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Total Synthesis of (-)-Acutumine

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Total Synthesis of (-)-Acutumine

by

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GRADUATE COMMITTEE APPROVAL

of a thesis submitted by

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BRIGHAM YOUNG UNIVERSITY

As chair of the candidate's graduate committee, I have read the thesis of Fang Li in its final form and have found that (1) its format, citations, and bibliographical style are consistent and acceptable and fulfill university and department style requirements; (2) its illustrative materials including figures, tables, and charts are in place; and (3) the final manuscript is satisfactory to the graduate committee and is ready for submission to the university library.

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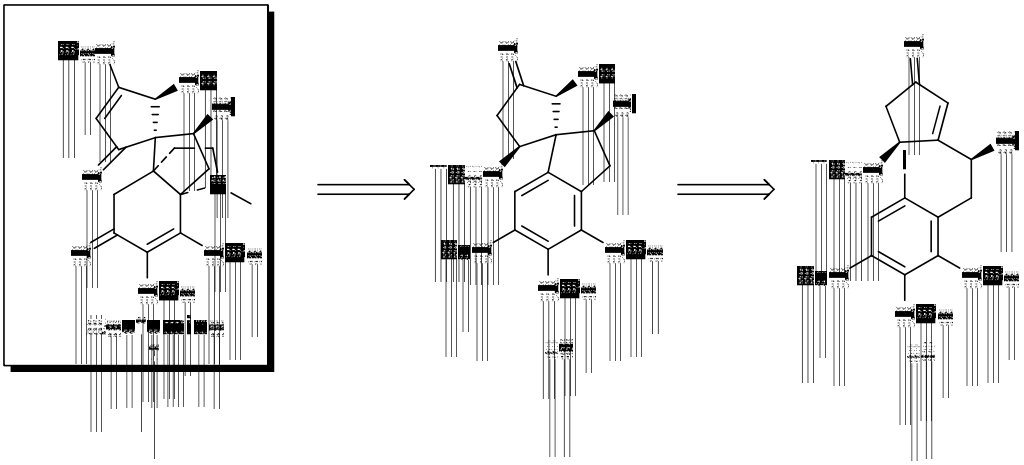
ABSTRACT

TOTAL SYNTHESIS OF (-)-ACUTUMINE

Fang Li

Department of Chemistry and Biochemistry

Doctor of Philosophy



Acutumine is a tetracyclic alkaloid isolated from the Asian vine *Menispermum dauricum* with selective T-cell cytotoxicity and antiamnestic properties. We have developed a total synthetic route to this congested alkaloid, during which we also found a novel, stereoselective radical-crossover reaction that combines an intramolecular

radical conjugate addition with a subsequent enolate hydroxylation. Key features of this synthesis also include a reagent-controlled diastereoselective ketone allylation, an anionic oxy-Cope rearrangement to form a congested quaternary sterocenter, a pyridine-mediated selective ozonolysis, and a Lewis acid promoted Michael-type cyclization.

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Most of all I want to express my appreciation to my wife, Chunyan, for bearing a heavy family burden over the past six years. She has been a wonderful wife and mother. Without her significant personal sacrifices my recent scholastic accomplishments would not have come to pass. It is to her and my lovely daughter Amber that I dedicate this dissertation.

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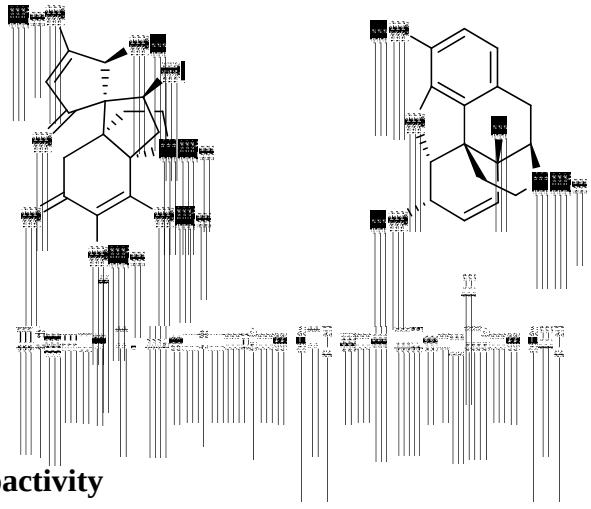
Chapter 1. Introduction

1.1 Background

Alkaloids are a group of natural products with at least one basic nitrogen atom. Many of them are from plants and have strong bioactivity.[1] Since morphine (**2**, Figure 1), the first active member of this family was discovered by Sertürner in 1817, alkaloids have attracted extensive attention from organic chemists not only for their strong pharmacological effects, but also for the intriguing structures which have inspired the development of several novel reactions, catalysts, and techniques.



1.2 Discovery and Bioactivity

The tetracyclic alkaloid acutumine (**1**, Figure 1) is found to be the major constituent of the vines *Menispermum dauricum,*[2] *Sinomenium acutum,*[3] and

Menispermum canadense.[4] *Menispermum dauricum* is a widespread plant in China, and its rhizome is a traditional Chinese medicine which is officially documented in the Chinese Pharmacopoeia as an analgesic and antipyretic agent.[5] It was reported that acutumine possesses selective T-cell cytotoxicity by Yu et al. in 2002.[6] Additionally, the antiamnesic properties of **1** were also described in Qin's patent in 2004. These data were based on experiments with animal models.[7]

Acutumine **1** was isolated by K. Goto and H. Sudzuki in 1929,[2] but the structure and the stereochemistry were not determined until thirty-eight years later by Tomita and coworkers through X-ray crystallographic studies in 1967.[4, 8, 9] This benzylisoquinoline alkaloid is characterized by a propellane-like [4.3.3.0] fused tricycle, a spirocycle, and a neopentylic secondary chloride, which bears some structural resemblance to the morphine (**2**) alkaloids. Several derivatives such as dechlorodauricumine **3**, dauricumine **4**[10], dauricumidine **5**[11], dechloroacutumine **6**, and acutumidine **7** (Figure 2) are also isolated from the same plant and reported to share similar core structures. Recently Sugimoto et al. proposed a biosynthetic relationship among those similar alkaloids, in which dechlorodauricumine **3** is the original precursor. Then the chloride atom was installed regioselectively and stereoselectively with the help of enzyme(s) to get dauricumine **4**, which could lead to acutumine **1** by epimerization. Catalyzed by same or similar chlorination enzyme(s), acutumine **1** could also be formed by dechloroacutumine (**6**), although the detailed mechanisms are still under investigation.

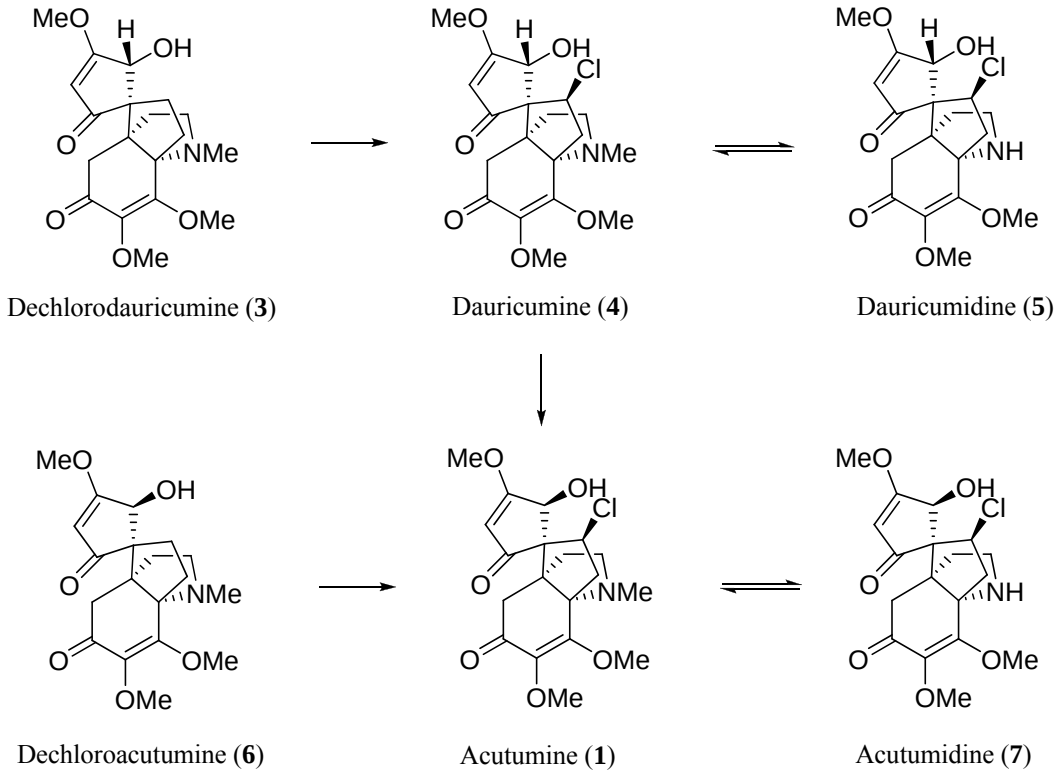
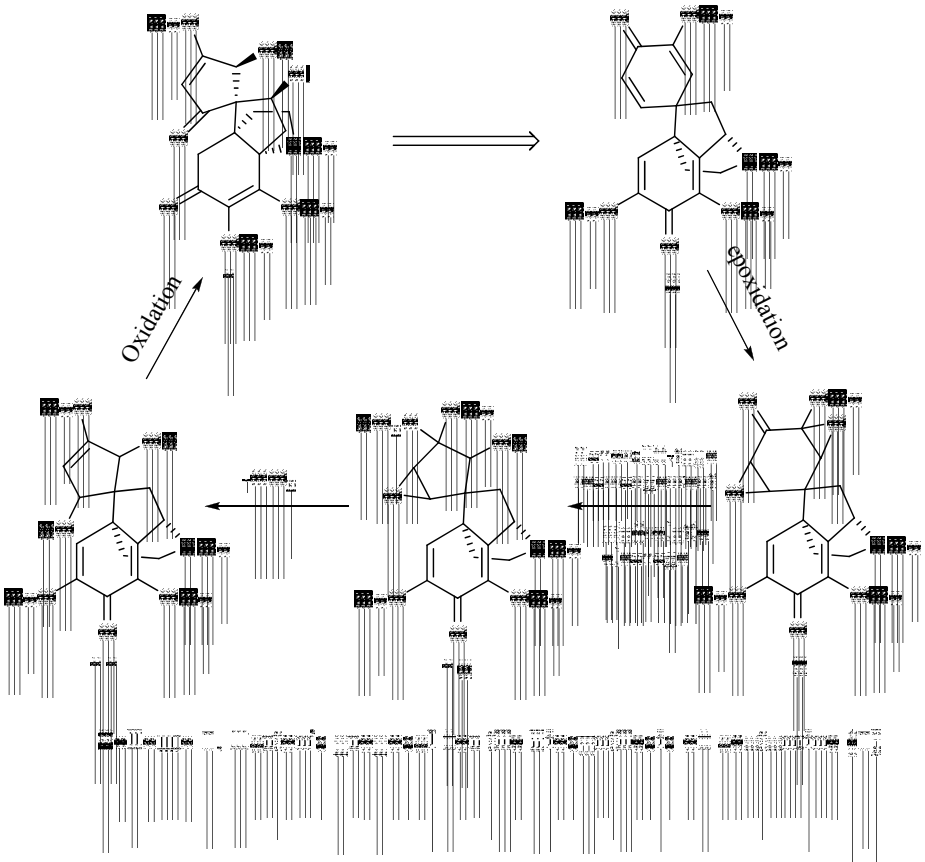


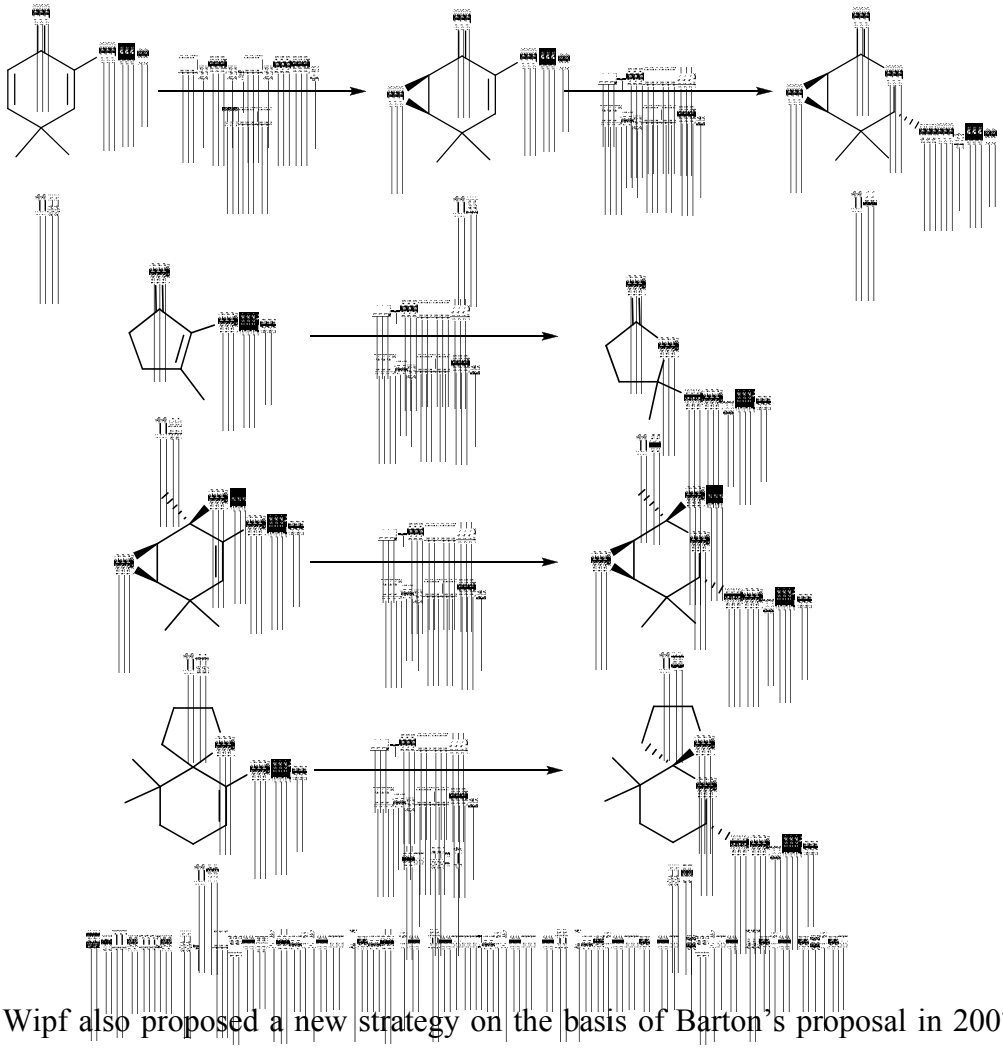
Figure 2. Proposed biosynthetic relationship among acutumine alkaloids

1.3 Biosynthesis

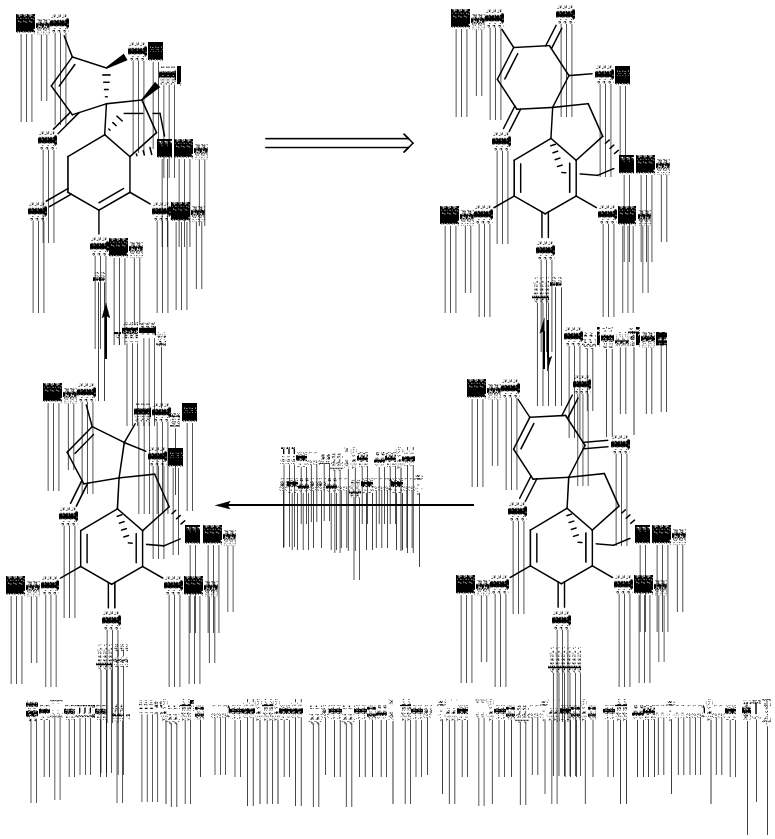
Barton and co-workers proposed an idea for the biosysnthesis of **1** in 1968,[12] in which spirodienone **8** (Scheme 1) undergoes a double epoxidation follow by a hydrolytic Favorskii-type rearrangement to furnish acutumine.



However, in 1984, Matoba and co-workers tested the diepoxidation on a simpler subsrate (Scheme 2).[13] They reported that *m*-CPBA can only provid monoepoxidation product while over-oxidation lead to unexpected Bayer-Villiger rearrangement. Wipf and co-workers confirmed this recently and proposed an oxidative rearrangement methodology of alkyl enol ethers to lactone and spiroketal ester based on this discovery (Scheme 2). [14]

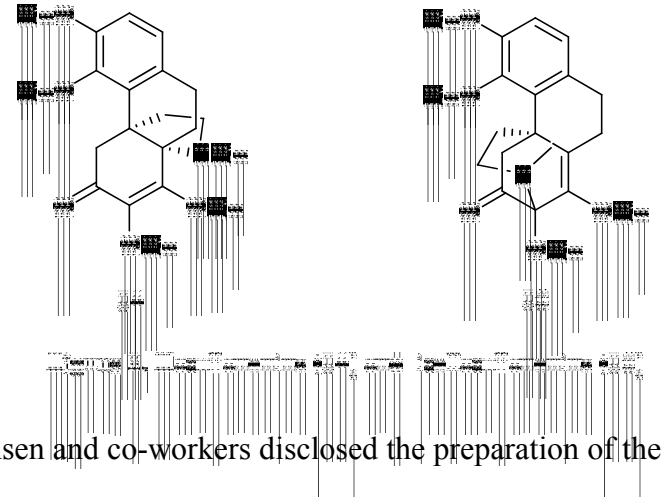


Wipf also proposed a new strategy on the basis of Barton's proposal in 2007, in which tricarbonyl tyrosine dimer **21** (Scheme 3) undergoes an oxidation and benzilic acid rearrangement, followed by decarboxylation to give the cyclopentanone subunit.

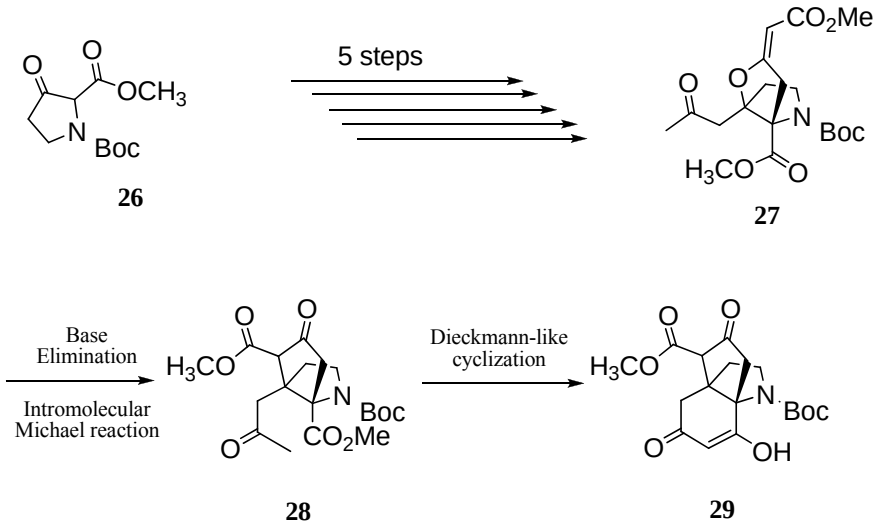


1.4 Total Synthesis

The chloride of acutumine resides in the cyclopentane ring along with three contiguous quaternary stereocenters, two of which are all carbon quaternary centers. Forming quaternary stereocenters is a major challenge in organic synthesis. Forming adjacent ones poses an even more significant hurdle because of the extreme steric hindrance. So this unique, chlorine-containing alkaloid has never been synthesized in the eighty years after its discovery. Several hasubanan alkaloid syntheses, which share the same propellane [4.4.3.0] core structure, have been reported by our group[15, 16] and Kobayashi[17] recently (Figure 3).



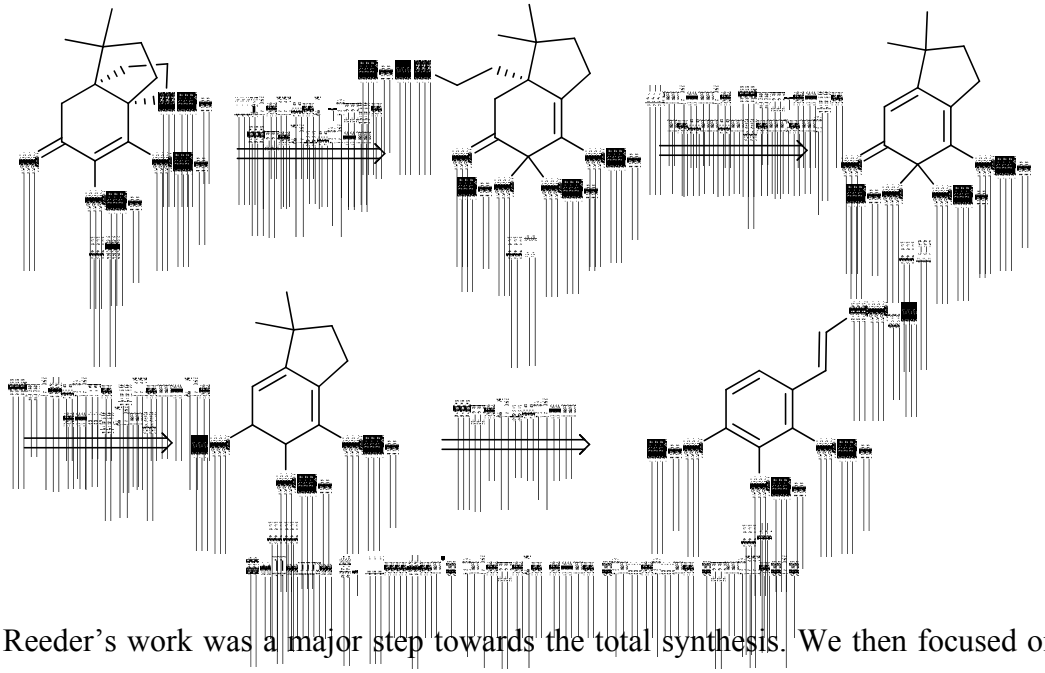
In 2007, Sorensen and co-workers disclosed the preparation of the propellane-like [4.3.3.0] fused tricyclic core of acutumine by a short synthesis, which consisted of a series of remarkable carbonyl chemistry reactions including intromolecular Michael reaction and Dieckmann-like cyclization (Scheme 4).[5] Despite this progress, a total synthesis has never been reported before 2009.



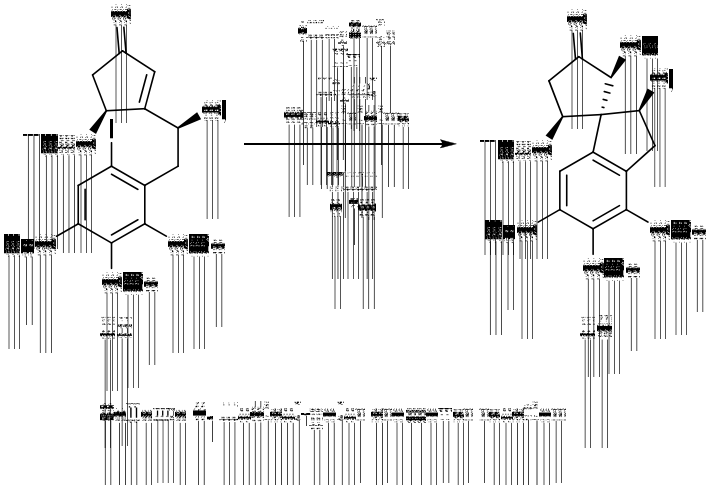
Scheme 4. Sorensen's synthesis of tricyclic core structure of Acutumine (**1**)

In 2005, Matthew D. Reeder in our group synthesized tricyclic compound **28**,[18] representative of the core of acutumine, in which he developed a strategy for the construction of an all-carbon quaternary center and an adjacent amine-bearing quaternary

carbon that relies on an anionic oxy-Cope rearrangement followed by a Lewis acid mediated Michael-type cyclization (Scheme 5).



Reeder's work was a major step towards the total synthesis. We then focused on developing a synthesis of the spirocycle core structure first and then applying Reeder's chemistry to the total synthesis. Key to our successful total synthesis was the novel radical-polar crossover reaction (Scheme 6).[19]



Details of our work applying this methodology to the total synthesis of acutumine will be provided in the following chapters.

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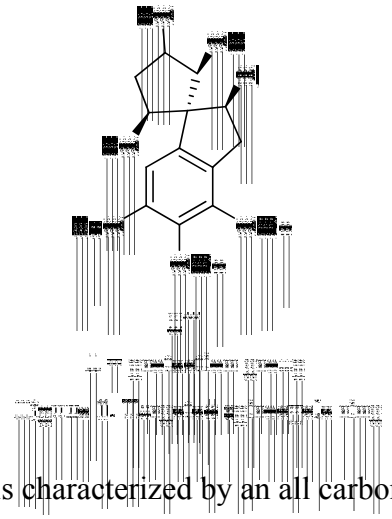
Chapter 2. Investigation of 5-*exo* Friedel-Crafts Cyclization onto An Epoxide

2.1 Targeted Spirocycle Ring

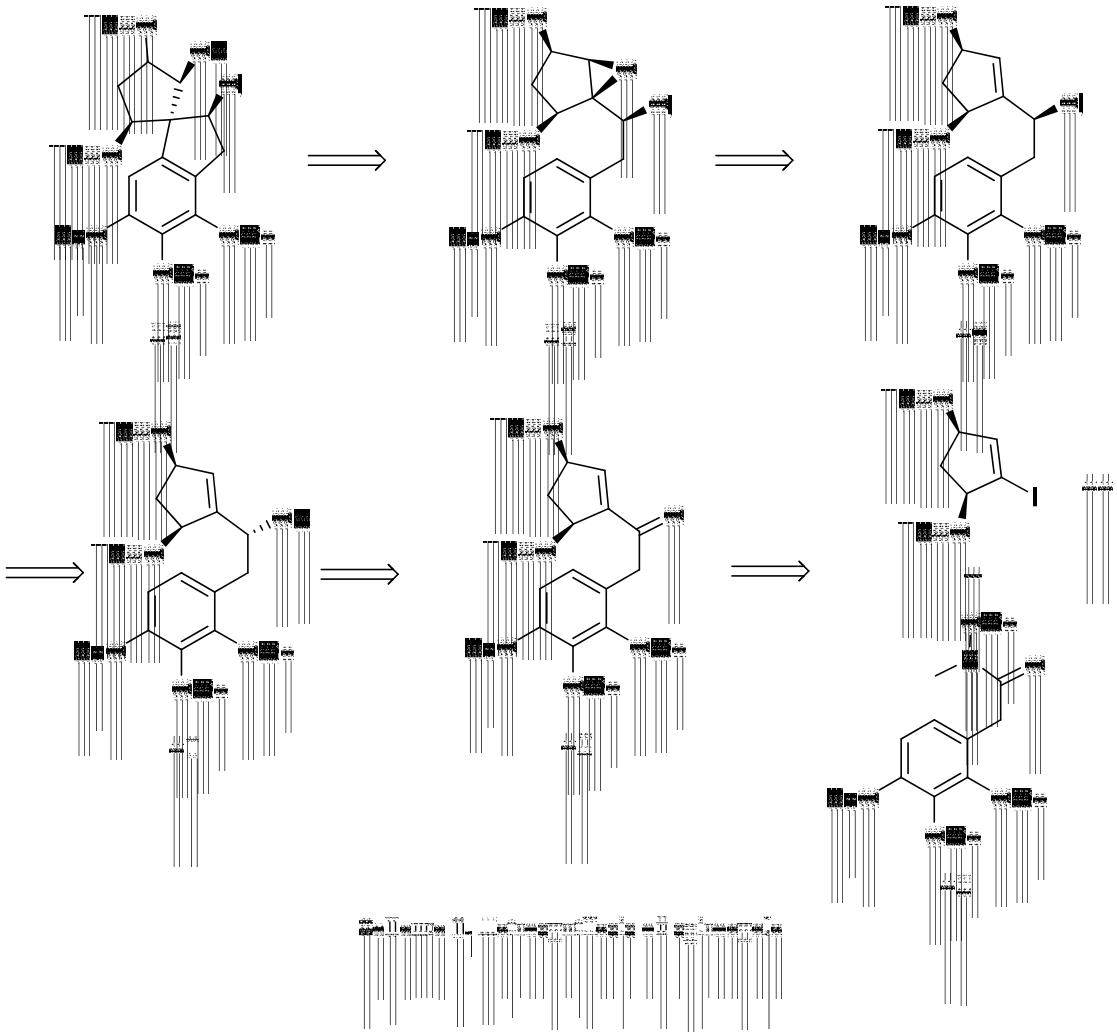
With the establishement of a route to the propellane-type core of acutumine by Reeder et al,[1] we needed to construct a spirocyclic substrate to test this strategy in the total synthesis (Figure 1). My work on the project began at this point.



The fused spirocycle is characterized by an all carbon quaternary stereocenter and a neopentylic secondary chloride. As mentioned in the introduction, building an all carbon quaternary stereocenter is still a big challenge in synthetic chemistry. Moreover, the stability of the chloride is another concern.

2.2 Retrosynthesis

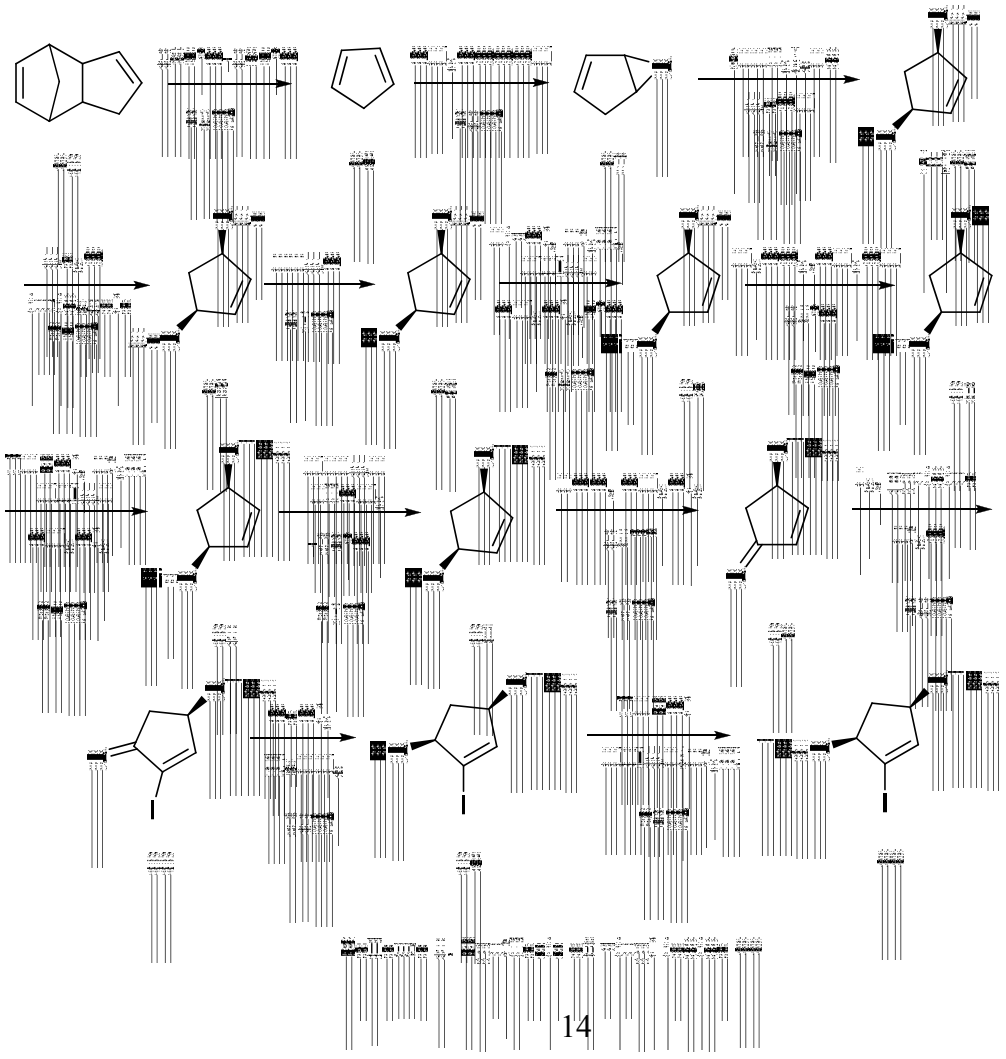
Our first retrosynthesis of the acutumine spirocycle is outlined in Scheme 1. Exposure of epoxide **39** to Lewis acids or Brønsted acids should result in formation of the desired spirocycle **38** via regioselective 5-*exo* Friedel-Crafts cyclization.[2] Sharpless epoxidation of allyl chloride **40** could afford epoxide **39** directly. Allyl alcohol **41** could be provided after coupling with Weinreb amide **43** and vinyl iodide **44** followed by stereoselective reduction of **42**. Though we realized the stability of the chloride in subsequent reactions might be a challenging problem, we hoped that the neighboring quaternary carbon center would shield this sensitive group from undesired reactions. Also, we hoped to obtain data about the stability of alkyl chlorides in various reactions.



2.3 Synthesis of Vinyl Iodide 44

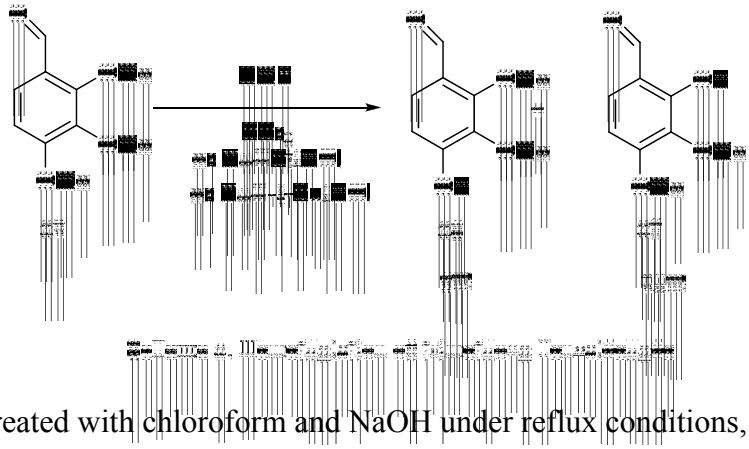
In order to achieve our total synthesis, as outlined in Scheme 1, we needed to prepare coupling partners **43** and **44**. To obtain enantiopure vinyl iodide **44**, we started from dicyclopentadiene **45** and followed the procedure of Deardoff and co-workers.[3, 4] Dicyclopentadiene is a white solid at room temperature, but it could be melted at 32 ºC and broken down to cyclopentadiene **46** through a retro Diels-Alder reaction when heated over 240 ºC. Cyclopentadiene **46** readily dimerizes to form its precursor **45** at room

temperature. So, the following epoxidation was conducted quickly to provide stable epoxide **47**. Treatment of **47** with tetrakis(triphenylphosphine)palladium afforded racemic *cis*-monoacetate **48**.[3] Enantiopure **48** would be obtained following acetylation and electric eel acetylcholinesterase (EEAC) mediated desymmetrization.[4] The exchange of protecting group from **48** to **51** was previously reported by Myers.[5] Conversion of **51** to **54** also followed Myers' strategy. Subsequent α-iodination and Luche reduction[6] of **54** gave **56** and followed the approach reported for different substrates by Johnson.[7] Silylation of **56** afforded enantiomerically pure vinyl iodide **44**.

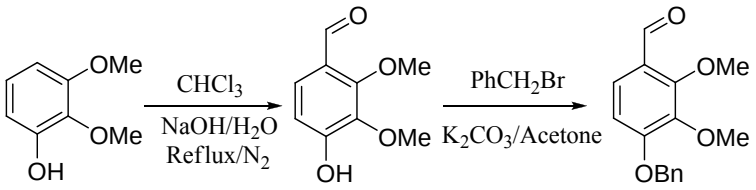


2.4 Synthesis of Weinreb amide 43

To obtain the Weinreb amide **43**, 4-hydroxy- 2,3-dimethoxybenzaldehyde **58** was chosen as the starting material. However, it is difficult to produce this benzaldehyde efficiently and conveniently. Initially, the demethoxylation of 2,3,4-trimethoxyaldehyde **57** (Scheme 3) was tested. At this stage, two selective demethylation reagents were investigated (BBr_3 and NaSEt). Unfortunately, we obtained the undesired regiosisomer **59** as the major product. NaS-*t*-Bu was also evalutated as the demethylation reagent. Some of the desired isomer **58** was formed. The ratio between **58** and **59** was 1:9-1:10. Obviously this was not synthetically useful.

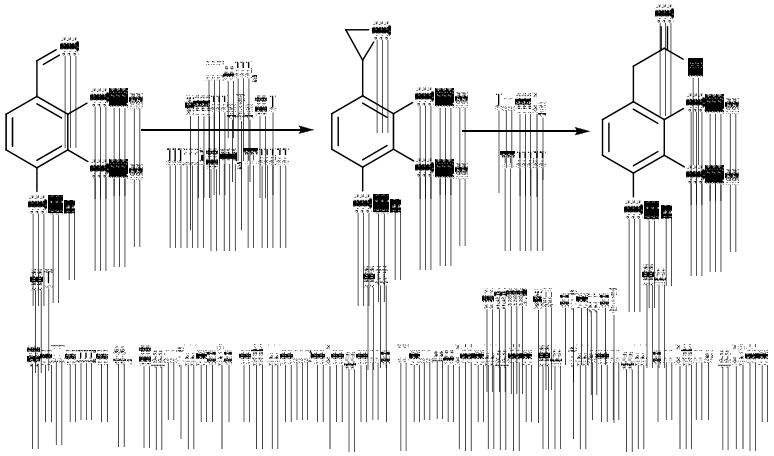


When treated with chloroform and NaOH under reflux conditions, 2,3-dimethoxybenzaldehyde **60** can be converted to **58.**[8] Though the yield is poor and not very reproducible (15-30%), it was the best way I found to make the benzaldehyde. Compound **61** could be formed in 37% (in two steps from **60**) by treating compound **58** with benzylbromide (Scheme 4).

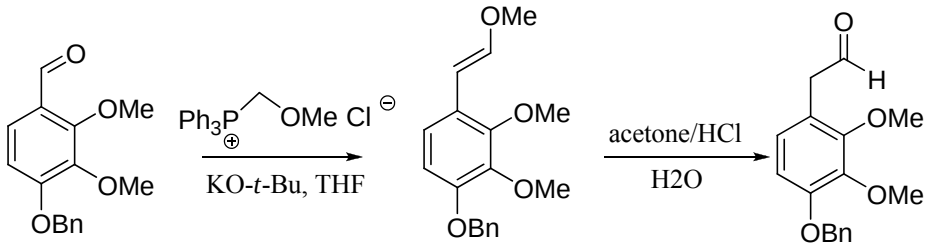


Scheme 4. Synthesis of benzaldehyde **61**

With **61** in hand, two protocols were investigated for converting **61** to **63**; the first of which involved formation of epoxide **62** followed by indium-chloride promoted rearrangement (Scheme 5). [9]



The second approach involved Wittig reaction of aldehyde **61** to give enol ether **64**, followed by hydrolysis to give **63**. [10, 11] Eventually, this route was chosen because it was more convenient and offered higher yields (Scheme 6).

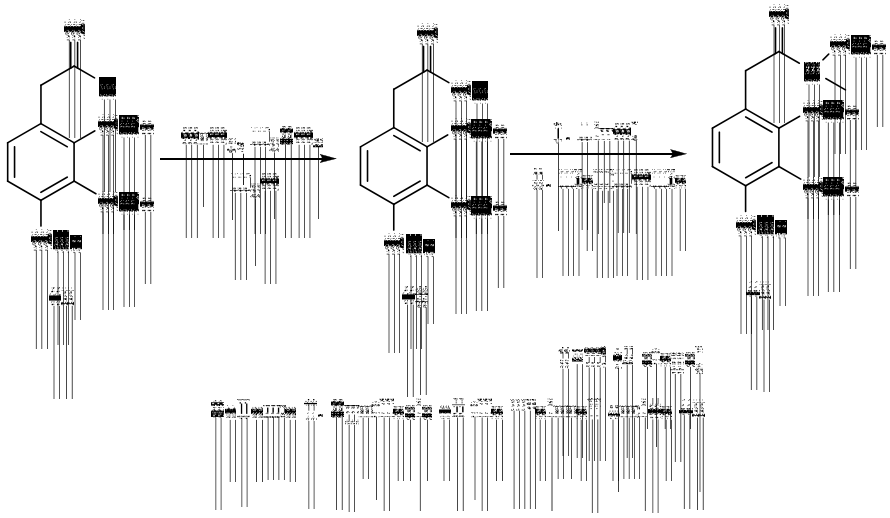


61 **64** **63**

75% (2 steps)

Scheme 6. Synthesis of homologous benzaldehyde **63** through Wittig reaction

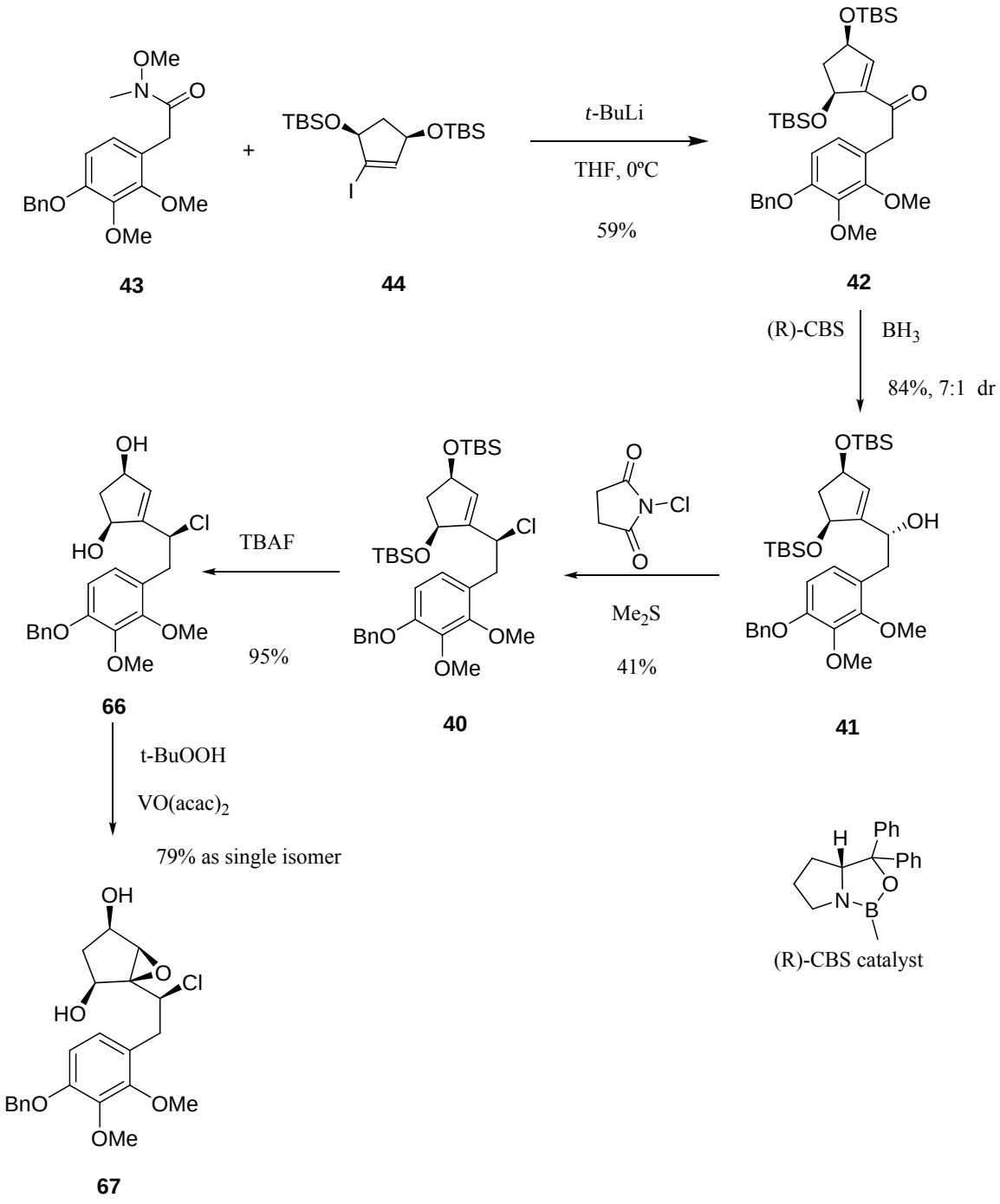
Conversion of **63** to **65** via Jones oxidation[12] followed by amidation of an intermediate mixed anhydride gave Weinreb amide **43** in 78% yield (Scheme 7).[13]



2.5 Coupling and Synthesis of Epoxide 67

With coupling partners **43** and **44** in hand, different coupling conditions including *n*-BuLi, *t*-BuLi, PhLi and CH_3MgBr were evaluated.[14] As it turned out, t-BuLi gave the best yield though it is very sensitive to moisture (Scheme 8). Stereoselective reduction of **42** has been performed by three kinds of catalyst: CBS (Corey-Bakshi-Shibata),[15] BINAL-H.[16, 17] and Tsdpen reduction.[18] The best yield is from CBS with 90% yield and 57% de, while BINAL-H provided 80% yield and 48% de; Tsdpen provided 59% yield

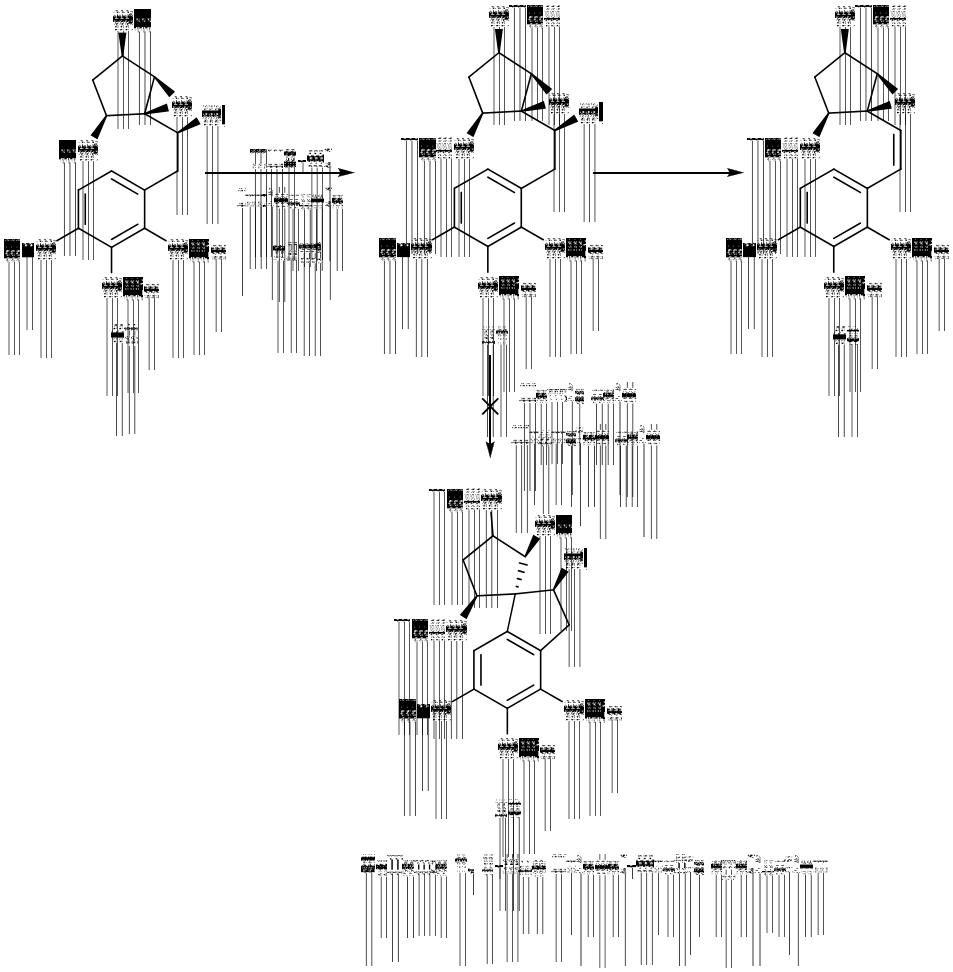
and 51% de. The configuration of the newly formed stereocenter of **41** was assigned by Mosher's method using R-MTPA.[19] The hydroxyl group of **41** was replaced by chlorine via treatment with NCS/$(CH_3)_2S$ to give **40**.[20] Both silyl ether groups were removed by TBAF to give **66**. The alcohol-directed epoxidation[21] was performed under Sharpless conditions with high yields and diastereoselectivity.



Scheme 8 Coupling and synthesis of epoxide **67**

2.6 5-*exo* Friedel-Crafts Cyclization

After protection of the secdondary hydroxyls of **67**, we attempted to install the spirocyclic quarternary center via a Lewis Acid promoted 5-*exo* cyclization (Scheme 9). Unfortunately, no matter what Lewis or Brønsted acid we used, no desired compound **38** was formed. Instead, the chloride elimination product **68** was obtained**.** It is obvious that the elimination product is stabilized by conjugation with the aromatic ring and this stabilization makes the secondary chloride too fragile to survive the epoxide opening conditions. As a result, we were forced to develop a new strategy.



2.7 References

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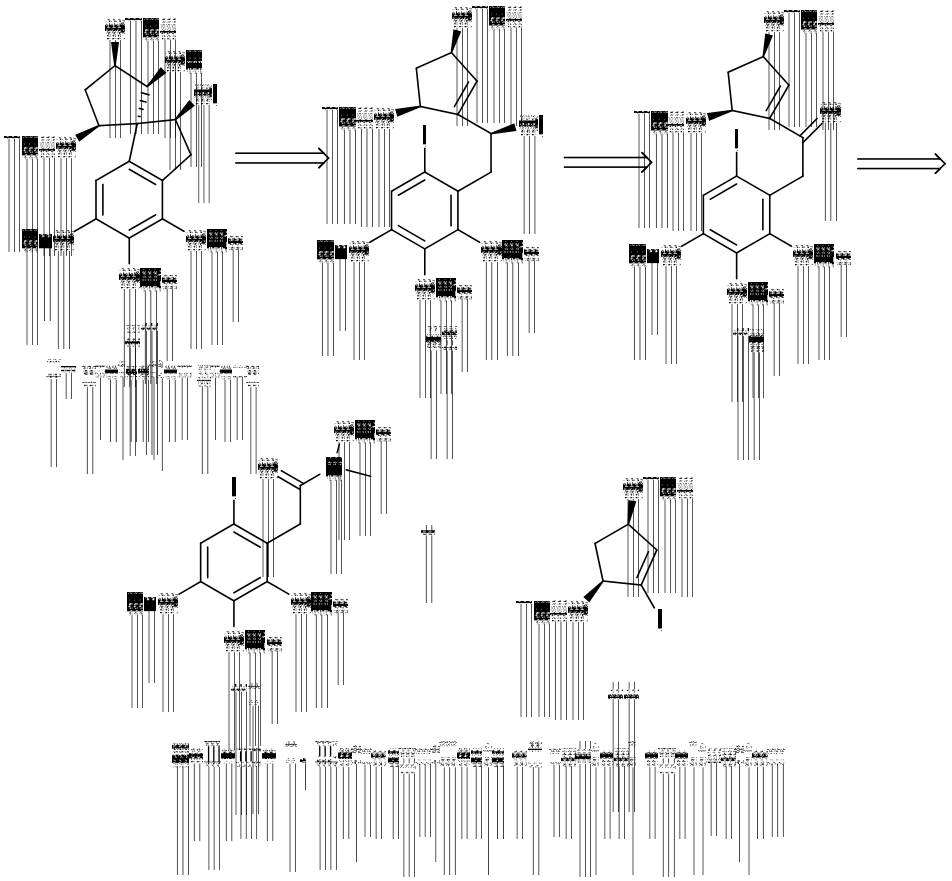
Chapter 3. Radical Cyclization Route to the Spirocycle of Acutumine

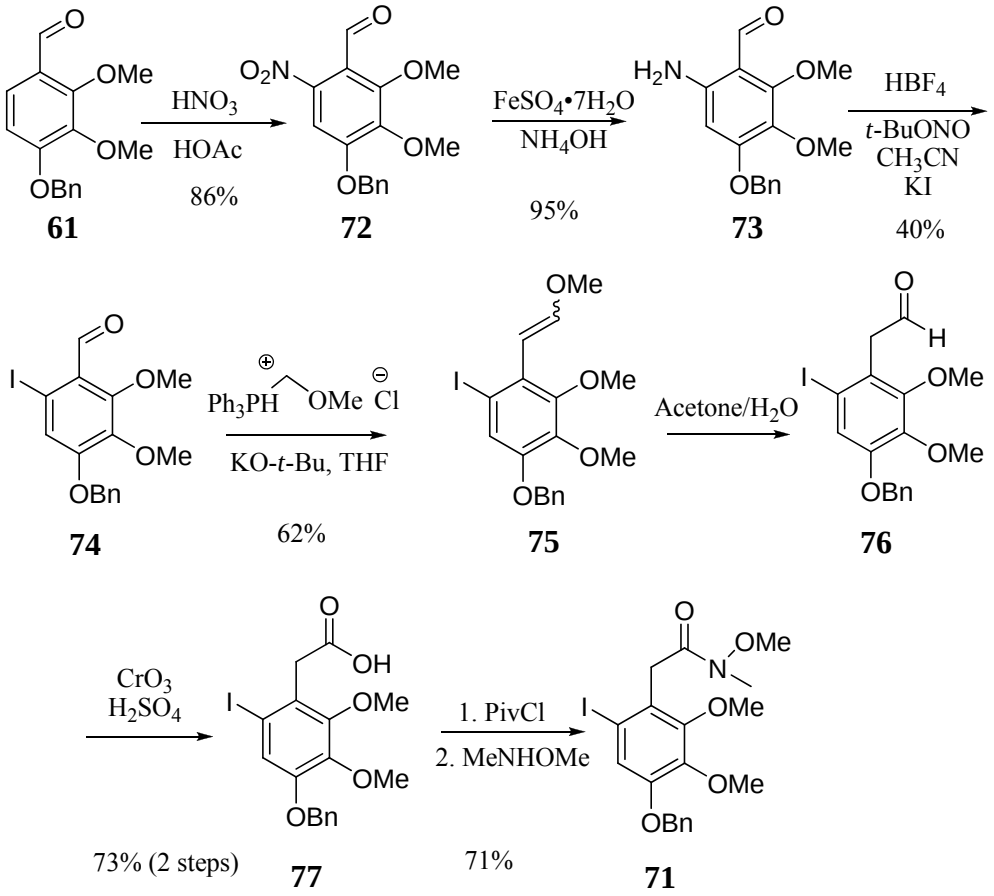
3.1 Retrosynthesis of Radical Cyclization Route

The failed Friedel-Crafts cyclization suggested that the secondary chloride might be too fragile to withstand exposure to Lewis and Brønsted acids. Thus a new cyclization strategy was employed. Radical cyclization has shown the strong potency to construct quaternary carbons,[1] so a 5-*exo*-trig radical cyclization strategy was devised to construct the spirocycle (Scheme 1).



3.2 Synthesis of Iodinated Weinreb Amide 71

To obtain the proper substrate for the radical cyclization, a similar strategy to the one shown in Chapter 2 was used to prepare coupling partner **71**, though a few extra steps to install the iodine atom were required (Scheme 2). Benzaldehyde **61** was nitrated in the ortho position to give **72**, and subsequent reduction and iodination afford iodinated benzaldehyde **74**. Though the yield for the iodination was not high, it was the only workable iodination strategy, which had been determined by Jones in his hasubanonine synthesis.[2] Weinreb amide **71** was then synthesized according to the same route depicted in Chapter 2.

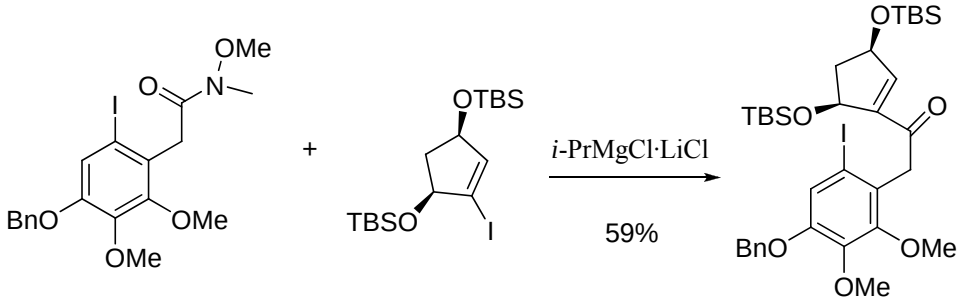


Scheme 2. Synthesis of iodinated Weinreb amide **71**

3.3 Coupling of the Weinreb Amide and Vinyl Iodide

The attempted coupling of iodinated Weinreb amide **71** with vinyl iodide **44** give low yields. Though this coupling reaction is almost the same as the one utilized in the chemistry discussed in Chapter 2, I obtained very low yields with the same conditions. The iodine atom was apprently cleaved by the organolithium reagent. When we switched to a Grignard reagent, the rich electron density of the cyclopentene ring decreased the I/Mg-exchange rate (only 5% vinlymagnisum formed in 7 days at room temperature).

Knochel and co-workers have reported that increased electron density slows halogen-magnesium exchange.[3] Knochel also reported that by adding lithium chloride, the reaction rate can be dramatically increased. This technique also worked in our case. When adding lithium chloride as additive and 15-crown-5 as the coordinating reagent, the I/Mg exchange and the coupling could be finished in one day (Scheme 3).[4, 5]

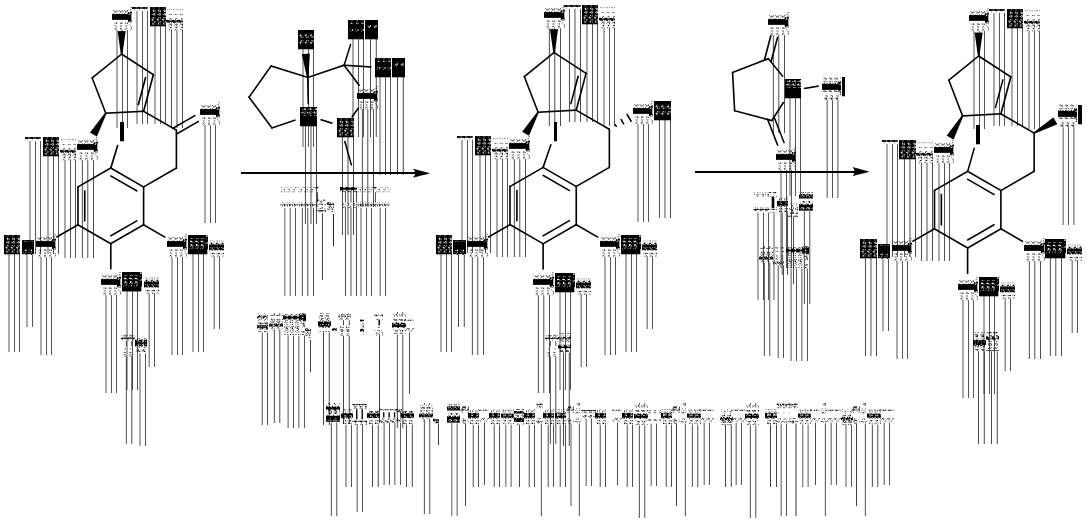


71 **44** **70**

Scheme 3. Grignard reagent promoted coupling reaction

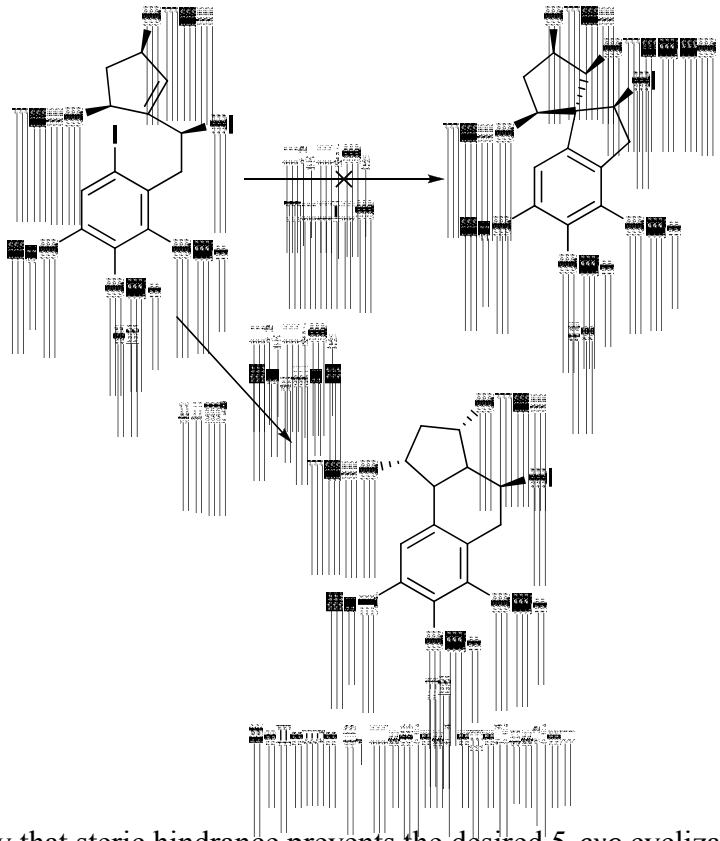
3.4 Stereoselective Reduction and Chlorination

Under the same conditions as those shown in Chapter 2, iodinated enone **70** was reduced diastereoselectively and the formed hydroxyl group of **78** was substituted by chlorine under Corey's conditions (Scheme 4).[6] By adjusting the equivalents of substrate, oxazaborolidine, and boron hydride (1: 0.2: 1.2), we improved the yield (84%) and de (87%) of the reduction. The chlorination yield was low, but we did not improve it because at this stage the goal was to get enough substrate to test our new cyclization strategy.



3.5 Radical Cyclization

To trigger the radical cyclization, different initiators were examined. To our surprise, treatment of **69** with Et_3B/O_2 and Bu_3SnH[7] afforded 6-*endo* cyclization product **79** instead of 5-*exo*. When TEMPO[8] was used in place of Bu_3SnH, no cyclization product **80** was detected (Scheme 5).



It is likely that steric hindrance prevents the desired 5-*exo* cyclization. Nevertheless, we are happy to find the fact that the sensitive allylic chloride could survive a radical reaction, which inspired us to test the radical-polar crossover reaction.

3.6 References

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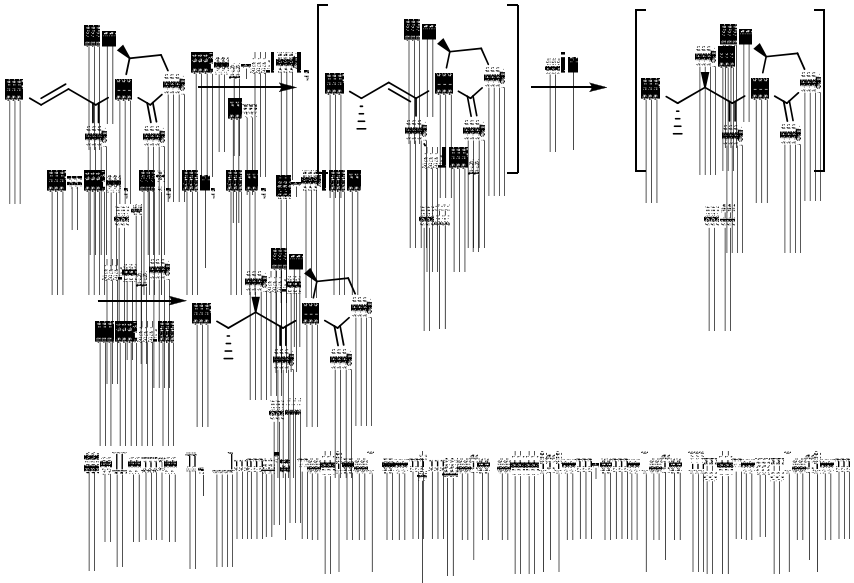
Chapter 4. Radical-Polar Cyclization and the Total synthesis of Acutumine

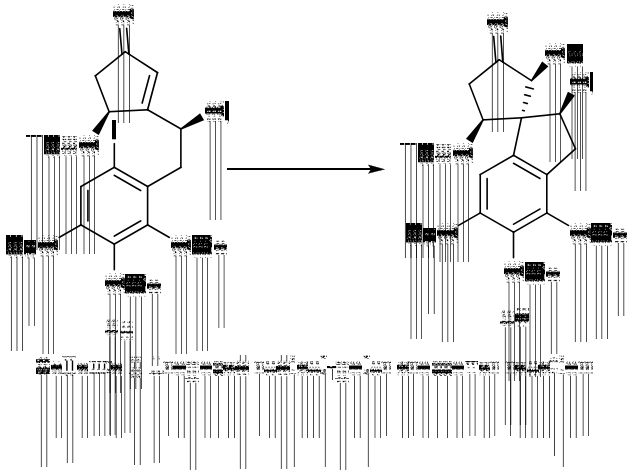
4.1 Background of Radical-Polar Crossover Reaction

In the last thirty years, radical chemistry has received increasing attention from synthetic chemists.[1, 2] The term radical-polar crossover reaction was introduced by Murphy in 1993[3] to describe cascade processes which transition from radical to polar chemistry. These processes can be called cascade radical/ionic reactions.[1, 2] Numerous radical-polar crossover reactions involve radical conjugate addition to an α,β-unstaturated carbonyl group, then formation of an enolate from an α-carbonyl radical. The latter step also helps to propagate the chain process, with the enolate eventually attacking an electrophile. The earliest example, reported by Oshima and coworkers in 1988, is the intermolecular radical conjugate addition and aldol reactions.[4, 5] Though the potential utility of these reactions are great, there are few examples reported in natural product synthesis. Kunz and co-workers reported a tandem radical conjugate addition-enolate hydroxylation in 1991 to install two adjacent stereocenters in one step, one of which is a secondary alcohol (Scheme 1).



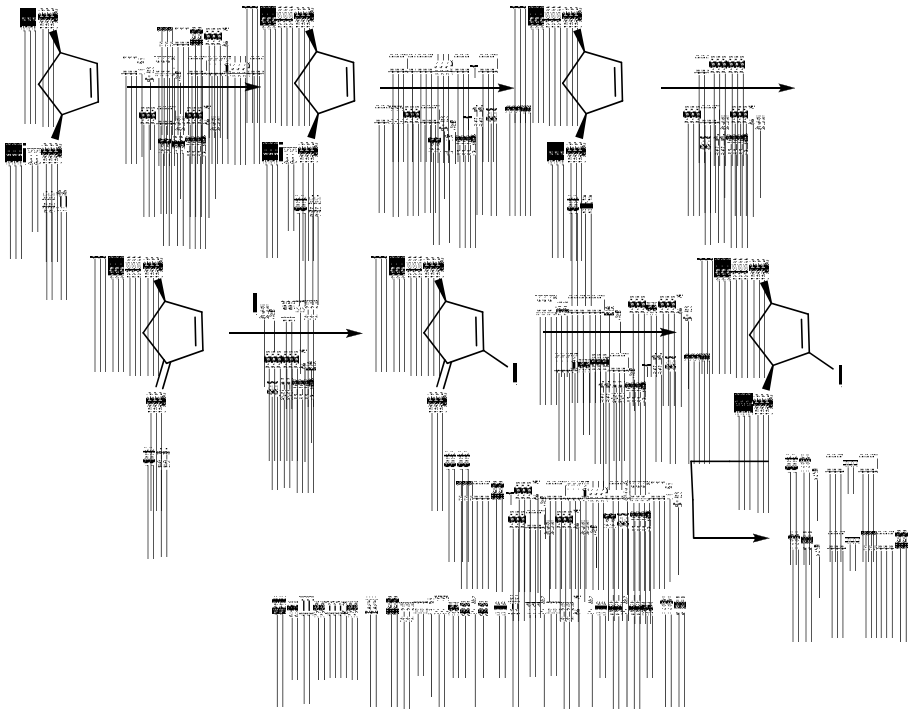
4.2 Proposed Radical-Polar Crossover Reaction on Our Substrate

As we revised our route to the acutumine spirocycle, we realized that enone **35** (Scheme 2) would be a suitable substrate for this radical-polar crossover reaction. We need to construct two stereocenters, which include a secondary alcohol and a quaternary carbon. Furthermore, we also need to cyclize to a spirocycle without disturbing the allylic chloride.



4.3 Synthesis of Vinyl Iodide 90

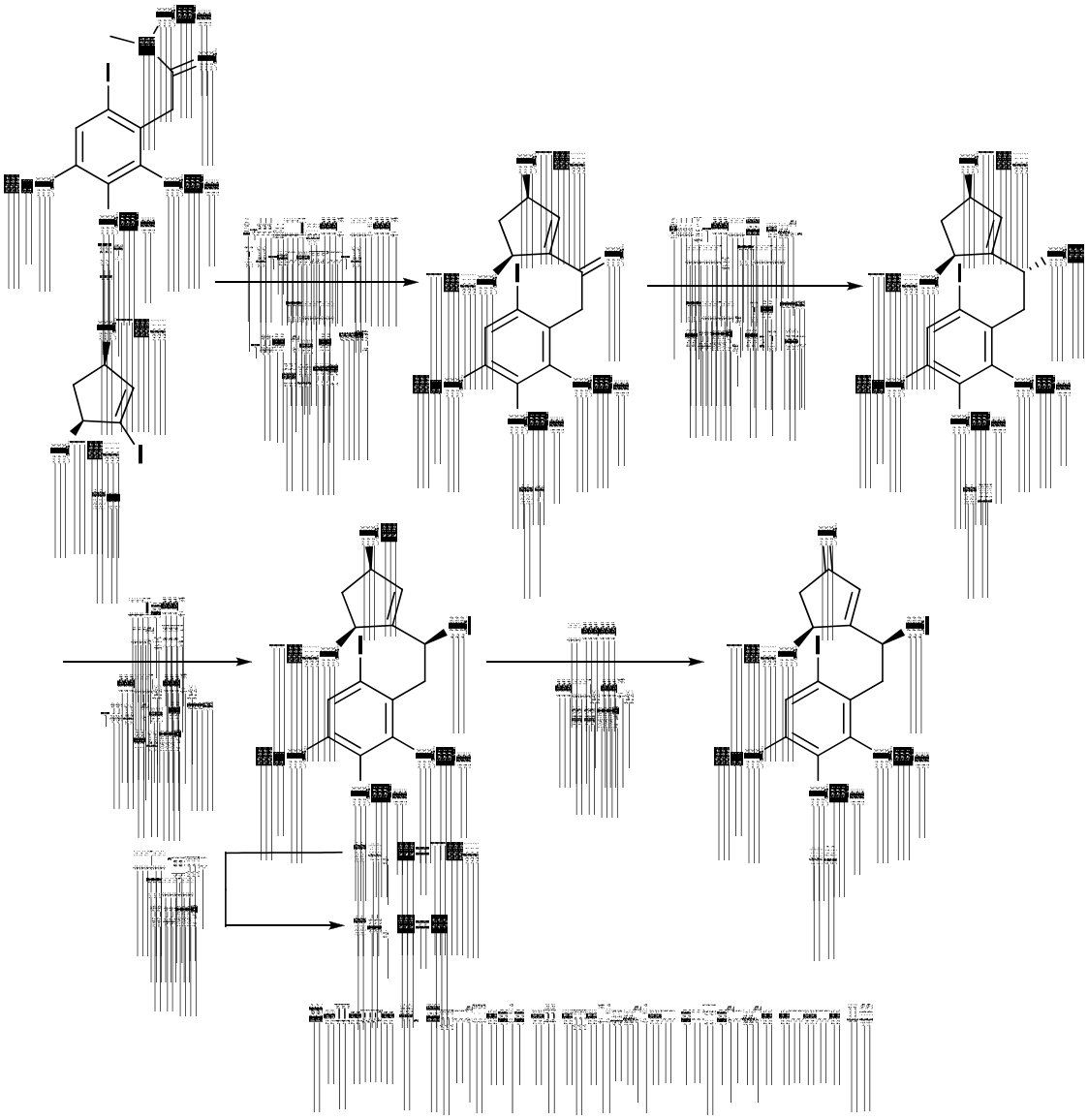
To obtain substrate **35**, we employed a similar strategy to the one used previously (Chapter 3). Vinyl iodide **90** was made according to the same procedures by Deardoff, [6, 7] though the two alcohols were differentiated by protecting with different silyl groups (Scheme 3).



4.4 Synthesis of Cyclization Substrate Enone 35

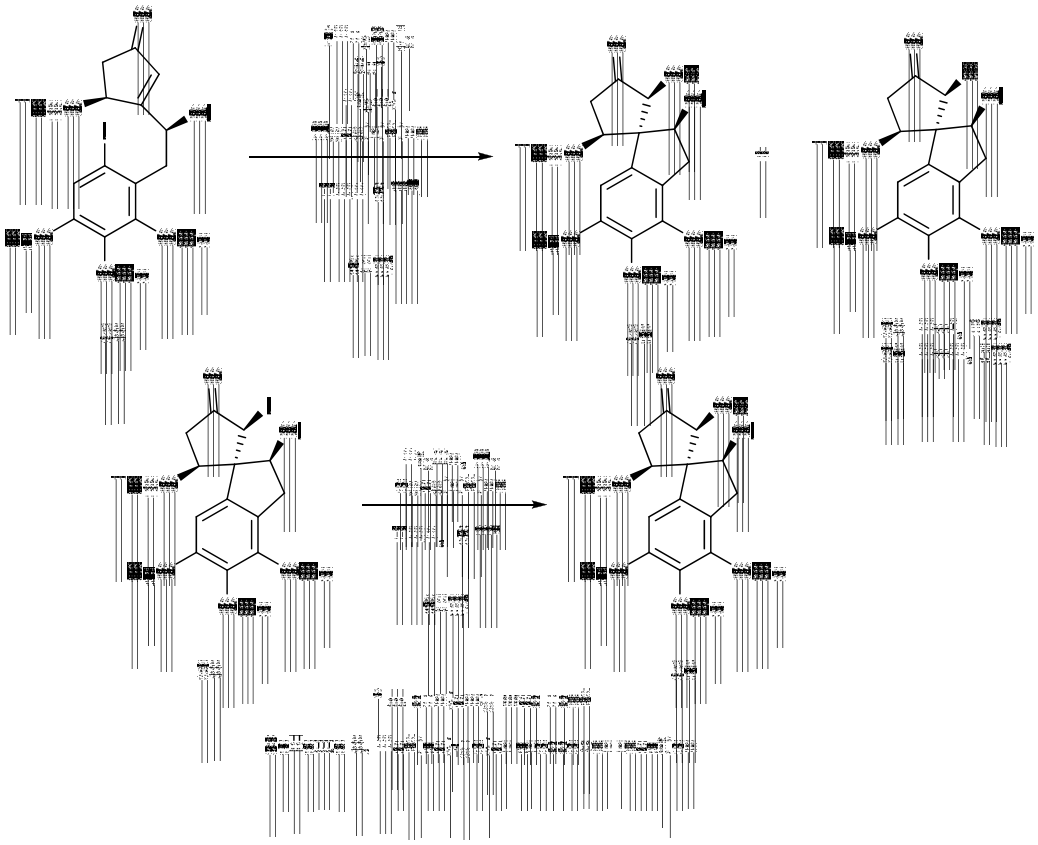
By applying the optimized reaction conditions from Chapter 3, coupling of iodinated Weinreb **71** and vinyl iodide **90** afforded enone **91**, which was stereoselectively reduced to allyl alcohol **92**. As mentioned in Chapter 3, chlorination under Corey's conditions[8] provided low yields. Consequently, different conditions to install the sensitive chloride were investigated. Most of them, such as MsCl/LiCl/collidine, provided

elimination products. Williams and co-workers met similar problems when synthesizing Stephacidins A, B and Notoamide B.[9] They solved the problem by switching to MsCl/TEA, which also worked in our case. The TES group of **93** was selectively cleaved in the presence of the TBS group, and subsequent oxidation afforded enone **35** directly.



4.5 Radical-Polar Crossover Reaction onto Spirocycle

To initiate the radical reaction (Scheme 5), we tried different initiators and found that Et_3B and Et_2Zn bring lower yields than Et_3Al. Different enolate hydroxylation reagents and different temperatures were also tested (Table 1).



entry	Reagent (equiv)	Oxidant (equiv)	Solvent	**36/95/96** (%)
1	Et_3B (1)	O_2	THF	21/20/19
2	Et_3B (1)	DMDO (10)	THF	16/18/24
3	Et_2Zn (4)	O_2	THF	28/23/5
4	Et_2Zn (4)	DMDO (10)	THF	20/18/3
5	Et_2Zn (4)	Oxaziridine* (4)	THF	29/27/17
6	Et_3Al (1)	O_2	THF	33/22/19
7	Et_3Al (1)	DMDO (10)	THF	25/11/9
8	**Et_3Al (3)**	**Oxaziridine* (5)**	**THF**	**62/7/3**
9	Et_3Al (3)	t-BuOOH (5)	THF	34/3/27
10	Et_3Al (3)	$(Me_3SiO)_2$	THF	12/-/-
11	Et_3Al (3)	Oxaziridine* (5)	CH_2Cl_2	42/11/3
12	Et_3Al (3)	Oxaziridine* (5)	$PhCF_3$	40/9/13
13	Et_3Al (3)	Oxaziridine* (5)	THF/PhH 1:1	47/10/5
14	Et_3Al (1)	Oxaziridine* (5)	THF	9/4/-
15	Et_3Al (5)	Oxaziridine* (10)	THF	45/6/4

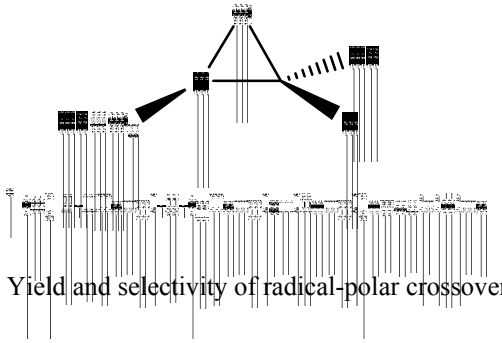
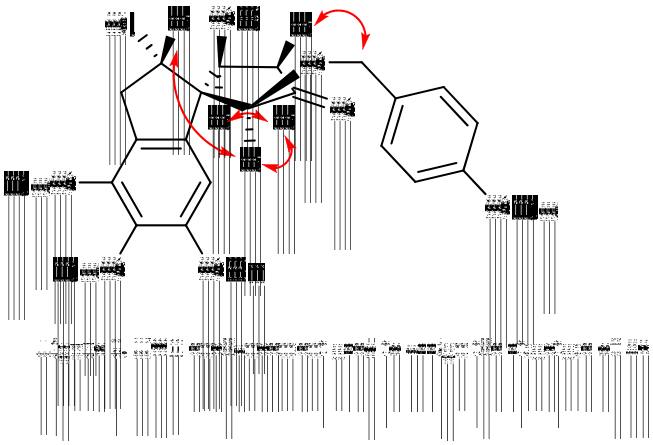


Table 1. Yield and selectivity of radical-polar crossover reaction

As shown in Table 1, entry 8 leads to the highest yield. In most cases, iodide **95** and reduced compound **96** were also formed, whereas **96** might come from reduction of α-keto radical or enolate. The origin of **95** is not certain yet. The α-keto radical intermediate might be attacked by I· or I_2, both of which come from photolytic cleavage of aryl Iodide (vide infra). Another possibility is that the α-keto radical or enolate reacts with Bu_3SnI, which is formed by abstraction from vinyl iodide **90** by tributyltin radical. To improve the yield of this reaction, we tried to explore the possibility for converting iodide **95** into the desired product **36**. We were delighted to find that this transformation could be accomplished under similar condition. Et_2Zn/O_2, together with the oxaziridine, provided 62% yield, compared to the lower yield (40%) of Et_3Al in this reaction. The material obtained from **95** via this route raised our overall yield of **36** to 66%.

The stereochemistry of **36** was assigned according to NOE experiments on a *p*-methoxybenzyl ether derivative. The diagnostic correlations are illustrated in Figure 1, and the assignment has been confirmed by the accomplishment of the total synthesis of (-)-**1** from **36.**



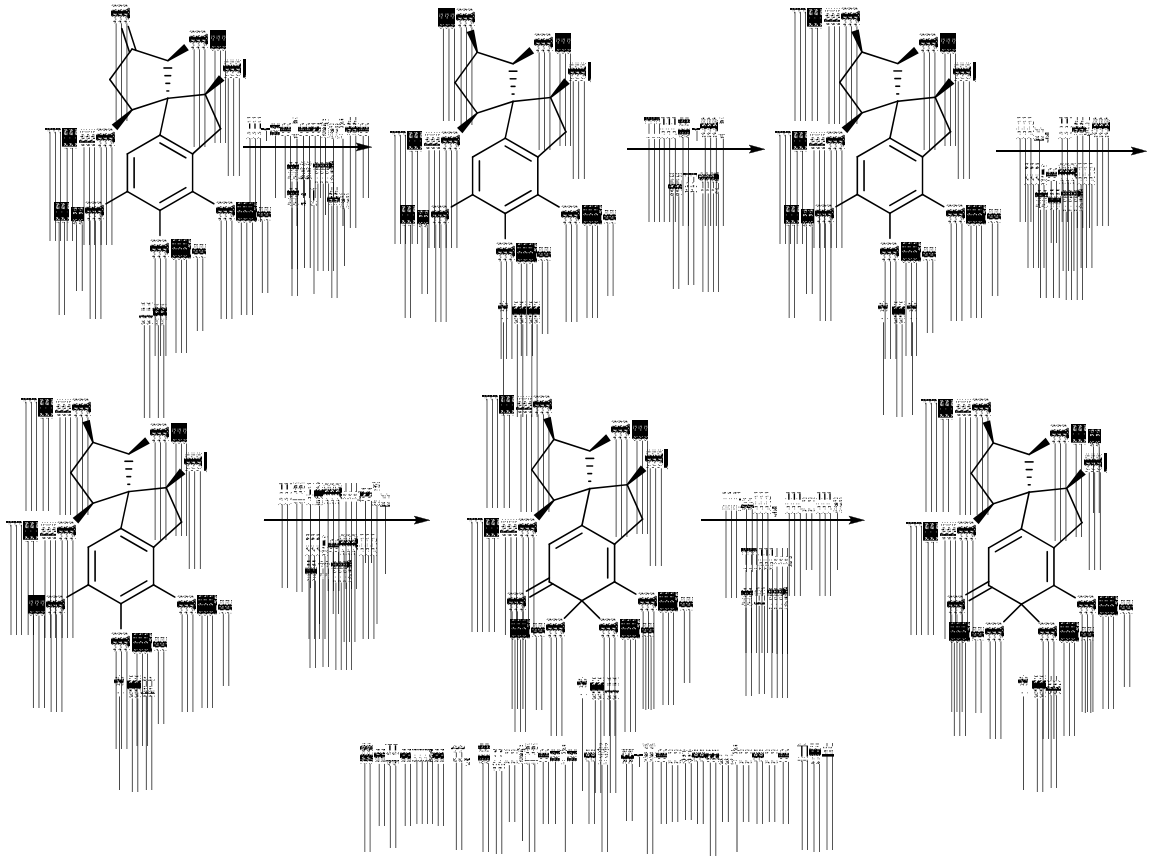
Its interesting that no diastereomers of **36**, **95**, and **96** were found in this reaction. Though the detailed mechanism of this reaction will require further study, we propose the following mechanism (Scheme 6). The enone subunit of **35** works as a sensitizer by absorbing visible light and transferring energy to the ditin reagent, facilitating its homolytic cleavage. The iodide was abstracted to form an aryl radical and undergo a 5-*exo*-trig cyclization. The aryl radical attacked the enone from the face opposite the bulky adjacent OTBS group. After formation of the spirocycle, the aromatic ring could shield one face of the enolate, causing a stereoselective hydroxylation to produce the desired diastereomer.

We also tried SmI_2/HMPA as radical initiator to generate the aryl radical. Unforturnately, α-hydroxy ketone **36** was obtained in low yields as 15%. Compounds **95**,

96 and other uncharacterized byproducts were also present. This is likely a result of several functional groups' reactivity with SmI_2, such as the enone and allylic chloride.

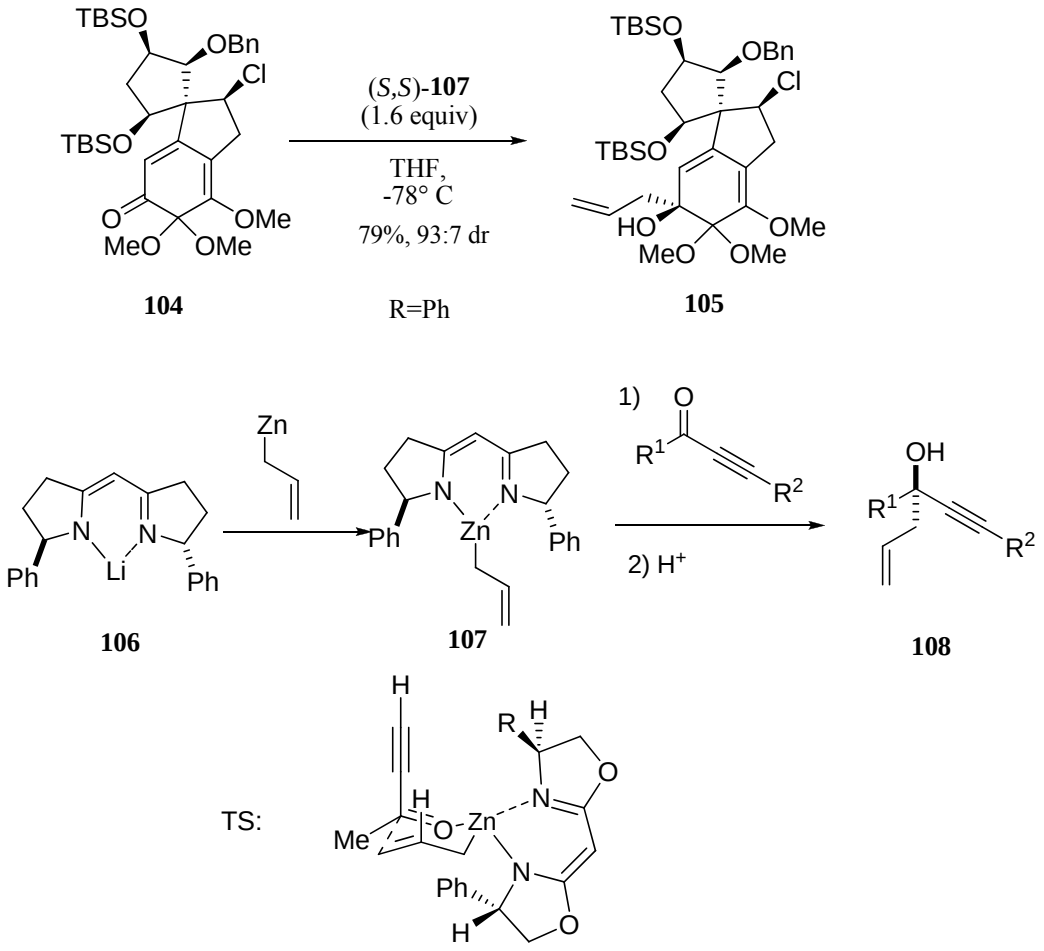
4.6 Synthesis of Masked *o*-Benzoquinone 104

To proceed with the total synthesis, α-hydroxy ketone **36** was selectively reduced to give diol **100**. Different reducing agents were evalutated and L-selectride afforded the largest ratio of diastereoisomers (9:1), while $NaBH_4$ only provided the products as a 1:1 mixture. Though the newly formed stereocenter would be destroyed in a later step, L-selectride was employed for the convenience in separating and characterization. The less hindered alcohol of **100** was selectively protected as a TBS ether and following hydrogenolysis cleaved the benzyl ether bond to form phenol **101**. After removal of the benzyl group by H_2, phenolic oxidation of **102** provided masked o-benzoquinone **103**, and the remaining alcohol was protected as a benzyl ether.



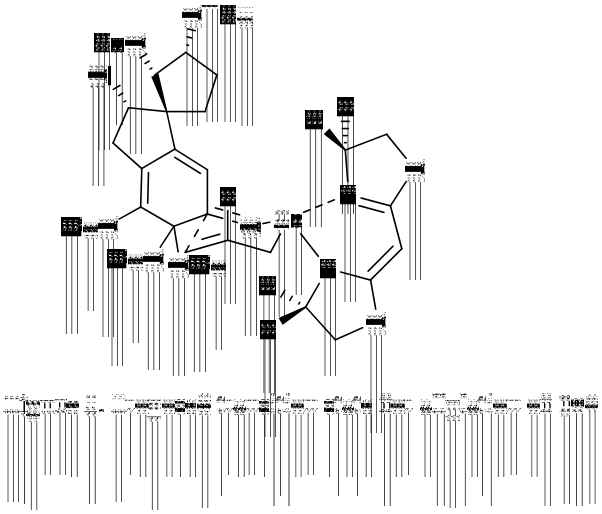
4.7 Stereoselective Allylation

Stereoselective 1,2-addition to the ketone of **104** was accomplished with a bisoxazoline ligated chiral allylzinc reagent by means of allylmagnesium chloride in 59% yield (Scheme 8). This reagent was developed for stereoselective allylation of alkynyl ketones by Nakamura in 1998,[10] and it has proven highly selective in the synthesis of isohasbanan alkaloids in our lab, in which the substrates share the same cyclopentenone subunit as acutumine. We obtained a 79% yield and 93:7 dr.



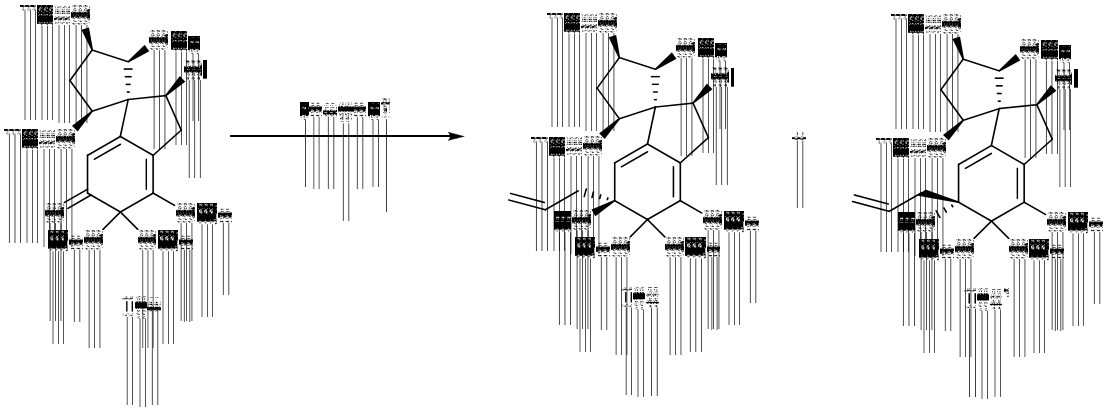
Scheme 8. Stereoselective allyl addition.

Although[9] a stoichiometric amount (1.6 equiv) of this reagent was required in this reaction, we were able to recover almost half of the chiral bisoxazoline ligand. The newly formed stereocenter was assigned according to the six-membered cyclic transition state for the asymmetric ketone allylation reported by Nakamura and co-workers(Figure 2).[10]



4.8 Exploration of Nakamura Reagent Allylation

To explore the reagent-directed stereocontrol ability of the Nakamura reagent, we also tried allylmagnesium bromide and *(R,R)*-**110** allylation as control. As depicted in Table 2, allylmagnesium bromide only afforded a 70:30 mixture of **105** and its diastereomer **105'** (entry 2), which confirmed that there is some substrate-directed stereocontrol in this reaction. When using (*R,R*)-**110**, this substrate control was overcome by reagent control to provide product with 13:87 ratio. Though the Nakamura reagent has been seldom used in organic synthesis from its discovery, its exciting performance in acutumine and isohasubanan alkaloids synthesis demonstrated that it not limited to alkynyl ketones for which it was designed.



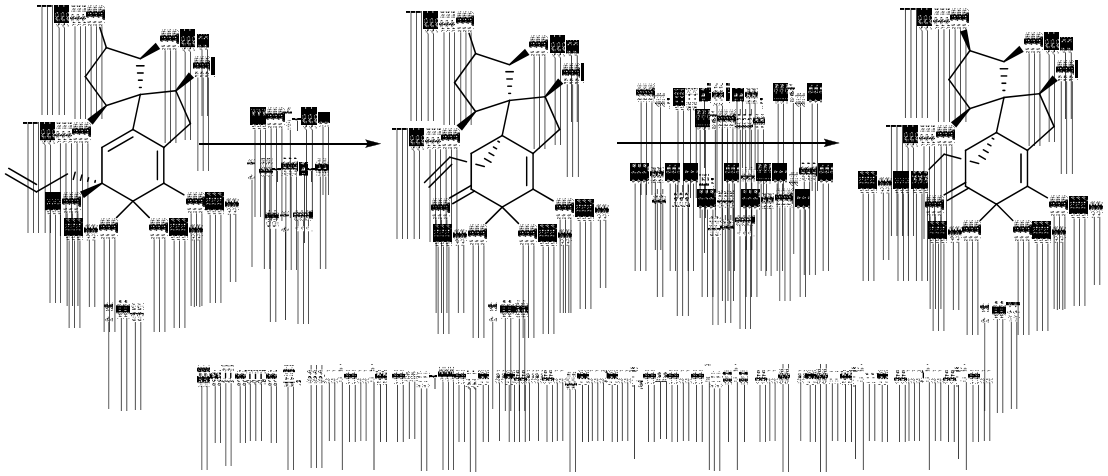
entry	*reagent*	*yield*	*105:105'*
1	(*S,S*)-**107**	79	93:7
2	allyMgBr	88	70:30
3	(*R,R*)-**107**	69	13:87

Table 2. Allylation of Ketone **104**

4.9 Anionic Oxy-Cope Rearrangement, Ozonolysis and Reductive Amination

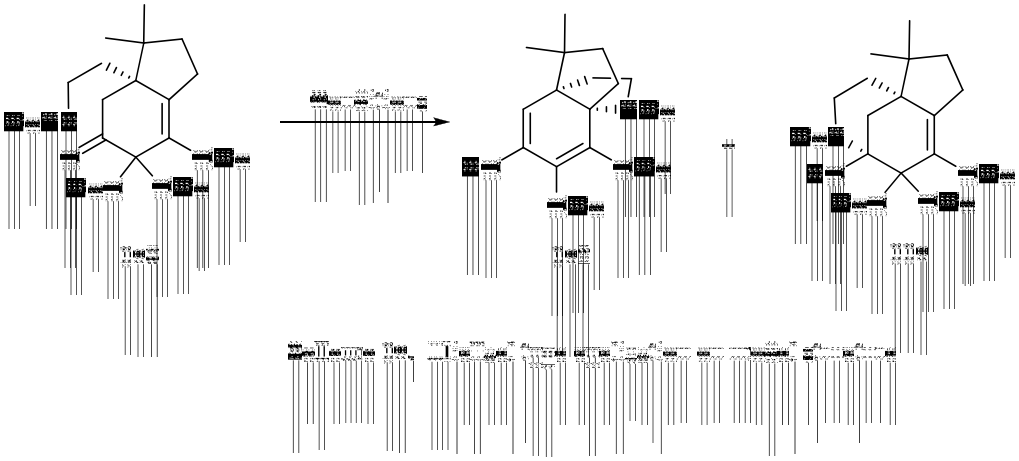
Exposure of **105** to potassium tert-butoxide and 18-crown-6 at 0 ºC provided ketone **106** through anionic oxy-Cope rearrangement (Scheme 9). To cleave the double bond in the allyl group, different methods were evaluated including $OsO_4/NaIO_4$. All reactions were unsuccessful except ozonoysis. Unfortunately, at first we could not accurately control the amount of ozone in the reaction system. Our substrate is very sensitive to ozone due to the presence of an electron-rich methyl enol ether, so it would decompose after three seconds of bubbling ozone. So selective ozonolysis of the allyl group required us to find a way to accurately control the equivalents of ozone. Wender and co-workers recently proposed an idea to control the ozone amount by dissolving

ozone in methylene chloride.[11] We used a similar approach by dissolving ozone in ethyl acetate and measuring the concentration by titration, which helped control the equivalents of ozone in the reaction system. The concentration of a saturated solution of O_3 in EtOAc is 0.007 M as determined by titrating with styrene. Treatment of **106** with 1.5 equiv of O_3 in EtOAc provided 30% aldehyde product and 30% recovered staring material. The yield could be optimized by moderating the reactivity of ozone by using pyridine as additive. The Donohoe group reported a similar approach in their recent synthesis of deoxypukalide.[12] The best yields (54% of amine, 27% recovered starting material) were obtained by adding 1.5 equiv of O_3/EtOAC solution to a solution of **106**, pyridine, and EtOAc mixture, the reductive amination was conducted in the same pot.



4.10 Development of Cyclization Conditions in Model System

To develop optimized cyclization from **108** to **109**, different conditions were tried on model system **108** (Scheme 10). Though we used TMSOTf to promote Michael addition in model syntheses before,[13] it provided low yields on this more complex molecule. After screening different Lewis and Brønsted acids including acid acetic acid, HCl, HFIP [14]and TFA, we found BCl_3 was the best catalyst to provide pyrrolidine **109** (Table 3). It is surprising that HCl (entry 3) afford undesired hemiaminal **110** as isohasubanan alkaloids. It is still under investigation why **109** was the only product under these conditions. HFIP can provide modest yields of enol **109** without adding any Lewis and Brønsted acids. But the yield was not improved by using HFIP as the only solvent with BCl_3.



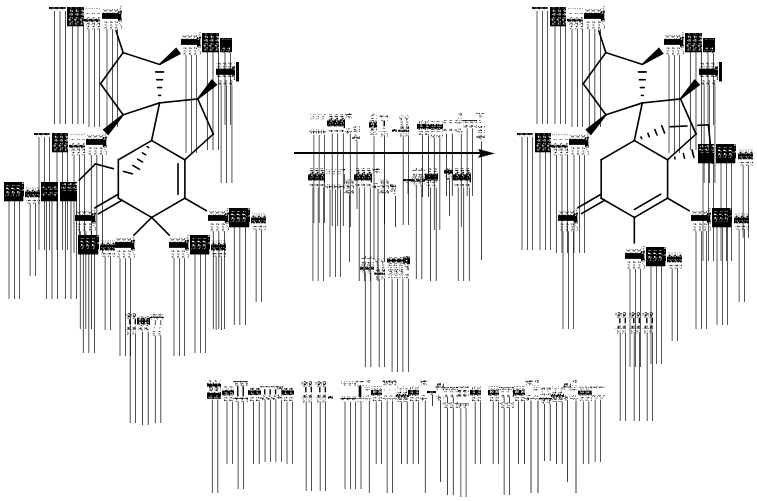
entry	*conditions* [a]	*product* [b]
1	TFA (5 equiv), CH_2Cl_2	**109**(31)
2	TFA (5 equiv), CH_2Cl_2, 0° C	**109** (41)
3	HCl (2 equiv), MeOH	**110**(10)
4	HOAc (3 equiv), MeOH	**109** (12)
5	BCl_3 (1 equiv), MeOH	**109**(19)[c]
6	BCl_3 (2 equiv), MeOH	**109** (27)
7	BCl_3 (3 equiv), MeOH	**109**(39)
8	BCl_3 (4 equiv), MeOH	**109**(38)
9	BCl_3 (3 equiv), CH_2Cl_2, 0° C	**109**(35)
10	BCl_3 (3 equiv), CH_2Cl_2, -15° C	**109**(39)
11	BCl_3 (3 equiv), CH_2Cl_2, -40° C	**109** (41)
12	BCl_3 (3 equiv), CH_2Cl_2, -78° C	**109** (37)
13	HFIP, [d] 0° C	**109** (27)
14	HFIP, -40° C	**109** (31)
15	BCl_3 (3 equiv), HFIP, -40° C	**109** (40)

[a] Reactions were conducted at room temperature in the presence of 4 Å MS unless otherwise indicated. [b] Percent yield is given in parentheses. [c] 27% of **108** was recovered. [d] 1,1,1,3,3,3-hexafluoro-2-propanol.

Table 3. Development of cyclization conditions in model system

4.11 BCl_3 Catalyzed Michael-Type Cyclization

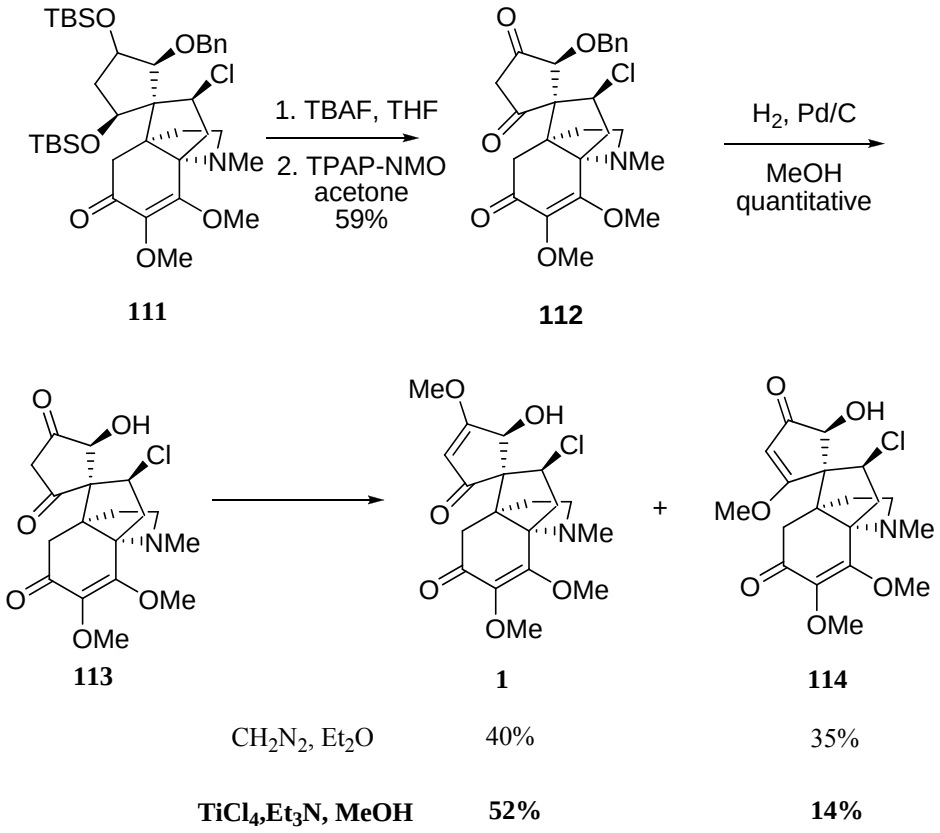
We obtained 45% yield when the optimized BCl_3 promoted cyzlization was applied to amine **107** (Scheme 11). It is noteworthy to mention that we did not observe any undesired cyclization byproduct as in our isohasubanan alkoloid synthesis. This exciting outcome might be attributed to the different electron density and different substituents in the spirocycle. Most importantly, we did not observe the hemiaminal isomer of **107** in the acutumine synthesis. Cyclization of the aminoketone to form a hemiaminal would have prevented the desired cyclization and would have formed undesired hasubanon alkaloids.[15]



4.12 Total Synthesis of (-)-Acutumine

Both TBS protecting groups of **111** were removed and the resulting diol was oxidized by TPAP-NMO to diketone **112** (Scheme 11). The diol product is very unstable even when stored in the freezer. So the subsequent oxidation was performed as soon as possible after cleavage of the TBS protection. The following steps in the synthesis consist

of deprotection and methylation. Two different orders for these reactions were tested. Deprotection and then methylation proved slightly better than methylation followed by deprotection. Also, in the last step, CH_2N_2 proved to be a better methylation reagent then $TMSCHN_2$. The drawback is that undesired regioisomer **114** was also obtained. We obtained a 1.3:1 mixture of products favoring acutumine. Fortunately, treatment of **113** with the Lewis acid $TiCl_4$ in the presence of Et_3N produced **1** as the major product with 3.7:1 ratio in favor of **1** (Scheme 12).[16]



Scheme 12. Synthesis of acutumine

Synthetic acutumine was identical to the authentic sample by TLC, MS, ^{1}H NMR, and ^{13}C NMR. The rotation of synthetic acutumine is $[\alpha]^{25}_D$ –171 (*c* 0.81, pyridine),

while natural acutumine was reported to be $[\alpha]^{25}_{D}$ –206 (*c* 0.69, pyridine). The ^{1}H and ^{13}C NMR spectroscopy comparison is shown below (Figure 3, 4).

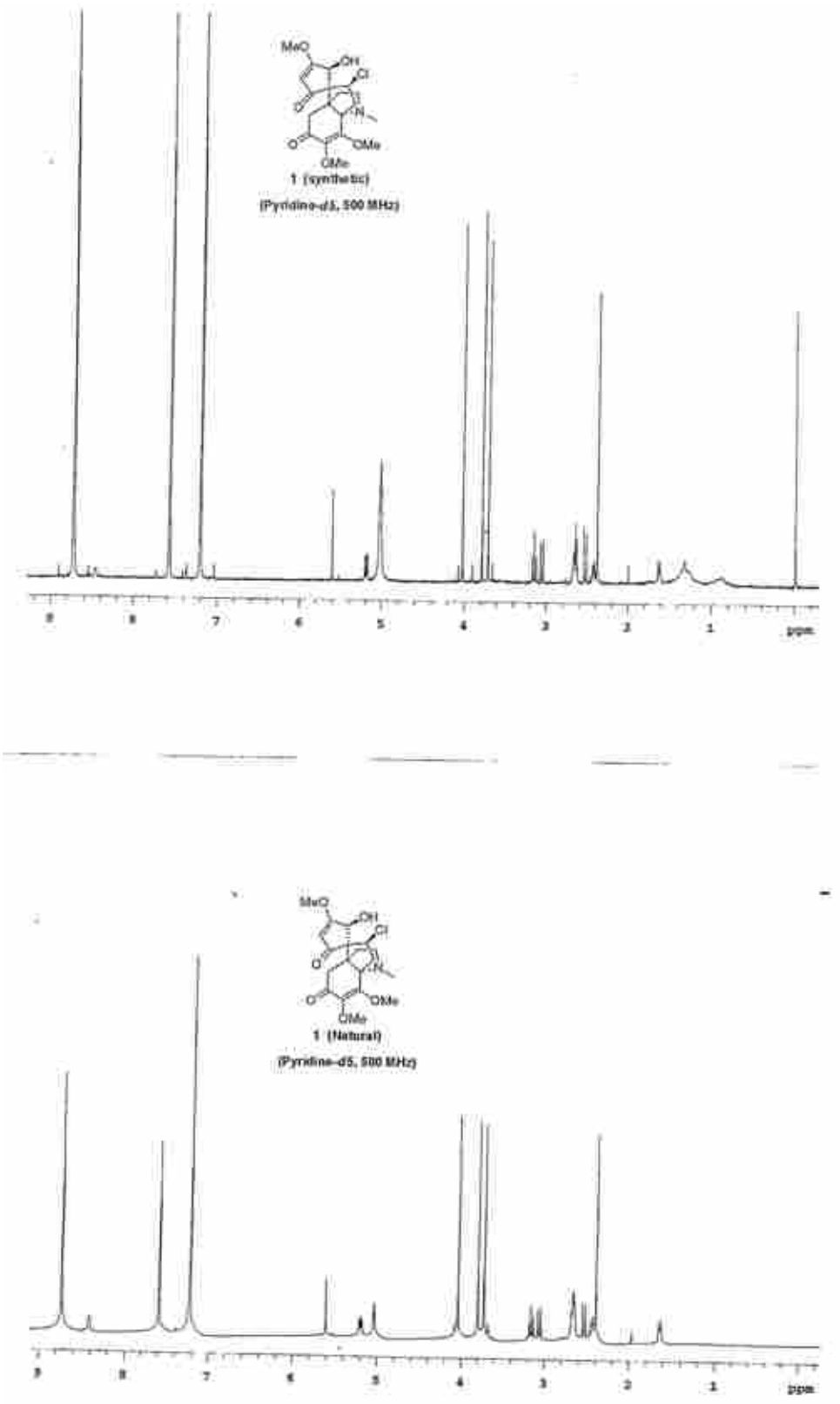


Figure 3. Comparison of ^{1}H NMR spectroscopy between synthetic and natural acutumine

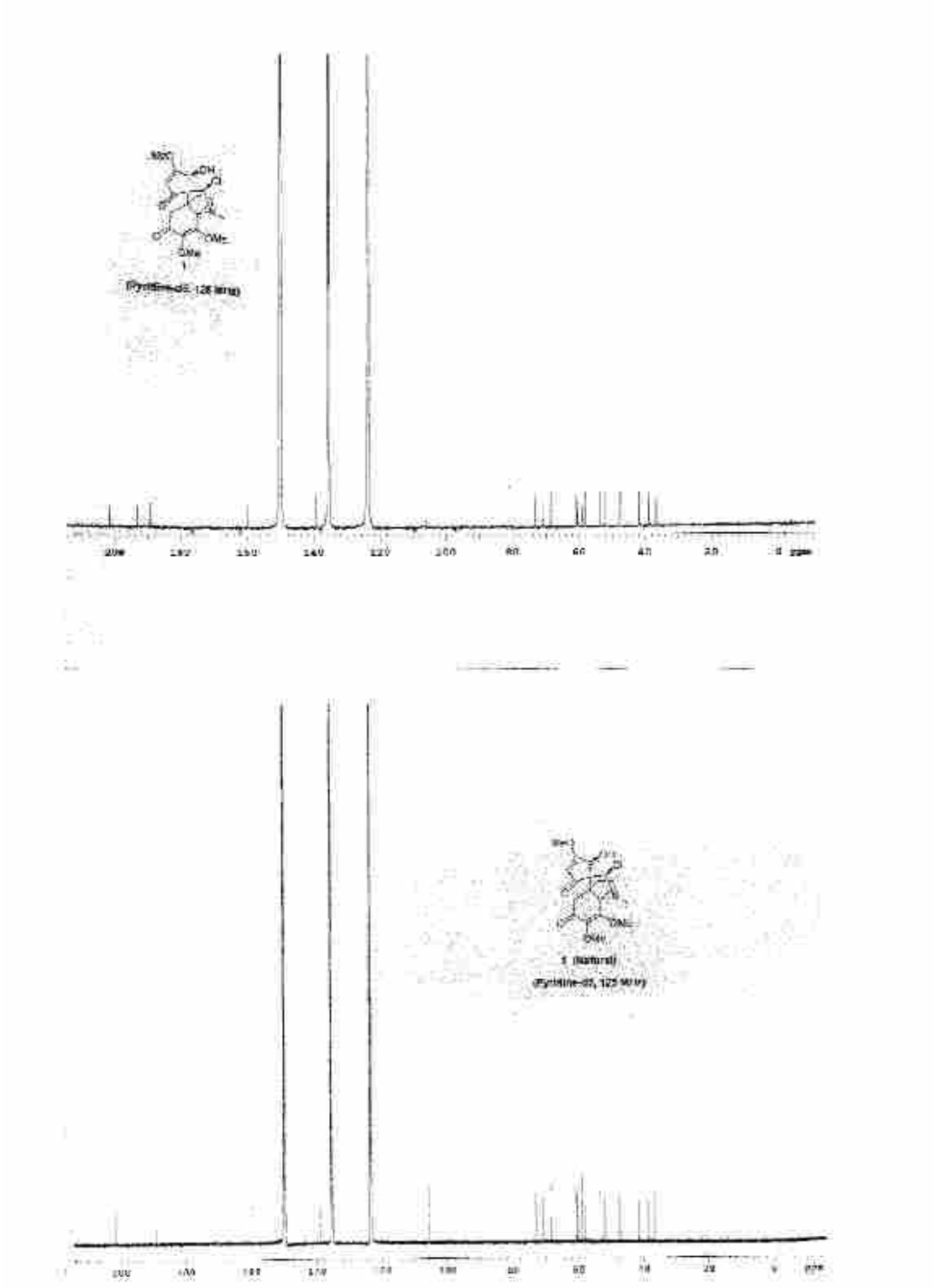


Figure 3. Comparison of ^{13}C NMR spectroscopy between synthetic and natural acutumine

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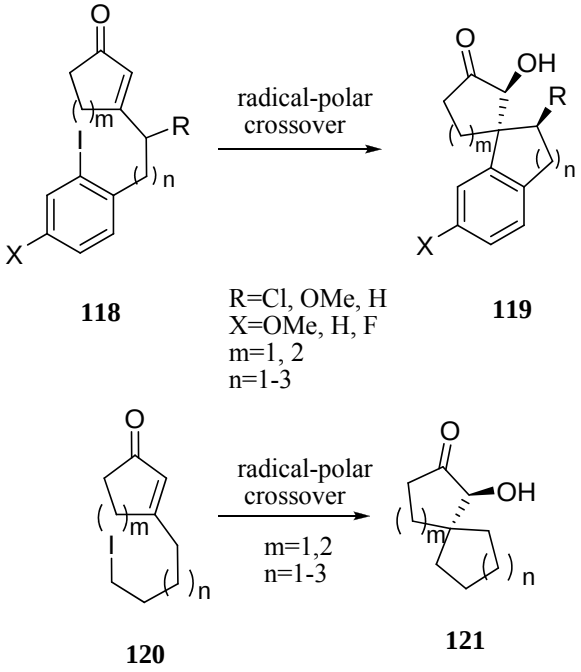
Chapter 5. Conclusion and Future Work

5.1 Conclusion and Future Work

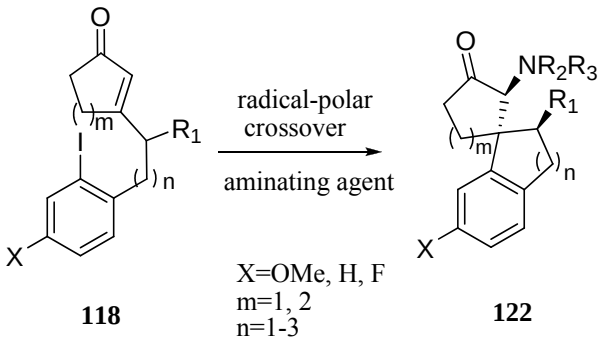
In conclusion, we have finished the total synthesis of enantiopure natural product acutumine, which is the first total synthesis of this challenging alkaloid.

During the exploration, we discovered a novel radical-polar crossover reaction consisting of an intramolecular aryl radical conjugate addition and hydroxylation of an enolate. One spirocycle and two stereocenters were created in this step, and an alcohol was installed. We believe this tandem reaction will be very useful in organic synthesis. So it is worthy to do more investigation on this methodology in the future by testing different substrates to explore the scope and limitations of this reaction (Scheme 1).



Scheme 1. Radical-polar crossover reactions on different substrate

Also, replacing the hydroxylation step with an electrophilic amination would lead to α-amino ketone derivatives (Scheme 2).[1-3]



118 **122**

Scheme 2. Tandem cyclization-amination

The Nakamura reagent was not used after its discovery because it was thought to be limited to alkynyl ketones. Also, it has never been used in natural product total syntheses before our group's isohasubanan alkaloids synthesis.[4] So it is a breakthrough to find it also works on complicated cyclic ketone substrates. It could be very useful in reagent-controlled stereoselective allylation of different ketones. Our group has started the research to explore the scope and limitations of Nakamura reagent. Other noteworthy reactions include a pyridine adjusted selective ozonolysis, an anionic oxy-Cope rearrangement to build a congested quaternary carbon and a Lewis acid promoted Michael-type cyclization.

5.2 Reference

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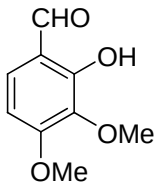
Chapter 6 Experimental Section

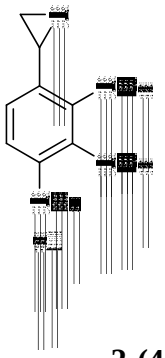
Benzene, dimethylformamide, methanol, methylene chloride, tetrahydrofuran, and toluene were dried by passage through a solvent drying system containing cylinders of activated alumina. Flash chromatography was carried out using 60–230 mesh silica gel. ^{1}H NMR spectra were acquired on 300 or 500 MHz spectrometers with chloroform (7.27 ppm) or pyridine (8.74 ppm) as internal references. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), br s (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). ^{13}C NMR spectra were acquired on spectrometers operating at 75 or 125 MHz with chloroform (77.23 ppm) or pyridine (149.80) as internal references. Infrared spectra were obtained on an FT-IR spectrometer. Mass spectral data were obtained using ESI techniques.



59

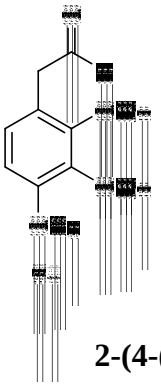
2-hydroxy-3,4-dimethoxybenzaldehyde (59). A solution of **57** (764 mg, 3.9 mmol) in anhydrous DMF (15 ml) was treated with sodium 2-methylpropane-2-thiolate (*t*-BuNaS, 0.437 g, 3.9 mmol) at 100°C and stirred for 30 min. The resultant mixture was

slowly cooled to room temperature and stirred for 1 hour. It was then diluted with $CHCl_3$ (15 ml) and washed with Sat aq NH_4Cl (15 ml). The combined aqueous layers were back-extracted with $CHCl_3$ (3 × 10 ml), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 × 10 cm. 10% EtOAc-hexane elution) afforded **59** (511 mg, 2.8 mmol, 71.8%) as yellow oil: ^{1}H NMR (300 MHz, $CHCl_3$) δ 11.21 (s, 1H), 7.57 (d, *J* = 9 Hz, 1H), 7.54 (s, 1H), 6.82 (d, *J* = 9 Hz, 1H), 4.01 (s, 3H), 3.94 (s, 3H); ^{13}C (300 MHz, $CDCl_3$) δ 191.5, 157.5, 151.2, 140.3, 124.5, 121.2, 107.6, 56.4, 55.2; IR (film) ν_{max} 2054, 1766, 877, 556 cm^{-1}; HRMS (ESI) *m/z* 182.0573 (M^+, $C_9H_{10}O_4$ requires 182.0579).



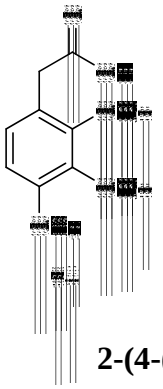
2-(4-(benzyloxy)-2, 3-dimethoxyphenyl)oxirane (62). Solid NaH (0.125 g, 3.12 mmol) was washed with 1-2ml hexane in an over-dried round bottom flask, then removeed hexane with syringe. 2.46 ml DMSO was added and stirred at 70° C for 45 min under nitrogen (use flushing nitrogen, an evolution of gas will create excess pressure). The resultant mixture was slowly cooled to room temperature and stirred for 40 min under nitrogen. 2.5 ml THF was added and the mixture was cool to 0-5° C in ice bath. Solid $(CH_3)_3SI$ (0.64 g, 3.12 mmol) was added over 10 min under 0-5°C. A solution of **61** (0.2 g, 0.75 mmol) in 1ml THF was added and stirred for 25 min. Then the mixture was

warmed back to room temperature and stirred for 12 hour, diluted with water (3 ml), extracted with EtOAC (3 × 3 ml). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 × 18cm. 10% EtOAc-hexane elution) afforded **62** (0.19 g, 0.66 mmol, 88%) as colorless oil: ^{1}H NMR (300MHz,$CHCl_3$) δ 7.56-7.44 (m, 5H), 6.63 (d, 1H, *J* = 9 Hz), 6.44 (d, 1H, *J* = 9 Hz), 5.34 (s, 2H), 3.90 (m, 1H), 3.83 (s, 3H), 3.81(s, 3H), 2.84(m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 152.3, 148.4, 142.5, 140.1, 129.7, 124.3, 124.1, 119.5, 117.7, 106.3, 70.1, 61.4, 53.2, 51.7; IR (film) ν_{max} 2088, 1542, 922, 855, 787 cm^{-1}; HRMS (ESI) *m/z* 286.1233 (M^+, $C_{17}H_{18}O_4$ requires 286.1205).



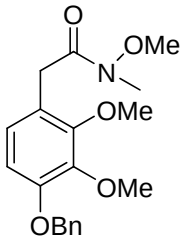
2-(4-(benzyloxy)-2,3-dimethoxyphenyl)acetaldehyde (63). A solution of (methoxymethyl)triphenylphosphonium chloride (0.61 g, 1.77 mmol) in anhydrous THF (2.0 mL) at 0 °C was treated dropwise with a solution of KOt-Bu (210 mg, 1.77 mmol) in anhydrous THF (0.7 mL). The resultant mixture was warmed to rt and stirred under N_2 for 30 min, then treated with a solution of **61** (223 mg, 0.84 mmol) in anhydrous THF (1.5 mL) and stirred at rt under N_2 for 16 h. The reaction was quenched by the addition of brine (4mL), extracted with EtOAc (3 × 4 mL), and concentrated in vacuo. The crude enol ether was dissolved in acetone (4.0 mL), then treated with concentrated HCl (1.0 mL)

and H_2O (1.0 mL). The resultant mixture was refluxed for 12 h, extracted with Et2O (3 × 5 mL), dried (MgSO4), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 12 cm, 10% EtOAc–hexanes elution) afforded **63** (192 mg, 0.67 mmol, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.82 (s, 1H) 7.45-7.22 (m, 5H), 6.82 (d, 1H, *J* = 9 Hz), 6.59 (d, 1H, *J* = 9 Hz), 5.15 (s, 2H), 3.91(s, 1H), 3.89 (s, 1H), 3.57 (s, 2H); ^{13}C NMR (CDCl3, 75 MHz) δ174.2, 155.2, 153.3, 143.6, 137.1, 127.4, 126.1, 126.0, 125.8, 122.4, 109.2, 78.3, 78.1, 75.9, 72.6, 62.5, 61.8, 37.2, 35.6; IR (film) ν_{max} 2832, 1734, 1523, 1410, 961, 758,621 cm^{-1}; HRMS (ESI) m/z 286.1198 (M^+, $C_{17}H_{18}O_4$ requires 286.1201).



2-(4-(benzyloxy)-2,3-dimethoxyphenyl)acetic acid (63). A solution of **63** in 5 ml acetone at 0°C and treated with Jones reagent (0.2 ml). The resultant mixure was stirred overnight (16 h) at 0°C. The reaction was quenched by the addition of sat aq sodium bisulfide till till the brown color has disappeared from the upper layer, extracted with EtOAc (3 × 15 mL), dried (MgSO4), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 12 cm, 10% EtOAc–hexanes elution) afforded **65** (192 mg, 0.67 mmol, 80%) as white solid crystal: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47-7.26 (m, 5H), 6.87 (d, 1H, *J* = 9Hz), 6.71 (d, 1H, *J* = 9 Hz), 5.17 (s, 2H), 3.94 (s, 1H), 3.92 (s, 1H), 3.62 (s, 2H); ^{13}C(300MHz;$CDCl_3$) δ177.8, 152.8, 152.3, 142.9, 137.2, 128.8, 128.2, 127.5, 125.1, 120.6, 109.4, 77.7, 77.3, 76.9, 71.2, 61.1, 61.0, 35.6, 31.2; IR (film) ν_{max} 2915,

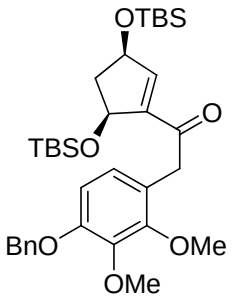
2822, 1779, 1647, 1510 , 1022, 773 cm^{-1}; HRMS (ESI) *m/z* 303.1222 (MH^+, $C_{17}H_{18}O_5$ requires 303.1232).



43

2-(4-(benzyloxy)-2,3-dimethoxyphenyl)-N-methoxy-N-methylacetamide (43).

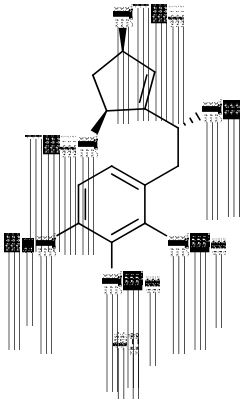
A solution of acid **65** (0.064 g, 0.21 mmol) in 3ml CH_2Cl_2 was treated with Et_3N (0.032 ml, 0.23 mmol) and stirred for 15 min. The resultant mixture was treated with PivCl (0.025 ml, 0.21 mmol), $MeO(CH_3)NH{\cdot}HCl$(0.02g,0.01mmol) and Et_3N (0.058ml,0.42mmol) dropwisely. After stirring for 2 more hours, the reaction was quenched with water, extracted with CH_2Cl_2 (3×3ml), dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 8 cm, 10% EtOAc–hexanes elution) afforded **43** (0.056 g,0.16 mmol, 78%) as pale yellow solid: ^1H NMR (300MHz,$CHCl_3$) δ 7.48-7.37 (m, 5H), 6.88 (d, 1H, *J* =9 Hz),6.70 (d,1H, *J* = 9 Hz), 5.12 (s, 2H), 3.92 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H), 3.24 (s, 2H); ^{13}C (75MHz, $CDCl_3$) δ 152.3,143.0, 137.4, 128.8, 128.1, 127.5, 125.1, 122.1, 109.6, 71.2, 61.4, 61.1, 61.0, 60.6, 33.4, 32.7, 29.9, 14.4; IR (film) ν_{max} 2829, 2514, 1739, 1566 , 1087, 922, 773 cm^{-1}; HRMS (ESI) *m/z* 346.1642 (MH^+, $C_{19}H_{24}NO_5$, requires 346.1654).



42

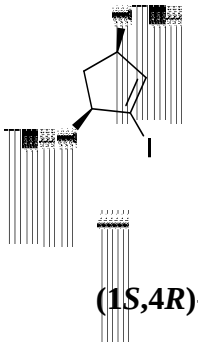
2-(4-(benzyloxy)-2,3-dimethoxyphenyl)-1-((3R,5S)-3,5-bis(tert-butyldimethylsilyloxy)cyclopent-1-enyl)ethanone (42). A portion of the *t*-BuLi (1.6 M solution in THF, 36 μL, 0.058 mmol) was added to a solution of **44** (26.4 mg, 0.058 mmol) in anhydrous THF (200 μL) at –78 °C, and the mixture was stirred at –78 °C for 10 min and treated with a precooled (–78 °C) solution of **43** (18.3 mg, 0.053 mmol) in anhydrous THF (200 μL). The resultant mixture was stirred at –78 °C for 1 h, then treated with sat aq NH_4Cl (1 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 8 cm, 10% EtOAc–hexanes elution) afforded **42** (22.4 mg, 0.036 mmol, 59%) as a pale yellow oil: $[\alpha]^{25}_D$ + 16.7 (*c* 1.01, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52–7.37 (m, 5H), 7.45 (d, 1H, *J* = 8.5 Hz), 7.25 (d, 1H, *J* = 8.5 Hz), 5.18 (s, 2H), 4.88–4.85 (m, 1H), 4.62–4.59 (m, 1H), 4.05 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 2.75 (dt, J = 12.5, 8 Hz, 1H), 1.69 (dt, J = 12.5, 8 Hz, 1H), 1.23 (s, 9H), 1.15 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H), 0.15 (s, 6H); 13C NMR (CDCl3, 75 MHz) δ 201.2, 156.4, 153.2, 147.9, 145.3, 139.2, 138.1, 135.1, 130.6 (2C), 129.6, 126.8(2C), 125.2, 122.4, 84.9, 82.3, 76.1, 74.7, 73.2, 44.3, 42.7, 24.9 (6C), 17.8 (2C), –4.1(2C) , –4.0 (2C); IR (film) νmax 3010, 2898,

1778, 1450, 1209, 955, 802 cm–1; HRMS (ESI) *m/z* 613.33668 (MH+, $C_{34}H53O_6Si_2$ requires 613.33807).

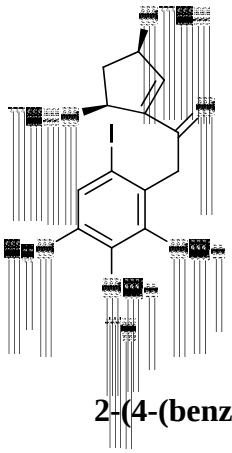


(R)-2-(4-(benzyloxy)-2,3-dimethoxyphenyl)-1-((3R,5S)-3,5-bis(tert-butyldimethylsilyloxy)cyclopent-1-enyl)ethanol (41). BH_3·THF (1.0 M solution in THF, 150 μL, 0.15 mmol) was added to the (*R*)-Corey–Bakshi–Shibata catalyst (0.038 M solution in THF, 670 μL, 0.0255 mmol) at 10 °C under N_2. The mixture was treated with a solution of **42** (78 mg, 0.127 mmol) in anhydrous THF (1 mL), stirred at 10 °C for 3 h, filtered through Celite (washed with Et_2O), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 12 cm, 5% EtOAc–hexanes elution) afforded **41** (67 mg, 0.11 mmol, 86%) as a 7:1 mixture of diastereomers that was a light yellow oil (data for major diastereomer): $[\alpha]^{25}_D$ +12.8 (*c* 0.79, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41–7.25(m, 5H), 7.18 (d, 1H, *J* = 8.5 Hz), 7.10 (d, 1H, *J* = 8.5 Hz), 6.48 (s, 1H), 5.15 (s, 2H), 4.85–4.81 (m, 1H), 4.66–4.60 (m, 1H), 4.39–4.35 (m, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 2.91–2.87 (m, 2H), 2.59 (dt, *J* = 12.5, 8 Hz, 1H), 1.75 (dt, *J* = 12.5, 8 Hz, 1H), 1.22 (s, 9H), 1.19 (s, 9H), 0.18 (s, 3H), 0.16(s, 3H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.2, 147.7, 143.3, 139.7, 134.2, 129.8, 126.0 (2C), 124.7, 123.5 (2C), 121.9, 118.3,

84.8, 77.1, 75.2, 68.7, 68.0, 65.4, 62.9, 42.1, 25.1 (6C), 15.8 (2C). –4.2 (2C), –4.3 (2C); IR (film) ν_{max} 3011, 2858, 1621, 1522, 1187, 828 cm^{-1}; HRMS (ESI) *m/z* 741.24971 (MH^+, $C_{34}H_{53}O_6ISi_2H$ requires 741.24981).



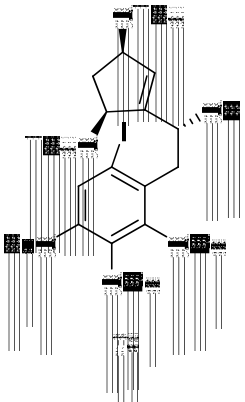
(1*S*,4*R*)-1,4-di-(*tert*-butyldimethylsilyloxy)-2-iodocyclopent-2-ene (44). A solution of **56** (1.02 g, 3 mmol) in anhydrous CH_2Cl_2 at rt under Ar was treated with DMAP (184 mg, 1.5 mmol) and Et_3N (1.95 mL, 1.42 g, 15 mmol), then cooled to 0 °C and treated with TBS-Cl (743 mg, 4.5 mmol). The resultant mixture was warmed to rt, stirred under Ar for 12 h, and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 × 14 cm, 5% EtOAc–hexanes elution) afforded **44** (1.33 g, 2.94 mmol, 98%) as a yellow oil: $[\alpha]^{25}_D$ +19.2 (*c* 1.05, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ6.22–6.19 (m, 1H), 4.59–4.54 (m, 1H), 4.48–4.44 (m, 1H), 2.68-2.63 (m, 1H), 1.72-1.67 (m, 1H), 0.94 (s, 9H), 0.88 (s, 9H),0.18 (s, 3H), 0.13 (s, 3H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.1, 106.7, 78.8, 75.6, 44.5, 26.0 (6C), 18.4 (2C), –4.3 (2C), –4.4(2C); IR (film) ν_{max} 2928, 2855, 1252, 1087, 835, 776 cm^{-1}; HRMS (ESI) *m/z* 477.11092 (MNa^+, $C_{17}H_{35}O_2ISi_2Na$ requires 477.11125).



2-(4-(benzyloxy)-6-iodo-2,3-dimethoxyphenyl)-1-((3*R*,5S)-3,5-di-*tert*-butyldimethylsilyloxycyclopent-1-enyl)ethanone (70). A round-bottomed flask under Ar was charged with Mg turnings (264 mg, 11.0 mmol), LiCl (420 mg, 10.0 mmol), and anhydrous THF (2.5 mL). A solution of *i*-PrCl (0.91 mL, 10.0 mmol) in anhydrous THF (2.5 mL) was added dropwise to this mixture at rt. The resultant mixture was stirred at rt under Ar for 12 h, then transferred to another Ar-filled flask via syringe (this step removed most of the unreacted Mg).

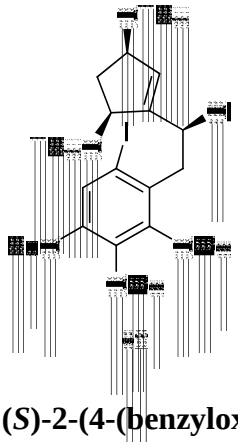
A portion of the *i*-PrMgCl·LiCl prepared above (2.0 M solution in THF, 775 μL, 1.55 mmol) was treated with 15-crown-5 (310 μL, 345 mg, 1.55 mmol). The resultant mixture was added to a solution of **44** (217.0 mg, 0.477 mmol) in anhydrous THF (1mL) at 0 °C, and the mixture was stirred at 0 °C for 15 min, then at rt for 1 h. It was cooled to –20 °C, and treated with a precooled (–20 °C) solution of **71** (203 mg, 0.43 mmol) in anhydrous THF (1mL). The resultant mixture was stirred at –20 °C for 8 h and at 0 °C for 4 h, then treated with sat aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 × 12 cm, 5% EtOAc–hexanes elution) afforded **70** (187 mg, 0.25 mmol, 59%) as a pale yellow oil: $[\alpha]^{25}_D$ +26.3 (*c* 1.05, CH_2Cl_2); ^{1}H NMR ($CDCl_3$,

300 MHz) δ 7.49–7.36 (m, 5H), 7.46 (s, 1H), 6.63 (s, 1H), 5.12 (s, 2H), 4.96–4.91 (m, 1H), 4.70–4.65 (m, 1H), 4.20 (s, 2H), 3.91 (s, 3H), 3.86 (s, 3H), 2.73 (dt, *J* = 12.6, 6.9 Hz, 1H), 1.70 (dt, *J* = 12.6, 6.9 Hz, 1H), 0.94 (s, 9H), 0.88 (s, 9H), 0.14-0.13 (m, 9H), 0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.2, 152.4, 147.0, 146.2, 143.4, 142.9, 137.4, 128.7 (2C), 128.1, 127.5(2C), 125.3, 109.4, 98.1, 74.2, 73.5, 73.1, 71.2, 61.2, 45.1, 41.6, 26.1 (6C), 18.4 (2C), –4.3 (2C) , –4.6 (2C); IR (film) ν_{max} 2933, 2858, 1728, 1509, 1389, 1198, 1020cm^{-1}; HRMS (ESI) *m/z* 761.21357 (MNa^+, $C_{34}H_{51}O_6ISi_2Na$ requires 761.21611).



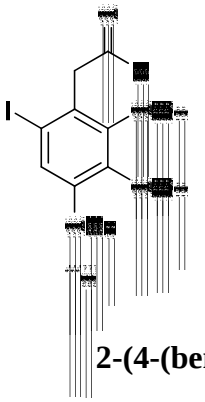
(*R*)-2-(4-(benzyloxy)-6-iodo-2,3-dimethoxyphenyl)-1-((3*R*,5*S*)-3,5-di-*tert*-butyldimethylsilyloxycyclopent-1-enyl)ethanol (78). BH_3·THF (1.0 M solution in THF, 171 μL, 0.17 mmol) was added to the (*R*)-Corey–Bakshi–Shibata catalyst (0.038 M solution in THF, 760 μL, 0.029 mmol) at 10 °C under N_2. The mixture was treated with a solution of **70** (107 mg, 0.144 mmol) in anhydrous THF (1.5 mL), stirred at 10 °C for 3 h, filtered through Celite (washed with Et_2O), and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 × 9 cm, 5% EtOAc–hexanes elution) afforded **78** (89.5 mg, 0.121 mmol, 84%) as a 6.7:1 mixture of diastereomers that was a light yellow oil (data for major diastereomer): $[\alpha]^{25}_D$ +15.9 (*c* 0.92, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44–7.27(m, 5H), 7.20 (s, 1H), 6.75 (s, 1H), 5.10 (s, 2H), 4.88–4.82 (m, 1H), 4.63–4.59

(m, 1H), 4.37–4.33 (m, 1H), 3.86(s, 3H), 3.82 (s, 3H), 2.95–2.89 (m, 2H), 2.64 (dt, J = 12.6, 6.9 Hz, 1H), 1.70 (dt, J = 12.6, 6.9 Hz, 1H), 1.20 (m, 9H), 1.18 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.9, 147.5, 141.9, 138.5, 133.8, 128.0, 125.1 (2C), 124.2, 123.3 (2C), 121.4, 117.5, 96.2, 83.1, 75.2, 74.9, 69.2, 68.5, 65.3, 62.0, 41.7, 23.3 (6C), 15.6 (2C). –4.4 (2C), –4.5 (2C); IR (film) ν_{max} 2947, , 2892, 1534, 1251, 1137, 1065, 821 cm^{-1}; HRMS (ESI) *m/z* 741.24971 (MH^+, $C_{34}H_{53}O_6ISi_2H$ requires 741.24981).



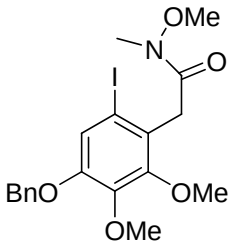
(*S*)-2-(4-(benzyloxy)-6-iodo-2,3-dimethoxyphenyl)-1-((3*R*,5*S*)-3,5-di-*tert*-butyldimethylsilyloxycyclopent-1-enyl)-1-chloroethane (69). A solution of **78** (71 mg, 0.095 mmol) in anhydrous CH_2Cl_2 (500 μL) at 0 °C was treated with anhydrous Me_2S (14 μL, 11.9 mg, 0.192 mmol) and NCS (15 mg, 0.114 mmol), stirred for 6 hours at 0 °C, and then quenched with sat aq NH_4Cl (3 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 12 cm, 6% EtOAc–hexanes elution) afforded **69** (31 mg, 0.041 mmol) as yellow oil: $[\alpha]^{25}_D$ +25.1 (*c* 1.02, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44–7.29 (m, 5H), 7.27 (s, 1H), 6.60 (s, 1H), 5.08 (s, 2H), 4.88 (m, 1H), 4.65 (m, 1H), 4.19 (m, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.11 (m, 1H), 3.06 (m, 1H), 2.68 (dt, J = 12.6,

6.9 Hz, 1H), 1.65 (dt, J = 12.6, 6.9 Hz, 1H), 1.21 (s, 9H), 1.18 (s, 9H), 0.24 (s, 3H), 0.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.1, 147.8, 143.0, 138.5, 132.2, 130.8, 124.5(2C), 122.6, 121.8 (2C), 120.6, 97.8, 71.6, 70.5, 68.4, 68.0, 67.2, 55.6, 40.8, 32.7, 25.2 (6C), 16.2 (2C), –4.4 (2C), –4.3 (2C); IR (film) ν_{max} 3035, 2744, 1328, 1298, 1011, 952 cm^{-1}; HRMS (ESI) *m/z* 781.19769 (MNa^+, $C_{34}H_{52}ClINaO_5Si_2$ requires 781.19842).



2-(4-(benzyloxy)-6-iodo-2,3-dimethoxyphenyl)acetaldehyde (76). A solution of (methoxymethyl)triphenylphosphonium chloride (0.92 g, 2.64 mmol) in anhydrous THF (3.0 mL) at 0 °C was treated dropwise with a solution of KO*t*-Bu (300 mg, 2.52 mmol) in anhydrous THF (1.0 mL). The resultant mixture was warmed to rt and stirred under N_2 for 30 min, then treated with a solution of 4-benzyloxy-4-iodo-2,3-dimethoxybenzaldehyde (**74**)[1] (500 mg, 1.26 mmol) in anhydrous THF (1.5 mL) and stirred at rt under N_2 for 16 h. The reaction was quenched by the addition of brine (5 mL), extracted with EtOAc (3 × 5 mL), and concentrated in vacuo. The crude enol ether was dissolved in acetone (5.0 mL), then treated with concentrated HCl (1.0 mL) and H_2O (1.0 mL). The resultant mixture was refluxed for 12 h, extracted with Et_2O (3 × 6 mL), dried

($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 15 cm, 10% EtOAc–hexanes elution) afforded **76** (423 mg, 1.03 mmol, 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (s, 1H), 7.48–7.30 (m, 5H), 7.25 (s, 1H), 5.09 (s, 2H), 3.89 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.0, 153.2, 152.6, 143.4, 136.5, 128.9 (2C), 128.5, 127.7 (2C), 124.1, 120.2, 93.5, 71.5, 61.4, 61.1, 49.8; IR (film) ν_{max} 2944, 2874, 1704, 1595, 1524, 1488, 1456, 1380, 1336, 1309, 1256, 1193, 1116 cm^{-1}; HRMS (ESI) *m/z* 413.02423 (MH^+, $C_{17}H_{17}O_4IH$ requires 413.02443).



71

2-(4-(benzyloxy)-6-iodo-2,3-dimethoxyphenyl)-*N*-methoxy-*N*-methylacetamide (71). A solution of **77** (31.0 mg, 0.075 mmol) in *t*-BuOH (0.9 mL) and H_2O (0.2 mL) at rt was treated with 2-methyl-2-butene (100 μL, 66 mg, 0.92 mmol), NaH_2PO_4 (12 mg, 0.097 mmol), and $NaClO_2$ (42 mg, 0.47 mmol). The resulting mixture was stirred for 1 h, diluted with H_2O (2 mL), and extracted with CH_2Cl_2 (3 × 4 mL). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. The crude acid was used directly in the next reaction.

A solution of the carboxylic acid (ca. 0.075 mmol) in anhydrous CH_2Cl_2 (0.5 mL) at 0 °C was treated with Et_3N (12 μL, 8.7 mg, 0.086 mmol) and stirred for 15 min.

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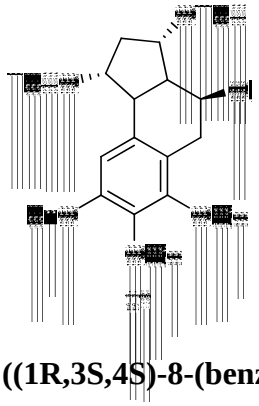
[1] Jones, S. B.; He, L.; Castle, S. L. *Org. Lett.* **2006**, *8*, 3757.

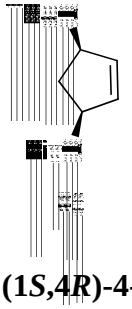
Pivaloyl chloride (9 μL, 0.075 mmol) was then added to the mixture, and it was stirred for 1 h prior to the addition of MeO(Me)NH·HCl (14 mg, 0.15 mmol) and Et_3N (20 μL, 15 mg, 0.14 mmol). The resultant mixture was stirred at 0 °C for 2 h, then treated with brine (0.5 mL) and extracted with CH_2Cl_2 (3 × 1 mL). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 0.5 × 7 cm, 20% EtOAc–hexanes elution) afforded **71** (31.8 mg, 0.0675 mmol, 90%) as a pale yellow solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49–7.37 (m, 5H), 7.25 (s, 1H), 5.09 (s, 2H), 3.98 (s, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5, 152.4, 152.3, 143.0, 136.4, 128.5 (2C), 128.0, 127.3 (2C), 126.2, 119.6, 93.8, 71.0, 61.2, 61.1, 60.7, 38.7, 32.4; IR (film) ν_{max} 2936, 1666, 1493, 1467, 1418, 1381, 1275, 1258, 1194, 1090, 1044 cm^{-1}; HRMS (ESI) *m/z* 494.03968 (MNa^+, $C_{19}H_{22}O_5NINa$ requires 494.04349).



((1R,3S,4S)-8-(benzyloxy)-4-chloro-6,7-dimethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[a]naphthalene-1,3-diyl)bis(oxy)bis(tert-butyldimethylsilane)

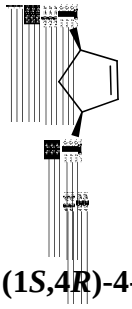
A solution of **69** (18 mg, 0.024 mmol) in toluene (0.5 ml) was treated with Et_3B (0.048 mL of a 1.0 M solution in hexanes, 0.048 mmol) at –30 °C, and a constant supply of dry air was provided by passing compressed air through a short tube of Drierite and over the solution (venting with a needle allowed a continuous flow). An additional portion of

Et3B (0.24 mL of a 1.0 M solution in hexanes, 1.0 mmol) was added by syringe pump over 8 h while the solution was stirred and exposed to dry air as explained above. The solution was stirred for an additional 3 h then concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 1.5 × 10 cm, 10% EtOAc in hexanes elution) to afford **79** (8 mg, 0.0127 mmol, 53%) as a yellow oil: $[\alpha]^{25}_D$ 31.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42-7.19 (m, 5H), 6.92 (s, 1H), 4.66-4.59 (dd, *J* = 12.6, 7.2 Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.58-3.48 (m, 1H), 3.39-3.31 (m, 1H), 3.00 (t, *J* = 7.5 Hz, 1H), 2.83 (t, *J* = 12 Hz, 1H), 2.69-2.63 (dd, *J* = 12.6, 7.2 Hz, 1H), 2.13-2.04 (m, 1H), 2.00-1.90 (m, 1H), 1.73-1.62 (m, 1H), 0.97 (s, 9H), 0.91 (s, 9H), 0.11 (s, 6H), 0.08 (s, 6H) 2.83 (dt, *J* = 13.8, 7.2 Hz, 1H), 1.60 (dt, *J* = 13.8, 5.4 Hz, 1H) 1.20 (s, 9H), 0.99 (t, *J* = 7.8 Hz, 9H), 0.64 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.0, 152.1, 147.8, 143.8, 137.8, 133.4, 132.3, 127.6 (2C), 126.9, 126.0 (2C), 75.7, 75.4, 71.5, 71.0, 69.3, 47.7, 43.5, 38.7, 32.4, 27.9, 24.1, 24.1, 16.5, –4.3 (2C), –4.3 (2C); IR (film) ν_{max} 3521, 2844, 1652, 1397, 885 cm^{-1}; HRMS (ESI) *m/z* 633.31854 (MH^+, $C_{34}H_{54}ClO_5Si_2$ requires 633.31983).



(1*S*,4*R*)-4-(triethylsilyloxy)cyclopent-2-enyl pivalate (85). A solution of **51**[2] (5.30 g, 28.8 mmol) in anhydrous CH_2Cl_2 (100 mL) at rt under Ar was treated with

DMAP (1.80 g, 14.7 mmol) and Et_3N (20 mL), then cooled to 0 °C and treated with a solution of chlorotriethylsilane (9.02 g, 59.8 mmol) in anhydrous CH_2Cl_2 (20 mL, solution added over a period of 5 min). The resultant mixture was warmed to rt and stirred for 1 h, then diluted with Et_2O (30 mL) and washed with brine (50 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 5 × 14 cm, 8% EtOAc–hexanes elution) afforded **85** (7.75 g, 26.0 mmol, 90%) as a colorless oil: $[\alpha]^{25}_D$ –9.5 (*c* 1.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.00–5.98 (m, 1H), 5.91–5.89 (m, 1H), 5.48–5.44 (m, 1H), 4.76–4.71 (m, 1H), 2.83 (dt, *J* = 13.8, 7.2 Hz, 1H), 1.60 (dt, *J* = 13.8, 5.4 Hz, 1H) 1.20 (s, 9H), 0.99 (t, *J* = 7.8 Hz, 9H), 0.64 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.6, 138.8, 131.9, 76.9, 74.8, 41.5, 38.8, 27.3 (3C), 7.0 (3C), 5.0 (3C); IR (film) ν_{max} 2956, 2877, 1728, 1157 cm^{-1}; HRMS (ESI) *m/z* 321.18496 (MNa^+, $C_{16}H_{30}O_3SiNa$ requires 321.18564).



(1*S*,4*R*)-4-(triethylsilyloxy)cyclopent-2-enol (86). A solution of **85** (7.75 g, 26.0 mmol) in anhydrous toluene (50 mL) was cooled to –78 °C under Ar (precipitates formed) and treated with DIBAL-H (1 M solution in toluene, 52 mL, 52 mmol). The resultant mixture was stirred at –78 °C for 2 h, and the reaction was quenched by the addition of

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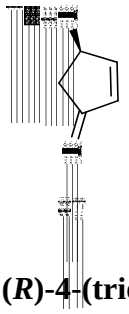
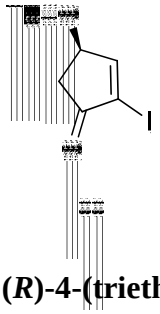
[2] Myers, A. G.; Hammond, M.; Wu, Y. *Tetrahedron Lett.* **1996**, *37*, 3083.

toluene–CH_3OH (1:1, 50 mL, added over a period of 5 min). The mixture was then treated with 1 N HCl (30 mL), stirred for 30 min, and filtered through Celite (washed with EtOAc). The layers were seprated, and the aqueous layer was extracted with EtOAc (5 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 5 × 14 cm, 15% EtOAc–hexanes elution) afforded **86** (5.08 g, 23.7 mmol, 91%) as a colorless oil: $[\alpha]^{25}_D$ +17.2 (*c* 1.4, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.00–5.97 (m, 1H), 5.94–5.91 (m, 1H), 4.70–4.58 (m, 2H), 2.73 (dt, *J* = 13.8, 7.2 Hz, 1H), 1.81–1.73 (m, 1H), 1.55 (dt, *J* = 13.8, 4.5 Hz, 1H), 1.00 (t, *J* = 7.8 Hz, 9H), 0.65 (q, *J* = 8.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3, 135.9, 75.5, 75.0, 45.0, 7.0 (3C), 5.0 (3C); IR (film) ν_{max} 3363, 2955, 2877, 1459, 1366, 1239 cm^{-1}; HRMS (ESI) *m/z* 237.12831 (MNa^+, $C_{11}H_{22}O_2SiNa$ requires 237.12813).

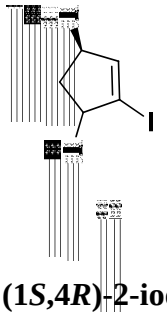


(*R*)-4-(triethylsilyloxy)-cyclopent-2-enone (87). A solution of **86** (5.07 g, 23.6 mmol) in anhydrous CH_2Cl_2 (70 mL) was treated with NaOAc (620 mg, 7.6 mmol) and powdered 4 Å molecular sieves (9.60 g), cooled to 0 °C, and treated with PCC (7.60 g, 35.2 mmol). The resultant mixture was warmed to rt and stirred under Ar for 1 h. The chromium salts were precipitated by the addition of Et_2O (300 mL), and the mixture was filtered through Celite and SiO_2 (both plugs washed with 200 mL total of EtOAc). Concentration in vacuo followed by flash chromatography (SiO_2, 5 × 12 cm, 12% EtOAc–hexanes elution) afforded **87** (4.39 g, 20.7 mmol, 87%) as a yellow oil: $[\alpha]^{25}_D$

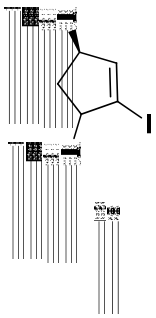
+41.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49 (dd, *J* = 5.7, 2.4 Hz, 1H), 6.22 (dd, *J* = 5.7, 1.5 Hz, 1H), 5.03–4.99 (m, 1H), 2.75 (dd, *J* = 18.3, 6.3 Hz, 1H), 2.29 (dd, *J* = 18.3, 2.4 Hz, 1H), 1.02 (t, *J* = 7.8 Hz, 9H), 0.68 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.7, 164.1, 134.8, 70.8, 45.3, 6.9 (3C), 4.9 (3C); IR (film) ν_{max} 2956, 2878, 1725, 1109, 1072 cm^{-1}; HRMS (ESI) *m/z* 213.13032 (MH^+, $C_{11}H_{20}O_2SiH$ requires 213.13053).



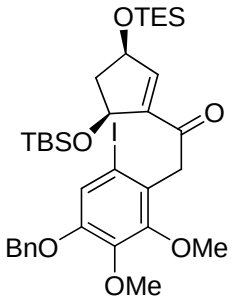
(*R*)-4-(triethylsilyloxy)-2-iodocyclopent-2-enone (88). A solution of **87** (920 mg, 4.33 mmol) in CCl_4–pyridine (1:1, 30 mL) at 0 °C under Ar was treated dropwise with a solution of I_2 (4.6 g, 18.2 mmol) in CCl_4–pyridine (1:1, 30 mL). The resultant mixture was stirred at 0 °C for 5 min, then warmed to rt and stirred for 5 h. It was diluted with Et_2O (30 mL), washed with H_2O (20 mL), 1 N HCl (25 mL), sat aq $Na_2S_2O_3$ (30 mL), and sat aq $NaHCO_3$ (30 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 3.5 × 16 cm, 7% EtOAc–hexanes elution) afforded **88** (1.20 g, 3.55 mmol, 82%) as a yellow oil: $[\alpha]^{25}_D$ +18.5 (*c* 1.6, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, *J* = 2.4 Hz, 1H), 5.00–4.95 (m, 1H), 2.90 (dd, *J* = 18.3, 6.3 Hz, 1H), 2.39 (dd, *J* = 18.3, 2.1 Hz, 1H), 1.01 (t, *J* = 8.4 Hz, 9H), 0.68 (q, *J* = 8.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.4, 169.3, 105.1, 72.0, 42.5, 6.8 (3C), 4.8 (3C); IR (film) ν_{max} 2955, 2876, 1726, 1086 cm^{-1}; HRMS (ESI) *m/z* 361.00911 (MNa^+, $C_{11}H_{19}O_2ISiNa$ requires 361.00912).



(1*S*,4*R*)-2-iodo-4-(triethylsilyloxy)cyclopent-2-enol (89). A solution of $CeCl_3 \cdot 7H_2O$ (220 mg, 0.59 mmol) in CH_3OH (2.0 mL) was stirred at rt for 30 min, then treated with a solution of **88** (400 mg, 1.18 mmol) in CH_3OH (1 mL). The resultant mixture was cooled to –60 °C, treated with $NaBH_4$ (45 mg, 1.18 mmol), and stirred at –30 °C for 1 h. It was then diluted with Et_2O (3 mL) and washed with sat aq $NaHCO_3$ (3 mL) and brine (3 mL). The combined aqueous layers were back-extracted with Et_2O (3 × 2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 10 cm, 10% EtOAc–hexanes elution) afforded **89** (290 mg, 0.85 mmol, 72%) as a pale yellow oil: $[\alpha]^{25}_D$ +27.5 (*c* 0.28, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.28 (s, 1H), 4.63–4.58 (m, 1H), 4.51–4.42 (m, 1H), 2.76 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.57 (d, *J* = 7.5 Hz, 1H), 1.74 (dt, *J* = 13.5, 4.8 Hz, 1H), 0.97 (t, *J* = 7.8 Hz, 9H), 0.63 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.0, 106.2, 79.7, 75.3, 43.5, 7.0 (3C), 5.0 (3C); IR (film) ν_{max} 3395, 2954, 2876, 1077, 1005 cm^{-1}; HRMS (ESI) *m/z* 363.02374 (MNa^+, $C_{11}H_{21}O_2ISiNa$ requires 363.02477).



(1*S*,4*R*)-1-(*tert*-butyldimethylsilyloxy)-4-(triethylsilyloxy)2-iodocyclopent-2-ene (90). A solution of **89** (721 mg, 2.12 mmol) in anhydrous CH_2Cl_2 at rt under Ar was treated with DMAP (130 mg, 1.06 mmol) and Et_3N (1.50 mL, 1.09 g, 10.7 mmol), then cooled to 0 °C and treated with TBS-Cl (700 mg, 4.24 mmol). The resultant mixture was warmed to rt, stirred under Ar for 16 h, and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 × 8 cm, 5% EtOAc–hexanes elution) afforded **90** (940 mg, 2.07 mmol, 98%) as a yellow oil: $[\alpha]^{25}_D$ +22.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.23–6.21 (m, 1H), 4.61–4.54 (m, 1H), 4.51–4.45 (m, 1H), 2.68 (dt, *J* = 12.9, 7.2 Hz, 1H), 1.73 (dt, *J* = 12.6, 6.3 Hz, 1H), 1.00–0.90 (m, 9H), 0.95 (s, 9H), 0.62 (q, *J* = 8.1 Hz, 6H), 0.18 (s, 3H), 0.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.1, 106.9, 78.9, 75.4, 44.6, 26.1 (3C), 18.4, 7.0 (3C), 5.0 (3C), –4.2, –4.3; IR (film) ν_{max} 2955, 2877, 1251, 1086 cm^{-1}; HRMS (ESI) *m/z* 477.11035 (MNa^+, $C_{17}H_{35}O_2ISi_2Na$ requires 477.11125).

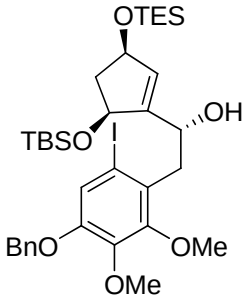


91

2-(4-(benzyloxy)-6-iodo-2,3-dimethoxyphenyl)-1-((3*R*,5S)-5-*tert*-butyldimethylsilyloxy-3-(triethylsilyloxy)cyclopent-1-enyl)ethanone (91). A round-bottomed flask under Ar was charged with Mg turnings (264 mg, 11.0 mmol), LiCl (420 mg, 10.0 mmol), and anhydrous THF (2.5 mL). A solution of *i*-PrCl (0.91 mL, 10.0

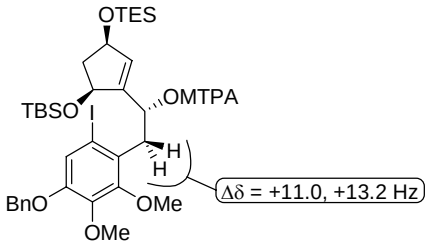
mmol) in anhydrous THF (2.5 mL) was added dropwise to this mixture at rt. The resultant mixture was stirred at rt under Ar for 12 h, then transferred to another Ar-filled flask via syringe (this step removed most of the unreacted Mg).

A portion of the *i*-PrMgCl·LiCl prepared above (2.0 M solution in THF, 50 μL, 0.10 mmol) was treated with 15-crown-5 (20 μL, 22.3 mg, 0.10 mmol). The resultant mixture was added to a solution of **90** (14.0 mg, 0.0308 mmol) in anhydrous THF (200 μL) at 0 °C, and the mixture was stirred at 0 °C for 10 min, then at rt for 1 h. It was cooled to –20 °C, and treated with a precooled (–20 °C) solution of **71** (13.1 mg, 0.0278 mmol) in anhydrous THF (200 μL). The resultant mixture was stirred at –20 °C for 2 h and at 0 °C for 5 h, then treated with sat aq NH_4Cl (1 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 7.5 cm, 8% EtOAc–hexanes elution) afforded **91** (12.9 mg, 0.0175 mmol, 63%) as a pale yellow oil: $[\alpha]^{25}_D$ +22.3 (*c* 1.03, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49–7.34 (m, 5H), 7.41 (s, 1H), 6.81 (s, 1H), 5.12 (s, 2H), 4.96–4.91 (m, 1H), 4.70–4.65 (m, 1H), 4.00 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 2.74 (dt, *J* = 13.2, 7.5 Hz, 1H), 1.71 (dt, *J* = 13.2, 6.0 Hz, 1H), 1.19–1.09 (m, 9H), 1.14 (s, 9H), 0.72 (q, *J* = 8.1 Hz, 6H), 0.18 (s, 3H), 0.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.2, 153.2, 152.4, 147.1, 143.4, 137.4, 137.1, 128.8 (2C), 128.1, 127.5 (2C), 125.3, 121.8, 97.1, 80.0, 79.5, 73.5, 73.1, 71.2, 45.2, 43.7, 26.1 (3C), 18.4, 8.7 (3C), 6.1 (3C), –4.3, –4.4; IR (film) ν_{max} 2928, 2855, 2360, 1685, 1493, 1469, 1362, 1253, 1087 cm^{-1}; HRMS (ESI) *m/z* 761.21196 (MNa^+, $C_{34}H_{51}O_6ISi_2Na$ requires 761.21611).

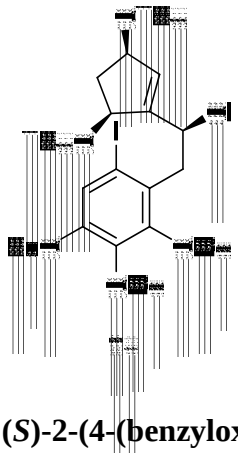


92

(*R*)-2-(4-(benzyloxy)-6-iodo-2,3-dimethoxyphenyl)-1-((3*R*,5*S*)-5-*tert*-butyldimethylsilyloxy-3-(triethylsilyloxy)cyclopent-1-enyl)ethanol (92). BH_3·THF (1.0 M solution in THF, 16 μL, 0.016 mmol) was added to the (*R*)-Corey–Bakshi–Shibata catalyst (0.038 M solution in THF, 71 μL, 0.0027 mmol) at 10 °C under N_2. The mixture was treated with a solution of **91** (10.0 mg, 0.0135 mmol) in anhydrous THF (500 μL), stirred at 10 °C for 3 h, filtered through Celite (washed with Et_2O), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 7.5 cm, 5% EtOAc–hexanes elution) afforded **92** (9.2 mg, 0.0125 mmol, 92%) as a 9:1 mixture of diastereomers that was a light yellow oil (data for major diastereomer): $[\alpha]^{25}_D$ +10.3 (*c* 0.78, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.23 (m, 5H), 7.18 (s, 1H), 6.70 (s, 1H), 5.01 (s, 2H), 4.85–4.80 (m, 1H), 4.59–4.55 (m, 1H), 4.35–4.31 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.90–2.83 (m, 2H), 2.63 (dt, *J* = 13.2, 7.2 Hz, 1H), 1.96 (s, 1H), 1.60 (dt, *J* = 13.2, 5.7 Hz, 1H), 1.27–1.16 (m, 9H), 1.21 (s, 9H), 0.79 (q, *J* = 7.8 Hz, 6H), 0.24 (s, 3H), 0.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.3, 148.1, 142.8, 139.1, 133.2, 128.6, 124.7 (2C), 124.2, 124.0 (2C), 121.8, 117.7, 95.4, 82.8, 75.8, 75.3, 69.5, 69.0, 66.5, 61.1, 40.9, 22.1 (3C), 13.9, 9.7 (3C), 6.5 (3C), –4.4, –4.5; IR (film) ν_{max} 3129, 2958, 2913, 2878, 1532, 1433, 1289, 1110, 1072 cm^{-1}; HRMS (ESI) *m/z* 741.25032 (MH^+, $C_{34}H_{53}O_6ISi_2H$ requires 741.24981).

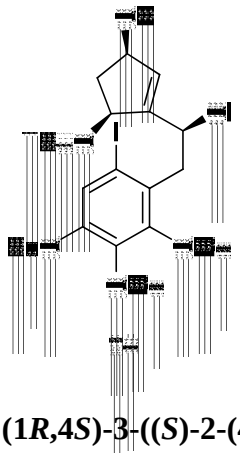


Analysis of MTPA ester of **92**.



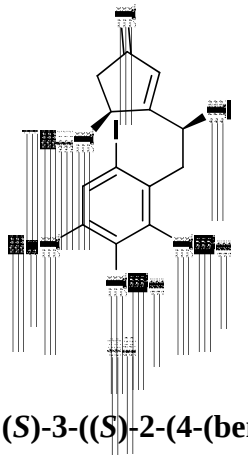
(*S*)-2-(4-(benzyloxy)-6-iodo-2,3-dimethoxyphenyl)-1-((3*R*,5*S*)-5-*tert*-butyldimethylsilyloxy-3-(triethylsilyloxy)cyclopent-1-enyl)-1-chloroethane (93). A solution of **92** (6.0 mg, 0.0081 mmol) in anhydrous CH_2Cl_2 (100 μL) at –25 °C was treated with anhydrous Et_3N (1.0 μL, 0.73 mg, 0.0072 mmol), stirred for 10 min, and then treated with methanesulfonyl chloride (1.5 μL, 2.2 mg, 0.019 mmol). The resultant mixture was slowly warmed to 0 °C and stirred under Ar for 4 h, then concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 7.5 cm, 8% EtOAc–hexanes elution) afforded **93** (4.0 mg, 0.0053 mmol, 65%) as a pale yellow oil: $[\alpha]^{25}_D$ +39.4 (*c* 1.14, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42–7.27 (m, 5H), 7.22 (s, 1H), 6.56 (s, 1H), 5.03 (s, 2H), 4.85 (t, *J* = 6.6 Hz, 1H), 4.61 (t, *J* = 6.3 Hz, 1H), 4.16 (t, *J* = 5.7 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.09 (d, *J* = 5.7 Hz, 1H), 3.02 (d, *J* = 5.4 Hz, 1H), 2.68 (dt, *J* = 11.4, 6.0 Hz, 1H), 1.65 (dt, *J* = 11.7, 5.7 Hz, 1H), 1.27–1.17 (m, 9H), 1.21 (s, 9H), 0.79 (q, *J* = 6.6 Hz,

6H), 0.24 (s, 3H), 0.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.4, 147.2, 142.1, 137.9, 132.4, 130.1, 123.8 (2C), 123.1 (2C), 122.5 (2C), 120.2, 96.6, 72.0, 71.9, 69.2, 68.5, 68.0, 56.0, 40.1, 36.6, 21.1 (3C), 13.3, 9.5 (3C), 6.0 (3C), –4.5, –4.6; IR (film) ν_{max} 2928, 2856, 1252, 1087 cm^{-1}; HRMS (ESI) *m/z* 776.24489 ($M(NH_4)^+$, $C_{34}H_{52}O_5ClISi_2NH_4$ requires 776.24247).



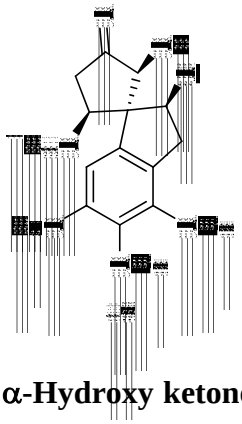
(1*R*,4*S*)-3-((*S*)-2-(4-(benzyloxy)-6-iodo-2,3-dimethoxyphenyl)-1-chloroethyl)-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-enol (94). A solution of **93** (10.0 mg, 0.013 mmol) in anhydrous THF (500 μL) at 0 °C was treated with HF·pyridine (1.2 M solution in THF, 10 μL, 0.12 mmol), stirred at 0 °C for 30 min, then warmed to rt and stirred for 30 min. The resultant mixture was diluted with EtOAc (2 mL), treated with sat aq $NaHCO_3$ (1 mL), extracted with EtOAc (3 × 1 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 6 cm, 15% EtOAc–hexanes elution) afforded **94** (6.1 mg, 0.0095 mmol, 72%) as a light yellow oil: $[\alpha]^{25}_D$ +31.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49–7.34 (m, 5H), 7.29 (s, 1H), 6.64 (s, 1H), 5.13 (s, 2H), 4.96–4.92 (m, 1H), 4.69–4.63 (m, 1H), 4.18–4.14 (m, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.08 (d, *J* = 4.8 Hz, 1H), 3.02 (d, *J* = 5.4 Hz, 1H), 2.77–2.67 (m, 1H), 2.01 (s, 1H), 1.75–1.67 (m, 1H), 0.89 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.3,

145.0, 141.3, 140.9, 135.4, 126.7 (2C), 126.0, 125.5 (2C), 123.2, 119.5, 107.4, 98.2, 71.5, 71.0, 69.1, 59.1, 59.0, 43.1, 39.6, 27.9, 24.0 (3C), 16.4, –4.4, –4.5; IR (film) ν_{max} 3395, 2954, 2911, 2876, 2360, 1605, 1458, 1414, 1355, 1290, 1239, 1117, 1077 cm^{-1}. HRMS (ESI) *m/z* 662.15397 ($M(NH_4)^+$, $C_{28}H_{42}ClINO_5Si$+ requires 662.15600).



(*S*)-3-((*S*)-2-(4-(benzyloxy)-6-iodo-2,3-dimethoxyphenyl)-1-chloroethyl)-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-enone (35). A solution of **94** (5.0 mg, 0.0078 mmol) in anhydrous CH_2Cl_2 (100 μL) was treated with anhydrous NaOAc (2.5 mg, 0.034 mmol) and 4Å MS (37 mg), then cooled to 0 °C and treated with pyridinium chlorochromate (33 mg, 0.15 mmol). The resultant mixture was warmed to rt and stirred for 30 min, then treated with Et_2O (1 mL), extracted with Et_2O (3 × 1 mL), filtered through Celite (washed with Et_2O), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 6 cm, 6% EtOAc–hexanes elution) afforded **35** (4.4 mg, 0.0068 mmol, 88%) as a colorless oil: $[\alpha]^{25}_D$ +10.7 (*c* 0.56, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.31 (m, 6H), 6.80 (s, 1H), 5.09 (s, 2H), 4.93–4.89 (m, 1H), 4.32–4.27 (m, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.25 (d, *J* = 6.6 Hz, 1H), 3.20 (d, *J* = 6.9 Hz, 1H), 2.75 (d, *J* = 7.2 Hz, 1H), 1.69 (d, *J* = 6.9 Hz, 1H), 0.91 (s, 9H), 0.08 (s, 3H), 0.00 (s, 3H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.5, 157.2, 147.7, 147.6, 142.5, 138.7, 132.8, 124.1 (2C), 123.5, 122.9 (2C), 120.6, 111.6, 95.7, 72.3, 68.9, 68.4, 66.6, 56.6, 40.5, 37.0, 21.5 (3C), 13.8, –5.0, –5.1; IR (film) ν_{max} 2955, 2876, 1726, 1274, 1167, 1086 cm^{-1}; HRMS (ESI) *m/z* 643.11247 (MH^+, $C_{28}H_{36}O_5ClISiH$ requires 643.11380).



α-Hydroxy ketone 97: A solution of **35** (7.0 mg, 0.011 mmol) in anhydrous THF (100 μL) at 0 °C was treated with hexabutylditin (5.8 μL, 6.7 mg, 0.011 mmol) and triethylaluminum (1.0 M solution in THF, 32 μL, 0.032 mmol). The resultant mixture was irradiated at 0 °C with a sunlamp for 6 h (frequent addition of ice to the cooling bath was necessary to maintain this temperature). Then, 3-phenyl-2-(phenylsulfonyl)-oxaziridine[3] (ca. 0.5 M solution in THF, 100 μL, 0.05 mmol) was added to the mixture, and it was stirred at 0 °C (without irradiation) for 5 h, then at rt for 2 h. The resultant mixture was extracted with EtOAc (3 × 0.5 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 9 cm, 10–15% EtOAc in hexanes gradient elution) afforded **96** (3.6 mg, 0.0067 mmol, 62%) as a colorless oil: $[\alpha]^{25}_D$ +26 (*c* 0.23, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53–7.32 (m, 6H), 5.06 (s, 2H), 4.82 (t, *J* = 7.2

Hz, 1H), 4.45 (t, *J* = 6.6 Hz, 1H), 4.25 (s, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 2.99 (d, *J* = 6.9 Hz, 1H), 2.91 (d, *J* = 6.6 Hz, 1H), 2.62 (d, *J* = 6.9 Hz, 1H), 2.11 (d, *J* = 7.2 Hz, 1H), 1.51 (br s, 1H), 0.88 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.5, 149.7, 149.6, 146.4, 142.5, 134.8, 127.8 (2C), 127.3, 126.4 (2C), 121.8, 103.4, 92.2, 72.1, 66.2, 64.2, 63.8, 63.1, 49.7, 42.7, 38.8, 22.2 (3C), 16.1, –4.9, –5.0; DEPT NMR ($CDCl_3$, 75 MHz) **C:** 207.5, 149.7, 149.6, 146.4, 142.5, 134.8, 121.8, 64.2, 16.1 **CH:** 127.8, 127.3, 126.4, 103.4, 92.2, 66.2, 49.7 **CH_2:** 72.1, 42.7, 38.8 **CH_3:** 63.8, 63.1, 22.2, –4.9, –5.0; 2D ^{1}H–^{1}H COSY NMR ($CDCl_3$, 500 MHz) 4.82/2.62 (s), 4.82/2.11 (s), 4.45/2.99 (s), 4.45/2.91 (s); 2D ^{1}H–^{13}C HMQC NMR ($CDCl_3$, 500 MHz) 7.53–7.32/127.8, 7.53–7.32/127.3, 7.53–7.32/126.4, 7.53–7.32/103.4, 5.06/72.1, 4.82/66.2, 4.45/49.7, 4.25/92.2, 3.90 and 3.84/63.8 and 63.1, 2.99/38.8, 2.91/38.8, 2.62/42.7, 2.11/42.7, 0.88/22.2, 0.13 and 0.11/–4.9 and –5.0; IR (film) ν_{max} 3012, 2955, 2878, 2857, 1728, 1471, 1356, 1251, 1134, 1087 cm^{-1}; HRMS (ESI) *m/z* 533.21177 (MH^+, $C_{28}H_{37}O_6ClSiH$ requires 533.21207).

The iodide **95** (0.5 mg, 0.00076 mmol, 7%) and reduced compound **96** (0.2 mg, 0.00037 mmol, 3%) were also obtained. For **95**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49–7.34 (m, 6H), 5.13 (s, 2H), 4.98–4.92 (m, 1H), 4.72–4.63 (m, 1H), 4.59 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.00 (d, *J* = 6.6 Hz, 1H), 2.93 (d, *J* = 6.6 Hz, 1H), 2.65 (d, *J* = 6.6 Hz, 1H), 2.02 (d, *J* = 6.9 Hz, 1H), 0.89 (s, 9H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.1, 146.3, 146.2, 144.4, 139.1, 139.0, 120.8 (2C), 120.1 (2C), 119.5, 113.6, 91.4, 71.2,

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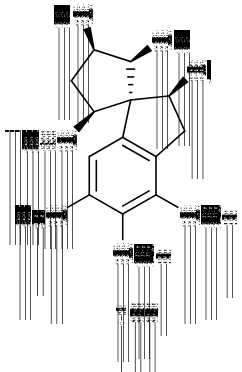
[3] Davis, F. A.; Vishawakarma, L. C.; Billmers, J. G.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241.

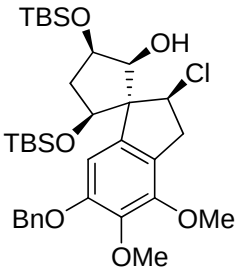
67.1, 63.9, 63.5, 63.0, 53.2, 47.4, 41.1, 37.3, 22.0 (3C), 14.4, –4.4, –4.5; HRMS (ESI) *m/z* 643.11245 (MH^+, $C_{28}H_{36}O_5ClISiH$ requires 643.11380). For **96**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.31 (m, 6H), 5.10 (s, 2H), 4.93–4.88 (m, 1H), 4.65 (t, *J* = 6.3 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.92 (d, *J* = 6.6 Hz, 1H), 2.85 (d, *J* = 6.6 Hz, 1H), 2.65 (d, *J* = 6.9 Hz, 1H), 2.49 (s, 1H), 2.05 (s, 1H), 2.00 (d, *J* = 6.9 Hz, 1H), 0.92 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.2, 145.4, 144.1, 143.8, 142.6, 139.8, 120.1 (2C), 118.8, 118.3 (2C), 114.4, 96.5, 73.0, 69.6, 65.5, 63.9, 62.7, 51.2, 40.6, 40.0, 39.2, 25.8 (3C), 17.6, –4.3, –4.4; HRMS (ESI) *m/z* 534.23974 ($M(NH_4)^+$, $C_{28}H_{37}O_5ClSiNH_4$ requires 534.24370).

Conversion of **95** into **36**. A solution of **95** (9.6 mg, 0.015 mmol) in anhydrous THF (200 μL) at 0 °C was treated with Et_2Zn (1.0 M solution in hexane, 45 μL, 0.045 mmol) and stirred vigorously under O_2 (balloon) for 2 h. Then, 3-phenyl-2-(phenylsulfonyl)-oxaziridine (ca. 0.5 M solution in THF, 150 μL, 0.075 mmol) was added to the mixture, and it was stirred for 4 h, treated with 1 N HCl (50 μL) and H_2O (1 mL), and extracted with EtOAc (3 × 1 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 7 cm, 10–15% EtOAc in hexanes gradient elution) afforded **36** (5.0 mg, 0.0094 mmol, 62%) as a colorless oil.



(+)-(1*R*,2*S*,2'*S*,3*R*,5*S*)-6'-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2'-chloro-4',5'-dimethoxy-2',3'-dihydrospiro[cyclopentane-1,1'-indene]-2,3-diol (100). A solution of **96** (150 mg, 0.281 mmol) in anhydrous THF (2 mL) at 0 °C under Ar was treated with L-Selectride (1.0 M solution in THF, 280 μL, 0.28 mmol). The resultant mixture was stirred at 0 °C for 1.5 h, then treated with sat aq NH_4Cl (1 mL) and warmed to rt. The mixture was extracted with EtOAc (3 × 3 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 × 11 cm, 20% EtOAc–hexanes elution) afforded **100** (132 mg, 0.247 mmol, 88%) as a pale yellow solid in 9:1 dr. A diastereomerically pure sample could be obtained after further purification: $[\alpha]^{25}_D$ +22.7 (*c* 1.39, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42–7.12 (m, 5H), 6.75 (s, 1H), 5.07 (s, 2H), 4.87 (dd, *J* = 11.1, 5.7 Hz, 1H), 4.27 (d, *J* = 6.6 Hz, 1H), 4.08 (br s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.64 (br s, 1H), 3.56–3.38 (m, 2H), 3.06 (t, *J* =12.0 Hz, 1H), 2.89 (dd, *J* =12.6, 7.2 Hz, 1H), 2.03–1.98 (m, 1H), 1.70–1.61 (m, 1H), 0.88 (s, 9H), 0.21 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.6, 146.4, 146.3, 144.3, 139.1, 139.0, 120.8 (2C), 120.1, 119.5 (2C), 113.6, 73.5, 71.2, 67.2, 64.0, 63.5, 63.0, 53.2, 47.4, 41.1, 37.3, 23.9, 22.0 (3C), –4.4, –4.5; IR (film) ν_{max} 3548, 2911, 1626, 1450, 1219, 1091, 933 cm^{-1}; HRMS (ESI) *m/z* 557.20989 (MNa^+, $C_{28}H_{39}ClO_6SiNa^+$ requires 557.20966).

The *cis* relative stereochemistry of **100** was assigned based on the 6.6 Hz coupling constant of the two α-hydroxy hydrogens. This value is similar to coupling constants reported by Hartung and Paquette[4] for related *cis* compounds (4.2–5.8 Hz) and differs markedly from the value reported by Christol and Vanel[5] for a related *trans* compound (10 Hz). Additionally, molecular models of **77** demonstrate that approach of the reducing agent to the top (*re*) face of the carbonyl, which would afford the *trans* isomer, is hindered by the neighboring chloride substituent.



101

(+)-(1*R*,2*S*,2'*S*,3*R*,5*S*)-6'-(benzyloxy)-3,5-bis(*tert*-butyldimethylsilyloxy)-2'-chloro-4',5'-dimethoxy-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-2-ol (101). A solution of **100** (140 mg, 0.262 mmol) in anhydrous CH_2Cl_2 (5.0 mL) under Ar was treated with Et_3N (450 μL), then cooled to 0 °C. TBS-Cl (59 mg, 0.39 mmol, 1.5 equiv) was added portionwise to the mixture, and it was stirred at 0 °C for 2 h, then at rt for 1 h. The resultant mixture was diluted with EtOAc (5 mL), treated with sat aq NH_4Cl (3 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL),

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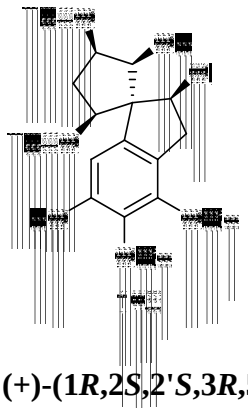
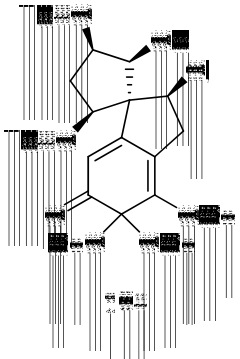
[4] Hartung, R. E.; Paquette, L. A. *Synthesis* **2005**, 3209.
[5] Christol, H.; Vanel, R. *Bull. Soc. Chim. Fr.* **1968**, 1393.

dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 × 10 cm, 7.5% EtOAc–hexanes elution) afforded **101** (148 mg, 0.228 mmol, 87%) as a light yellow oil: $[\alpha]^{25}_D$ +17 (*c* 1.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49–7.27 (m, 5H), 6.54 (s, 1H), 5.07 (s, 2H), 4.67 (dd, *J* = 12.6, 7.2 Hz, 1H), 4.16 (d, *J* = 6.9 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.71 (br s, 1H), 3.62–3.44 (m, 2H), 3.05 (t, *J* = 12.0 Hz, 1H), 2.70 (dd, *J* = 12.6, 7.5 Hz, 1H), 2.01–1.94 (m, 1H), 1.67–1.63 (m, 1H), 1.17 (s, 9H), 0.99 (s, 9H), 0.20 (s, 6H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.2, 160.4, 155.1, 151.8, 145.9, 145.6, 137.6 (2C), 136.9, 136.0 (2C), 133.7, 79.9, 79.5, 75.2, 72.6, 72.2, 70.3, 53.7, 51.8, 38.1, 34.1 (3C), 34.0 (3C), 33.2, 26.3, 17.1,–4.4 (2C), –4.5 (2C); IR (film) ν_{max} 3577, 2897, 1610, 1442, 989 cm^{-1}; HRMS (ESI) *m/z* 649.31418 (MH^+, $C_{34}H_{53}ClO_6Si_2H^+$ requires 649.31420).



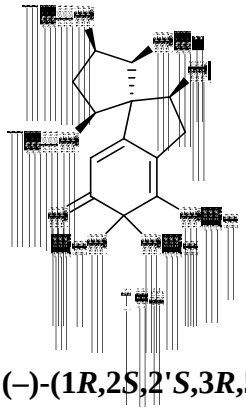
(+)-(1*R*,2*S*,2'*S*,3*R*,5*S*)-3,5-bis(*tert*-butyldimethylsilyloxy)-2'-chloro-4',5'-dimethoxy-2',3'-dihydrospiro[cyclopentane-1,1'-indene]-2,6'-diol (102). A solution of **101** (148 mg, 0.228 mmol) in anhydrous MeOH (5.0 mL) was treated with 10% Pd/C (40 mg, 0.27 wt equiv). The resultant mixture was stirred at rt under H_2 (1 atm) for 4 h, then filtered through a plug of Celite (washed with CH_2Cl_2), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 8 cm, 10% EtOAc–hexanes elution) afforded **102** (123 mg, 0.220 mmol, 96%) as a pale yellow oil: $[\alpha]^{25}_D$ +27 (*c* 1.7,

$CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.82 (s, 1H), 4.43 (dd, *J* = 12.6, 7.2 Hz, 1H), 4.21 (d, *J* = 6.9 Hz, 1H), 3.91 (s, 3H), 3.88–3.84 (br s, 1H), 3.84 (s, 3H), 3.63 (br s, 1H), 3.54–3.31 (m, 2H), 2.87 (t, *J* = 12.0 Hz, 1H), 2.66 (dd, *J* = 12.6, 7.2 Hz, 1H), 2.00–1.90 (m, 1H), 1.74–1.62 (m, 1H), 1.16 (s, 9H), 1.10 (s, 9H), 0.19 (s, 6H), 0.16 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.1, 142.8, 139.1, 133.2, 128.6, 128.1, 82.7, 75.8, 75.3, 69.5, 69.0, 66.5, 61.1, 40.8, 36.7, 25.8, 22.1 (6C), 13.8, –4.4 (2C), –4.5 (2C); IR (film) ν_{max} 3212, 1258, 1122, 1077 cm^{-1}; HRMS (ESI) *m/z* 559.26731 (MH^+, $C_{27}H_{47}ClO_6Si_2H^+$ requires 559.26725).



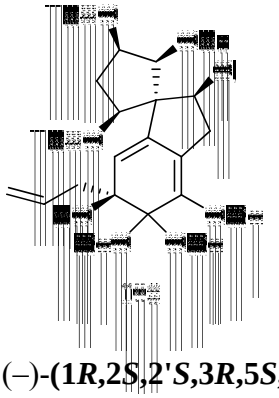
(–)-(1*R*,2*S*,2'*S*,3*R*,5*S*)-3,5-bis(*tert*-butyldimethylsilyloxy)-2'-chloro-2-hydroxy-4',5',5'-trimethoxy-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-6'(5'H)-one (103). A solution of **102** (98.0 mg, 0.175 mmol) in anhydrous CH_3OH (3.0 mL) was added to a mixture of $KHCO_3$ (30 mg, 0.35 mmol, 2.0 equiv), $PhI(OAc)_2$ (62 mg, 0.19 mmol, 1.1 equiv), and anhydrous CH_3OH (3.0 mL) at –10 °C under Ar. The resulting yellow–orange mixture was stirred for 10 min, diluted with CH_2Cl_2 (5 mL), and washed with brine (10 mL). The layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 × 10 cm, 10% EtOAc–hexanes elution) afforded **103** (69.0 mg, 0.117 mmol, 67%) as a yellow oil: $[\alpha]^{25}_D$ –15 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.25 (s, 1H), 4.55 (dd, *J* = 12.6, 7.5 Hz, 1H), 4.13

(d, J = 6.9 Hz, 1H), 3.98 (s, 3H), 3.61 (br s, 1H), 3.49–3.24 (m, 2H), 3.37 (s, 3H), 3.32 (s, 3H), 2.79 (t, J = 11.8 Hz, 1H), 2.58 (dd, J = 12.6, 7.5 Hz, 1H), 1.93–1.81 (m, 1H), 1.58–1.49 (m, 1H), 0.91 (s, 9H), 0.86 (s, 9H), 0.10 (s, 6H) 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.1, 142.8, 139.1, 133.2, 121.4, 117.7, 82.8, 69.9, 69.5, 69.0, 66.5, 61.1, 56.5, 56.4, 40.9, 37.7, 23.8, 22.1 (6C), 13.8, –4.4 (2C), –4.6 (2C); IR (film) ν_{max} 3337, 2450, 1755, 1233, 956 cm^{-1}; HRMS (ESI) *m/z* 606.30440 (MNH_4^+, $C_{28}H_{49}ClO_7Si_2NH_4^+$ requires 606.30436).



(–)-(1*R*,2*S*,2'*S*,3*R*,5*S*)-2-(benzyloxy)-3,5-bis(*tert*-butyldimethylsilyloxy)-2'-chloro-4',5',5'-trimethoxy-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-6'(5'H)-one (104). A solution of **103** (110 mg, 0.187 mmol) in anhydrous DMF (1.5 mL) at rt under Ar was treated with NaH (60% dispersion in mineral oil, 7.6 mg, 4.6 mg NaH, 0.19 mmol), tetrabutylammonium iodide (70 mg, 0.190 mmol), and benzyl bromide (23 μL, 32.9 mg, 0.192 mmol). The resultant brown solution was stirred at 60 °C for 5 h, cooled to rt, diluted with CH_2Cl_2 (2 mL), and washed with brine (2 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 × 3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 12 cm, 1% Et_3N in 5% EtOAc–hexanes elution) afforded **104** (111 mg, 0.163 mmol, 88%) as a brown oil: $[\alpha]^{25}_D$ –21 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ

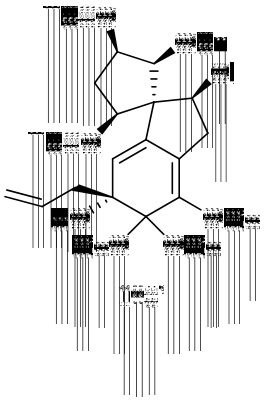
7.42–7.18 (m, 5H), 6.39 (s, 1H), 5.20 (s, 2H), 4.99 (dd, *J* = 12.6, 7.5 Hz, 1H), 4.76–4.72 (m, 1H), 3.92 (s, 3H), 3.63–3.46 (m, 2H), 3.56 (s, 3H), 3.51, (s, 3H), 3.14 (t, *J* = 11.8 Hz, 1H), 2.77 (dd, *J* = 12.6, 7.5 Hz, 1H), 1.83–1.71 (m, 1H), 1.49–1.38 (m, 1H), 0.98 (s, 9H), 0.97 (s, 9H); 0.089 (s, 6H), 0.086 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.7, 150.3, 145.1, 141.3, 135.4, 126.6 (2C), 126.0, 125.4 (2C), 123.1, 107.4, 72.1, 71.5, 71.0, 69.5, 66.0, 59.2, 59.0, 55.1, 43.4, 39.6, 27.8, 24.1 (3C), 24.0 (3C), 16.3 (2C), –4.4 (2C), –4.5 (2C); IR (film) ν_{max} 3284, 2566, 1727 cm^{-1}; HRMS (ESI) *m/z* 679.32488 (MH^+, $C_{35}H_{55}ClO_7Si_2H^+$ requires 679.32476).



(–)-**(1*R*,2*S*,2'*S*,3*R*,5*S*,6'*S*)-6'-allyl-2-(benzyloxy)-3,5-bis(*tert*-butyldimethylsilyloxy)-2'-chloro-4',5',5'-trimethoxy-2',3',5',6'-tetrahydrospiro [cyclopentane-1,1'-inden]-6'-ol (105).** A solution of bis((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)methane[6] (76 mg, 0.24 mmol) and 2,2′-dipyridyl (2 crystals), in anhydrous THF (200 μL) under Ar at 0 °C was treated dropwise with *n*-BuLi (1.6 M in hexanes, 250 μL, 0.40 mmol) until the mixture turned a reddish-brown color. The solution was warmed to rt and stirred for 1 h, then treated dropwise with allylzinc

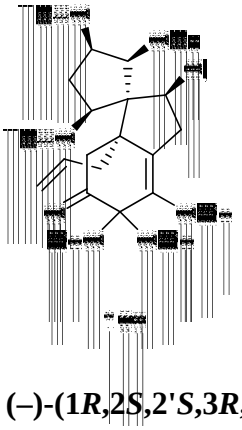
[6] Hall, J.; Lehn, J.-M.; DeCian, A.; Fischer, J. *Helv. Chim. Acta* **1991**, *74*, 1.

bromide (1.0 M in THF, 240 μL, 0.24 mmol) and cooled to –78 °C. A solution of ketone **104** (95 mg, 0.14 mmol) in anhydrous THF (220 μL) was added dropwise, and the resultant mixture was stirred at –78 °C under Ar for 1 h. The reaction was quenched by the addition of MeOH–H_2O (1:1, 1 mL), and the mixture was extracted with Et_2O (3 × 1 mL). The combined organic layers were washed with NaOH (0.5 M, 1 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2:23:75 Et_3N/EtOAc/hexanes elution) afforded **105** (79 mg, 0.11 mmol, 93:7 dr, 79%) as a colorless oil: $[\alpha]^{25}_D$ –36 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47–7.31 (m, 5H), 6.37–6.27 (m, 1H), 6.21 (s, 1H), 5.24 (dd, *J* = 12.3, 7.2 Hz, 1H), 5.19 (s, 2H), 4.93–4.79 (m, 2H), 4.65 (d, *J* = 6.9 Hz, 1H), 3.82 (s, 3H), 3.47–3.27 (m, 3H), 3.41 (s, 3H), 3.37 (s, 3H), 3.09 (t, *J* = 12.0 Hz, 1H), 2.74 (dd, *J* = 12.3, 7.2 Hz, 1H), 1.85–1.77 (m, 1H), 1.73–1.65 (m, 1H), 1.57–1.53 (m, 1H), 1.50–1.37 (m, 1H), 0.91 (s, 9H), 0.85 (s, 9H), 0.11 (s, 6H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.3, 145.1, 141.3, 140.9, 135.4, 126.7 (2C), 126.1, 125.5 (2C), 123.3, 123.2, 107.4, 73.8, 72.1, 71.5, 71.0, 69.1, 65.4, 59.1, 59.0, 55.5, 48.0, 43.1, 39.6, 27.9, 24.1 (3C), 24.0 (3C), 16.4 (2C), –4.4 (2C), –4.5 (2C); IR (film) ν_{max} 3087, 2991, 2836, 1629, 1467, 933 cm^{-1}; HRMS (ESI) *m/z* 721.37162 (MH^+, $C_{38}H_{61}ClO_7Si_2H^+$ requires 721.37171).



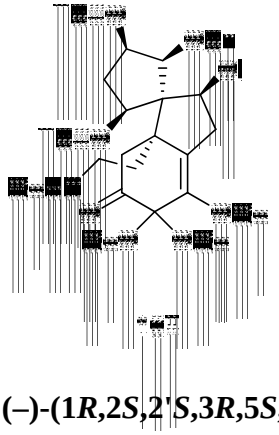
(1R,2S,2'S,3R,5S,6'R)-6'-allyl-2-(benzyloxy)-3,5-bis(tert-butyldimethylsilyloxy)-2'-chloro-4',5',5'-trimethoxy-2',3',5',6'-tetrahydrospiro [cyclopentane-1,1'-inden]-6'-ol

A solution of bis((*R*)-4-phenyl-4,5-dihydrooxazol-2-yl)methane (9.5 mg, 0.03 mmol) and 2,2′-dipyridyl (1 crystals), in anhydrous THF (25 μL) under Ar at 0 °C was treated dropwise with *n*-BuLi (1.6 M in hexanes, 32 μL, 0.05 mmol) until the mixture turned a reddish-brown color. The solution was warmed to rt and stirred for 1 h, then treated dropwise with allylzinc bromide (1.0 M in THF, 30 μL, 0.03 mmol) and cooled to –78 °C. A solution of ketone **104** (12 mg, 0.018 mmol) in anhydrous THF (30 μL) was added dropwise, and the resultant mixture was stirred at –78 °C under Ar for 1 h. The reaction was quenched by the addition of MeOH–H_2O (1:1, 0.5 mL), and the mixture was extracted with Et_2O (3 × 0.5 mL). The combined organic layers were washed with NaOH (0.5 M, 0.5 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2:23:75 Et_3N/EtOAc/hexanes elution) afforded **105'** (8.9 mg, 0.012 mmol, 13:87 dr, 69%) as a colorless oil: $[\alpha]^{25}_D$ 12.4 (*c* 0.88, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48–7.34 (m, 5H), 6.50–6.40 (m, 1H), 6.21 (s, 1H), 5.26 (dd, *J* = 12.3, 7.2 Hz, 1H), 5.22 (s, 2H), 5.00–4.87 (m, 2H), 4.66 (d, *J* = 6.9 Hz, 1H), 3.83 (s, 3H), 3.51–3.30 (m, 3H), 3.44 (s, 3H), 3.40 (s, 3H), 3.12 (t, *J* = 12.0 Hz, 1H), 2.76 (dd, *J* = 12.3, 7.2 Hz, 1H), 1.95–1.88 (m, 1H), 1.75–1.68 (m, 1H), 1.60–1.58 (m, 1H), 1.53–1.40 (m, 1H), 0.94 (s, 9H), 0.88 (s, 9H), 0.14 (s, 6H), 0.11 (s, 6H); IR (film) ν_{max} 3054, 2980, 1655, 1521, 1458, 917, 632 cm^{-1}; HRMS (ESI) *m/z* 721.37180 (MH^+, $C_{38}H_{61}ClO_7Si_2H^+$ requires 721.37171).



(–)-(1*R*,2*S*,2'*S*,3*R*,5*S*,7a'*R*)-7a'-allyl-2-(benzyloxy)-3,5-bis(*tert*-butyldimethylsilyloxy)-2'-chloro-4',5',5'-trimethoxy-2',3',7',7a'-tetrahydrospiro [cyclopentane-1,1'-inden]-6'(5'H)-one (106). A mixture of 18-crown-6 (34 mg, 0.13 mmol), KO*t*-Bu (14 mg, 0.13 mmol), and anhydrous THF (700 μl) at 0 °C under Ar was stirred for 15 min, then treated with a solution of **105** (30.0 mg, 0.0416 mmol) in anhydrous THF (150 μL, added dropwise over 3 min). The resulting mixture was stirred at 0 °C under Ar for 1 h. The reaction was quenched by the addition of H_2O (1 mL), and the mixture was diluted with Et_2O (2 mL). The layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 1% Et_3N in 10% EtOAc–hexanes elution) afforded **106** (27.5 mg, 0.0381 mmol, 92%) as a colorless oil: $[\alpha]^{25}_D$ –22 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52–7.34 (m, 5H), 5.88–5.76 (m, 1H), 5.27 (dd, *J* = 12.2, 7.0 Hz, 1H), 5.20 (s, 2H), 5.00–4.88 (m, 2H), 4.60 (d, *J* = 6.9 Hz, 1H), 3.91 (s, 3H), 3.58–3.42 (m, 2H), 3.50 (s, 3H), 3.45 (s, 3H), 3.10 (t, *J* = 11.8 Hz, 1H), 2.98 (d, *J* = 14.7 Hz, 1H), 2.72 (dd, *J* = 12.2, 7.0 Hz, 1H), 2.56 (d, *J* = 15.0 Hz, 1H), 1.89–1.81 (m, 1H), 1.78–1.69 (m, 1H), 1.67–1.62 (m, 1H), 1.58–1.51 (m, 1H). 0.97 (s, 9H), 0.94 (s, 9H), 0.10 (s, 6H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.5, 147.7, 142.5, 138.8, 132.8, 124.2 (2C), 123.5, 122.9 (2C), 120.7, 104.8, 71.1, 69.6,

68.9, 68.4, 66.6, 56.6, 56.4, 52.9, 49.8, 41.2, 40.5, 37.0, 36.3, 25.3, 21.5 (3C), 21.4 (3C), 13.9 (2C), –5.0 (2C), –5.1 (2C); IR (film) ν_{max} 3055, 2978, 2844, 1782, 1631, 1423, 1012, 941 cm^{-1}; HRMS (ESI) *m/z* 721.37180 (MH^+, $C_{38}H_{61}ClO_7Si_2H^+$ requires 721.37171).



(–)-(1*R*,2*S*,2'*S*,3*R*,5*S*,7a'*R*)-2-(benzyloxy)-3,5-bis(*tert*-butyldimethylsilyloxy)-2'-chloro-4',5',5'-trimethoxy-7a'-(2-(methylamino)ethyl)-2',3',7',7a'-tetrahydrospiro [cyclopentane-1,1'-inden]-6'(5'H)-one (107). A saturated solution of O_3 in EtOAc was prepared by bubbling ozone through EtOAc at –78 °C for 10 min. The concentration was determined to be 0.007 M as measured by titration with styrene.[7] Then, a solution of **106** (27 mg, 0.037 mmol), pyridine (10 μL), and Et_3N (16.0 μL, 11.6 mg, 0.115 mmol, 3.1 equiv) in EtOAc (0.5 mL) was cooled to –40 ° C. A portion of the previously prepared solution of O_3 in EtOAc (0.007 M, 8 mL, 0.056 mmol, 1.5 equiv), which was precooled to –78 ° C, was then added to this solution. The resultant mixture was stirred at –78 °C for 5 min, then diluted with anhydrous MeOH (1.0 mL) and treated with powdered 4 Å molecular sieves (30 mg) and CH_3NH_2 (2.0 M in MeOH, 76 μL, 0.15 mmol, 4.1 equiv). This mixture was stirred at rt under Ar for 30 min, then treated with $NaBH_3CN$ (4.8 mg,

0.076 mmol) and stirred for 16 h. It was then diluted with EtOAc (2 mL), washed with aq KOH (10 M, 1 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 1% Et_3N in 15–20% EtOAc–hexanes gradient elution) afforded recovered **106** (7.3 mg, 27% recovery) and **107** (15 mg, 0.020 mmol, 54%, 74% based on recovered **106**) as a yellow oil: $[\alpha]^{25}_D$ –25 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52–7.32 (m, 5H), 5.05 (s, 2H), 4.83 (dd, *J* = 12.0, 6.9 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 1H), 4.02 (s, 3H), 3.87–3.73 (m, 2H), 3.62 (s, 3H), 3.57 (s, 3H), 3.06 (t, *J* = 11.8 Hz, 1H), 2.97 (s, 3H), 2.71–2.62 (m, 2H), 2.38 (dd, *J* = 12.2, 7.0 Hz, 1H), 2.28 (d, *J* = 15.0 Hz, 1H), 2.23 (br s, 1H), 2.18–2.13 (m, 1H), 2.00 (d, *J* = 15.0 Hz, 1H), 1.69–1.61 (m, 1H), 1.44–1.38 (m, 1H), 1.35–1.28 (m, 1H), 0.87 (s, 9H), 0.81 (s, 9H), 0.10 (s, 6H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.1, 152.4, 147.1, 137.4, 128.8 (2C), 128.1, 127.5 (2C), 109.4, 75.1, 74.1, 73.6, 73.0, 71.2, 61.2, 61.0, 54.1, 50.0, 47.0, 45.9, 45.1, 41.7, 40.9, 39.2, 29.9, 26.1 (3C), 26.0 (3C), 18.2 (2C), –4.5 (2C), –5.0 (2C); IR (film) ν_{max} 3125, 2923, 2810, 1741, 1633, 1420, 1208, 1138, 982 cm^{-1}; HRMS (ESI) *m/z* 760.38014 (MNa^+, $C_{38}H_{64}ClNO_7Si_2Na^+$ requires 760.38021).

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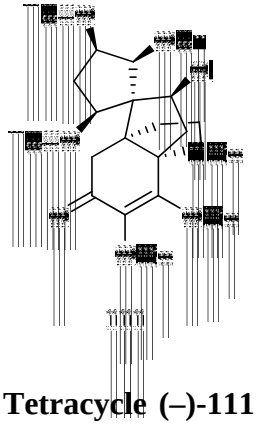
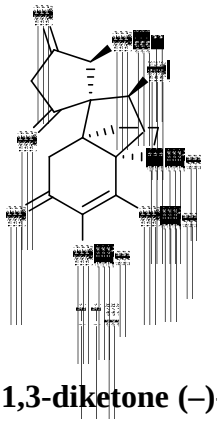
[7] Wender, P. A.; DeChristopher, B. A.; Schrier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 6658.

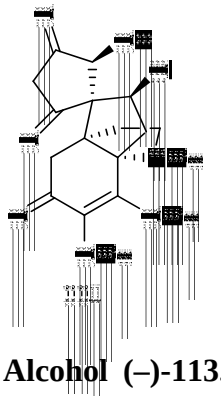


Tetracycle (–)-111. A mixture of **107** (15 mg, 0.020 mmol), 4 Å MS (80 mg), and anhydrous CH_2Cl_2 (2.0 mL) was stirred at rt under Ar for 10 min, then cooled to –40 ° C. Next, BCl_3 (1.0 M in CH_2Cl_2, 30 μL, 0.030 mmol, 1.5 equiv) was added dropwise, and the resultant mixture was stirred at –40 °C under Ar for 18 h, then concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 2:30:68 Et_3N/EtOAc/hexanes elution), affording **111** (6.4 mg, 0.0091 mmol, 45%) as a colorless oil: $[\alpha]^{25}_D$ –79 (*c* 1.2, $CHCl_3$); ^{1}H NMR (pyridine-d_5, 500 MHz) δ 7.44–7.41 (m, 3H), 7.36–7.33 (m, 2H), 5.25 (dd, *J* = 12.2, 6.8 Hz, 1H), 5.12 (s, 2H), 4.80 (d, *J* = 7.0 Hz, 1H), 4.14 (s, 3H), 3.84 (s, 3H), 3.50–3.44 (m, 1H), 3.41–3.36 (m, 1H), 3.20 (t, *J* = 12.0 Hz, 1H), 3.11 (d, *J* =15.5 Hz, 1H), 2.75–2.69 (m, 3H), 2.61 (d, *J* = 15.5 Hz, 1H), 2.52–2.47 (m, 1H), 2.46 (s, 3H), 1.71–1.68 (m, 1H), 1.55–1.50 (m, 1H), 1.46–1.40 (m, 1H), 0.96 (s, 9H), 0.92 (s, 9H), 0.26 (s, 3H), 0.22 (s, 3H), 0.13 (s, 6H); ^{13}C NMR (pyridine-d_5, 125 MHz) δ 192.0, 158.8, 142.3, 138.1, 129.9 (2C), 129.2, 128.4 (2C), 76.2, 75.8, 75.3, 74.2, 72.0, 67.4, 59.5, 59.2, 56.9, 52.3, 50.8, 46.3, 44.0, 40.5, 37.6, 35.4, 30.0 (3C), 29.8 (3C), 20.0 (2C), –4.1 (2C), –4.2 (2C); IR (film) ν_{max} 3209, 2974, 2795, 1763, 1651, 1402, 1265, 912 cm^{-1}; HRMS (ESI) *m/z* 706.37199 (MH^+, $C_{37}H_{60}ClNO_6Si_2H^+$ requires 706.37205).

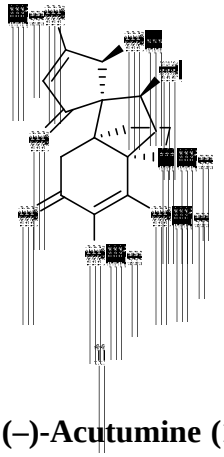


1,3-diketone (–)-115. A solution of **111** (8.7 mg, 0.012 mmol) in anhydrous THF (100 μL) at 0 °C under Ar was treated with TBAF (1.0 M in THF, 27 μL, 0.027 mmol, 2.2 equiv) in one portion. The resulting mixture was stirred at 0 °C for 20 min. The reaction was quenched by the addition of ice water (0.5 mL), and the mixture was extracted with cold CH_2Cl_2 (cooled in ice bath, 3 × 0.5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo in an ice bath. The unstable crude diol was dissolved in acetone (0.5 mL) at 0 °C, then 4 Å MS (50 mg), NMO (4.2 mg, 0.036 mmol), and TPAP (0.4 mg, 0.001 mmol) were added in order to the solution. The resulting mixture was stirred at 0 °C under Ar for 30 min, then slowly warmed to rt over 1 h and stirred at rt for 1 additional h. It was then filtered through a plug of SiO_2 (rinsed with 5 mL EtOAc), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1% Et_3N in 2% MeOH–CH_2Cl_2 elution) afforded **112** (3.3 mg, 0.0070 mmol, 57%) as a white solid: $[\alpha]^{25}_D$ –122 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (pyridine-d_5, 500 MHz) δ 7.46–7.42 (m, 3H), 7.39–7.37 (m, 2H), 5.20 (dd, *J* = 12.0, 6.5 Hz, 1H), 5.02 (s, 2H), 4.87 (s, 1H), 4.10 (s, 3H), 3.92 (d, *J* = 14.0 Hz, 1H), 3.80 (s, 3H), 3.74 (d, *J* = 14.0 Hz, 1H), 3.16 (t, *J* = 12.5 Hz, 1H), 3.07 (d, *J* =16.0 Hz, 1H), 2.70–2.63 (m, 3H), 2.55 (d, *J* = 15.5 Hz, 1H), 2.45–2.41 (m, 1H), 2.40 (s, 3H), 1.65–1.62 (m, 1H); ^{13}C NMR (pyridine-d_5, 125

MHz) δ 202.8, 201.4, 193.3, 160.2, 143.6, 139.4, 131.6 (2C), 130.9, 130.3 (2C), 73.4, 71.9, 71.2, 69.1, 60.9, 60.6, 59.3, 58.3, 52.1, 47.7, 46.9, 41.9, 39.0, 36.8; IR (film) ν_{max} 3024, 2931, 2795, 1825, 1633, 1429, 1176, 955 cm^{-1}; HRMS (ESI) *m/z* 474.16785 (MH^+, $C_{25}H_{28}ClNO_6H^+$ requires 474.16779).



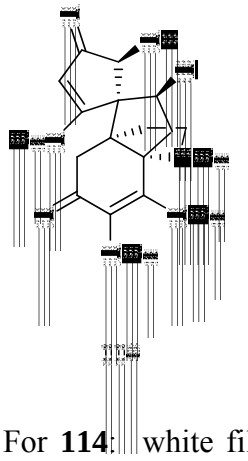
Alcohol (–)-113. To a solution of **112** (3.0 mg, 0.0063 mmol) in anhydrous MeOH (1.0 mL) under Ar was added 10% Pd/C (10 mg, 3.3 wt equiv). The resulting mixture was stirred at rt under H_2 (1 atm) for 2 h, then filtered through a plug of Celite (washed with CH_2Cl_2), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 8 cm, 5% MeOH–CH_2Cl_2 elution) afforded **113** (2.4 mg, 0.0063 mmol, 99%) as a pale yellow oil: $[\alpha]^{25}_D$ –135 (*c* 0.6, CH_2Cl_2); ^1H NMR (pyridine-d_5, 500 MHz) δ 8.66 (br s, 1H), 5.30 (dd, *J* = 12.0, 6.5 Hz, 1H), 5.13 (s, 1H), 4.14 (s, 3H), 4.03 (d, *J* = 14.0 Hz, 1H), 3.83 (s, 3H), 3.76 (d, *J* = 14.0 Hz, 1H), 3.26 (t, *J* = 12.2 Hz, 1H), 3.17 (d, *J* = 15.5 Hz, 1H), 2.82–2.74 (m, 3H), 2.65 (d, *J* = 15.5 Hz, 1H), 2.55–2.52 (m, 1H), 2.50 (s, 3H), 1.76–1.73 (m, 1H); ^{13}C NMR (pyridine-d_5, 125 MHz) δ 203.1. 201.7, 194.1, 160.9, 140.2, 72.9, 71.7, 69.3, 60.2, 59.9, 56.8, 55.5, 53.2, 48.9, 46.1, 42.0, 38.4, 36.4; IR (film) ν_{max} 3054, 2832, 1836, 1477, 1201, 934 cm^{-1}; HRMS (ESI) *m/z* 406.10270 (MNa^+, $C_{18}H_{22}ClNO_6Na^+$ requires 406.10279).



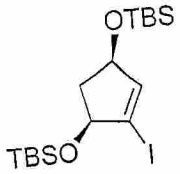
(–)-Acutumine (1). $TiCl_4$ (0.04 M solution in CH_2Cl_2, 20 μL, 0.0008 mmol) was added to a solution of **113** (2.0 mg, 0.0052 mmol) in anhydrous MeOH (100 μL). The solution was stirred at rt for 15 min, then treated with Et_3N (4 μL, 2.9 mg, 0.029 mmol) and stirred at rt for 45 min. The mixture was concentrated in vacuo, and the residue was purified by flash chromatography (SiO_2, 1.5 × 6 cm, 1% Et_3N in 5–15% MeOH–CH_2Cl_2 gradient elution), affording **1** (1.1 mg, 0.0027 mmol, 52%) and enol ether regioisomer **114** (0.3 mg, 0.00075 mmol, 14%). For **1**: white film, $[\alpha]^{25}_D$ –171 (*c* 0.81, pyridine), lit[8] $[\alpha]^{25}_D$ –206 (*c* 0.69, pyridine); ^{1}H NMR (pyridine-d_5, 500 MHz) δ 8.47 (br, s, 1H), 5.61 (s, 1H), 5.20 (dd, *J* = 11.8, 6.8 Hz, 1H), 5.03 (s, 1H, obscured by H_2O), 4.04 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.16 (t, *J* = 12.0 Hz, 1H), 3.07 (d, *J* = 15.5 Hz, 1H), 2.69–2.63 (m, 3H), 2.54 (d, *J* = 15.5 Hz, 1H), 2.45–2.42 (m, 1H), 2.39 (s, 3H), 1.65–1.62 (m, 1H); ^{13}C NMR (pyridine-d_5, 125 MHz) δ 201.3, 192.8, 188.9, 159.7, 138.9, 105.5, 72.9, 70.7, 68.3, 60.4, 60.1, 58.8, 57.8, 53.2, 51.6, 47.2, 41.4, 38.5, 36.3; IR (film) ν_{max} 3410, 2899, 2817,

[8] Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Tetrahedron Lett.* **1967**, 2421.

1655, 1641, 1364, 1205, 1079, 935 cm^{-1}; HRMS (ESI) *m/z* 398.13655 (MH^+, $C_{19}H_{24}ClNO_6H^+$ requires 398.13649).

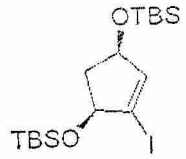


For **114**: white film, $[\alpha]^{25}_D$ –112 (*c* 0.3, pyridine), ^1H NMR (pyridine-d_5, 500 MHz) δ 8.40 (br, s, 1H), 5.32 (s, 1H), 5.16 (dd, *J* = 12.0, 7.0 Hz, 1H), 4.94 (s, 1H), 4.07 (s, 3H), 3.74 (s, 3H), 3.57 (s, 3H), 3.13 (t, *J* = 12.5 Hz, 1H), 3.02 (d, *J* = 16.5 Hz, 1H), 2.67–2.60 (m, 3H), 2.48 (d, *J* = 15.5 Hz, 1H), 2.43–2.38 (m, 1H), 2.36 (s, 3H), 1.62–1.60 (m, 1H); HRMS (ESI) *m/z* 398.13664 (MH^+, $C_{19}H_{24}ClNO_6H^+$ requires 398.13649).



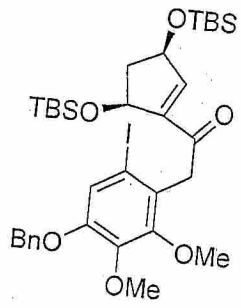
44

$CDCl_3$, 500 MHz



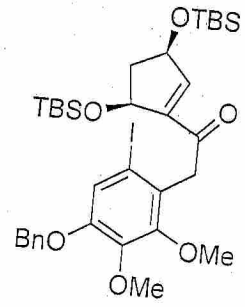
~~44~~

$CDCl_3$. 125 MHz



70

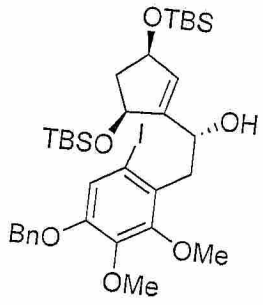
$CDCl_3$, 300 MHz



70

$CDCl_3$, 75 MHz

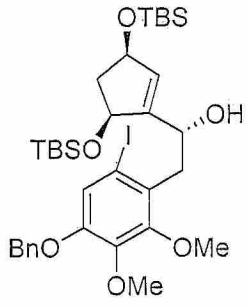
78.



78

$CDCl_3$, 300 MHz

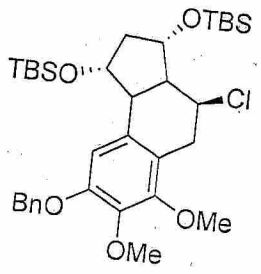
78



78

$CDCl_3$, 75 MHz

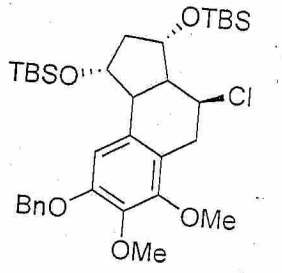
794



79

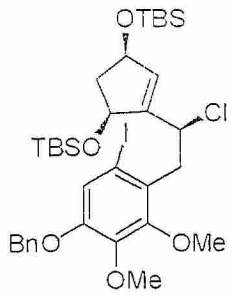
$CDCl_3$, 300 MHz

79c



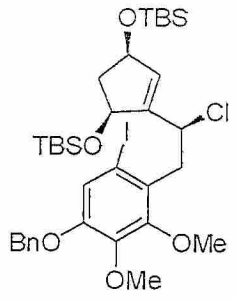
79

$CDCl_3$, 75 MHz



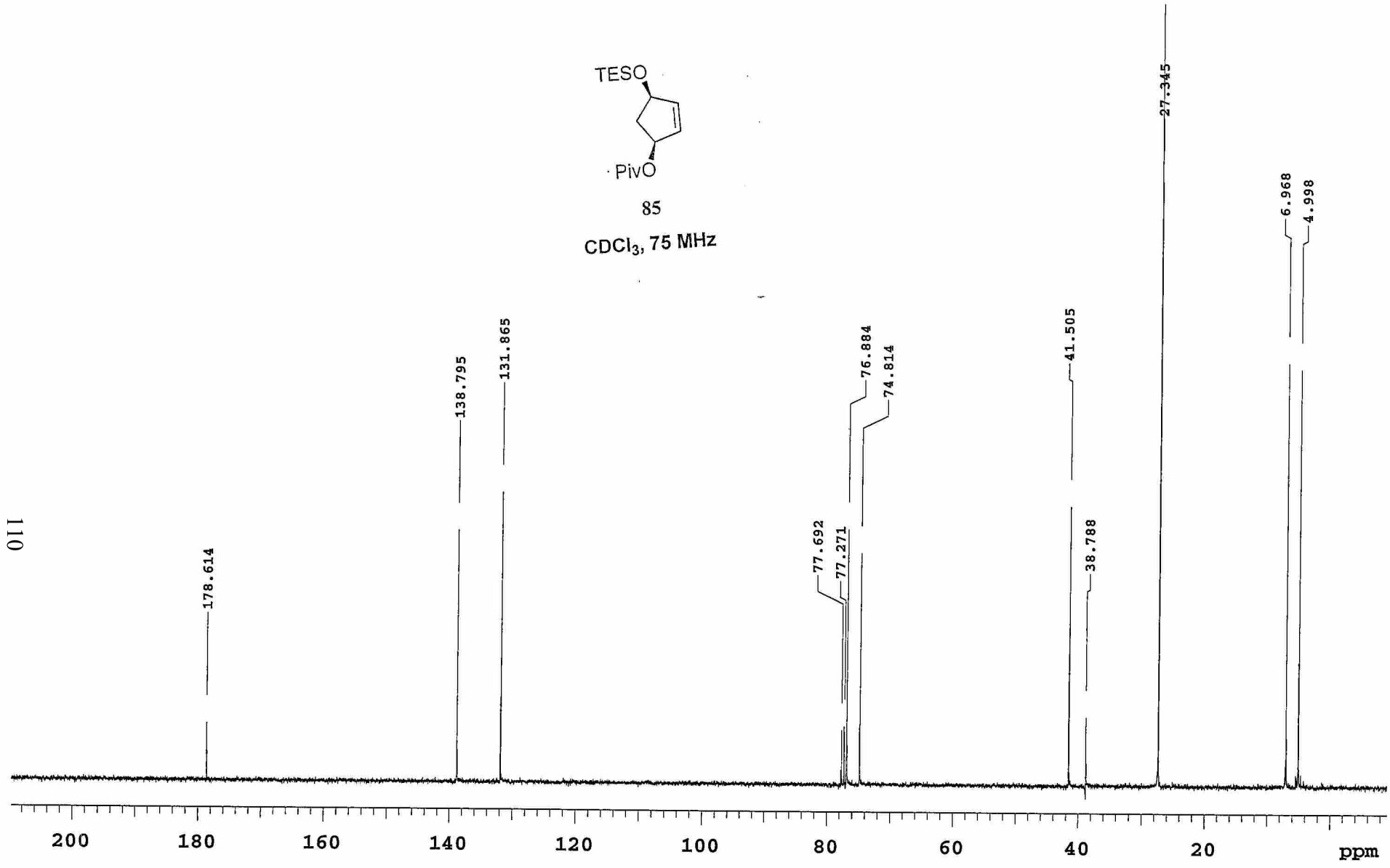
69

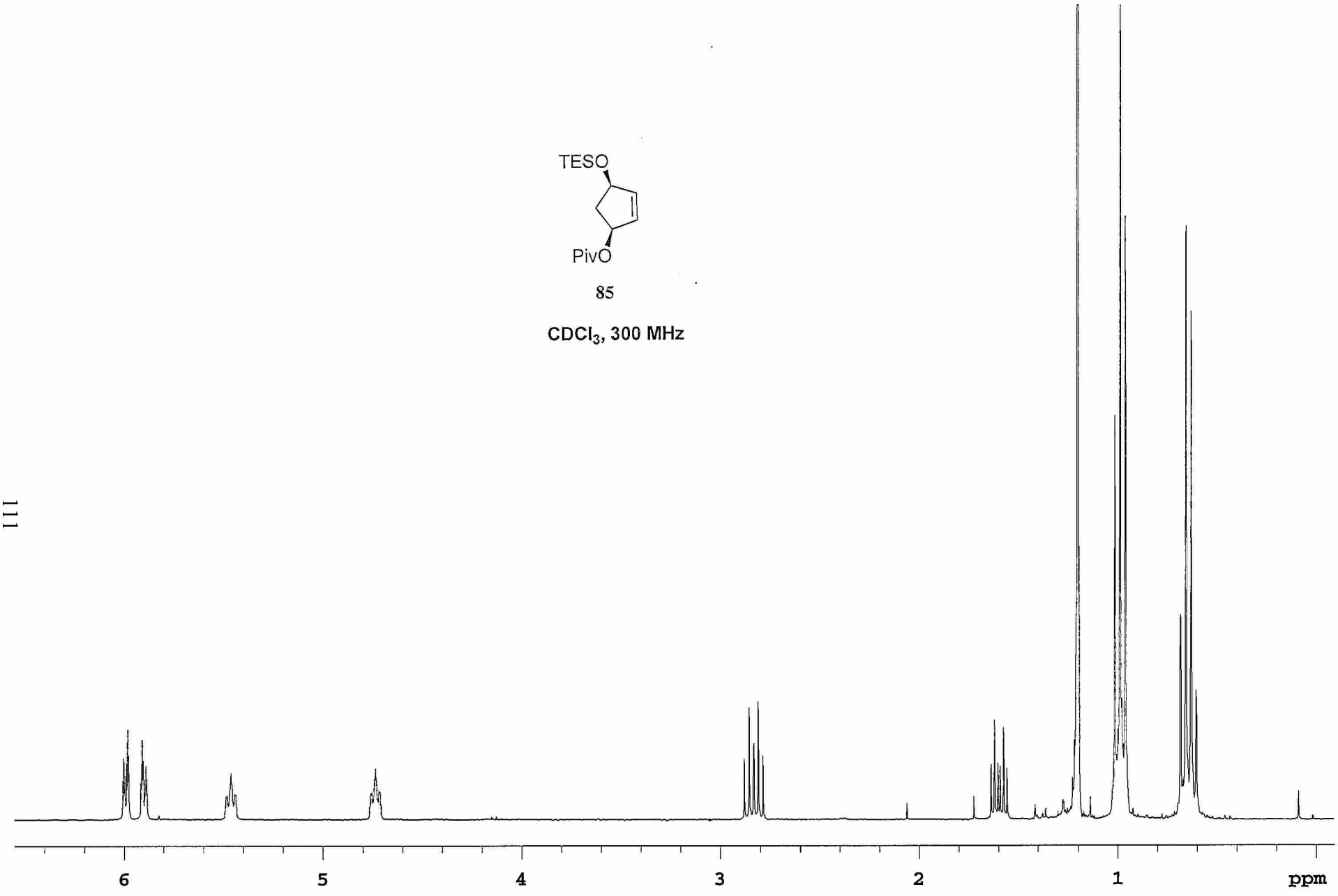
$CDCl_3$, 75 MHz

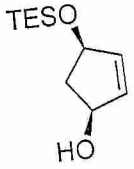


69

$CDCl_3$, 300 MHz

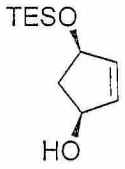

TESO
PivO
85
CDCl3, 75 MHz
178.614
138.795
131.865
77.692
77.271
76.884
74.814
41.505
38.788
27.345
6.968
4.998
200
180
160
140
120
100
80
60
40
20
ppm

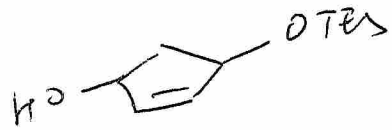

TESO
PivO
85
CDCl3, 300 MHz
6
5
4
3
2
1
ppm



86

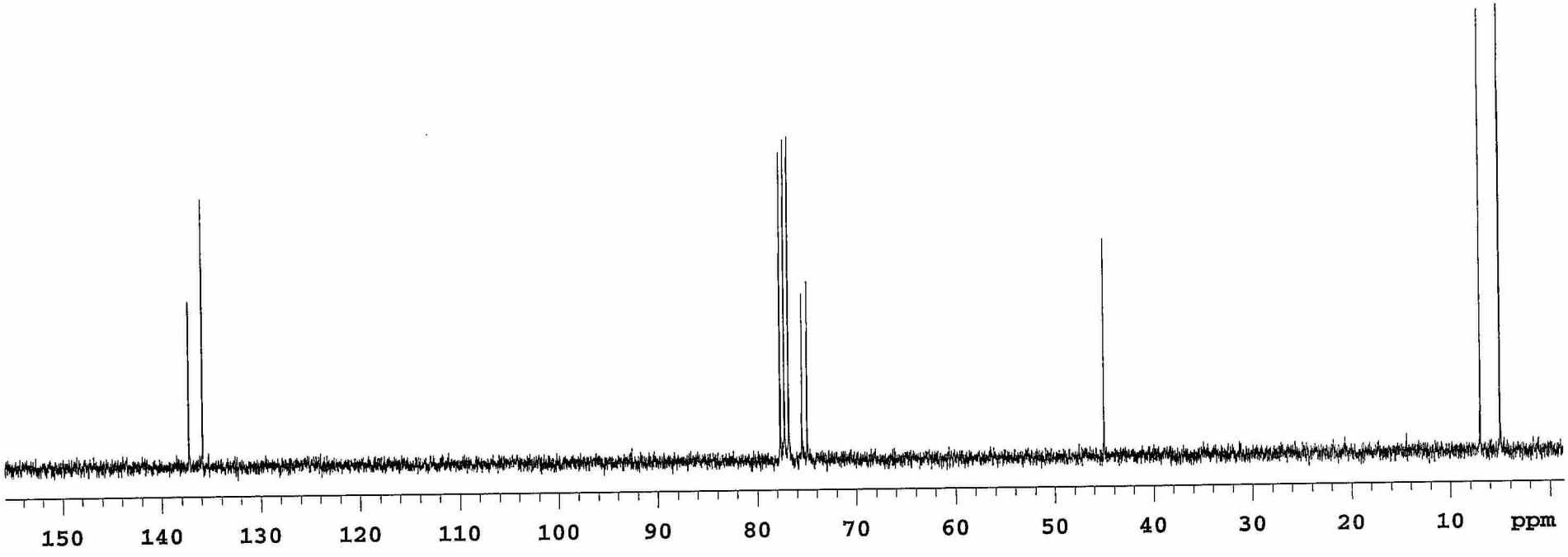
$CDCl_3$, 75 MHz

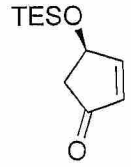




86

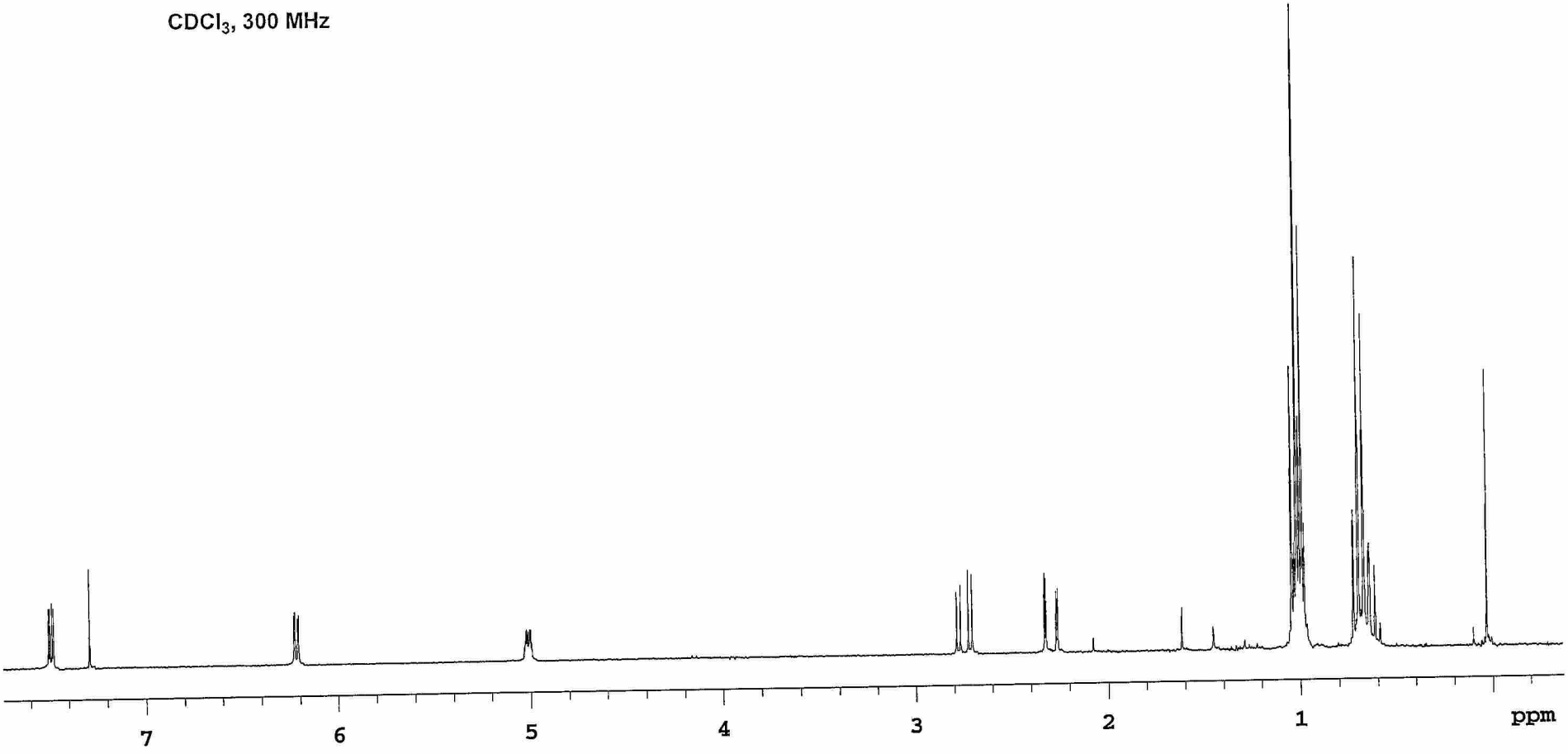
$CDCl_3$, 300 MHz

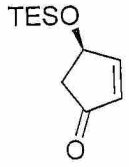




87

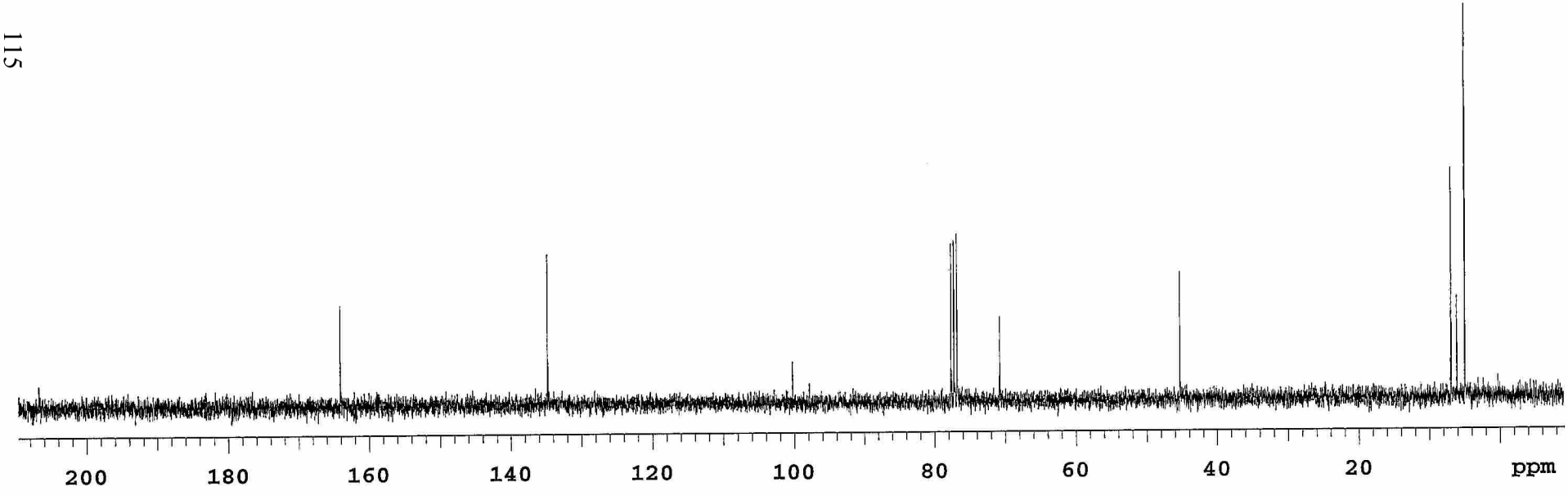
$CDCl_3$, 300 MHz

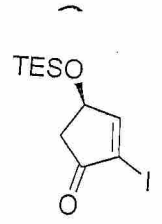




87

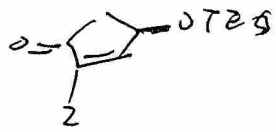
$CDCl_3$, 75 MHz





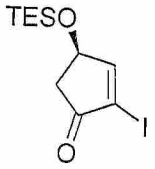
88

$CDCl_3$, 300 MHz



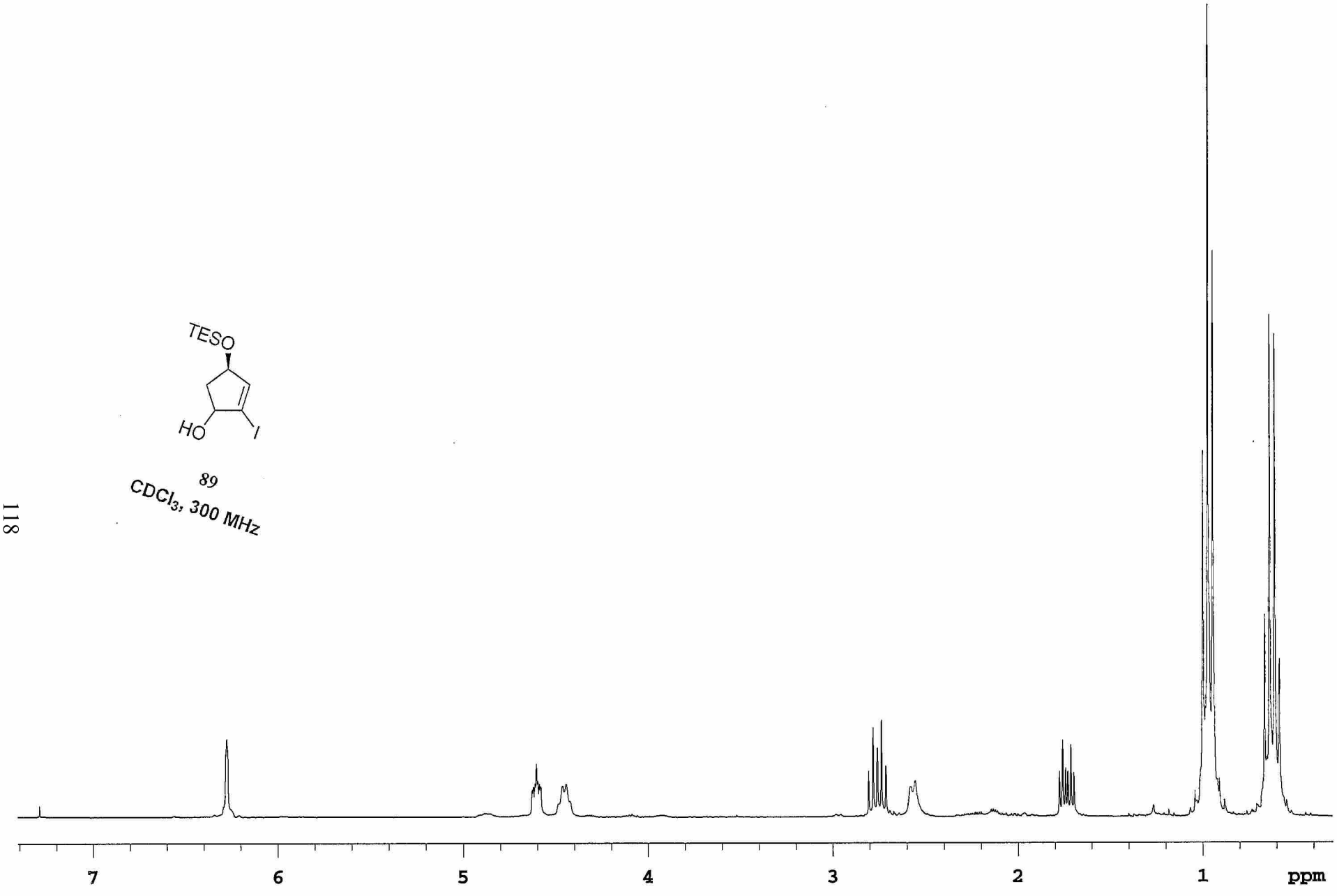
Cpd 9 13C (CDCl3, 125 MHz)

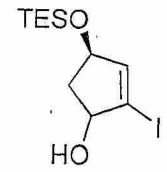
Pulse Sequence: s2pul



88

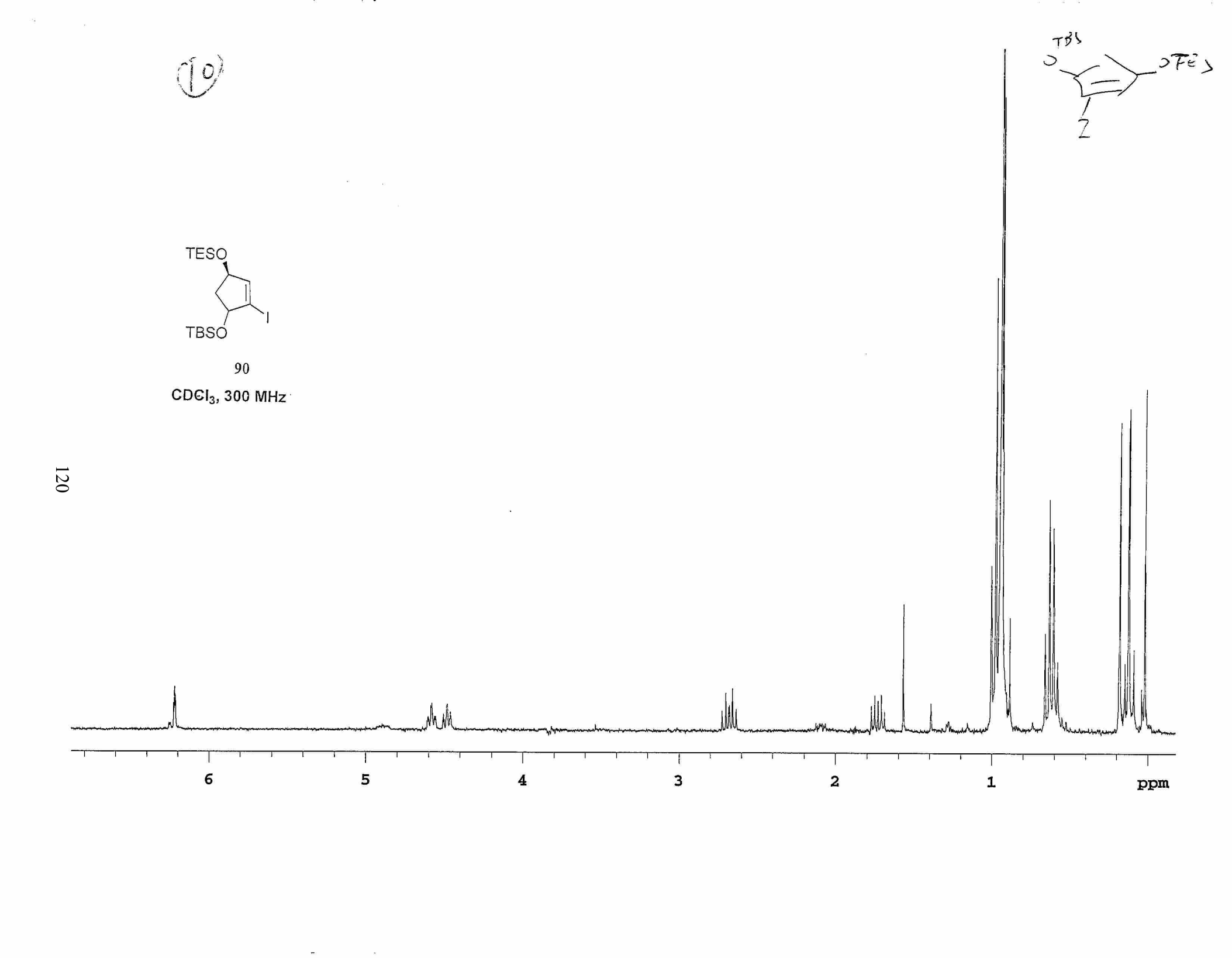
$CDCl_3$, 75 MHz


TESO
HO
I
89
CDCl3, 300 MHz
7
6
5
4
3
2
1
ppm

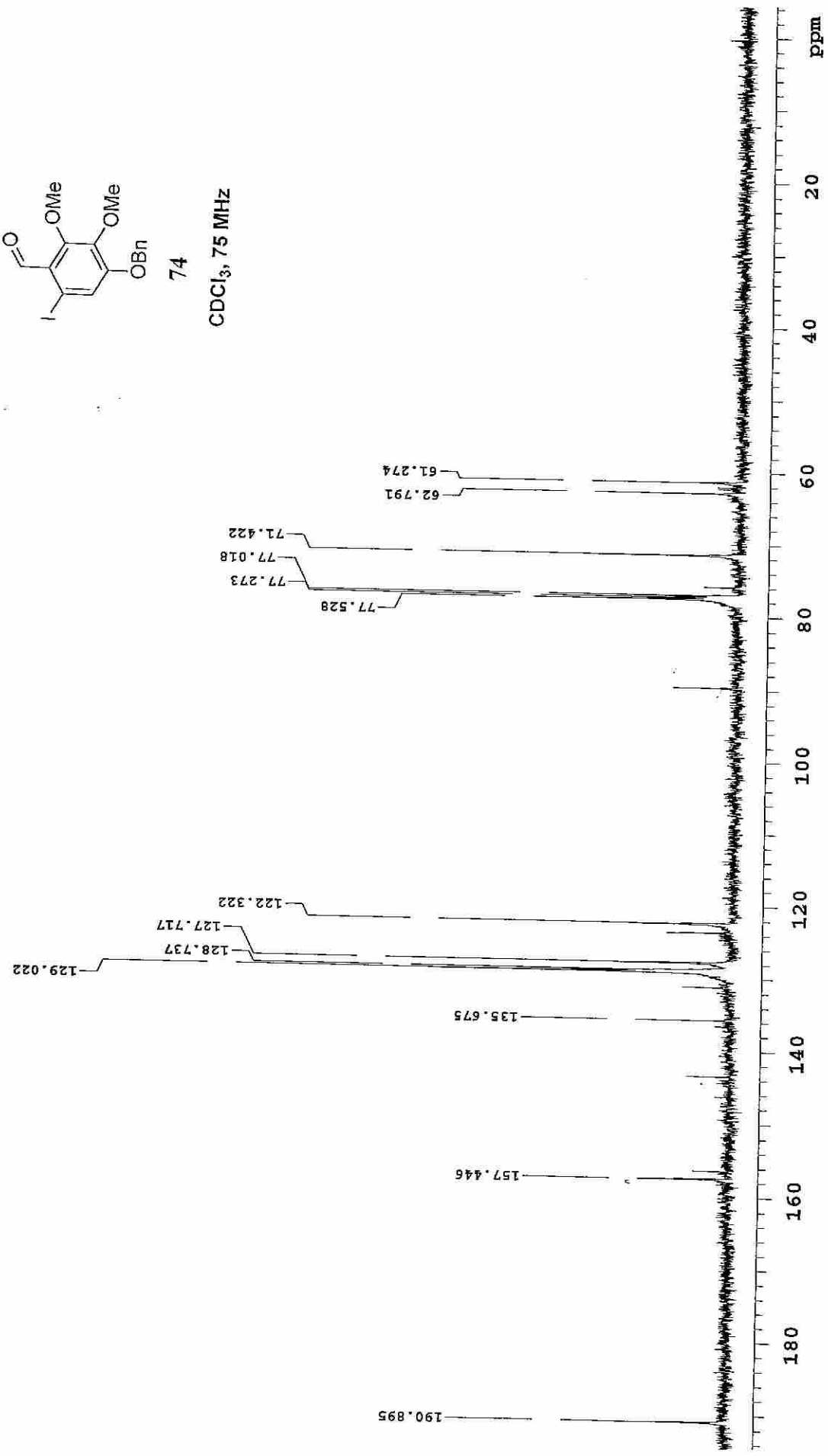


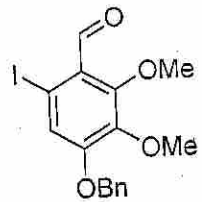
89

$CDCl_3$, 75 MHz


(10)
TBS
OTES
Z
TESO
TBSO
I
90
CDCl3, 300 MHz
120
6
5
4
3
2
1
ppm

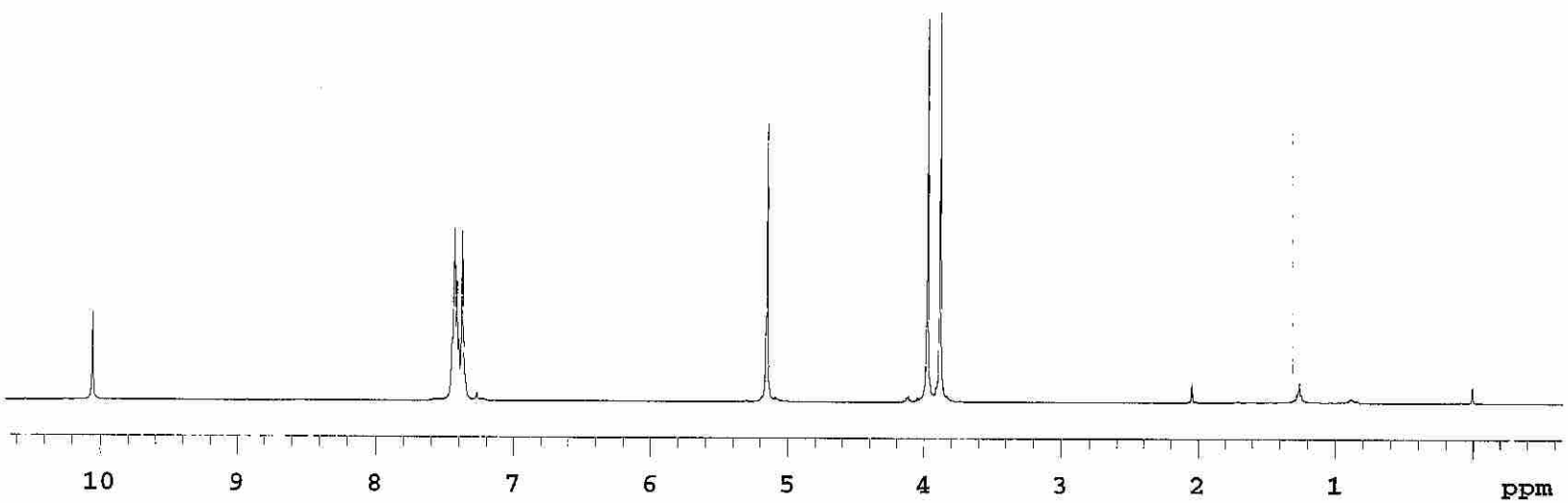
-4.275
-4.182
-3.327
0.238
5.012
6.981
18.432
25.889
26.083
44.610
75.355
76.831
77.258
77.679
78.907
106.908
144.110
TESO
TBSO
I
90
CDCl3, 75 MHz
ppm
200
180
160
140
120
100
80
60
40
20

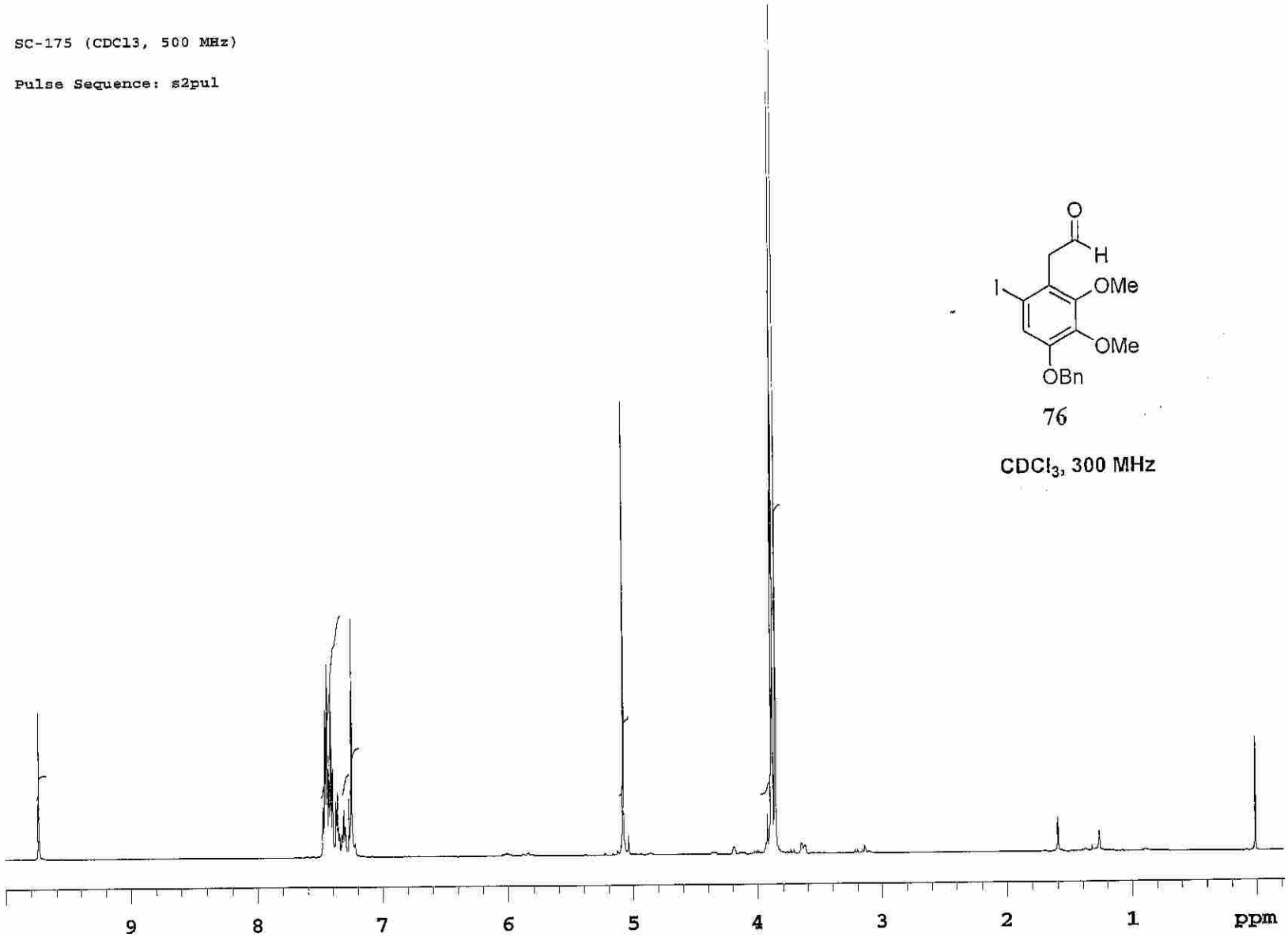

OMe
OMe
OBn
I
74
CDCl3, 75 MHz
190.895
157.446
135.675
129.022
128.737
127.717
122.322
77.528
77.273
77.018
71.422
62.791
61.274
ppm
180
160
140
120
100
80
60
40
20



74

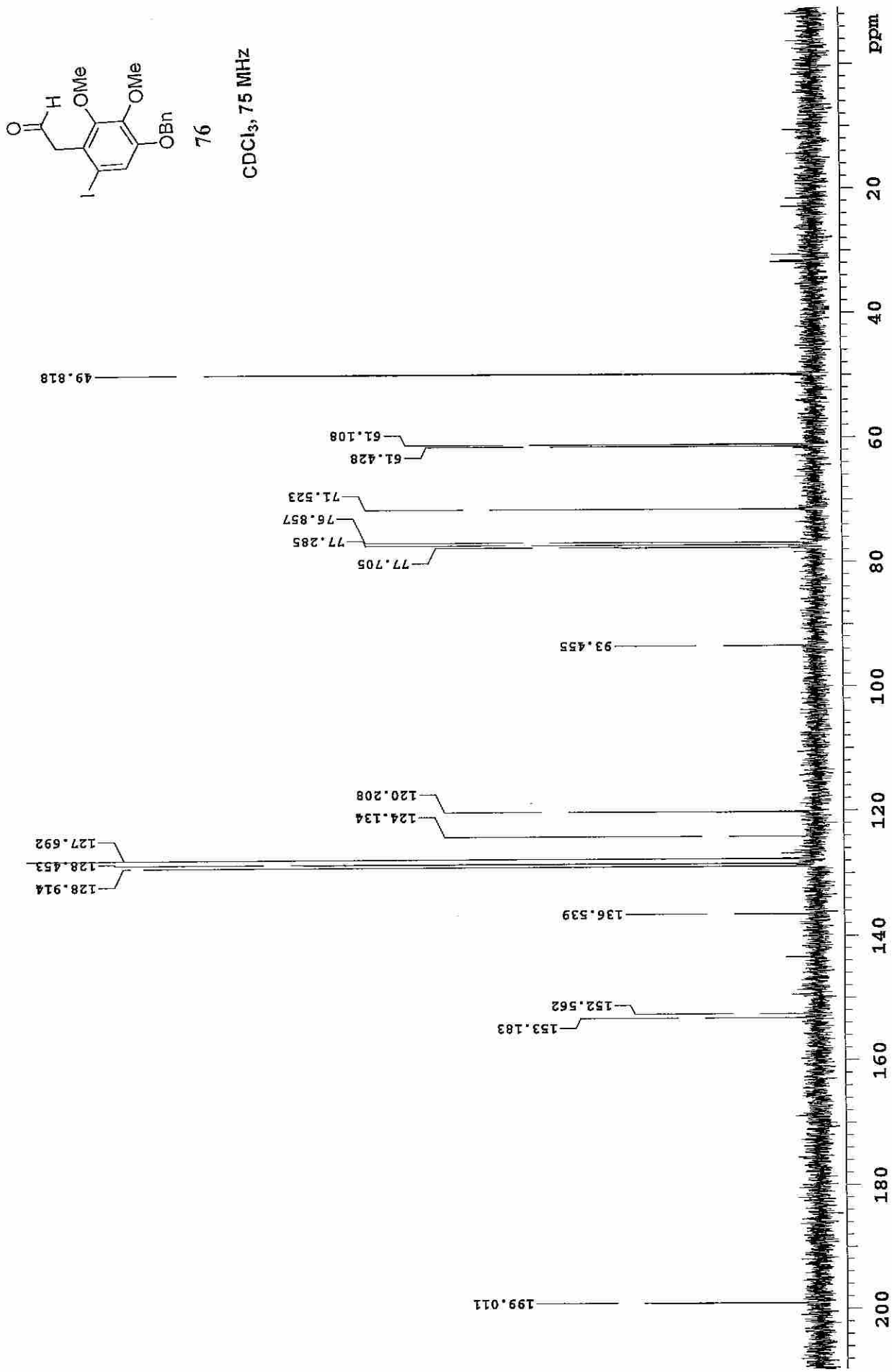
$CDCl_3$, 300 MHz

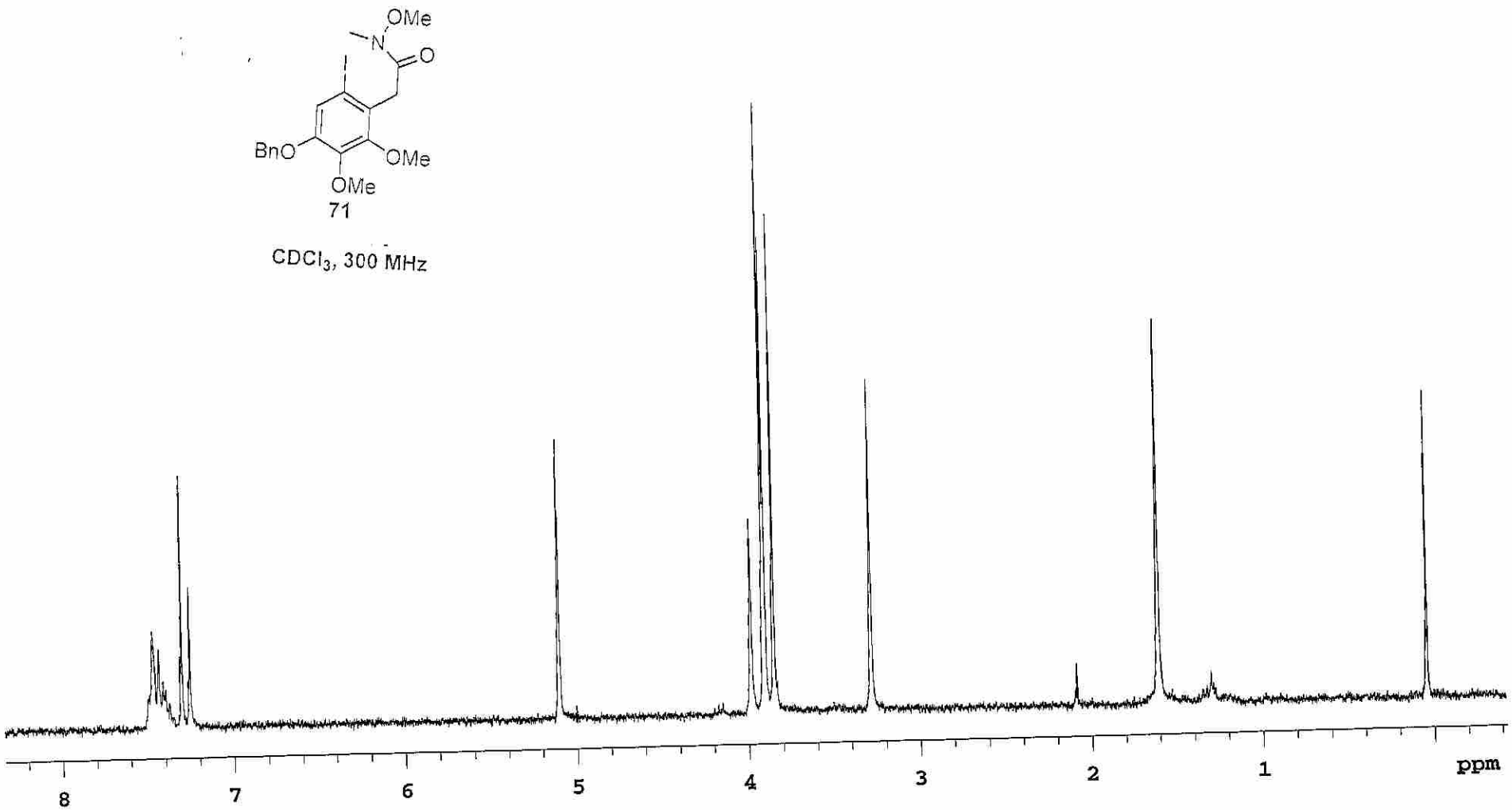


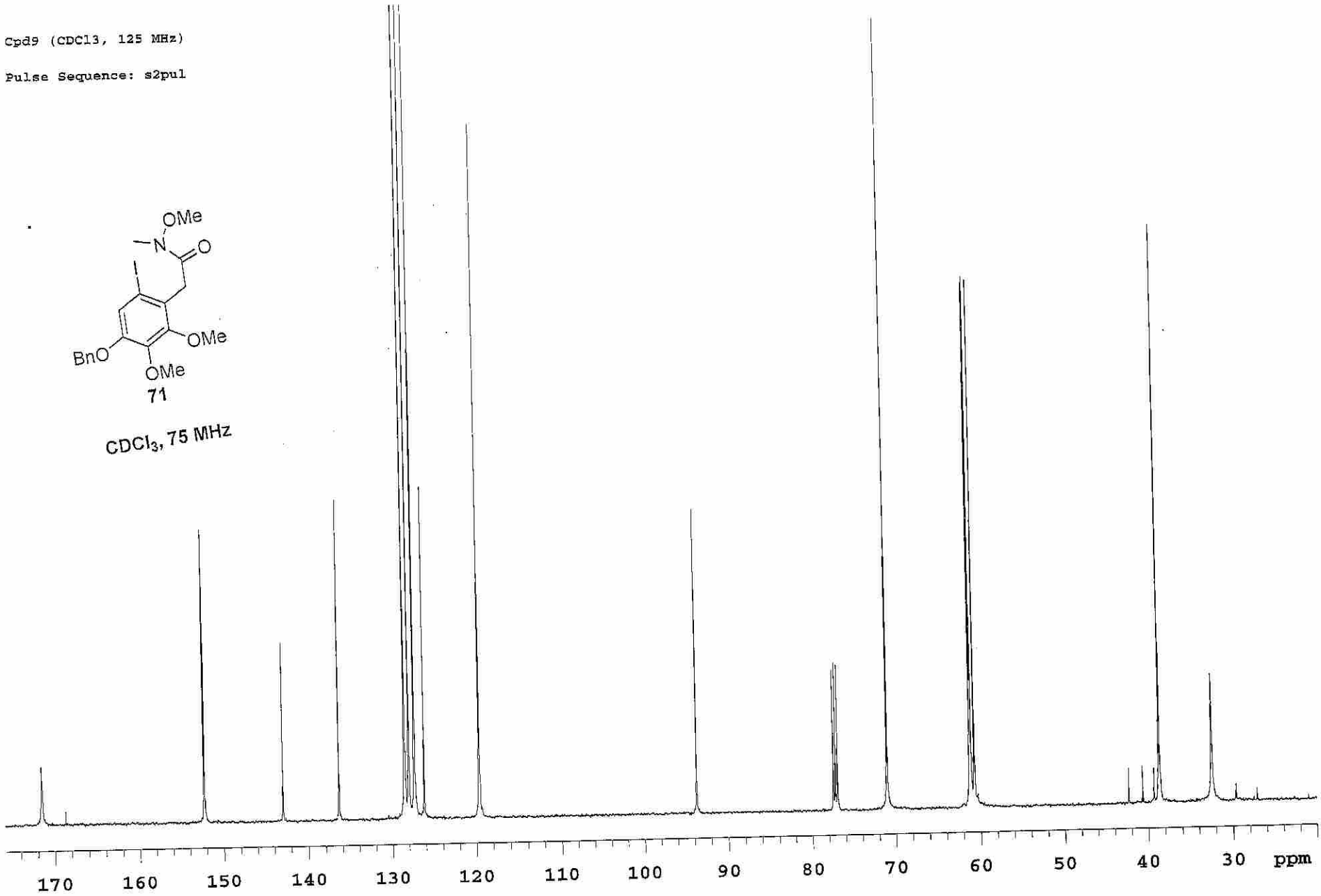


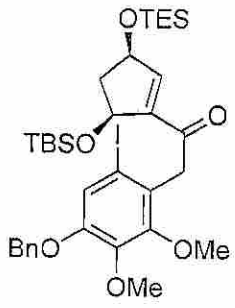
76

$CDCl_3$, 300 MHz


O
H
OMe
OMe
OBn
I
76
CDCl3, 75 MHz
49.818
61.108
61.428
71.523
76.857
77.285
77.705
93.455
120.208
124.134
127.692
128.453
128.914
136.539
152.562
153.183
199.011
ppm
20
40
60
80
100
120
140
160
180
200

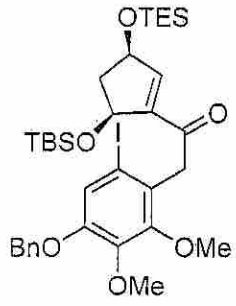

OMe
N
O
BnO
OMe
OMe
71
CDCl3, 300 MHz
8
7
6
5
4
3
2
1
ppm


Cpd9 (CDCl3, 125 MHz)
Pulse Sequence: s2pul
OMe
N
O
BnO
OMe
OMe
71
CDCl3, 75 MHz
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm



91

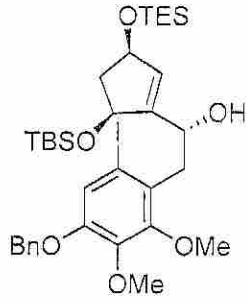
$CDCl_3$, 300 MHz



91

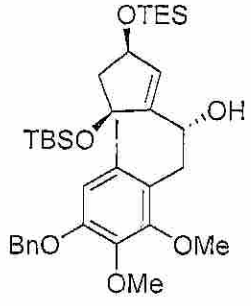
$CDCl_3$, 75 MHz

(12)



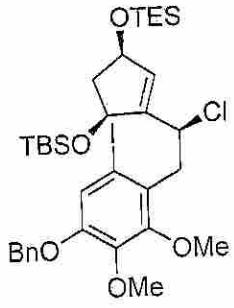
92

$CDCl_3$, 300 MHz



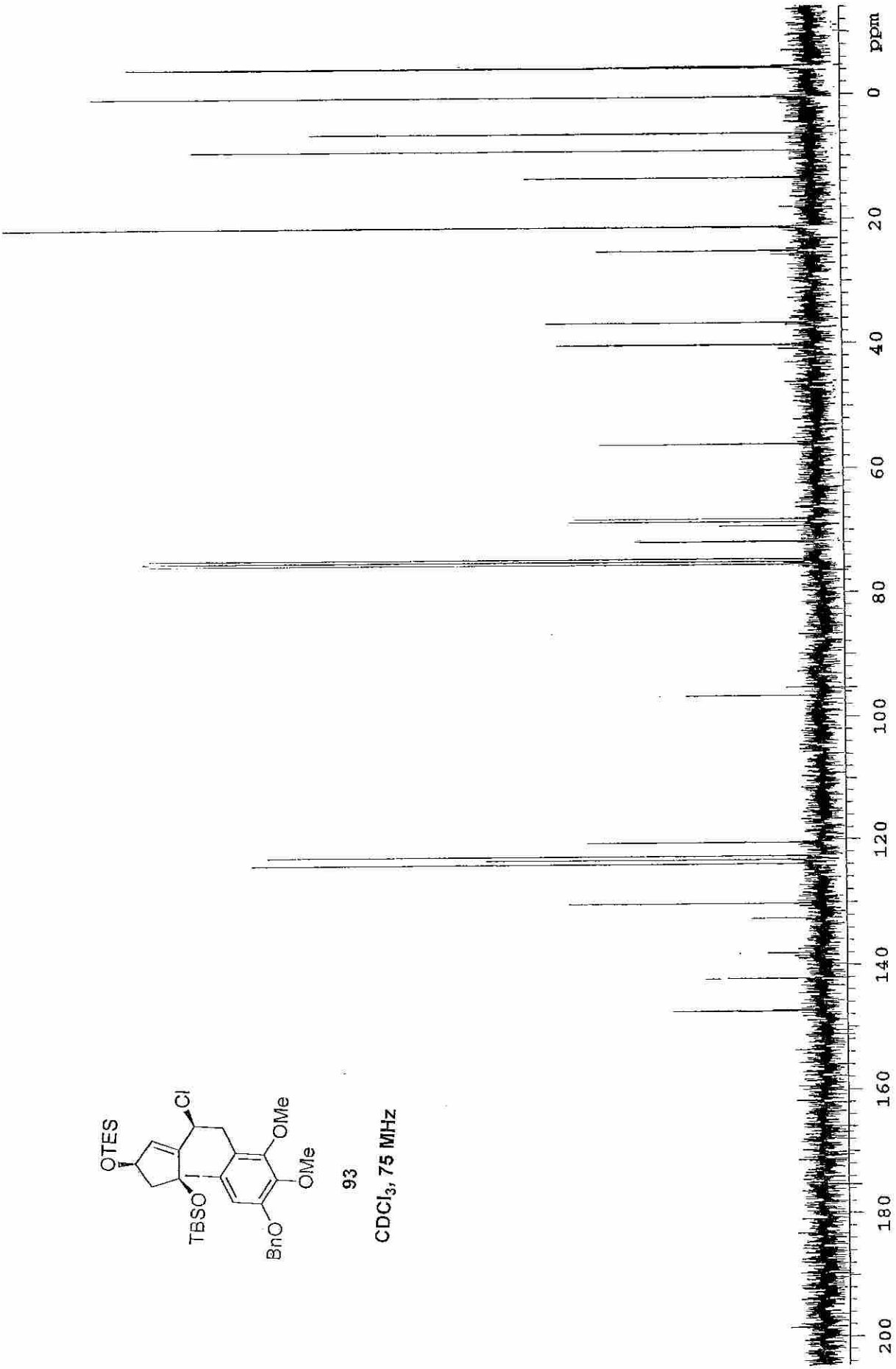
92

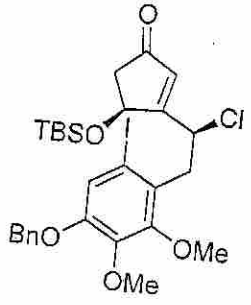
$CDCl_3$, 75 MHz



93

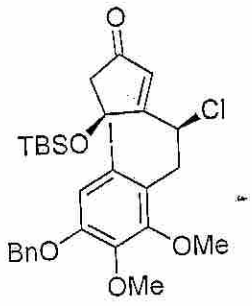
$CDCl_3$, 300 MHz


OTES
Cl
OMe
OMe
TBSO
BnO
93
CDCl3, 75 MHz
ppm
0
20
40
60
80
100
120
140
160
180
200



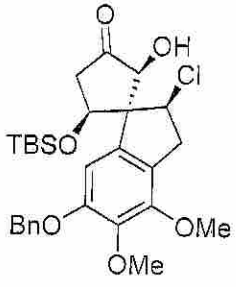
35

$CDCl_3$, 300 MHz



35

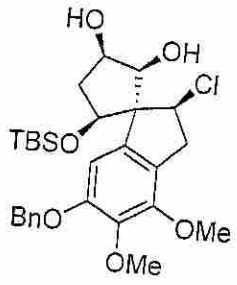
$CDCl_3$, 75 MHz



36

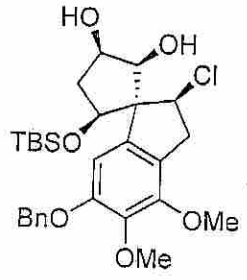
$CDCl_3$, 75 MHz

OH
Cl
O
TBSO
BnO
OMe
OMe
36
CDCl3, 300 MHz
ppm
200
180
160
140
120
100
80
60
40
20



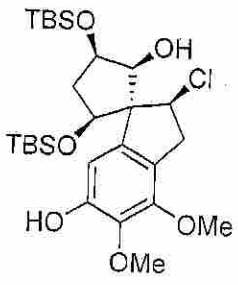
100

$CDCl_3$, 300 MHz



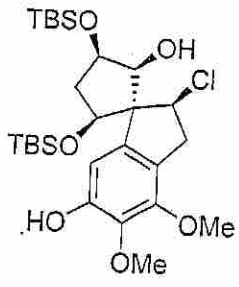
100

$CDCl_3$, 75 MHz



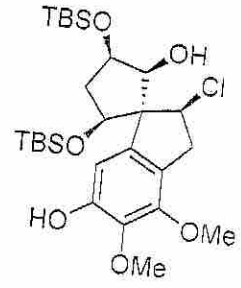
101

$CDCl_3$, 300 MHz



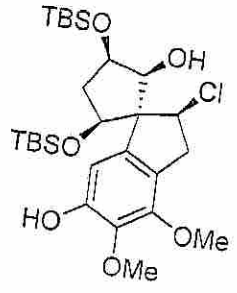
101

$CDCl_3$, 75 MHz



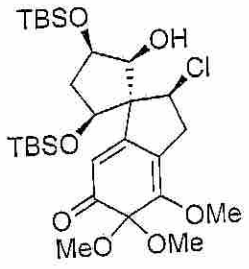
102

$CDCl_3$, 300 MHz



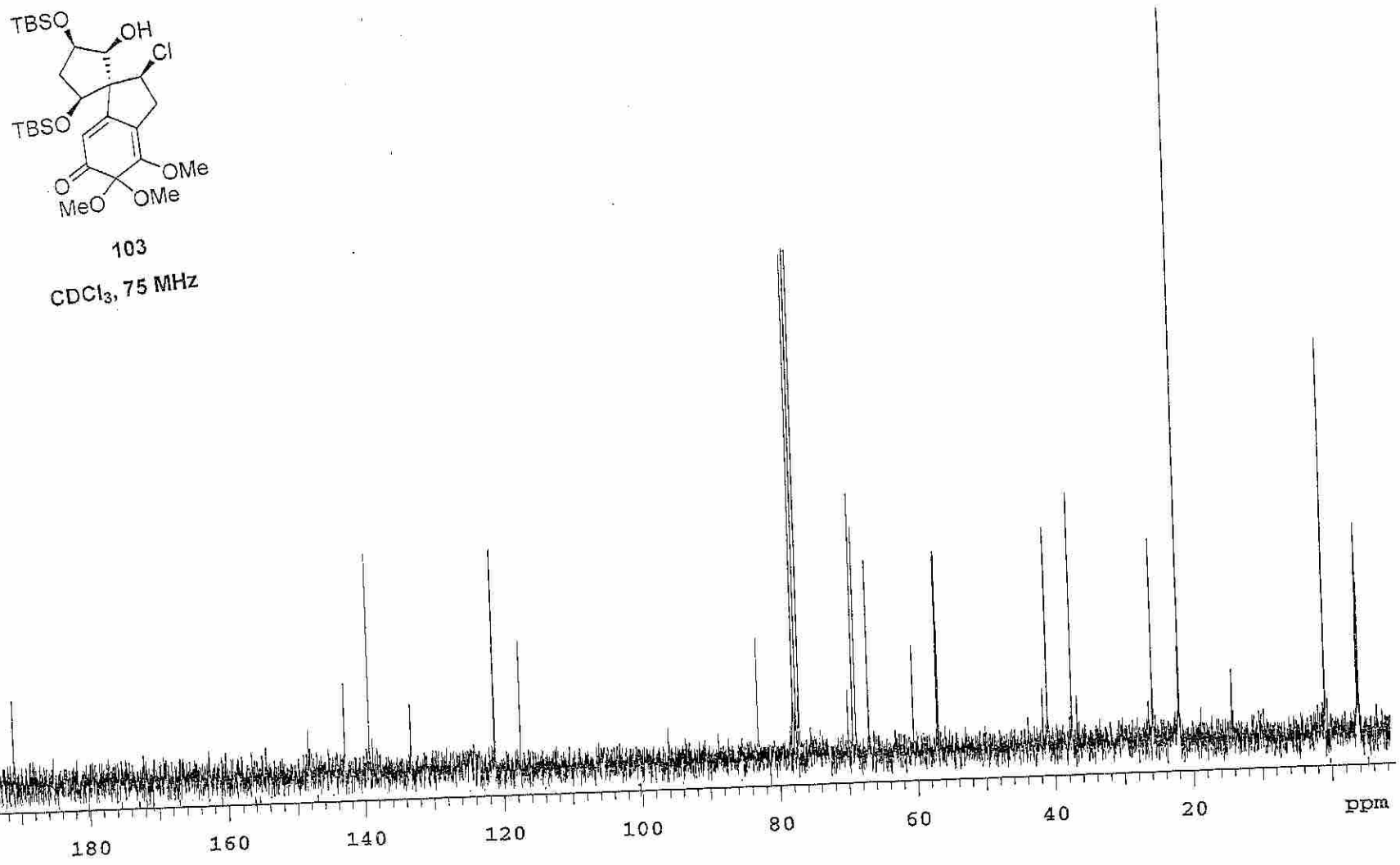
102

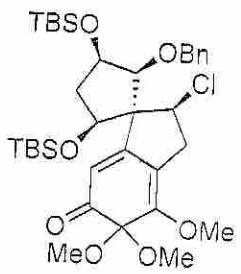
$CDCl_3$, 75 MHz



103

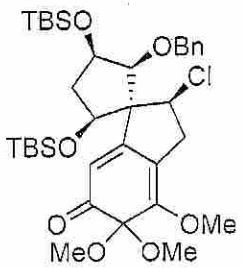
$CDCl_3$, 300 MHz


TBSO
OH
Cl
TBSO
OMe
O
MeO
OMe
103
CDCl3, 75 MHz
200
180
160
140
120
100
80
60
40
20
ppm



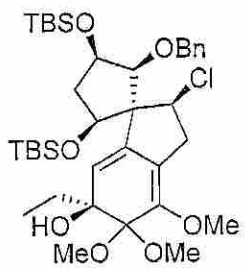
104

$CDCl_3$; 300 MHz



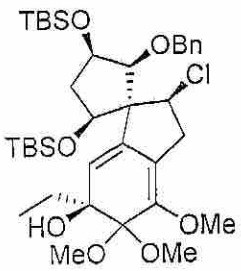
104

$CDCl_3$, 75 MHz



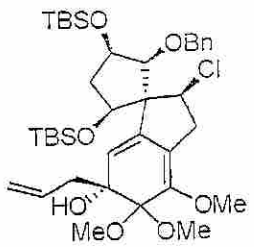
105

$CDCl_3$, 300 MHz



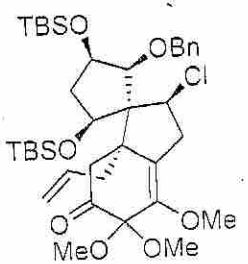
105

$CDCl_3$, 75 MHz



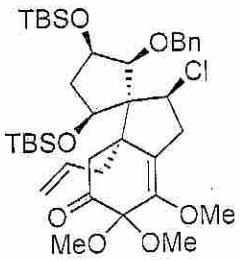
105'

$CDCl_3$, 300 MHz



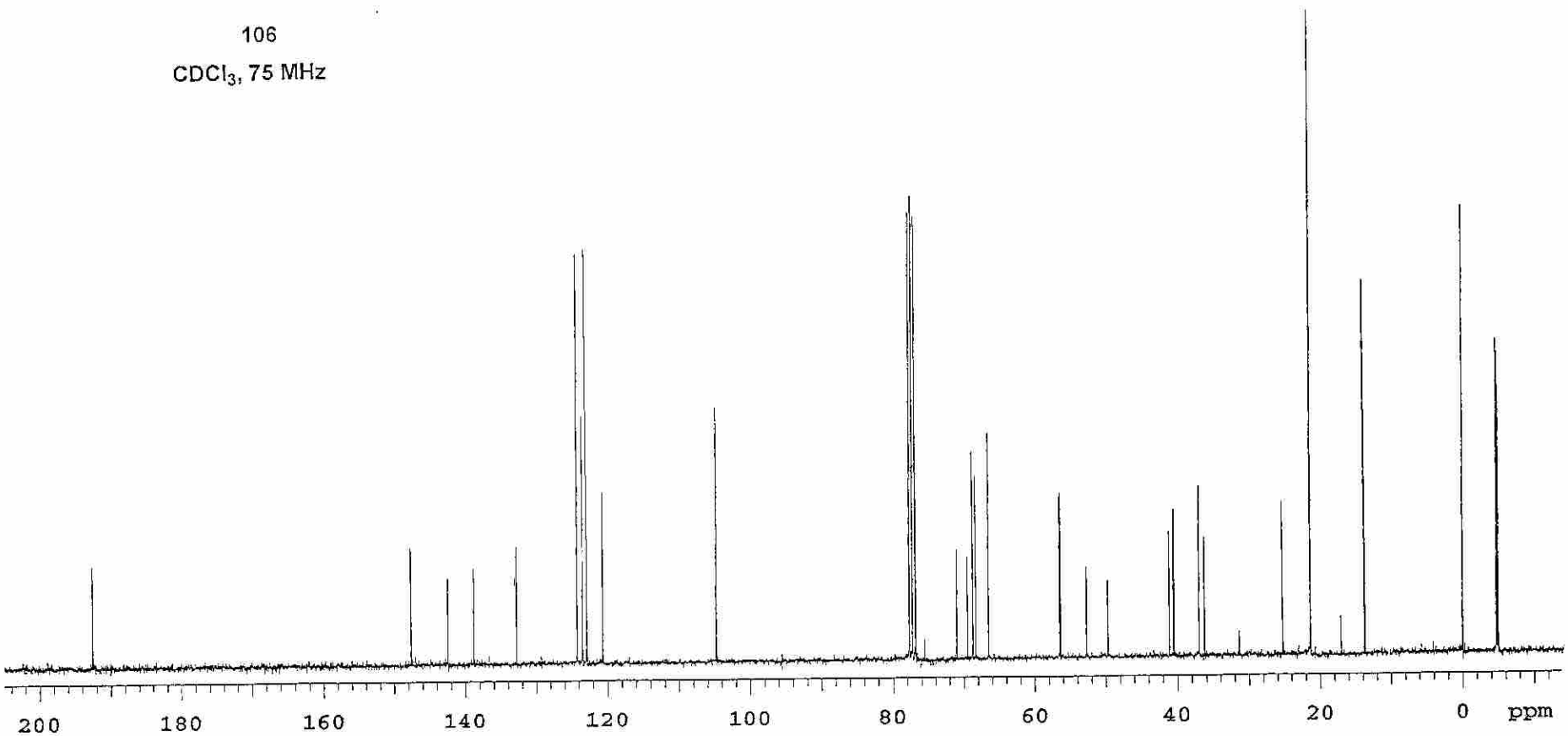
106

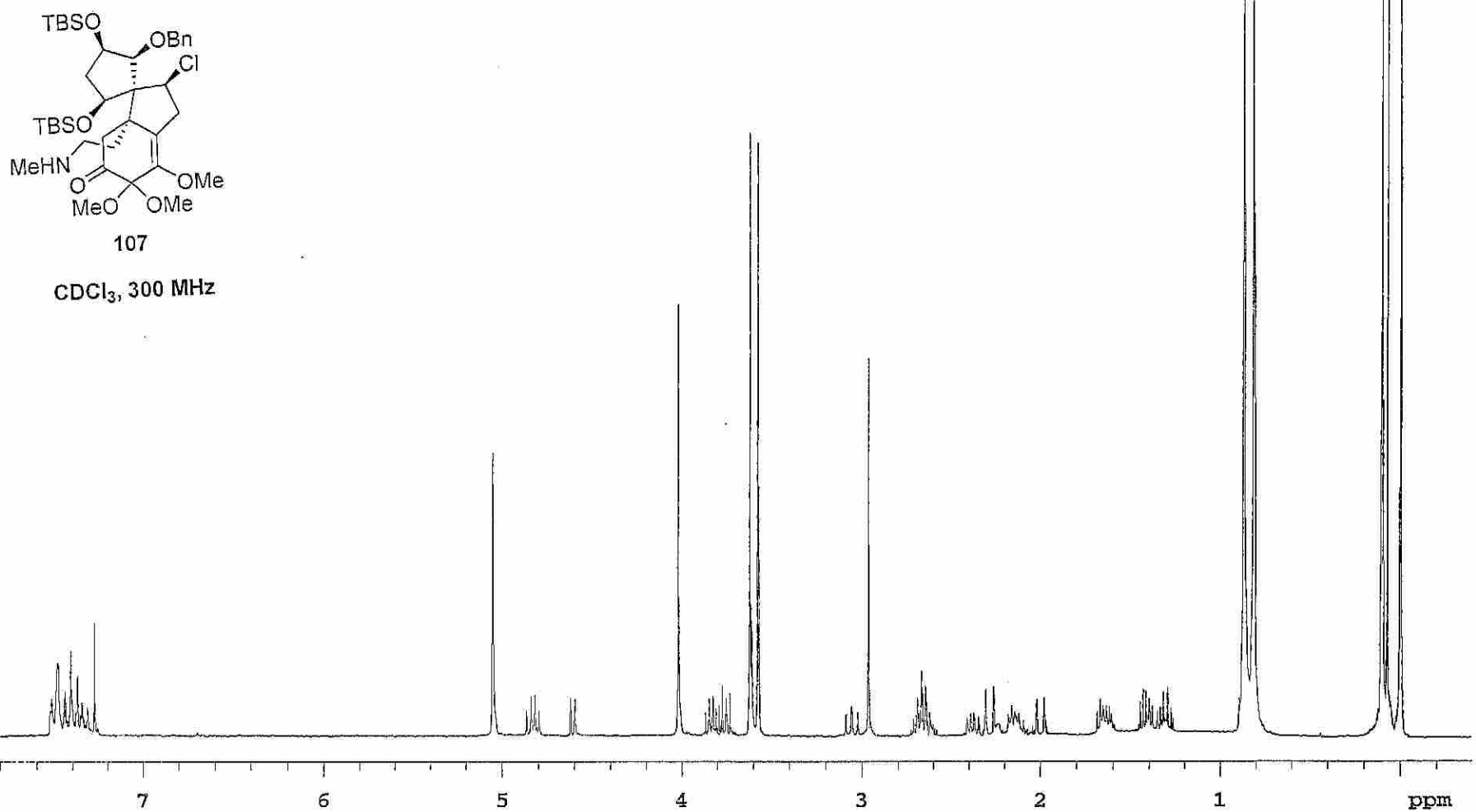
$CDCl_3$,300 MHz

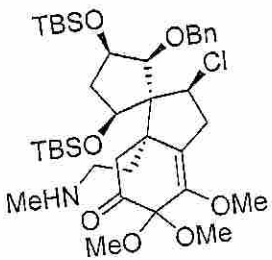


106

$CDCl_3$, 75 MHz

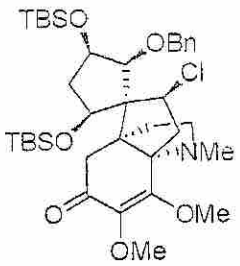



TBSO
OBn
Cl
TBSO
MeHN
O
OMe
MeO
OMe
107
CDCl3, 300 MHz
8
7
6
5
4
3
2
1
ppm



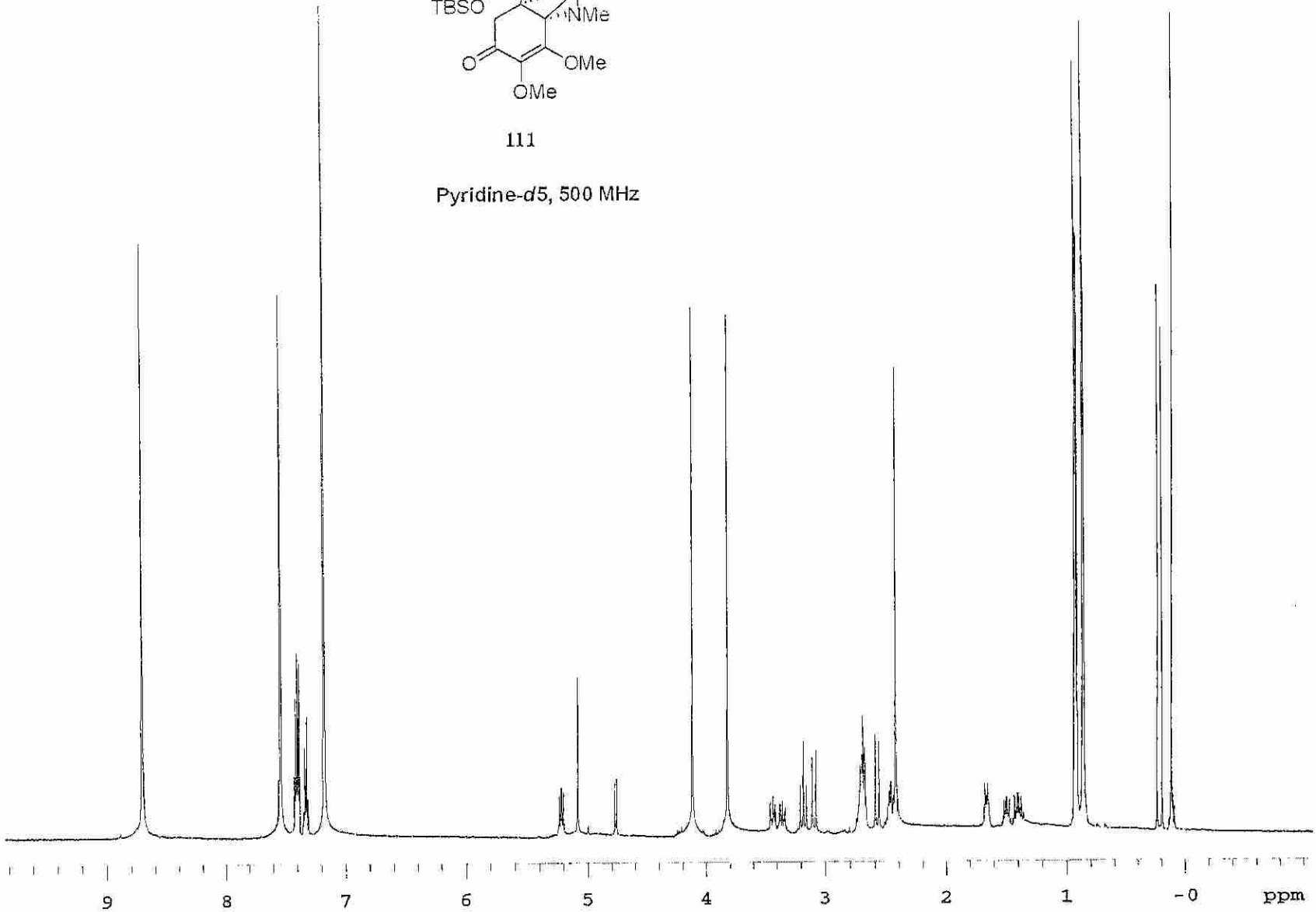
107

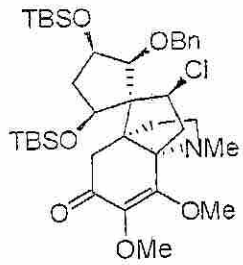
$CDCl_3$, 75 MHz



111

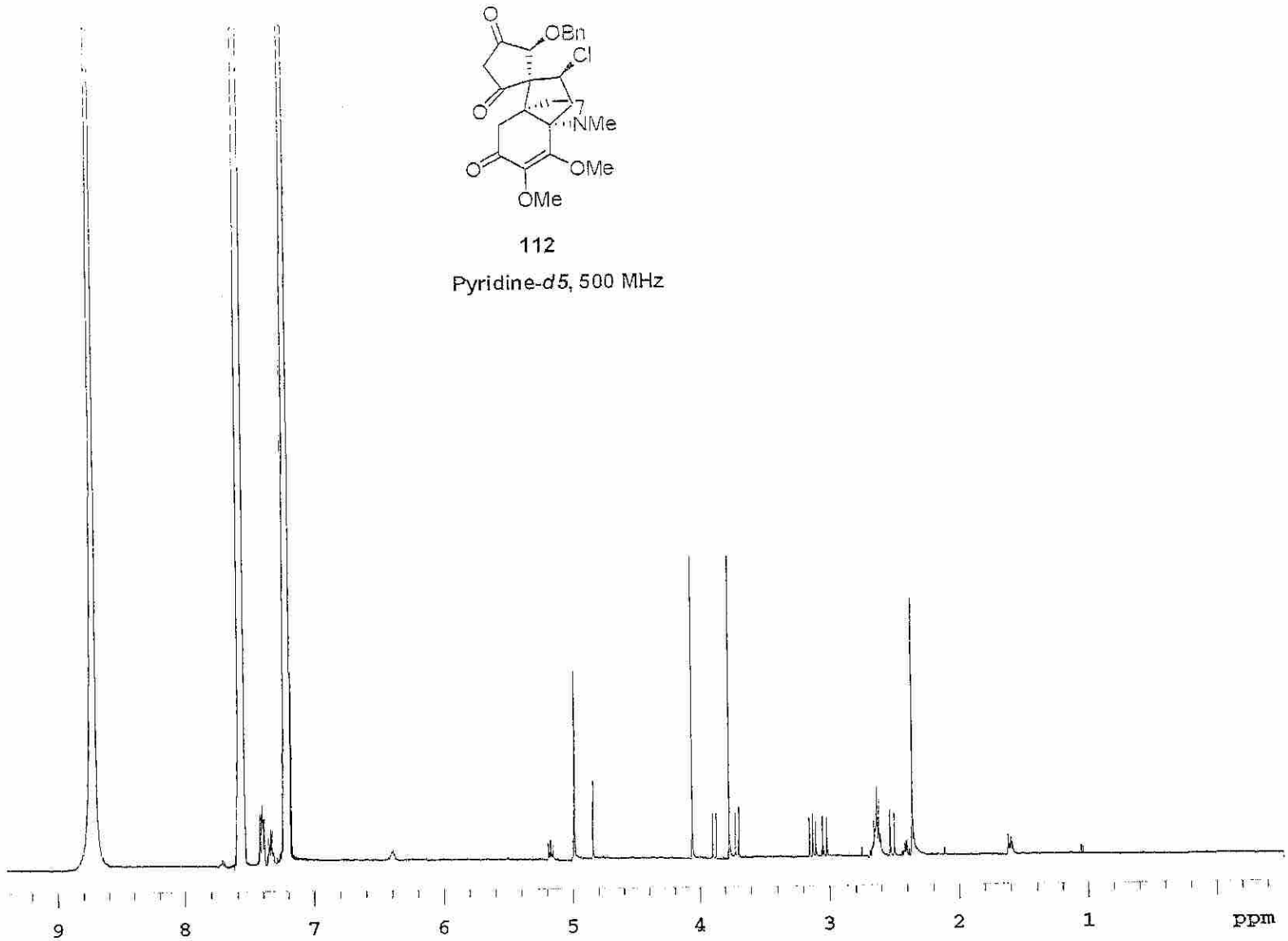
Pyridine-*d*5, 500 MHz





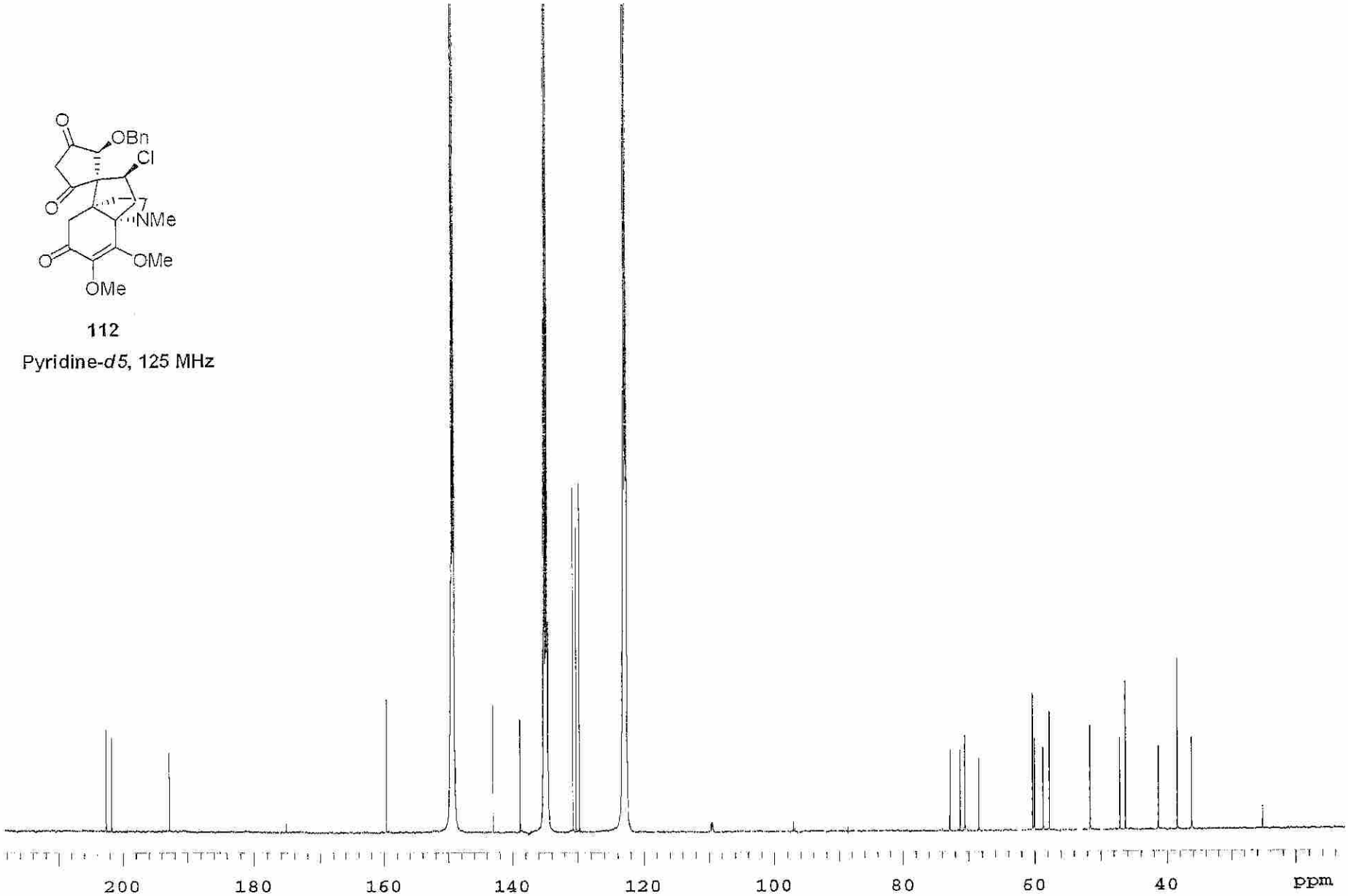
111

Pyridine-*d*5, 125 MHz



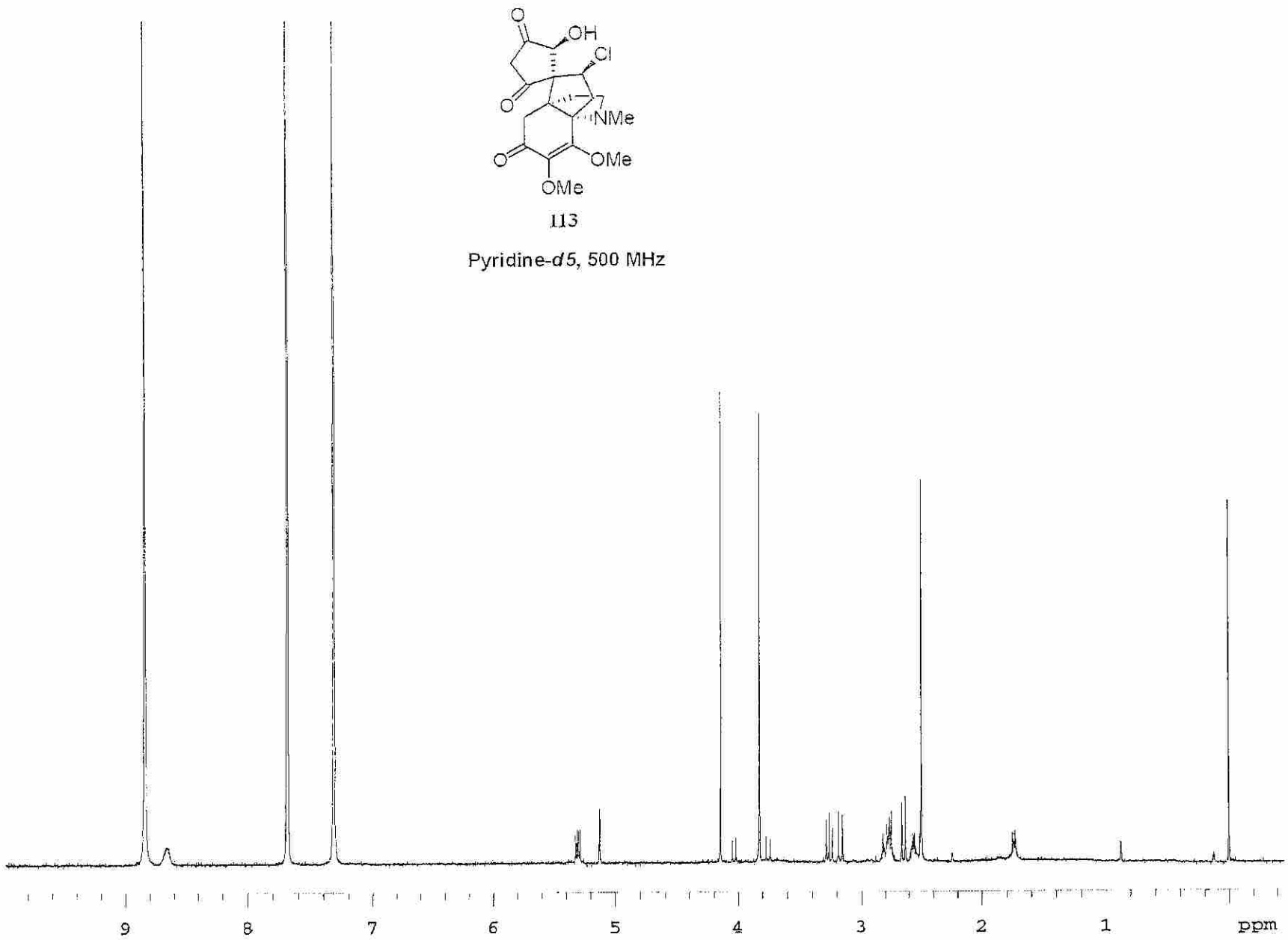
112

Pyridine-*d5*, 500 MHz



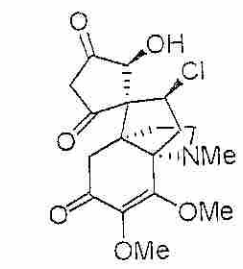
112

Pyridine-*d5*, 125 MHz



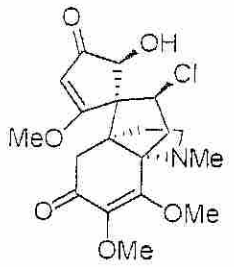
113

Pyridine-*d5*, 500 MHz



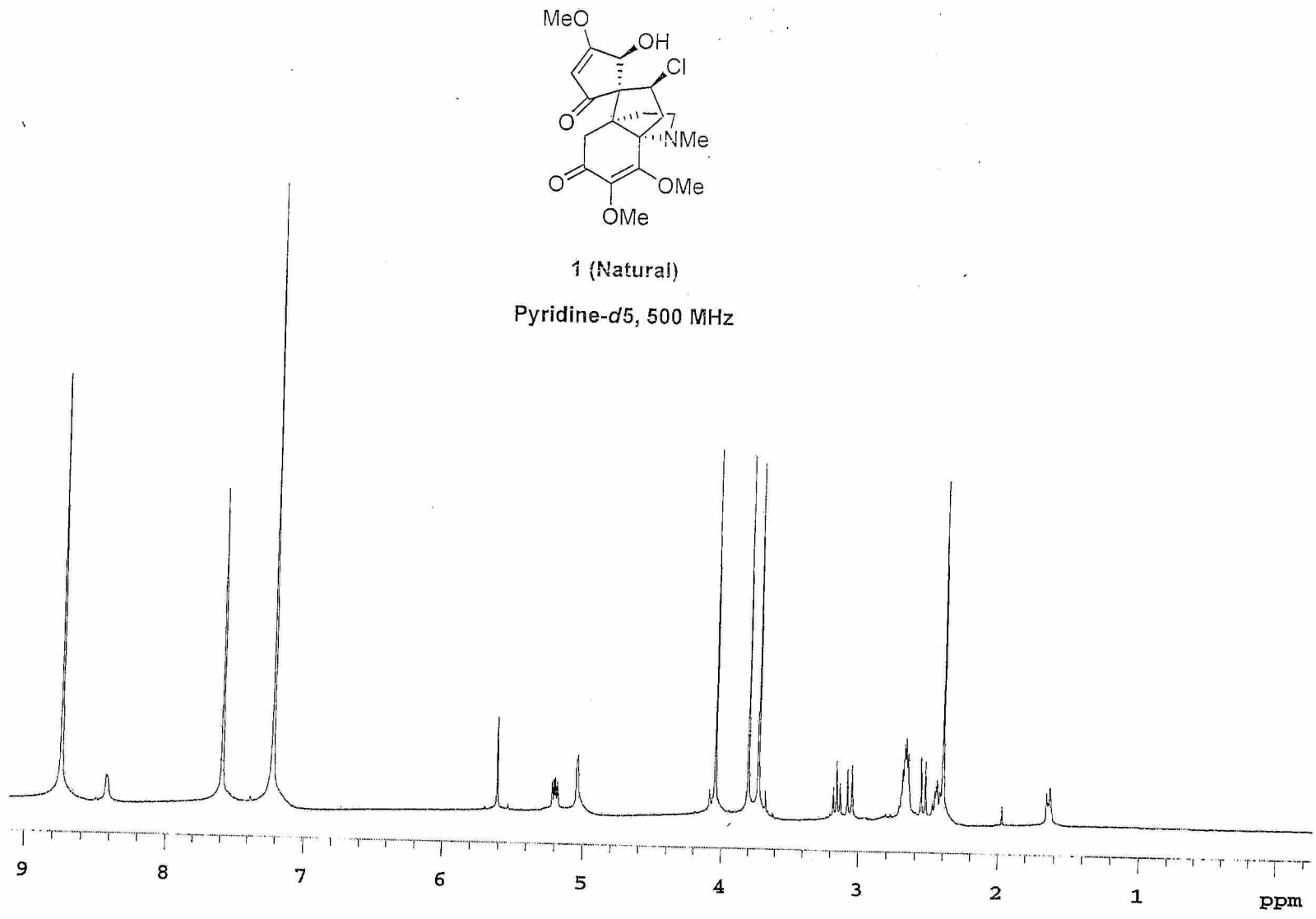
113

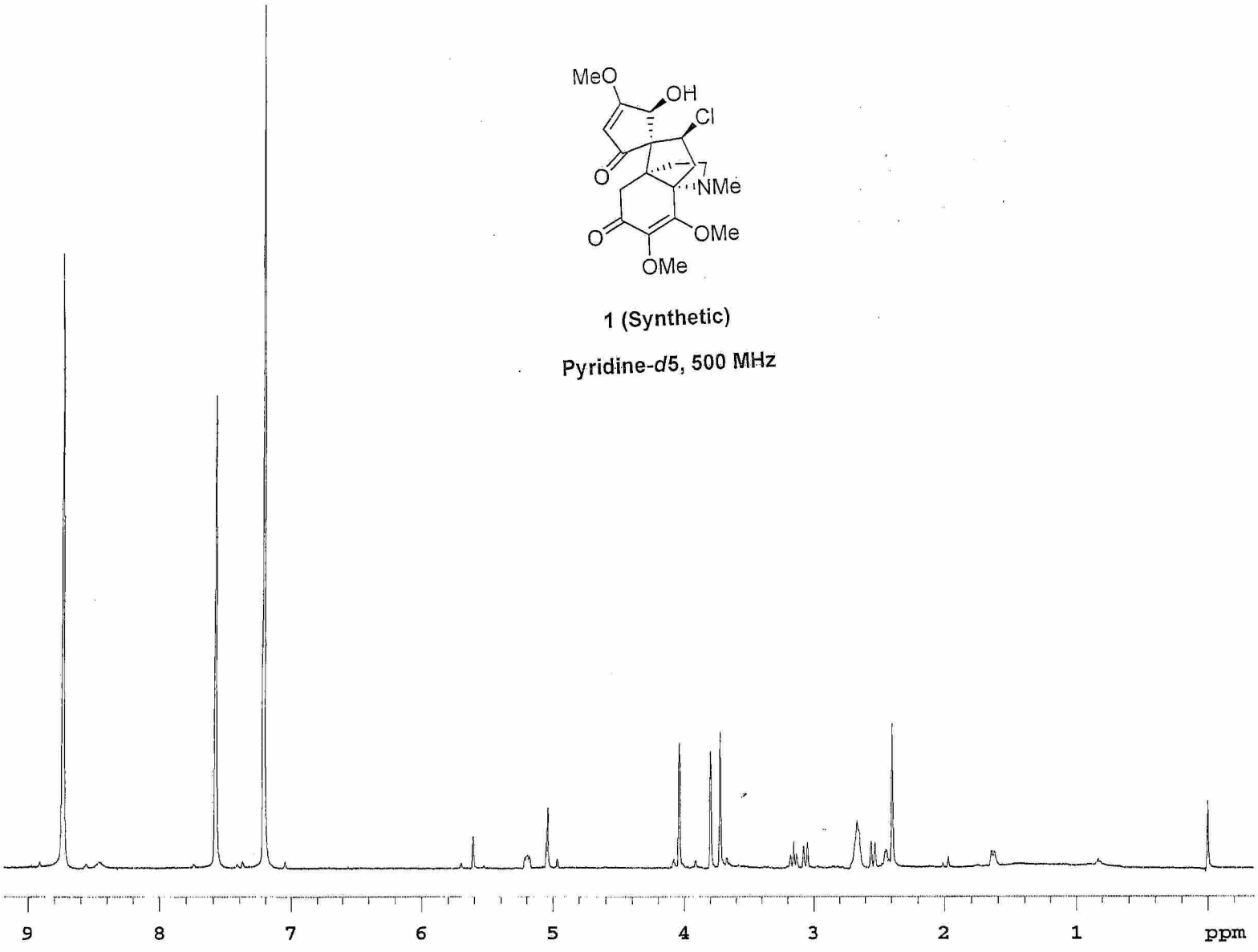
Pyridine-*d5*, 125 MHz



114

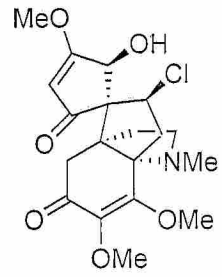
Pyridine-*d5*, 500 MHz


MeO
OH
Cl
O
NMe
O
OMe
OMe
1 (Natural)
Pyridine-d5, 500 MHz
9
8
7
6
5
4
3
2
1
ppm



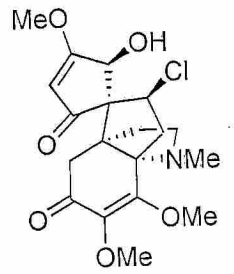
1 (Synthetic)

Pyridine-*d*5, 500 MHz



1 (Natural)

Pyridine-*d*5, 125 MHz



1 (Synthetic)

Pyridine-*d*5, 125 MHz