with $CHCl_3$ (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:3 to 1:1) to give 8.3 mg of **95** (92%): a colorless oil; IR (film) 3297, 3095, 2954, 1651, 1557, 1411, 1248, 1157, 852, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.47 (bs, 1H), 5.46 (dtt, *J* = 14.9, 8.0, 1.2 Hz, 1H), 5.23 (dtt, *J* = 14.9, 6.6, 1.2 Hz, 1H), 2.79 (d, *J* = 4.9 Hz, 3H), 2.31 (td, *J* = 6.9, 6.6 Hz, 2H), 2.21 (t, *J* = 6.9 Hz, 2H), 1.40 (dt, *J* = 8.0, 1.2 Hz, 2H), –0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5 (C), 127.7 (CH), 126.8 (CH), 36.9 (CH_2), 28.9 (CH_2), 26.2 (CH_3), 22.7 (CH_2), –2.0 (CH_3); HRMS (FAB), calcd for $C_{10}H_{22}NOSi^+$ $(M+H)^+$ 200.1471, found 200.1475.

Preparation of *N*-methoxyamide *Z*-42





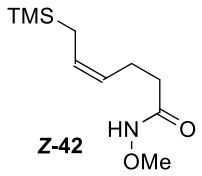
88

(*Z*)-6-(trimethylsilyl)hex-4-enoic acid (88)

Sulfur trioxide pyridine complex (55.4 mg, 348 μmol) was added to a solution of alcohol **86** (30.0 mg, 174 μmol),[5] DMSO (220 μL) and CH_2Cl_2 (660 μL) at room temperature. The solution was maintained for

2 h at room temperature, and quenched with H_2O (5 mL). The resulting mixture was extracted with CH_2Cl_2 (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/pentane 1:3) to give aldehyde **87**.

A solution of aldehyde **87** and EtOH (1.5 mL) was added to a mixture of silver nitrate (59.1 mg, 348 μmol), NaOH (27.8 mg, 696 μmol) and H_2O (3.0 mL) at 0 °C. The resulting mixture was stirred for 30 min at room temperature, and quenched with saturated aqueous NH_4Cl (10 mL). The resulting mixture was extracted with Et_2O (2x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:14) to give 22.4 mg of **88** (69%, 2 steps): a colorless oil; IR (film) 3011, 2956, 2679, 1714, 1417, 1292, 1249, 1152, 944, 856, 729, 701, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.47 (dtt, J = 10.6, 8.6, 1.4 Hz, 1H), 5.24 (dtt, J = 10.6, 6.9, 1.4 Hz, 1H), 2.42–2.37 (m, 2H), 2.37–2.30 (m, 2H), 1.49 (d, J = 8.6 Hz, 2H), 0.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6 (C), 127.6 (CH), 124.8 (CH), 34.3 (CH_2), 22.5 (CH_2), 18.7 (CH_2), –1.7 (CH_3); LRMS (EI) *m/z* 186 (M^+, 2.8%), 118 (6), 117 (56), 75 (64), 74 (10), 73 (100), 72 (7), 68 (12), 59 (6); HRMS (EI), calcd for $C_9H_{18}O_2Si$ M^+ 186.1076, found 186.1080.

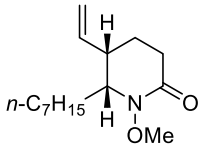


***Z*-42**

(*Z*)-*N*-methoxy-6-(trimethylsilyl)hex-4-enamide (*Z*-42)

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI, 487 mg, 2.54 mmol) was added to a solution of carboxylic acid **88** (432 mg, 2.31 mmol), *O*-methylhydroxylamine hydrochloride (212 mg, 2.54 mmol), HOBt·H_2O (342 mg, 2.54 mmol), triethylamine (670 μL, 5.1 mmol) and CH_2Cl_2 (23 mL) at room temperature. The solution was maintained for 21 h at room temperature, and quenched with saturated aqueous $NaHCO_3$ (20 mL). The resulting mixture was extracted with chloroform (2x 20 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:3 to 1:1) to give 470 mg of ***Z*-42**[4] (95%): a colorless oil; IR (film) 3183, 2955, 1660, 1423, 1248, 1152, 1078, 856 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.49 (dt, J = 9.7, 9.7 Hz, 1H), 5.30–5.18 (m, 1H), 3.76 (s, 3H), 2.35 (dt, J = 7.2, 7.2 Hz, 2H), 2.19–2.05 (m, 2H), 1.50 (d, J = 9.7 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (C), 127.8 (CH), 124.9 (CH), 64.5 (CH_3), 33.4 (CH_2), 23.0 (CH_2), 18.7 (CH_2), –1.7 (CH_3); HRMS (ESI), calcd for $C_{10}H_{22}NO_2Si^+$ $(M+H)^+$ 216.1420, found 216.1418.

Synthesis of *N*-methoxylactams 71a-j



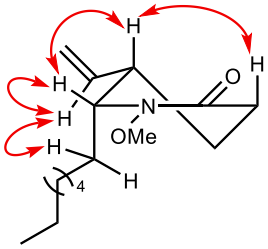
71a

[General Procedure A]

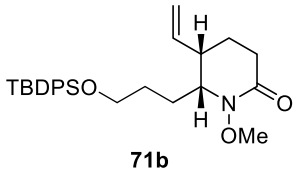
(5*S*,6*R*)-6-heptyl-1-methoxy-5-vinylpiperidin-2-one (71a)

Boron trifluoride diethyl ether complex (570 µL, 4.6 mmol) was added to a solution of octanal **94a** (540 µL, 3.5 mmol), ***E*-42** (500 mg, 2.32 mmol) and CH_2Cl_2 (12 mL) at –20 °C. After maintaining at –20 °C for 20 min, boron trifluoride diethyl ether complex (290 µL, 2.3 mmol) was added to the solution every 15 min four times. After maintaining at –20 °C for 20 min, the solution was quenched with H_2O (15 mL), and extracted with chloroform (2x 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:3 to 1:2) to give 529 mg of **71a** (90%): a colorless oil; IR (film) 2928, 2857, 1673, 1460, 1072, 999, 918 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddd, J = 17.2, 10.6, 7.5 Hz, 1H), 5.19 (ddd, J = 10.6, 1.2, 1.2 Hz, 1H), 5.17 (ddd, J = 17.2, 1.2, 1.2 Hz, 1H), 3.74 (s, 3H), 3.67 (ddd, J = 6.6, 5.2, 5.2 Hz, 1H), 2.77–2.70 (m, 1H), 2.53 (ddd, J = 17.5, 6.0, 6.0 Hz, 1H), 2.44 (ddd, J = 17.5, 6.2, 6.0 Hz, 1H), 1.87–1.76 (m, 2H), 1.72–1.64 (m, 1H), 1.59–1.50 (m, 1H), 1.43–1.19 (m, 10H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1 (C), 136.5 (CH), 117.1 (CH_2), 62.6 (CH), 61.4 (CH_3), 42.4 (CH), 31.8 (CH_2), 30.9 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.1 (CH_2), 27.0 (CH_2), 23.5 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI), calcd for $C_{15}H_{27}NO_2Na^+$ $(M+Na)^+$ 276.1939, found 276.1936.

NOESY experiment for **71a**



71a (500 MHz, $CDCl_3$)

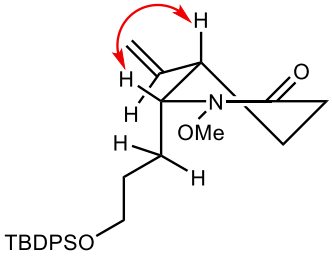


71b

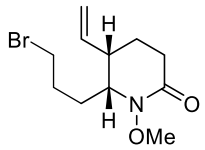
(5*S*,6*R*)-6-(3-((tert-butyldiphenylsilyl)oxy)propyl)-1-methoxy-5-vinylpiperidin-2-one (71b)

Following the general procedure A using boron trifluoride diethyl ether complex (6x 34 µL, 1.6 mmol), 4-((tert-butyldiphenylsilyl)oxy)butanal **94b**[6] (135 mg, 417 µmol) and ***E*-42** (60.0 mg, 278 µmol) were converted to 115 mg of **71b** (92%): a colorless oil; IR (film) 2931, 2857, 1672, 1428, 1111, 772, 703, 613 cm^{-1}; ^1H NMR (500 MHz, d-acetone) δ 7.71–7.68 (m, 4H), 7.49–7.41 (m, 6H), 5.97 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H), 5.18 (ddd, *J* = 17.5, 1.4, 1.4 Hz, 1H), 5.16 (ddd, *J* = 10.3, 1.4, 1.4 Hz, 1H), 3.77 (ddd, *J* = 6.0, 5.7, 4.6 Hz, 1H), 3.74–3.68 (m, 2H), 3.65 (s, 3H), 2.84–2.77 (m, 1H), 2.40 (ddd, *J* = 17.5, 6.3, 6.3 Hz, 1H), 2.44 (ddd, *J* = 17.5, 7.5, 7.5 Hz, 1H), 1.84–1.76 (m, 3H), 1.76–1.65 (m, 3H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1 (C), 136.4 (CH), 135.6 (CH), 133.9 (C), 129.7 (CH), 127.7 (CH), 117.3 (CH_2), 63.6 (CH_2), 62.4 (CH), 61.5 (CH_3), 42.5 (CH), 30.8 (CH_2), 30.0 (CH_2), 26.9 (CH_3), 26.5 (CH_2), 23.5 (CH_2), 19.3 (C); HRMS (ESI), calcd for $C_{27}H_{37}NO_3Na^+$ $(M+Na)^+$ 474.2440, found 474.2443.

NOESY experiment for **71b**



71b (500 MHz, *d*-acetone)

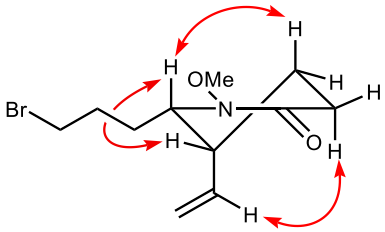


71c

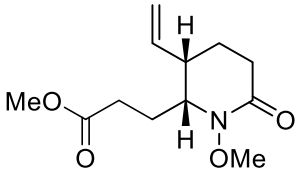
(5*S*,6*R*)-6-(3-bromopropyl)-1-methoxy-5-vinylpiperidin-2-one (71c)

Following the general procedure A using boron trifluoride diethyl ether complex (5x 60 µL, 2.4 mmol), 4-bromobutanal **94c**[4] (108 mg, 717 µmol) and ***E*-42** (103 mg, 478 µmol) were converted to 105 mg of **71c**[4] (80%): a colorless oil; IR (film) 3457, 2936, 1667, 1435, 1266, 999, 923 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddd, *J* = 17.5, 10.6, 7.2 Hz, 1H), 5.22 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H), 5.19 (ddd, *J* = 17.5, 1.4, 1.4 Hz, 1H), 3.75 (s, 3H), 3.71 (ddd, *J* = 5.8, 5.8, 4.9 Hz, 1H), 3.44–3.34 (m, 2H), 2.79–2.71 (m, 1H), 2.55 (ddd, *J* = 17.8, 5.7, 5.7 Hz, 1H), 2.46 (ddd, *J* = 17.8, 8.0, 8.0 Hz, 1H), 2.03 (ddddd, *J* = 14.3, 14.3, 6.3, 6.3, 6.3 Hz, 1H), 1.95 (ddddd, *J* = 14.3, 14.3, 6.9, 6.9, 6.9 Hz, 1H), 1.86–1.80 (m, 2H), 1.80–1.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9 (C), 136.2 (CH), 117.5 (CH_2), 61.7 (CH), 61.4 (CH_3), 42.6 (CH), 33.5 (CH_2), 30.9 (CH_2), 30.3 (CH_2), 28.9 (CH_2), 22.9 (CH_2); HRMS (ESI), calcd for $C_{11}H_{18}NO_2NaBr^+$ $(M+Na)^+$ 298.0419, found 298.0419.

NOESY experiment for **71c**



71c (500 MHz, $CDCl_3$)



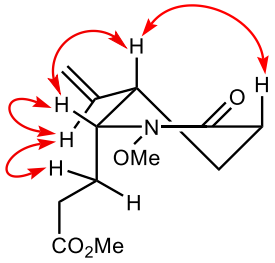
71d

[General Procedure B]

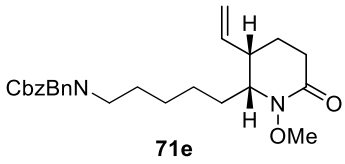
methyl 3-((2*R*,3*S*)-1-methoxy-6-oxo-3-vinylpiperidin-2-yl)propanoate (71d)

Boron trifluoride diethyl ether complex (68 µL, 550 µmol) was added to a solution of methyl 4-oxobutanoate **94d**[7] (78.0 mg, 433 µmol), ***E*-42** (60.0 mg, 279 µmol) and CH_2Cl_2 (1.4 mL) at –20 °C. After maintaining at –20 °C for 1 h, boron trifluoride diethyl ether complex (36 µL, 290 µmol) was added to the solution every 1 h four times. After maintaining at –20 °C for 12h, the solution was quenched with H_2O (5 mL), and extracted with chloroform (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:1 to 3:1 to 1:0) to give 61.4 mg of **71d** (92%): a colorless oil; IR (film) 2950, 1737, 1668, 1437, 1174, 1004, 925 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddd, J = 17.2, 10.3, 6.9 Hz, 1H), 5.19 (ddd, J = 10.3, 1.2, 1.2 Hz, 1H), 5.17 (ddd, J = 17.2, 1.2, 1.2 Hz, 1H), 3.80 (ddd, J = 6.3, 6.3, 4.6 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 2.78–2.71 (m, 1H), 2.53 (ddd, J = 17.5, 6.0, 6.0 Hz, 1H), 2.49 (t, J = 7.7 Hz, 2H), 2.46 (ddd, J = 17.5, 8.3, 8.3 Hz, 1H), 1.93–1.88 (m, 2H), 1.84–1.78 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6 (C), 166.8 (C), 136.4 (CH), 117.5 (CH_2), 61.4 (CH_3), 61.1 (CH), 51.7 (CH_3), 42.6 (CH), 31.5 (CH_2), 31.0 (CH_2), 25.6 (CH_2), 22.6 (CH_2); HRMS (ESI), calcd for $C_{12}H_{19}NO_4Na^+$ $(M+Na)^+$ 264.1212, found 264.1199.

NOESY experiment for **71d**



71d (500 MHz, $CDCl_3$)

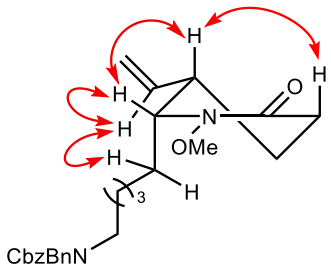


71e

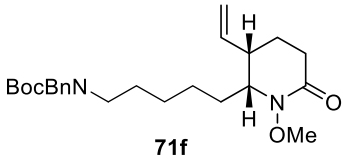
benzyl benzyl(5-((2*R*,3*S*)-1-methoxy-6-oxo-3-vinylpiperidin-2-yl)pentyl)carbamate (71e)

Following the general procedure B using boron trifluoride diethyl ether complex (4x 35 µL, 1.1 mmol), benzyl benzyl(6-oxohexyl)carbamate **94e** (142 mg, 418 µmol) and ***E*-42** (60.0 mg, 279 µmol) were converted to 119 mg of **71e** (92%): a colorless oil; IR (film) 2934, 2861, 1699, 1670, 1456, 1421, 1220, 914, 771, 744, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.42–7.12 (m, 10H), 5.82 (ddd, J = 17.5, 10.0, 7.5 Hz, 1H), 5.21–5.12 (m, 4H), 4.49 (s, 2H), 3.72 (s, 3H), 3.62 (ddd, J = 5.4, 5.4, 4.6 Hz, 1H), 3.24 (t, J = 6.9 Hz, 2H), 2.74–2.67 (m, 2H), 2.52 (ddd, J = 17.5, 6.0, 6.0 Hz, 1H), 2.43 (ddd, J = 17.5, 7.7, 7.7 Hz, 1H), 1.82–1.76 (m, 2H), 1.69–1.58 (m, 1H), 1.58–1.45 (m, 3H), 1.42–1.29 (m, 2H), 1.29–1.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 167.2 (C), 156.7 (C), 138.2 (C), 137.1 (C), 136.7 (CH), 128.64 (CH), 128.55 (CH), 128.01 (CH), 127.96 (CH), 127.7 (CH), 127.4 (CH), 117.2 (CH), 67.3 (CH_2), 62.8 (CH), 61.5 (CH_3), 50.7 (CH_2), 46.8 (CH_2), 42.7 (CH), 31.0 (CH_2), 30.0 (CH_2), 27.03 (CH_2), 26.96 (CH_2), 26.7 (CH_2), 23.6 (CH_2); HRMS (ESI), calcd for $C_{28}H_{37}N_2O_4^+$ $(M+H)^+$ 465.2753, found 465.2755.

NOESY experiment for **71e**



71e (500 MHz, $CDCl_3$)

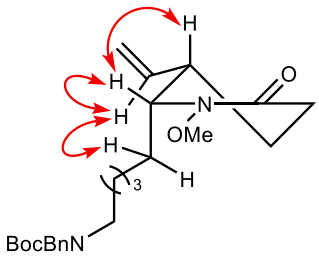


71f

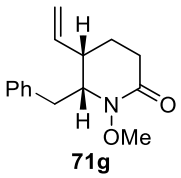
***tert*-butyl benzyl(5-((2*R*,3*S*)-1-methoxy-6-oxo-3-vinylpiperidin-2-yl)pentyl)carbamate (71f)**

Following the general procedure B using boron trifluoride diethyl ether complex (4x 33 µL, 1.1 mmol), *tert*-butyl benzyl(6-oxohexyl)carbamate **94f** (117 mg, 383 µmol) and ***E*-42** (57.0 mg, 264 µmol) were converted to 85.1 mg of **71f** (75%): a colorless oil; IR (film) 2974, 2932, 1687, 1418, 1365, 1170, 914, 772, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.34–7.18 (m, 5H), 5.84 (ddd, *J* = 17.5, 10.3, 7.2 Hz, 1H), 5.18 (d, *J* = 10.3 Hz, 1H), 5.16 (d, *J* = 17.5 Hz, 1H), 4.42 (s, 2H), 3.74 (s, 3H), 3.65 (ddd, *J* = 5.4, 5.4, 5.4 Hz, 1H), 3.16 (s, 2H), 2.76–2.68 (m, 1H), 2.52 (ddd, *J* = 17.5, 6.0, 6.0 Hz, 1H), 2.43 (ddd, *J* = 17.5, 7.7, 7.7 Hz, 1H), 1.86–1.76 (m, 2H), 1.70–1.62 (m, 1H), 1.60–1.45 (m, 12H), 1.45–1.30 (m, 2H), 1.29–1.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 167.1 (C), 156.0 (C), 138.9 (C), 136.8 (CH), 128.6 (CH), 127.6 (CH), 127.2 (CH), 117.2 (CH_2), 79.7 (C), 62.9 (CH), 61.5 (CH_3), 50.6 (CH_2), 46.8 (CH_2), 42.8 (CH), 31.1 (CH_2), 30.1 (CH_2), 28.6 (CH_3), 28.1 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 23.7 (CH_2); HRMS (ESI), calcd for $C_{25}H_{38}N_2O_4Na^+$ $(M+Na)^+$ 453.2729, found 453.2725.

NOESY experiment for **13f**



13f (500 MHz, $CDCl_3$)



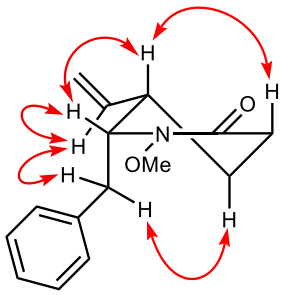
71g

(5*S*,6*R*)-6-benzyl-1-methoxy-5-vinylpiperidin-2-one (71g)

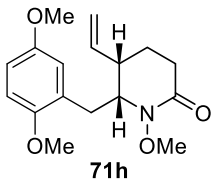
Following the general procedure B using boron trifluoride diethyl ether complex (5x 34 µL, 1.4 mmol), 2-phenylacetaldehyde **94g** (49 µL, 420 µmol) and ***E*-42** (60.0 mg, 279 µmol) were converted to 52.9 mg of **71g** (78%, dr = 11:1). For an analytical sample, **71g** was purified by HPLC (PEGASIL Silica 120-5, 250×20 mm, EtOAc, 10 mL/min, T_R = 15.8 min). **71g**: a colorless oil; IR (film) 2934, 1672, 1261, 1070,

923, 743, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 7.5, 6.9 Hz, 2H), 7.22–7.18 (m, 3H), 5.82 (ddd, *J* = 17.2, 10.3, 7.5 Hz, 1H), 5.25 (ddd, *J* = 10.3, 1.4, 1.4 Hz, 1H), 5.15 (ddd, J = 17.2, 1.4, 1.4 Hz, 1H), 4.17 (ddd, J = 7.7, 4.3, 3.7 Hz, 1H), 3.77 (s, 3H), 3.07 (dd, *J* = 14.0, 3.7 Hz, 1H), 2.93 (dd, J = 14.0, 7.7 Hz, 2H), 2.71–2.65 (m, 1H), 2.52 (ddd, *J* = 17.5, 6.6, 6.6 Hz, 1H), 2.43 (ddd, *J* = 17.5, 8.0, 6.6 Hz, 1H), 1.70 (dddd, *J* = 13.8, 6.6, 6.6, 3.4 Hz, 2H), 1.58 (dddd, *J* = 13.8, 9.5, 8.0, 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8 (C), 138.3 (C), 136.4 (CH), 129.8 (CH), 128.5 (CH), 126.6 (CH), 118.0 (CH_2), 64.0 (CH), 61.8 (CH_3), 42.0 (CH), 35.1 (CH_2), 30.9 (CH_2), 23.7 (CH_2); LRMS (EI) *m/z* 245 (M^+, 10.7%), 118 (19.9), 117 (74), 126 (13), 124 (6), 123 (29), 122 (5), 117 (19), 107 (8), 96 (9), 95 (17), 94 (11), 91 (50), 81 (8), 80 (12), 68 (6), 67 (5), 56 (8); HRMS (EI), calcd for $C_{15}H_{19}NO_2$ M^+ 245.1416, found 245.1412.

NOESY experiment for **71g**



71g (500 MHz, $CDCl_3$)



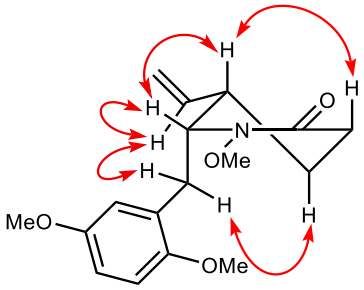
71h

(5*S*,6*R*)-6-(2,5-dimethoxybenzyl)-1-methoxy-5-vinylpiperidin-2-one (71h)

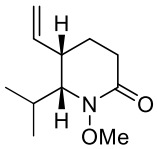
Following the general procedure B using boron trifluoride diethyl ether complex (4x 36 µL, 1.2 µmol), 2-(2,5-dimethoxyphenyl)acetaldehyde **94h**[8] (78.0 mg, 433 µmol) and ***E*-42** (62.1 mg, 288 µmol) were converted to 81.4 mg of **71h** (92%, dr = 11:1). For an analytical sample, **71h** was purified by HPLC (PEGASIL Silica 120-5, 250×20 mm, EtOAc, 10 mL/min, T_R = 19.8 min): **71h**: a colorless oil; IR (film) 3074, 2937, 2834, 1670, 1502, 1226, 1047, 923, 807 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.77–6.70 (m, 3H), 5.96 (ddd, *J* = 17.8, 10.6, 7.7 Hz, 1H), 5.18 (ddd, *J* = 10.3, 1.4, 1.4 Hz, 1H), 5.15 (ddd, *J* = 17.2, 1.4, 1.4 Hz, 1H), 4.17 (ddd, *J* = 8.0, 4.9, 4.0 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 3.18 (dd, *J* = 13.8, 4.9 Hz, 1H), 2.79 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.68–2.62 (m, 1H), 2.53 (ddd, *J* = 17.5, 6.9, 6.9 Hz, 1H), 2.43 (ddd, *J* = 17.5, 6.9, 6.9 Hz, 1H), 2.04 (sept-d, *J* = 7.2, 2.6 Hz, 1H), 1.80–1.73 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6 (C), 153.4 (C), 151.8 (C), 136.6 (CH), 127.6 (CH), 117.6 (CH_2), 117.5 (C),

112.2 (CH), 111.2 (CH), 62.2 (CH), 61.3 (CH_3), 55.82 (CH_3), 55.78 (CH_3), 42.3 (CH), 30.7 (CH_2), 30.3 (CH_2), 24.3 (CH_2); HRMS (ESI), calcd for $C_{17}H_{24}NO_4^+$ $(M+H)^+$ 306.1705, found 306.1696.

NOESY experiment for **71h**



71h (500 MHz, $CDCl_3$)

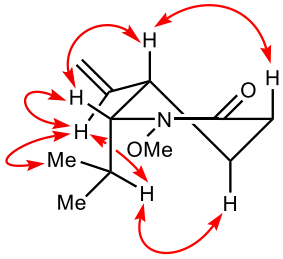


71i

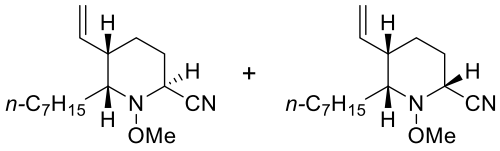
(5*S*,6*R*)-6-isopropyl-1-methoxy-5-vinylpiperidin-2-one (71i)

Boron trifluoride diethyl ether complex (68 µL, 550 µmol) was added to a solution of 2-methyl propanal **94i** (38 µL, 410 µmol), ***E*-42** (60.0 mg, 279 µmol) and CH_2Cl_2 (1.4 mL) at –20 °C. After maintaining at –20 °C for 1 h, boron trifluoride diethyl ether complex (34 µL, 280 mmol) was added to the solution every 1 h three times. After maintaining at –20 °C for 2 days, the solution was quenched with H_2O (5 mL), and extracted with chloroform (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:3 to 1:2 to 1:1) to give 36.8 mg of **71i** (67%): a colorless oil; IR (film) 2925, 2932, 1670, 1072, 913, 772, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (ddd, J = 16.9, 10.3, 6.0 Hz, 1H), 5.18 (ddd, J = 10.3, 1.4, 1.4 Hz, 1H), 5.15 (ddd, J = 16.9, 1.4, 1.4 Hz, 1H), 3.74 (s, 3H), 3.65 (dddd, J = 10.3, 6.0, 5.2, 4.9 Hz, 1H), 2.81–2.74 (m, 1H), 2.53 (ddd, J = 17.8, 6.0, 4.0 Hz, 1H), 2.43 (ddd, J = 17.8, 9.7, 8.3 Hz, 1H), 2.04 (sept-d, J = 7.2, 2.6 Hz, 1H), 1.87–1.76 (m, 2H), 1.05 (d, J = 7.2 Hz, 3H), 0.95 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8 (C), 137.8 (CH), 116.5 (CH_2), 66.6 (CH), 60.3 (CH_3), 43.5 (CH), 31.4 (CH_2), 29.0 (CH), 24.3 (CH_3), 22.3 (CH_2), 19.5 (CH_3); LRMS (EI) *m*/*z* 197 (M^+, 5.9%), 155 (9), 154 (100), 123 (12), 102 (51), 97 (10), 96 (9.8), 95 (8), 89 (9), 81 (6), 80 (6), 79 (7), 78 (64), 77 (13), 73 (7), 70 (7), 69 (20), 68 (27), 67 (16), 56 (29); HRMS (EI), calcd for $C_{11}H_{19}NO_2$ M^+ 197.1416, found 197.1408.

NOESY experiment for **71i**



71i (500 MHz, $CDCl_3$)



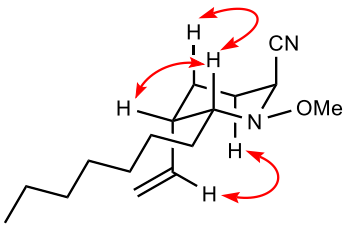
74a **122a**

(2*S*,5*S*,6*R*)-6-heptyl-1-methoxy-5-vinylpiperidine-2-carbonitrile (74a)

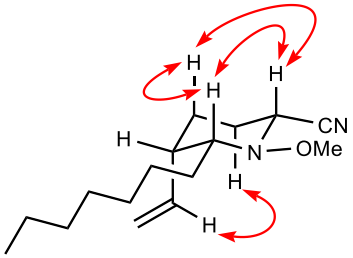
Diisobutylalminium hydride (1.5 M in toluene, 110 µL, 170 µmol) was added to a solution of **71a** (36.4 mg, 144 µmol) and CH_2Cl_2 (1.4 mL) at –78 °C. After stirring for 10 min, acetonitlile (480 µL), cyanotrimethylsilane (54 µL, 430 µmol) and tetrachlorostannane (20 µL, 170 µmol) were added to the solution. After stirring for 30 min at –78 °C, the resulting mixture was allowed to warm to room temperature, and maintained for 1 h at room temperature. This mixture was quenched with saturated aqueous (+)-potassium sodium tartrate (5 mL), and extracted with chloroform (2x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:120) to give 22.5 mg of **74a** (60%) and 10.4 mg of **122a** (27%): **74a**: a colorless oil; IR (film) 2929, 2857, 2234, 1466, 1044, 916 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.98 (ddd, *J* = 17.5, 9.8, 8.0 Hz, 1H), 5.10 (d, *J* = 9.8 Hz, 1H), 5.08 (d, *J* = 17.5 Hz, 1H), 4.28–4.21 (m, 1H), 3.54 (s, 3H), 3.00–2.89 (m, 1H), 2.61–2.52 (m, 1H), 2.05 (dddd, *J* = 13.8, 13.2, 4.0, 3.7 Hz, 1H), 1.93–1.82 (m, 2H), 1.82–1.71 (m, 1H), 1.63–1.54 (m, 1H), 1.39–1.21 (m, 11H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1 (CH), 117.9 (C), 116.9 (CH_2), 64.5 (CH), 61.2 (CH_3), 55.1 (CH), 41.1 (CH), 31.9 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 28.7 (CH_2), 27.3 (CH_2), 25.3 (CH_2), 24.7 (CH_2), 22.8 (CH_2), 14.2 (CH_3); HRMS (ESI), calcd for $C_{16}H_{29}N_2O^+$ $(M+H)^+$ 265.2280, found 265.2279; **122a**: a colorless oil; IR (film) 2928, 2857, 2250, 1467, 1040, 1001, 918 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 6.07 (ddd, *J* = 17.8, 9.7, 9.7 Hz, 1H), 5.15 (d, *J* = 9.7 Hz, 1H), 5.10 (d, *J* = 17.8 Hz, 1H), 3.70 (s, 3H), 3.43 (d, *J* = 11.5 Hz, 1H), 2.53–2.47 (m, 1H), 2.47–2.42 (m, 1H), 2.13 (dddd, *J* = 13.5, 13.5, 11.5, 3.2 Hz, 1H), 1.95–1.79 (m, 2H), 1.69 (dddd, *J* = 13.5, 3.2, 3.2, 3.2 Hz, 1H), 1.53 (dddd, *J* = 13.5, 13.5, 4.3, 4.3 Hz, 1H), 1.46–1.37 (m, 1H), 1.37–1.12 (m, 10H), 0.91 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6 (CH), 119.6 (C), 117.4 (CH_2), 69.9 (CH), 63.4 (CH_3), 58.5 (CH), 41.5

(CH), 31.9 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 26.7 (CH_2), 25.4 (CH_2), 22.8 (CH_2), 14.2 (CH_3); HRMS (ESI), calcd for $C_{16}H_{29}N_2O^+$ $(M+H)^+$ 265.2280, found 265.2280.

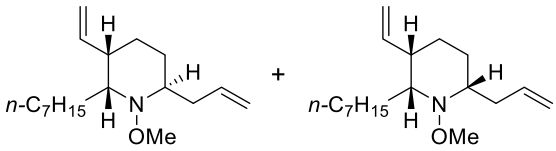
NOESY experiment for **74a** and **122a**



74a (500 MHz, $CDCl_3$)



122a (500 MHz, $CDCl_3$)



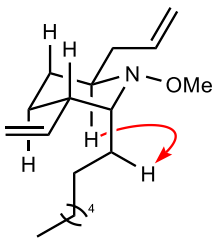
74b **122b**

(2*R*,3*S*,6*S*)-6-allyl-2-heptyl-1-methoxy-3-vinylpiperidine (74b)

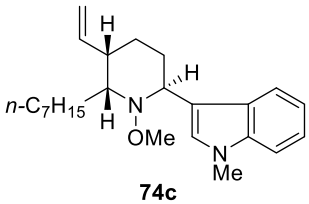
Diisobutylalminium hydride (1.5 M in toluene, 100 µL, 150 µmol) was added to a solution of **71a** (29.2 mg, 115 µmol) and CH_2Cl_2 (1.2 mL) at –78 °C. After stirring for 10 min, allyltributylstannane (110 µL, 346 µmol) and $Sc(OTf)_3$ (68.1 mg, 138 µmol) were added to the solution. After stirring for 30 min at –78 °C, the resulting mixture was allowed to warm to room temperature, and maintained for 1 h at room temperature. This mixture was quenched with saturated aqueous (+)-potassium sodium tartrate (5 mL), and extracted with chloroform (2x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:120 to 1:100) to give 32.9 mg of a mixture of **74b** and **122b** (86%, **74b**:**122b** = 4.1:1). For analytical samples, two diastereomers were purified by HPLC (PEGASIL Silica 120-5, 250×20 mm, EtOAc/hexane 1:80, 10 mL/min) **74b**: a colorless oil; IR (film) 2932, 2856, 1639, 1465, 1045, 910 cm^{-1}; ^1H NMR (500 MHz, *d*-acetone, 55 °C) δ 5.92 (dddd, *J* = 16.9, 10.0, 7.2, 6.9 Hz, 1H), 5.83 (ddd, *J* = 16.9, 9.2, 7.7 Hz, 1H), 5.08–4.96 (m, 4H), 3.46 (s, 3H), 3.22–3.15 (m, 1H), 2.87–2.79 (m, 1H), 2.87–2.64 (m, 1H), 2.46 (ddd, *J* = 14.0, 6.9, 6.9 Hz, 1H), 2.12 (ddd, *J* = 14.0, 7.2, 7.2 Hz, 1H), 1.61–1.54 (m, 1H), 1.54–1.39 (m, 4H), 1.39–1.26 (m, 11H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of two conformers) δ 141.6 (CH), 140.6 (CH), 137.5 (CH), 136.2 (CH), 116.4 (CH_2), 115.7 (CH_2), 114.2 (CH_2), 113.8 (CH_2), 63.5 (CH), 63.1 (CH), 60.5 (CH_3), 59.9 (CH_3), 58.0 (CH), 56.6 (CH), 44.5 (CH), 38.0 (CH_2), 37.7 (CH_2), 36.9 (CH), 32.1 (CH_2), 32.1 (CH_2), 31.1 (CH_2), 30.0 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 27.1 (CH_2), 26.2 (CH_2), 24.7 (CH_2), 24.2 (CH_2), 23.5 (CH_2), 23.5 (CH_2), 22.8 (CH_2),

22.8 (CH_2), 14.3 (CH_3), 14.3 (CH_3); HRMS (ESI), calcd for $C_{18}H_{34}NO$ $(M+H)^+$ 280.2640, found 280.2626; **122b**: a colorless oil; IR (film) 3074, 2926, 2856, 2823, 1640, 1467, 1442, 1047, 998, 912 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 6.13 (ddd, *J* = 16.6, 9.5, 9.5 Hz, 1H), 5.87 (dddd, *J* = 16.9, 9.8, 7.5, 7.5 Hz, 1H), 5.09–4.98 (m, 4H), 3.55 (s, 3H), 2.65–2.56 (m, 1H), 2.56–2.37 (m, 3H), 2.21 (ddd, *J* = 13.8, 7.7, 7.5 Hz, 1H), 1.86–1.76 (m, 1H), 1.65–1.24 (m, 15H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6 (CH), 136.3 (CH), 116.5 (CH_2), 116.0 (CH_2), 70.3 (CH), 67.9 (CH), 63.7 (CH_3), 42.5 (CH), 38.4 (CH_2), 32.0 (CH_2), 31.0 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 29.5 (CH_2), 26.9 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 14.3 (CH_3); HRMS (ESI), calcd for $C_{18}H_{34}NO$ $(M+H)^+$ 280.2640, found 280.2626.

NOE experiment for **74b**



74b (500 MHz, *d*-acetone, 55 °C)



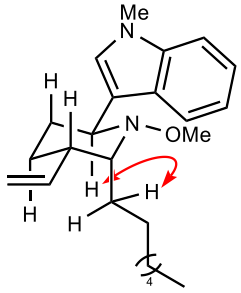
74c

3-((2*S*,5*S*,6*R*)-6-heptyl-1-methoxy-5-vinylpiperidin-2-yl)-1-methyl-1H-indole (74c)

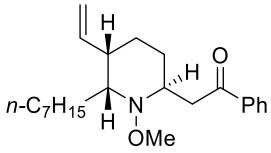
Diisobutylalminium hydride (1.5 M in toluene, 100 μL, 150 μmol) was added to a solution of **71a** (30.0 mg, 118 μmol) and CH_2Cl_2 (1.2 mL) at –78 °C. After stirring for 10 min, 1-methylindole (44 μL, 355 μmol) and $Sc(OTf)_3$ (69.8 mg, 142 μmol) were added to the solution. The resulting mixture was then allowed to warmed to –40 °C. The mixture was stirred for 22 h, quenched with saturated aqueous (+)-potassium sodium tartrate (5 mL) and extracted with chloroform (2x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:120 to 1:80) to give 38.3 mg of **74c** (88%, dr = 14:1). For an analytical sample, **74c** was purified by HPLC (P:EGASIL Silica 120-5, 250×20 mm, EtOAc/hexane 1:20, 10 mL/min, T_R = 14.1 min): **74c**: a colorless oil; IR (film) 2928, 2856, 1468, 1045, 910, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.88 (d, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.10 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.99 (s, 1H), 5.94–5.82 (m, 1H), 5.11–5.03 (m, 2H), 4.24 (d, *J* = 8.0 Hz, 1H), 3.77 (s, 3H), 3.37–3.27 (m, 1H), 3.10 (s, 3H), 3.00–2.80 (m, 1H), 2.35–2.15 (m, 1H),

1.89–1.56 (m, 5H), 1.56–1.27 (m, 10H), 0.92 (t, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 141.6 (CH), 137.4 (C), 128.0 (C), 127.4 (CH), 121.5 (CH), 120.8 (CH), 118.8 (CH), 116.9 (C), 113.9 (CH_2), 109.1 (CH), 64.0 (CH), 60.4 (CH_3), 52.8 (CH), 44.6 (CH_2), 37.0 (CH), 32.7 (CH_3), 32.1 (CH_2), 30.0 (CH_2), 29.5 (CH_2), 28.2 (CH_2), 26.4 (CH_2), 24.7 (CH_2), 22.8 (CH_2), 14.2 (CH_3); HRMS (FAB), calcd for $C_{24}H_{37}N_2O^+$ $(M+H)^+$ 369.2906, found 369.2921.

NOESY experiment for **74c**



74c (500 MHz, $CDCl_3$, 60 °C)

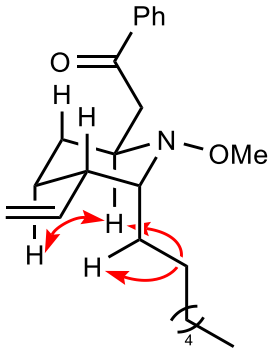


74d

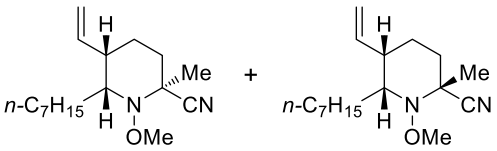
2-((2*S*,5*S*,6*R*)-6-heptyl-1-methoxy-5-vinylpiperidin-2-yl)-1-phenylethan-1-one (74d)

Zirconocene chloride hydride (46.0 mg, 178 μmol) was added to a solution of **71a** (32.8 mg, 129 μmol) and $(CH_2Cl)_2$ (1.3 mL) at room temperature. After stirring for 10 min, triisopropyl((1-phenylvinyl)oxy)silane (45.5 mg, 165 μmol) and $Sc(OTf)_3$ (12.7 mg, 25.8 μmol) were added to the solution. After stirring for 1 h at room temperature, this solution was quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with chloroform (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:120 to 1:100) to give 30.0 mg of **74d** (65%, single diastereomer): a colorless oil; IR (film) 2937, 2834, 1670, 1503, 1465, 1226, 1047, 923 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.97 (d, J = 7.5 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 5.80 (ddd, J = 17.5, 10.0, 6.9 Hz, 1H), 5.01 (d, J = 17.5 Hz, 1H), 4.99 (d, J = 10.0 Hz, 1H), 3.60–3.50 (m, 1H), 3.42 (s, 3H), 3.46–3.35 (m, 1H), 3.20–3.08 (m, 1H), 3.02–2.87 (m, 1H), 2.78–2.67 (m, 1H), 1.69–1.40 (m, 5H), 1.40–1.19 (m, 11H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7 (C), 141.2 (CH), 137.6 (C), 133.0 (CH), 128.7 (CH), 128.3 (CH), 114.1 (CH_2), 62.9 (CH), 60.4 (CH_3), 53.7 (CH), 37.1 (CH), 32.1 (CH_2), 29.8 (CH_2), 29.4 (CH_2), 27.0 (CH_2), 26.4 (CH_2), 25.1 (CH_2), 24.3 (CH_2), 23.5 (CH_2), 22.8 (CH_2), 14.3 (CH_3); HRMS (ESI), calcd for $C_{23}H_{36}NO_2^+$ $(M+H)^+$ 358.2746, found 358.2739.

NOESY experiment for **74d**



74d (500 MHz, $CDCl_3$)



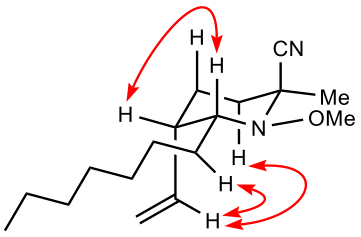
74e **122e**

(2*S*,5*S*,6*R*)-6-heptyl-1-methoxy-2-methyl-5-vinylpiperidine-2-carbonitrile (14e)

Methyl lithium (1.14 M in Et_2O, 150 µL, 170 µmol) was added to a solution of **13a** (36.0 mg, 142 µmol) and THF (1.4 mL, freshly distilled from sodium/benzophenone) at –78 °C. After stirring for 10 min, acetonitlile (470 µL), cyanotrimethylsilane (53 µL, 430 µmol) and tetrachlorostannane (20 µL, 170 µmol) were added to the solution. The resulting mixture was then allowed to warm to room temperature, and maintained for 24 h at room temperature. This mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with chloroform (2x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:80) to give 32.9 mg of a mixture of **14e** and **36e** (83%, **14e** : **36e** = 1:4.1). For analytical samples, two diastereomers was purified by HPLC (PEGASIL Silica 120-5, 250×20 mm, EtOAc/hexane 1:20, 10 mL/min) **14e**: a colorless oil; IR (film) 2928, 2856, 2228, 1452, 1041, 915 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.03 (ddd, J = 16.9, 10.6, 10.3 Hz, 1H), 5.13–5.07 (m, 2H), 3.58 (s, 3H), 2.87 (ddd, J = 10.0, 3.4, 3.4 Hz, 1H), 2.57–2.51 (m, 1H), 1.93–1.74 (m, 4H), 1.62, (s, 3H), 1.60–1.52 (m, 2H), 1.42–1.21 (m, 10H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0 (CH), 120.1 (C), 117.1 (CH_2), 66.5 (CH), 64.7 (CH_3), 63.8 (C), 41.5 (CH), 33.4 (CH_2), 31.9 (CH_2), 30.1 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 28.3 (CH_2), 26.1 (CH_2), 25.4 (CH_2), 22.8 (CH_2), 14.3 (CH_3); HRMS (ESI), calcd for $C_{17}H_{31}N_2O^+$ $(M+H)^+$ 279.2436, found 279.2428; **36e**: a colorless oil; IR (film) 2928, 2856, 2241, 1457, 1036, 916, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 6.11–5.96 (m, 1H), 5.12–5.04 (m, 2H), 3.64 (s, 3H), 3.10–2.89 (m, 1H), 2.49–2.41 (m, 1H), 2.28–2.16 (m, 1H), 2.05–1.86 (m, 1H), 1.74–1.59 (m, 3H), 1.55 (s, 3H), 1.44–1.35 (m, 1H), 1.35–1.17 (m, 10H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$,

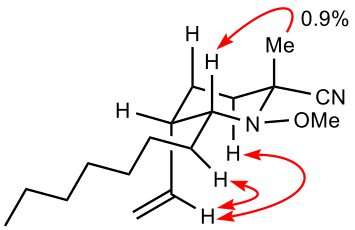
60 °C) δ 138.3 (CH), 123.1 (C), 116.0 (CH_2), 62.5 (CH_3), 62.5 (CH), 58.5 (C), 42.7 (CH), 33.7 (CH_2), 32.0 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 27.5 (CH_2), 27.5 (CH_3), 27.5 (CH_2), 24.3 (CH_2), 22.8 (CH_2), 14.1 (CH_3); HRMS (ESI), calcd for $C_{17}H_{31}N_2O^+$ $(M+H)^+$ 279.2436, found 279.2435

NOESY experiments for **74e**

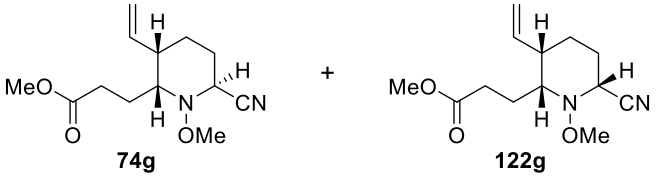


74e (500 MHz, $CDCl_3$)

NOE and NOESY experiments for **122e**



122e (500 MHz, $CDCl_3$, 60 °C)

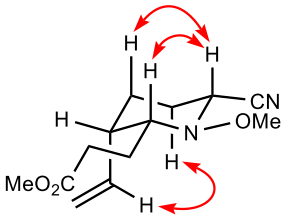


methyl 3-((2*R*,3*S*,6*S*)-6-cyano-1-methoxy-3-vinylpiperidin-2-yl)propanoate (74g)

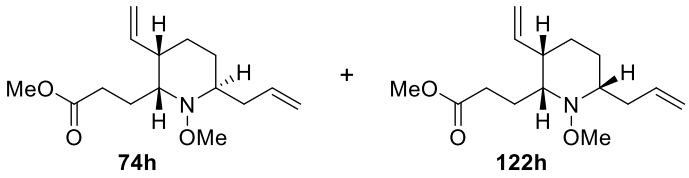
Zirconocene chloride hydride (39.9 mg, 155 μmol) was added to a solution of **71d** (26.1 mg, 108 μmol) and $(CH_2Cl)_2$ (1.1 mL) at room temperature. After stirring for 10 min, cyanotrimethylsilane (16 μL, 128 μmol) and $Sc(OTf)_3$ (5.3 mg, 10.8 μmol) were added to the solution. After stirring for 2.5 h at room temperature, this solution was quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with chloroform (2x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:5) to give 23.4 mg of a mixture of **74g** and **122g** (86%, **74g**:**122g** = 1:4.3). For analytical samples, two diastereomers were separated by HPLC (PEGASIL Silica 120-5, 250×20 mm, *i*-PrOH/hexane 1:120, 10 mL/min, **74g**: T_R = 19.7 min, **122g**: T_R = 21.0 min); **74g**: a colorless oil; IR (film) 2950, 2234, 1737, 1439, 1169, 1037, 921 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.95 (ddd, *J* = 17.8, 9.2, 8.6 Hz, 1H), 5.16 (d, *J* = 9.2 Hz, 1H), 5.11 (d, *J* = 17.8 Hz, 1H), 4.27–4.20 (m, 1H), 3.69 (s, 3H), 3.55 (s, 3H), 3.03–2.95 (m, 1H), 2.60–2.53 (m, 1H), 2.43–2.30 (m, 2H), 2.12–1.97 (m, 2H), 1.97–1.82 (m, 2H), 1.69 (dddd, J = 14.3, 7.2, 7.2, 7.2 Hz, 1H), 1.58 (dddd, J = 14.0, 4.3, 4.3, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9 (C), 136.7 (CH), 117.8 (C), 117.5 (CH_2), 63.7 (CH), 61.1 (CH_3), 54.6 (CH), 51.8 (CH_3), 41.2 (CH), 30.9 (CH_2), 26.9 (CH_2), 24.5 (CH_2), 24.5 (CH_2); HRMS (ESI), $C_{13}H_{20}N_2O_3Na^+$ $(M+Na)^+$ 275.1372, found 275.1366. **122g**: a colorless oil; IR (film) 2951, 2857, 2250, 1738, 1439, 1170, 1038, 922 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 6.07 (ddd, *J* = 17.2, 9.9, 9.6 Hz, 1H), 5.16 (d, *J* = 9.9 Hz, 1H), 5.11 (d, *J* =

17.2 Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.46 (d, J = 10.8 Hz, 1H), 2.55–2.48 (m, 1H), 2.48–2.42 (m, 1H), 2.40 (ddd, J = 15.8, 9.2, 6.6 Hz, 1H), 2.31 (ddd, J = 15.8, 6.9, 6.9 Hz, 1H), 2.24–2.08 (m, 2H), 1.95–1.86 (m, 1H), 1.76–1.67 (m, 2H), 1.56 (dddd, J = 13.5, 13.5, 4.4, 4.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8 (C), 136.1 (CH), 119.4 (C), 118.0 (CH_2), 68.6 (CH), 63.4 (CH_3), 58.4 (CH), 51.8 (CH_3), 42.2 (CH), 30.7 (CH_2), 29.8 (CH_2), 26.6 (CH_2), 25.7 (CH_2); HRMS (ESI), calcd for $C_{13}H_{20}N_2O_3Na^+$ $(M+Na)^+$ 275.1372, found 275.1374

NOESY experiment for **122g**



122g (500 MHz, $CDCl_3$)

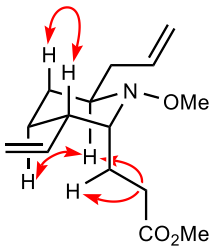


methyl 3-((2*R*,3*S*,6*S*)-6-allyl-1-methoxy-3-vinylpiperidin-2-yl)propanoate (74h)

Zirconocene chloride hydride (37.6 mg, 146 μmol) was added to a solution of **71d** (26.0 mg, 108 μmol) and $(CH_2Cl)_2$ (1.1 mL) at room temperature. After stirring for 10 min, the solution was cooled to –30 °C. Allyltributylstannane (67 μL, 216 μmol) and $Sc(OTf)_3$ (15.9 mg, 32.3 mmol) were then added to the solution. After maintaining at –30 °C for 17 h, the solution was quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with chloroform (3x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:80) to give 17.2 mg of **74h** (60%) and 4.1 mg of **122h** (14%): **74h**: a colorless oil; IR (film) 3077, 2938, 1740, 1437, 1169, 1043, 912 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.86 (dddd, J = 17.5, 10.0, 7.5, 7.5 Hz, 1H), 5.78 (ddd, J = 16.9, 10.3, 6.6 Hz, 1H), 5.08–4.98 (m, 4H), 3.67 (s, 3H), 3.44 (s, 3H), 3.23–3.13 (m, 1H), 2.82–2.64 (m, 2H), 2.50–2.41 (m, 2H), 2.35 (ddd, J = 16.0, 8.0, 8.0 Hz, 1H), 2.12 (ddd, J = 14.3, 7.2, 7.2 Hz, 1H), 1.95–1.65 (m, 2H), 1.65–1.56 (m, 1H), 1.56–1.37 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of two conformers, signals of the major conformer were reported) δ 174.5 (C), 140.9 (CH), 137.2 (CH), 115.9 (CH_2), 114.4 (CH_2), 62.6 (CH), 60.5 (CH_3), 56.4 (CH), 51.6 (CH_3), 37.8 (CH_2), 36.7 (CH), 31.7 (CH_2), 24.6 (CH_2), 24.0 (CH_2), 21.3 (CH_2); HRMS (ESI),

calcd for $C_{15}H_{26}NO_3^+$ $(M+H)^+$ 268.1913, found 268.1905; **122h**: a colorless oil; IR (film) 2947, 1742, 1438, 1171, 1045, 914, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 6.13 (ddd, *J* = 17.3, 9.5, 9.5 Hz, 1H), 5.86 (dddd, *J* = 17.2, 9.7, 6.9, 6.9 Hz, 1H), 5.11–4.99 (m, 4H), 3.67 (s, 3H), 3.56 (s, 3H), 2.64–2.56 (m, 1H), 2.56–2.47 (m, 2H), 2.45–2.27 (m, 3H), 2.21 (ddd, *J* = 14.6, 6.9, 6.6 Hz, 1H), 2.21–2.12 (m, 1H), 1.70 (dddd, *J* = 14.0, 6.6, 6.6, 6.6 Hz, 1H), 1.65–1.50 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3 (CH), 138.0 (CH), 136.1 (CH), 116.7 (CH_2), 116.6 (CH_2), 69.3 (CH), 67.9 (CH), 63.7 (CH_3), 51.7 (CH_3), 43.2 (CH), 38.2 (CH_2), 31.2 (CH_2), 30.9 (CH_2), 26.8 (CH_2), 26.3 (CH_2); HRMS (ESI), $C_{15}H_{26}NO_3^+$ $(M+H)^+$ 268.1913, found 268.1903.

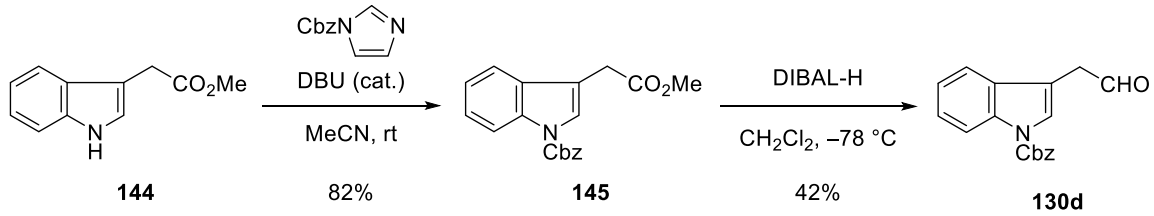
NOESY experiment for **74h**

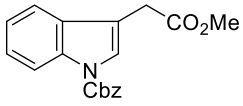


74h (500 MHz, $CDCl_3$)

A-2. Intramolecular Reductive Pictet-Spengler Reaction and Three-component Reaction

Synthesis of indolealdehyde 130d



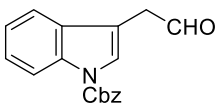


145

benzyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (145)

Benzyl alcohol (620 μL, 6.0 mmol) was added to a solution of 1,1'-Carbonyldiimidazole (1.14 mg, 9.00 mmol) and CH_2Cl_2 (20 mL) at 0 °C. The resulting mixture was gradually allowed to warm to room temperature, and maintained for 18 h at room temperature. The mixture was diluted with H_2O (10 mL), and extracted with CH_2Cl_2 (2x10 mL). The combined organic extracts were washed with H_2O (2x 30 mL), dried over Na_2SO_4, and concentrated to give benzyl 1*H*-imidazole-1-carboxylate[9], which was used in the next reaction without further purification.

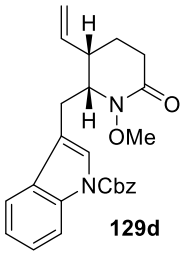
1,8-Diazabicyclo[5.4.0]undec-7-ene (150 μL, 993 μmol) was added to a solution of benzyl 1*H*-imidazole-1-carboxylate (1.00 g, 4.97 mmol), methyl 2-(1H-indol-3-yl)acetate **144** (940 mg, 4.97 mmol) and MeCN (25 mL) at room tempelature. The solution was maintained for 12 h at room temperature, diluted with H_2O (30 mL). The resulting mixture was extracted with AcOEt (2x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9) to give 1.33 g of **145** (82%): white crystals, mp 59.5–60.5 °C; IR (film) 2952, 1733, 1455, 1397, 1358, 1247, 1161, 1082, 745cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (bs, 1H), 7.62 (s, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.50–7.46 (m, 2H), 7.44–7.36 (m, 3H), 7.34 (t, J = 8.0 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 5.44 (s, 2H), 3.72 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5 (C), 150.9 (C), 135.6 (C), 135.2 (C), 130.2 (C), 128.91 (CH), 128.87 (CH), 128.6 (CH), 125.0 (CH), 124.2 (CH), 123.2 (CH), 119.2 (CH), 115.5 (CH), 114.2 (C), 68.8 (CH_2), 52.3 (CH_3), 31.0 (CH_2); HRMS (ESI), $C_{19}H_{17}NO_4Na^+$ $(M+Na)^+$ 346.1055, found 346.1048.



130d

benzyl 3-(2-oxoethyl)-1*H*-indole-1-carboxylate (130d)

A solution of diisobutylaluminium hydride (1.0 M in hexane, 430 μL, 430 μmol) and CH_2Cl_2 (4.0 mL) was added dropwise via cannula to a solution of ester **145** (138 mg, 427 μmol) and CH_2Cl_2 (4.5 mL) at –78 °C. The solution was stirred for 20 min, and quenched with saturated aqueous (+)-potassium sodium tartrate (10 mL). The resulting mixture was vigorously for 1 h, and extracted with chloroform (2x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:15) to give 52.5 mg of **130d** (42%): a pale yellow oil; IR (film) 3119, 3065, 3034, 2958, 2824, 2724, 1726, 1455, 1396, 1356, 1246, 1085, 1027, 746, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, *J* = 2.3 Hz, 1H), 8.20 (bs, 1H), 7.63 (s, 1H), 7.51–7.34 (m, 7H), 7.28 (ddd, *J* = 7.7, 6.9, 0.9 Hz, 1H), 5.46 (s, 2H), 3.76 (d, *J* = 2.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4 (CH), 150.7 (C), 135.6 (C), 135.1 (C), 130.2 (C), 128.9 (CH), 128.9 (CH), 128.6 (CH), 125.3 (CH), 124.5 (CH), 123.3 (CH), 118.9 (CH), 115.5 (CH), 112.1 (C), 68.9 (CH_2), 40.0 (CH_2); HRMS (ESI), calcd for $C_{18}H_{16}NO_3$ $(M+H)^+$ 294.1130, found 294.1130.

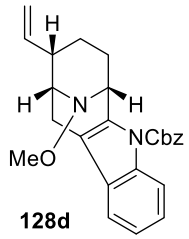


129d

benzyl 3-(((2*S*,3*R*)-1-methoxy-6-oxo-3-vinylpiperidin-2-yl)methyl)-1*H*-indole-1-carboxylate (129d)

Boron trifluoride diethyl ether complex (16 μL, 132 μmol) was added to a solution of 3-indole acetaldehyde **37** (29.0 mg, 98.9 μmol), ***E*-42** (14.2 mg, 65.9 μmol) and CH_2Cl_2 (1.0 mL) at –20 °C. After maintaining at –20 °C for 20 min, boron trifluoride diethyl ether complex (290 μL, 2.3 mmol) was added to the solution every 15 min twelve times. After maintaining at –20 °C for 20 min, the solution was quenched with H_2O (5 mL), and extracted with chloroform (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:2 to 1:11) to give 18.9 mg of **129d** (68%): a colorless oil; IR (film) 2928, 1736, 1671, 1455, 1399, 1249, 1090, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (bs, 1H), 7.56 (ddd, *J* = 7.7, 1.2, 0.9 Hz, 1H), 7.51–7.46 (m, 2H), 7.46–7.36 (m, 4H), 7.33 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.28–7.24 (m, 1H), 5.95 (ddd, *J* = 17.2, 10.6, 7.5 Hz, 1H), 5.45 (s, 2H), 5.24 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H), 5.16 (ddd, *J* = 17.2, 1.2, 1.2 Hz, 1H), 4.11 (ddd, *J* = 8.0, 4.0, 4.0 Hz, 1H), 3.80 (s, 3H), 3.20 (dd, *J* = 14.6, 4.0 Hz, 1H), 2.98 (dd, *J* = 14.6, 8.0 Hz, 1H), 2.77–2.70 (m, 1H), 2.53 (ddd, *J* = 17.5, 6.6, 6.6 Hz, 1H), 2.44 (ddd, *J* = 17.5, 7.2, 7.2 Hz, 1H), 1.81–1.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9 (C), 150.8 (C), 136.1 (CH), 135.6 (C), 135.3 (C), 130.4 (C), 128.9 (CH), 128.8 (CH), 128.5 (CH),

124.9 (CH), 124.2 (CH), 123.0 (CH), 119.3 (CH), 118.2 (CH_2), 117.8 (C), 115.4 (CH), 68.7 (CH_2), 62.3 (CH), 62.0 (CH_3), 42.0 (CH), 30.8 (CH_2), 25.0 (CH_2), 23.9 (CH_2); HRMS (ESI), calcd for $C_{25}H_{27}N_2O_4^+$ $(M+H)^+$ 419.1971, found 419.1971.

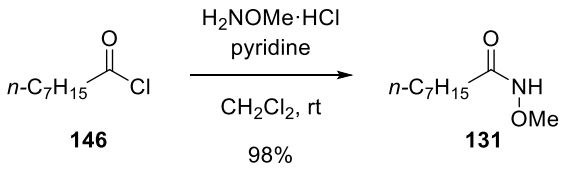


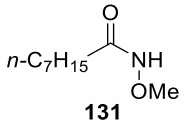
128d

benzyl (6*R*,9*S*,10*R*)-12-methoxy-9-vinyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[b]-indole-5-carboxylate (128d)

Zirconocene chloride hydride (23.4 mg, 90.7 μmol) was added to a solution of **129d** (33.4 mg, 79.8 μmol) and CH_2Cl_2 (800 μL) at room temperature. After stirring for 10 min, $Sc(OTf)_3$ (3.9 mg, 8.0 μmol) were added to the solution, and stirred for 1 h at room temperature. This solution was quenched with H_2O (5 mL), and extracted with chloroform (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:30) to give 15.7 mg of **128d** (49%): a colorless oil; IR (film) 2929, 1730, 1455, 1392, 1328, 1215, 1147, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.7 Hz, 1H), 7.51–7.47 (m, 2H), 7.45–7.35 (m, 4H), 7.26–7.20 (m, 2H), 5.82 (ddd, *J* = 16.3, 10.6, 5.4 Hz, 1H), 5.47 (d, *J* = 12.0, 1H), 5.43 (d, *J* = 12.0, 1H), 5.11 (ddd, *J* = 10.6, 1.7, 1.7 Hz, 1H), 5.05–5.01 (m, 1H), 5.02 (ddd, *J* = 16.3, 1.7, 1.7 Hz, 1H), 3.74 (dd, *J* = 6.9, 4.0 Hz, 1H), 3.53 (s, 3H), 2.94 (dd, *J* = 17.2, 6.9 Hz, 1H), 2.72–2.64 (m, 1H), 2.50 (d, *J* = 17.2 Hz, 1H), 1.99–1.94 (m, 2H), 1.38 (dddd, *J* = 13.2, 3.4, 3.4, 3.4 Hz, 1H), 1.09 (dddd, *J* = 13.2, 13.2, 10.3, 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6 (C), 140.2 (CH), 135.8 (C), 135.1 (C), 133.3 (C), 129.3 (C), 128.93 (CH), 128.89 (CH), 128.83 (CH), 124.1 (CH), 123.0 (CH), 118.2 (CH), 116.8 (C), 115.9 (CH), 115.5 (CH_2), 68.8 (CH_2), 59.7 (CH_3), 56.8 (CH), 55.6 (CH), 44.7 (CH), 29.0 (CH_2), 20.0 (CH_2), 17.7 (CH_2); HRMS (ESI), calcd for $C_{25}H_{27}N_2O_3^+$ $(M+H)^+$ 403.2022, found 403.2022.

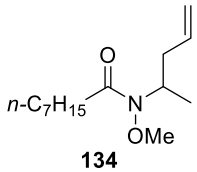
Synthesis of *N*-methoxyoctanamide 131





***N*-methoxyoctanamide (131)**

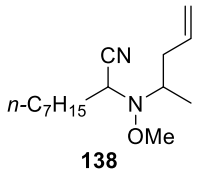
Octanoyl chloride **146** (2.4 mL, 14 mmol) was added to a solution of *O*-methylhydroxylamine hydrochloride (1.00 g, 12.0 mmol), pyridine (2.9 mL, 36 mmol) and CH_2Cl_2 (60 mL) at room temperature. The solution was maintained for 1 h at room temperature, poured into 0.5 M HCl (50 mL). The resulting mixture was extracted with chloroform (2x 40 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4 to 2:1) to give 2.03 g of **131** (98%): a colorless oil; IR (film) 3182, 2958, 2930, 2858, 1661, 1521, 1068 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.76 (s, 3H), 2.40 (bs, 1H), 2.07 (bs, 2H), 1.64 (tt, J = 7.5, 7.5 Hz, 2H), 1.37–1.20 (m, 8H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4 (C), 64.0 (CH_3), 33.2 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 25.6 (CH_2), 22.6 (CH_2), 14.1 (CH_3); LRMS (EI) *m/z* 173 (M^+, 3.5%), 128 (14), 127 (89), 109 (13), 102 (14), 89 (65), 84 (5), 83 (7), 78 (12), 10.3 (10), 59 (29), 58 (100), 56 (22); HRMS (EI), calcd for $C_9H_{19}NO_2$ M^+ 173.1416, found 173.1416.



***N*-methoxy-*N*-(pent-4-en-2-yl)octanamide (134)**

(±)-10-Camphorsulfonic acid (2.7 mg, 12 μmol) was added to a solution of *N*-methoxyoctanamide **131** (200 mg, 1.15 mmol), ethylvinylether **136** (130 mL, 1.35 mmol) and CH_2Cl_2 (2.3 mL) at 0 °C. After stirring for 3 h, allyltributylstannane (900 μL, 2.90 mmol) and boron trifluoride diethyl ether complex (280 μL, 2.3 mmol) were added to the solution at 0 °C. The mixture was stirred for 1 h at 0 °C, and allowed to warm to room temperature. After maintaining for 30 min at room temperature, the solution was quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with chloroform (2x 5 mL). The combined organic extracts were washed with brine (10 mL) dried over Na_2SO_4, and concentrated. The

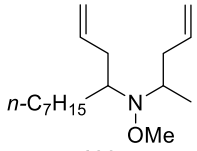
residue was purified by silica gel column chromatography (EtOAc/hexane 1:60 to 1:40) to give 229 mg of *N*-methoxyamide **134** (82%): a colorless oil; IR (film) 2930, 2857, 1672, 1456, 1385, 1157, 1027, 916 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.74 (dddd, *J* = 17.2, 10.3, 6.9, 6.9 Hz, 1H), 5.07 (ddd, *J* = 17.2, 1.4, 1.4 Hz, 1H), 5.02 (ddd, *J* = 10.3, 1.4, 1.4 Hz, 1H), 4.52 (bs, 1H), 3.75 (s, 3H), 2.48–2.31 (m, 3H), 2.24 (ddddd, *J* = 14.0, 6.9, 6.9, 1.4, 1.4 Hz, 1H), 1.62 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.35–1.25 (m, 8H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6 (C), 135.3 (CH), 117.2 (CH_2), 64.8 (CH_3), 53.4 (CH), 38.5 (CH_2), 32.8 (CH_2), 31.8 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 24.7 (CH_2), 22.7 (CH_2), 18.0 (CH_3), 14.2 (CH_3); HRMS (ESI), calcd for $C_{14}H_{28}NO_2^+$ $(M+H)^+$ 242.2120, found 242.2112.



138

2-(methoxy(pent-4-en-2-yl)amino)nonanenitrile (138)

Zirconocene chloride hydride (54.0 mg, 209 μmol) was added to a solution of **134** (36.0 mg, 150 μmol) and $(CH_2Cl)_2$ (1.5 mL) at room temperature. After stirring for 10 min, cyanotrimethylsilane (22 μL, 180 μmol) and $Sc(OTf)_3$ (7.4 mg, 15.0 μmol) were added to the solution. After stirring for 2.5 h at room temperature. This solution was quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with chloroform (2x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:80) to give 27.0 mg of **138** (72%, dr = 1.1:1): a colorless oil; IR (film) 2928, 2858, 2234, 1466, 1042, 914 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 5.85–5.74 (m, 1H), 5.13–5.03 (m, 2H), 3.78 (dd, *J* = 13.5, 6.3 Hz, 1/2H), 3.76 (dd, *J* = 13.5, 6.3 Hz, 1/2H), 3.62 (s, 3/2H), 3.62 (s, 3/2H), 3.11–3.02 (m, 1H), 2.56–2.49 (m, 1/2H), 2.37–2.49 (m, 1/2H), 2.19 (ddddd, *J* = 14.0, 6.3, 6.3, 1.2, 1.2 Hz, 1/2H), 2.13 (ddddd, *J* = 14.6, 7.4, 7.2, 1.2, 1.2 Hz, 1/2H), 1.96–1.80 (m, 2H), 1.59–1.44 (m, 2H), 1.39–1.23 (m, 8H), 1.20 (d, *J* = 6.3 Hz, 3/2H), 1.03 (d, *J* = 6.3 Hz, 3/2H), 0.89 (*t*, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 135.3 (CH), 134.7 (CH), 118.3 (C), 117.9 (C), 117.47 (CH_2), 117.44 (CH_2), 64.24 (CH_3), 64.17 (CH_3), 60.4 (CH), 60.4 (CH), 56.2 (CH), 56.1 (CH), 38.5 (CH_2), 38.4 (CH_2), 31.8 (CH_2), 31.8 (CH_2), 31.6 (CH_2), 31.5 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 22.7 (CH_2), 22.7 (CH_2), 16.7 (CH_3), 16.4 (CH_3), 14.2 (CH_3), 14.2 (CH_3); HRMS (ESI), calcd for $C_{15}H_{29}N_2O^+$ $(M+H)^+$ 253.2280, found 253.2269.



139

***O*-methyl-*N*-(pent-4-en-2-yl)-*N*-(undec-1-en-4-yl)hydroxylamine (45b)**

Zirconocene chloride hydride (44.4 mg, 172 μmol) was added to a solution of **134** (26.0 mg, 108 μmol) and $(CH_2Cl)_2$ (1.4 mL) at room temperature. After stirring for 10 min, allyltributylstannane (100 μL, 323 μmol) and $Sc(OTf)_3$ (63.6 mg, 129 μmol) were added to the solution. After stirring for 20 min at room temperature. This solution was quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with chloroform (2x 5 mL). The combined organic extracts were washed with brine (10 mL) dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:80 to 1:60) to give 16.9 mg of **139** (59%, dr = 1:1): a colorless oil; IR (film) 2927, 2855, 1458, 1375, 1043, 911, 772 cm^{-1}; ^1H NMR (500 MHz, CD_3OD, 1:1 mixture of diastereomers) δ 5.93–5.79 (m, 2H), 5.10–4.06 (m, 4H), 3.543 (s, 3/2H), 3.538 (s, 3/2H), 3.08–2.98 (m, 1H), 2.87–2.79 (m, 1H), 2.48–2.33 (m, 2H), 2.24–2.06 (m, 2H), 1.60–1.24 (m, 12H), 1.08–1.03 (m, 3/2H), 1.03–0.99 (m, 3/2H), 0.95–0.88 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ137.3 (CH), 137.1 (CH), 136.7 (CH), 136.6 (CH), 116.4 (CH_2), 116.4 (CH_2), 116.1 (CH_2), 116.0 (CH_2), 64.1 (CH_3), 64.1 (CH_3), 62.0 (CH), 61.8 (CH), 57.5 (CH), 57.5 (CH), 39.0 (CH_2), 38.8 (CH_2), 34.7 (CH_2), 33.8 (CH_2), 32.0 (CH_2), 32.0 (CH_2), 30.7 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 22.8 (CH_2), 22.8 (CH_2), 14.3 (CH_3), 14.3 (CH_3), 14.3 (CH_3), 14.3 (CH_3); HRMS (ESI), calcd for $C_{17}H_{34}NO^+$ $(M+H)^+$ 268.2640, found 268.2627.

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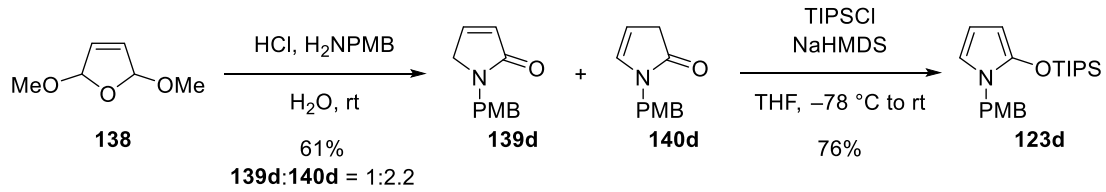
Unified Total Synthesis of Stemoamide-type Alkaloids

A-2. Gram-scale Total Synthesis of Stemoamide (1)

Synthesis of 2-Siloxypyrrole 123d

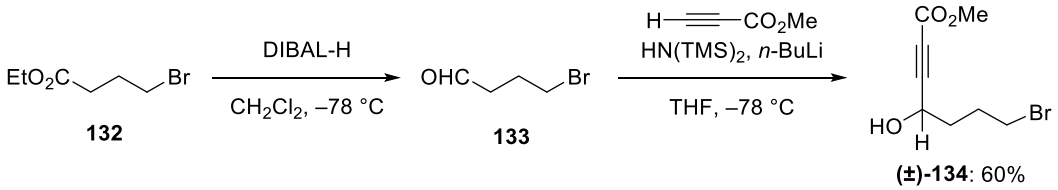


1-(4-Methoxybenzyl)-2-((triisopropylsilyl)oxy)-1*H*-pyrrole (123d)[1]

4-Methoxybenzylamine (6.5 mL, 50 mmol, 1.0 equiv) was added dropwise over 1 h to a mixture of 2,5-dihydro-2,5-dimethoxyfuran **30** (6.0 mL, 49 mmol, 1.0 equiv) and aqueous 0.04 M HCl (260 mL, 10 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred for 10 min, and extracted with EtOAc (3 x 300 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 2:1) to give 6.10 g of *α,β*-unsaturated lactam **139d** and enamide **140d** (61%, **139d**:**140d** = 1:2.2). For analytical samples, two diastereomers were separated by silica gel column chromatography (EtOAc/hexane 1:5 to 2:1); α,β-unsaturated lactam **139d**: a yellow solid; mp 48–49 °C; IR (film) 2837, 1673, 1513, 1455, 1245, 1177, 1032, 801 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20–7.15 (m, 2H), 7.03 (dt, *J* = 6.0, 1.7 Hz, 1H), 6.88–6.84 (m, 2H), 6.21 (dt, *J* = 6.0, 2.0 Hz, 1H), 4.57 (s, 2H), 3.85 (dd, *J* = 2.0, 1.7 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3 (C), 159.1 (C), 142.9 (CH), 129.5 (C), 129.4 (CH), 128.1 (CH), 114.2 (CH), 55.3 (CH_3), 52.2 (CH_2), 45.4 (CH_2); HRMS (ESI), calcd for $C_{12}H_{14}NO_2^+$ $(M+H)^+$ 204.1025, found 204.1021. enamide **140d**: a yellow solid; mp 45–46 °C; IR (film) 2934, 2836, 1692, 1514, 1356, 1247, 1176, 1032, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20–7.16 (m, 2H), 6.89–6.84 (m, 2H), 6.30 (dt, *J* = 4.9, 2.0 Hz, 1H), 5.26 (dt, *J* = 4.9, 2.3 Hz, 1H), 4.56 (s, 2H), 3.79 (s, 3H), 3.11 (dd, *J* = 2.3, 2.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0 (C), 159.3 (C), 132.7 (CH), 129.3 (CH), 128.9 (C), 114.3 (CH), 104.6 (CH), 55.4 (CH_3), 45.2 (CH_2), 37.6 (CH_2); HRMS (ESI), calcd for $C_{12}H_{14}NO_2^+$ $(M+H)^+$ 204.1025, found 204.1025.

Sodium bis(trimethylsilyl)amide (1.9 M in THF, 17 mL, 32 mmol, 1.1 equiv) was added to a solution of *α,β*-unsaturated lactam **139d** and enamide **140d** (**139d**:**140d** = 1:2.2, 6.10 g, 30.0 mmol, 1.0 equiv) and THF (60 mL) at –78 °C. After maintaining for 10 min at –78 °C, triisopropylsilyl chloride (6.4 mL, 30 mmol, 1.0 equiv) was added to the solution at –78 °C. The solution was allowed to warm to room temperature, and stirred for 12 h, and diluted with hexane (100 mL). The resulting mixture was filtered through a pad of Celite®, and concentrated. The residue was filtered through a pad of basic alumina, and washed with hexane. The filtrate was concentrated to give 8.15 g of 2-siloxypyrrole **123d** (76%): a pale yellow oil; IR (film) 2945, 2867, 1557, 1513, 1462, 1248, 1030, 913, 854, 684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.09–7.04 (m, 2H), 6.85–6.80 (m, 2H), 6.13 (dd, *J* = 3.2, 2.1 Hz, 1H), 5.90 (dd, *J* = 3.4, 3.2 Hz,

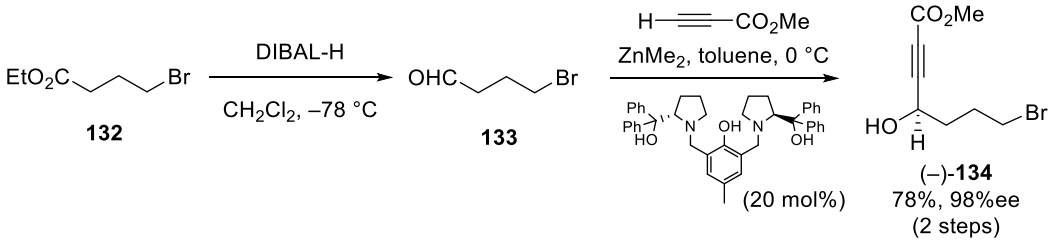
1H), 5.23 (dd, J = 3.4, 2.1 Hz, 1H), 4.88 (s, 2H), 3.78 (s, 3H), 1.26 (sep, J = 7.3 Hz, 3H), 1.07 (d, J = 7.3 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9 (C), 142.4 (C), 130.9 (C), 128.4 (CH), 114.0 (CH), 111.8 (CH), 105.1 (CH), 87.3 (CH), 55.4 (CH_3), 47.5 (CH_2), 18.0 (CH_3), 12.5 (CH); HRMS (ESI), calcd for $C_{21}H_{34}NO_2Si^+$ $(M+H)^+$ 360.2359, found 360.2344.



Methyl-7-bromo-4-hydroxyhept-2-ynoate ((±)-134)

Diisobutylaluminium hydride (1.0 M in Hexane, 23 mL, 23 mmol, 1.1 equiv) was added to a solution of ethyl 4-bromobutyrate **122** (3.0 mL, 21 mmol, 1.0 equiv) and CH_2Cl_2 (100 mL) at –78 °C. After stirring at –78 °C for 1 h, the solution was quenched with saturated aqueous (+)-potassium sodium tartrate (50 mL) at –78 °C, allowed to warm to room temperature, stirred vigorously for 1 h, and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, and concentrated to give 4-bromobutanal **133**, which was immediately used in the next reaction without further purification.

n-Butyllithium (1.55 M in hexane, 15 mL, 23 mmol, 1.1 equiv) was added to a solution of hexamethyldisilazane (5.0 mL, 23 mmol, 1.1 equiv) at –78 °C. After stirring at –78 °C for 10 min, methyl propiolate (2.6 mL, 31 mmol, 1.5 equiv) was added to the solution of $LiN(TMS)_2$ at –78 °C. After stirring at –78 °C for 1 h, a solution of the above aldehyde **133** and THF (16 mL) was added to a solution of the lithium acetylide via cannula at –78 °C. The resulting solution was stirred for 30 min at –78 °C, and quenched with aqueous saturated NH_4Cl (40 mL). The mixture was allowed to warm to room temperature, filtered, and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:5) to give 2.94 g of (±)-γ-hydroxypropiolate **134** (60%). The spectral data of **134** was identical to chiral γ-hydroxypropiolate **134**.



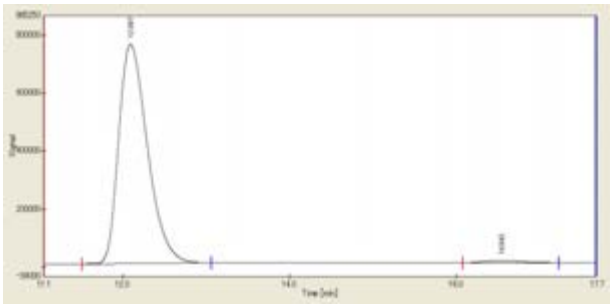
Methyl (*R*)-7-bromo-4-hydroxyhept-2-ynoate (134)

Diisobutylaluminium hydride (1.0 M solution in hexane, 31 mL, 31 mmol, 1.1 equiv) was added to a solution of ethyl 4-bromobutyrate **132** (4.0 mL, 28 mmol, 1.0 equiv) and CH_2Cl_2 (140 mL) at –78 °C. After stirring at –78 °C for 1 h, the solution was quenched with saturated aqueous (+)-potassium sodium tartrate (70 mL) at –78 °C, allowed to warm to room temperature, stirred vigorously for 1 h, and extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracts were washed with brine (400 mL), dried over Na_2SO_4, and concentrated to give 4-bromobutanal **133**, which was immediately used in the next reaction without further purification.

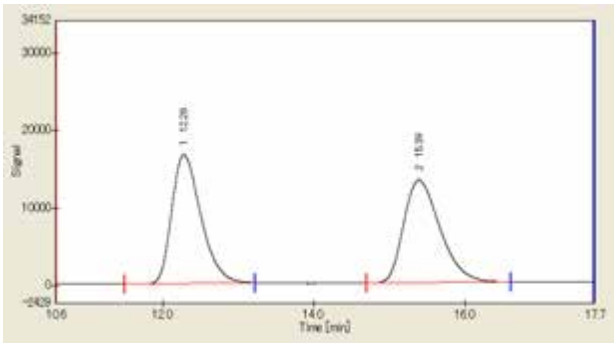
Dimethylzinc (1.2 M solution in toluene, 70 mL, 84 mmol, 3.0 equiv) was added dropwise to a solution of (*S*,*S*)-ProPhenol (3.53 g, 5.56 mmol, 20 mol%) and methyl propiolate (6.9 mL, 83 mmol, 3.0 equiv) and toluene (90 mL) at 0 °C. The solution was warmed to room temperature and stirred for 30 min. A solution of 4-bromobutanal **133** and toluene (90 mL) was added over 24 h at 0 °C using a syringe pump to the solution of the catalyst. The solution was stirred for an additional 3 h at 0 °C, and quenched with aqueous saturated NH_4Cl (120 mL). The mixture was filtered, and extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with brine (500 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:5) to give 5.13 g of γ-hydroxypropiolate **134** (78%, 98% ee determined by HPLC (CHIRALPAK OD-H, 250×4.6 mm, UV 210 nm, *i*PrOH/hexane 1:11 (v/v), 1.0 mL/min, **134**: T_R= 12.1 min, ***ent*-134**: T_R= 16.5 min)): a pale yellow oil; $[\alpha]_D^{22}$ = +0.76 (*c* 1.0, $CHCl_3$); IR (film) 3409, 2956, 2239, 1715, 1436, 1255, 1058, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.57 (dd, *J* = 6.6, 6.6 Hz, 1H), 3.70 (s, 3H), 3.46 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.11–2.03 (m, 2H), 1.98 (bs, 1H), 1.97–1.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8 (C), 87.5 (C), 76.7 (C), 61.4 (CH), 53.1 (CH_3), 35.3 (CH_2), 33.1 (CH_2), 28.2 (CH_2); HRMS (ESI), calcd for $C_8H_{12}O_3Br^+$ $(M+H)^+$ 234.9970, found 234.9967.

Chiral HPLC chart of 134 (98% ee)

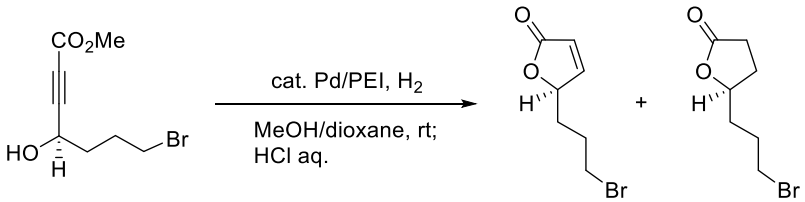
CHIRALPAK OD-H, 250×4.6 mm, UV 210 nm, *i*PrOH/hexane 1:11 (v/v), 1.0 mL/min



No.	T_R	Area	Height	Area (%)
1	12.10	18055812	755803	98.8339
2	16.54	213034	7256	1.1661



No.	T_R	Area	Height	Area (%)
1	12.28	444358	16586	49.9345
2	15.39	445524	13284	50.0655



(–)-**134** (98% ee) **122**: 72% **136**: 3%

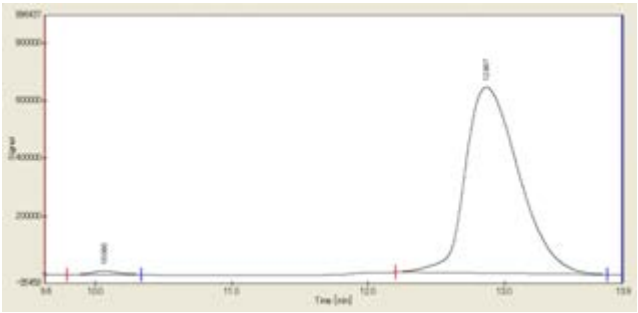
(*R*)-5-(3-Bromopropyl)furan-2(5*H*)-one (122)

A suspension of palladium on polyethyleneimine (4.3 wt% on polyethyleneimine, 101 mg) and MeOH (36 mL) was added to a solution of γ-hydroxypropiolate **134** (5.06 g, 21.5 mmol) and 1,4-dioxane (36 mL) at room temperature using Pasteur pipette. The flask was purged with hydrogen. After stirring under hydrogen atmosphere (1 atm) at room temperature for 14 h, 1 M aqueous HCl (70 mL) was added to the mixture. The resulting mixture was stirred for 2 h at room temperature, extracted with EtOAc (3 x 70 mL), dried over Na_2SO_4, and concentrated. The residue was diluted with aqueous saturated $NaHCO_3$ and extracted with EtOAc (3 x 70 mL), dried over Na_2SO_4, and concentrated. The residue was filtered through a pad of silica gel (EtOAc/Hexane 1:3), and then purified by MPLC (Yamazen Ultra Pack Column B, 26×300 mm, EtOAc/hexane 24:76 to 45:55, 20 mL/min, T_R = 28 min) to give 3.32 g of an inseparable mixture of butenolide **122** (3.18 g, 72%) and lactone **136** (0.14 g, 3%). Butenolide **122**: 98% ee determined by HPLC (CHIRALPAK AS-H, 250×4.6 mm, UV 210 nm, EtOH/hexane 1:3 (v/v), 1.0 mL/min, ***ent*-122**:

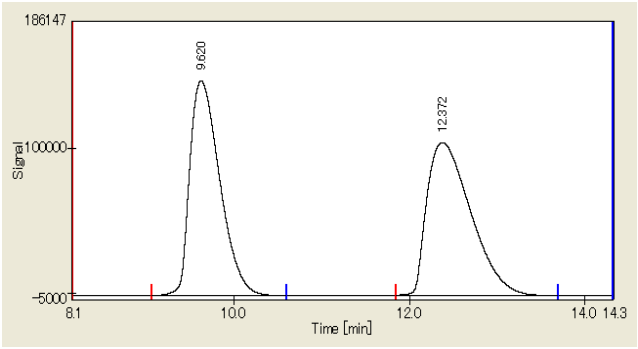
T_R= 10.1 min, **122**: T_R= 12.9 min); a pale yellow oil; $[\alpha]_D^{23}$ = –77.7 (*c* 1.0, $CHCl_3$); IR (film) 3087, 2923, 2850, 1749, 1163, 814 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 5.7, 1.4 Hz, 1H), 6.14 (dd, *J* = 5.7, 2.0 Hz, 1H), 5.08 (dddd, *J* = 8.3, 3.7, 2.0, 1.4 Hz, 1H), 3.51–3.41 (m, 2H), 2.11–1.96 (m, 3H), 1.80–1.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9 (C), 155.9 (CH), 122.1 (CH), 82.4 (CH), 32.9 (CH_2), 31.8 (CH_2), 28.1 (CH_2); HRMS (ESI), calcd for $C_7H_{10}O_2Br^+$ $(M+H)^+$ 204.9864, found 204.9865.

Chiral HPLC chart of 122 (98% ee)

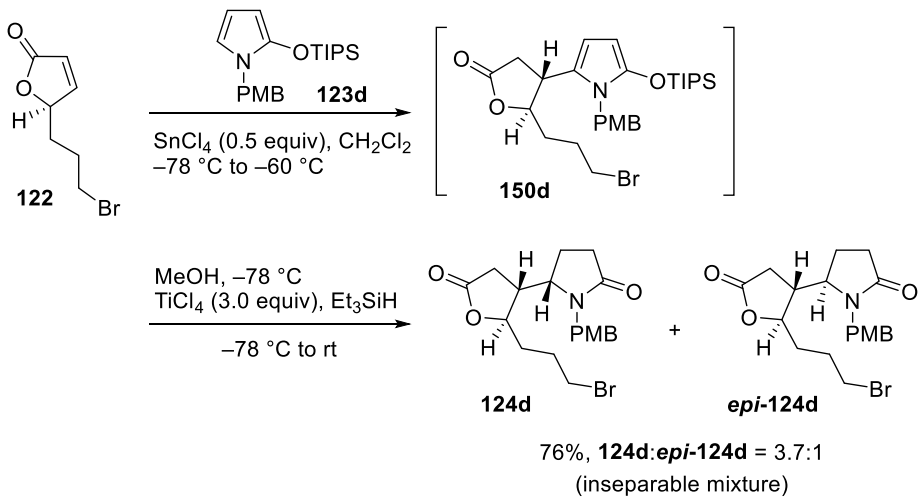
CHIRALPAK AS-H, 250×4.6 mm, UV 210 nm, EtOH/hexane 1:3 (v/v), 1.0 mL/min



No.	T_R	Area	Height	Area (%)
1	10.06	173635	12095	0.9764
2	12.87	17608930	644765	99.0236



No.	T_R	Area	Height	Area (%)
1	9.62	3509745	147434	49.0203
2	12.37	3650031	104912	50.9797



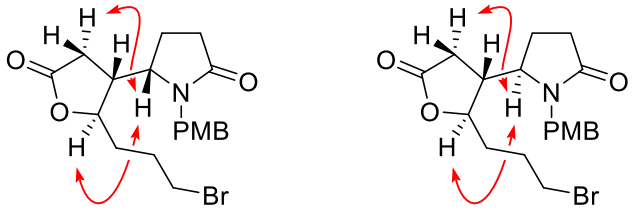
(*S*)-5-((2*R*,3*R*)-2-(3-Bromopropyl)-5-oxotetrahydrofuran-3-yl)-1-(4-methoxybenzyl)-pyrrolidin-2-one (124) and

(*R*)-5-((2*R*,3*R*)-2-(3-bromopropyl)-5-oxotetrahydrofuran-3-yl)-1-(4-methoxybenzyl)-pyrrolidin-2-one (*epi*-124)

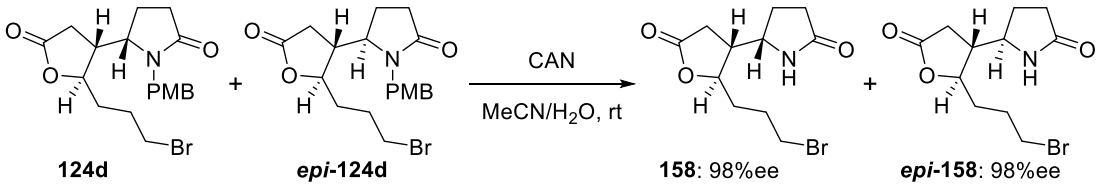
Tin (IV) tetrachloride (890 μL, 7.6 mmol, 0.5 equiv) was added to a solution of a 3.11 g mixture of butenolide **122** and lactone **136** (**122**: 2.98 g, 14.5 mmol, 1.0 equiv, **136**: 0.13 g, 0.63 mmol), 2-siloxypyrrole **123d** (6.54 g, 18.2 mmol, 1.2 equiv) and CH_2Cl_2 (380 mL) at –78 °C. The solution was allowed to warm to –60 °C, and stirred for 12 h at –60 °C. The resulting deep green solution was re-cooled to –78 °C. Methanol (1.5 mL, 37 mmol, 2.5 equiv) was added to the solution at –78 °C. Then, triethylsilane (36 mL, 220 mmol, 14 equiv) and titanium (IV) tetrachloride (5.0 mL, 46 mmol, 3.0 equiv) were added dropwise to the solution at –78 °C. The resulting white suspension was allowed to warm to room temperature, and stirred vigorously for 35 h at room temperature. The mixture was quenched with saturated aqueous $NaHCO_3$ (200 mL), and vigorously stirred for 1 h at room temperature. The resulting mixture was filtered through Celite®, washed with $CHCl_3$, and concentrated carefully. The resulting mixture was extracted with $CHCl_3$ (5 x 200 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, and concentrated. The residue was filtered through a pad of silica gel (EtOAc), and then purified by MPLC (Yamazen Ultra Pack Column D, 26×300 mm, EtOAc/hexane 46:54 to 67:33, 45 mL/min, T_R = 63 min) to give 4.52 g of a mixture of lactams **124** and ***epi*-124** (76%, **124**:***epi*-124** = 3.7:1). For analytical samples, two diastereomers were separated by HPLC (PEGASIL Silica 120-5, 250×20 mm, EtOAc/MeCN 4:1, 10 mL/min, **124**: T_R = 12.3 min, ***epi*-124**: T_R = 16.0 min); lactam **124**: a colorless oil; $[\alpha]_D^{21}$ = –6.3 (*c* 1.0, $CHCl_3$); IR (film) 2935, 2838, 1773, 1684, 1513, 1418, 1247, 1177, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.17–7.13 (m, 2H), 6.88–6.84 (m, 2H), 4.71 (d, *J* = 15.2 Hz, 1H), 4.22 (ddd, *J* = 10.0, 3.2, 3.2 Hz, 1H), 4.12 (d, *J* = 15.2 Hz, 1H), 3.79 (s, 3H), 3.60 (ddd, *J* = 8.0, 6.3, 3.7 Hz, 1H), 3.36 (ddd, *J* = 10.0, 6.6, 6.0 Hz, 1H), 3.32 (ddd, *J* = 10.0, 7.7, 5.7 Hz, 1H), 2.71 (dd, *J* = 18.0, 10.0 Hz, 1H), 2.56 (dddd, *J* = 10.0, 4.0, 3.7, 3.2 Hz, 1H), 2.53 (ddd, *J* = 17.5, 10.0, 5.7 Hz, 1H), 2.45 (ddd,

J = 17.5, 10.0, 7.2 Hz, 1H), 2.19 (dd, J = 18.0, 4.0 Hz, 1H), 2.09 (dddd, J = 13.2, 10.0, 8.0, 5.7 Hz, 1H), 2.04–1.94 (m, 1H), 1.85–1.76 (m, 1H), 1.72 (dddd, J = 13.2, 10.0, 7.2, 6.3 Hz, 1H), 1.52 (dddd, J = 14.0, 10.3, 10.0, 4.6 Hz, 1H), 1.19 (dddd, J = 14.0, 10.6, 5.4, 3.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9 (C), 175.4 (C), 159.5 (C), 129.3 (CH), 128.4 (C), 114.5 (CH), 79.4 (CH), 59.3 (CH), 55.4 (CH_3), 45.0 (CH_2), 40.9 (CH), 34.4 (CH_2), 32.9 (CH_2), 30.9 (CH_2), 30.1 (CH_2), 28.7 (CH_2), 19.6 (CH_2); HRMS (ESI), calcd for $C_{19}H_{25}NO_4Br^+$ $(M+H)^+$ 410.0967, found 410.0963. lactam ***epi*-124**: a colorless oil; $[\alpha]_D^{22}$ = +5.5 (*c* 1.0, $CHCl_3$); IR (film) 2932, 2837, 1176, 1681, 1513, 1246, 1177, 1031 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18–7.13 (m, 2H), 6.89–6.85 (m, 2H), 4.78 (d, J = 14.9 Hz, 1H), 4.11 (ddd, J = 8.6, 5.7, 4.0 Hz, 1H), 4.01 (d, J = 14.9 Hz, 1H), 3.80 (s, 3H), 3.62 (ddd, J = 8.3, 6.3, 4.0 Hz, 1H), 3.41 (ddd, J = 10.3, 7.2, 5.4 Hz, 1H), 3.40 (ddd, J = 10.3, 7.2, 5.4 Hz, 1H), 2.62 (dddd, J = 9.5, 7.2, 5.7, 4.0 Hz, 1H), 2.52 (ddd, J = 17.5, 10.0, 6.0 Hz, 1H), 2.46 (ddd, J = 17.5, 9.7, 7.2 Hz, 1H), 2.30 (dd, J = 18.6, 9.2 Hz, 1H), 2.24 (dd, J = 18.6, 7.5 Hz, 1H), 2.07 (dddd, J = 13.8, 9.7, 8.3, 6.0 Hz, 1H), 2.04–1.95 (m, 1H), 1.89–1.79 (m, 1H), 1.79–1.64 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2 (C), 175.1 (C), 159.5 (C), 129.5 (CH), 128.1 (C), 114.5 (CH), 80.5 (CH), 57.3 (CH), 55.4 (CH_3), 44.6 (CH_2), 41.6 (CH), 34.2 (CH_2), 33.0 (CH_2), 30.1 (CH_2), 28.6 (CH_2), 28.3 (CH_2), 18.9 (CH_2); HRMS (ESI), calcd for $C_{19}H_{25}NO_4Br^+$ $(M+H)^+$ 410.0967, found 410.0969.

NOESY experiment for **124** and ***epi*-124**



124 and ***epi*-124** (500 MHz, $CDCl_3$)



124d **epi-124d** **158**: 98%ee ***epi*-158**: 98%ee

124:***epi*-124** = 3.7:1 94%, **158**:***epi*-158** = 3.7:1 (inseparable)

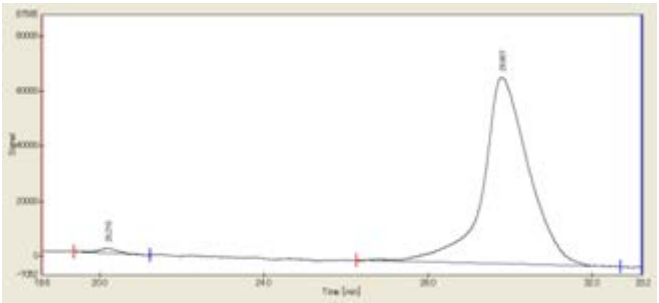
(*S*)-5-((2*R*,3*R*)-2-(3-Bromopropyl)-5-oxotetrahydrofuran-3-yl)pyrrolidin-2-one (158) and (*R*)-5-((2*R*,3*R*)-2-(3-bromopropyl)-5-oxotetrahydrofuran-3-yl)pyrrolidin-2-one (*epi*-158)

Cerium ammonium nitrate (18.0 g, 32.8 mmol, 3.0 equiv) was added to a solution of lactam **124** and ***epi*-124** (4.48 g, **124**:***epi*-124** = 3.7:1, 10.9 mmol, 1.0 equiv), MeCN (550 mL) and H_2O (55 mL) at room temperature. After stirring at room temperature for 24 h, the solution was concentrated at 0 °C to 1/5 volume. Then, solid $NaHCO_3$ (ca. 20 g) was added to the solution. The resulting mixture was filtered, and

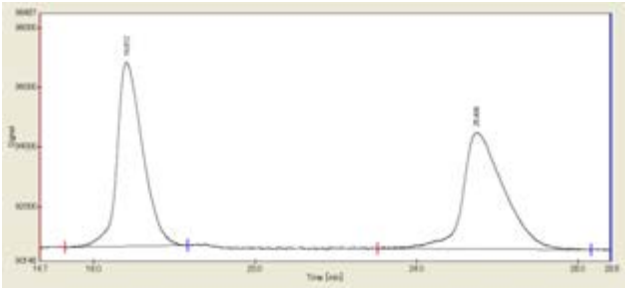
extracted with $CHCl_3$ (5 x 100 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH 1:0 to 19:1) to give 2.97 g of secondary lactams **158** and ***epi*-158** (94%, **158**: ***epi*-158** = 3.7:1). For analytical samples, two diastereomers were separated by HPLC (PEGASIL Silica 120-5, 250×10 mm, Et_2O/MeCN 2:3, 10 mL/min, **158**: T_R = 34.0 min, ***epi*-158**: T_R = 37.5 min). The ee of secondary lactam **158** was determined as 98% ee by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV 210 nm, EtOH/hexane 1:1 (v/v), 1.0 mL/min, ***ent*-158**: T_R= 20.2 min, **158**: T_R= 29.8 min). The ee of secondary lactam ***epi*-158** was determined as 98% ee by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV 210 nm, EtOH/hexane 1:1 (v/v), 1.0 mL/min, ***epi*-158**: T_R= 11.3 min, ***ent-epi*-158**: T_R= 15.9 min): lactam **158**: a white solid; $[\alpha]_D^{22}$ = 33.1 (*c* 1.0, $CHCl_3$); mp 109–110 °C; IR (film) 3216, 2932, 1771, 1693, 1438, 1423, 1268, 1201, 1181 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (bs, 1H), 4.30 (ddd, *J* = 9.5, 6.3, 3.2 Hz, 1H), 3.80 (ddd, *J* = 7.2, 6.6, 6.0 Hz, 1H), 3.49 (ddd, *J* = 10.0, 7.2, 5.2 Hz, 1H), 3.45 (ddd, *J* = 10.0, 6.8, 6.0 Hz, 1H), 2.68 (dd, *J* = 18.0, 9.2 Hz, 1H), 2.47 (dd, *J* = 18.0, 7.7 Hz, 1H), 2.39–2.25 (m, 4H), 2.14–2.03 (m, 1H), 2.03–1.88 (m, 2H), 1.79–1.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.4 (C), 175.3 (C), 81.1 (CH), 55.3 (CH), 45.9 (CH), 33.7 (CH_2), 33.2 (CH_2), 30.5 (CH_2), 30.3 (CH_2), 28.5 (CH_2), 25.3 (CH_2); HRMS (ESI), calcd for $C_{11}H_{17}NO_3Br^+$ $(M+H)^+$ 290.0392, found 290.0398. lactam ***epi*-158**: a colorless oil; $[\alpha]_D^{19}$ = 52.4 (*c* 0.5, $CHCl_3$); IR (film) 3216, 2927, 1773, 1692, 1262, 1200, 1183 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (bs, 1H), 4.37 (ddd, *J* = 8.3, 4.9, 3.4 Hz, 1H), 3.72 (ddd, *J* = 7.5, 7.2, 6.6 Hz, 1H), 3.51 (ddd, *J* = 10.0, 7.2, 5.4 Hz, 1H), 3.45 (ddd, *J* = 10.0, 7.2, 5.7 Hz, 1H), 2.77–2.69 (m, 1H), 2.46–2.26 (m, 5H), 2.15–2.06 (m, 1H), 2.06–1.97 (m, 1H), 1.97–1.89 (m, 1H), 1.79–1.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2 (C), 175.1 (C), 82.0 (CH), 56.7 (CH), 46.2 (CH), 34.7 (CH_2), 33.5 (CH_2), 31.2 (CH_2), 30.0 (CH_2), 28.6 (CH_2), 25.2 (CH_2); HRMS (ESI), calcd for $C_{11}H_{17}NO_3Br^+$ $(M+H)^+$ 290.0392, found 290.0389.

Chiral HPLC chart of 158 (98% ee)

CHIRALPAK AD-H, 250×4.6 mm, UV 210 nm, EtOH/hexane 1:1 (v/v), 1.0 mL/min



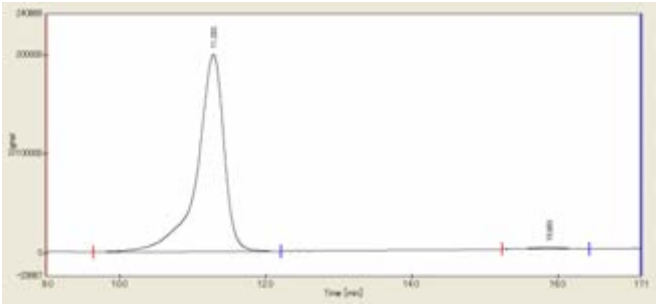
No.	T_R	Area	Height	Area (%)
1	20.21	50178	1700	0.9481
2	29.81	5242525	67533	99.0519



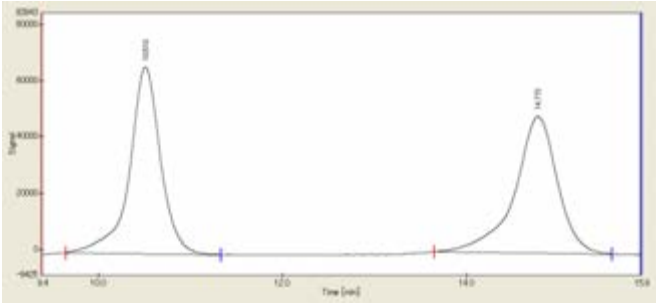
No.	T_R	Area	Height	Area (%)
1	16.81	273165	6184	49.7531
2	25.49	275876	3897	50.2469

Chiral HPLC chart of *epi*-158 (98% ee)

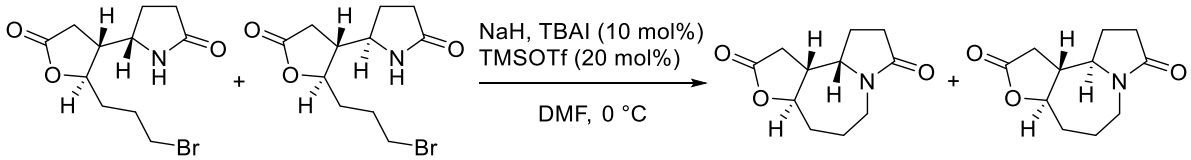
CHIRALPAK AD-H, 250×4.6 mm, UV 210 nm, EtOH/hexane 1:1 (v/v), 1.0 mL/min



No.	T_R	Area	Height	Area (%)
1	11.28	5093292	198311	99.1763
2	15.88	42304	1596	0.8237



No.	T_R	Area	Height	Area (%)
1	10.51	1555834	66392	49.7829
2	14.77	1569405	48490	50.2171



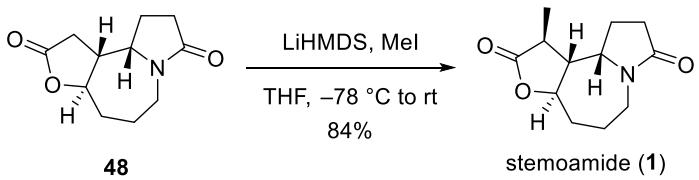
158 ***epi*-158** **158**:***epi*-**158** = 3.7:1

48: 57% ***epi*-48**: 19%

(3*aR*,10*aS*,10*bR*)-Octahydro-2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine-2,8(1*H*)-dione (48) and (3*aR*,10*aR*,10*bR*)-octahydro-2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine-2,8(1*H*)-dione (*epi*-48)

Trimethylsilyl trifluoromethanesulfonate (TMSOTf; 360 μL, 2.0 mmol, 20 mol%) was added to a mixture of NaH (63% in mineral oil, 570 mg, 15 mmol, 1.5 equiv), tetrabutylammonium iodide (369 mg, 999

μmol, 10 mol%) and DMF (100 mL) at room temperature. After stirring for 10 min at room temperature, the resulting mixture was cooled to 0 °C. A solution of secondary lactams **158** and ***epi*-158** (2.90 g, **158**:***epi*-158** = 3.7:1, 9.99 mmol, 1.0 equiv) and DMF (90 mL) was added to the mixture at 0 °C via cannula. The reaction mixture was stirred for 6 h, quenched with aqueous 1 M HCl (100 mL), and stirred for 30 min. Then, solid LiCl was added to the mixture until the mixture was saturated. The resulting mixture was filtered and extracted with $CHCl_3$ (6 x 100 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated. The remaining DMF was azeotropically removed with toluene. The residue was filtered through a pad of silica gel (EtOAc/MeOH 9:1), and then purified by MPLC (Yamazen Ultra Pack Column D, 26×300 mm, EtOAc/MeOH 85:15, 45 mL/min) to give 1.19 g of desired tricyclic compound **48** (57%) and 393 mg of undesired tricyclic compound ***epi*-48** (19%); tricyclic compound **48**: a colorless oil; $[\alpha]_D^{21}$ = –122.9 (*c* 1.0, $CHCl_3$); IR (film) 2937, 1776, 1681, 1418, 1185, 1015 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.29 (ddd, *J* = 10.3, 10.3, 2.9 Hz, 1H), 4.18–4.12 (m, 1H), 3.99 (ddd, *J* = 10.6, 6.3, 6.3 Hz, 1H), 2.85 (dddd, *J* = 12.6, 10.3, 8.6, 6.3 Hz, 1H), 2.71–2.63 (m, 1H), 2.65 (dd, *J* = 17.5, 8.6 Hz, 1H), 2.51 (dd, *J* = 17.5, 12.6 Hz, 1H), 2.45–2.37 (m, 3H), 2.07 (dddd, *J* = 12.0, 6.3, 5.7, 4.0 Hz, 1H), 1.91-1.81 (m, 1H), 1.71 (dddd, *J* = 12.0, 10.9, 10.6, 10.6 Hz, 1H), 1.63–1.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8 (C), 174.1 (C), 79.9 (CH), 56.1 (CH), 44.9 (CH), 40.2 (CH_2), 34.6 (CH_2), 31.1 (CH_2), 30.6 (CH_2), 25.5 (CH_2), 22.7 (CH_2); HRMS (ESI), calcd for $C_{11}H_{16}NO_3^+$ $(M+H)^+$ 210.1130, found 210.1128. tricyclic compound ***epi*-48**: a white solid; $[\alpha]_D^{20}$ = 30.3 (*c* 1.0, $CHCl_3$); mp 114–115 °C; IR (film) 2936, 2870, 1773, 1683, 1290, 1201 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.36 (ddd, *J* = 10.9, 9.7, 5.4 Hz, 1H), 3.84 (ddd, *J* = 14.6, 10.0, 3.2 Hz, 1H), 3.54 (ddd, *J* = 9.2, 7.5, 7.2 Hz, 1H), 3.18 (ddd, *J* = 14.6, 8.9, 3.4 Hz, 1H), 2.64 (dd, *J* = 16.0, 6.9 Hz, 1H), 2.52–2.25 (m, 5H), 2.20 (dddd, *J* = 12.9, 8.6, 7.2, 4.3 Hz, 1H), 1.93–1.81 (m, 2H), 1.75 (dddd, *J* = 13.2, 10.9, 7.2, 5.7 Hz, 1H), 1.65 (dddd, *J* = 12.9, 9.5, 9.5, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5 (C), 174.1 (C), 83.4 (CH), 61.0 (CH), 48.8 (CH), 40.5 (CH_2), 33.1 (CH_2), 30.5 (CH_2), 30.3 (CH_2), 24.3 (CH_2), 22.3 (CH_2); HRMS (ESI), calcd for $C_{11}H_{16}NO_3^+$ $(M+H)^+$ 210.1130, found 210.1133.



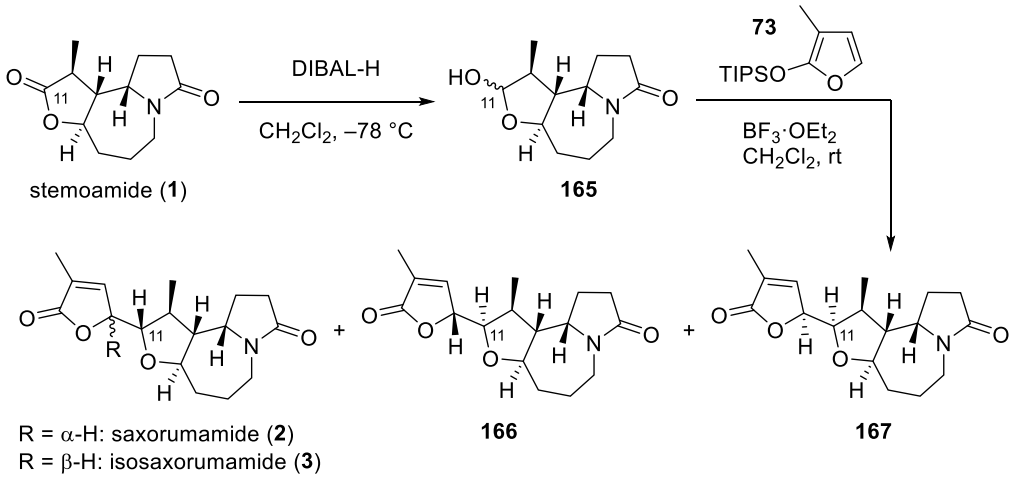
48 stemoamide (**1**)

Stemoamide (1)

n-Butyllithium (1.55 M in hexane, 4.4 mL, 6.8 mmol, 1.2 equiv) was added to a solution of $(Me_3Si)_2NH$ (1.4 mL, 6.7 mmol, 1.2 equiv) and THF (7 mL) at –78 °C. The solution was maintained for 15 min at –78 °C. The solution of $LiN(TMS)_2$ was added to a solution of tricyclic compound **48** (1.19 g, 5.69 mmol, 1.0 equiv) and THF (50 mL) via cannula at –78 °C. The resulting white suspension was allowed to warm

to –40 °C, stirred for 1 h at –40 °C, and cooled to –78 °C. Methyl iodide (460 μL, 7.4 mmol, 1.3 equiv) was then added dropwise to the solution at –78 °C. After stirring for 15 min at –78 °C, the mixture was allowed to warm to room temperature. After stirring for 2 h at room temperature, the mixture was quenched with aqueous 1 M HCl (30 mL). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (5 x 50 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH 1:0 to 19:1) to give 1.07 g of (–)-stemoamide (**1**: 84%): a white solid; $[\alpha]_D^{20}$ = –213.1 (*c* 0.5, MeOH) [lit. $[\alpha]_D^{26}$ −181 (*c* 0.89, MeOH)[2a], $[\alpha]_D^{30}$ −219.3 (*c* 0.5, MeOH)[2b], $[\alpha]_D^{25}$ −183.5 (*c* 1.36, MeOH)[2c], $[\alpha]_D^{25}$ −191.6 (*c* 0.5, MeOH)[2d]]; mp 190–191 °C; [lit. mp 190–191 °C,[2a] mp 187–188 °C,[2b] mp 186–187 °C,[2c] mp 185–186 °C[2d]]; IR (film) 2932, 1762, 1683, 1425, 1193, 998 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.20 (ddd, *J* = 10.3, 10.3, 2.9 Hz, 1H), 4.19-4.13 (m, 1H), 3.99 (ddd, *J* = 10.9, 6.3, 6.3 Hz, 1H), 2.69–2.62 (m, 1H), 2.60 (dq, *J* = 12.3, 6.9 Hz, 1H), 2.45–2.36 (m, 4H), 2.08–2.01 (m, 1H), 1.91–1.81 (m, 1H), 1.71 (dddd, *J* = 12.0, 10.9, 10.9, 10.9 Hz, 1H), 1.59–1.49 (m, 2H), 1.31 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5 (C), 174.1 (C), 77.7 (CH), 55.9 (CH), 52.7 (CH), 40.2 (CH_2), 37.4 (CH), 34.8 (CH_2), 30.7 (CH_2), 25.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (ESI), calcd for $C_{12}H_{18}NO_3^+$ $(M+H)^+$ 224.1287, found 224.1287.

A-2. Total Syntheses of Saxorumamide (2) and Isosaxorumamide (3)

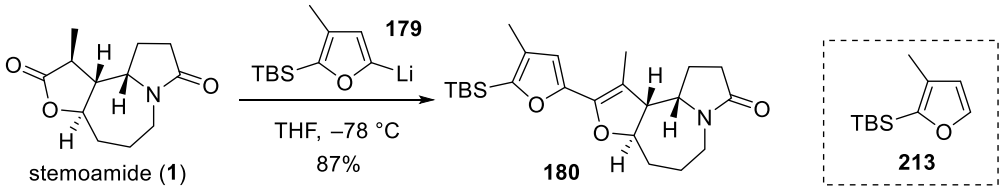


Saxorumamide (2), isosaxorumamide (3), 11-*epi*-saxorumamides (166 and 167)

Diisobutylalminium hydride (1 M in hexane, 120 μL, 120 μmol, 3.0 equiv) was added to a solution of stemoamide (**1**: 8.9 mg, 40 μmol, 1.0 equiv) and CH_2Cl_2 at –78 °C. The resulting solution was maintained for 1 h at –78 °C, and quenched with aqueous saturated (+)-potassium sodium tertrate (10 mL). The mixture was vigorously stirred for 1 h, extracted with $CHCl_3$ (3 x 10 mL). The combined organic extract was washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The crude lactol **165** was used in the next reaction without further purification. For analytical sample, the crude mixture was purified by silica gel column chromatography (EtOAc/MeOH 1:0 to 9:1) to give two diastereomers of lactol **165** (dr = 1.1:1); a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, 1.1:1 mixture of C11-diastereomers) δ 5.25 (d, *J* = 4.6 Hz, 1/2H), 5.11 (d, *J* = 3.4 Hz, 1/2H), 4.09–4.02 (m, 3/2H), 3.95–3.87 (m, 2/2H), 3.83 (ddd, *J* = 10.3, 2.3, 2.3 Hz, 1/2H), 2.70–2.58 (m, 2/2H), 2.42 (ddd, *J* = 12.3, 9.7, 6.9 Hz, 1/2H), 2.40–2.31 (m, 4/2H), 2.23–2.13 (m, 2/2H), 2.13–2.05 (m, 2/2H), 2.05–1.97 (m, 2/2H), 1.94 (dddd, *J* = 12.3, 6.3, 6.3, 2.3 Hz, 1/2H), 1.84 (dddd, *J* = 12.0, 10.6, 10.6, 10.6 Hz, 1/2H), 1.78–1.70 (m, 2/2H), 1.65 (dddd, *J* = 12.0, 10.6, 10.6, 10.6 Hz, 1/2H), 1.58–1.37 (m, 4/2H), 1.13 (d, *J* = 6.9 Hz, 3/2H), 1.06 (d, *J* = 6.6 Hz, 3/2H).

Boran trifluoride diethylether complex (25 μL, 200 μmol, 5.0 equiv) was added to a solution of lactol **165** and 2-siloxyfuran **73** (36 μL, 120 μmol, 3.0 equiv), and CH_2Cl_2 (1.3 mL) at room temperature. After stirring for 36 h, the reaction mixture was quenched with aqueous saturated $NaHCO_3$ (5 mL) and extracted with $CHCl_3$ (4 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH 19:1 to 9:1) to give 5.9 mg of a mixture of four diastereomers **2**, **3**, **166**, and **167** (**2**:**3**:**166**:**167** = 25:19:32:24). For analytical samples, four diastereomers were separated by HPLC (PEGASIL Silica 120-5, 250×10 mm, EtOAc/MeOH 4:1, 10 mL/min, an inseparable mixture of **3** and **166**: T_R = 12.3 min, **2**: T_R = 13.4 min, **167**: T_R = 18.4 min). The spectral data of saxorumamide (**2**) and isosaxorumamide (**3**) are reported in page 124. 11-epimer **166**: ^{1}H NMR (500 MHz, $CDCl_3$, an inseparable mixture of **166** and **3**, peaks of **166** were reported) δ 7.28 (dq, *J* = 1.7, 1.4 Hz, 1H), 4.76 (ddq, *J* = 9.2, 1.7, 1.7 Hz, 1H), 4.13–4.06 (m, 1H), 3.98 (ddd, *J* = 10.6, 6.3, 6.3

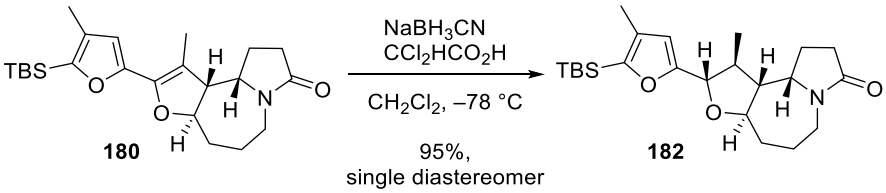
Hz, 1H), 3.72 (ddd, *J* = 10.3, 2.9, 2.9 Hz, 1H), 3.59 (dd, *J* = 9.2, 7.5 Hz, 1H), 2.68–2.61 (m, 1H), 2.48 (ddq, *J* = 9.5, 7.2, 7.2 Hz, 1H), 2.42–2.31 (m, 2H), 2.26–2.19 (m, 1H), 2.15–1.99 (m, 2H), 1.93 (dd, *J* = 1.7, 1.4 Hz, 3H), 1.81–1.62 (m, 2H), 1.55–1.33 (m, 2H), 1.23 (d, *J* = 7.2 Hz, 3H). 11-epimer **167**: pale yellow crystals; $[\alpha]_D^{23}$ = –37.9 (*c* 0.1, $CHCl_3$); mp 193–194 °C; IR (film) 2925, 2855, 1756, 1667, 1455, 1261, 1083, 802 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (dq, *J* = 1.7, 1.4 Hz, 1H), 4.89–4.86 (m, 1H), 4.22 (dd, *J* = 8.3, 0.9 Hz, 1H), 4.07–4.01 (m, 1H), 3.92 (ddd, *J* = 10.9, 6.9, 6.3 Hz, 1H), 3.73 (ddd, *J* = 10.2, 9.7, 2.9 Hz, 1H), 2.72–2.65 (m, 1H), 2.59–2.51 (m, 1H), 2.47 (ddd, *J* = 12.0, 9.7, 6.9 Hz, 1H), 2.42–2.31 (m, 2H), 2.00–1.92 (m, 2H), 1.95 (dd, *J* = 1.7, 1.4 Hz, 3H), 1.74–1.60 (m, 2H), 1.45–1.29 (m, 2H), 1.24 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7 (C), 174.1 (C), 146.7 (CH), 131.1 (C), 80.6 (CH), 80.3 (CH), 80.0 (CH), 56.3 (CH), 51.3 (CH), 40.5 (CH_2), 38.5 (CH), 35.1 (CH_2), 31.0 (CH_2), 25.9 (CH_2), 22.1 (CH_2), 13.1 (CH_3), 10.9 (CH_3); HRMS (ESI), calcd for $C_{17}H_{24}NO_4^+$ $(M+H)^+$ 306.1705, found 306.1703.



(3*aR*,10*aS*,10*bR*)-2-(5-(*Tert*-butyldimethylsilyl)-4-methylfuran-2-yl)-1-methyl-3a,4,5,6,9,10,10a,10b-octahydro-8*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepin-8-one (180)

n-Butyllithium (1.64 M in hexane, 210 μL, 340 μmol, 1.5 equiv) was added to a solution of *tert*-butyldimethyl(3-methylfuran-2-yl)silane **213**[3] (79 μL, 340 μmol, 1.5 equiv) and THF (1.1 mL) at –78 °C. The resulting solution was allowed to warm to 0 °C, stirred for 30 min at 0 °C, and re-cooled to –78 °C. The resulting solution of lithiated furan was added to a suspension of stemoamide (**1**, 51.0 mg, 228 μmol, 1.0 equiv) and THF (1.2 mL) via cannula at –78 °C. The resulting solution was maintained for 2 h at –78 °C, quenched with aqueous saturated NH_4Cl (5 mL), allowed to warm to room temperature, and stirred for 1 h. The mixture was extracted with $CHCl_3$ (5 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:1 to 4:1) to give 79.5 mg of enol ether **180** (87%); a white solid; $[\alpha]_D^{21}$ = –137.8 (*c* 1.0, $CHCl_3$); mp 132–133 °C; IR (film) 2929, 2858, 1689, 1419, 823, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.28 (s, 1H), 4.25 (ddd, *J* = 12.0, 10.9, 2.6 Hz, 1H), 4.12–4.05 (m, 2H), 3.46 (ddq, *J* = 12.0, 6.9, 1.7 Hz, 1H), 2.71 (ddd, *J* = 12.6, 12.6, 1.5 Hz, 1H), 2.42 (ddd, *J* = 16.9, 11.7, 8.9 Hz, 1H), 2.34 (ddd, *J* = 16.9, 9.5, 1.7 Hz, 1H), 2.34–2.29 (m, 1H), 2.08 (s, 3H), 2.08–1.92 (m, 2H), 1.97 (d, *J* = 1.7 Hz, 3H), 1.80–1.56 (m, 3H), 0.91 (s, 9H), 0.28 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7 (C), 154.1 (C), 150.4 (C), 143.6 (C), 132.4 (C), 111.5 (CH), 105.5 (C), 81.0 (CH), 56.9 (CH), 56.7 (CH), 40.5 (CH_2), 34.1 (CH_2), 30.9 (CH_2), 26.5 (CH_3), 25.3 (CH_2), 21.2 (CH_2), 18.0 (C), 11.4 (CH_3), 10.6 (CH_3),

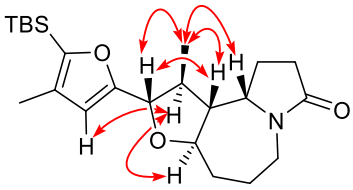
–5.7 (CH_3); HRMS (ESI), calcd for $C_{23}H_{36}NO_3Si^+$ $(M+H)^+$ 402.2464, found 402.2460.



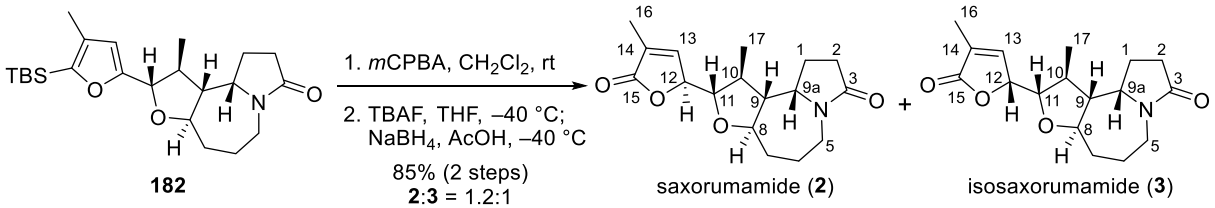
(1*S*,2*S*,3*aR*,10*aS*,10*bR*)-2-(5-(*Tert*-butyldimethylsilyl)-4-methylfuran-2-yl)-1-methyldecahydro-8*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepin-8-one (182)

Dichloroacetic acid (44 µL, 540 µmol, 5.0 equiv) was added to a solution of enol ether **180** (42.6 mg, 106 µmol, 1.0 equiv), sodium cyanoborohydride (33.1 mg, 527 µmol, 5.0 equiv) and CH_2Cl_2 (11 mL) at –78 °C. The resulting suspension was stirred for 14 h at –78 °C, quenched with saturated aqueous $NaHCO_3$ (10 mL), and extracted with $CHCl_3$ (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 2:1 to 1:0) to give 40.5 mg of furan **182** (95%); a white solid; $[\alpha]_D^{23}$ = –108.2 (*c* 1.0, MeOH); mp 111–112 °C; IR (film) 2930, 2856, 1692, 1459, 1420, 824 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.13 (s, 1H), 4.56 (d, *J* = 9.2 Hz, 1H), 4.11–4.06 (m, 1H), 4.01–3.95 (m, 1H), 3.95 (ddd, *J* = 10.6, 6.3, 6.3 Hz, 1H), 2.65 (dd, *J* = 12.8, 12.8 Hz, 1H), 2.43 (ddq, *J* = 13.2, 9.2, 6.6 Hz, 1H), 2.40–2.35 (m, 2H), 2.21–2.14 (m, 2H), 2.05 (s, 3H), 2.03–1.95 (m, 1H), 1.82–1.71 (m, 2H), 1.52–1.40 (m, 2H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.23 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3 (C), 157.2 (C), 153.5 (C), 132.1 (C), 111.0 (CH), 81.0 (CH), 79.2 (CH), 56.4 (CH), 55.7 (CH), 41.2 (CH), 40.6 (CH_2), 36.2 (CH_2), 31.0 (CH_2), 26.5 (CH_3), 26.0 (CH_2), 22.4 (CH_2), 17.9 (C), 15.5 (CH_3), 11.5 (CH_3), –5.6 (CH_3), –5.7 (CH_3); HRMS (ESI), calcd for $C_{23}H_{38}NO_3Si^+$ $(M+H)^+$ 404.2621, found 404.2619.

NOESY experiment for **182**



182 (500 MHz, $CDCl_3$)

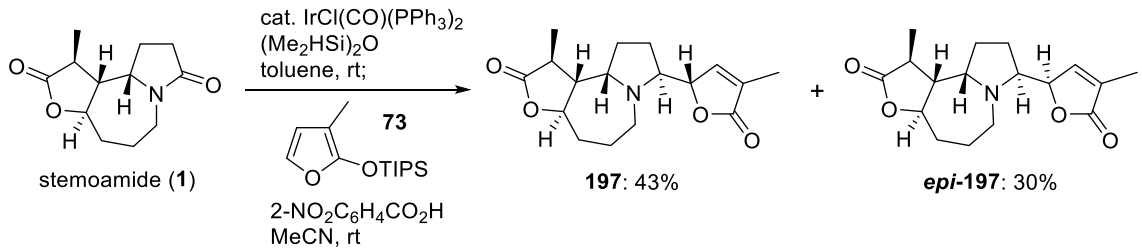


Saxorumamide (2) and Isosasorumamide (3)

*m*Chloroperbenzoic acid (69~75 wt% containing H_2O, 9.4 mg, 38 μmol, 1.2 equiv) was added to a solution of furan **182** (9.8 mg, 24 μmol, 1.0 equiv) and CH_2Cl_2 (3.3 mL) at room temperature. The resulting mixture was stirred for 2 h at room temperature, filtered through a pad of silica gel (EtOAc/Hexane 1:1 to 1:0), and concentrated. The residue was dissolved in THF (3.3 mL), and cooled to –40 °C. Tetrabutylammonium fluoride (94 μL, 94 μmol, 3.0 equiv) was added to the solution at –40 °C. After stirring for 30 min at –40 °C, AcOH (5 μL, 90 μmol, 3 equiv) and $NaBH_4$ (6.1 mg, 160 μmol, 5.0 equiv) were added to the solution at –40 °C. The resulting solution was stirred for 30 min, quenched with aqueous 1 M HCl (5 mL), and extracted with $CHCl_3$ (4 x 10 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated. The residue was purified by preparative layer chromatography (EtOAc/MeOH 9:1) to give 4.5 mg of saxorumamide (**2**: 46%) and 3.8 mg of isosaxorumamide (**3**: 39%). saxorumamide (**2**): a white amorphous solid; $[\alpha]_D^{22}$ = –107.3 (*c* 0.35, MeOH); IR (film) 3294, 2939, 2872, 1755, 1646, 1461, 1074 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.00 (dq, *J* = 1.7, 1.7 Hz, 1H), 4.93 (ddq, *J* = 2.3, 1.7, 1.7 Hz, 1H), 4.08 (ddd, *J* = 14.3, 2.9, 2.9 Hz, 1H), 3.92 (ddd, *J* = 10.6, 6.3, 6.3 Hz, 1H), 3.86 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.78 (ddd, *J* = 10.3, 10.3, 2.9 Hz, 1H), 2.60 (ddd, *J* = 13.9, 12.3, 1.2 Hz, 1H), 2.43–2.33 (m, 3H), 2.15–2.06 (m, 2H), 2.00 (dddd, *J* = 12.3, 6.3, 6.3, 2.9 Hz, 1H), 1.95 (dd, *J* = 1.7, 1.7 Hz, 3H), 1.83–1.69 (m, 2H), 1.47–1.32 (m, 2H), 1.14 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6 (C), 174.3 (C), 146.0 (CH), 131.3 (C), 83.7 (CH), 80.3 (CH), 80.2 (CH), 56.3 (CH), 55.2 (CH), 40.6 (CH_2), 37.8 (CH), 36.1 (CH_2), 30.9 (CH_2), 25.9 (CH_2), 22.6 (CH_2), 16.0 (CH_3), 11.0 (CH_3); HRMS (ESI), calcd for $C_{17}H_{24}NO_4^+$ $(M+H)^+$ 306.1705, found 306.1700. isosaxorumamide (**3**): a white amorphous solid; $[\alpha]_D^{22}$ = –59.7 (*c* 0.13, MeOH); IR (film) 3296, 2933, 2872, 1757, 1682, 1456, 1072, 1043, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (dq, *J* = 1.7, 1.7 Hz, 1H), 4.80 (ddq, *J* = 6.9, 1.7, 1.7 Hz, 1H), 4.12–4.06 (m, 1H), 3.92 (ddd, *J* = 10.6, 6.0, 6.0 Hz, 1H), 3.88 (ddd, *J* = 10.0, 10.0, 2.9 Hz, 1H), 3.52 (dd, *J* = 8.0, 6.9 Hz, 1H), 2.62 (ddd, *J* = 13.8, 12.0, 1.2 Hz, 1H), 2.38 (dd, *J* = 10.6, 4.6 Hz, 2H), 2.19–2.08 (m, 3H), 2.06–1.99 (m, 1H), 1.94 (dd, *J* = 1.7, 1.7 Hz, 3H), 1.81–1.61 (m, 2H), 1.50–1.35 (m, 2H), 1.14 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2 (C), 174.1 (C), 147.3 (CH), 130.9 (C), 85.7 (CH), 83.1 (CH), 79.8 (CH), 56.0 (CH), 55.7 (CH), 40.5 (CH_2), 39.8 (CH), 36.1 (CH_2), 31.0 (CH_2), 26.0 (CH_2), 22.7 (CH_2), 16.7 (CH_3), 10.9 (CH_3); HRMS (ESI), calcd for $C_{17}H_{24}NO_4^+$ $(M+H)^+$ 306.1705, found 306.1710.

*The optical rotations for natural samples of saxorumamide (**2**) and isosaxorumamide (**3**) were reported as $[\alpha]_D^{20}$ = –15.4 (*c* 0.35, MeOH) and $[\alpha]_D^{20}$ = –152 (*c* 0.13, MeOH), respectively.[4] Unfortunately, ^1H NMR spectra of their natural samples apparently contain impurities, see their supporting information.

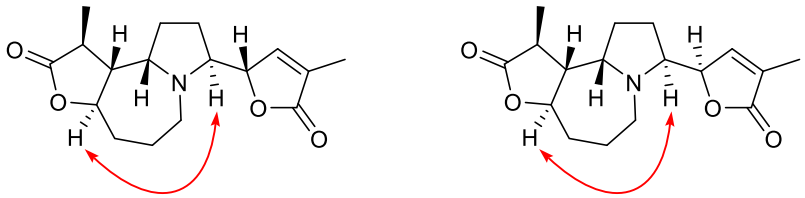
A-3. Total Synthesis of Stemonine (4)



14,15-Dehydrostemonine (197) and 13-*epi*-14,15-dehydrostemonine (*epi*-197)

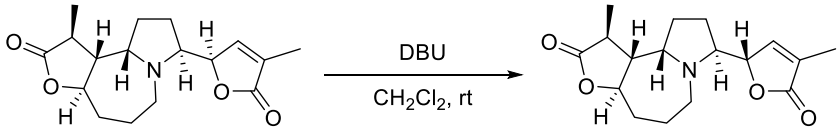
1,1,3,3-Tetramethyldisiloxane (24 μL, 130 μmol, 1.5 equiv) was added to a mixture of stemoamide (**1**, 19.9 mg, 89.1 μmol, 1.0 equiv), $IrCl(CO)(PPh_3)_2$ (0.7 mg, 0.9 μmol, 1 mol %) and toluene (6.0 mL), which was kept in water bath at 20 °C. The resulting solution was stirred for 1 h at 20 °C. Then, MeCN (30 mL) and triisopropyl((3-methylfuran-2-yl)oxy)silane **73**[5] (75 μL, 250 μmol, 2.8 equiv) and 2-nitrobenzoic acid (75.0 mg, 449 μmol, 5.0 equiv) were added to the solution at 20 °C. After stirring for 24 h at 20 °C, the solution was acidified with aqueous 0.05 M HCl (10 mL). The mixture was extracted with aqueous 0.05 M HCl (3 x 10 mL). The combined extracts were basified with aqueous saturated $NaHCO_3$ (10 mL), and extracted with $CHCl_3$ (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated. The residue was purified by preparative layer chromatography (EtOAc) to give 11.6 mg of **197** (43%) and 8.3 mg of ***epi*-197** (30%): 14,15-dehydrostemonine (**197**): a white solid; $[\alpha]_D^{23}$ = –202.3 (*c* 1.0, MeOH); mp 64–65 °C; IR (film) 2934, 2873, 1759, 1456, 1359, 1324, 1185, 1007, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.99 (qd, *J* = 1.6, 1.4 Hz, 1H), 4.84–4.79 (m, 1H), 4.20 (ddd, *J* = 10.9, 10.3, 3.7 Hz, 1H), 3.66–3.60 (m, 1H), 3.43–3.37 (m, 1H), 3.33 (ddd, *J* = 8.0, 6.6, 6.6 Hz, 1H), 2.92 (ddd, *J* = 15.8, 10.6, 1.7 Hz, 1H), 2.42 (dq, *J* = 12.3, 6.9 Hz, 1H), 2.35–2.29 (m, 1H), 2.25 (ddd, *J* = 12.3, 10.3, 5.4 Hz, 1H), 1.99–1.90 (m, 1H), 1.94 (dd, *J* = 1.6, 1.4 Hz, 3H), 1.87–1.79 (m, 1H), 1.63–1.50 (m, 4H), 1.41 (dddd, *J* = 12.6, 12.3, 10.9, 5.4 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4 (C), 174.2 (C), 146.5 (CH), 131.4 (C), 85.0 (CH), 79.1 (CH), 63.2 (CH), 58.3 (CH), 53.1 (CH), 46.5 (CH_2), 39.4 (CH), 34.5 (CH_2), 27.3 (CH_2), 26.8 (CH_2), 21.4 (CH_2), 14.1 (CH_3), 10.9 (CH_3); HRMS (ESI), calcd for $C_{17}H_{24}NO_4^+$ $(M+H)^+$ 306.1705, found 306.1701. 13-*epi*-14,15-dehydrostemonine (***epi*-197**): a colorless oil; $[\alpha]_D^{23}$ = –83.7 (*c* 1.0, MeOH); IR (film) 2934, 2872, 1748, 1455, 1323, 1186, 1097, 1003, 727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.01 (dq, *J* = 2.0, 1.7 Hz, 1H), 5.00–4.96 (m, 1H), 4.26 (ddd, *J* = 10.6, 10.6, 3.4 Hz, 1H), 3.58 (ddd, *J* = 9.5, 5.7, 5.7 Hz, 1H), 3.47 (ddd, *J* = 6.9, 6.9, 3.7 Hz, 1H), 3.13–3.07 (m, 1H), 2.89 (ddd, *J* = 15.2, 11.5, 0.6 Hz, 1H), 2.43 (dq, *J* = 12.6, 6.9 Hz, 1H), 2.36–2.30 (m, 1H), 2.20 (ddd, *J* = 12.6, 10.6, 5.7 Hz, 1H), 1.94 (dd, *J* = 2.0, 1.7 Hz, 3H), 1.84–1.75 (m, 2H), 1.63–1.35 (m, 5H), 1.24 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6 (C), 174.4 (C), 146.8 (CH), 131.2 (C), 82.1 (CH), 79.0 (CH), 62.8 (CH), 57.9 (CH), 53.0 (CH), 46.0 (CH_2), 39.7 (CH), 34.6 (CH_2), 27.1 (CH_2), 24.6 (CH_2), 23.3 (CH_2), 14.2 (CH_3), 11.0 (CH_3); HRMS (ESI), calcd for $C_{17}H_{24}NO_4^+$ $(M+H)^+$ 306.1705, found 306.1702.

NOESY experiment for **197** and ***epi*-197**



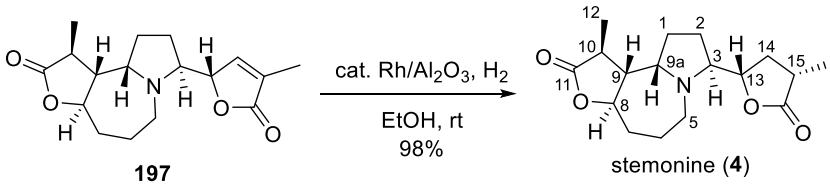
197 and ***epi*-197** (500 MHz, $CDCl_3$)

Isomerization of 13-epi-14,15-dehydrostemonine (*epi*-197)



epi*-197** 95% **197**:epi*-197 = 1.2:1

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 5 µL, 30 µmol, 2 equiv) was added to a solution of ***epi*-197** (4.4 mg, 14.4 µmol, 1.0 equiv) and CH_2Cl_2 (1 mL) at room temperature. After stirring for 3 h, the resulting solution was quenched with H_2O (5 mL), and extracted with $CHCl_3$ (3 x 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified with silica gel column chromatography (EtOAc/Hexane 2:1 to 1:0) to give 4.2 mg of **197** and ***epi*-197** (95%, **197**: ***epi*-197** = 1.2:1).



197 stemonine (**4**)

Stemonine (4)

Rhodium on alumina (5 wt%, 2.9 mg) was added to a solution of butenolide **197** (5.8 mg, 19 µmol) and EtOH (1.0 mL). The flask was purged with hydrogen. The mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 3 h, filtered through a pad of Celite®, washed with EtOAc, and concentrated. The residue was filtered through a pad of basic alumina, and then purified with silica gel column chromatography (EtOAc/Hexane 2:1 to 1:0) to give 5.7 mg of stemonine (**4**) (98%): a white solid; $[\alpha]_D^{22}$ = –108.6 (*c* 0.2, acetone) [lit.[6] $[\alpha]_D^{21}$ –81.1 (*c* 0.2, acetone)]; mp 53–54 °C; IR (film) 2934, 2874, 1768, 1455, 1188, 1009, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.22 (ddd, *J* = 10.9, 10.0, 3.4 Hz, 1H), 4.18 (ddd, *J* = 11.2, 7.5, 5.4 Hz, 1H), 3.68 (ddd, *J* = 11.7, 5.7, 5.2 Hz, 1H), 3.53 (dd, *J* = 15.8, 4.0 Hz, 1H), 3.30 (ddd, *J* = 9.5, 7.5, 6.3 Hz, 1H), 2.89 (dd, *J* = 15.8, 11.2 Hz, 1H), 2.61 (ddq, *J* = 12.3, 8.6, 6.9 Hz, 1H),

2.42 (dq, *J* = 12.3, 6.9 Hz, 1H), 2.37 (ddd, *J* = 12.6, 8.6, 5.4 Hz, 1H), 2.35–2.29 (m, 1H), 2.26 (ddd, *J* = 12.3, 10.0, 5.2 Hz, 1H), 1.95 (dddd, *J* = 13.1, 7.2, 6.3, 1.2 Hz, 1H), 1.85 (dddd, *J* = 11.7, 7.2, 7.2, 1.2 Hz, 1H), 1.65 (ddddd, *J* = 14.9, 13.2, 11.2, 4.0, 1.7 Hz, 1H), 1.60–1.49 (m, 3H), 1.48–1.36 (m, 2H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.24 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6 (C), 178.5 (C), 83.4 (CH), 79.1 (CH), 64.3 (CH), 58.8 (CH), 53.2 (CH), 46.5 (CH_2), 39.4 (CH), 35.0 (CH), 34.54 (CH_2), 34.49 (CH_2), 27.3 (CH_2), 26.7 (CH_2), 20.9 (CH_2), 15.1 (CH_3), 14.1 (CH_3); HRMS (ESI), calcd for $C_{17}H_{26}NO_4^+$ $(M+H)^+$ 308.1862, found 308.1864.

References in Unified Total Synthesis of Stemoamide-type Alkaloids

[1] Alves, J. C. F. *J. Braz. Chem. Soc.* **2007**, *18*, 855.

[2] (a) Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett.* **1994**, *35*, 6417. (b) Kinoshita, A.; Mori, M. *Heterocycles* **1997**, *46*, 287. (c) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc*. **1997**, *119*, 3409. (d) Sibi, M. P.; Subramanian, T. *Synlett* **2004**, 1211.

[3] Mace, L. H.; Shanmugham, M. S.; White, J. D.; Drew, M. G. B. *Org. Biomol. Chem.* **2006**, *4*, 1020.

[4] Wang, Y.-Z.; Tang, C.-P.; Dien, P.-H.; Ye, Y. *J. Nat. Prod.* **2007**, *70*, 1356.

[5] (a) Rosso, G. B.; Pilli, R. A. *Tetrahedron Lett.* **2006**, *47*, 185–188. (b) Funakoshi, Y.; Miura, T.; Murakami, M. *Org. Lett.* **2016**, *18*, 6284.

[6] Williams, D. R.; Shamim, K.; Reddy, J. P.; Amato, G. S.; Shaw, S. M. *Org. Lett.* **2003**, *5*, 3361.

[7] Koyama, H.; Oda, K. *J. Chem. Soc. B* **1970**, 1330.

B. Comparison of Synthetic Routes for Total Syntheses and Formal Syntheses of Stemoamides

1. Enantioselective Total Synthesis

group	year	starting material	LLS	total yield	scale of stemoamide
Williams	1994	(*R*)-(–)-methyl-3-hydroxy-2-methyl propionate	25 steps	5.6%	N/A
Mori	1996	(5*S*)-5-(hydroxymethyl)-2-pyrrolidinone	13 steps	8.3%	6.3 mg
Jacobi	2000	(5*S*)-5-(hydroxymethyl)-2-pyrrolidinone	7 steps	4.2%	18 mg
Sibi	2004	(5*S*)-5-(hydroxymethyl)-2-pyrrolidinone	14 steps	7.0%	N/A
Olivo	2006	succiniimide	13 steps	<14.1%*	25 mg
Somfai	2007	(5*S*)-5-(hydroxymethyl)-2-pyrrolidinone	12 steps	19.6%	6.8 mg
Honda	2011	(5*S*)-5-(hydroxymethyl)-2-pyrrolidinone	9 steps	23.4%	32.2 mg
Hong	2012	4-chlorobutanoyl chloride	12 steps	18.7%	24.7 mg
Sato/Chida	2016	(+)-dimethyl L-tartrate	22 steps	2.2%	8.9 mg
Sato/Chida	2017	ethyl 4-bromobutyrate	7 steps	19.2%	1.07 g

* Yields of first three steps are not reported

2. Racemic Total Synthesis

group	year	starting material	LLS	total yield	scale of stemoamide
Narasaka	1996	4-Methyl-3-penten-2-one	14 steps	1.1%	12 mg
Jacobi	1997	4-chlorobutanoyl chloride	7 steps	19.9%	438 mg
Bates	2009	succinimide	11 steps	5.70%	N/A
Hong	2011	propargyl bromide	9 steps	30.1%**	166 mg
Zhang, Qiu	2014	3-Methyl-2(5*H*)-furanone	7 steps	5.1%	24 mg

** They originally counted the steps starting from 4-buromobutanal, which is not generally commercially available.

3. Enantioselective Formal Synthesis

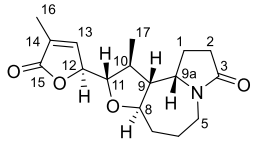
group	Year	starting material	possible LLS
Gurjar	2002	diacetone-D-glucose	22 steps
Cossy	2006	2,4-pentanedione	11 steps
Chavan	2012	(–)-methyl Pyroglutamate	18 steps

4. Racemic Formal Synthesis

group	Year	starting material	possible LLS
Cossy	2006	dihydrofuran	12 steps
Rosales/Rodriguez-Garcia/ Oltra	2014	succinimide	6 steps
Pilli	2015	TMS-siloxyfuran	6 steps

C. Comparison of Spectral Data with Natural Products

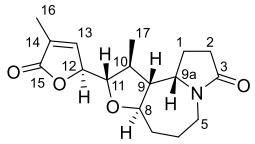
Comparison of ^{1}H NMR of saxorumamide (2)



saxorumamide (**2**)

	our synthetic sample	natural sample
Proton	^{1}H NMR (500 MHz, $CDCl_3$)	^{1}H NMR (300 MHz, $CDCl_3$)
13	7.00 (qd, *J* = 1.7, 1.7 Hz, 1H)	6.99 (m, 1H)
12	4.92 (ddq, *J* = 2.3, 1.7, 1.7 Hz, 1H)	4.96 (dd, *J* = 3.8, 2.0 Hz, 1H)
5	4.08 (ddd, *J* = 14.3, 2.9, 2.9 Hz, 1H)	4.08 (dd, *J* = 14.0, 2.3 Hz, 1H)
9a	3.92 (ddd, *J* = 10.9, 6.3, 6.3 Hz, 1H)	3.93 (m, 1H)
11	3.86 (dd, *J* = 8.9, 2.3 Hz, 1H)	3.87 (dd, *J* = 8.8, 2.0 Hz, 1H)
8	3.78 (ddd, *J* = 10.3, 10.3, 2.9 Hz, 1H)	3.78 (ddd, *J* = 13.0, 10.2, 2.7 Hz, 1H)
5	2.60 (ddd, *J* = 13.8, 12.3, 1.2 Hz, 1H)	2.60 (dd, *J* = 14.0, 12.4 Hz, 1H)
2, 10	2.43–2.33 (m, 3H)	2.38 (m, 1H), 2.37 (m, 2H)
7, 9	2.15–2.06 (m, 2H)	2.12 (m, 1H), 2.10 (m, 1H)
1	2.00 (dddd, *J* = 12.3, 6.3, 6.3, 2.9 Hz, 1H)	2.02 (m, 1H)
16	1.95 (dd, *J* = 1.7, 1.7 Hz, 3H)	1.94 (dd, *J* = 1.7, 1.7 Hz, 3H)
1, 6	1.83–1.69 (m, 2H)	1.77 (m, 1H), 1.74 (m, 1H)
6, 7	1.47–1.32 (m, 2H)	1.42 (m, 1H), 1.38 (m, 1H)
17	1.14 (d, *J* = 6.6 Hz, 3H)	1.10 (d, *J* = 6.6 Hz, 3H)

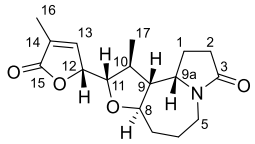
Comparison of ^{13}C NMR of saxorumamide (2)



saxorumamide (**2**)

	our synthetic sample	natural sample
Carbon	^{13}C NMR (125 MHz, $CDCl_3$)	^{13}C NMR (100 MHz, $CDCl_3$)
3, 15	174.6 (C), 174.3 (C)	174.1 (C), 174.1 (C)
13	146.0 (CH)	145.8 (CH)
14	131.3 (C)	131.2 (C)
11	83.7 (CH)	83.6 (CH),
8, 12	80.3 (CH), 80.2 (CH)	80.1 (CH), 80.1 (CH)
9a	56.3 (CH)	56.0 (CH)
9	55.2 (CH)	55.1 (CH)
5	40.6 (CH_2)	40.4 (CH_2)
10	37.8 (CH)	37.6 (CH)
7	36.1 (CH_2)	36.0 (CH_2)
2	30.9 (CH_2)	30.7 (CH_2)
6	25.9 (CH_2)	25.8 (CH_2)
1	22.6 (CH_2)	22.4 (CH_2)
17	16.0 (CH_3)	15.9 (CH_3)
16	11.0 (CH_3)	10.8 (CH_3)

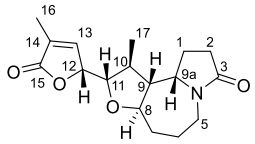
Comparison of ^{1}H NMR of isosaxorumamide (3)



isosaxorumamide (**3**)

	our synthetic sample	natural sample
Proton	^{1}H NMR (500 MHz, $CDCl_3$)	^{1}H NMR (300 MHz, $CDCl_3$)
13	7.17 (dq, *J* = 1.7, 1.7 Hz, 1H)	7.15 (t, *J* = 1.6 Hz, 1H)
12	4.80 (ddq, *J* = 6.9, 1.7, 1.7 Hz, 1H)	4.78 (ddd, *J* = 6.9, 3.9, 1.8 Hz, 1H)
5	4.12–4.06 (m, 1H)	4.08 (m, 1H)
9a	3.92 (ddd, *J* = 10.6, 6.0, 6.0 Hz, 1H)	3.92 (m, 1H)
8	3.88 (ddd, *J* = 10.0, 10.0, 2.9 Hz, 1H)	3.88 (m, 1H)
11	3.52 (dd, *J* = 8.0, 6.9 Hz, 1H)	3.52 (dd, *J* = 7.9, 6.9 Hz, 1H)
5	2.62 (ddd, *J* = 13.8, 12.0, 1.2 Hz, 1H)	2.62 (m, 1H)
2	2.38 (dd, *J* = 10.6, 4.6 Hz, 2H)	2.38 (dd, *J* = 10.5, 4.4 Hz, 2H)
7, 9, 10	2.19–2.08 (m, 3H)	2.15 (m, 1H), 2.12 (m, 1H), 2.12 (m, 1H)
1	2.06–1.99 (m, 1H)	2.01 (m, 1H)
16	1.94 (dd, *J* = 1.7, 1.7 Hz, 3H)	1.93 (dd, *J* = 1.9, 1.7 Hz, 3H)
1, 6	1.81–1.61 (m, 2H)	1.75 (m, 1H), 1.70 (m, 1H)
6, 7	1.50–1.35 (m, 2H)	1.42 (m, 1H), 1.40 (m, 1H)
17	1.14 (d, *J* = 6.0 Hz, 3H)	1.13 (d, *J* = 8.0 Hz, 3H)

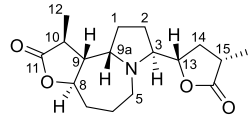
Comparison of ^{13}C NMR of isosaxorumamide (3)



isosaxorumamide (**3**)

	our synthetic sample	natural sample
Carbon	^{13}C NMR (125 MHz, $CDCl_3$)	^{13}C NMR (100 MHz, $CDCl_3$)
3, 15	174.2 (C), 174.1 (C)	174.0 (C), 174.0 (C)
13	147.3 (CH)	147.0 (CH)
14	130.9 (C)	130.8 (C)
11	85.7 (CH)	85.6 (CH)
12	83.1 (CH)	82.9 (CH)
8	79.8 (CH)	79.7 (CH)
9a	56.0 (CH)	55.9 (CH)
9	55.7 (CH)	55.6 (CH)
5	40.5 (CH_2)	40.4 (CH_2)
10	39.8 (CH)	39.7 (CH)
7	36.1 (CH_2)	36.0 (CH_2)
2	31.0 (CH_2)	30.8 (CH_2)
6	26.0 (CH_2)	25.9 (CH_2)
1	22.7 (CH_2)	22.6 (CH_2)
17	16.7 (CH_3)	16.5 (CH_3)
16	10.9 (CH_3)	10.7 (CH_3)

Comparison of ^{1}H NMR of stemonine (4)

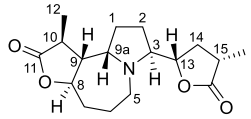


stemonine (**4**)

	our synthetic sample	Williams' synthetic sample
Proton	^{1}H NMR (500 MHz, $CDCl_3$)	^{1}H NMR (400 MHz, $CDCl_3$)
8	4.22 (ddd, *J* = 10.9, 10.0, 3.4 Hz, 1H)	4.24–4.12 (m, 2H)
13	4.18 (ddd, *J* = 11.2, 7.5, 5.4 Hz, 1H)	
9a	3.68 (ddd, *J* = 11.7, 5.7, 5.2 Hz, 1H)	3.67 (dt, *J* = 10.1, 5.0, 5.0 Hz, 1H)
5	3.53 (dd, *J* = 15.8, 4.0 Hz, 1H)	3.53 (dd, *J* = 15.9, 4.8 Hz, 1H)
3	3.30 (ddd, *J* = 9.5, 7.5, 6.3 Hz, 1H)	3.33–3.27 (m, 1H)
5	2.89 (dd, *J* = 15.8, 11.2 Hz, 1H)	2.88 (dd, *J* = 15.8, 11.1 Hz, 1H)
15	2.61 (ddq, *J* = 12.3, 8.6, 6.9 Hz, 1H)	2.61 (ddq, *J* = 12.3, 8.4, 6.9 Hz,
10	2.42 (dq, *J* = 12.3, 6.9 Hz, 1H)	2.46–2.22 (m, 4H)
14	2.37 (ddd, *J* = 12.6, 8.6, 5.4 Hz, 1H)	
7	2.35–2.29 (m, 1H)	
9	2.26 (ddd, *J* = 12.3, 10.0, 5.2 Hz, 1H)	
2	1.95 (dddd, *J* = 13.1, 7.2, 6.3, 1.2 Hz, 1H)	1.96–1.90 (m, 1H)
1	1.85 (dddd, *J* = 11.7, 7.2, 7.2, 1.2 Hz, 1H)	1.88–1.81 (m, 1H)
6	1.65 (ddddd, *J* = 14.9, 13.2, 11.2, 4.0, 1.7 Hz,	1.69–1.30 (m, 6H)
1, 6, 14	1.60–1.49 (m, 3H)	
2, 7	1.48–1.36 (m, 2H)	
17	1.26 (d, *J* = 6.9 Hz, 3H)	1.26 (d, *J* = 7.1 Hz, 3H)
12	1.24 (d, *J* = 6.9 Hz, 3H)	1.23 (d, *J* = 7.8 Hz, 3H)

*The structure of stemonine was unambiguously determined by X-ray crystallographic analysis by Koyama and Oda in 1970.[7] However, ^{1}H and ^{13}C NMR data of the natural sample were not reported. The Williams' group compared with an authentic sample of stemonine, as well as ^{1}H NMR, IR, and mass spectra of the natural product gifted by Yang Ye, Shanghai Institute of Materia Medica.[6]

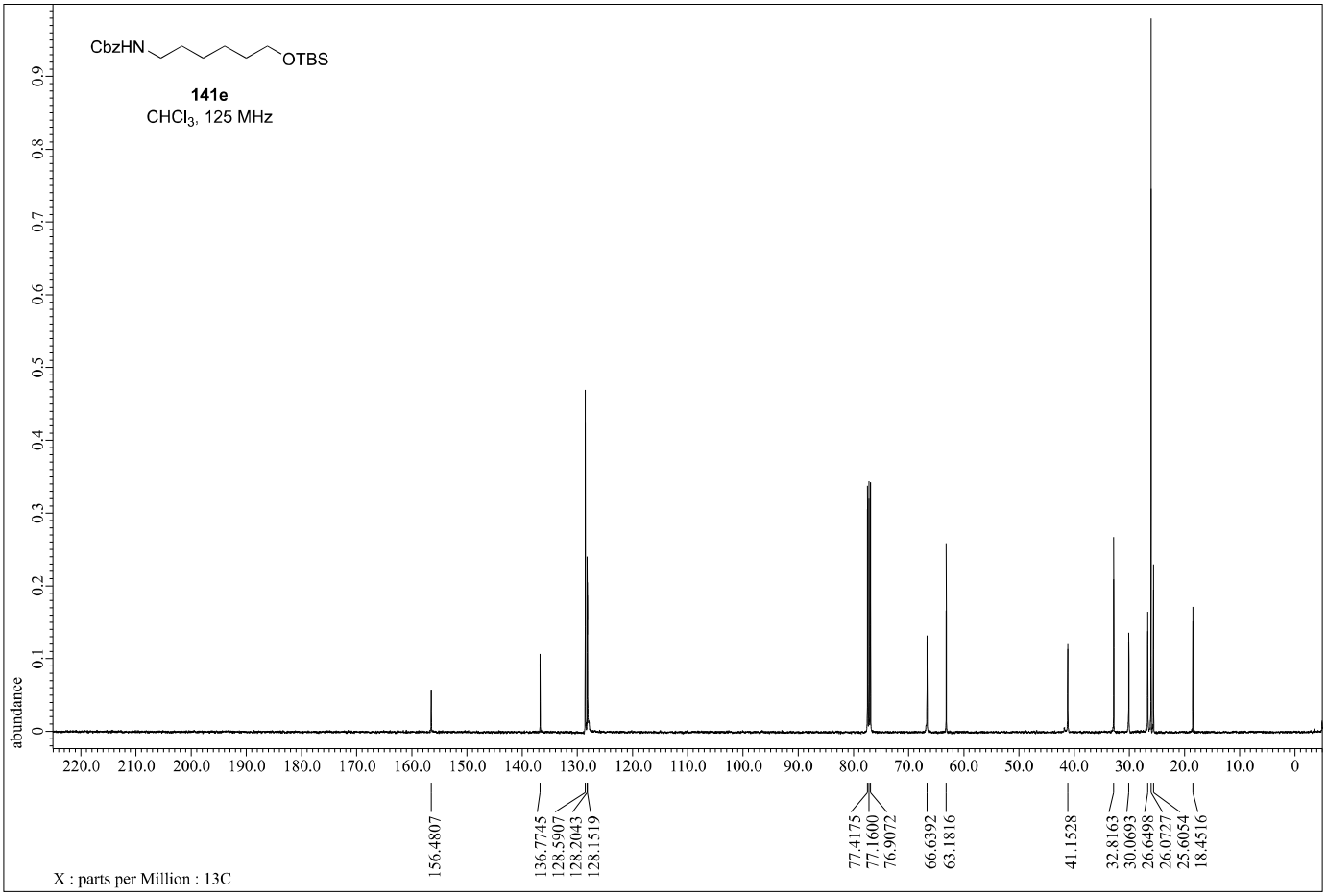
Comparison of ^{13}C NMR of stemonine (4)



stemonine (**4**)

our synthetic sample	Williams' synthetic sample
^{13}C NMR (125 MHz, $CDCl_3$)	^{13}C NMR (100 MHz, $CDCl_3$)
179.6 (C)	179.5 (C)
178.5 (C)	178.4 (C)
83.4 (CH)	83.4 (CH)
79.1 (CH)	78.9 (CH)
64.3 (CH)	64.1 (CH)
58.8 (CH)	58.5 (CH)
53.2 (CH)	53.1 (CH)
46.5 (CH_2)	46.3 (CH_2)
39.4 (CH)	39.2 (CH)
35.0 (CH)	34.9 (CH)
34.54 (CH_2)	34.3 (CH_2)
34.49 (CH_2)	
27.3 (CH_2)	27.2 (CH_2)
26.7 (CH_2)	26.6 (CH_2)
20.9 (CH_2)	20.7 (CH_2)
15.1 (CH_3)	14.9 (CH_3)
14.1 (CH_3)	13.9 (CH_3)

*The structure of stemonine was unambiguously determined by X-ray crystallographic analysis by Koyama and Oda in 1970.[7] However, ^{1}H and ^{13}C NMR data of the natural sample were not reported. The Williams' group compared with an authentic sample of stemonine, as well as ^{1}H NMR, IR, and mass spectra of the natural product gifted by Yang Ye, Shanghai Institute of Materia Medica.[6]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OTBS
141e
CHCl3, 125 MHz
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128.5907
128.2043
128.1519
77.4175
77.1600
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63.1816
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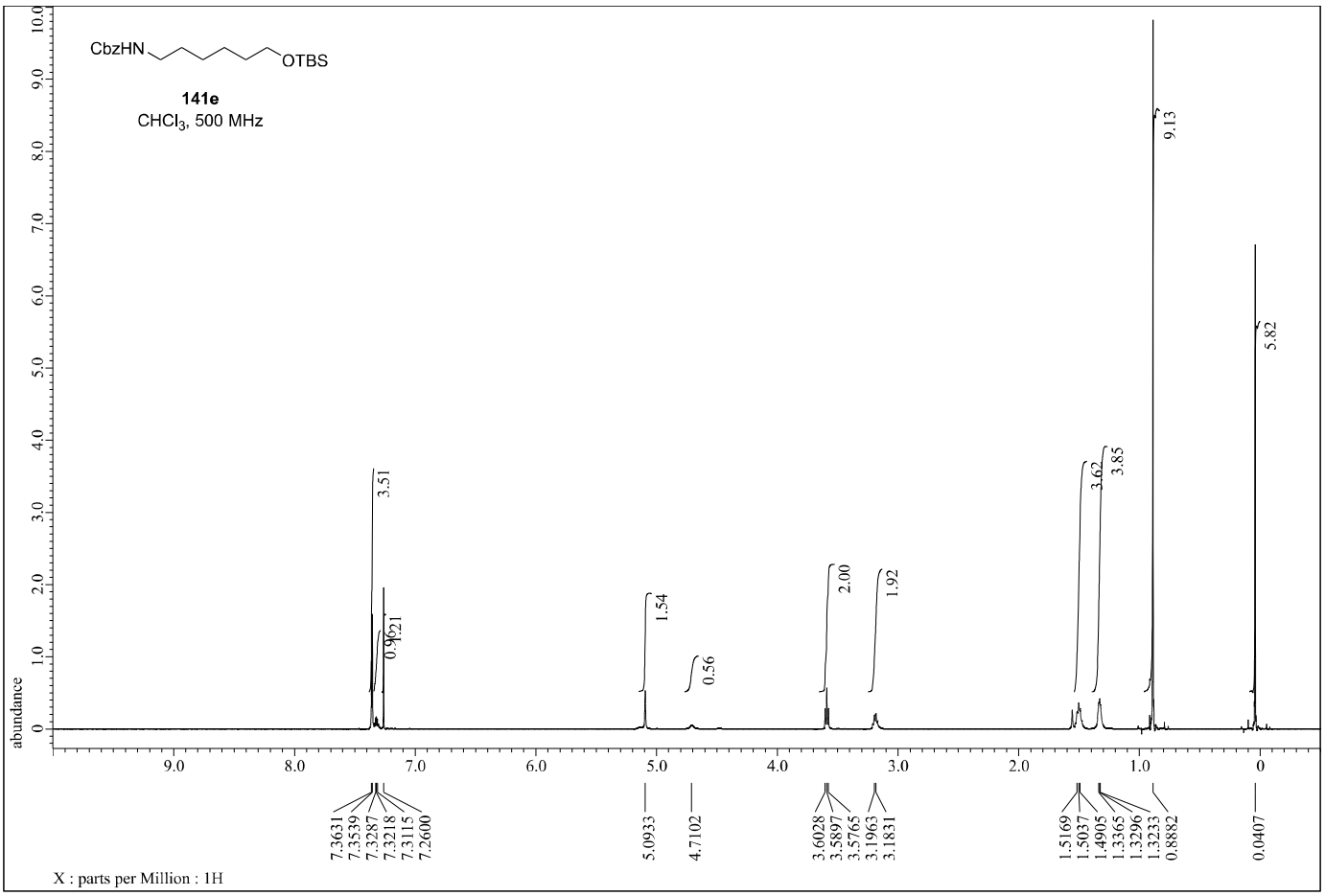
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OTBS
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CHCl3, 500 MHz
abundance
X : parts per Million : 1H
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3.85
3.62
3.51
2.00
1.92
1.54
0.56
0.921
7.3631
7.3539
7.3287
7.3218
7.3115
7.2600
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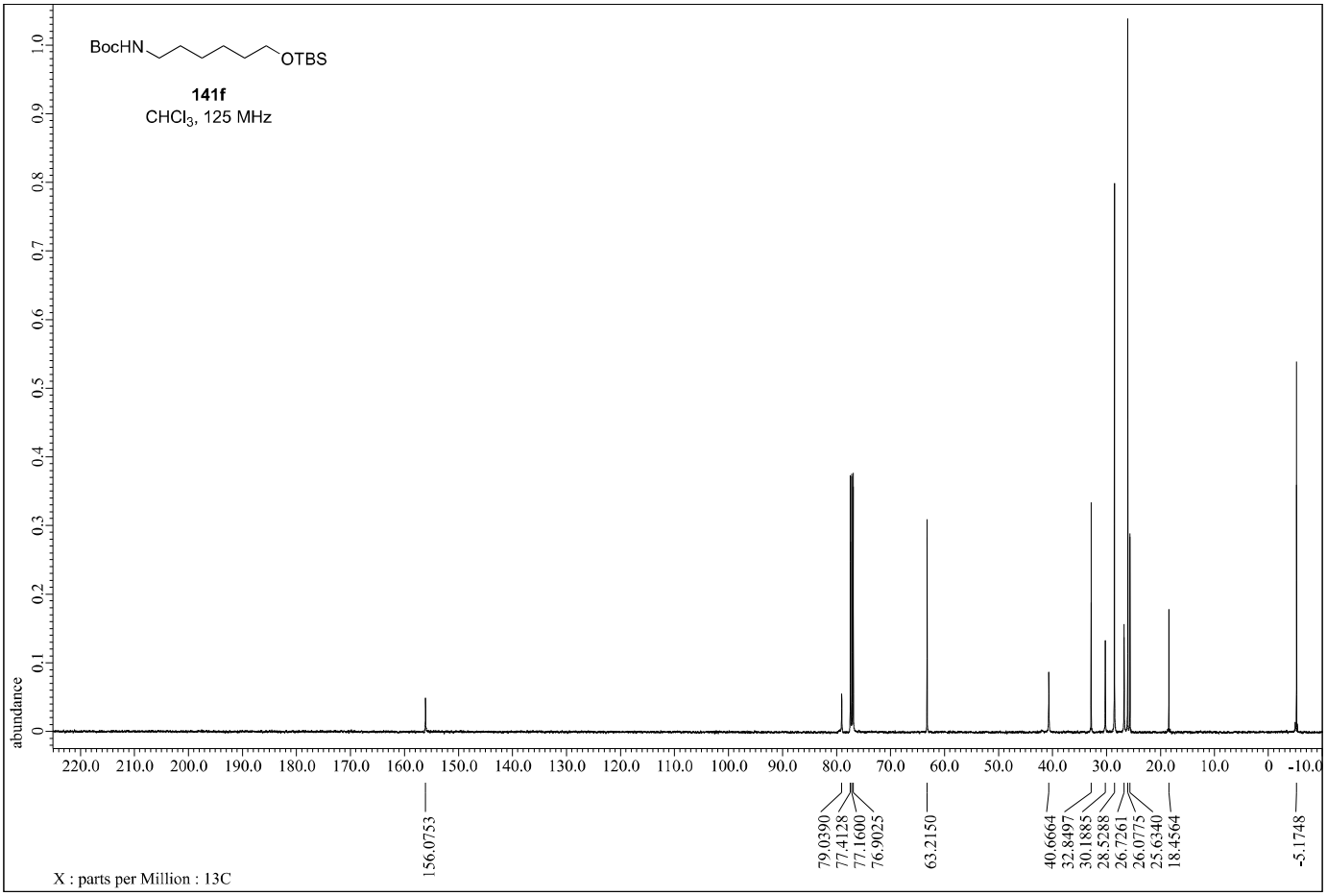
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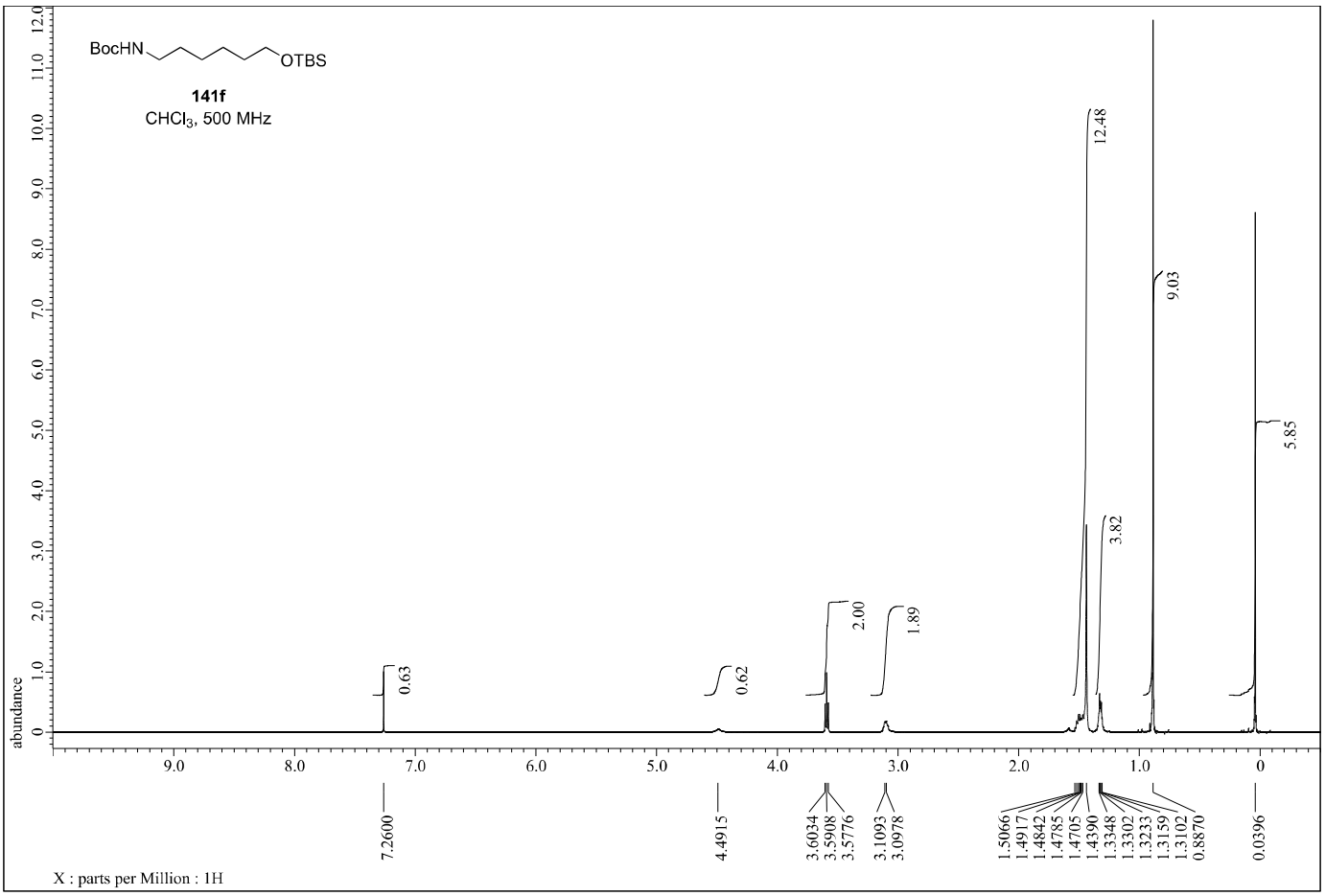
X : parts per Million : 13C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OTBS
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CHCl3, 500 MHz
abundance
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2.00
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0.62
7.2600
4.4915
3.6034
3.5908
3.5776
3.1093
3.0978
1.5066
1.4917
1.4842
1.4785
1.4705
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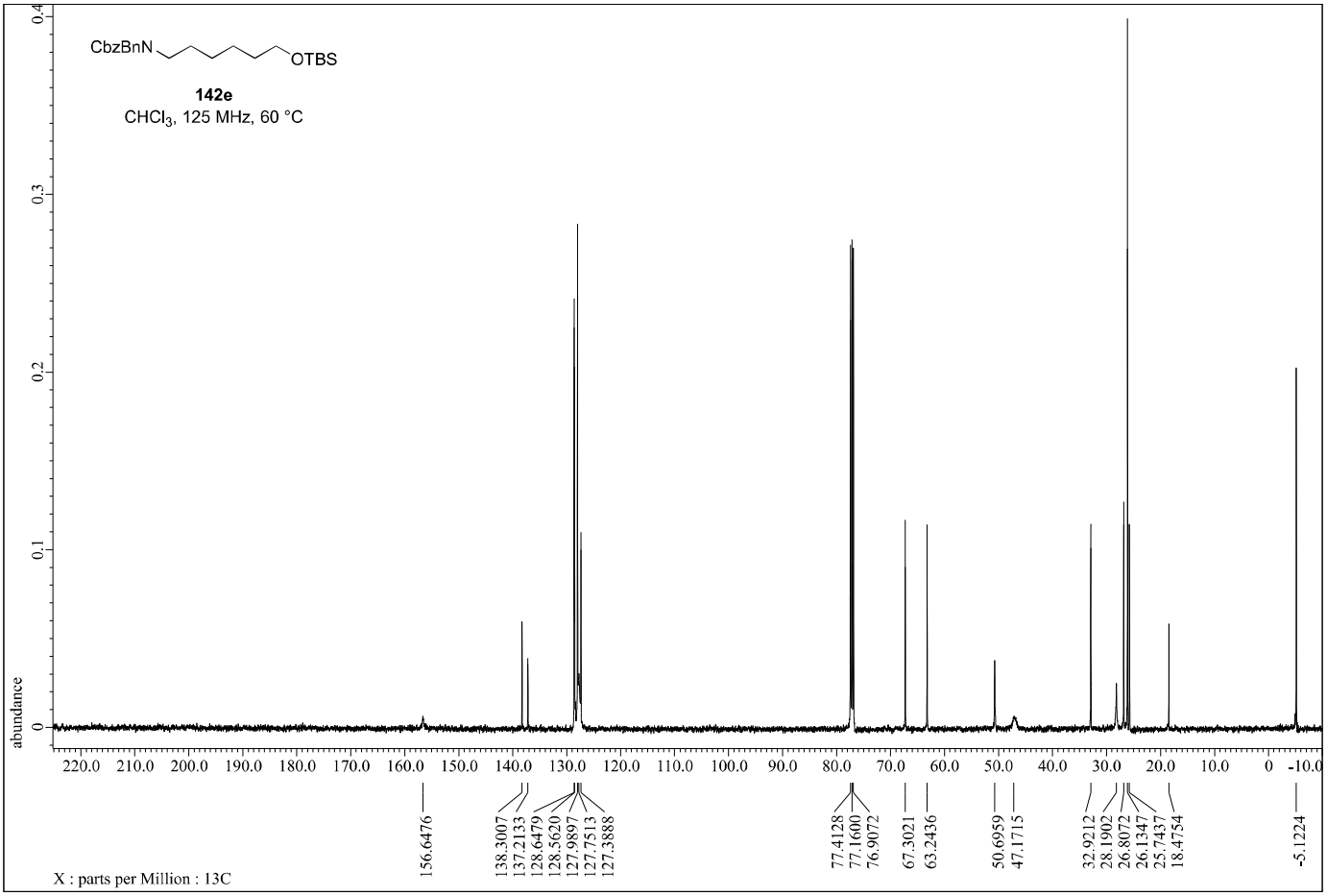
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OTBS
142e
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abundance
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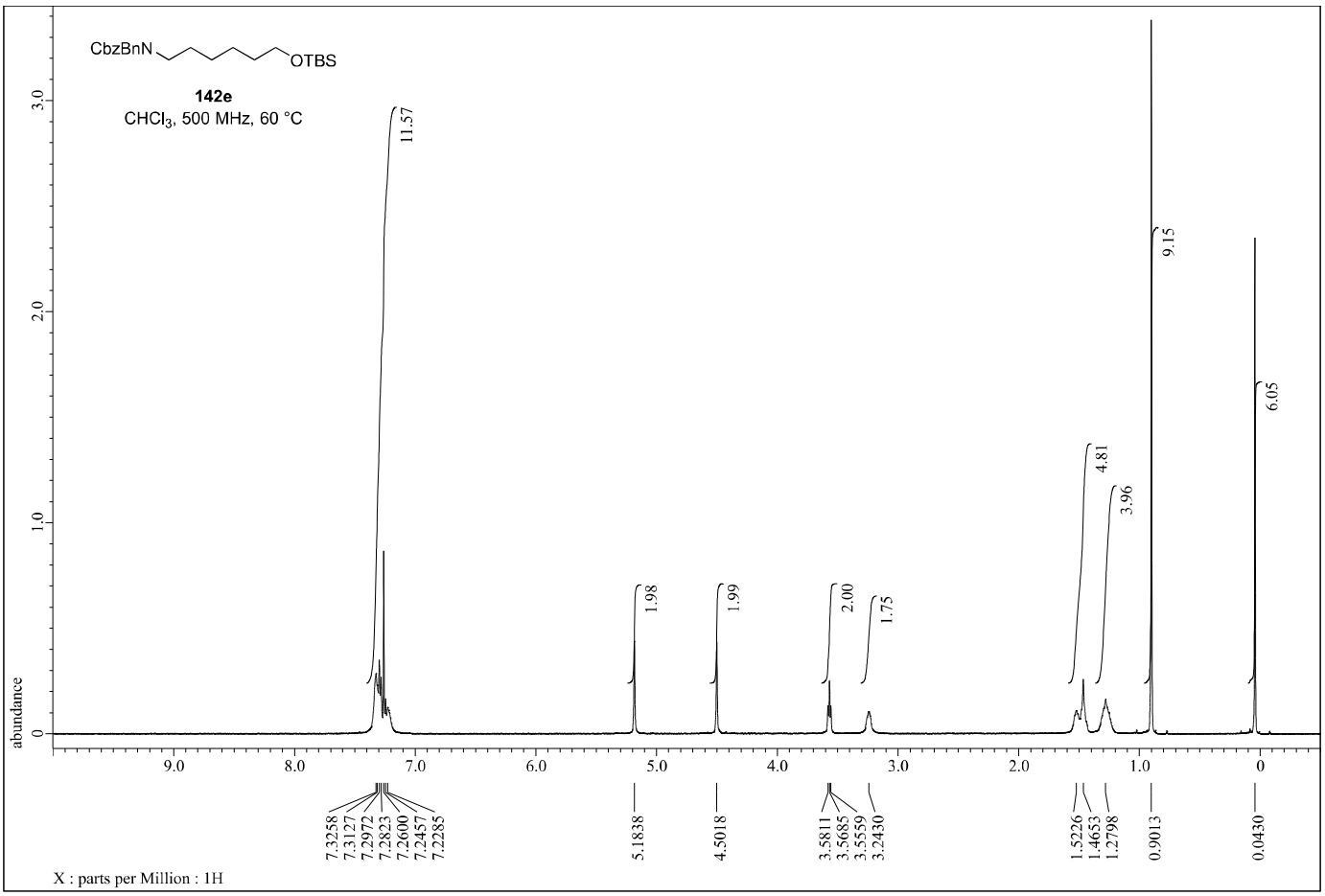
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CHCl3, 500 MHz, 60 °C
abundance
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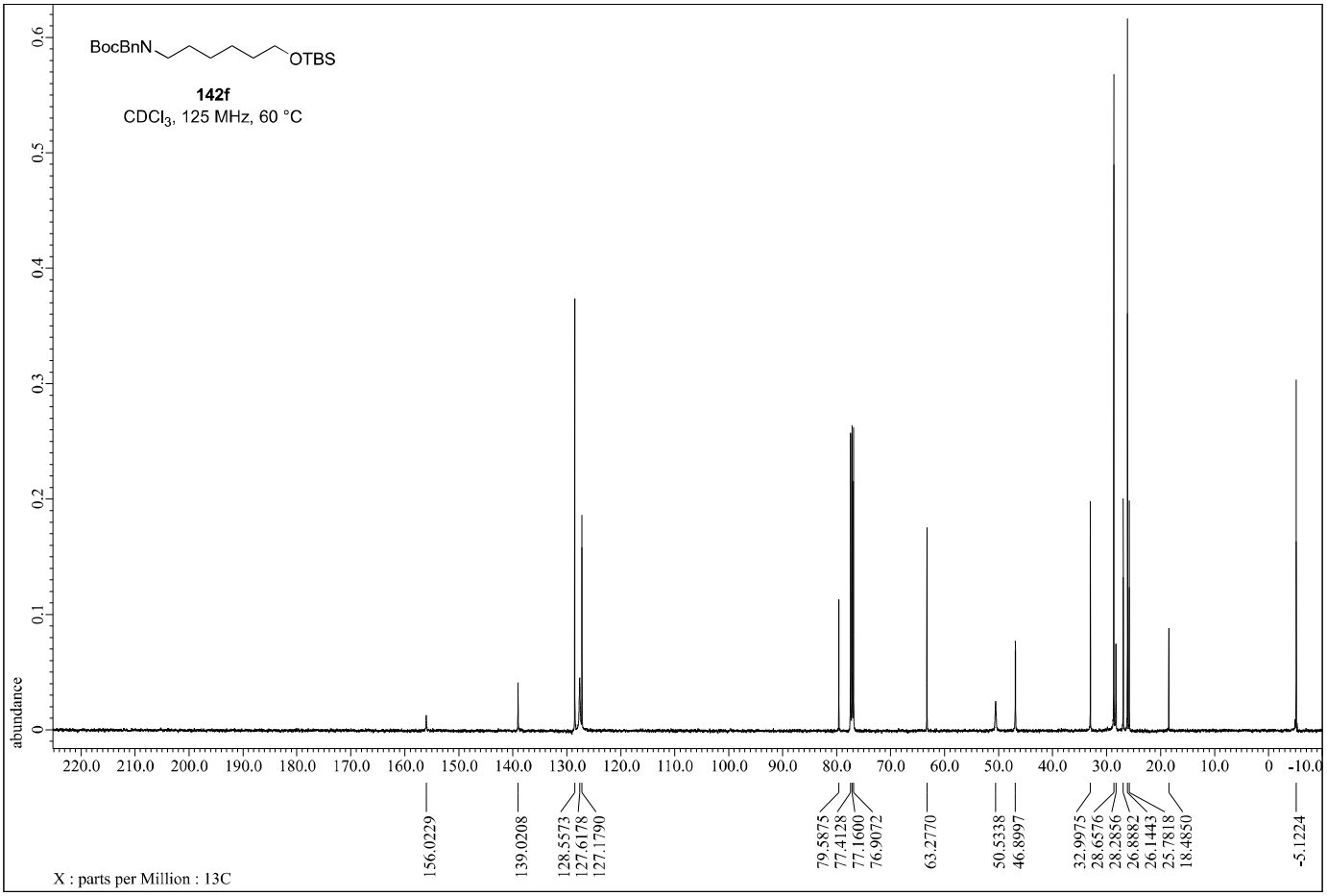
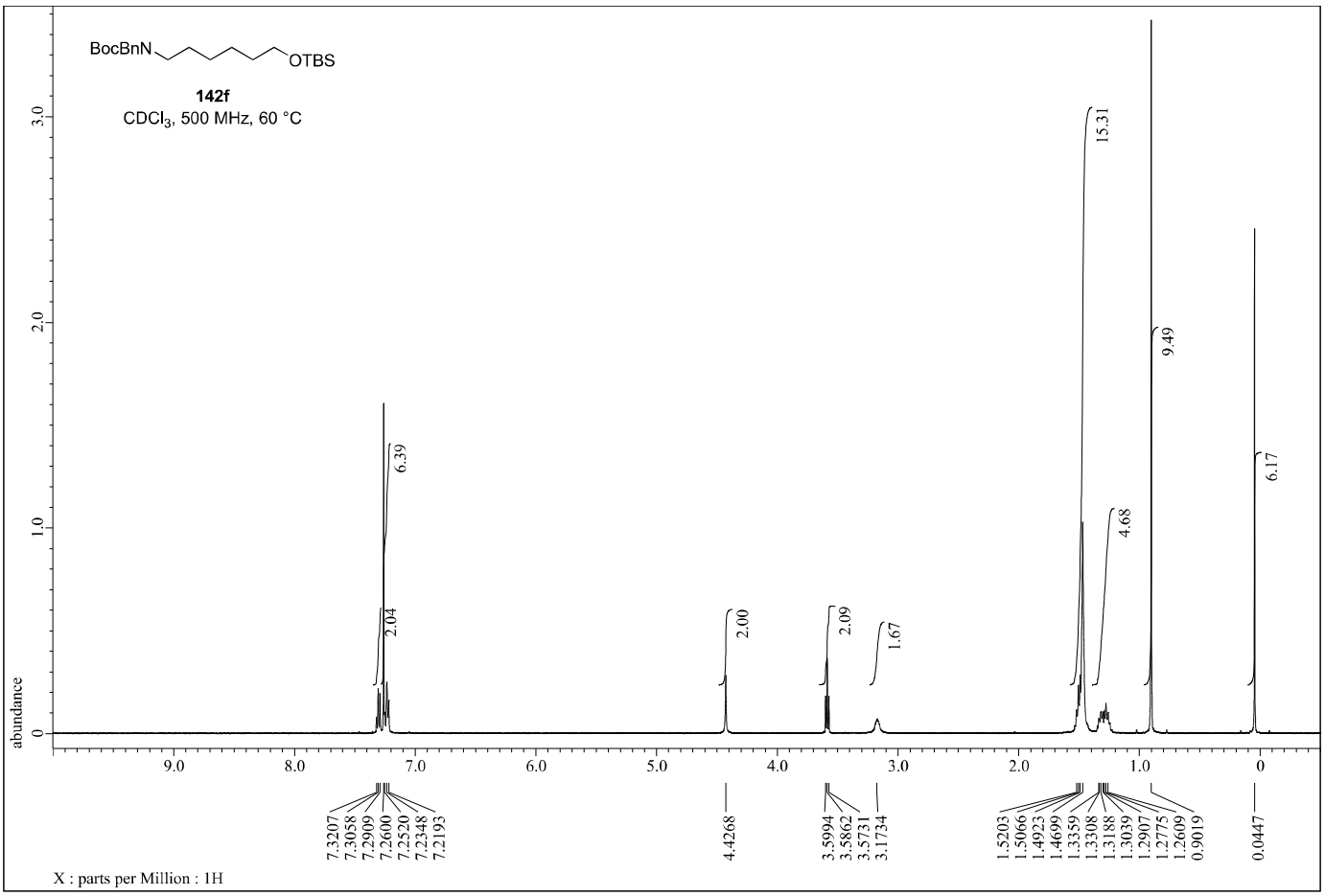
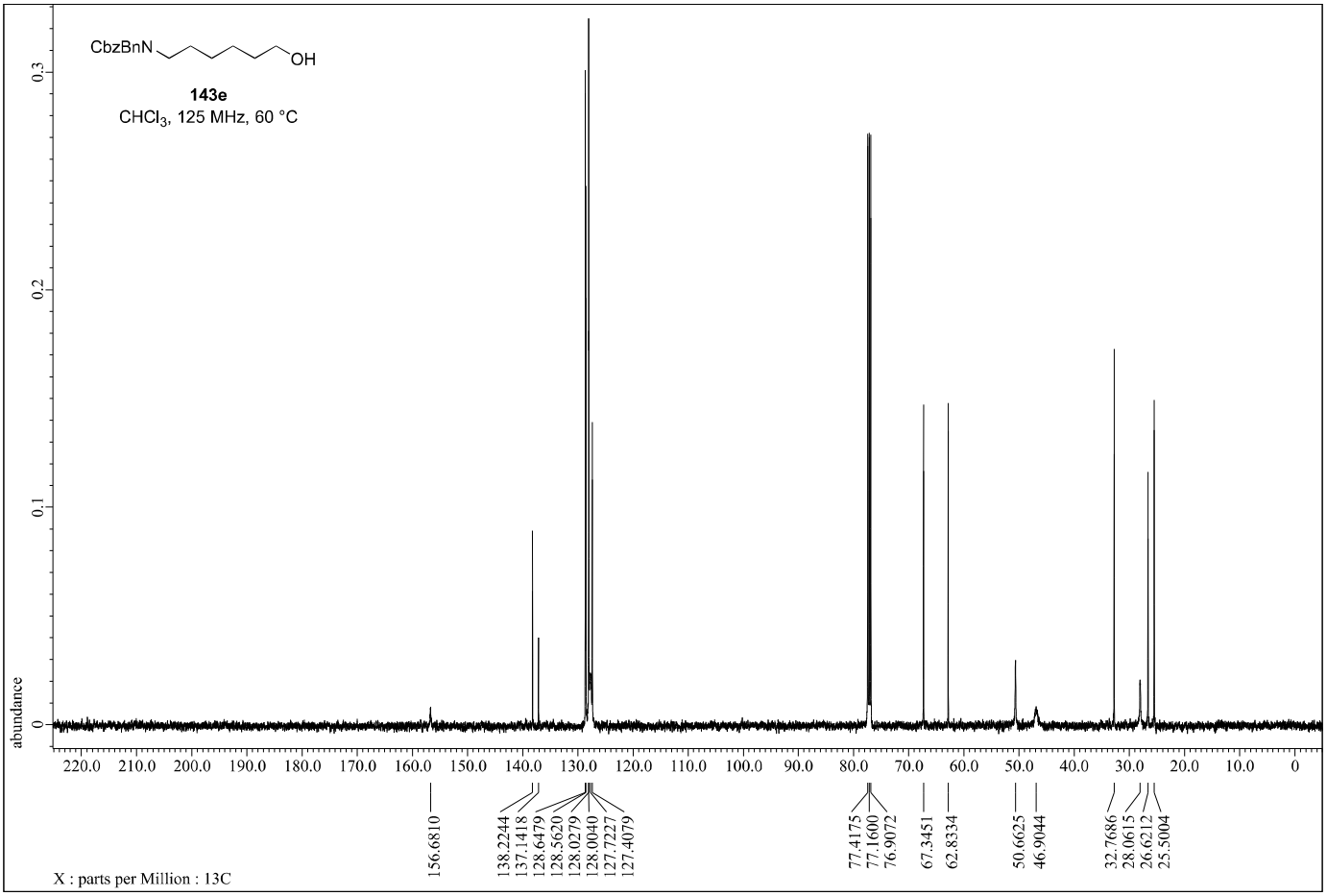
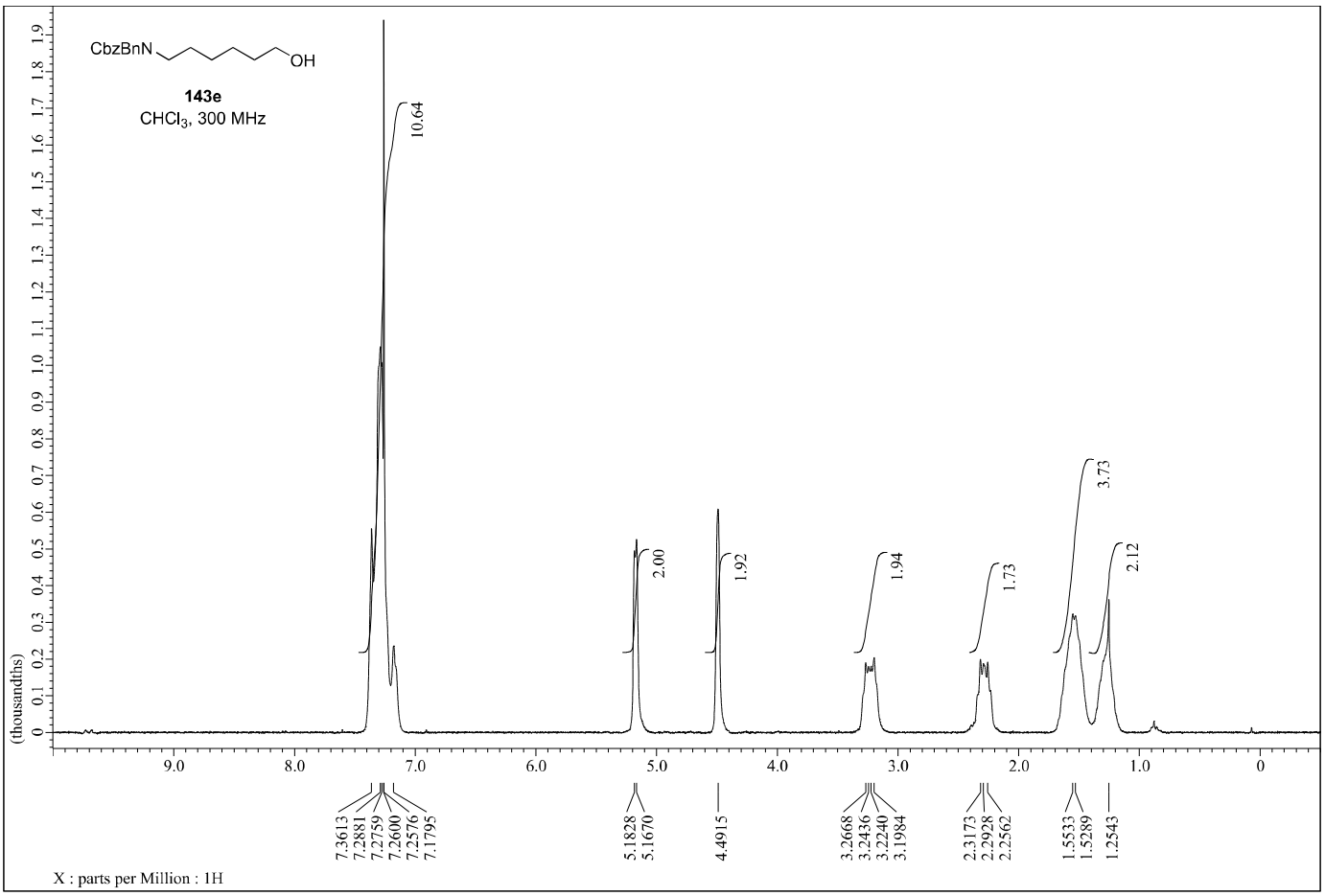
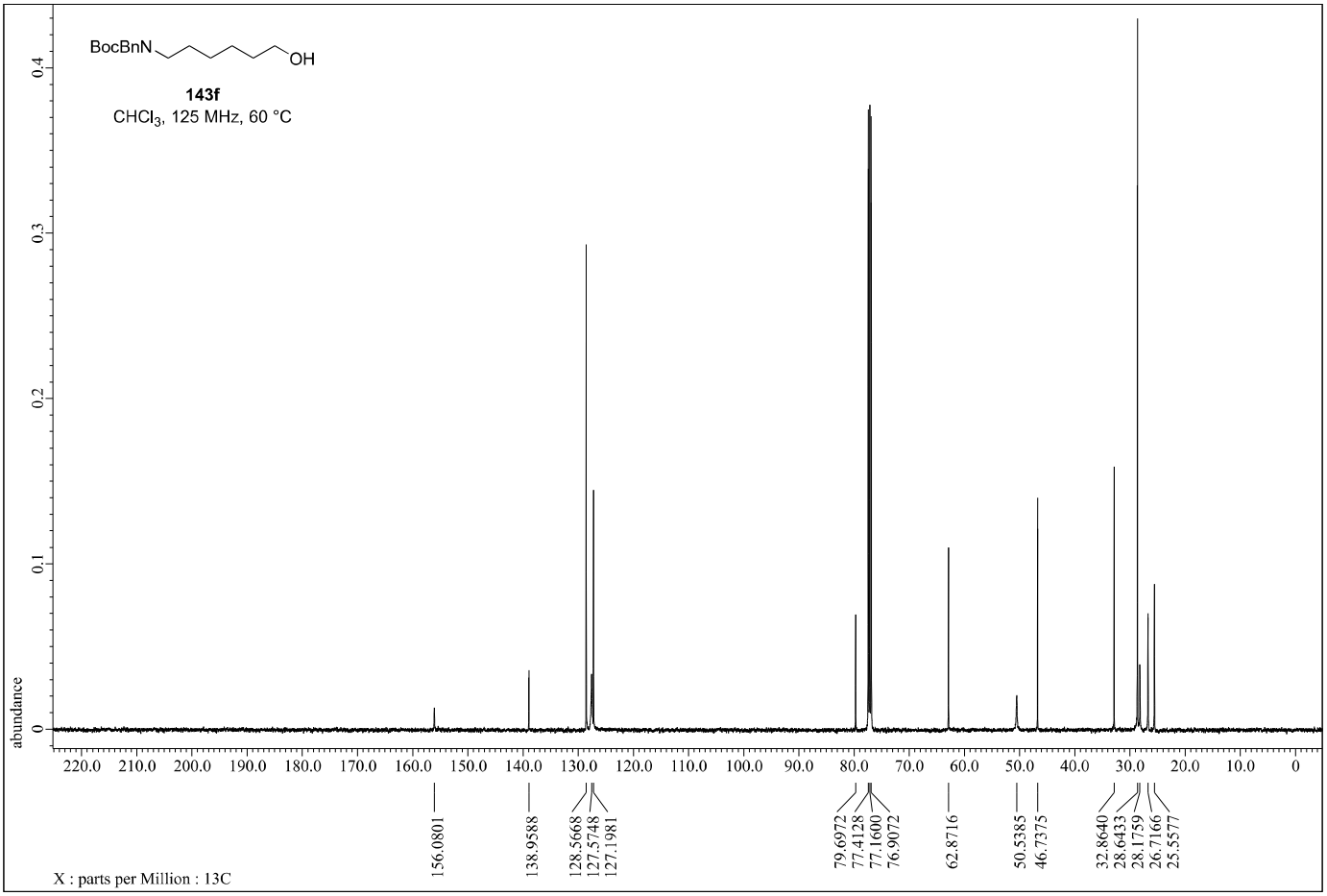
1.99
2.00
1.75
4.81
3.96
9.15
6.05
7.3258
7.3127
7.2972
7.2823
7.2600
7.2457
7.2285
5.1838
4.5018
3.5811
3.5685
3.5559
3.2430
1.5226
1.4653
1.2798
0.9013
0.0430

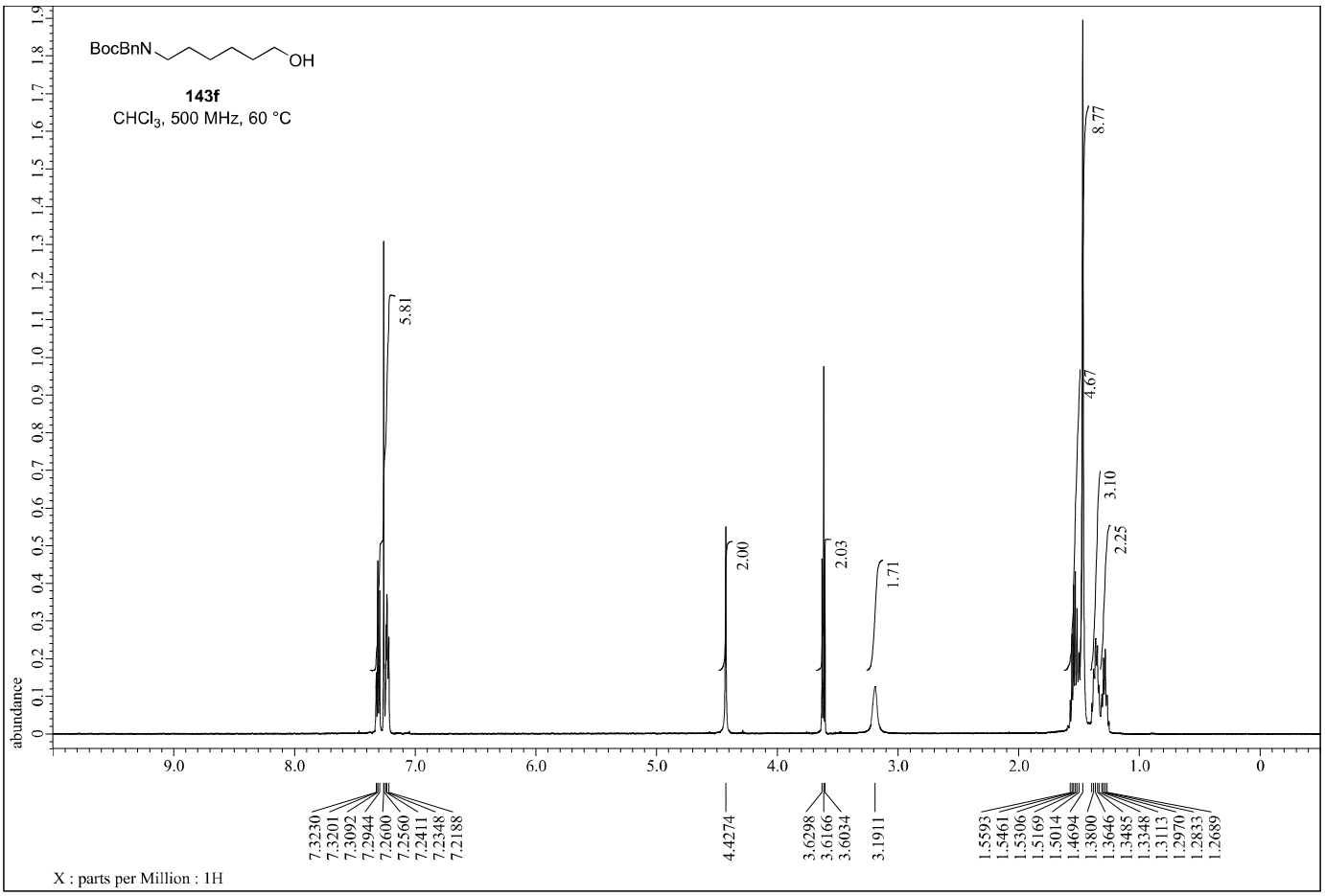

BocBnN
OTBS
142f
CDCl3, 125 MHz, 60 °C
abundance
X : parts per Million : 13C
156.0229
139.0208
128.5573
127.6178
127.1790
79.5875
77.4128
77.1600
76.9072
63.2770
50.5338
46.8997
32.9975
28.6576
28.2856
26.8882
26.1443
25.7818
18.4850
-5.1224

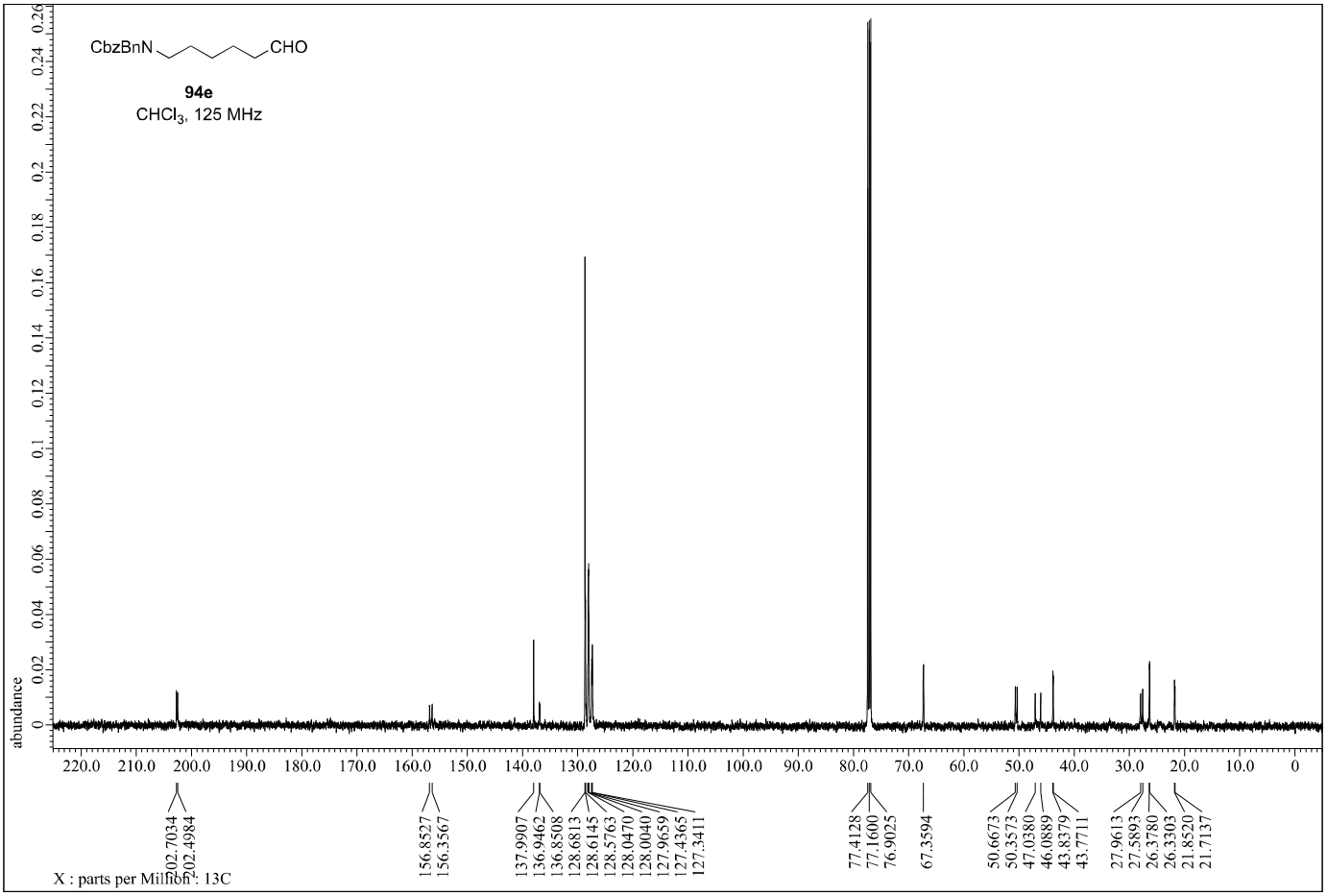

BocBnN
OTBS
142f
CDCl3, 500 MHz, 60 °C
abundance
X : parts per Million : 1H
7.3207
7.3058
7.2909
7.2600
7.2520
7.2348
7.2193
4.4268
3.5994
3.5862
3.5731
3.1734
1.5203
1.5066
1.4923
1.4699
1.3359
1.3308
1.3188
1.3039
1.2907
1.2775
1.2609
0.9019
0.0447
6.39
2.04
2.00
2.09
1.67
15.31
4.68
9.49
6.17

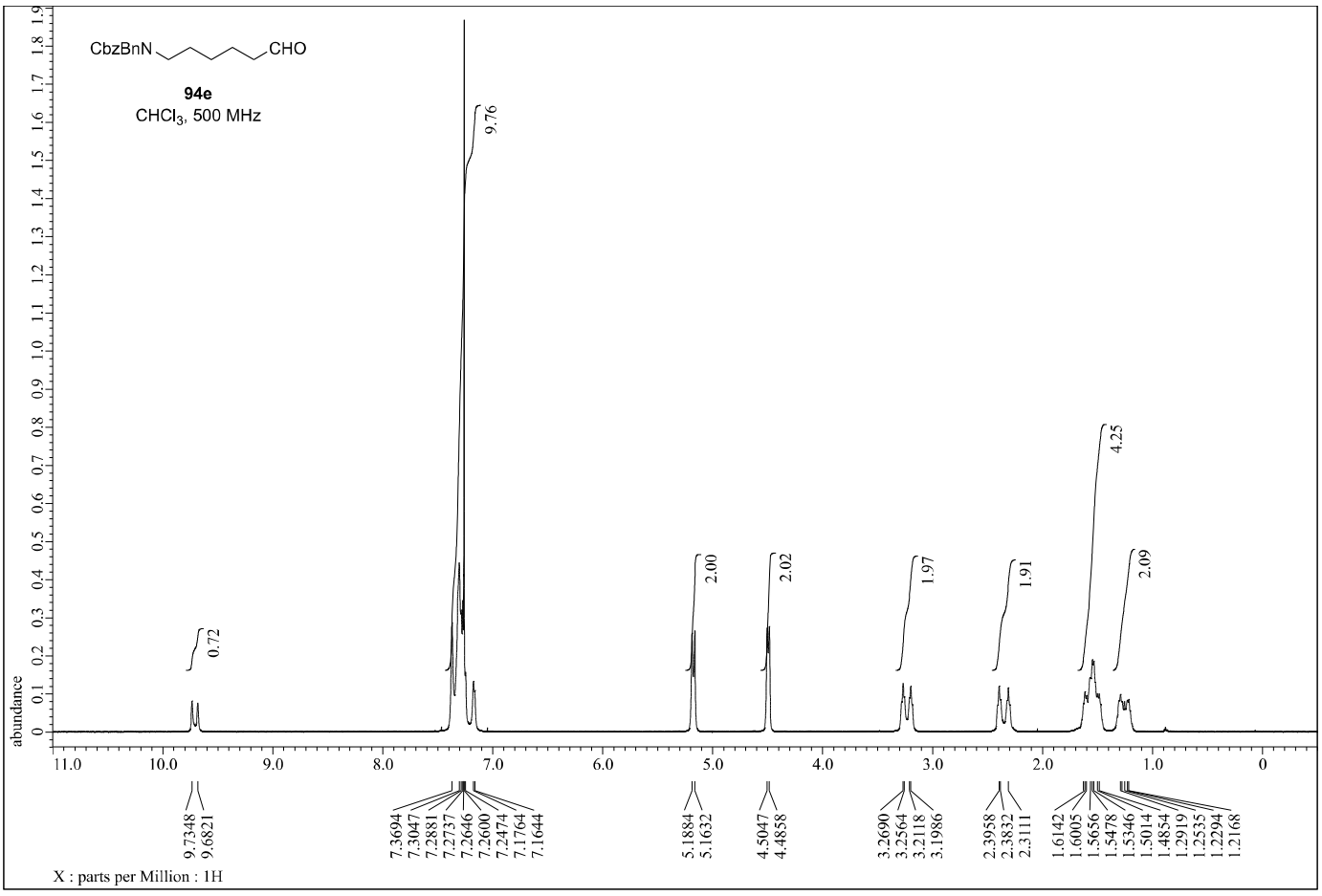

CbzBnN
OH
143e
CHCl3, 125 MHz, 60 °C
abundance
X : parts per Million : 13C
156.6810
138.2244
137.1418
128.6479
128.5620
128.0279
128.0040
127.7227
127.4079
77.4175
77.1600
76.9072
67.3451
62.8334
50.6625
46.9044
32.7686
28.0615
26.6212
25.5004

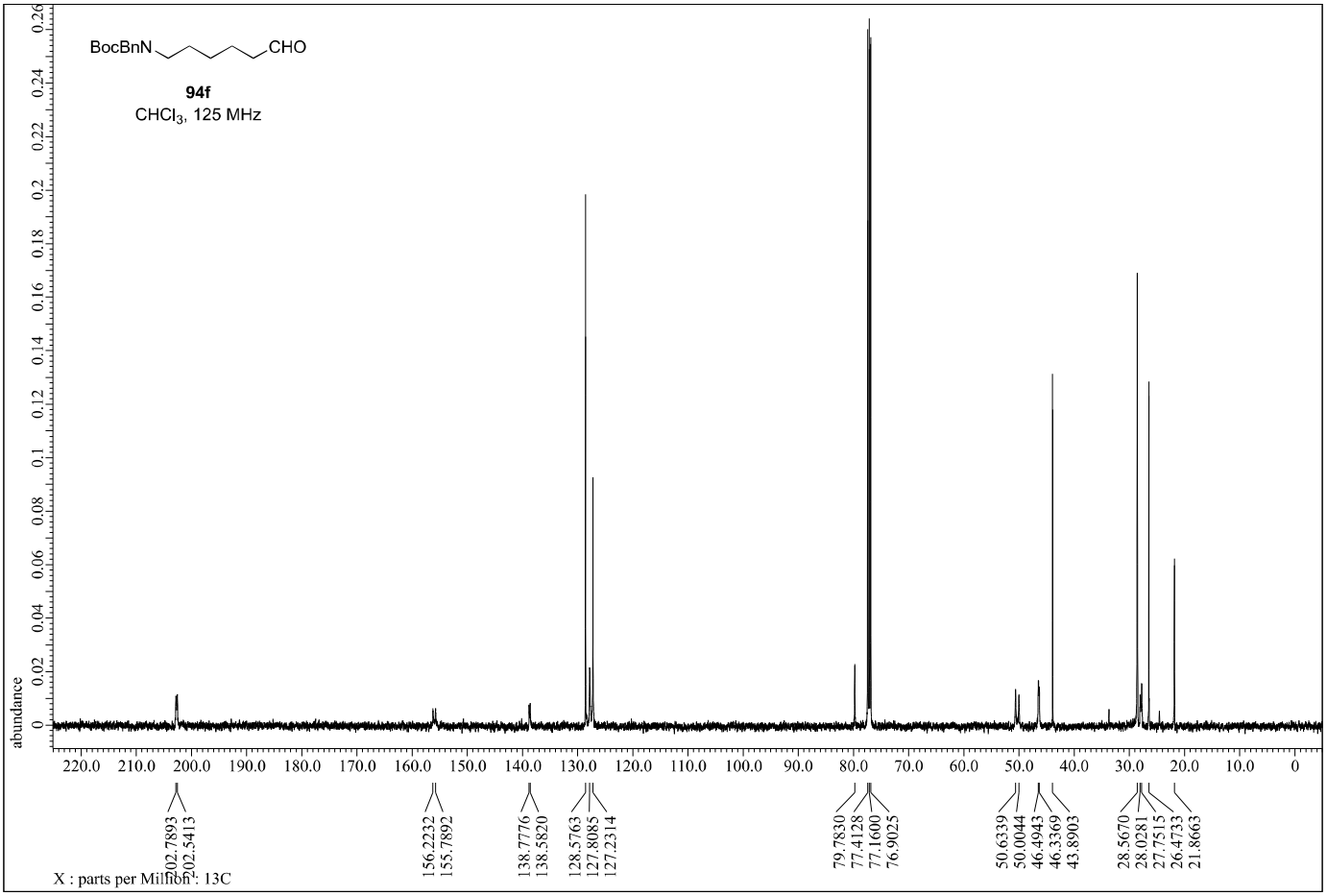

CbzBnN
OH
143e
CHCl3, 300 MHz
(thousandths)
X : parts per Million : 1H
10.64
2.00
1.92
1.94
1.73
3.73
2.12
7.3613
7.2881
7.2759
7.2600
7.2576
7.1795
5.1828
5.1670
4.4915
3.2668
3.2436
3.2240
3.1984
2.3173
2.2928
2.2562
1.5533
1.5289
1.2543

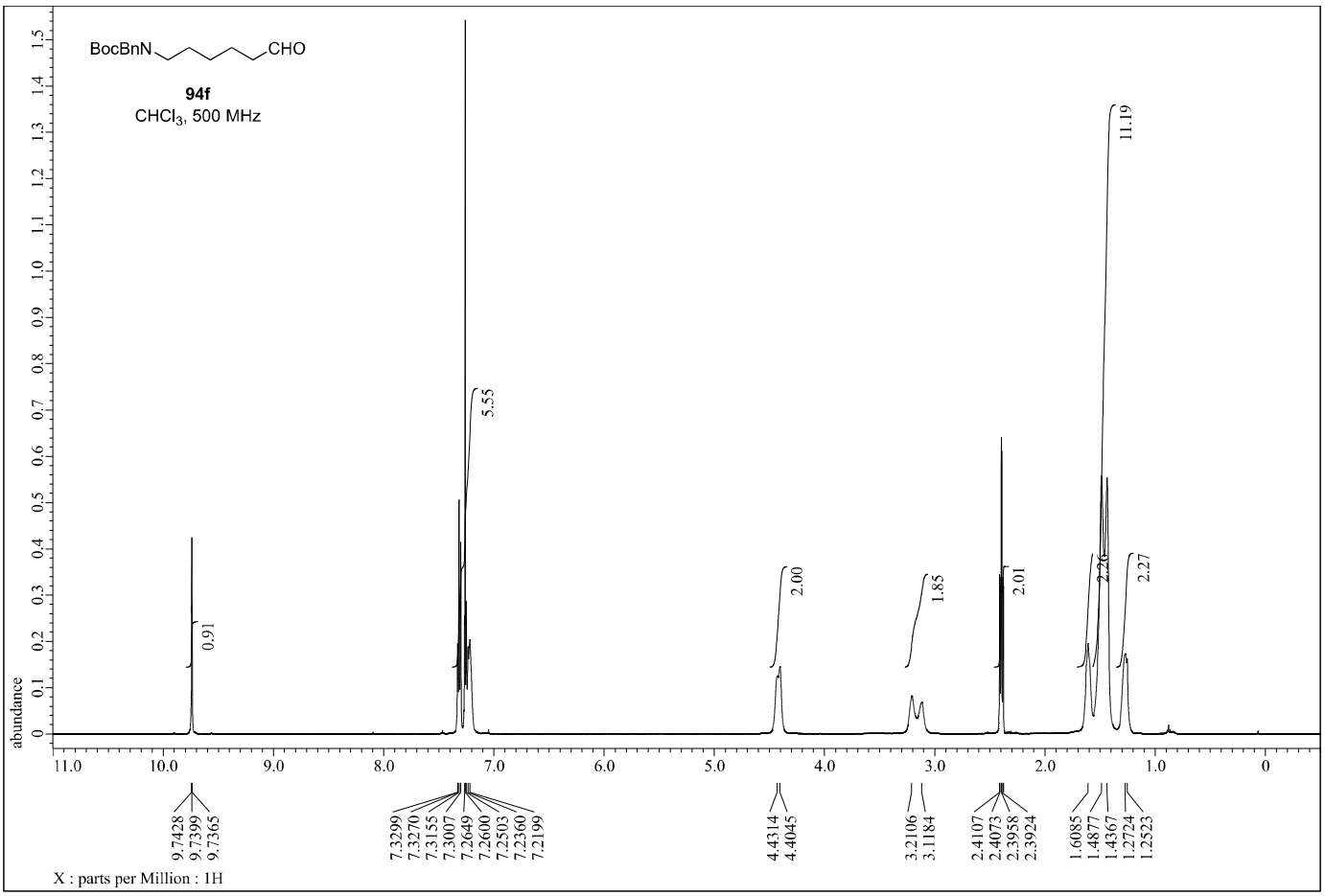

BocBnN
OH
143f
CHCl3, 125 MHz, 60 °C
abundance
156.0801
138.9588
128.5668
127.5748
127.1981
79.6972
77.4128
77.1600
76.9072
62.8716
50.5385
46.7375
32.8640
28.6433
28.1759
26.7166
25.5577
X : parts per Million : 13C

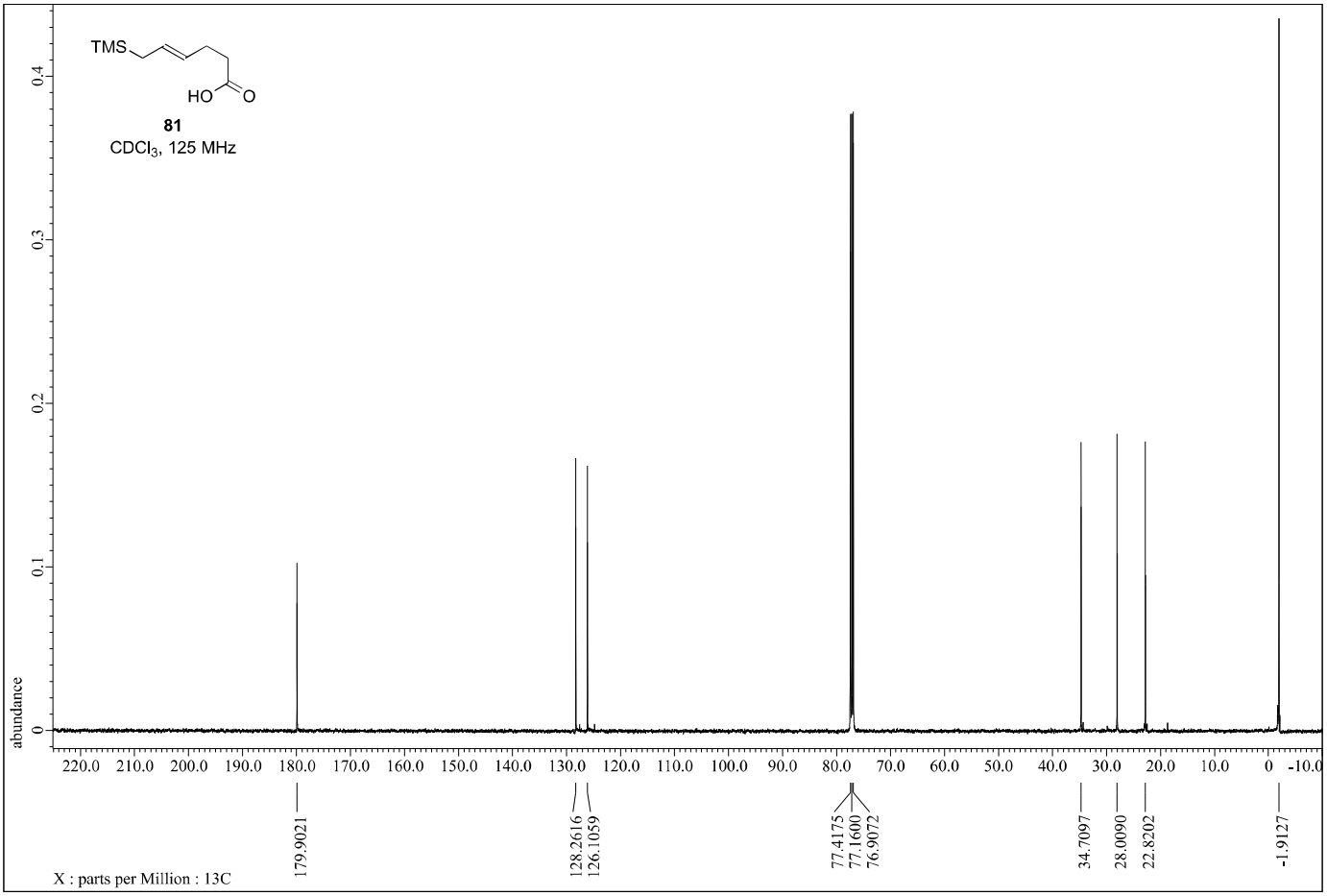

BocBnN
OH
143f
CHCl3, 500 MHz, 60 °C
abundance
8.77
5.81
4.67
3.10
2.25
2.00
2.03
1.71
7.3230
7.3201
7.3092
7.2944
7.2600
7.2560
7.2411
7.2348
7.2188
4.4274
3.6298
3.6166
3.6034
3.1911
1.5593
1.5461
1.5306
1.5169
1.5014
1.4694
1.3800
1.3646
1.3485
1.3348
1.3113
1.2970
1.2833
1.2689
X : parts per Million : 1H

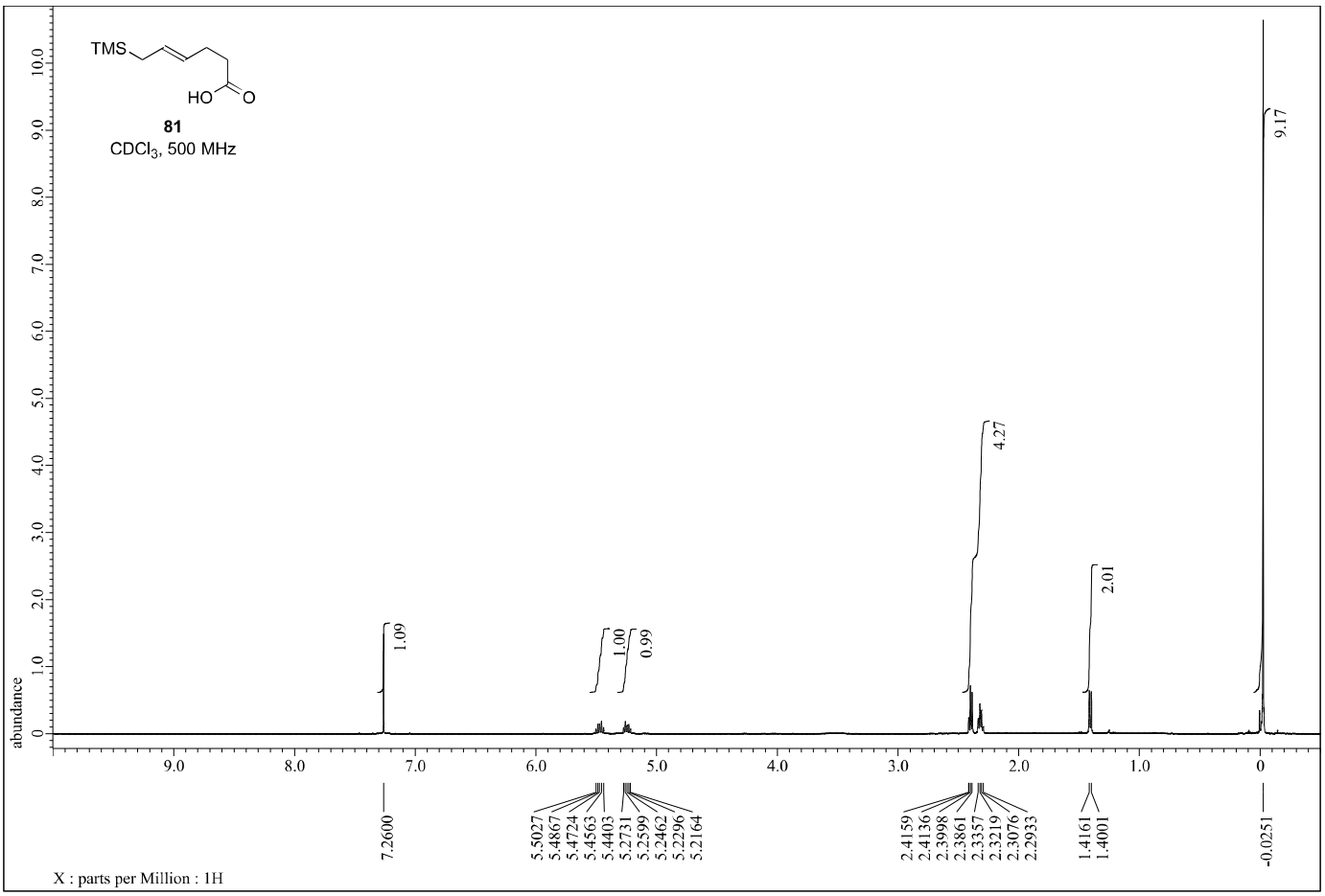

CbzBnN
CHO
94e
CHCl3, 125 MHz
abundance
X : parts per Million : 13C

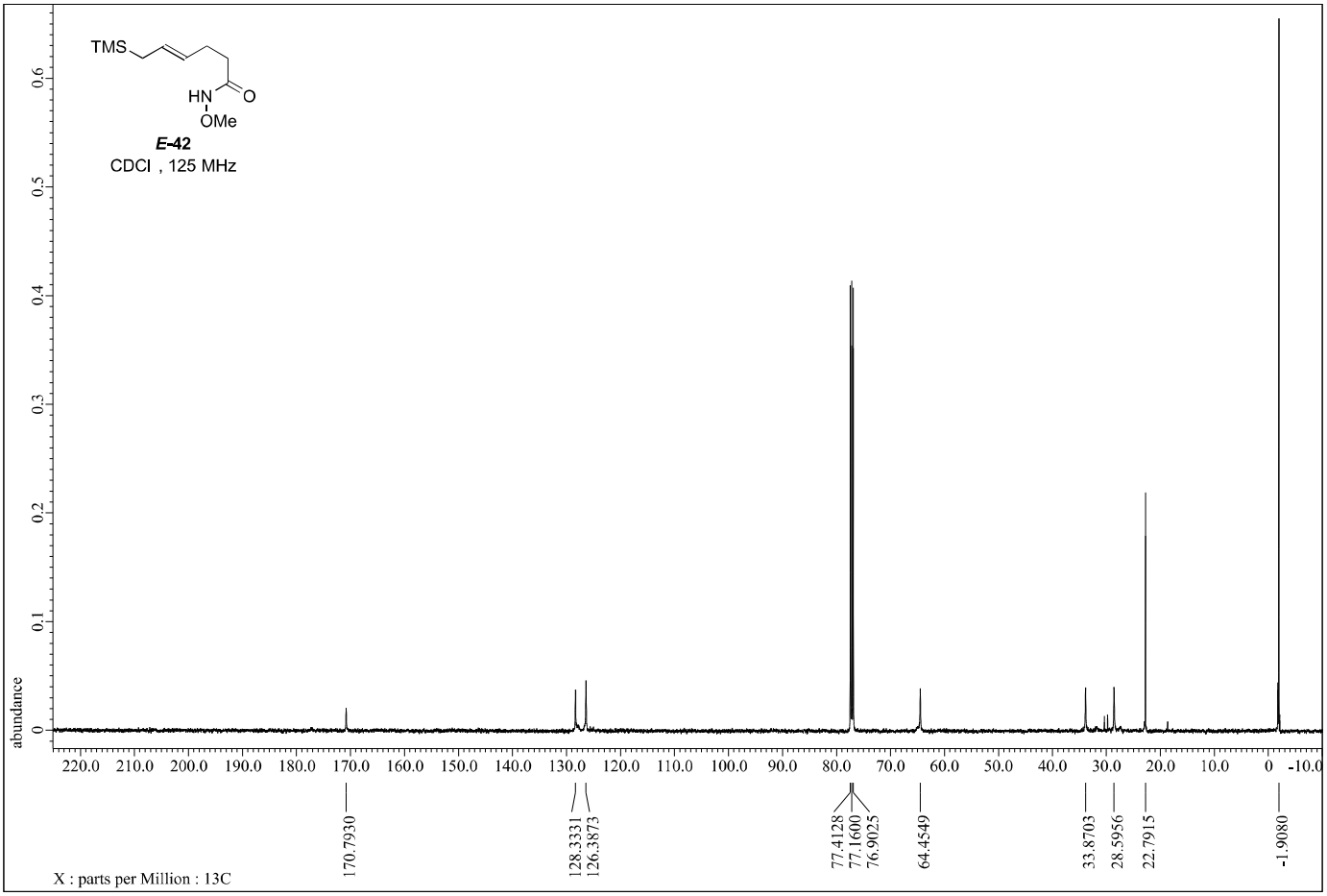

CbzBnN
CHO
94e
CHCl3, 500 MHz
9.76
0.72
2.00
2.02
1.97
1.91
4.25
2.09
abundance
X : parts per Million : 1H

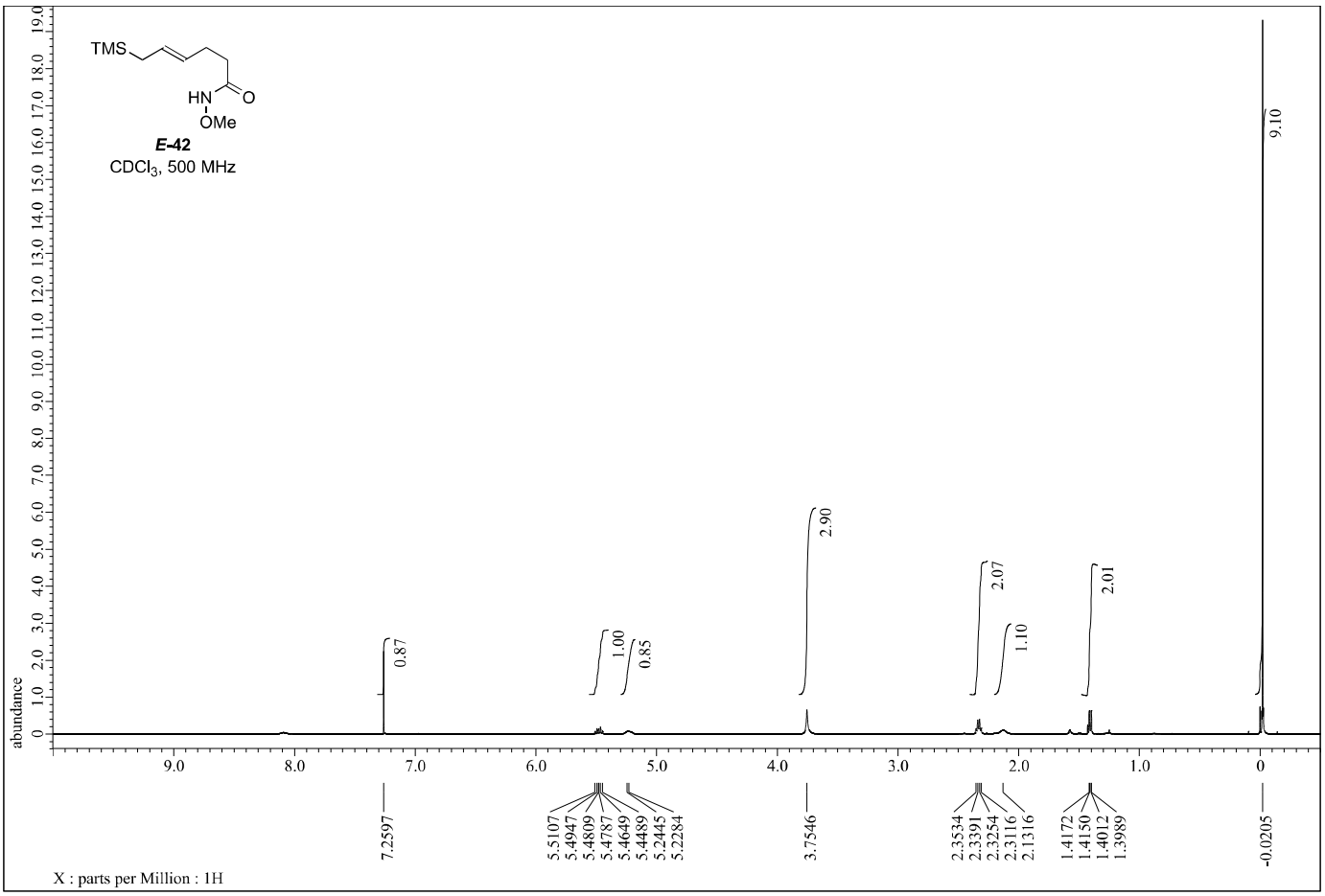

BocBnN
CHO
94f
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
202.7893
202.5413
156.2232
155.7892
138.7776
138.5820
128.5763
127.8085
127.2314
79.7830
77.4128
77.1600
76.9025
50.6339
50.0044
46.4943
46.3369
43.8903
28.5670
28.0281
27.7515
26.4733
21.8663

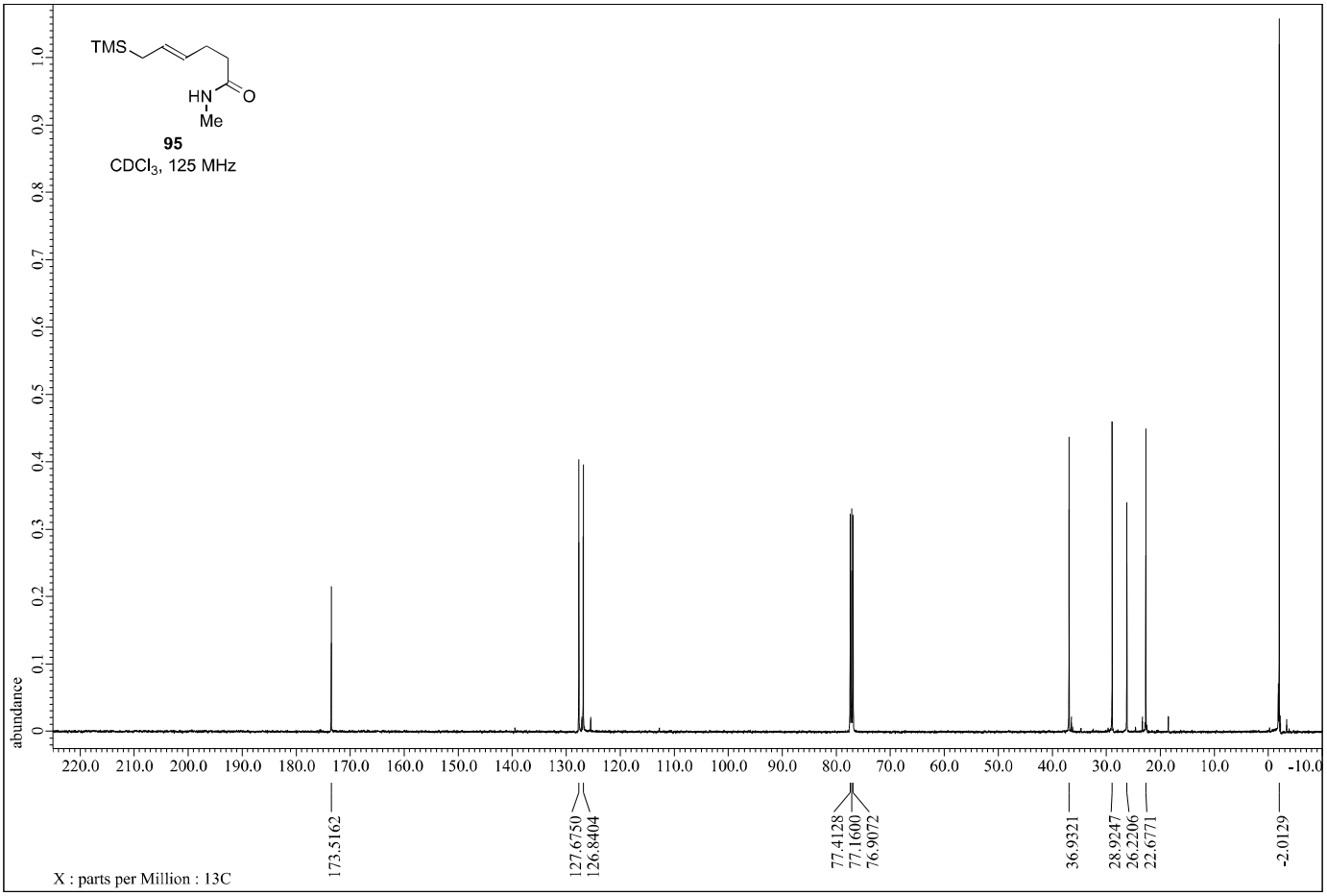

BocBnN
CHO
94f
CHCl3, 500 MHz
abundance
X : parts per Million : 1H
0.91
5.55
2.00
1.85
2.01
2.26
2.27
11.19
9.7428
9.7399
9.7365
7.3299
7.3270
7.3155
7.3007
7.2649
7.2600
7.2503
7.2360
7.2199
4.4314
4.4045
3.2106
3.1184
2.4107
2.4073
2.3958
2.3924
1.6085
1.4877
1.4367
1.2724
1.2523

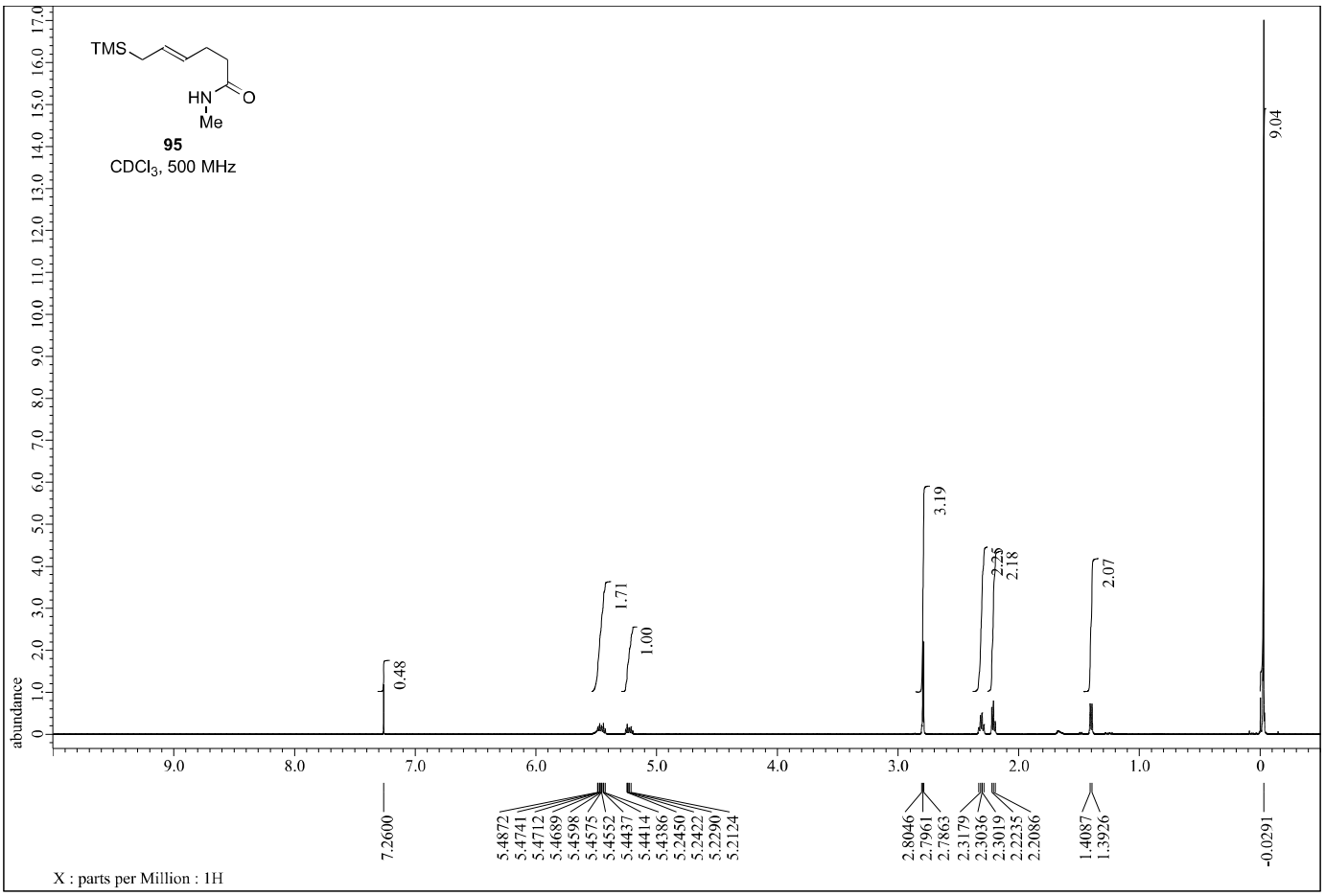

TMS
HO
O
81
CDCl3, 125 MHz
abundance
179.9021
128.2616
126.1059
77.4175
77.1600
76.9072
34.7097
28.0090
22.8202
-1.9127
X : parts per Million : 13C

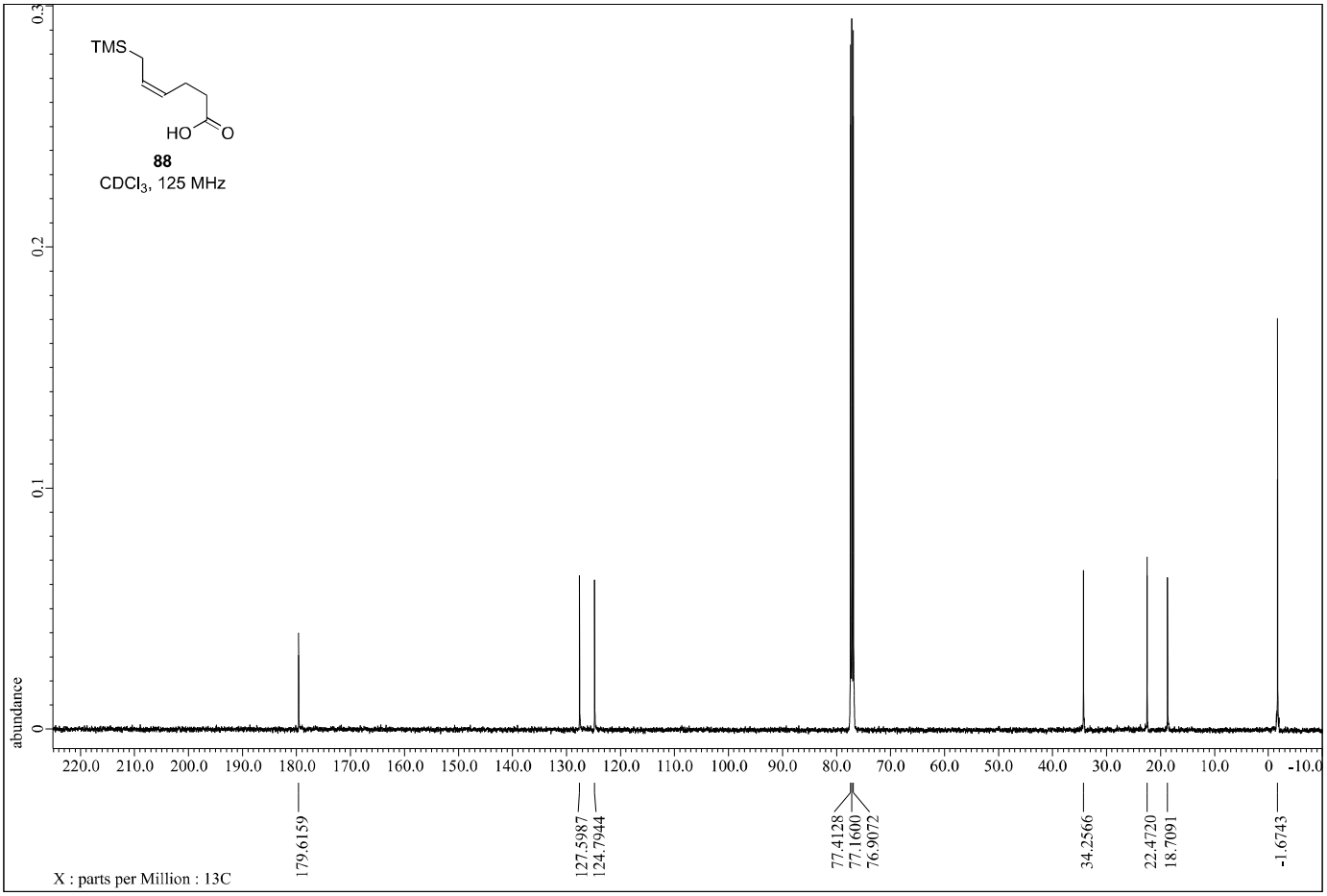

TMS
HO
O
81
CDCl3, 500 MHz
abundance
1.09
1.00
0.99
4.27
2.01
9.17
7.2600
5.5027
5.4867
5.4724
5.4563
5.4403
5.2731
5.2599
5.2462
5.2296
5.2164
2.4159
2.4136
2.3998
2.3861
2.3357
2.3219
2.3076
2.2933
1.4161
1.4001
-0.0251
X : parts per Million : 1H

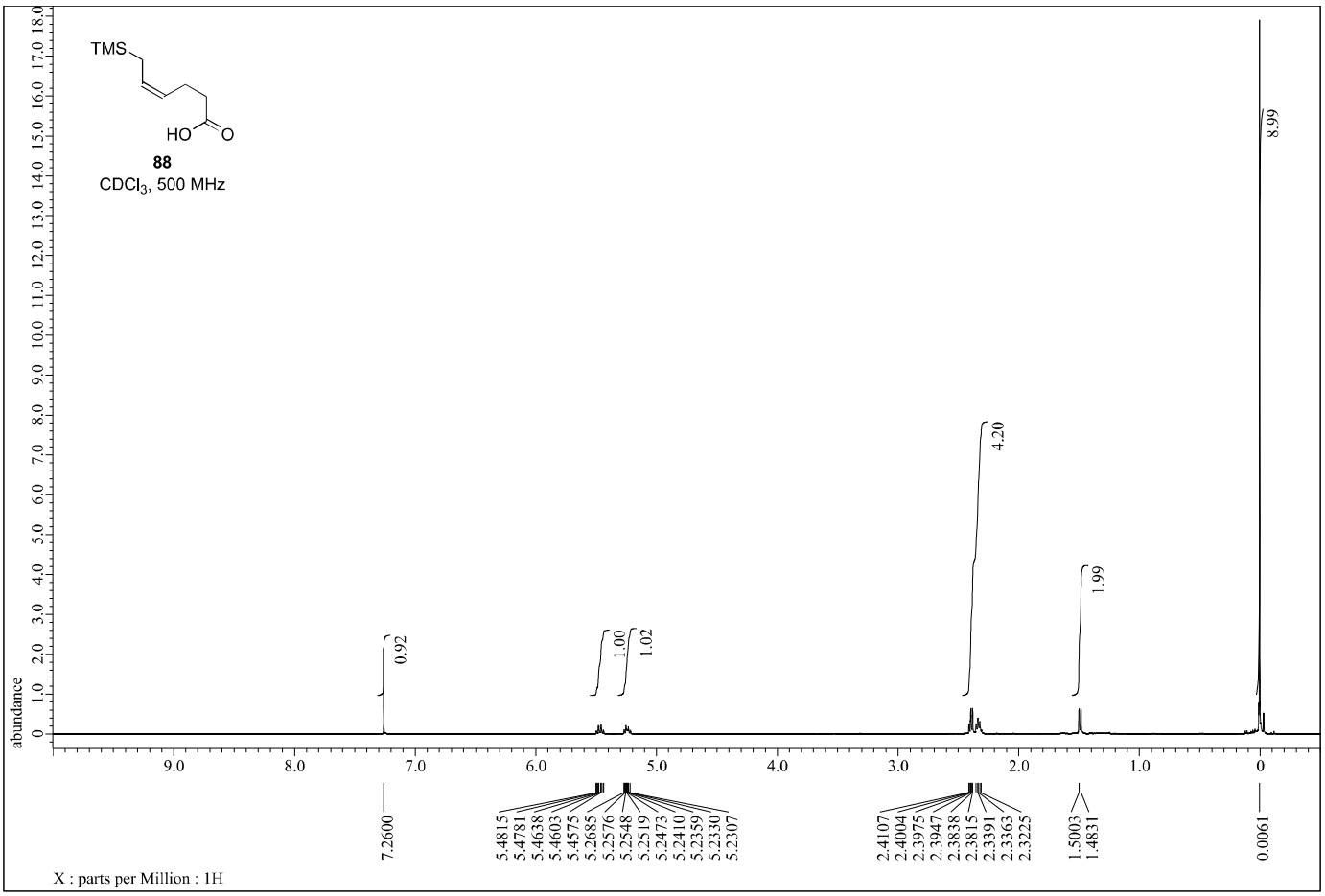

TMS
HN
O
OMe
E-42
CDCl , 125 MHz
abundance
170.7930
128.3331
126.3873
77.4128
77.1600
76.9025
64.4549
33.8703
28.5956
22.7915
-1.9080
X : parts per Million : 13C

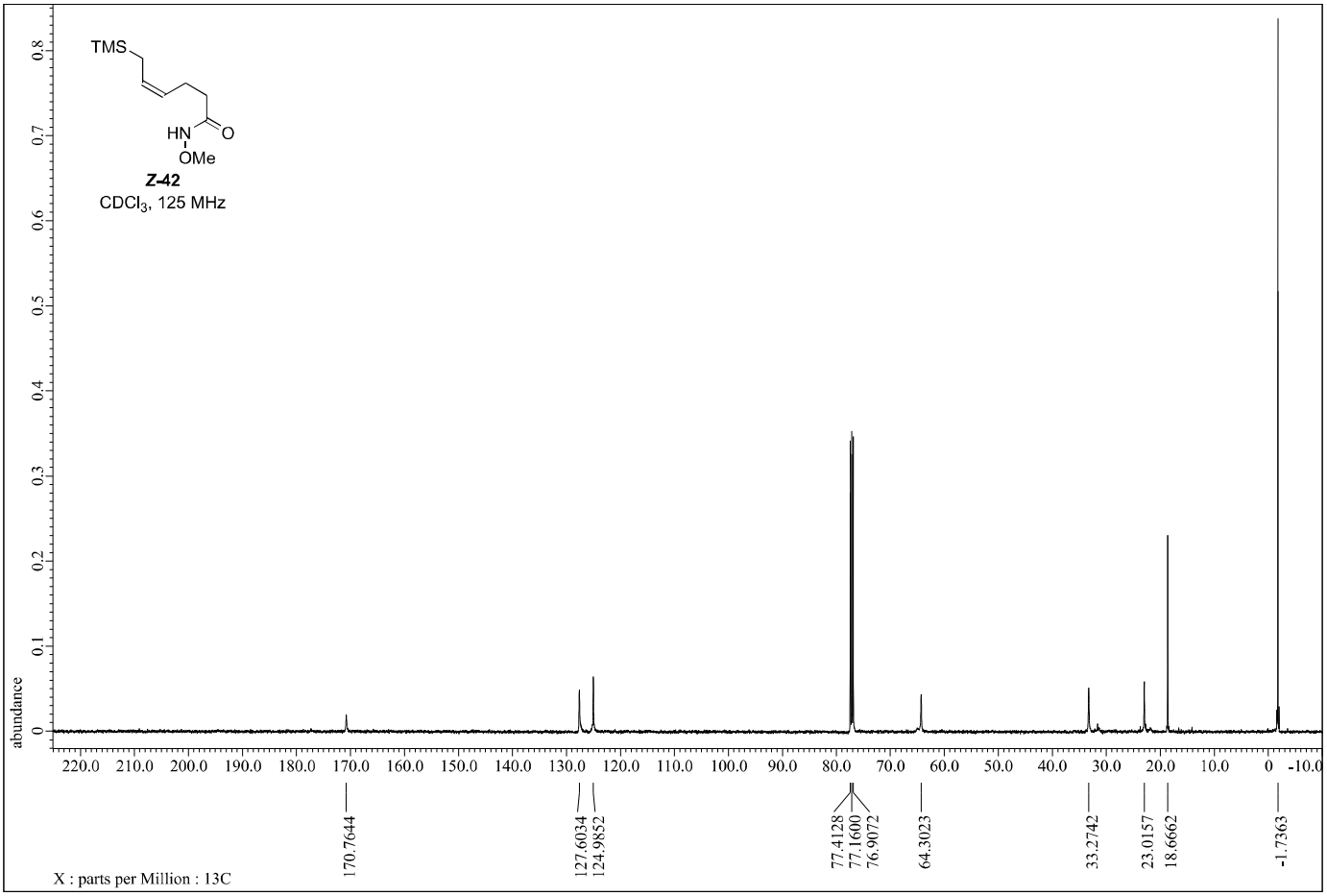

TMS
HN
O
OMe
E-42
CDCl3, 500 MHz
abundance
0.87
1.00
0.85
2.90
2.07
1.10
2.01
9.10
7.2597
5.5107
5.4947
5.4809
5.4787
5.4649
5.4489
5.2445
5.2284
3.7546
2.3534
2.3391
2.3254
2.3116
2.1316
1.4172
1.4150
1.4012
1.3989
-0.0205
X : parts per Million : 1H

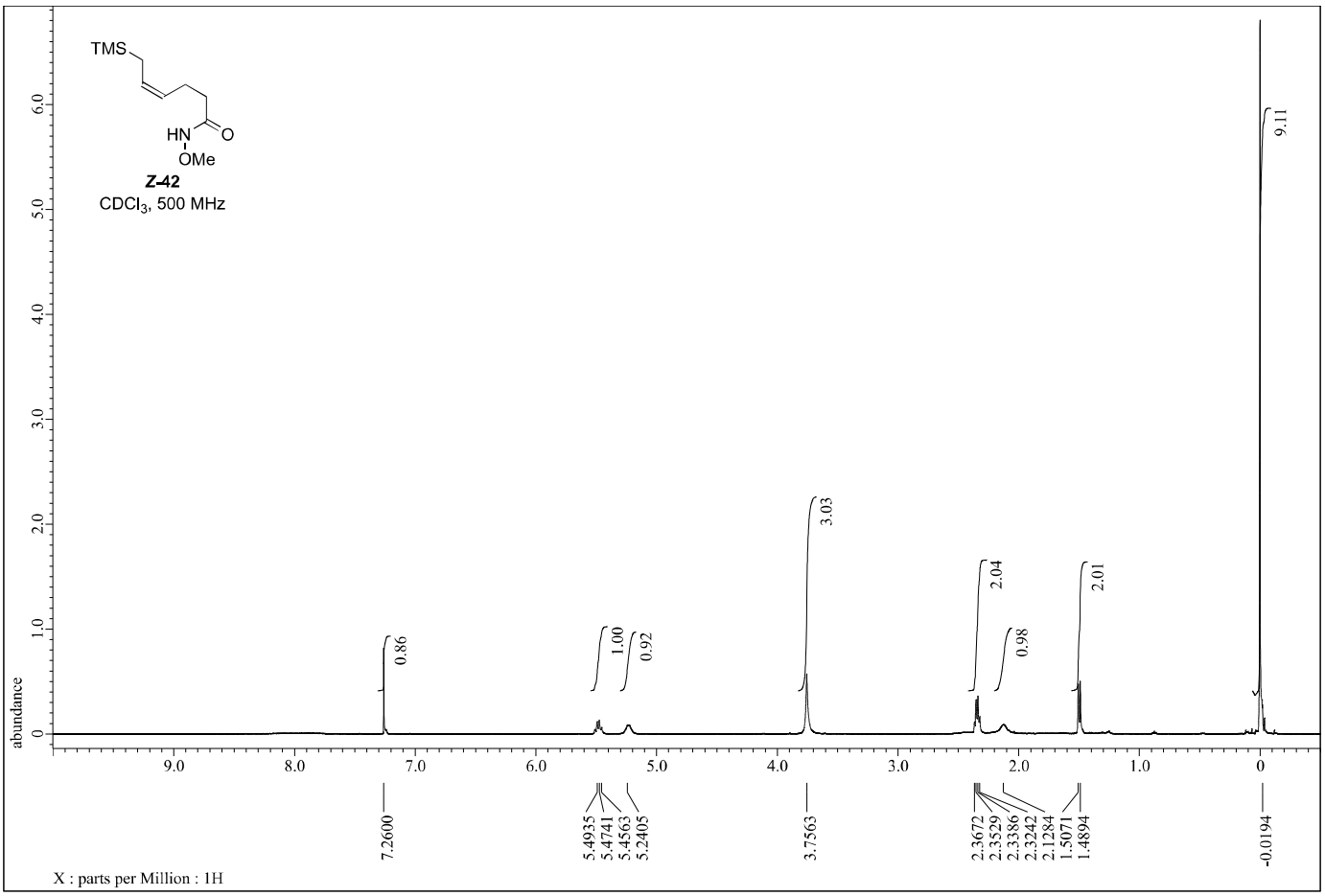

TMS
HN
O
Me
95
CDCl3, 125 MHz
abundance
X : parts per Million : 13C
173.5162
127.6750
126.8404
77.4128
77.1600
76.9072
36.9321
28.9247
26.2206
22.6771
-2.0129

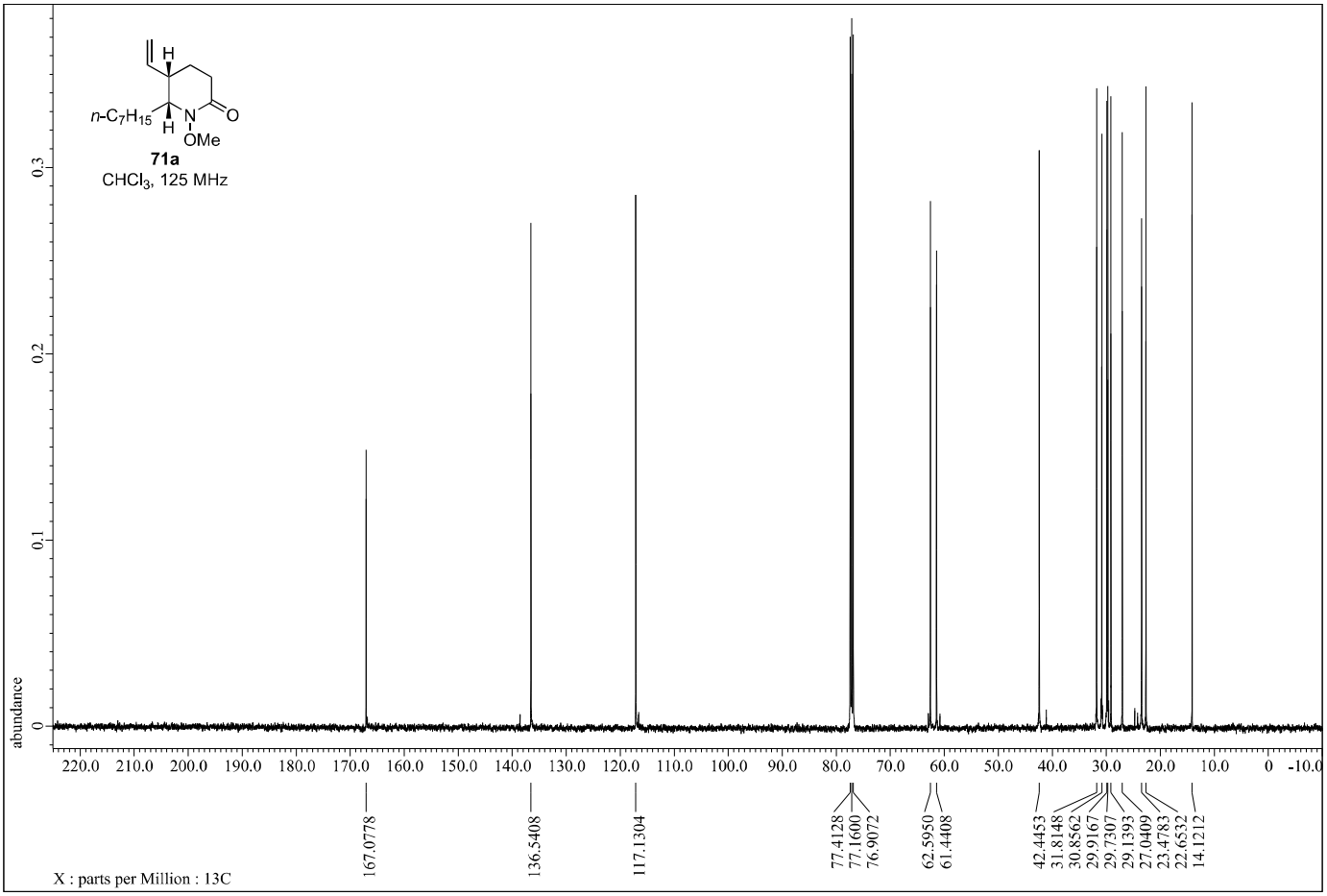

TMS
HN
O
Me
95
CDCl3, 500 MHz
abundance
X : parts per Million : 1H
9.04
3.19
2.25
2.18
2.07
1.71
1.00
0.48
7.2600
5.4872
5.4741
5.4712
5.4689
5.4598
5.4575
5.4552
5.4437
5.4414
5.4386
5.2450
5.2422
5.2290
5.2124
2.8046
2.7961
2.7863
2.3179
2.3036
2.3019
2.2235
2.2086
1.4087
1.3926
-0.0291

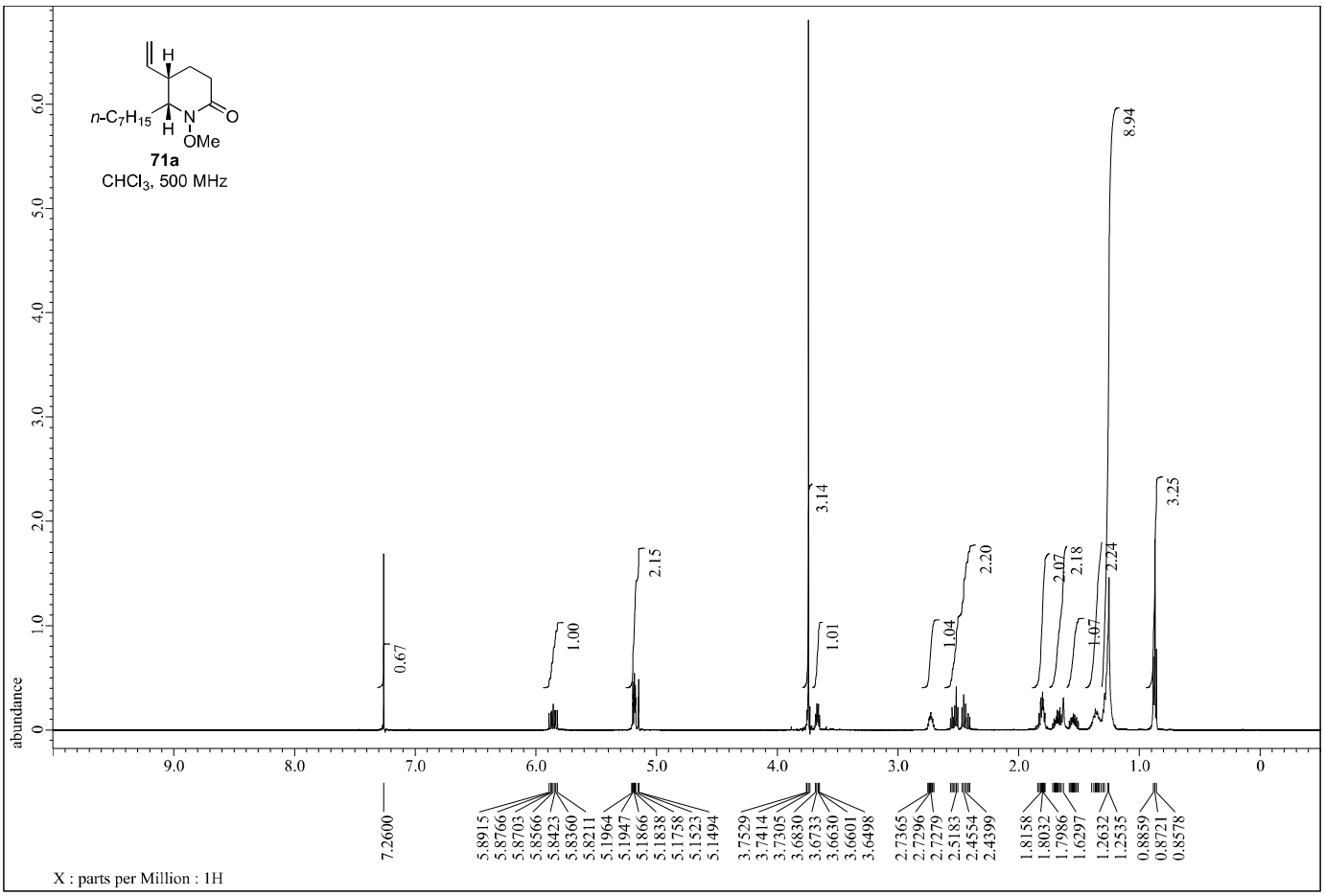

TMS
HO
O
88
CDCl3, 125 MHz
abundance
179.6159
127.5987
124.7944
77.4128
77.1600
76.9072
34.2566
22.4720
18.7091
-1.6743
X : parts per Million : 13C

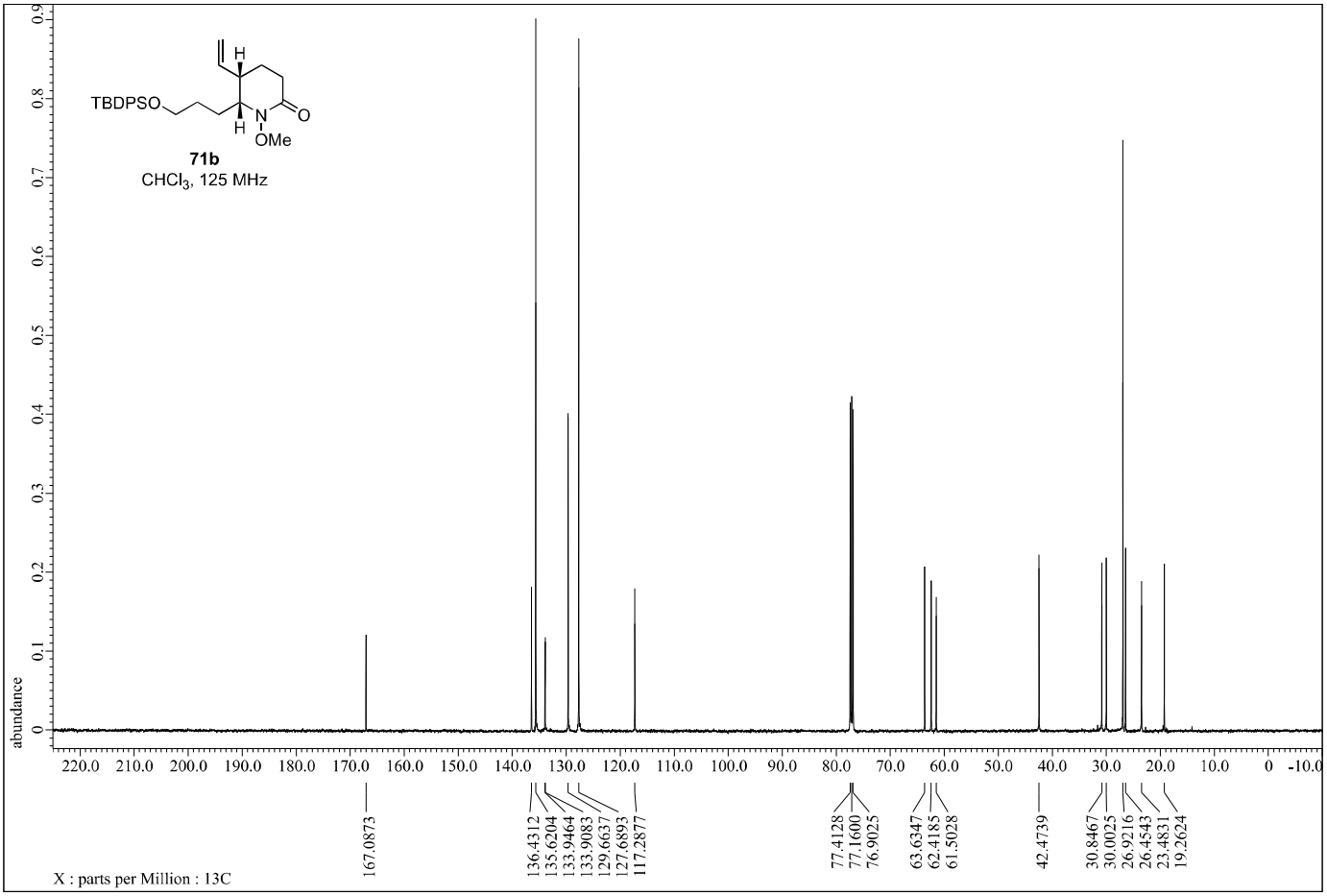

TMS
HO
O
88
CDCl3, 500 MHz
abundance
0.92
1.00
1.02
4.20
1.99
8.99
7.2600
5.4815
5.4781
5.4638
5.4603
5.4575
5.2685
5.2576
5.2548
5.2519
5.2473
5.2410
5.2359
5.2330
5.2307
2.4107
2.4004
2.3975
2.3947
2.3838
2.3815
2.3391
2.3363
2.3225
1.5003
1.4831
0.0061
X : parts per Million : 1H

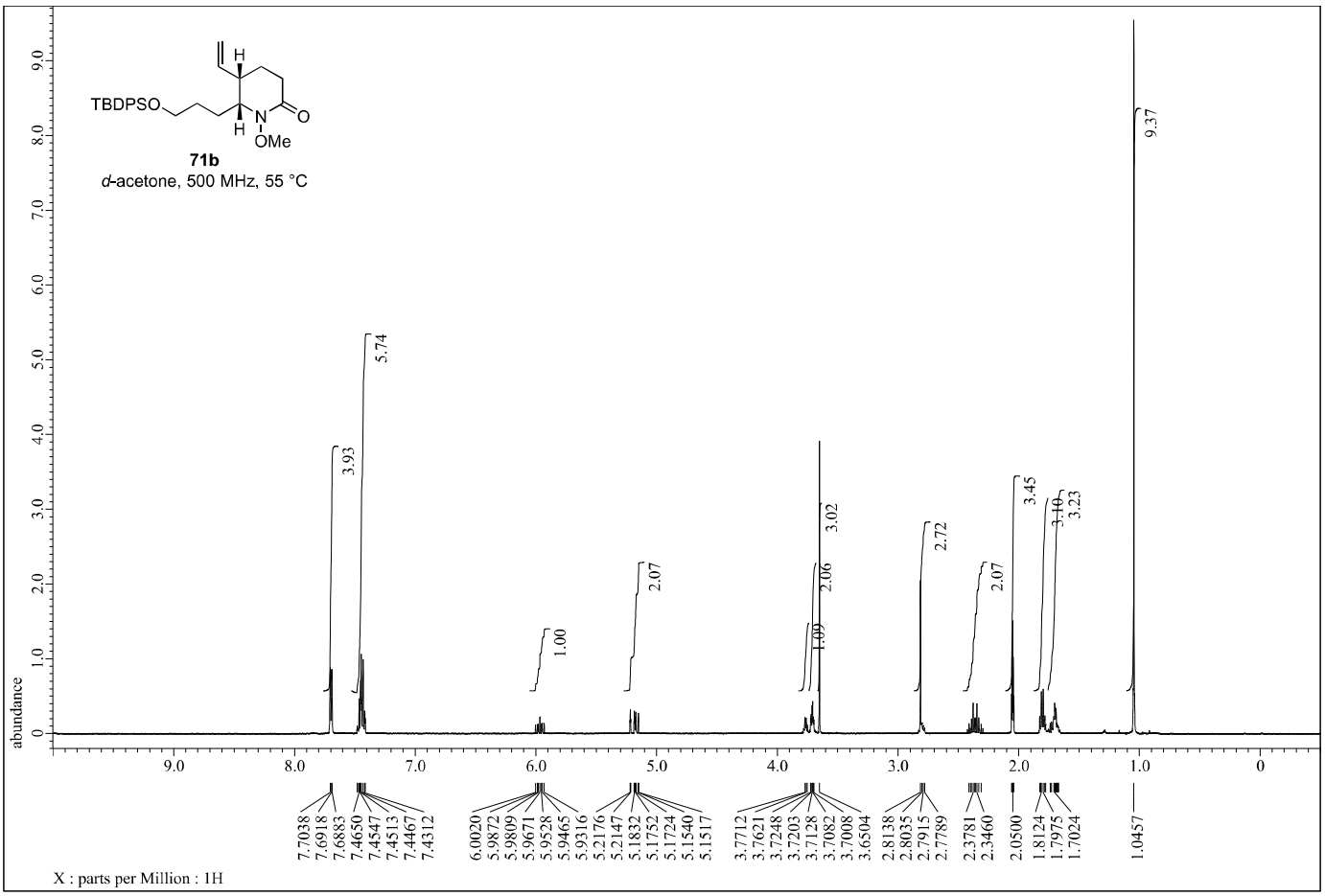

TMS
HN
O
OMe
Z-42
CDCl3, 125 MHz
abundance
X : parts per Million : 13C
170.7644
127.6034
124.9852
77.4128
77.1600
76.9072
64.3023
33.2742
23.0157
18.6662
-1.7363

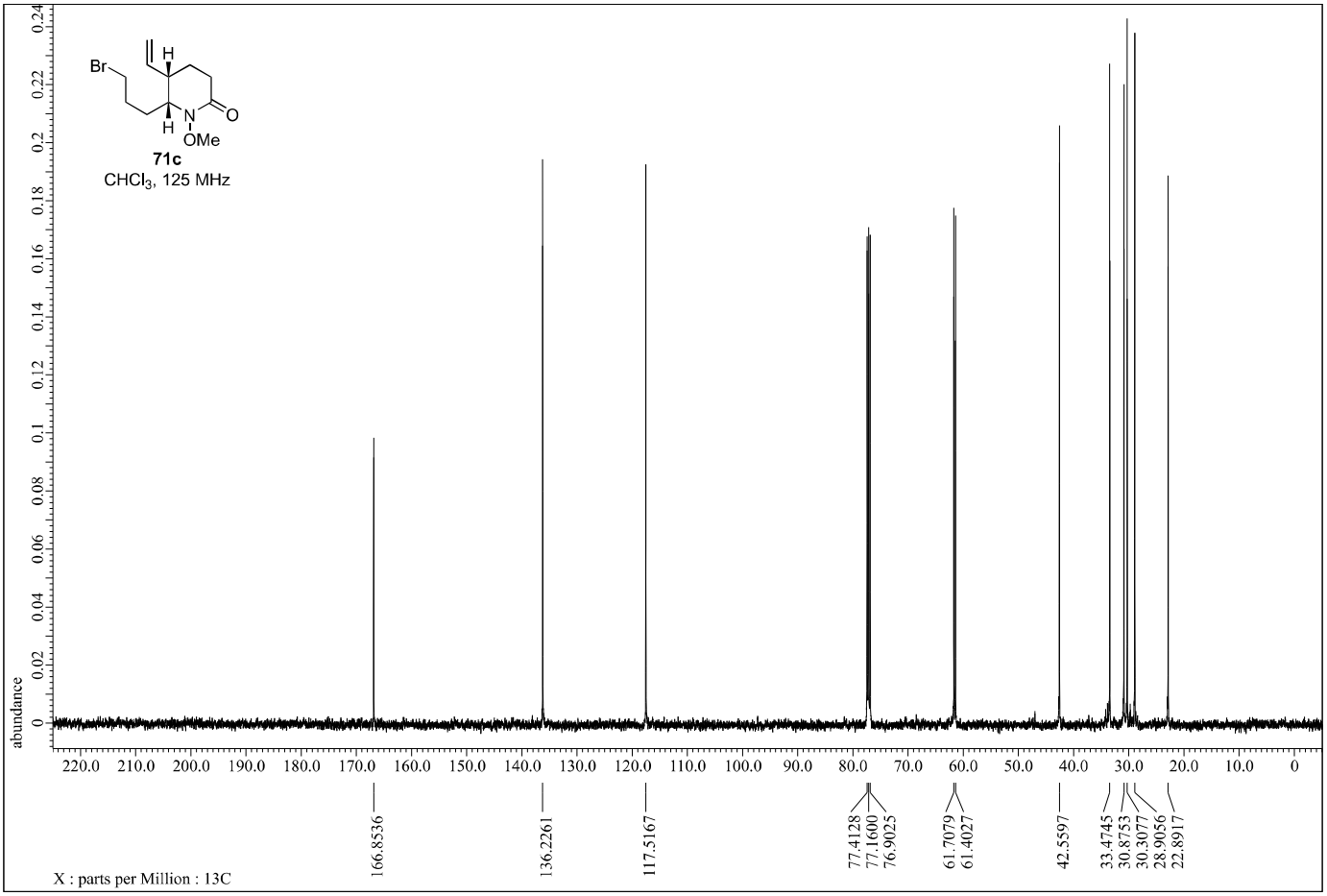

TMS
HN
O
OMe
Z-42
CDCl3, 500 MHz
abundance
X : parts per Million : 1H
0.86
1.00
0.92
3.03
2.04
0.98
2.01
9.11
7.2600
5.4935
5.4741
5.4563
5.2405
3.7563
2.3672
2.3529
2.3386
2.3242
2.1284
1.5071
1.4894
-0.0194

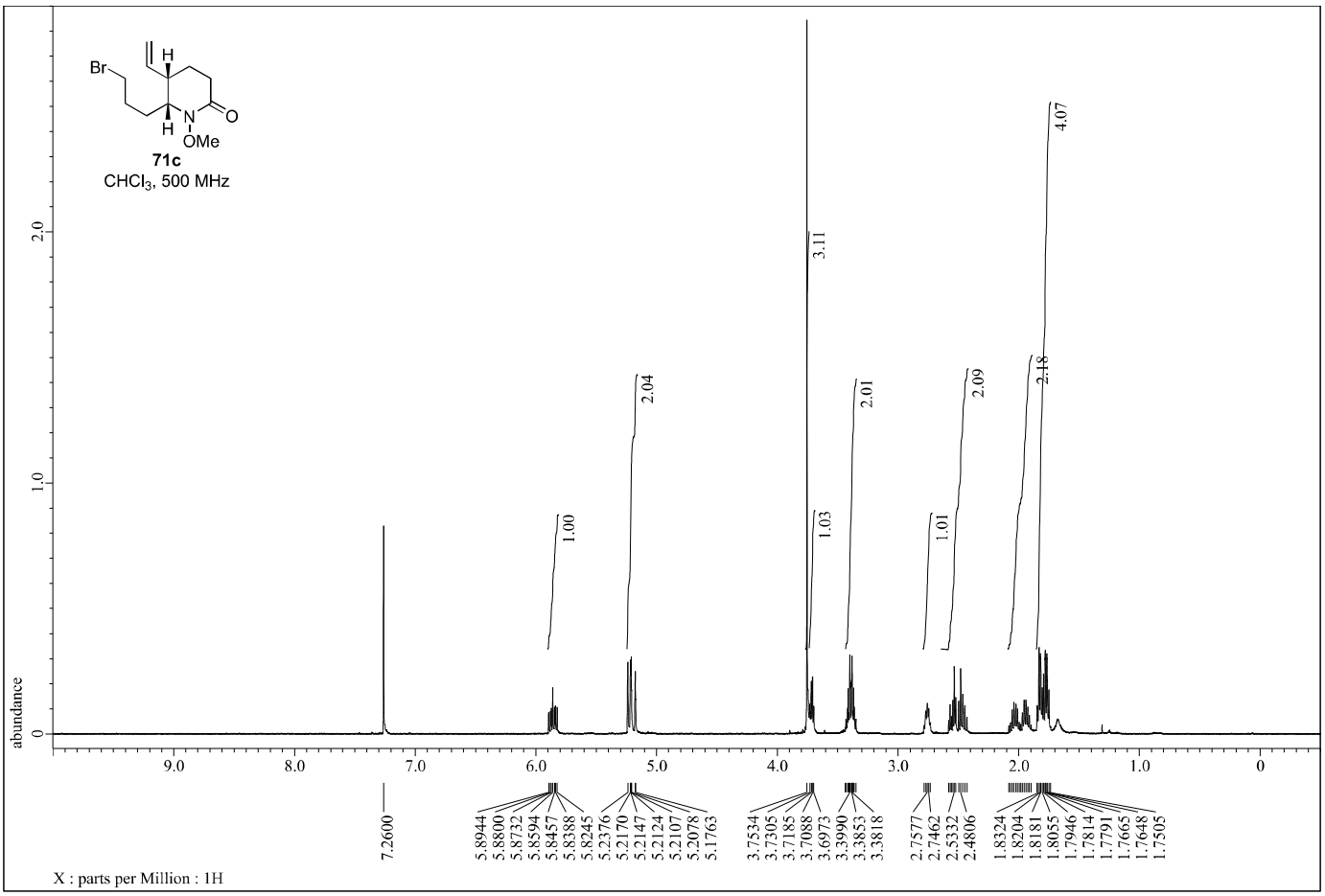

n-C7H15
H
N
O
OMe
71a
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
167.0778
136.5408
117.1304
77.4128
77.1600
76.9072
62.5950
61.4408
42.4453
31.8148
30.8562
29.9167
29.7307
29.1393
27.0409
23.4783
22.6532
14.1212

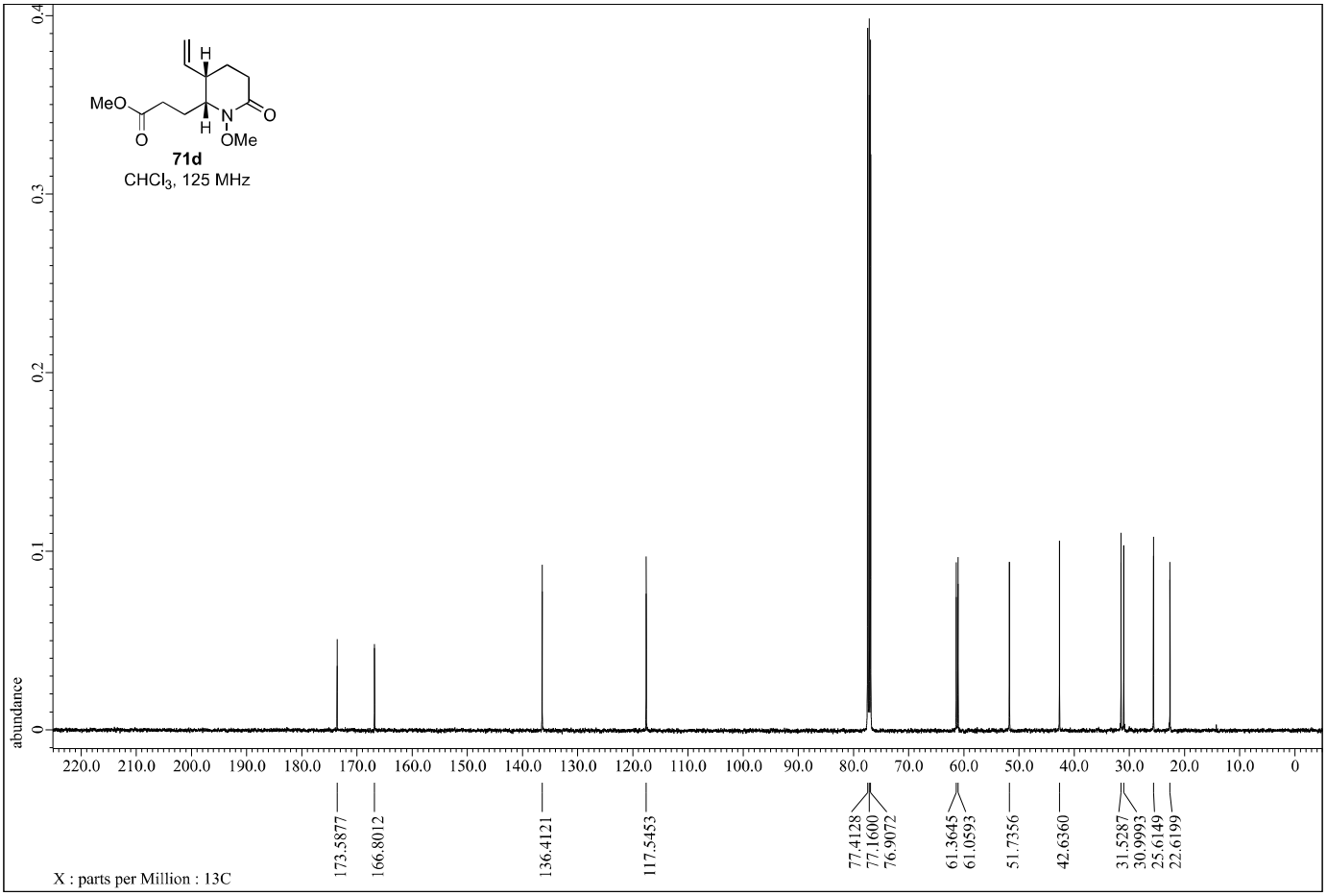

n-C7H15
H
N
O
OMe
71a
CHCl3, 500 MHz
abundance
X : parts per Million : 1H
7.2600
0.67
1.00
2.15
3.14
1.01
1.04
2.20
1.07
2.07
2.18
2.24
8.94
3.25

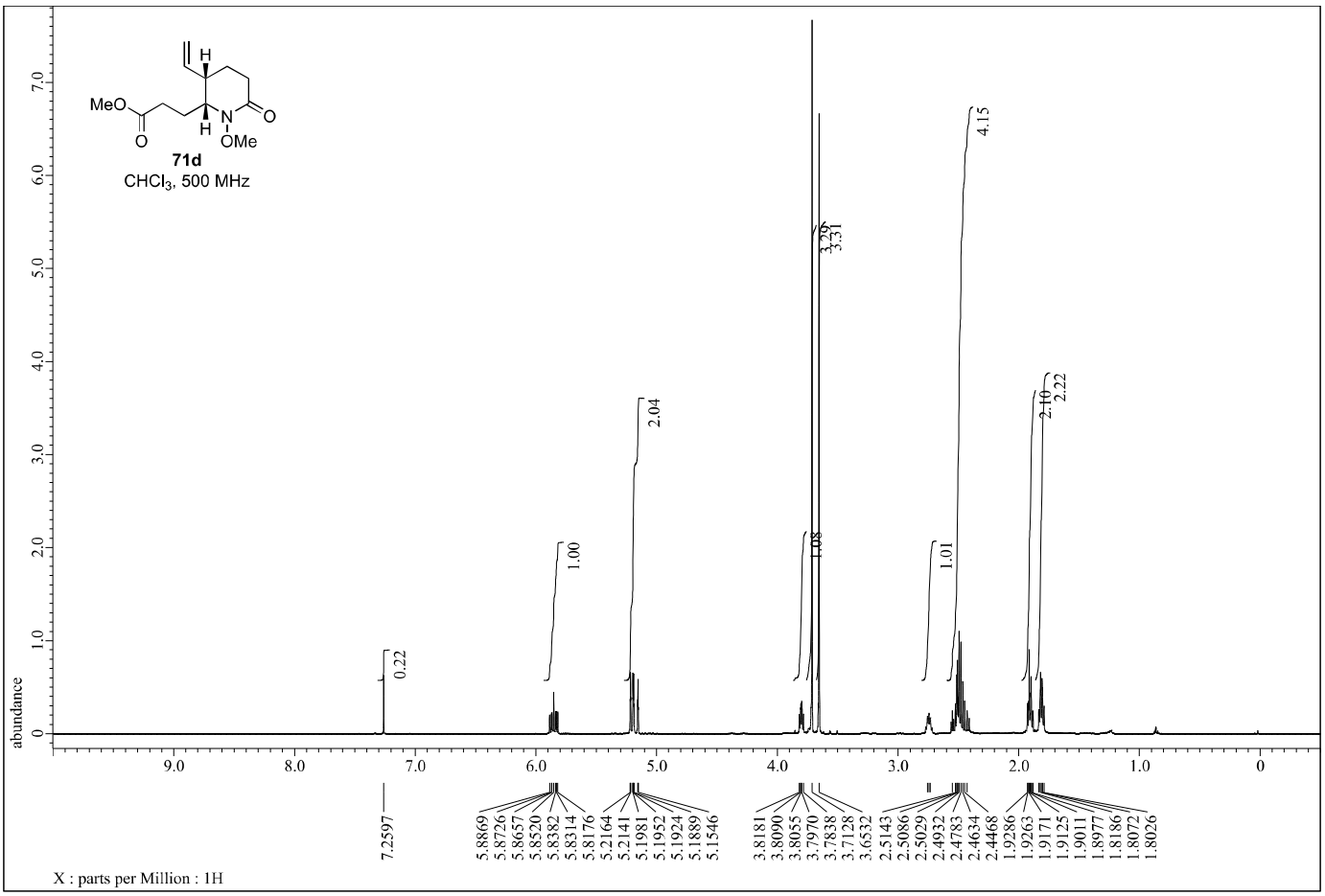

TBDPSO
H
N
O
H
OMe
71b
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
167.0873
136.4312
135.6204
133.9464
133.9083
129.6637
127.6893
117.2877
77.4128
77.1600
76.9025
63.6347
62.4185
61.5028
42.4739
30.8467
30.0025
26.9216
26.4543
23.4831
19.2624

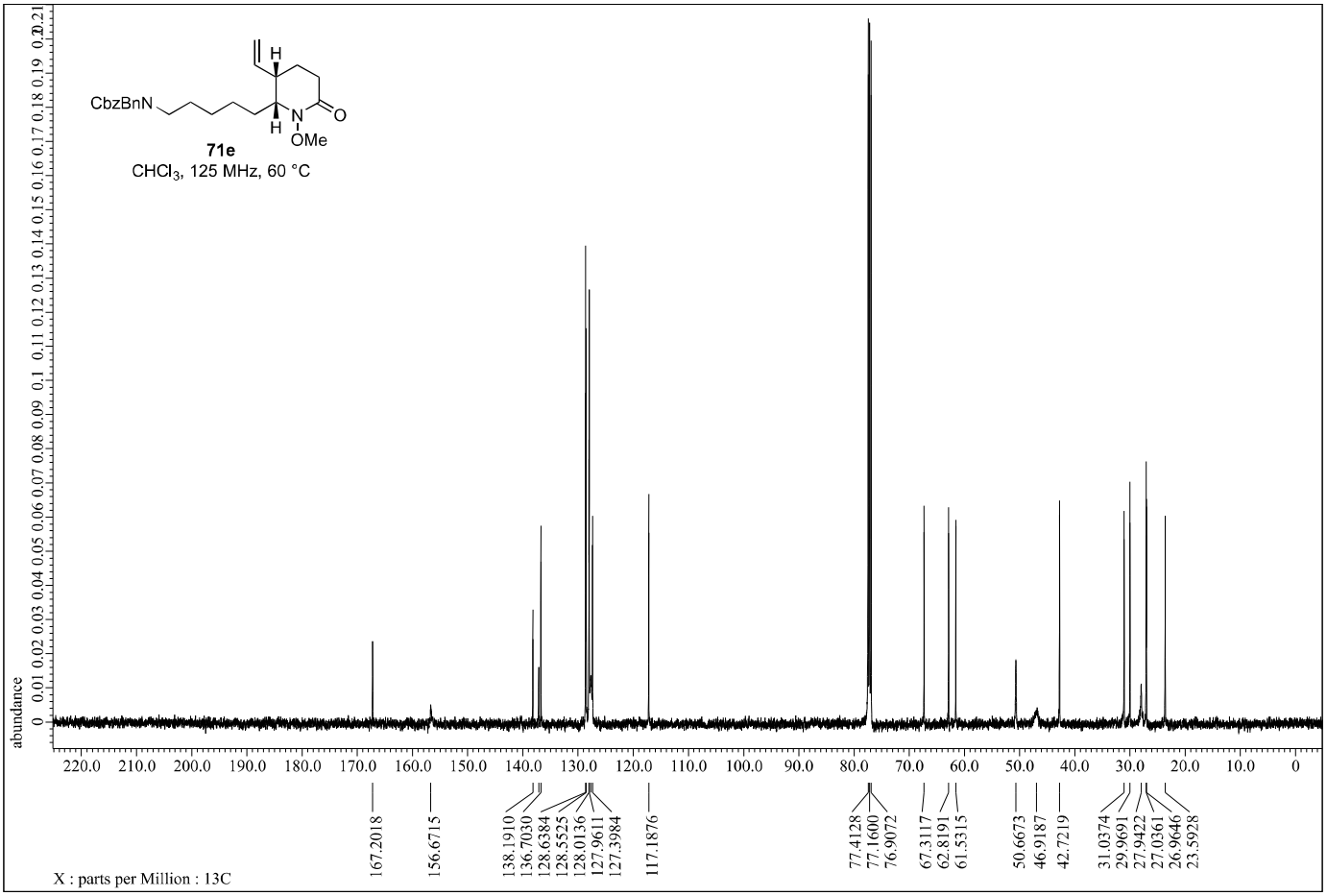

TBDPSO
H
N
O
H
OMe
71b
d-acetone, 500 MHz, 55 °C
abundance
X : parts per Million : 1H
9.37
5.74
3.93
3.02
2.72
2.07
2.06
3.45
3.10
3.23
2.07
1.00
1.09
7.7038
7.6918
7.6883
7.4650
7.4547
7.4513
7.4467
7.4312
6.0020
5.9872
5.9809
5.9671
5.9528
5.9465
5.9316
5.2176
5.2147
5.1832
5.1752
5.1724
5.1540
5.1517
3.7712
3.7621
3.7248
3.7203
3.7128
3.7082
3.7008
3.6504
2.8138
2.8035
2.7915
2.7789
2.3781
2.3460
2.0500
1.8124
1.7975
1.7024
1.0457

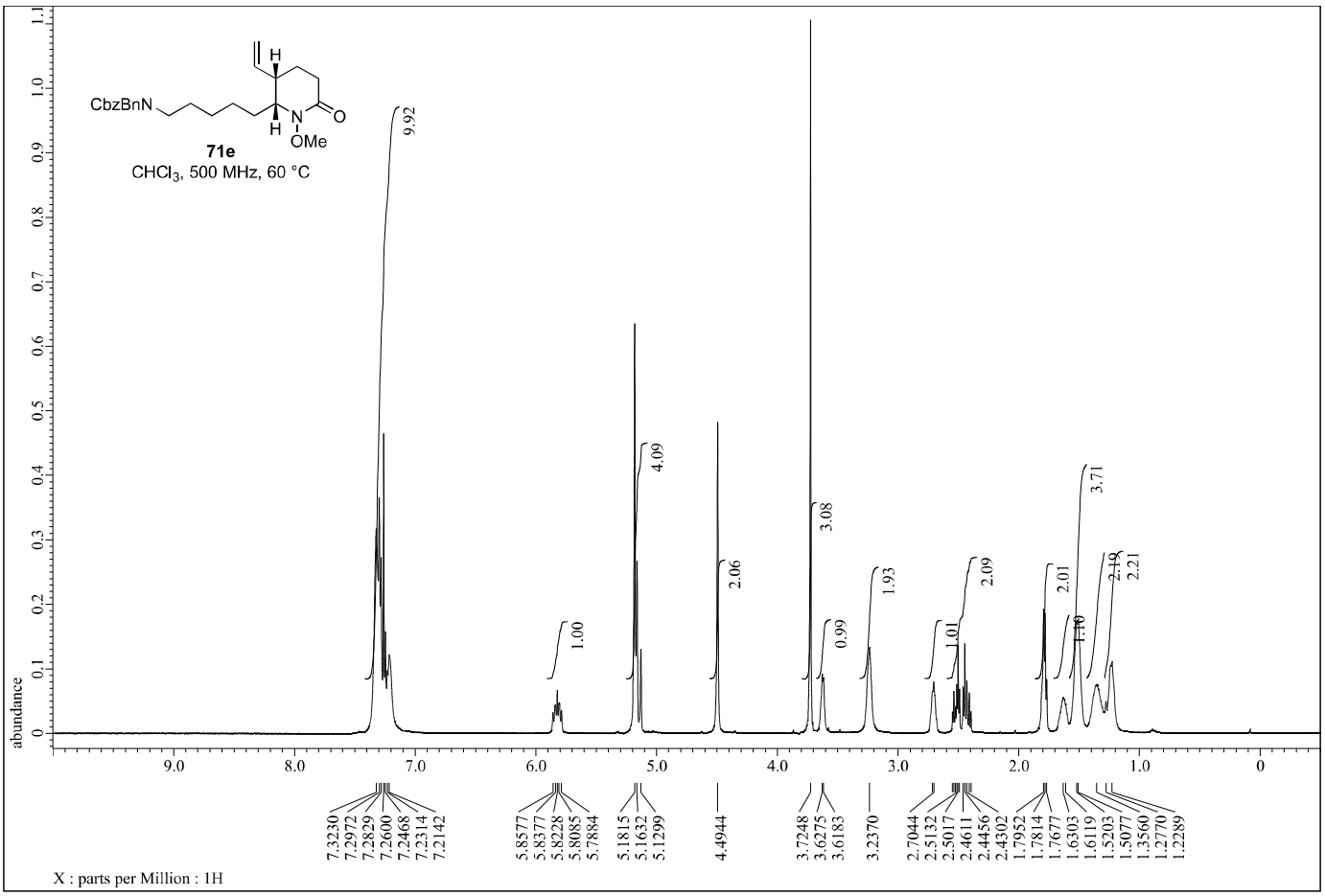

Br
H
N
O
H
OMe
71c
CHCl3, 125 MHz
abundance
166.8536
136.2261
117.5167
77.4128
77.1600
76.9025
61.7079
61.4027
42.5597
33.4745
30.8753
30.3077
28.9056
22.8917
X : parts per Million : 13C

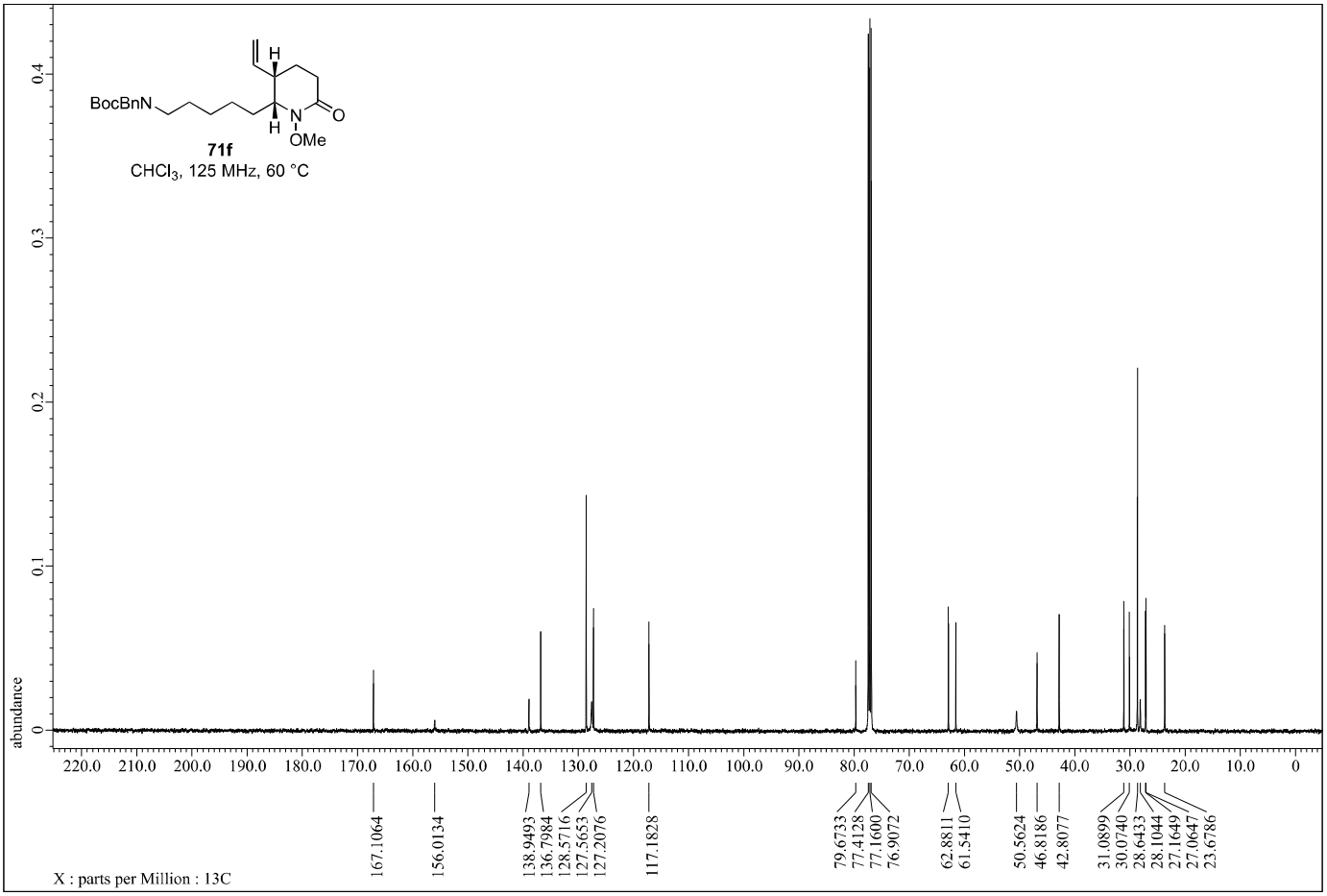

Br
H
N
O
H
OMe
71c
CHCl3, 500 MHz
abundance
1.00
2.04
3.11
1.03
2.01
1.01
2.09
2.18
4.07
7.2600
5.8944
5.8800
5.8732
5.8594
5.8457
5.8388
5.8245
5.2376
5.2170
5.2147
5.2124
5.2107
5.2078
5.1763
3.7534
3.7305
3.7185
3.7088
3.6973
3.3990
3.3853
3.3818
2.7577
2.7462
2.5332
2.4806
1.8324
1.8204
1.8181
1.8055
1.7946
1.7814
1.7791
1.7665
1.7648
1.7505
X : parts per Million : 1H

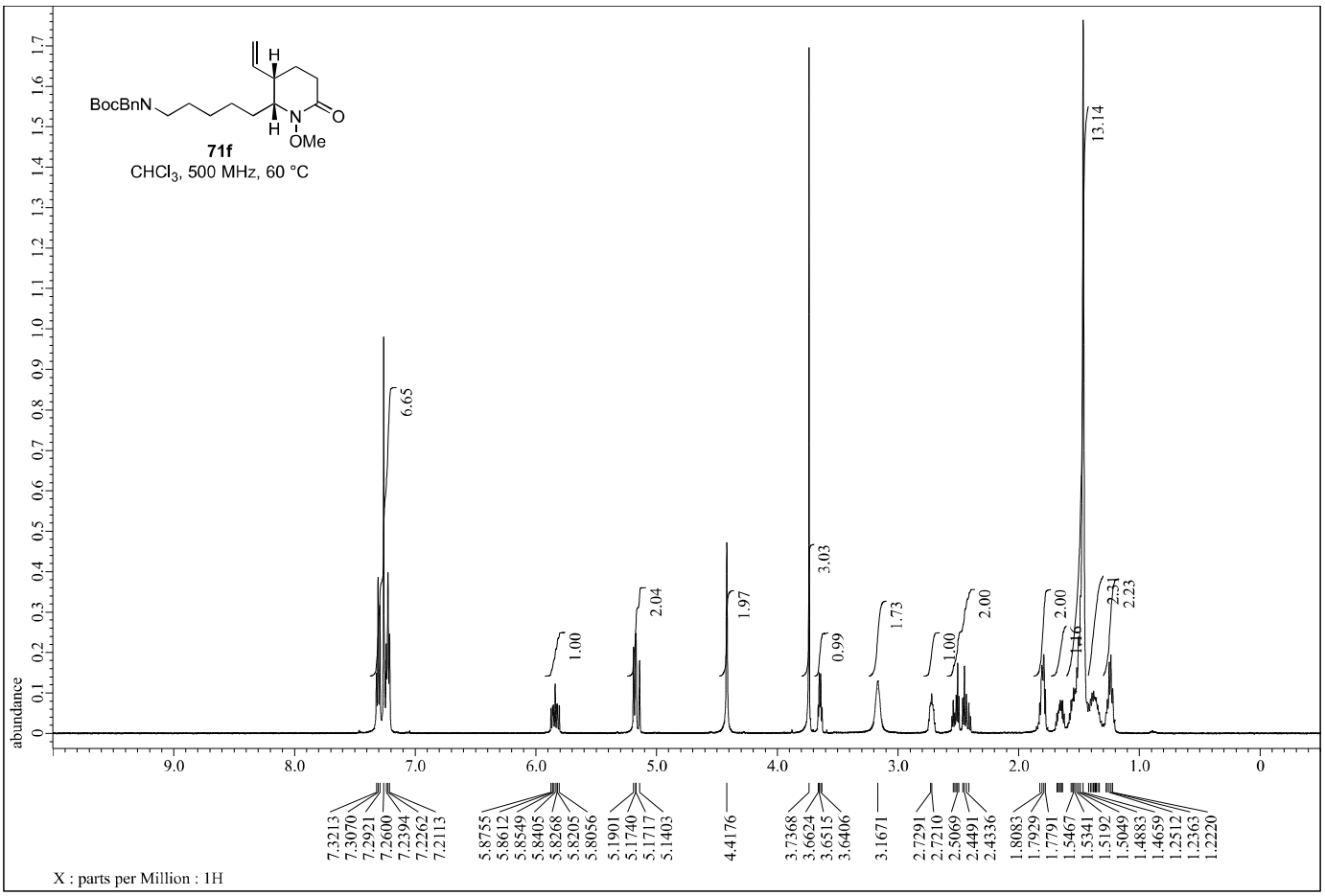

MeO
O
N
H
OMe
O
71d
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
173.5877
166.8012
136.4121
117.5453
77.4128
77.1600
76.9072
61.3645
61.0593
51.7356
42.6360
31.5287
30.9993
25.6149
22.6199

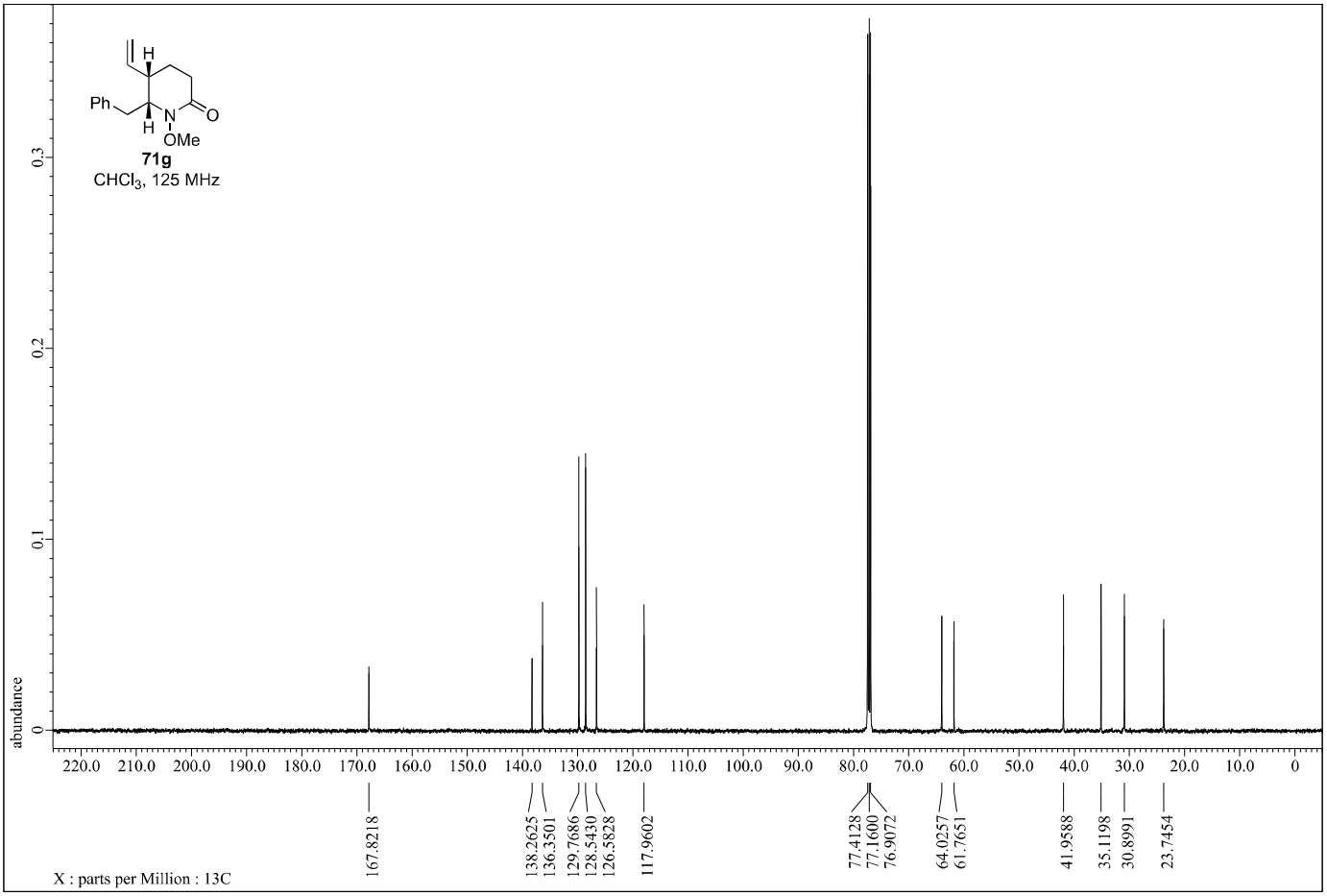

MeO
O
N
H
OMe
O
71d
CHCl3, 500 MHz
abundance
X : parts per Million : 1H
0.22
1.00
2.04
1.08
3.29
3.31
1.01
4.15
2.10
2.22
7.2597
5.8869
5.8726
5.8657
5.8520
5.8382
5.8314
5.8176
5.2164
5.2141
5.1981
5.1952
5.1924
5.1889
5.1546
3.8181
3.8090
3.8055
3.7970
3.7838
3.7128
3.6532
2.5143
2.5086
2.5029
2.4932
2.4783
2.4634
2.4468
1.9286
1.9263
1.9171
1.9125
1.9011
1.8977
1.8186
1.8072
1.8026

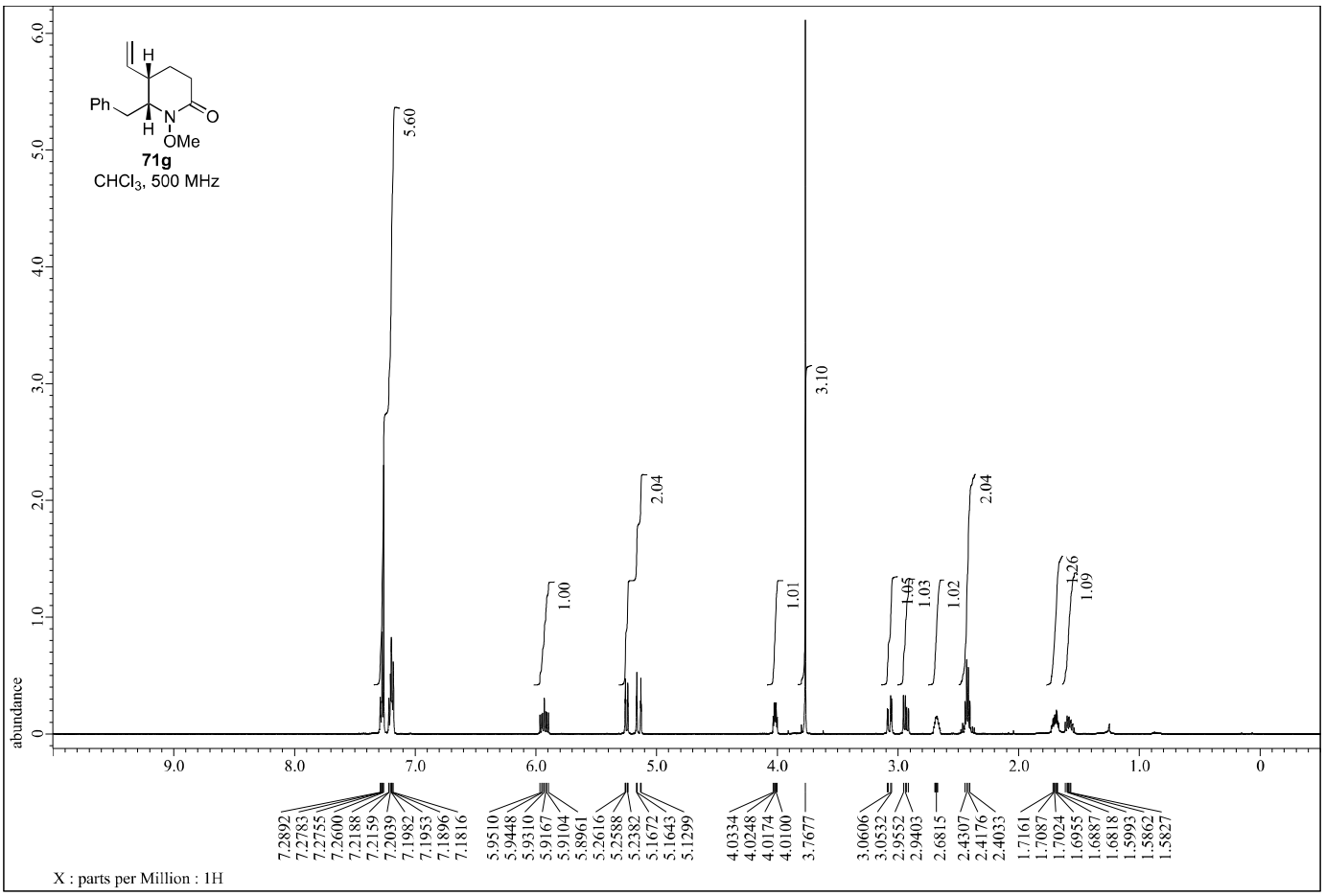

CbzBnN
H
N
H
OMe
O
71e
CHCl3, 125 MHz, 60 °C
abundance
X : parts per Million : 13C
167.2018
156.6715
138.1910
136.7030
128.6384
128.5525
128.0136
127.9611
127.3984
117.1876
77.4128
77.1600
76.9072
67.3117
62.8191
61.5315
50.6673
46.9187
42.7219
31.0374
29.9691
27.9422
27.0361
26.9646
23.5928

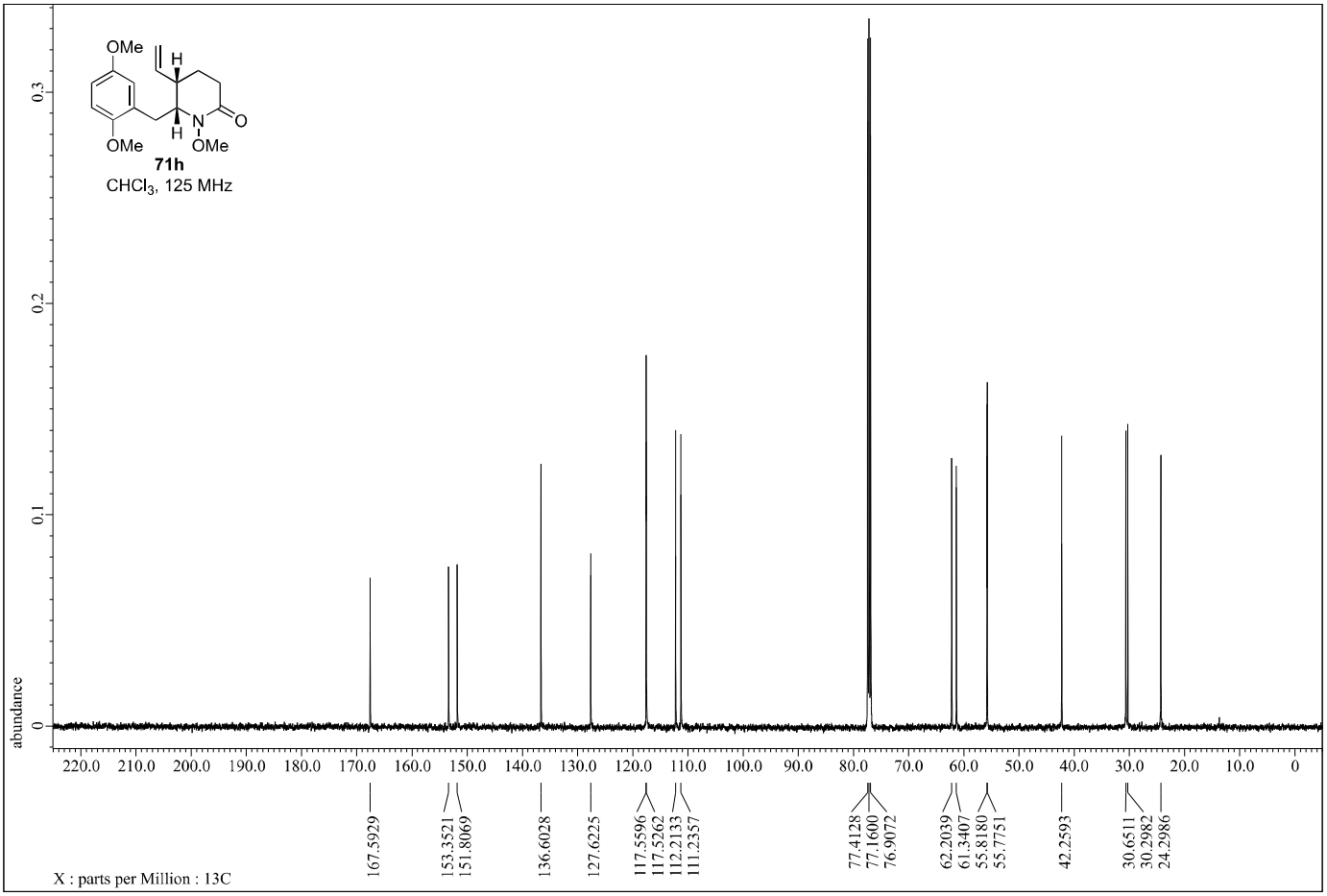

CbzBnN
H
N
H
OMe
O
71e
CHCl3, 500 MHz, 60 °C
abundance
X : parts per Million : 1H
9.92
1.00
4.09
2.06
3.08
0.99
1.93
1.01
2.09
2.01
1.10
3.71
2.19
2.21
7.3230
7.2972
7.2829
7.2600
7.2468
7.2314
7.2142
5.8577
5.8377
5.8228
5.8085
5.7884
5.1815
5.1632
5.1299
4.4944
3.7248
3.6275
3.6183
3.2370
2.7044
2.5132
2.5017
2.4611
2.4436
2.4302
1.7952
1.7814
1.7677
1.6303
1.6119
1.5203
1.5077
1.3560
1.2770
1.2289

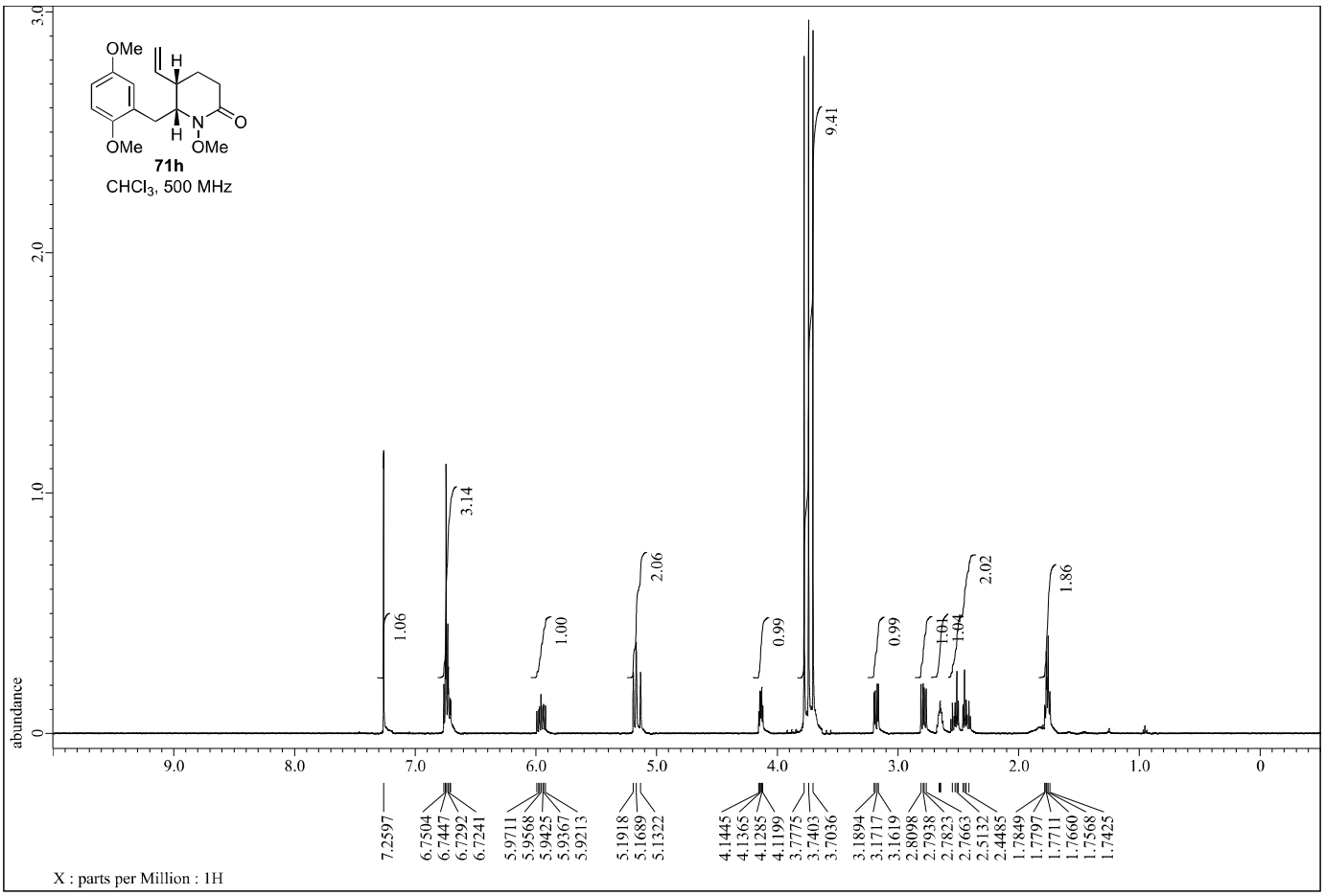

BocBnN
H
N
O
H
OMe
71f
CHCl3, 125 MHz, 60 °C
abundance
X : parts per Million : 13C
167.1064
156.0134
138.9493
136.7984
128.5716
127.5653
127.2076
117.1828
79.6733
77.4128
77.1600
76.9072
62.8811
61.5410
50.5624
46.8186
42.8077
31.0899
30.0740
28.6433
28.1044
27.1649
27.0647
23.6786

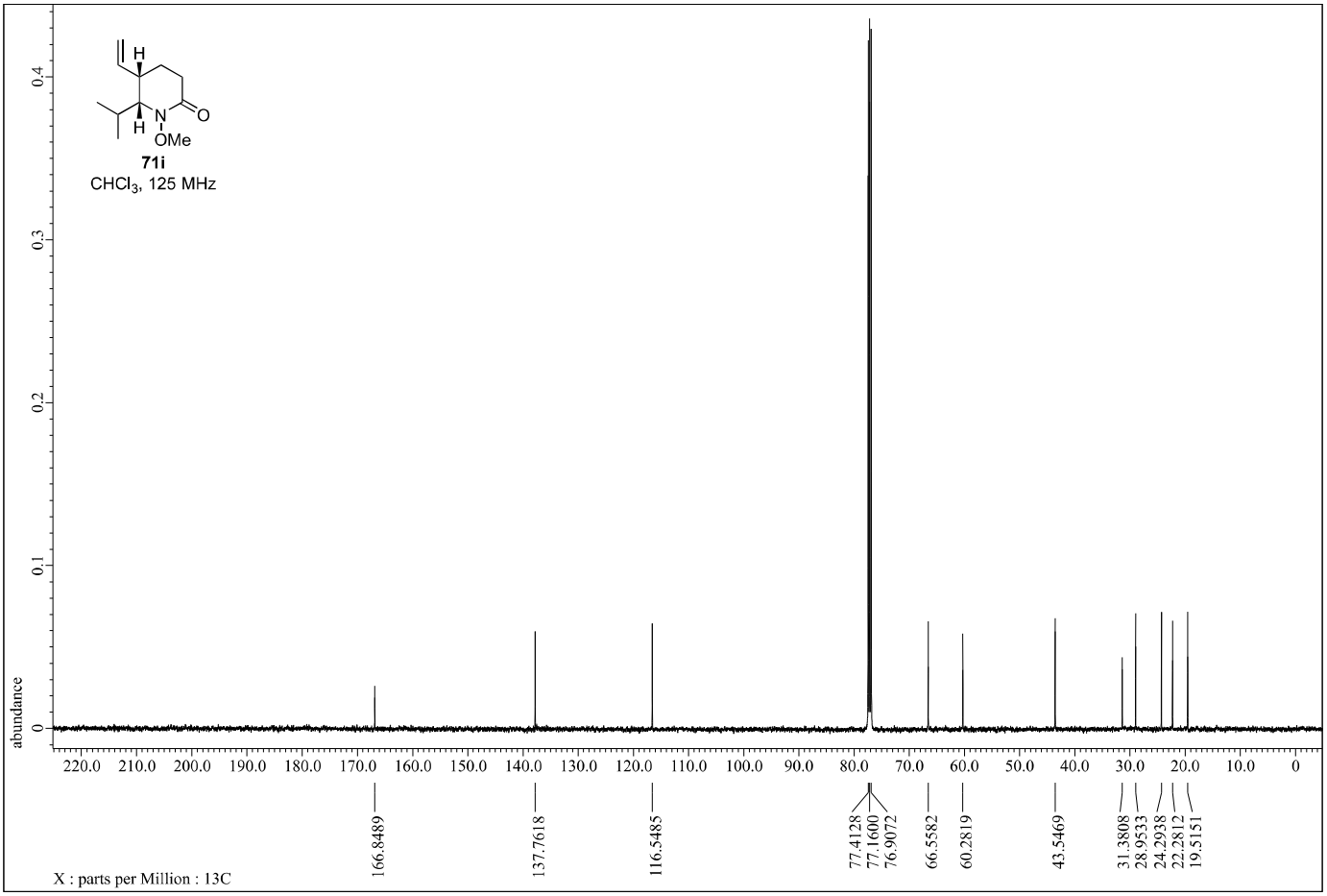

BocBnN
H
N
O
H
OMe
71f
CHCl3, 500 MHz, 60 °C
abundance
X : parts per Million : 1H
6.65
1.00
2.04
1.97
3.03
0.99
1.73
1.00
2.00
1.16
2.00
2.31
2.23
13.14
7.3213
7.3070
7.2921
7.2600
7.2394
7.2262
7.2113
5.8755
5.8612
5.8549
5.8405
5.8268
5.8205
5.8056
5.1901
5.1740
5.1717
5.1403
4.4176
3.7368
3.6624
3.6515
3.6406
3.1671
2.7291
2.7210
2.5069
2.4491
2.4336
1.8083
1.7929
1.7791
1.5467
1.5341
1.5192
1.5049
1.4883
1.4659
1.2512
1.2363
1.2220

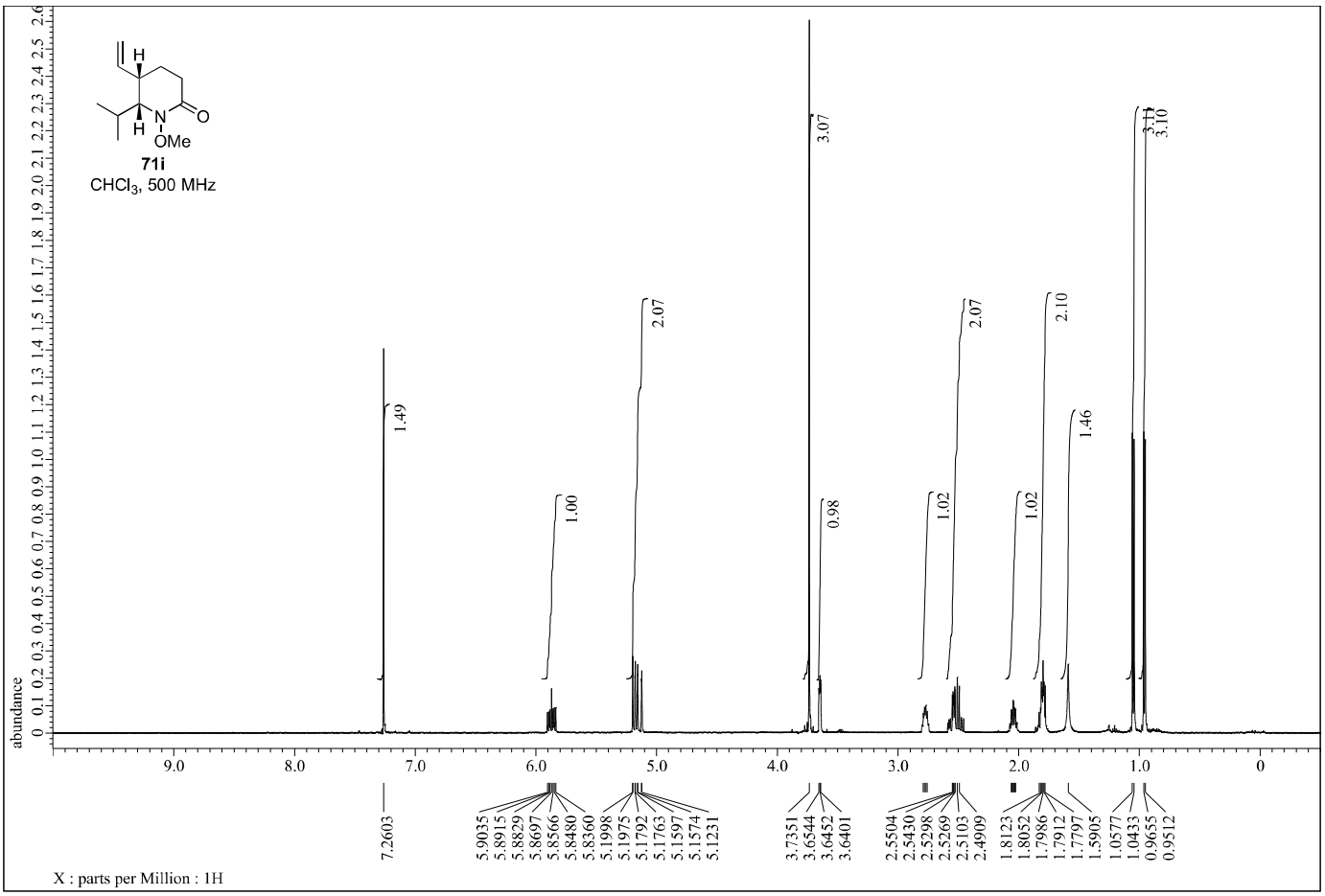

71g
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
167.8218
138.2625
136.3501
129.7686
128.5430
126.5828
117.9602
77.4128
77.1600
76.9072
64.0257
61.7651
41.9588
35.1198
30.8991
23.7454

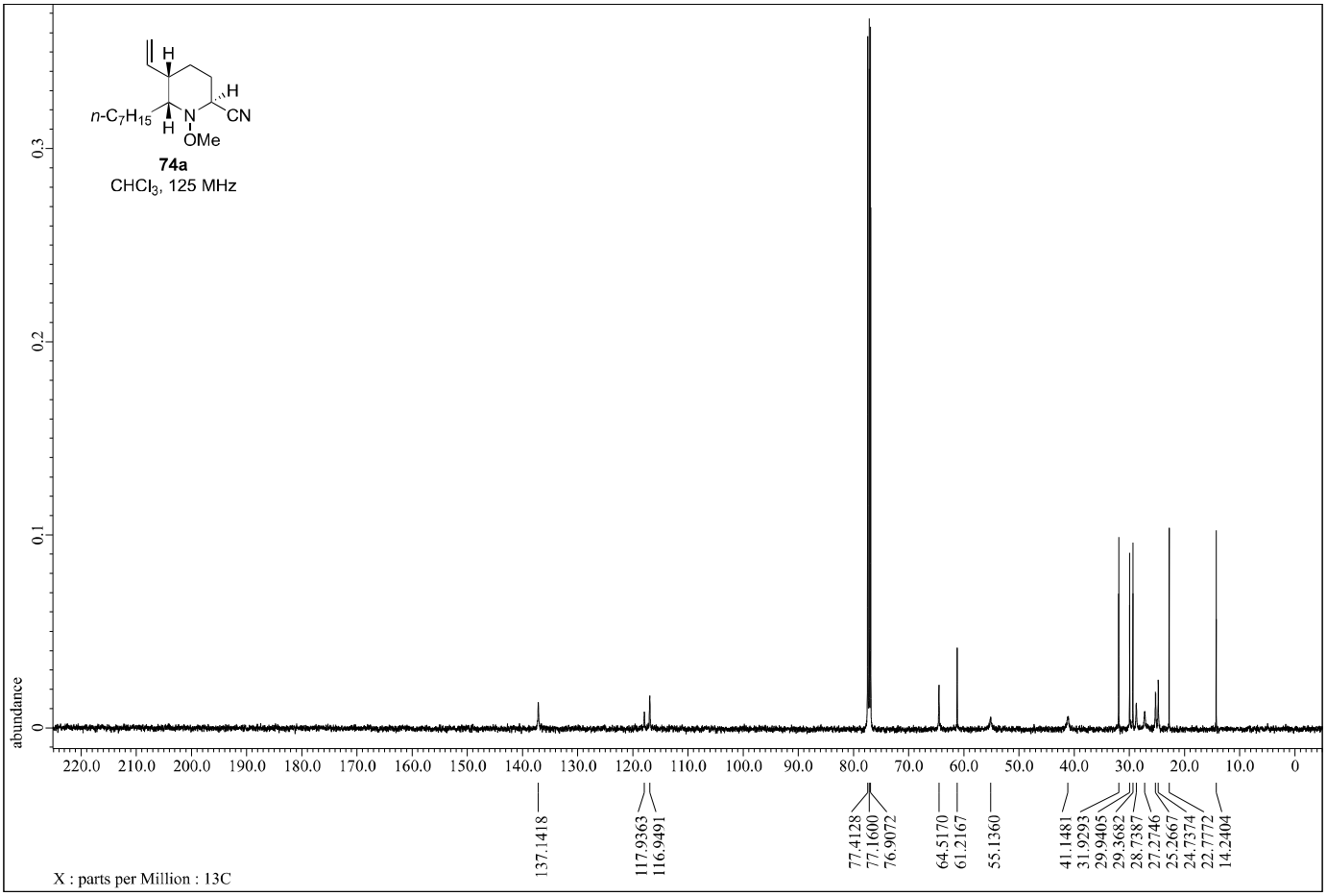

71g
CHCl3, 500 MHz
abundance
X : parts per Million : 1H
5.60
1.00
2.04
1.01
3.10
1.05
1.03
1.02
2.04
1.26
1.09
7.2892
7.2783
7.2755
7.2600
7.2188
7.2159
7.2039
7.1982
7.1953
7.1896
7.1816
5.9510
5.9448
5.9310
5.9167
5.9104
5.8961
5.2616
5.2588
5.2382
5.1672
5.1643
5.1299
4.0334
4.0248
4.0174
4.0100
3.7677
3.0606
3.0532
2.9552
2.9403
2.6815
2.4307
2.4176
2.4033
1.7161
1.7087
1.7024
1.6935
1.6887
1.6818
1.5993
1.5862
1.5827

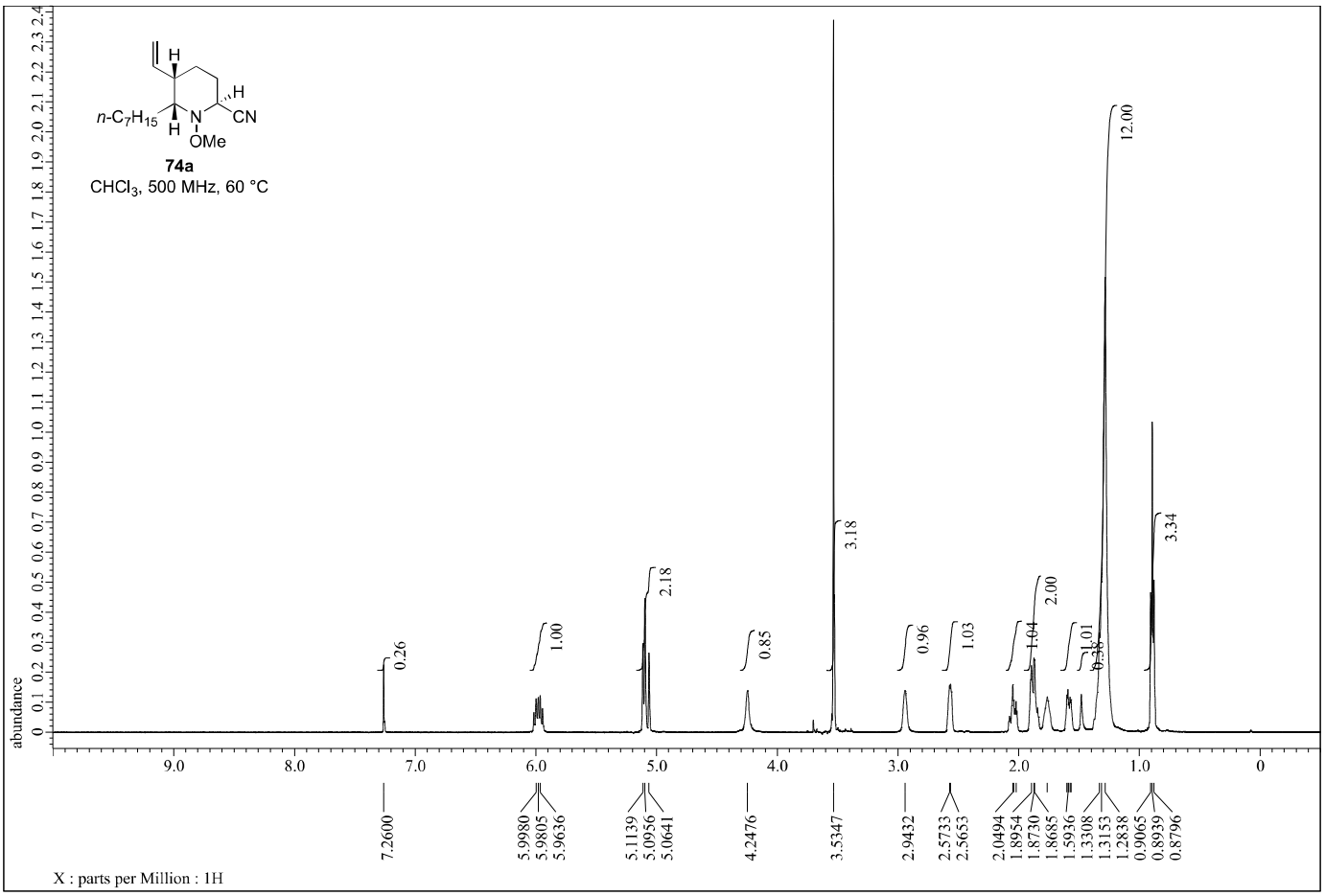

OMe
H
OMe
N
O
H
OMe
71h
CHCl3, 125 MHz
abundance
0.3
0.2
0.1
0
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
167.5929
153.3521
151.8069
136.6028
127.6225
117.5596
117.5262
112.2133
111.2357
77.4128
77.1600
76.9072
62.2039
61.3407
55.8180
55.7751
42.2593
30.6511
30.2982
24.2986
X : parts per Million : 13C

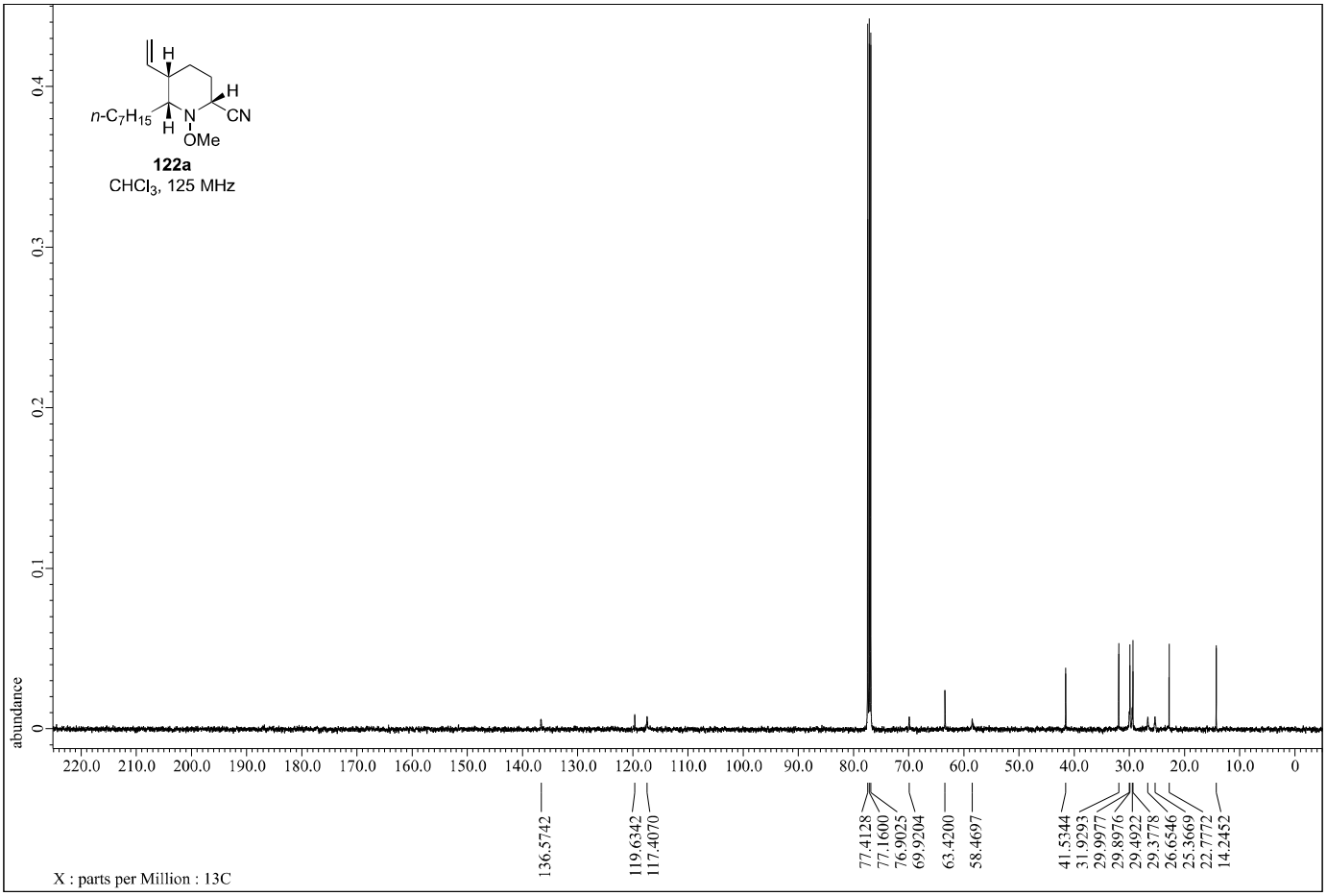

OMe
H
OMe
N
O
H
OMe
71h
CHCl3, 500 MHz
abundance
3.0
2.0
1.0
0
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0
1.06
3.14
1.00
2.06
0.99
9.41
0.99
1.01
1.04
2.02
1.86
7.2597
6.7504
6.7447
6.7292
6.7241
5.9711
5.9568
5.9425
5.9367
5.9213
5.1918
5.1689
5.1322
4.1445
4.1365
4.1285
4.1199
3.7775
3.7403
3.7036
3.1894
3.1717
3.1619
2.8098
2.7938
2.7823
2.7663
2.5132
2.4485
1.7849
1.7797
1.7711
1.7660
1.7568
1.7425
X : parts per Million : 1H

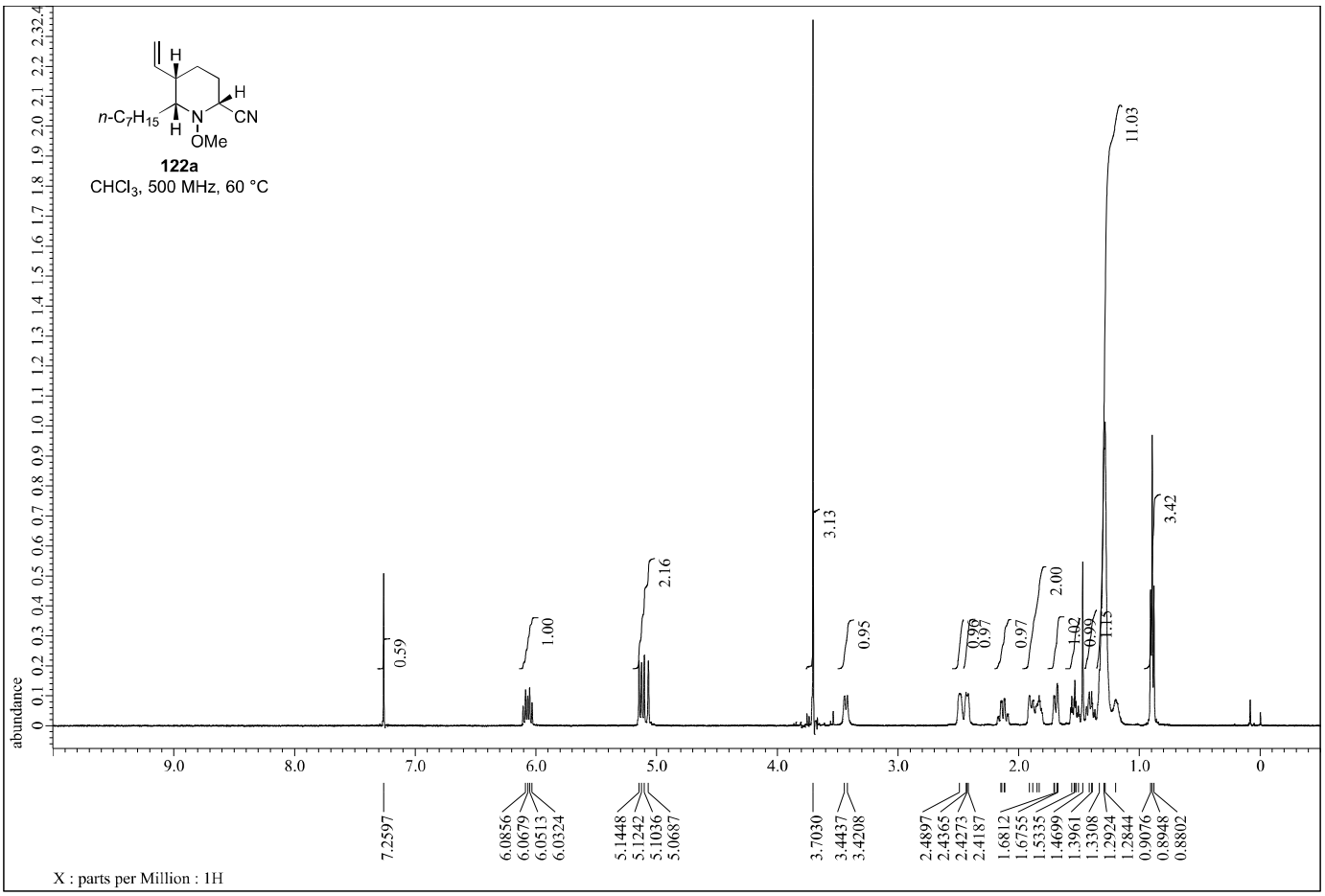

71i
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
166.8489
137.7618
116.5485
77.4128
77.1600
76.9072
66.5582
60.2819
43.5469
31.3808
28.9533
24.2938
22.2812
19.5151

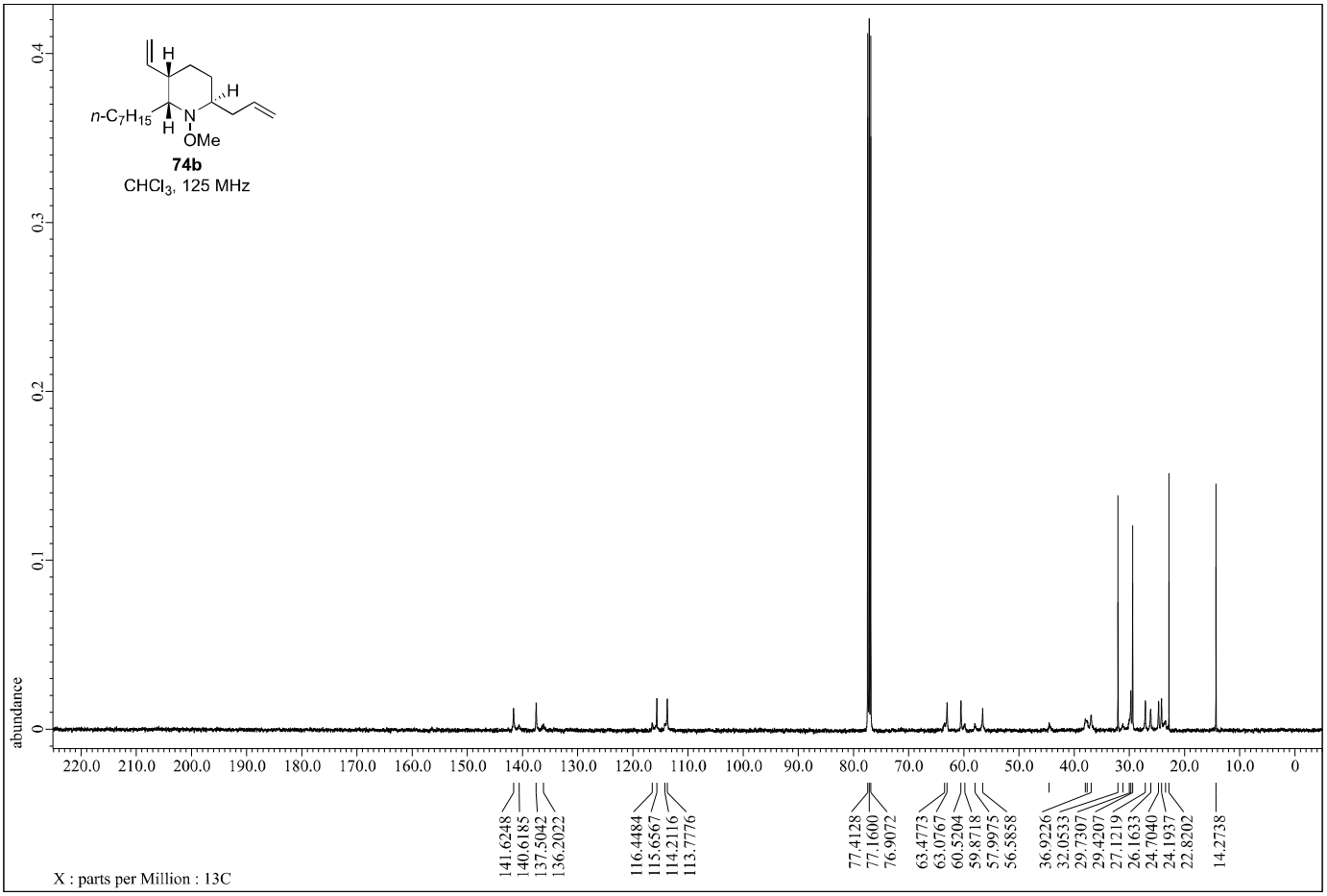

71i
CHCl3, 500 MHz
abundance
X : parts per Million : 1H
7.2603
5.9035
5.8915
5.8829
5.8697
5.8566
5.8480
5.8360
5.1998
5.1975
5.1792
5.1763
5.1597
5.1574
5.1231
3.7351
3.6544
3.6452
3.6401
2.5504
2.5430
2.5298
2.5269
2.5103
2.4909
1.8123
1.8052
1.7986
1.7912
1.7797
1.5905
1.0577
1.0433
0.9655
0.9512
1.49
1.00
2.07
3.07
0.98
1.02
2.07
1.02
2.10
1.46
3.11
3.10

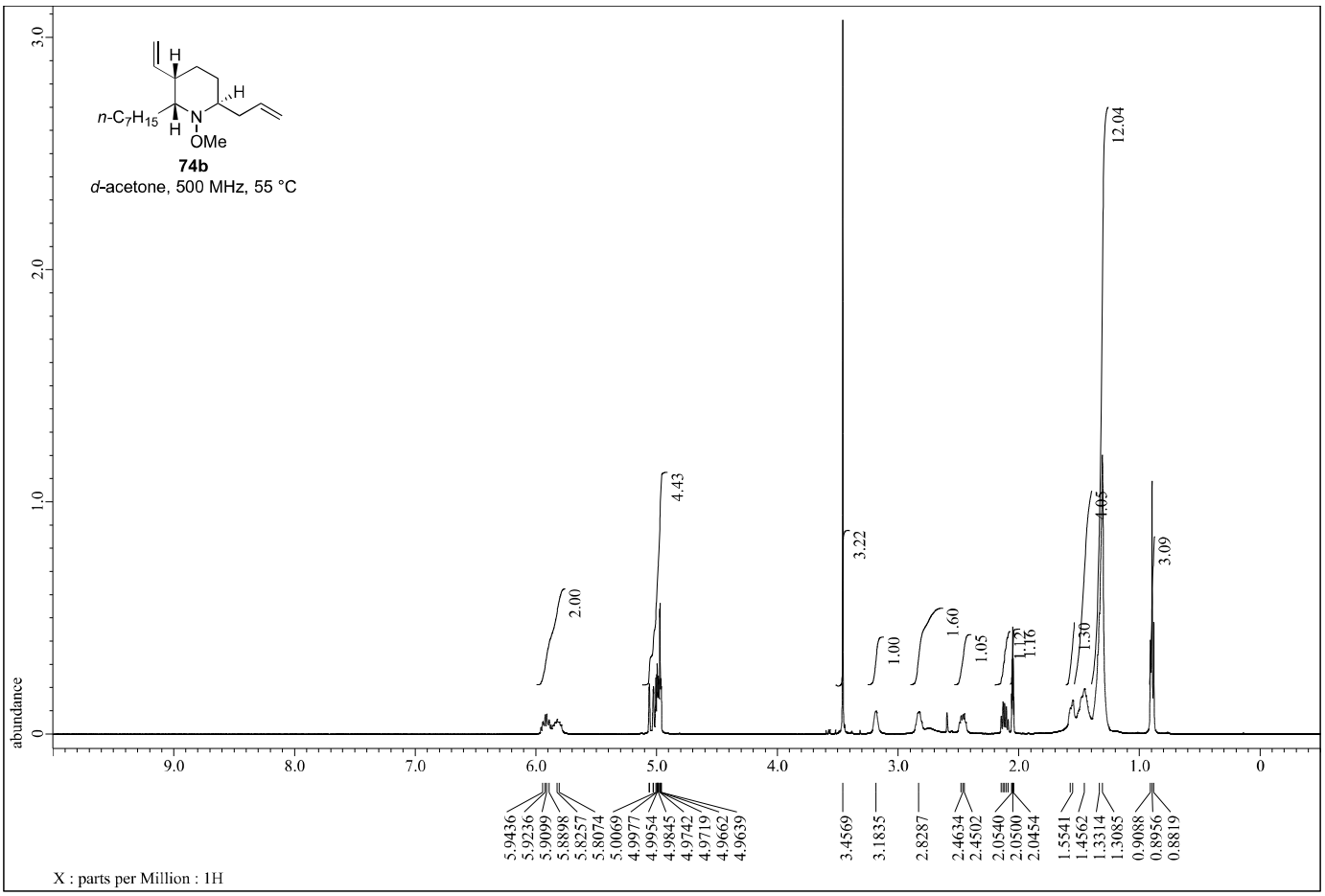

74a
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
137.1418
117.9363
116.9491
77.4128
77.1600
76.9072
64.5170
61.2167
55.1360
41.1481
31.9293
29.9405
29.3682
28.7387
27.2746
25.2667
24.7374
22.7772
14.2404

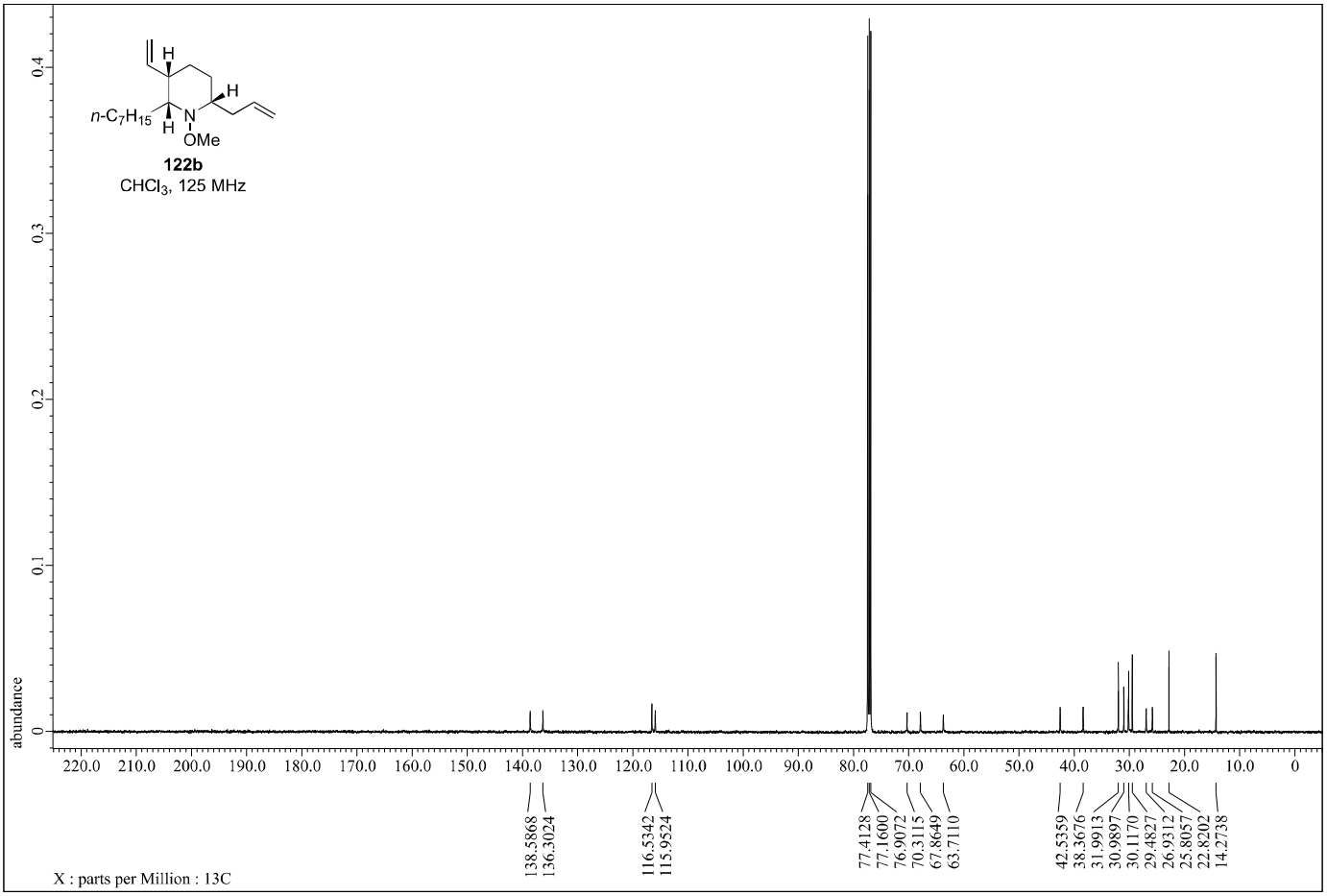

74a
CHCl3, 500 MHz, 60 °C
abundance
X : parts per Million : 1H
7.2600
5.9980
5.9805
5.9636
5.1139
5.0956
5.0641
4.2476
3.5347
2.9432
2.5733
2.5653
2.0494
1.8954
1.8730
1.8685
1.5936
1.3308
1.3153
1.2838
0.9065
0.8939
0.8796
0.26
1.00
2.18
0.85
3.18
0.96
1.03
1.04
2.00
1.01
0.38
12.00
3.34

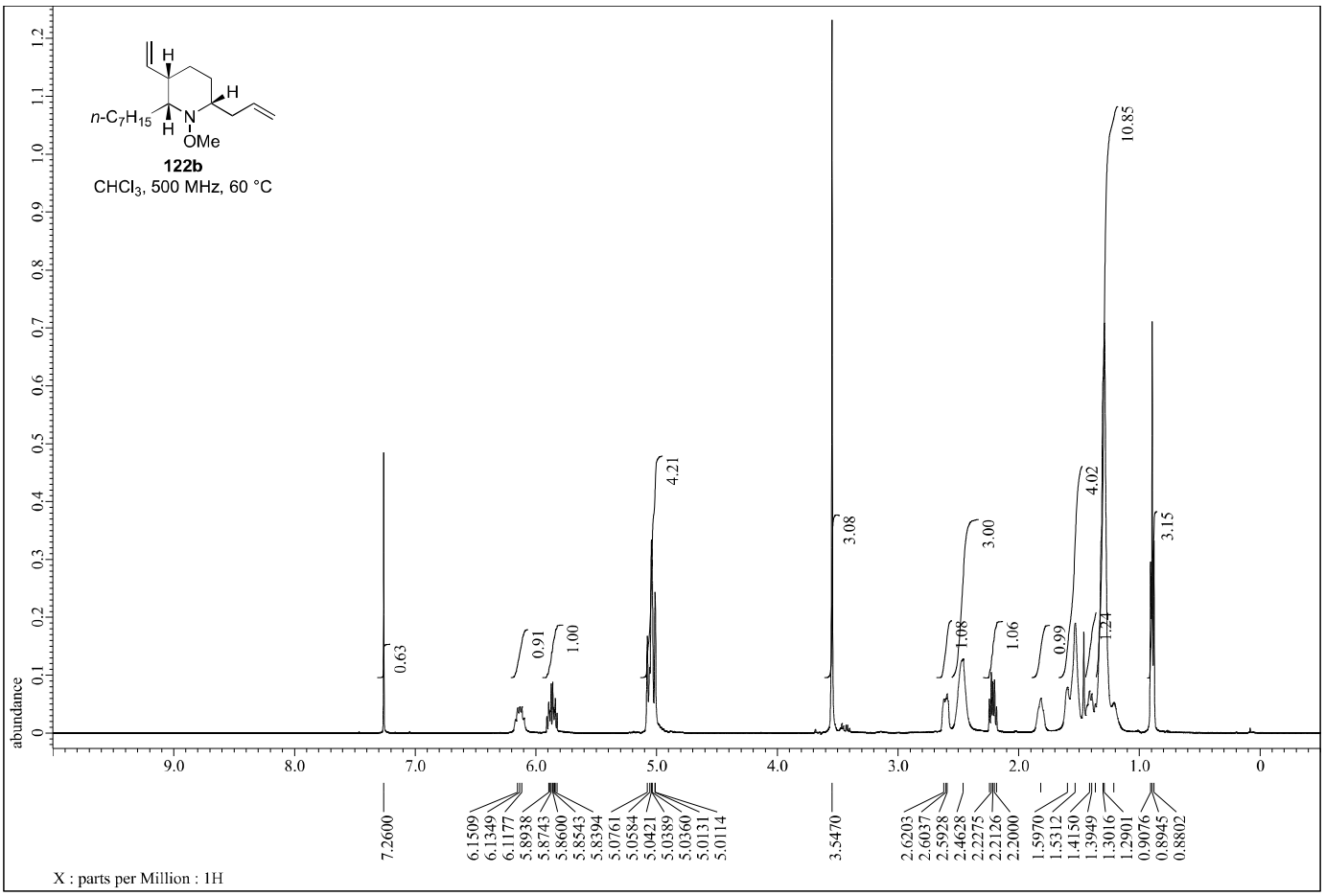

122a
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
136.5742
119.6342
117.4070
77.4128
77.1600
76.9025
69.9204
63.4200
58.4697
41.5344
31.9293
29.9977
29.8976
29.4922
29.3778
26.6546
25.3669
22.7772
14.2452

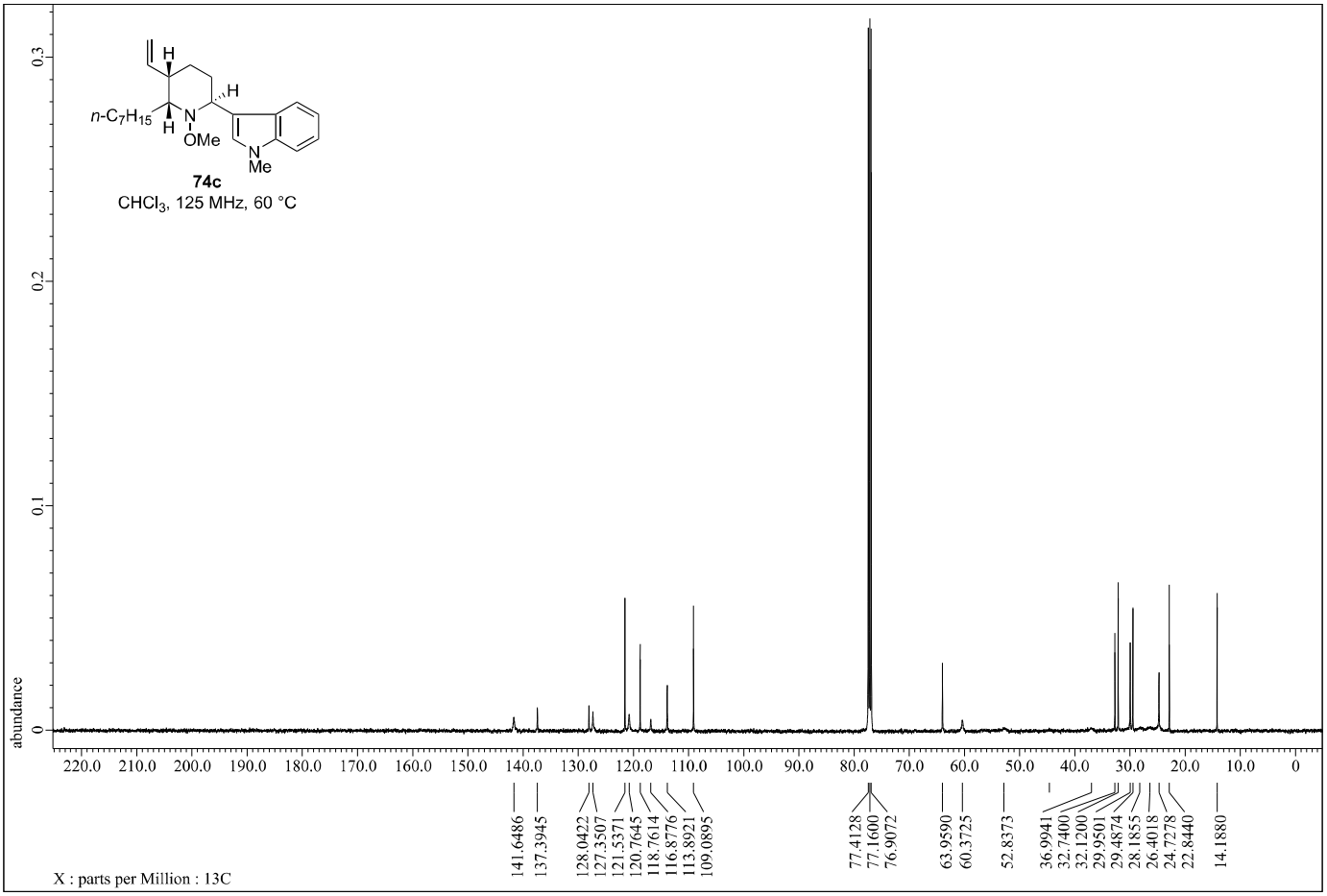

122a
CHCl3, 500 MHz, 60 °C
abundance
X : parts per Million : 1H
7.2597
6.0856
6.0679
6.0513
6.0324
5.1448
5.1242
5.1036
5.0687
3.7030
3.4437
3.4208
2.4897
2.4365
2.4273
2.4187
1.6812
1.6755
1.5335
1.4699
1.3961
1.3308
1.2924
1.2844
0.9076
0.8948
0.8802
0.59
1.00
2.16
3.13
0.95
0.96
0.97
0.97
2.00
1.02
0.99
1.15
11.03
3.42

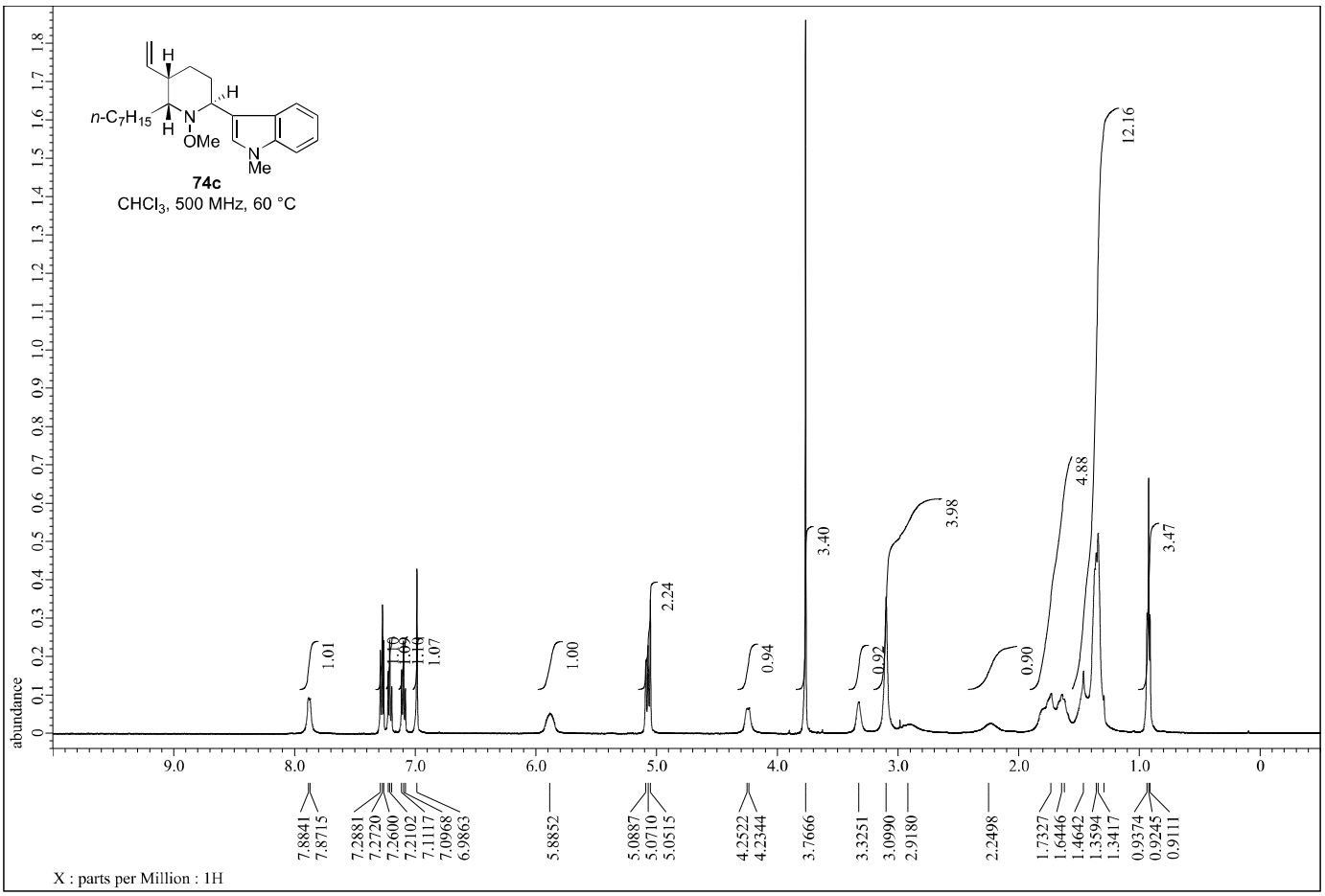

n-C7H15
OMe
74b
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
141.6248
140.6185
137.5042
136.2022
116.4484
115.6567
114.2116
113.7776
77.4128
77.1600
76.9072
63.4773
63.0767
60.5204
59.8718
57.9975
56.5858
36.9226
32.0533
29.7307
29.4207
27.1219
26.1633
24.7040
24.1937
22.8202
14.2738

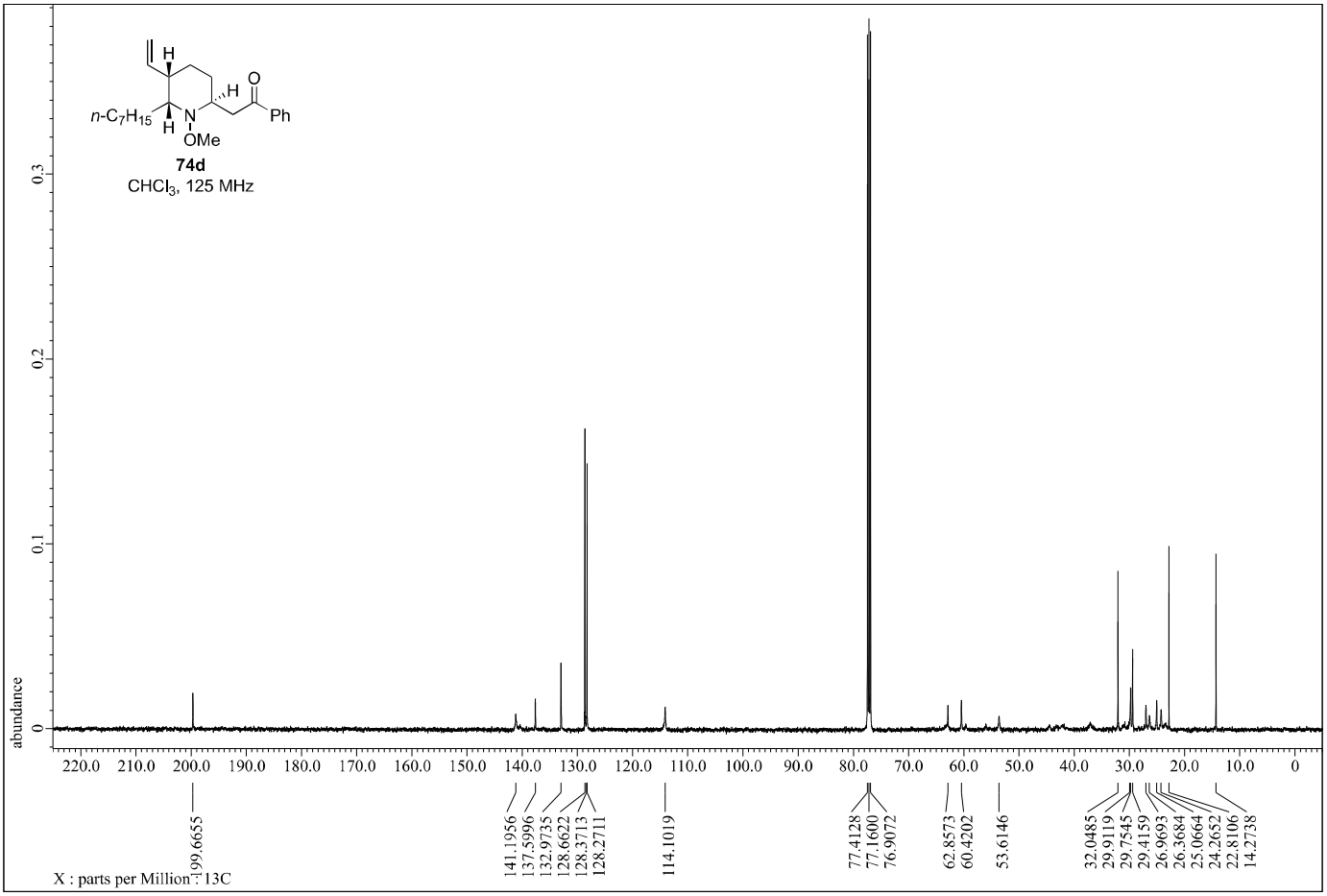

n-C7H15
OMe
74b
d-acetone, 500 MHz, 55 °C
abundance
X : parts per Million : 1H
2.00
4.43
3.22
1.00
1.60
1.05
1.12
1.16
1.30
4.05
12.04
3.09
5.9436
5.9236
5.9099
5.8898
5.8257
5.8074
5.0069
4.9977
4.9954
4.9845
4.9742
4.9719
4.9662
4.9639
3.4569
3.1835
2.8287
2.4634
2.4502
2.0540
2.0500
2.0454
1.5541
1.4562
1.3314
1.3085
0.9088
0.8956
0.8819

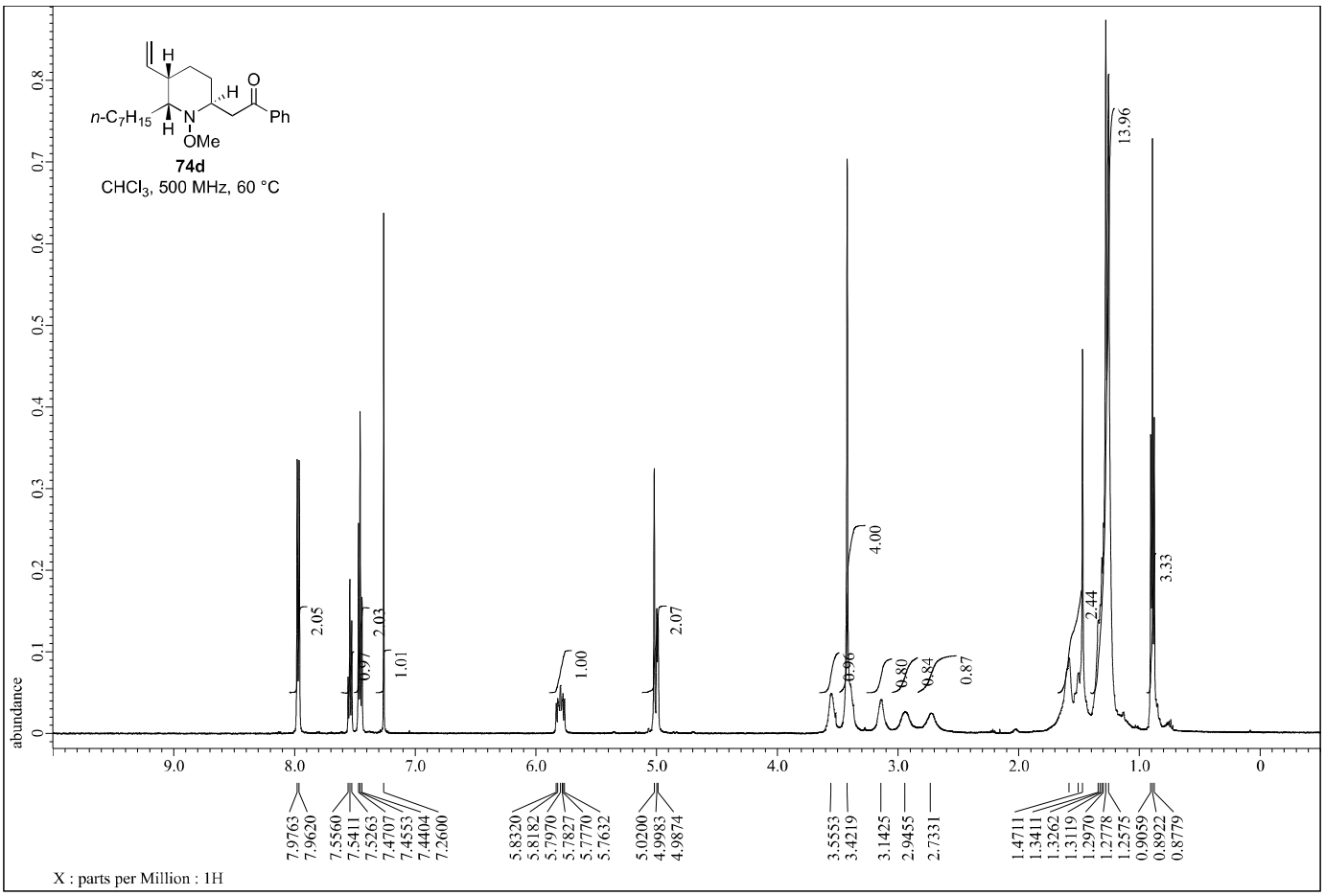

122b
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
138.5868
136.3024
116.5342
115.9524
77.4128
77.1600
76.9072
70.3115
67.8649
63.7110
42.5359
38.3676
31.9913
30.9897
30.1170
29.4827
26.9312
25.8057
22.8202
14.2738

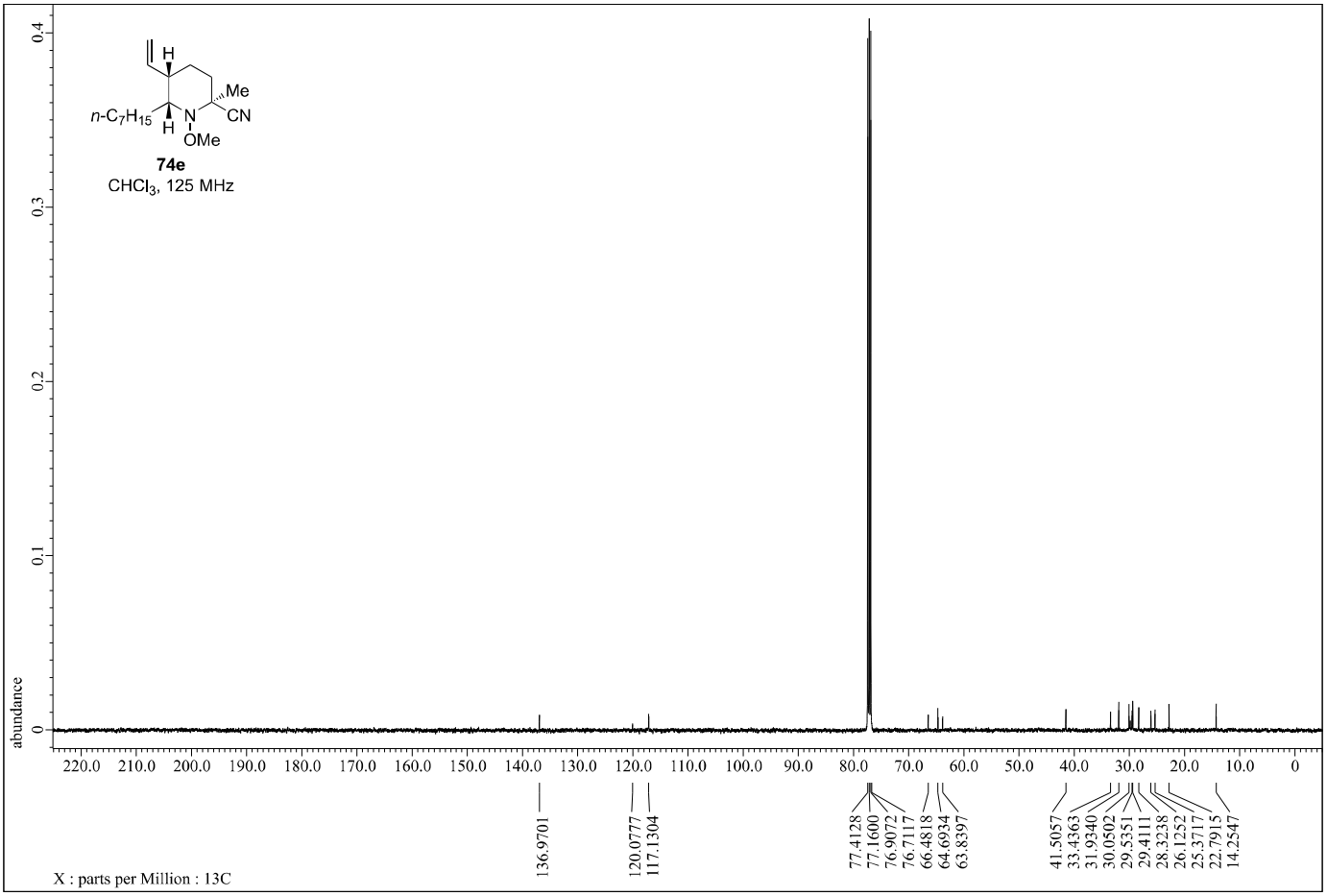

122b
CHCl3, 500 MHz, 60 °C
abundance
X : parts per Million : 1H
7.2600
6.1509
6.1349
6.1177
5.8938
5.8743
5.8600
5.8543
5.8394
5.0761
5.0584
5.0421
5.0389
5.0360
5.0131
5.0114
3.5470
2.6203
2.6037
2.5928
2.4628
2.2275
2.2126
2.2000
1.5970
1.5312
1.4150
1.3949
1.3016
1.2901
0.9076
0.8945
0.8802
0.63
0.91
1.00
4.21
3.08
1.08
3.00
1.06
0.99
4.02
1.21
10.85
3.15

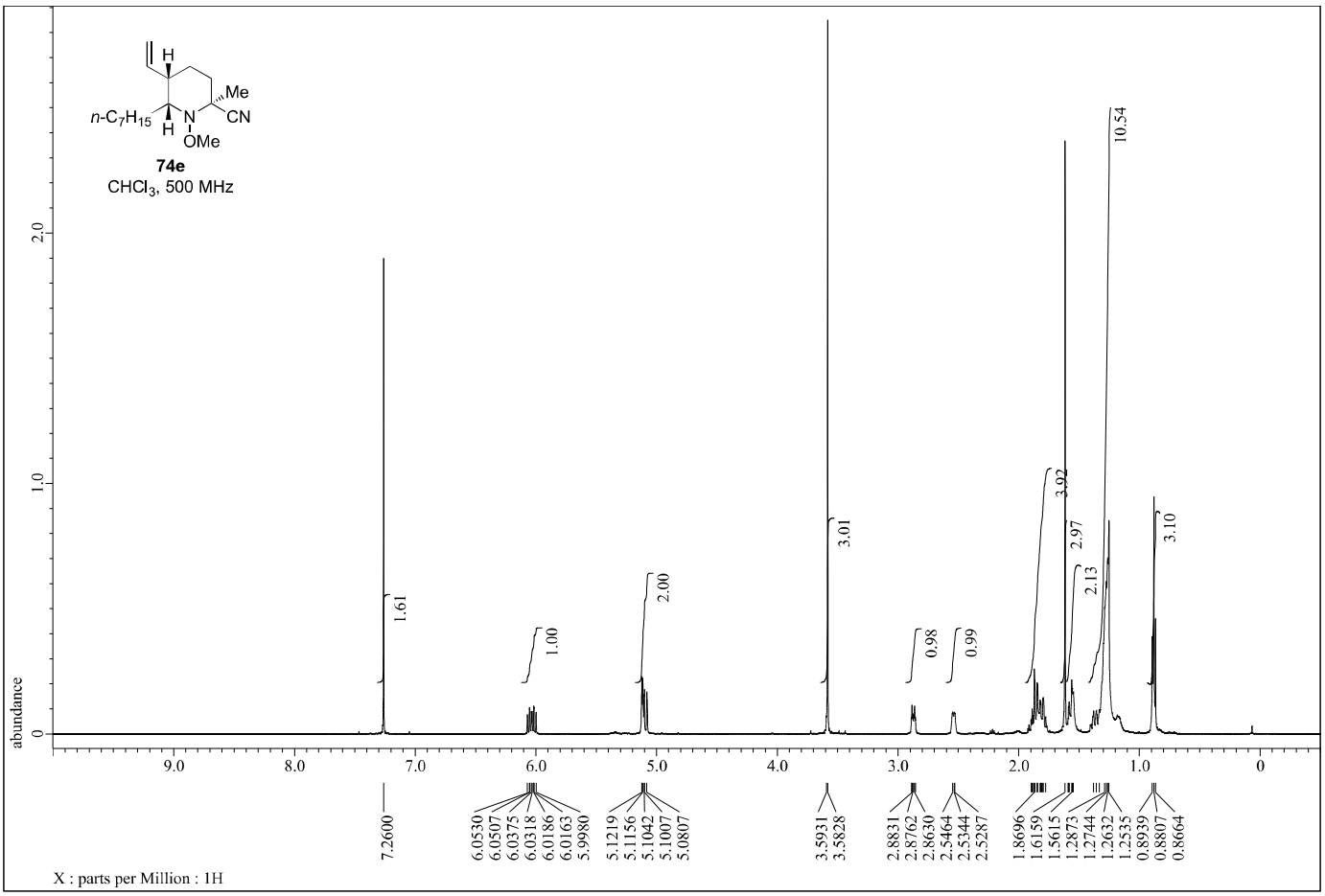

74c
CHCl3, 125 MHz, 60 °C
X : parts per Million : 13C

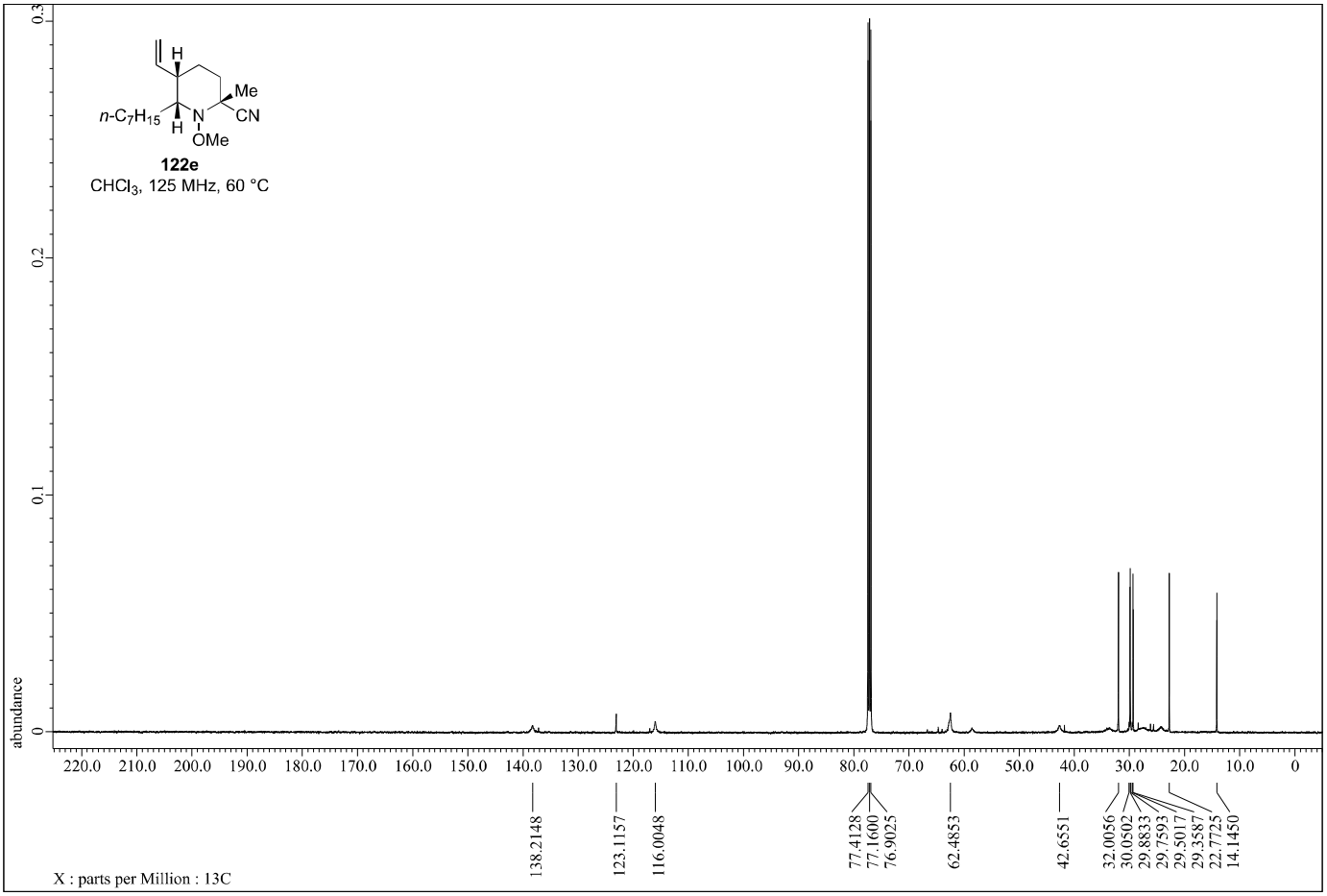

74c
CHCl3, 500 MHz, 60 °C
X : parts per Million : 1H

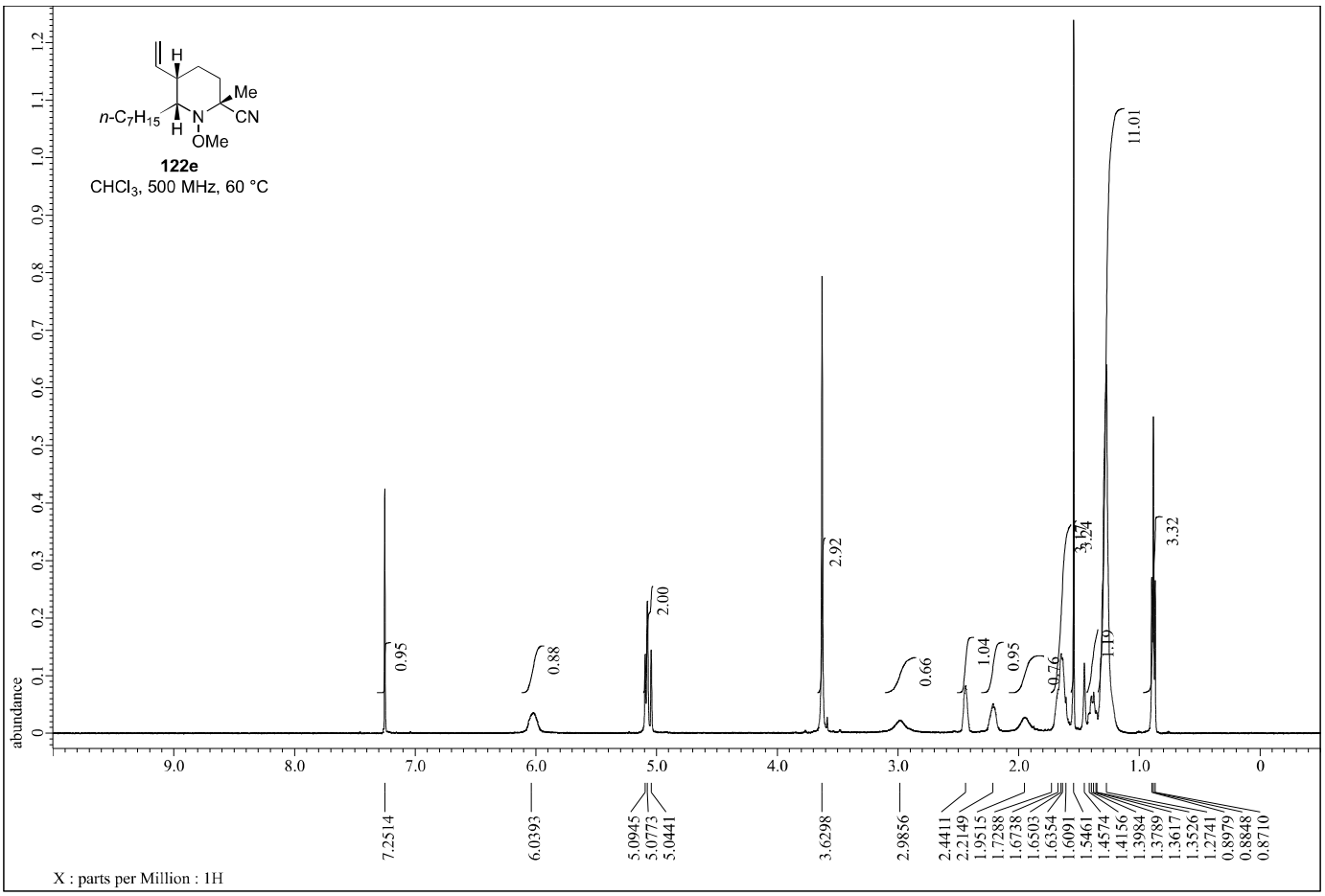

74d
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
199.6655
141.1956
137.5996
132.9735
128.6622
128.3713
128.2711
114.1019
77.4128
77.1600
76.9072
62.8573
60.4202
53.6146
32.0485
29.9119
29.7545
29.4159
26.9693
26.3684
25.0664
24.2652
22.8106
14.2738

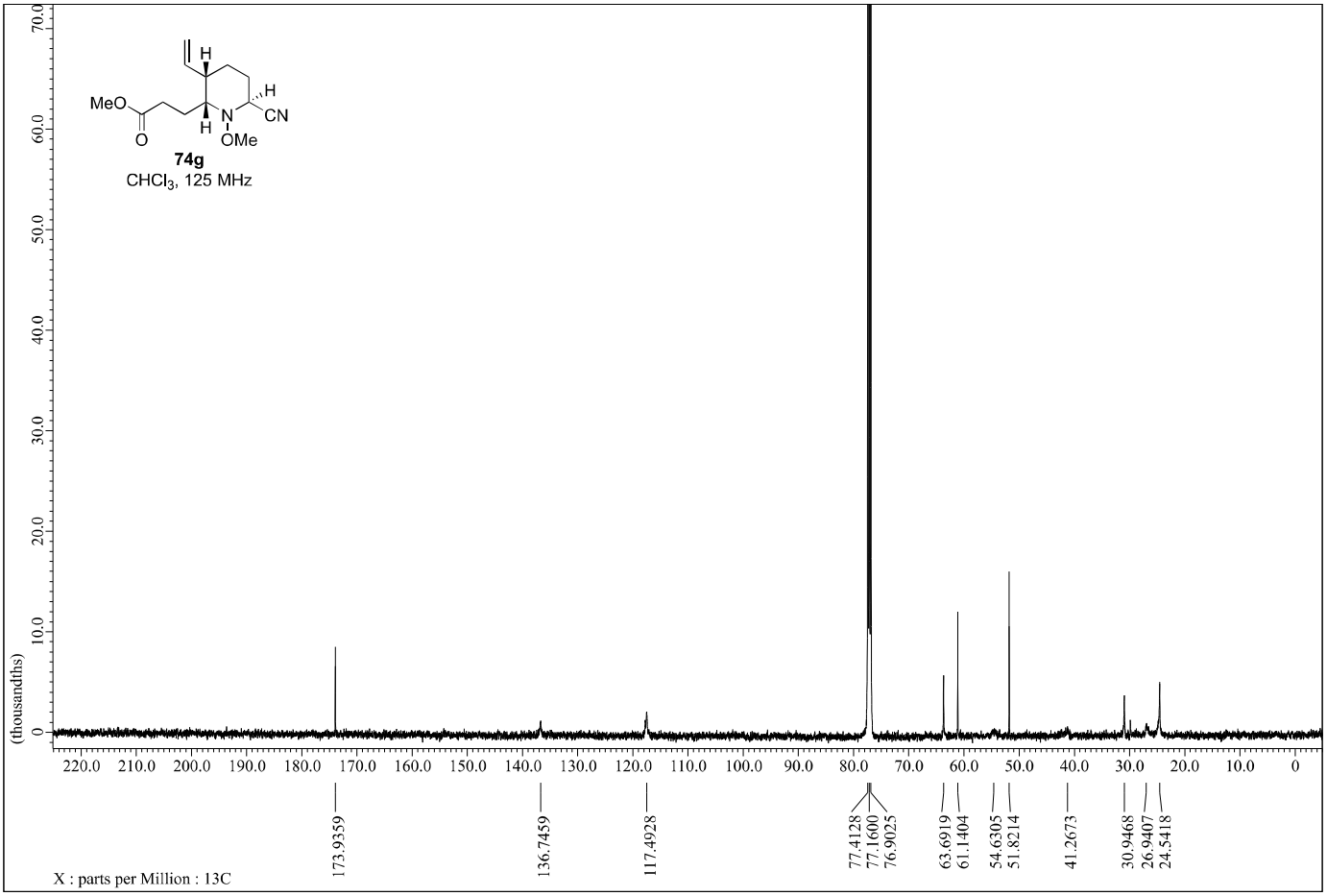

74d
CHCl3, 500 MHz, 60 °C
abundance
X : parts per Million : 1H
7.9763
7.9620
7.5560
7.5411
7.5263
7.4707
7.4553
7.4404
7.2600
5.8320
5.8182
5.7970
5.7827
5.7770
5.7632
5.0200
4.9983
4.9874
3.5553
3.4219
3.1425
2.9455
2.7331
1.4711
1.3411
1.3262
1.3119
1.2970
1.2778
1.2575
0.9059
0.8922
0.8779
2.05
2.03
1.01
1.00
2.07
0.96
4.00
0.80
0.84
0.87
2.44
13.96
3.33

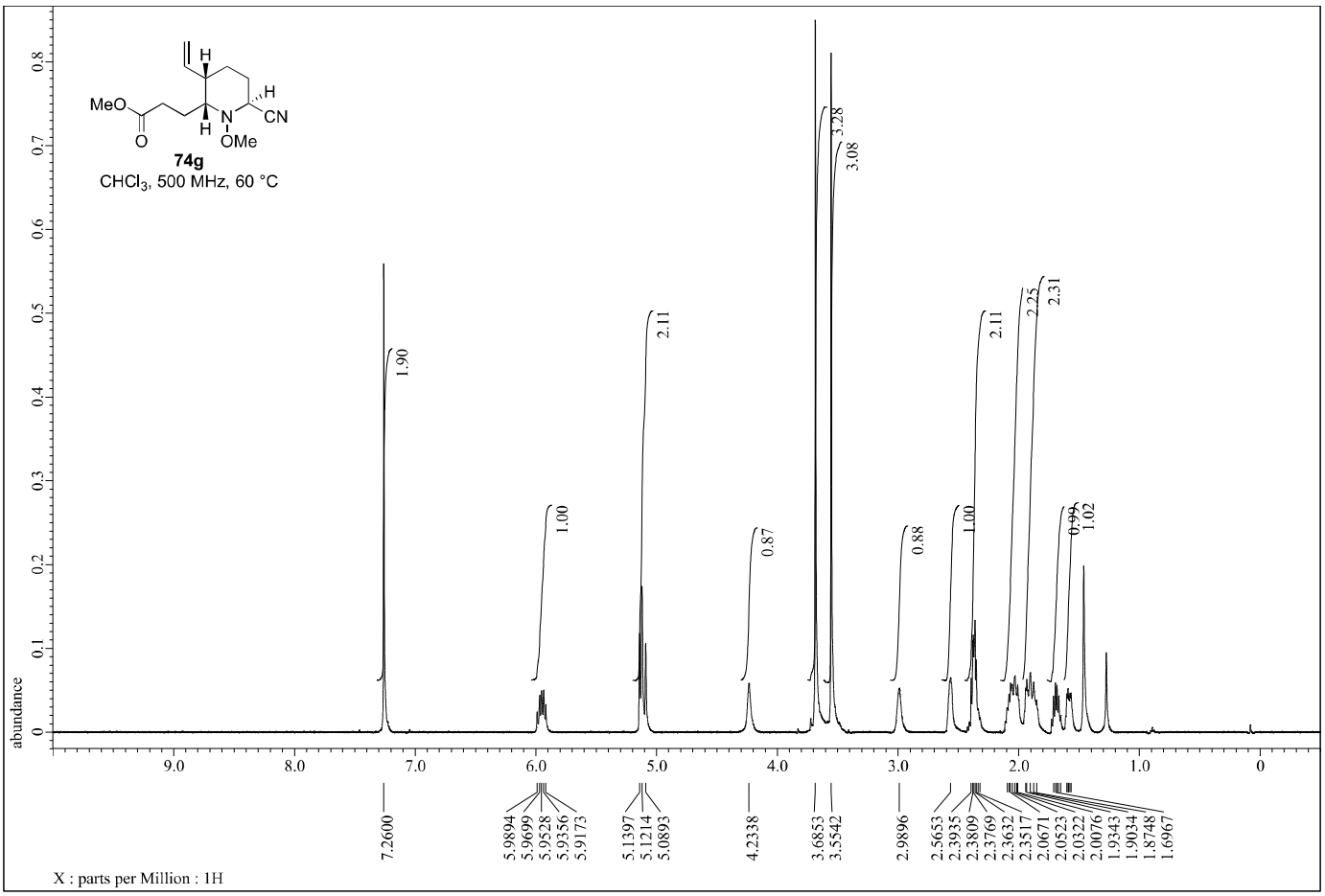

74e
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
136.9701
120.0777
117.1304
77.4128
77.1600
76.9072
76.7117
66.4818
64.6934
63.8397
41.5057
33.4363
31.9340
30.0502
29.5351
29.4111
28.3238
26.1252
25.3717
22.7915
14.2547

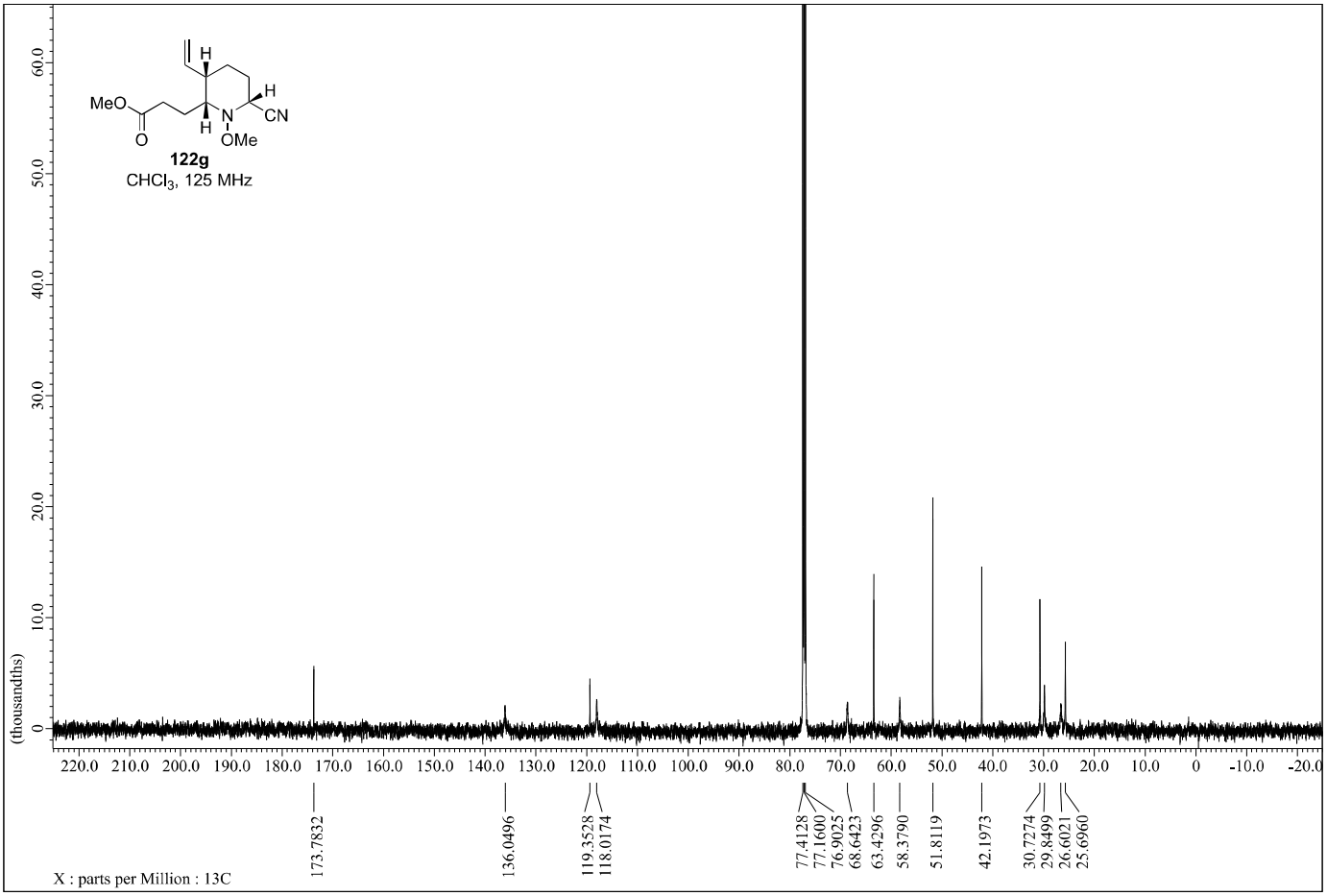

74e
CHCl3, 500 MHz
abundance
X : parts per Million : 1H
1.61
1.00
2.00
3.01
0.98
0.99
3.92
2.97
2.13
10.54
3.10
7.2600
6.0530
6.0507
6.0375
6.0318
6.0186
6.0163
5.9980
5.1219
5.1156
5.1042
5.1007
5.0807
3.5931
3.5828
2.8831
2.8762
2.8630
2.5464
2.5344
2.5287
1.8696
1.6159
1.5615
1.2873
1.2744
1.2632
1.2535
0.8939
0.8807
0.8664

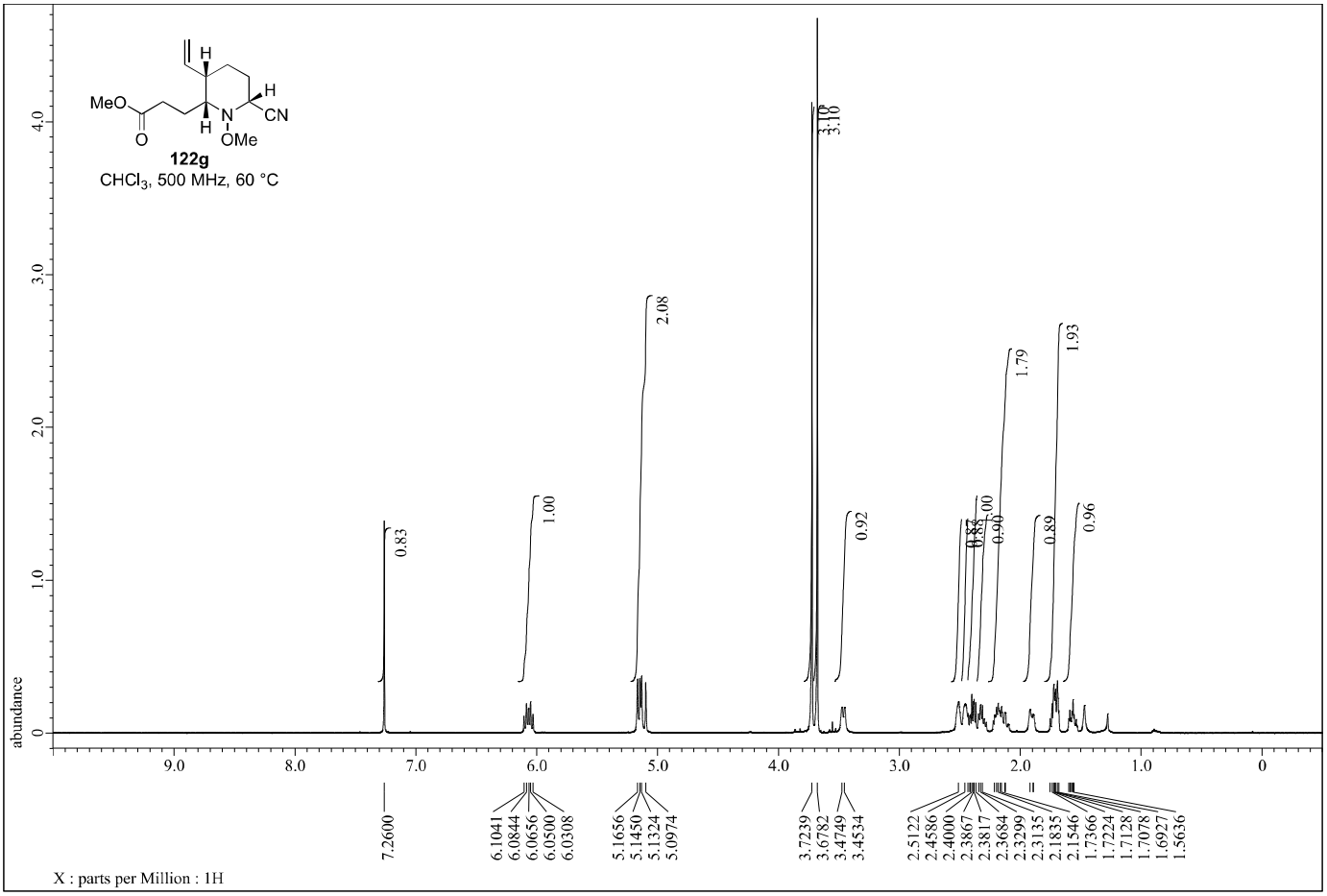

122e
CHCl3, 125 MHz, 60 °C
abundance
X : parts per Million : 13C
138.2148
123.1157
116.0048
77.4128
77.1600
76.9025
62.4853
42.6551
32.0056
30.0502
29.8833
29.7593
29.5017
29.3587
22.7725
14.1450

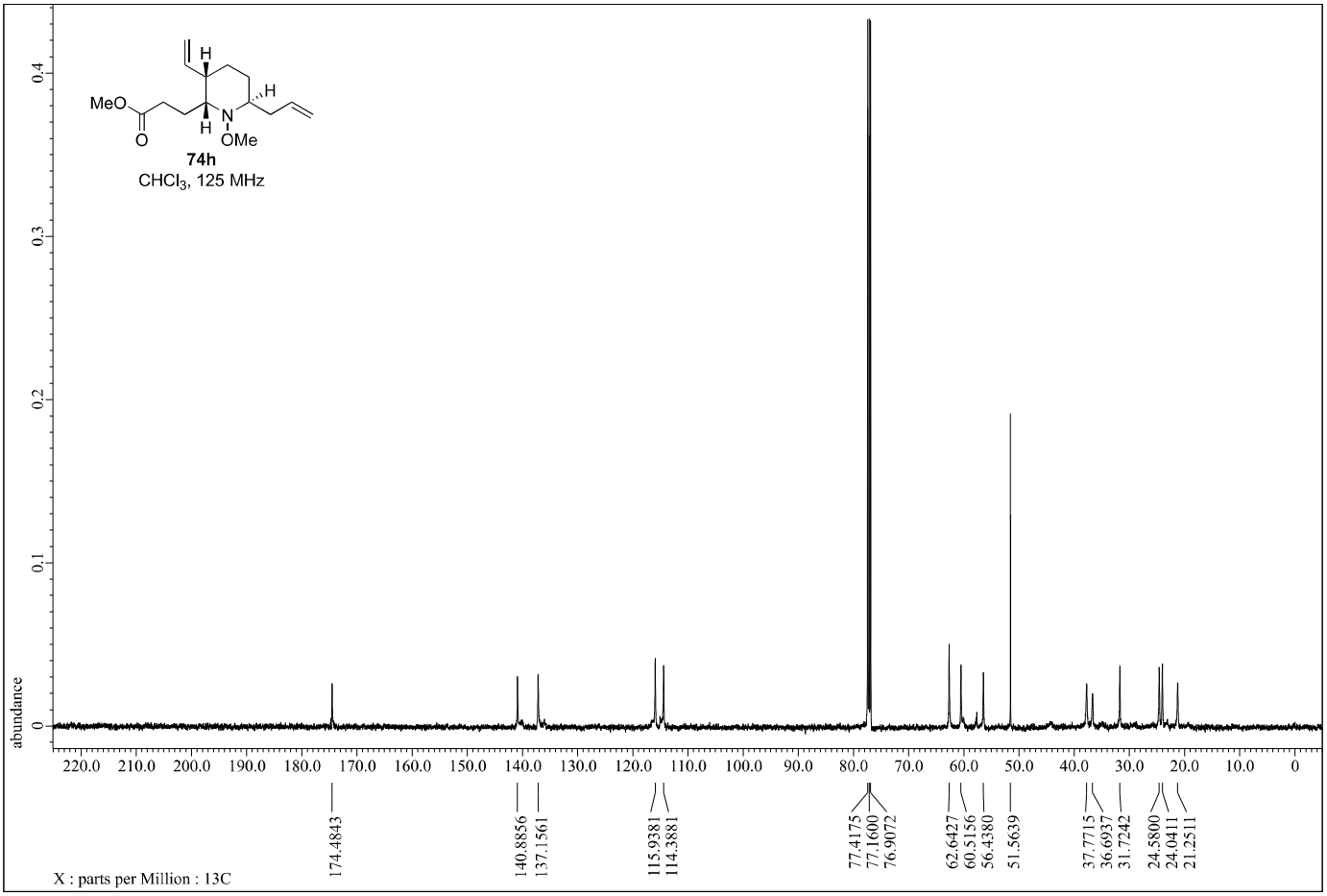

122e
CHCl3, 500 MHz, 60 °C
abundance
X : parts per Million : 1H
0.95
0.88
2.00
2.92
0.66
1.04
0.95
0.76
3.17
3.24
1.19
11.01
3.32
7.2514
6.0393
5.0945
5.0773
5.0441
3.6298
2.9856
2.4411
2.2149
1.9515
1.7288
1.6738
1.6503
1.6354
1.6091
1.5461
1.4574
1.4156
1.3984
1.3789
1.3617
1.3526
1.2741
0.8979
0.8848
0.8710

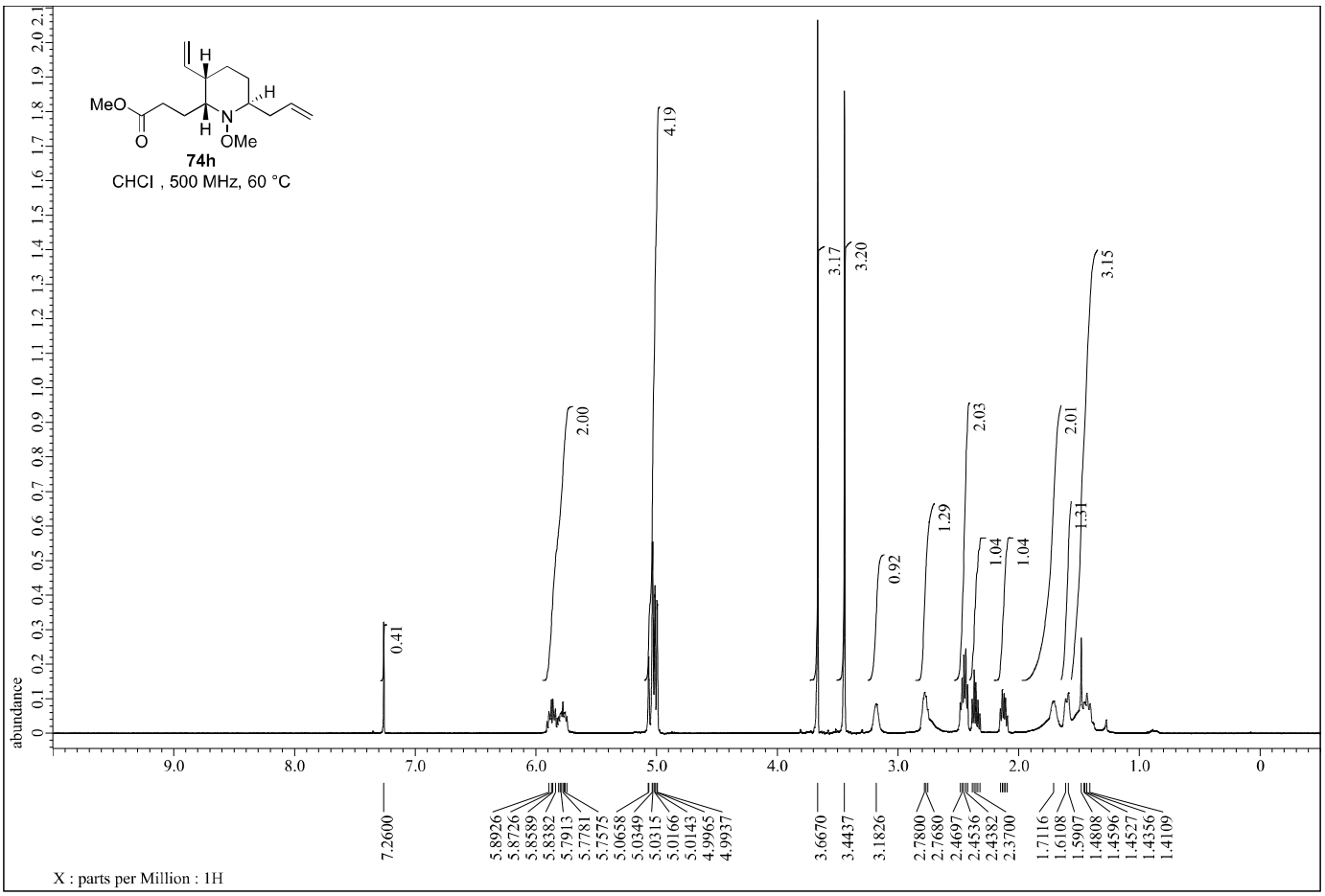

MeO
O
H
N
H
OMe
H
CN
74g
CHCl3, 125 MHz
(thousandths)
173.9359
136.7459
117.4928
77.4128
77.1600
76.9025
63.6919
61.1404
54.6305
51.8214
41.2673
30.9468
26.9407
24.5418
X : parts per Million : 13C

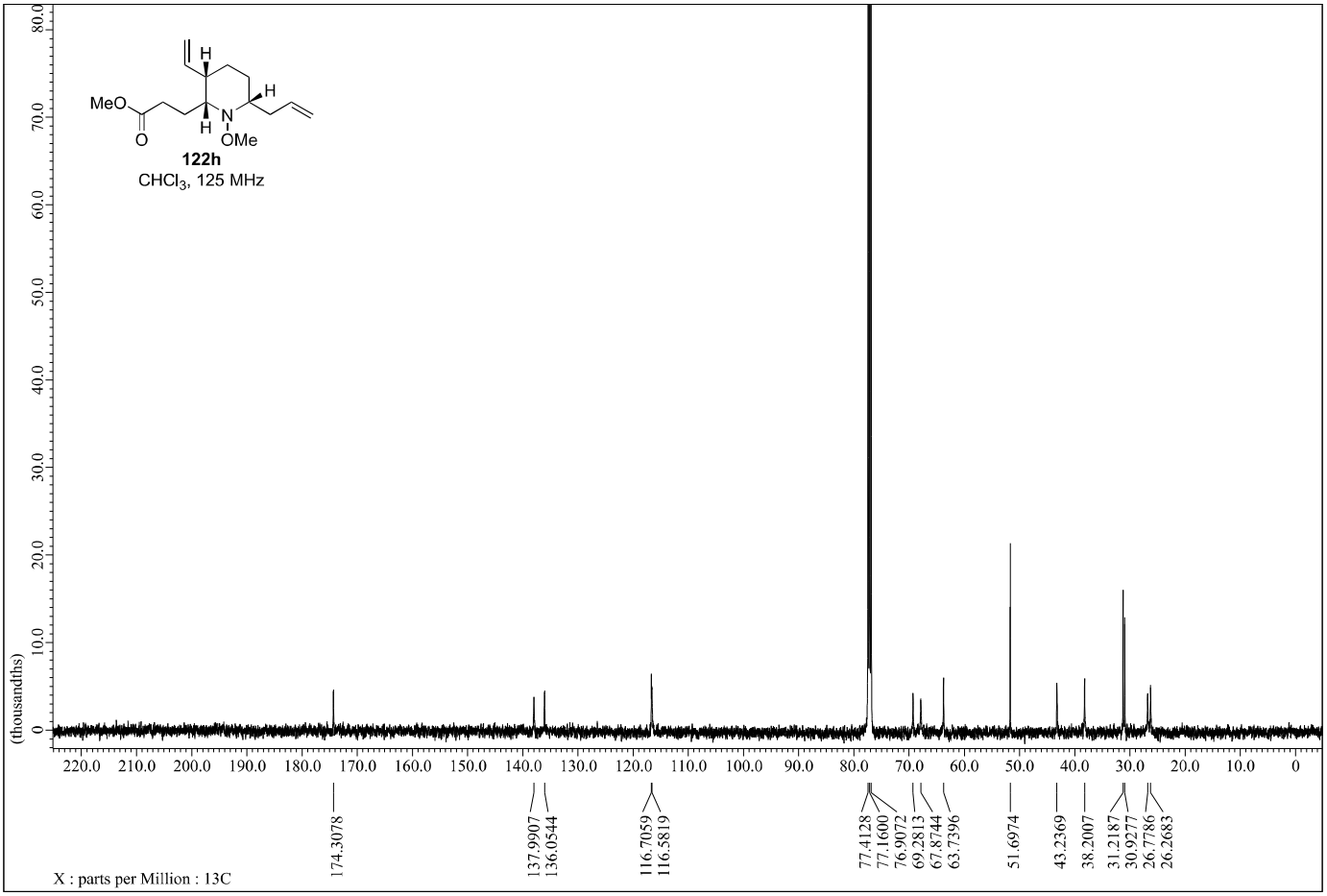

MeO
O
H
N
H
OMe
H
CN
74g
CHCl3, 500 MHz, 60 °C
abundance
1.90
1.00
2.11
0.87
3.28
3.08
0.88
1.00
2.11
2.25
2.31
0.99
1.02
7.2600
5.9894
5.9699
5.9528
5.9356
5.9173
5.1397
5.1214
5.0893
4.2338
3.6853
3.5542
2.9896
2.5653
2.3935
2.3809
2.3769
2.3632
2.3517
2.0671
2.0523
2.0322
2.0076
1.9343
1.9034
1.8748
1.6967
X : parts per Million : 1H

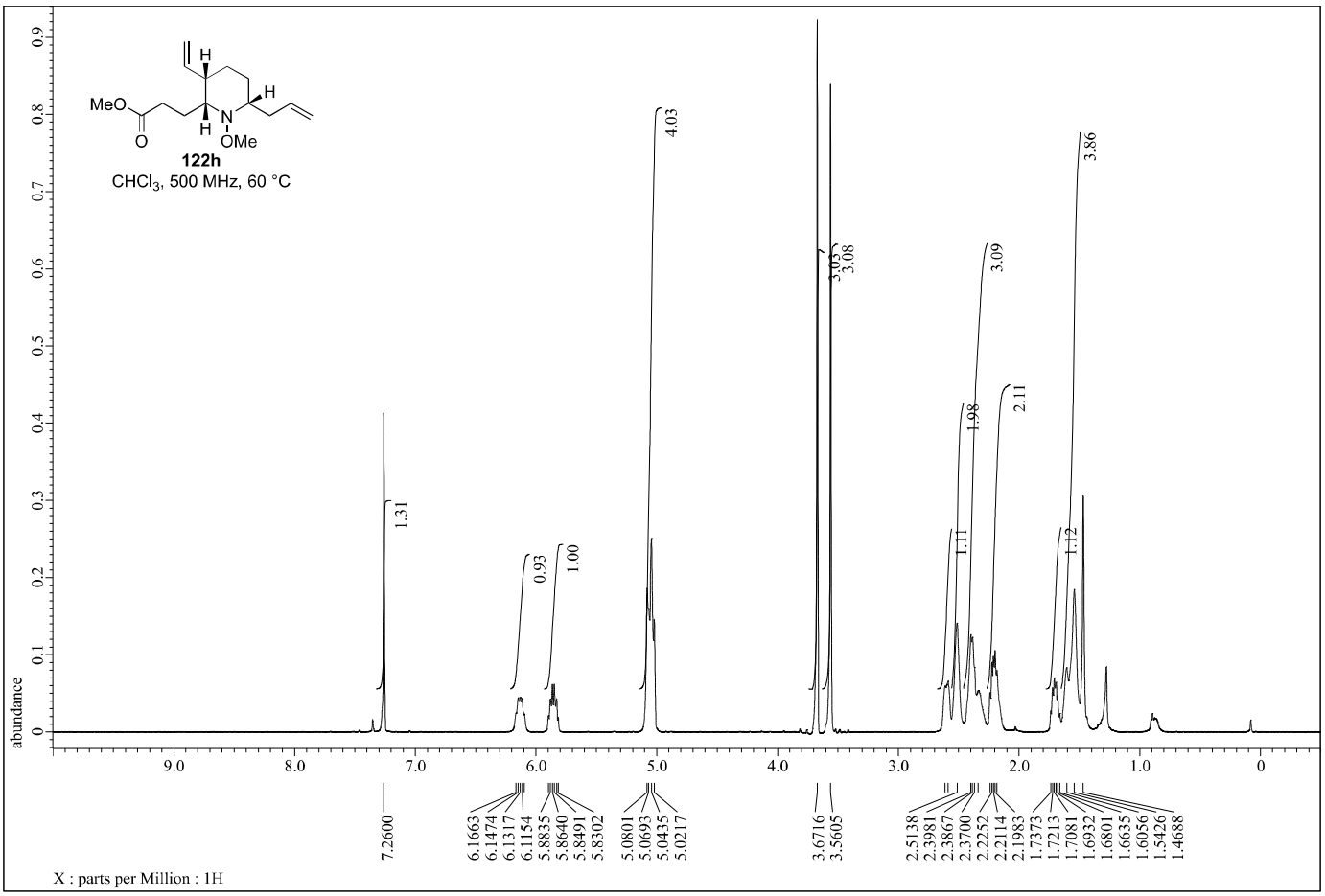

MeO
O
H
N
H
OMe
CN
122g
CHCl3, 125 MHz
(thousandths)
X : parts per Million : 13C
173.7832
136.0496
119.3528
118.0174
77.4128
77.1600
76.9025
68.6423
63.4296
58.3790
51.8119
42.1973
30.7274
29.8499
26.6021
25.6960

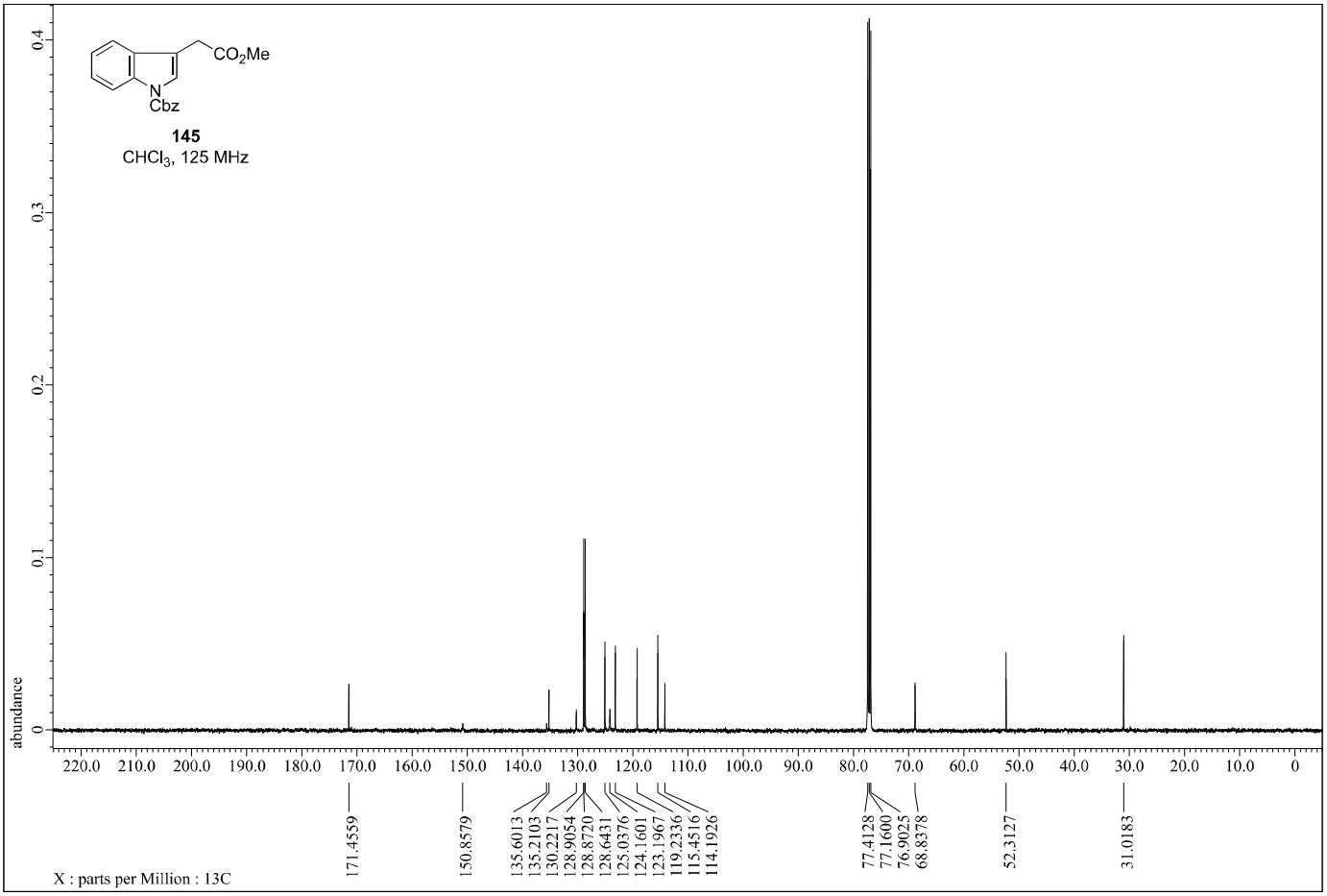

MeO
O
H
N
H
OMe
CN
122g
CHCl3, 500 MHz, 60 °C
abundance
X : parts per Million : 1H
0.83
1.00
2.08
3.10
0.92
0.87
0.90
1.79
0.89
1.93
0.96
7.2600
6.1041
6.0844
6.0656
6.0500
6.0308
5.1656
5.1450
5.1324
5.0974
3.7239
3.6782
3.4749
3.4534
2.5122
2.4586
2.4000
2.3867
2.3817
2.3684
2.3299
2.3135
2.1835
2.1546
1.7366
1.7224
1.7128
1.7078
1.6927
1.5636

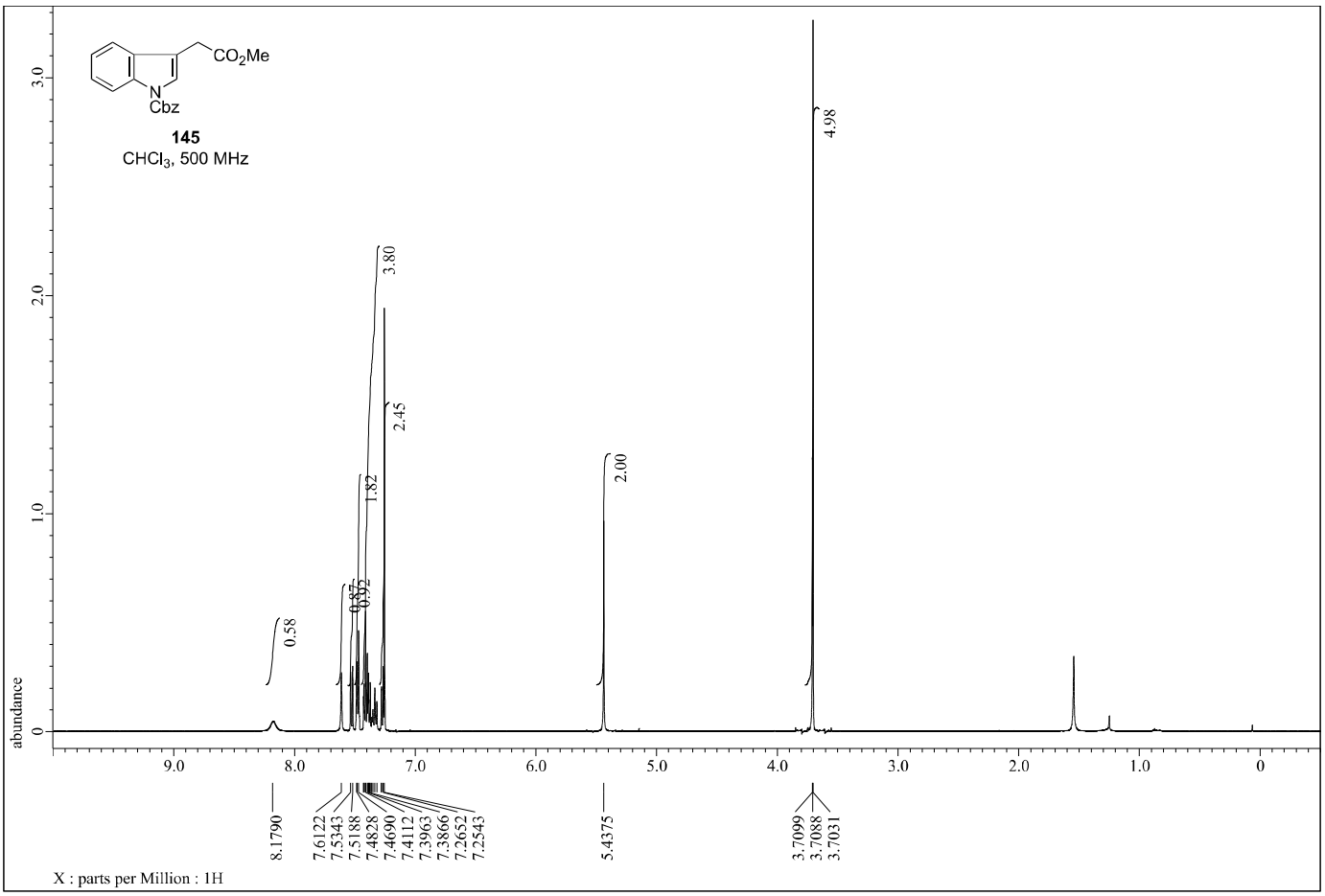

74h
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
174.4843
140.8856
137.1561
115.9381
114.3881
77.4175
77.1600
76.9072
62.6427
60.5156
56.4380
51.5639
37.7715
36.6937
31.7242
24.5800
24.0411
21.2511

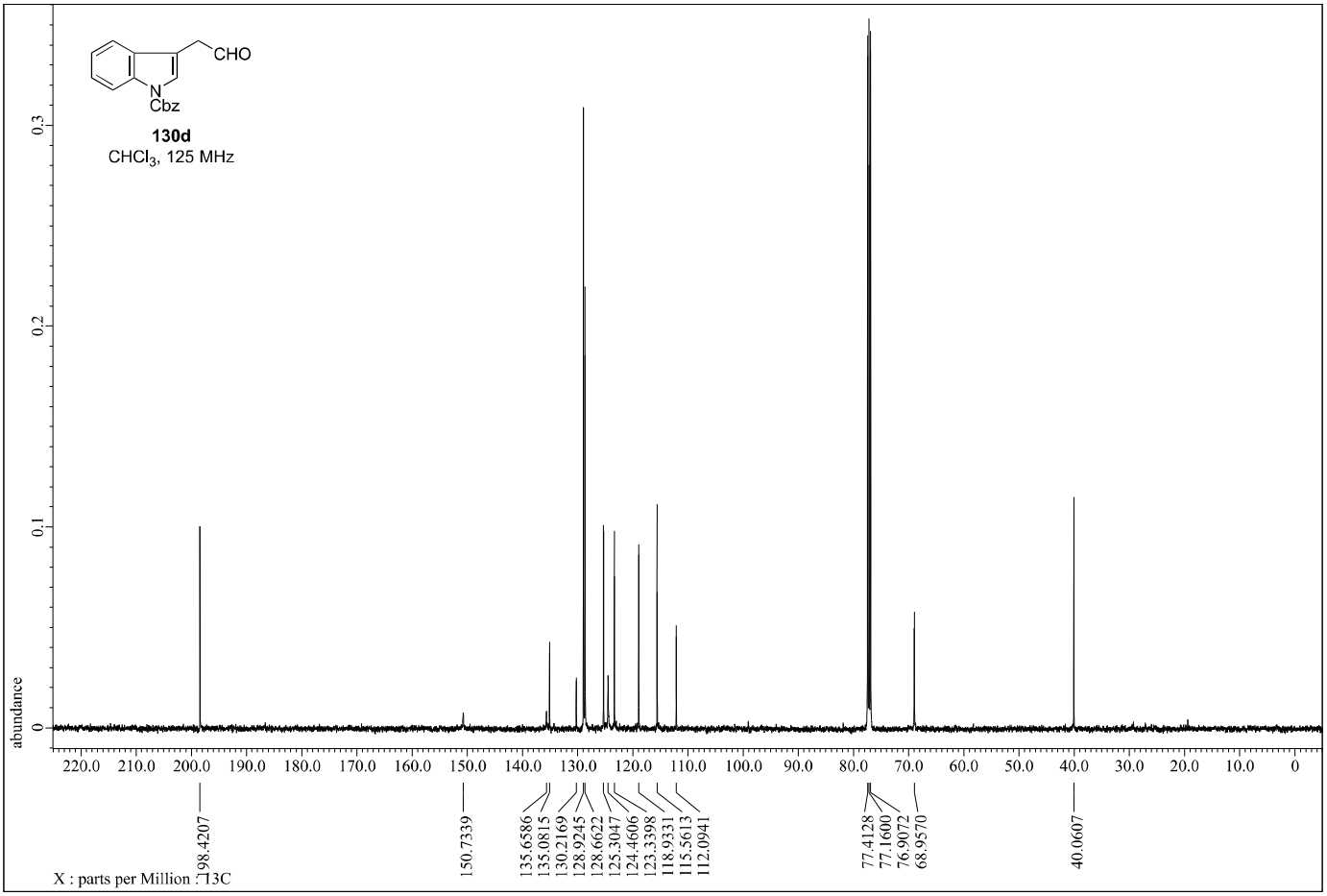

74h
CHCl , 500 MHz, 60 °C
abundance
X : parts per Million : 1H
7.2600
5.8926
5.8726
5.8589
5.8382
5.7913
5.7781
5.7575
5.0658
5.0349
5.0315
5.0166
5.0143
4.9965
4.9937
3.6670
3.4437
3.1826
2.7800
2.7680
2.4697
2.4536
2.4382
2.3700
1.7116
1.6108
1.5907
1.4808
1.4596
1.4527
1.4356
1.4109
0.41
2.00
4.19
3.17
3.20
0.92
1.29
2.03
1.04
1.04
2.01
1.31
3.15

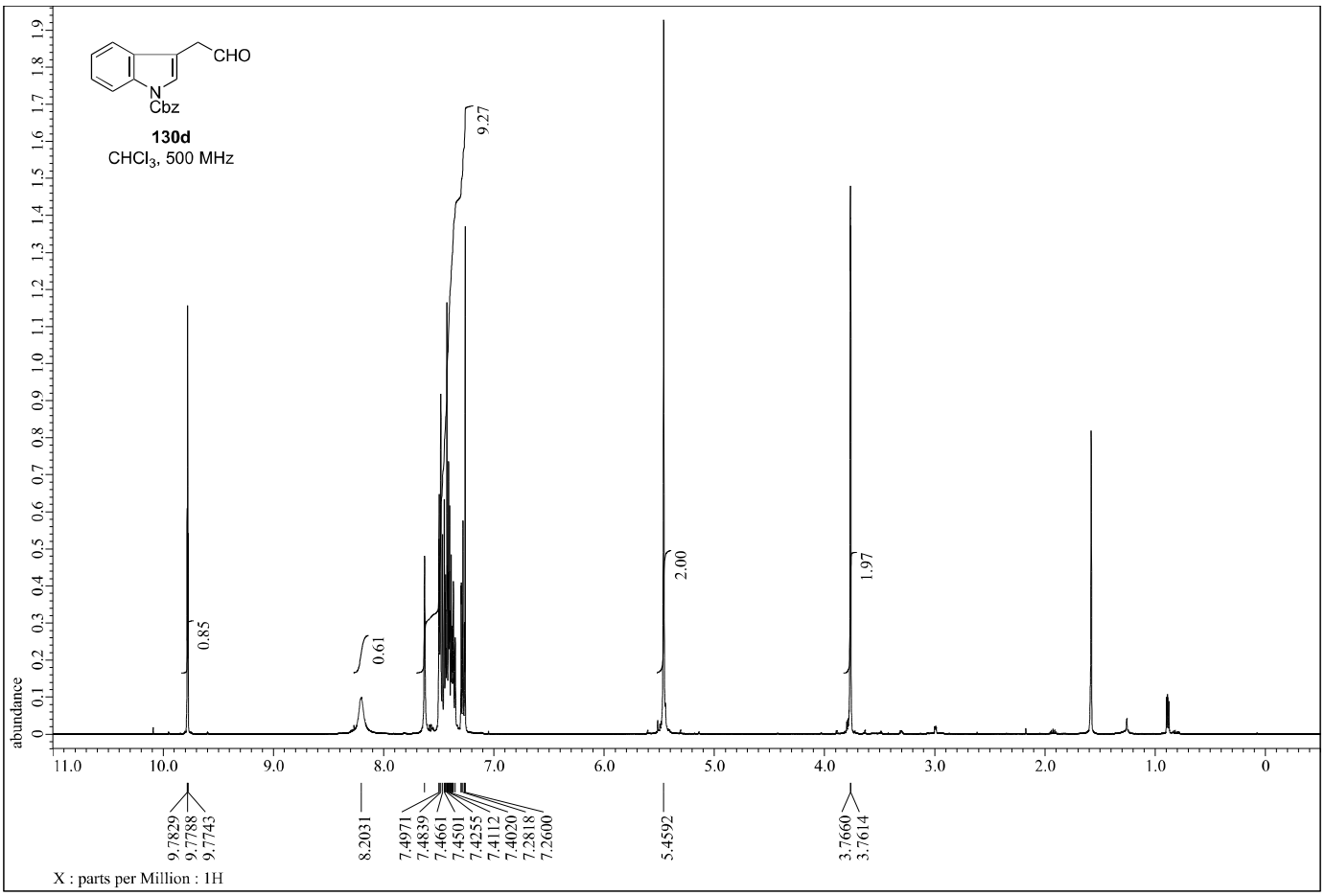

MeO
O
H
N
OMe
122h
CHCl3, 125 MHz
(thousandths)
174.3078
137.9907
136.0544
116.7059
116.5819
77.4128
77.1600
76.9072
69.2813
67.8744
63.7396
51.6974
43.2369
38.2007
31.2187
30.9277
26.7786
26.2683
X : parts per Million : 13C

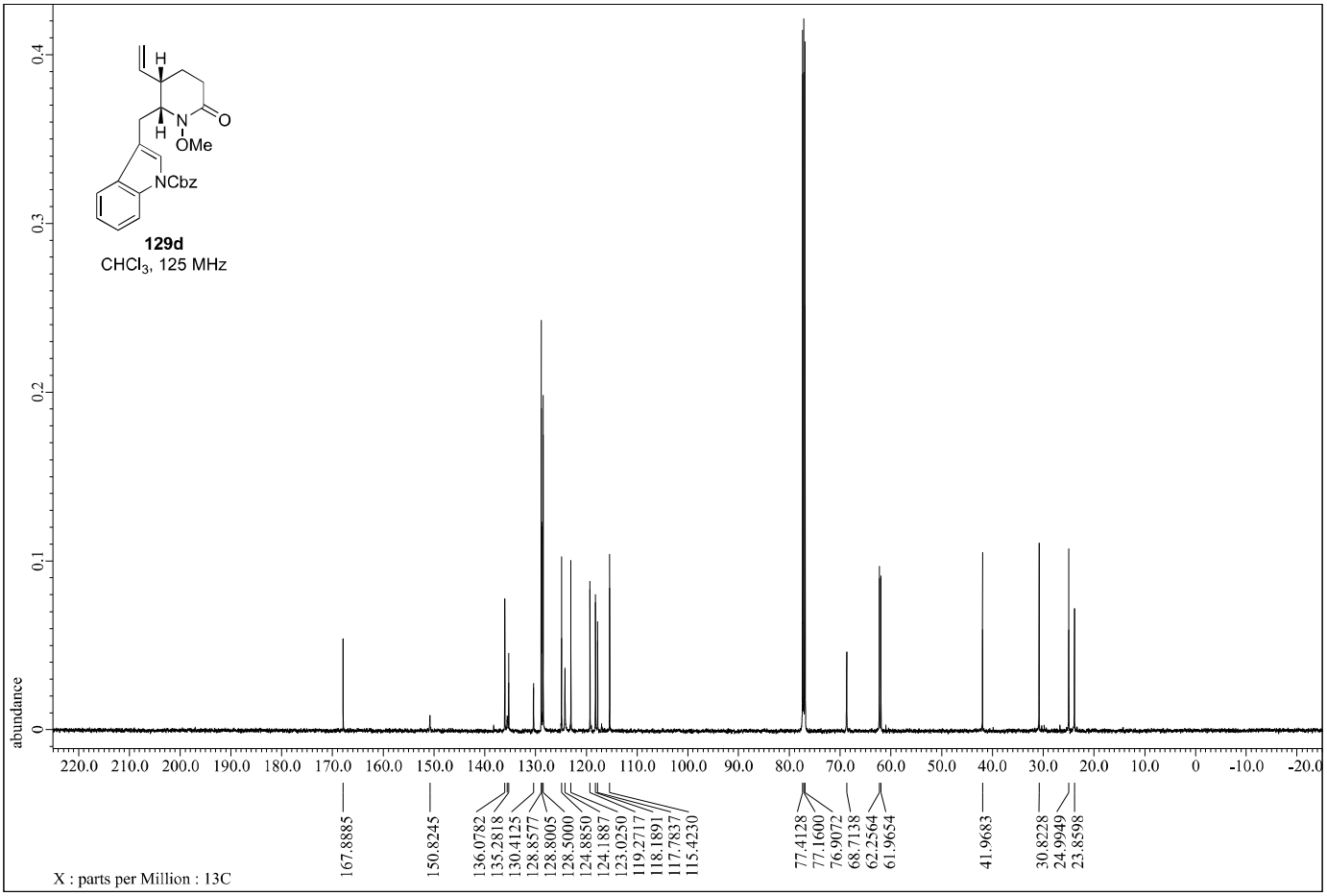

MeO
O
H
N
OMe
122h
CHCl3, 500 MHz, 60 °C
abundance
1.31
0.93
1.00
4.03
3.05
3.08
1.11
1.98
3.09
2.11
1.12
3.86
7.2600
6.1663
6.1474
6.1317
6.1154
5.8835
5.8640
5.8491
5.8302
5.0801
5.0693
5.0435
5.0217
3.6716
3.5605
2.5138
2.3981
2.3867
2.3700
2.2252
2.2114
2.1983
1.7373
1.7213
1.7081
1.6932
1.6801
1.6635
1.6056
1.5426
1.4688
X : parts per Million : 1H

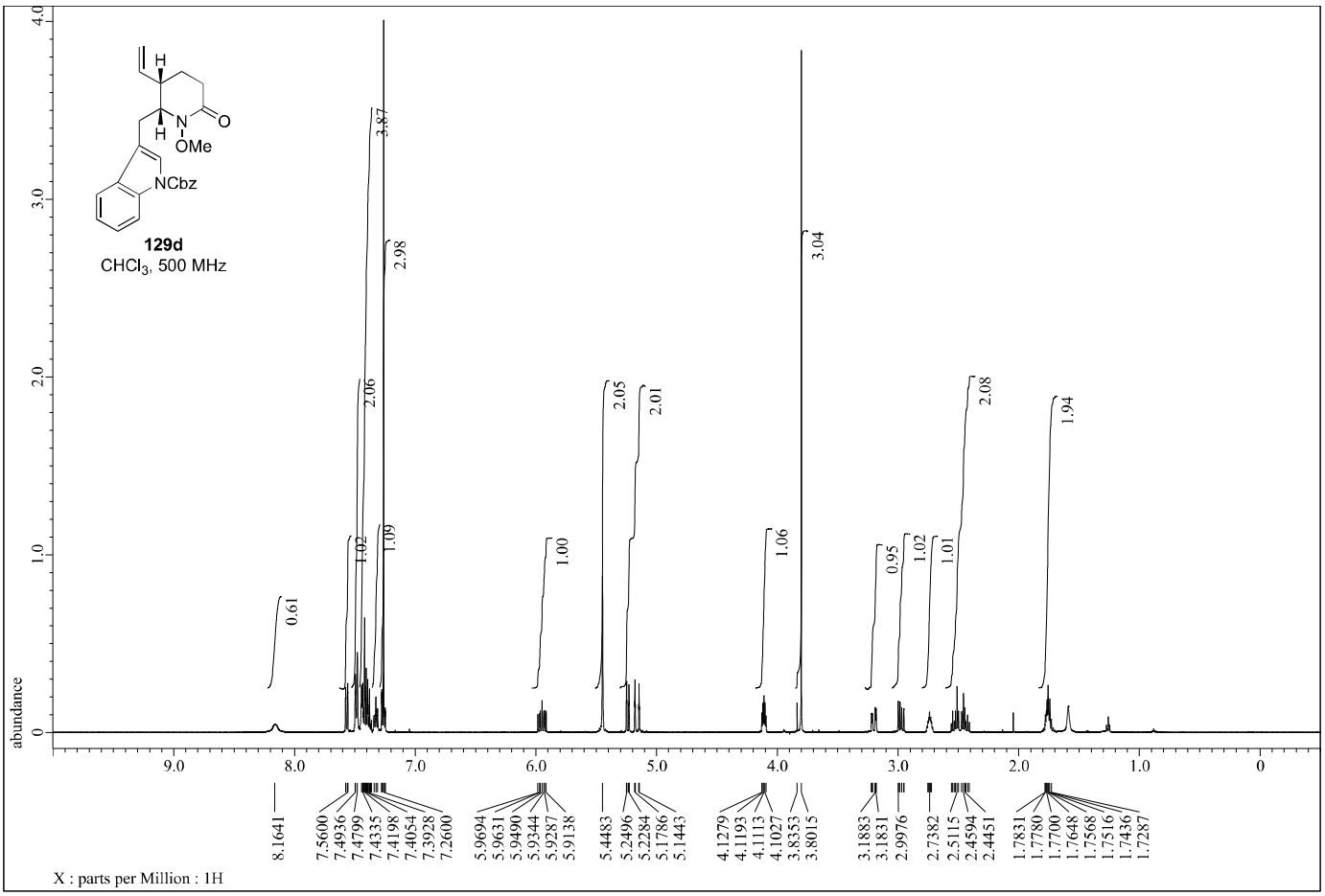

CO2Me
N
Cbz
145
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
171.4559
150.8579
135.6013
135.2103
130.2217
128.9054
128.8720
128.6431
125.0376
124.1601
123.1967
119.2336
115.4516
114.1926
77.4128
77.1600
76.9025
68.8378
52.3127
31.0183

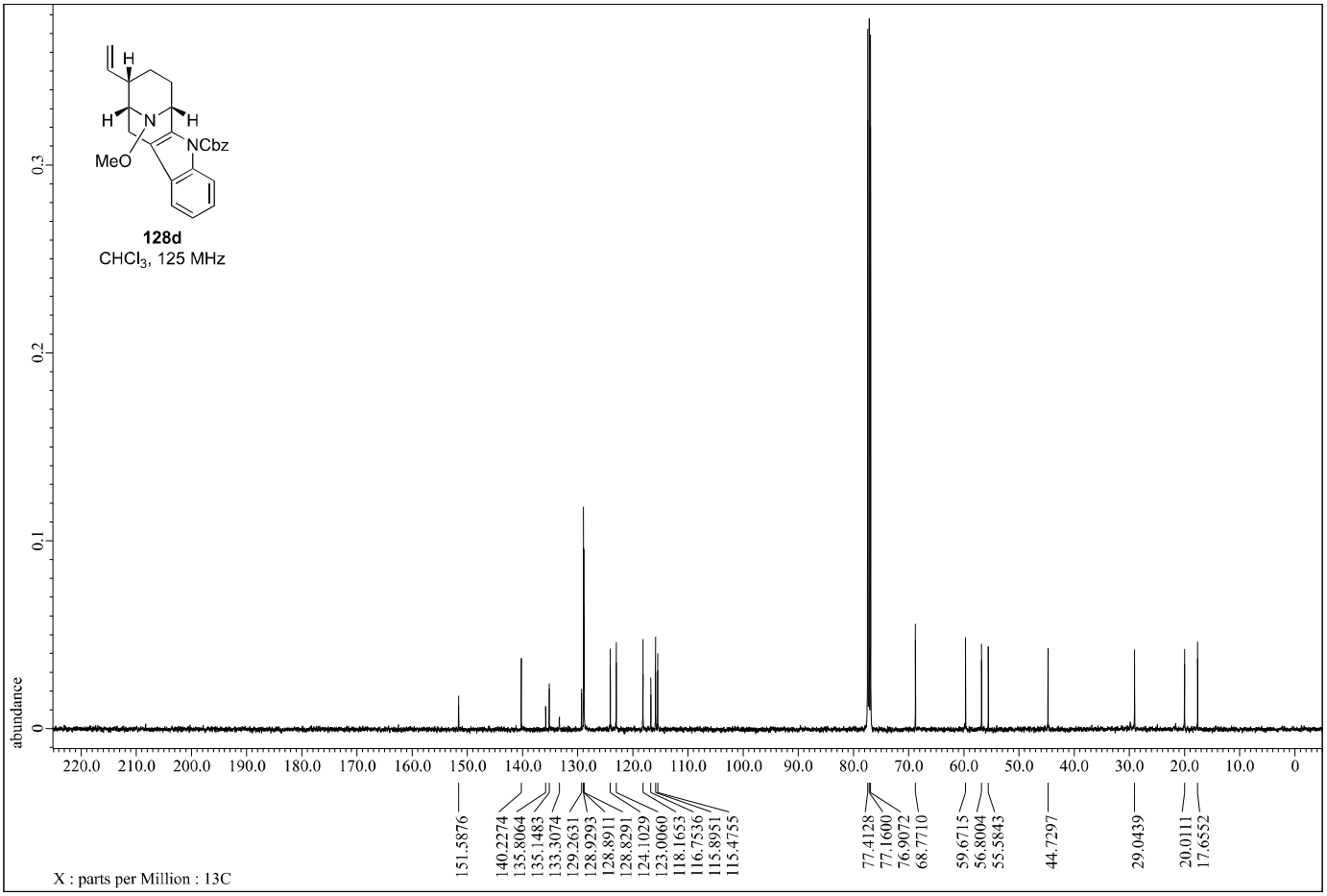

CO2Me
N
Cbz
145
CHCl3, 500 MHz
abundance
X : parts per Million : 1H
8.1790
7.6122
7.5343
7.5188
7.4828
7.4690
7.4112
7.3963
7.3866
7.2652
7.2543
5.4375
3.7099
3.7088
3.7031
0.58
0.87
0.92
1.82
3.80
2.45
2.00
4.98

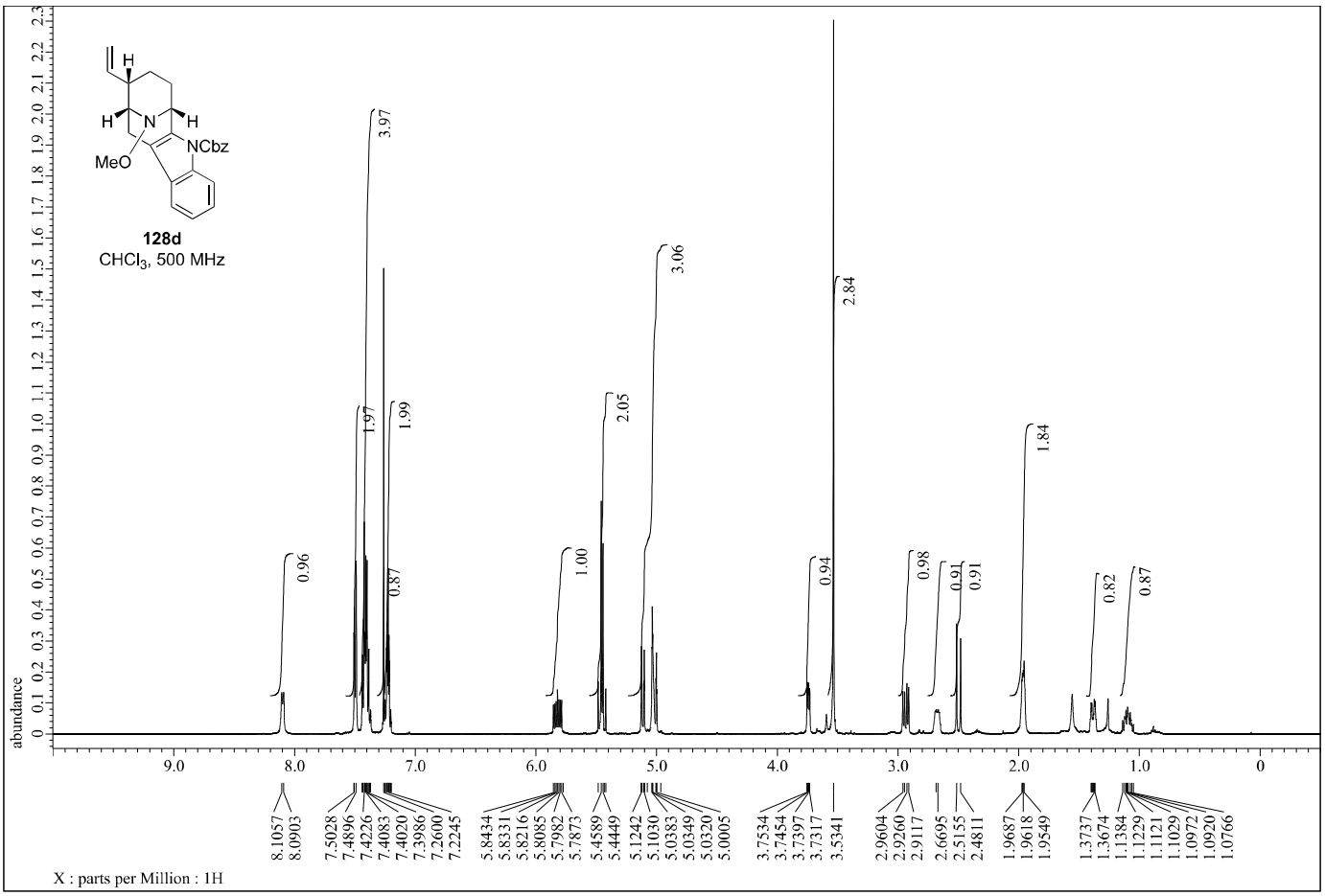

CHO
N
Cbz
130d
CHCl3, 125 MHz
abundance
198.4207
150.7339
135.6586
135.0815
130.2169
128.9245
128.6622
125.3047
124.4606
123.3398
118.9331
115.5613
112.0941
77.4128
77.1600
76.9072
68.9570
40.0607
X : parts per Million : 13C

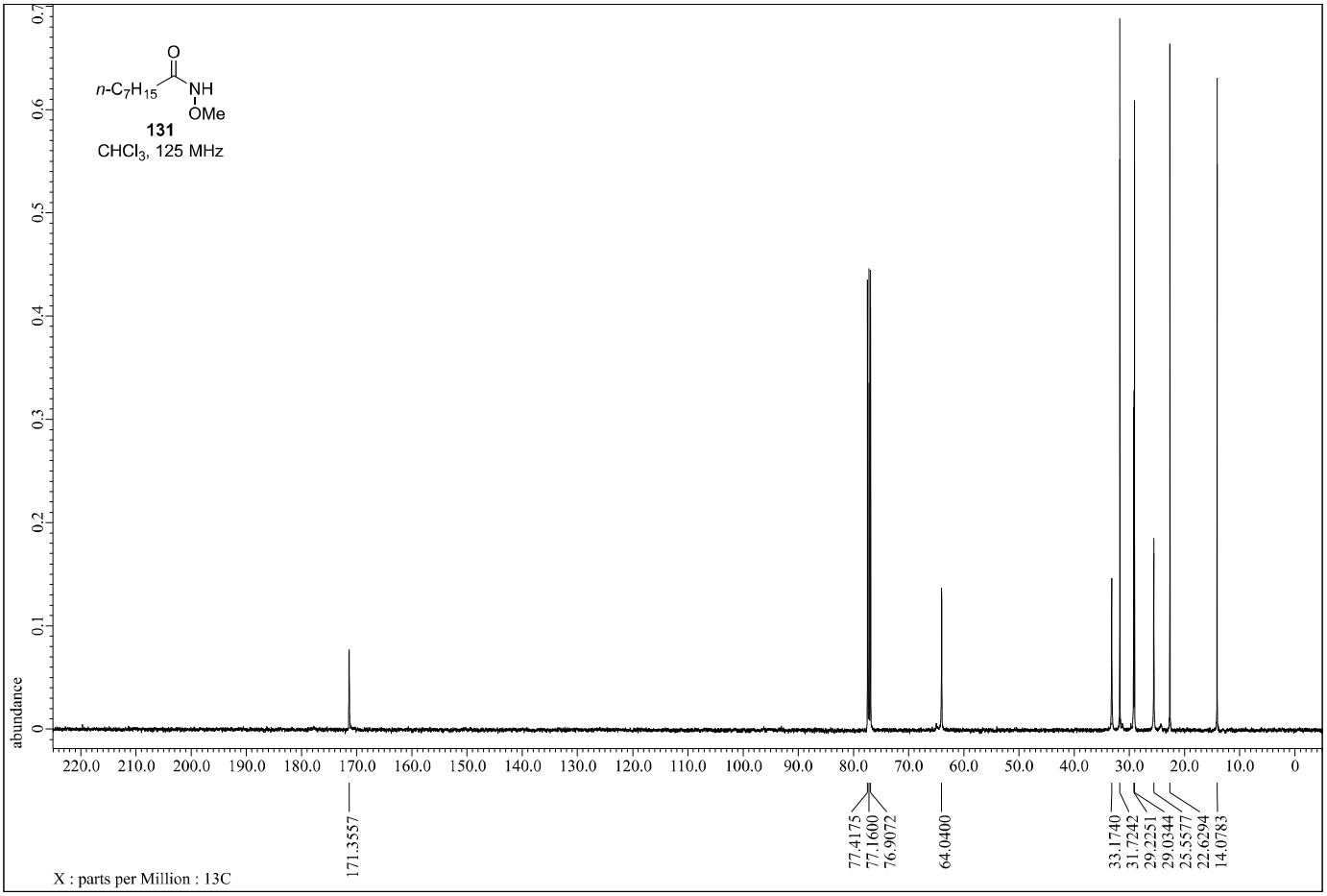

CHO
N
Cbz
130d
CHCl3, 500 MHz
abundance
0.85
0.61
9.27
2.00
1.97
9.7829
9.7788
9.7743
8.2031
7.4971
7.4839
7.4661
7.4501
7.4255
7.4112
7.4020
7.2818
7.2600
5.4592
3.7660
3.7614
X : parts per Million : 1H

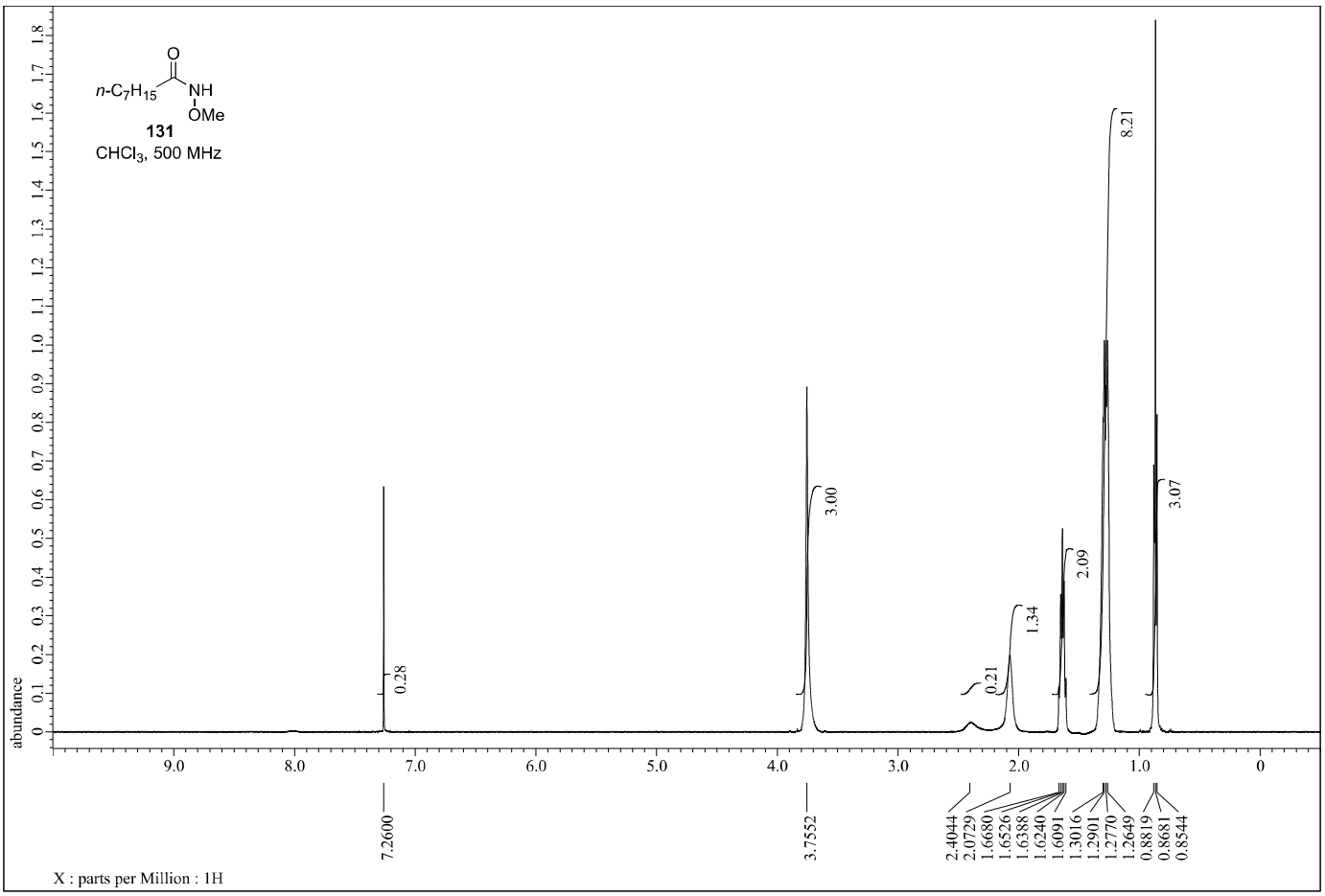

129d
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
167.8885
150.8245
136.0782
135.2818
130.4125
128.8577
128.8005
128.5000
124.8850
124.1887
123.0250
119.2717
118.1891
117.7837
115.4230
77.4128
77.1600
76.9072
68.7138
62.2564
61.9654
41.9683
30.8228
24.9949
23.8598

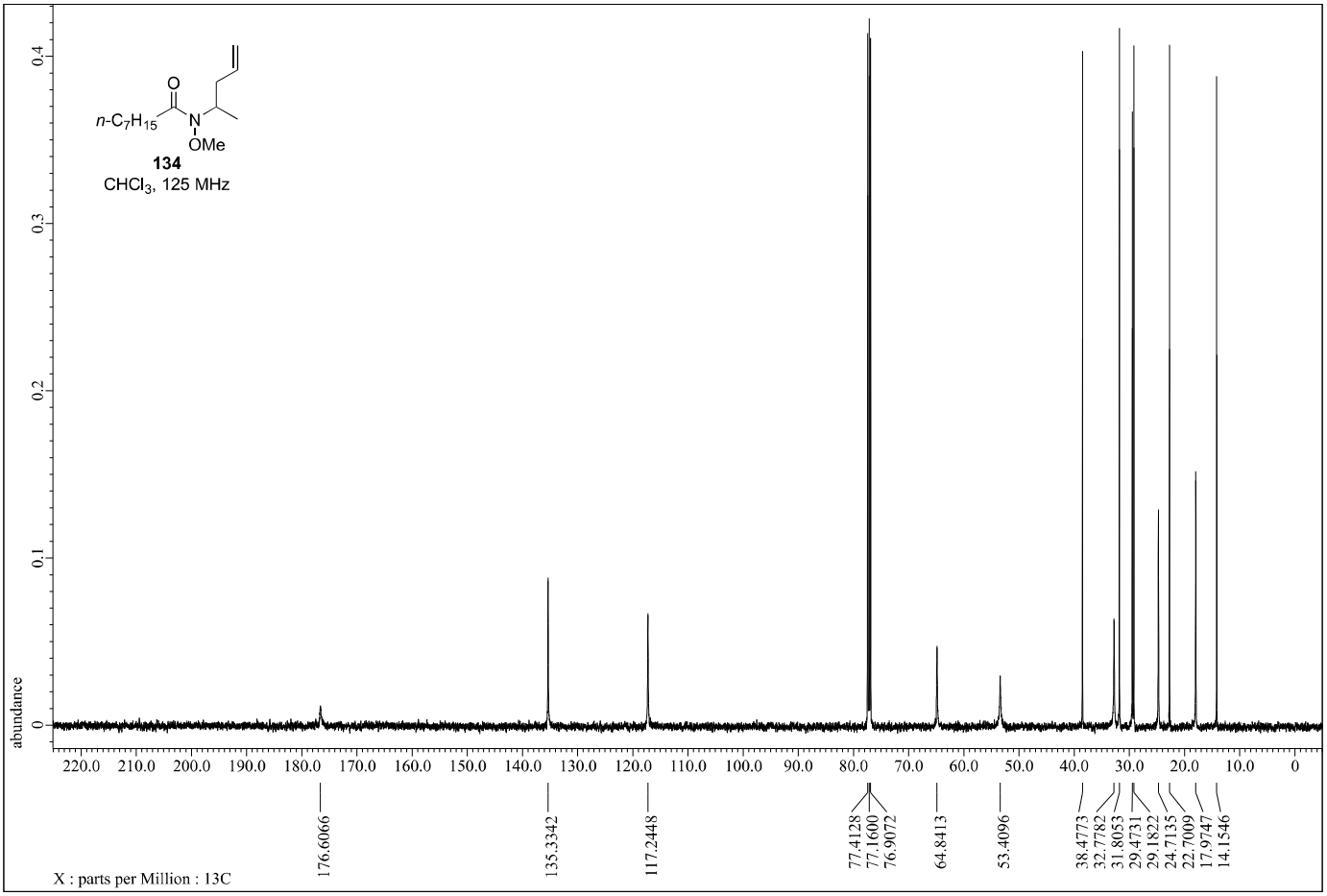

129d
CHCl3, 500 MHz
abundance
X : parts per Million : 1H
0.61
1.02
2.06
3.87
1.09
2.98
1.00
2.05
2.01
1.06
3.04
0.95
1.02
1.01
2.08
1.94
8.1641
7.5600
7.4936
7.4799
7.4335
7.4198
7.4054
7.3928
7.2600
5.9694
5.9631
5.9490
5.9344
5.9287
5.9138
5.4483
5.2496
5.2284
5.1786
5.1443
4.1279
4.1193
4.1113
4.1027
3.8353
3.8015
3.1883
3.1831
2.9976
2.7382
2.5115
2.4594
2.4451
1.7831
1.7780
1.7700
1.7648
1.7568
1.7516
1.7436
1.7287

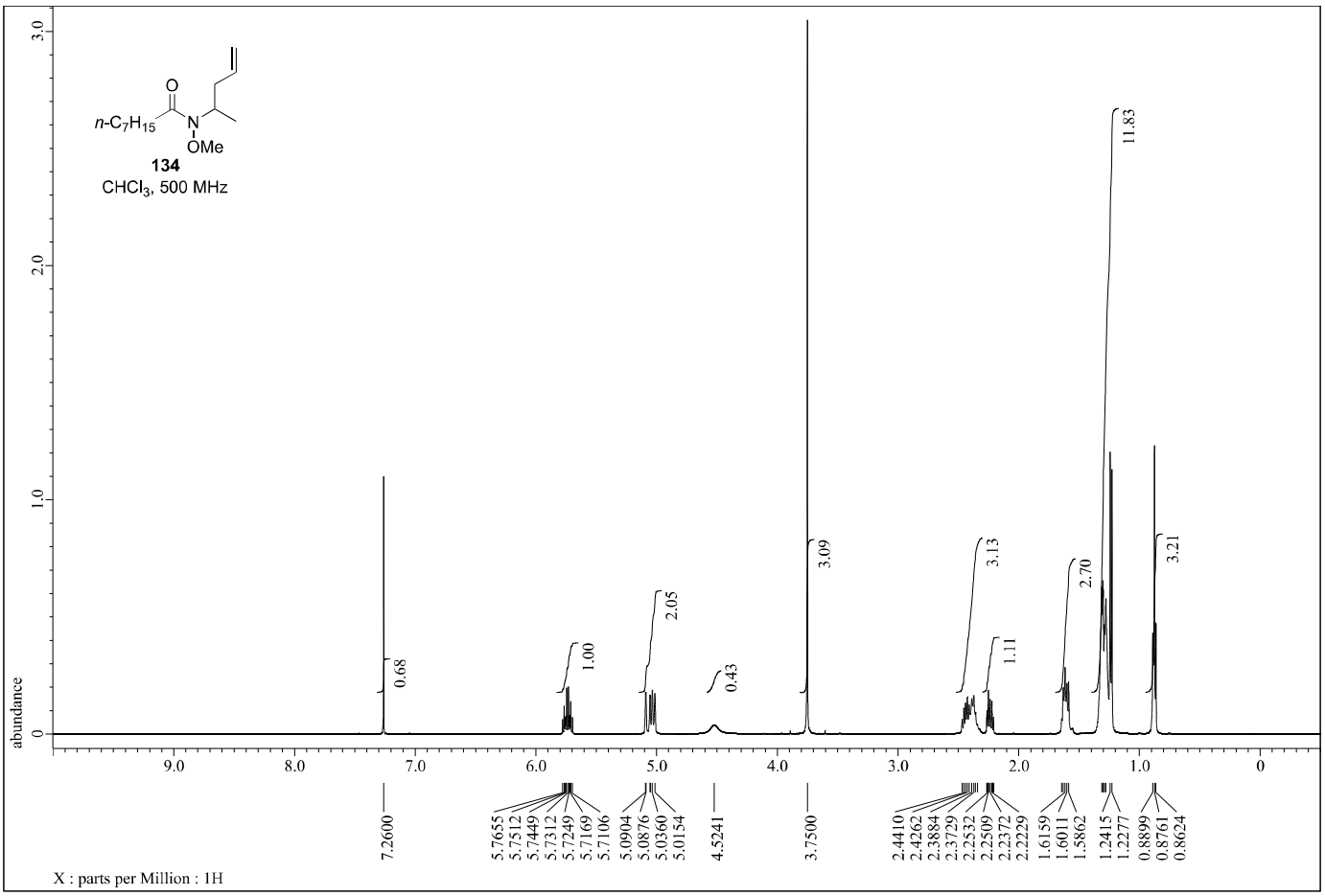

128d
CHCl3, 125 MHz
MeO
NCbz
abundance
X : parts per Million : 13C
151.5876
140.2274
135.8064
135.1483
133.3074
129.2631
128.9293
128.8911
128.8291
124.1029
123.0060
118.1653
116.7536
115.8951
115.4755
77.4128
77.1600
76.9072
68.7710
59.6715
56.8004
55.5843
44.7297
29.0439
20.0111
17.6552

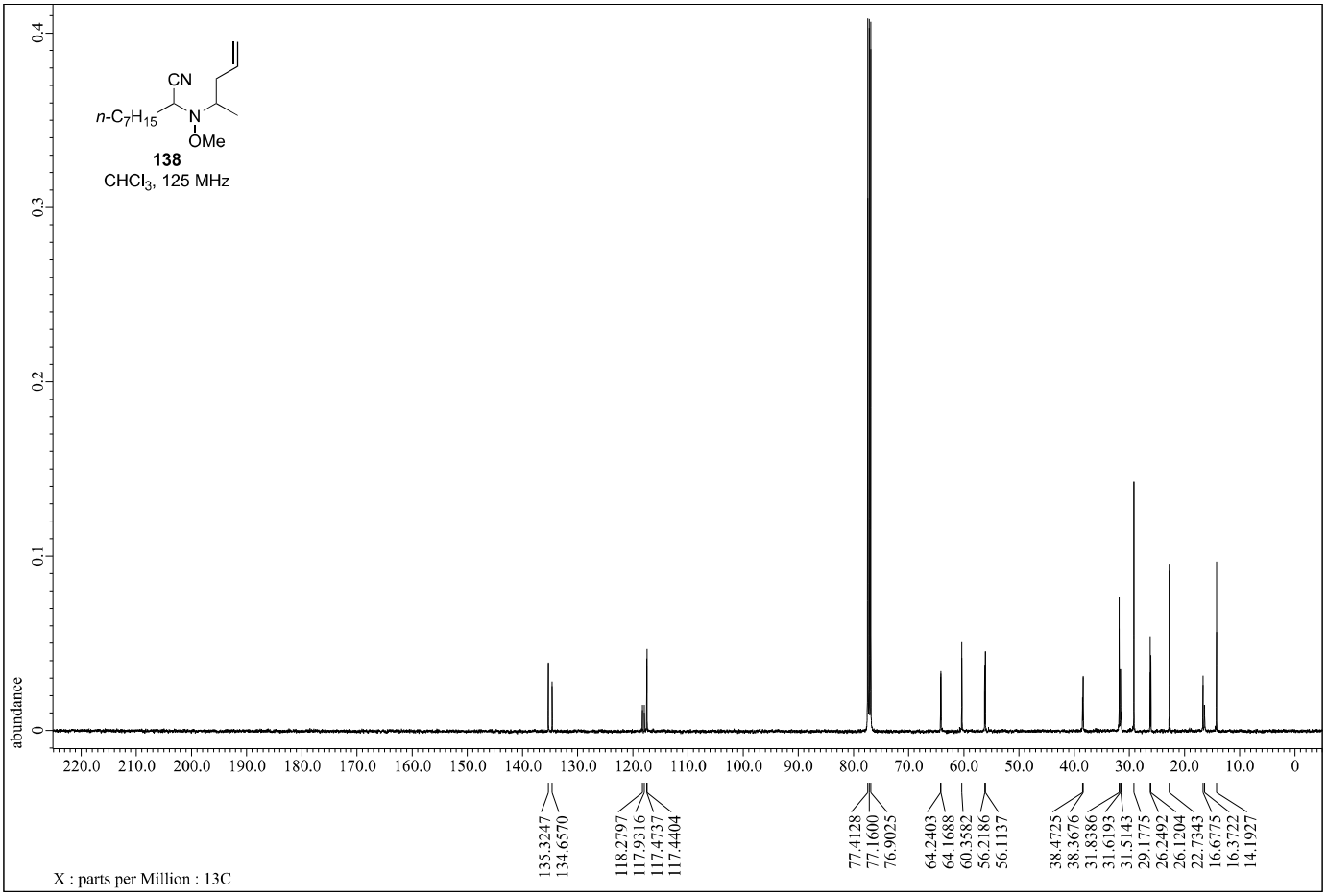

128d
CHCl3, 500 MHz
MeO
NCbz
abundance
X : parts per Million : 1H
0.96
3.97
1.97
1.99
0.87
1.00
2.05
3.06
2.84
0.94
0.98
0.91
0.91
1.84
0.82
0.87
8.1057
8.0903
7.5028
7.4896
7.4226
7.4083
7.4020
7.3986
7.2600
7.2245
5.8434
5.8331
5.8216
5.8085
5.7982
5.7873
5.4589
5.4449
5.1242
5.1030
5.0383
5.0349
5.0320
5.0005
3.7534
3.7454
3.7397
3.7317
3.5341
2.9604
2.9260
2.9117
2.6695
2.5155
2.4811
1.9687
1.9618
1.9549
1.3737
1.3674
1.1384
1.1229
1.1121
1.1029
1.0972
1.0920
1.0766

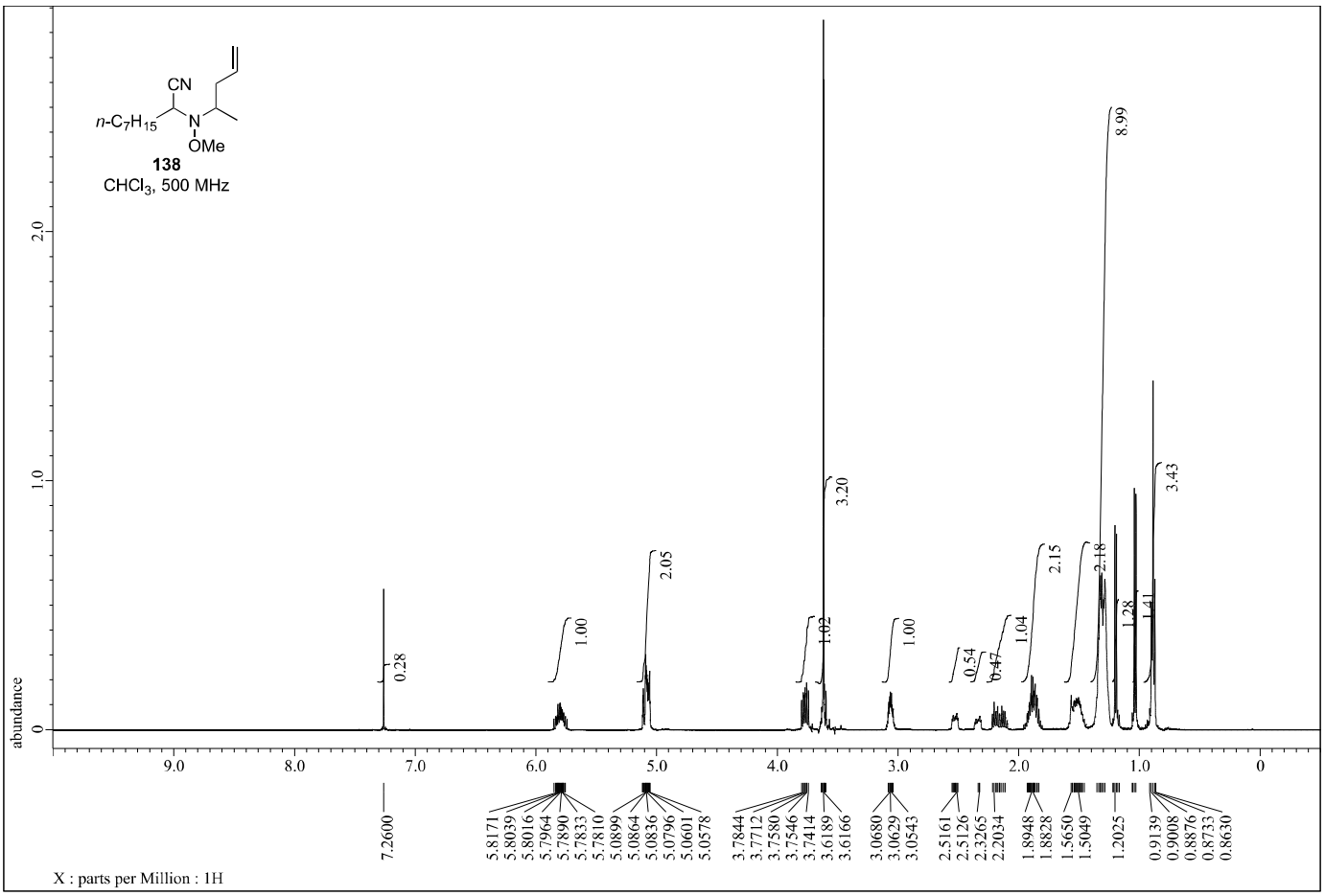

n-C7H15
O
NH
OMe
131
CHCl3, 125 MHz
abundance
171.3557
77.4175
77.1600
76.9072
64.0400
33.1740
31.7242
29.2251
29.0344
25.5577
22.6294
14.0783
X : parts per Million : 13C

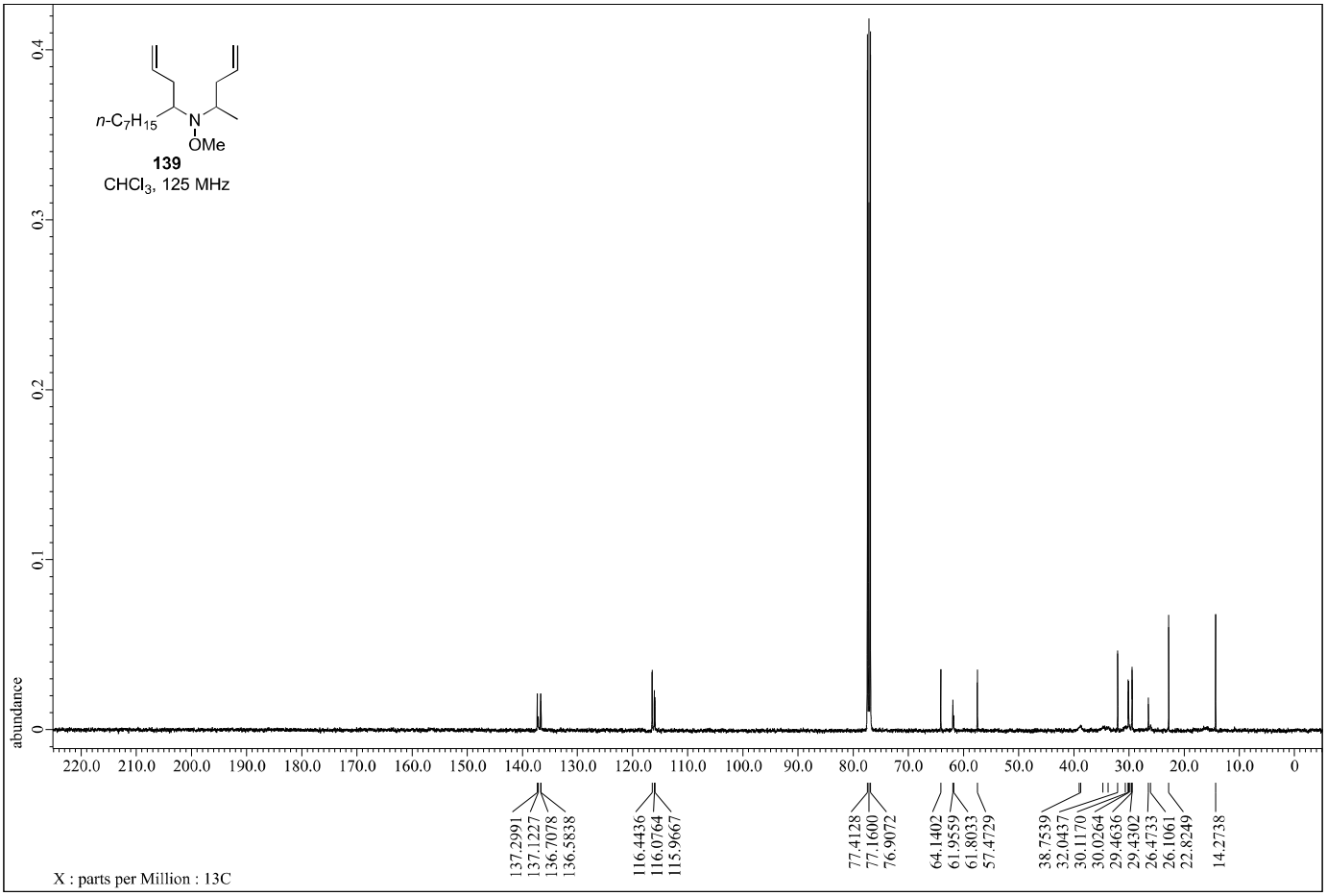

n-C7H15
O
NH
OMe
131
CHCl3, 500 MHz
abundance
0.28
3.00
0.21
1.34
2.09
8.21
3.07
7.2600
3.7552
2.4044
2.0729
1.6680
1.6526
1.6388
1.6240
1.6091
1.3016
1.2901
1.2770
1.2649
0.8819
0.8681
0.8544
X : parts per Million : 1H

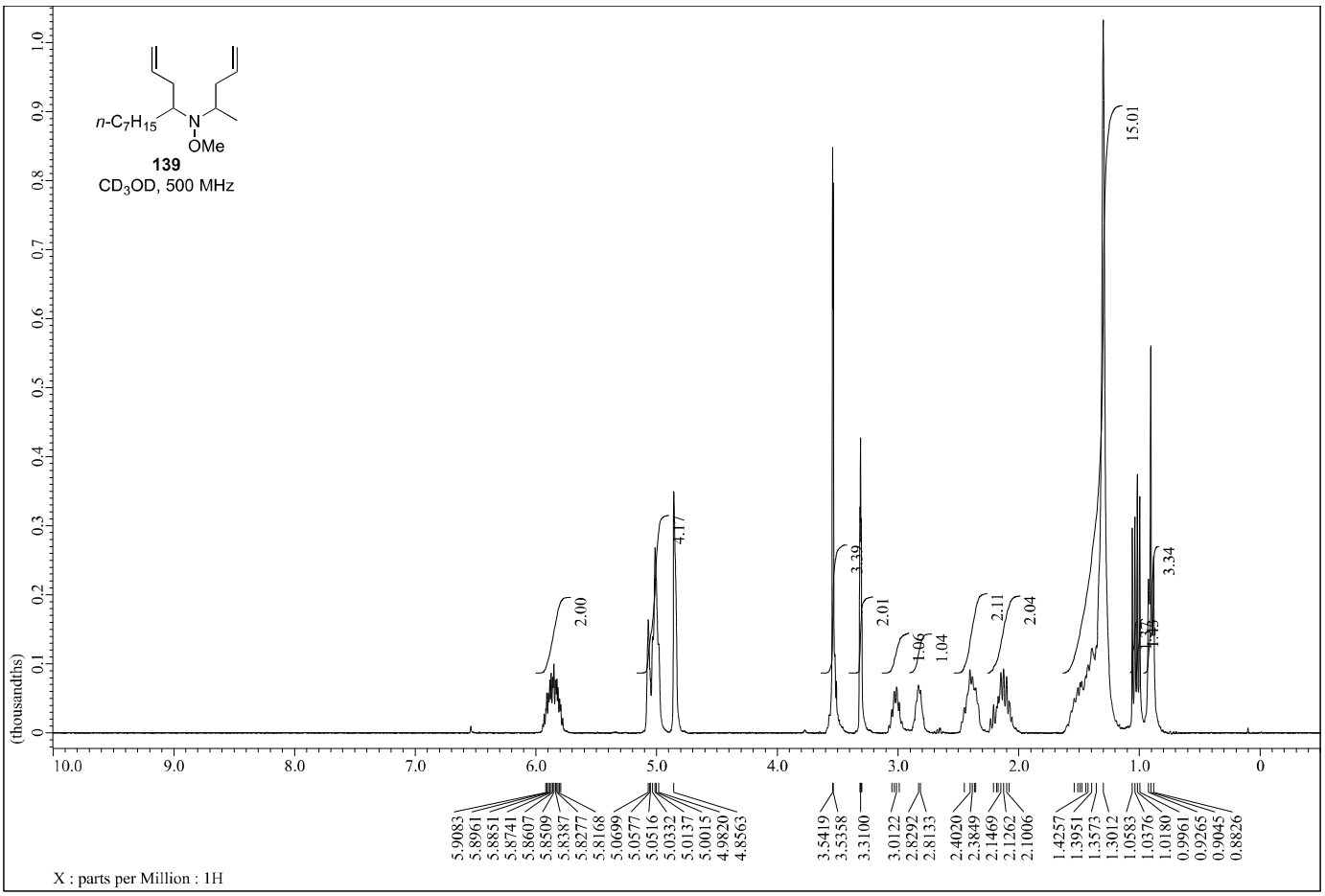

n-C7H15
O
N
OMe
134
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
176.6066
135.3342
117.2448
77.4128
77.1600
76.9072
64.8413
53.4096
38.4773
32.7782
31.8053
29.4731
29.1822
24.7135
22.7009
17.9747
14.1546

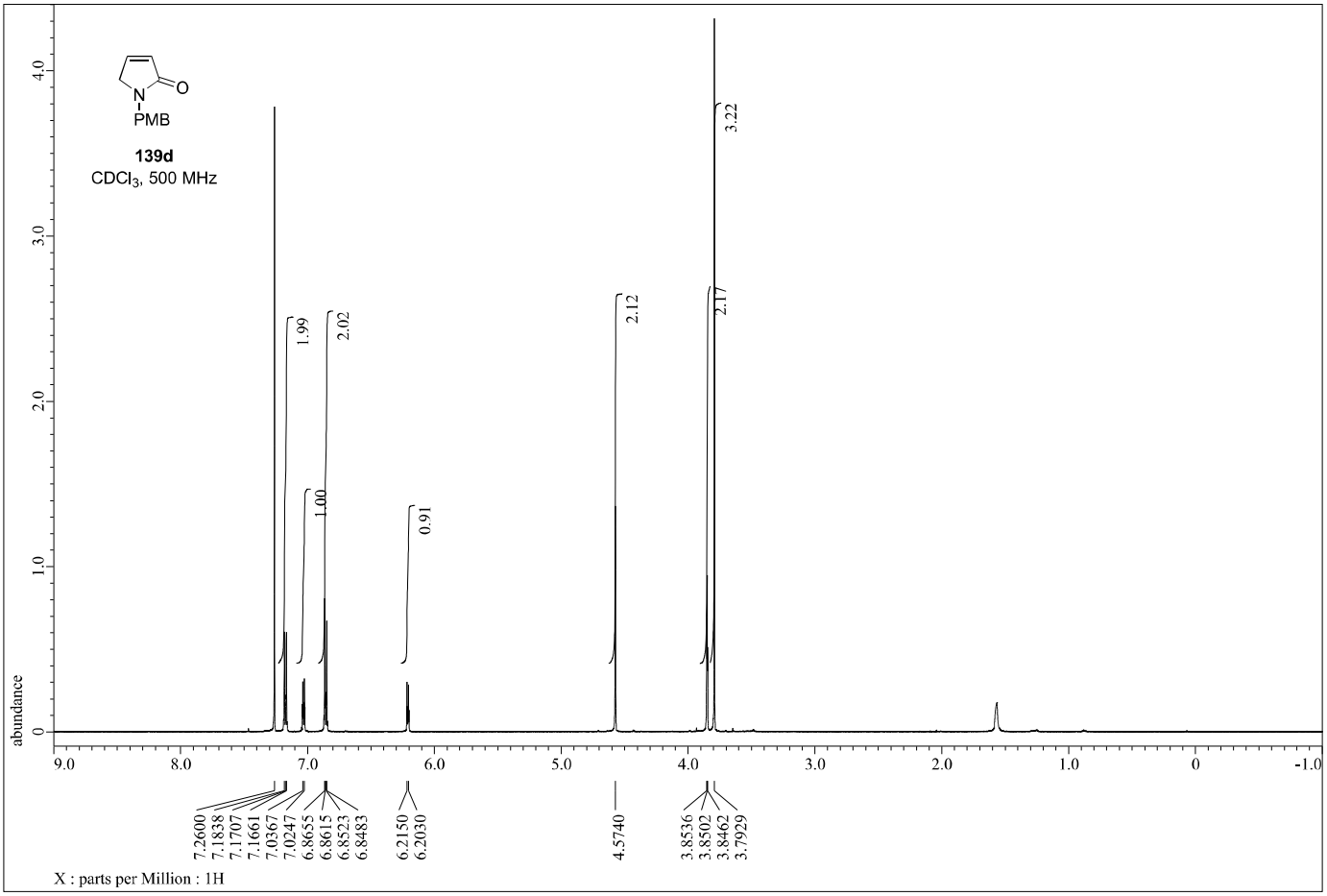

n-C7H15
O
N
OMe
134
CHCl3, 500 MHz
abundance
X : parts per Million : 1H
0.68
1.00
2.05
0.43
3.09
3.13
1.11
2.70
11.83
3.21
7.2600
5.7655
5.7512
5.7449
5.7312
5.7249
5.7169
5.7106
5.0904
5.0876
5.0360
5.0154
4.5241
3.7500
2.4410
2.4262
2.3884
2.3729
2.2532
2.2509
2.2372
2.2229
1.6159
1.6011
1.5862
1.2415
1.2277
0.8899
0.8761
0.8624

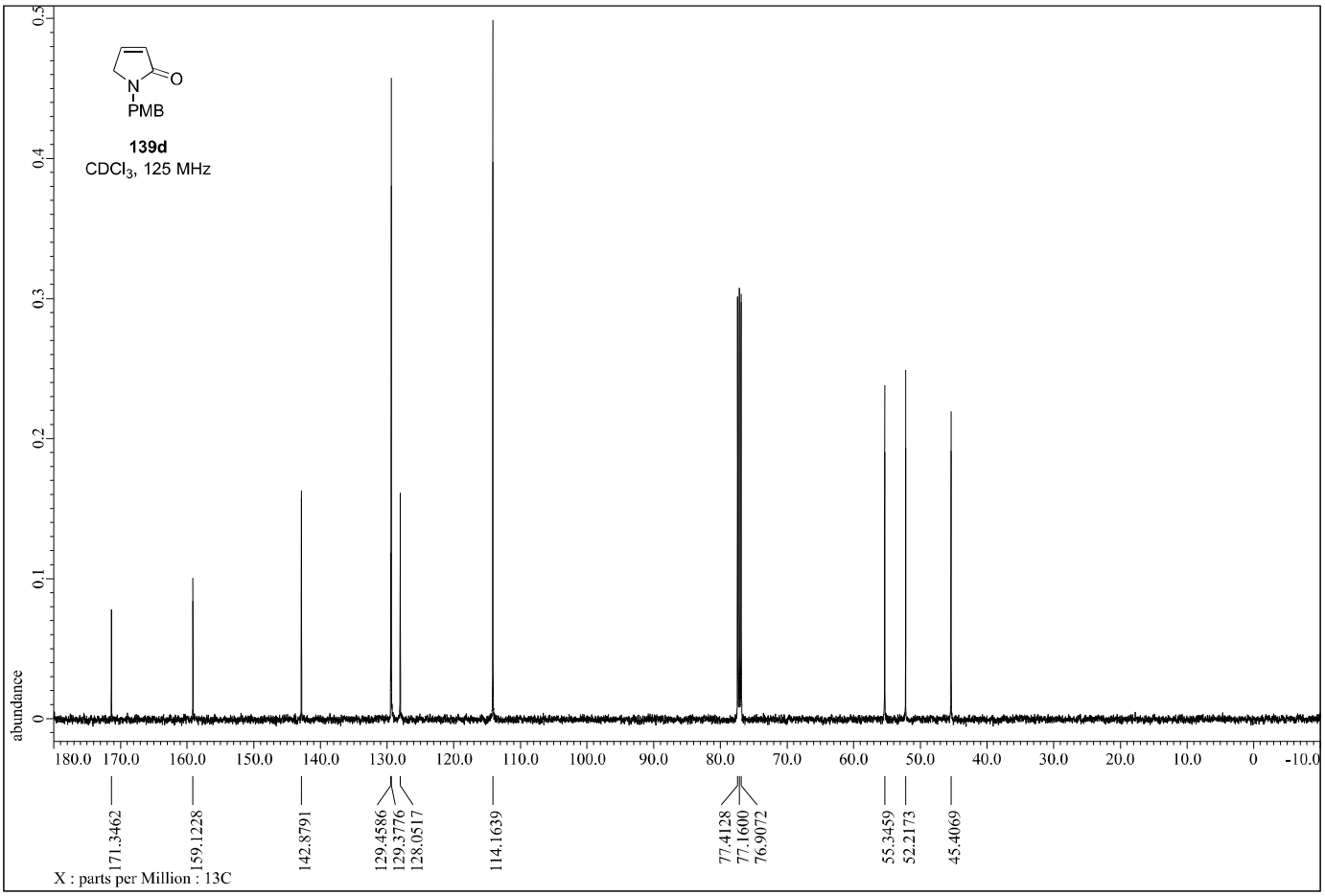

CN
n-C7H15
N
OMe
138
CHCl3, 125 MHz
abundance
X : parts per Million : 13C
135.3247
134.6570
118.2797
117.9316
117.4737
117.4404
77.4128
77.1600
76.9025
64.2403
64.1688
60.3582
56.2186
56.1137
38.4725
38.3676
31.8386
31.6193
31.5143
29.1775
26.2492
26.1204
22.7343
16.6775
16.3722
14.1927

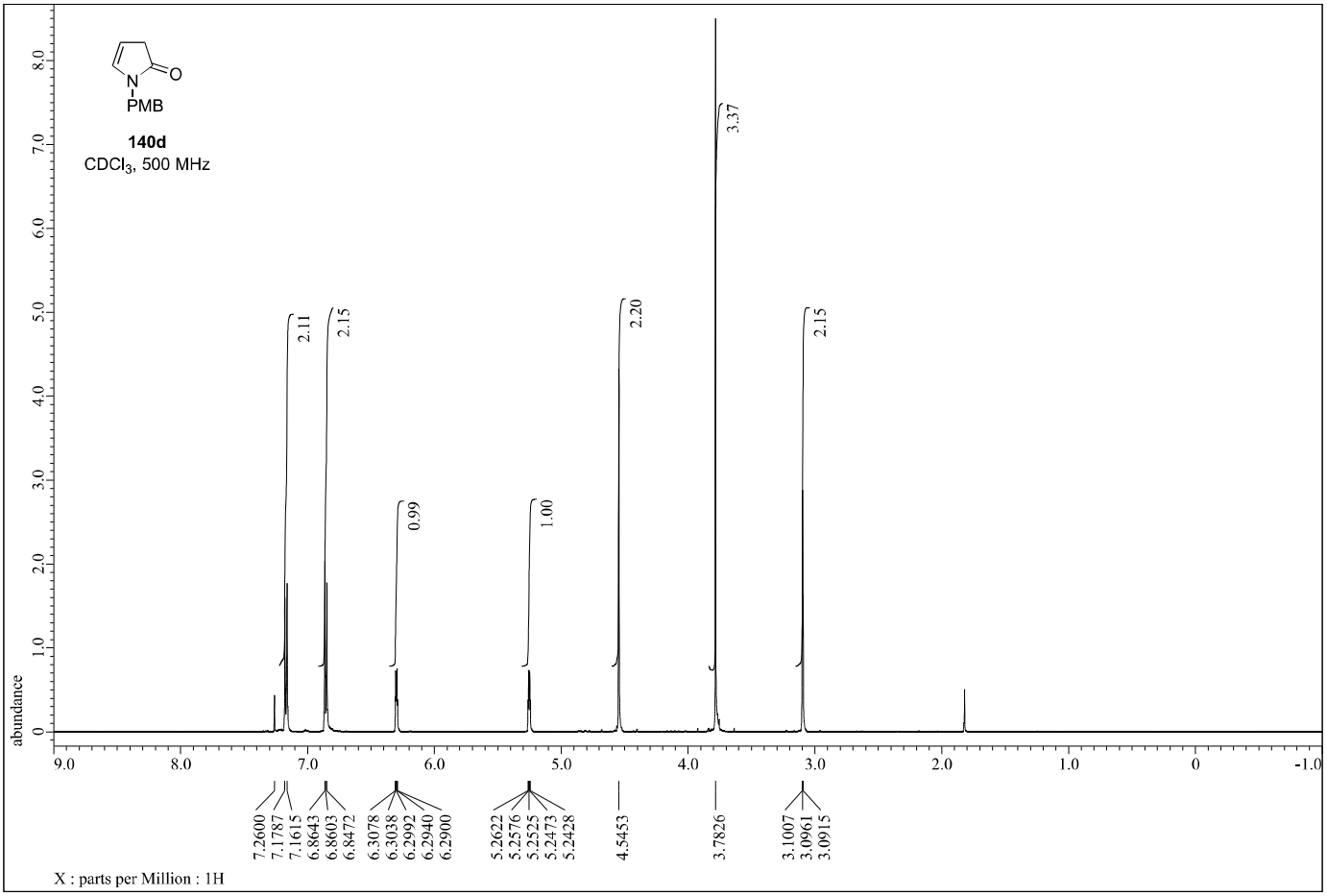

CN
n-C7H15
N
OMe
138
CHCl3, 500 MHz
abundance
X : parts per Million : 1H
7.2600
5.8171
5.8039
5.8016
5.7964
5.7890
5.7833
5.7810
5.0899
5.0864
5.0836
5.0796
5.0601
5.0578
3.7844
3.7712
3.7580
3.7546
3.7414
3.6189
3.6166
3.0680
3.0629
3.0543
2.5161
2.5126
2.3265
2.2034
1.8948
1.8828
1.5650
1.5049
1.2025
0.9139
0.9008
0.8876
0.8733
0.8630
0.28
1.00
2.05
1.02
3.20
1.00
0.54
0.47
1.04
2.15
2.18
8.99
1.28
1.41
3.43

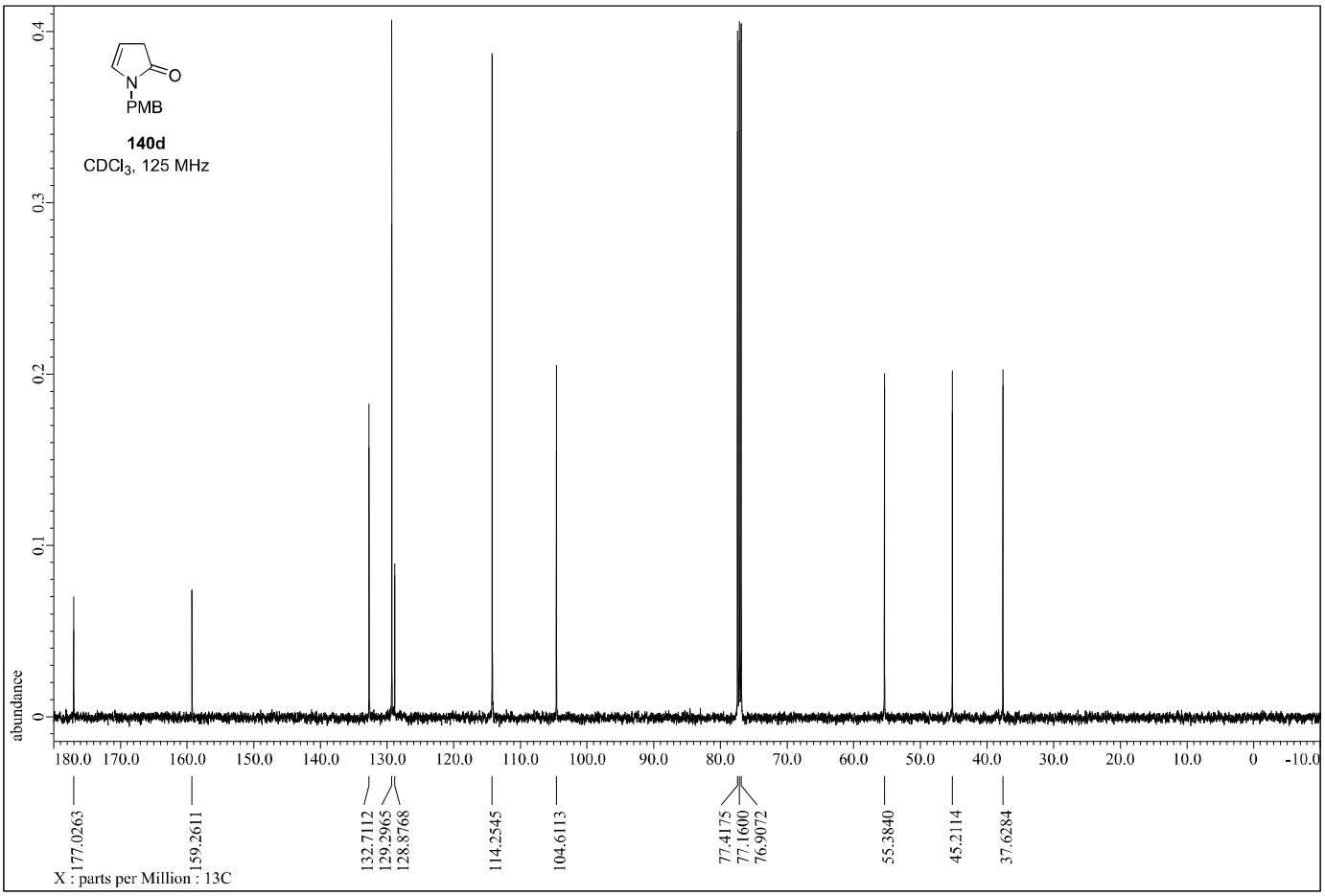

n-C7H15
N
OMe
139
CHCl3, 125 MHz
abundance
137.2991
137.1227
136.7078
136.5838
116.4436
116.0764
115.9667
77.4128
77.1600
76.9072
64.1402
61.9559
61.8033
57.4729
38.7539
32.0437
30.1170
30.0264
29.4636
29.4302
26.4733
26.1061
22.8249
14.2738
X : parts per Million : 13C

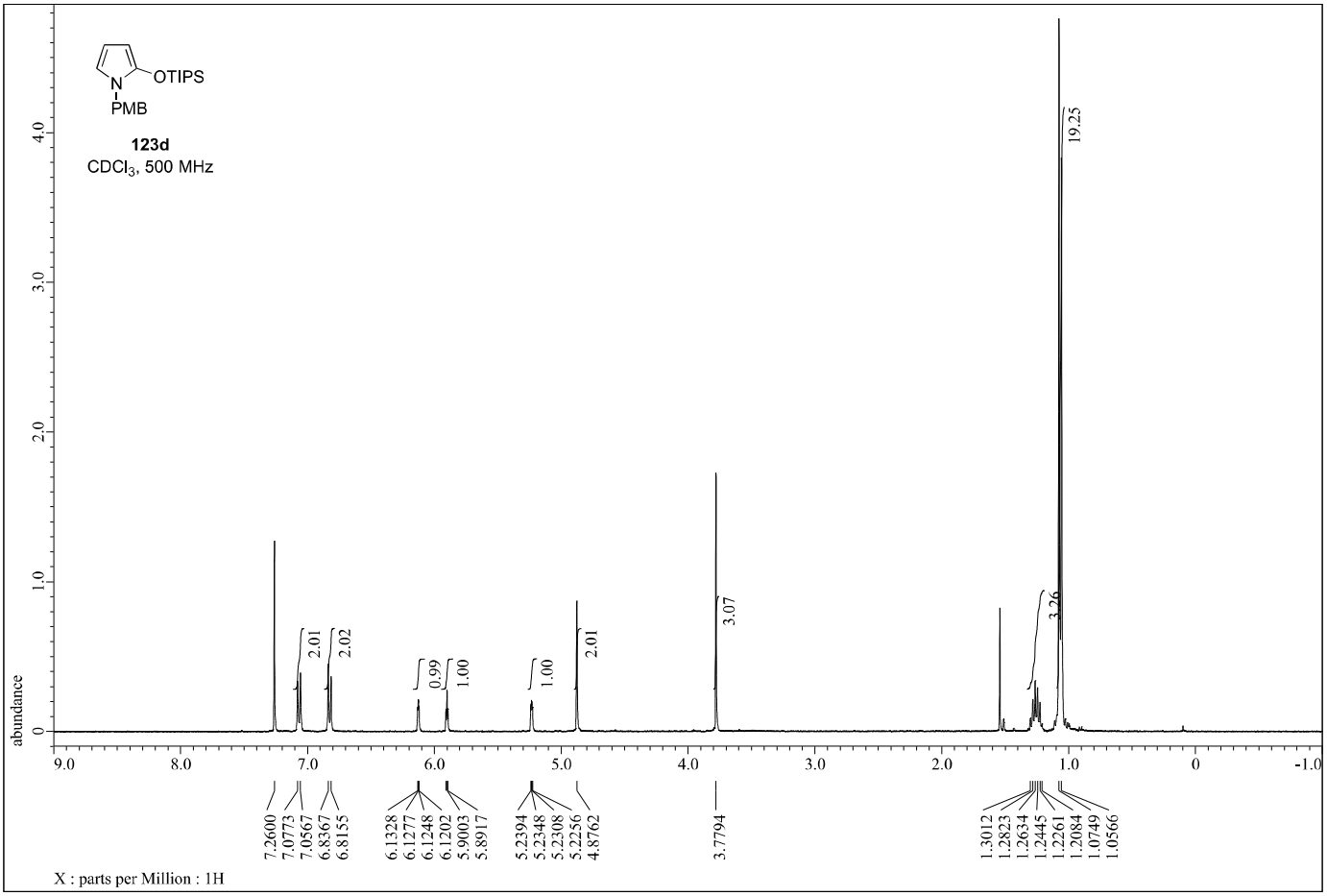

n-C7H15
N
OMe
139
CD3OD, 500 MHz
(thousandths)
2.00
4.17
3.39
2.01
1.06
1.04
2.11
2.04
15.01
3.34
5.9083
5.8961
5.8851
5.8741
5.8607
5.8509
5.8387
5.8277
5.8168
5.0699
5.0577
5.0516
5.0332
5.0137
5.0015
4.9820
4.8563
3.5419
3.5358
3.3100
3.0122
2.8292
2.8133
2.4020
2.3849
2.1469
2.1262
2.1006
1.4257
1.3951
1.3573
1.3012
1.0583
1.0376
1.0180
0.9961
0.9265
0.9045
0.8826
X : parts per Million : 1H

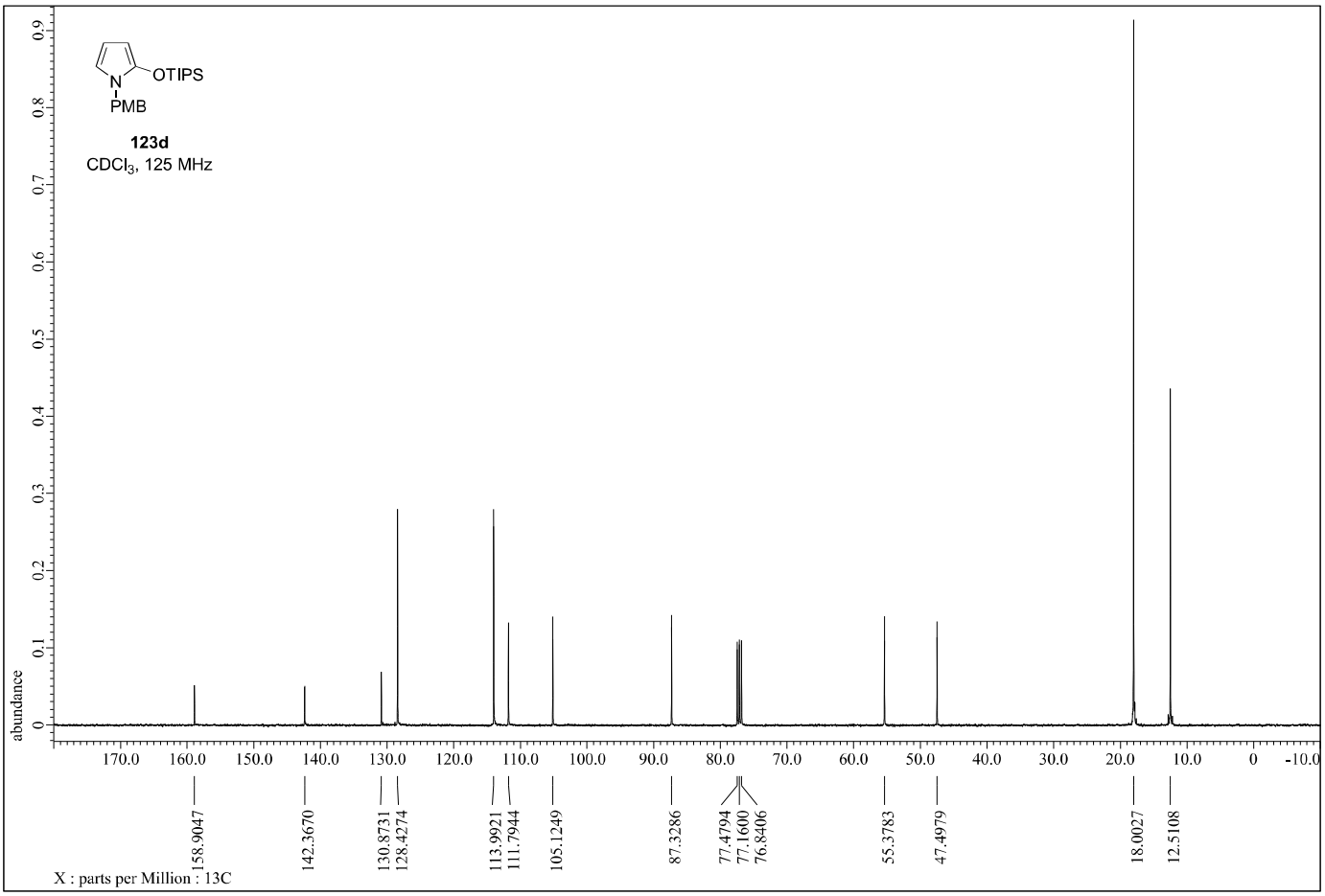

PMB
139d
CDCl3, 500 MHz
abundance
1.99
2.02
1.00
0.91
2.12
2.17
3.22
7.2600
7.1838
7.1707
7.1661
7.0367
7.0247
6.8655
6.8615
6.8523
6.8483
6.2150
6.2030
4.5740
3.8536
3.8502
3.8462
3.7929
X : parts per Million : 1H

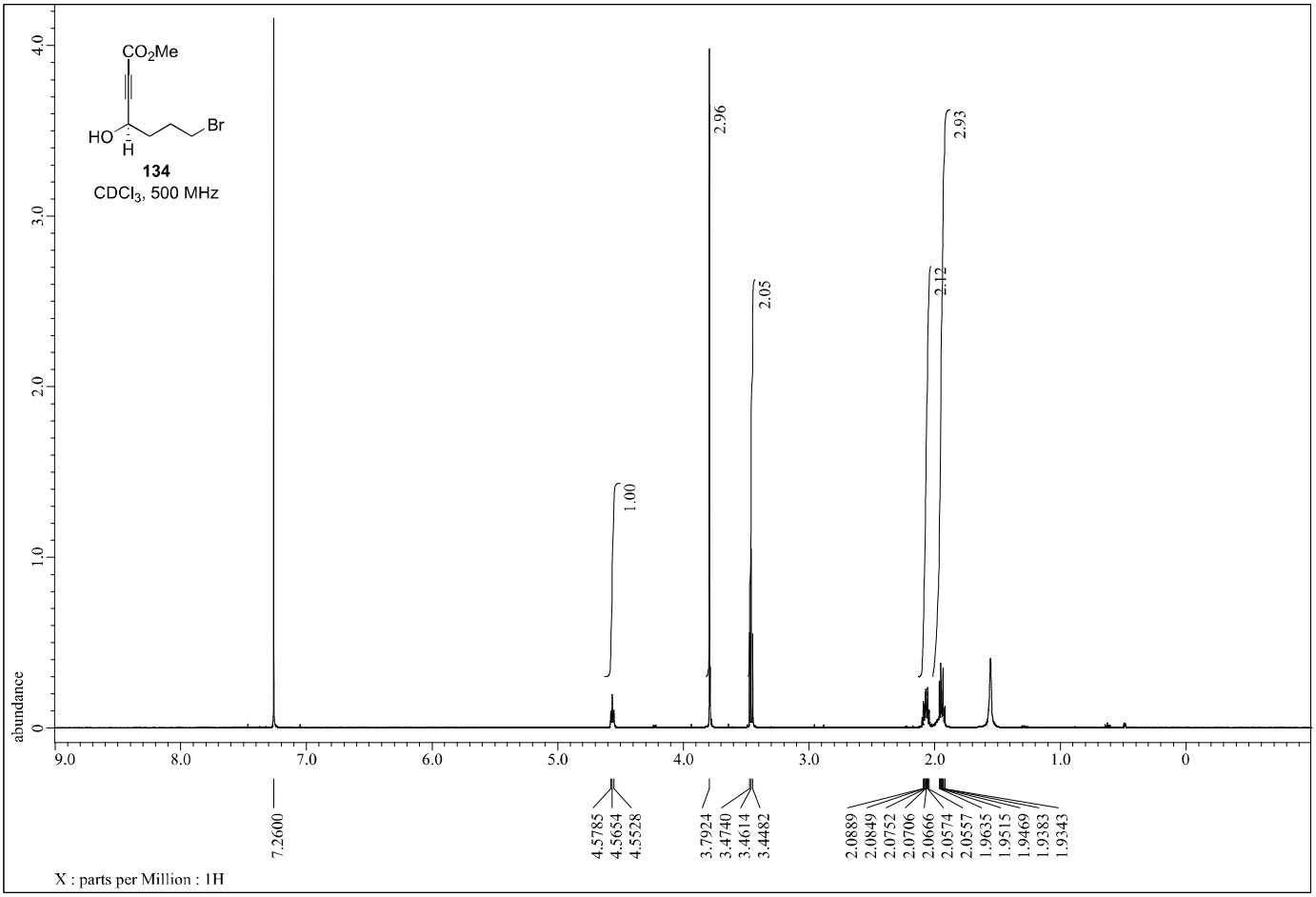

PMB
139d
CDCl3, 125 MHz
abundance
171.3462
159.1228
142.8791
129.4586
129.3776
128.0517
114.1639
77.4128
77.1600
76.9072
55.3459
52.2173
45.4069
X : parts per Million : 13C

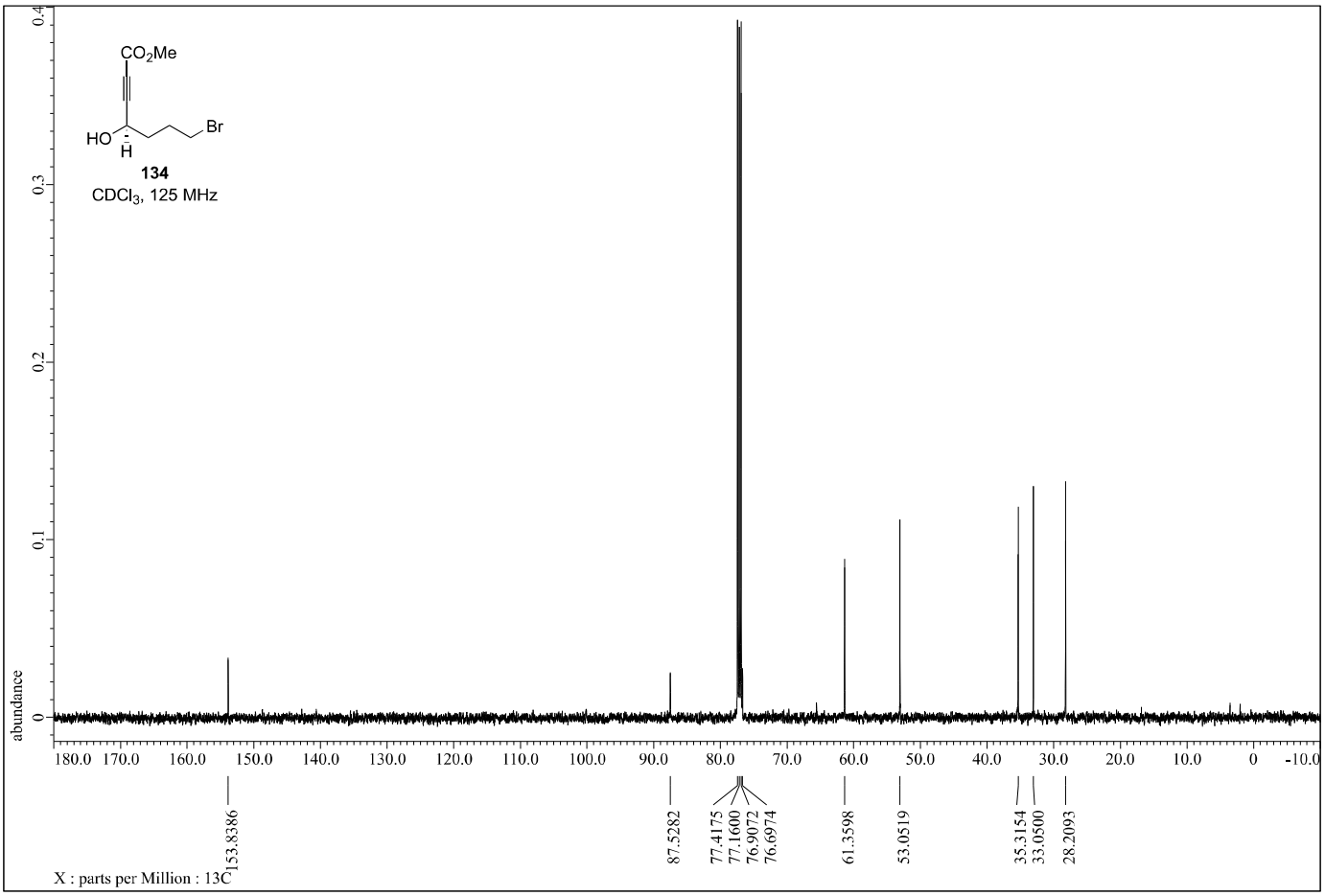

PMB
140d
CDCl3, 500 MHz
abundance
X : parts per Million : 1H
2.11
2.15
0.99
1.00
2.20
3.37
2.15
7.2600
7.1787
7.1615
6.8643
6.8603
6.8472
6.3078
6.3038
6.2992
6.2940
6.2900
5.2622
5.2576
5.2525
5.2473
5.2428
4.5453
3.7826
3.1007
3.0961
3.0915

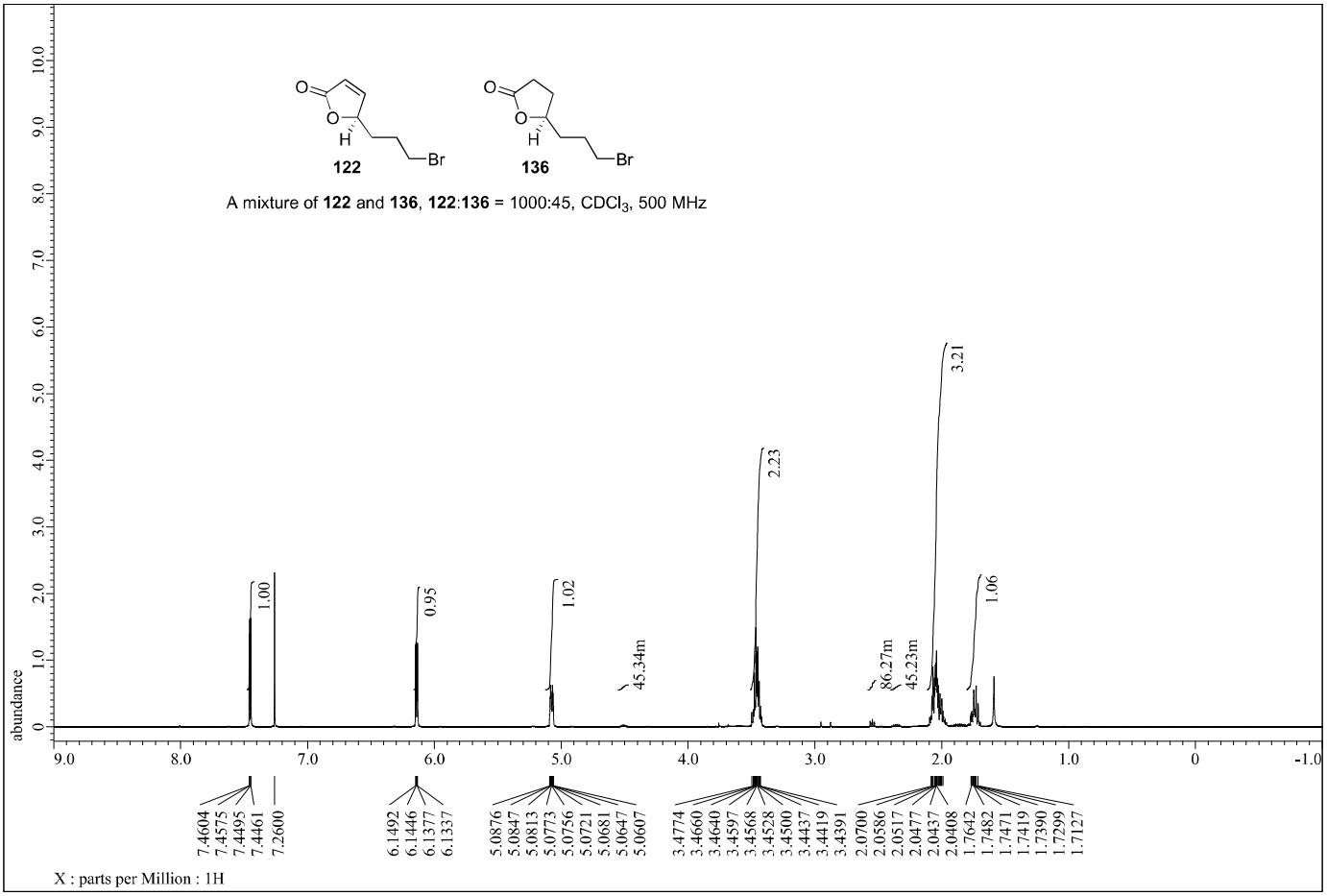

PMB
140d
CDCl3, 125 MHz
abundance
X : parts per Million : 13C
177.0263
159.2611
132.7112
129.2965
128.8768
114.2545
104.6113
77.4175
77.1600
76.9072
55.3840
45.2114
37.6284

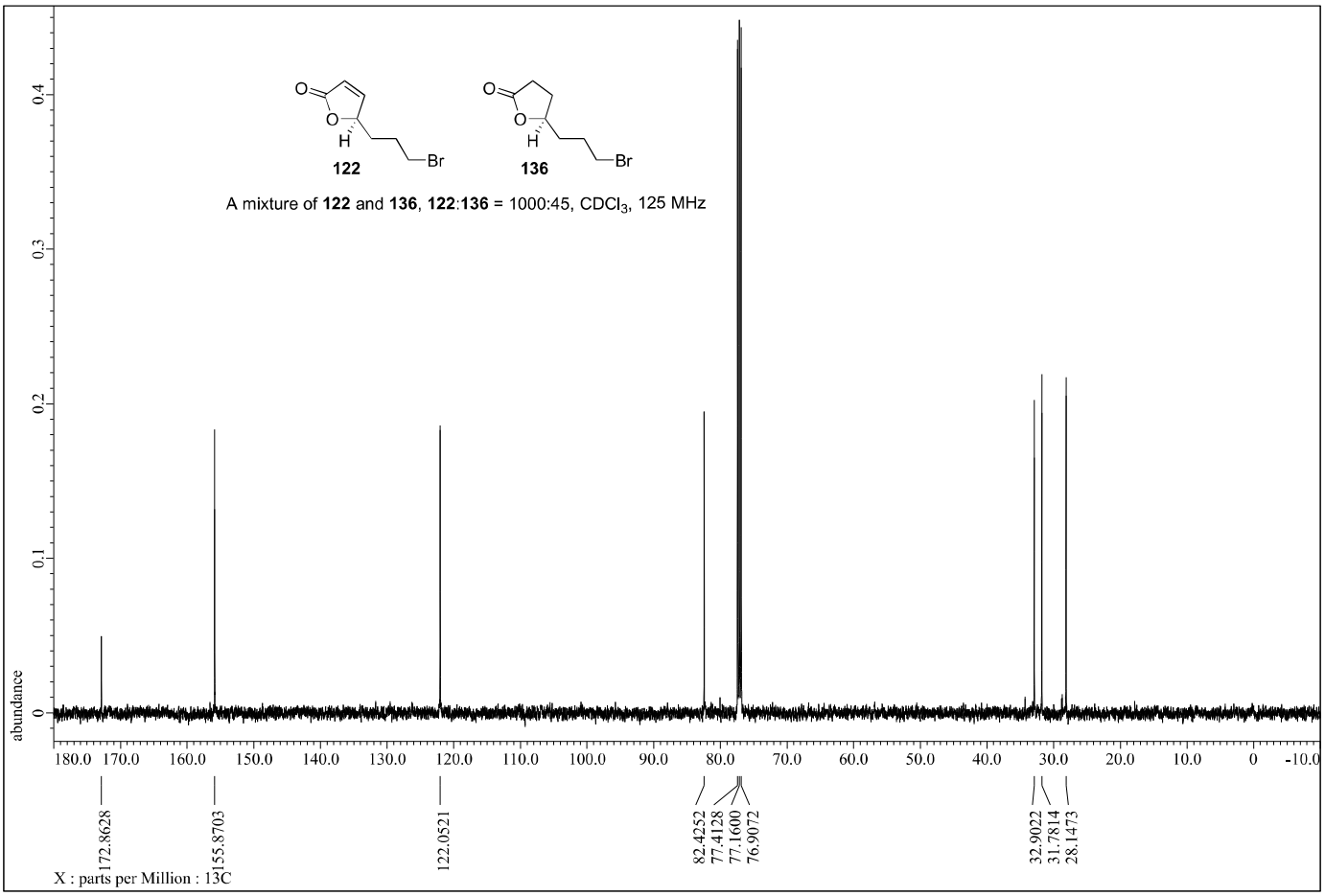

OTIPS
N
PMB
123d
CDCl3, 500 MHz
abundance
19.25
3.26
3.07
2.01
2.02
0.99
1.00
1.00
2.01
7.2600
7.0773
7.0567
6.8367
6.8155
6.1328
6.1277
6.1248
6.1202
5.9003
5.8917
5.2394
5.2348
5.2308
5.2256
4.8762
3.7794
1.3012
1.2823
1.2634
1.2445
1.2261
1.2084
1.0749
1.0566
X : parts per Million : 1H

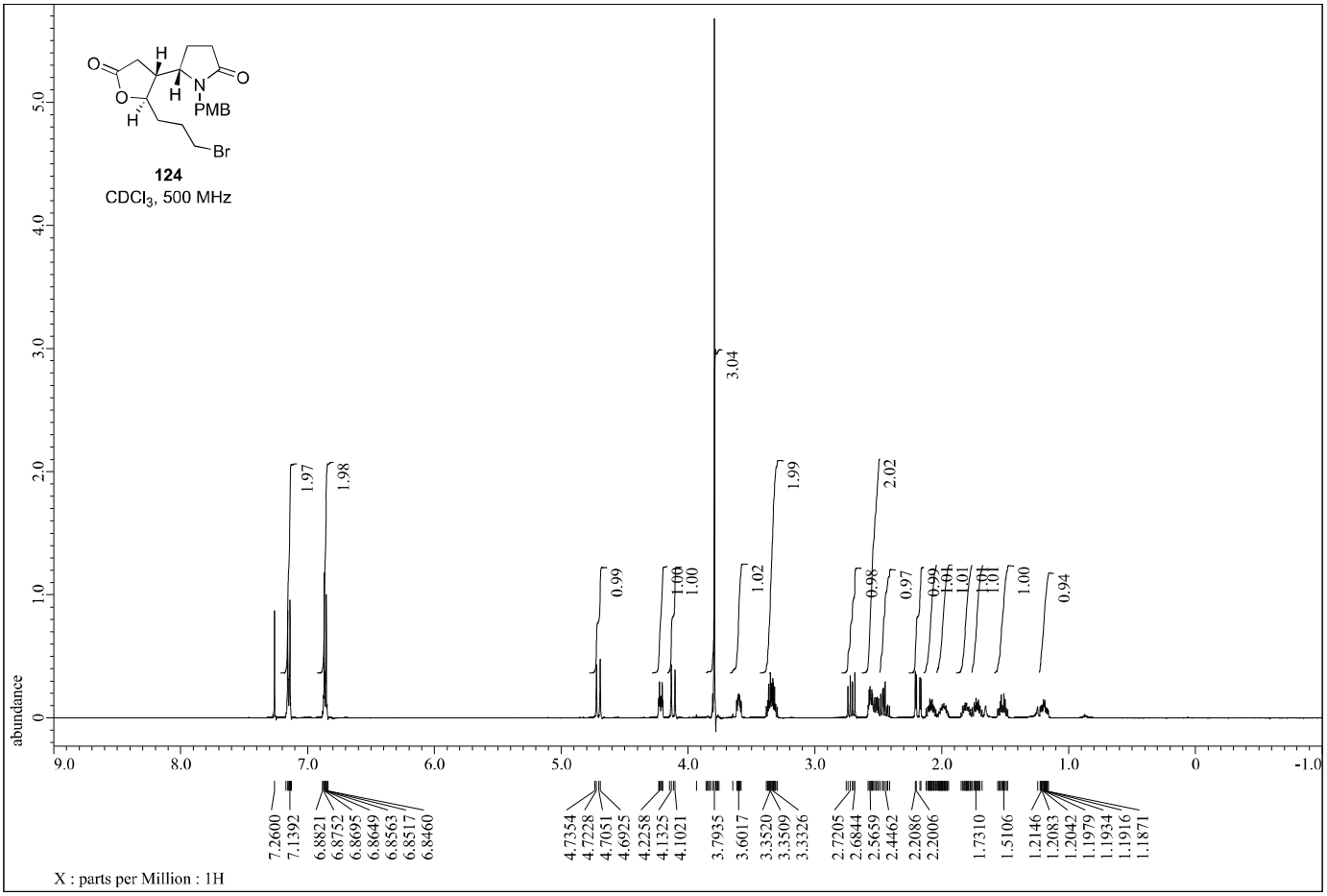

OTIPS
N
PMB
123d
CDCl3, 125 MHz
abundance
158.9047
142.3670
130.8731
128.4274
113.9921
111.7944
105.1249
87.3286
77.4794
77.1600
76.8406
55.3783
47.4979
18.0027
12.5108
X : parts per Million : 13C

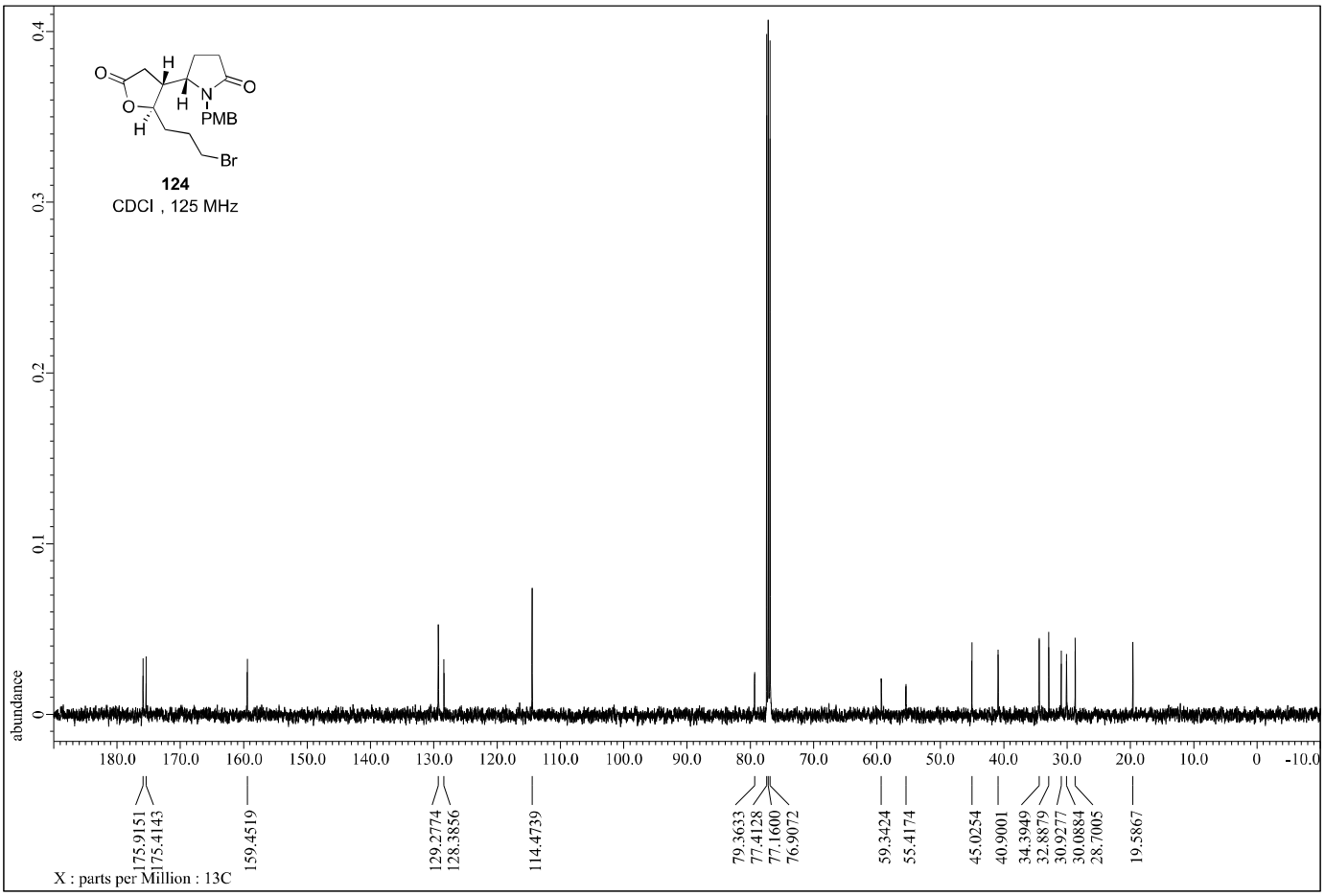

CO2Me
HO
H
Br
134
CDCl3, 500 MHz
abundance
2.96
2.93
2.12
2.05
1.00
7.2600
4.5785
4.5654
4.5528
3.7924
3.4740
3.4614
3.4482
2.0889
2.0849
2.0752
2.0706
2.0666
2.0574
2.0557
1.9635
1.9515
1.9469
1.9383
1.9343
X : parts per Million : 1H

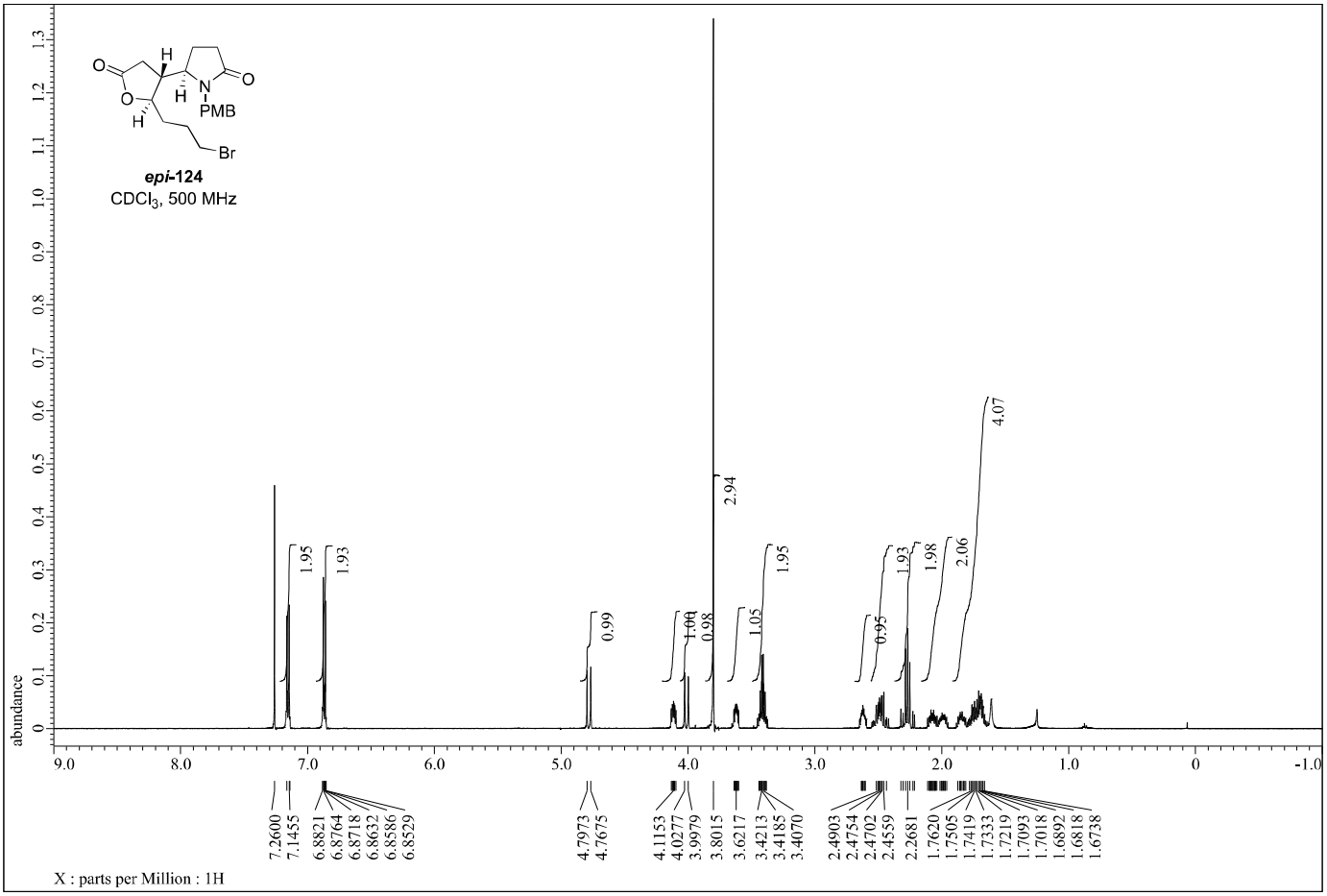

CO2Me
HO
H
Br
134
CDCl3, 125 MHz
abundance
153.8386
87.5282
77.4175
77.1600
76.9072
76.6974
61.3598
53.0519
35.3154
33.0500
28.2093
X : parts per Million : 13C

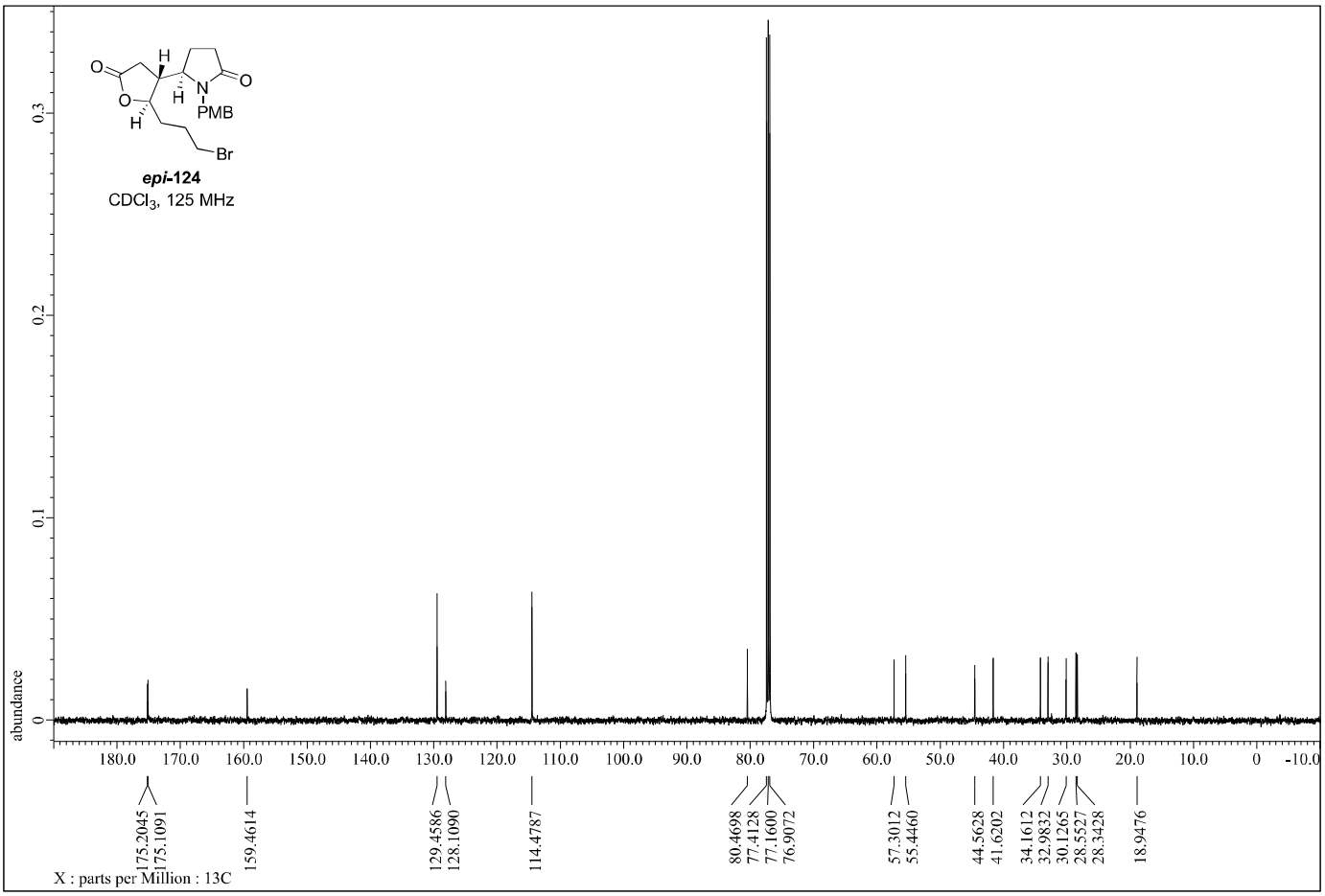

122
136
A mixture of 122 and 136, 122:136 = 1000:45, CDCl3, 500 MHz
abundance
1.00
0.95
1.02
45.34m
2.23
86.27m
45.23m
3.21
1.06
7.4604
7.4575
7.4495
7.4461
7.2600
6.1492
6.1446
6.1377
6.1337
5.0876
5.0847
5.0813
5.0773
5.0756
5.0721
5.0681
5.0647
5.0607
3.4774
3.4660
3.4640
3.4597
3.4568
3.4528
3.4500
3.4437
3.4419
3.4391
2.0700
2.0586
2.0517
2.0477
2.0437
2.0408
1.7642
1.7482
1.7471
1.7419
1.7390
1.7299
1.7127
X : parts per Million : 1H

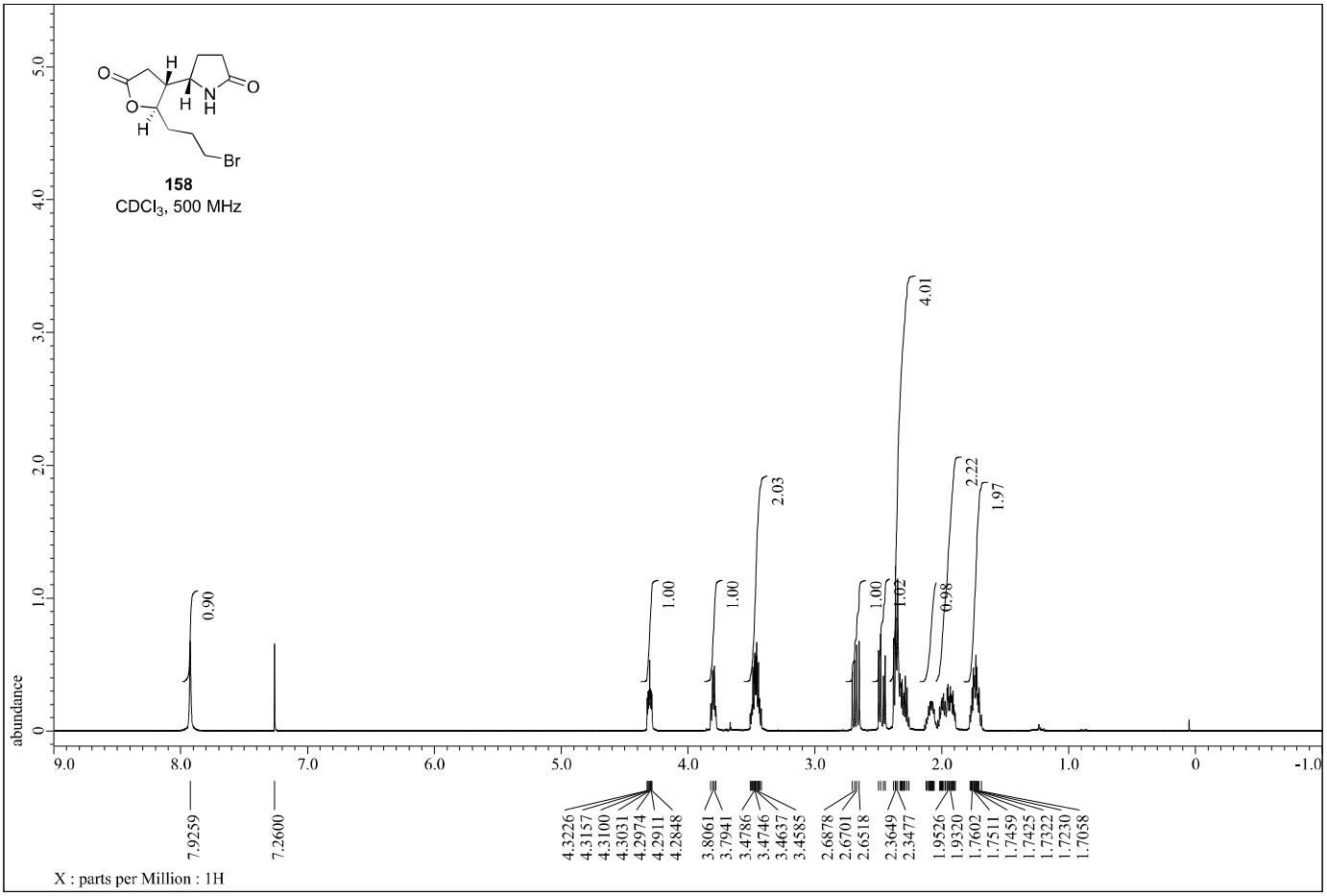

122
136
A mixture of 122 and 136, 122:136 = 1000:45, CDCl3, 125 MHz
abundance
172.8628
155.8703
122.0521
82.4252
77.4128
77.1600
76.9072
32.9022
31.7814
28.1473
X : parts per Million : 13C

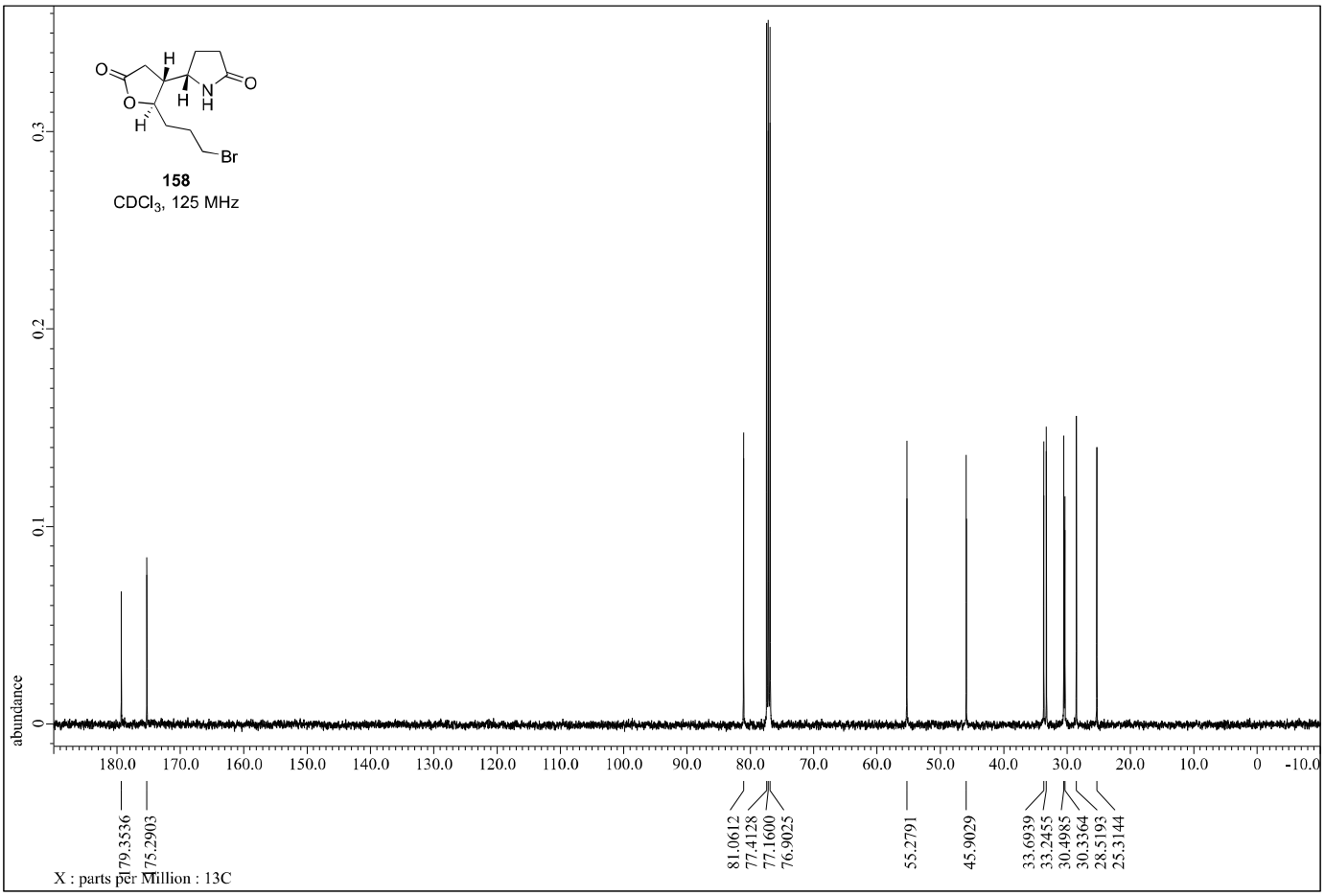

124
CDCl3, 500 MHz
abundance
X : parts per Million : 1H

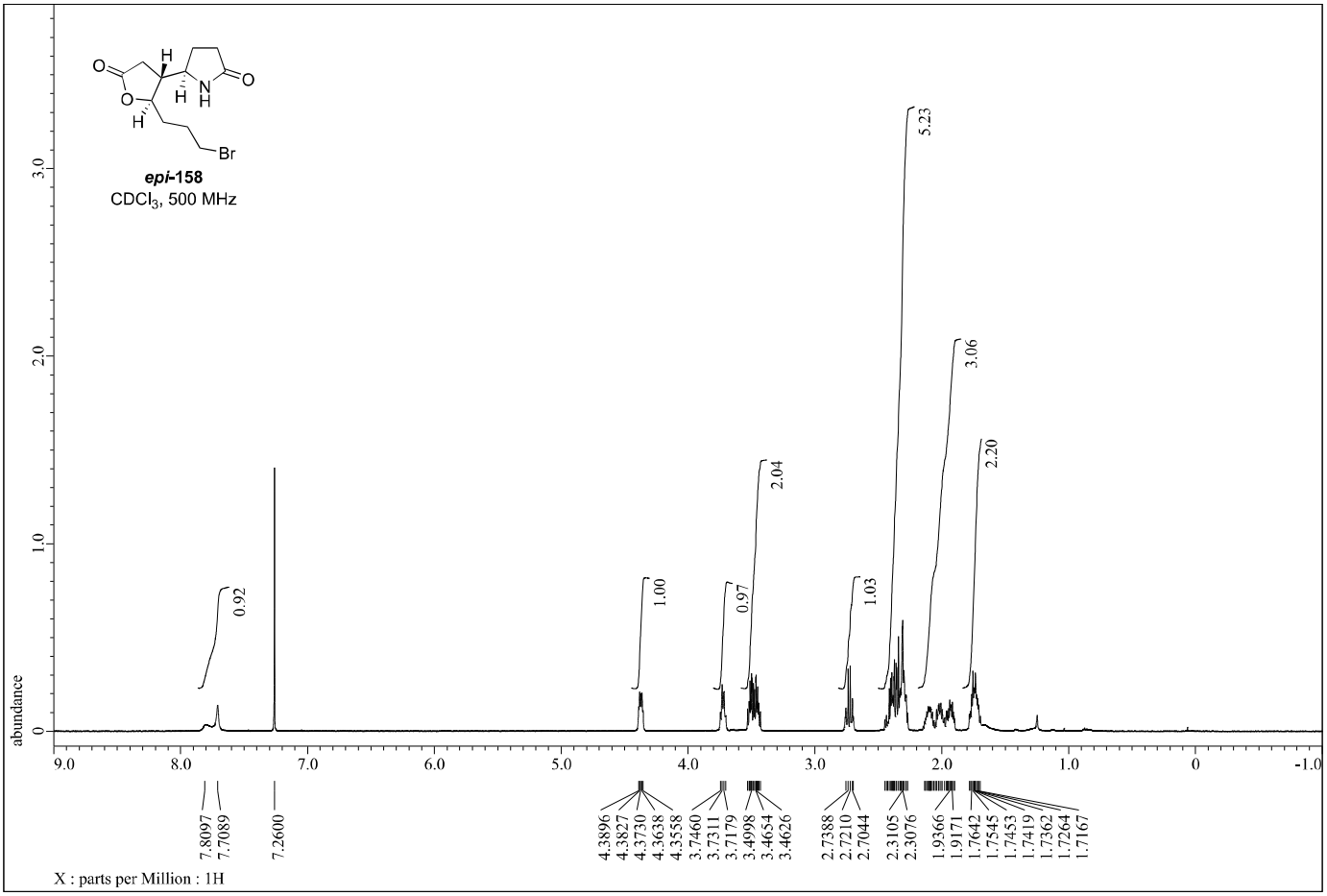

124
CDCl , 125 MHz
abundance
X : parts per Million : 13C

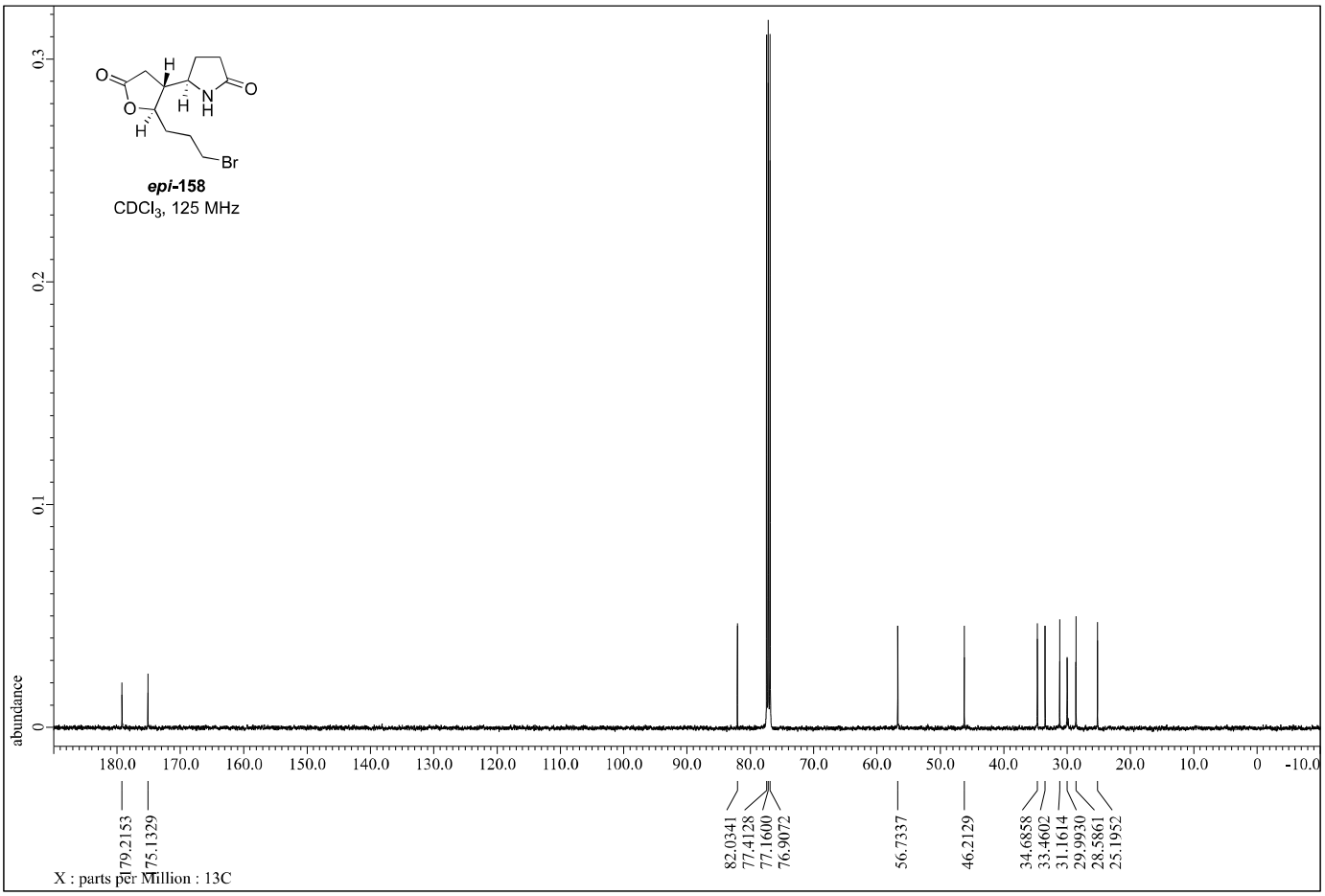

epi-124
CDCl3, 500 MHz
abundance
X : parts per Million : 1H

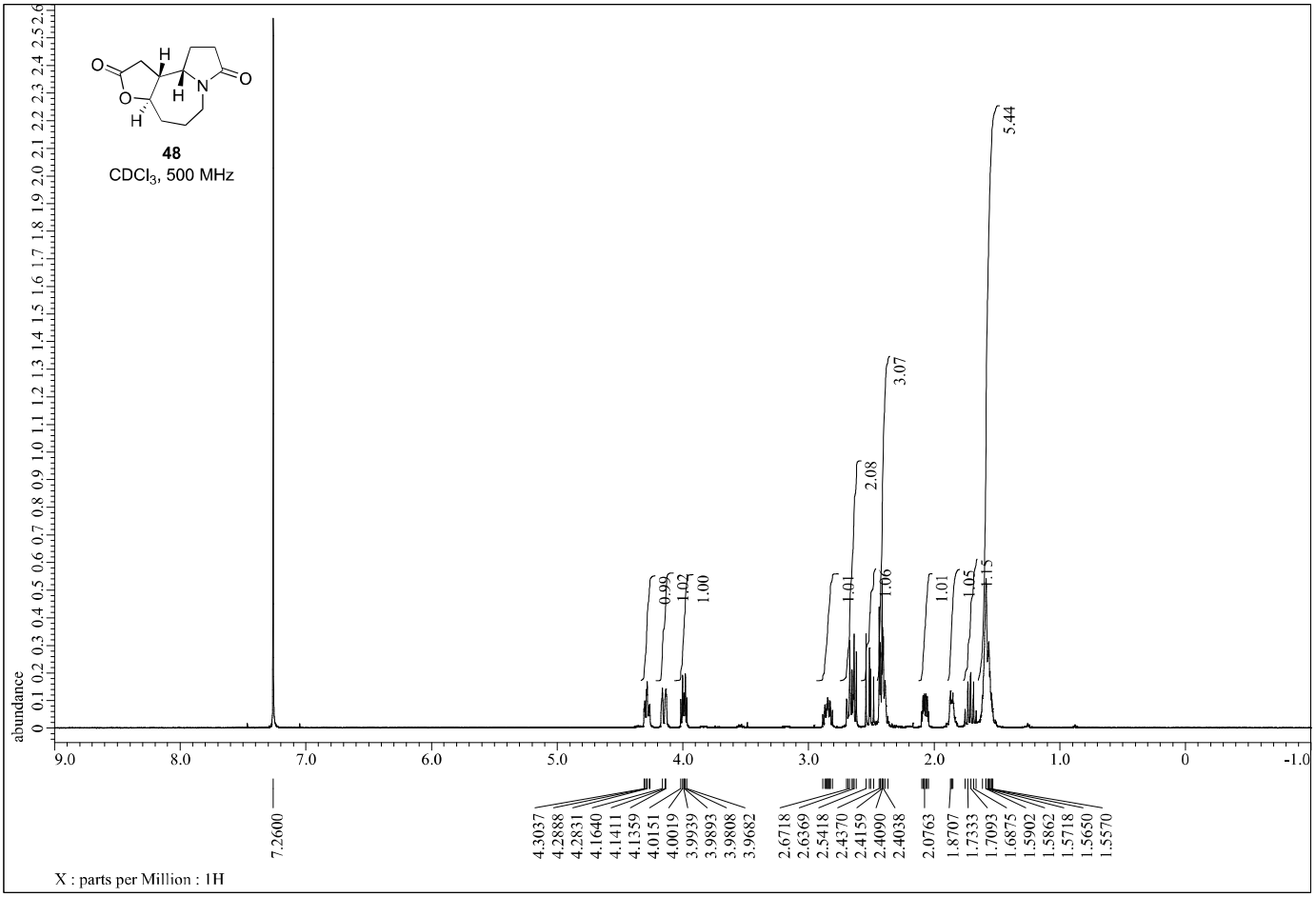

epi-124
CDCl3, 125 MHz
abundance
X : parts per Million : 13C

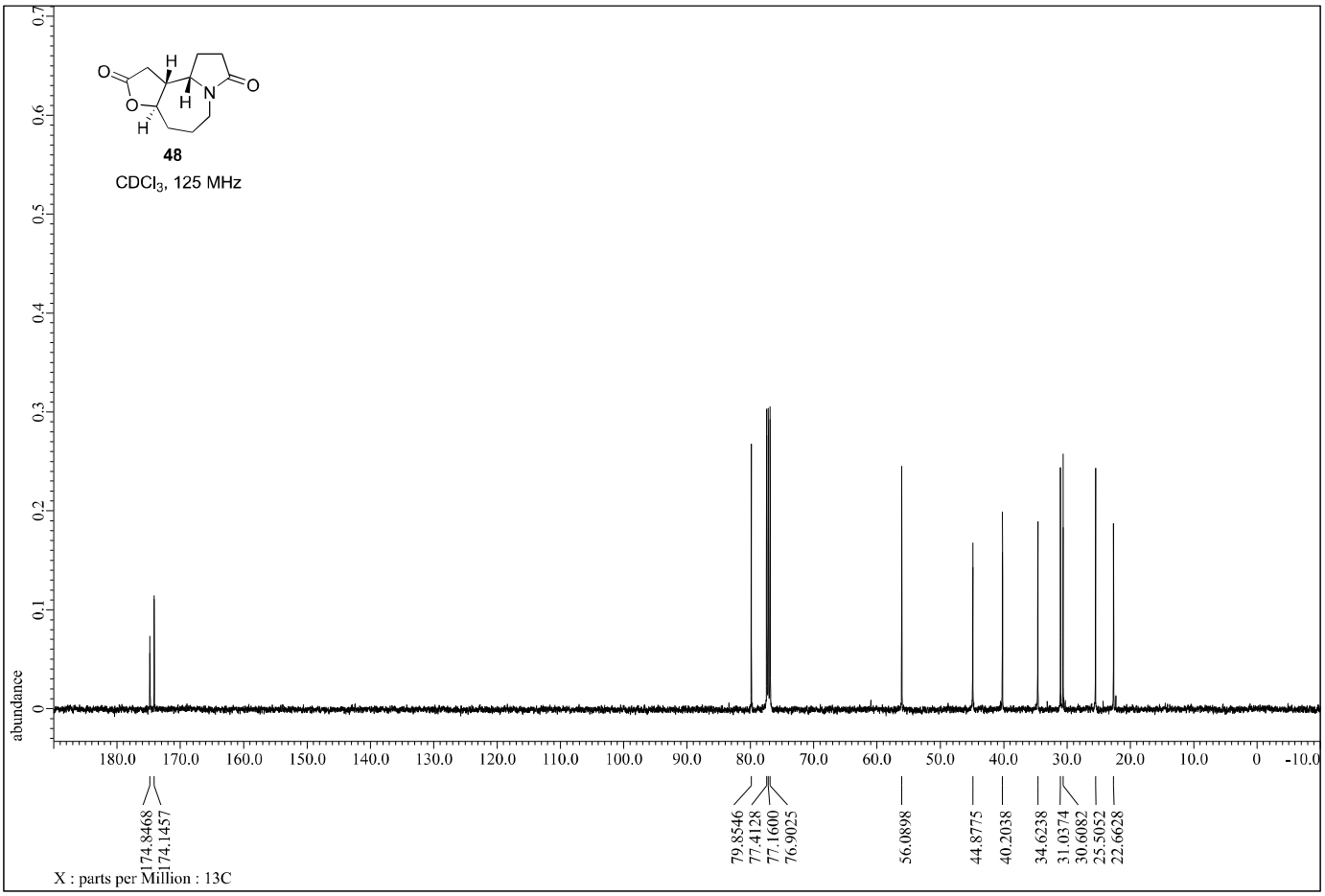

158
CDCl3, 500 MHz
abundance
X : parts per Million : 1H
7.9259
7.2600
4.3226
4.3157
4.3100
4.3031
4.2974
4.2911
4.2848
3.8061
3.7941
3.4786
3.4746
3.4637
3.4585
2.6878
2.6701
2.6518
2.3649
2.3477
1.9526
1.9320
1.7602
1.7511
1.7459
1.7425
1.7322
1.7230
1.7058
0.90
1.00
1.00
2.03
1.00
1.02
4.01
0.98
2.22
1.97

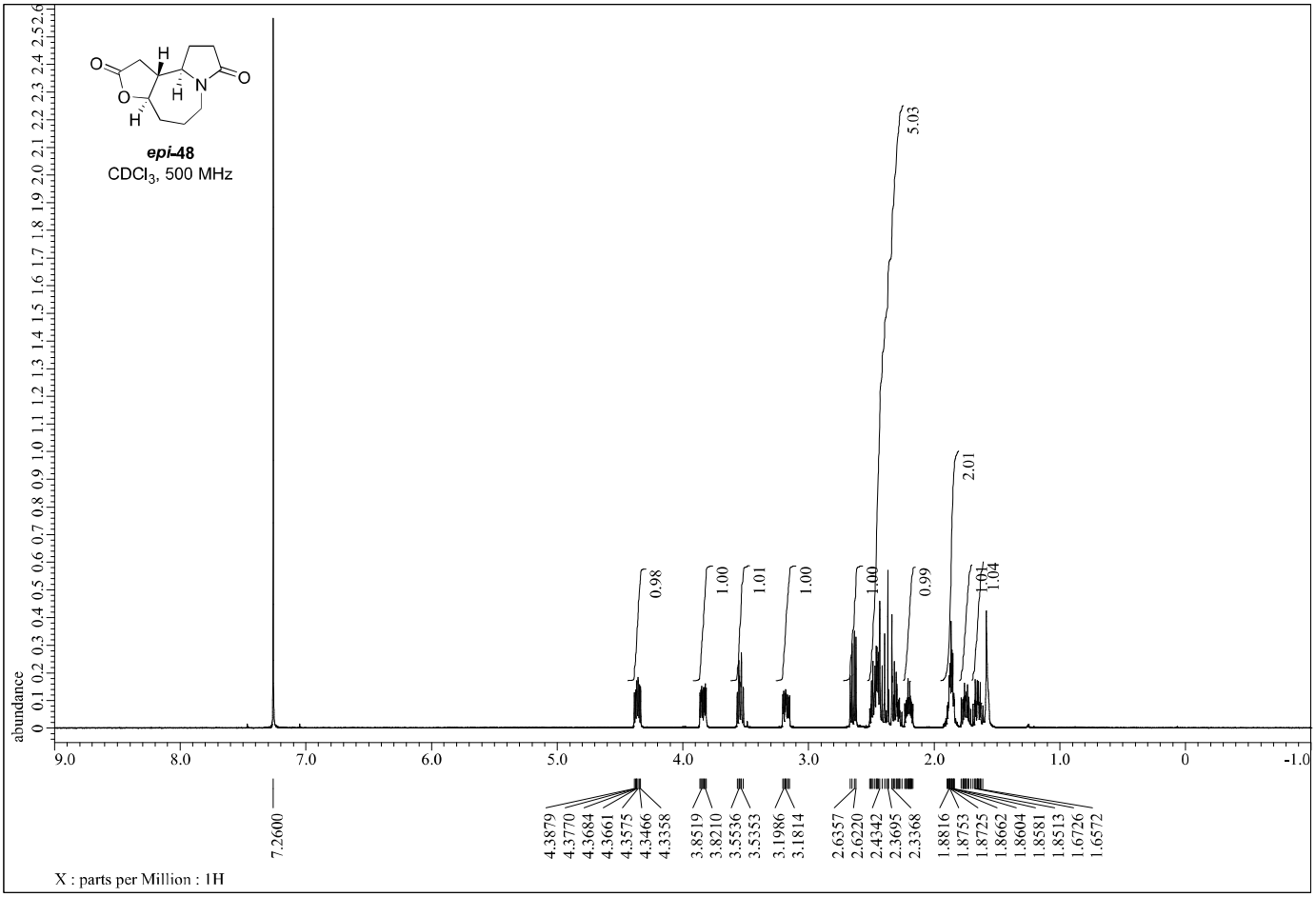

158
CDCl3, 125 MHz
abundance
X : parts per Million : 13C
179.3536
175.2903
81.0612
77.4128
77.1600
76.9025
55.2791
45.9029
33.6939
33.2455
30.4985
30.3364
28.5193
25.3144

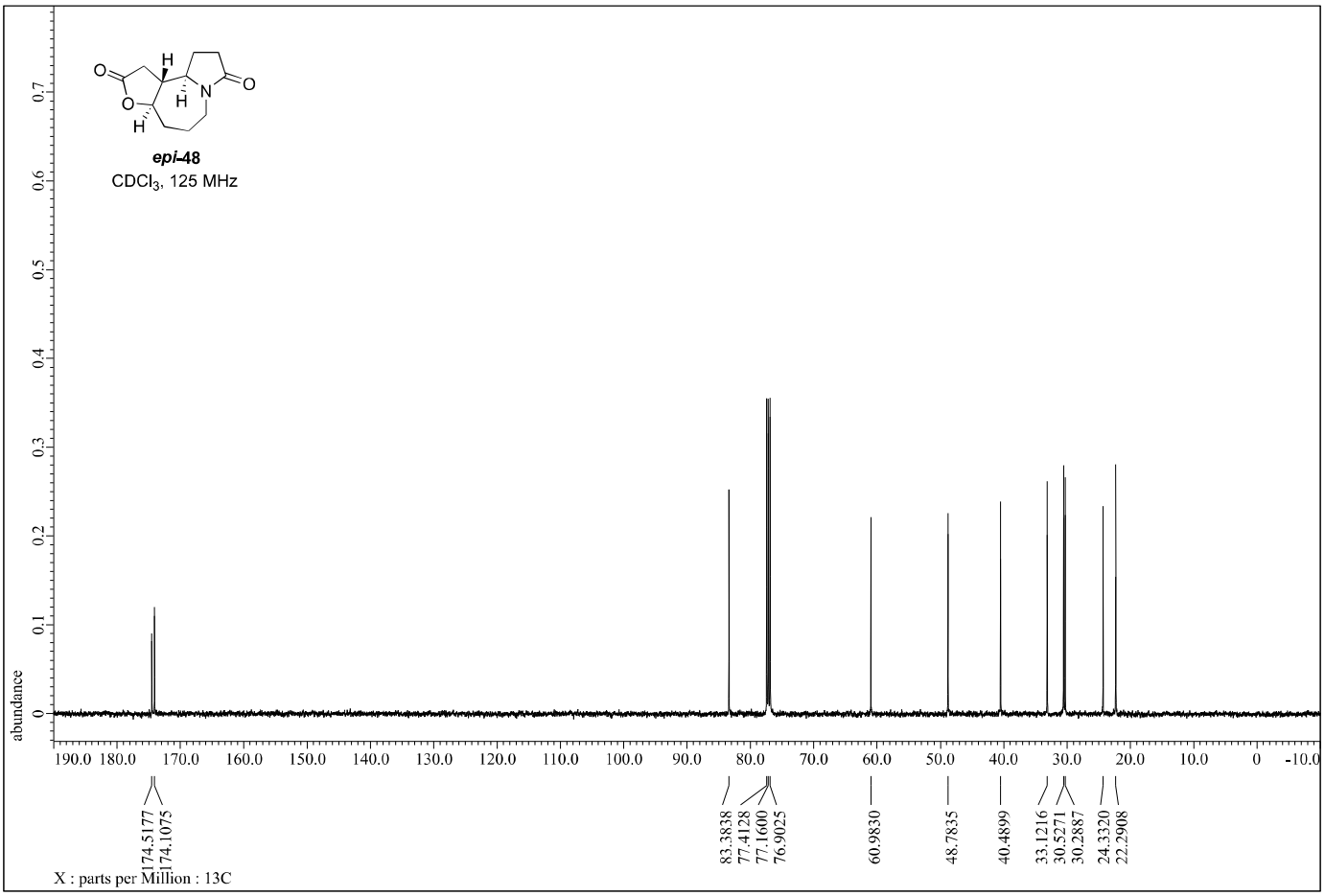

epi-158
CDCl3, 500 MHz
abundance
X : parts per Million : 1H
0.92
1.00
0.97
2.04
1.03
5.23
3.06
2.20
7.8097
7.7089
7.2600
4.3896
4.3827
4.3730
4.3638
4.3558
3.7460
3.7311
3.7179
3.4998
3.4654
3.4626
2.7388
2.7210
2.7044
2.3105
2.3076
1.9366
1.9171
1.7642
1.7545
1.7453
1.7419
1.7362
1.7264
1.7167

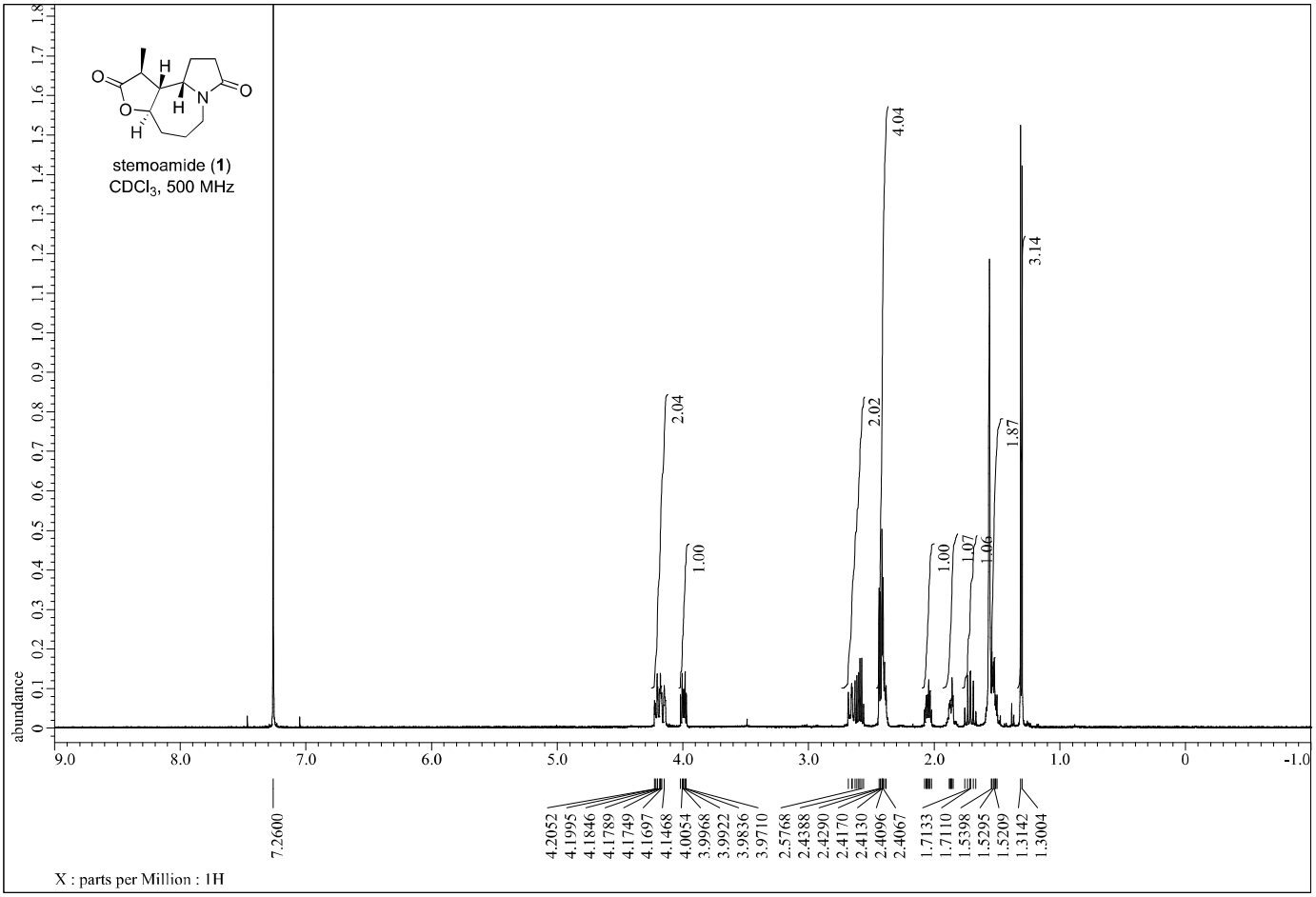

epi-158
CDCl3, 125 MHz
abundance
X : parts per Million : 13C
179.2153
175.1329
82.0341
77.4128
77.1600
76.9072
56.7337
46.2129
34.6858
33.4602
31.1614
29.9930
28.5861
25.1952

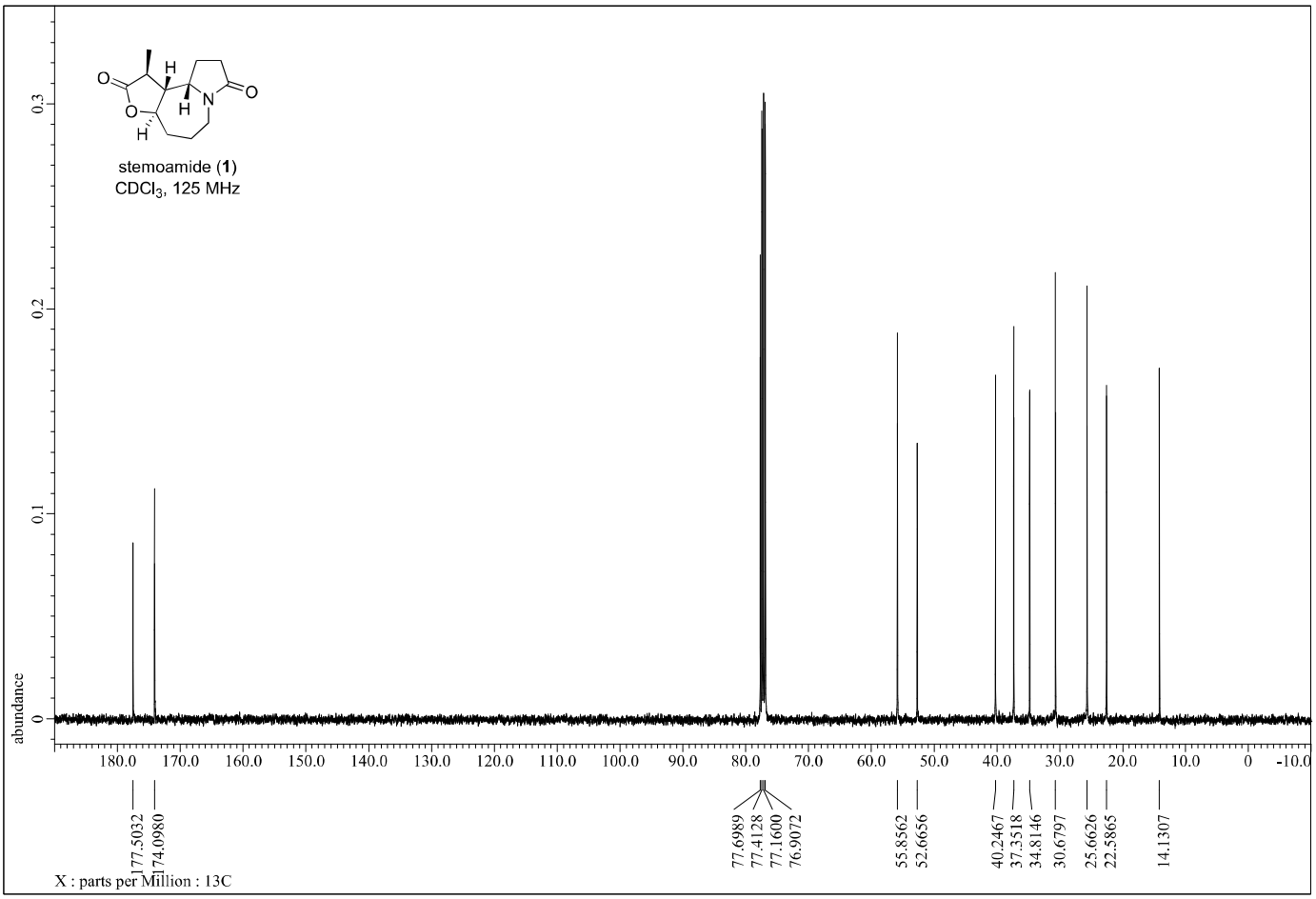

48
CDCl3, 500 MHz
abundance
X : parts per Million : 1H
7.2600
4.3037
4.2888
4.2831
4.1640
4.1411
4.1359
4.0151
4.0019
3.9939
3.9893
3.9808
3.9682
2.6718
2.6369
2.5418
2.4370
2.4159
2.4090
2.4038
2.0763
1.8707
1.7333
1.7093
1.6875
1.5902
1.5862
1.5718
1.5650
1.5570
0.99
1.02
1.00
1.01
2.08
3.07
1.06
1.01
1.05
1.15
5.44

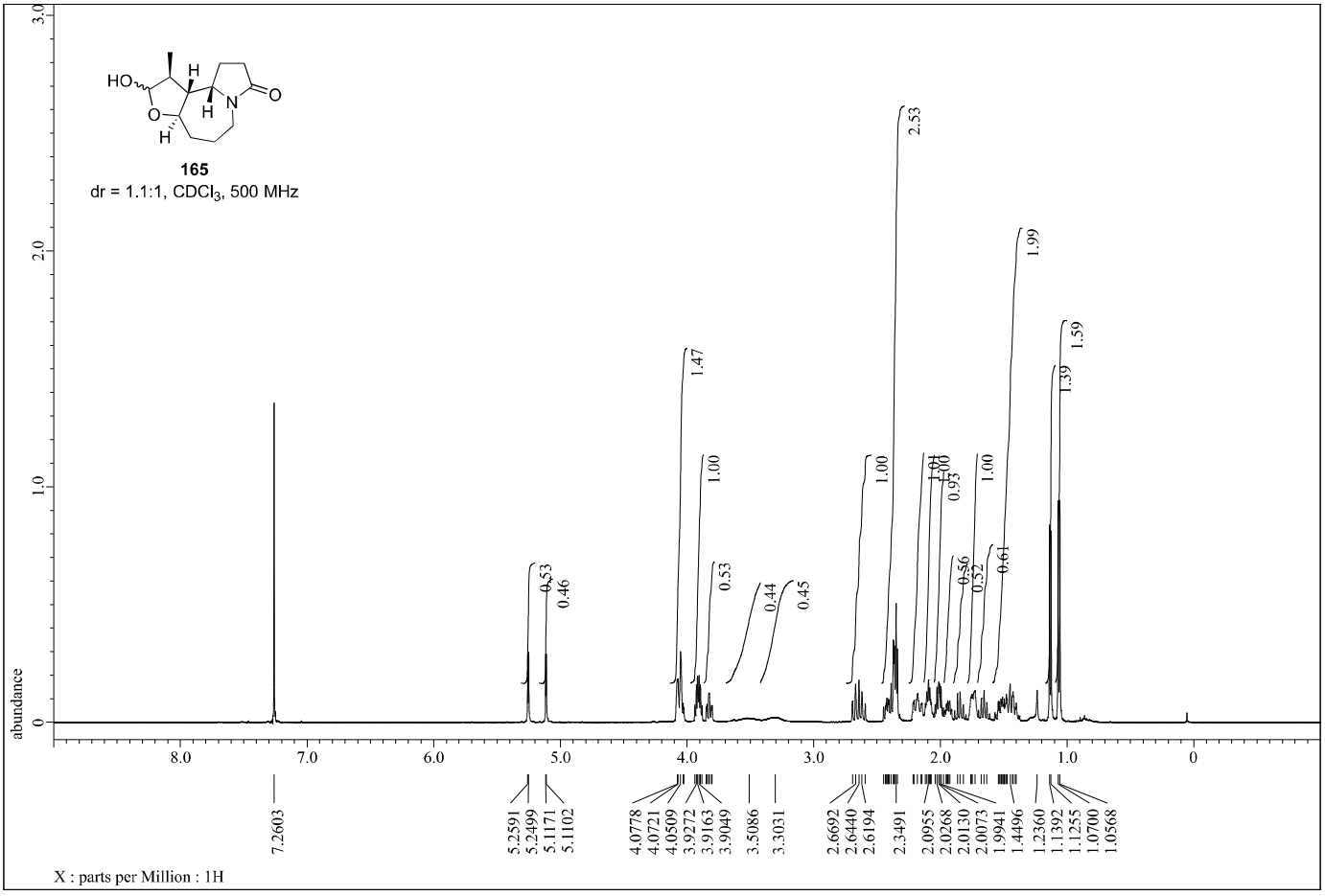

48
CDCl3, 125 MHz
abundance
X : parts per Million : 13C
174.8468
174.1457
79.8546
77.4128
77.1600
76.9025
56.0898
44.8775
40.2038
34.6238
31.0374
30.6082
25.5052
22.6628

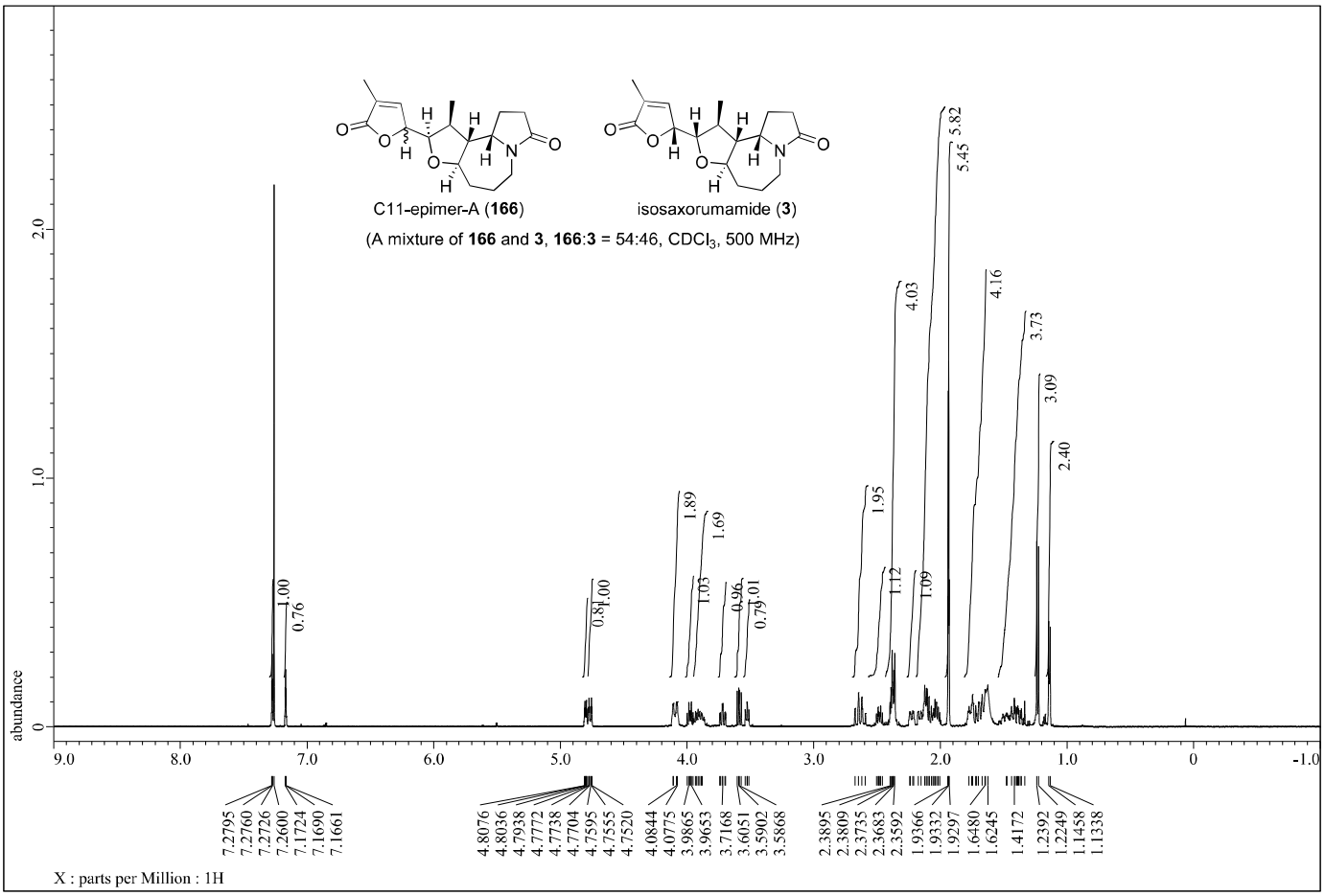

epi-48
CDCl3, 500 MHz
abundance
X : parts per Million : 1H
7.2600
4.3879
4.3770
4.3684
4.3661
4.3575
4.3466
4.3358
3.8519
3.8210
3.5536
3.5353
3.1986
3.1814
2.6357
2.6220
2.4342
2.3695
2.3368
1.8816
1.8753
1.8725
1.8662
1.8604
1.8581
1.8513
1.6726
1.6572
0.98
1.00
1.01
1.00
1.00
0.99
1.01
1.04
2.01
5.03

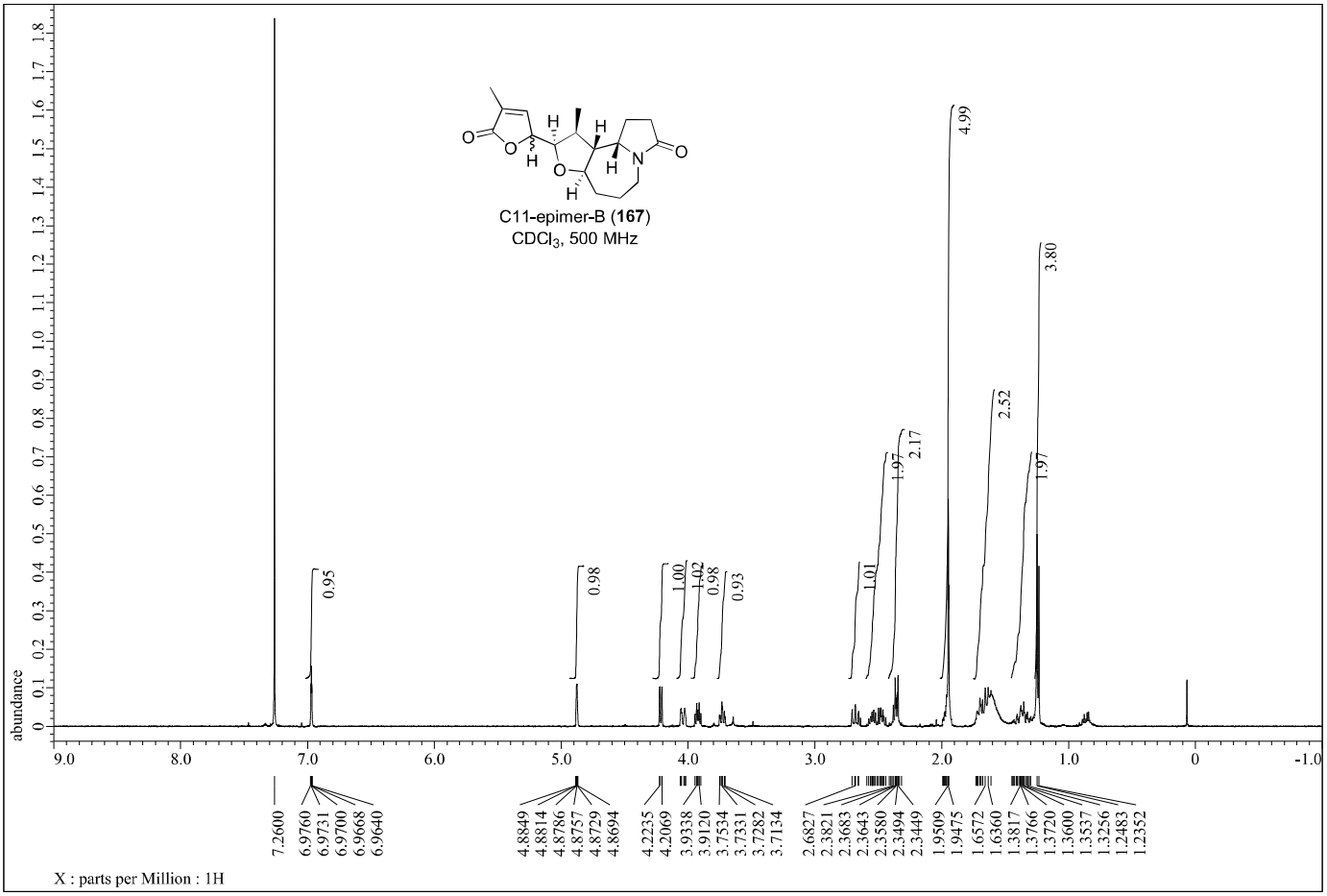

epi-48
CDCl3, 125 MHz
abundance
X : parts per Million : 13C
174.5177
174.1075
83.3838
77.4128
77.1600
76.9025
60.9830
48.7835
40.4899
33.1216
30.5271
30.2887
24.3320
22.2908

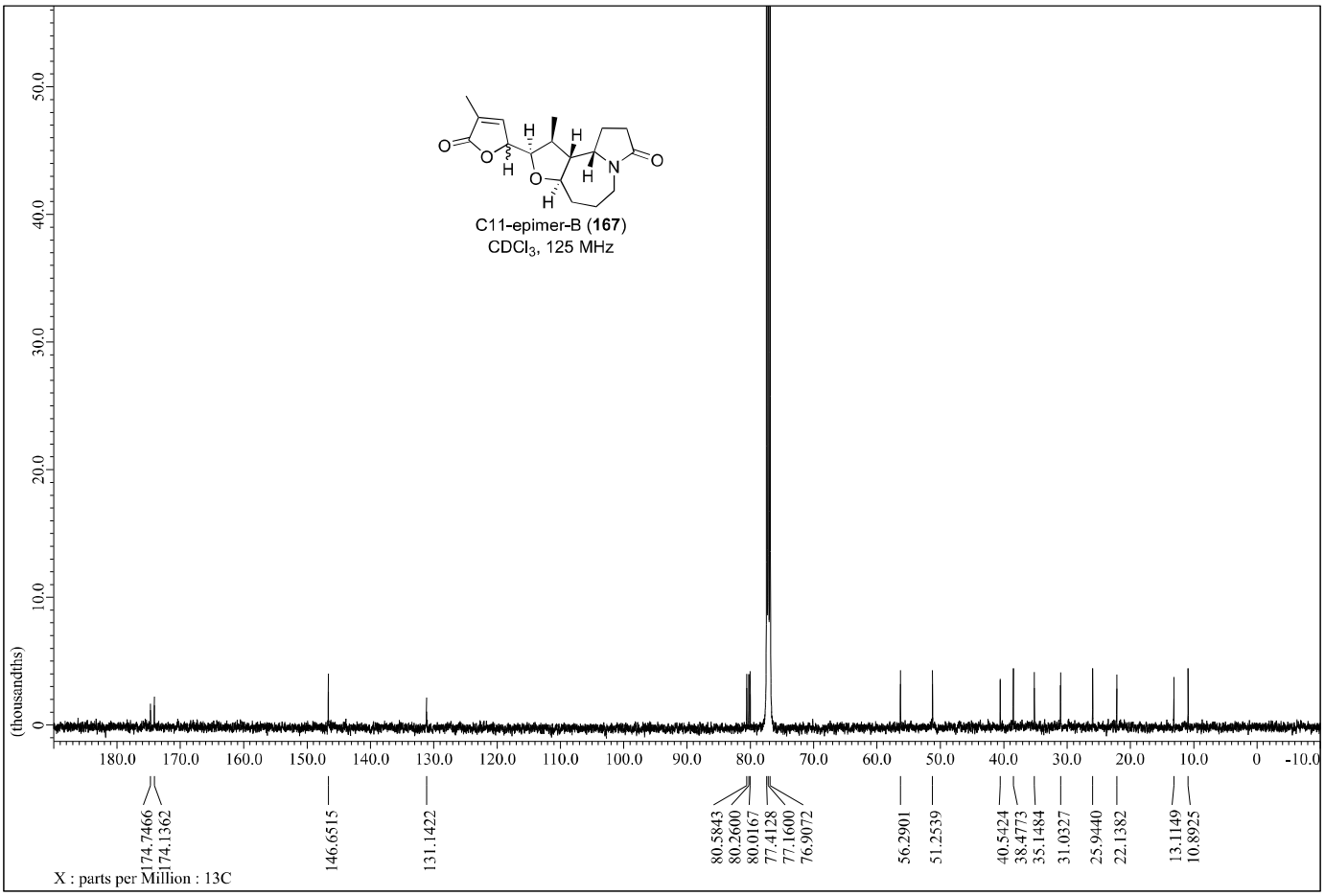

stemoamide (1)
CDCl3, 500 MHz
abundance
X : parts per Million : 1H
7.2600
4.2052
4.1995
4.1846
4.1789
4.1749
4.1697
4.1468
4.0054
3.9968
3.9922
3.9836
3.9710
2.5768
2.4388
2.4290
2.4170
2.4130
2.4096
2.4067
1.7133
1.7110
1.5398
1.5295
1.5209
1.3142
1.3004
2.04
1.00
2.02
4.04
1.00
1.07
1.06
1.87
3.14

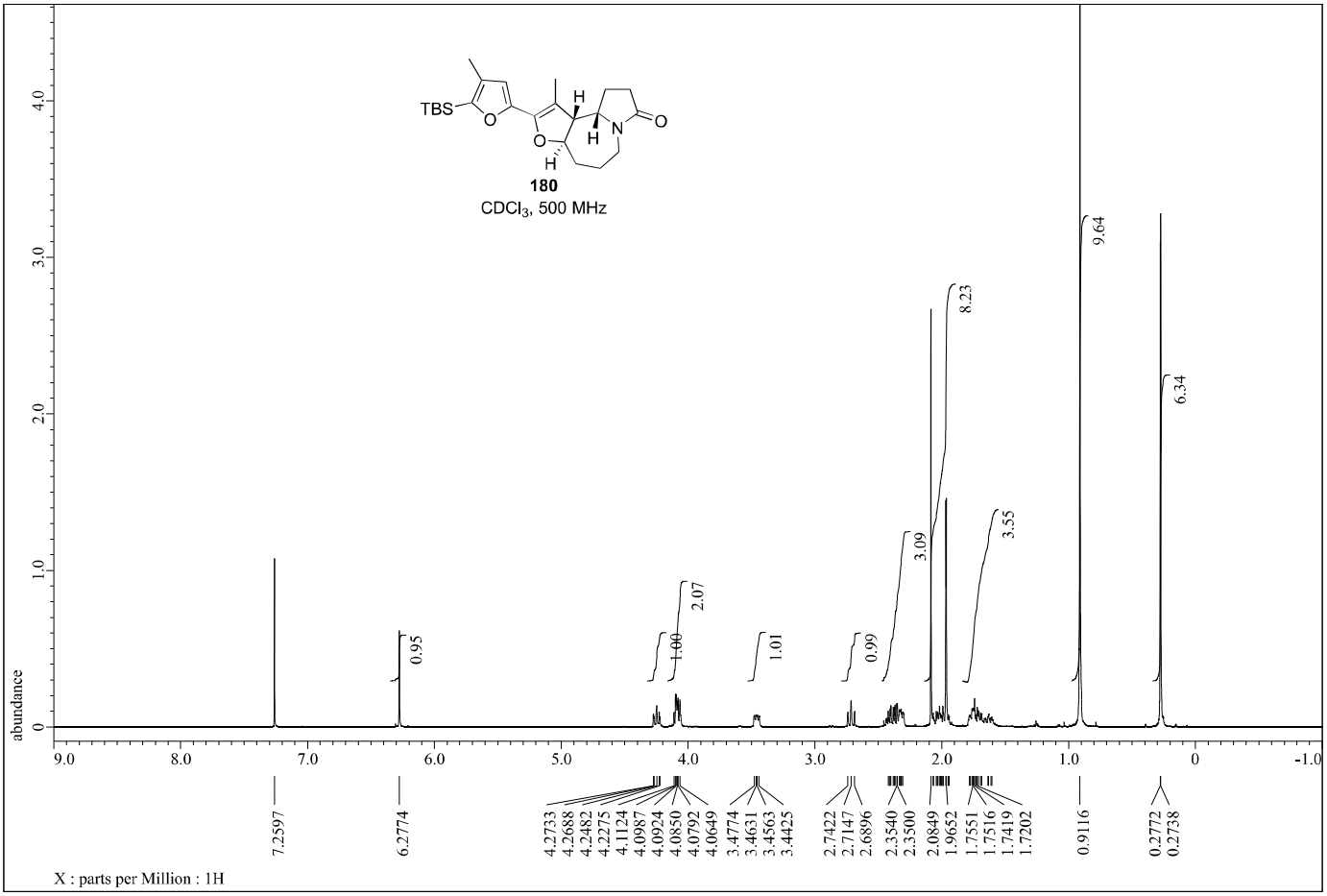

stemoamide (1)
CDCl3, 125 MHz
abundance
X : parts per Million : 13C
177.5032
174.0980
77.6989
77.4128
77.1600
76.9072
55.8562
52.6656
40.2467
37.3518
34.8146
30.6797
25.6626
22.5865
14.1307

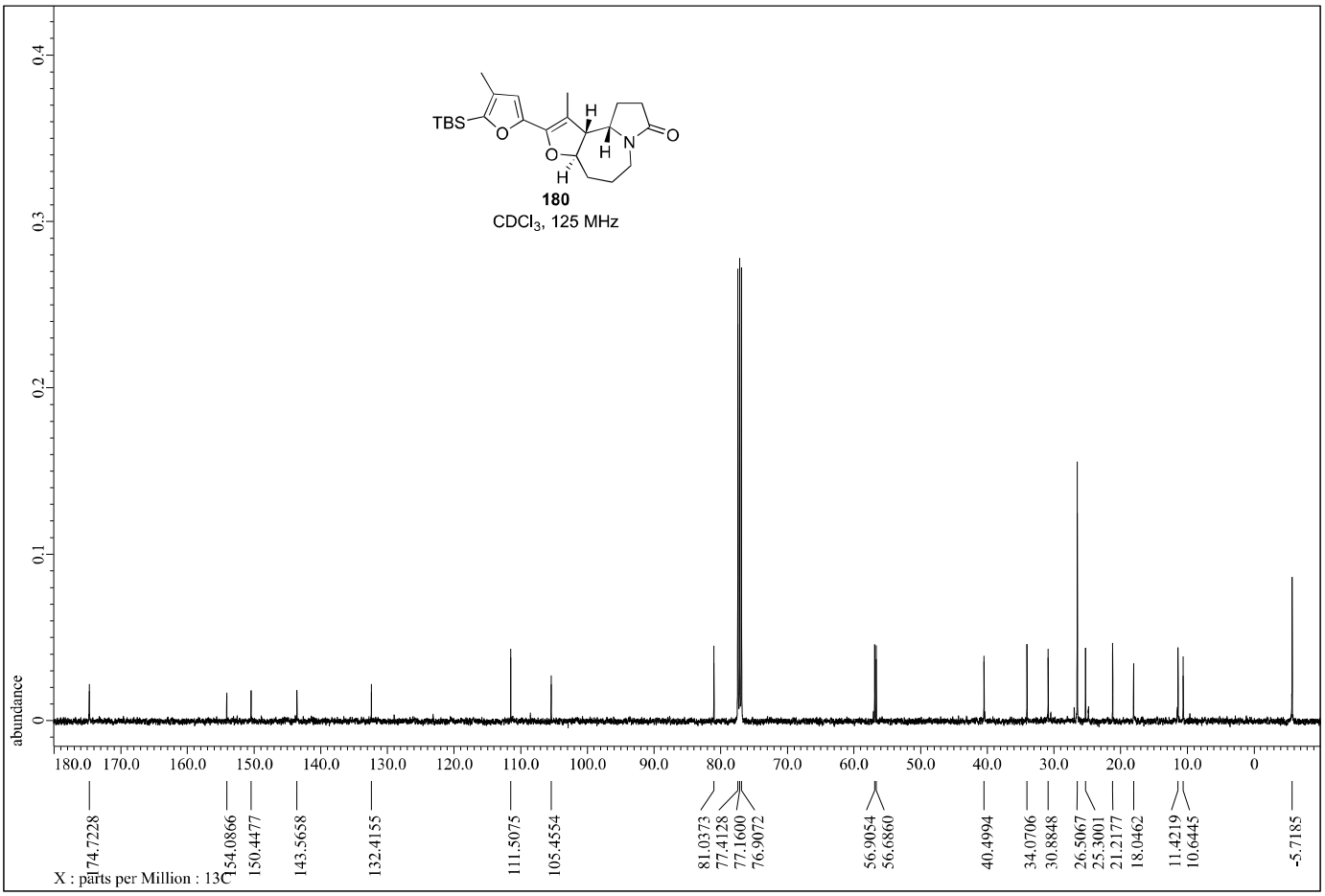

HO
H
O
N
H
O
H
165
dr = 1.1:1, CDCl3, 500 MHz
abundance
X : parts per Million : 1H

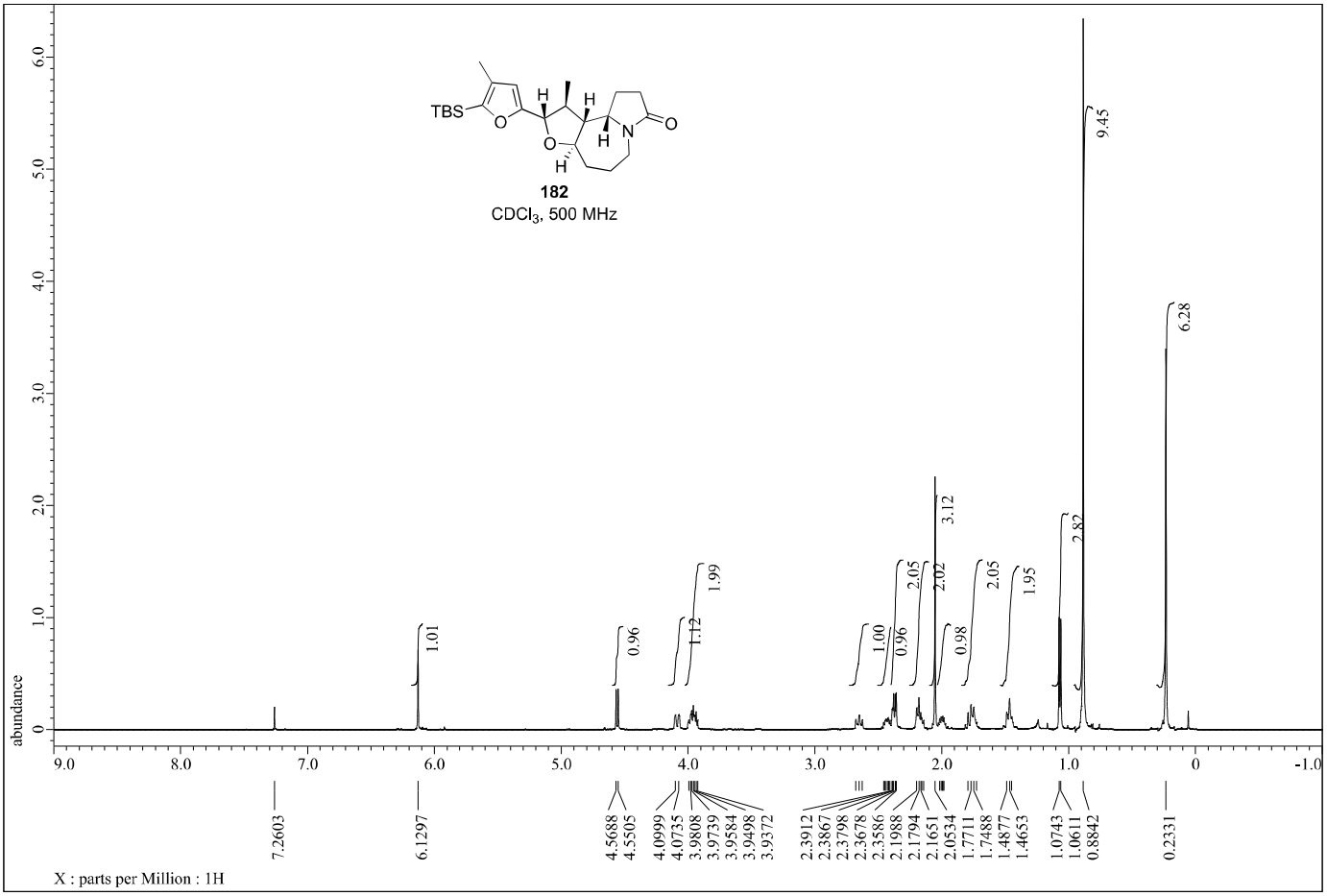

C11-epimer-A (166)
isosaxorumamide (3)
(A mixture of 166 and 3, 166:3 = 54:46, CDCl3, 500 MHz)
abundance
X : parts per Million : 1H

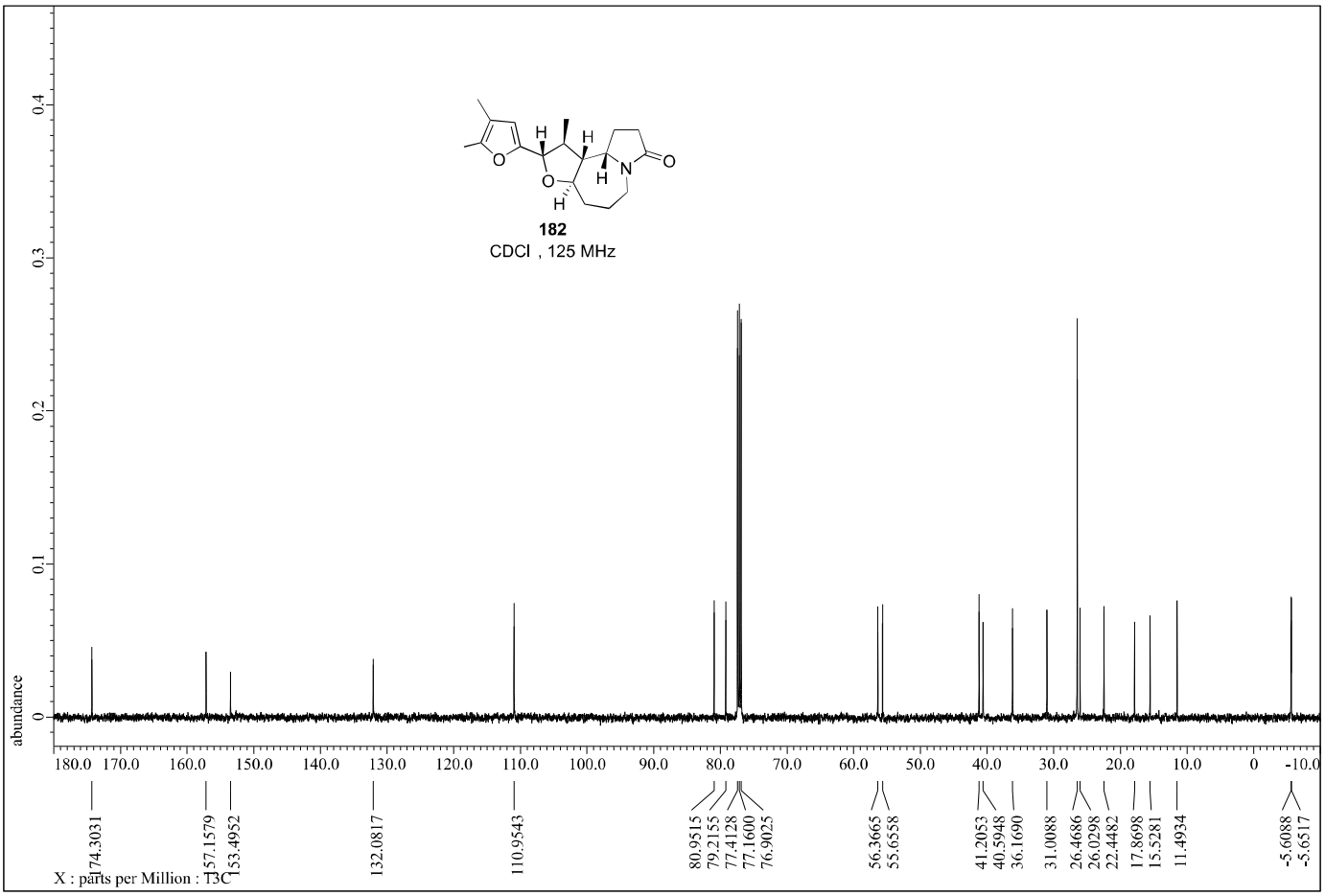

C11-epimer-B (167)
CDCl3, 500 MHz
abundance
X : parts per Million : 1H

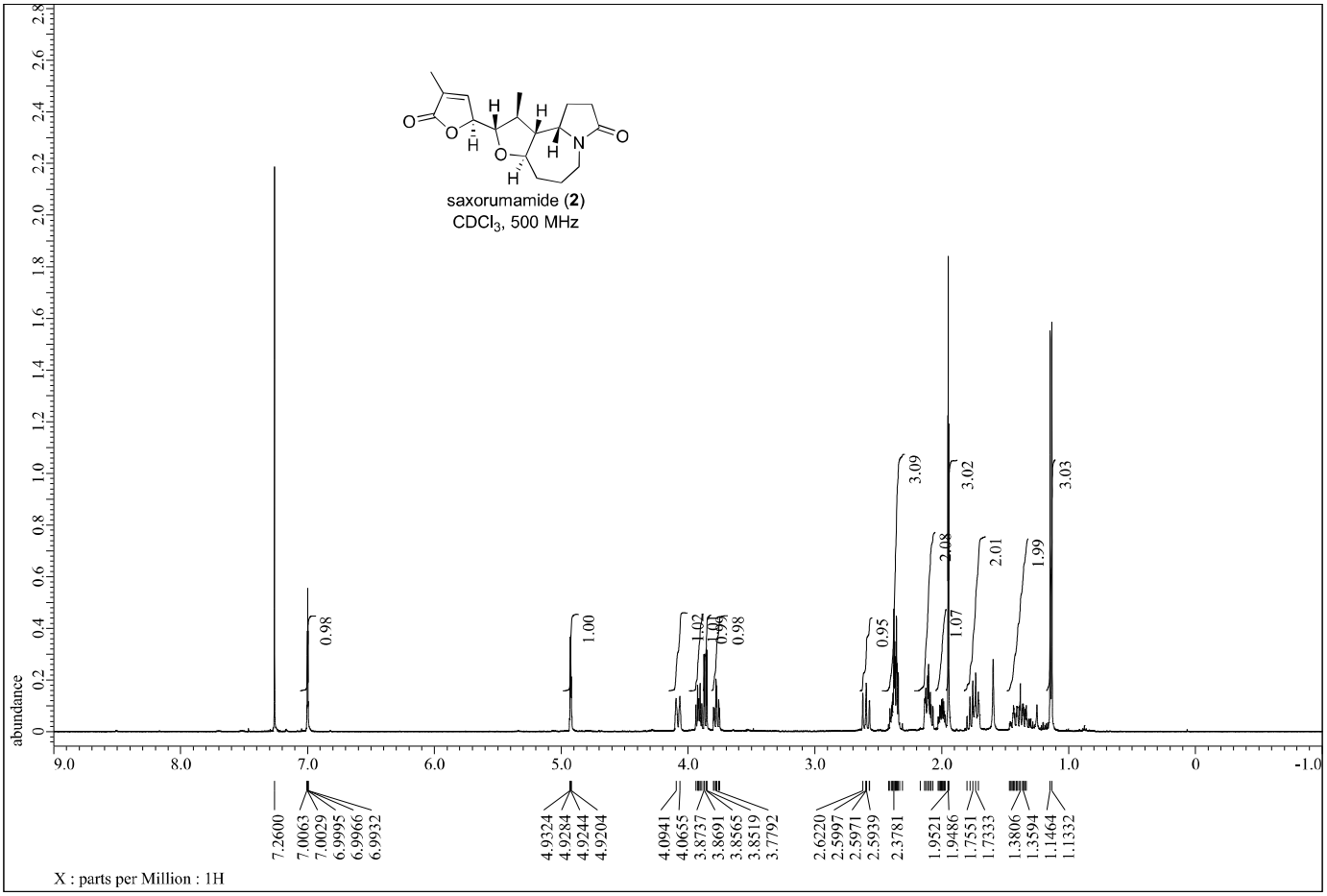

C11-epimer-B (167)
CDCl3, 125 MHz
(thousandths)
X : parts per Million : 13C

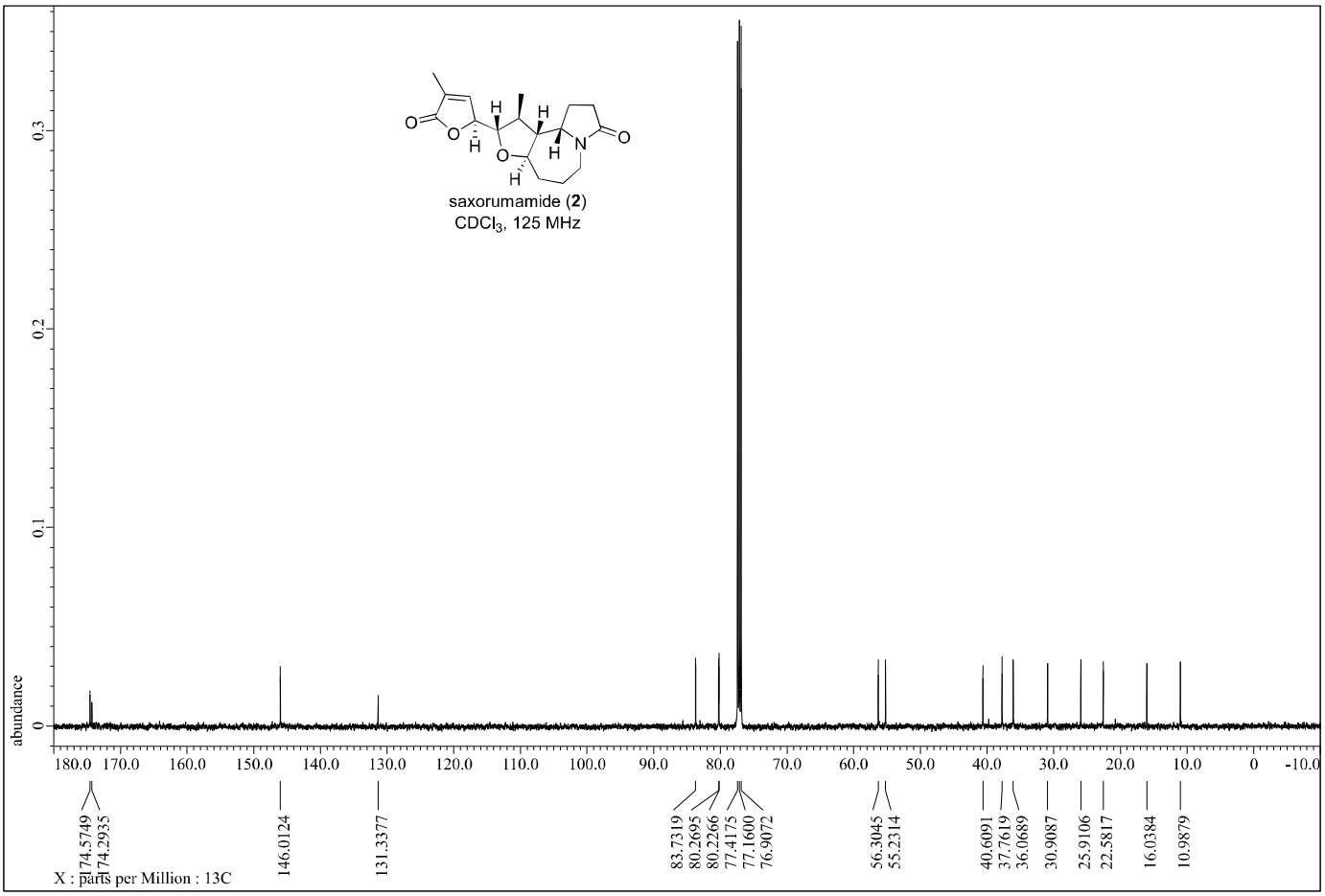

TBS
O
O
H
H
N
O
H
180
CDCl3, 500 MHz
abundance
4.0
3.0
2.0
1.0
0
9.64
8.23
6.34
3.55
3.09
2.07
1.00
0.95
1.01
0.99
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
-1.0
7.2597
6.2774
4.2733
4.2688
4.2482
4.2275
4.1124
4.0987
4.0924
4.0850
4.0792
4.0649
3.4774
3.4631
3.4563
3.4425
2.7422
2.7147
2.6896
2.3540
2.3500
2.0849
1.9652
1.7551
1.7516
1.7419
1.7202
0.9116
0.2772
0.2738
X : parts per Million : 1H

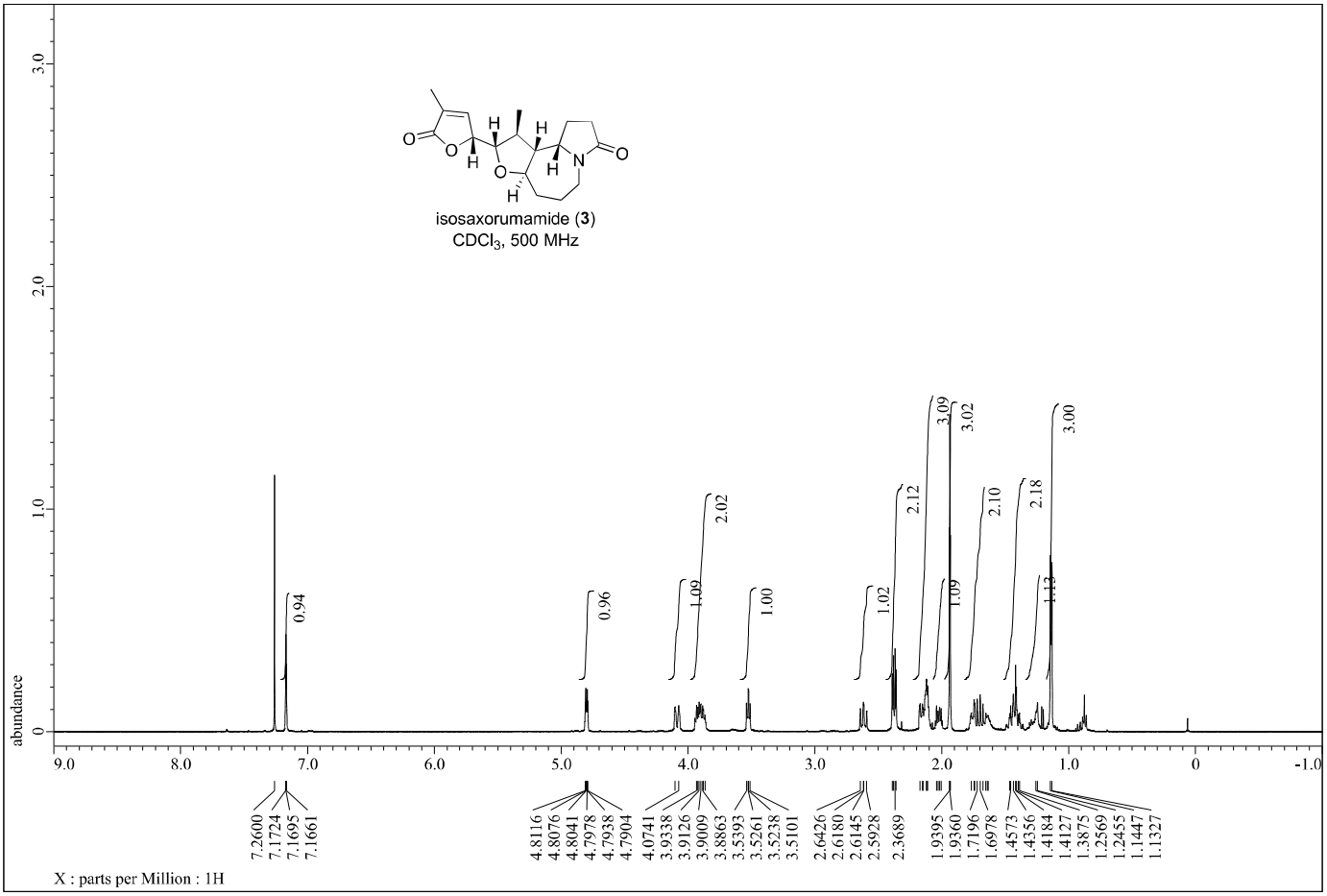

TBS
O
O
H
H
N
O
H
180
CDCl3, 125 MHz
abundance
0.4
0.3
0.2
0.1
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
174.7228
154.0866
150.4477
143.5658
132.4155
111.5075
105.4554
81.0373
77.4128
77.1600
76.9072
56.9054
56.6860
40.4994
34.0706
30.8848
26.5067
25.3001
21.2177
18.0462
11.4219
10.6445
-5.7185
X : parts per Million : 13C

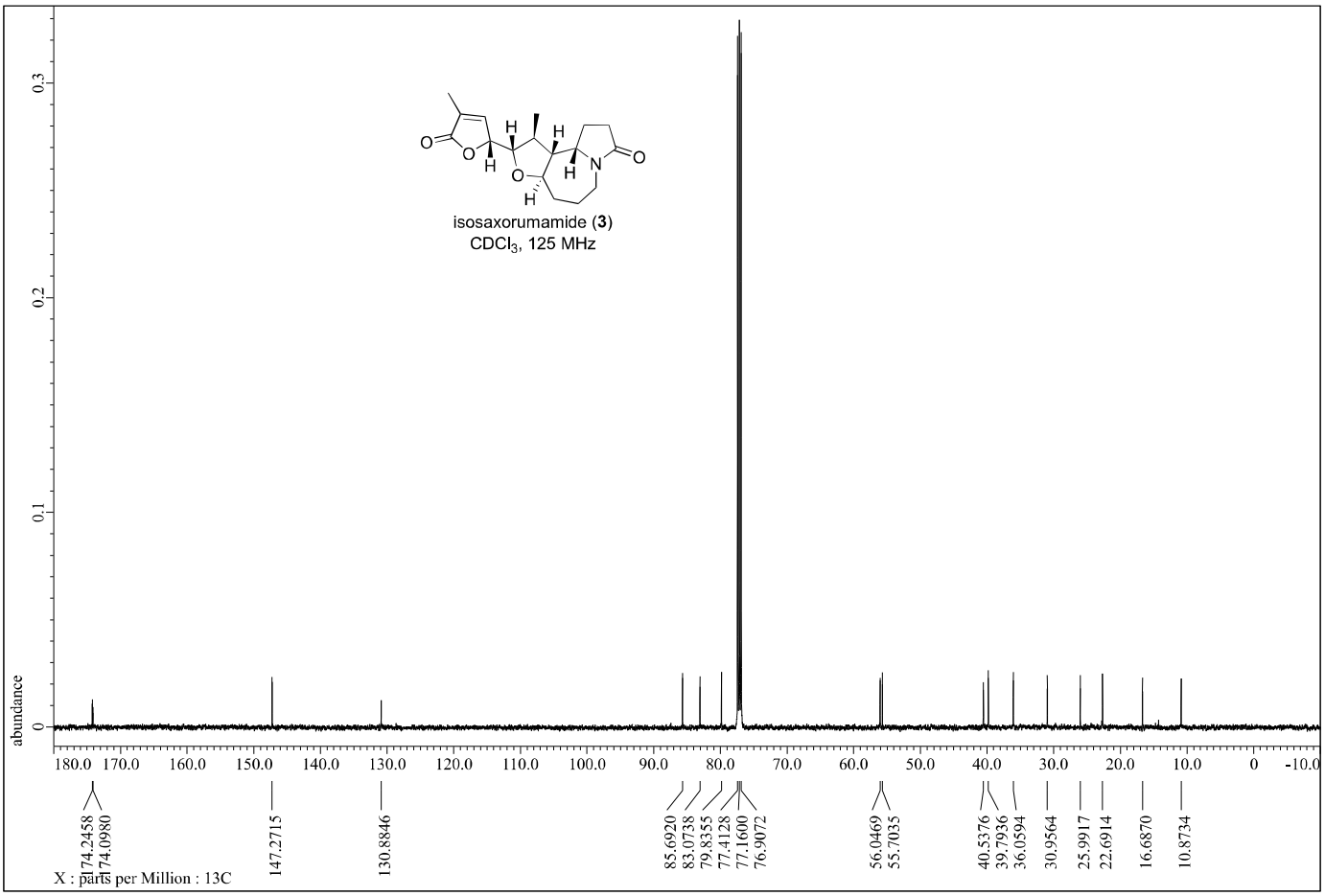

TBS
O
H
H
O
H
N
O
182
CDCl3, 500 MHz
abundance
9.45
6.28
3.12
2.82
2.05
2.05
2.02
1.99
1.95
1.12
1.01
1.00
0.98
0.96
0.96
7.2603
6.1297
4.5688
4.5505
4.0999
4.0735
3.9808
3.9739
3.9584
3.9498
3.9372
2.3912
2.3867
2.3798
2.3678
2.3586
2.1988
2.1794
2.1651
2.0534
1.7711
1.7488
1.4877
1.4653
1.0743
1.0611
0.8842
0.2331
X : parts per Million : 1H

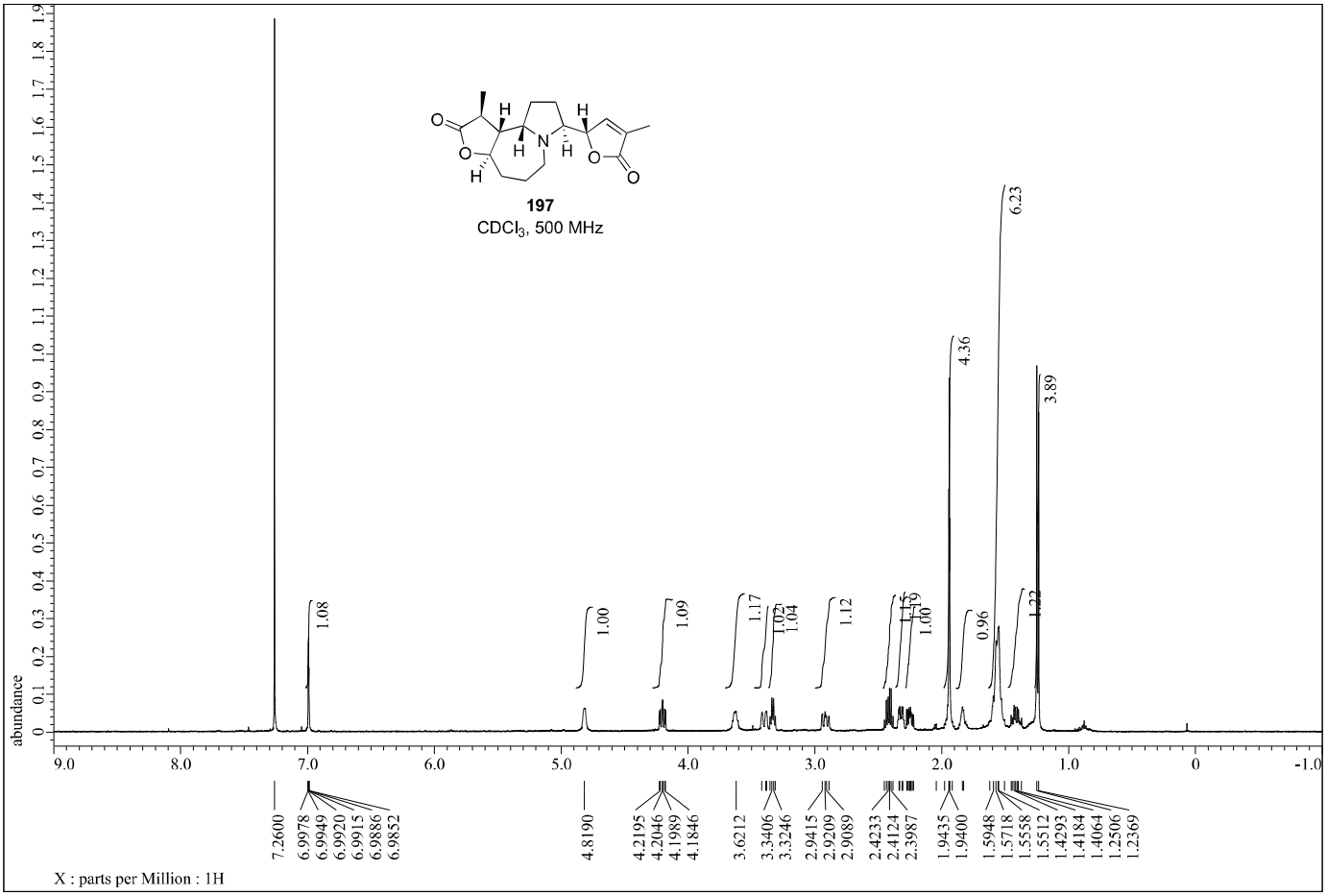

O
H
H
O
H
N
O
182
CDCl , 125 MHz
abundance
174.3031
157.1579
153.4952
132.0817
110.9543
80.9515
79.2155
77.4128
77.1600
76.9025
56.3665
55.6558
41.2053
40.5948
36.1690
31.0088
26.4686
26.0298
22.4482
17.8698
15.5281
11.4934
-5.6088
-5.6517
X : parts per Million : 13C

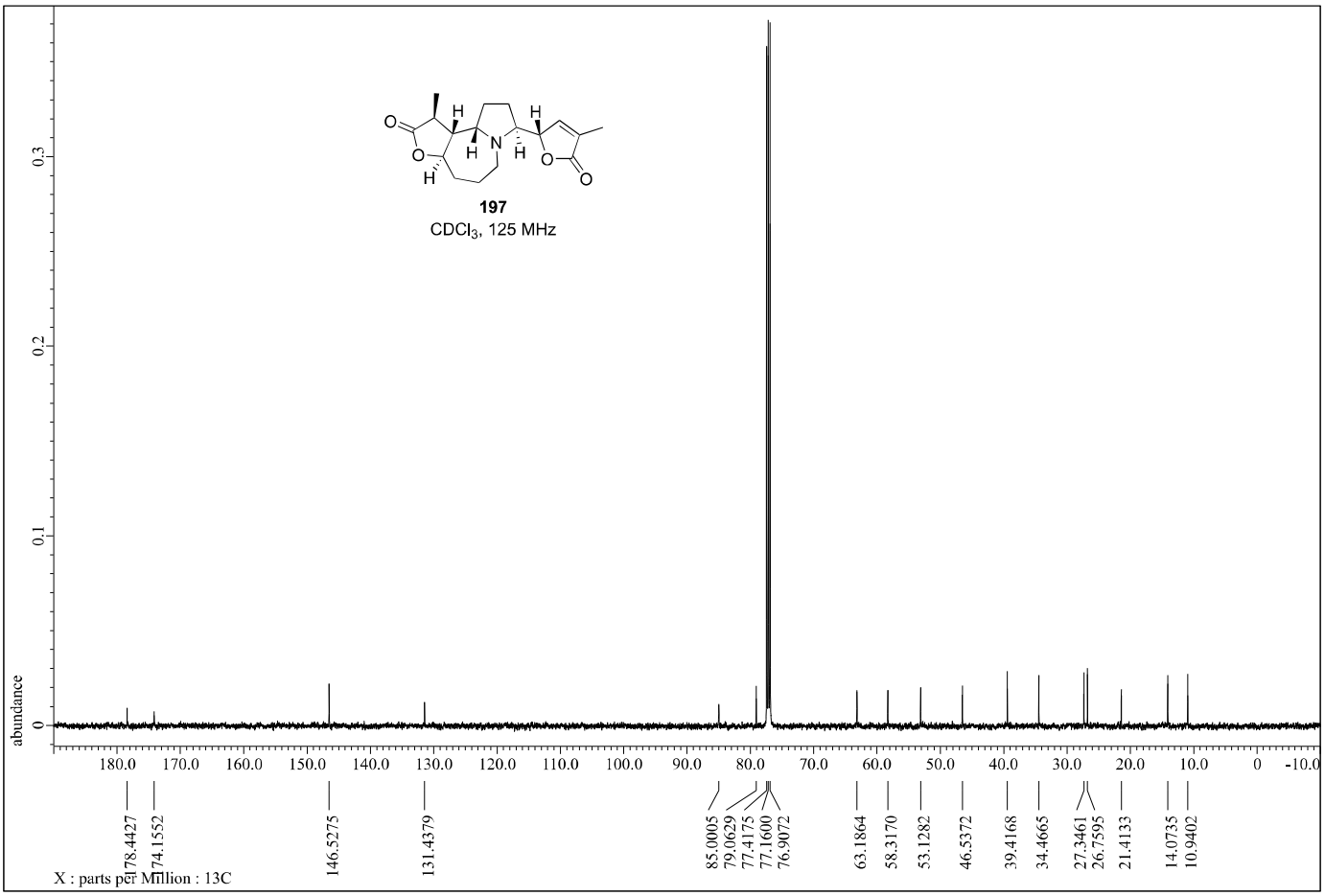

saxorumamide (2)
CDCl3, 500 MHz
abundance
X : parts per Million : 1H
7.2600
7.0063
7.0029
6.9995
6.9966
6.9932
4.9324
4.9284
4.9244
4.9204
4.0941
4.0655
3.8737
3.8691
3.8565
3.8519
3.7792
2.6220
2.5997
2.5971
2.5939
2.3781
1.9521
1.9486
1.7551
1.7333
1.3806
1.3594
1.1464
1.1332
0.98
1.00
1.02
1.01
0.93
0.98
0.95
3.09
2.08
3.02
1.07
2.01
1.99
3.03

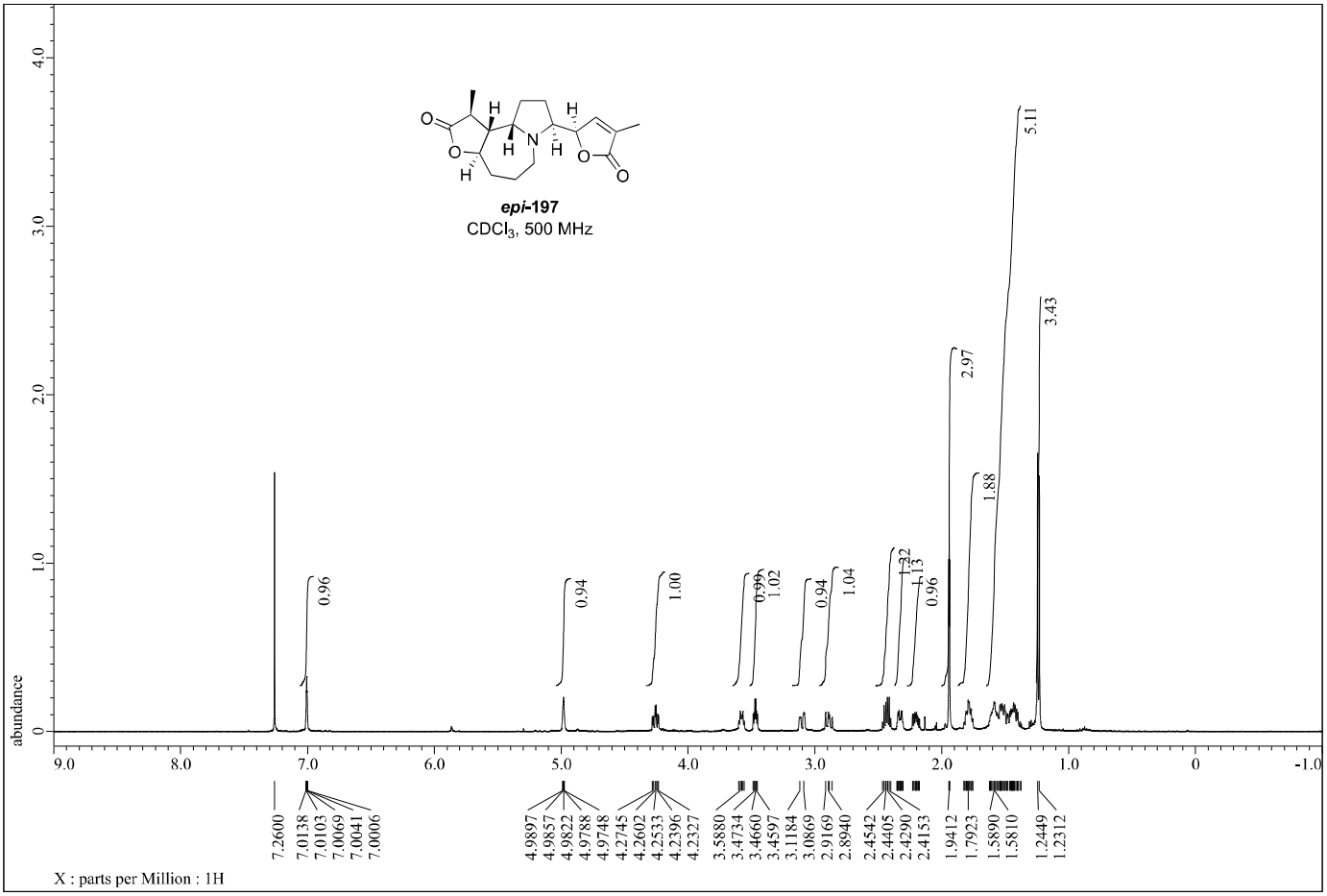

saxorumamide (2)
CDCl3, 125 MHz
abundance
X : parts per Million : 13C
174.5749
174.2935
146.0124
131.3377
83.7319
80.2695
80.2266
77.4175
77.1600
76.9072
56.3045
55.2314
40.6091
37.7619
36.0689
30.9087
25.9106
22.5817
16.0384
10.9879

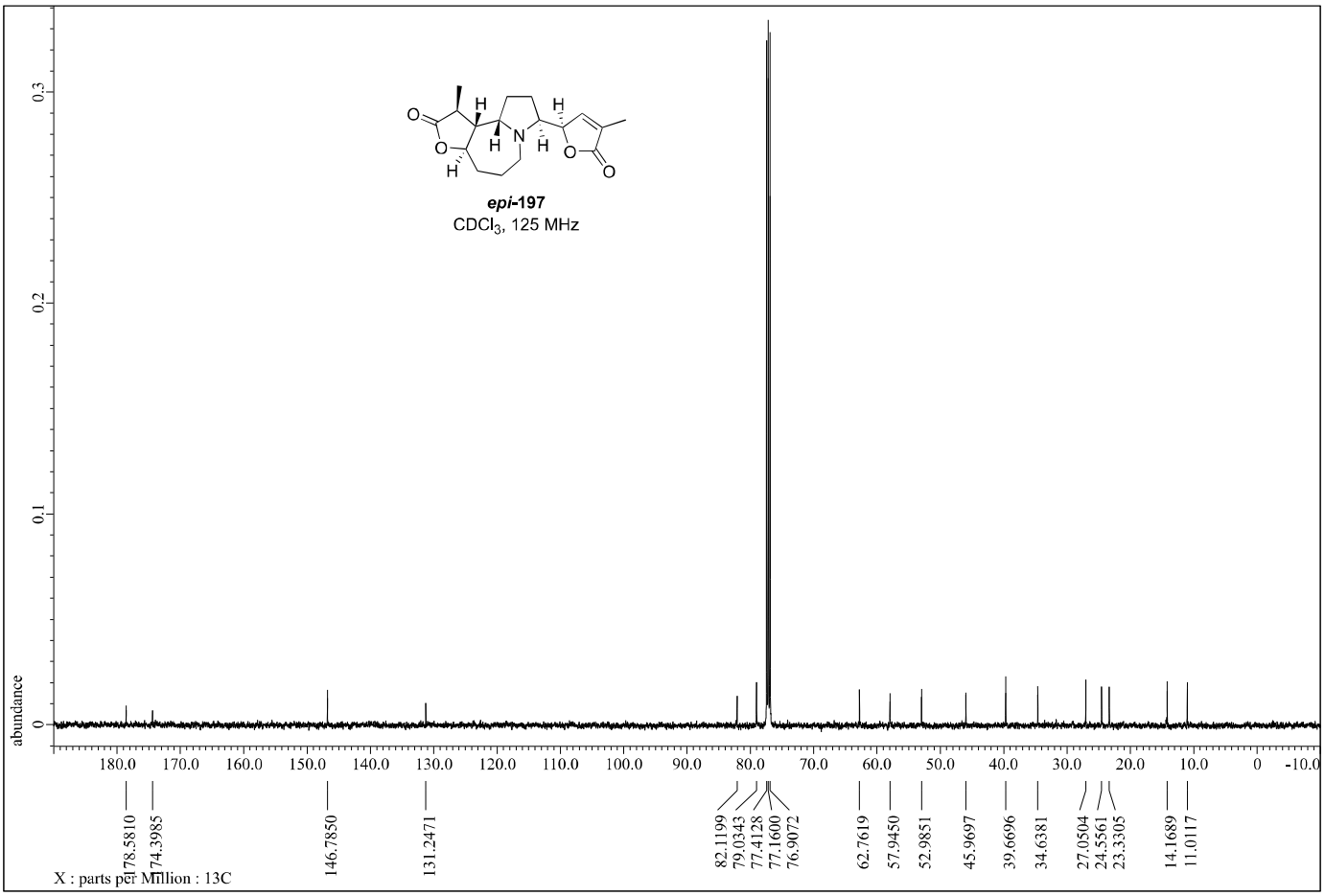

isosaxorumamide (3)
CDCl3, 500 MHz
abundance
X : parts per Million : 1H
0.94
0.96
1.09
2.02
1.00
1.02
2.12
3.09
1.09
3.02
2.10
2.18
1.13
3.00
7.2600
7.1724
7.1695
7.1661
4.8116
4.8076
4.8041
4.7978
4.7938
4.7904
4.0741
3.9338
3.9126
3.9009
3.8863
3.5393
3.5261
3.5238
3.5101
2.6426
2.6180
2.6145
2.5928
2.3689
1.9395
1.9360
1.7196
1.6978
1.4573
1.4356
1.4184
1.4127
1.3875
1.2569
1.2455
1.1447
1.1327

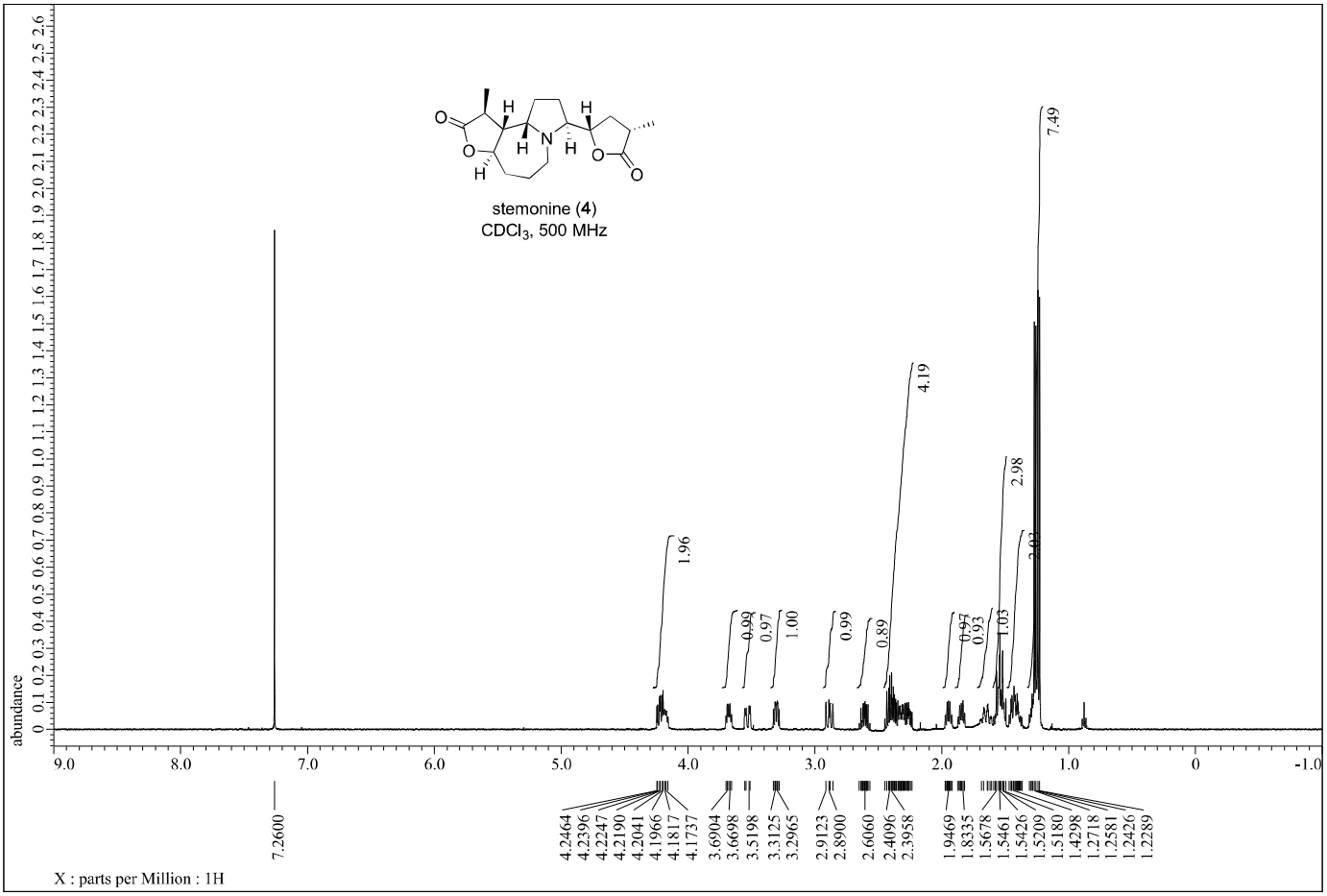

isosaxorumamide (3)
CDCl3, 125 MHz
abundance
X : parts per Million : 13C
174.2458
174.0980
147.2715
130.8846
85.6920
83.0738
79.8355
77.4128
77.1600
76.9072
56.0469
55.7035
40.5376
39.7936
36.0594
30.9564
25.9917
22.6914
16.6870
10.8734

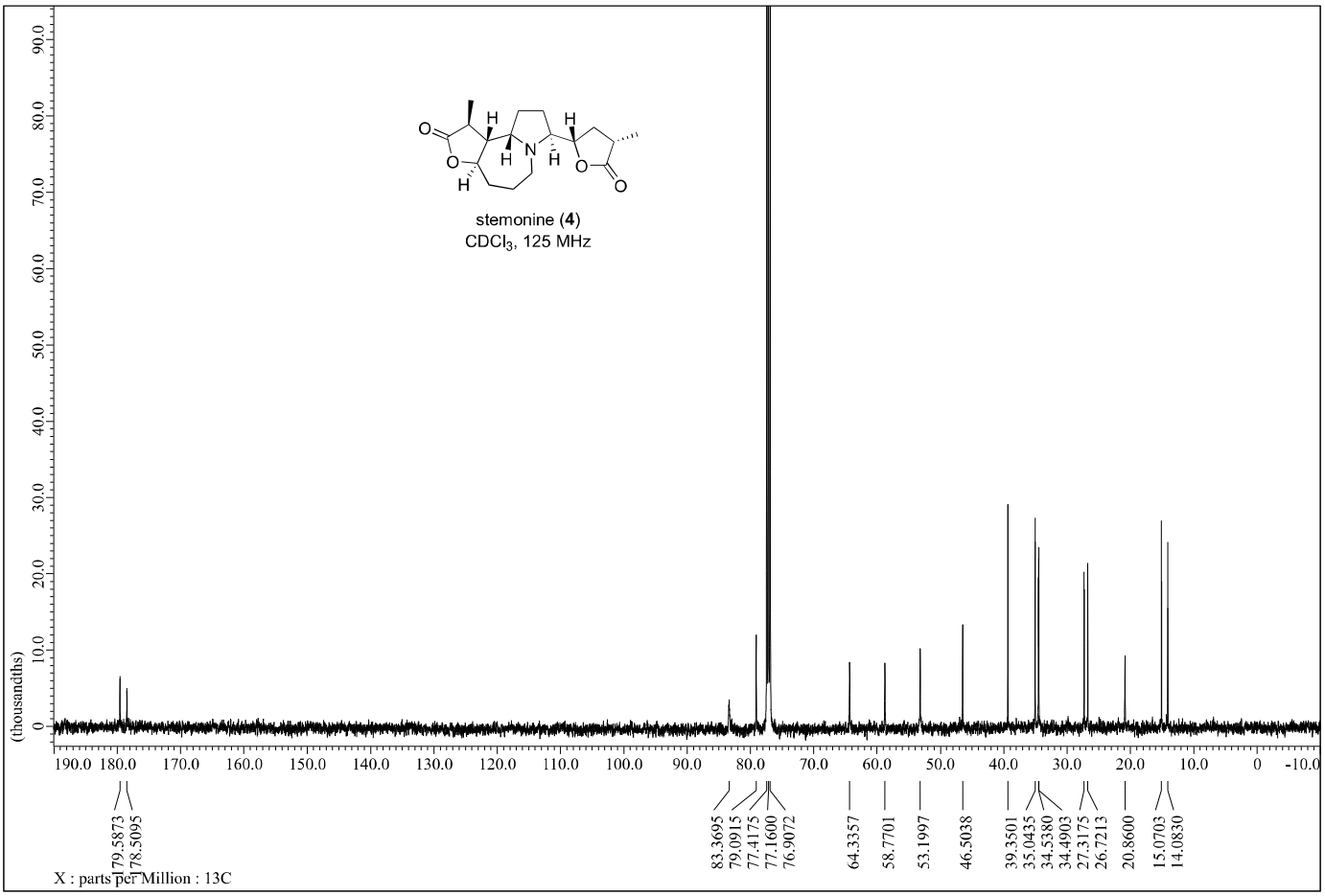

197
CDCl3, 500 MHz
abundance
X : parts per Million : 1H


197
CDCl3, 125 MHz
abundance
X : parts per Million : 13C


epi-197
CDCl3, 500 MHz
abundance
X : parts per Million : 1H


epi-197
CDCl3, 125 MHz
abundance
X : parts per Million : 13C


stemonine (4)
CDCl3, 500 MHz
abundance
X : parts per Million : 1H


stemonine (4)
CDCl3, 125 MHz
(thousandths)
X : parts per Million : 13C

E. References

Complete lists of references on nucleophilic addition to amides

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