Total Synthesis of Plakortide E and Biomimetic Synthesis of Plakortone B

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Abstract

Plakortide E (**85**), which is isolated from the Jamaican marine sponge *Plakortis halichondrioides,* contains a five-membered peroxide ring, with the oxygen atoms are linked to tertiary C4 and C6 centers.[34,57] In this thesis, the total synthesis of plakortide E (**85**) is described. A novel palladium-catalyzed approach towards 1,2-dioxolanes has been developed. A lipase-catalyzed kinetic resolution was employed to provide optically pure 1,2-dioxolane central cores. Coupling of the central cores and side chains was achieved by a Negishi reaction. All four isomeric structures of plakortide E methyl ester, namely, **86a-d** were synthesized, and one of these molecules, **86d** proved to be natural plakortide E methyl ester on the basis of ^{1}H, ^{13}C NMR spectra and specific rotation. With plakortide E methyl ester (4*S*,6*R*,10*R*)-(–)-*cis*-(**86d**) and its other three isomers in hand, we successfully converted them into plakortone B (3*S*,4*S*,6*R*,10*R*)-(**87a**), and its isomers *ent*-**87a**, **87b** and *ent*-**87b** via an intramolecular oxa-Michael addition/lactonization cascade reaction. Saponification converted 1,2-dioxolane **86d** into plakortide E (**85a**) whose absolute configuration (4*S*,6*R*,10*R*) was confirmed by comparison of spectral and physical data with those previously reported.[35b]

摘要

Plakortide E (**85**) 是从牙买加海绵 *Plakortis halichondrioides* 中分离到的一个带有五员环状过氧结构的天然产物。[34,57] 本论文描述了 Plakortide E (**85**) 的全合成。我们发展了一种新型的钯催化制备五员环状过氧化合物的方法。利用酶催化的动力学拆分得到了光学纯的五员环状过氧母核。采用 Negishi 反应实现了手性侧链和母核的连接。Plakortide E 甲酯的四种可能结构（**86a-d**）全部被合成出来，通过与文献报道的核磁以及比旋光数据的比较，我们确定了 **86d** 是天然产物 Plakortide E 的甲酯。通过分子内氧杂-迈克尔加成/内酯关环的串联反应，我们将 **86a-d** 成功转化为已经报道的天然产物 plakortone B ((3*S*,4*S*,6*R*,10*R*)-(**87a**)) 及其异构体 *ent*-**87a**, **87b** 和 *ent*-**87b**。[35b] 通过核磁以及比旋光数据的比较，我们从 plakortone B 及其异构体的已知绝对构型出发，成功确定了化合物 **86a-d** 的绝对构型。水解 **86d** 得到了天然产物 Plakortide E，其绝对构型为(4*S*,6*R*,10*R*)。

Abbreviations

[α]	specific rotation
Å	Ångstrom (s)
Ac	Acetyl
AIBN	Azobisisobutyronitrile
Anal.	Analytical
aq.	aqueous
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
BDE	Bond dissociation energy
BHT	2,6-di-*tert*-butyl-4-methyl phenol
cat.	catalytic
conc.	concentrated
δ	chemical shift in parts per million downfield from tetramethylsilane
d	day (s), doublet (spectral)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	dimethyl formamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
EA	ethyl acetate
Et	ethyl
EI	electron impact (in mass spectrometry)
ESI	Electrospray Ionization
equiv	equivalent
FAB	Fast Atom Bombardment
FT	Fourier Transform
HPLC	High-performance liquid chromatography
HRMS	high-resolution mass spectrum
HWE	Horner-Wadsworth-Emmons
IR	infrared
J	coupling constant (in NMR)
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
lit.	literature
DCC	*N,N'*-Dicyclohexylcarbodiimide
m	multiplet (spectral)，milli-
Me	methyl
m.p.	melting point
MS	mass spectrometry; molecular sieves
m/z	mass to charge ratio (in mass spectrometry)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy

PDC	pyridinium dichromate
Ph	phenyl
ppm	parts per million (in NMR)
^{i}Pr	isopropyl
q	quartet
R_f	retention factor
rt	room temperature
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TEA	triethylamine
tert-	tertiary
THF	tetrahydrofuran
TLC	thin-layer chromatography
p-TsOH	*p*-toluenesulfonic acid

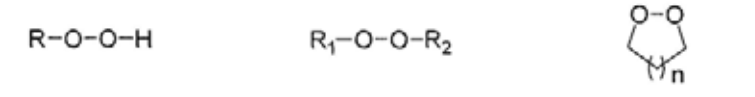
Index of spectra of compounds

Chapter 1
Introduction

1.1 Introduction to organic peroxides

Organic peroxides are compounds containing an O-O bond. The O-O group is called the peroxide group. The peroxide bond is one of the weakest bonds in organic molecules, with BDE of approximately 34 kcal/mol (C-C: 81 kcal/mol, C-H: 98 kcal/mol, C-O: 79 kcal/mol, C-N: 66 kcal/mol).[1] The O-O bond is unstable and easily splits into reactive radicals via homolytic cleavage. For this reason, peroxides are found in nature only in small quantities, in water, atmosphere, plants, animals and man. According to the substitution patterns, organic peroxides can be classified into hydroperoxides, acyclic dialkyl peroxide and cyclic peroxides (Figure 1).

Figure 1. Categories of peroxides

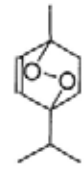


Hydroperoxides Acyclic dialkyl peroxide Cyclic peroxides

1.2 Cyclic peroxide natural products and their potential biological activities

Ascaridole, used as a remedy for worms, which was isolated from chenopodium oil and named by Hüthig in 1908,[2] was the first studied naturally occurring organic peroxide (Figure 2). Hüthig described its explosive character and determined its chemical formula as $C_{10}H_{16}O_2$. In 1911, these results were confirmed by Nelson in his detailed study of ascaridole.[2]

Figure 2. The first studied naturally occurring organic peroxide



Ascaridole

One of the most important medical applications of organic peroxides has been in the treatment of malarial. In the worldwide scale, there are 300 to 500 million clinical cases of people that are infected by malaria every year, and between one to three million deaths, mostly of children, are attributable to this disease. Every 40 seconds a child dies of malaria, resulting in a daily loss of more than 2,000 young lives worldwide. These estimates made malaria one of the top three killers among communicable diseases.[3]

In the search for antimalarial drugs, yingzhaosu A was isolated by Liang and coworkers in 1979 from *Artabotrys uncinatus* (Annonaceae),[4] which was used in China as a traditional remedy for the treatment of malaria (Figure 3). Further work from this lab resulted in the isolation of yingzhaosu C. (Figure 3).[5] Yingzhaosus A and C both contain a 1,2-dioxane core structure. These compounds have been extensively studied for their potential antimalarial activity.

Figure 3. Antimalarial natural cyclic peroxides

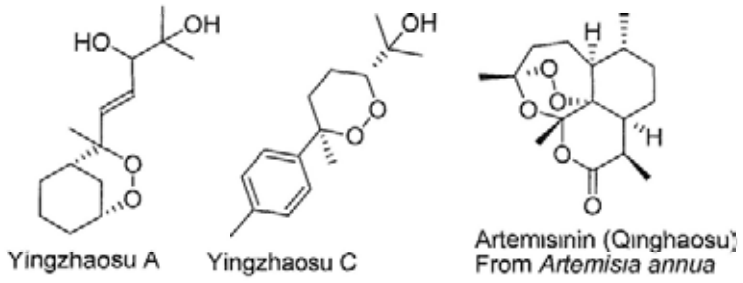


Figure 4. ***Artemisia annua***

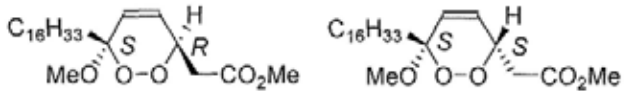
At about the same time, artemisinin, a naturally occurring organic peroxide with a 1,2,4-trioxane core, also known as qinghaosu, was isolated from the plant *Artemisia annua*, a herb described in Chinese traditional medicine by Wu and coworkers (Figure 3 and Figure 4).[6a] Artemisinin and its derivatives are a group of drugs that possess the most rapid action of all current drugs against falciparum malaria. The discovery of strong antimalarial activity from artemisinin and yinghaosu motivated the worldwide exploration of antimalarial cyclic peroxide drugs. Since scientists recognized the pivotal role of cyclic peroxides in various vital biological processes,[6b] the chemistry of cyclic peroxides has been rejuvenated in the 1970s. More and more naturally occurring cyclic peroxides have been isolated and identified.

Chondrillin, isolated from a Great Barrier Reef sponge of the genus *Chondrilla* by

Wells in 1976, was the first cyclic peroxide to be isolated from marine sources.[7] Later, it was also isolated from another marine sponge *Plakortis lita* by DeGuzman and Christophersen,[8] and its diastereomer plakorin and a number of other alkoxydioxines were isolated from this marine sponge (Figure 5).[9]

These peroxides have shown interesting biological properties. For example, chondrillin was found to have an *in vitro* IC_{50} of 5 μg/mL against P388 leukemia cells.[8] Plakorin is a potent activator of sarcoplasmic reticulum calcium-ATPase, and it also has an *in vitro* IC_{50} = 0.85 μg/mL against murine lymphoma L1210 cells and IC_{50} = 1.8 μg/mL against human epidermoid carcinoma KB cells.[10]

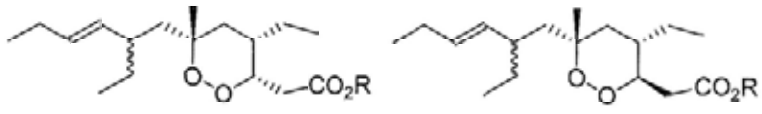
Figure 5. Six-membered cyclic peroxides



Chondrillin Plakorin

Many natural peroxides with 1,2-dioxine or 1,2-dioxane subunits have been isolated from the marine sponge, *Plakortis sp.*, especially from *Plakortis halichondrioides*. For example, plakortin (**1**), 3-epi-plakortin (**2**), plakortic acid (**3**) all share a common six-membered cyclic peroxide core (Figure 6). The marine cyclic peroxide plakortic acid (**3**) is a potent antifungal and antibacterial agent; however, the corresponding methyl ester, plakortin (**1**), is inactive.[11]

Figure 6. Natural products with 1,2-dioxane cores

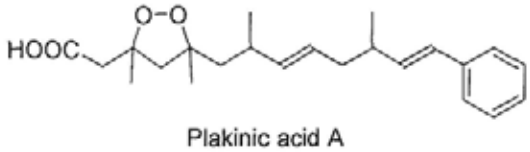


1 R = Me
3 R = H

2

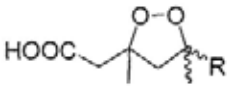
Plakinic acid A, a 3,3,5,5-tetrasubstituted 1,2-dioxolane isolated from a Caribbean sponge, was the first isolated five-membered ring peroxide among marine natural products (Figure 7).[12,13] In the last decades, many additional plakinates have been isolated and characterized, which usually exhibited remarkable cytotoxicity against fungal and cancer cell lines.[13-21] As shown in Table 1, all the plakinic acids contained a 3,3,5,5-tetrasubstituted 1,2-dioxolane core.

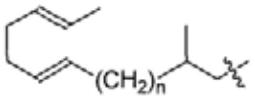
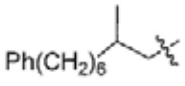
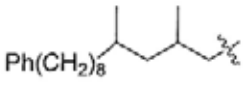
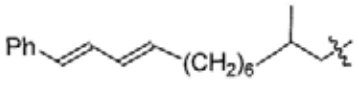
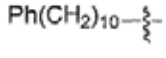
Figure 7. The first isolated five-membered ring peroxide



Plakinic acid A

Table 1. Plakinates from marine sponge

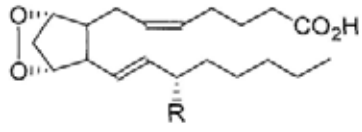


R		Plakinate	Reference
$C_{16}H_{33}$ $C_{15}H_{31}$		unnamed	14
	n = 4	C (3,5-*cis*); epi-C (3,5-*trans*)	13
	n = 2	D (3,5-*cis*); epi-D (3,5-*trans*)	13
		epi-E (3,5-*trans*)	16
		F (3,5-*cis*); epi-F (3,5-*trans*)	17
		G (3,5-*cis*); epi-G (3,5-*trans*)	18
		unnamed (3,5-cis); unnamed (3,5-trans)	57
		andavadoic acid (3,5-*trans*)	20

The highly unstable prostaglandin H_2 (PGH_2) and prostaglandin G_2 (PGG_2), containing a five-membered ring peroxide, were isolated and identified as key intermediates in prostaglandin's biosynthesis from arachidonic acid (Figure 8).[22-24] PGH_2 and PGG_2 were also biosynthetic precursors for many other physiological important compounds, such as prostacyclins and thromboxanes.[25,26] Afterwards, the total syntheses of PGH_2 and PGG_2 were reported by Porter and coworkers[54] and Johnson and coworkers.[114] The early studies on prostaglandin endoperoxides and their

analogs were reviewed by Nicolaou and Salomon.[27,28]

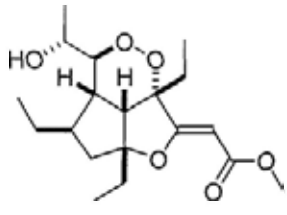
Figure 8. Prostaglandin G_2 and H_2



R =OOH, Prostaglandin G_2
R = OH, Prostaglandin H_2

In the course of their continuing search for drug leads from Japanese marine invertebrates, Nakao and Fusetani isolated graciliorther A from the deep-sea sponge *Agelas gracilis* in 2009, which show considerable antimalarial activity (Figure 9).[29] The absolute stereochemistry of graciliorther A was confirmed by application of the modified Mosher's method.

Figure 9. A polycyclic natural product with 1,2-dioxane core

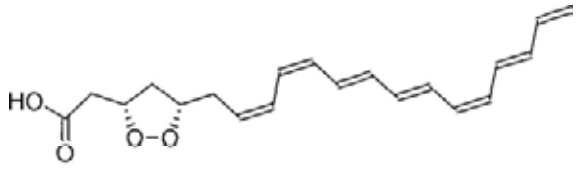


Gracilioether A

Clardy and coworkers in their study of the southern pine beetle system, have discovered another symbiont (Streptomyces sp. SPB74) that produces a polyene peroxide, which was named mycangimycin (Figure 10). It was found that mycangimycin selectively inhibits the beetle's fungal antagonist. The complete

structure was fully elucidated including the absolute configuration.[30]

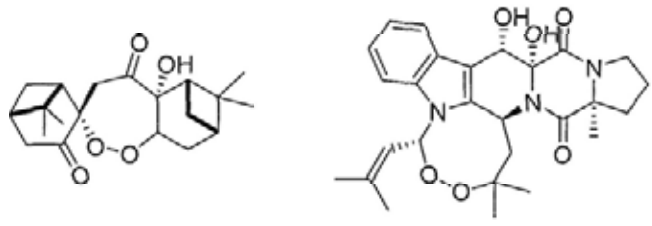
Figure 10. A novel linear polyene peroxide



Mycangimycin

Although majority of cyclic peroxide natural products contain dioxanes or dioxolanes, some medium ring cyclic peroxides discovered in nature (Figure 11). The terpenic peroxide **4** was isolated from the spice cardamom, the fruit of *Amomum krervanh* Pierre, which contained a seven-membered cyclic peroxide core. Compound **4** also exhibited moderate antimalarial activity *in vitro* against *Plasmodium falciparum* (IC_{50} = 170 nM).[31] Verruculogen (**5**), containing a novel eight-membered cyclic peroxide core, was obtained from a strain of *Penicillium verruculosum* Peyronel isolated from peanuts, which was fully characterized by Clardy and coworkers in 1974.[32]

Figure 11. Natural products containing medium ring cyclic peroxides



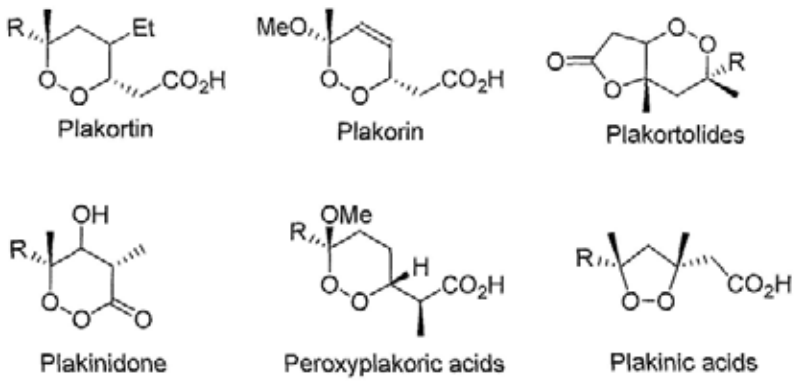
4 Verruculogen (**5**)

1.3 Natural products from marine sponges of the genus *Plakortis*

Marine sponges have been among the most studied of marine organisms. The genus *Plakortis* has attracted particularly interests as a source of novel metabolites. Many unusual metabolites isolated from the genus *Plakortis* exhibited anti-fungal, anti-tumor, anti-bacterial and other important pharmacological activities. Based on their work, the structures, stereochemistry, pharmacological activities and selected syntheses of the *Plakortis* derived metabolites have been reviewed by Kitching and coworkers in 2004.[33]

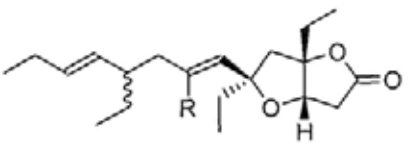
Examples of cyclic peroxides isolated from the genus *Plakortis* are illustrated in Figure 12. These cyclic peroxide natural products are very fascinating because of their novel structure and activities.

Figure 12. Natural products from the genus *Plakortis*

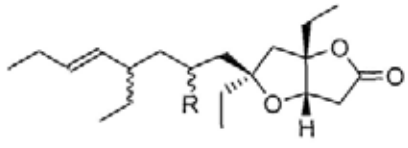


In their continuing search for biologically active natural products to cure cardiac disease, Patil and coworkers employed a high throughput screening to evaluate the ability of natural products to stimulate cardiac SR-Ca^{2+} ATPase.[34] A screening of over 2400 plant and marine extracts found an extract of sponge *Plakortis halichondrioides* with the ability to stimulate cardiac SR-Ca^{2+} ATPase activity. This led to the discovery of four novel polyketides, plakortones A-D, four novel acids, plakortides E-H and one known compound 3-epi-plakortin (**2**) were isolated from the sponge *Plakortis halichondrioides* (Figure 13).

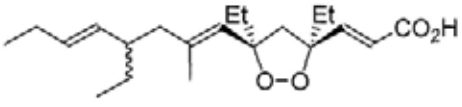
Figure 13. Natural products from the sponge *Plakortis halichondrioides*



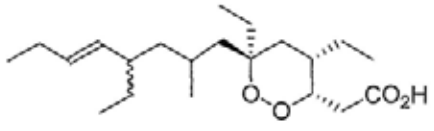
Plakortones A (R = Et), B (R = Me)



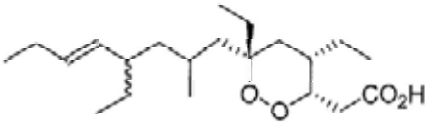
Plakortones C (R = Me), D (R = H)



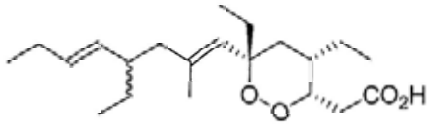
Plakortide E



Plakortide F



Plakortide G

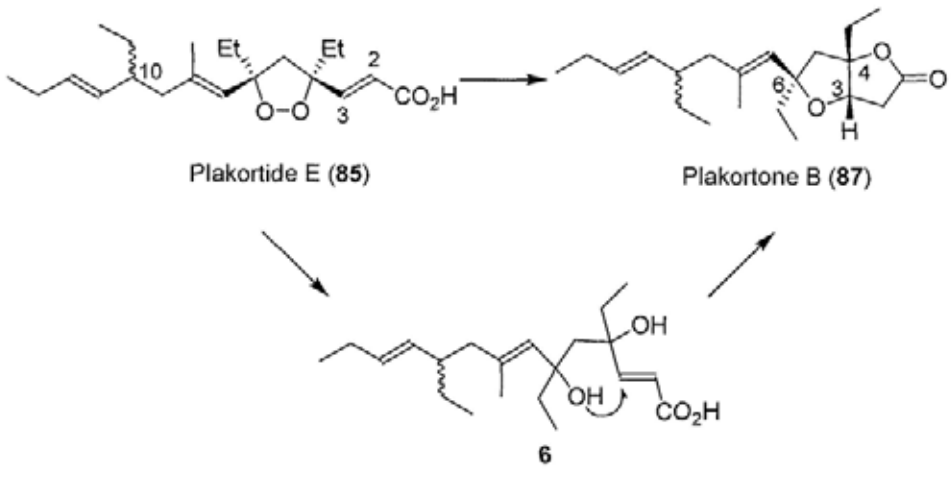


Plakortide H

In 2002, Kitching and coworkers reported the first total synthesis of plakortone D, which not only confirmed the absolute stereochemistry of plakortone D, but also enabled the acquisition of other plakortones and analogs.[33a] In 2010, they reported the total syntheses and configuration assignments of plakortone C and F.[33c] Our group were also interested in the synthetic chemistry of the *Plakortis* derived metabolites. Our preliminary synthetic efforts towards plakortide E were recorded in 2007.[35a] In 2010, we have reported the total syntheses and configuration assignments of all four isomers of plakortone B,[35b] whose total synthesis was reported by Semmelhack and coworkers in 2006.[36] In consideration that plakortone B was isolated from the same animal source together with plakortide E,[34] we reasoned that diol **6** could be converted to plakortone B (Scheme 1).[59] Kitching has also suggested that the 1,3-diol notionally

derived from reductive cleavage of 1,2-dioxolane are perhaps the actual precursors of the plakortone series.[33b,33c]

Scheme 1. Biosynthesis of plakortone B

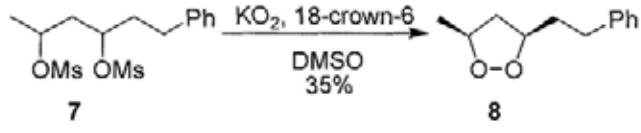


1.4 Methodologies for synthesis of cyclic peroxides

Construction of cyclic peroxides is a particularly challenging issue because of the low O-O bond dissociation energy (37±1 kcal mol^{-1}).[1a] Numerous approaches have been developed in the past for the synthesis of five- and six-membered ring peroxides.[39-45] Syntheses of cyclic peroxides were well-reviewed by Nojima and coworkers,[37] and Bachi and coworker.[38] Many of these methodologies demand low temperature operations and mild conditions. These approaches can be categorized into three types: 1. cyclization of hydroperoxides through intramolecular nucleophilic reactions; 2. cycloaddition of triplet oxygen with radicals; 3. cycloaddition of singlet oxygen with 1,3-dienes.

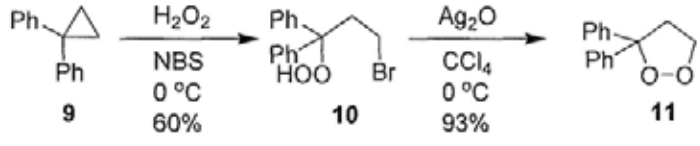
Cyclization via intramolecular nucleophilic reaction In 1975, Corey and coworkers reported a method to obtain the 1,2-dioxolane through a intramolecular substitution. Bis(mesylate) **7** was treated with potassium superoxide to give the *cis*-disubstituted 1,2-dioxolane **8** in a moderate yield (Scheme 2).[45a]

Scheme 2. Corey's synthesis of 1,2-dioxolanes



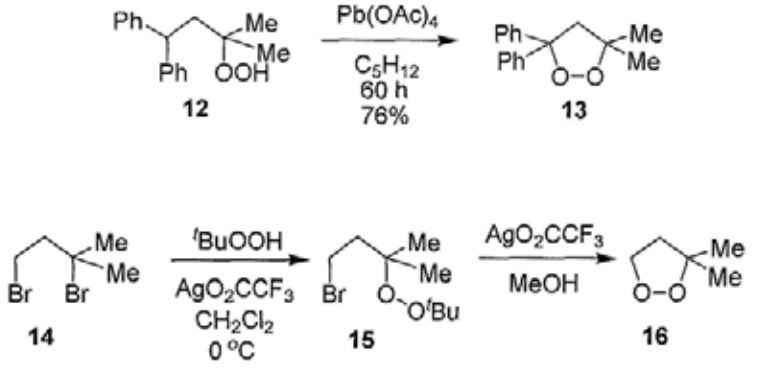
In 1978, Adam treated cyclopropane **9** with H_2O_2/NBS to afford β-bromohydro peroxide **10**, which was cyclized to 1,2-dioxolane **11** in the presence of silver(I) oxide in good yield (Scheme 3).[45b]

Scheme 3. Adam's route to 1,2-dioxolanes



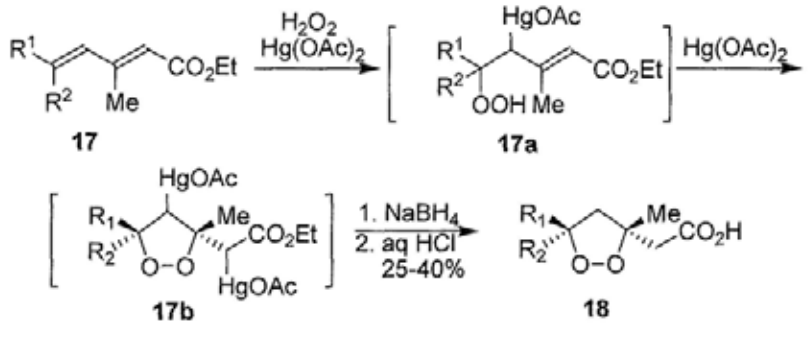
Kropf[39i] prepared 1,2-dioxolanes by treating hydroperoxides with $Pb(OAc)_4$, which involves 1,5-hydrogen abstraction by an intermediate peroxyl radical. Alternatively, the treatment of 1,3-dibromopropane **14** with *tert*-butylhydroperoxide in the presence of AgO_2CCF_3 also led to 1,2-dioxolane **16** (Scheme 4).[45c]

Scheme 4. Formations of 1,2-dioxolanes via nucleophilic reactions



Bloodworth[40] prepared four non-natural plakinic acids via a peroxymercuration reaction as shown below (Scheme 5). A similar strategy was used by Gunstone[41] for his preparation of 1,2-dioxolanes from methyl oleate. A cycloperoxyiodination route also gave rise to 1,2-dioxolane frameworks. The difference between Bloodwoworth's and Gunstone's approach is five-*exo* vs. 5-*endo* peroxymercuration.

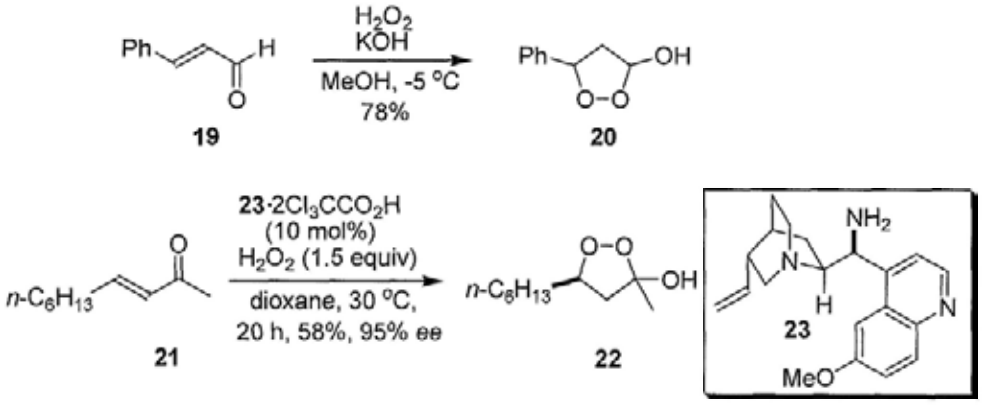
Scheme 5. Intramolecular hydroperoxide addition to double bond



Intramolecular nucleophilic addition of hydroperoxide to a carbonyl group was one of the earliest methods to prepare cyclic peroxides. For example, the α,β-unsaturated

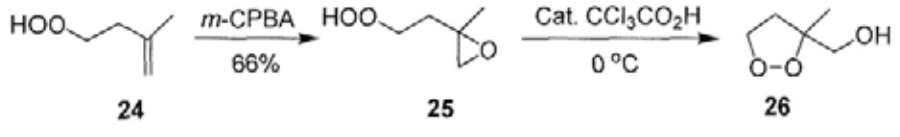
aldehyde **19** reacted with hydrogen peroxide at room temperature in the presence of KOH to form the 1,2-dioxolane **20** in 78% yield.[46] An asymmetric version of this reaction was reported by List and coworkers in 2008 (Scheme 6).[46c]

Scheme 6. Intramolecular hydroperoxide addition to carbonyl group



Acid-catalyzed intramolecular attack of hydroperoxide on an epoxide to form the 1,2-dioxolane was reported in 1976 (Scheme 7).[47] This type of reaction was applicable to more complex substrates, and has been applied to the total syntheses of natural products.[53]

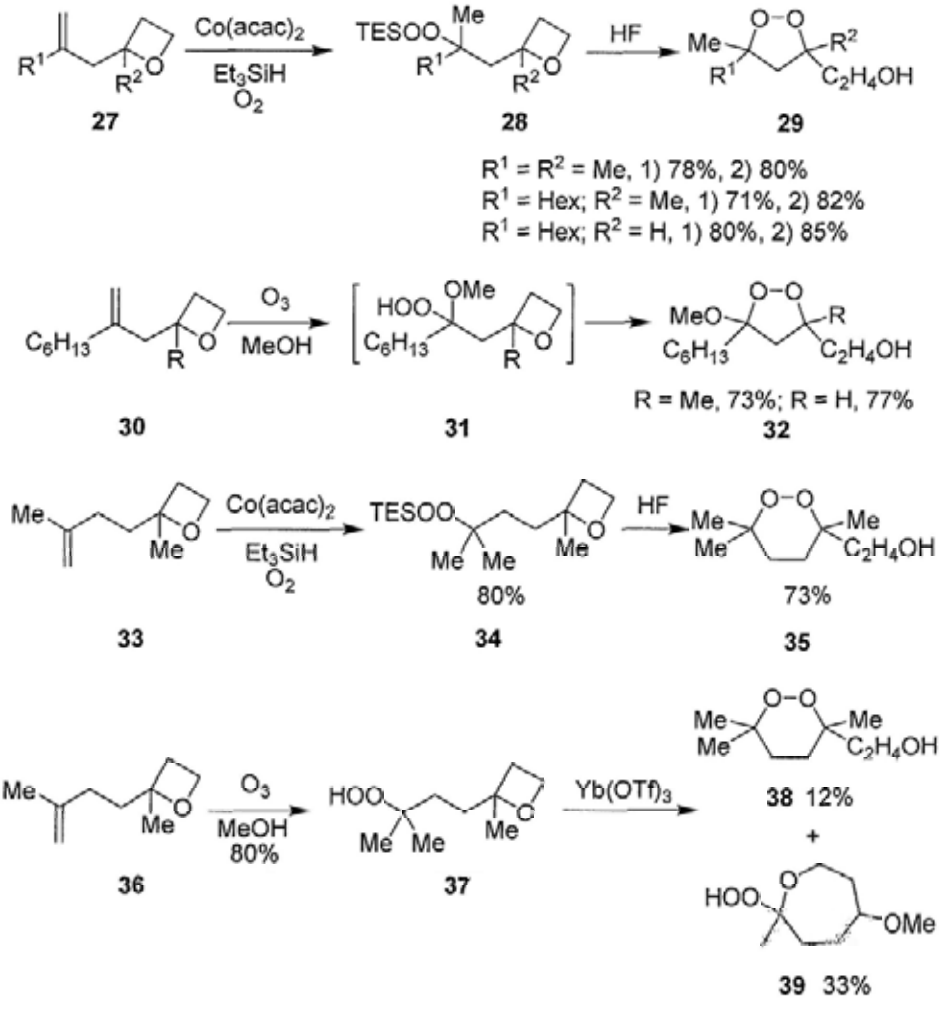
Scheme 7. Formation of 1,2-dioxolane via intramolecular opening of epoxide with hydroperoxide



Methods to synthesize the cyclic peroxides by the intramolecular opening of oxetanes with hydroperoxides have been developed by Dussault and coworkers.[43g]

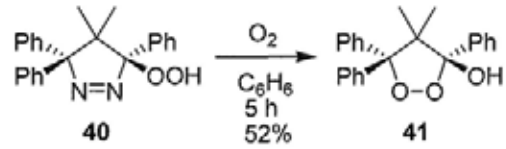
The method was used to synthesize the 1,2-dioxolanes, 1,2-dioxanes and 3-alkoxy-1,2-dioxolanes with good stereoselectivity and good yields (Scheme 8).

Scheme 8. Formations of 1,2-dioxolane via intramolecular opening of oxetanes with hydroperoxides



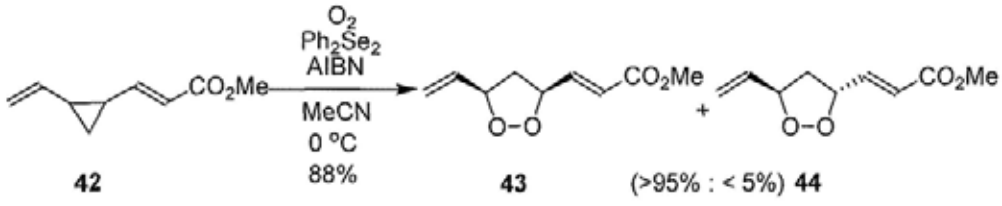
Cycloaddition of triplet oxygen with radicals. As can be seen in Scheme 9, pentasubstituted 3-hydroxy-1,2-dioxolanes were realized via oxygen trapping during thermolysis of cyclic α-azohydroperoxides.[45d]

Scheme 9. Cycloaddition of triplet oxygen with diradicals



Feldman developed a convenient approach for the formation of 1,2-dioxolanes from vinylcyclopropanes by a free radical-mediated ring expansion with oxygen as demonstrated in Scheme 10. In their experiments, the *cis*-1,2-dioxolanes **43** were obtained in good yield.[44]

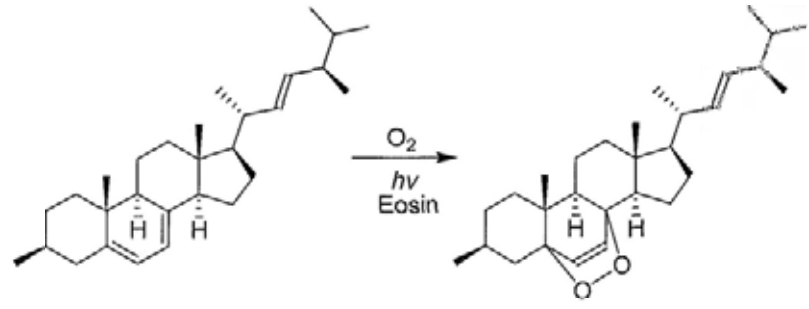
Scheme 10. Formations of 1,2-dioxolanes reported by Feldman and coworkers



Cycloaddition of singlet oxygen with 1,3-dienes. Singlet oxygen ($^1O_2$) can be generated by a chemical process on a synthetically useful scale or in a photosensitized process by energy transfer from dye molecules such as rose bengal, methylene blue or porphyrins.[48] The electron occupancy of the shells of the singlet oxygen is different from those of ground state oxygen. The energy difference between ground state and singlet oxygen is 94.3 kJ/mol.[49] The damages caused by the sunlight to many organic materials are always attributed to the effects of singlet oxygen. Singlet oxygen reacting with a variety of 1,3-dienes gives the corresponding six-membered cyclic

peroxides. This is one of the oldest and the most general methods to generate cyclic peroxides. Windaus and Brunken isolated the cyclic peroxide of ergosteryl acetate in 1928,[50] which was prepared through singlet oxygen cycloaddition to ergosteryl acetate (**45**) (Scheme 11).

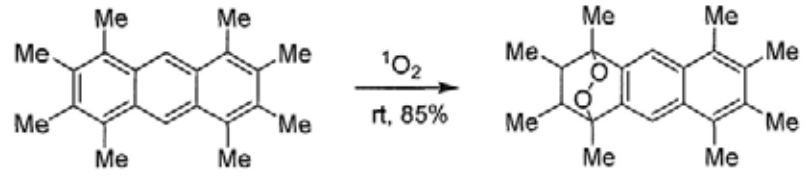
Scheme 11. Ergosteryl acetate oxidation with oxygen



Ergosteryl Acetate (**45**) **46**

Anthracene derivatives reacted with singlet oxygen to furnish the corresponding 1,4-endoperoxides or 9,10-endoperoxides. For example, singlet oxygen cycloaddition to 1,2,3,4,5,6,7,8-octamethylanthracene (**47**) mainly led to 1,4-endoperoxide **48** (Scheme 12).[51]

Scheme 12. Anthracene derivatives peroxydation with singlet oxygen

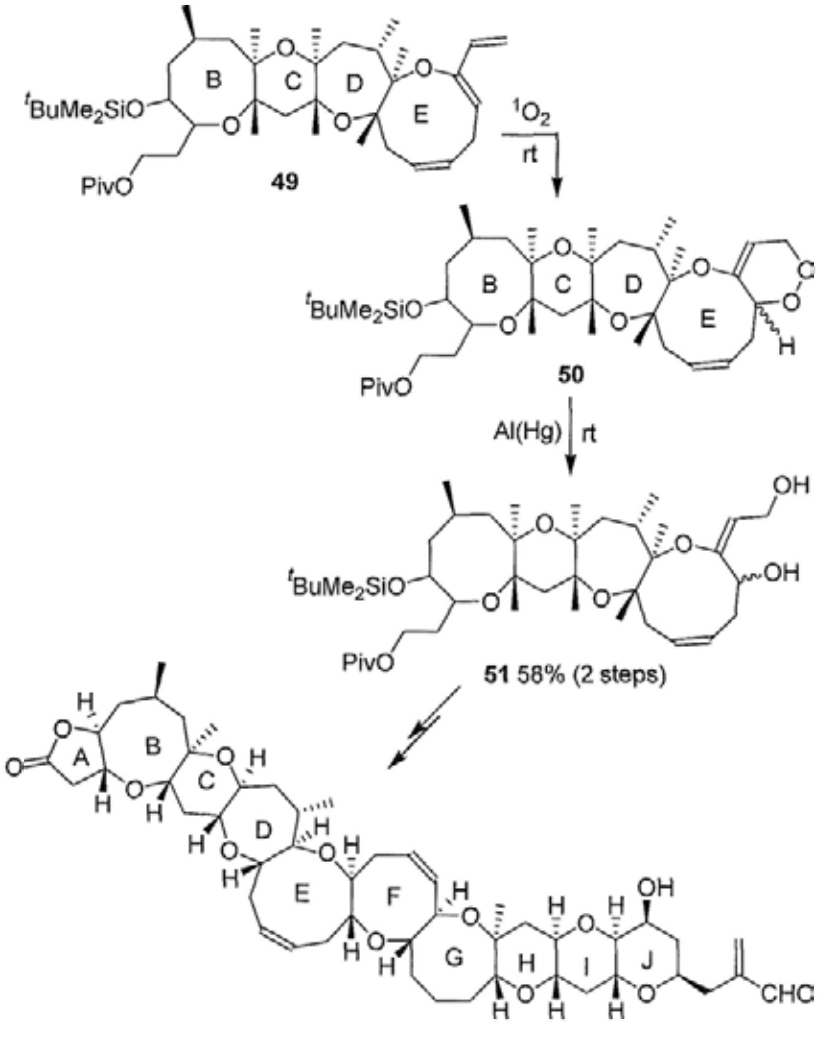


47 **48**

Singlet oxygen [4+2]-cycloadditions to 1,3-dienes were widely used in the total

syntheses of non-peroxide containing natural products. For example, in the total synthesis of brevetoxin A (**52**), 1,3-diene **49** reacted with singlet oxygen to furnish the cyclic peroxide containing intermediate **50** (Scheme 13).[52]

Scheme 13. Application of singlet oxygen [4+2]-cycloaddition to 1,3-dienes in total synthesis of brevetoxin A

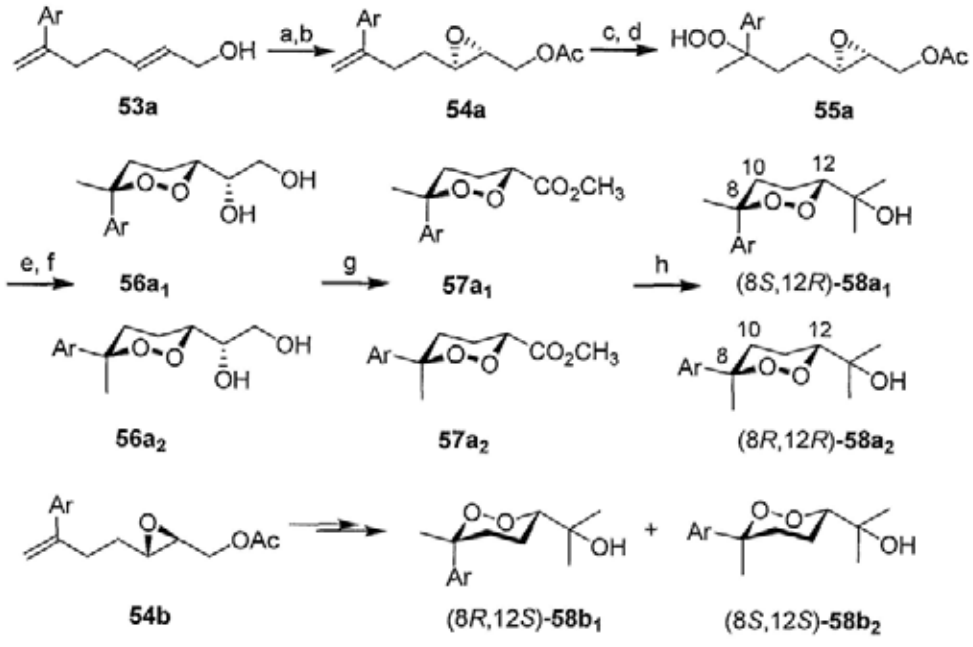


1.5 Total syntheses of cyclic peroxide natural products

The discovery of antimalarial and anticancer activity in cyclic peroxide natural products has resulted in increased interest in the total syntheses of cyclic peroxide natural products in the last decades. In this section, the total syntheses of cyclic peroxide natural products will be reviewed.

Xu and coworkers reported the total synthesis of all four stereoisomers of yingzhaosu C in 1995.[53] The core structure of the 1,2-dioxane was constructed by intramolecular epoxide opening under acidic conditions (Amberlyst-15), with the stereochemistry of the ring-closure controlled by the stereochemistry of the epoxide (Scheme 14). Compounds **58a$_1$** and **58a$_2$** were prepared from **53a**. Dioxanes **58b$_1$** and **58b$_2$** were synthesized in a similar manner. These four samples are two pairs of enantiomers (**58a$_1$** and **58b$_1$**, **58a$_2$** and **58b$_2$**). The NMR spectra of **58a$_1$** and **58b$_1$** were identical with that of the natural yingzhaosu C. On the basis of the observed optical rotation, Xu and coworkers concluded that natural yingzhaosu C may be considered to be a mixture of enantiomeric (8*S*,12*R*)-**58a$_1$** and (8*R*,12*S*)-**58b$_1$** with the former being in excess, because the optical rotation of the natural yingzhaosu C was only +2.89 (MeOH). However, the strategy employed in this study is not suitable for the substrates with unsaturated side chains.

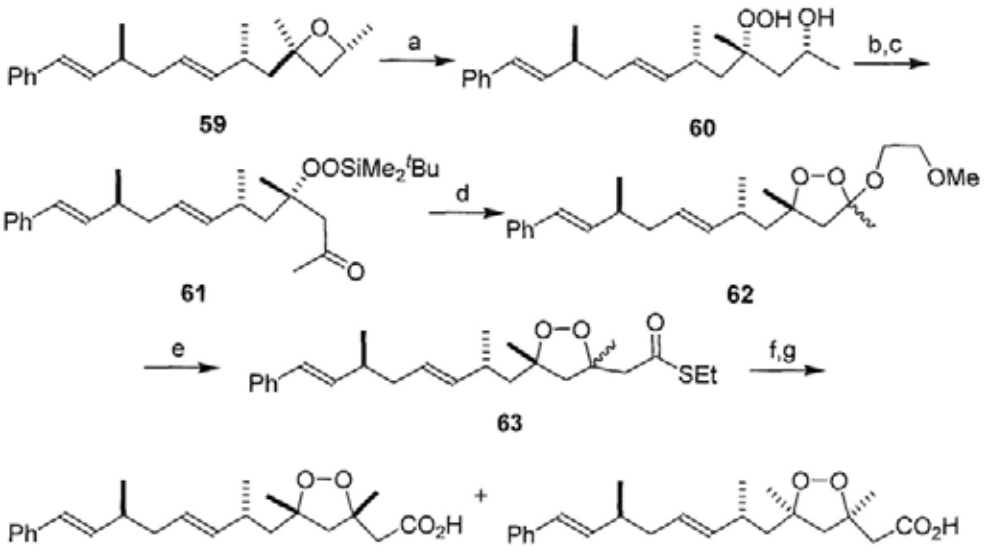
Scheme 14. Total syntheses of yingzhaosu C and its isomers



Reagents and conditions: (a) L-(+)-DIPT, Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2; (b) Ac_2O/Pyr; (c) Et_3SiH, O_2, Co(modh)$_2$; (d) KF/18-crown-6, THF; (e) Amberlyst-15, CH_2Cl_2; (f) K_2CO_3/MeOH, then $H_2C_2O_4$ $2H_2O$; (g) $NaIO_4$/$RuCl_3$, MeCN:CCl_4:H_2O (2:2:3, v/v), rt, then CH_2N_2/Et_2O; (h) 2 equiv of MeLi/Et_2O, –78 °C, then aqueous NH_4Cl.

Based on elegant synthetic routes,[43] Dussault and coworkers achieved for the first time the asymmetric synthesis and configurational assignment of plakinic acid A (**65**) in 2006.[43h] The synthetic pathway for the (3*S*,5*S*,7*R*,11*S*)-stereoisomer of plakinic acid is shown in Scheme 15. As can be seen, a regio- and stereoselective opening of an enantiomerically enriched oxetane by hydrogen peroxide led to an intermediate, which was further elaborated into the 1,2-dioxolane product. After preparing four possible structural candidates of plakinic acid A (**65**), Dussault concluded that the most likely configuration for plakinic acid A should be (3*R*,5*R*,7*R*,11*R*).

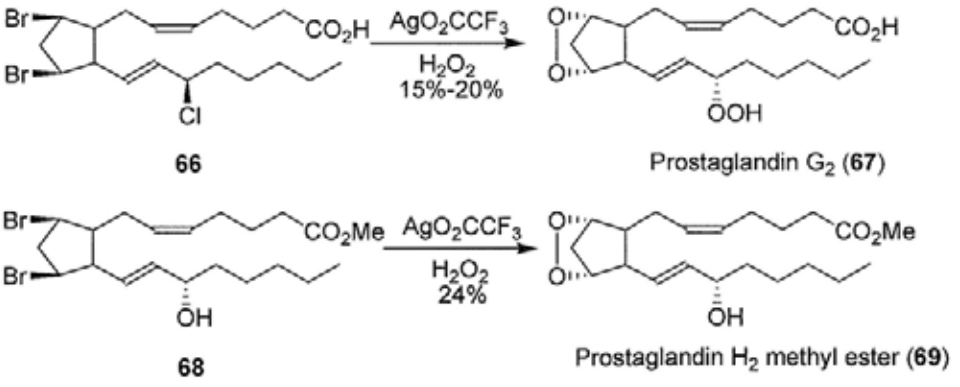
Scheme 15. Total synthesis of plakinic acid A



Reagents and conditions: (a) Me_3SiOTf, H_2O_2, Et_2O, −78 °C, 57%; (b) $LiN(SiMe_3)_2$, *t*-$BuMe_2SiCl$; (c) Dess-Martin periodinane, 80%; (d) HF, $MeOCH_2CH_2OH$, 2 days, 88%; (e) $TiCl_4$, $CH_2{=}CH_2(OSiMe_3)SEt$, −50 to 0 °C, 88%; (f) NaOMe, MeOH; g. LiOH, H_2O_2, THF, 71%.

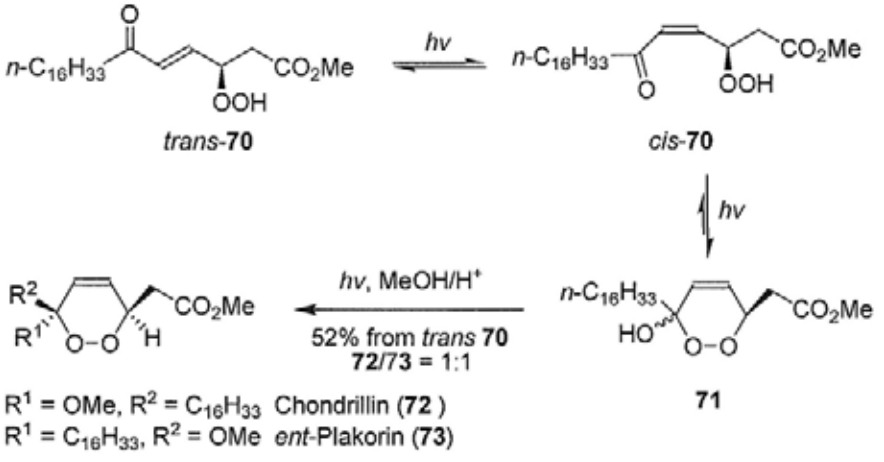
Porter and coworkers reported the semi-syntheses of prostaglandin H_2 and prostaglandin G_2 (Scheme 16). 1,3-Dibromide **68** was treated with hydrogen peroxide and silver trifluoroacetate to give prostaglandin H_2 (**69**) in 24% yield. In a similar manner, prostaglandin G_2 was obtained in 15%-20% yield.[54]

Scheme 16. Semi-syntheses of prostaglandin H_2 and prostaglandin G_2



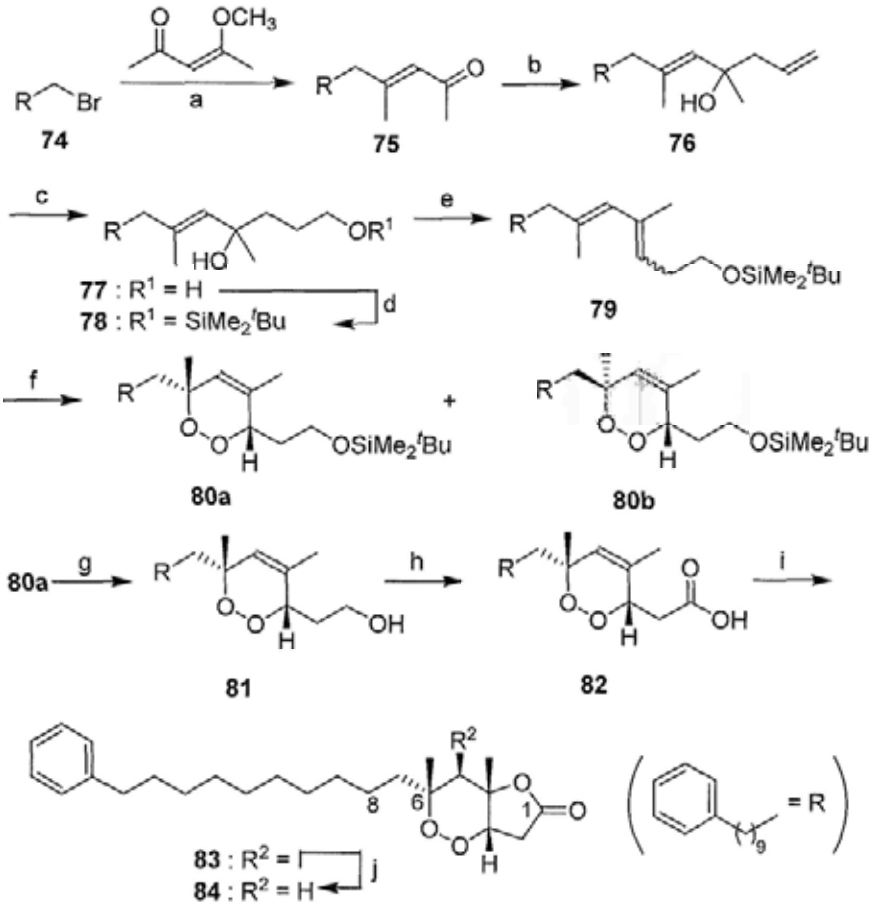
Total syntheses of chondrillin and *ent*-plakorin were accomplished by Dussault and coworkers. The final key step was based on the cyclization of *trans*-**70** as shown in Scheme 17. Compound *trans*-**70** was subjected to photocyclization and transetherification to give a mixture of chondrillin (**72**) and *ent*-plakorin (**73**) in good yield.[55]

Scheme 17. Total syntheses of chondrillin and *ent*-plakorin



In 2002, Jung and coworkers reported the first total synthesis of racemic 6-epiplakortolide E (Scheme 17).[56] Thus, the intermediate diene **79** underwent singlet oxygen [4+2]-cycloaddition to provide the six-membered cyclic peroxide containing compound **80**, which was a mixture of *cis*-**80a** and *trans*-**80b**. The ability to perform a [4+2]-cycloaddition on intermediate **79** was related to a substitution pattern. Compound *cis*-**80a** was subjected to desilylation giving alcohol **81** in 87% yield. Oxidation of **81** with Jones' reagent furnished acid **82**, which was subjected to iodolactonization to give **83**. A chemoselective free-radical reductive deiodination of **83** led to the natural product 6-epiplakortolide E (**84**).

Scheme 18. Total synthesis of 6-epiplakortolide E



Reagents and conditions: (a) Mg/ether, rt, 2 h, 69%; (b) allylmagnesium bromide, ether, 0 °C, 1.5 h, 60%; (c) 9-BBN, rt, 3 N $NaOH/H_2O_2$, 2 h, 90%; (d) *t*-$BuMe_2SiCl$, imidazole, DMF, rt, 4 h, 98%; (e) $TsOH/CaCl_2$, benzene, rt, 2 h, 80%; (f) O_2, 500-W lamp, rose bengal, 0 °C, 6 h, CH_2Cl_2/MeOH (19:1), 45%; (g) 10% HCl, THF/MeOH, rt, 1 h, 87%; (h) Jones' reagent, acetone, rt, 1.5 h, 78%; (i) $NaHCO_3/I_2$, $CHCl_3/H_2O$, rt, 2 days, 55%; (j) AIBN/Bu_3SnH, benzene, 80 °C, 1 h, 68%.

Chapter 2

Results and Discussion

2.1 Introduction

Plakortide E (**85**) and plakortone B (**87**) were first isolated from the Jamaican marine sponge *Plakortis halichondrioides* along with plakortones A, C, D in 1996 by Patil and coworkers (Figure 14 and Figure 15).[34] In 1999, plakortone B (**87**) was also isolated from the Caribbean sponge *Plakortis simplex* along with plakortones C-F by Fattorusso and coworkers.[58] In their continuing program to identify compounds with antifungal properties, Wright and coworkers also isolated a molecule identified as plakortide E (**85**) from the sponge *Plakortis halichondrioides* in 2002.[57]

Figure 14. The Jamaican marine sponge *Plakortis halichondrioides*

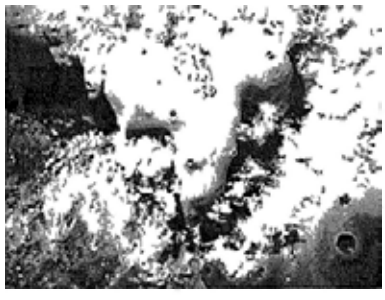
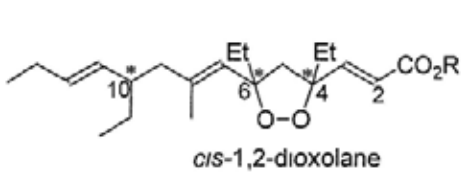
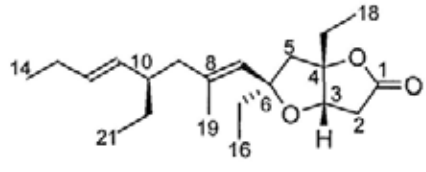


Figure 15. Plakortide E (85) and plakortone B (87)



cis-1,2-dioxolane

R = H plakortide E (**85**)
R = Me plakortide E methyl ester (**86**)



(3*S*,4*S*,6*R*,10*R*)-Plakortone B (**87**)

Plakortide E (**85**), $[\alpha]_D^{20}$ = 63.9 (*c* = 2.0, $CHCl_3$), isolated as a low melting solid, was first characterized in 1996 by Patil and coworkers.[34] The molecular formula of plakortide E (**85**) was determined as $C_{22}H_{36}O_4$ from the LRESIMS 351$(M+H)^+$. The basic skeleton was determined by interpretation of the IR, ^1H NMR (Table 2), ^{13}C NMR (Table 2), COSY, and HMBC spectra. In the IR spectrum, a sharp and intense absorption at 1690 cm^{-1} indicated that the carbonyl was an α,β-unsaturated acid. Treatment of **85** with diazomethane furnished methyl ester **86**, confirming the presence of an acid group in **85**. The data of methyl ester **86** is summarized in Table 4. The NMR spectra indicated that plakortide E (**85**) contained five methyl groups and two double bonds. The methyl group was at C-8 in the side chain. The coupling constants of the double bond (15.8 Hz) suggested *trans* stereochemistry. Additionally, the NMR data indicated that the remaining oxygen in **85** must be attached via a peroxide functionality in the form of a 1,2-dioxolane. A combination of COSY, and HMBC spectra confirmed that plakortide E (**85**) contained a *tetra*-substituted *cis*-1,2-dioxolane, whose oxygen atoms were linked to two tertiary C4 and C6 centers. However, only the relative configuration was established. The absolute configuration at C4, C6 and C10 were not revealed in the initial structure elucidation.

Table 2. The data of Plakortide E (85) reported by Patil and coworkers

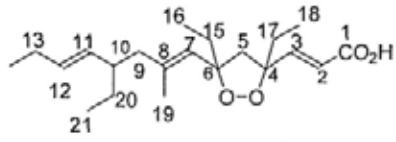
Source	Natural Product[34]		
Reference	*Tetrahedron*, **1996**, *52*, 377.		
Assigned Structure			
EIHRMS	*m/z* $[M+H]^+$: 351		
$[\alpha]_D^t$	$[\alpha]_D^{20}$ = 63.9(*c* = 2.0, $CHCl_3$)		
NMR ($CDCl_3$)	^1H (ppm)	^{13}C (ppm)	
equipment	Bruker AMX-400 spectrometer		
H-1		C-1	173.0
H-2	5.98 (1 H, d , 15.8)	C-2	123.9
H-3	6.69 (1 H, d, 15.8)	C-3	146.9
H-4		C-4	87.2
H-5	2.53 β (1 H, d, 12.0) 2.42 α (1 H, d, 12.0)	C-5	55.8
H-6		C-6	89.1
H-7	5.12 (1 H, m)	C-7	126.9
H-8		C-8	136.5
H-9	2.00 (1 H, m) 1.85 (1 H, m)	C-9	46.6
H-10	2.00 (1 H, m)	C-10	42.6
H-11	5.05 (1 H, ddt, 15.2, 8.3, 1.4)	C-11	132.8
H-12	5.34 (1 H , dt, 6.3, 15.2)	C-12	131.9
H-13	1.98 (2 H, m)	C-13	25.6
H-14	0.93 (3 H, t, 7.4)	C-14	14.0
H-15	1.85 (1H, m) 1.63 (1H, m)	C-15	32.1
H-16	0.87 (3 H, t, 7.4)	C-16	8.8
H-17	1.77 (2 H, m)	C-17	31.0
H-18	0.87 (3 H, t, 7.4)	C-18	8.9
H-19	1.61 (3 H, d, 1.0)	C-19	17.7
H-20	1.35 (1 H, m) 1.11(1 H, m)	C-20	27.6
H-21	0.80 (3 H, t, 7.4)	C-21	11.6

Table 3. The data of Plakortide E (85) reported by Wright and coworkers

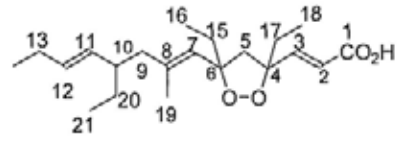
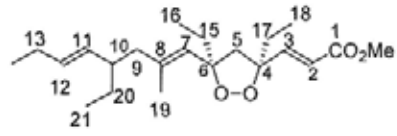
Source	Natural Product[57]		
Reference	*J. Nat. Prod.*, **2002**, *65*, 1509.		
Assigned Structure			
EIHRMS			
$[\alpha]_D^T$	$[\alpha]_D^{25} = 63$ ($c = 0.001$, $CHCl_3$)		
NMR ($CDCl_3$)	^1H (ppm)	^{13}C (ppm)	
equipment	Bruker AMX-500 spectrometer		
H-1		C-1	172.0
H-2	6.09 (1 H, d , 15)	C-2	120.5
H-3	6.93 (1 H, d, 15)	C-3	152.1
H-4		C-4	87.2
H-5	2.53 β (1 H, d, 12.0) 2.42 α (1 H, d, 12.0)	C-5	56.0
H-6		C-6	89.3
H-7	5.10 (1 H, s)	C-7	126.6
H-8		C-8	136.7
H-9	2.00 (1 H, m) 1.85 (1 H, m)	C-9	46.6
H-10	2.00 (1 H, m)	C-10	42.6
H-11	5.04 (1 H, dd, 15, 8)	C-11	132.8
H-12	5.33 (1 H , dt, 6.5, 15)	C-12	132.0
H-13	1.95 (2 H, m)	C-13	25.6
H-14	0.92 (3 H, t, 7.5)	C-14	14.1
H-15	1.86 (1H, m) 1.64 (1H, m)	C-15	32.2
H-16	0.86 (3 H, t, 7.5)	C-16	8.9
H-17	1.78 (2 H, m)	C-17	30.8
H-18	0.88 (3 H, t, 7.5)	C-18	8.9
H-19	1.60 (3 H, s)	C-19	17.8
H-20	1.37 (1 H, m) 1.24(1 H, m)	C-20	27.7
H-21	0.80 (3 H, t, 7.5)	C-21	11.6

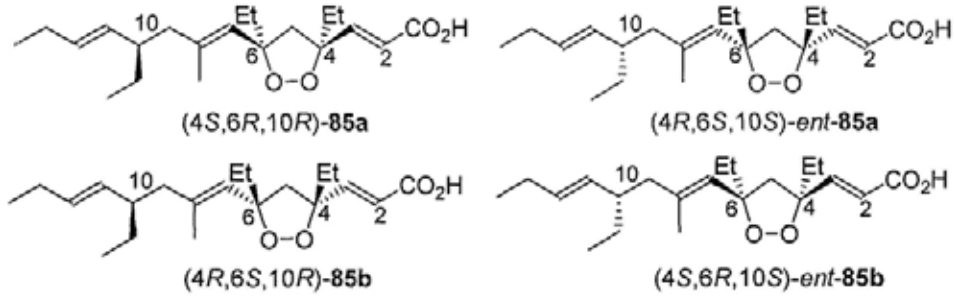
Table 4. The data of Plakortide E methyl ester (86) reported by Patil and coworkers

Source	Natural Product[34]		
Reference	*Tetrahedron*, **1996**, *52*, 377.		
Assigned Structure			
EIHRMS	*m/z* $[M+H]^+$: calcd for $C_{22}H_{37}O_4$: 365.2692, found: 365.2681		
$[\alpha]_D^t$	$[\alpha]_D^{20}$ = 75.1(*c* = 2.23, $CHCl_3$)		
NMR ($CDCl_3$)	^1H (ppm)	^{13}C (ppm)	
equipment	Bruker AMX-400 spectrometer		
H-1		C-1	166.9
H-2	6.07 (1 H , d , 15.8)	C-2	119.9
H-3	6.85 (1 H , d , 15.8)	C-3	149.6
H-4		C-4	87.1
H-5	2.54 β (1 H , d , 12.0) 2.44 α (1 H , d , 12.0)	C-5	55.9
H-6		C-6	89.1
H-7	5.11 (1 H , q, 1.3)	C-7	126.7
H-8		C-8	136.4
H-9	2.00 (1 H , m); 1.85 (1 H , m)	C-9	46.5
H-10	2.00 (1 H , m)	C-10	42.5
H-11	5.05 (1 H, ddt, 1.5, 8.4, 15.3)	C-11	132.7
H-12	5.34 (1 H , dt, 6.43, 15.3)	C-12	131.9
H-13	1.97 (2 H , m)	C-13	25.5
H-14	0.93 (3 H , t, 7.4)	C-14	14.0
H-15	1.86 (1H, m); 1.64 (1H, m)	C-15	32.1
H-16	0.88 (3 H , t, 7.4)	C-16	8.8
H-17	1.78 (2 H , m)	C-17	30.8
H-18	0.90 (3 H , t, 7.4)	C-18	8.8
H-19	1.61 (3 H , d, 1.3)	C-19	17.7
H-20	1.35 (1 H , m); 1.10 (1 H , m)	C-20	27.6
H-21	0.80 (3 H , t, 7.4)	C-21	11.5
	3.73 (3H, s, OCH_3)		51.1

In 2002, Wright and coworkers[57] also characterized plakortide E (**85**), however, the absolute configurations of C4, C6 and C10 were still unknown. The NMR and specific rotation data, depicted in Table 3, were nearly identical to those reported by Patil and coworkers. However, a chemical shift difference at C3 was observed in both the ^{1}H NMR and ^{13}C NMR spectra, although both samples were measured in $CDCl_3$ (Table 2 and Table 3). The proton and carbon signals were observed at δ 6.69 (d, J = 15.8 Hz) and 146.9 respectively by Patil and coworkers. While the proton and carbon were observed at δ 6.93 (d, J = 15 Hz) and 152.07 respectively by Wright and coworkers. The isolation procedures used in both isolations were similar. Wright and coworkers have not given any explanations on the differences of the chemical shift at C3 in the NMR spectra. They thought that some form of tautomerism was occurring, and it was possible that their isolation was of the sodium or other salt.[57]

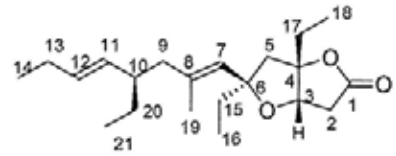
So far, the absolute configuration of plakortide E has not been determined. Based on the stereochemical data of the isolation papers, we can conclude that plakortide E had four possible configurations (Figure 16).

Figure 16. Four possible isomers of plakortide E



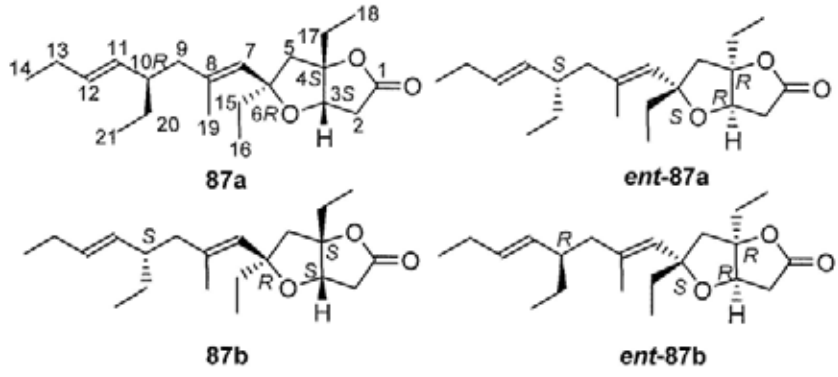
Plakortone B (**87**), $[\alpha]_D^{20} = -9.2$ ($c = 0.72$, $CHCl_3$), isolated as a colorless oil, was first characterized in 1996 by Patil and coworkers. The molecular formula of plakortone B (**87**) was determined as $C_{21}H_{34}O_3$ by 335.2586 $(M+H)^+$. The basic skeleton was established by NMR methods (Table 5). NOE difference data provided the relative configuration. Many similarities were observed between the ^1H NMR spectra of plakortone B (**87**) and plakortide E (**85**). However, the absolute configurations of their stereocenters were not revealed in the initial structure elucidation.[34]

Table 5. The data of plakortone B (87) reported by Patil and coworkers

Source	Natural Product[34]		
Reference	*Tetrahedron*, **1996**, *52*, 377.		
Assigned Structure			
EIHRMS	*m/z* $[M+H]^+$: calcd for $C_{21}H_{35}O_3$: 335.2586, found: 335.2541		
$[\alpha]_D^T$	$[\alpha]_D^{20} = -9.2$ ($c = 0.72$, $CHCl_3$)		
NMR ($CDCl_3$)	^1H (ppm)	^{13}C (ppm)	
equipment	Bruker AMX-400 spectrometer		
H-1		C-1	175.6
H-2	2.71 β (dd, 5.1, 18.4, 1 H) 2.64 α (dd, 1.3, 18.4, 1 H)	C-2	36.7
H-3	4.21 (dd, 1.3, 5.1, 1 H)	C-3	79.5
H-4		C-4	97.2
H-5	2.24 α (d, 13.7, 1H) 2.13 β (d, 13.7, 1 H)	C-5	49.0
H-6		C-6	86.9
H-7	5.03 (q, 1.3, 1 H)	C-7	129.5
H-8		C-8	137.1
H-9	2.00 (m, 1 H); 1.85 (m, 1 H)	C-9	46.9
H-10	1.98(m, 1 H)	C-10	42.6
H-11	5.06 (ddt, 1.5, 8.4, 15.3, 1 H)	C-11	132.7
H-12	5.36 (dt, 6.3, 15.3, 1 H)	C-12	131.9
H-13	1.96 (m, 2 H)	C-13	25.5
H-14	0.95 (t, 7.4, 3 H)	C-14	14.0
H-15	1.73 (m, 2 H)	C-15	33.7
H-16	0.86 (t, 7.4, 3 H)	C-16	8.7
H-17	1.73 (m, 2 H)	C-17	30.3
H-18	0.96 (t, 7.4, 3 H)	C-18	8.3
H-19	1.69 (d, 1.3, 3 H)	C-19	16.7
H-20	1.35 (m, 1 H); 1.15 (m, 1 H)	C-20	27.8
H-21	0.83 (t, 7.4, 3 H)	C-21	11.5

According to the stereochemical data, there are four possible structures for plakortone B (Figure 17). In 2006, the absolute configuration of plakortone B was established as **87a** by total synthesis.[36] Recently, our group has reported the total syntheses and stereochemical assignments of all four isomers of plakortone B.[35b]

Figure 17. Four possible isomers of plakortone B



The novel structural features of plakortide E (**85**) as well as its potential bioactivities have stimulated our considerable interest in the quest for its total synthesis. Our first plan was to synthesize all four possible isomers of plakortide E (Figure 16) and to realize the determination of the absolute configuration of plakortide E. We were also intrigued by the biosynthesis of plakortone B (**87**). So our second plan was to convert plakortide E to plakortone B, which would support the hypothesis that plakortide E was the precursor of plakortone B in nature.

2.2 Retrosynthesis

Our studies of the total synthesis of plakortide E (**85**) began as early as 2002. Initially, in consideration of the instability of the cyclic peroxide, we planned to

construct the cyclic peroxide ring in the final step. We designed the model substrate **88** to investigate the Feldman reaction (Scheme 18). However, to our disappointment, the starting material decomposed, but no desired product **89** was obtained.[59] Assuming that the failure resulted from the steric hindrance in **88**, we designed an alternative convergent strategy.

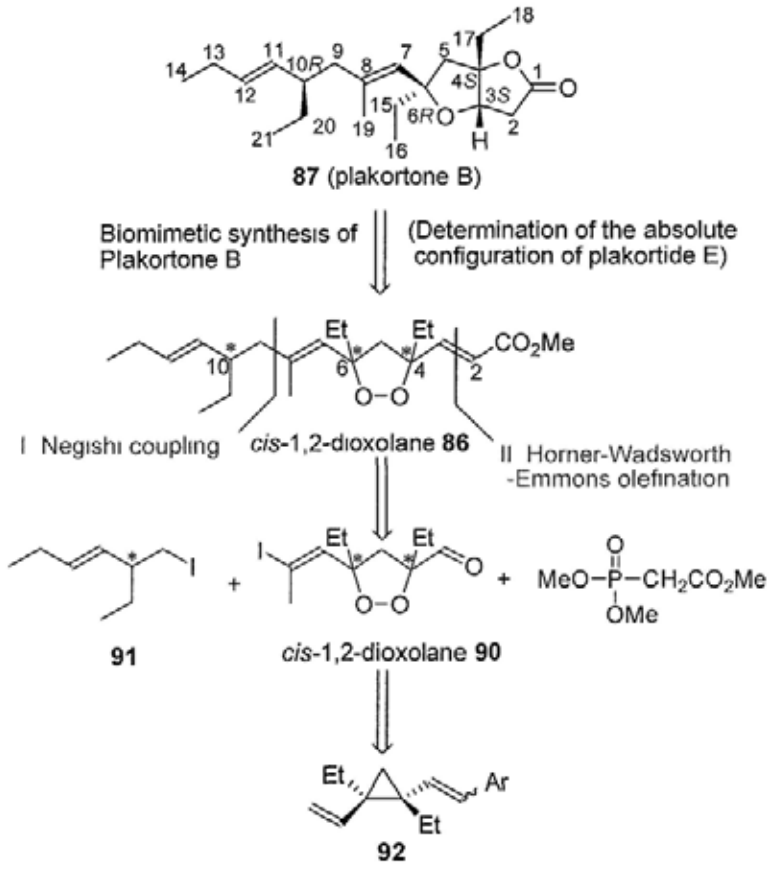
Scheme 18. Feldman reaction of the model substrate

88 **89**

Retrosynthetic analysis. According to the convergent synthetic strategy as shown in Scheme 19, we envisioned that the assembly of the target molecule **86** can be achieved by coupling the corresponding central core **90** with the side chain **91**. Formation of the C8-C9 single bond is realized by a metal-catalyzed sp^2–sp^3 coupling reaction.[60,90,91] Realization of the *trans* double bond, in turn, can be accomplished by a Horner-Wadsworth-Emmons olefination reaction.[61] Variations in the structure of central core **90** and the side chain **91** would provide the four possible absolute configurations of plakortide E. In our synthetic strategy, lipase-catalyzed kinetic resolution of racemic 1,2-dioxolane **90** would be employed to generate the two enantiomerically pure central cores.[62] The racemic 1,2-dioxolane **90** would be prepared from vinylcyclopropane **92**. When the four possible isomers of plakortide E are obtained, we plan to convert them into the four possible isomers of plakortone B

(**87**), whose total synthesis has been reported by us recently.[35b] This conversion will not only provide a biomimetic synthesis towards plakortone B, but will also help to confirm the absolute configuration of plakortide E (Scheme 19).

Scheme 19. Retrosynthetic analysis of plakortide E and plakortone B

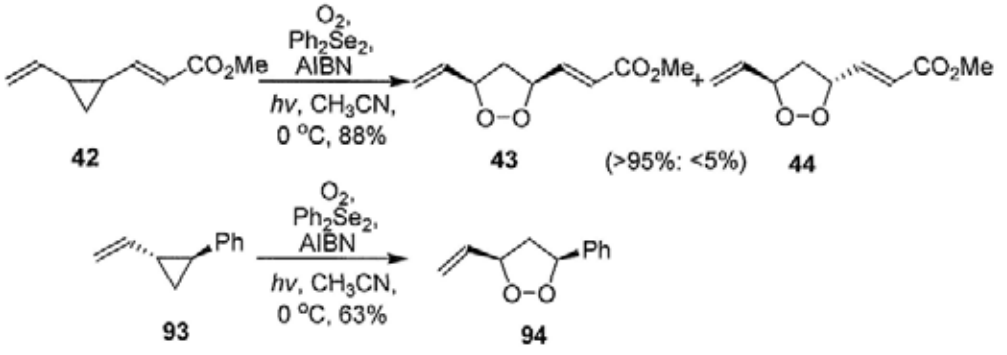


2.3 Synthesis of *cis*-1,2-dioxolane

2.3.1 Syntheses of 1,2-dioxolanes by the Feldman reaction

In 1986, Feldman developed a convenient method for the synthesis of 1,2-dioxolanes. In this reaction, vinylcyclopropanes react with molecular oxygen via a radical-mediated [3+2] addition to form 1,2-dioxolanes (Scheme 20). The experimental results support the notion that *cis*-1,2-dioxolanes should predominate.[44]

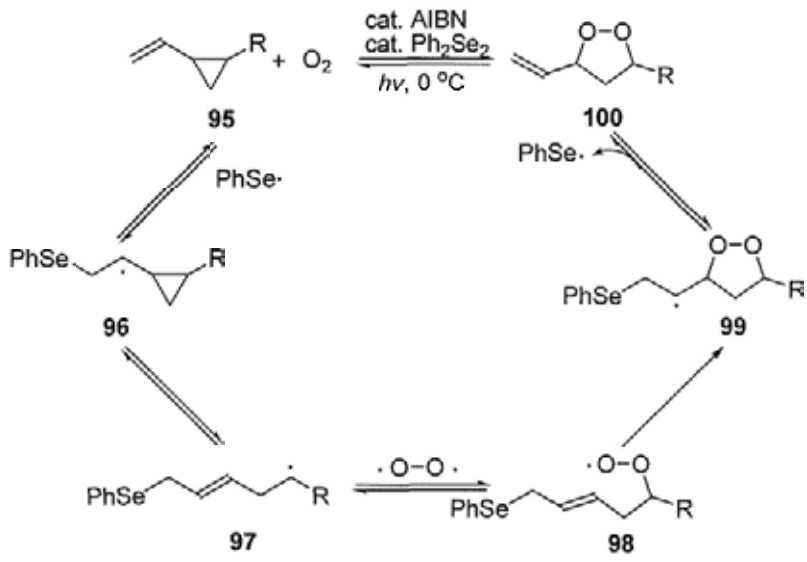
Scheme 20. Formations of 1,2-dioxolanes via Feldman reactions



The mechanism of the Feldman reaction is depicted in Scheme 21. The free radical PhSe· is produced by using AIBN as an initiator, which reacts with the double bond of vinylcyclopropane **95**, leading to cyclopropylcarbinyl radical **96**. Then cyclopropylcarbinyl radical **96** opens to the homoallylic radical **97**, which is trapped by oxygen to generate 5-hexenylperoxy **98**. Cyclization of the intermediate **98** leads to **99**. Finally, expulsion of PhSe· radical from peroxyl radical **99** results in the formation of 1,2-dioxolane **100**. The rate-determining step is the irreversible

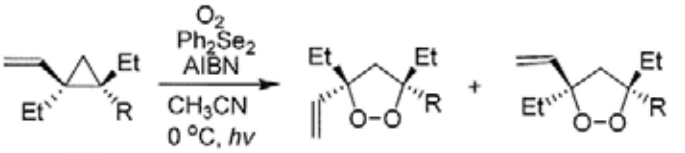
cyclization of 5-hexenylperoxy **98** to peroxyl radical **99**.[44]

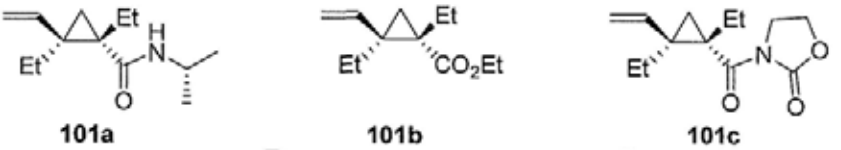
Scheme 21. The mechanism of the Feldman reaction

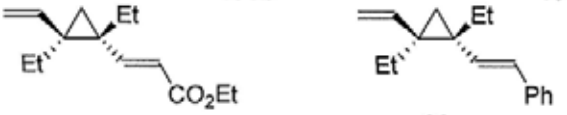


Our previous research. Our preliminary synthetic efforts towards plakortide E were recorded in 2007,[35a] in which Zhao studied the application of the Feldman reaction to synthesize highly substituted 1,2-dioxolanes. Initially, substrate **101d** was prepared and used to investigate the Feldman reaction. Irradiation with a 300 W sunlamp at 0 °C under an atmosphere of oxygen and in the presence of catalytic amounts of Ph_2Se_2 and AIBN furnished 1,2-dioxolane in 88% yield and as a 1/7 mixture of diastereomers, as determined by ^1H NMR and HPLC. The major product was determined to have *trans* configuration based upon nOe studies. A subsequent study applied the same peroxidation to a series of vinyl cyclopropanes. The results are depicted in Table 6.

Table 6. Investigations of Feldman reaction





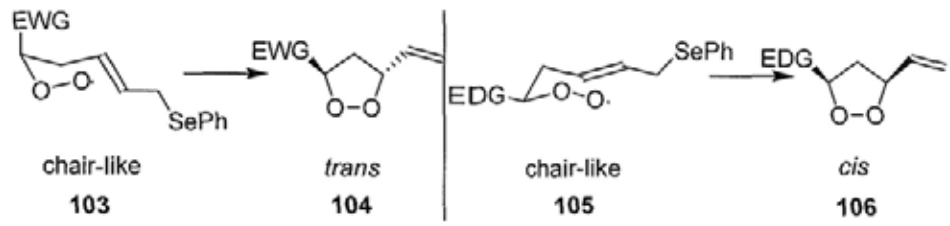


Entry	Substrate	Yield(%)	*cis/trans*[a]
1	**101a**	quant	*trans*
2	**101b**	75%	1/22
3	**101c**	quant	1/13
4	**101d**	88%	1/7
5	**92a**	82%	1/2.8

[a] Determined by ^{1}H NMR analysis.

In studies on less substituted vinylcyclopropane substrates, Feldman found that *cis*-1,2-dioxolanes predominated.[44] Weinreb and Feldman[44d] utilized *ab initio* computation methods at the MP2/6-31G*//UHF/6-31G* level to probe the predicted energies between these species (5-hexenylperoxy **98** and peroxyl radical **99** in Scheme 21) in order to explain the *cis/trans* ratio in the product. Their results indicate that a chair-like transition state is always favorable, and an electron-withdrawing group would prefer an axial disposition that leads to a *trans*-product. On the other hand, an electron-donating group will occupy an equatorial position to give a *cis*-product (Scheme 22).

Scheme 22. Chair-like transition states in Feldman reaction

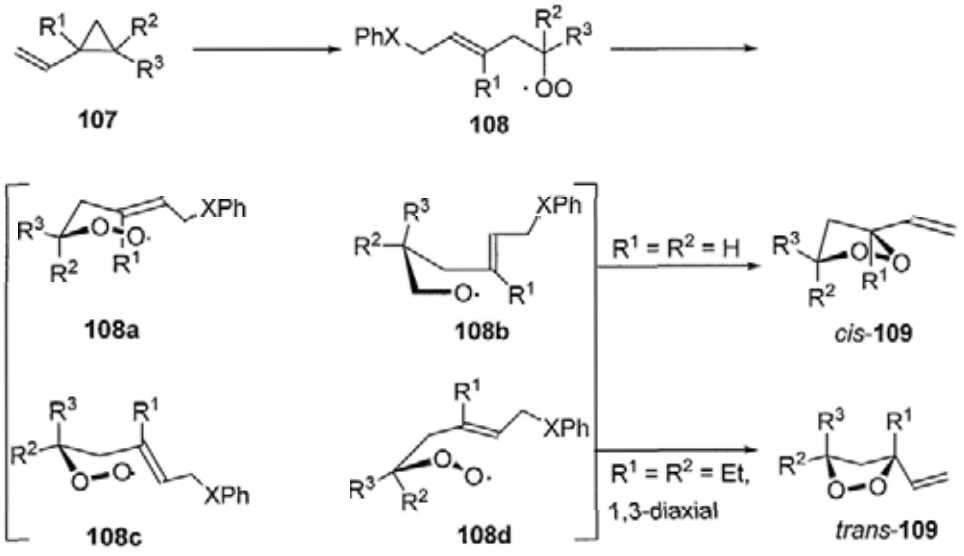


In the less substituted substrates, both experimental and computational results support the notion that *cis*-1,2-dioxolanes should predominate.[44] However, to our disappointment, during our construction of 3,5-tetrasubstituted-1,2-dioxolanes, we observed that the Feldman reaction predominantly furnished the *trans*-stereoisomer when both oxygen atoms were on tertiary carbons (Table 6).[35a] Even substrate **92a**, which had an electron-rich styrenyl substituent, under Feldman reaction conditions as described above furnished the *trans*-product (*cis*/*trans* = 1:2.8) as the major product. These results were different from the traditional results as reported by Feldman and coworkers.

To explain our experimental results, we reinvestigate the transition states for cyclization of the hexenyl peroxyl radical which were developed by Feldman and coworkers to interpret the stereochemistry of 1,2-dioxolane formation.[44b] After the equilibration studies with 1,2-dioxolanes and a trapping experiment with 1,2-dioxolane, Feldman and coworkers had predicted that the cyclization was irreversible and that the stereoselectivity reflected kinetic control. In the cyclization of 5-hexenylperoxy radical **108**, there were four transition states, the chair-like transition state **108a** featuring a pseudoequatorial substituent R^3, a boat-like transition state

108b with pseudoaxial R^3, the chair-like transition state **108c** featuring a pseudoaxial substituent R^3 and a boat-like transition state **108d** with pseudoequatorial R^3 (Scheme 23). Reaction is believed to proceed through the more stable chair-like transition states **108a** or **108c** to generate the *cis*-product or *trans*-product respectively. When $R^1 = R^2 = H$, the reaction mainly proceeded through conformer **108a** to furnish the *cis*-1,2-dioxolane as the major product. However, when $R^1 = R^2 = Et$, the two Et groups would suffer from a 1,3-diaxial interaction in **108a**. As a result, cyclizations of substrates with $R^1 = R^2 = R^3 =$ alkyl proceed mainly via conformer **108c,** leading to the *trans*-1,2-dioxolane as the major product.

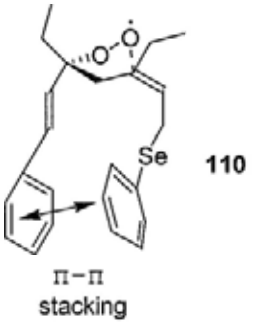
Scheme 23. Stereochemistry of 1,2-dioxolane formation



We also have studied this issue by employing DFT computional methods (courtesy of Dr Yu-Xue Li, Shanghai Institute of Organic Chemistry, The Chinese Academy of Science). As expected, UB3LYP/6-31G* level computations indicated that the

chair-like transition state going towards tertiary *trans*-peroxide was about 0.2 kcal/mol more stable in energy than those leading to *cis*-products.

Figure 18. π–π stacking interaction in the formation of 1,2-dioxolane



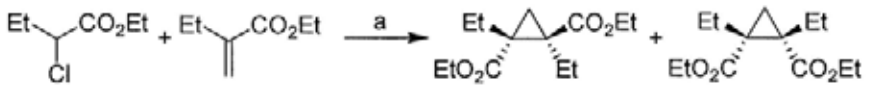
110

Comparing the *cis*/*trans* ratio of the peroxides in Table 6, we found that the substrate **92a** gave the best value (*cis*/*trans* = 1: 2.8). We envisioned that *cis*/*trans* ratio can be improved with a benzyl group. This result might suggest that the aryl group plays an important role in the stereocontrol process. We presumed that a π–π stacking interaction might be a crucial factor to control *cis*-selectivity (Figure 18). To address this issue, we planned to reinvestigate the Feldman reaction with a series of divinylcyclopropanes containing a range of arene substituents on the alkenes. It was anticipated that the realization of *cis*-1,2-dioxolane could be accomplished by this strategy.

Syntheses of *trans*-divinyl cyclopropanes. The key intermediate **113** was prepared according to McCoy's procedure.[63] As depicted in Scheme 24, ethyl α-chlorobutyrate (**111**) and ethyl α-ethylacrylate (**112**) underwent tandem Michael/alkylation for the

generation of diethyl 1,2-diethyl-1,2-cyclopropanedicarboxylate (**113**). Ethyl α-chlorobutyrate (**111**)[65] was prepared from butyric acid (**114**) (Scheme 25) and ethyl α-ethylacrylate (**112**)[64] was formed from diethyl 2-ethylmalonate (**116**) (Scheme 26).

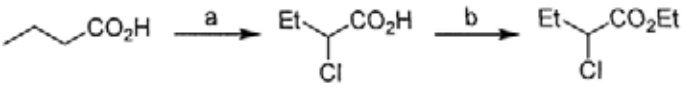
Scheme 24. Preparation of diethyl 1,2-diethyl-1,2-cyclopropanedicarboxylate



111 **112** ***trans*-113** ***cis*-113**

Reagents and conditions: (a) NaH, DMF, 88%.

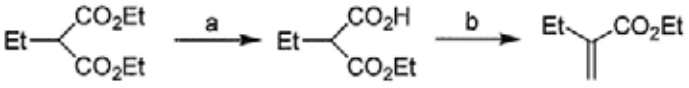
Scheme 25. preparation of ethyl α-chlorobutyrate



114 **115** **111**

Reagents and conditions: (a) DMF, SO_2Cl_2, 90-95 °C, 29% ; (b) EtOH, H_2SO_4, benzene, 70%.

Scheme 26. preparation of ethyl α-ethylacrylate



116 **117** **112**

Reagents and conditions: (a) KOH, EtOH; (b) Piperidine, $(HCHO)_2$, Pyridine, 70% (2 steps).

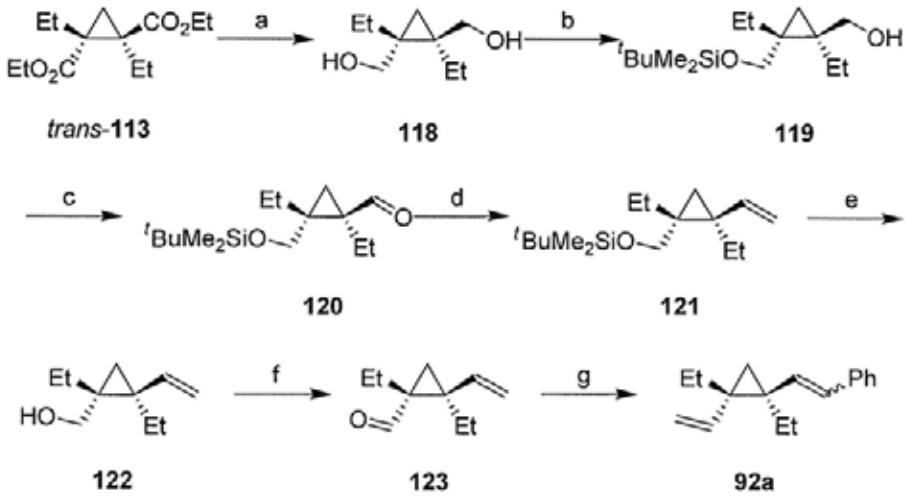
Our previous studies towards plakortide E showed that the *cis*-divinyl cyclopropane might undergo Cope rearrangement to furnish cycloheptadiene.[35a] Therefore, we resorted to the use of the *trans*-divinyl cyclopropane as a precursor for our

investigation of the Feldman reaction (Scheme 27). Reduction of diester **113** gave diol **118** in 93% yield by employing $LiAlH_4$.[35a,59]

After reduction with $LiAlH_4$, mono-protection of alcohol group was necessary. Diol **118** was treated with Et_3N and *t*-$BuMe_2SiCl$ to afford the desired mono-protected product **119** as a colorless oil in 80% yield (Scheme 27).[35a,59] The mono-protected alcohol **119** was then subjected to Swern oxidation to generate aldehyde **120** as a colorless oil. Subsequently, aldehyde **120** was used directly for the Wittig reaction affording vinylcyclopropane **121** as a colorless oil in 65% yield (Scheme 27).[35a,59]

Then *p*-TsOH mediated desilylation of **121** furnished the free hydroxyl intermediate **122** as a colorless oil in 98% yield. Then the alcohol was subjected to Swern oxidation as above to furnish aldehyde **123** a colorless oil. Subsequently, Wittig reaction was performed, and the desired product divinylcyclopropane **92a** was prepared in 70% yield (two steps) (Scheme 27).[35a,59]

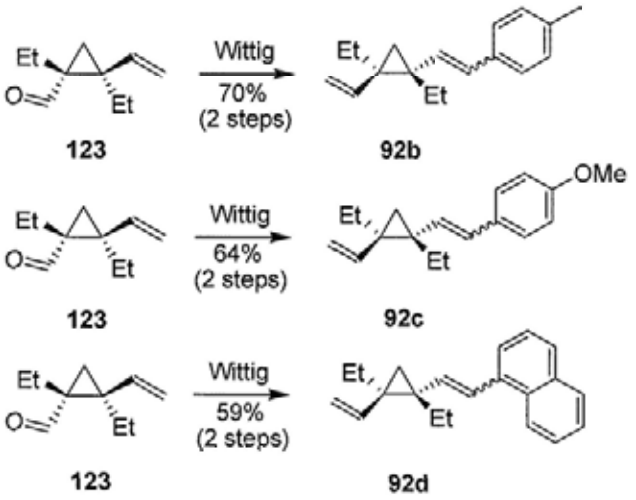
Scheme 27. Synthesis of *trans*-divinyl cyclopropane



Reagents and conditions: (a) $LiAlH_4$, Et_2O, rt, 84%; (b) *t*-$BuMe_2SiCl$, Et_3N, CH_2Cl_2, 0 °C, 2 h, 78%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 81%; (d) *n*-BuLi, PPh_3CH_3I, THF, –78 °C to rt, 74%; (e) *p*-TsOH, CH_2Cl_2/CH_3OH, 90%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C; (g) *n*-BuLi, PPh_3BnBr, THF, –78 °C to rt, 70% (2 steps).

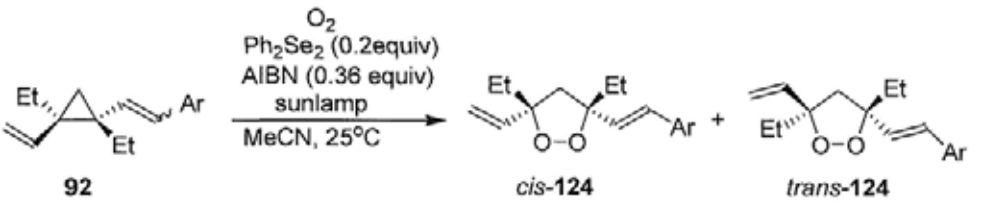
Starting from the 1,2-diethyl-2-vinyl- cyclopropanecarbaldehyde (**123**), three other aryl-substituted divinylcyclopropanes were prepared by Wittig reactions in a similar manner (Scheme 28).[35a,59]

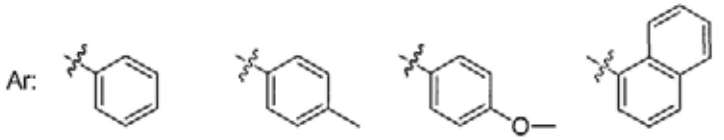
Scheme 28. Syntheses of *trans*-divinyl cyclopropanes



Syntheses of 1,2-dioxolanes by the Feldman reaction. With the desired substrates in hand, we began our studies on the effect of aryl π–π stacking interaction in the Feldman reaction. The reactions were performed under standard Feldman reaction conditions. All the experimental results are summarized in Table 7. However, to our disappointment, we found that there was no significant improvement to the *cis*/*trans* ratio when various substrates were used. The best value in the table was *cis*/*trans* = 1:2.6, when the substrate **92c** was used. However, the major product was still the *trans*-1,2-dioxolane. The natural product plakortide E[34] was a *cis*-tetrasubstituted peroxide, so we sought to develop a complementary approach to synthesize the *cis*-tetrasubstituted 1,2-dioxolanes.

Table 7. Syntheses of 1,2-dioxolanes by Feldman reaction





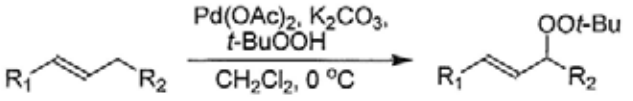
Entry	Substrate	Yield (%)	*cis*/*trans*[a]
1	**92a**	72%	1:3.1
2	**92b**	75%	1:4
3	**92c**	84%	1:2.6
4	**92d**	62%	1:2.5

[a] Determined by ^{1}H NMR analysis.

2.3.2 Palladium-catalyzed approach towards 1,2-dioxolanes

Ru-catalyzed oxidation of amides with *tert*-butyl hydroperoxide to give the corresponding *tert*-butyldioxy amides has been reported.[66a] A Co-mediated peroxidation of alkenes in the presence of oxygen and triethylsilane was also known.[39k-39m,66b-66d] To the best of our knowledge, only two examples of Pd-catalyzed reaction resulting in peroxide-containing products have been reported.[67] Corey's method only furnished allylic *tert*-butylperoxy ethers as the major products (Scheme 29).[67a]

Scheme 29. Formation of allylic *tert*-butylperoxy ethers catalyzed by $Pd(OAc)_2$

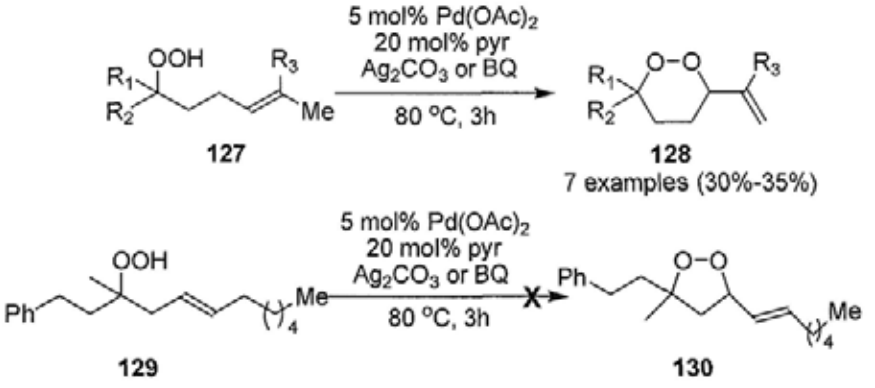


125 **126**

6 examples (yield: 40%-72%)

Woerpel reported a palladium-catalyzed intramolecular cyclization of unsaturated hydroperoxides for the formation six-membered cyclic peroxides.[67b] However, yields of this method were reportedly low (30%-35%). Furthermore, this method has not been known to afford 1,2-dioxolanes (Scheme 30).

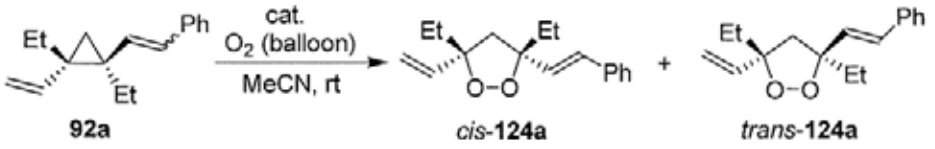
Scheme 30. Formations of 1,2-dioxanes reported by Woerpel and coworkers



Our initial studies involved the use of **92a**[35a] as a substrate. Thus, under O_2 (oxygen balloon), we examined a number of catalysts to identify the optimal catalytic system. Our results are summarized in Table 8. As can be seen, $Pd(PPh_3)_4$ was found to give the best result. In the absence of the catalyst, the reaction did not take place. In the presence of the $CuSO_4$, or Pd^{2+} [$Pd(OAc)_2$, $Pd(PCy_3)_2Cl_2$ and $PdCl_2$], no

1,2-dioxolane was resulted. In the presence of the Pd(0) catalyst, the desired product was obtained, and the ratio of the *cis*/*trans* is 1:1. When $Pd(PPh_3)_4$ was used as the catalyst, the yield of the reaction was found to be higher than that of $Pd_2(dba)_3$.

Table 8. Catalyst screening



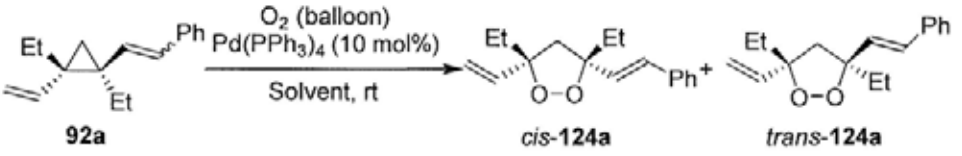
92a *cis*-**124a** *trans*-**124a**

Catalyst (mol %)	Temp (°C)	Time (h)	Yield (%)	*cis*/*trans*[a]
No catalyst	25	48	NR[b]	-
$Pd(PCy_3)_2Cl_2$ (10)	25	24	NR[b]	-
$Pd(PPh_3)_4$ (10)	25	24	25	1:1
$Pd_2(dba)_3$ (10)	25	48	20	1:1
$PdCl_2$ (10)	25	24	NR[b]	-
$Pd(OAc)_2$ (10)	25	24	NR[b]	-
$CuSO_4$ (100)	25	24	NR[b]	-

[a] Determined by ^1H NMR analysis . [b] NR = No reaction.

For further optimization, we examined the reaction in a variety of solvents. All results are summarized in Table 9. In DMSO or $MeNO_2$, there was no reaction. When MeCN was used as the solvent, the reaction gave a higher yield than in other solvents.

Table 9. Solvent screening

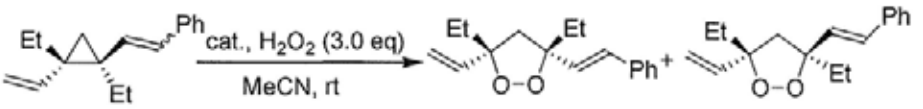


Entry	Solvent	Time	Yield (%)	*cis*/*trans*[a]
1	THF	48	19	1:1
2	DMF	48	13	1:1
3	Toluene	48	15	1:1
4	DMSO	48	NR[b]	-
5	MeNO2	48	NR[b]	-
6	MeCN	24	25	1:1

[a] Determined by ^{1}H NMR analysis . [b] NR = No reaction.

In the syntheses of peroxides, H_2O_2 is a widely used reagent. For further screening of reaction conditions for the oxidation of **92a**, aqueous H_2O_2 (30%) was used instead of oxygen balloon. The reaction was performed at room temperature in the presence of various catalysts with aqueous H_2O_2 solution in MeCN. The results are shown in Table 10. To our delight, in the presence of Pd (0) catalyst, substrate **92a** reacted with aqueous H_2O_2 solution, leading to the desired 1,2-dioxolane. However, the yields were not good. In the presence of 20 mol% $Pd(PPh_3)_4$, the mixture of 1,2-dioxolanes (*cis*/*trans* =1:1.5) was obtained in 26% yield (Table 10).

Table 10. Catalyst screening



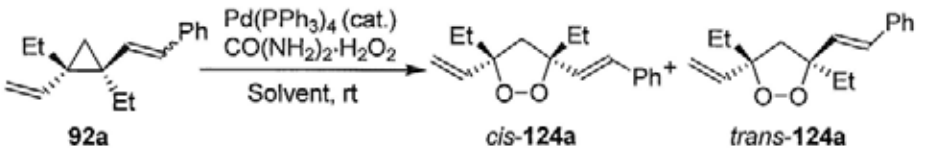
92a *cis*-**124a** *trans*-**124a**

Entry	Catalyst (mol %)	Time (h)	Yield (%)	*cis*/*trans*[a]
1	$Pd(PPh_3)_4$ (10)	24	15	1:1.5
2	$Pd(PPh_3)_4$ (20)	24	26	1:1.5
3	$CuCl_2$ (20)	24	NDP[b]	-
4	$Pd(PPh_3)_4$ (10) $CuCl_2$ (20)	24	trace	-
5	$PdCl_2$ (10)	24	NDP[b]	-
6	$Pd_2(dba)_3$ (10)	24	9	1:1.5

[a] Determined by ^{1}H NMR analysis . [b] NDP = No desired product

Consideration of the effect of water in the reaction, urea hydrogen peroxide (UHP), a white crystalline solid, was used instead of aqueous H_2O_2. The reaction was performed at room temperature in the presence of $Pd(PPh_3)_4$ with urea hydrogen peroxide in dry organic solvents. The experimental results are summarized in Table 11. In these studies, we observed that the reaction with urea peroxide led to a better result (yield = 33%, *cis*/*trans* = 1:1.5) than that with aqueous H_2O_2 solution (yield = 15%, *cis*/*trans* = 1:1.5). By increasing the $Pd(PPh_3)_4$ catalyst loading from 10 mol% to 20 mol%, an isolated yield of 57% was realized. We also screened other solvents (THF and benzene), but it was found that MeCN was the best solvent for this reaction.

Table 11. Optimizations for the Pd-catalyzed approach towards 1,2-dioxolane



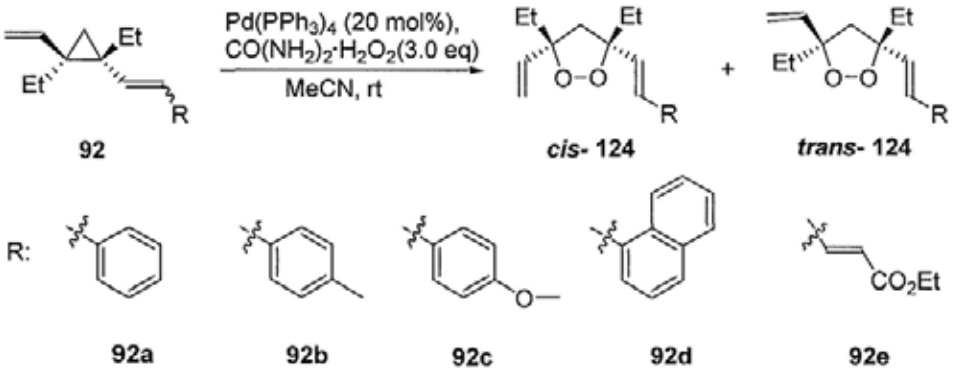
92a *cis*-**124a** *trans*-**124a**

Entry	Catalyst (mol %)	H_2O_2 (equiv)	Solvent	Time (h)	Yield (%)	*Cis/trans*[a]
1	$Pd(PPh_3)_4$ (10)	2.0	MeCN	12	33	1:1.5
2	$Pd(PPh_3)_4$ (20)	2.0	MeCN	12	53	1:1.5
3	$Pd(PPh_3)_4$ (20)	2.0	Benzene	36	46	1:1.9
4	$Pd(PPh_3)_4$ (20)	2.0	THF	12	17	1:1.2
5	$Pd(PPh_3)_4$ (20)	3.0	MeCN	12	57	1:1.5

[a] Determined by ^1H NMR analysis.

The application of this palladium-catalyzed approach towards various 1,2-dioxolanes under the optimized condition is shown in Table 12. We have still not been able to obtain exclusively *cis*-1,2-dioxolanes by this method although the *cis/trans* ratio of this palladium approach (*cis/trans* = 1:1.4) is much better than that of the Feldman reaction (*cis/trans* = 1:2.8).[35a] Further optimization and search for asymmetric versions of this palladium-catalyzed process towards 1,2-dioxolanes are in progress.

Table 12. Palladium-catalyzed approach towards 1,2-dioxolanes

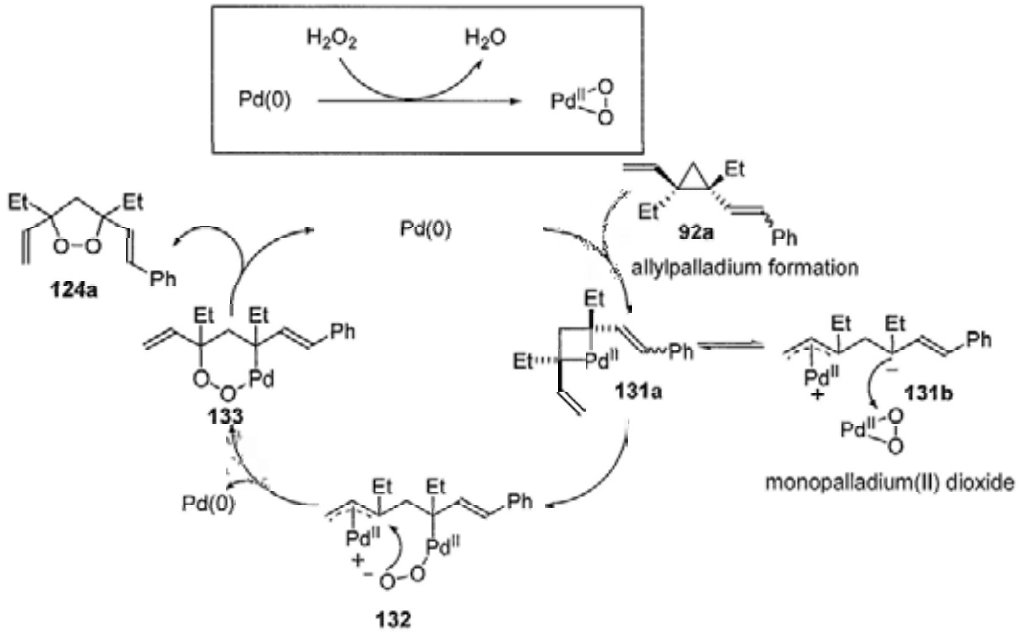


Entry	Substrate	Yield (%)	*cis*/*trans*[a]
1	a	57	1:1.5
2	b	70	1:1.4
3	c	40	1:1.6
4	d	67	1:1.8
5	e	NR[b]	-

[a] Determined by ^{1}H NMR analysis. [b] NR = no product formed

An attempt to gain insight into the mechanism of this reaction was carried out. A radical scavenger, 2,6-di-*tert*-butyl-4-methylphenol (BHT), was used in the reaction between **92a** and urea peroxide. Despite the presence of a radical scavenger, the desired product was still obtained in 42% yield. This result implies that the reaction is not expected to proceed through a free radical process. As illustrated in Scheme 31, a mechanism is proposed in light of other palladium-catalyzed reactions involving vinylcyclopropanes.[68a] Divinylcyclopropane **92a** may react with Pd(0) to generate a π-allylpalladium complex **131b**, which can attack the monopalladium(II) dioxide [O_2Pd^{II}][68b] to form **132**. Ring closure by an intramolecular attack therefore yields **133**, which undergoes reductive elimination to yield the 1,2-dioxolane **124a** and regenerate the Pd(0) catalyst.

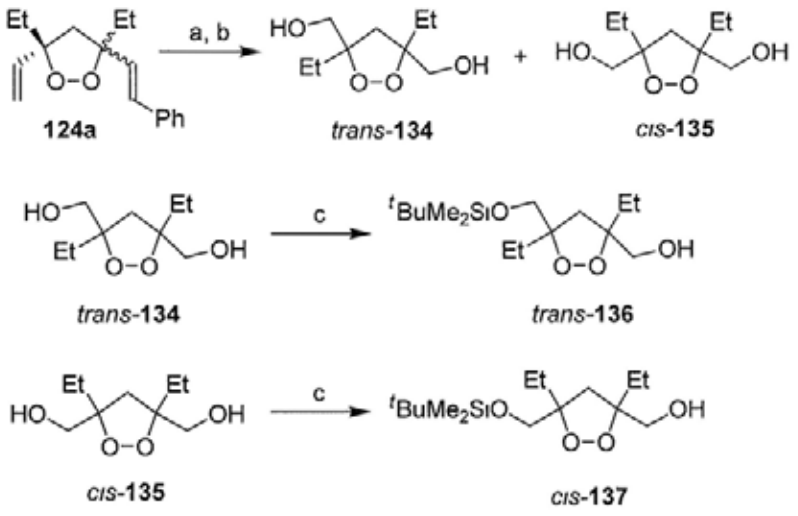
Scheme 31. Proposed mechanism for a palladium-catalyzed approach towards 1,2-dioxolane



2.3.3 Synthesis of cis-1,2-dioxolane

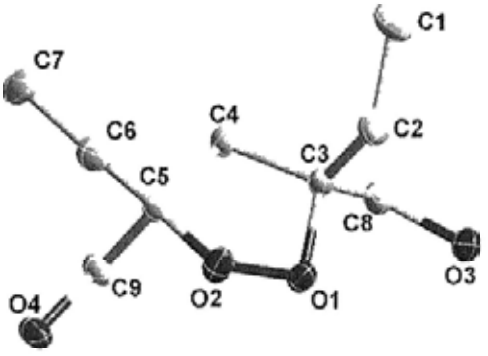
The mixture of *cis*/*trans* 1,2-dioxolanes **124a** was subjected to ozonolysis, which on reductive workup with $NaBH_4$ gave two chromatographically separable diols *trans*-**134** and *cis*-**135.** (Scheme 31).[35a] Peroxide *cis*-**135** was isolated as a colorless solid, whose stereochemistry was confirmed by an X-ray crystallographic analysis (Figure 19). Peroxides *trans*-**134** and *cis*-**135** were monoprotected with *t*-$BuMe_2SiCl$ to give *trans*-**136** and *cis*-**137**, respectively.

Scheme 31. Synthesis of *cis*-1,2-dioxolane 137



Reagents and conditions: (a) O_3, CH_2Cl_2/MeOH (7:1), 78 °C; (b) $NaBH_4$ (1.5 equiv), –78 °C to 0 °C, 5 h, 90% (2 steps), (c) *t*-$BuMe_2SiCl$ (1.0 equiv), imidazole (1.0 equiv), DMAP (5 mol%), DMF, 0 °C to rt, 74% (reacted yield).

Figure 19. X-ray crystallographic analysis of *cis*-135



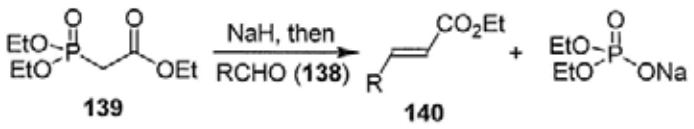
2.4 Studies on the model reactions

cis-1,2-Dioxolane **137** is the key synthetic precursor towards the total synthesis of plakortide E, while the *trans*-product **136** is useful for model studies. Due to the weak O-O bond dissociation energy (37±1 kcal mol^{-1}),[1a] the functionalization of the 1,2-dioxolanes are expectedly difficult. Generally, it is widely believed that peroxides are unstable compounds. Metals and metal ions such as Co and Pd, Sn(II), Fe(II) and Zn(II) are able to function as single- or two electron donors or Lewis acids to decompose peroxides. Strong bases, strong acids and high temperature are all detrimental to peroxides.[1a, 38] According to these facts, it goes without saying that the studies on the model reactions for the total synthesis are by no means trivial.

2.4.1 Construction of *trans*-double bond

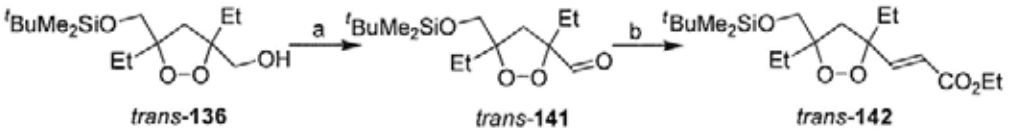
In 1958, Horner developed a modified Wittig reaction between aldehydes or ketones **138** and stabilized phosphonate **139** (Scheme 32).[61,69] Compared to phosphonium ylides, phosphonate-stabilized carbanions are more nucleophilic and more basic. Wadsworth and Emmons did further studies on this reaction.[61b] The stereoselectivity of Horner-Wadsworth-Emmons reaction is usually pretty high, which favors the formation of *E*-alkenes. Another advantage is that the phosphate by-product can be washed away by aqueous solution of *p*H>2.

Scheme 32. Horner-Wadsworth-Emmons reaction



Starting from the mono-protected *trans*-1,2-dioxolane containing alcohol **136**, we began to construct the *trans* double bond, which is a substituent of the tertiary peroxide center. In light of the good stereoselectivity and mild reaction conditions of Horner-Wadsworth-Emmons olefination reaction, we envisioned that this reaction would meet our requirements. The synthetic route is depicted in Scheme 33. Oxidation of **136** with Dess-Martin periodinane (DMP) generated the 1,2-dioxolane-containing aldehyde **141**. Aldehyde **141** as an unstable species that had to be freshly prepared for each olefination. To our delight, the Horner-Wadsworth-Emmons olefination of aldehyde **141** with triethyl phosphonoacetate resulted exclusively in the desired product **142** in 79% yield (two steps).[61,69] The stereochemistry was determined by the ^{1}H NMR, with the 15.8 Hz $^{3}J_{H\text{-}H}$ coupling confirming the *trans* stereochemistry.

Scheme 33. Construction of *trans*-double bond



Reagents and conditions: (a) Dess-Martin periodinane (1.5 equiv), CH_2Cl_2; (b) $(EtO)_2P(O)CH_2CO_2Et$ (3.0 equiv), NaH (2.8 equiv), THF, 0 °C, 79% (2 steps).

Encouraged by the success of the Horner-Wadsworth-Emmons olefination, we next investigated the application of a Wittig olefination for introduction of *tri*-substituted alkene adjacent to the 1,2-dioxolane. The model reaction is shown in Scheme 34. Although two kinds of Wittig reactions have been tried, we failed to obtain the desired product (Table 13). In both cases, no obvious product spot was observed on TLC, although all starting material was consumed. We presumed that the steric hindrance between the 1,2-dioxolane-containing aldehyde **141** and the side chain **144**[59] or **145**[59] led to the failure of these coupling reactions. When the desired Wittig reaction did not take place, the unstable 1,2-dioxolane-containing aldehyde decomposed under these conditions. For this reason, we abandoned this Wittig reaction approach. Next, we place our focus on the Pd-catalyzed cross-coupling reaction, which has been widely used in carbon–carbon bond-forming reactions.

Scheme 34. Construction of trisubstituted double bond

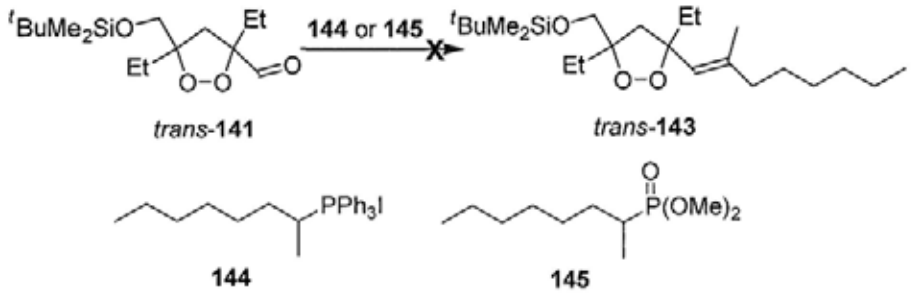


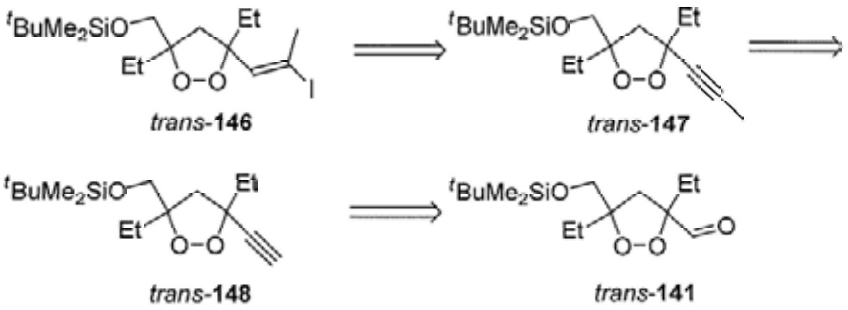
Table 13. Reaction conditions for Wittig reaction

Entry	Reaction conditions	Results
1	*n*-BuLi (1.2 equiv), **144**[59] (1.3 equiv), THF, −78 °C to rt	decomposed
2	*n*-BuLi (1.2 equiv), **145**[59] (1.3 equiv), THF, −78 °C to rt	decomposed

2.4.2 Synthesis of alkenyl iodide

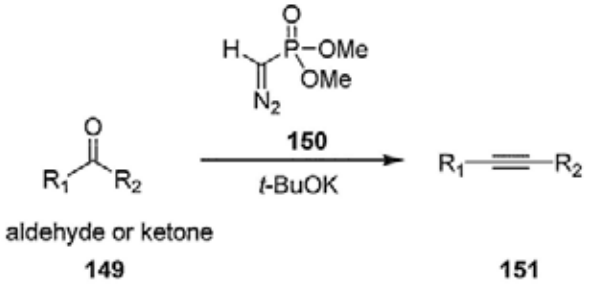
In our retrosynthesis of plakortide E, 1,2-dioxolane-containing-alkenyl iodide **90** was an important key precursor. To prepare for the synthesis of the *cis*-1,2-dioxolane-containing alkenyl iodide **90**, we intended to initially model the synthetic steps on the *trans* isomer, **146**. As shown in Scheme 35, starting from the *trans*-1,2-dioxolane-containing-aldehyde **141** to prepare the *trans*-1,2-dioxolane-containing-alkenyl iodide **146**, we need as the first step to prepare the intermediate terminal alkyne **148**. With terminal alkyne **148** in hand, subsequent methylation afforded the alkyne **147**. The conversion of an alkyne to an alkenyl iodide has been reported in the literature.[35b,36,79b]

Scheme 35. Retrosynthesis of alkenyl iodide 146

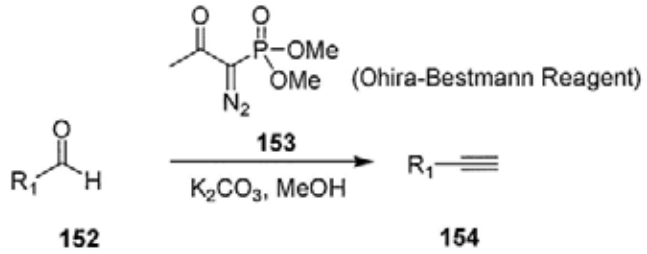


Preparation of terminal alkyne 148. The one-pot conversion of ketones or aldehydes to the corresponding internal or terminal alkynes by using diazophosphonates under basic conditions is called Seyferth-Gilbert homologation (Scheme 36). In 1973, Colvin and coworkers reported that aryl ketone **149** (or aldehyde) reacted with dimethyl (diazomethyl)phosphonate **150** in the presence of a base to give substituted alkynes **151**.[71] Dimethyl (diazomethyl)phosphonate **150** was often called the Seyferth-Gilbert reagent,[70] which was first synthesized by Seyferth. In 1979 Gilbert and coworkers improved the procedure of the reaction, and extended its scope.[72] Ohira and Bestmann made a further modification of this reaction based upon generation of the dimethyl (diazomethyl)phosphonate *in situ* from dimethyl(1-diazo-2-oxopropyl)phosphonate (**153**), which was called Ohira-Bestmann reagent (Scheme 37).[73] The Ohira-Bestmann procedure is now widely used in organic syntheses. The mild reaction conditions are tolerant most functional groups and various aldehydes can be homologated in excellent yields.

Scheme 36. Seyferth-Gilbert homologation

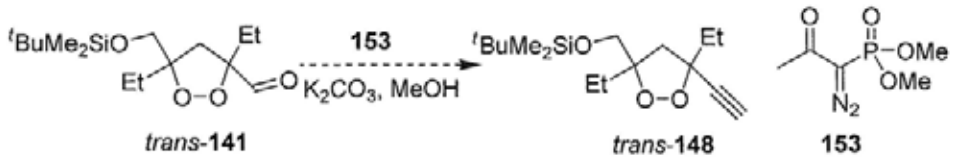


Scheme 37. Modification of Seyferth-Gilbert homologation (Ohira-Bestmann reagent)



In the light of the advantages of the Ohira-Bestmann procedure and its wide synthetic applications, we planned to use this reaction to introduce the terminal alkyne to our 1,2-dioxolane-containing substrate. As shown in Scheme 38, freshly prepared aldehyde **141** was subjected to the standard Ohira-Bestmann procedure.[73] To our disappointment, none of the desired terminal alkyne **148** was obtained, although the TLC showed that all starting material was consumed. We presumed that the 1,2-dioxolane-containing aldehyde **141** decomposed under the basic conditions due to its instability.

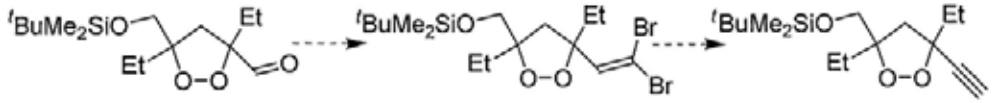
Scheme 38. Synthesis of terminal alkyne via Ohira-Bestmann procedure



trans-**141** *trans*-**148** **153**

Due to the fact that a one-pot conversion of the 1,2-dioxolane-containing aldehyde **141** to terminal alkyne **148** failed, we planned to convert the 1,2-dioxolane-containing aldehyde **141** to the 1,1-dibromoalkene **155**, which can be treated with *n*-BuLi to generate the desired terminal alkyne **148** (Scheme 39).

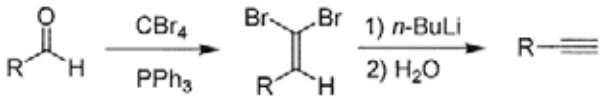
Scheme 39. Synthesis of terminal alkyne



trans-**141** *trans*-**155** *trans*-**148**

The Corey-Fuchs reaction[75] included two sequential reactions, the formation of the 1,1-dibromoolefin and the formation of the terminal alkyne. Starting from aldehyde **156**, and through these two sequential transformations, a terminal alkyne **158** was obtained (Scheme 40). The formation of 1,1-dibromoolefins via phosphine-dibromomethane was originally developed by Desai and McKelvie.[74]

Scheme 40. Corey-Fuchs reaction



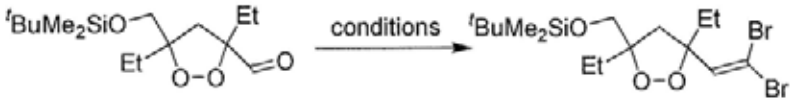
156 **157** **158**

In consideration of the good functional group tolerance of the Corey-Fuchs reaction, we intended to employ it in our preparation of the terminal alkyne **148**. Freshly prepared aldehyde **141** was used to investigate the Corey–Fuchs reaction. The reaction was performed under standard Corey-Fuchs reaction conditions.[75] However, to our disappointment, we failed to obtain the desired 1,1-dibromoalkene **155** (Table 14). Under these reaction conditions, no obvious spot was observed on TLC although all starting material was consumed. We thought that the 1,2-dioxolane-containing aldehyde **141** decomposed during the reaction.

Then we adopted the Rassat's procedure which has also been widely used in total synthesis.[77] Thus to a slurry of freshly prepared Ph_3P-$CHBr_3$[76] (2.5 equiv) in THF at 0 °C was added *t*-BuOK (2.4 equiv). The bright yellow slurry was stirred for 15 min and the temperature was allowed to warm to room temperature. Then the solution of the aldehyde **141** (1.0 equiv) in THF was added to the mixture and stirred for 30 min, the reaction was complete as monitored by TLC. To our delight, the desired 1,1-dibromoalkene **155** was prepared in 79% yield starting from the 1,2-dioxolane-containing alcohol **136** (two steps). It was necessary to warm the reaction system after the addition of *t*-BuOK. If the reaction were kept at 0 °C, an inseparable side product was formed along with the 1,1-dibromoalkene **155**. The

reaction time for the Wittig salt Ph_3P-$CHBr_3$ and *t*-BuOK and the amount of *t*-BuOK were also important. It is essential to allow a complete consumption of the base *t*-BuOK; otherwise, the base would decompose 1,2-dioxolane-containing aldehyde **141**.

Table 14. Reaction conditions for the preparation of 1,1-dibromoalkene 155

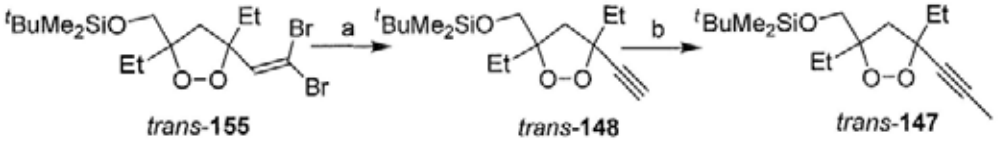


trans-**141** *trans*-**155**

Entry	Reaction conditions	Results
1	CBr_4, Ph_3P, CH_2Cl_2 (Corey-Fuchs reaction)	decomposed
2	CBr_2HPPh_3Br, *t*-BuOK,	79% (2 steps)

Preparation of the alkyne 147. With dibromoalkene **155** in hand, we treated it with *n*-BuLi (2.2 equiv) at –78 °C to provide the terminal alkyne **148** in 95% yield. Then the terminal alkyne **148** was deprotonated with *n*-BuLi (1.2 equiv) at –78 °C, followed by methylation to afford *trans*-1,2-dioxolane-containing alkyne **147** in 70% yield (Scheme 41).[35b, 36]

Scheme 41. Preparation of *trans*-1,2-dioxolane-containing alkyne

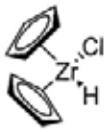


trans-**155** *trans*-**148** *trans*-**147**

Reagents and conditions: (a) *n*-BuLi (2.2 equiv), THF, –78 °C, 0.5 h, 95%; (b) *n*-BuLi (1.2 equiv), MeOTf (1.5 equiv), THF, –78 °C, 1 h, 70%.

Preparation of the alkenyl iodide 146. In 1970, Wailes and Weigold first prepared zirconocene hydrochloride (Cp_2ZrHCl) by the reduction of Cp_2ZrCl_2,[78] and then Schwartz examined the reactions of Cp_2ZrHCl with a wide range of substrates and developed it to become a useful reagent for organic synthesis (Figure 20).[79] Zirconocene hydrochloride reacts with alkenes or alkynes to form alkenylzirconium or alkylzirconium compounds and this reaction is called Schwartz hydrozirconation. Zirconocene hydrochloride (Cp_2ZrHCl) is called the Schwartz reagent. Generally, the addition of the Zr-H proceeds with *syn*-addition.[80]

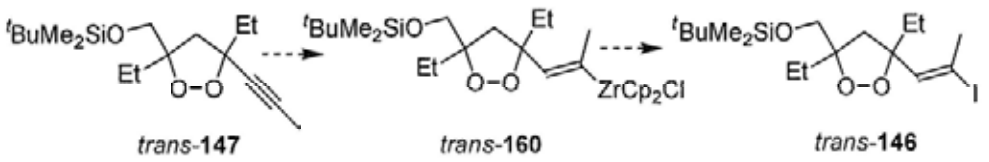
Figure 20. Schwartz reagent



159

To prepare the alkenyl iodide **146**, we attempted to employ the Schwartz reagent in our transformation. Hydrozirconation of the alkyne **147** should lead to the formation of the alkenylzirconium **160**, iodination of which affords the desired alkenyl iodide **146** (Scheme 42).

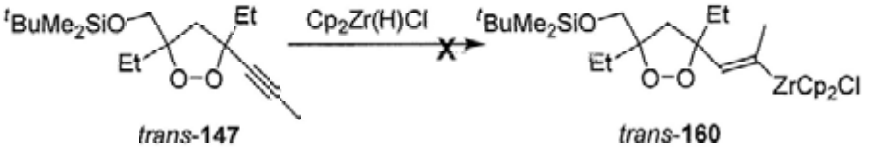
Scheme 42. Preparation of *trans*-1,2-dioxolane-containing alkenyl iodide 23 by Schwartz hydrozirconation



trans-**147** *trans*-**160** *trans*-**146**

The Schwartz hydrozirconation reaction of the alkyne **147** was performed under standard reacion conditions reported in the literature.[79,81] To a suspension of $Cp_2Zr(H)Cl$ in THF at 0 °C was added a solution of the alkyne **147** in benzene under nitrogen. The temperature was allowed to warm to room temperature. The reaction was examined by ^1H NMR. Although the reaction mixture was stirred for 24 hours, no reaction took place (Table 15). Then the reaction was performed at 50 °C, and was monitored by ^1H NMR. To our disappointment, no desired product **160** resulted. However, the starting material was consumed. Decomposition of the starting material made the reaction very messy.

Table 15. Reaction conditions for Schwartz hydrozirconation



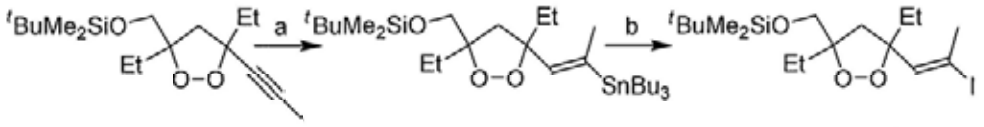
trans-**147** *trans*-**160**

Entry	Reaction conditions	Results
1	$Cp_2Zr(H)Cl$, benzene, THF, 0 °C-rt	No reaction
2	$Cp_2Zr(H)Cl$, benzene, THF, 50 °C	Complicated

After the failure of the Schwartz hydrozirconation reaction, we sought to employ a milder reaction to prepare the 1,2-dioxolane-containing alkenyl iodide **146**. This time, we resorted to the palladium-catalyzed hydrostannylation of alkynes. Compared to other methods, the palladium-catalyzed hydrostannylation offers these advantages: (1) mild reaction conditions; (2) good functional group tolerance; (3) good

stereoselectivity (*cis*-addition);[82] (4) wide application in total synthesis. It was recently reported that hexane minimized the competitive stannane dimerization in palladium-catalyzed hydrostannylations.[83] In light of these findings, our synthetic route was designed in Scheme 43. The palladium-catalyzed hydrostannylation of the alkyne **147** regiospecifically furnished **161**. Then subsequent iodination of **161** cleanly led to the 1,2-dioxolane-containing alkenyl iodide **146**.

Scheme 43. Preparation of *trans*-1,2-dioxolane-containing alkenyl iodide 146 by palladium-catalyzed hydrostannylation of the alkyne 147.



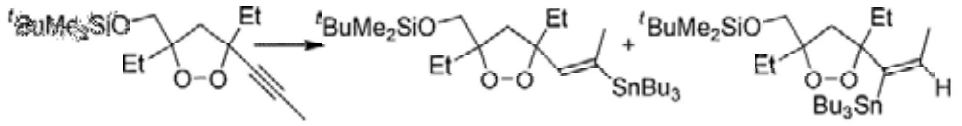
trans-**147** *trans*-**161** *trans*-**146**

Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$ (10 mol%), *n*-Bu_3SnH (3.0 equiv), Hexane, 1 h, 84%; (f) I_2 (1.0 equiv), CH_2Cl_2, 0 °C, 86%;

Employing alkyne **147** as the substrate, we studied the palladium-catalyzed hydrostannylation of 1,2-dioxolane-containing alkyne. To a solution of $Pd(PPh_3)_2Cl_2$ (10 mol%) and alkyne **147** in THF, tributyltin hydride was added dropwise at room temperature. The dark brown reaction mixture was stirred for 1 hour, and the reaction was monitored by TLC. The starting material alkyne **147** was completely consumed. After flash column chromatography, both **161** and **162** were obtained in 66% yield, and the **161/162** ratio is 1:1. Although we obtained our desired product **161**, the regioselectivity was not acceptable. We optimized the reactions by screening several palladium catalysts, ligands and solvents. All the results are summarized in Table 16.

Gratifyingly, we found the best reaction conditions. In the presence of $Pd(PPh_3)_2Cl_2$ (10 mol%), alkyne **147** reacted with tributyltin hydride in hexane, and regioselectively resulted in the desired product in 84% yield. With the intermediate **161** in hand, its iodination led to 1,2-dioxolane-containing alkenyl iodide **146** in 86% yield.

Table 16. Optimization of the Palladium-catalyzed hydrostannylation



trans-**147** *trans*-**161** *trans*-**162**

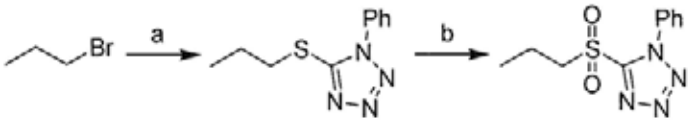
catalyst	solvent	$(n\text{-}Bu)_3SnH$	**161**	**162**	SM
$Pd(PPh_3)_2Cl_2$ (10 mol%)	THF	4.0 equiv	33%	33%	-
$Pd(PCy_3)_2Cl_2$ (10 mol%)	THF	2.0 equiv	trace	trace	56%
$Pd(OAc)_2$ (10 mol%) PCy_3 (20 mol%)	THF	4.0 equiv	24%	trace	-
$Pd(PPh_3)_2Cl_2$ (10 mol%) PCy_3 (30 mol%)	THF	4.0 equiv	30%	33%	-
$Pd(PPh_3)_4$ (10 mol%)	THF	4.0 equiv	31%	35%	-
$Pd(OAc)_2$ (10 mol%) PCy_3 (30 mol%)	Hexane	2.0 equiv	17%	7%	46%
$Pd(PPh_3)_2Cl_2$ (10 mol%)	Hexane	4.0 equiv	84%	trace	-
$Pd(PPh_3)_2Cl_2$ (10 mol%)	Hexane	2.0 equiv	71%	trace	SM residual
$Pd(PPh_3)_2Cl_2$ (10 mol%)	Hexane	2.5 equiv	80%	trace	-

2.4.3 Synthesis of the racemic side chain

To continue our basic model study, the racemic side chain needed to be prepared. The route is shown in Scheme 45. The synthetic paradigm was step-economical and starting material was commercially available and cheap.

As shown in Scheme 45, Julia olefination was used to construct the *trans*-double bond of the side chain. We first prepared the Julia reagent **165** by literature reported methods (Scheme 44).[59] Commercially available *n*-propyl bromide **163** was allowed to react with 1-phenyl-1H-tetrazole-5-thiol (Hspt) in THF in the presence of NaH furnishing the intermediate thioether **164** in 96% yield, which was in turn oxidized to the sulfone **165** with H_2O_2 in the presence of a catalytic amounts of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 92% yield.

Scheme 44. Preparation of the Julia reagent



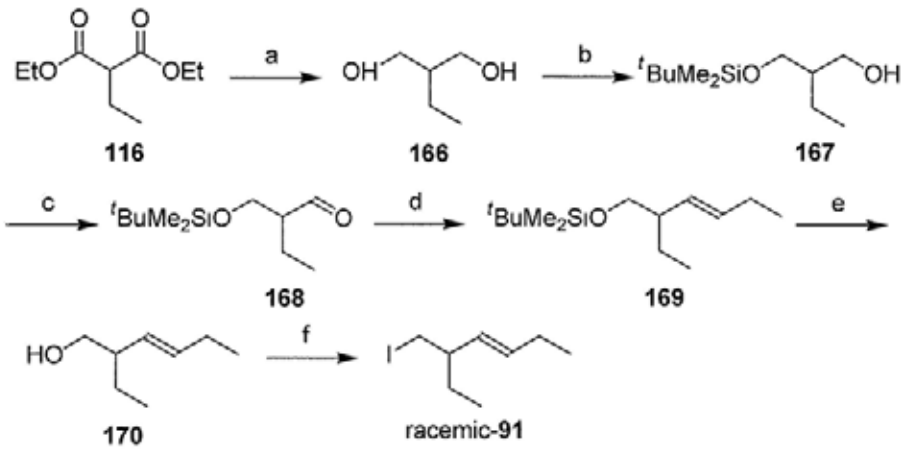
163 **164** **165**

Reagents and conditions: (a) NaH, Hspt, THF, 0 °C to rt, overnight, 96%; (b) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2(30%), EtOH, overnight, 92%.

We next prepared the aldehyde substrate for the Julia olefination. Commercially available ethyl diethyl malonate (**116**) was reduced to diol **166** in 60% yield by using $LiAlH_4$. Diol **166** was then treated with *n*-BuLi and *t*-$BuMe_2SiCl$ at –78 °C to afford the desired mono-protected product **167** as a colorless oil in excellent yield.[84] The

mono-protected alcohol **167** was then subjected to Swern oxidation. After oxidation, a colorless oil of aldehyde **168** was obtained and was directly used for the Julia olefination (Scheme 45).

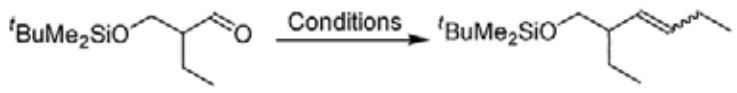
Scheme 45. Synthesis of the racemic side chain



Reagents and conditions: (a) $LiAlH_4$, THF, reflux, 24h, 60%; (b) *n*-BuLi, *t*-$BuMe_2SiCl$, THF, –78 °C to rt, 99%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C; (d) KHMDS (solid), Julia reagent , THF, –78 °C –rt, 89% (2 steps); (e) *p*-TsOH, CH_2Cl_2/CH_3OH, 86%; f. PPh_3, imidazole, I_2, CH_2Cl_2, 0 °C to rt, 86%.

When we used Julia olefination to construct the *trans*-double bond, we found that the stereoselectivity of the reaction was problematic. We found that the *trans*/*cis* ratio was affected by the base. Initially, LDA was used, the *trans*/cis *ratio* is 10:1.2 as determined by ^1H NMR spectrometry. Then we optimized the reaction by screening bases and solvents. The results are summarized in Table 17. When KHMDS was used as a base, the desired 1,2-disubstituted olefin **169** was obtained in 89% yield (two steps). The *trans*/*cis* ratio of the 1,2-disubstituted olefin **169** obtained under these reaction conditions was also acceptable (*trans*/*cis* = 25:1).

Table 17. Optimization of the Julia olefination



168 169

Entry	Reaction conditions	Trans/Cis[a]	Yield(2 steps)
1	LDA, THF, −78 °C -rt	10:1.2	56%
2	KHMDS (Toluene), THF, −78 °C -rt	11:1	30%
3	KHMDS (solid), THF, −78 °C -rt	25:1	89%

[a] Determined by ^{1}H NMR analysis .

The 1,2-disubstituted alkene **169** underwent *p*-TsOH mediated desilylation to furnish the free hydroxy intermediate **170** as a colorless oil in 86 % yield. Alcohol **170** was converted to (±)-**91** in 86% yield with PPh_3/I_2/imidazole (Scheme 45).[35b,36]

2.4.4 Pd-Catalyzed Sp^2-Sp^3 coupling

"In studying the evolution of organic chemistry and grasping its essence, one comes quickly to the conclusion that no other type of reaction plays as large a role in shaping this domain of science than carbon–carbon bond-forming reactions."—K. C. Nicolaou[85]

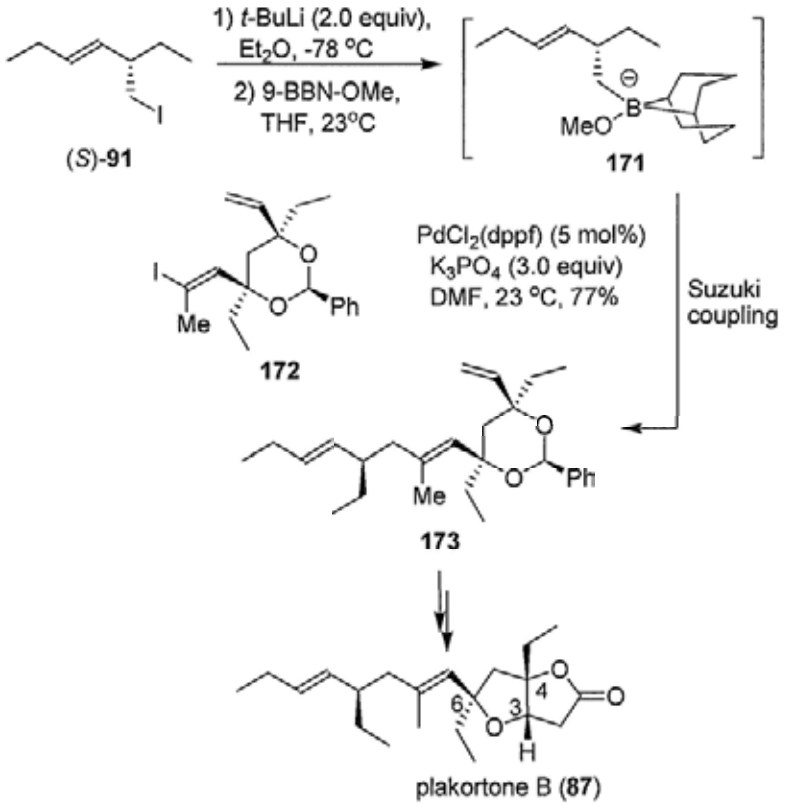
In the last quarter of the 20th century, transition metal-catalyzed cross coupling reactions have been greatly developed. Nowadays, these types of cross coupling reactions have become the most powerful and useful C-C formation reactions in synthetic organic chemistry. Amongst them, the palladium-catalyzed cross coupling reactions are the most visible. It is only natural that Pd-catalyzed coupling has been

used as a pivotal reaction in many total syntheses.[86]

Palladium-catalyzed cross-coupling reactions in total synthesis have been comprehensively reviewed by Nicolaou and coworkers.[85] Below, I have provided some examples relevant to our total synthesis of plakortide E. These beautiful applications of palladium-catalyzed cross-coupling reactions in total synthesis have shed light on our own program in the quest for plakortide E.

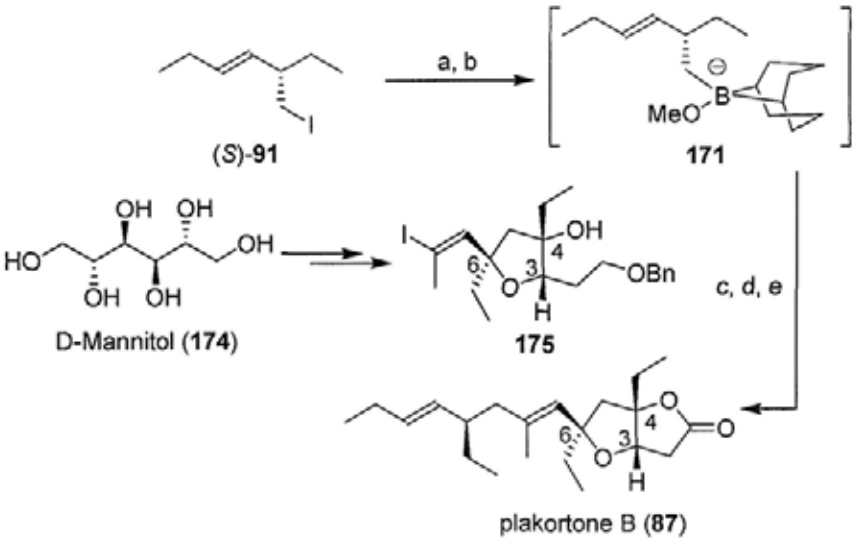
In 2006, Semmelhack and coworkers reported the synthesis of plakortone B (**87**) and analogs.[36] The connection of the side chain (*S*)-**91** to the core structure **172** was achieved by a palladium-catalyzed Suzuki reaction (Scheme 46).

Scheme 46. Application of Suzuki reaction in total synthesis of plakortone B



Recently, starting from D-mannitol (**174**), our group accomplished the total syntheses of all four possible isomers of plakortone B.[35b] And one of these molecules, **87**, was found to be identical with the natural plakortone B on the basis of ^{1}H, ^{13}C NMR spectra and specific rotation, demonstrating that absolute configuration of the natural plakortone B is (3*S*,4*S*,6*R*,10*R*). In our synthesis, a Suzuki reaction was also used to connect the central core **175** and side chain (*S*)-**91** (Scheme 47).

Scheme 47. Application of Suzuki reaction in total synthesis of plakortone B

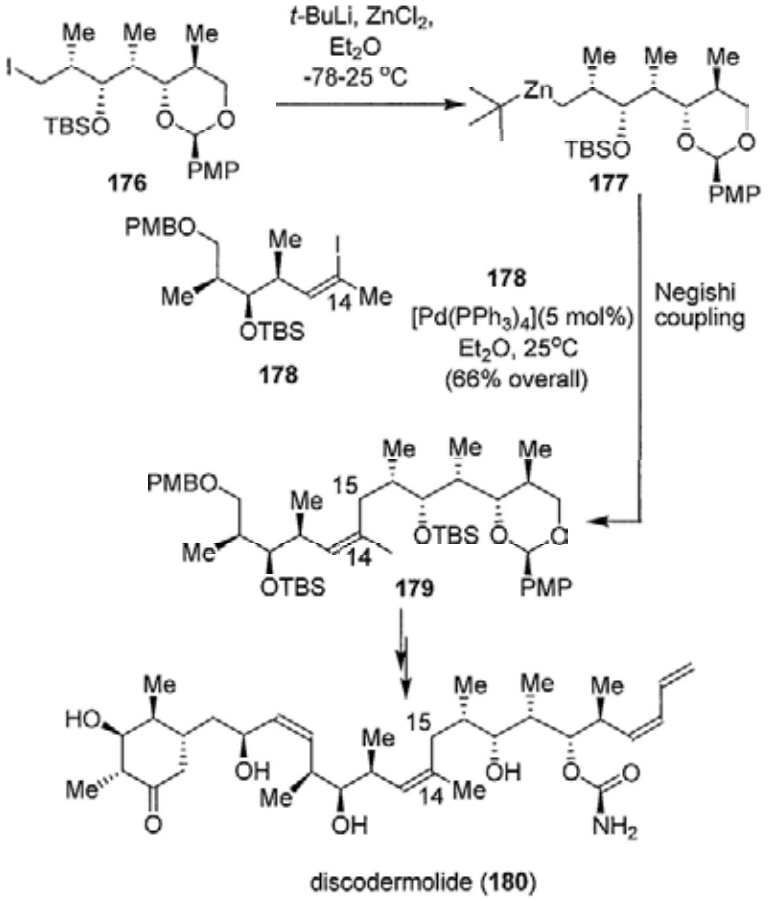


Reagents and conditions: (a) *t*-BuLi, Et_2O, −78 °C, 5 min; (b) 9-BBN-OMe, THF, −78°C, 10 min, then warm to 23 °C, 1 h; (c) 3N K_3PO_4 (aq.), 3 min; then **175**, [$PdCl_2$ $(dppf)_2$]·CH_2Cl_2, DMF, 23°C, 20 h; (d) Na/NH_3 (liq.), THF, −78 °C, 0.5 h; (e) PDC, DMF, 23 °C, 20 h, 60% over 3 steps.

In 1977, Negishi and coworkers developed a new carbon-carbon bond formation reaction, which was used to couple organozinc reagents and organic halides.[87] The synthesis of β-carotene demonstrates the utility of this reaction both as a *sp*-*sp*^{2} and

sp^2-sp^2 coupling method.[88] Generally, diorganozinc species (R_2Zn) and organozinc halides (RZnX) can be employed in the Negishi reaction. Organozinc halides (RZnX), typically prepared either by the direct insertion of zinc (zinc dust) into organic halides or by transmetalation from other organometallic species, are widely used in organic synthesis.[89] Alkylzinc reagents were used in the cross coupling process, which have greatly expanded the scope of the Negishi reaction beyond standard C(sp^2)-C(sp^2) couplings. Smith and coworkers reported a gram-scale synthesis of discodermolide (**180**), which was a clinically relevant microtubule-stabilizing agent. In their total synthesis, the Negishi coupling reaction was beautifully utilized to achieve the coupling of two fragments (Scheme 48). This application was a good example of the use of alkylzinc reagents in the process of sp^2-sp^3 carbon–carbon bond-formation.[90]

Scheme 48. Application of the Negishi reaction in the total synthesis of discodermolide

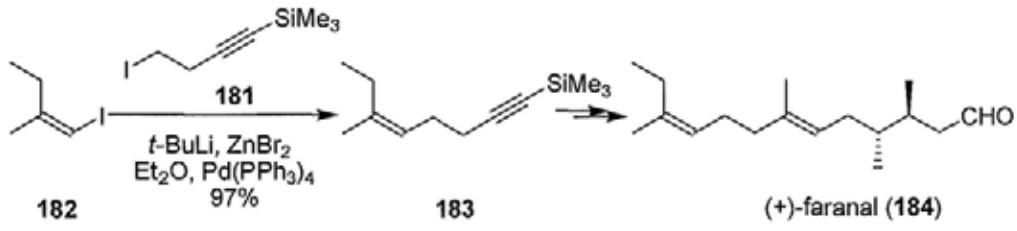


In this approach, the two fragments **176** and **178** were coupled to form the C_{14}-C_{15} bond of the target product. Significantly, it was found that 3 equivalents of *t*-BuLi were needed in the initial lithium–halogen exchange process after the optimization. If the customary 2 equivalents were used, the product was a 1:1 mixture of the iodide starting material **176** and the expected product **179**. To explain such modified Negishi protocol, they speculated that the mixed *tert*-butyl-alkyl zinc intermediate (**177**) was in fact the reactive alkyl donor in the coupling process (Scheme 48).[90]

Recently, Aggarwal and coworkers reported the total synthesis of (+)-faranal.

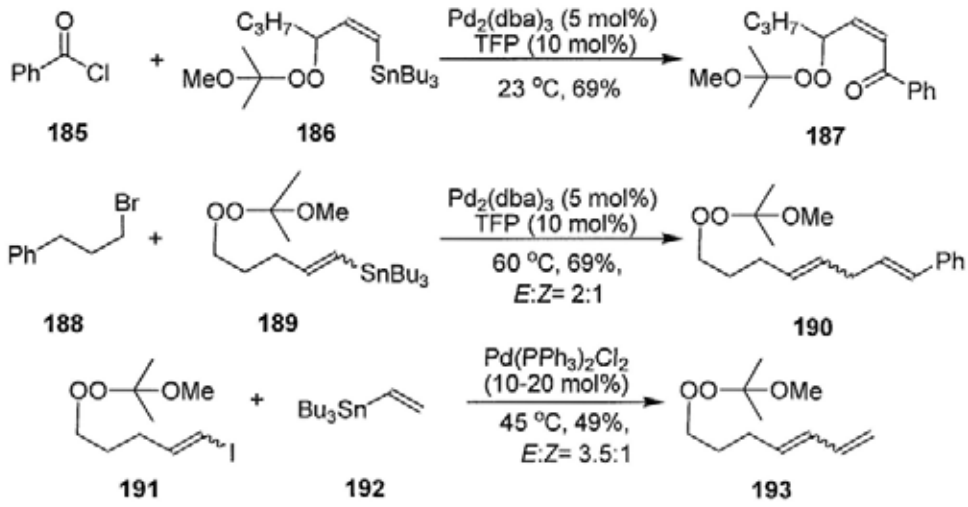
Remarkably, this synthesis was completed in only six steps from propyne, which was quite step-economical. The key reaction in the total synthesis was the coupling of the two fragments **182** and **181** from Negishi coupling. Zinc bromide was used to generate the alkyl-zinc intermediate from the corresponding organolithium (Scheme 49). This application was also an example of sp^2-sp^3 carbon–carbon bond-formation achieved by Negishi cross-coupling.[91]

Scheme 49. Application of Negishi reaction in the total synthesis of (+)-faranal

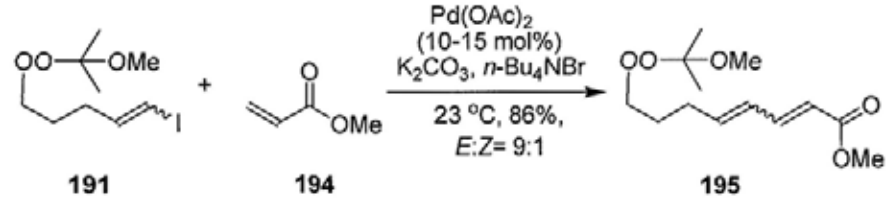


In 1998, Dussault and coworker reported their studies on the application of palladium-mediated carbon-carbon bond forming reactions to functionalized peroxides.[92] They found that the peroxides are compatible with a series of Pd-catalyzed cross coupling reactions. In that paper, they used acyclic peroxides in Stille (Scheme 50), Heck (Scheme 51), and Pd-catalyzed carbonylation reactions of vinyl iodides (Scheme 52). These examples demonstrated that peroxides are stable to the conditions for a series of palladium-catalyzed carbon-carbon bond formation reactions.

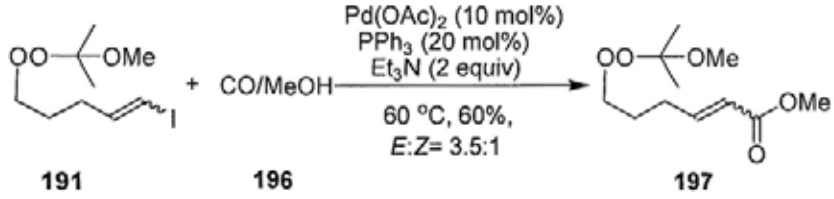
Scheme 50. Stille reaction



Scheme 51. Heck reaction



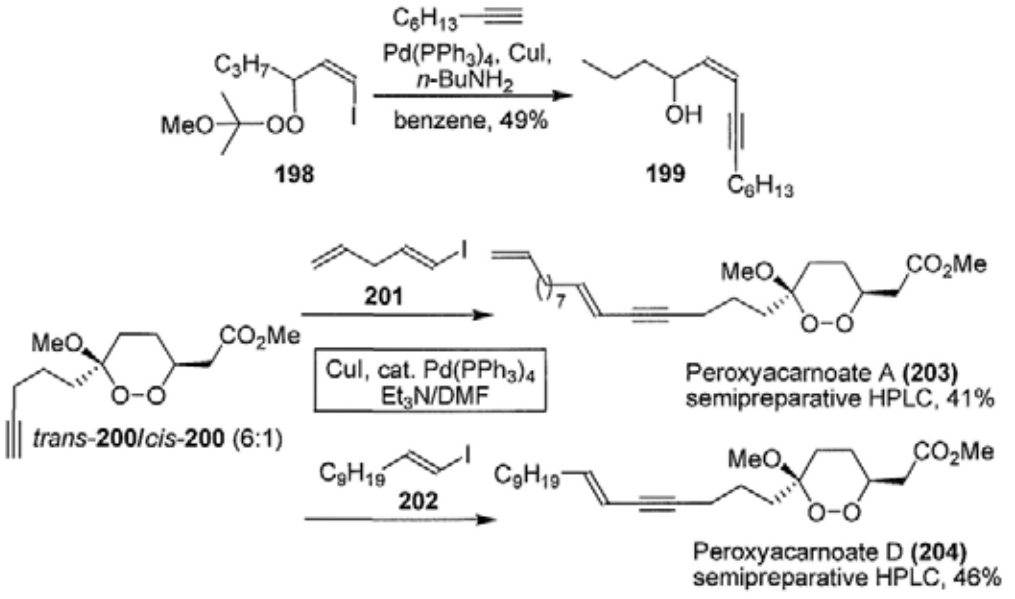
Scheme 52. Pd-catalyzed carbonylations of vinyl iodide reactions



Dussault and coworkers observed that acyclic peroxides were reduced under the conditions of the Sonogashira reaction. However, in the syntheses of polyunsaturated

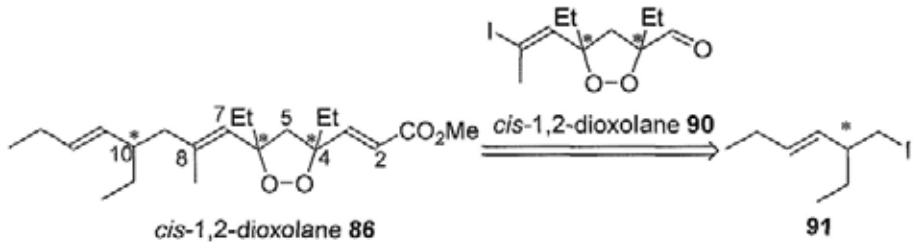
peroxides peroxyacarnoate A (**203**) and peroxyacarnoate D (**204**),[93] the Sonogashira reaction was successfully employed for the key coupling reactions (Scheme 53). Taken together, these results encouraged us in our planned use of Pd-catalyzed cross coupling reactions in our total synthesis of plakortide E.

Scheme 53. syntheses of Polyunsaturated Peroxides



In our retrosynthetic analysis of the total synthesis of plakortide E, the coupling of the side chain **91** with the cyclic peroxide containing central core **90** is one of the challenging issues (Scheme 54). Side chain **91** is an alkyl iodide, and the centre core is an 1,2-dioxolane-containing alkenyl iodide. So the C7-C8 bond formation is in fact an issue concerning $C(sp^2)$-$C(sp^3)$ coupling.

Scheme 54. The coupling of the side chain 91 and the central core 90

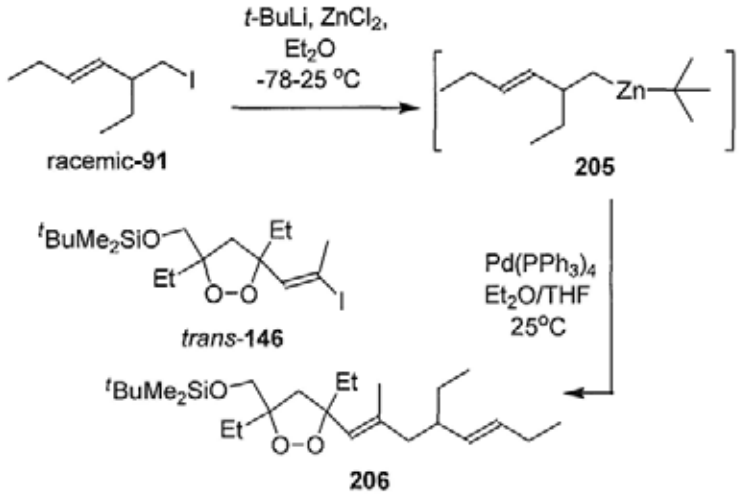


The organozinc reagents mentioned before show only moderate reactivity towards many organic electrophiles, However, they are among the most reactive of nucleophilic species in palladium-catalyzed cross-coupling reactions. This is due to the fact that in contrast to other organometallic reagents, organozinc reagents undergo rapid transmetalation with transition-metal salts, most notably those of palladium.[85] Based on these facts, we thought the Negishi cross-coupling reaction was suitable for application to the peroxide-containing substrate, because the moderate nucleophilicity of organozinc reagents would decrease their reactivity towards organic peroxides.

We proceeded to test this reaction with a model study. With the side chain (±)-**91** and *trans*-1,2-dioxolane-containing alkenyl iodide **146** in hand, we attempted to couple the two components together. The modified Negishi coupling protocol developed by Smith's group was demonstrated as an efficient method for C(sp^2)-C(sp^3) bond formation in their gram-scale synthesis of discodermolide.[90] Inspired by their success, we directly employed the modified Negishi coupling protocol to our model reaction (Scheme 55). To a solution of iodide (±)-**91** (1.2 equiv) and $ZnCl_2$ (1.2 equiv) in Et_2O at −78 °C, *t*-BuLi (3.6 equiv) was added, and was followed by warming the

reaction mixture to room temperature. Then alkenyl iodide **146** (1.0 equiv) and $Pd(PPh_3)_4$ (10 mol %) in THF were added to the reaction mixture. The reaction mixture was stirred at room temperature for 16 hours. After work-up and flash column chromatography, a colorless oil was obtained. The ^1H NMR spectrum indicated that a 4:1 mixture of our expected coupling product **206** and an unknown side product was furnished. Unfortunately the side product cannot be removed by column chromatography.

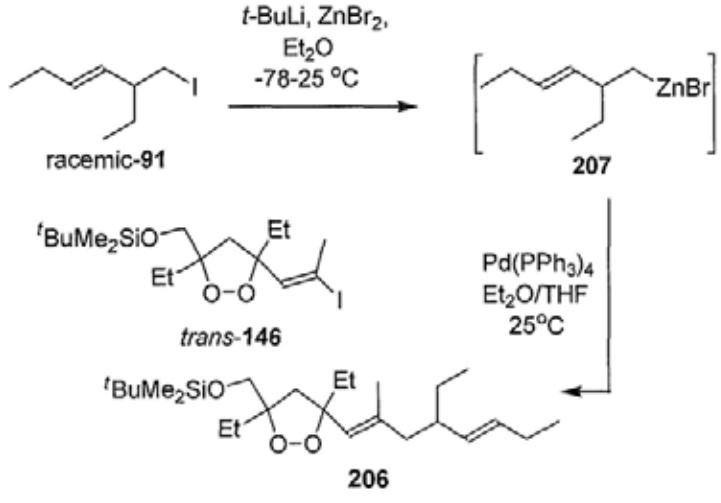
Scheme 55. Negishi coupling (Condition I)



To obtain the pure coupling product **206**, we optimized the Negishi cross-coupling reaction. The side chain was easily prepared by reported methods.[35b,84] However, the 1,2-dioxolane-containing alkenyl iodide was not readily available. Due to the above facts, we considered to use an excess of the side chain in order to improve the yield and the purity of the expected coupling product. In accordance with the literature,

$ZnBr_2$ was used instead of $ZnCl_2$.[91] The reaction was then performed under the improved conditions (Scheme 3). To a solution of iodide (±)-**91** (1.0 equiv) and $ZnBr_2$ (1.3 equiv) in Et_2O, *t*-BuLi (2.0 equiv) was added at –78 °C. The mixture was stirred at –78 °C for 30 min. Then the temperature was allowed to warm to room temperature and the reaction mixture was stirred for 1 hour. Subsequently, alkenyl iodide **146** (0.4 equiv) and $Pd(PPh_3)_4$ (4 mol %) in THF were added to the above reaction mixture. The reaction mixture was stirred at room temperature for 16 hours (Scheme 56). After flash column chromatography, the desired coupling product was obtained in good yield (> 80%) as the only product. No side product was found by ^1H NMR spectroscopy.

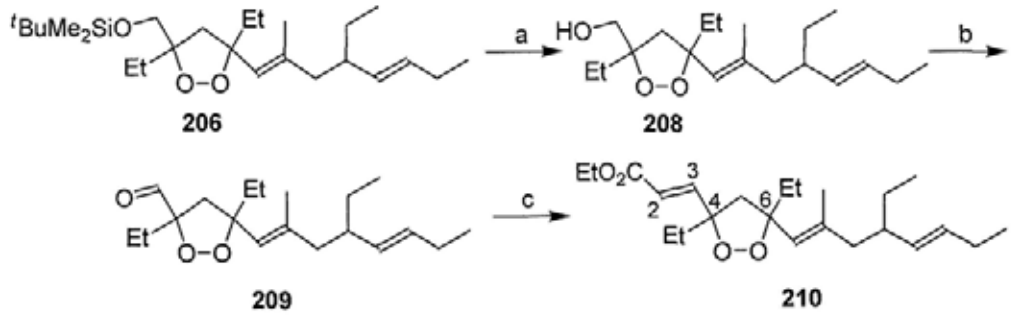
Scheme 56. Negishi coupling (Condition II)



After we successfully obtained the crossing coupling product **206**, we continued to study the total synthesis of plakortide E. To our delight, the successive conversions

were achieved smoothly (Scheme 57). The crossing coupling product **206** was subjected to a *p*-TsOH mediated desilylation to give the free hydroxy intermediate **208** in 89% yield.[35a] Dess-Martin oxidation of **208** afforded an aldehyde **209**, whose Horner–Wadsworth–Emmons olefination with triethyl phosphonoacetate gave **210** in a good yield.[61] The coupling constant between H-2 and H-3 of **210** was found to be 15.8 Hz, indicating *trans* stereochemistry of the C2-C3 disubstituted double bond (Scheme 6). Until now, all fundamental reactions related to the total synthesis of plakortide E were well studied. The successful completion of this model sequence was very helpful to our total synthesis of plakortide E.

Scheme 57. Synthesis of model product 210



Reagents and conditions: (a) *p*-TsOH (10 mol%), CH_2Cl_2/MeOH (1:2), 89%; (b) Dess-Martin periodinane (1.5 equiv), CH_2Cl_2; (c) $(EtO)_2P(O)CH_2CO_2Et$ (2.0 equiv), NaH (1.9 equiv), THF, 0 °C, 80% (2 steps).

2.5 Synthesis of chiral side chains

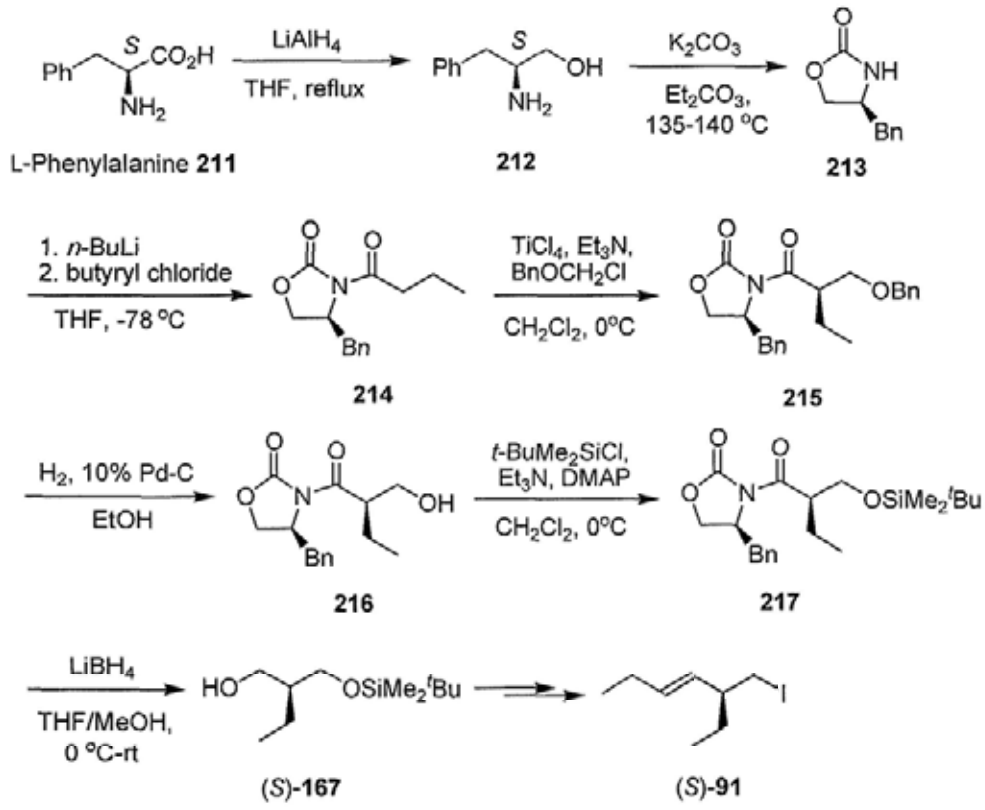
Figure 21. Enantiomerically pure side chains

(*R*)-**91** (*S*)-**91**

In our project, the four possible structures of plakortide E will be synthesized. For this reason, both chiral side chains (*R*)-**91** and (*S*)-**91** were needed (Figure 21). The syntheses of these two compounds have been reported in the literature (Scheme 58).[35b,36,94]

Commercially available L-phenylalanine (**211**) was reduced by $LiAlH_4$ to give amino alcohol **212** in good yield, which was converted to (*S*)-4-benzyl-2-oxazolidinone (**213**) with potassium dicarbonate/diethyl carbonate.[94e] Then the Evans reagent **213** was treated with *n*-BuLi/ butyryl chloride to furnish imide **214**.[94d] The subsequent reaction of **214** with (benzyloxy)methyl chloride (BOMCl) in the presence of $TiCl_4$ and Et_3N at 0 °C produced imide **215** as a single stereoisomer in 77% yield. Hydrogenolysis of **215**, followed by protection of the resulting alcohol **216** with *t*-$BuMe_2Si$ group, quantitatively provided **217** (Scheme 58).[94c] Reduction of **217** with $LiBH_4$ furnished (*S*)-**167** in 85% yield.[94c]

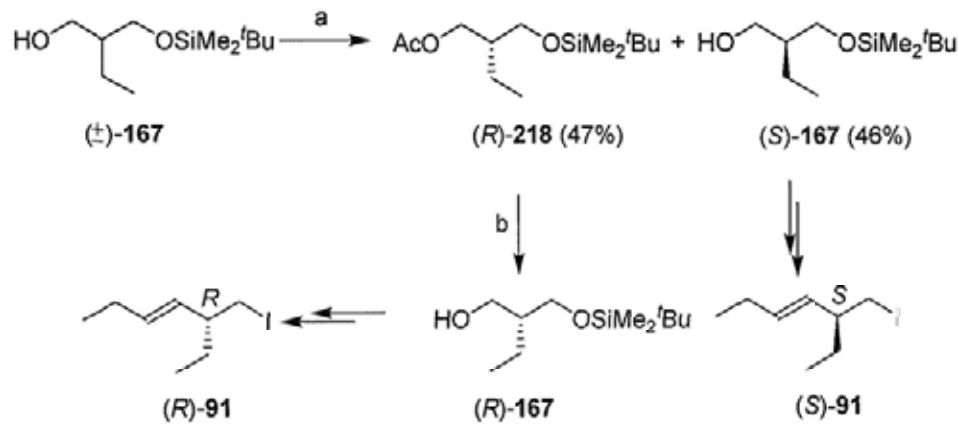
Scheme 58. Synthesis of side enantiomerically pure side chain



As shown in Scheme 58, 7 steps were needed in the synthesis of the chiral intermediate (*S*)-**167**, starting from the commercial available L-phenylalanine (**211**). The synthesis of its enantiomer of (*R*)-**167** also should involve similar steps. In consideration of a step-economic synthetic strategy, we sought to develop an alternative synthetic route to realize the chiral side chain (*R*)-**91** and (*S*)-**91** (Scheme 59). In our model studies for the synthesis of the racemic side chain, the racemic-**167** as the intermediate was easily prepared in only two steps from commercially available ethyl diethyl malonate (**116**). The lipase catalyzed kinetic resolution of racemic-**167** was employed in the total synthesis of rutamycin B and oligomycin C, and showed

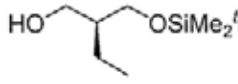
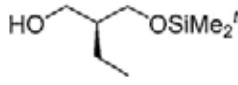
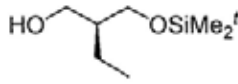
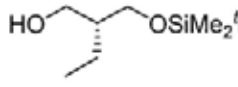
excellent enantiomeric excess.[84] We envisioned to use this method to prepare the optically pure (*S*)-**167** and (*R*)-**167** in only one step. If we employed the synthetic route described in Scheme 58, there were totally 14 steps required to prepare (*S*)-**167** and (*R*)-**167**. According to the literature, the kinetic resolution of racemic **167** was performed. To a solution of racemic **167** in pentane, the lipase extract and vinyl acetate were added. The reaction mixture was stirred vigorously for 24 h. Then the reaction mixture was filtered to remove the lipase catalyst. Purification by column chromatography furnished acetate (*R*)-**218** in 47% yield and alcohol (*S*)-**167** in 46% yield. On the other hand, hydrolysis of acetate (*R*)-**218** gave the enantiomeric alcohol (*R*)-**167** (Scheme 59). A comparison of the specific rotation with literature values is shown in Table 18.[112,113]

Scheme 59. An alternative synthetic route for enantiomerically pure side chains



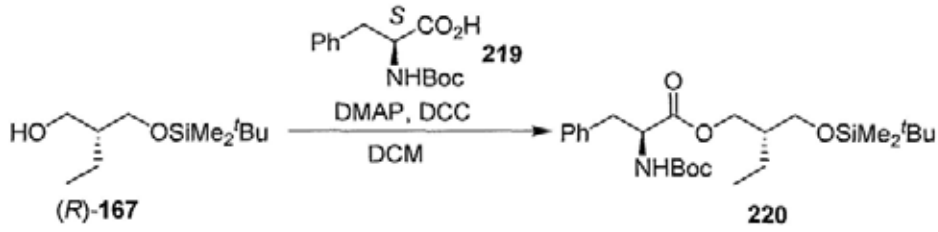
Reagents and conditions : (a) Lipase PS30, vinyl acetate, pentane, rt, 24h; (b) K_2CO_3, MeOH, 99%.

Table 18. Comparison of specific rotations

Entry	Compound	$[\alpha]_D^{20}$	Literature
1		$[\alpha]_D^{20}$ = -10.6 (*c*, 0.99, $CHCl_3$) (nearly 100% *ee*)	*J. Org. Chem.* **1994**, *59*, 5317-5323.
2		$[\alpha]_D^{20}$ = -11.41 (*c*, 1.42, $CHCl_3$) (> 99% *ee*)	*J. Chem. Soc., Chem. Commun.*, **1987**, 619-620.
3	 (*S*)-**167**	$[\alpha]_D^{20}$ = -10.7 (*c*, 1.37, $CHCl_3$)	Our synthetic compound
4	 (*R*)-**167**	$[\alpha]_D^{20}$ = 10.6 (*c*, 1.67, $CHCl_3$)	Our synthetic compound

We also assessed the enantiomeric purity of (*S*)- and (*R*)-**167** by analyses of the ^1H NMR and ^{13}C NMR spectra of the diastereomeric derivative **220**. Our synthetic chiral compound (*R*)-**167** reacted with optically pure *N*-Boc protected L-phenylalanine (**219**) to afford the diastereomeric derivative **220**,[95] which was analyzed by the ^1H NMR and ^{13}C NMR spectroscopy (Scheme 60). The NMR spectra indicated that compound **220** was very pure, with virtually no trace of the diastereoisomer (dr > 95%).

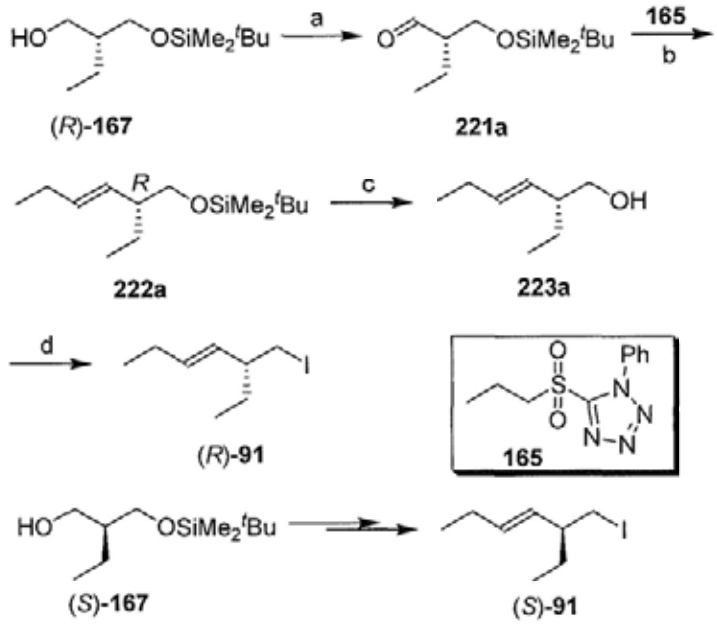
Scheme 60. Formation of the diastereomeric derivative 220



(*R*)-**167** **220**

After the enantiomerically pure (*R*)-**167** and (*S*)-**167** were obtained, we proceeded to continue the syntheses of enantiomerically pure side chains of plakortide E. Since all related reactions have been well studied in model studies, we found it straightforward to convert the desired enantiomerically pure side chains (*R*)-**91** and (*S*)-**91**. The synthetic route is shown in Scheme 61. The enantiomerically pure alcohol (*R*)-**167** was first subjected to Swern oxidation. After oxidation, a colorless oil of aldehyde **221a** was generated and was used immediately in the Julia olefination. When KHMDS was used as the base, the desired 1,2-disubstituted olefin **222a** was obtained in 89% yield (two steps).[35b,36] From 1,2-disubstituted olefin **222a**, *p*-TsOH mediated desilylation helped to remove the *t*-$BuMe_2Si$ group to give the free hydroxy intermediate **223a** as a colorless oil in 86 % yield. Alcohol **223a** was converted with PPh_3/I_2/imidazole to iodide (*R*)-**91** in 86% yield. In a similar manner, enantiomerically pure side chain (*S*)-**91** was also synthesized.[35b,36]

Scheme 61. Syntheses of enantiomerically pure side chains



Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (b) KHMDS (solid), Julia reagent , THF, −78 °C- rt, 89% (2 steps); (c) *p*-TsOH, CH_2Cl_2/CH_3OH, 86%; (d) PPh_3, imidazole, I_2, CH_2Cl_2, 0 °C to rt, 86%.

2.6 Syntheses of enantiomerically pure dioxolane cores

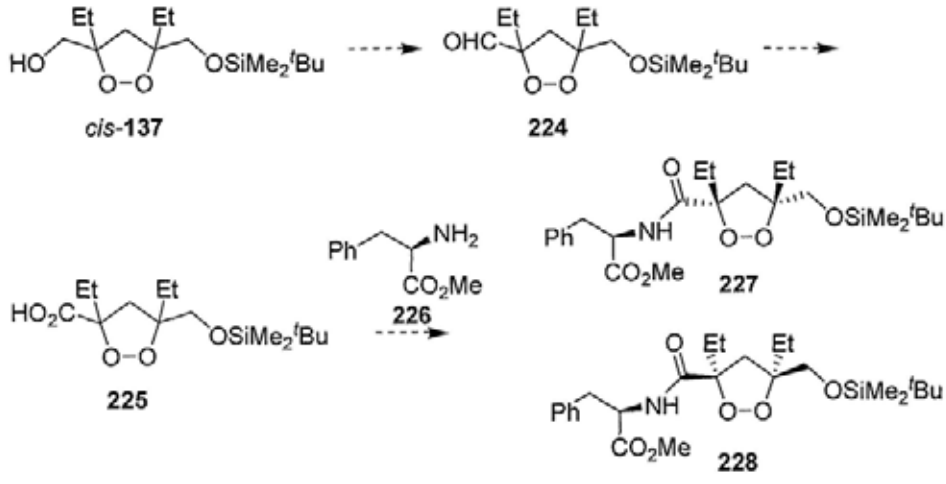
Syntheses of enantiomerically pure central cores via chemical resolution

Chemical resolution is an established method for producing optically pure compound as single enantiomers. A racemic compound is reacted with an optically pure reagent to form a pair of diastereomers, which can be separated by conventional techniques, such as column chromatography. This method was first introduced by Louis Pasteur in 1853, who successfully resolved racemic tartaric acid with optically active (+)-cinchotoxine.

Scheme 62 illustrates the planned resolution. To prepare the optically pure cyclic peroxide, we planned to start from *cis*-**137**. Thus, oxidation of the aldehyde **224** leads to the acid **225**, which is allowed to react with the chiral amine **226** to furnish a pair of

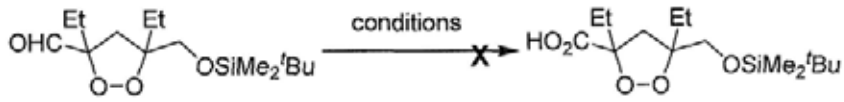
diastereomers **227** and **228**. Then the diastereomers are separated by column chromatography.

Scheme 62. Chemical resolution of racemic *cis*-1,2-dioxolane alcohol



To our disappointment, oxidation of aldehyde **224** with $NaClO_2$ did not successfully furnish the corresponding acid **225**; instead, the aldehyde decomposed. TLC indicated that the reaction was very complicated. On the other hand, attempts to oxidize aldehyde **224** with PDC in DMF also did not lead to the desired acid **225**.[96] The results are summarized in Table 19.

Table 19. Oxidations of racemic cis-1,2-dioxolane alcohol

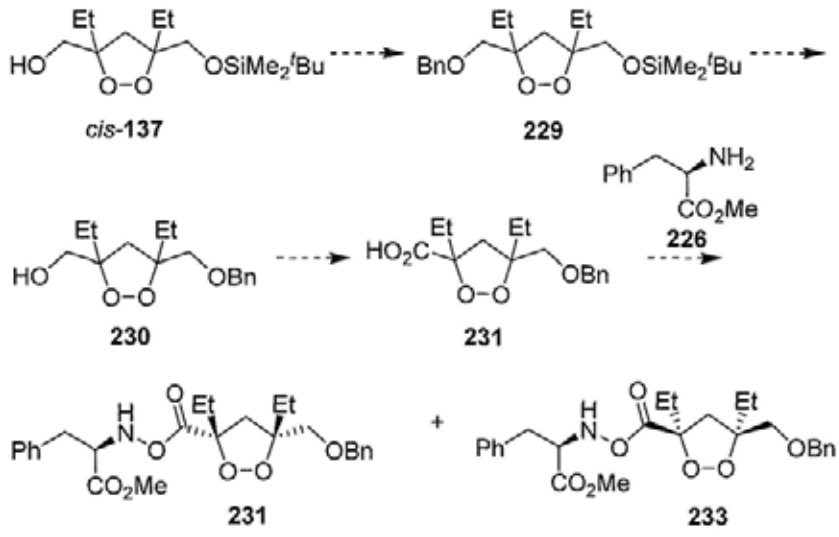


224 **225**

Entry	Reaction conditions	Results
1	$NaClO_2$, H_2O_2, NaH_2PO_4, THF, rt	Complicated
2	PDC, DMF, rt, 10 h	Complicated

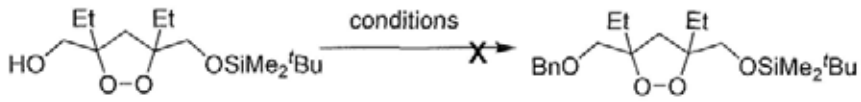
One reason for these failures was presumably due to the sensitivity of the *t*-$BuMe_2Si$ group. We therefore designed an alternate route replacing the *t*-$BuMe_2Si$ protecting group with a Bn group. Another route of chemical resolution was therefore designed (Scheme 63). Thus, racemic *cis*-1,2-dioxolane alcohol **137** is protected with Bn group to give **229**, whose *t*-$BuMe_2Si$ group is removed to afford the free alcohol **230**. Oxidation of the racemic *cis*-1,2-dioxolane alcohol **230** leads to the acid **231**, which reacts with enantiomerically pure amine **226** to furnish the diastereomers **231** and **232**. Then the diastereomers are separated by column chromatography.

Scheme 63. An alternative chemical resolution route of racemic *cis*-1,2-dioxolane alcohol 137



However, the protection of the racemic *cis*-1,2-dioxolane alcohol **137** with benzyl bromide is problematic. The reaction conditions are depicted in Table 20.[97] In all cases, TLC indicated that no expected product was produced. However, the starting material was consumed. The racemic *cis*-1,2-dioxolane alcohol **137** was found to decompose easily under these reaction conditions. For this reason, we had to abandon this chemical resolution route.

Table 20. Reaction conditions for protection of the racemic *cis*-1,2-dioxolane alcohol 137 with benzyl bromide

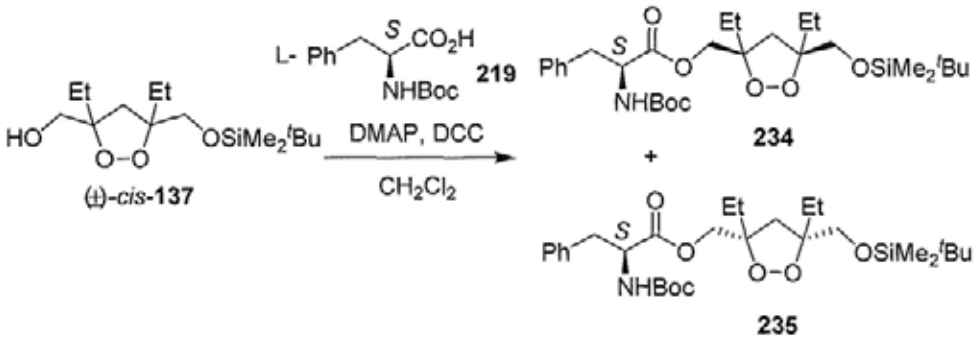


cis-**137** **229**

Entry	Reaction conditions	Results
1	BnBr, NaH, DMF	Complicated
2	BnBr, Ag_2O, DMF	Complicated
3	BnBr, NaH, TBAI, THF	Complicated

Due to the aforementioned failure, we had to seek other milder reactions to accomplish the resolution of racemic *cis*-1,2-dioxolane alcohol **137**. Finally, we found the racemic *cis*-1,2-dioxolane alcohol **137** reacted with *N*-Boc protected L-phenylalanine (**219**) smoothly in the presence of DMAP/DCC to furnish the diastereomers **234** and **235** (Scheme 64).[95] However, their diastereomers could not be separated by column chromatography. In principle, diastereomers **234** and **235** could be converted to other derivatives that might be separable. However, this approach is not step-economical for our total synthesis of plakortide E. We therefore moved onto enzymatic resolution of the 1,2-dioxolane core.

Scheme 64. Formation of diastereomeric derivatives of racemic *cis*-1,2-dioxolane alcohol



Syntheses of enantiomerically pure central cores by lipase-catalyzed kinetic resolution. Enzymes are proteins that catalyze a vast number of chemical reactions.[62, 98] The history of enzyme is very long, which can go back to thousands of years to ancient Egypt.[62] Over the last few years, more and more organic chemists have recognized the potential of biocatalysis as a viable and popular technique in organic synthesis. Compared to other catalysts, the advantages of enzymes are quite obvious. It is known that reactions catalyzed by enzymes are more selective and efficiently performed.

Firure 22. A computer-generated image of a type of pancreatic lipase (PLRP2) from the guinea pig.

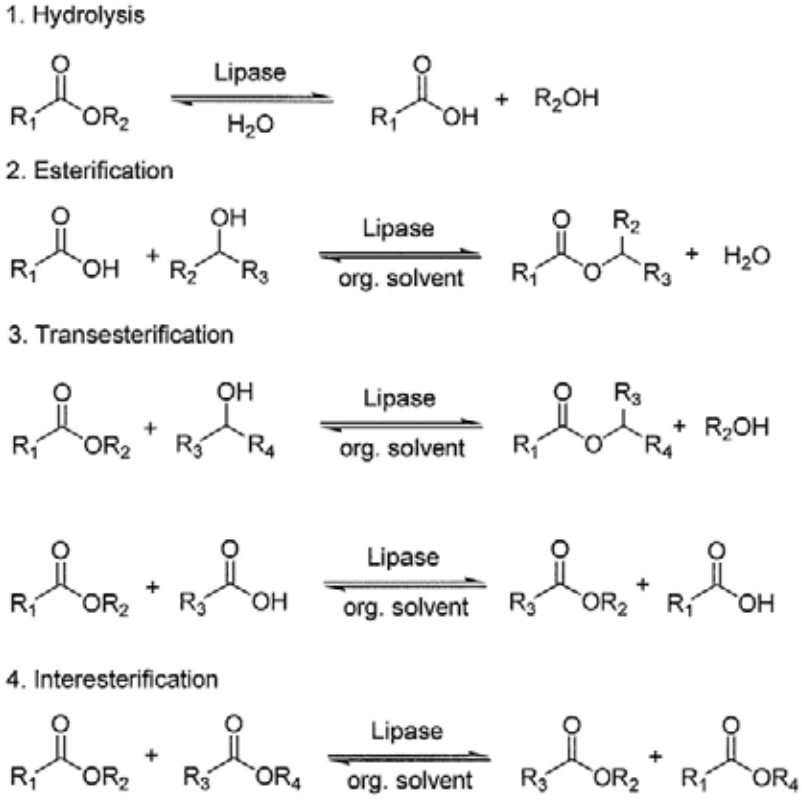
There has been a dramatic increase in the number of publications in the field of lipase-catalyzed reactions. Lipases are ubiquitous water-soluble enzymes that catalyze the hydrolysis of ester chemical bonds and can be found in animals, plants, fungi and bacteria.[62,99] A computer-generated image of a type of pancreatic lipase from the guinea pig is showed in Figure 22. Traditionally, biocatalysis are performed in aqueous medium. However, water is a poor solvent for organic chemistry, since most organic compounds are very sparingly soluble and are sometimes unstable in aqueous solutions. Side reactions such as hydrolysis, racemization, polymerization and decomposition often take place easily in water medium. As a result, chemists have developed procedures for the use of enzymes in organic solvents. Now, enzymatic catalysis in non-aqueous media has significantly benefited the chemistry of lipase

catalysis.[100]

Lipases as organocatalysts are widely used in three main types of asymmetric transformations.[19] They are (a) kinetic resolution of racemic carboxylic acids or alcohols, (b) transformations of meso dicarboxylic acids or meso diols and (c) transformations of prochiral dicarboxylic acid and diol derivatives. In kinetic resolutions, theoretical yields are limited to 50%. Through enantiotopic group differentiation of meso dicarboxylic acids or meso diols, yields of up to 100% are possible.[101] Some typical reactions catalyzed by lipases are depicted in Scheme 65.

According to IUPAC recommendation, kinetic resolution (KR) is defined as the achievement of partial or complete resolution by virtue of unequal rates of reaction of the enantiomers in a racemate with a chiral agent (reagent, catalyst, solvent, etc.).[101]

Scheme 65. Reactions catalyzed by lipase

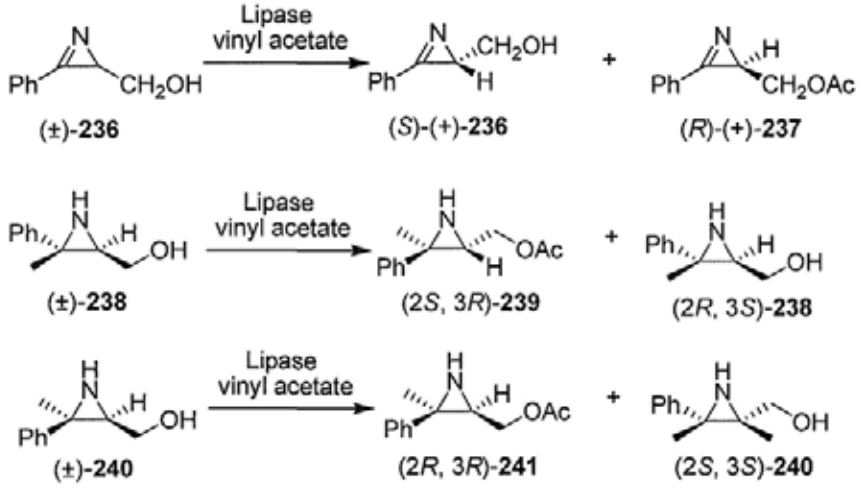


The enzyme catalyzed reactions and the lipase-catalyzed kinetic resolutions have been reviewed.[62] The following section describes some selected examples of lipase-catalyzed resolutions.

In 1997, an efficient method[102] to prepare enantiomerically pure (*S*)-(+)-**236** and (*R*)-(+)-**237** by a lipase-catalyzed kinetic resolution was reported by Sakai. Their reactions were carried out preferentially at –40°C (Scheme 66). Recently, in their continuing program, porous ceramic (Toyonite)-immobilized lipase (PSCII) was used in the resolution of (±)-**238** at low temperature, giving the synthetically useful (2*R*,3*S*)-**238** and its acetate (2*S*,3*R*)-**239** with (2*S*)-selectivity ($E = 55$ at –40 °C), while a similar reaction of (±)-**240** gave (2*S*,3*S*)-**240** and its acetate (2*R*,3*R*)-**241** with

(2*R*)-selectivity (E = 73 at –20 °C) (Scheme 66). Two special points in this example are intriguing and are worthy of mentioning. First, substrates (±)-**238** and (±)-**240** belong to an interesting class of primary aziridine alcohols, which feature two stereogenic centers at the β- and γ-carbons. Before this report, there were few examples of the lipase-catalyzed reaction for such 2-aziridinemethanols. Second, the substrates without *N*-protection were directly used in the reactions. These outcomes inspired us to use the lipase-catalyzed resolution to realize the enantiomerically pure *cis*-1,2-dioxolane containing alcohols, which also feature two stereogenic centers.[102]

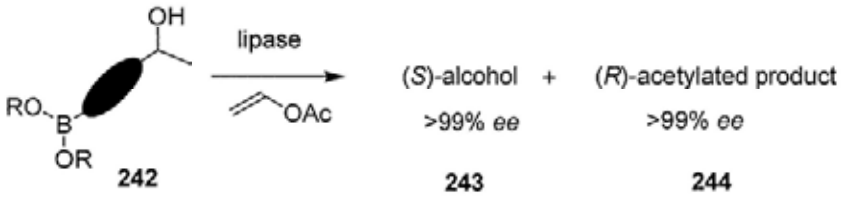
Scheme 66. An efficient method to prepare enantiomerically pure alcohols by lipase-catalyzed kinetic resolution



Boron compounds are useful as potential enzyme inhibitors. Recently, a highly enantioselective lipase-catalyzed kinetic resolution of boron-containing alcohols was reported. It was found that aromatic, allylic, and aliphatic secondary alcohols containing a boronate ester or boronic acid group (*viz.* **242**) were resolved by lipase

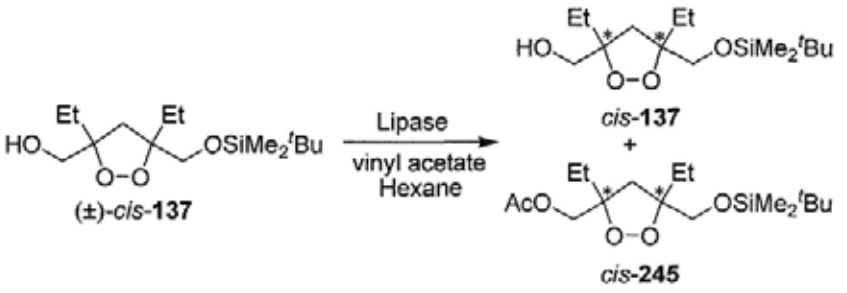
from *Candida antartica* (CALB). Excellent *E* values ($E > 200$) and high enantiomeric excesses (>99%) of **243** and **244** were obtained (Scheme 67).[103] This example extends the scope of the lipase-catalyzed kinetic resolutions.

Scheme 67. The lipase-catalyzed kinetic resolution of boron-containing alcohols



With the desired mono-protected alcohol (±)-*cis*-**137** in hand, the lipase-catalyzed kinetic resolution of *cis*-1,2-dioxolane-containing alcohol was investigated.[62,84] Results of these studies are summarized in Table 21. Lipase PS from *Burkholderia cepaci* was found to give the best kinetic resolution outcome. We observed that prolongation of the reaction time to 29 hours provided the optically pure alcohol, which showed excellent enantiomeric excess (>99% *ee*). When the reaction was quenched after 3 hours, the optically pure ester was obtained (94% *ee*). We were able to secure the optically pure ester in excellent enantiomeric excess (>99% *ee*) by repeating the resolution on partially resolved material.

Table 21. Optimization for the kinetic resolution of (±)-*cis*-137



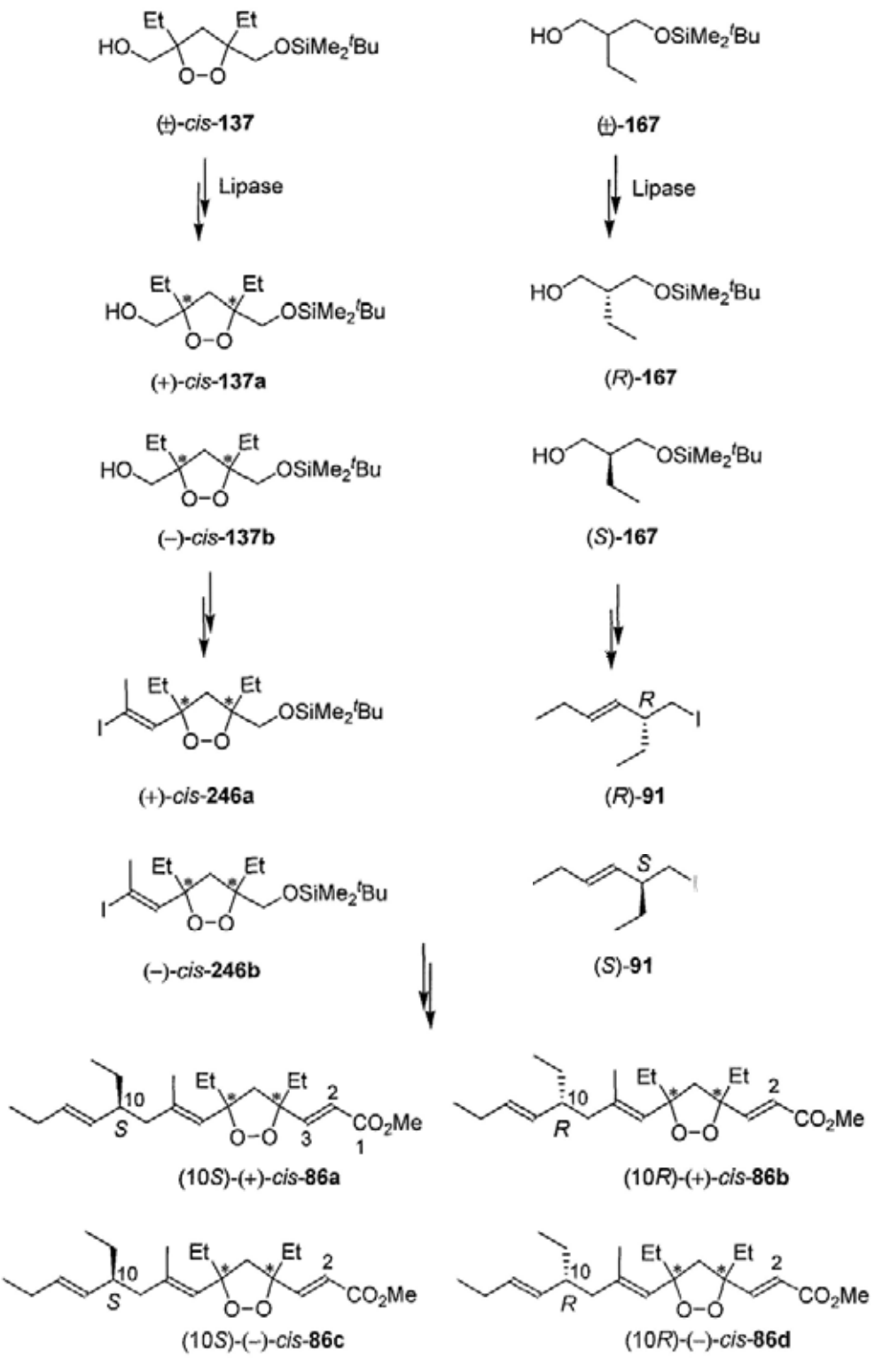
Lipase source	Time	Alcohol			Ester		
		yield	*ee*	Specific rotation	yield	*ee*	Specific rotation
Lipase CR	40	68%	34%	-6.6	31%	49%	10.0
Lipase BC	3	53%	78%	23.5	45%	94%	-21.5
	5	49%	89%	26.3	46%		-21.5
	29	43%	>99%	28.5	55%		
	3	56%			41%	>99% [a]	-21.5

Lipase CR: Candida rugosa lipase; Lipase BC: Lipase PS from Burkholderia cepaci;
[a] Resolution two times; The *ee* was determined by chiral HPLC.

2.7 Total synthesis of four possible structures of plakortide E methyl ester

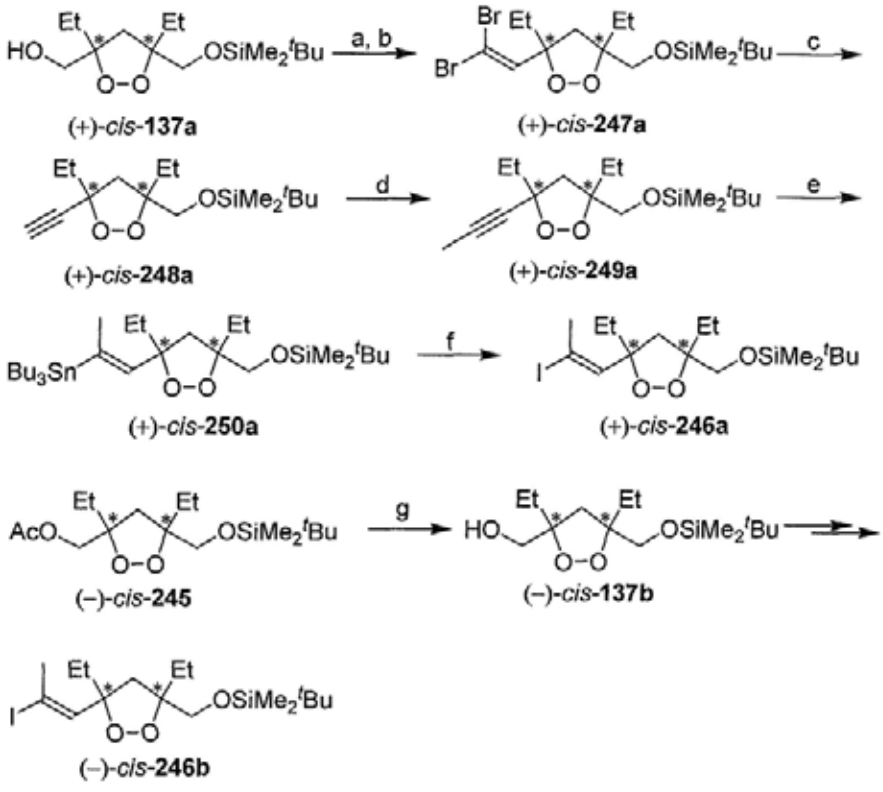
With the enantiomerically pure 1,2-dioxolane-containing alcohol *cis*-**137** and ester *cis*-**245**, enantiomerically pure side chain (*R*)-**91** and (*S*)-**91** in hand, we assembled the four possible plakortide E methyl esters structures using the chemistry worked out in our model sequences. The routes are illustrated in Scheme 68.

Scheme 68. Total synthesis of four possible structures of Plakortide E methyl ester



Preparation of enantiomerically pure *cis*-1,2-dioxolane-containing alkenyl iodide 246a and 246b. As shown in Scheme 69, oxidation of **137a** with Dess-Martin periodinane (DMP) produced a 1,2-dioxolane-containing aldehyde. Thus, the 1,2-dioxolane-containing aldehyde was treated with freshly prepared $CHBr_2PPh_3Br$ and *t*-BuOK, giving dibromoalkene **247a** in good yield with excellent reproducibility.[77] Preparation of terminal alkyne **248a** was subsequently achieved by treatment of **247a** with *n*-BuLi, followed by methylation to provide **249a**.[35b] In the presence of a catalytic amount of $PdCl_2(PPh_3)_2$, **249a** underwent regiospecific hydrostannylation to furnish **250a** in 84% yield. Subsequent iodination of **250a** led to the formation of the key alkenyl iodide **246a**. On the other hand, hydrolysis of **245** gave the enantiomeric **137b** in a good yield. In a similar manner, optically pure **246b** was also synthesized (Scheme 69). Because all the related reactions had been well executed in the model studies, the syntheses of **246a** and **246b** were achieved smoothly.

Scheme 69. Syntheses of enantiomerically pure 246a and 246b

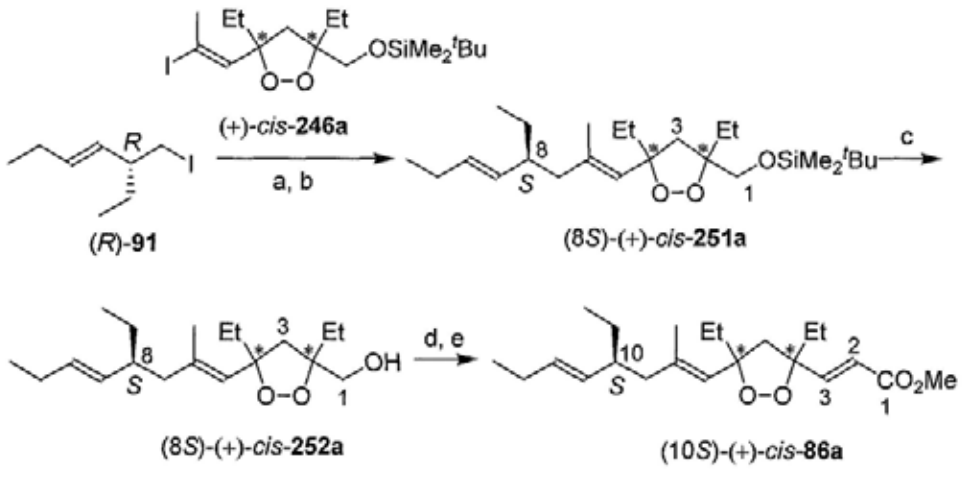


Reagents and conditions: (a) Dess-Martin periodinane (1.5 equiv), CH_2Cl_2; (b) $CHBr_2P^+Ph_3Br^-$ (2.5 equiv), *t*-BuOK (2.4 equiv), THF, rt, 79% (2 steps); (c) *n*-BuLi (2.2 equiv), THF, −78 °C, 0.5 h, 95%; (d) *n*-BuLi (1.2 equiv), MeOTf (1.5 equiv), THF, −78 °C, 1 h, 70%; (e) $Pd(PPh_3)_2Cl_2$ (10 mol%), *n*-Bu_3SnH (3.0 equiv), Hexane, 1 h, 84%; (f) I_2 (1.0 equiv), CH_2Cl_2, 0 °C, 86%; (g) K_2CO_3 (1.0 equiv), MeOH, 94%.

Total synthesis of four possible isomers of plakortide E methyl ester. With the central core (+)-**246a** and side chain (*R*)-**91** in hand, the Negishi cross coupling reaction was carried out to join the two partners together,[91] from which the desired molecule **251a** was generated as the only product. Subsequent *p*-TsOH mediated desilylation of the *t*-$BuMe_2Si$ group furnished the free hydroxy intermediate **252a** in 89% yield.[35a] Dess-Martin oxidation of **252a** afforded an aldehyde, whose Horner–Wadsworth–Emmons olefination with trimethyl phosphonoacetate gave **86a**

in a good yield.[61] The coupling constant between H-2 and H-3 of **86a** was found to be 15.8 Hz, indicating the *trans* stereochemistry of the C2-C3 disubstituted double bond (Scheme 70).

Scheme 70. Synthesis of 86a



Reagents and conditions: (a) $ZnBr_2$ (1.3 equiv), *t*-BuLi(2.0 equiv), Et_2O/THF, −78 °C to rt; (b) $Pd(PPh_3)_4$ (10 mol%), THF, 16h, 93%; (c) *p*-TsOH (10 mol%), CH_2Cl_2/MeOH (1:2), 89%; (d) Dess-Martin Periodinane (1.5 equiv), CH_2Cl_2; (e) $(MeO)_2P(O)CH_2CO_2Me$ (10.0 equiv), NaH (10.0 equiv), THF, 0 °C, 80% (2 steps).

With the two enantiomerically pure central cores (**246a** and **246b**) and two side chains (*R*)-**91** and (*S*)-**91** available, the other three possible isomers of plakortide E methyl ester were synthesized through similar sequences. All reactions proceeded smoothly to give the other three isomers in good yields (Scheme 71).

Scheme 71. Syntheses of three other possible isomers of plakortide E methyl ester

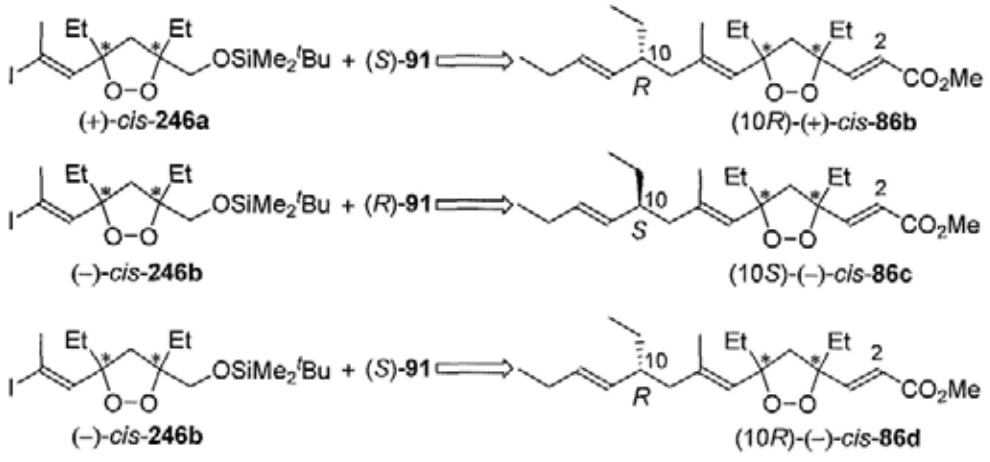


Table 22. Comparison of selected ^{1}H NMR chemical shifts (*J* values) and specific rotations.

	H5	H7	H19	$[\alpha]_D^{20}$
86a	2.54 (11.9) 2.44 (11.9)	5.11	1.61	–86.0
86b	2.58 (11.8) 2.44 (11.8)	5.15	1.59	–74.8
86c	2.58 (11.9) 2.44 (11.9)	5.15	1.59	+75.0
86d	2.54 (11.9) 2.44 (11.9)	5.11 (1.3) [a]	1.61 (1.3) [a]	+87.0
plakortide E Methyl ester[34]	2.54 (12.0) 2.44 (12.0)	5.11 (1.3)	1.61 (1.3)	+75.1

[a] Coupling constants were measured by 2D J-Resolved NMR experiment on an Advance Bruker 600M spectrometer.

Table 23. Comparison of selected ^{13}C chemical shifts.

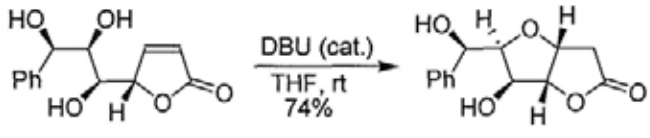
	C-1	C-2	C-3	C-5	C-7	C-8	C-11	C-12
86d	167.1	119.9	149.8	56.0	126.7	136.6	132.8	132.0
plakortide E methyl ester[34]	166.9	119.9	149.6	55.9	126.7	136.4	132.7	131.9

All four possible isomers of plakortide E methyl ester were synthesized so that a comparison of their NMR spectral data with those of the natural plakortide E methyl ester could be made.[34] All ^{1}H and ^{13}C NMR spectra and specific rotation data are included in the Experimental section, with the most crucial data being summarized in Table 22 and Table 23. As can be seen, the four synthetic samples can be divided into two pairs of enantiomers (**86a** and **86d**, **86b** and **86c**). Although the differences in their ^{1}H NMR spectra are generally very small, there are considerable differences in the chemical shifts of H-5, H-7 and H-19. While the ^{1}H NMR spectra of the synthetic molecules **86a** and **86d** show good agreement with those of the natural compound, the ^{1}H NMR spectra of compounds **86b** and **86c** exhibit significant differences. It is therefore clear that **86b** and **86c** are not related to the natural product. Because the specific rotation $[\alpha]_D^{20}$ of the natural plakortide E methyl ester ($[\alpha]_D^{20} = +75.1$, $c = 2.23$ in $CHCl_3$)[34] was found to be in positive value, the value of **86a** is negative ($[\alpha]_D^{20} = -86$, $c = 0.28$ in $CHCl_3$), indicating that this enantiomer can also be ruled out. It was found therefore that only the ^{1}H NMR spectrum and specific rotation ($[\alpha]_D^{20} = +87.1$, $c = 0.39$ in $CHCl_3$) of **86d** fit closely with those of the natural plakortide E methyl ester. These results confirm that **86d** possesses an identical structure to the natural plakortide E methyl ester.

2.8 Biomimetic synthesis of plakortone B and determination of the absolute configuration of plakortide E.

Over the past few years, the intramolecular Michael addition has become one of the most efficient and simple approaches to the synthesis of furanofuran bicyclic lactone skeleton, which has been widely applied to the total synthesis of natural products containing furanofuran bicyclic lactone skeleton. For example, Shing and coworkers[104] reported the total synthesis of (+)-goniofufurone through an intramolecular Michael addition reaction (Scheme 72). Thus, treatment of the butenolide **253** with a catalytic amount of DBU in THF provided the desired lactone **254** in 74% yield.

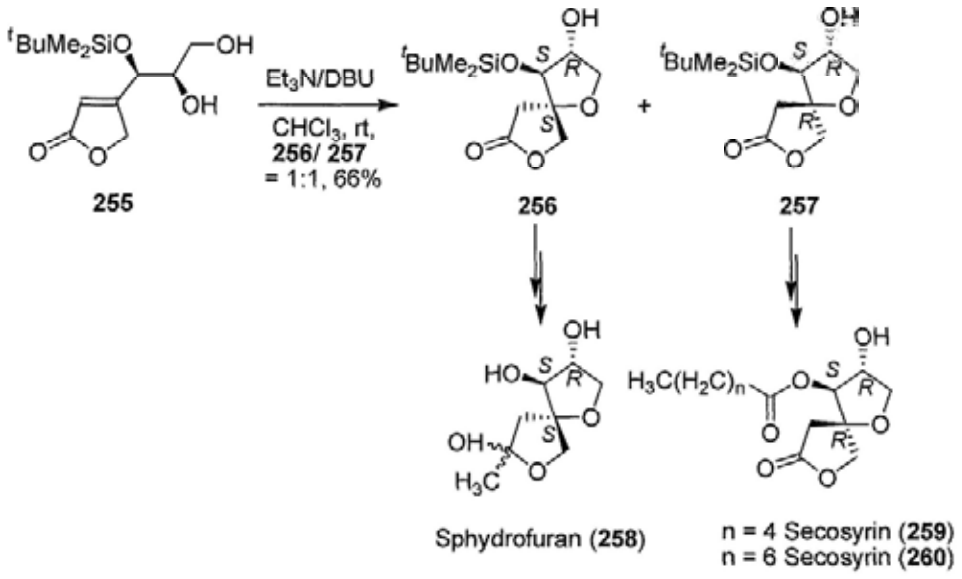
Scheme 72. Application of intramolecular Michael addition reaction in the total synthesis of (+)-goniofufurone



253 **254**

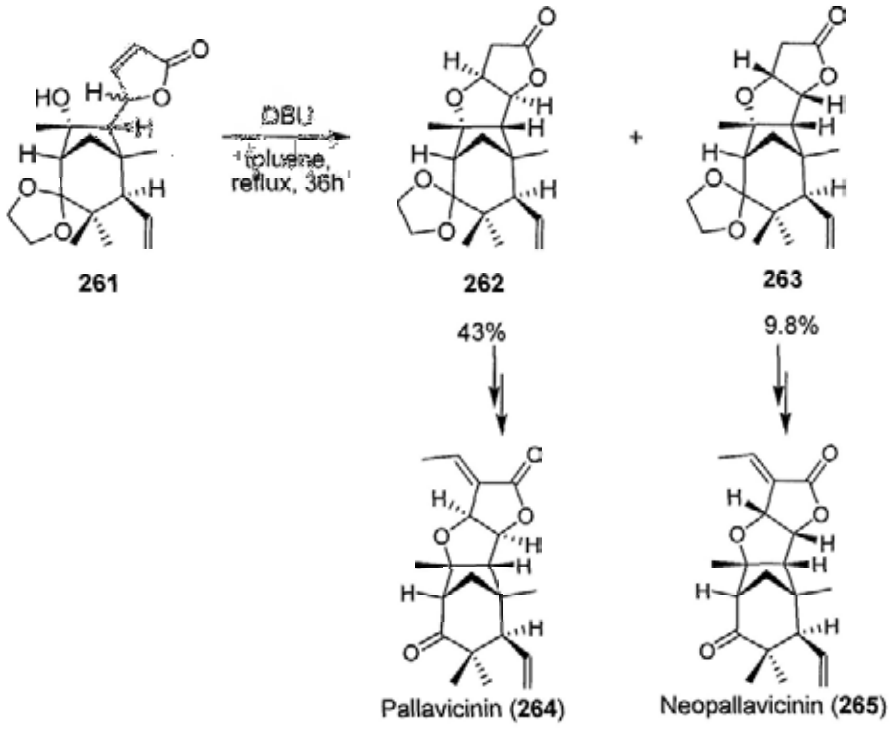
Our group has used intramolecular Michael addition to prepare the dioxaspiro framework in the syntheses of natural products, including the total synthesis of sphydrofuran and secosyrin (Scheme 73).[105]

Scheme 73. Application of intramolecular Michael addition in the total syntheses of sphydrofuran and secosyrins



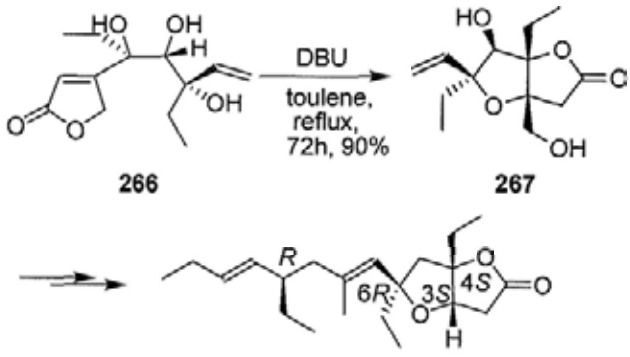
Peng also applied the same protocol to realize the total syntheses of natural products pallavicinin (**264**) and neopallavicinin (**265**) (Scheme 74). Treatment of the butenolide mixture **261** with DBU in toluene provided a 4:1 mixture of **262** and **263**.[106]

Scheme 74. Application of intramolecular Michael addition in the total syntheses of pallavicinin and neopallavicinin



Recently, our group has reported the total syntheses and configuration assignments of all four isomers of plakortone B. The synthesis of the furanofuran bicyclic lactone skeleton was achieved through a stereoselective intramolecular conjugate addition of an alcohol to an unsaturated lactone; the transformation is chemoselective for one alcohol in the triol substrate (Scheme 75).[35b]

Scheme 75. Application of intramolecular Michael addition in the total synthesis of plakortone B

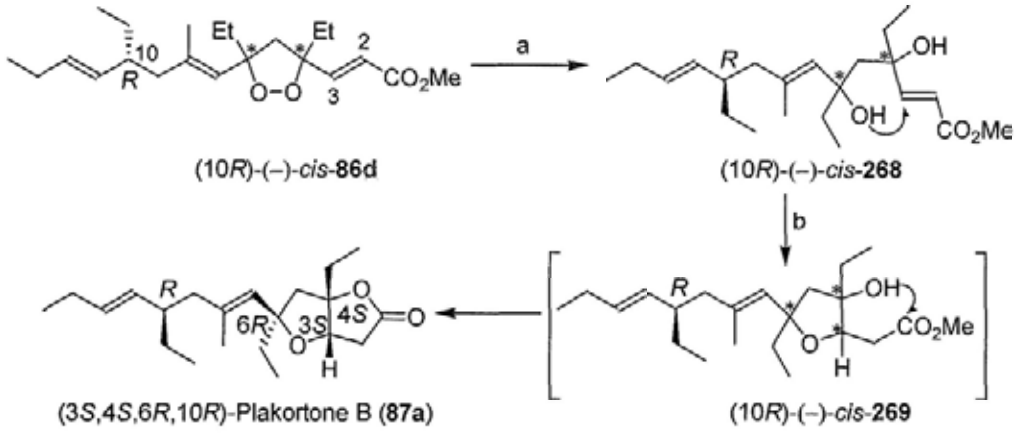


266 267

(3*S*,4*S*,6*R*,10*R*)-Plakortone B (**87**)

In consideration that plakortone B (**87a**) was isolated from the same marine sponge together with plakortide E (**85**),[34] we reasoned that plakortide E methyl ester **86d** could be converted to plakortone B (**87a**). In this way, the determination of the absolute configuration of plakortide E methyl ester (**86d**) would be achieved, and this conversion would also provide a concise biomimetic synthesis pathway to plakortone B (**87a**). To begin with, cleavage of the O-O bond of plakortide E methyl ester (**86d**) with zinc in acetic acid provided 1,3-diol **268** in an excellent yield.[107] With the 1,3-diol **268** in hand , our next objective was to convert it to the corresponding isomer of plakortone B. Encouraged by our recent success in the preparation of various tetrahydrofurofuranone frameworks towards the syntheses of naturally occurring molecules, an intramolecular Michael addition was employed to achieve this conversion. Thus, the 1,3-diol **268** was subjected to an intramolecular oxa-Michael addition/lactonization cascade reaction. To our delight, our target **87a** was afforded exclusively in 90% yield (Scheme 76).[106,108]

Scheme 76. Biomimetic synthesis of plakortone B



Reagents and conditions: (a) Zn (50 equiv), AcOH/CH_2Cl_2 (1:2), 0 °C to rt, 2 h, 99%; (b) DBU (0.2 equiv), toluene, reflux, overnight, 90%.

The other three possible isomers of plakortone B were prepared in a similar manner from the three corresponding isomers of plakortide E methyl ester, as can be seen in Scheme 77. A comparison of the NMR spectra and the specific rotations of the four synthetic isomers and the reported data of plakortone B (**87a**) and its isomers[35b] confirms the absolute configurations of **86a**, **86b**, **86c and 86d** to be (4*R*,6*S*,10*S*), (4*R*,6*S*,10*R*), (4*S*,6*R*,10*S*) and (4*S*,6*R*,10*R*). All absolute configurations of plakortide E methyl ester and its isomers are depicted in Figure 23.

Scheme 77. Syntheses of the other three isomers of plakortone B

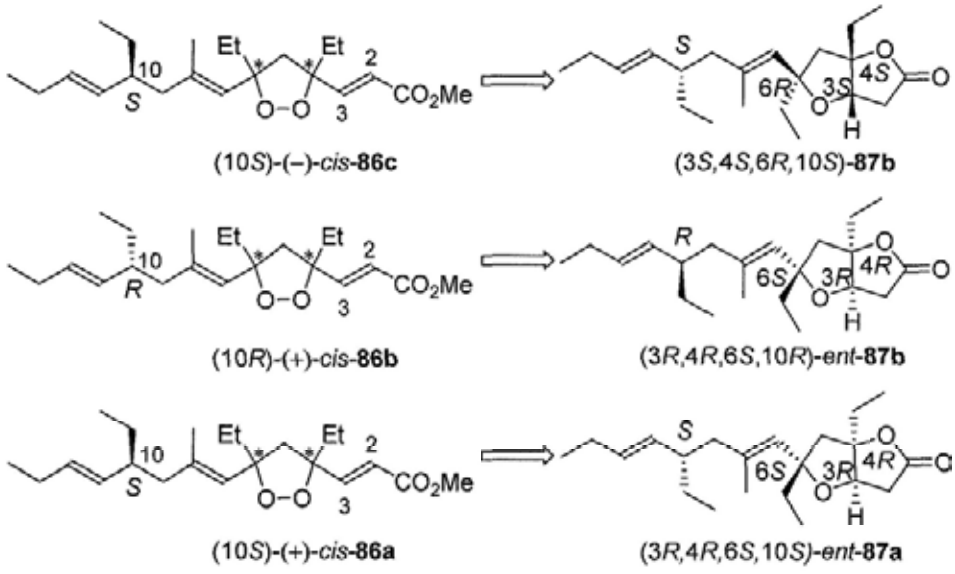
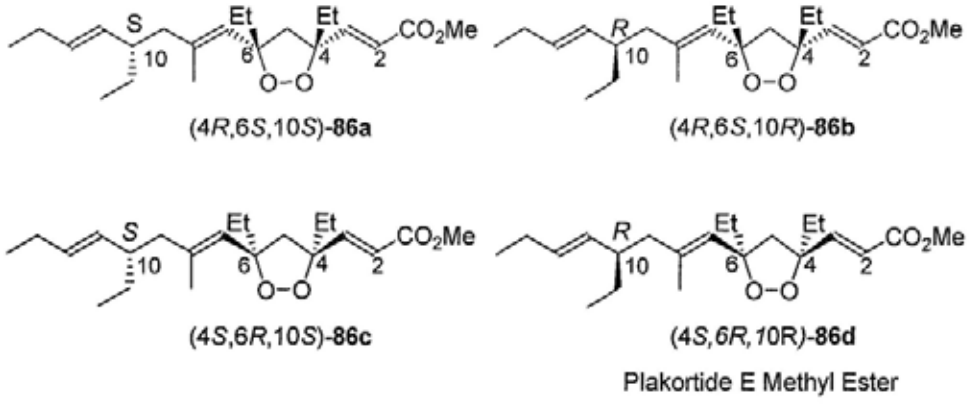


Figure 23. Absolute configurations of four isomers of plakortide E methyl ester

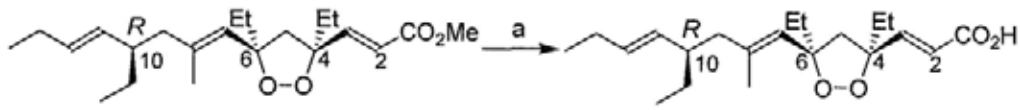


2.9 Synthesis of plakortide E

As depicted in Scheme 78, compound **86d** was then saponified to provide the plakortide E (**85a**). Comparisons of the chemical shifts and coupling constants for the synthetic compound and the literature values for plakortide E are summarized in Table 24. Our values are identical to those reported by Wright.[57] However, our results

and those of Patil[34] show some differences for the ^{13}C NMR chemical shifts of C-1, C-2 and C-3.

Scheme 78. Synthesis of plakortide E



(*4S,6R,10R*)-**86d** (*4S,6R,10R*)-**85a**

Reagents and conditions: (a) LiOH (5.0 equiv), THF/H_2O (4:1), 0 °C to rt, 24 h, 90%.

Table 24. Comparison of Selected NMR Shifts (*J* values) and Specific Rotations.

	H-2	H-3	H-5	C-1	C-2	C-3	C-5	$[\alpha]_D^{20}$
85a	6.09 (15.7)	6.93 (15.7)	2.43 (12.0) 2.53 (12.0)	171.1	119.6	152.1	56.0	66.6
Wright[57]	6.09 (15)	6.93 (15)	2.43 (12) 2.53 (12)	172.0	120.5	152.1	56.0	63
Patil[34]	5.98 (15.8)	6.69 (15.8)	2.43 (12) 2.53 (12)	173.0	123.9	146.9	55.8	63.9

Chapter 3
Conclusion

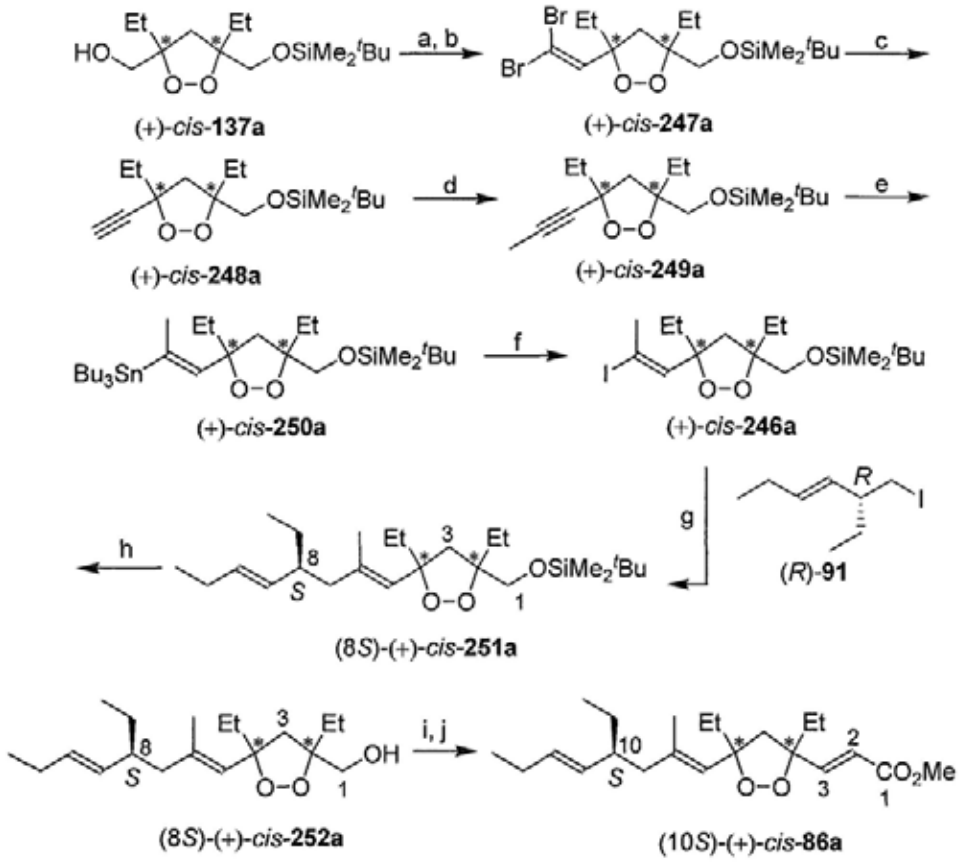
The key steps included the synthesis of enantiomerically pure dioxolane cores through lipase resolution of a racemic precursor, the introduction of an alkynyl sidechain on a 1,2-dioxolane via a Corey-Fuchs homologation, and the introduction of the sidechain of the natural product through Pd-catalyzed sp^2/sp^3 cross-coupling.

Synthesis of plakortide E methyl ester **86a** (one of the plakortide E candidate structures) was completed in ten steps from (+)-*cis*-**137a** (Scheme 79). The other three possible isomers of plakortide E methyl ester (**86b**, **86c** and **86d**) were synthesized in a similar manner. One of these molecules **86d** was identical to the natural plakortide E methyl ester on the basis of ^{1}H, ^{13}C NMR spectra and specific rotation comparisons.

With the plakortide E methyl ester **86d** and its other three isomers in hand, we successfully converted them into plakortone B (3*S*,4*S*,6*R*,10*R*)-(**87a**), and its isomers *ent*-**87a**, **87b** and *ent*-**87b** via an intramolecular oxa-Michael addition/lactonization cascade reaction. A comparison of the NMR spectra and the specific rotations of the four synthetic isomers (**87a**, *ent*-**87a**, **87b** and *ent*-**87b**) and the reported data of plakortone B and its isomers[35b] confirmed the absolute configurations of **86a**, **86b**, **86c and 86d** to be (4*R*,6*S*,10*S*), (4*R*,6*S*,10*R*), (4*S*,6*R*,10*S*) and (4*S*,6*R*,10*R*). The conversion not only provided a concise biomimetic synthesis pathway to plakortone B (**87a**), but also proved the hypothesis that plakortide E was the precursor of the plakortone B in nature.

Saponification converted 1,2-dioxolane **86d** into plakortide E (**85a**) whose absolute configuration (4*S*,6*R*,10*R*) was confirmed by comparison of spectral and physical data with those of reported.

Scheme 79. Synthesis of 86a



Reagents and conditions: (a) Dess-Martin periodinane (1.5 equiv), CH_2Cl_2; (b) $CHBr_2P^+Ph_3Br^-$ (2.5 equiv), *t*-BuOK (2.4 equiv), THF, rt, 79% (2 steps); (c) *n*-BuLi (2.2 equiv), THF, –78 °C, 0.5 h, 95%; (d) *n*-BuLi (1.2 equiv), MeOTf (1.5 equiv), THF, –78 °C, 1 h, 70%; (e) $Pd(PPh_3)_2Cl_2$ (10 mol%), *n*-Bu_3SnH (3.0 equiv), Hexane, 1 h, 84%; (f) I_2 (1.0 equiv), CH_2Cl_2, 0 °C, 86%; (g) $ZnBr_2$ (1.3 equiv), *t*-BuLi(2.0 equiv), Et_2O/THF, –78 °C to rt, then $Pd(PPh_3)_4$ (10 mol%), THF, 16h, 93%; (h) *p*-TsOH (10 mol%), CH_2Cl_2/MeOH (1:2), 89%; (i) Dess-Martin periodinane (1.5 equiv), CH_2Cl_2; (j) $(MeO)_2P(O)CH_2CO_2Me$ (10.0 equiv), NaH (10.0 equiv), THF, 0 °C, 80% (2 steps).

Chapter 4

Experimental Section

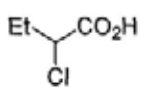
General Information

All non-aqueous reactions were carried out using oven-dried glassware under a positive pressure of dry nitrogen unless otherwise noted. All reagents and solvents were reagent grade. Further purifications and drying by standard methods were used when necessary. Except as indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light. In addition, compounds on TLC plate were visualized with a spray of 5% w/v dodecamolybdophosphoric acid in ethanol and with subsequent heating. Chromatographic purification of products (flash chromatography) was performed on E. Merck silica gel 60 (230-400 mesh). All evaporation of organic solvents was carried out with a rotary evaporator. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated.

NMR spectra were recorded on Bruker DRX300 spectrometer, Brucker Advanced III 400 spectrometer and Advanced Brucker 600 M spectrometer. Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (δ 7.26) or tetramethylsilane (δ 0.00) for ^{1}H and chloroform (δ 77.1) for ^{13}C. Data are reported as follows: brs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants in Hz. ^{1}H NMR measurements were carried out at room temperature in deuterated chloroform solution unless otherwise stated. Mass spectra (EIMS and HRMS (ESI)) were obtained with a HP 5989B spectrometer and determined

at an ionizing voltage of 70eV unless otherwise stated; relevant data were tabulated as *m/z*. HPLC analysis was performed on a Hewlett Packard Series 1050 HPLC, or Hewlett Packard Series 1100 HPLC, or Agilent 1100 HPLC with a diode array UV detector (λ = 214-258 nm), using Chiralpak AD-H (0.46 cm × 25 cm). Optical rotations were measured on a Perkin-Elmer model 241 polarimeter operating at the sodium D line with a 100 mm path length cell and at 20 °C, and were reported as follows: $[\alpha]_D^T$, concentration (g/100 mL), and solvent.

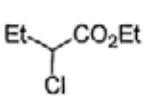
2-Chlorobutyric acid (115).[59,65a]



115

Sulfuryl chloride (366 mL, 4.5 mol) was added dropwise to a solution of butyric acid **114** (265 g, 3 mol) in dimethylformamide (5 mL) in a 3-necked round flask fitted with a condenser, drying tube and HCl gas convertor. The reaction mixture was heated to 80-85 °C and then the yellow solution was heated to 90-95 °C for 2 h. Colour change from yellow to colorless was observed. The resulting mixture was distilled carefully to yield 2-chlorobutyric acid (**115**) (106 g) in 29% yield. b.p.: 112 °C/25 torr (Lit: [65a] 123 °C/34 torr); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, J = 7.2 Hz, 3H), 1.93-2.17 (m, 2H), 4.28 (t, J = 6 Hz, 1H), 10.77 (s, 1H) ppm; MS (ESI): *m/z* $(M)^+$ 122.

Ethyl 2-chlorobutyrate (111).[59,65c]

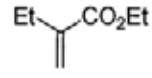


111

Concentrated sulfuric acid (9 mL) was added to a solution of 2-chlorobutyric acid (**115**)

(76.1 g, 0.62 mol) in ethanol (95%, 110 mL) and benzene (40 mL) in a 3-necked round flask fitted with condenser, thermometer. The reaction mixture was heated to reflux for 14 h (monitored by TLC) and the solvent was removed *in vacuo*. The residue was washed with water (70 mL x 2) and the *p*H of solution was adjusted to *p*H 5-6 using saturated sodium hydrogen carbonate. The solution was extracted with Et_2O (70 mL x 2) and the combined layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield **111** (65.0 g) as a colorless oil in 70% yield. b.p.: 85 °C/35 torr (Lit:[65c] 64 °C/20 torr); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, J = 7.5 Hz, 3H), 1.27 (t, J = 7.5 Hz, 3H), 1.92-2.10 (m, 2H), 4.16-4.26 (m, 3H) ppm; MS (ESI): *m/z* $(M+H)^+$ 151.

Ethyl 2-ethylacrylate (112).[59,64]



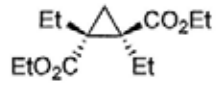
112

Diethyl 2-ethylmalonate (35 g, 186 mmol, 1 equiv) in anhydrous ethanol (50 mL) was added to potassium hydroxide (10.5 g, 186 mmol, 1 equiv) in anhydrous ethanol (100 mL) at 0 °C. The reaction mixture was stirred for 10 h. White precipitate was formed and solvent was removed. Water (10 mL) was added to dissolve the white solid and the solution was acidified to *p*H 3-4 using hydrochloric acid (10%). The solution was extracted with Et_2O (70 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was concentrated *in vacuo* to yield a colorless oil.

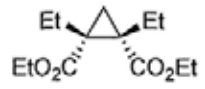
Pyridine (40 mL) was added to the crude, $(HCHO)_n$ (5.58 g, 186 mmol, 1 equiv) and piperidine (1.8 mL) were added to the solution. The reaction mixture was heated to reflux for 1 h and then cooled to room temperature. The mixture was poured into water (100 mL), and washed with *n*-pentane (70 mL x 3). The combined layers were washed

with hydrochloric acid (10%, 100 mL), water (100 mL), sodium hydrogen carbonate (5%, 100 mL), then dried over Na_2SO_4, filtered and concentrated *in vacuo*. It was purified by using distillation at 68 °C *in vacuo* to yield a colorless oil (16.7 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.04 (t, J = 7.5 Hz , 3H), 1.26 (t, , J = 7.3 Hz , 3H), 2.30 (q, J = 7.5 Hz , 2H), 4.17 (q, J = 7.5 Hz , 2H), 5.47 (s, 1H), 6.09 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 12.7, 14.2, 24.8, 60.5, 123.2, 142.5, 167.3 ppm; MS (ESI): *m/z* $(M+Na)^+$ 151.

Diethyl *cis*-1,2-diethylcyclopropane-1,2-dicarboxylate (*cis*-**113**) and **Diethyl *trans*-1,2-diethylcyclopropane-1,2-dicarboxylate** (*trans*-**113**).[59,109]



trans-**113**



cis-**113**

NaH (60%, 5.6 g, 140.4 mmol, 1.5 equiv) in DMF (25 mL) was cooled in an ice-bath. A solution of α-ethylacrylate **112** (12.0 g, 93.6 mmol) and α-chlorobutyrate **111** (11.1 g, 93.6 mmol) in DMF (50 mL) were added dropwise to the solution with temperature below 30 °C (gas released). The reaction mixture was stirred at room temperature for 17 h (monitored by TLC). MeOH (15 mL) was added to quench the excess NaH, then washed with water (100 mL). The mixture was extracted with Et_2O (70 mL x 3) and the combined layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was subjected to purification using column chromatography on silica gel (800 g) eluting with hexanes/EtOAc (20:1) to yield *trans*-**113** (14.3 g, 63%), and *cis*-**113** (5.7 g, 25%). *trans*-**113** R_f = 0.6 (hexanes/EtOAc, 20:1); *cis*-**113** R_f = 0.4 (hexanes/EtOAc, 20:1); *cis*-**113**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.65 (d, 1H, J = 4.5 Hz), 1.01 (t, J = 7.5 Hz, 6H), 1.24 (t, J = 7.5 Hz, 6H), 1.43-1.50 (m, 2H), 1.86 (d, J = 4.5 Hz, 1H), 1.94-2.02 (m, 2H), 4.10 (q, J = 7.5 Hz, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8, 14.2, 23.0,

23.9, 38.1, 60.8, 172.1 ppm; MS (ESI): *m/z* $(M+Na)^+$ 265.

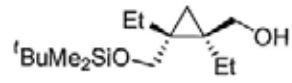
trans-**113:** ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.5 Hz, 6H), 1.10-1.15 (m, 2H), 1.24 (t, *J* = 7.5 Hz, 6H), 1.28 (s, 2H), 1.98-2.06 (m, 2H), 4.08-4.20 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.6, 14.3, 20.1, 23.6, 38.0, 60.9, 171.6 ppm; IR (Film): 2974, 2939, 2880, 1729, 1458, 1382, 1309, 1234, 1182, 1139, 1031 cm^{-1}; MS (ESI): *m/z* $(M+Na)^+$ 265.

***trans*-1,2-Diethyl-1,2-bis (hydroxymethyl) cyclopropane (118).**[59,110]

118

Compound *trans*-**113** (10 g, 41.3 mmol) in Et_2O (50 mL) was added dropwise to a solution of $LiAlH_4$ (3.4 g, 90.8 mmol, 2.2 equiv) in Et_2O (50 mL) at 0 °C and the reaction mixture was heated to reflux for 17 h (monitored by TLC). NaOH (5%, 20 mL) was added to the reaction mixture to quench the excess $LiAlH_4$, then filtered and extracted with Et_2O (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was subjected to purification using column chromatography on silica gel (250 g) eluting with hexanes/EtOAc (1:2) to yield a colorless oil (6.1 g, 93%). R_f = 0.3 (hexanes/EtOAc, 1:2); ^1H NMR (400 MHz, $CDCl_3$) *δ* = 0.19 (s, 2H), 0.93 (t, *J* = 7.4 Hz , 6H), 1.25-1.34 (m, 2H), 1.82-1.91 (m, 2H), 3.28 (d, *J* = 11.3 Hz, 2H), 3.69 (s, 2H), 3.79 (d, *J* = 11.4 Hz , 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* = 11.2, 19.2, 21.9, 32.9, 63.4 ppm; MS (ESI): *m/z* $(M+Na)^+$ 181.

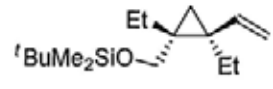
***trans*-1,2-Diethyl-2-(hydroxymethyl)-[(*tert*-butyl-dimethylsiloxy)methyl]-cyclopropane (119).**[59,110]



119

Et_3N (11.0 g, 15.1 mL, 108.4 mmol, 2.2 equiv) was added to a solution of **118** (7.8 g, 49.3 mmol) in CH_2Cl_2 (60 mL) at 0 °C and stirred for 10 min. *t*-$BuMe_2SiCl$ (8.2 g, 54.2 mmol, 1.1 equiv) in CH_2Cl_2 (20 mL) was then added dropwise to the solution at 0 °C and stirred for 4 h (monitored by TLC). White precipitate was formed. The reaction mixture was washed with water (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was subjected to purification using column chromatography on silica gel (400 g) eluting with hexanes : ethyl acetate (5 : 1) to yield a colorless oil **119** (10.73 g) in 80% yield. R_f = 0.3 (hexanes/EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.02 (s, 3H), 0.03 (s, 3H), 0.28 (q, J = 4.8 Hz , 2H), 0.88 (s, 9H), 0.92 (t, J = 7.5 Hz, 3H), 0.98 (t, J = 7.5 Hz, 3H), 1.24 (s, 1H), 1.41-1.70 (m, 4H), 3.40 (d, J = 10.7 Hz, 1H), 3.54 (d, J = 11.5 Hz, 1H), 3.65 (d, J = 11.6 Hz, 1H), 3.70 (d, J = 10.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = −5.4, −5.4, 11.3, 11.4, 18.3, 20.3, 22.9, 23.1, 26.0, 32.7, 32.9, 64.1, 64.9 ppm; MS (ESI): *m/z* $(M+Na)^+$ 295.

***trans*-1,2-Diethyl-1-(*tert*-butyldimethylsiloxymethyl)-2-vinylcyclopropane (121).**[59]



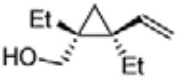
121

DMSO (7.2 g, 6.6 mL, 91.7 mmol, 2.5 equiv) in CH_2Cl_2 (20 mL) was added carefully to a solution of $(COCl)_2$ (5.6 g, 3.8 mL, 44.0 mmol, 1.2 equiv) in CH_2Cl_2 (60 mL) at −78 °C and stirred for 15 min. **119** (10 g, 36.7 mmol) in CH_2Cl_2 (20 mL) was added to the mixture and followed by Et_3N (19.3 g, 26.6 mL, 190.8 mmol, 5.2 equiv). The reaction mixture was allowed to stir at room temperature for 20 min. Water (50 mL) was added to

the mixture and stirred for a further 30 min. The mixture was extracted with CH_2Cl_2 (70 mL x 3) and the combined layers were washed with hydrochloric acid (10%, 70 mL) sodium hydrogen carbonate solution (10%, 70 mL) and saturated brine solution (70 mL), then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was used directly for the next step.

n-BuLi (1.6 M, 35 mL, 30.3 mmol, 1.3 equiv) was added to a solution of PPh_3CH_3I (19.3 g, 47.7 mmol, 1.3 equiv) in THF (100 mL) at −78 °C. The solution was stirred at room temperature until no solid left and then re-cooled to −78 °C. The crude material in THF (10 mL) was added dropwise to the solution and left stirring at room temperature for overnight. saturated aq. NH_4Cl (70 mL) was added to the reaction mixture and extracted with Et_2O (70 mL x 3). The combined layers were washed with water (100 mL), saturated brine solution (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield a yellow solid. The crude material was subjected to purification using column chromatography on silica gel (250 g) eluting with hexane to yield a colorless oil **121** (5.9 g) in 60% yield (two steps); R_f = 0.3 (hexanes/EtOAc, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.04 (s, 3H), 0.05 (s, 3H), 0.34 (d, J = 4.2 Hz , 1H), 0.57 (d, J = 4.7 Hz , 1H), 0.87 (t, J = 7.5 Hz, 3H), 0.90 (s, 9H), 0.92 (t, J = 7.5 Hz, 3H), 1.39-1.49 (m, 3H), 1.57-1.62 (m, 1H), 3.56 (d, J = 10.7 Hz, 1H), 3.70 (d, J = 10.7 Hz, 1H), 4.95 (d, J = 17.2 Hz, 1H), 5.07 (d, J =10.5 Hz, 1H), 5.86 (dd, J =10.5, 17.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = −5.3, −5.4, 11.2, 11.7, 18.4, 20.6, 23.8, 25.7, 26.0, 33.3, 34.4, 64.2, 114.6, 140.8 ppm; MS (EI): *m/z* $(M)^+$ 268.

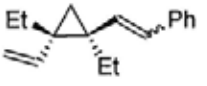
***trans*-1,2-Diethyl-2-vinylcyclopropyl)methanol (122).**[59]



122

p-TsOH (242.5 mg, 1.42 mmol, 10 mol%) was added to a solution of **121** (3.8 g, 14.2 mmol) in CH_2Cl_2/ MeOH (1 : 2, 80 mL) at 0 °C with stirring. The reaction mixture was stirred at room temperature for 4 h (monitored by TLC). The mixture was then extracted with CH_2Cl_2 (40 mL x 3). The combined layers were washed with $NaHCO_3$ solution (5%, 40 mL), saturated brine solution (40 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo* to the crude. The crude material was subjected to purification using column chromatography on silica gel (100 g) eluting with hexane/EtOAc (5:1) to yield a colorless oil (2.0 g, 90%); R_f = 0.3 (hexanes/EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.34 (d, J = 4.8 Hz , 1H), 0.63 (d, J = 4.8 Hz , 1H), 0.90 (t, J = 7.4 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H), 1.37-1.52 (m, 4H), 1.60-1.68 (m, 1H), 3.64 (d, J = 12.5 Hz, 1H), 3.72 (d, J = 12.5 Hz, 1H), 4.97 (d, J = 17.2 Hz, 1H), 5.10 (d, J =10.5 Hz, 1H), 5.83 (dd, J = 10.5, 17.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.2, 11.7, 20.7, 23.4, 25.7, 33.7, 34.7, 64.4, 115.3, 139.9 ppm; MS (ESI): *m/z* $(M+Na)^+$ 177.

1-(2-(*trans*-1,2-Diethyl-2-vinylcyclopropyl)vinyl)benzene (92a).[35a,59]

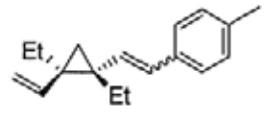


92a

A solution of DMSO (0.13 mL, 1.85 mmol) in CH_2Cl_2 (2 mL) was added to a solution of $(COCl)_2$ (0.07 mL, 0.74 mmol) in CH_2Cl_2 (2 mL) at −78 °C over 30 min, followed by a solution of *trans*-**122** (114 mg, 0.74 mmol) in CH_2Cl_2 (2 mL). The resulting mixture was stirred at the same temperature for 30 min, and then Et_3N (0.5 mL, 3.7 mmol) was added. After another 20 min, water (10 mL) and CH_2Cl_2 (10 mL) were added, and the whole was

partitioned. The aqueous layer was extracted with CH_2Cl_2 (20 mL×3). The combined organic layers were successively washed with 1% HCl (30 mL), H_2O (30 mL), saturated aq. $NaHCO_3$ (30 mL), and brine (30 mL), and dried over Na_2SO_4. After removal of the solvents, the crude product was used without purification in the next step. $BnPPh_3Br$ (415.6 mg, 1.0 mmol, 1.3 equiv) was suspended in anhydrous THF (5 mL) under nitrogen. *n*-BuLi (1.6 M in hexane, 0.63 mL, 1.00 mmol) was added into the reaction flask dropwise at −78 °C. After warming to room temperature, the resulting ylide mixture was allowed to stir for 30 min and then cooled to 0 °C again. A solution of the crude aldehyde in THF (2 mL) was added dropwise into the cooled reaction mixture, and was then allowed to warm slowly to room temperature. After 20 h, saturated aq. NH_4Cl (10 mL) was added to the mixture followed by Et_2O (30 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (30 mL×2). The combined organic layers were dried over Na_2SO_4., filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (8 g) eluting with hexane to afford **92a** as a colorless oil (117.1 mg, 70% in 2 steps): R_f = 0.85 (Hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.41 (d, J = 4.5 Hz, 1H), 0.87 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H), 1.34-2.04 (m, 4H), 1.87 (d, J = 4.5 Hz, 1H), 4.93-5.22 (d, J = 17.1 Hz, 2H), 5.23-5.37 (m, 1H), 5.75-6.05 (m, 1H), 6.22-6.75 (m, 1H), 7.09-7.50 (m, 5H) ppm; IR (Film): 3082, 3026, 2961, 2854, 1640, 1601, 1495, 1463, 1378, 1164, 959, 694 cm^{-1}; MS (EI): *m/z* 226 [M$^+$];

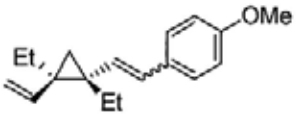
1-(2-(*trans*-1,2-Diethyl-2-vinylcyclopropyl)vinyl)-4-methylbenzene (92b).[59]



92b

Compound **92b** was prepared by a similar procedure as **92a** : yield = 70% (2 steps); (*E*/*Z* = 7/3); R_f = 0.85 (Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.44 (d, *J* = 4.7 HZ, 0.3 H), 0.79-0.96 (m, 7.7H), 1.25-1.65 (m, 4H), 2.34 (s, 2.1 H), 2.35 (s, 0.9 H), 4.99 (dd, 1H, *J* = 1.1, 11.9 Hz), 5.16 (m, 1H), 5.74 (d, *J* = 11.9 Hz, 0.3H), 5.86-5.96 (m, 1H), 6.26-6.45 (m, 1.7H), 7.12 (d, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 1.4H), 7.33 (d, *J* = 7.8 Hz, 0.6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.6, 11.7, 11.8, 12.4, 21.2, 21.2, 24.8, 26.4, 26.5, 26.7, 27.2, 32.9, 35.6, 36.6, 36.6, 115.3, 115.4, 125.9, 128.7, 129.1, 129.3, 130.5, 131.3, 131.5, 132.5, 134.3, 135.1, 136.5, 136.7, 139.7, 139.9 ppm; MS (EI): *m/z* 240 [M^+]; HRMS (EI) *m/z* [$M]^+$ calcd for $C_{18}H_{24}$: 240.1873, found: 240.1884.

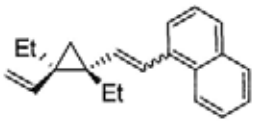
1-(2-(*trans*-1,2-Diethyl-2-vinylcyclopropyl)vinyl)-4-methoxybenzene (92c).



92c

Compound **92c** was prepared by a similar procedure as **92a** : yield = 64% (2 steps); R_f = 0.60 (Hexanes/EtOAc, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.43 (d, *J* = 4.8 HZ, 1H), 0.84 (t, *J* = 7.3 Hz, 3H), 0.87 (d, *J* = 4.7 HZ, 1H), 0.94 (t, *J* = 7.4 Hz, 3H), 1.48-1.68 (m, 4H), 3.81 (s, 3H), 4.99 (dd, 1H, *J* = 1.8, 17.2 Hz), 5.16 (dd, 1H, *J* = 1.7, 10.5 Hz), 5.67 (d, *J* = 11.9 Hz, 1H), 5.86 (dd, *J* = 10.5, 17.2 Hz, 1H), 6.38 (d, *J* = 12.0 Hz, 1H), 6.84 (d, *J* = 6.8 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.6, 12.3, 24.8, 26.5, 27.2, 32.8, 36.6, 55.3, 113.4, 115.3, 130.0, 130.4, 131.0, 131.3, 139.7, 158.5 ppm; MS (FAB): *m/z* 256 [M^+]; HRMS (FAB) *m/z* [$M]^+$ calcd for $C_{18}H_{24}O$: 256.1822, found: 256.1811.

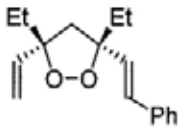
1-(2-(*trans*-1,2-Diethyl-2-vinylcyclopropyl)vinyl)naphthalene (92d).



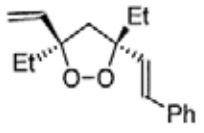
92d

Compound **92d** was prepared by a similar procedure as **92a** (the *E*/*Z* ratio is about 5/2): yield = 59% (2 steps); R_f = 0.85 (Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.11 (d, *J* = 5.1 HZ, 0.4 H), 0.60 (d, *J* = 5.0 HZ, 0.4 H),0.79-0.96 (m, 7.7H), 0.80 (t, *J* = 7.3 Hz, 1.2H), 0.86-0.96 (m, 8H), 1.4-1.67 (m, 5.6H), 4.90 (dd, *J* = 1.8, 17 Hz, 0.4H), 5.04-5.10 (m, 1.4H), 5.17 (dd, *J* = 1.6, 10.5 Hz, 1H), 5.84 (dd, *J* = 10.4, 17.2 Hz, 0.4H), 5.96 (dd, *J* = 10.5, 17.2 Hz, 1H), 6.05 (d, *J* = 11.8 Hz, 0.4H), 6.33 (d, *J* = 15.6 Hz, 1H), 7.03 (d, *J* = 11.8 Hz, 0.4H), 7.10 (d, *J* = 15.7 Hz, 1H), 7.40-7.56 (m, 5.6H), 7.75 (d, *J* = 8.1 Hz, 1.4H), 7.84 (d, *J* = 7.4 Hz, 1.4H), 8.0 (d, *J* = 8.0 Hz, 0.4H), 8.11 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.6, 11.7, 11.8, 12.2, 21.6, 23.9, 26.5, 26.6, 26.8, 28.0, 31.9, 33.1, 35.9, 36.1, 36.6, 115.2, 115.4, 123.4, 124.0, 124.7, 125.1, 125.6, 125.6, 125.7, 125.8, 126.5, 127.1, 127.3, 127.9, 128.4, 128.5, 129.3, 131.1, 131.5, 133.4, 133.6, 134.7, 134.8, 135.8, 139.5, 139.7 ppm; MS (ESI): *m/z* 277 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{25}$: 277.1951, found: 277.1957.

(*E*)-*cis*-3,5-Diethyl-3-styryl-5-vinyl-1,2-dioxolane (*cis*-**124a**) and **(*E*)-*trans*-3,5-Diethyl-3-styryl-5-vinyl-1,2-dioxolane** (*trans*-**124a**).[59]



cis-**124a**



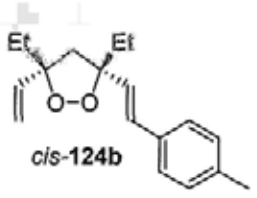
trans-**124a**

Feldman procedure. To a stirring solution of the vinylcyclopropane **92a** (226 mg, 1 mmol) in CH_3CN (10 mL) at room temperature was added diphenyl diselenide (32 mg, 0.1 mmol) and AIBN (13 mg, 0.08 mmol). The reaction was placed under a balloon of

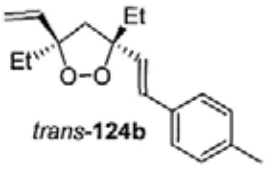
oxygen and irradiated with a 300 W sunlamp. When starting material was consumed as shown by TLC, the reaction mixture was concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel (8 g, hexane/EtOAc, 10/1) to afford **124** (*cis*/*trans* = 1:3.1) as a colorless oil (185.8 mg, 72%); R_f = 0.50 (hexanes/EtOAc, 20:1);

Pd-catalyzed procedure. To a 25-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar was added **92a** (57 mg, 0.25 mmol), urea peroxide (35%, 73 mg, 0.75 mmol, 3.0 equiv) and Pd $(PPh_3)_4$ (57 mg, 20 mol%). The flask was placed under an argon atmosphere, and MeCN (2 mL) was added via syringe. The resulting mixture was stirred at room temperature for 24 hours. The reaction mixture concentrated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (8 g, hexanes/EtOAc, 20:1) to give the pure product in which the *cis*/*trans* ratio is about 1/1.5 as a colorless oil (37 mg, 57%); R_f = 0.50 (hexanes/EtOAc, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.86-0.98 (m, 15 H), 1.67-1.83 (m, 10H), 2.38 (d, J = 12.1 Hz, 1H), 2.52 (s, 3H), 2.64 (d, J = 12.0 Hz, 1H), 5.16 (dd, J = 1.0, 11.0 Hz, 1H), 5.20 (dd, J = 1.0, 10.9 Hz, 1.5H), 5.25 (dd, J = 1.0, 17.6 Hz, 1H), 5.31 (dd, J = 1.0, 17.5 Hz, 1.5H), 5.82-5.94 (m, 2.5H), 6.21 (t, J = 16.5 Hz, 2.5H), 6.62 (t, J = 16.3 Hz, 2.5H), 7.23-7.25 (m, 2.5H), 7.28-7.41 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 8.7, 8.9, 30.5, 30.9, 31.0, 31.5, 53.3, 53.9, 88.4, 88.5, 88.5, 88.6, 114.1, 114.8, 126.4, 127.5, 128.5, 128.9, 129.6, 130.8, 131.8, 136.7, 139.4, 140.2 ppm; MS (EI): *m/z* 258 $[M]^+$; HRMS (EI) *m/z* $[M]^+$ calcd for $C_{17}H_{22}O_2$: 258.1614, found: 258.1613.

(*E*)-3-(4-Methystyryl)-*cis*-3,5-diethyl-5-vinyl-1,2-dioxolane (*cis*-**124b**) and **(*E*)-3-(4-Methystyryl)-*trans*-3,5-diethyl-5-vinyl-1,2-dioxolane** (*trans*-**124b**).[59]



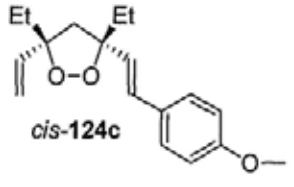
cis-**124b**



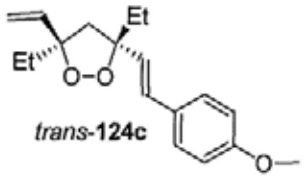
trans-**124b**

Compound **124b** was prepared by a similar procedure as **124a**; Feldman procedure: yield = 75%, (*cis*/*trans* = 1:4); Pd-catalyzed procedure: yield = 70% (*cis*/*trans* = 1:1.4); R_f = 0.50 (hexanes/EtOAc, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.86-0.97 (m, 14.4H), 1.69-1.84 (m, 9.6H), 2.33 (s, 3H), 2.34 (s, 4.2H), 2.37 (d, J = 12.0 Hz, 1H), 2.52 (s, 2.8H), 2.65 (d, J = 12.0 Hz, 1H), 5.16 (dd, J = 1.1, 11.0 Hz, 1H), 5.19 (dd, J = 1.1, 10.9 Hz, 1.4H), 5.26 (dd, J = 1.1, 17.6 Hz, 1H), 5.30 (dd, J = 1.1, 17.5 Hz, 1.4H), 5.86-5.93 (m, 2.4H), 6.16 (t, J = 16.4 Hz, 2.4H), 6.57 (t, J = 17.0 Hz, 2.4H), 7.11-7.14 (m, 4.8H), 7.28-7.31 (m, 4.8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 8.9, 9.0, 9.0, 21.2, 30.7, 31.1, 31.2, 31.6, 53.4, 54.0, 88.6, 88.7, 88.7, 88.7, 114.2, 114.9, 126.4, 126.4, 128.9, 129.3, 129.3, 129.7, 129.9, 130.9, 134.1, 137.5, 139.7, 140.4 ppm; MS(ESI): *m/z* 290 $[M+NH_4]^+$; HRMS (ESI) *m/z* $[M+ NH_4]^+$ calcd for $C_{18}H_{28}NO_2$: 290.2115, found: 290.2113.

(*E*)-3-(4-Methoxystyryl)-*cis*-3,5-diethyl-5-vinyl-1,2-dioxolane (*cis*-**124c**) and **(*E*)-3-(4-Methoxystyryl)-*trans*-3,5-diethyl-5-vinyl-1,2-dioxolane** (*trans*-**124c**)



cis-**124c**

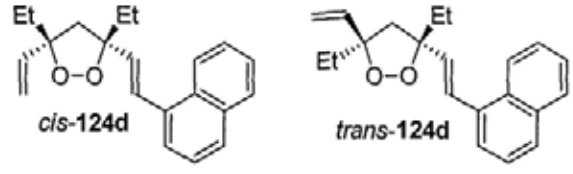


trans-**124c**

Compound **124c** was prepared by a similar procedure as **124a**; Feldman procedure: yield = 84%, (*cis*/*trans* = 1:2.6); Pd-catalyzed procedure: yield = 40% (*cis*/*trans* = 1:1.6); R_f = 0.50 (hexanes/EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.86-0.97 (m, 16.2H), 1.67-1.84 (m, 10.8H), 2.37 (d, J = 12.0 Hz, 1H), 2.51 (s, 3.4H), 2.64 (d, J = 12.0 Hz, 1H),

3.80 (s, 3H), 3.81 (s, 5.1H), 5.16 (dd, J = 1.0, 11.0 Hz, 1H), 5.19 (dd, J = 1.0, 11.0 Hz, 1.7H), 5.28 (dt, J = 1.0, 17.6 Hz, 2.7H), 5.82-5.93 (m, 2.7H), 6.07 (t, J = 16.8 Hz, 2.7H), 6.54 (t, J = 16.6 Hz, 2.7H), 6.84-6.88 (m, 5.4H), 7.30-7.35 (m, 5.4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 8.9, 9.0, 30.7, 31.0, 31.2, 31.6, 53.4, 53.9, 55.4, 88.6, 88.6, 88.7, 88.7, 114.0, 114.0, 114.2, 114.9, 127.7,128.5, 128.6, 129.3,129.6, 139.7, 140.3, 159.3 ppm; IR (Neat): 2964, 2934, 1607, 1511, 1251, 1175, 1036, 839 cm^{-1}; MS (FAB): *m/z* 288 [M]$^+$; HRMS (EI) *m/z* [M]$^+$ calcd for $C_{18}H_{24}O_3$: 288.1720, found: 288.1716.

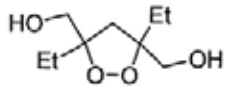
(*E*)-*cis*-3,5-Diethyl-3-(2-(naphthalen-1-yl)vinyl)-5-vinyl-1,2-dioxolane (*cis*-**124d**) and **(*E*)-*trans*-3,5-Diethyl-3-(2-(naphthalen-1-yl)vinyl)-5-vinyl-1,2-dioxolane** (*trans*-**124d**)



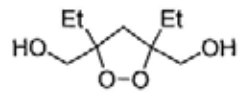
cis-**124d** *trans*-**124d**

Compound **124d** was prepared by a similar procedure as **124a**; Feldman procedure: yield = 62%, (*cis*/*trans* = 1:2.5); Pd-catalyzed procedure: yield = 67% (*cis*/*trans* = 1:1.8); R_f = 0.50 (hexanes/EtOAc, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.91-1.06 (m, 16.8H), 1.73-1.91 (m, 11.2H), 2.44 (d, J = 12.1 Hz, 1H), 2.61 (s, 3.6H), 2.75 (d, J = 12.0 Hz, 1H), 5.20 (dd, J = 1.1, 10.8 Hz, 1H), 5.23 (dd, J = 1.1, 10.9 Hz, 1.8H), 5.31 (dd, J = 1.0, 18 Hz, 1H), 5.36 (dd, J = 1.0, 17.4 Hz, 1.8H), 5.89-5.98 (m, 2.8 Hz), 5.18 (d, J = 16 Hz, 1H), 6.22 (d, J = 16 Hz, 1.8H), 7.36-7.60 (m, 14H), 7.79 (dd, J = 3.8, 8.2 Hz, 2.8H), 7.85 (dd, J = 2.6, 7.4 Hz, 2.8H), 8.09 (d, J = 7.4 Hz, 1H), 8.13 (d, J = 7.9 Hz, 1.8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 8.9, 9.1, 30.7, 31.2, 31.7, 53.5, 54.2, 88.6, 88.7, 88.8, 88.8, 114.2, 115.0, 123.7, 124.0, 124.0, 125.6, 125.8, 126.1, 126.1, 126.5, 127.3, 127.9, 128.5, 131.4, 133.6. 134.3, 135.0, 135.1, 139.6, 140.5 ppm; MS (ESI): *m/z* 326 [M+NH_4]$^+$; HRMS (ESI) *m/z* [M+NH_4]$^+$ calcd for $C_{21}H_{28}NO_2$: 326.2115, found: 326.2120.

(*trans*-3,5-Diethyl-1,2-dioxolane-3,5-diyl)dimethanol (*trans*-**134**) and **(*cis*-3,5-Diethyl-1,2-dioxolane-3,5-diyl)dimethanol** (*cis*-**135**).[59]



trans-**134**



cis-**135**

To a –78 °C solution of **92a** (440 mg, 1.6 mmol) in CH_2Cl_2 (14 mL)/ MeOH (2 mL) was bubbled O_3. After the mixture turned light blue and TLC analysis displayed little or no starting material, ozonolysis was stopped and the ozone was removed by passage of O_2 or N_2 through the solution. $NaBH_4$ (91 mg, 2.4 mmol) was added to the reaction mixture at the same temperature and the reaction was slowly (5 h) warm to room temperature. The reaction was diluted with water (2 mL) and the mixture extracted with EtOAc (15 mL × 2). The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (10 g, hexanes/EtOAc, 2:1–1:1) to afford firstly *trans*-**134** (178 mg, 55%), followed by *cis*-**135** (113 mg, 35%); *trans*-**134**: R_f = 0.25 (hexanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.93 (t, J = 7.6 Hz, 6H), 1.51-1.60 (m, 2H), 1.74-1.83 (m, 2H), 2.05 (s, 2H), 2.25 (brs, 2H), 3.43 (d, J = 11.8 Hz, 2H), 3.72 (d, J = 11.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.2, 25.0, 44.7, 64.5, 89.5 ppm; MS (ESI): *m/z* 208 $[M+NH_4]^+$; HRMS (ESI) *m/z* $[M+NH_4]^+$ calcd for $C_9H_{22}NO_4$: 208.1543, found: 208.1540.

cis-**135**: R_f = 0.22 (hexanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.94 (t, J = 7.6 Hz, 6H), 1.58-1.67 (m, 2H), 1.74-1.83 (m, 2H), 2.14 (d, J = 12.4 Hz, 1H), 2.46 (d, J = 12.4 Hz, 1H), 2.60 (s, 2H), 3.63 (q, J = 12.2 Hz, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 8.7, 27.4, 44.2, 63.9, 89.5 ppm; MS (ESI): *m/z* 213 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_9H_{18}O_4Na$: 213.1097, found: 213.1093.

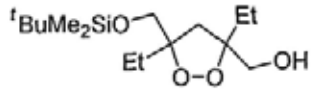
(5-((*tert*-Butyldimethylsilyloxy)methyl)-*cis*-3,5-diethyl-1,2-dioxolan-3-yl)methanol (*cis*-**137**) and **3,5-bis((*tert*-Butyldimethylsilyloxy)methyl)-*cis*-3,5-diethyl-1,2-dioxolane** (*cis*-**270**).

cis-**137** *cis*-**270**

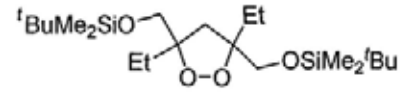
To a stirring solution of *cis*-**135** (741 mg, 3.89 mmol) in DMF (10 mL) cooled at 0 °C were added imidazole (265 mg, 3.89 mmol), DMAP (24 mg, 0.19 mmol), and *tert*-butyldimethylsilyl chloride (587 mg, 3.89 mmol). The reaction was stirred overnight, and it was allowed to warm to room temperature slowly. Then quenched by addition of saturated aq. NH_4Cl (10 mL), and the resulting solution was stirred at room temperature for 30 min. The mixture was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography on silica gel (8 g, hexane/EtOAc, 20:1 - 10:1) to afford *cis*-**270** (83 mg, 5%), *cis*-**137** (532 mg, 45%) and *cis*-**135** (259 mg, 35%) as colorless oil. *cis*-**137**: R_f = 0.50 (hexanes/EtOAc, 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 6H), 0.89 (s, 9H), 0.90 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H), 1.57-1.66 (m, 2H), 1.75-1.83 (m, 2H), 2.07-2.12 (m, 1H), 2.06 (d, J = 12.3 Hz, 1H), 2.32 (d, J = 12.3 Hz, 1H), 3.46 (dd, J = 7.6 Hz, 11.9 Hz, 1H), 3.58 (d, J = 3.0 Hz, 2H), 3.72 (dd, J = 4.6 Hz, 11.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.4, 8.5, 8.9, 18.4, 25.9, 26.4, 28.0, 44.8, 63.9, 64.1, 89.1, 89.2 ppm; IR (Neat): 2956, 2931, 2883, 2858, 1463, 1254, 1113, 1060, 838, 778 cm^{-1}; MS (ESI): *m/z* 305 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{33}O_4Si$: 305.2143, found: 305.2141.

cis-**270**: R_f = 0.9 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 12H), 0.89 (s, 18 H), 0.90 (t, J = 7.5 Hz, 6H), 1.55-1.64 (m, 2H), 1.75-1.84 (m, 2H), 1.98 (d, J = 12.4 Hz, 1H), 2.28 (d, J = 12.3 Hz, 1H), 3.49 (d, J = 10.6 Hz, 2H), 3.65 (d, J = 10.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.4, –5.3, 8.6, 18.3, 25.9, 27.2, 45.3, 64.0, 88.8, ppm; MS (ESI): *m/z* 419 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{47}O_4Si_2$: 419.3007, found: 419.3018.

(5-((*tert*-Butyldimethylsilyloxy)methyl)-*trans*-3,5-diethyl-1,2-dioxolan-3-yl)methanol (*trans*-**136**) and **3,5-bis((*tert*-Butyldimethylsilyloxy)methyl)-*trans*-3,5-diethyl-1,2-dioxolane** (*trans*-**271**)



trans-**136**



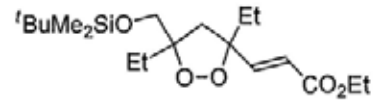
trans-**271**

trans-**136** and *trans*-**271** were prepared by a similar procedure as *cis*-**137** and *cis*-**270**; *trans*-**137**: R_f = 0.50 (hexanes/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 6H), 0.89 (s, 9H), 0.91 (t, J = 7.4 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H), 1.49-1.59 (m, 2H), 1.70-1.80 (m, 2H), 1.96 (d, J = 12.6 Hz, 1H), 2.04-2.10 (m, 1H), 2.17 (d, J = 12.6 Hz, 1H), 3.44 (dd, J = 8.3 Hz, 11.6 Hz, 1H), 3.49 (d, J = 10.9 Hz, 1H), 3.68 (d, J = 10.9 Hz, 1H), 3.71 (dd, J = 8.3 Hz, 11.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.4, –5.3, 8.8, 9.0, 18.3, 25.4, 25.9, 25.9, 44.6, 64.4, 65.0, 88.9, 89.1 ppm; IR (Neat): 2955, 2933, 2884, 2862, 1464, 1254, 1112, 1059, 842, 779 cm^{-1}; MS (ESI): *m/z* 305 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{33}O_4Si$: 305.2143, found: 305.2141.

trans-**271**: R_f = 0.9 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 12H), 0.89 (s, 18 H), 0.91 (t, J = 7.5 Hz, 6H), 1.55-1.62 (m, 2H), 1.72-1.80 (m, 2H), 2.10 (s, 2H), 3.50 (d, J = 10.2 Hz, 2H), 3.65 (d, J = 10.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.5,

–5.3, 8.6, 18.3, 25.9, 26.3, 44.4, 64.9, 88.5 ppm; MS (ESI): *m/z* 441 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{21}H_{46}O_4Si_2Na$: 441.2827, found: 441.2831.

(*E*)-Ethyl 3-(5-((butyldimethylsilyloxy)methyl)-*trans*-3,5-diethyl-1,2-dioxolan-3-yl)acrylate *trans*-142.

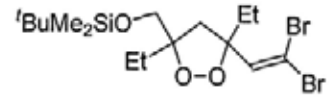


trans-**142**

To a solution of *trans*-**136** (38 mg, 0.125 mmol) in CH_2Cl_2 (2.0 mL) was added DMP (80 mg, 0.188 mmol). The reaction mixture was stirred until the starting material had disappeared, $NaHCO_3$ (84 mg, 1.0 mmol) was added. Then added saturated aq. $NaHCO_3$ (5.0 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography on silica gel (8 g, hexanes/EtOAc, 10:1) to afford the desired aldehyde *trans*-**141**, which was used in the next step. To a 0 °C spension of NaH (14 mg, 60% in mineral oil, 2.8 equiv) in THF (1 mL) was added a solution of triethyl phosphonoacetate (84 mg, 0.375 mmol, 3.0 equiv) in THF (0.5 mL). After stirring for 0.5 h, the aldehyde **141** in THF (1 mL) was added slowly. The reaction mixture was warmed to room temperature, stirred until no starting material remained (TLC). Quenched the reaction with saturated aq. NH_4Cl extracted with Et_2O three times and combined the organic layers and washed with brine and water, and dried over $MgSO_4$ and filtered. Removed the solvent with rotary evaporation. Flash chromatography on silica gel (8 g) of the residue gave the product (37 mg, 79% in 2 steps) as a colorless oil. R_f = 0.50 (hexanes/EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ =0.07 (s, 6H), 0.86 (t, J = 7.5 Hz, 3H), 0.89 (s, 9H), 0.91 (t, J = 7.5 Hz, 3H), 1.30 (t, J = 7.1 Hz,

3H), 1.52-1.58 (m, 1H), 1.68-1.78 (m, 3H), 2.31 (q, J = 12.5 Hz, 2H), 3.50 (d, J = 10.3 Hz, 1H), 3.65 (d, J = 10.3 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 6.11 (d, J = 15.8 Hz, 1H), 6.87 (d, J = 15.8 Hz, 1H)ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = −5.5, −5.3, 8.7, 8.8, 14.3, 18.3, 25.9, 26.2, 30.4, 49.0, 60.6, 65.0, 87.7, 89.0, 120.5, 149.8, 166.7 ppm; IR (Neat): 2956, 2930, 2857, 1722, 1658, 1463, 1304, 1259, 1178, 1113, 1039, 838, 778 cm^{-1}; MS (ESI): m/z $[M+H]^+$ 373; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{37}O_5Si$: 373.2405, found: 373.2402.

***tert*-Butyl((5-(2,2-dibromovinyl)-*trans*-3,5-diethyl-1,2-dioxolan-3-yl)methoxy)dimethylsilane (*trans*-155)**

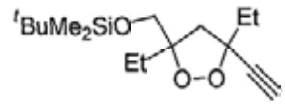


trans-**155**

To a slurry of Ph_3P-$CHBr_3$[76] (322 mg, 0.625 mmol) in THF (2.0 mL) at 0 °C was added *t*-BuOK (67 mg, 0.6 mmol). The bright yellow slurry was stirred for 15 min and the temperature was allowed to warm to room temperature. Then added the aldehyde **141** in THF (1.0 mL) to the mixture and stirred for 30 min, TLC, the reaction completed. Quenched the reaction with saturated aq. NH_4Cl extracted with Et_2O three times and combined the organic layers and washed with brine and water, and dried over $MgSO_4$ and filtered. Removed the solvent with rotary evaporation. Flash chromatography on silica gel (8 g) of the residue gave the product (90 mg, 79%, 2 steps) as a colorless oil : R_f = 0.75 (hexanes/EtOAc, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.07 (s, 6H), 0.89 (s, 9H), 0.91 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H), 1.56-1.63 (m, 1H), 1.70-1.81 (m, 2H), 2.15-2.20 (m, 1H), 2.25 (d, J = 12.7 Hz, 1H), 2.69 (d, J = 12.7 Hz, 1H), 3.48 (d, J = 10.2 Hz, 1H), 3.63 (d, J = 10.2 Hz, 1H), 6.91 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ =

−5.4, −5.3, 8.5, 8.9, 18.3, 25.9, 26.2, 28.0, 49.1, 65.5, 87.1, 88.8, 90.3, 144.9 ppm; IR (Neat): 2954, 2930, 2858, 1461, 1256, 1115, 838 cm^{-1}; MS (ESI): *m/z* 481 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{30}Br_2O_3SiNa$: 481.0203, found: 481.0190.

***tert*-Butyl((*trans*-3,5-diethyl-5-ethynyl-1,2-dioxolan-3-yl)methoxy)dimethylsilane (*trans*-148)**

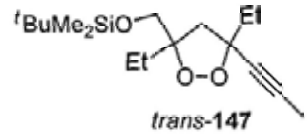


trans-**148**

To a two necked round-bottomed flask equipped with a magnetic stirring bar was added *trans*-**155** (114 mg, 0.25mmol) under an argon atmosphere, and THF (2 mL) was added via syringe. The mixture was cooled to −78 °C and *n*-butyllithium (0.55 mmol, 1.6 M solution in hexanes, 0.344 mL) was added dropwise via syringe. The mixture was stirred at −78 °C for 30 min, then saturated aq. NH_4Cl water solution was added. The mixture was warmed to 25 °C, diluted with Et_2O, transferred to a separatory flask, and the layers separated. The aqueous layer was extracted with Et_2O and the combined organic extracts washed with saturated brine and water, dried by $MgSO_4$, filtered and the solvent removed by rotary evaporation. The residue was purified by column chromatography on silica gel (8 g) to yield **148** (71 mg, 95%) as a colorless oil, R_f = 0.55 (hexanes/ Et_2O 20:1); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 0.95 (t, *J* = 7.5 Hz, 3H), 1.08 (t, *J* = 7.4 Hz, 3H), 1.70-1.81 (m, 2H), 1.80-1.87 (m, 2H), 2.33 (d, *J* = 12.4 Hz, 1H), 2.51 (s, 1H), 2.56 (d, *J* = 12.4 Hz, 1H), 3.47 (d, *J* = 10.3 Hz, 1H), 3.63 (d, *J* = 10.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = −5.5, −5.3, 8.5, 9.6, 18.3, 25.9, 26.2, 31.2, 51.6, 65.3, 73.0, 82.7, 84.8, 89.0, ppm; IR (Neat): 3311, 2955, 2930, 2858,

1471, 1463, 1258, 1111, 1007, 839 cm^{-1}; MS (ESI): *m/z* 321 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{30}O_3SiNa$: 321.1856, found: 321.1854.

***tert*-Butyl((*trans*-3,5-diethyl-5-(prop-1-ynyl)-1,2-dioxolan-3-yl)methoxy)dimethylsilane** (*trans*-**147**).



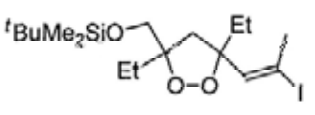
trans-**147**

To a 25-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar was added **148** (89 mg, 0.3 mmol). The flask was placed under an argon atmosphere, and THF (2.5 mL) was added via syringe. The mixture was cooled to −78 °C and *n*-butyllithium (0.36 mmol, 1.6 M solution in hexanes, 0.225 mL) was added dropwise via syringe. The mixture was stirred at −78 °C for 5 min and methyl trifluoromethanesulfonate (0.45 mmol, 74 mg, 0.052 mL) was added dropwise via syringe. The mixture was stirred at −78 °C for 30 min, then saturated aq. $NaHCO_3$ was added. The mixture was warmed to 25 °C, diluted with Et_2O, transferred to a separatory flask, and the layers separated. The aqueous layer was extracted with Et_2O and the combined organic extracts washed with saturated brine and water, dried by $MgSO_4$, filtered and the solvent removed by rotary evaporation. The residue was purified by column chromatography on silica gel (8 g) to yield **147** (66 mg, 70%) as a colorless oil, R_f = 0.55 (hexanes/ Et_2O 20:1); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 0.96 (t, J = 7.5 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H), 1.66-1.73 (m, 2H), 1.73-1.83 (m, 2H), 1.85 (s, 3H), 2.27 (d, J = 12.3 Hz, 1H), 2.48 (d, J = 12.3 Hz, 1H), 3.45 (d, J = 10.4 Hz, 1H), 3.60 (d, J = 10.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = −5.5, −5.3, 3.7, 8.5, 9.8, 18.3, 25.9, 26.4, 31.7, 51.9, 65.3, 80.2, 81.1, 83.1, 88.9 ppm; MS

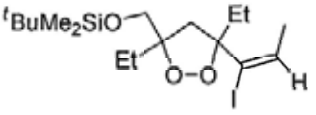
(ESI): *m/z* 335 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{32}O_3SiNa$: 335.2013, found: 335.2017.

(*E*)-*tert*-Butyl((*trans*-3,5-diethyl-5-(2-iodoprop-1-enyl)-1,2-dioxolan-3-yl)methoxy)dimethylsilane (*trans*-**146**)

(*E*)-*tert*-Butyl((*trans*-3,5-diethyl-5-(1-iodoprop-1-enyl)-1,2-dioxolan-3-yl)methoxy)dimethylsilane (*trans*-**162b**)



trans-**146**



trans-**162b**

Procedure I: To a 10-mL, argon-filled, two-necked round-bottomed flask equipped with a magnetic stirring bar was added *trans*-**147** (64 mg, 0.206 mmol) and $Pd(PPh_3)_2Cl_2$ (10 mol%). The flask was evacuated and filled with argon three times, and then freshly distilled THF (2 mL) was added via a syringe. Tributyltin hydride (4.0 equiv) was added slowly (about over 10 min) via a syringe. The reaction was stirred at 23 °C for 1 h, then immediately transferred to a silica gel column (8 g) and rapidly eluted with hexanes until the excess $Bu_3SnH/(Bu_3Sn)_2$ is removed, followed by elution with a mixture of hexanes and EtOAc (10:1) to afford *trans*-**161** (41 mg, 33%), *trans*-**162** (41 mg, 33%) as colorless oil; *trans*-**162**: R_f = 0.70 (hexanes/EtOAc, 20:1); *trans*-**161**: R_f = 0.60 (hexanes/EtOAc, 20:1); The obtained stannane compound *trans*-**162** was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. I_2 (17 mg, 0.07 mmol) in CH_2Cl_2 (1 mL) was added and the resulting mixture was stirred at 0 °C for 5-8 min then worked up by a saturated aq. $Na_2S_2O_3$ solution (3 mL) and extracted by Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by flash column

chromatography on silica gel (8 g, hexanes/EtOAc, 20:1) to give **162b** (26 mg, 86%) as an oil: R_f = 0.60 (hexanes/EtOAc, 20:1); In a similar manner of iodination, *trans*-**146** was prepared as a colorless oil: R_f = 0.50 (hexanes/EtOAc, 20:1);

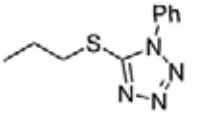
trans-**146**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 6H), 0.90 (s, 9H), 0.92 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H), 1.55-1.64 (m, 1H), 1.70-1.76 (m, 3H), 2.28 (d, J = 1.6 Hz, 2H), 2.58 (d, J = 1.3 Hz, 3H), 3.48 (d, J = 10.2 Hz, 1H), 3.61 (d, J = 10.2 Hz, 1H), 6.17 (d, J = 1.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = −5.4, −5.3, 8.5, 9.1, 18.3, 25.9, 26.4, 29.8, 30.9, 50.8, 65.4, 88.4, 90.8, 96.4, 144.1 ppm; MS (ESI): *m/z* $[M+Na]^+$ 463; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{33}IO_3SiNa$: 463.1136, found: 463.1137.

trans-**162b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 6H), 0.90 (s, 9H), 0.92 (t, J = 7.5 Hz, 6H), 1.60-1.68 (m, 1H), 1.70-1.77 (m, 2H), 1.87 (d, J = 7.5 Hz, 3H), 2.11-2.19 (m, 1H), 2.26 (d, J = 12.9 Hz, 1H), 2.87 (q, J = 12.8 Hz, 1H), 3.50 (d, J = 10.1 Hz, 3H), 3.62 (d, J = 10.1 Hz, 1H), 6.45 (d, J = 7.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = −5.4, −5.3, 8.2, 8.6, 18.0, 18.4, 26.0, 26.0, 30.9, 51.7, 65.8, 88.6, 93.2, 107.1, 138.8 ppm; MS (ESI): *m/z* $[M+Na]^+$ 463; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{33}IO_3SiNa$: 463.1136, found: 463.1138.

Procedure II (*trans*-146): To a 10-mL, argon-filled, two-necked round-bottomed flask equipped with a magnetic stirring bar was added *trans*-**147** (64 mg, 0.206 mmol) and $Pd(PPh_3)_2Cl_2$ (10 mol%). The flask was evacuated and filled with argon three times, and then freshly distilled *n*-hexane (2 mL) was added via a syringe. Tributyltin hydride (4.0 equiv) was added slowly (about over 10 min) via a syringe. The reaction was stirred at 23 °C for 1 h, then immediately transferred to a silica gel column (8 g) and rapidly eluted with hexanes until the excess $Bu_3SnH/(Bu_3Sn)_2$ is removed, followed by elution with a

mixture of hexanes and ethyl acetate (10:1) to give the stannane compound *trans*-**161** (105 mg, 84%) as a colorless oil: R_f = 0.60 (hexanes/EtOAc, 20:1). The obtained stannane compound was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. I_2 (43 mg, 0.17 mmol) in CH_2Cl_2 (1 mL) was added and the resulting mixture was stirred at 0 °C for 5-8 min then worked up by a saturated aq. $Na_2S_2O_3$ solution (3 mL) and extracted by Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (8 g, /EtOAc, 20:1) to give *trans*-**146** (64 mg, 86%) as an oil: R_f = 0.50 (hexanes/EtOAc, 20:1);

1-Phenyl-5-(propylthiol)-1*H*-tetrazole (164).[59,111]

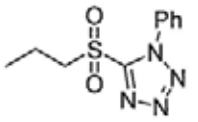


164

To a solution of *n*-propyl bromide **163** (1.3 g, 10.6 mmol) in THF (40 mL) was added NaH (424 mg, 60% in mineral oil, 12 mmol) and 1-phenyl-1h-tetrazole-5-thiol (HSPT) (2.16 g, 12 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with saturated aq. NH_4Cl and extracted with EtOAc. The organic layer were dried over MgSO4, filtered and concentrated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (100 g, hexanes/EtOAc, 20:1) to give the desired **164** (2.25 g) in 96% yield. R_f = 0.70 (hexanes/EtOAc, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.03 (t, J = 7.4 Hz, 3H), 1.79-1.89 (m, 2H), 3.35 (t, 2H, J = 7.2 Hz), 7.52-7.56 (m, 5H)

ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.2, 22.6, 35.2, 123.9, 129.8, 130.1, 133.7, 154.5 ppm; MS (ESI): *m/z* $[M+H]^+$ 221;

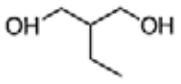
1-Phenyl-5-(propylsulfonyl)-1*H*-tetrazole (165).[59,111]



165

To a solution of **164** (0.22 g, 1.0 mmol) in EtOH (5 mL) was added $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ (0.13 g, 0.1 mmol) and H_2O_2 (30% in H_2O, 1 mL, 10 mmol) at room temperature. The reaction mixture was stirred for 14 h. The reaction mixture was extracted with Et_2O (25 mL×3). The organic layer were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (8 g, hexanes/EtOAc, 6:1) to give the desired **165** (0.23 g) in 92% yield; R_f = 0.50 (hexanes/EtOAc, 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ = 1.12 (t, J = 7.4 Hz, 3H), 1.94-2.01 (m, 2H), 3.68-3.72 (m, 2H), 7.56-7.68 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 12.8, 16.0, 57.6, 125.1, 129.7, 131.5, 133.0, 153.5 ppm; MS (ESI): *m/z* $[M+H]^+$ 253;

2-Ethylpropane-1,3-diol (166).[84]

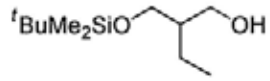


166

To a solution of ethyl diethyl malonate (10 g, 0.053 mol) in THF (90 mL) was slowly added $LiAlH_4$ (3.9 g, 0.103 mol) at 0 °C. The reaction mixture was stirred at rt for 1h and refluxed for 15h. The reaction mixture was cooled to 0 °C and quenched with 20% NaOH solution. The mixture was further diluted with Et_2O (300 mL), filtered and the

precipitated aluminum salts were washed with additional 200 mL of Et_2O. The combined filtrates were concentrated under reduced pressure to give a yellow oil which was distilled under reduced pressure at 110 °C, to provide diol as a colorless oil in a 60% yield (3.3 g). ^1H NMR (400 MHz, $CDCl_3$) δ = 0.89 (t, J = 7.4 Hz, 3H), 1.20-1.27 (m, 2H), 1.55-1.61 (m, 1H), 3.52-3.58 (m, 2H), 3.67-3.71 (m, 2H), 3.81 (s, 1H), 3.87 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.6, 20.6, 43.7, 64.8, 64.9 ppm; MS (ESI): *m/z* $[M+H]^+$ 105;

2-((*tert*-Butyldimethylsilyloxy)methyl)butan-1-ol (167).[84]

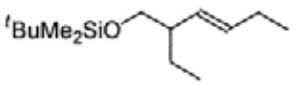


167

To a solution of diol **166** (3.3 g, 0.032 mol) in THF (90 mL) was slowly added *n*-BuLi (1.6 M, 19.8 mL, 1.0 equiv) at –78 °C. The reaction mixture was stirred at –78 °C for 1h, the reaction mixture was warmed to –30 °C, and *t*-$BuMe_2SiCl$ was added (1.0 equiv). After stirring for 1 at –30 °C, the reaction mixture was allowed to warm to room perature, quenched with saturated aq. NH_4Cl and extracted with EtOAc. The organic layer were dried over MgSO4, filtered and concentrated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (hexanes/EtOAc, 20:1) to give the desired mono protected alcohol **167** (7.0 g) as an oil in quantitative yield.

R_f = 0.50 (hexanes/EtOAc, 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 6H), 0.88 (s, 9H); 0.91 (t, J = 7.4 Hz, 3H), 1.22-1.30 (m, 2H), 1.60-1.65 (m, 1H), 2.95 (s, 1H), 3.60 (q, J = 7.4 Hz, 2H), 3.72 (d, J = 10.4 Hz, 1H), 3.79 (dd, J = 3.8, 9.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.6, –5.5, 11.8, 18.2, 20.6, 25.9, 43.7, 66.4, 67.2 ppm; MS (ESI): *m/z* $[M+H]^+$ 219;

(*E*)-*tert*-Butyl(2-ethylhex-3-enyloxy)dimethylsilane (169).[35b]



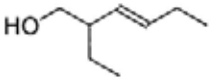
169

To a stirring solution of $(COCl)_2$ (0.75 mL, 8.6 mmol) in CH_2Cl_2 (50 mL) was added DMSO (1 mL, 14.0 mmol) dropwise via a syringe at –78 °C. The mixture was stirred at –78 °C for 15 min and then a solution of **167** (1.08 g, 4.95 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture via a syringe. After stirring for 1 h at –78 °C, Et_3N (2.5 mL, 18.0 mmol) was added and the reaction was allowed to warm to 23 °C and stirred at this temperature for 0.5 h. Then it was successively washed with an aq. HCl solution (10 mL, 1 N), a saturated aq. $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude aldehyde **168** as a pale yellow oil which was used directly in the next step without further purification.

To a solution of compound **165** (1.26 g, 5 mmol) of THF (20 mL) was added dropwise KHMDS (4.5 mL, 1.0 M in THF, 4.5 mmol) at –78 °C. After stirring at –78 °C for 2 h, a solution of the above freshly prepared aldehyde **168** in THF (5 mL) was added dropwise. The resulting mixture was stirred from –78 °C to 23 °C overnight, and quenched with a saturated aq. NH_4Cl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide a residue which was purified by flash column chromatography on silica gel (40 g, hexanes/Et_2O 20:1) to give **169** (1.07 g, 89% in 2 steps) as a 25:1 *E*/*Z* mixture: R_f = 0.35 (hexanes/Et_2O 20:1); ^1H NMR (400 MHz, $CDCl_3$)

δ = 0.03 (s, 6H), 0.85 (t, J = 7.4 Hz, 3H), 0.90 (s, 9H), 0.98 (t, J = 7.6 Hz, 3H), 1.16-1.26 (m, 1H), 1.49-1.59 (m, 1H), 1.97-2.05 (m, 3H), 3.43-3.51 (m, 2H), 5.15 (ddt, J = 1.4, 7.2, 15.4 Hz, 1H), 5.48 (dt, J = 6.5, 15.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.2, –5.2, 11.7, 14.0, 18.5, 24.1, 25.9, 26.0, 47.2, 67.0, 130.4, 133.4 ppm; MS (ESI): *m/z* $[M+Na]^+$ 265; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{14}H_{30}NaOSi$: 265.1958, found: 265.1955.

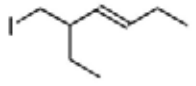
(*E*)-2-Ethylhex-3-en-1-ol (170).[35b,36]



170

To a solution of **169** (35 mg, 0.14 mmol) in CH_2Cl_2/MeOH (0.7/1.4 mL) was added *p*-TsOH (10 mol%). The reaction was stirred at room temperature until no starting material remained (TLC). After removal of the solvents, the crude product was purified by column chromatography on silica gel (8 g, hexanes/EtOAc, 5:1) to yield **170** (18 mg, 86%); R_f = 0.35 (hexanes/Et_2O 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.85 (t, J = 7.4 Hz, 3H), 0.98 (t, J = 7.6 Hz, 3H), 1.16-1.27 (m, 1H), 1.38-1.43 (m, 2H), 2.01-2.09 (m, 3H), 3.35 (t, J = 10.6 Hz, 1H), 3.51-3.57 (m, 1H), 5.13 (ddt, J = 1.4, 7.4, 15.4 Hz, 1H), 5.60 (dt, J = 6.3, 15.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.7, 14.1, 24.1, 25.8, 47.7, 65.8, 130.0, 135.9 ppm; MS (EI): *m/z* $[M+Na]^+$ 151;

(*E*)-5-(Iodomethyl)hept-3-ene (recemic-**91**).[35b,36]

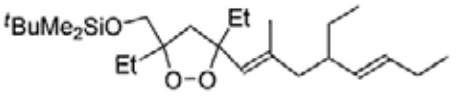


racemic-**91**

170 (179 mg, 1.40 mmol) was dissolved in CH_2Cl_2 (5 mL) and stirred at 0 °C. PPh_3 (628 mg, 2.4 mmol) and imidazole (204 mg, 3 mmol) was added to the solution followed

by I_2 (558 mg, 2.2 mmol) at 0 °C. The resulting mixture was stirred from 0 °C to 23 °C for 4 h and then worked up by adding a saturated aq. $Na_2S_2O_3$ solution (5 mL). The organic layer was separated and the aqueous layer was extracted with pentane (3 × 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated at 25°C under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (10 g, pentane) to give recemic-**91** (286 mg, 86%): R_f = 0.80 (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.86 (t, J = 7.4 Hz, 3H), 0.99 (t, J = 7.5 Hz, 3H), 1.26-1.33 (m, 1H), 1.52-1.58 (m, 1H), 1.96-2.07 (m, 3H), 3.16 (d, J = 6.1 Hz, 2H), 5.13 (dd, J = 8.4, 15.2 Hz, 1H), 5.52 (dt, J = 6.4, 15.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.6, 13.9, 14.8, 25.7, 27.9, 45.9, 130.9, 134.5 ppm; MS (ESI): *m/z* $[M]^+$ 238.

***tert*-Butyl((*trans*-3,5-diethyl-5-((1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)methoxy)dimethylsilane (206).**

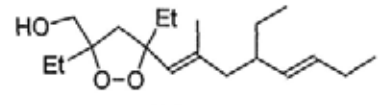


206

Negishi Coupling: To a 25-mL, two-necked, round-bottomed flash equipped with a magnetic stirring bar was added $ZnBr_2$ (70mg, 0.312 mmol). The flask was placed under an argon atmosphere, and the side chain racemic-**91** (57 mg, 0.24 mmol) in Et_2O (3 mL) was added via syringe. The solution was cooled to –78 °C and *t*-butyllithium (0.48 mmol, 1.6 M solution in hexanes, 0.32 mL) was added dropwise via syringe. The mixture was stirred at –78 °C for 30 min and THF (0.75 mL) was stirred for1 hr and the temperature was allowed to warm to room temperature. The core **146** (40 mg, 0.09 mmol) in THF (1.5 mL) with $Pd(PPh_3)_4$ was added via syringe. The mixture was stirred overnight in the

absence of light. Quenched with saturated aq. NH_4Cl. The mixture was diluted with Et_2O, and the layers was separated. The water layer was separated with Et_2O, and the combined organic layers were washed with brine and water, dried over $MgSO_4$, filtered and solvent was removed by rotary evaporation. Chromatography on silica gel (8 g) gave the product **206** (36 mg, 93%) as a colorless oil: R_f = 0.50 (hexanes/EtOAc, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 3H), 0.07 (s, 3H), 0.83 (t, J = 7.4 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H), 0.89 (s, 9H), 0.95 (t, J = 7.4 Hz, 3H), 1.09- 1.20 (m, 1H), 1.32- 1.44 (m, 1H), 1.52-1.62 (m, 1H), 1.63 (s, 1.5 H), 1.64 (s, 1.5 H), 1.66-1.81 (m, 3H), 1.90-2.04 (m, 5H), 2.21-2.45 (m, 2H), 3.49 (d, J = 12.4 Hz, 1H), 3.61 (d, J = 12.8 Hz, 1H), 5.08 (dd, J = 8.3, 15.3 Hz, 1H), 5.27 (s, 0.5H), 5.30 (s, 0.5H), 5.33-5.40 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.4, –5.3, 8.6, 9.1, 9.2, 11.7, 11.7, 14.1, 14.1, 17.5, 17.6, 18.4, 25.7, 26.0, 27.0, 27.8, 27.9, 31.3, 42.6, 42.8, 46.6, 46.7, 51.5, 51.7, 64.9, 65.0, 88.3, 88.4, 88.8, 130.0, 130.5, 131.9, 133.0, 135.1, 135.5 ppm; IR (Neat): 2962, 2930, 2880, 2857, 1462, 1438, 1263, 1118, 838 cm^{-1}; MS (ESI): *m/z* 447 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{48}O_3SiNa$: 447.3265, found: 447.3269.

(*trans*-3,5-Diethyl-5-((1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)methanol (208).

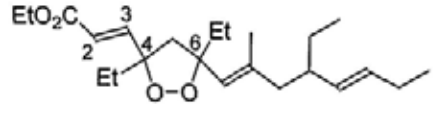


208

To a solution of **206** (35 mg, 0.08 mmol) in CH_2Cl_2/MeOH (0.7/1.4 mL) was added *p*-TsOH (10 mol%). The reaction was stirred at room temperature until no starting material remained (TLC). After removal of the solvents, the crude product was purified by column chromatography on silica gel (8 g, hexanes/EtOAc, 5:1) to yield **208** (22 mg, 89%): R_f =

0.30 (hexanes/EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.84 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 1.11- 1.20 (m, 1H), 1.33- 1.44 (m, 1H), 1.56-1.60 (m, 1H), 1.65 (d, J = 1.0 Hz, 1.5 H), 1.67 (d, J = 1.0 Hz, 1.5 H), 1.72-1.79 (m, 3H), 1.19-2.07 (m, 6H), 2.24 (dd, J = 3.2, 11.8 Hz, 1H), 2.40 (t, J = 11.8 Hz, 1H), 3.49 (dd, J = 7.5, 11.7 Hz, 1H), 3.64 (dd, J = 5.8, 11.7 Hz, 1H), 5.09 (dd, J = 8.1, 15.3 Hz, 1H), 5.26 (s, 0.5H), 5.30 (s, 0.5H), 5.33-5.40 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.0, 9.2, 9.3, 11.7, 11.7, 14.0, 14.1, 17.3, 17.5, 25.7, 26.1, 27.9, 27.9, 31.1, 42.6, 42.8, 46.7, 46.8, 51.1, 51.2, 65.3, 88.6, 88.7, 89.3, 130.0, 130.4, 132.0, 132.0, 132.9, 133.0, 135.6, 136.0 ppm; MS (ESI): *m/z* 333 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{34}O_3Na$: 333.2400, found: 333.2403.

(*E*)-Ethyl 3-(*trans*-3,5-diethyl-5-((1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)acrylate (*E*)-ethyl acrylate (210).

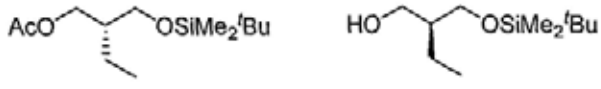


210

To a solution of **208** (22 mg, 0.07 mmol) in CH_2Cl_2 (1 mL) was added DMP (45 mg, 0.105 mmol). The reaction mixture was stirred until the starting material had disappeared, $NaHCO_3$ (25 mg, 0.30 mmol) was added. Then added saturated aq. $NaHCO_3$ solution (5 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexanes/ethyl acetate) to afford the desired aldehyde, which was used in the next step. To a 0 °C spension of NaH (5.3 mg, 60% in mineral oil, 0.13 mmol) in THF (0.8 mL) was added a solution of triethyl phosphonoacetate (31.4 mg, 0.14 mmol) in THF (0.5 mL). After stirring for 0.5 h,

the aldehyde in THF (0.7 mL) was added slowly. The reaction mixture was warmed to room temperature, stirred until no starting material remained (TLC). Quenched the reaction with saturated aq. NH_4Cl extracted with Et_2O three times and combined the organic layers and washed with brine and water, and dried over $MgSO_4$ and filtered. Removed the solvent with rotary evaporation. Flash chromatography on silica gel (8 g) of the residue gave the product **210** (21 mg, 80% in 2 steps) as a colorless oil : R_f = 0.50 (hexanes/EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.81 (t, J = 7.4 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H), 1.10-1.20 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.33-1.40 (m, 1H), 1.63 (d, J = 1.1 Hz, 1.5H), 1.64 (d, J = 1.0 Hz, 1.5H), 1.65-1.70 (m, 2H), 1.72-1.86 (m, 2H), 1.87-1.93 (m, 1H), 1.94-2.10 (m, 4H), 2.49 (s, 1H), 2.51 (d, J = 2.3 Hz, 1H), 4.20 (q, J = 7.2 Hz, 1H), 5.07 (dd, J = 8.3, 15.2 Hz, 1H), 5.27 (d, J = 10.6 Hz, 1H), 5.33-5.40 (m, 1H), 6.06 (d, J = 15.8 Hz, 1H), 6.88 (d, J = 15.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.8, 9.0, 9.1, 11.7, 11.7, 14.1, 14.1, 14.3, 17.6, 17.7, 25.7, 27.9, 28.0, 30.9, 31.0, 31.5, 31.5, 42.7, 42.8, 46.6, 46.6, 55.9, 56.0, 60.6, 87.3, 87.4, 89.3, 120.1, 129.0, 129.3, 132.0, 132.1, 132.8, 132.9, 135.9, 136.2, 149.2, 149.2, 166.7 ppm; MS (ESI): *m/z* 382 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{38}O_4Na$: 401.2662, found: 401.2661.

(*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)butyl acetate ((*R*)-**218**) and **(*S*)-2-((*tert*-butyldimethylsilyloxy)methyl)butan-1-ol** ((*S*)-**167**)[84,112,113]



(*R*)-**218** (*S*)-**167**

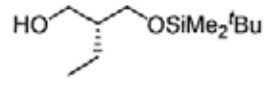
To a solution of racemic primary alcohol **167** (5.16 g,) in pentane was added the lipase extract PS3O (250 mg) and freshly distilled vinyl acetate. The heterogeneous mixture is

stirred vigorously at room temperature for 24h.Then filtered through a sintered glass funnel to recover the enzymatic extract. The ertracted was washed with Et_2O, and combined the solutions and removed the solvents under vacuum. Purification by column chromatography on silica gel (200 g, hexanes/EtOAc, 10:1) to afford (*R*)-**218** (2.91 g, 47%) and (*S*)-**167** (2.40 g, 46%);

(*R*)-**218** : R_f = 0.60 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = 1.2 (*c*, 1.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.02 (s, 6H), 0.87 (s, 9H); 0.91 (t, *J* = 7.4 Hz, 3H), 1.30-1.40 (m, 2H), 1.68-1.70 (m, 1H), 2.03 (s, 3H), 3.52-3.60 (m, 2H), 4.05 (d, *J* = 5.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.5, 11.5, 18.3, 20.8, 21.0, 25.9, 41.9, 62.4, 64.5, 171.3 ppm; MS (ESI): *m/z* $[M+Na]^+$ 283; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{13}H_{28}O_3SiNa$: 283.1700, found: 283.1704.

(*S*)-**167** : R_f = 0.50 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = –10.7 (*c*, 1.37, CHCl3); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 6H), 0.88 (s, 9H); 0.91 (t, *J* = 7.4 Hz, 3H), 1.22-1.30 (m, 2H), 1.60-1.65 (m, 1H), 2.95 (s, 1H), 3.60 (q, *J* = 7.4 Hz, 2H), 3.72 (d, *J* = 10.4 Hz, 1H), 3.79 (dd, *J* = 3.8, 9.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.6, –5.5, 11.8, 18.2, 20.6, 25.9, 43.7, 66.4, 67.2 ppm; MS (ESI): *m/z* $[M+H]^+$ 219;

(*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)butan-1-ol ((*R*)-**167**).[84,35b]

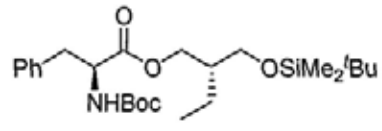


(*R*)-**167**

To a solution of (*R*)-**218** (426.4 mg, 1.64 mmol) in MeOH (30 mL) was added K_2CO_3 (226 mg, 1.64 mmol). The reaction mixture was stirred until the starting material had disappeared. Removed the solvent under reduced pressure. Water (20 mL) was added. The mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed

with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography on silica gel (20 g, hexanes/EtOAc, 8:1) to afford (*R*)-**167** (354 mg, 99%) as colorless oil; R_f = 0.50 (hexanes/EtOAc, 10:1); (*R*)-**167** : $[\alpha]_D^{20}$ = 10.6 (*c*, 1.67, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 6H), 0.88 (s, 9H); 0.91 (t, *J* = 7.4 Hz, 3H), 1.22-1.30 (m, 2H), 1.60-1.65 (m, 1H), 2.95 (s, 1H), 3.60 (q, *J* = 7.4 Hz, 2H), 3.72 (d, *J* = 10.4 Hz, 1H), 3.79 (dd, *J* = 3.8, 9.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.6, –5.5, 11.8, 18.2, 20.6, 25.9, 43.7, 66.4, 67.2 ppm; MS (ESI): *m/z* $[M+H]^+$ 219;

(*S*)-((*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)butyl) 2-(*tert*-butoxycarbonyl)-3-phenylpropanoate (220)

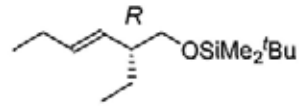


220

To a solution of (*R*)-**167** (34.9 mg, 0.16 mmol) and optically pure *N*-Boc protected *L*-phenylalanine **219** (46 mg, 1.05 equiv) in CH_2Cl_2 (2 mL) was added DMAP (10 mol%) and DCC (41 mg, 1.2 equiv) at 0 °C. The temperature was allowed to warm to room temperature. The reaction mixture was stirred overnight. Quenched the reaction with saturated aq. NH_4Cl extracted with Et_2O three times and combined the organic layers and washed with 10% aqueous HCl, brine and water, and dried over $MgSO_4$ and filtered. Removed the solvent with rotary evaporation. Flash chromatography on silica gel (8 g) of the residue gave the product (74.0 mg, 99%) as a colorless oil; R_f = 0.40 (hexanes/EtOAc, 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.03 (s, 6H), 0.88 (s, 9H); 0.91 (t, *J* = 7.5 Hz, 3H), 1.23-1.38 (m, 2H), 1.41 (s, 9H), 1.61-1.67 (m, 1H), 3.02-3.12 (m, 2H), 3.50 (d, *J* = 5.0

Hz, 2H), 4.07 (dd, J = 5.4, 10.8 Hz, 1H), 4.14 (dd, J = 6.2, 10.8 Hz, 1H), 4.56-4.60 (m, 1H), 4.97 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 6.8 Hz, 2H), 7.2-7.3 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.4, –5.4, 11.4, 18.3, 20.6, 25.9, 28.4, 38.6, 42.0, 54.5, 62.2, 65.4, 79.9, 127.0, 128.6, 129.4, 136.2, 155.1, 172.0 ppm; MS (ESI): *m/z* $[M+Na]^+$ 488; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{43}NNaO_5Si$: 488.2803, found: 488.2811.

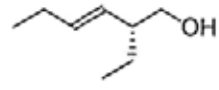
(*R*,*E*)-*tert*-Butyl(2-ethylhex-3-enyloxy)dimethylsilane (222a).[35b]



222a

The procedure was similar to that for the preparation of **169** (*vide supra*): yield = 89% (two steps); R_f = 0.35 (hexanes/EtOAc, 20:1); $[\alpha]_D^{20}$ = –16.6 (*c*, 1.49, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.03 (s, 6H), 0.85 (t, J = 7.4 Hz, 3H), 0.90 (s, 9H), 0.98 (t, J = 7.6 Hz, 3H), 1.16-1.26 (m, 1H), 1.49-1.59 (m, 1H), 1.97-2.05 (m, 3H), 3.43-3.51 (m, 2H), 5.15 (ddt, J = 1.4, 7.2, 15.4 Hz, 1H), 5.48 (dt, J = 6.5, 15.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.2, –5.2, 11.7, 14.0, 18.5, 24.1, 25.9, 26.0, 47.2, 67.0, 130.4, 133.4 ppm; MS (ESI): *m/z* $[M+Na]^+$ 265; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{14}H_{30}NaOSi$: 265.1958, found: 265.1952.

(*R*,*E*)-2-Ethylhex-3-en-1-ol (223a).[35b]

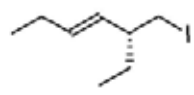


223a

The procedure was similar to that for the preparation of **170** (*vide supra*): yield = 86%; R_f = 0.35 (hexanes/EtOAc, 9:1); $[\alpha]_D^{20}$ = –3.0 (*c*, 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.85 (t, J = 7.4 Hz, 3H), 0.98 (t, J = 7.6 Hz, 3H), 1.16-1.27 (m, 1H), 1.38-

1.43 (m, 2H), 2.01-2.09 (m, 3H), 3.35 (t, J = 10.6 Hz, 1H), 3.51-3.57 (m, 1H), 5.13 (ddt, J = 1.4, 7.4, 15.4 Hz, 1H), 5.60 (dt, J = 6.3, 15.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.7, 14.1, 24.1, 25.8, 47.7, 65.8, 130.0, 135.9 ppm; MS (EI): m/z $[M]^+$ 128; HRMS (EI) m/z $[M]^+$ calcd for $C_8H_{16}O$: 128.1196, found: 128.1197.

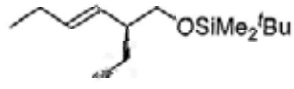
(*R*,*E*)-5-(Iodomethyl)hept-3-ene ((*R*)-**91**)[35b,33c]



(*R*)-**91**

The procedure was similar to that for the preparation of recemic-**91** (*vide supra*); yield = 86%; R_f = 0.80 (hexanes); R_f = 0.80 (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.86 (t, J = 7.4 Hz, 3H), 0.99 (t, J = 7.5 Hz, 3H), 1.26-1.33 (m, 1H), 1.52-1.58 (m, 1H), 1.96-2.07 (m, 3H), 3.16 (d, J = 6.1 Hz, 2H), 5.13 (dd, J = 8.4, 15.2 Hz, 1H), 5.52 (dt, J = 6.4, 15.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.6, 13.9, 14.8, 25.7, 27.9, 45.9, 130.9, 134.5 ppm; MS (ESI): m/z $[M]^+$ 238.

(*S*,*E*)-*tert*-Butyl(2-ethylhex-3-enyloxy)dimethylsilane (222b).[35b]

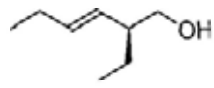


222b

The procedure was similar to that for the preparation of **169** (*vide supra*): yield = 89% (two steps); R_f = 0.35 (hexanes/EtOAc, 20:1); $[\alpha]_D^{20}$ = 16.2 (*c*, 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.03 (s, 6H), 0.85 (t, J = 7.4 Hz, 3H), 0.90 (s, 9H), 0.98 (t, J = 7.6 Hz, 3H), 1.16-1.26 (m, 1H), 1.49-1.59 (m, 1H), 1.97-2.05 (m, 3H), 3.43-3.51 (m, 2H), 5.15 (ddt, J = 1.4, 7.2, 15.4 Hz, 1H), 5.48 (dt, J = 6.5, 15.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = −5.2, −5.2, 11.7, 14.0, 18.5, 24.1, 25.9, 26.0, 47.2, 67.0, 130.4, 133.4

ppm; MS (ESI): *m/z* $[M+Na]^+$ 265; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{14}H_{30}NaOSi$: 265.1958, found: 265.1948.

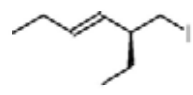
(*S*,*E*)-2-Ethylhex-3-en-1-ol (223b).[35b,36]



223b

The procedure was similar to that for the preparation of **170** (*vide supra*): yield = 86%; R_f = 0.35 (hexanes/EtOAc, 9:1); $[\alpha]_D^{20}$ = 2.9 (*c*, 0.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.85 (t, *J* = 7.4 Hz, 3H), 0.98 (t, *J* = 7.6 Hz, 3H), 1.16-1.27 (m, 1H), 1.38-1.43 (m, 2H), 2.01-2.09 (m, 3H), 3.35 (t, *J* = 10.6 Hz, 1H), 3.51-3.57 (m, 1H), 5.13 (ddt, *J* = 1.4, 7.4, 15.4 Hz, 1H), 5.60 (dt, *J* = 6.3, 15.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.7, 14.1, 24.1, 25.8, 47.7, 65.8, 130.0, 135.9 ppm; MS (EI): *m/z* $[M]^+$ 128; HRMS (EI) *m/z* $[M]^+$ calcd for $C_8H_{16}O$: 128.1196, found: 128.1196.

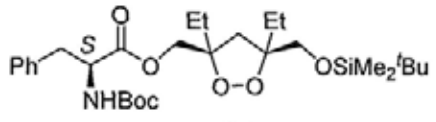
(*S*,*E*)-5-(Iodomethyl)hept-3-ene ((*S*)-91).[35b,36c]



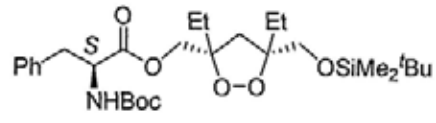
(*S*)-91

The procedure was similar to that for the preparation of recemic-**91** (*vide supra*); yield = 86%; R_f = 0.80 (hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.86 (t, *J* = 7.4 Hz, 3H), 0.99 (t, *J* = 7.5 Hz, 3H), 1.26-1.33 (m, 1H), 1.52-1.58 (m, 1H), 1.96-2.07 (m, 3H), 3.16 (d, *J* = 6.1 Hz, 2H), 5.13 (dd, *J* = 8.4, 15.2 Hz, 1H), 5.52 (dt, *J* = 6.4, 15.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.6, 13.9, 14.8, 25.7, 27.9, 45.9, 130.9, 134.5 ppm; MS (ESI): *m/z* $[M]^+$ 238.

(*S*)-((3*R*,5*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-3,5-diethyl-1,2-dioxolan-3-yl)methyl 2-(*tert*-butoxycarbonyl)-3-phenylpropanoate (234) and **(*S*)-((3*S*,5*R*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-3,5-diethyl-1,2-dioxolan-3-yl)methyl 2-(*tert*-butoxycarbonyl)-3-phenylpropanoate (235)**



234

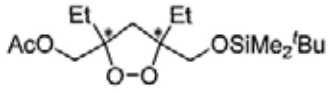


235

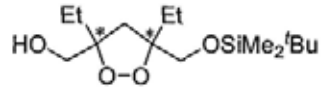
To a solution of *cis*-**137** (53.7 mg, 0.18 mmol) and optically pure *N*-Boc protected L-phenylalanine **219** (70.2 mg, 1.5 equiv) in CH_2Cl_2 (2 mL) was added DMAP (10 mol%) and DCC (54.7 mg, 1.5 equiv) at 0 °C. The temperature was allowed to warm to room temperature. The reaction mixture was stirred overnight. Quenched the reaction with saturated aq. NH_4Cl extracted with Et_2O three times and combined the organic layers and washed with 10% aqueous HCl, brine and water, and dried over $MgSO_4$ and filtered. Removed the solvent with rotary evaporation. Flash chromatography on silica gel (10 g) of the residue gave the product (90.9 mg, 93%) as a colorless oil; R_f = 0.30 (hexanes/EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.08 (s, 6H), 0.87-0.93 (m, 6H), 0.90 (s, 9H), 1.41 (s, 9H), 1.54-1.64 (m, 2H), 1.70-1.82 (m, 2H), 2.05 (dd, J = 4.5 Hz, 12.4 Hz, 1H), 2.25-2.30 (m, 1H), 3.03-3.15 (m, 2H), 3.52-3.62 (m, 2H), 3.97-4.03 (m, 1H), 4.33 (d, J = 11.6 Hz, 1H), 4.58-4.63 (m, 1H), 4.98 (s, 1H), 7.13-7.16 (m, 2H), 7.21-7.30 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.5, –5.4, –5.4, 8.5, 8.7, 8.7, 18.4, 18.4, 25.9, 26.4, 26.7, 27.8, 28.2, 28.4, 38.4, 45.6, 45.6, 54.4, 54.5, 63.4, 63.6, 65.2, 65.2, 79.9, 86.8, 86.9, 89.1, 127.0, 127.1, 128.6, 129.3, 129.5, 136.0, 136.0, 155.1, 171.7, 171.7 ppm; IR (Neat): 3381, 2957, 2931, 2883, 2858, 1745, 1718, 1497, 1472, 1462, 1366,

1253, 1169, 1115, 1007, 838, 779, 738, 701 cm^{-1}; MS (ESI): *m/z* $[M+Na]^+$ 574; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{29}H_{49}NNaO_7Si$: 574.3171, found: 574.3190.

(–)-(5-((*tert*-Butyldimethylsilyloxy)methyl)-*cis*-3,5-diethyl-1,2-dioxolan-3-yl)methyl acetate ((–)-*cis*-**245**) and **(+)-(5-((*tert*-Butyldimethylsilyloxy)methyl)-*cis*-3,5-diethyl-1,2-dioxolan-3-yl)methanol** ((+)-*cis*-**137a**)



(–)-*cis*-**245**



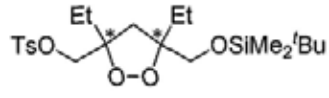
(+)-*cis*-**137a**

To a solution of racemic alcohol (±)-*cis*-**137** (1.11 g, 3.65 mmol) in hexane (40 mL) was added the Lipase PS from *Burkholderia cepaci* (555 mg) and vinyl acetate (1.68 mL, 18.3 mmol). The heterogeneous mixture was stirred vigorously at rt for 29 h before being filtered through a sintered glass funnel to recover the lipase catalyst. The catalyst was washed with Et_2O (20 mL), and the combined filtrates were concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (25 g, hexanes/EtOAc, 10:1) to afford (–)-*cis*-**245** (695 mg, 55%) and (+)-*cis*-**137a** (477 mg, 43%) as colorless oil;

(–)-*cis*-**245**: R_f = 0.50 (hexanes/EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.05 (s, 6H), 0.88 (s, 9H), 0.90 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.6 Hz, 3H), 1.56-1.66 (m, 2H), 1.73-1.82 (m, 2H), 2.05 (d, J = 12.4 Hz, 1H), 2.06 (s, 3H), 2.33 (d, J = 12.4 Hz, 1H), 3.53 (d, J = 10.8 Hz, 1H), 3.60 (d, J = 10.8 Hz, 1H), 4.02 (d, J = 11.8 Hz, 1H), 4.21 (d, J = 11.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.5, - 5.4, 8.4, 8.6, 18.3, 20.9, 25.9, 27.0, 27.7, 45.5, 63.6, 64.4, 86.9, 89.0, 170.8 ppm; MS (ESI): *m/z* 347 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{35}O_5Si$: 347.2248, found: 347.2248.

(+)-*cis*-**137a**: R_f = 0.35 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = 28.5 (*c* 1.13, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 6H), 0.89 (s, 9H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H), 1.57-1.66 (m, 2H), 1.75-1.83 (m, 2H), 2.02 (s, 1H), 2.06 (d, *J* = 12.3 Hz, 1H), 2.32 (d, *J* = 12.3 Hz, 1H), 3.46 (dd, *J* = 7.6 Hz, 11.9 Hz, 1H), 3.58 (d, *J* = 3.0 Hz, 2H), 3.72 (dd, *J* = 4.6 Hz, 11.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.4, 8.5, 8.9, 18.4, 25.9, 26.3, 28.0, 44.8, 63.8, 64.00, 89.1, 89.2 ppm; MS (ESI): *m/z* 305 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{33}O_4Si$: 305.2143, found: 305.2141.

(+)-(5-((*tert*-Butyldimethylsilyloxy)methyl)-*cis*-3,5-diethyl-1,2-dioxolan-3-yl)methyl 4-methylbenzenesulfonate ((+)-*cis*-**272a**)

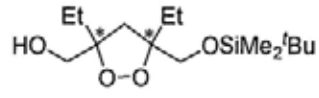


(+)-*cis*-**272a**

To a solution of acetate (+)-*cis*-**137a** (46 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) was added *p*-TsCl (34 mg, 1.8 mmol), Et_3N (2.0 eq) and DMAP (10 mol %). The reaction mixture was stirred until the starting material had disappeared. Removed the solvent, the residue was purified by flash chromatography on silica gel (10 g, hexanes/EtOAc, 10:1) to afford **272a** (61 mg, 89%): R_f = 0.40 (hexanes/EtOAc, 10: 1); *ee* >99%; The *ee* values were determined by chiral HPLC; CHIRALPAK AD–H column; hexane/2-propanol 95/5; flow rate 1.0 mL/min; temp 25 °C; wavelength = 254 nm; retention time: 4.9 min; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.00 (s, 3H), 0.01 (s, 3H), 0.85 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 6H), 1.52-1.66 (m, 2H), 1.71-1.82 (m, 2H), 2.03 (d, *J* = 12.6 Hz, 1H), 2.33 (d, *J* = 12.6 Hz, 1H), 2.44 (s, 3H), 3.48 (s, 2H), 3.91 (d, *J* = 10.1 Hz, 1H), 4.15 (d, *J* = 10.1 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.5, –5.4, 8.4, 18.3, 21.7, 25.9, 26.4, 28.1, 45.3, 63.2, 69.4, 86.7, 89.2, 128.0, 129.9, 132.9,

144.9 ppm; MS (ESI): *m/z* 459 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{39}O_6SSi$: 459.2231, found: 459.2225.

(−)-(5-((*tert*-Butyldimethylsilyloxy)methyl)-*cis*-3,5-diethyl-1,2-dioxolan-3-yl)methanol ((−)-*cis*-**137b**)



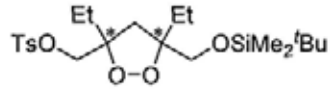
(−)-*cis*-**137b**

To a solution of racemic alcohol (±)-*cis*-**137** (1.11 g, 3.65 mmol) in hexane (40 mL) was added the Lipase PS from Burkholderia cepaci (555 mg) and vinyl acetate (1.68 mL, 18.3 mmol). The heterogeneous mixture is stirred vigorously at rt for 3 h before being filtered through a sintered glass funnel to recover the lipase catalyst. The catalyst was washed with Et_2O (20 mL), and the combined filtrates were concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (30 g, hexanes/EtOAc, 10:1) to afford (−)-*cis*-**245** (568 mg, 45%) and (+)-*cis*-**137a** (588 mg, 53%). (−)-*cis*-**245**: R_f = 0.50 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = −21.5 (*c*, 0.89, $CHCl_3$);

To a solution of acetate (−)-*cis*-**245** (568 mg, 1.64 mmol) in MeOH (30 mL) was added K_2CO_3 (226 mg, 1.64 mmol). The reaction mixture was stirred until the starting material had disappeared, the reaction mixture was acidified to *p*H 6 with 10% aqueous HCl. Removed the solvent under reduced pressure. The residue was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography on silica gel (30 g, hexanes/EtOAc, 10:1) to afford (−)-*cis*-**137b** (469 mg, 94%) as colorless oil : R_f = 0.35 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = −27.5 (*c* 0.47,

$CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 6H), 0.89 (s, 9H), 0.90 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H), 1.57-1.66 (m, 2H), 1.75-1.83 (m, 2H), 2.02 (bs, 1H), 2.06 (d, J = 12.3 Hz, 1H), 2.32 (d, J = 12.3 Hz, 1H), 3.46 (dd, J = 7.6 Hz, 11.9 Hz, 1H), 3.58 (d, J = 3.0 Hz, 2H), 3.72 (dd, J = 4.6 Hz, 11.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.4, 8.5, 8.9, 18.4, 25.9, 26.3, 28.0, 44.8, 63.9, 64.00, 89.1, 89.2 ppm; MS (ESI): *m/z* 327 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{15}H_{32}O_4SiNa$: 327.1962, found: 327.1968.

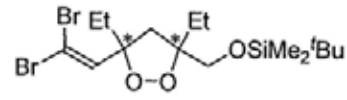
(–)-(5-((*tert*-Butyldimethylsilyloxy)methyl)-*cis*-3,5-diethyl-1,2-dioxolan-3-yl)methyl 4-methylbenzenesulfonate ((–)-*cis*-**272b**)



(–)-*cis*-**272b**

To increase the *ee*, (–)-*cis*-**137b** was resolved again. Then it was converted into (–)-*cis*-**272b** to determine the *ee* value. The procedure was similar to that for the preparation of (+)-*cis*-**272a** (*vide supra*): R_f = 0.40 (hexanes/EtOAc, 10:1); *ee* >99%; The *ee* values were determined by chiral HPLC; CHIRALPAK AD–H column; hexane/2-propanol 95/5; flow rate 1.0 mL/min; temp 25 °C; wavelength = 254 nm; retention time: 5.4 min; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.00 (s, 3H), 0.01 (s, 3H), 0.85 (s, 9H), 0.87 (t, J = 7.0 Hz, 6H), 1.52-1.66 (m, 2H), 1.71-1.82 (m, 2H), 2.03 (d, J = 12.6 Hz, 1H), 2.33 (d, J = 12.6 Hz, 1H), 2.44 (s, 3H), 3.48 (s, 2H), 3.91 (d, J = 10.1 Hz, 1H), 4.15 (d, J = 10.1 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.5, –5.4, 8.4, 18.3, 21.7, 25.9, 26.4, 28.1, 45.3, 63.2, 69.4, 86.7, 89.2, 128.0, 129.9, 132.9, 144.9 ppm; MS (ESI): *m/z* 459 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{39}O_6SSi$: 459.2231, found: 459.2225.

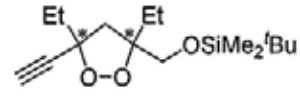
(+)-*tert*-Butyl((5-(2,2-dibromovinyl)-*cis*-3,5-diethyl-1,2-dioxolan-3-yl)methoxy)dimethylsilane ((+)-*cis*-**247a**)



(+)-*cis*-**247a**

The procedure was similar to that for the preparation of *trans*-**155** (*vide supra*); yield = 79% (two steps); R_f = 0.75 (hexanes/EtOAc, 20:1); $[\alpha]_D^{20}$ = −11.0 (*c*, 0.75, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H), 1.60-1.66 (m, 1H), 1.75-1.87 (m, 2H), 2.07-2.12 (m, 1H), 2.23 (d, *J* = 12.5 Hz, 1H), 2.80 (d, *J* = 12.5 Hz, 1H), 3.49 (d, *J* = 10.5 Hz, 1H), 3.58 (d, *J* = 10.5 Hz, 1H), 6.79 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.4, –5.3, 8.5, 8.9, 18.4, 25.9, 27.4, 29.1, 50.0, 64.1, 87.4, 88.9, 90.1, 142.5 ppm; IR (Neat): 2955, 2929, 2883, 2858, 1462, 1256, 1115, 838, 777 cm^{-1}; MS (ESI): *m/z* 459 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{31}Br_2O_3Si$: 459.0383, found: 459.0391.

(+)-*tert*-Butyl((*cis*-3,5-diethyl-5-ethynyl-1,2-dioxolan-3-yl)methoxy)dimethylsilane ((+)-*cis*-**248a**)

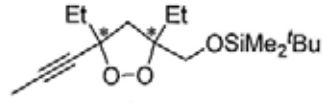


(+)-*cis*-**248a**

The procedure was similar to that for the preparation of *trans*-**148** (*vide supra*); yield = 95%; R_f = 0.55 (hexanes/ Et_2O 20:1); $[\alpha]_D^{20}$ = 17.0 (*c*, 1.60, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 0.92 (t, *J* = 7.5 Hz, 3H), 1.07 (t, *J* = 7.4 Hz, 3H), 1.60-1.67 (m, 1H), 1.67-1.80 (m, 2H), 1.85-1.92 (m, 1H), 2.25 (d, *J* = 12.4 Hz, 1H), 2.51 (s, 1H), 2.70 (d, *J* = 12.4 Hz, 1H), 3.70 (q, *J* = 10.3 Hz, 2H) ppm; ^{13}C

NMR (100 MHz, $CDCl_3$) δ = –5.4, –5.3, 8.4, 9.4, 18.3, 25.9, 27.1, 32.1, 52.5, 64.2, 73.7, 82.3, 83.4, 89.2, ppm; IR (Neat): 3311, 2956, 2931, 2883, 2858, 1472, 1463, 1259, 1111, 1007, 838, 670 cm^{-1}; MS (ESI): *m/z* 299 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{31}O_3Si$: 299.2037, found: 299.2037.

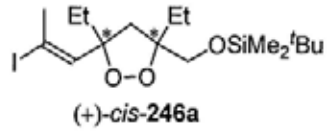
(+)-*tert*-Butyl((*cis*-3,5-diethyl-5-(prop-1-ynyl)-1,2-dioxolan-3-yl)methoxy)dimethylsilane ((+)-*cis*-**249a**)



(+)-*cis*-**249a**

The procedure was similar to that for the preparation of *trans*-**147** (*vide supra*); yield = 70%; R_f = 0.55 (hexanes/ Et_2O 20:1); $[\alpha]_D^{20}$ = 9.5 (*c*, 1.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 0.90 (t, *J* = 7.5 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H), 1.61-1.67 (m, 2H), 1.69-1.77 (m, 1H), 1.81-1.88 (m, 1H), 1.85 (s, 3H), 2.20 (d, *J* = 12.3 Hz, 1H), 2.60 (d, *J* = 12.3 Hz, 1H), 3.68 (q, *J* = 10.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.5, –5.3, 3.7, 8.4, 9.5, 18.3, 25.9, 26.9, 32.5, 52.3, 64.4, 78.6, 82.0, 82.7, 89.1, ppm; MS (ESI): *m/z* 335 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{32}O_3SiNa$: 335.2013, found: 335.2008.

(+)-(*E*)-*tert*-Butyl((*cis*-3,5-diethyl-5-(2-iodoprop-1-enyl)-1,2-dioxolan-3-yl)methoxy)dimethylsilane ((+)-*cis*-**246a**)

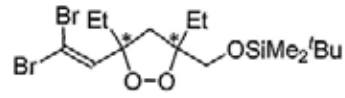


(+)-*cis*-**246a**

To a 10-mL, argon-filled, two-necked round-bottomed flask equipped with a magnetic stirring bar was added (+)-*cis*-**249a** (64 mg, 0.206 mmol) and $Pd(PPh_3)_2Cl_2$ (10 mol%).

The flask was evacuated and filled with argon three times, and then freshly distilled *n*-hexane (2 mL) was added via a syringe. Tributyltin hydride (4.0 equiv) was added slowly (about over 10 min) via a syringe. The reaction was stirred at 23 °C for 1 h, then immediately transferred to a silica gel column and rapidly eluted with hexanes until the excess $Bu_3SnH/(Bu_3Sn)_2$ is removed, followed by elution with a mixture of hexanes and ethyl acetate (10:1) to obtain the stannane compound **250a** (104 mg, 84%) as a colorless oil: R_f = 0.60 (hexanes/EtOAc, 20:1). The obtained stannane compound was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. I_2 (43 mg, 0.17 mmol) in CH_2Cl_2 (1 mL) was added and the resulting mixture was stirred at 0 °C for 5-8 min then worked up by a saturated aq. $Na_2S_2O_3$ solution (3 mL) and extracted by Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (hexanes/EtOAc, 20:1) to give **246a** (65 mg, 86%) as an oil: R_f = 0.50 (hexanes/EtOAc, 20:1); $[\alpha]_D^{20}$ = 1.2 (*c*, 2.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H), 1.58-1.74 (m, 2H), 1.76-1.88 (m, 2H), 2.18 (d, *J* = 12.2 Hz, 1H), 2.42 (d, *J* = 12.2 Hz, 1H), 2.53 (d, *J* = 0.7 Hz, 3H), 3.50 (d, *J* = 10.4 Hz, 1H), 3.62 (d, *J* = 10.4 Hz, 1H), 6.14 (d, *J* = 0.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.4, –5.3, 8.5, 9.0, 18.3, 25.9, 27.0, 30.3, 31.8, 51.3, 64.4, 88.4, 90.6, 96.6, 142.2 ppm; MS (ESI): *m/z* 441 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{34}IO_3Si$: 441.1316, found: 441.1320.

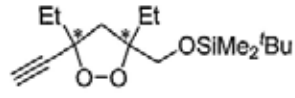
(–)-*tert*-Butyl((5-(2,2-dibromovinyl)-*cis*-3,5-diethyl-1,2-dioxolan-3-yl)methoxy)dimethylsilane ((–)-*cis*-247b)



(–)-*cis*-**247b**

The procedure was similar to that for the preparation of *trans*-**155** (*vide supra*); yield = 79% (two steps); R_f = 0.75 (hexanes/EtOAc, 20:1); $[\alpha]_D^{20}$ = 10.0 (*c*, 2.55, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H), 1.60-1.66 (m, 1H), 1.75-1.87 (m, 2H), 2.07-2.12 (m, 1H), 2.23 (d, *J* = 12.5 Hz, 1H), 2.80 (d, *J* = 12.5 Hz, 1H), 3.49 (d, *J* = 10.5 Hz, 1H), 3.58 (d, *J* = 10.5 Hz, 1H), 6.79 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.4, –5.3, 8.5, 8.9, 18.4, 25.9, 27.4, 29.1, 50.0, 64.1, 87.4, 88.9, 90.1, 142.5 ppm; MS (ESI): *m/z* 459 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{31}Br_2O_3Si$: 459.0383, found: 459.0385.

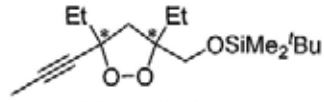
(–)-*tert*-Butyl((*cis*-3,5-diethyl-5-ethynyl-1,2-dioxolan-3-yl)methoxy)dimethylsilane ((–)-*cis*-248b)



(–)-*cis*-**248b**

The procedure was similar to that for the preparation of *trans*-**148** (*vide supra*); yield = 95%; R_f = 0.55 (hexanes/EtOAc, 20:1); $[\alpha]_D^{20}$ = –17.5 (*c* 0.64, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 0.92 (t, *J* = 7.5 Hz, 3H), 1.07 (t, *J* = 7.4 Hz, 3H), 1.56-1.65 (m, 1H), 1.67-1.80 (m, 2H), 1.85-1.94 (m, 1H), 2.25 (d, *J* = 12.4 Hz, 1H), 2.52 (s, 1H), 2.70 (d, *J* = 12.4 Hz, 1H), 3.70 (q, *J* = 10.3 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.4, –5.3, 8.4, 9.4, 18.3, 25.9, 27.1, 32.1, 52.5, 64.2, 73.7, 82.3, 83.4, 89.2 ppm; MS (ESI): *m/z* 299 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{31}O_3Si$: 299.2037, found: 299.2032.

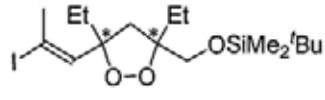
(−)-*tert*-Butyl((*cis*-3,5-diethyl-5-(prop-1-ynyl)-1,2-dioxolan-3-yl)methoxy)dimethylsilane ((−)-*cis*-**249b**)



(−)-*cis*-**249b**

The procedure was similar to that for the preparation of *trans*-**147** (*vide supra*); yield = 70%; R_f = 0.75 (hexanes/EtOAc, 20:1); $[\alpha]_D^{20}$ = –9.0 (*c*, 2.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 0.90 (t, *J* = 7.5 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H), 1.61-1.67 (m, 2H), 1.69-1.77 (m, 1H), 1.81-1.88 (m, 1H), 1.85 (s, 3H), 2.20 (d, *J* = 12.3 Hz, 1H), 2.60 (d, *J* = 12.3 Hz, 1H), 3.69 (q, *J* = 10.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.5, –5.3, 3.7, 8.4, 9.5, 18.3, 25.9, 26.9, 32.5, 52.3, 64.4, 78.6, 82.0, 82.7, 89.1 ppm; MS (ESI): *m/z* 335 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{32}O_3SiNa$: 335.2013, found: 335.2016.

(−)-(*E*)-*tert*-Butyl((*cis*-3,5-diethyl-5-(2-iodoprop-1-enyl)-1,2-dioxolan-3-yl)methoxy)dimethylsilane ((−)-*cis*-**246b**)

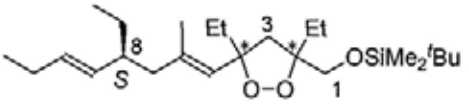


(−)-*cis*-**246b**

The procedure was similar to that for the preparation of (+)-*cis*-**246a** (*vide supra*): yield = 72% (two steps); R_f = 0.50 (hexanes/EtOAc, 20:1); $[\alpha]_D^{20}$ = -1.5 (*c*, 1.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H), 1.58-1.74 (m, 2H), 1.76-1.88 (m, 2H), 2.18 (d, *J* = 12.2 Hz, 1H), 2.42 (d, *J* = 12.2 Hz, 1H), 2.53 (d, *J* = 0.7 Hz, 3H), 3.50 (d, *J* = 10.4 Hz, 1H), 3.62 (d, *J* = 10.4 Hz, 1H), 6.14 (d, *J* = 0.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ

= –5.4, –5.3, 8.5, 9.0, 18.3, 25.9, 27.0, 30.3, 31.8, 51.3, 64.4, 88.4, 90.6, 96.6, 142.2 ppm; MS (ESI): *m/z* 441 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{34}IO_3Si$: 441.1316, found: 441.1322.

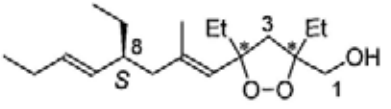
***tert*-Butyl(((+)-*cis*-3,5-diethyl-5-((*S*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)methoxy)dimethylsilane** ((8*S*)-(+)-*cis*-**251a**)



(8*S*)-(+)-*cis*-**251a**

The synthesis of (8*S*)-(+)-*cis*-**251a** was similar to that for the preparation of **206** (*vide supra*): yield = 93%; R_f = 0.50 (hexanes/EtOAc, 20:1); $[\alpha]_D^{20}$ = 60.5 (*c*, 0.47, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = -0.04 (s, 3H), 0.05 (s, 3H), 0.83 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.88 (s, 9H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H), 1.09- 1.17 (m, 1H), 1.34- 1.41 (m, 1H), 1.58-1.65 (m, 2H), 1.63 (d, *J* = 1.1 Hz, 3H), 1.73-1.83 (m, 1H), 1.85-1.92 (m, 2H), 1.94-2.04 (m, 4H), 2.03 (d, *J* = 12.6 Hz, 1H), 2.24 (s, 2H), 3.42 (d, *J* = 10.3 Hz, 1H), 3.64 (d, *J* = 10.3 Hz, 1H), 5.07 (dd, *J* = 8.3, 15.3 Hz, 1H), 5.18 (s, 1H), 5.36 (dt, *J* = 6.3, 15.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.5, –5.2, 8.8, 9.0, 11.7, 14.1, 17.9, 18.3, 25.7, 25.9, 26.3, 27.6, 32.2, 42.6, 46.6, 51.9, 64.5, 88.3, 88.7, 127.3, 131.9, 132.9, 135.9 ppm; MS (ESI): *m/z* 447 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{48}O_3SiNa$: 447.3265, found: 447.3279.

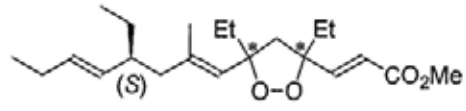
((+)-*cis*-3,5-Diethyl-5-((*S*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)methanol ((8*S*)-(+)-*cis*-**252a**).



(8*S*)-(+)-*cis*-**252a**

The procedure was similar to that for the preparation of **208** (*vide supra*): yield = 89%; R_f = 0.30 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = −81.2 (*c*, 0.29, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.83 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.6 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H), 1.09- 1.20 (m, 1H), 1.31- 1.40 (m, 1H), 1.54-1.68 (m, 2H), 1.64 (d, *J* = 0.8 Hz, 3H), 1.73-1.83 (m, 1H), 1.85-1.92 (m, 2H), 1.94-2.06 (m, 5H), 2.28 (q, *J* = 11.9 Hz, 2H), 3.40 (dd, *J* = 7.0, 11.7 Hz, 1H), 3.62 (dd, *J* = 4.0, 11.8 Hz, 1H), 5.05 (dd, *J* = 8.4, 15.2 Hz, 1H), 5.17 (s, 1H), 5.36 (dt, *J* = 6.3, 15.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.0, 9.0, 11.7, 14.1, 17.9, 25.7, 26.0, 27.9, 32.2, 42.7, 46.6, 51.2, 64.5, 88.8, 89.5, 126.7, 132.1, 132.7, 136.7 ppm; MS (ESI): *m/z* 333 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{34}O_3Na$: 333.2400, found: 333.2400.

(*E*)-Methyl 3-((+)-*cis*-3,5-diethyl-5-((*S*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)acrylate (*S*-(+)-*cis*-**86a**).

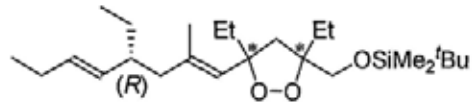


S-(+)-*cis*-**86a**

The procedure was similar to that for the preparation of **210** (*vide supra*): yield = 80% (two steps); R_f = 0.50 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = -86.0 (*c*, 0.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.80 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H), 1.07-1.14 (m, 1H), 1.31-1.38 (m, 1H), 1.61 (d, *J* = 0.7 Hz, 3H), 1.62-1.69 (m, 1H), 1.70-1.82 (m, 2H), 1.83-1.93 (m, 2H), 1.94-2.02 (m, 4H), 2.44 (d, *J* = 11.9 Hz, 1H), 2.54 (d, *J* = 11.9 Hz, 1H), 3.73 (s, 3H), 5.05 (dd, *J* = 8.3, 15.2 Hz, 1H), 5.11 (s, 1H), 5.34 (dt, *J* = 15.2, 6.3 Hz, 1H), 6.07 (d, *J* = 15.8 Hz, 1H), 6.85 (d, *J* = 15.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.9, 8.9, 11.6, 14.1, 17.8, 25.6, 27.6, 30.9, 32.2, 42.6, 46.6, 51.6, 56.0, 87.2, 89.3, 119.9 126.7, 132.0, 132.8, 136.6,

149.80, 167.1 ppm; IR (Neat): 2963, 2919, 2849, 1720, 1656, 1461, 1262, 798 cm^{-1}; MS (ESI): *m/z* 382 $[M+NH_4]^+$; HRMS (ESI) *m/z* $[M+NH_4]^+$ calcd for $C_{22}H_{40}O_4N$: 382.2952, found: 382.2943.

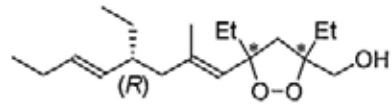
***tert*-Butyl(((−)-*cis*-3,5-diethyl-5-((*R*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)methoxy)dimethylsilane** ((8*R*)-(−)-*cis*-**251d**)



(8*R*)-(−)-*cis*-**251d**

The synthesis of **251d** was similar to that for the preparation of **206** (*vide supra*): yield = 93%; R_f = 0.50 (hexanes/EtOAc, 20:1); $[\alpha]_D^{20}$ = 62.0 (*c*, 1.12, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.04 (s, 3H), 0.05 (s, 3H), 0.83 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.88 (s, 9H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H), 1.09- 1.17 (m, 1H), 1.34- 1.41 (m, 1H), 1.58-1.65 (m, 2H), 1.63 (d, *J* = 1.1 Hz, 3H), 1.73-1.83 (m, 1H), 1.85-1.92 (m, 2H), 1.94-2.04 (m, 4H), 2.03 (d, *J* = 12.6 Hz, 1H), 2.24 (s, 2H), 3.42 (d, *J* = 10.3 Hz, 1H), 3.64 (d, *J* = 10.3 Hz, 1H), 5.07 (dd, *J* = 8.3, 15.3 Hz, 1H), 5.18 (s, 1H), 5.36 (dt, *J* = 6.3, 15.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.5, –5.2, 8.8, 9.0, 11.7, 14.1, 17.9, 18.3, 25.7, 25.9, 26.3, 27.6, 32.2, 42.6, 46.6, 51.9, 64.5, 88.3, 88.7, 127.3, 131.9, 132.9, 135.9 ppm; IR (Neat): 2961, 2930, 2857, 1463, 1263, 1119, 741 cm^{-1}; MS (ESI): *m/z* 447 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{48}O_3SiNa$: 447.3265, found: 447.3259.

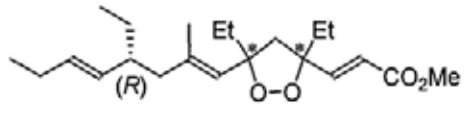
((−)-*cis*-3,5-Diethyl-5-((*R*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)methanol ((8*R*)-(−)-*cis*-**252d**).



(8*R*)-(–)-*cis*-**252d**

The procedure was similar to that for the preparation of **208** (*vide supra*): yield = 86%; R_f = 0.30 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = 80.0 (*c*, 0.80, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.82 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.6 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H), 1.09- 1.20 (m, 1H), 1.31- 1.40 (m, 1H), 1.54-1.68 (m, 2H), 1.63 (d, *J* = 0.5 Hz, 3H), 1.73-1.83 (m, 1H), 1.85-1.92 (m, 2H), 1.94-2.06 (m, 5H), 2.28 (q, *J* = 11.9 Hz, 2H), 3.40 (dd, *J* = 7.8, 11.8 Hz, 1H), 3.62 (dd, *J* = 5.3, 11.8 Hz, 1H), 5.05 (dd, *J* = 8.4, 15.2 Hz, 1H), 5.17 (s, 1H), 5.35 (dt, *J* = 6.3, 15.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.0, 9.0, 11.7, 14.1, 17.9, 25.7, 26.0, 27.9, 32.2, 42.7, 46.6, 51.2, 64.5, 88.8, 89.5, 126.7, 132.1, 132.7, 136.7 ppm; MS (ESI): *m/z* 333 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{34}O_3Na$: 333.2400, found: 333.2404.

(*E*)-Methyl 3-((–)-*cis*-3,5-diethyl-5-((*R*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)acrylate (*R*-(–)-*cis*-**86d**).[34]

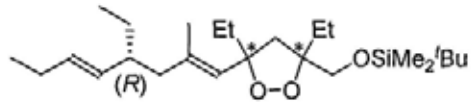


R-(–)-*cis*-**86d**

The procedure was similar to that for the preparation of **210** (*vide supra*): yield = 80% (two steps); R_f = 0.50 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = 87.0 (*c*, 0.85, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H), 1.07-1.14 (m, 1H), 1.31-1.38 (m, 1H), 1.61 (d, *J* = 0.7 Hz, 3H), 1.62-1.69 (m, 1H), 1.70-1.82 (m, 2H), 1.83-1.93 (m, 2H), 1.94-2.02 (m, 4H),

2.44 (d, J = 11.9 Hz, 1H), 2.54 (d, J = 11.9 Hz, 1H), 3.73 (s, 3H), 5.05 (dd, J = 8.3, 15.2 Hz, 1H), 5.11 (s, 1H), 5.34 (dt, J = 15.2, 6.3 Hz, 1H), 6.07 (d, J = 15.8 Hz, 1H), 6.85 (d, J = 15.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.9, 8.9, 11.6, 14.1, 17.8, 25.6, 27.6, 30.9, 32.2, 42.6, 46.6, 51.6, 56.0, 87.2, 89.3, 119.9 126.7, 132.0, 132.8, 136.6, 149.80, 167.1 ppm; IR (Neat): 2963, 2920, 2875, 2850, 1720, 1657, 1462, 1303, 1262, 1038, 798 cm^{-1}; MS (ESI): *m/z* 387 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{36}O_4Na$: 387.2506, found: 387.2505.

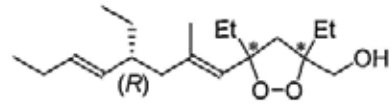
***tert*-Butyl(((+)-*cis*-3,5-diethyl-5-((*R*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)methoxy)dimethylsilane** ((8*R*)-(+)-*cis*-**251b**)



(8*R*)-(+)-*cis*-**251b**

The synthesis of **251b** was similar to that for the preparation of **206** (*vide supra*): yield = 93%; R_f = 0.50 (hexanes/EtOAc, 20:1); $[\alpha]_D^{20}$ = –47.1 (*c*, 0.93, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3H), 0.05 (s, 3H), 0.81 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H), 0.88 (s, 9H), 0.92 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 1.59-1.64 (m, 2H), 1.61 (d, J = 0.6 Hz, 3H), 1.74-1.81 (m, 2H), 1.83-1.92 (m, 2H), 1.94-2.04 (m, 4H), 2.23 (d, J = 12.0 Hz, 1H), 2.31 (d, J = 12.0 Hz, 1H), 3.43 (d, J = 10.2 Hz, 1H), 3.64 (d, J = 10.2 Hz, 1H), 5.06 (dd, J = 8.3, 15.2 Hz, 1H), 5.20 (s, 1H), 5.36 (dt, J = 6.3, 15.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5, –5.2, 8.7, 8.9, 11.7, 14.1, 17.8, 18.3, 25.7, 25.9, 26.4, 27.9, 32.2, 42.7, 46.6, 51.8, 64.7, 88.3, 88.7, 127.6, 132.0, 132.9, 135.5 ppm; MS (ESI): *m/z* 447 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{48}O_3SiNa$: 447.3265, found: 447.3265.

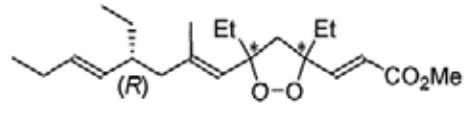
((+)-*cis*-3,5-Diethyl-5-((*R*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)methanol ((8*R*)-(+)-*cis*-**252b**).



(8*R*)-(+)-*cis*-**252b**

The procedure was similar to that for the preparation of **208** (*vide supra*): yield = 86%; R_f = 0.30 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = −43.5 (*c*, 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 6H), 1.13- 1.18 (m, 1H), 1.31- 1.41 (m, 1H), 1.56-1.68 (m, 2H), 1.62 (d, *J* = 1.2 Hz, 3H), 1.72-1.80 (m, 1H), 1.82-1.91 (m, 2H), 1.94-2.07 (m, 5H), 2.31 (s, 2H), 3.41 (dd, *J* = 6.3, 11.8 Hz, 1H), 3.61 (dd, *J* = 4.0, 11.8 Hz, 1H), 5.05 (ddt, *J* = 1.4, 8.5, 15.2 Hz, 1H), 5.18 (s, 1H), 5.36 (dt, *J* = 6.3, 15.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 8.9, 9.0, 11.7, 14.1, 17.8, 25.7, 26.2, 28.0, 32.1, 42.7, 46.6, 51.2, 64.5, 88.8, 89.5, 126.9, 132.3, 132.7, 136.5 ppm; MS (ESI): *m/z* 333 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{34}O_3Na$: 333.2400, found: 333.2391.

(*E*)-Methyl 3-((+)-*cis*-3,5-diethyl-5-((*R*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)acrylate (*R*-(+)-*cis*-**86b**).

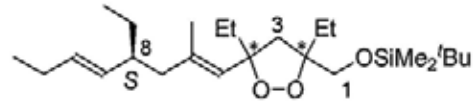


R-(+)-*cis*-**86b**

The procedure was similar to that for the preparation of **210** (*vide supra*): yield = 80% (two steps); R_f = 0.50 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = -74.8 (*c*, 0.39, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H), 1.10-1.13 (m, 1H), 1.30-1.35 (m, 1H), 1.59 (s, 3H),

1.61-1.67 (m, 1H), 1.70-1.81 (m, 2H), 1.82-1.89 (m, 2H), 1.89-2.02 (m, 4H), 2.44 (d, J = 11.9 Hz, 1H), 2.58 (d, J = 11.8 Hz, 1H), 3.74 (s, 3H), 5.04 (dd, J = 8.0, 15.2 Hz, 1H), 5.15 (s, 1H), 5.34 (dt, J = 15.2, 6.4 Hz, 1H), 6.08 (d, J = 15.8 Hz, 1H), 6.86 (d, J = 15.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.9, 8.9, 11.7, 14.1, 17.8, 25.7, 27.8, 30.9, 32.2, 42.7, 46.5, 51.7, 55.8, 87.4, 89.2, 120.0, 127.1, 132.0, 132.8, 136.1, 149.8, 167.1 ppm; MS (ESI): *m/z* 387 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{36}O_4Na$: 387.2506, found: 387.2507.

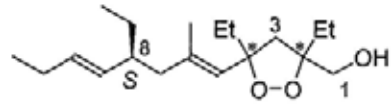
***tert*-Butyl(((−)-*cis*-3,5-diethyl-5-((*S*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)methoxy)dimethylsilane** ((8*S*)-(−)-*cis*-**251c**)



(8*S*)-(−)-*cis*-**251c**

The synthesis of **251c** was similar to that for the preparation of **206** (*vide supra*): yield = 93%; R_f = 0.50 (hexanes/EtOAc, 20:1); $[\alpha]_D^{20}$ = 46.5 (*c*, 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3H), 0.05 (s, 3H), 0.81 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H), 0.88 (s, 9H), 0.92 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 1.59-1.64 (m, 2H), 1.61 (s, 3H), 1.74-1.81 (m, 2H), 1.83-1.92 (m, 2H), 1.94-2.04 (m, 4H), 2.23 (d, J = 12.0 Hz, 1H), 2.31 (d, J = 12.0 Hz, 1H), 3.43 (d, J = 10.2 Hz, 1H), 3.64 (d, J = 10.2 Hz, 1H), 5.06 (dd, J = 8.2, 15.2 Hz, 1H), 5.20 (s, 1H), 5.36 (dt, J = 6.2, 15.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.5, −5.2, 8.7, 8.9, 11.7, 14.1, 17.8, 18.3, 25.7, 25.9, 26.4, 27.9, 32.2, 42.7, 46.6, 51.8, 64.7, 88.3, 88.7, 127.6, 132.0, 132.9, 135.5 ppm; MS (ESI): *m/z* 447 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{48}O_3SiNa$: 447.3265, found: 447.3254.

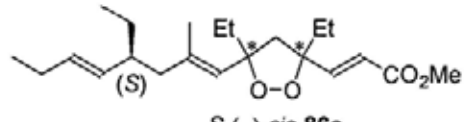
((–)-*cis*-3,5-Diethyl-5-((*S*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)methanol ((8*S*)-(–)-*cis*-**252c**).



(8*S*)-(–)-*cis*-**252c**

The procedure was similar to that for the preparation of **208** (*vide supra*): yield = 86%; R_f = 0.30 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = 44.0 (*c*, 0.27, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 6H), 1.13- 1.18 (m, 1H), 1.31- 1.41 (m, 1H), 1.56-1.68 (m, 2H), 1.62 (d, *J* = 1.2 Hz, 3H), 1.72-1.80 (m, 1H), 1.82-1.91 (m, 2H), 1.94-2.07 (m, 5H), 2.31 (s, 2H), 3.41 (dd, *J* = 6.3, 11.8 Hz, 1H), 3.61 (dd, *J* = 4.0, 11.8 Hz, 1H), 5.05 (ddt, *J* = 1.4, 8.5, 15.2 Hz, 1H), 5.18 (s, 1H), 5.36 (dt, *J* = 6.3, 15.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 8.9, 9.0, 11.7, 14.1, 17.8, 25.7, 26.2, 28.0, 32.1, 42.7, 46.6, 51.2, 64.5, 88.8, 89.5, 126.9, 132.3, 132.7, 136.5 ppm; MS (ESI): *m/z* 333 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{34}O_3Na$: 333.2400, found: 333.2395.

(*E*)-Methyl 3-((–)-*cis*-3,5-diethyl-5-((*S*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)acrylate (*S*-(–)-*cis*-**86c**).

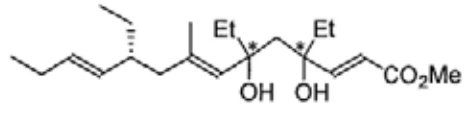


S-(–)-*cis*-**86c**

The procedure was similar to that for the preparation of **210** (*vide supra*): yield = 80% (two steps); R_f = 0.50 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = 75.0 (*c*, 0.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.5

Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H), 1.10-1.13 (m, 1H), 1.30-1.35 (m, 1H), 1.59 (s, 3H), 1.61-1.67 (m, 1H), 1.70-1.81 (m, 2H), 1.82-1.89 (m, 2H), 1.89-2.02 (m, 4H), 2.44 (d, J = 11.9 Hz, 1H), 2.58 (d, J = 11.8 Hz, 1H), 3.74 (s, 3H), 5.04 (dd, J = 8.0, 15.2 Hz, 1H), 5.15 (s, 1H), 5.34 (dt, J = 15.2, 6.4 Hz, 1H), 6.08 (d, J = 15.8 Hz, 1H), 6.86 (d, J = 15.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.9, 8.9, 11.7, 14.1, 17.8, 25.7, 27.8, 30.9, 32.2, 42.7, 46.5, 51.7, 55.8, 87.4, 89.2, 120.0, 127.1, 132.0, 132.8, 136.1, 149.8, 167.1 ppm; MS (ESI): *m/z* 382 $[M+NH_4]^+$; HRMS (ESI) *m/z* $[M+NH_4]^+$ calcd for $C_{22}H_{40}O_4N$: 382.2952, found: 382.2961.

(−)-(2*E*,7*E*,10*R*,11*E*)-Methyl 4,6,10-triethyl-4,6-dihydroxy-8-methyltetradeca-2,7,11-trienoate (*R*-(−)-*cis*-**268d**).

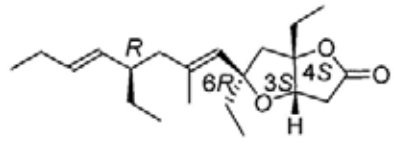


R-(−)-*cis*-**268d**

To a 25-mL round-bottomed flask equipped with a magnetic stirring bar was added **86d** (18 mg, 0.05 mmol) and Zn power (160 mg, 2.5 mmol), CH_2Cl_2 (1 mL) was added via syringe, and then 0.5 mL AcOH was added dropwiseat 0 °C. The mixture was stirred at room temperature, TLC monitor the reaction until the starting material disappeared. Two hours later, the reaction completed. Chromatography gave the product (18 mg, 99%): R_f = 0.30 (hexanes/EtOAc, 4:1); $[\alpha]_D^{20}$ = −34.4 (*c*, 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, J = 7.4 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H), 1.09-1.19 (m, 1H), 1.28-1.35 (m, 2H), 1.45-1.60 (m, 5H), 1.63 (d, J = 0.7 Hz, 3H), 1.75-1.81 (m, 1H), 1.87-2.06 (m, 6H), 3.71 (s, 3H), 4.87 (s, 1H), 5.02 (dd, J = 8.6, 15.2 Hz, 1H), 5.32 (dt, J = 15.2, 6.3 Hz, 1H), 6.03 (d, J = 15.5 Hz, 1H), 6.93

(d, J = 15.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.4, 7.5, 11.8, 14.1, 17.1, 25.9, 28.3, 35.6, 37.1, 42.7, 47.7, 50.4, 51.4, 76.0, 78.6, 117.6, 130.5, 132.0, 133.0, 135.7, 155.0, 167.4 ppm; MS (ESI): *m/z* 389 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{38}O_4Na$: 389.2662, found: 389.2668.

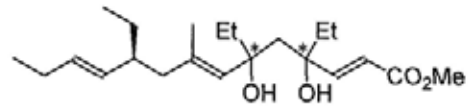
(3a*S*,5*R*,6a*S*)-5,6a-Diethyl-5-((*R*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-tetrahydrofuro[3,2-b]furan-2(5*H*)-one ((3*S*,4*S*,6*R*,10*R*)-Plakortone B (**87a**)).[34,35b,36]



(3*S*,4*S*,6*R*,10*R*)-Plakortone B (**87a**)

To a solution of **268d** (16 mg, 0.044 mmol) in toluene (5 mL) was added DBU (20 mol%) at 25 °C. The reaction mixture was allowed to reflux for 24 h and then concentrated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (hexanes/EtOAc, 10:1) to afford **87a** (13 mg, 90%). R_f = 0.30 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = −15.4 (*c*, 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, J = 7.4 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 1.09-1.17 (m, 1H), 1.32-1.39 (m, 1H), 1.63-1.67 (m, 2H), 1.69 (d, J = 1.1 Hz, 3H), 1.70-1.81 (m, 2H), 1.82-1.90 (m, 1H), 1.94-2.04 (m, 4H), 2.14 (d, J = 13.8 Hz, 1H), 2.24 (d, J = 13.8 Hz, 1H), 2.64 (dd, J = 1.2, 18.4 Hz, 1H), 2.71 (dd, J = 5.1, 18.4 Hz, 1H), 4.21 (dd, J = 1.1, 5.0 Hz, 1H), 5.03 (s, 1H), 5.06 (ddt, J = 1.0, 8.4, 15.3 Hz, 1H), 5.36 (dt, J = 6.3, 15.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.4, 8.8, 11.7, 14.1, 16.8, 25.7, 27.9, 30.4, 33.9, 36.8, 42.8, 47.0, 49.1, 79.6, 87.1, 97.4, 129.6, 132.1, 132.8, 137.3, 175.8 ppm; MS (ESI): *m/z* 335 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{35}O_3$: 335.2581, found: 335.2574.

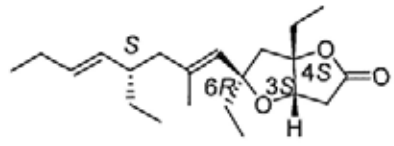
(−)-(2*E*,7*E*,10*S*,11*E*)-Methyl 4,6,10-triethyl-4,6-dihydroxy-8-methyltetradeca-2,7,11-trienoate (*S*-(−)-*cis*-**268c**)



S-(−)-*cis*-**268c**

The procedure was similar to that for the preparation of *R*-(−)-*cis*-**268d** (*vide supra*): R_f = 0.30 (hexanes/EtOAc, 4:1); $[\alpha]_D^{20}$ = –48.5 (*c*, 0.20, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.5 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 6H), 0.94 (t, *J* = 7.4 Hz, 3H), 1.07-1.14 (m, 1H), 1.28-1.38 (m, 2H), 1.45-1.65 (m, 5H), 1.63 (d, *J* = 0.8 Hz, 3H), 1.75-1.77 (m, 1H), 1.92-2.01 (m, 6H), 3.71 (s, 3H), 4.93 (s, 1H), 5.04 (dd, *J* = 8.3, 15.2 Hz, 1H), 5.34 (dt, *J* = 15.3, 6.3 Hz, 1H), 6.03 (d, *J* = 15.5 Hz, 1H), 6.93 (d, *J* = 15.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.4, 7.5, 11.6, 14.1, 17.3, 25.7, 27.8, 35.6, 36.8, 42.6, 47.5, 50.3, 51.4, 76.0, 78.3, 117.7, 131.1 132.0, 133.1, 135.5, 155.2, 167.4 ppm; MS (ESI): *m/z* 389 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{38}O_4Na$: 389.2662, found: 389.2663.

(3a*S*,5*R*,6a*S*)-5,6a-Diethyl-5-((*S*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-tetrahydrofuro[3,2-b]furan-2(5*H*)-one ((3*S*,4*S*,6*R*,10*S*)-**87b**).[35b]

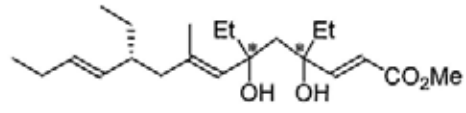


(3*S*,4*S*,6*R*,10*S*)-**87b**

The procedure was similar to that for the preparation of **87a** (*vide supra*): R_f = 0.3 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = –31.0 (*c*, 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.98 (t, *J* = 7.4

Hz, 3H), 1.09-1.17 (m, 1H), 1.32-1.38 (m, 1H), 1.63-1.76 (m, 4H), 1.68 (d, J = 1.1 Hz, 3H), 1.82-1.90 (m, 1H), 1.94-2.04 (m, 4H), 2.14 (d, J = 13.7 Hz, 1H), 2.24 (d, J = 13.7 Hz, 1H), 2.64 (dd, J = 1.2, 18.6 Hz, 1H), 2.71 (dd, J = 5.1, 18.6 Hz, 1H), 4.19 (dd, J = 1.1, 5.0 Hz, 1H), 5.04 (s, 1H), 5.05 (dd, J = 8.8, 15.3 Hz, 1H), 5.36 (dt, J = 6.3, 15.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.5, 8.9, 11.7, 14.2, 16.8, 25.8, 28.1, 30.4, 33.8, 36.8, 42.7, 47.0, 48.9, 79.7, 87.0, 97.4, 129.7, 132.1, 132.9, 137.3, 175.7 ppm; MS (ESI): m/z 357 $[M+Na]^+$; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{22}H_{34}O_3Na$: 357.2400, found: 357.2403.

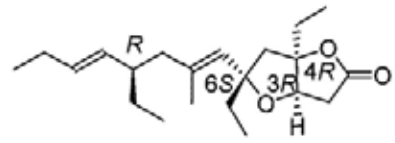
(+)-(2*E*,7*E*,10*R*,11*E*)-Methyl 4,6,10-triethyl-4,6-dihydroxy-8-methyltetradeca-2,7,11-trienoate (*R*-(+)-*cis*-268b)



R-(+)-*cis*-**268b**

The procedure was similar to that for the preparation of **268d** (*vide supra*): R_f = 0.30 (hexanes/EtOAc, 4:1); $[\alpha]_D^{20}$ = 45.5 (*c*, 0.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, J = 7.5 Hz, 3H), 0.83 (t, J = 7.4 Hz, 6H), 0.94 (t, J = 7.4 Hz, 3H), 1.07-1.14 (m, 1H), 1.28-1.38 (m, 2H), 1.45-1.65 (m, 5H), 1.63 (d, J = 0.8 Hz, 3H), 1.75-1.77 (m, 1H), 1.92-2.01 (m, 6H), 3.71 (s, 3H), 4.93 (s, 1H), 5.04 (dd, J = 8.3, 15.2 Hz, 1H), 5.34 (dt, J = 15.3, 6.3 Hz, 1H), 6.03 (d, J = 15.5 Hz, 1H), 6.93 (d, J = 15.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.3, 7.4, 11.6, 14.0, 17.1, 25.6, 27.7, 35.5, 36.7, 42.5, 47.4, 50.1, 51.3, 76.0, 78.3, 117.6, 131.0, 132.0, 133.0, 135.4, 155.2, 167.4 ppm; MS (ESI): m/z 389 $[M+Na]^+$; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{22}H_{38}O_4Na$: 389.2662, found: 389.2677.

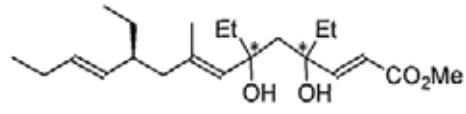
(3a*R*,5S,6a*R*)-5,6a-Diethyl-5-((*R*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-tetrahydrofuro[3,2-b]furan-2(5*H*)-one ((3*R*,4*R*,6*S*,10*R*)-*ent*-**87b**).[35b]



(3*R*,4*R*,6*S*,10*R*)-*ent*-**87b**

The procedure was similar to that for the preparation of **87a** (*vide supra*): R_f = 0.30 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = 33.0 (*c*, 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.98 (t, *J* = 7.4 Hz, 3H), 1.09-1.17 (m, 1H), 1.32-1.38 (m, 1H), 1.63-1.76 (m, 4H), 1.68 (d, *J* = 1.1 Hz, 3H), 1.82-1.90 (m, 1H), 1.94-2.04 (m, 4H), 2.14 (d, *J* = 13.7 Hz, 1H), 2.24 (d, *J* = 13.7 Hz, 1H), 2.64 (dd, *J* = 1.2, 18.6 Hz, 1H), 2.71 (dd, *J* = 5.1, 18.6 Hz, 1H), 4.19 (dd, *J* = 1.1, 5.0 Hz, 1H), 5.04 (s, 1H), 5.05 (dd, *J* = 8.8, 15.3 Hz, 1H), 5.36 (dt, *J* = 6.3, 15.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.5, 8.9, 11.7, 14.2, 16.8, 25.8, 28.1, 30.4, 33.8, 36.8, 42.7, 47.0, 48.9, 79.7, 87.0, 97.4, 129.7, 132.1, 132.9, 137.3, 175.8 ppm; MS (ESI): *m/z* 335 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{35}O_3$: 335.2581, found: 335.2580.

(+)-(2*E*,7*E*,10*S*,11*E*)-Methyl 4,6,10-triethyl-4,6-dihydroxy-8-methyltetradeca-2,7,11-trienoate (*S*-(+)-*cis*-**268a**)

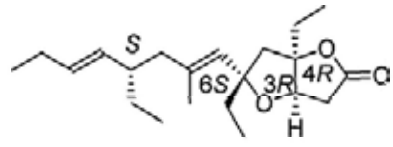


S-(+)-*cis*-**268a**

The procedure was similar to that for the preparation of **268d** (*vide supra*): R_f = 0.30 (hexanes/EtOAc, 4:1); $[\alpha]_D^{20}$ = 33.9 (*c*, 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ =

0.81 (t, J = 7.4 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H), 1.09-1.19 (m, 1H), 1.28-1.35 (m, 2H), 1.45-1.60 (m, 5H), 1.63 (d, J = 0.7 Hz, 3H), 1.75-1.81 (m, 1H), 1.87-2.06 (m, 6H), 3.71 (s, 3H), 4.87 (s, 1H), 5.02 (dd, J = 8.6, 15.2 Hz, 1H), 5.32 (dt, J = 15.2, 6.3 Hz, 1H), 6.04 (d, J = 15.5 Hz, 1H), 6.94 (d, J = 15.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.4, 7.5, 11.8, 14.1, 17.1, 25.9, 28.3, 35.6, 37.1, 42.7, 47.7, 50.4, 51.4, 76.0, 78.6, 117.6, 130.5, 132.0, 133.0, 135.7, 155.0, 167.4 ppm; MS (ESI): *m/z* 389 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{38}O_4Na$: 389.2662, found: 389.2657.

(3a*R*,5*S*,6a*R*)-5,6a-Diethyl-5-((*S*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-tetrahydrofuro[3,2-b]furan-2(5*H*)-one ((3*R*,4*R*,6*S*,10*S*)-*ent*-**87a**).[35b]

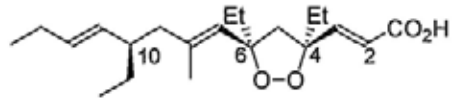


(3*R*,4*R*,6*S*,10*S*)-***ent*-87a**

The procedure was similar to that for the preparation of **87a** (*vide supra*): R_f = 0.30 (hexanes/EtOAc, 10:1); $[\alpha]_D^{20}$ = 15.0 (*c*, 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, J = 7.4 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 1.09-1.17 (m, 1H), 1.32-1.39 (m, 1H), 1.63-1.67 (m, 2H), 1.69 (d, J = 1.1 Hz, 3H), 1.70-1.81 (m, 2H), 1.82-1.90 (m, 1H), 1.94-2.04 (m, 4H), 2.14 (d, J = 13.8 Hz, 1H), 2.24 (d, J = 13.8 Hz, 1H), 2.64 (dd, J = 1.2, 18.4 Hz, 1H), 2.71 (dd, J = 5.1, 18.4 Hz, 1H), 4.21 (dd, J = 1.1, 5.0 Hz, 1H), 5.03 (s, 1H), 5.06 (ddt, J = 1.0, 8.4, 15.3 Hz, 1H), 5.36 (dt, J = 6.3, 15.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.4, 8.8, 11.7, 14.1, 16.8, 25.7, 27.9, 30.4, 33.9, 36.8, 42.8, 47.0, 49.1, 79.6, 87.1, 97.4, 129.6, 132.1, 132.8, 137.3,

175.8 ppm; MS (ESI): *m/z* 335 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{35}O_3$: 335.2581, found: 335.2590.

(*E*)-3-((3*S*,5*R*)-3,5-Diethyl-5-((*R*,1*E*,5*E*)-4-ethyl-2-methylocta-1,5-dienyl)-1,2-dioxolan-3-yl)acrylic acid ((4*S*,6*R*,10*R*)-Plakortide E (**85a**)).[34,57]

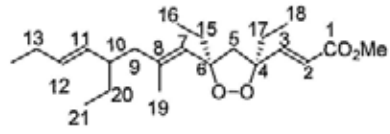
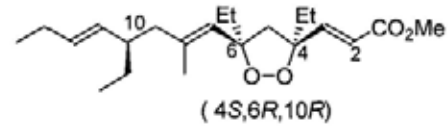


(4*S*,6*R*,10*R*)-Plakortide E (**85a**)

To a 0 °C solution of **86d** (13 mg, 0.037 mmol) in THF/H_2O (4:1, 2 mL) was added LiOH (4.5 mg, 0.19 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. TLC monitor the reaction until the starting material disappeared. The reaction mixture was acidified to *p*H 2 with 10% aqueous HCl. The resulting solution was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexanes//EtOAc/AcOH 100/10/1) to afford **85a** (11.6 mg, 90%) as a colorless oil: R_f = 0.25 (hexanes/EtOAc/AcOH, 100:10:1); $[\alpha]_D^{20}$ = 66.6 (*c*, 0.24, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.4 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H), 1.07-1.14 (m, 1H), 1.31-1.38 (m, 1H), 1.61 (d, *J* = 0.6 Hz, 3H), 1.62-1.69 (m, 1H), 1.70-1.82 (m, 2H), 1.83-1.93 (m, 2H), 1.94-2.02 (m, 4H), 2.43 (d, *J* = 12.0 Hz, 1H), 2.53 (d, *J* = 12.0 Hz, 1H), 5.05 (dd, *J* = 8.3, 15.2 Hz, 1H), 5.11 (s, 1H), 5.34 (dt, *J* = 6.4, 15.2 Hz, 1H), 6.09 (d, *J* = 15.7 Hz, 1H), 6.93 (d, *J* = 15.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.9, 8.9, 11.6, 14.1, 17.8, 25.6, 27.7, 30.8, 32.3, 42.6, 46.6, 56.0, 87.2, 89.3, 119.6, 126.6, 132.0, 132.8, 136.7, 152.1, 171.1 ppm; MS (ESI):

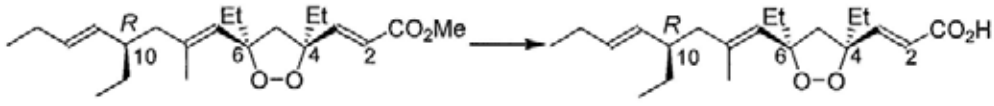
m/z 351 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{35}O_4$: 351.2530, found: 351.2533.

Table 1. The data reported for natural Plakortide E methyl ester and the data for our Synthetic compound **86d** (for comparison)

Source	Natural Product[34]			Our synthetic compound **86d**			
Reference	*Tetrahedron*, **1996**, *52*, 377-394.						
Assigned Structure				 (4*S*,6*R*,10*R*)			
EIHRMS	*m/z* $[M+H]^+$: calcd for $C_{22}H_{37}O_4$: 365.2692, found: 365.2681			*m/z* $[M+Na]^+$: calcd for $C_{22}H_{36}O_4Na$: 387.2506, found: 387.2509			
$[\alpha]_D^T$	$[\alpha]_D^{26}$= 75.1 (*c* = 2.23, $CHCl_3$)			$[\alpha]_D^{26}$= 87.0 (*c* = 0.85, $CHCl_3$)			
NMR ($CDCl_3$)	^1H (ppm)	^{13}C (ppm)		^1H (ppm)		^{13}C (ppm)	
equipment	Bruker AMX-400 spectrometer			Bruker Advance III 400 spectrometer			
H-1		C-1	166.9	H-1		C-1	167.1
H-2	6.07 (1H , d , 15.8)	C-2	119.9	H-2	6.07 (1H , d , 15.8)	C-2	119.9
H-3	6.85 (1H , d , 15.8)	C-3	149.6	H-3	6.85 (1H , d , 15.8)	C-3	149.8
H-4		C-4	87.1	H-4		C-4	87.2
H-5	2.54 β (1H , d , 12.0) 2.44 α (1H , d , 12.0)	C-5	55.9	H-5	2.54 β (1H , d , 11.9) 2.44 α (1H , d , 11.9)	C-5	56.0
H-6		C-6	89.1	H-6		C-6	89.3
H-7	5.11 (1H , q, 1.3)	C-7	126.7	H-7	5.11 (1H , q, 1.3)	C-7	126.7
H-8		C-8	136.4	H-8		C-8	136.6
H-9	2.00 (1H , m) 1.85 (1H , m)	C-9	46.5	H-9	2.00 (1H , m) 1.85 (1H , m)	C-9	46.5
H-10	2.00 (1H , m)	C-10	42.5	H-10	2.00 (1H , m)	C-10	42.6
H-11	5.05 (1H, ddt, 1.5, 8.4, 15.3)	C-11	132.7	H-11	5.05 (1H, dd, 15.1, 8.3)[a]	C-11	132.8
H-12	5.34 (1H, dt, 6.43, 15.3)	C-12	131.9	H-12	5.34 (1 H , dt, 6.3, 15.2)	C-12	132.0
H-13	1.97 (2H , m)	C-13	25.5	H-13	1.97 (2H , m)	C-13	25.6

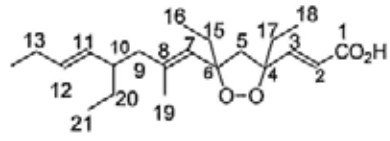
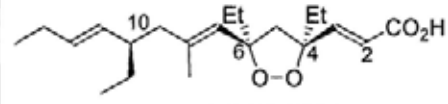
H-14	0.93 (3H , t, 7.4)	C-14	14.0	H-14	0.93 (3H , t, 7.4)	C-14	14.1
H-15	1.86 (1H, m) 1.64 (1H, m)	C-15	32.1	H-15	1.86 (1H, m) 1.64 (1H, m)	C-15	32.2
H-16	0.88 (3H , t, 7.4)	C-16	8.8	H-16	0.88 (3H , t, 7.4)	C-16	8.9
H-17	1.78 (2H , m)	C-17	30.8	H-17	1.78 (2H , m)	C-17	30.9
H-18	0.90 (3H , t, 7.4)	C-18	8.8	H-18	0.90 (3H , t, 7.4)	C-18	8.9
H-19	1.61 (3H , d, 1.3)	C-19	17.7	H-19	1.61 (3H , d, 1.3)	C-19	17.8
H-20	1.35 (1 H , m) 1.10 (1H , m)	C-20	27.6	H-20	1.35 (1H , m) 1.10 (1H , m)	C-20	27.6
H-21	0.80 (3H , t, 7.4)	C-21	11.5	H-21	0.81 (t, 7.4, 3H)	C-21	11.6
	3.73 (3H, S, OCH_3)		51.1		3.74 (3H, s, OCH_3)		51.6

(a) Coupling constants were measured by 2D J-Resolved NMR experiment on an Advance Bruker 600M spectrometer.



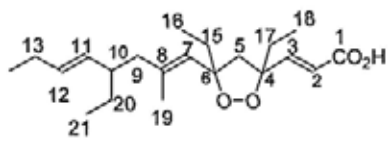
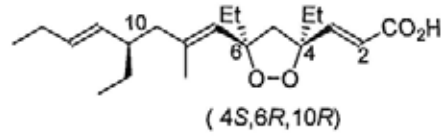
(*4S,6R,10R*)-**86d** (*4S,6R,10R*)-**85a**

Table 2-1. The data reported for natural Plakortide E and the data for our Synthetic compound **85a** (for comparison)

Source	Natural Product[34]			Our synthetic compound **85a**			
Reference	*Tetrahedron*, **1996**, *52*, 377-394.						
Assigned Structure				 (*4S,6R,10R*)			
EIHRMS	*m/z* $[M+H]^+$: 351			*m/z* $[M+H]^+$: calcd for $C_{21}H_{35}O_4$: 351.2530, found: 365.2522			
$[\alpha]_D^T$	$[\alpha]_D^{25}$= 63.9 (*c* = 2.0, $CHCl_3$)			$[\alpha]_D^{25}$= 66.6 (*c* = 0.24, $CHCl_3$)			
NMR ($CDCl_3$)	^1H (ppm)	^{13}C (ppm)		^1H (ppm)		^{13}C (ppm)	
equipment	Bruker AMX-400 spectrometer			Bruker Advance III 400 spectrometer			
H-1		C-1	173.0	H-1		C-1	171.1
H-2	5.98 (1H, d , 15.8)	C-2	123.9	H-2	6.09 (1H, d , 15.7)	C-2	119.6

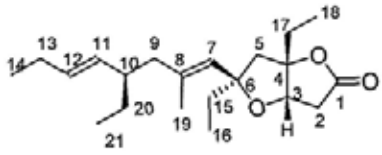
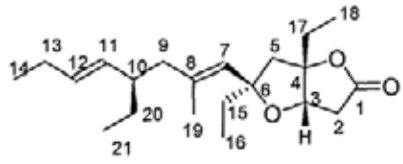
H-3	6.69 (1H, d, 15.8)	C-3	146.9	H-3	6.93 (1H, d, 15.7)	C-3	152.1
H-4		C-4	87.2	H-4		C-4	87.2
H-5	2.53 β (1H, d, 12.0) 2.42 α (1H, d, 12.0)	C-5	55.8	H-5	2.53 β (1H, d , 12.0) 2.43 α (1H, d , 12.0)	C-5	56.0
H-6		C-6	89.1	H-6		C-6	89.3
H-7	5.12 (1H, m)	C-7	126.9	H-7	5.11 (1H, s)	C-7	126.6
H-8		C-8	136.5	H-8		C-8	136.7
H-9	2.00 (1H, m) 1.85 (1H, m)	C-9	46.6	H-9	2.00 (1H, m) 1.85 (1H, m)	C-9	46.6
H-10	2.00 (1 H, m)	C-10	42.6	H-10	2.00 (1H, m)	C-10	42.6
H-11	5.05 (1H, ddt, 15.2, 8.3, 1.4)	C-11	132.8	H-11	5.05 (1H, dd, 15.2, 8.3)[a]	C-11	132.8
H-12	5.34 (1H , dt, 6.3, 15.2)	C-12	131.9	H-12	5.34 (1H, dt, 6.4, 15.2)	C-12	132.0
H-13	1.98 (2H, m)	C-13	25.6	H-13	1.97 (2H, m)	C-13	25.6
H-14	0.93 (3H, t, 7.4)	C-14	14.0	H-14	0.92 (3H, t, 7.4)	C-14	14.1
H-15	1.85 (1H, m) 1.63 (1H, m)	C-15	32.1	H-15	1.86 (1H, m) 1.64 (1H, m)	C-15	32.3
H-16	0.87 (3 H, t, 7.4)	C-16	8.8	H-16	0.86 (3 H, t, 7.4)	C-16	8.9
H-17	1.77 (2H, m)	C-17	31.0	H-17	1.78 (2H, m)	C-17	30.8
H-18	0.87 (3H, t, 7.4)	C-18	8.9	H-18	0.88 (3H, t, 7.4)	C-18	8.9
H-19	1.61 (3H, d, 1.0)	C-19	17.7	H-19	1.61 (3H, d, 0.9)	C-19	17.8
H-20	1.35 (1H, m) 1.11 (1H, m)	C-20	27.6	H-20	1.36 (1H, m) 1.11 (1H, m)	C-20	27.7
H-21	0.80 (3H, t, 7.4)	C-21	11.6	H-21	0.80 (t, 7.4, 3H)	C-21	11.6

Table 2-2. The data reported for natural plakortide E and the data for our synthetic compound **85a** (for comparison)

Source	Natural Product[57]	Our synthetic compound **85a**
Reference	*J. Nat. Prod.*, **2002**, *65*, 1509-1512.	
Assigned Structure		 (4*S*,6*R*,10*R*)

EIHRMS				*m/z* $[M+H]^+$: calcd for $C_{21}H_{35}O_4$: 351.2530, found: 365.2522			
$[\alpha]_D^T$	$[\alpha]_D^{20}$= 63 (*c* = 0.001, $CHCl_3$)			$[\alpha]_D^{20}$= 66.6 (*c* = 0.24, $CHCl_3$)			
NMR ($CDCl_3$)	^1H (ppm)	^{13}C (ppm)		^1H (ppm)		^{13}C (ppm)	
equipment	Bruker AMX-500 spectrometer			Bruker Advance III 400 spectrometer			
H-1		C-1	172.0	H-1		C-1	171.1
H-2	6.09 (1H, d , 15)	C-2	120.5	H-2	6.09 (1H, d , 15.7)	C-2	119.6
H-3	6.93 (1H, d, 15)	C-3	152.1	H-3	6.93 (1H, d, 15.7)	C-3	152.1
H-4		C-4	87.2	H-4		C-4	87.2
H-5	2.53 β (1H, d, 12.0) 2.42 α (1H, d, 12.0)	C-5	56.0	H-5	2.53 β (1H, d , 12.0) 2.43 α (1H, d , 12.0)	C-5	56.0
H-6		C-6	89.3	H-6		C-6	89.3
H-7	5.10 (1H, s)	C-7	126.6	H-7	5.11 (1H, s)	C-7	126.6
H-8		C-8	136.7	H-8		C-8	136.7
H-9	2.00 (1H, m) 1.85 (1H, m)	C-9	46.6	H-9	2.00 (1H, m) 1.85 (1H, m)	C-9	46.6
H-10	2.00 (1H, m)	C-10	42.6	H-10	2.00 (1H, m)	C-10	42.6
H-11	5.04 (1H, dd, 15, 8)	C-11	132.8	H-11	5.05 (1H, dd, 15.2, 8.3)[a]	C-11	132.8
H-12	5.33 (1H , dt, 6.5, 15)	C-12	132.0	H-12	5.34 (1H, dt, 6.4, 15.2)	C-12	132.0
H-13	1.95 (2H, m)	C-13	25.6	H-13	1.97 (2H, m)	C-13	25.6
H-14	0.92 (3H, t, 7.5)	C-14	14.1	H-14	0.92 (3H, t, 7.4)	C-14	14.1
H-15	1.86 (1H, m) 1.64 (1H, m)	C-15	32.2	H-15	1.86 (1H, m) 1.64 (1H, m)	C-15	32.3
H-16	0.86 (3H, t, 7.5)	C-16	8.9	H-16	0.86 (3H, t, 7.4)	C-16	8.9
H-17	1.78 (2H, m)	C-17	30.8	H-17	1.78 (2H, m)	C-17	30.8
H-18	0.88 (3H, t, 7.5)	C-18	8.9	H-18	0.88 (3H, t, 7.4)	C-18	8.9
H-19	1.60 (3H, s)	C-19	17.8	H-19	1.61 (3H, d, 0.9)	C-19	17.8
H-20	1.37 (1H, m) 1.24 (1H, m)	C-20	27.7	H-20	1.36 (1H, m) 1.11 (1H, m)	C-20	27.7
H-21	0.80 (3H, t, 7.5)	C-21	11.6	H-21	0.80 (3H, t, 7.4)	C-21	11.6

Table 3. The data reported for natural plakortone B and the data for our Synthetic compound **87a** (for comparison)

Source	Natural Product[34]			Our synthetic compound **87a**			
Reference	*Tetrahedron*, **1996**, *52*, 377-394.						
Assigned Structure	 plakortone B (relative configuration) The biclyclic furanolactone core is *cis* confused.			 (3*S*,4*S*,6*R*,10*R*)			
EIHRMS	*m/z* $[M+H]^+$: calcd for $C_{21}H_{35}O_3$: 335.2586, found: 335.2541			$[M+H]^+$ calcd for $C_{21}H_{35}O_3$: 335.2581, found: 335.2574			
$[\alpha]_D^T$	$[\alpha]_D^{26}$= –9.2 (*c* = 0.72, $CHCl_3$)			$[\alpha]_D^{26}$= –15.5 (*c* = 0.17, $CHCl_3$)			
NMR ($CDCl_3$)	^1H (ppm)	^{13}C (ppm)		^1H (ppm)		^{13}C (ppm)	
equipment	Bruker AMX-400 spectrometer			Bruker Advance III 400 spectrometer			
H-1		C-1	175.6	H-1		C-1	175.8
H-2	2.71 β (dd, 5.1, 18.4, 1H) 2.64 α (dd, 1.3, 18.4, 1H)	C-2	36.7	H-2	2.71 β (dd, 5.1, 18.6, 1H) 2.64 α (dd, 1.1, 18.6, 1H)	C-2	36.8
H-3	4.21 (dd, 1.3, 5.1, 1H)	C-3	79.5	H-3	4.21 (dd, 1.1, 5.0, 1H)	C-3	79.6
H-4		C-4	97.2	H-4		C-4	97.4
H-5	2.24 α (d, 13.7, 1H) 2.13 β (d, 13.7, 1H)	C-5	49.0	H-5	2.24 α (d, 13.7, 1H) 2.14 β (d, 13.7, 1H)	C-5	49.1
H-6		C-6	86.9	H-6		C-6	87.1
H-7	5.03 (q, 1.3, 1H)	C-7	129.5	H-7	5.03 (s, 1H)	C-7	129.6
H-8		C-8	137.1	H-8		C-8	137.3
H-9	2.00 (m, 1H) 1.85 (m, 1H)	C-9	46.9	H-9	1.99-2.04 (m, 1H) 1.82-1.87 (m, 1H)	C-9	47.0
H-10	1.98 (m, 1H)	C-10	42.6	H-10	1.99-2.04 (m, 1H)	C-10	42.8
H-11	5.06 (ddt, 1.5, 8.4, 15.3, 1H)	C-11	132.7	H-11	5.06 (dd, 8.4, 15.3, 1H)	C-11	132.8
H-12	5.36 (dt, 6.3, 15.3, 1H)	C-12	131.9	H-12	5.36 (dt, 6.3, 15.3, 1H)	C-12	132.1
H-13	1.96 (m, 2H)	C-13	25.5	H-13	1.99- 2.04 (m, 2H)	C-13	25.7
H-14	0.95 (t, 7.4, 3H)	C-14	14.0	H-14	0.95 (t, 7.4, 3H)	C-14	14.1

H-15	1.73 (m, 2H)	C-15	33.7	H-15	1.66-1.77 (m, 2H)	C-15	33.9
H-16	0.86 (t, 7.4, 3H)	C-16	8.7	H-16	0.86 (t, 7.4, 3H)	C-16	8.8
H-17	1.73 (m, 2H)	C-17	30.3	H-17	1.66-1.77 (m, 2H)	C-17	30.4
H-18	0.96 (t, 7.4, 3H)	C-18	8.3	H-18	0.96 (t, 7.2, 3H)	C-18	8.4
H-19	1.69 (d, 1.3, 3H)	C-19	16.7	H-19	1.69 (d, 1.4, 3H)[a]	C-19	16.8
H-20	1.35 (m, 1H) 1.15 (m, 1H)	C-20	27.8	H-20	1.32-1.38 (m, 1H) 1.10-1.17 (m, 1H)	C-20	27.9
H-21	0.83 (t, 7.4, 3H)	C-21	11.5	H-21	0.83 (t, 7.4, 3H)	C-21	11.7

Chapter 5

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Table 1. Crystal data and structure refinement for xysun-1.

Identification code	xysun-1
Empirical formula	C9 H18 O4
Formula weight	190.23
Temperature	296(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 5.6535(3) A alpha = 77.5980(10) deg. b = 8.1968(5) A beta = 86.4690(10) deg. c = 11.5406(7) A gamma = 77.1180(10) deg.
Volume	509.12(5) A^3
Z, Calculated density	2, 1.241 Mg/m^3
Absorption coefficient	0.096 mm^-1
F(000)	208
Crystal size	0.4 x 0.3 x 0.3 mm
Theta range for data collection	1.81 to 25.25 deg.
Limiting indices	-6<=h<=6, -9<=k<=9, -13<=l<=13
Reflections collected / unique	9128 / 1842 [R(int) = 0.0585]
Completeness to theta = 25.25	100.0 %
Absorption correction	None

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1842 / 0 / 118
Goodness-of-fit on F^2	1.036
Final R indices [I>2sigma(I)]	R1 = 0.0517, wR2 = 0.1433
R indices (all data)	R1 = 0.0569, wR2 = 0.1504
Largest diff. peak and hole	0.539 and -0.501 e.A^-3

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

	x	y	z	U(eq)
O(1)	-4154(2)	8764(2)	6738(1)	43(1)
O(2)	-5883(2)	10086(2)	7204(1)	46(1)
O(3)	-77(3)	6246(2)	6413(1)	46(1)
O(4)	-7398(3)	13420(2)	5588(1)	58(1)
C(1)	247(5)	7491(3)	9301(2)	65(1)
C(2)	-1905(4)	7587(3)	8560(2)	46(1)
C(3)	-1906(3)	8680(2)	7313(2)	31(1)
C(4)	-1943(3)	10564(2)	7284(2)	34(1)
C(5)	-4623(3)	11467(2)	7088(2)	32(1)
C(6)	-5750(4)	12407(3)	8058(2)	47(1)
C(7)	-4723(5)	13945(3)	8099(2)	66(1)
C(8)	62(3)	7922(2)	6510(2)	39(1)
C(9)	-4946(4)	12574(3)	5847(2)	43(1)

Table 3. Bond lengths [A] and angles [deg] for A.

O(1)-C(3)	1.451(2)
O(1)-O(2)	1.4596(18)
O(2)-C(5)	1.446(2)
O(3)-C(8)	1.422(2)
O(3)-H(3)	0.8200
O(4)-C(9)	1.424(2)
O(4)-H(4)	0.8200
C(1)-C(2)	1.508(3)
C(1)-H(1A)	0.9600
C(1)-H(1B)	0.9600
C(1)-H(1C)	0.9600
C(2)-C(3)	1.523(3)
C(2)-H(2A)	0.9700
C(2)-H(2B)	0.9700
C(3)-C(8)	1.515(2)
C(3)-C(4)	1.533(2)
C(4)-C(5)	1.538(2)
C(4)-H(4B)	0.9700
C(4)-H(4C)	0.9700
C(5)-C(9)	1.519(3)
C(5)-C(6)	1.522(2)
C(6)-C(7)	1.512(3)
C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700
C(7)-H(7A)	0.9600
C(7)-H(7B)	0.9600
C(7)-H(7C)	0.9600
C(8)-H(8A)	0.9700
C(8)-H(8B)	0.9700
C(9)-H(9C)	0.9700
C(9)-H(9A)	0.9700
C(3)-O(1)-O(2)	103.37(11)

C(5)-O(2)-O(1)	104.13(11)
C(8)-O(3)-H(3)	109.5
C(9)-O(4)-H(4)	109.5
C(2)-C(1)-H(1A)	109.5
C(2)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
C(2)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
C(1)-C(2)-C(3)	115.21(18)
C(1)-C(2)-H(2A)	108.5
C(3)-C(2)-H(2A)	108.5
C(1)-C(2)-H(2B)	108.5
C(3)-C(2)-H(2B)	108.5
H(2A)-C(2)-H(2B)	107.5
O(1)-C(3)-C(8)	104.45(13)
O(1)-C(3)-C(2)	109.22(14)
C(8)-C(3)-C(2)	113.30(15)
O(1)-C(3)-C(4)	102.98(13)
C(8)-C(3)-C(4)	111.98(14)
C(2)-C(3)-C(4)	113.90(14)
C(3)-C(4)-C(5)	104.29(13)
C(3)-C(4)-H(4B)	110.9
C(5)-C(4)-H(4B)	110.9
C(3)-C(4)-H(4C)	110.9
C(5)-C(4)-H(4C)	110.9
H(4B)-C(4)-H(4C)	108.9
O(2)-C(5)-C(9)	109.98(15)
O(2)-C(5)-C(6)	104.07(14)
C(9)-C(5)-C(6)	113.55(15)
O(2)-C(5)-C(4)	104.27(13)
C(9)-C(5)-C(4)	110.01(15)
C(6)-C(5)-C(4)	114.32(15)
C(7)-C(6)-C(5)	113.66(18)
C(7)-C(6)-H(6A)	108.8
C(5)-C(6)-H(6A)	108.8
C(7)-C(6)-H(6B)	108.8
C(5)-C(6)-H(6B)	108.8

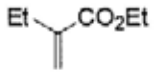
H(6A)-C(6)-H(6B)	107.7
C(6)-C(7)-H(7A)	109.5
C(6)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(6)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
O(3)-C(8)-C(3)	112.50(15)
O(3)-C(8)-H(8A)	109.1
C(3)-C(8)-H(8A)	109.1
O(3)-C(8)-H(8B)	109.1
C(3)-C(8)-H(8B)	109.1
H(8A)-C(8)-H(8B)	107.8
O(4)-C(9)-C(5)	113.31(16)
O(4)-C(9)-H(9C)	108.9
C(5)-C(9)-H(9C)	108.9
O(4)-C(9)-H(9A)	108.9
C(5)-C(9)-H(9A)	108.9
H(9C)-C(9)-H(9A)	107.7

Symmetry transformations used to generate equivalent atoms:

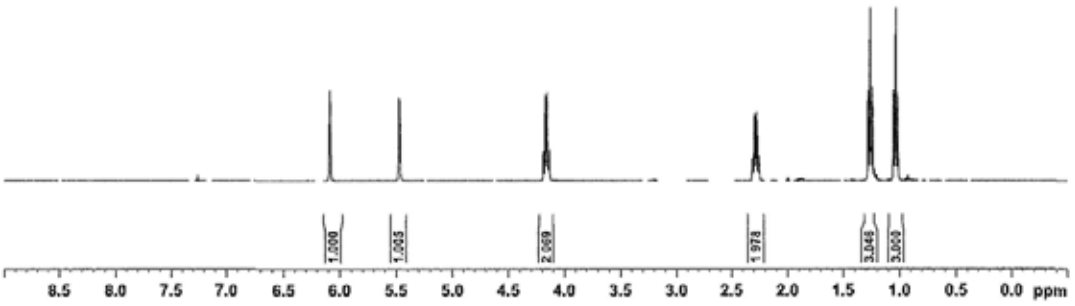
Table 4. Anisotropic displacement parameters (A^2 x 10^3) for A.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

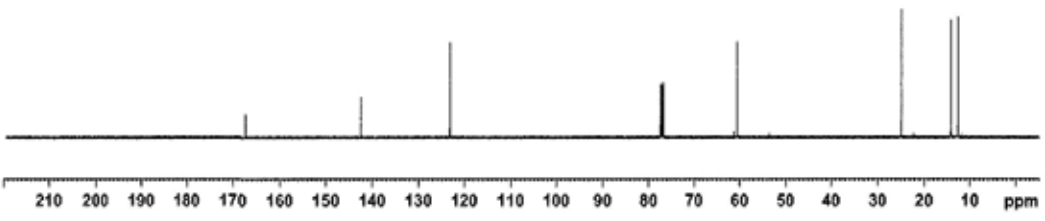
	U11	U22	U33	U23	U13	U12
O(1)	33(1)	36(1)	63(1)	-23(1)	-10(1)	-2(1)
O(2)	27(1)	39(1)	75(1)	-22(1)	0(1)	-6(1)
O(3)	46(1)	37(1)	56(1)	-23(1)	-8(1)	7(1)
O(4)	55(1)	54(1)	60(1)	-27(1)	-28(1)	21(1)

C(1)	75(2)	66(2)	45(1)	−4(1)	−16(1)	1(1)
C(2)	56(1)	40(1)	41(1)	−7(1)	2(1)	−10(1)
C(3)	29(1)	28(1)	36(1)	−10(1)	−4(1)	−4(1)
C(4)	28(1)	29(1)	46(1)	−10(1)	−5(1)	−3(1)
C(5)	27(1)	30(1)	40(1)	−12(1)	−2(1)	−3(1)
C(6)	43(1)	52(1)	44(1)	−20(1)	1(1)	1(1)
C(7)	69(2)	55(1)	80(2)	−42(1)	−21(1)	6(1)
C(8)	39(1)	36(1)	42(1)	−12(1)	1(1)	−2(1)
C(9)	41(1)	43(1)	40(1)	−12(1)	−7(1)	6(1)



112


1.000
1.005
2.069
1.978
3.046
3.000
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm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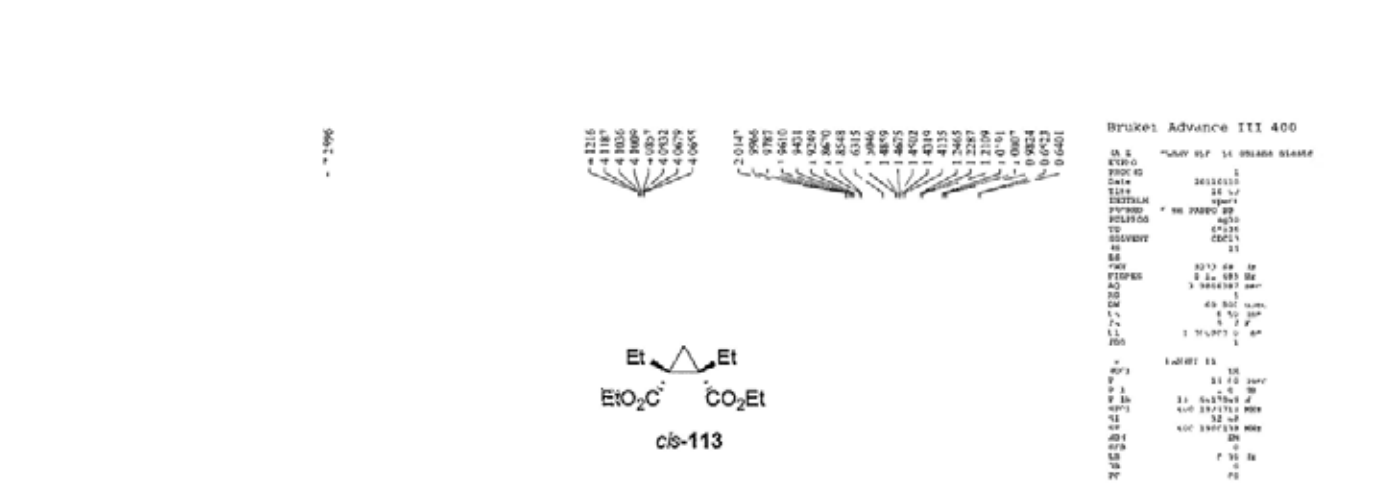
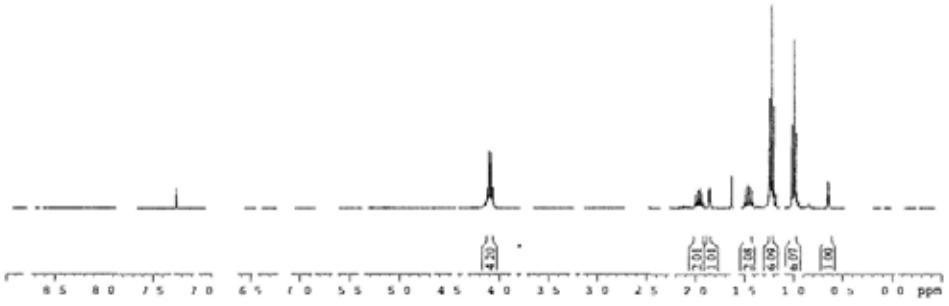

Bruker Advance III 400

Et
Et
EtO2C
CO2Et

cis-113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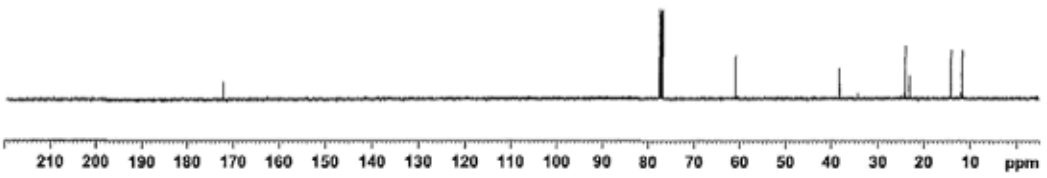
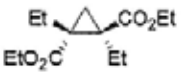
2.01
1.03
2.08
6.09
6.07
1.00
ppm

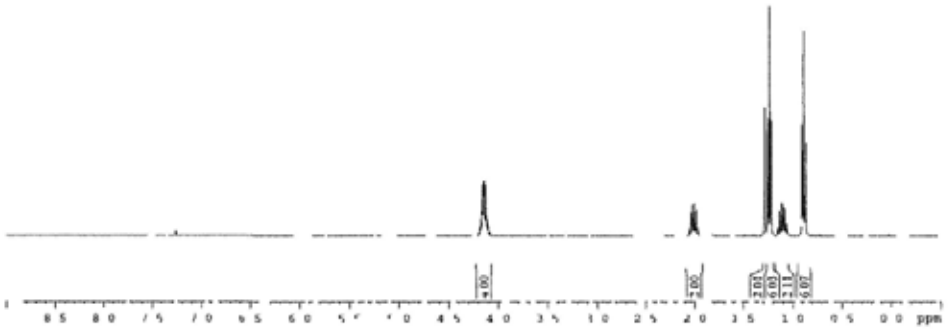

Bruker Advance 1.1 400


ppm


Et
CO2Et
EtO2C
Et

trans-**113**


Bruker Advance III 400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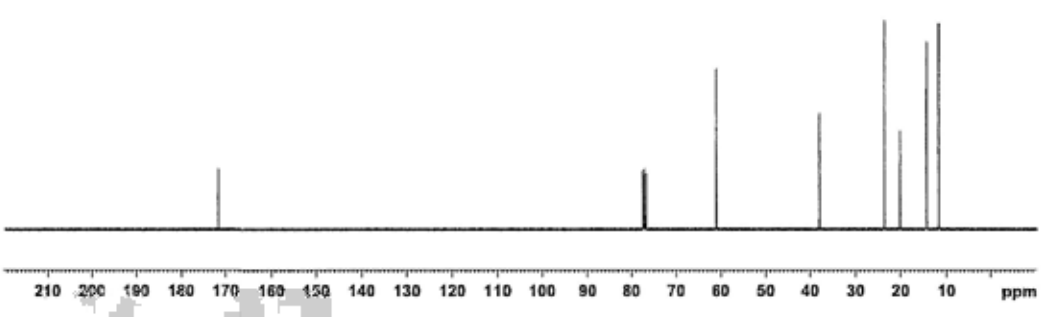
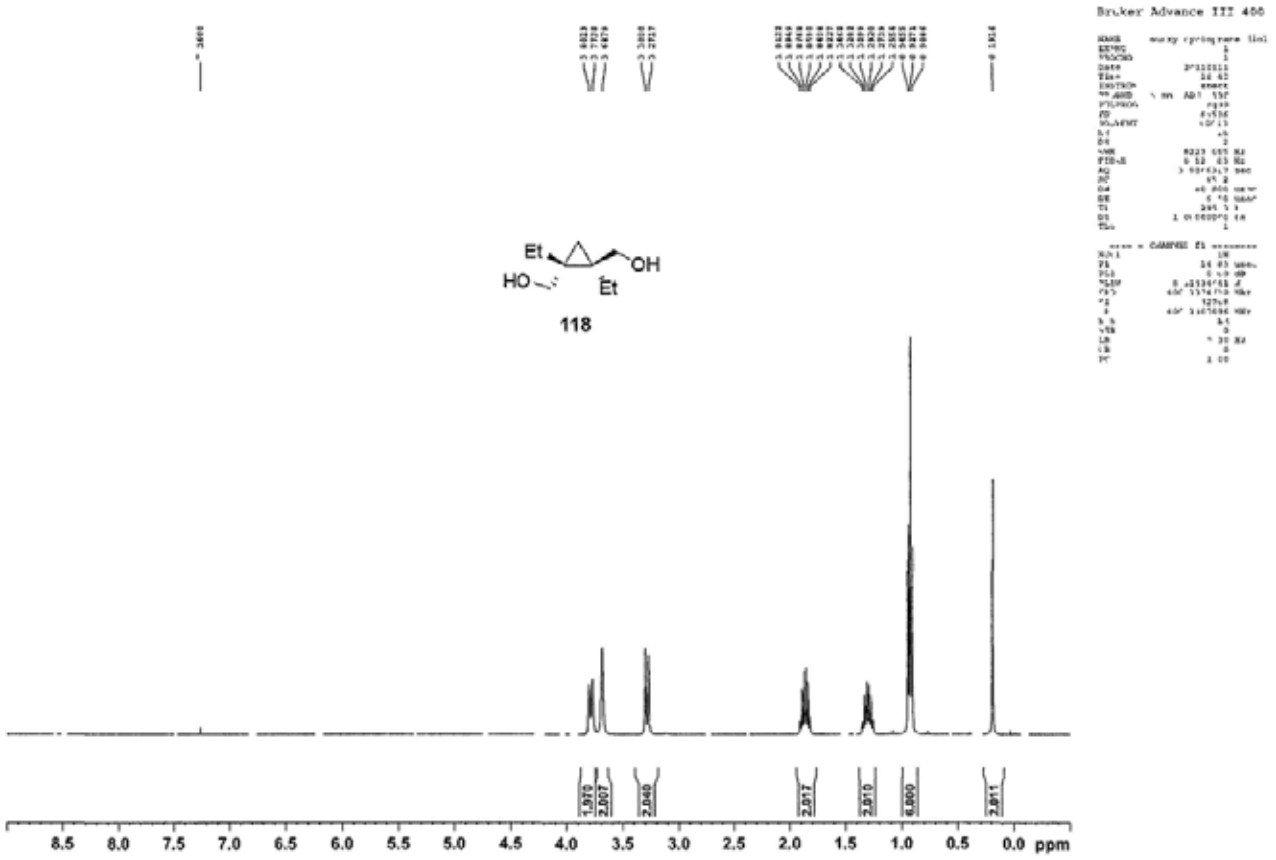
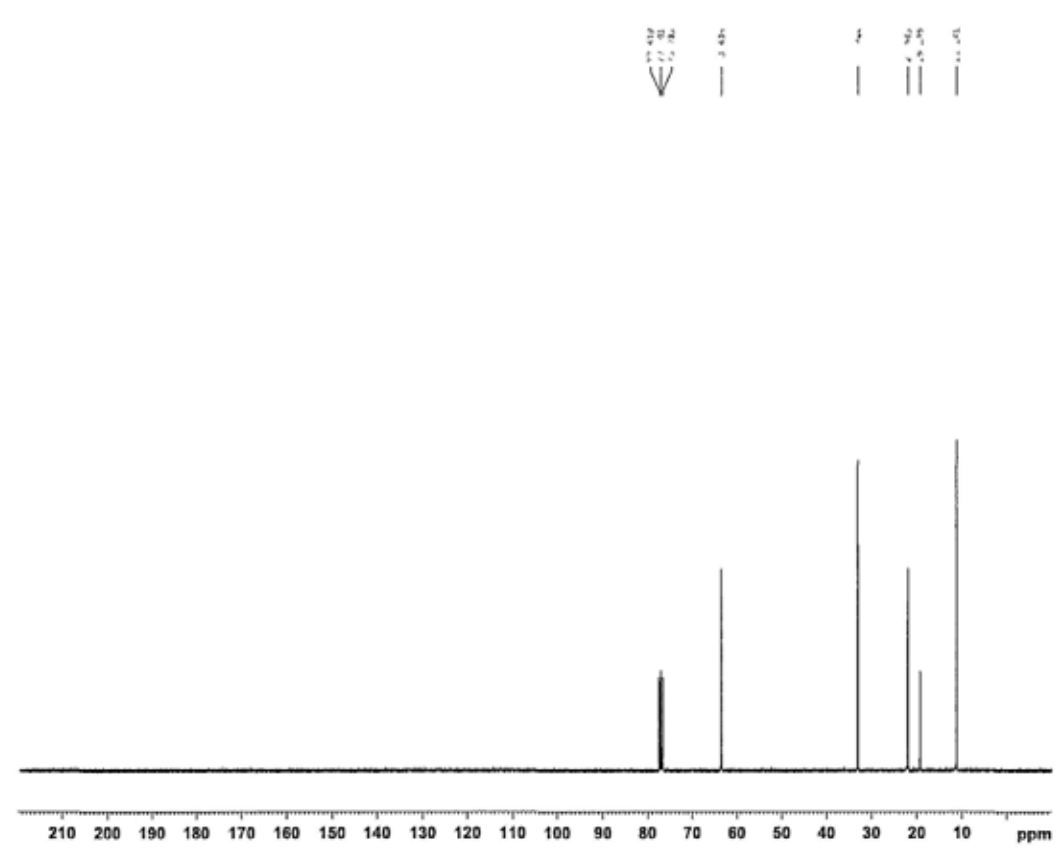
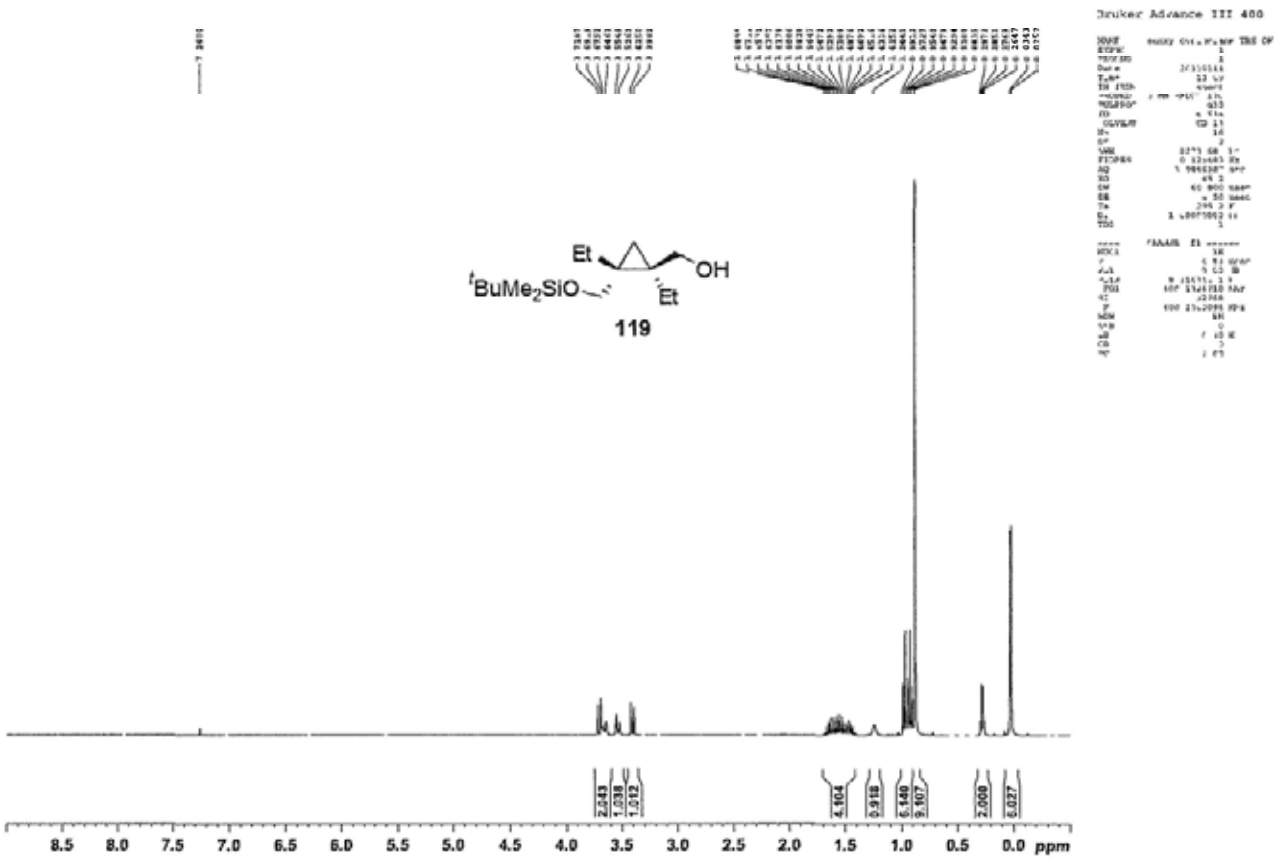
2.00
2.01
1.03
3.11
6.07
ppm

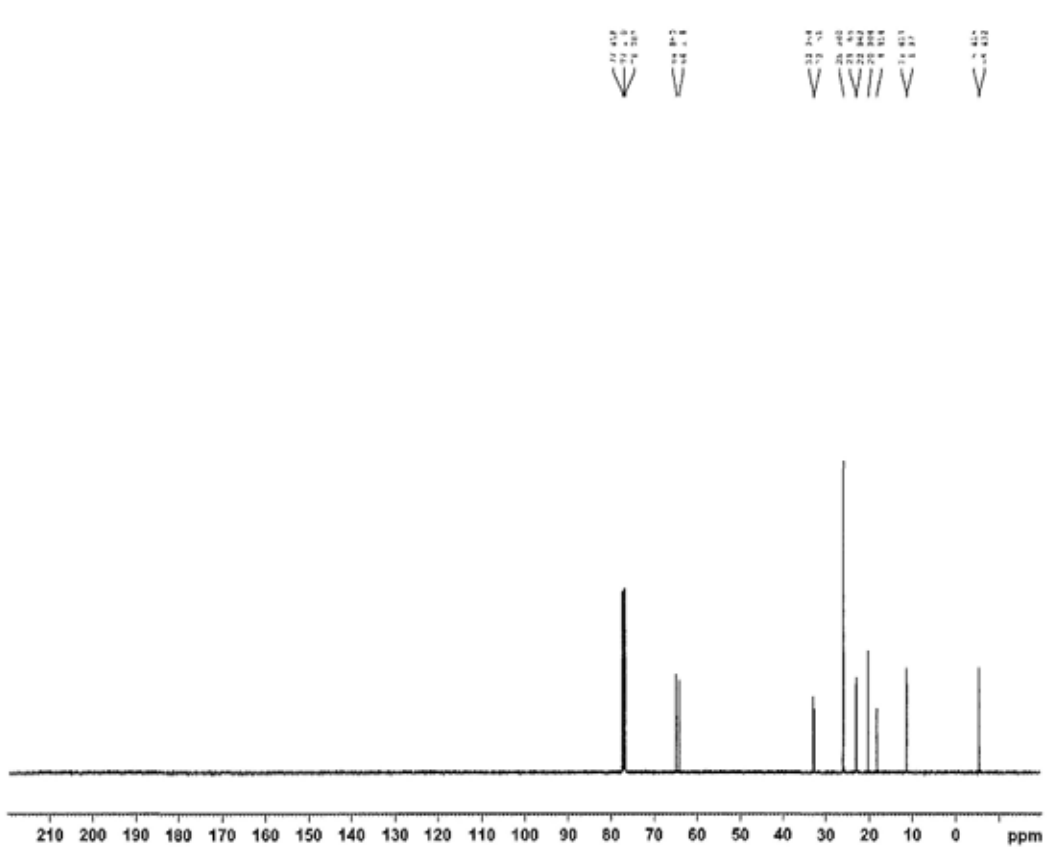

Bruker Advance III 400


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Et
OH
HO
Et
118
1.970
2.007
2.040
2.017
2.010
6.000
2.011
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


Et
OH
tBuMe2SiO
Et
119
2.043
1.038
1.012
4.104
0.918
6.140
9.107
2.000
6.027
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm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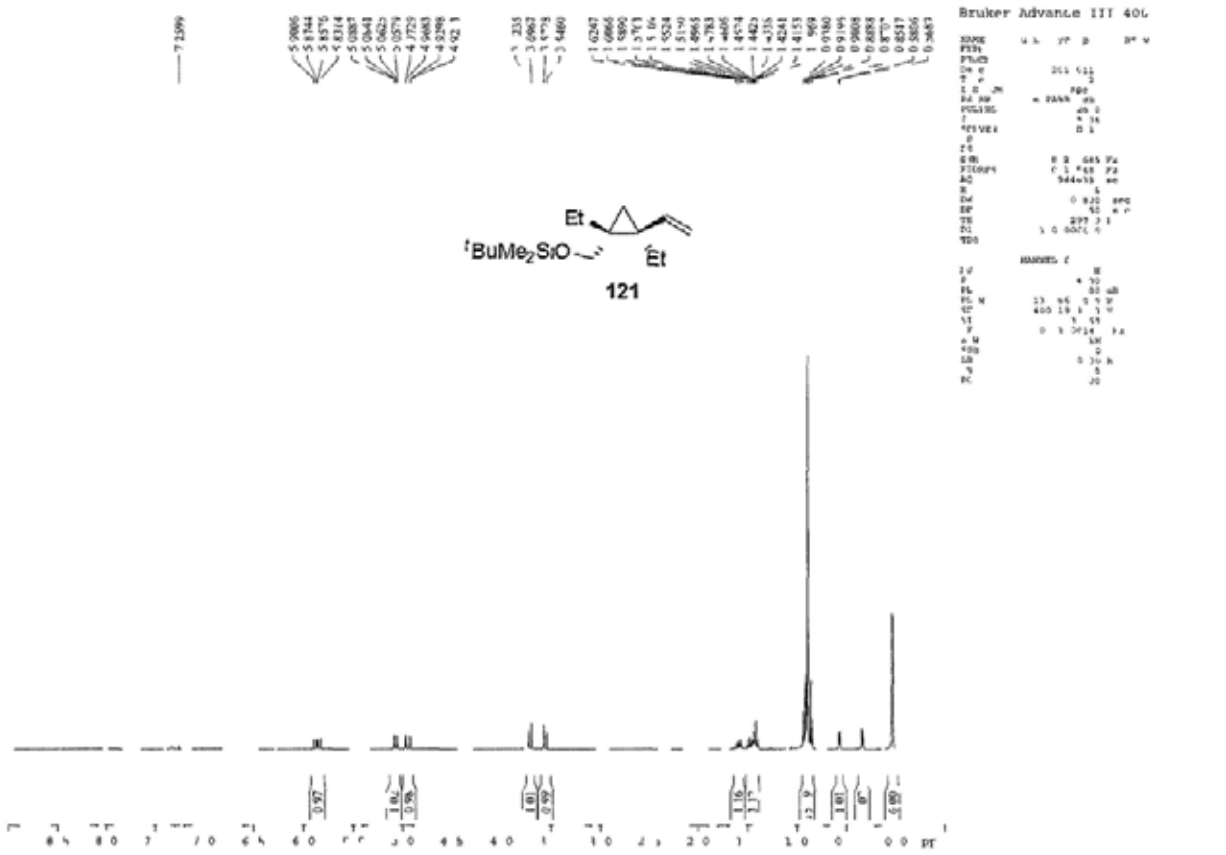
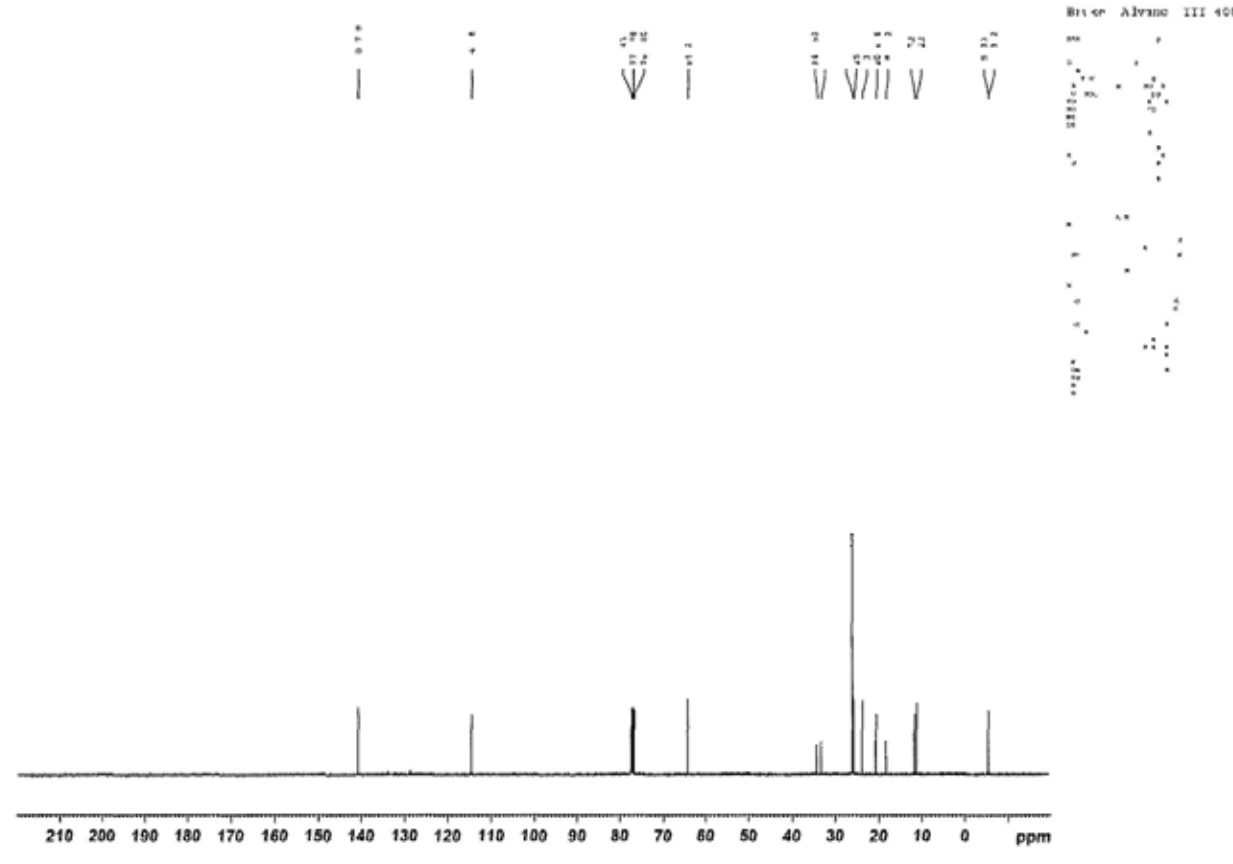
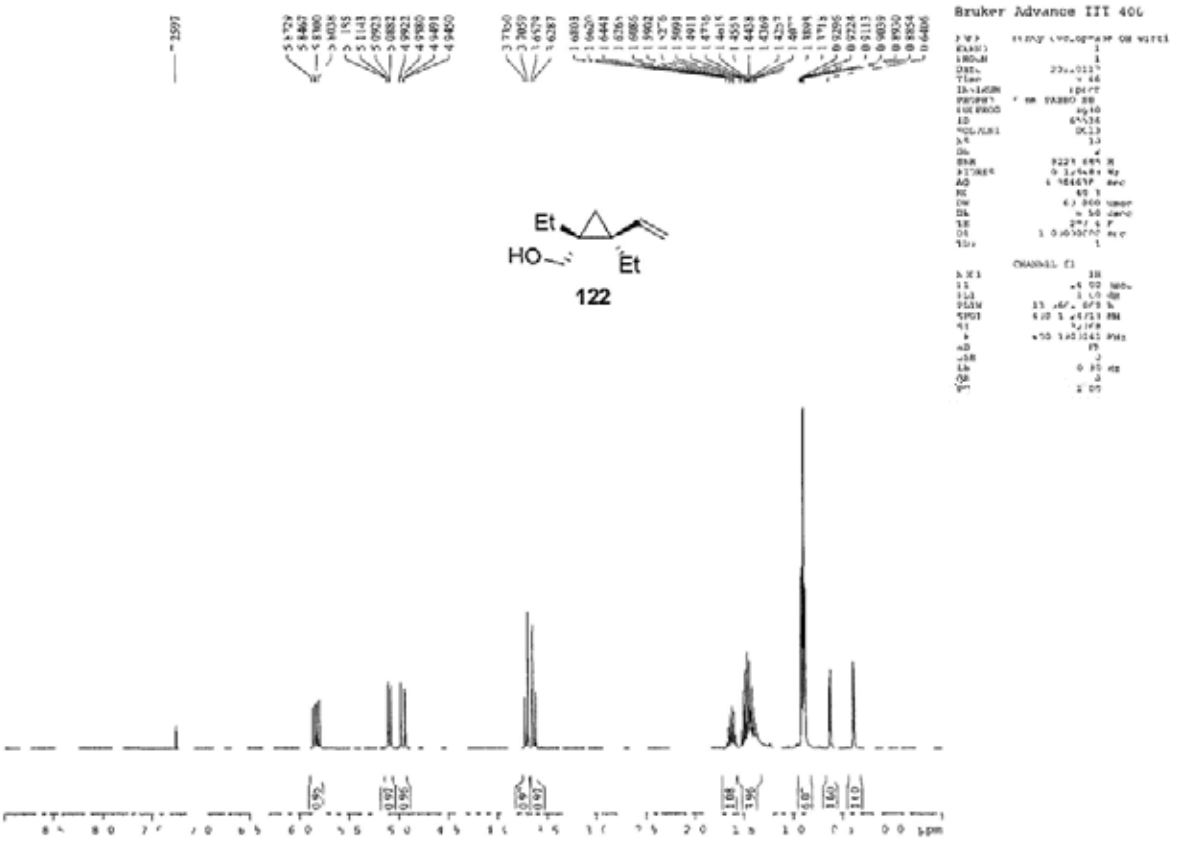


121



207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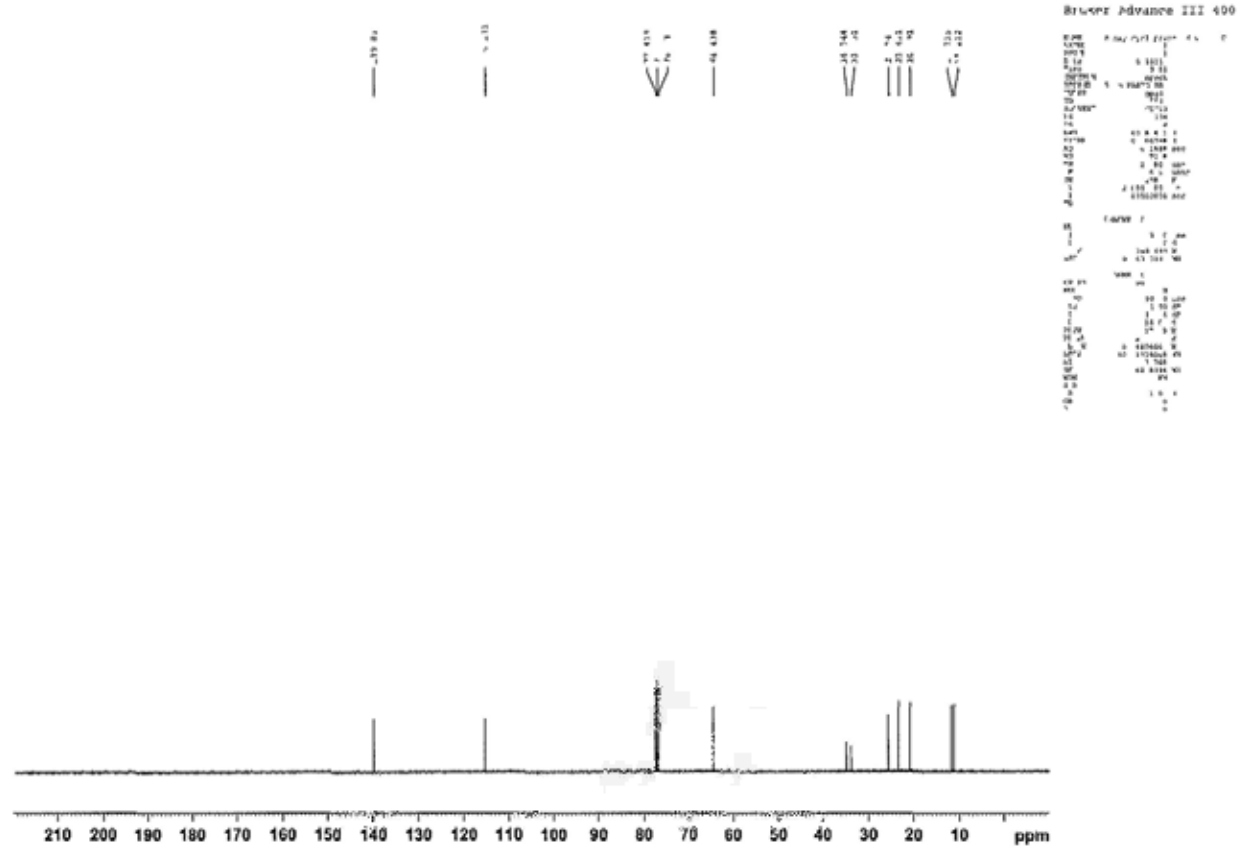
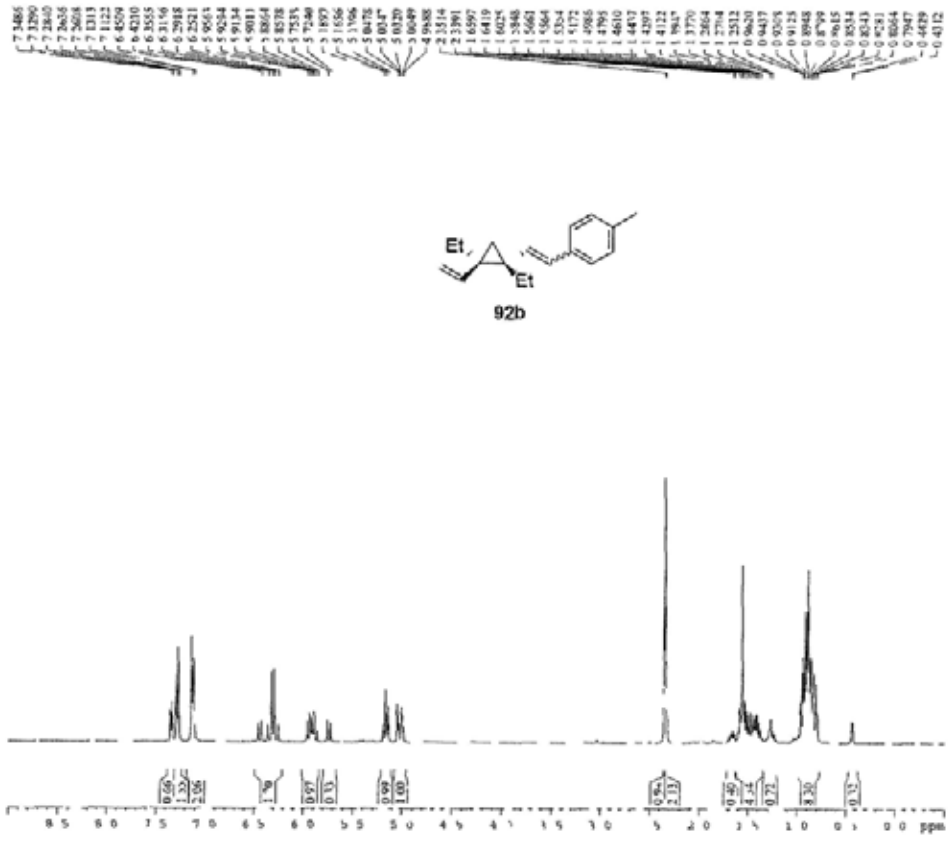
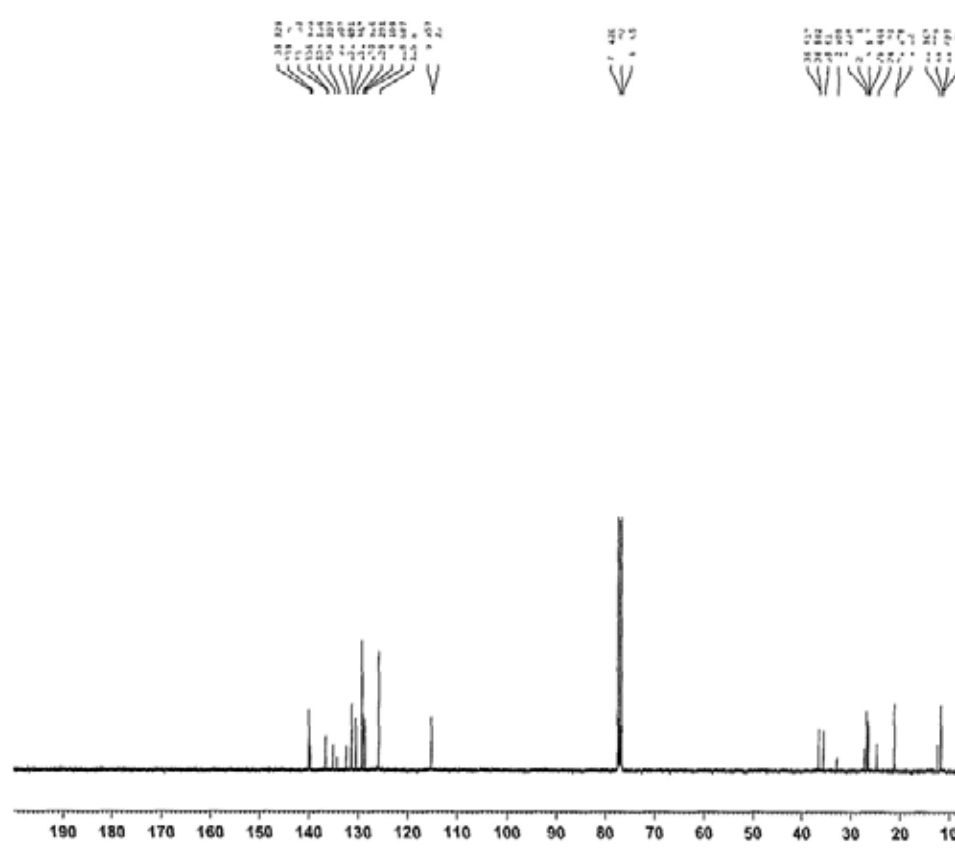
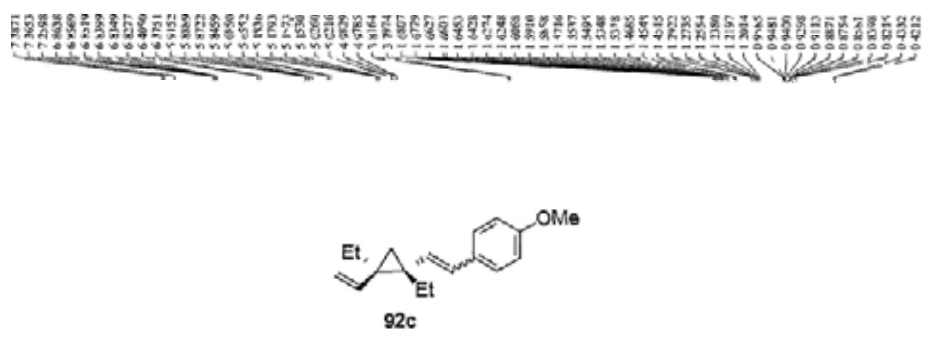
Et
HO
Et
122
0.95
0.95
0.97
0.97
1.68
1.96
0.68
1.60
3.10
ppm

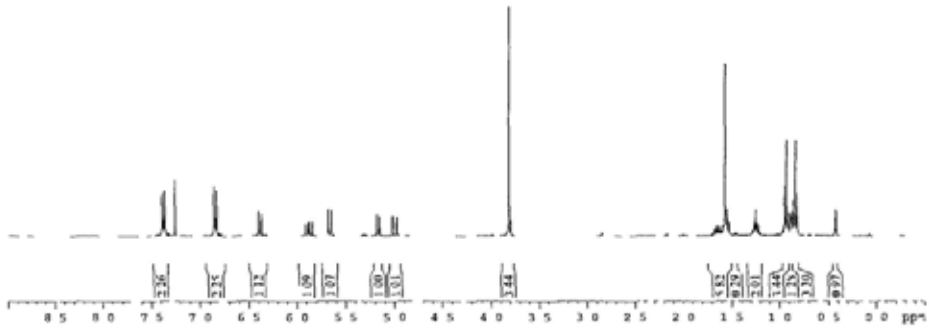

Bruker Advance III 400
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

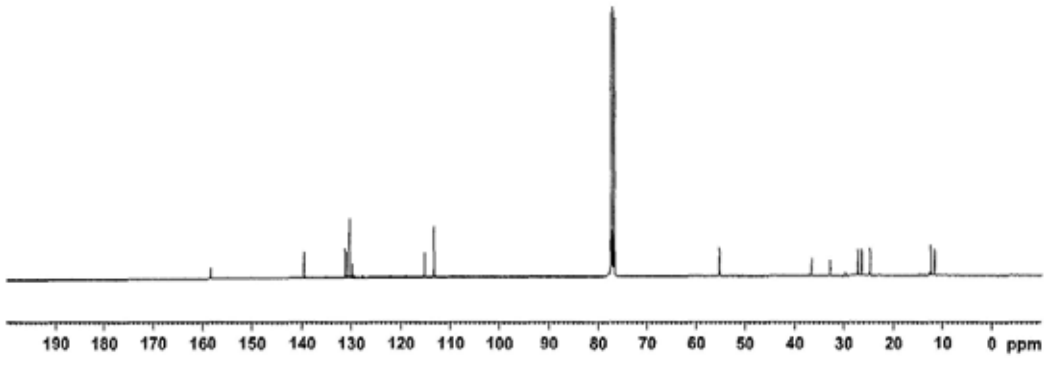

Et
Et
92b

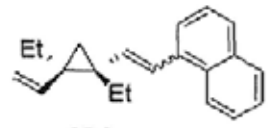




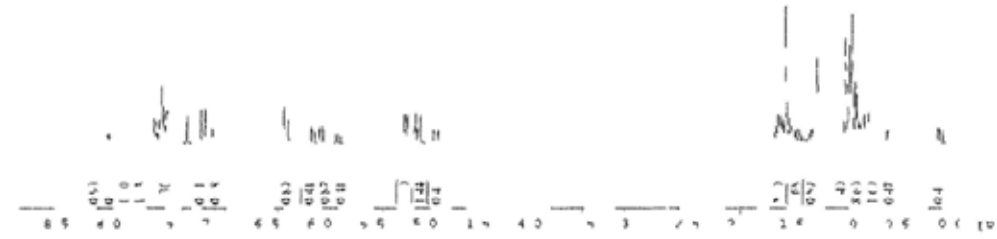
92c

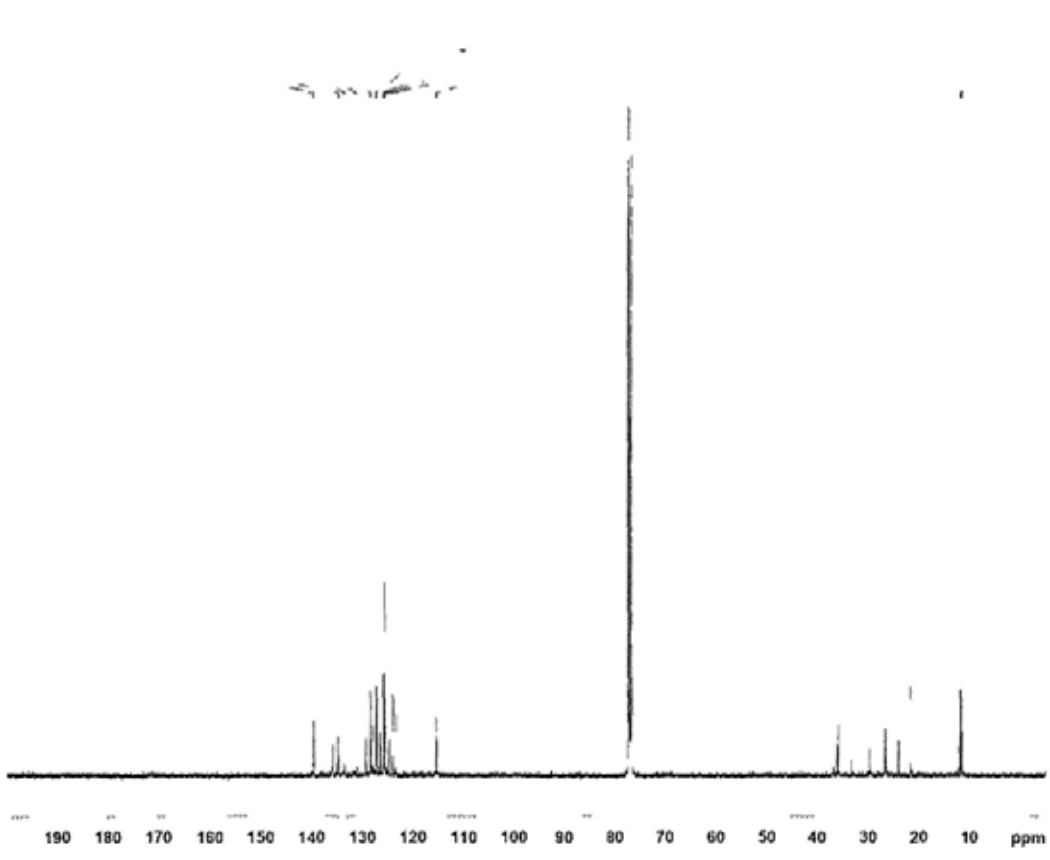





Et
Et

92d

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180
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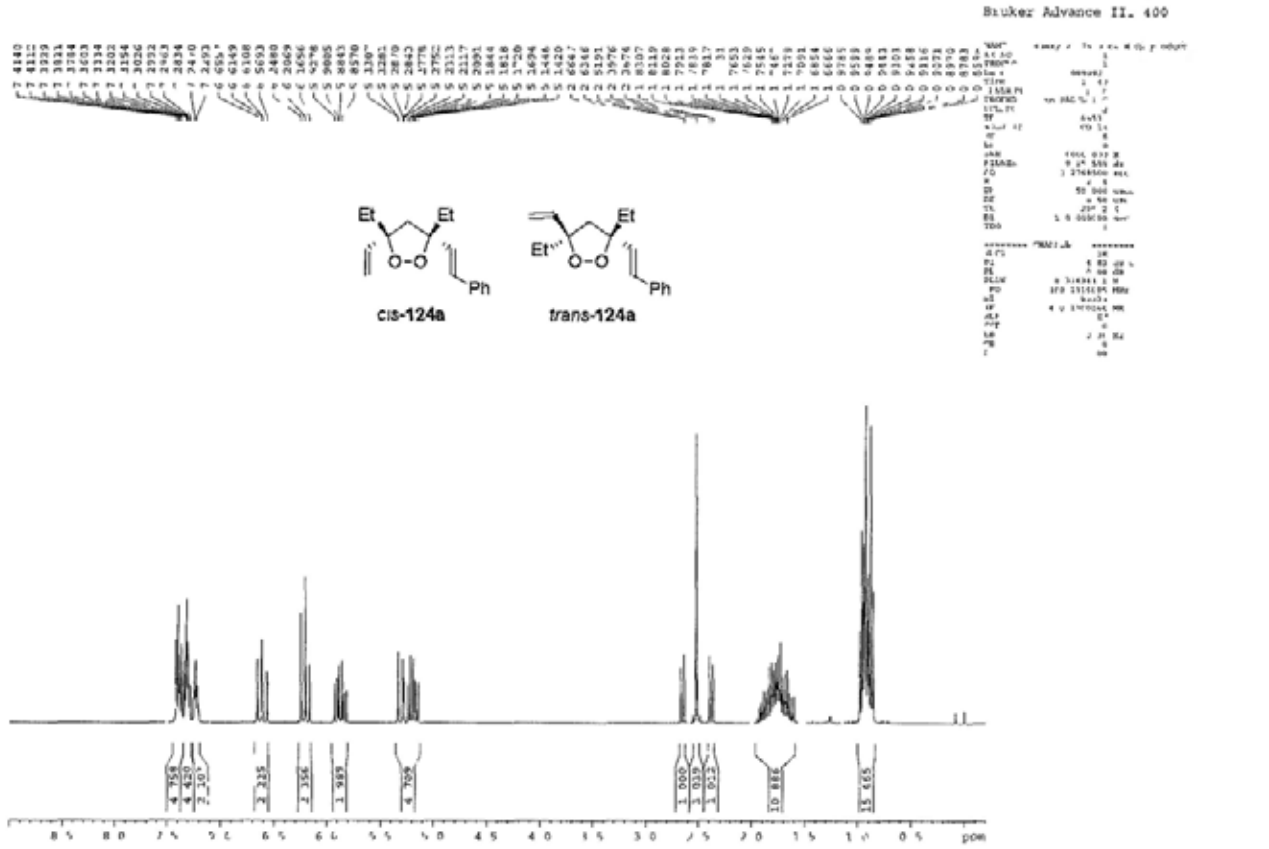
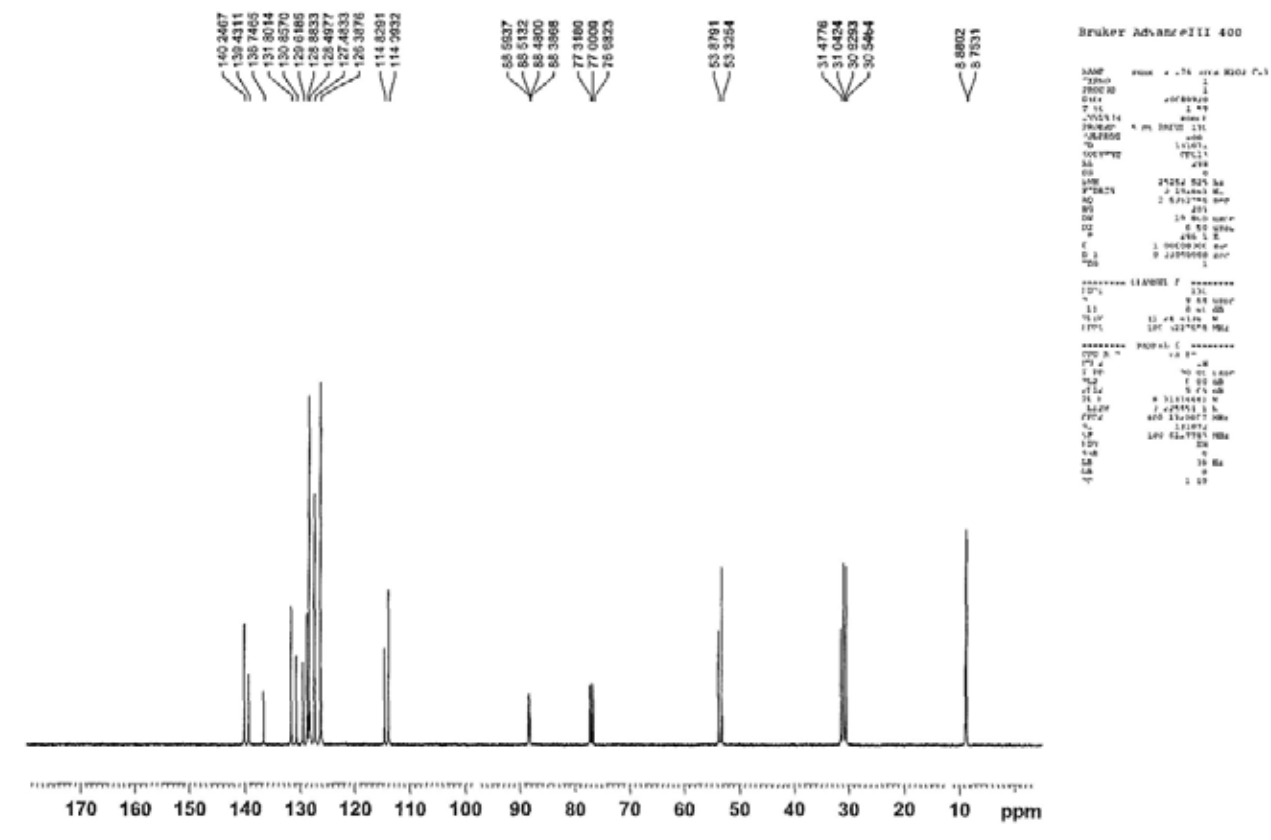
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Bruker Advance II. 400
Et
Et
O-O
Ph
cis-124a
Et
Et
O-O
Ph
trans-124a
4.758
4.420
2.301
2.225
2.356
1.989
4.704
1.000
1.039
1.025
10.886
15.465
ppm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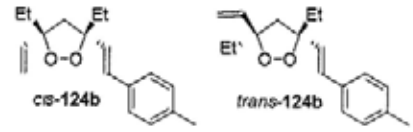
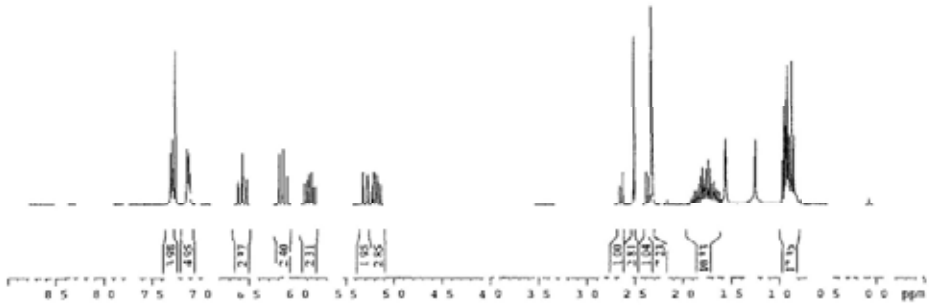
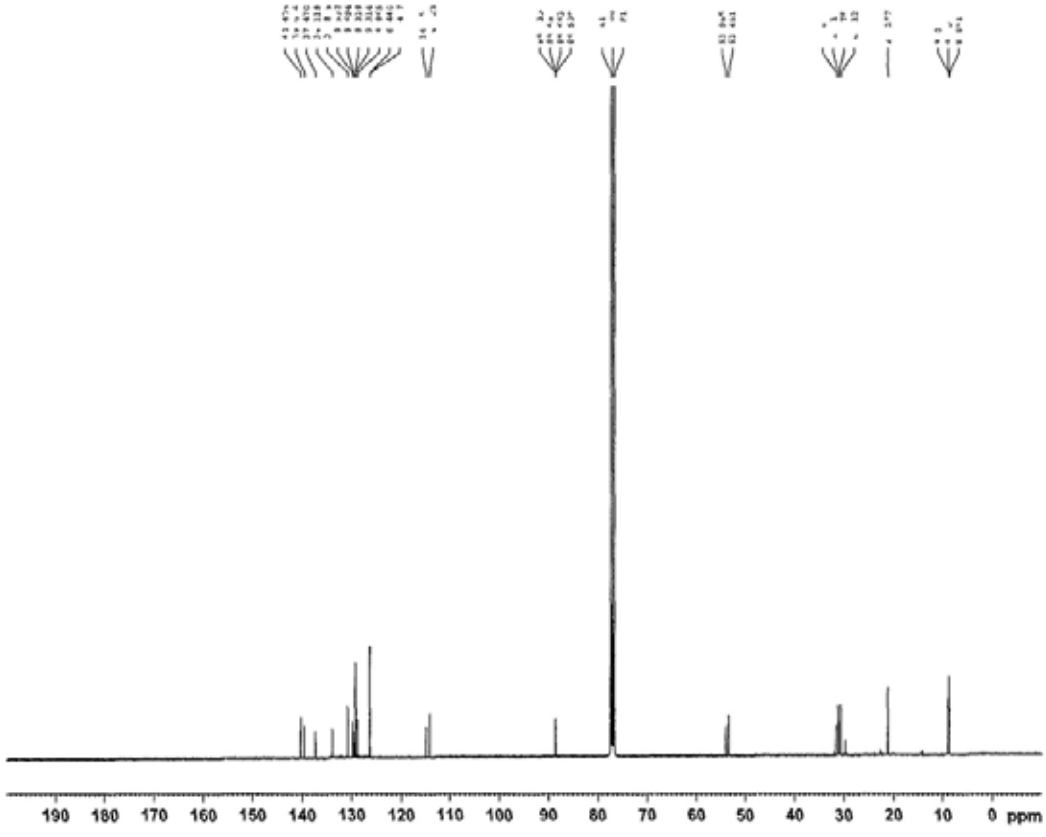
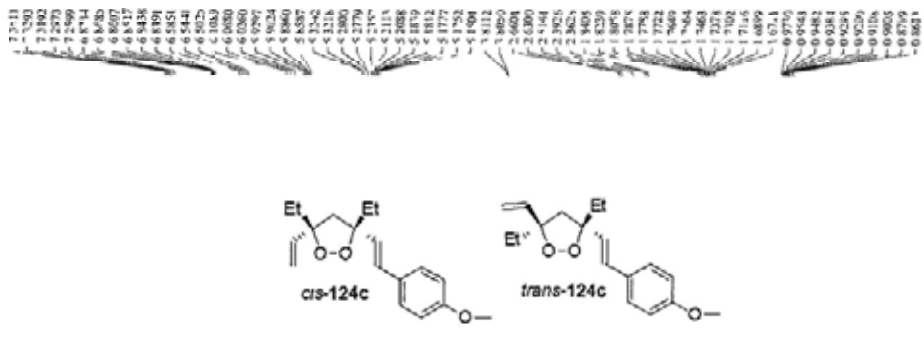
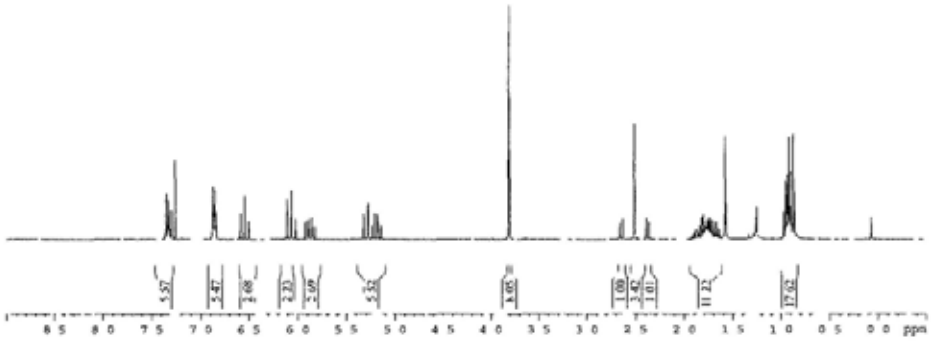
130.8570
129.6186
128.8833
128.4977
127.4833
126.3876
114.8291
114.0932
68.5937
68.5132
68.4800
68.3868
77.3180
77.0009
76.6823
53.8791
53.3264
31.4776
31.0424
30.5283
30.0464
8.8802
8.7531
Bruker Advance III 400
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

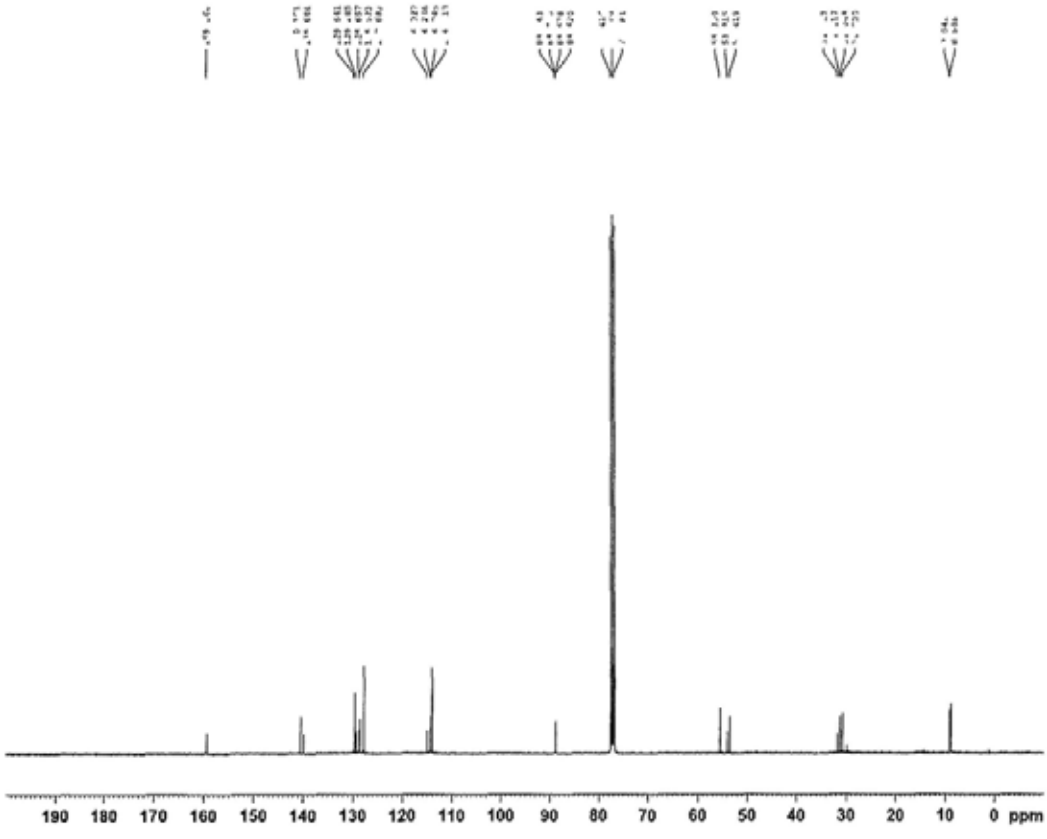

Et
Et
cis-124b
Et
Et
trans-124b

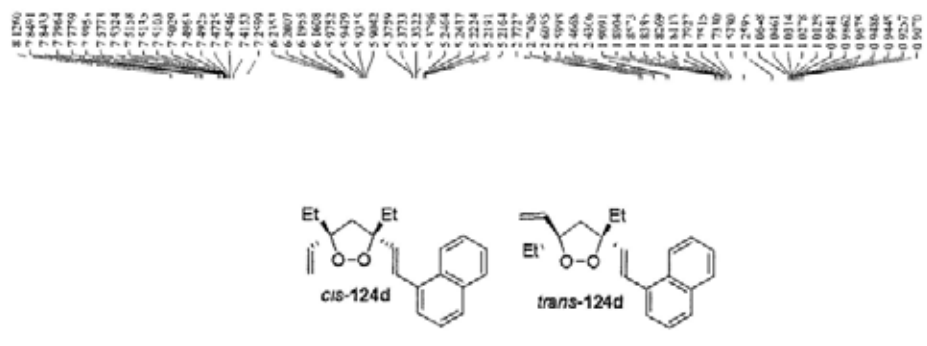


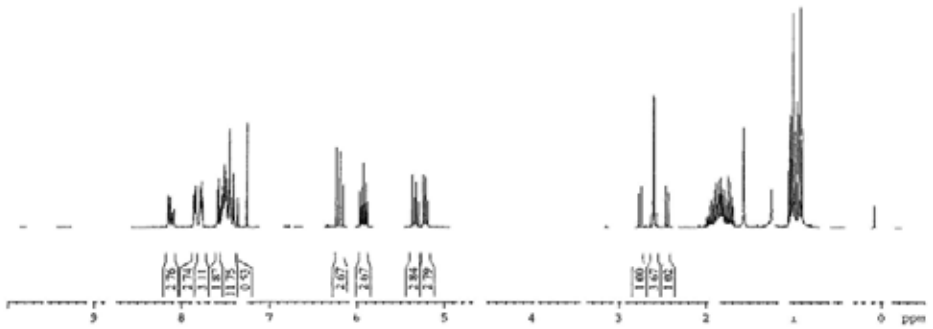


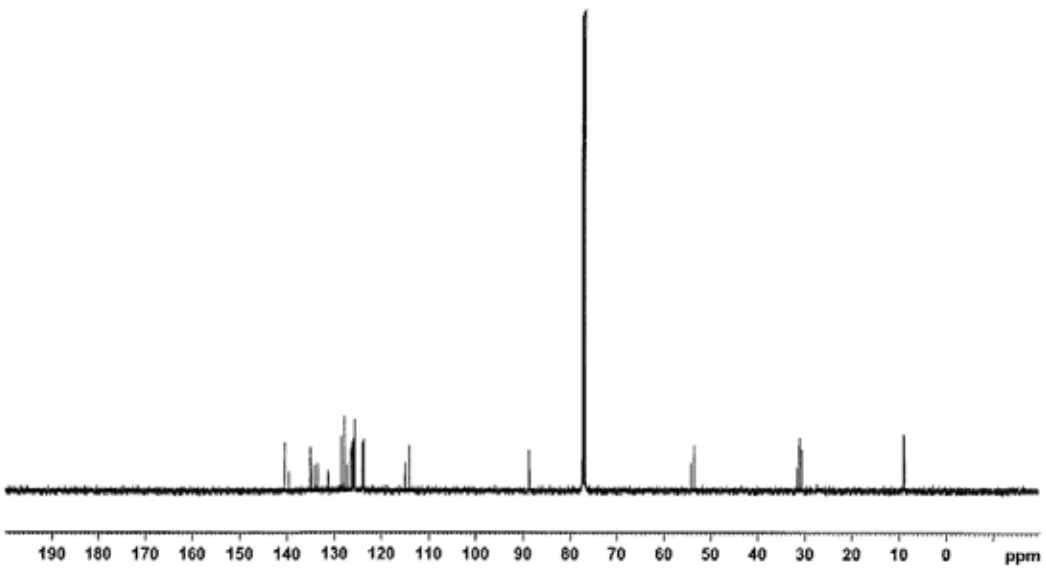

Et
Et
O-O
cis-124c
Et
Et
O-O
trans-124c
O—

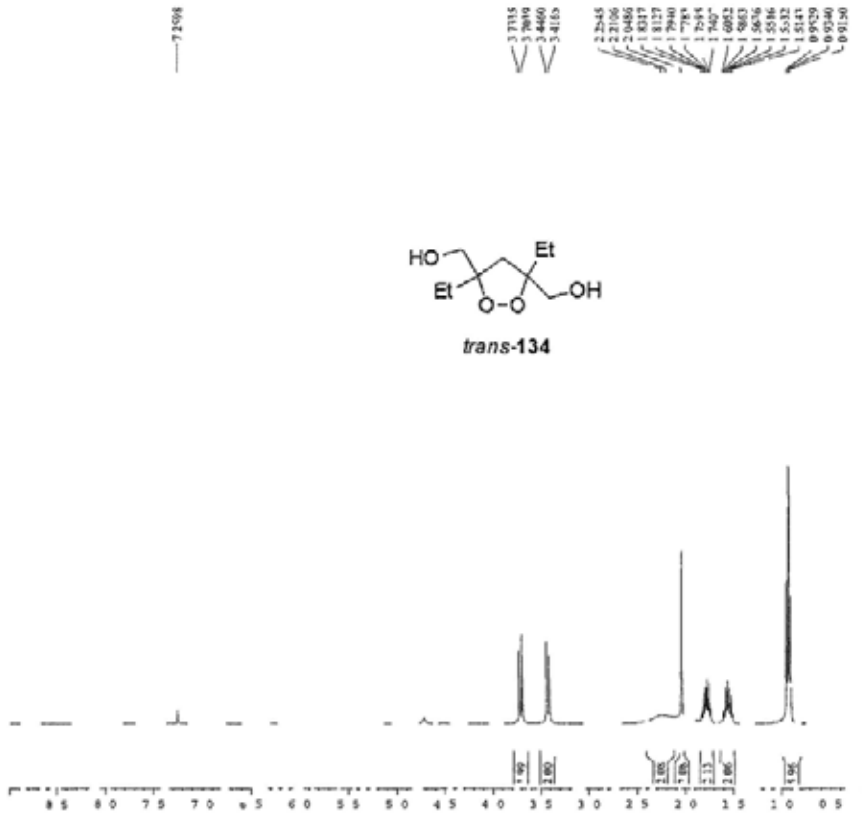

5.57
2.47
3.08
2.23
2.08
5.32
4.05
1.00
2.42
1.01
11.22
17.02
85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 05 00 ppm


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


Et
Et
O-O
cis-124d
Et
Et
O-O
trans-124d

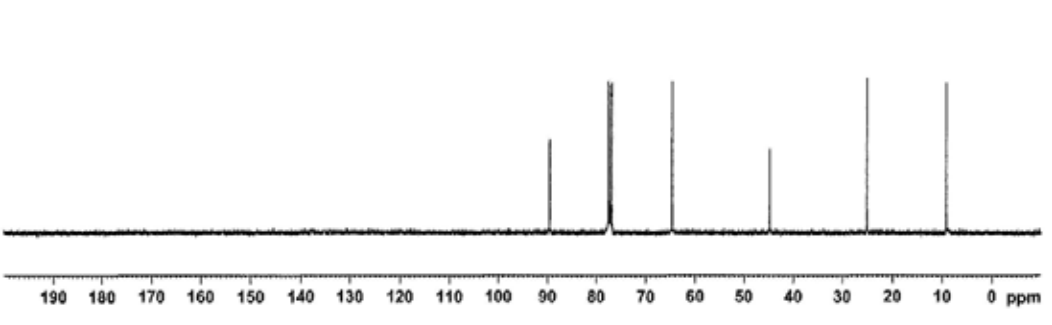

ppm

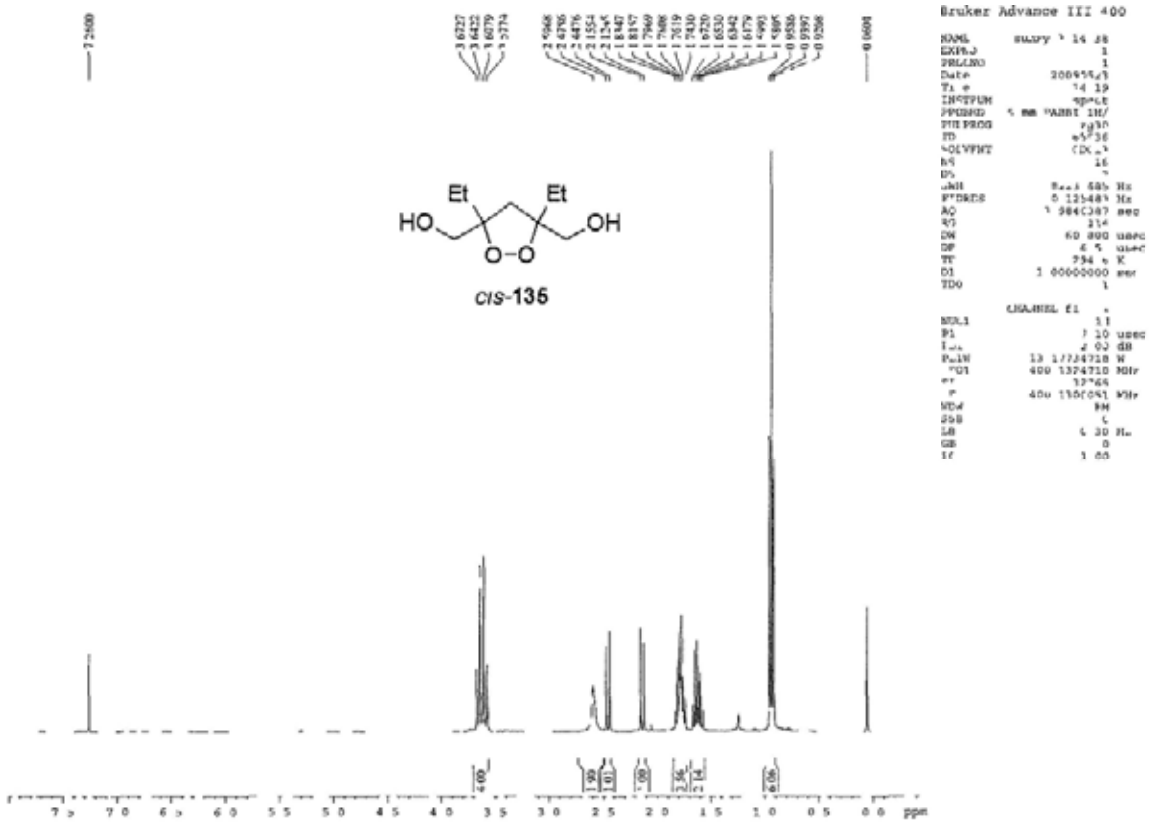

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

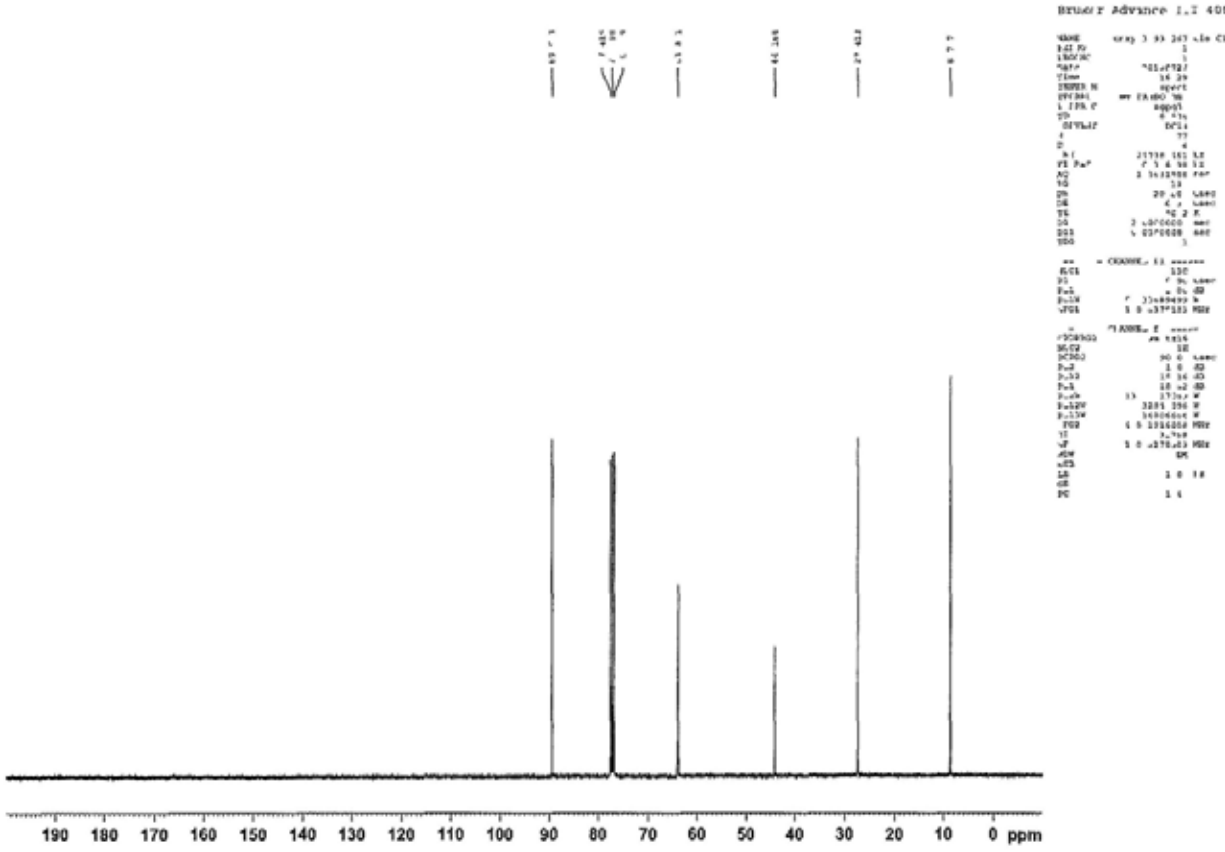

HO
Et
Et
O–O
OH

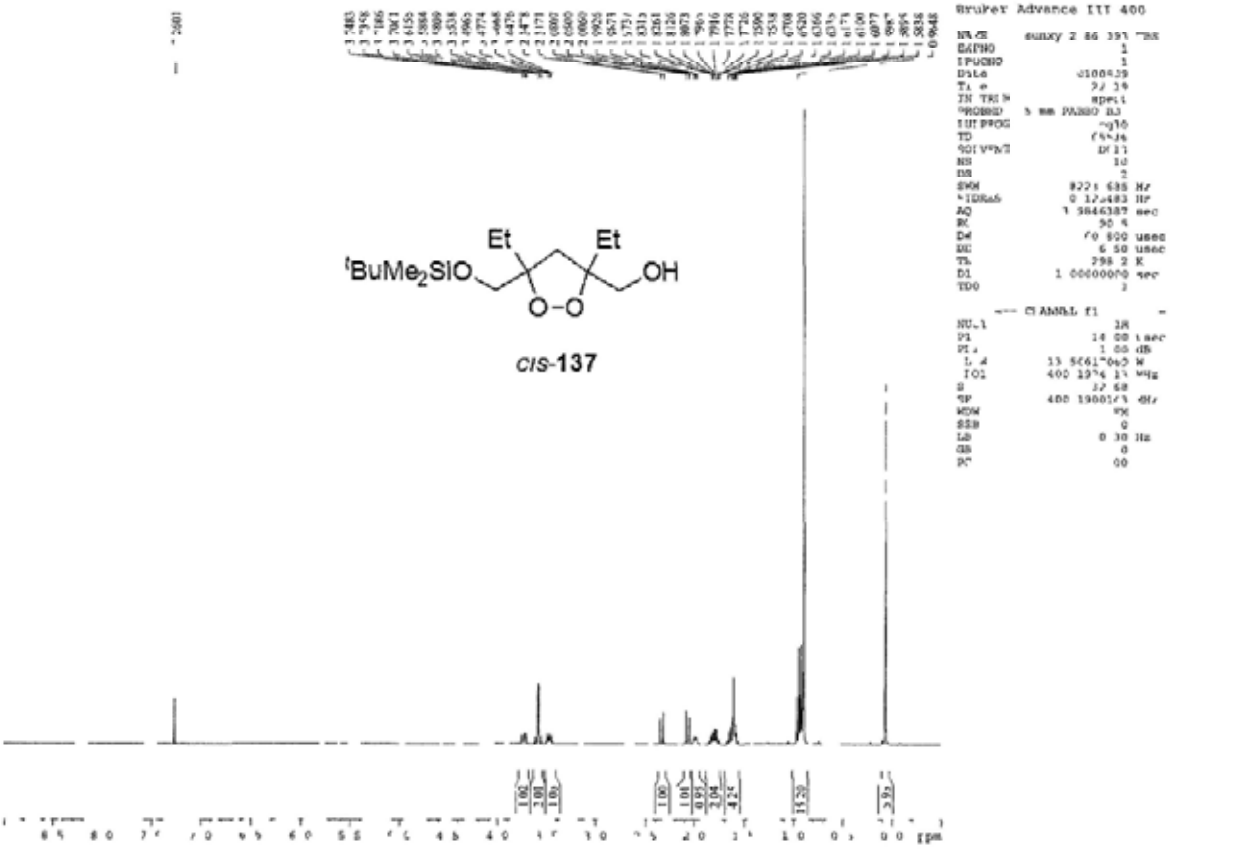
trans-**134**

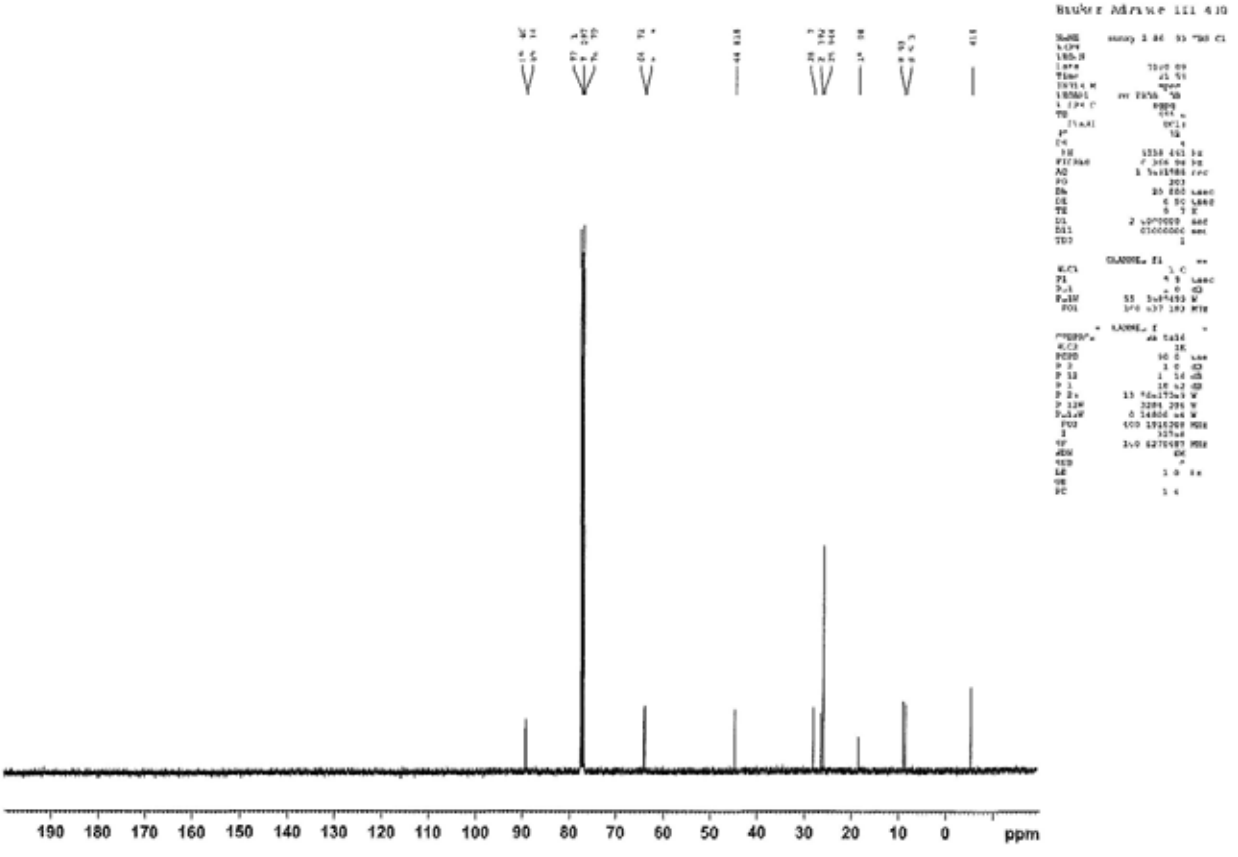
85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 05 00 ppm

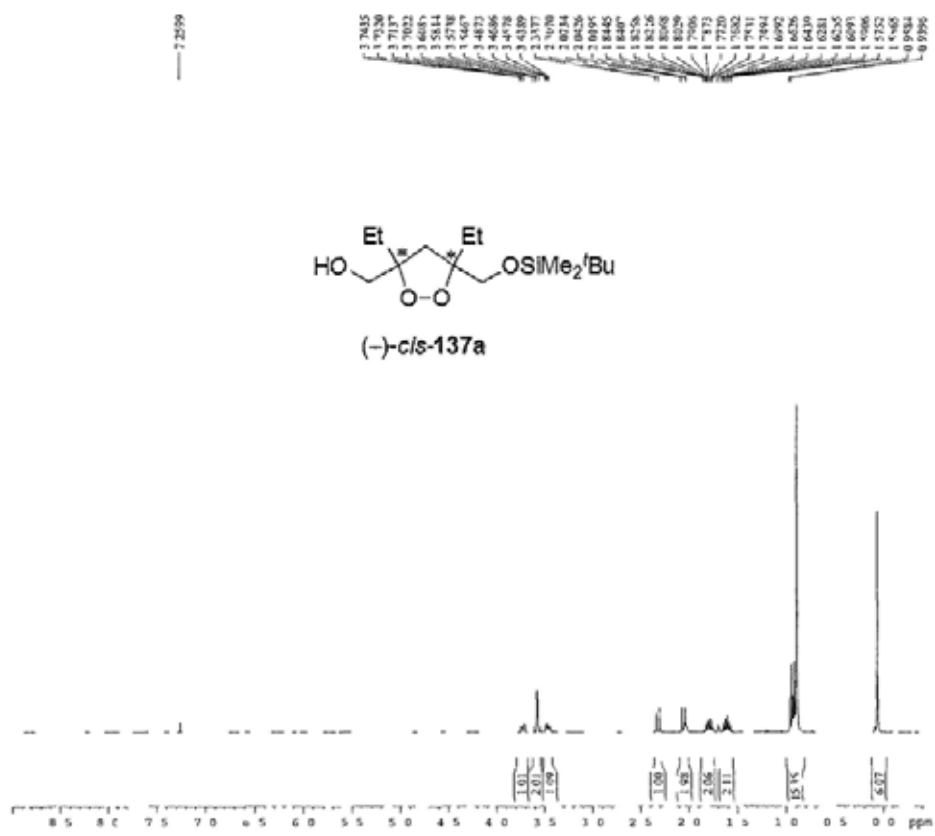

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

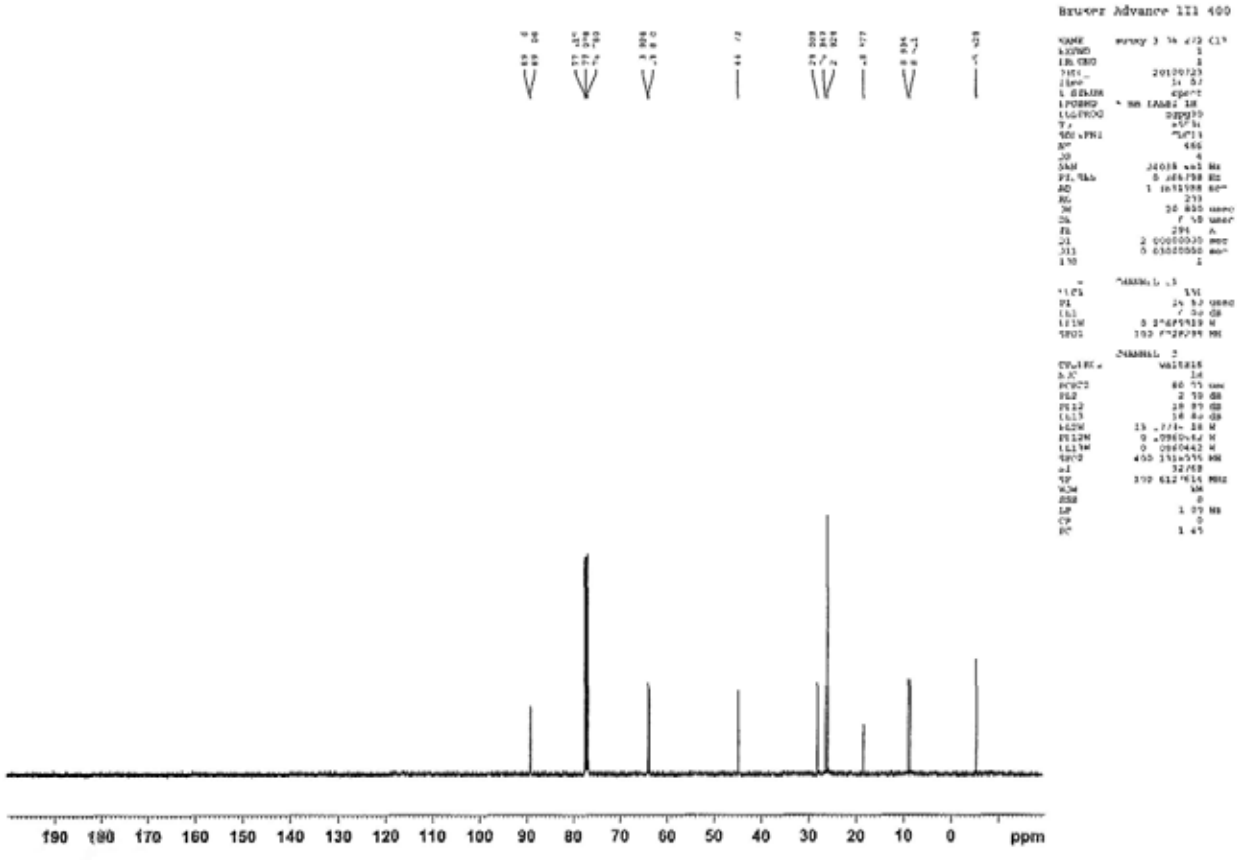

Et
Et
HO
OH
O–O
cis-135
Bruker Advance III 400
ppm

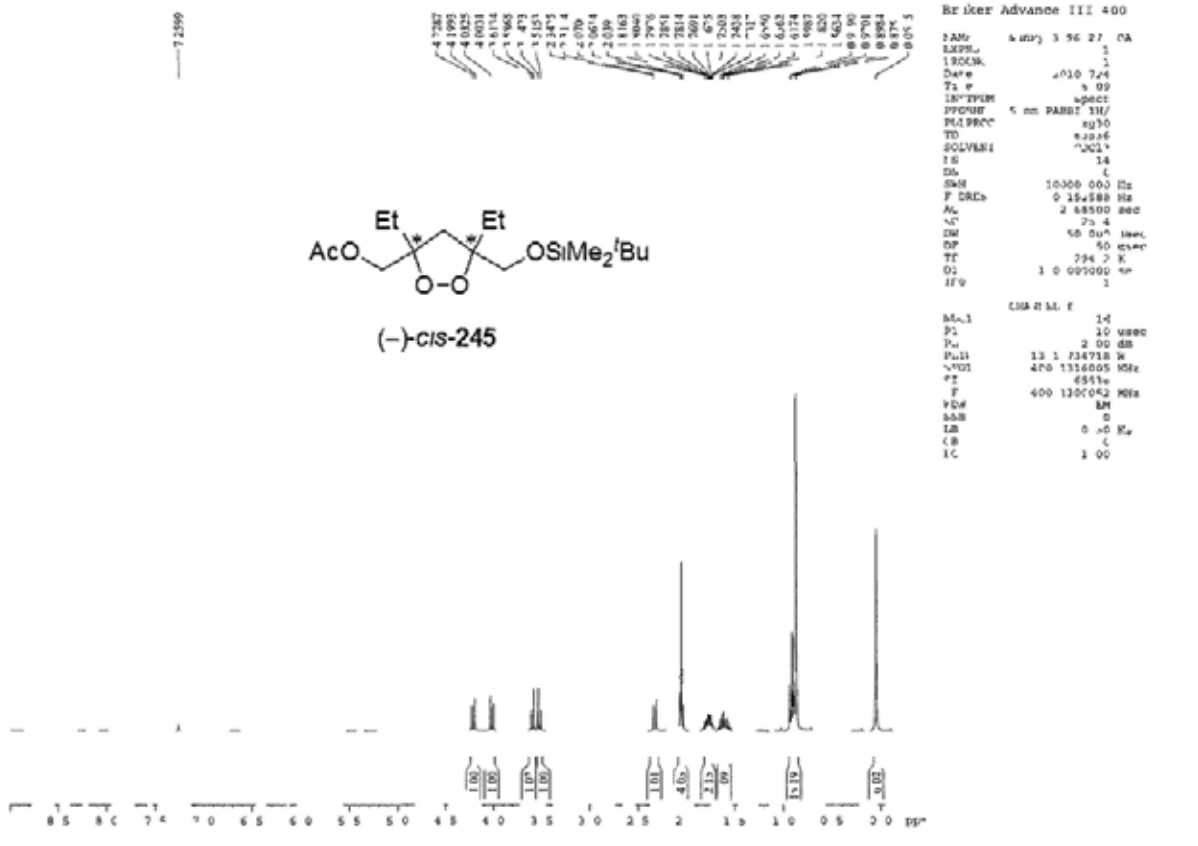

Bruker Advance
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

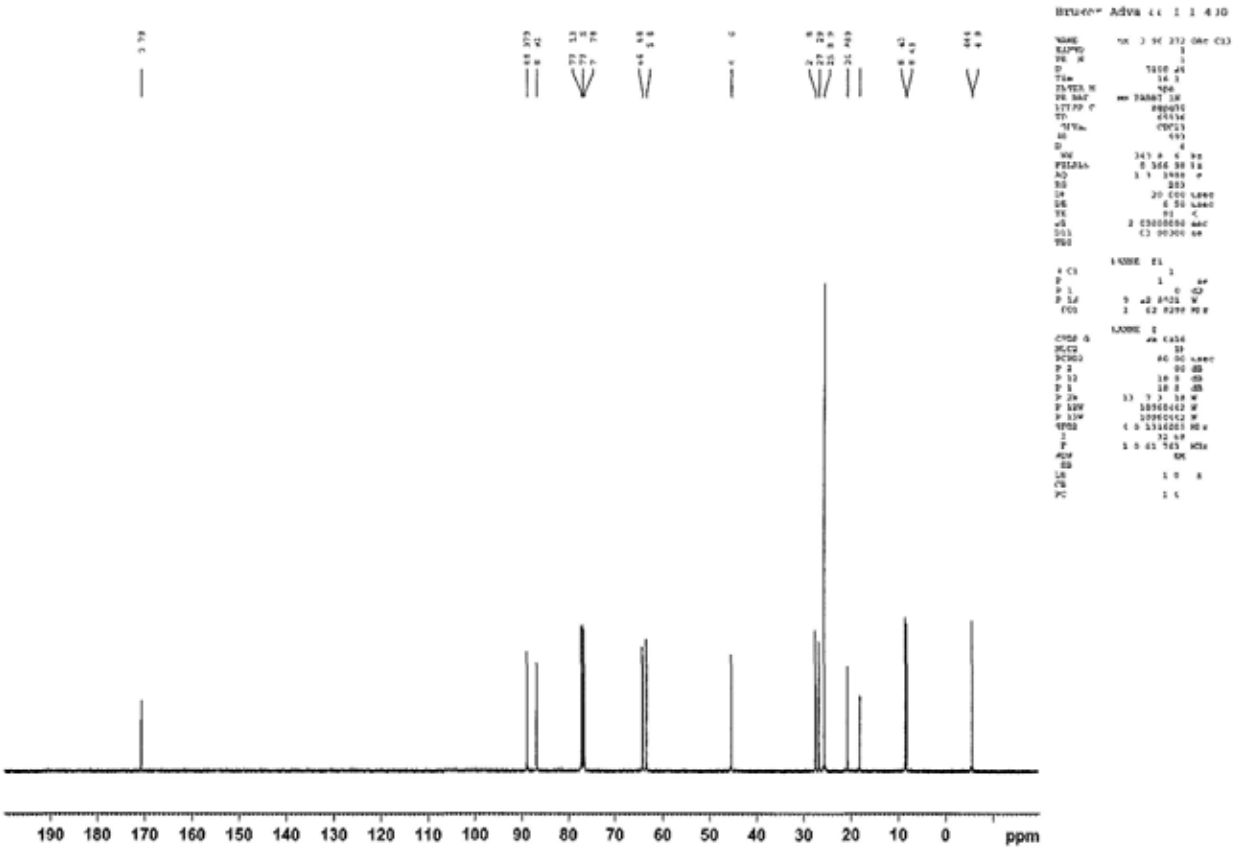

Et
Et
tBuMe2SiO
OH
O-O
cis-137
Bruker Advance III 400
ppm

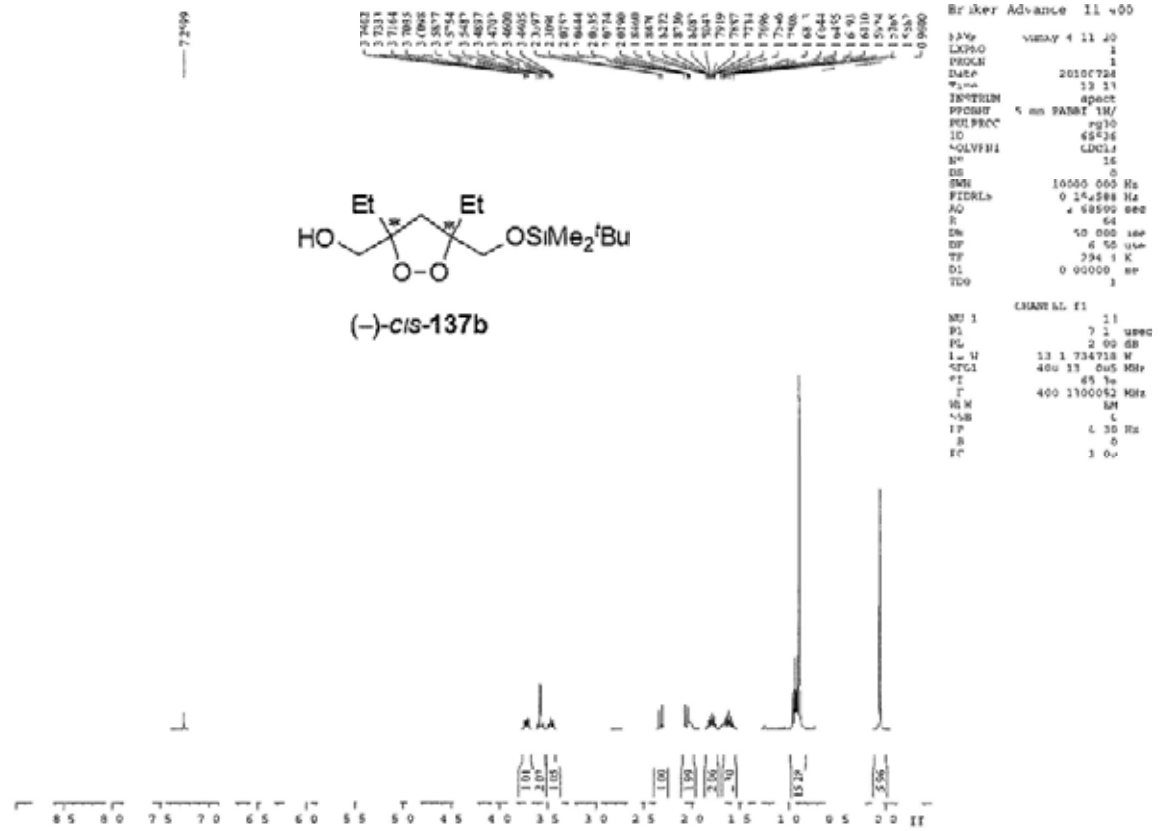

Bruker Advance III 400
ppm


Et
Et
HO
OSiMe2tBu
O–O
(–)-cis-137a
ppm

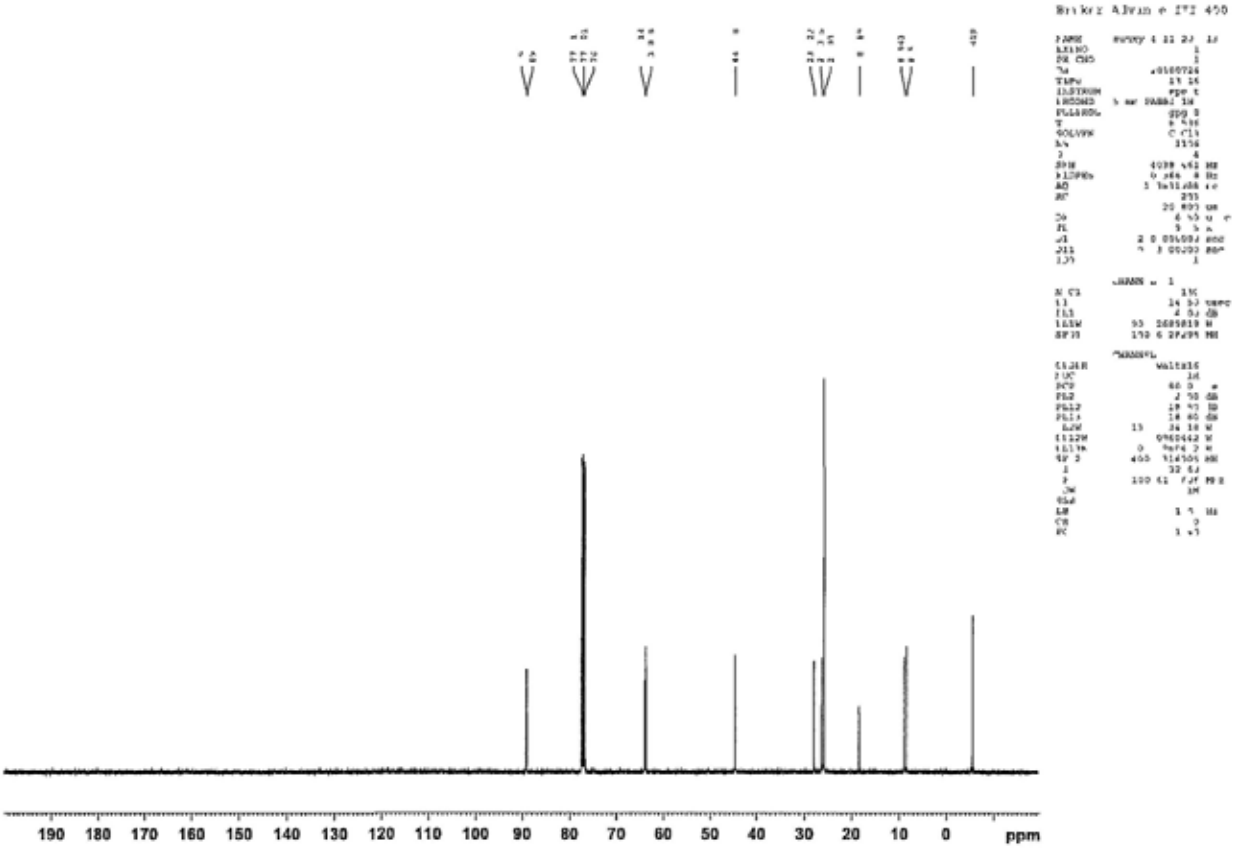

ppm

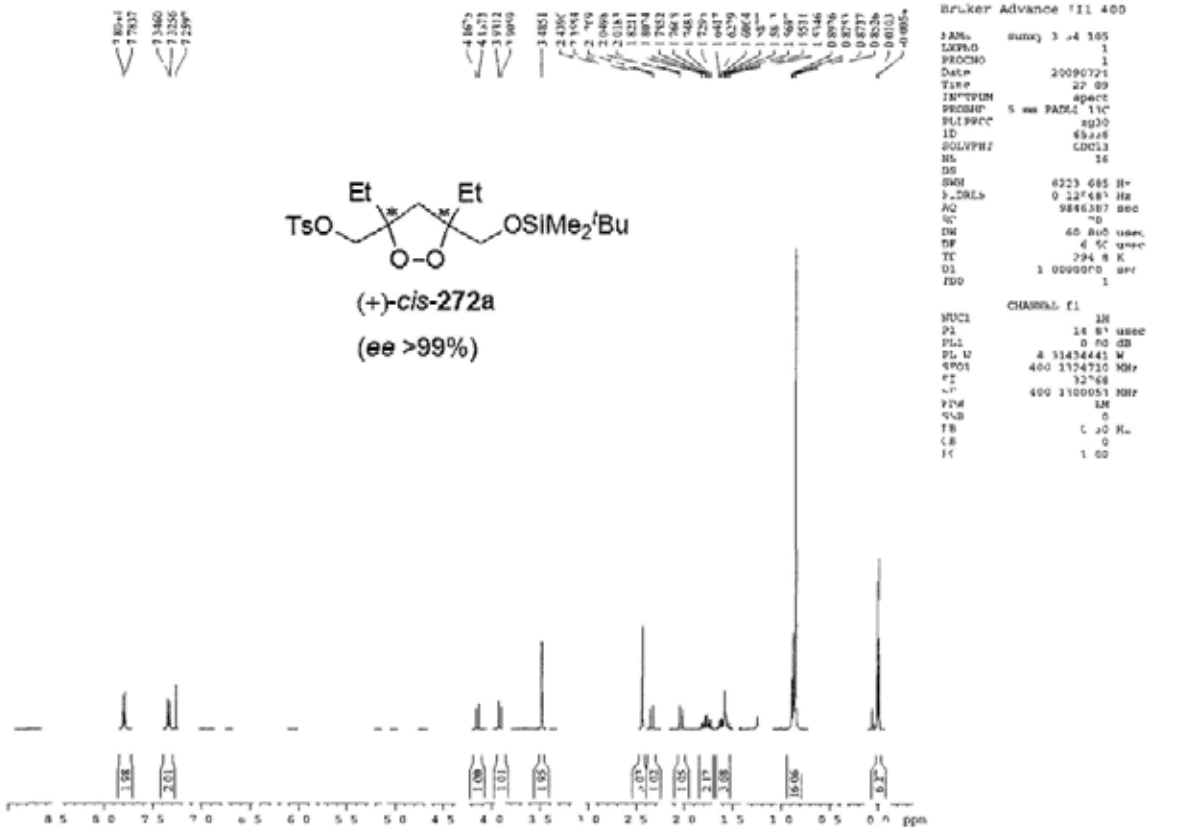

Et
Et
AcO
OSiMe2tBu
O–O
(–)-cis-245

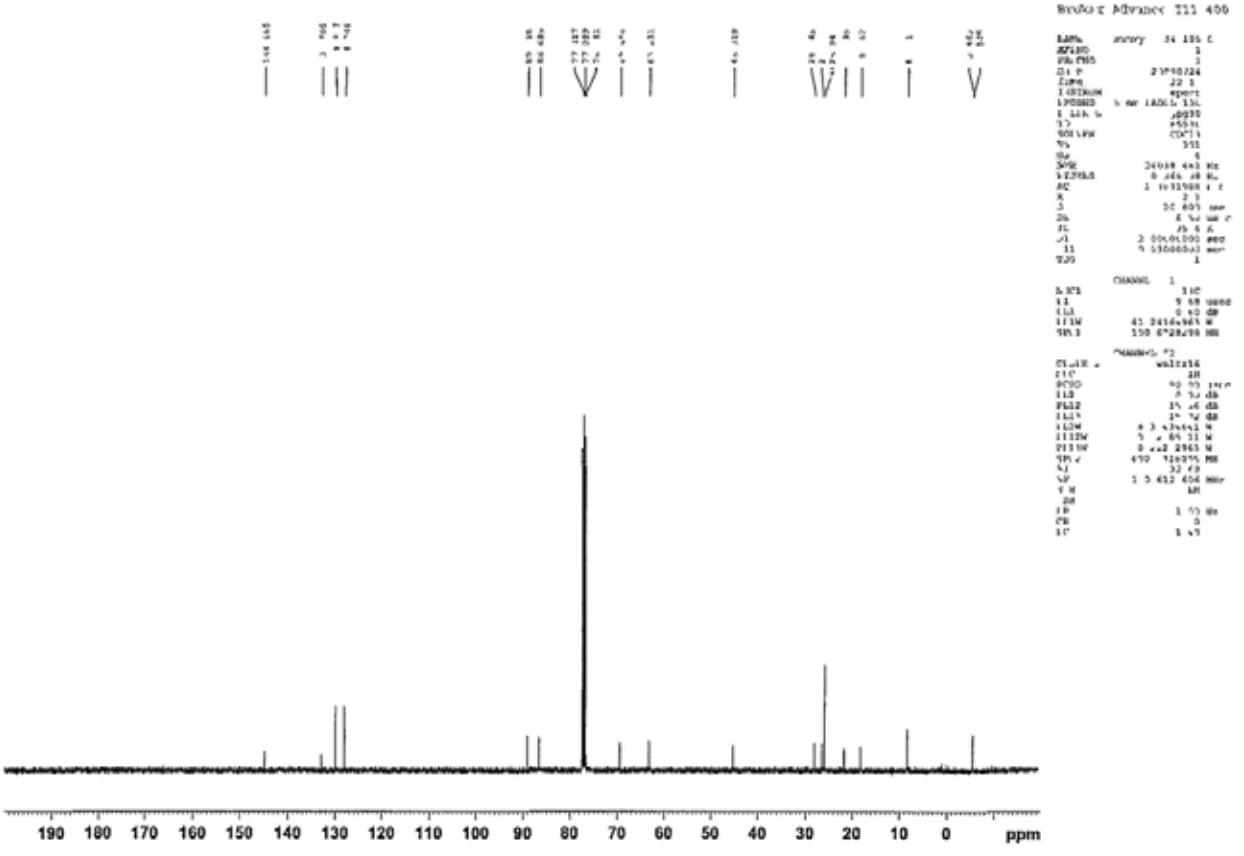


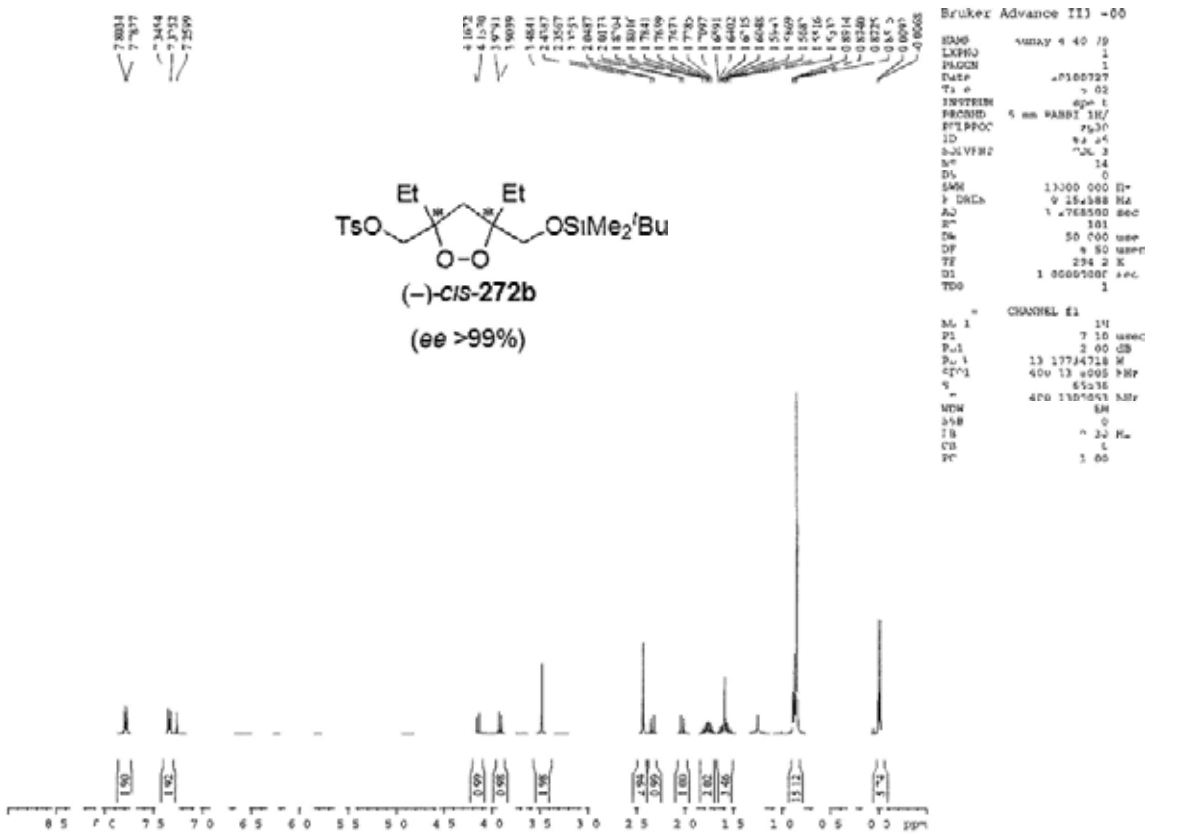


(–)-*cis*-137b



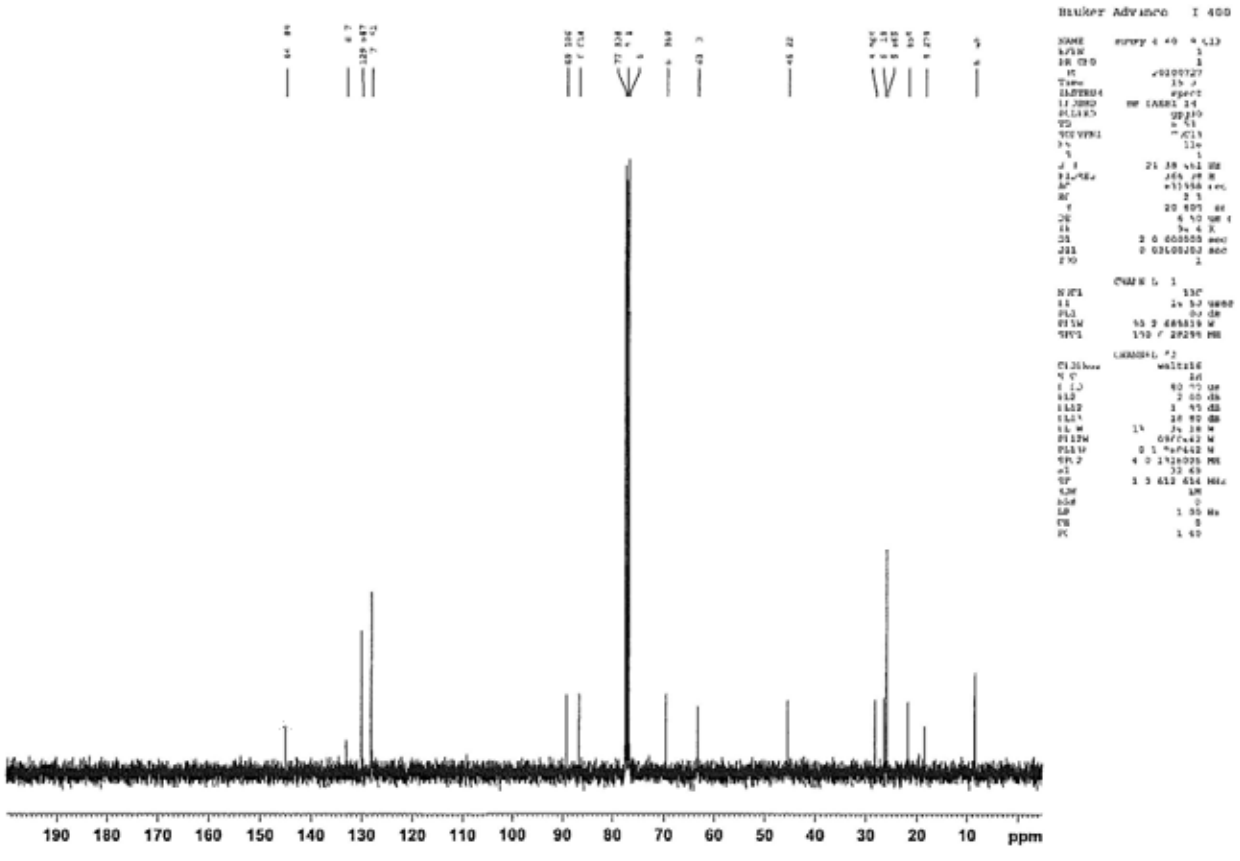

Et
Et
TsO
OSiMe2tBu
O–O
(+)-cis-272a
(ee >99%)
ppm

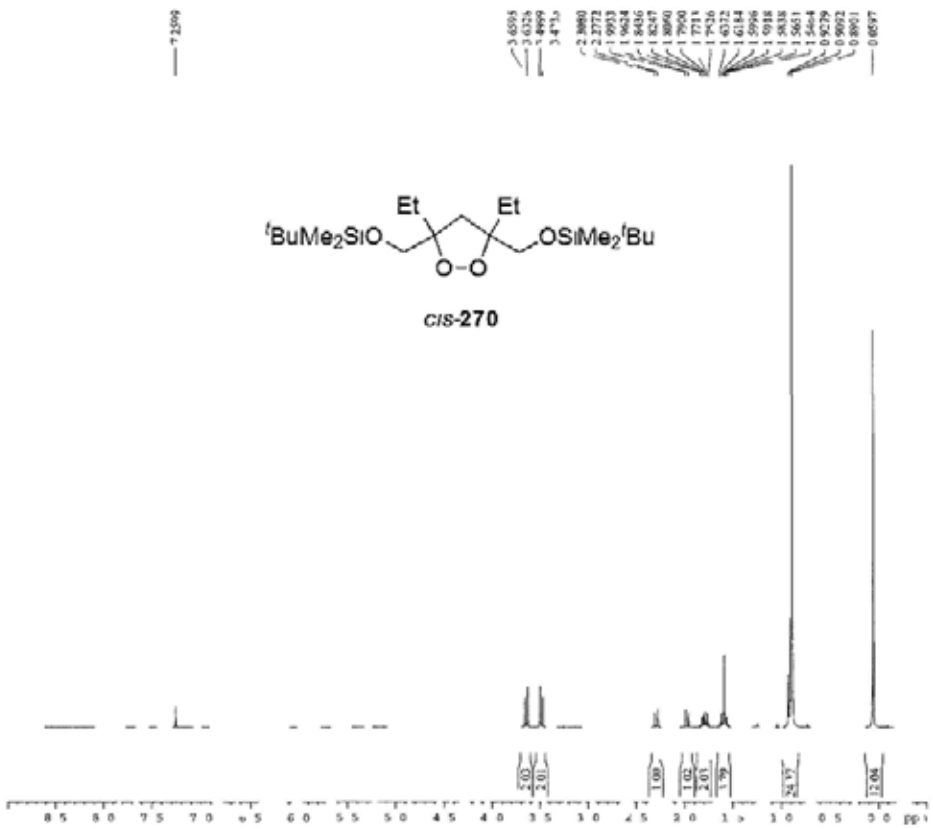

ppm

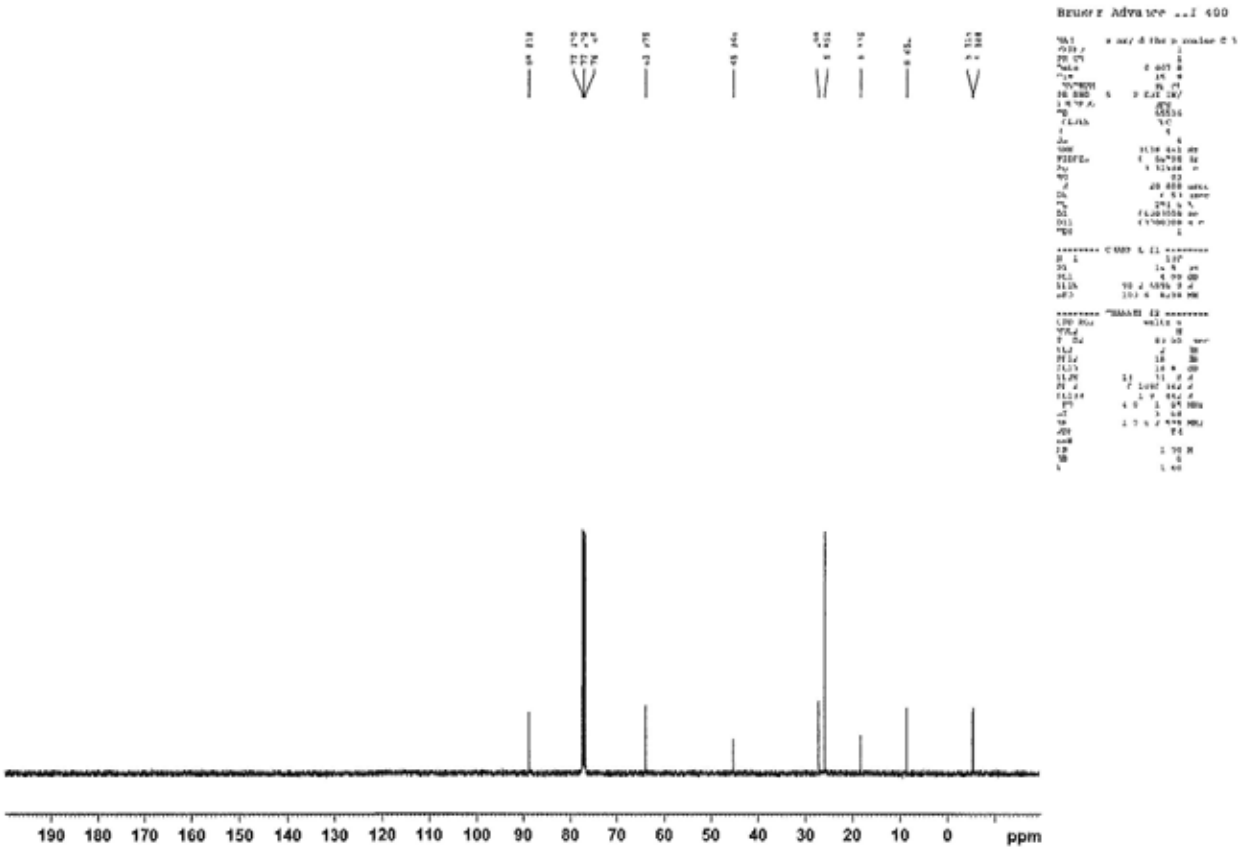


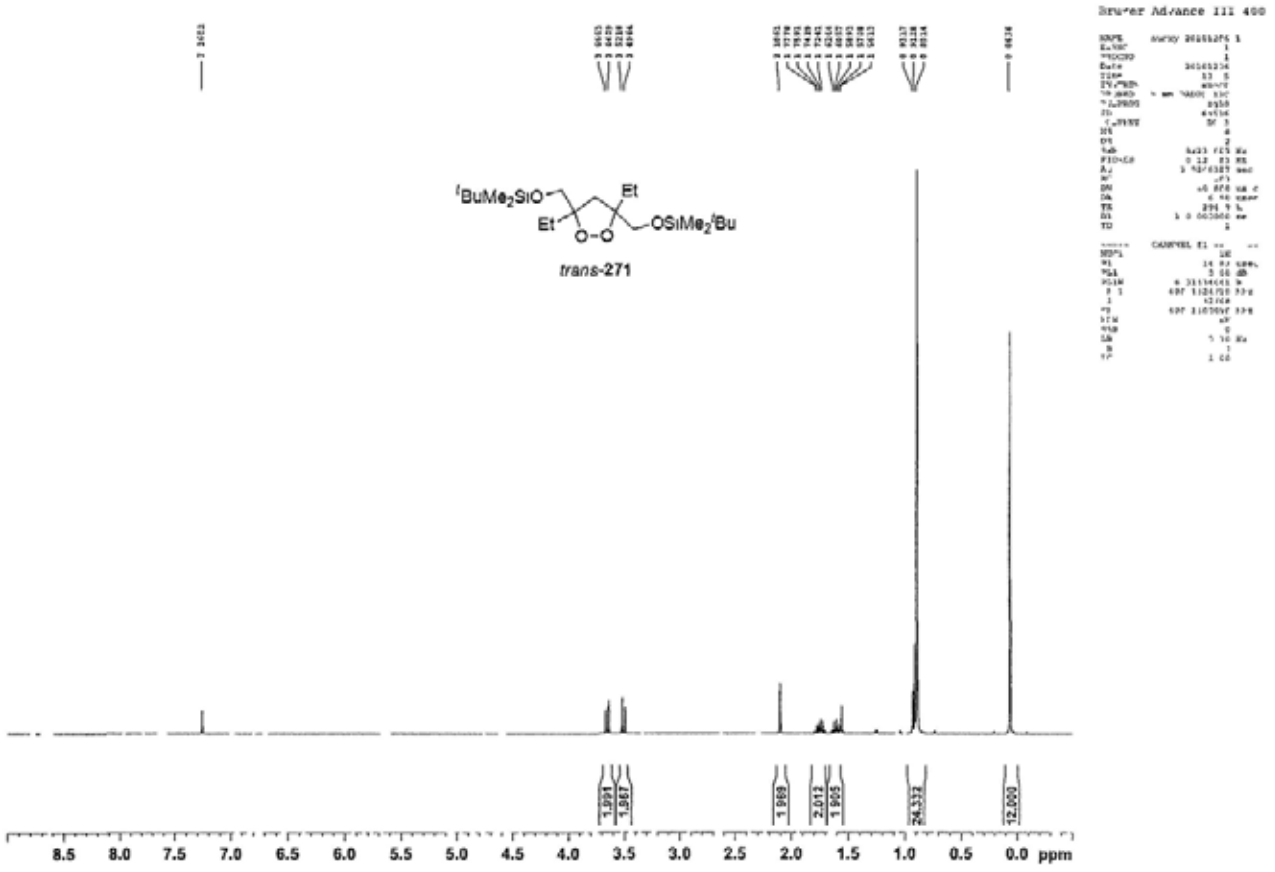
(–)-*cis*-272b

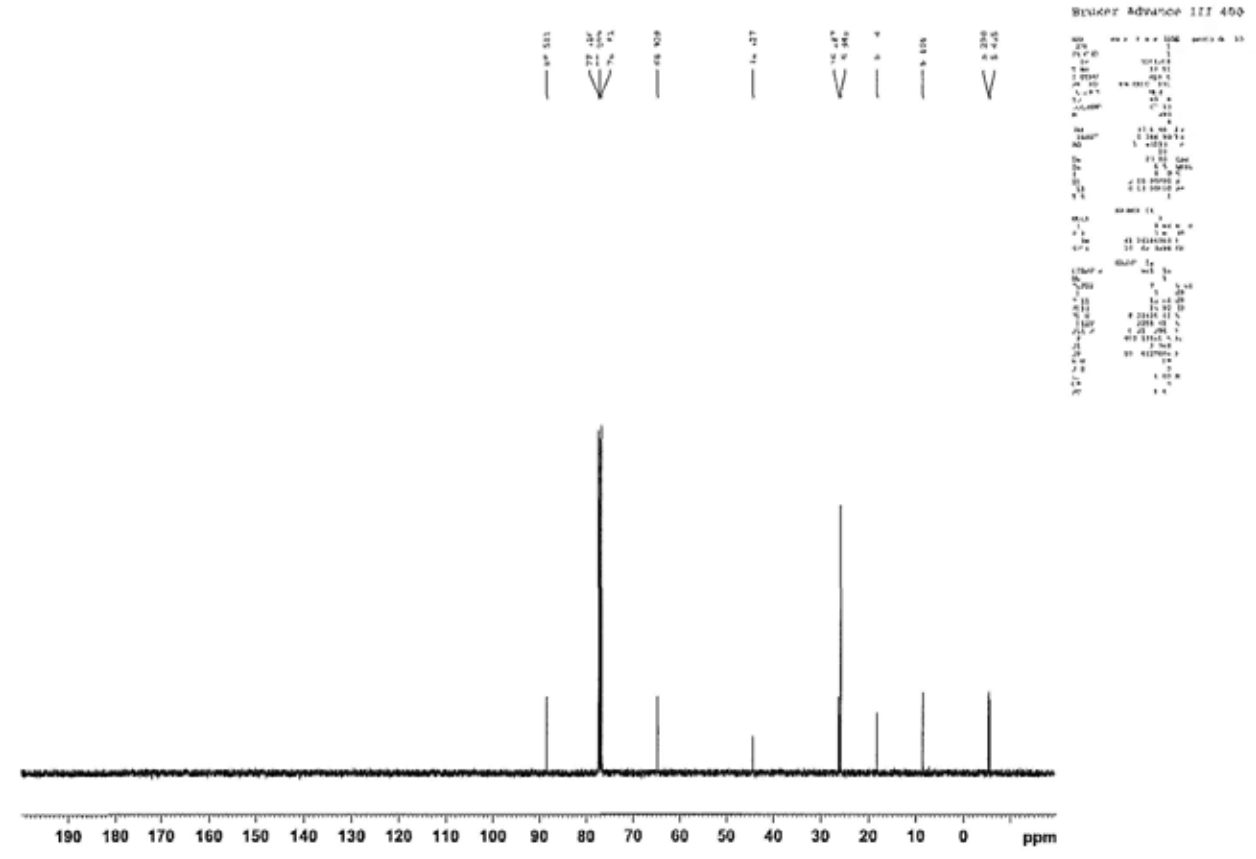
(*ee* >99%)

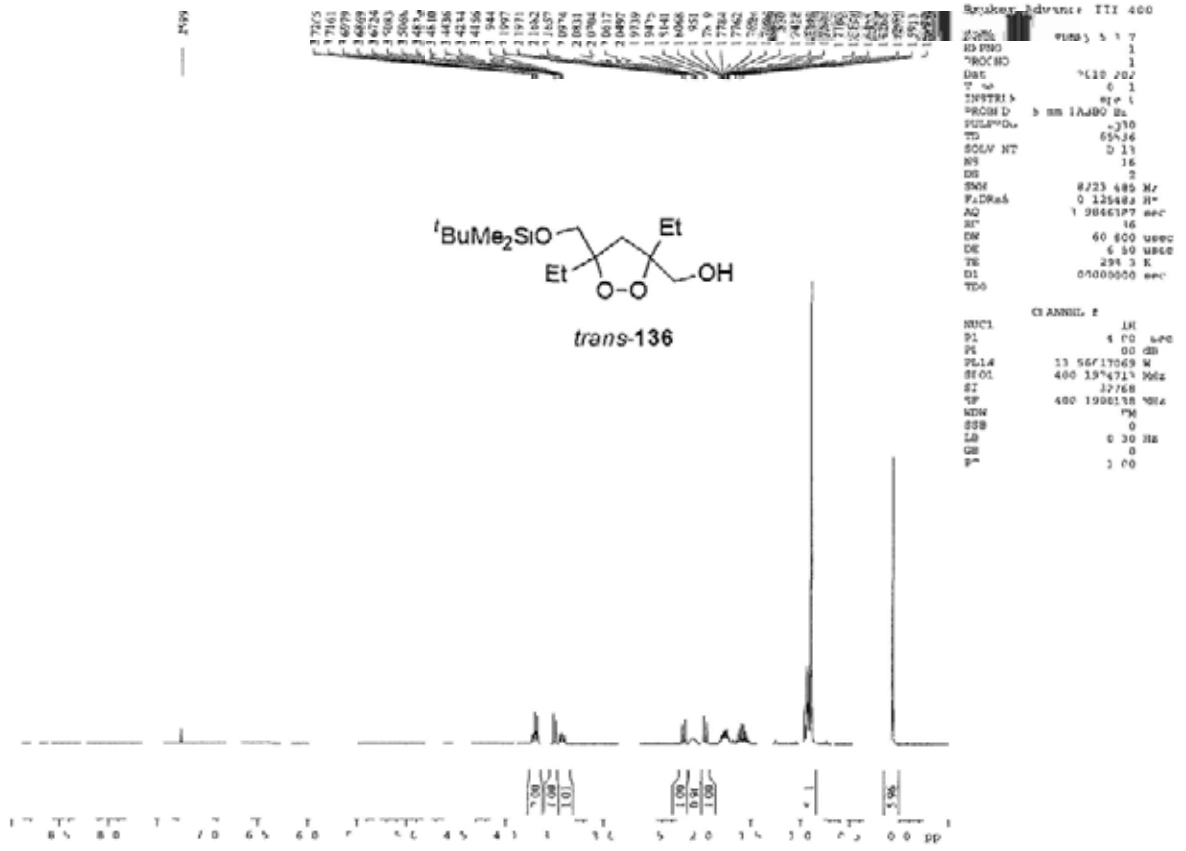


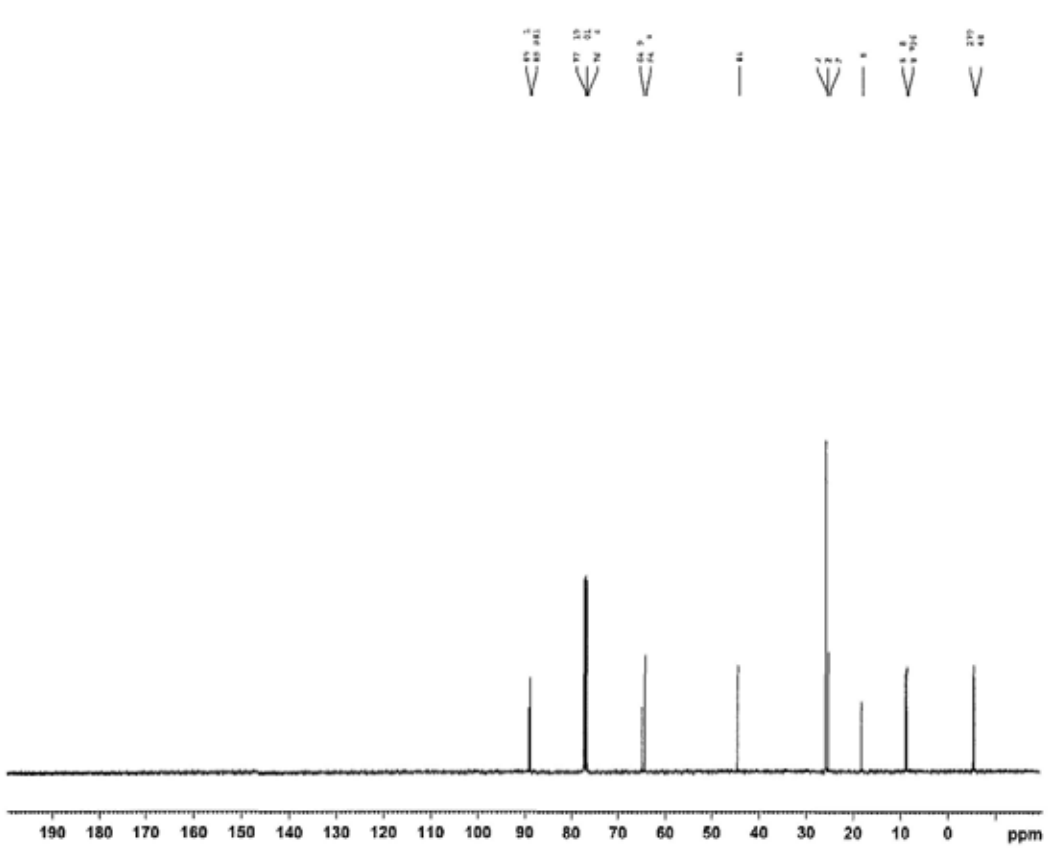

Et
Et
tBuMe2SiO
OSiMe2tBu
O–O
cis-270

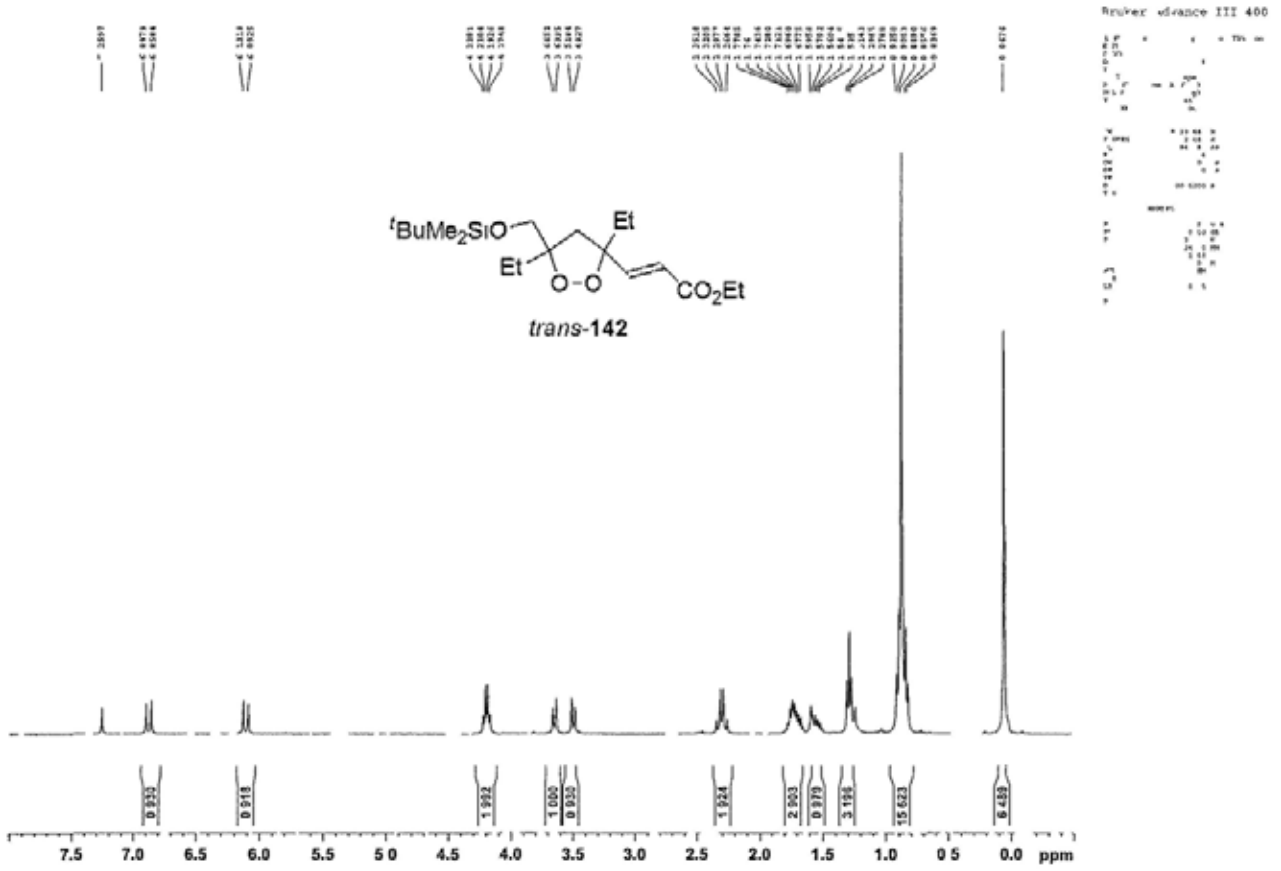


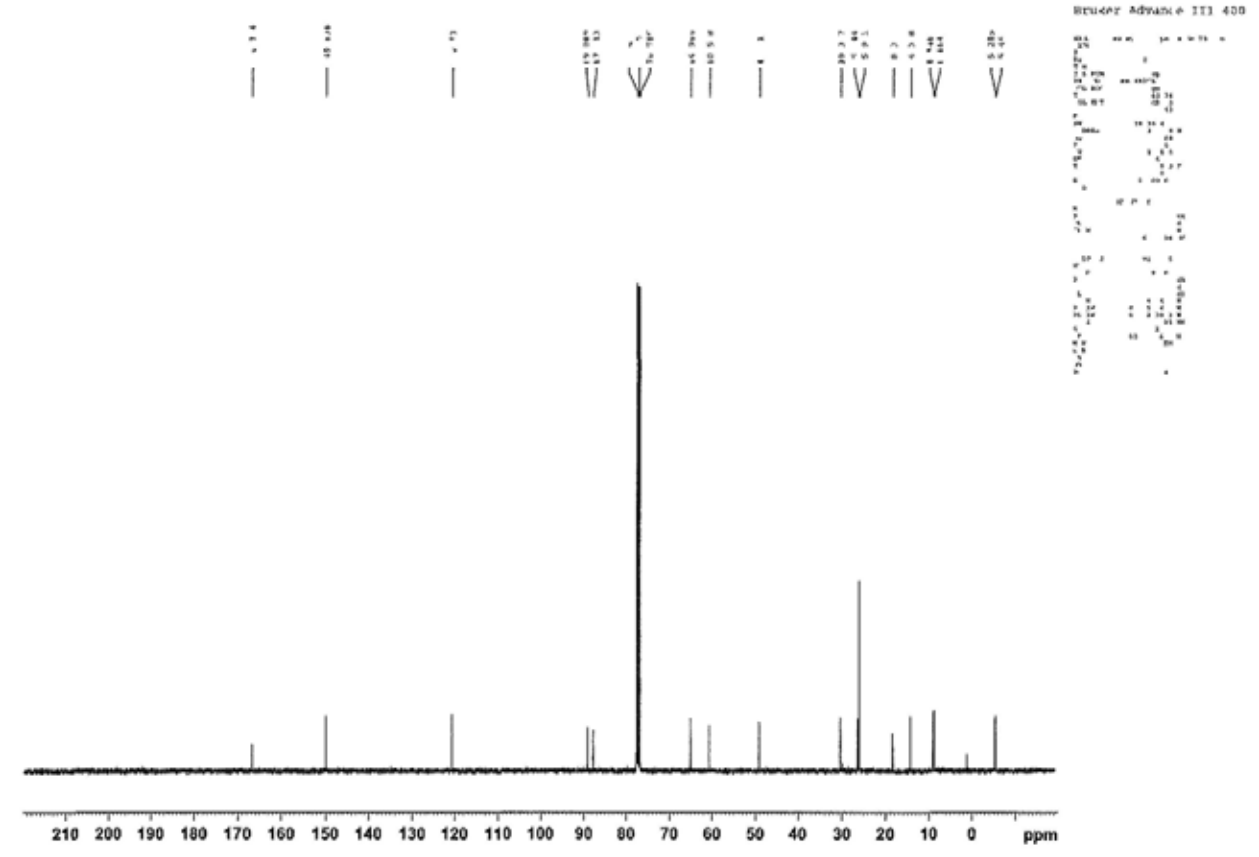

Bruker Advance III 400
tBuMe2SiO
Et
Et
OSiMe2tBu
trans-271
3.991
1.867
1.988
2.012
1.905
24.332
12.000
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

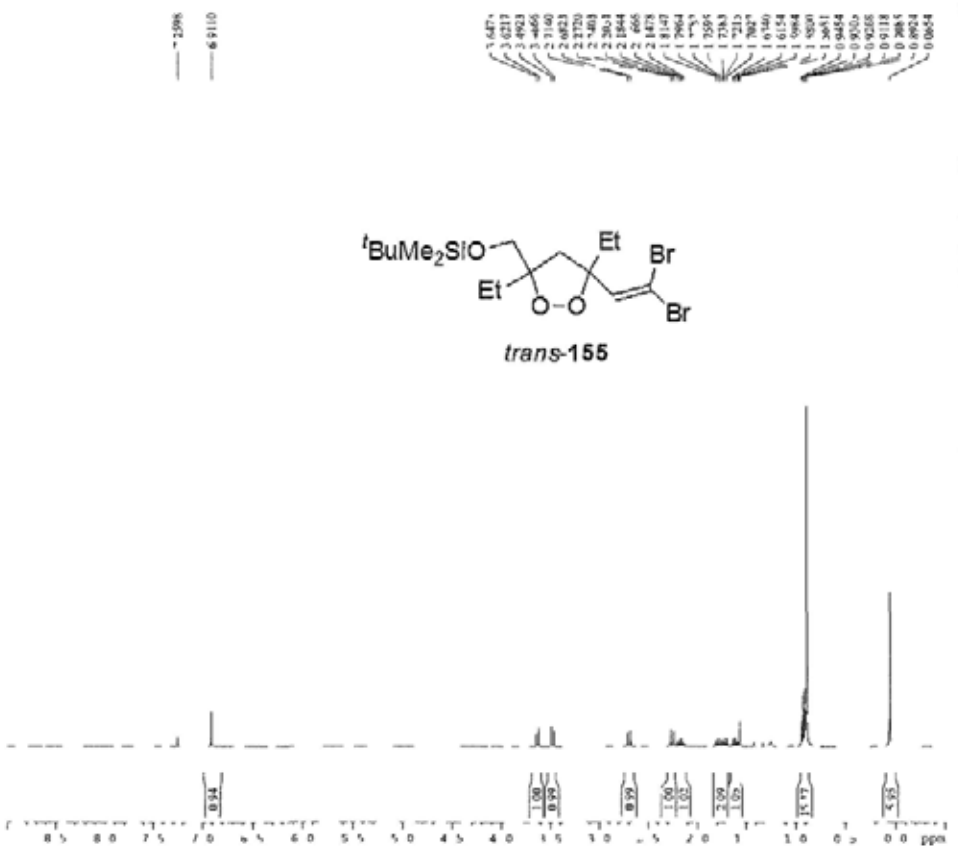

Bruker Advance III 400
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

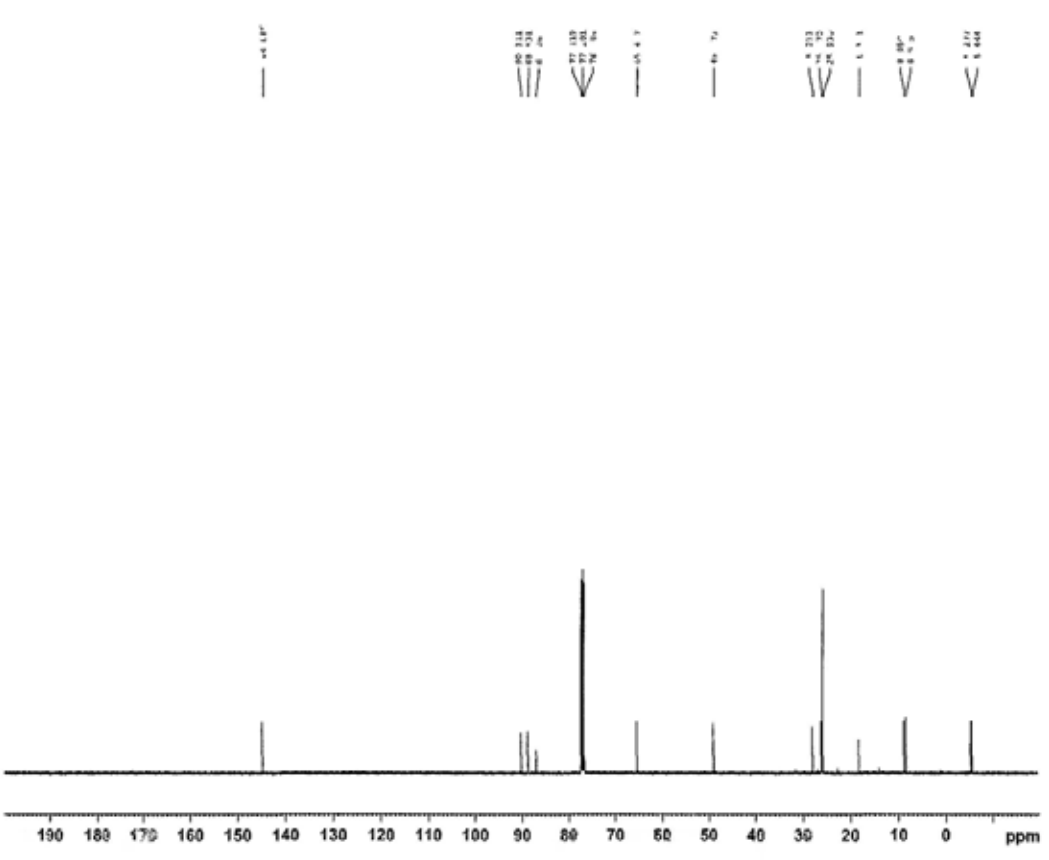

tBuMe2SiO
Et
Et
O-O
OH
trans-136

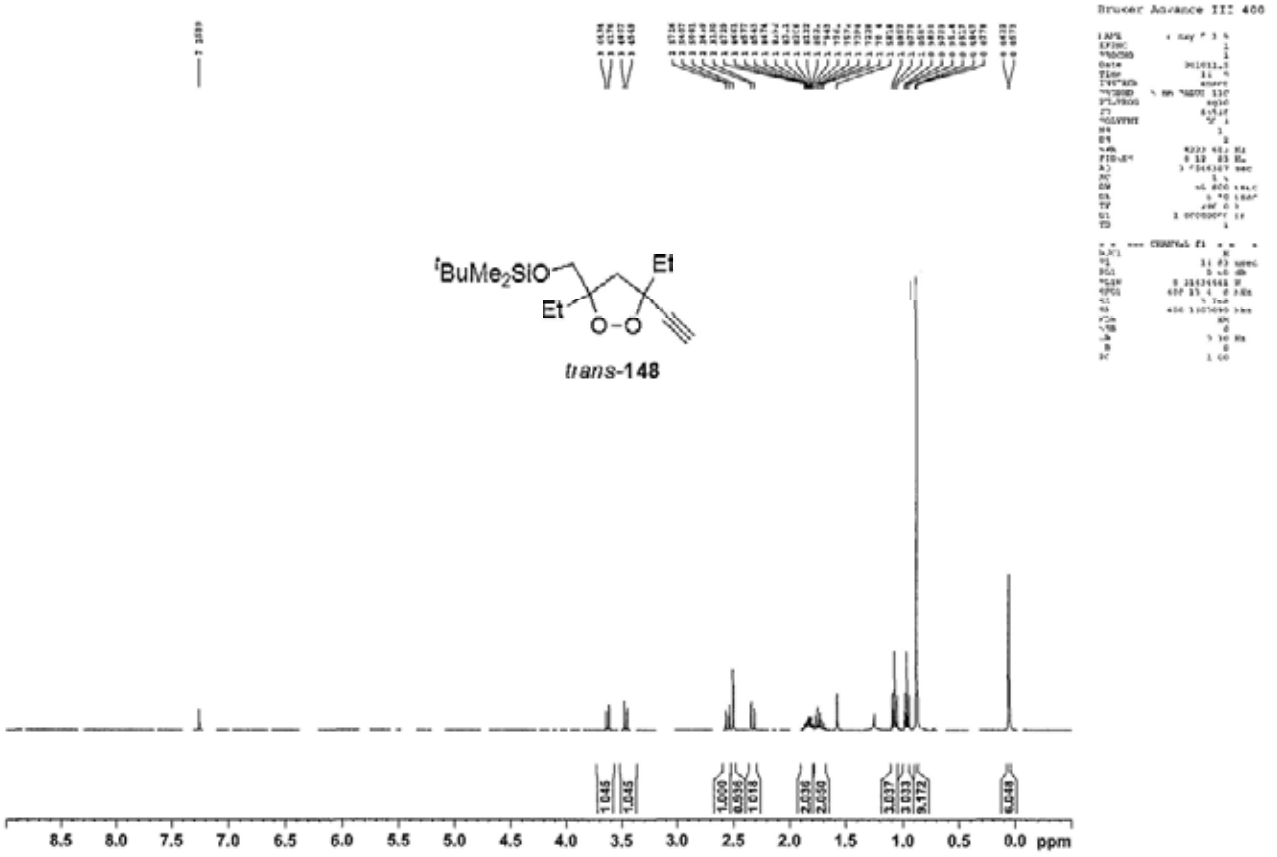

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

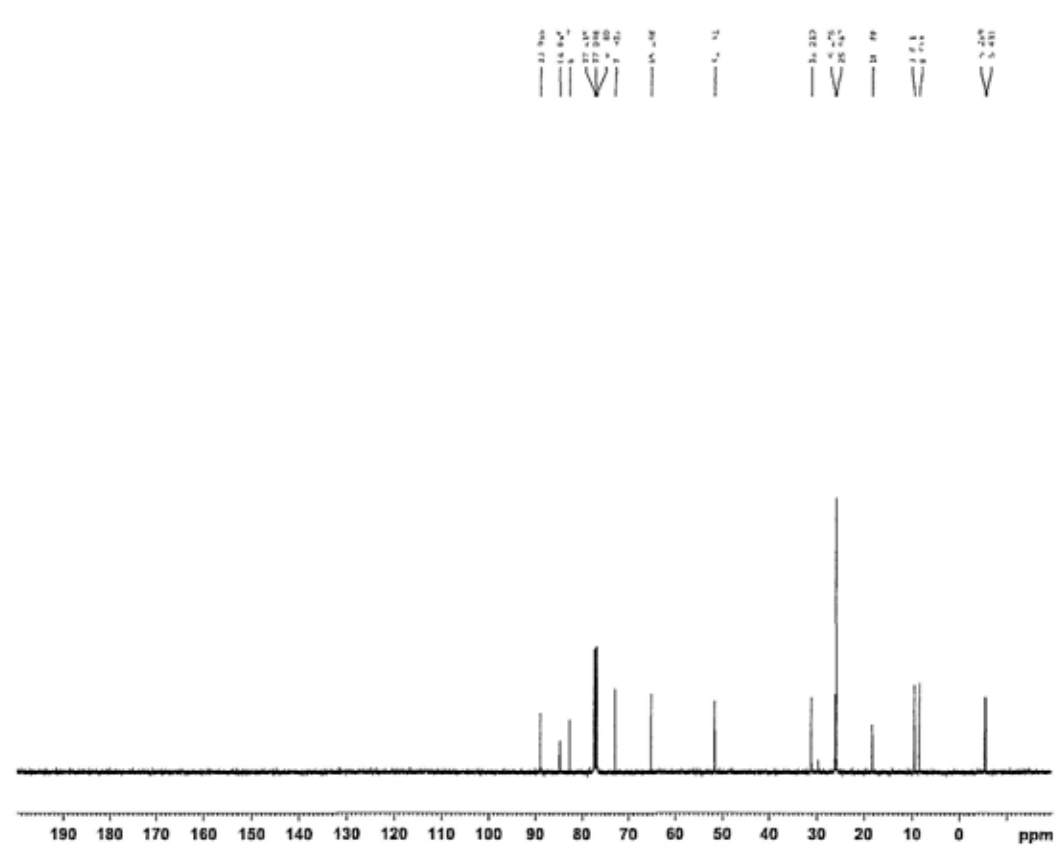

Bruker advance III 400
tBuMe2SiO
Et
Et
O-O
CO2Et
trans-142
0.833
0.918
1.992
1.000
0.938
1.924
2.903
0.979
3.196
15.623
6.489
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

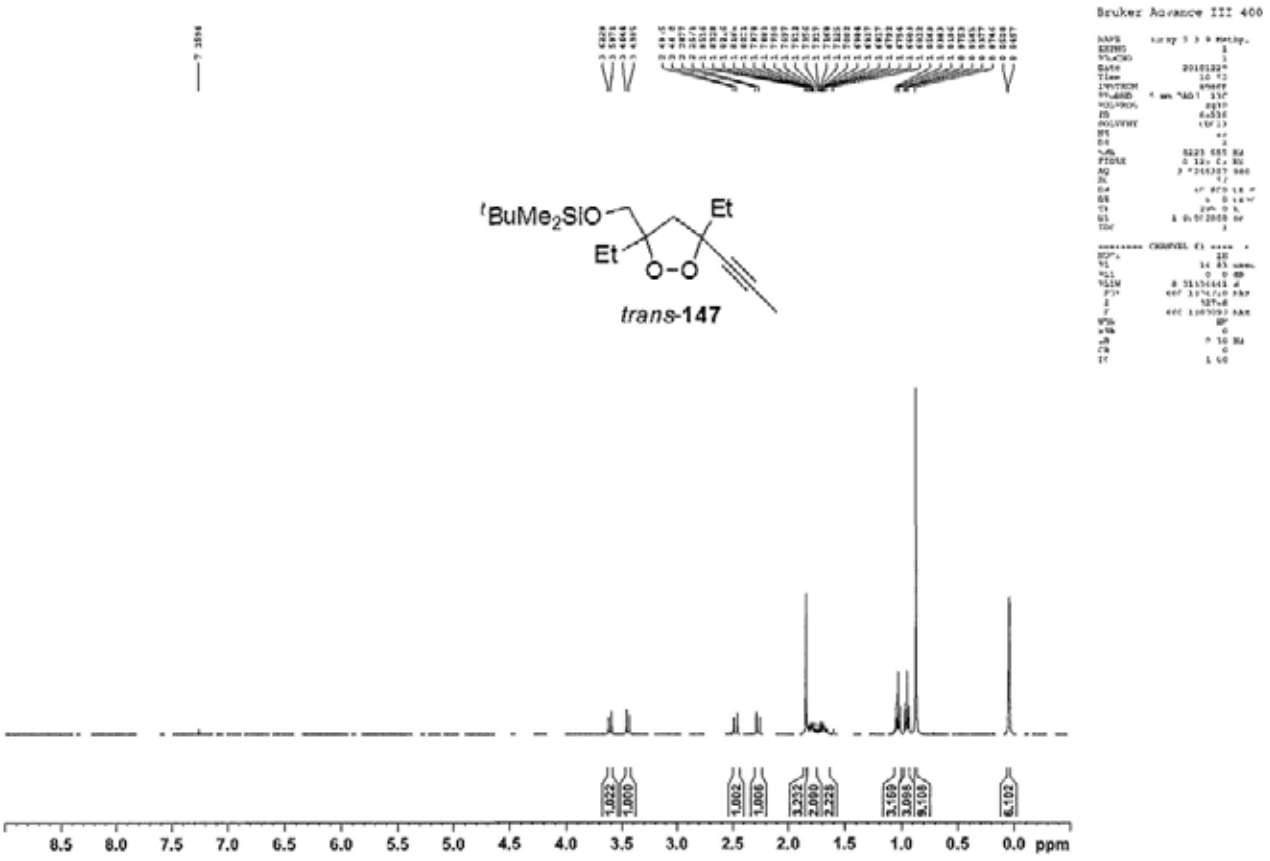

Bruker Advance III 400
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

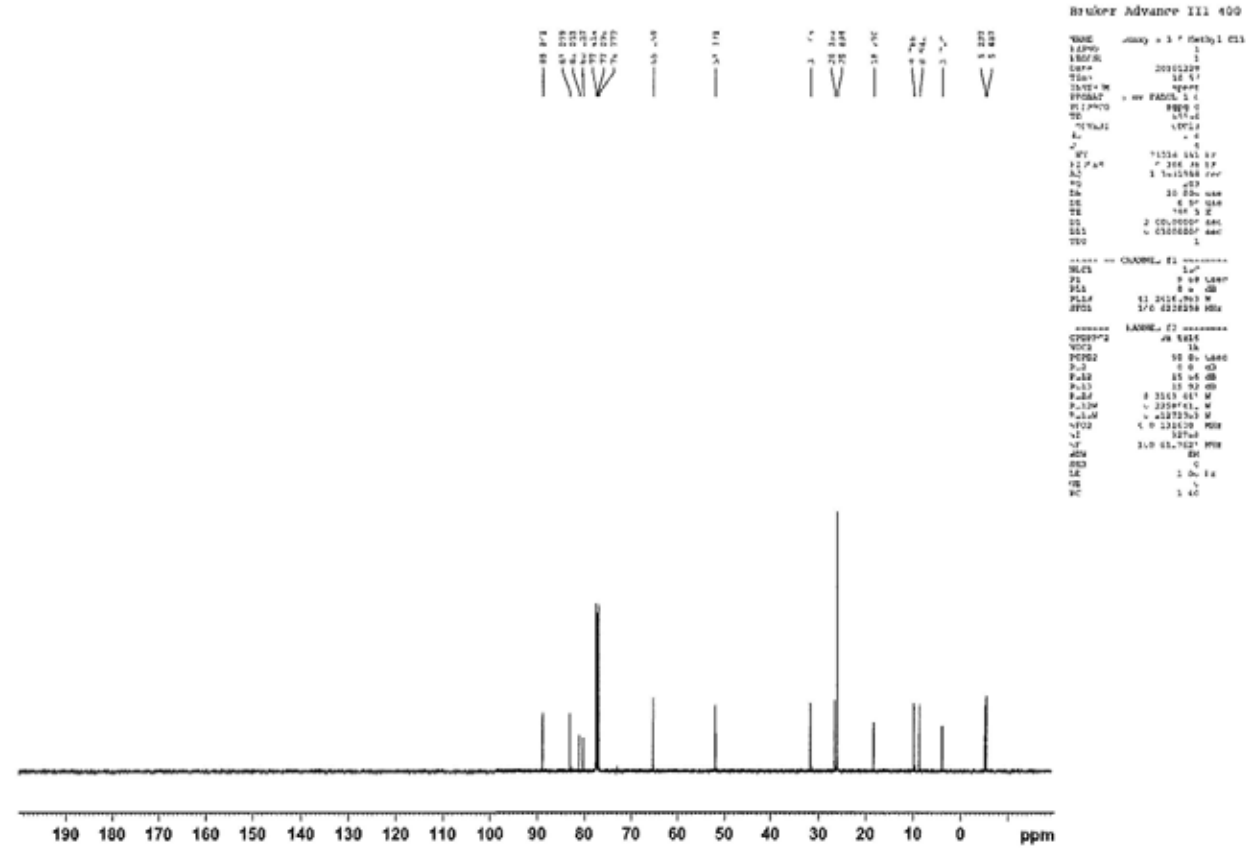

Bruker Advance III 400
^{t}BuMe$_2$SiO
Et
Et
Br
Br
trans-155
ppm

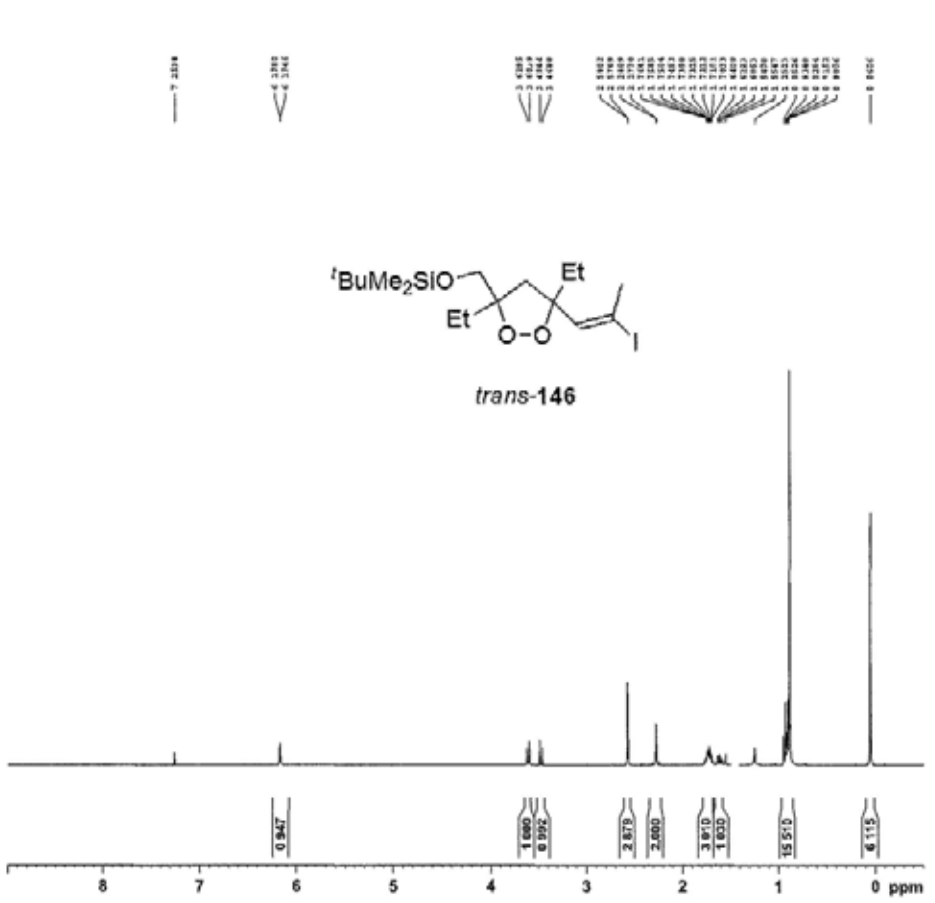

Bruker Advance III 400
ppm

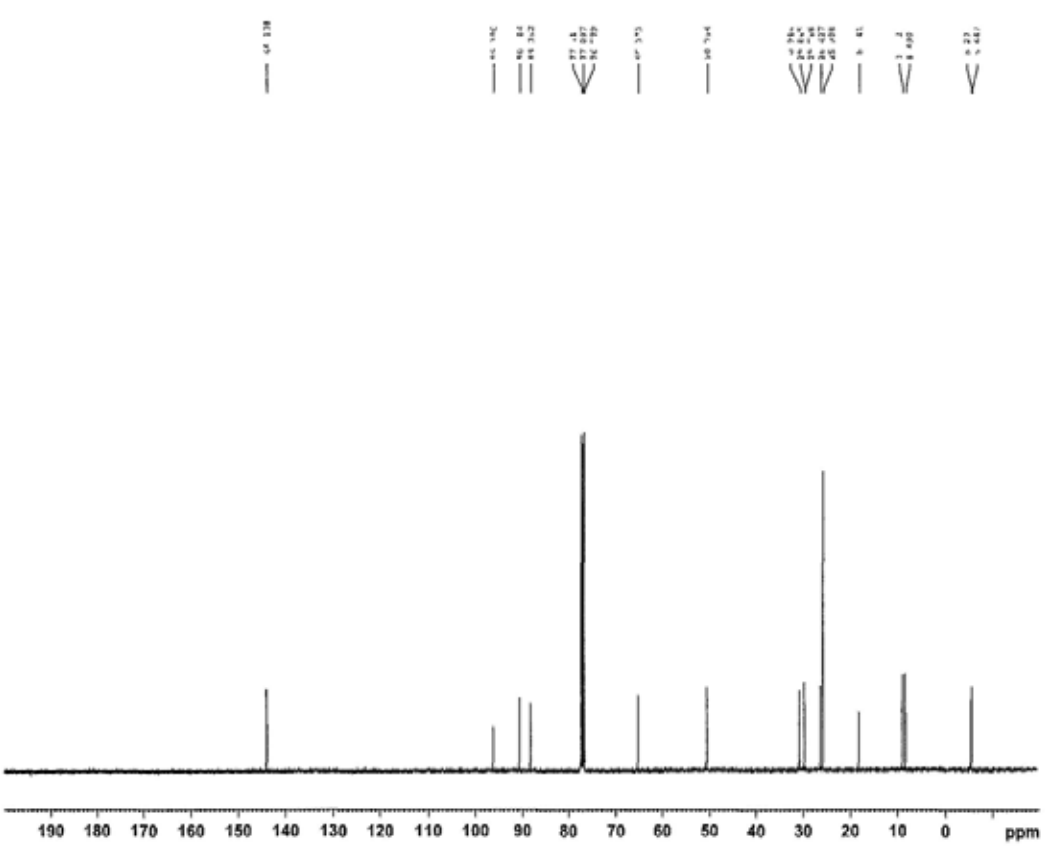

tBuMe2SiO
Et
Et
O–O
trans-148
1.045
1.045
1.000
0.936
1.618
2.036
2.000
3.037
3.033
9.172
6.048
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

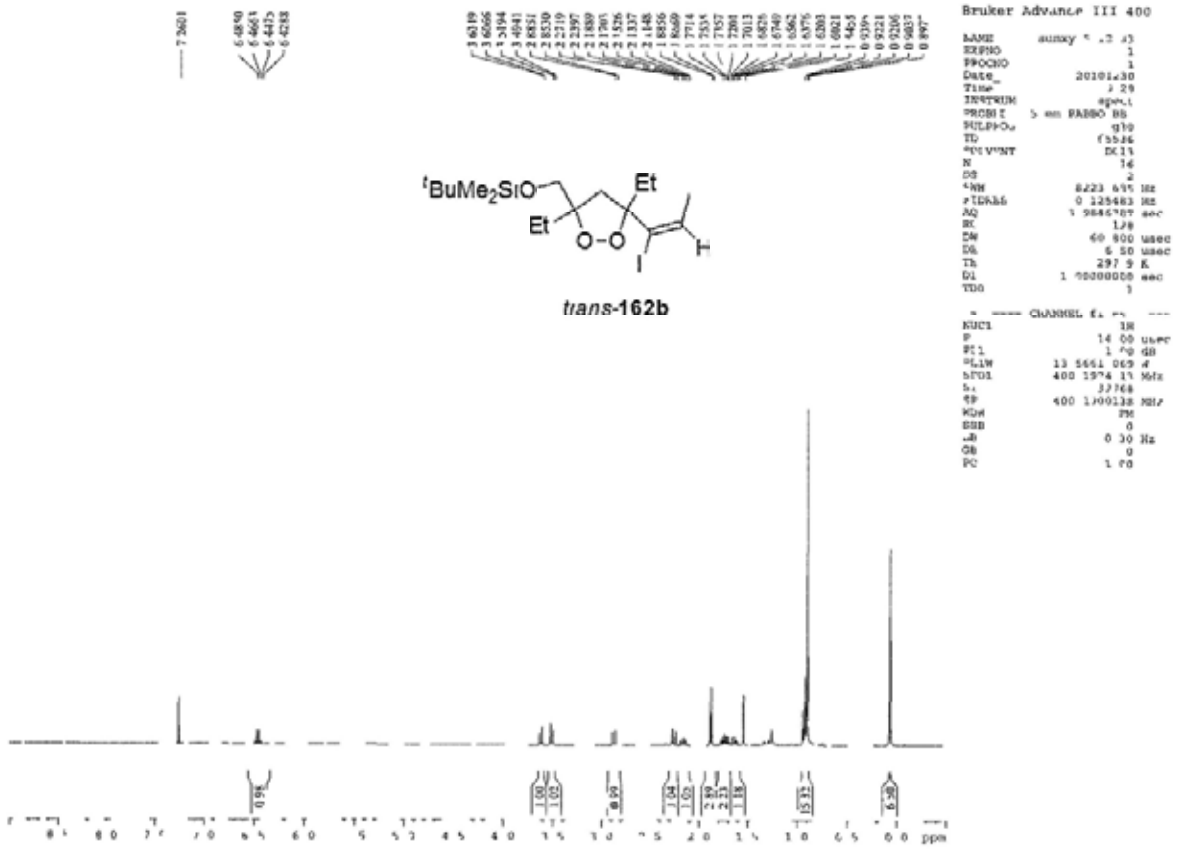

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


Bruker Advance III 400
tBuMe2SiO
Et
Et
O-O
trans-147
1.022
1.000
1.002
1.006
3.232
2.000
2.228
3.169
3.095
9.108
6.102
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

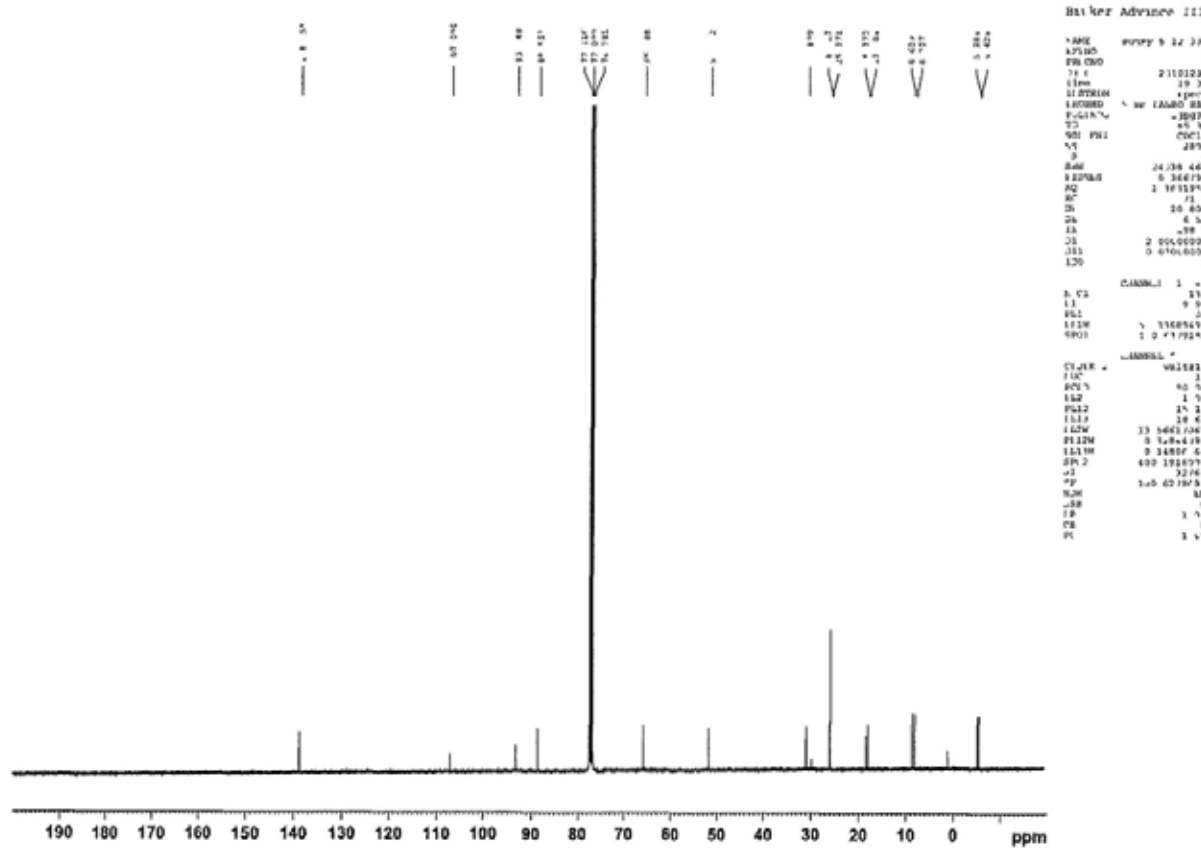

Bruker Advance III 400
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

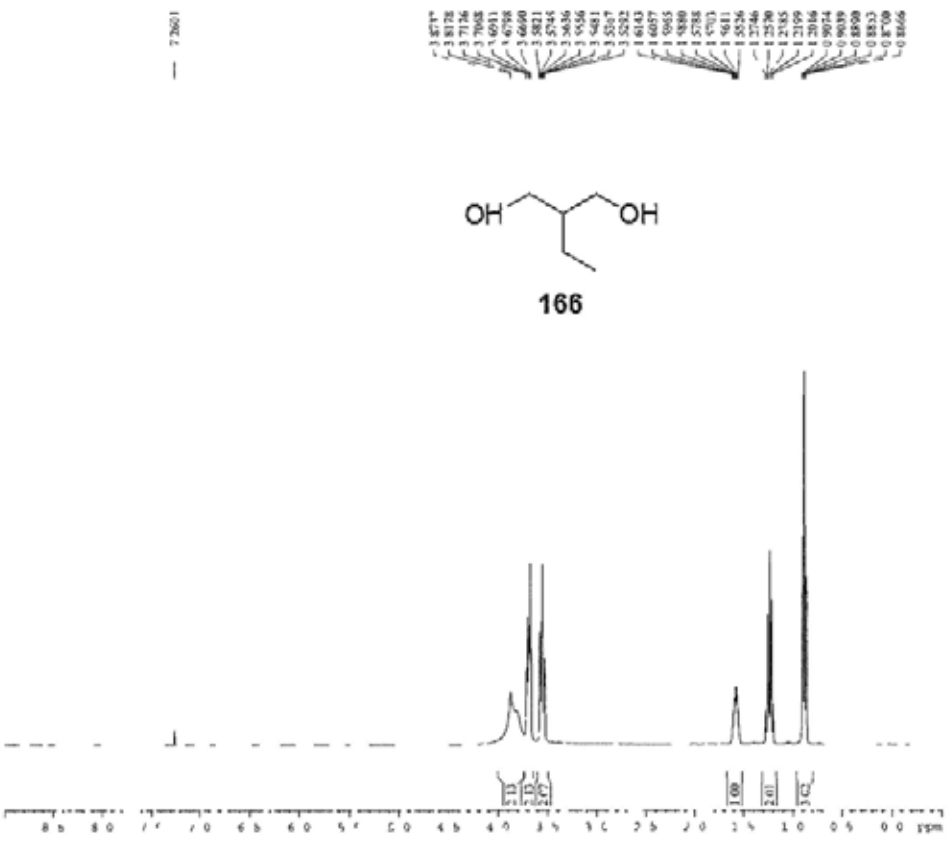

Bruker Advance III 400
tBuMe2SiO
Et
Et
O-O
I
trans-146
0.947
1.000
0.992
2.879
3.000
3.810
1.830
15.570
6.115
8 7 6 5 4 3 2 1 0 ppm


Bruker Advance III 400
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

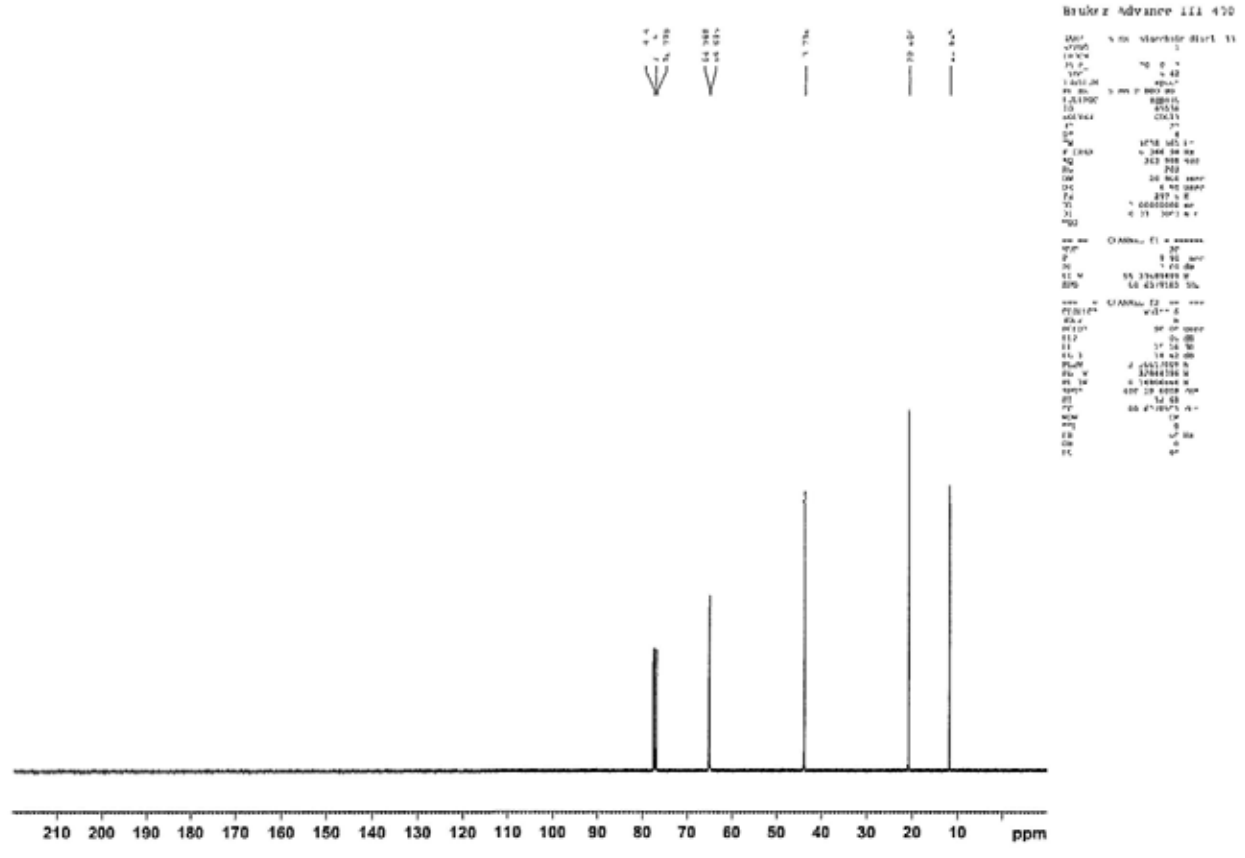

Bruker Advance III 400
$^tBuMe_2SiO$
Et
Et
O-O
I
H
ppm

trans-**162b**

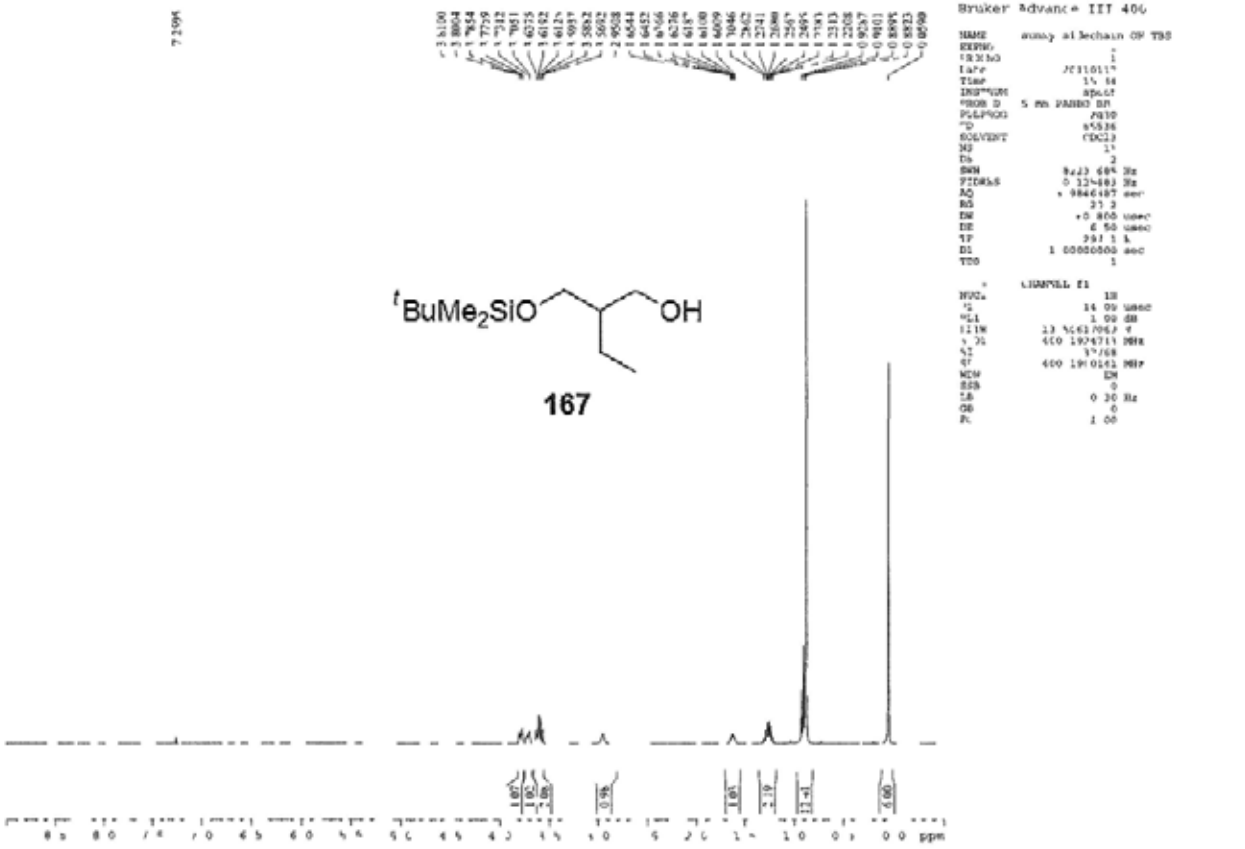

Bruker Advance III 400
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

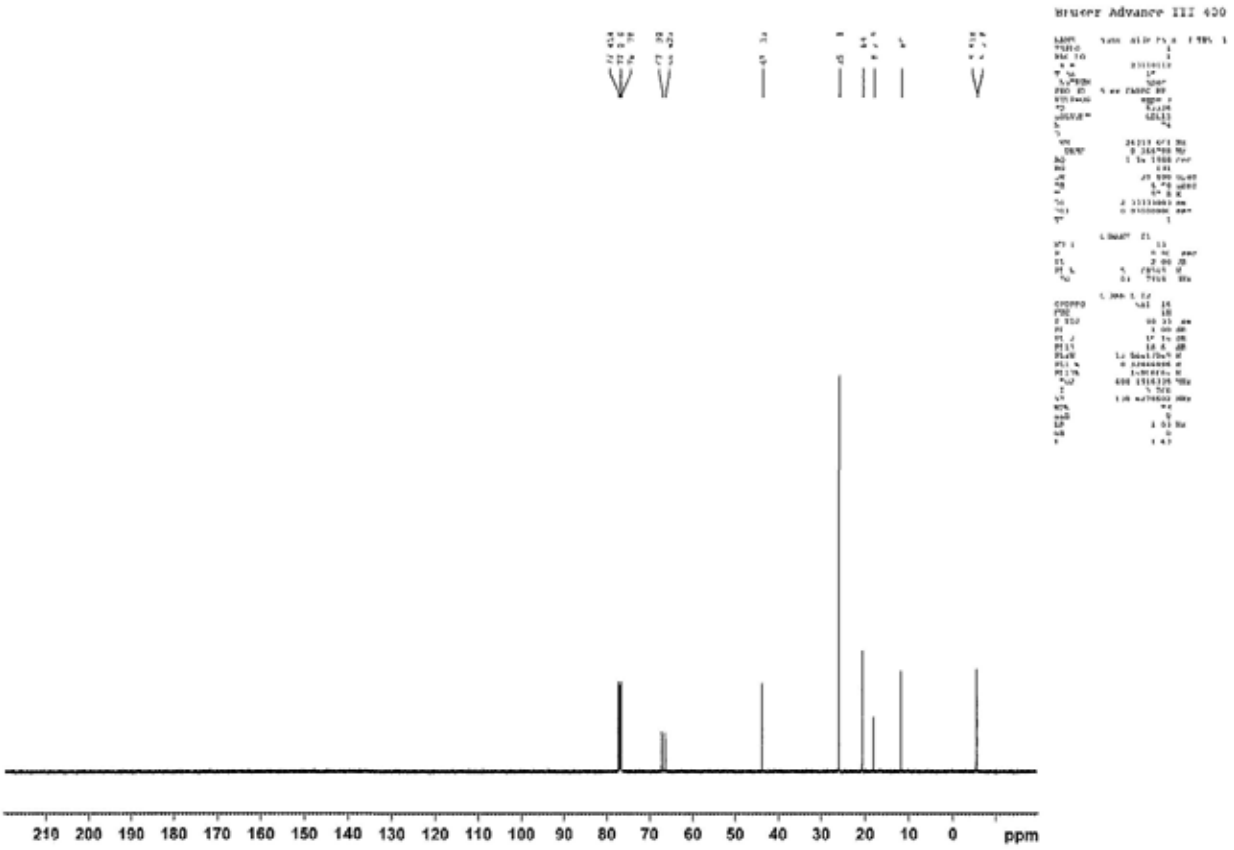

OH
OH

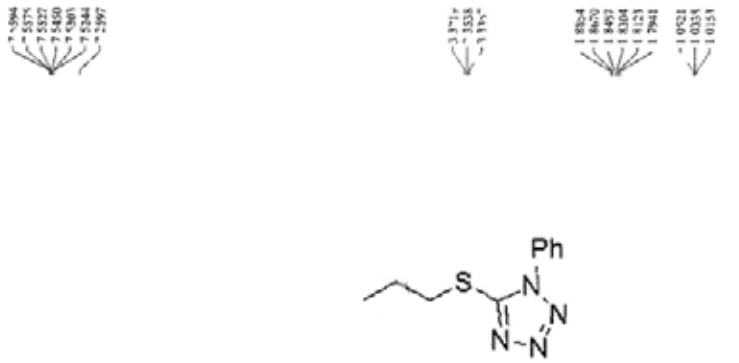
166



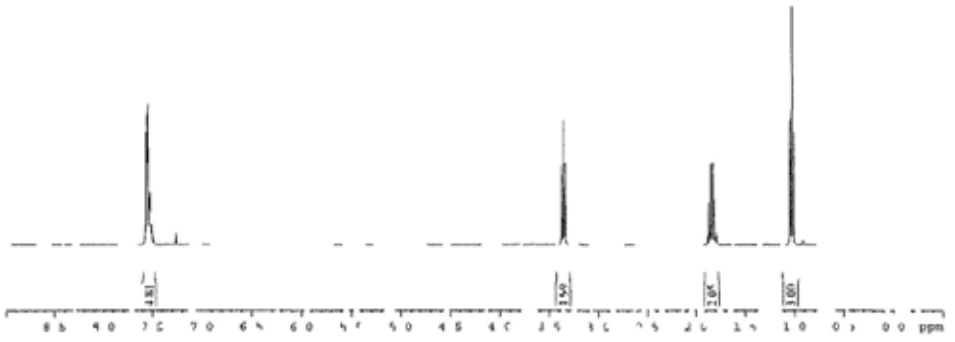
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

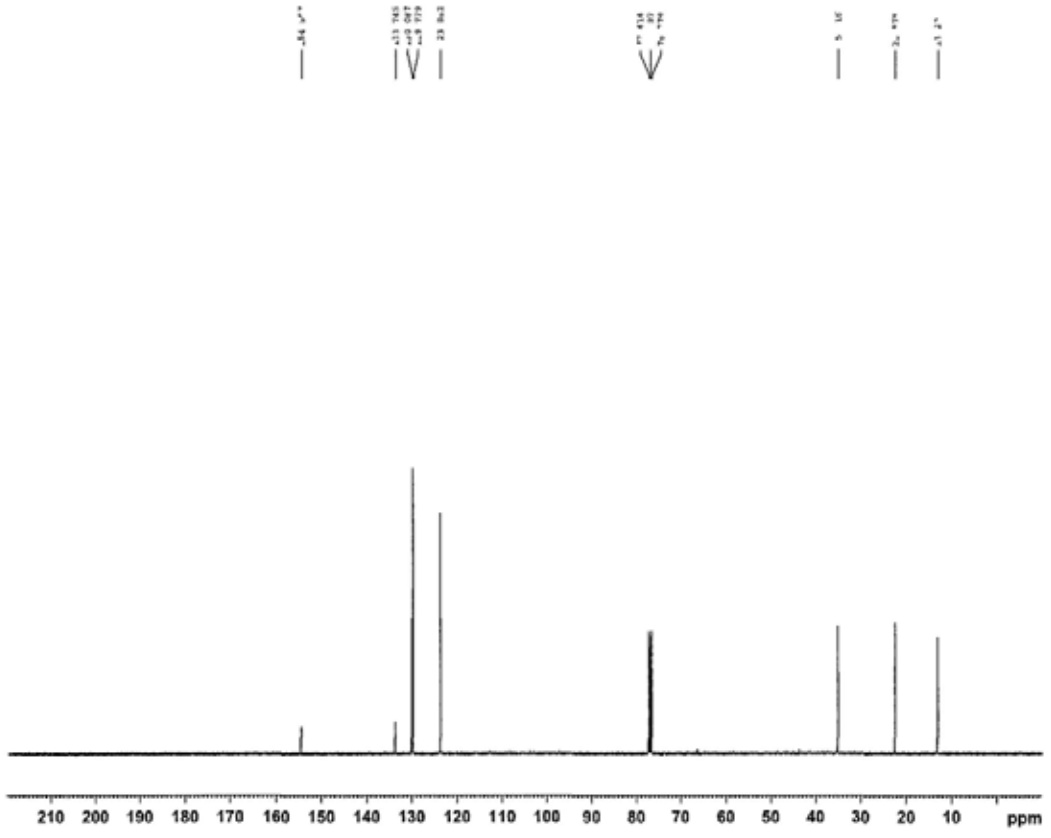

Bruker Advance III 400
^{t}BuMe$_2$SiO
OH
167
ppm

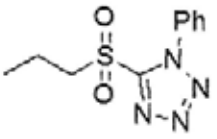

Bruker Advance III 400
ppm


Ph
S
N
N
N
N

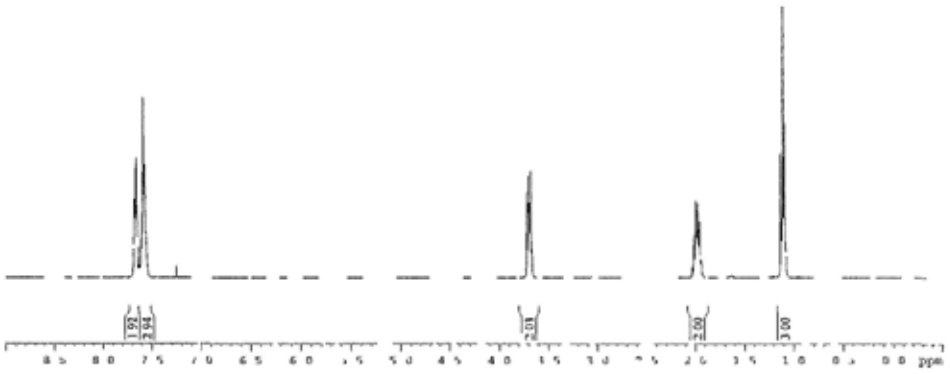
164

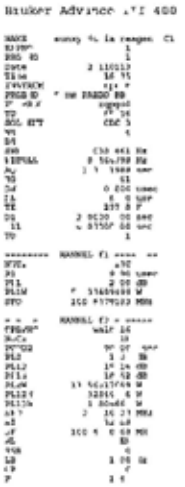

ppm

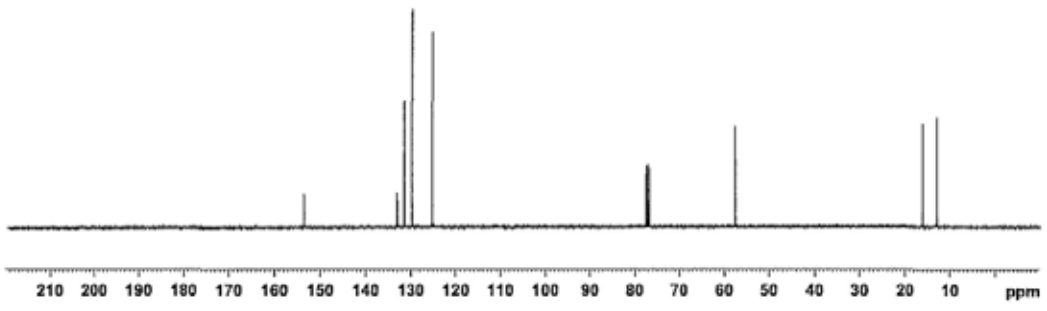

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

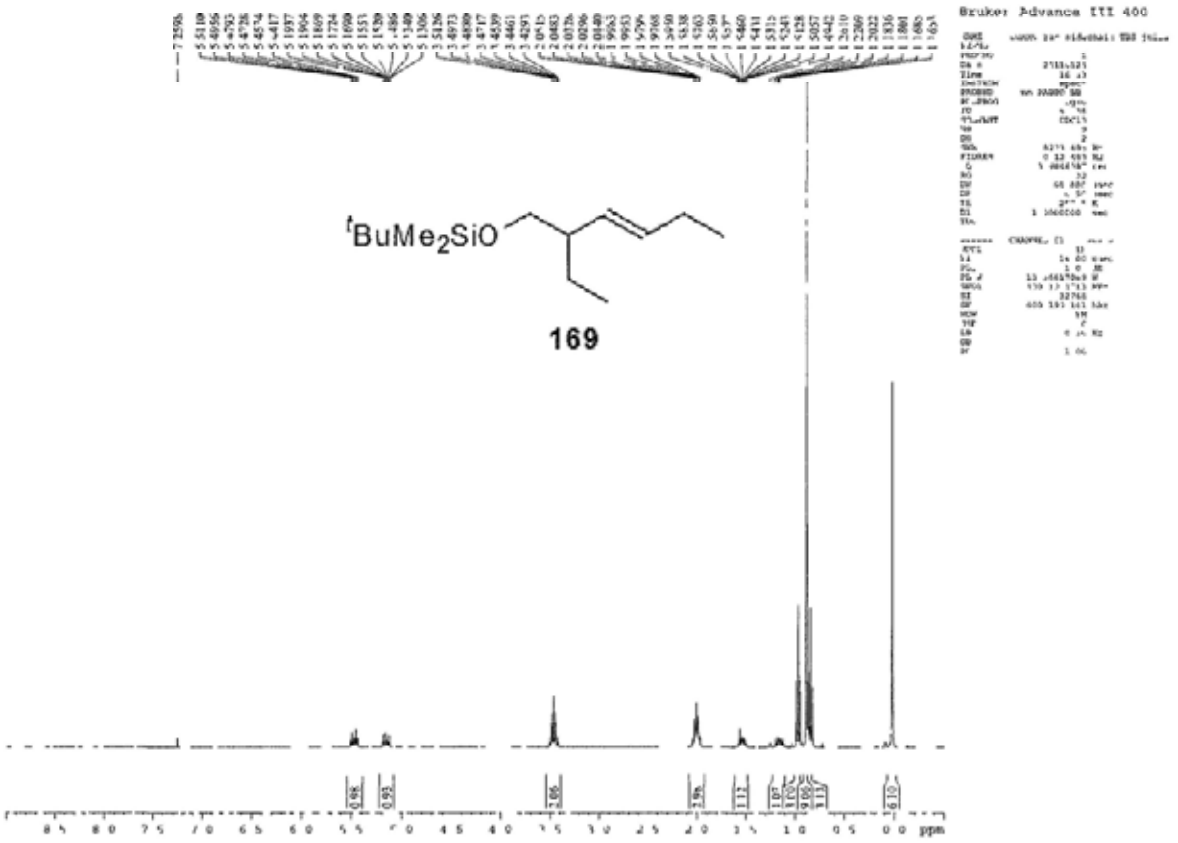


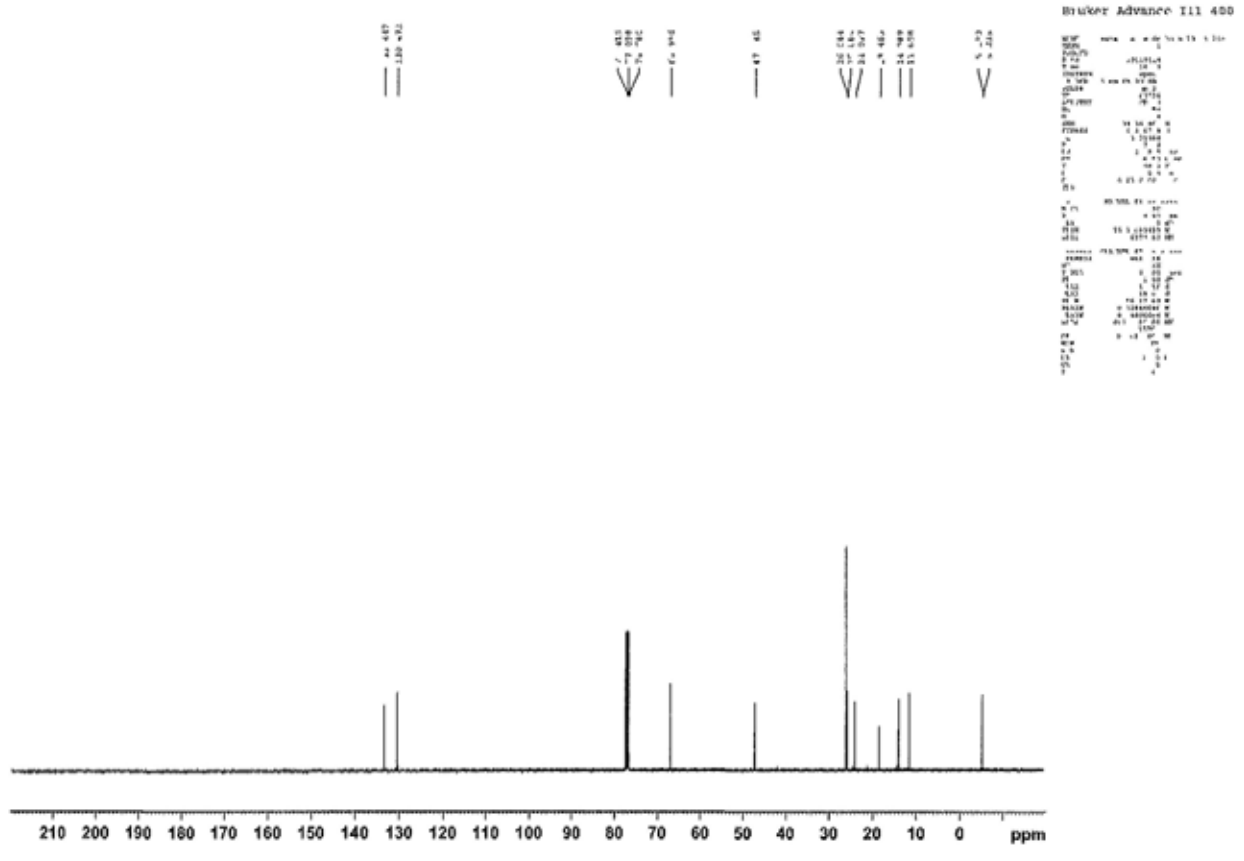
165

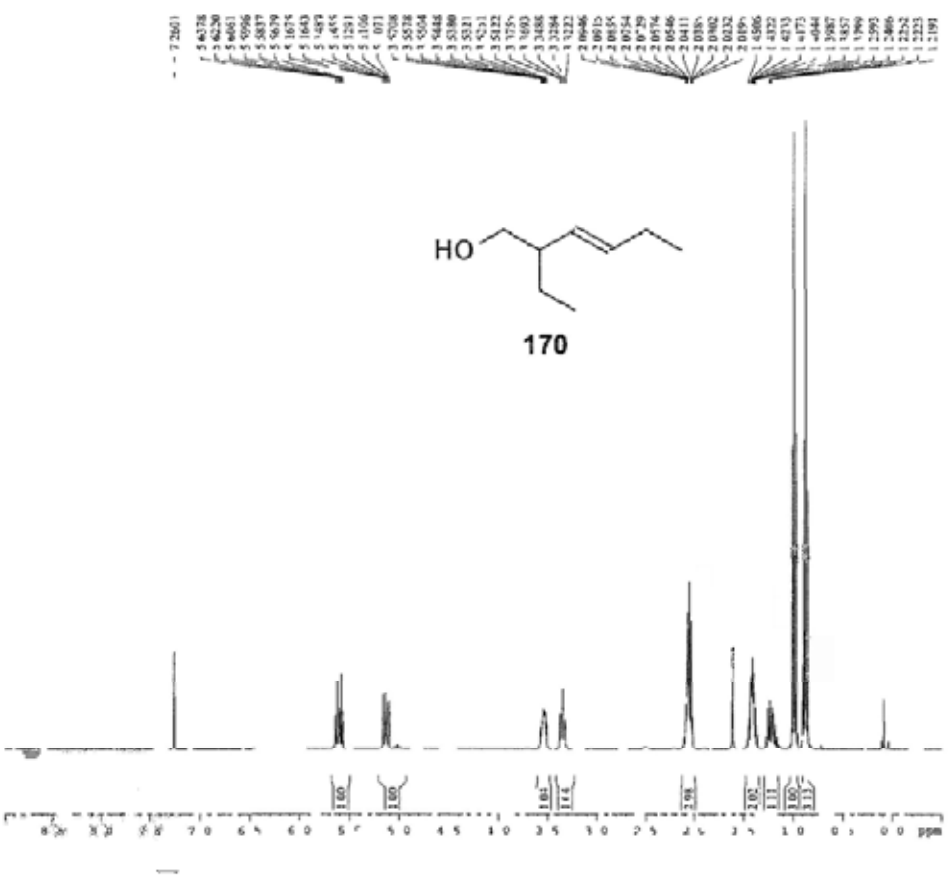


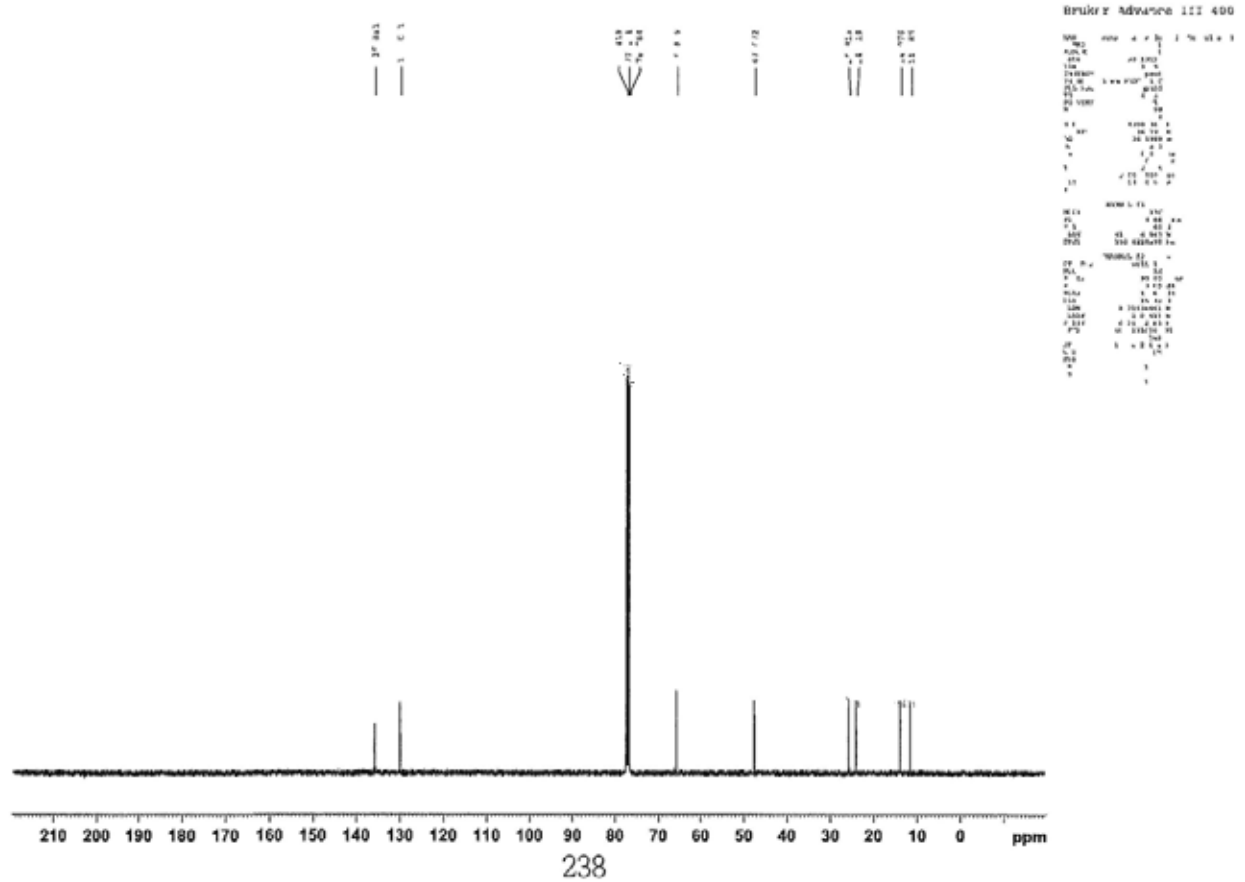


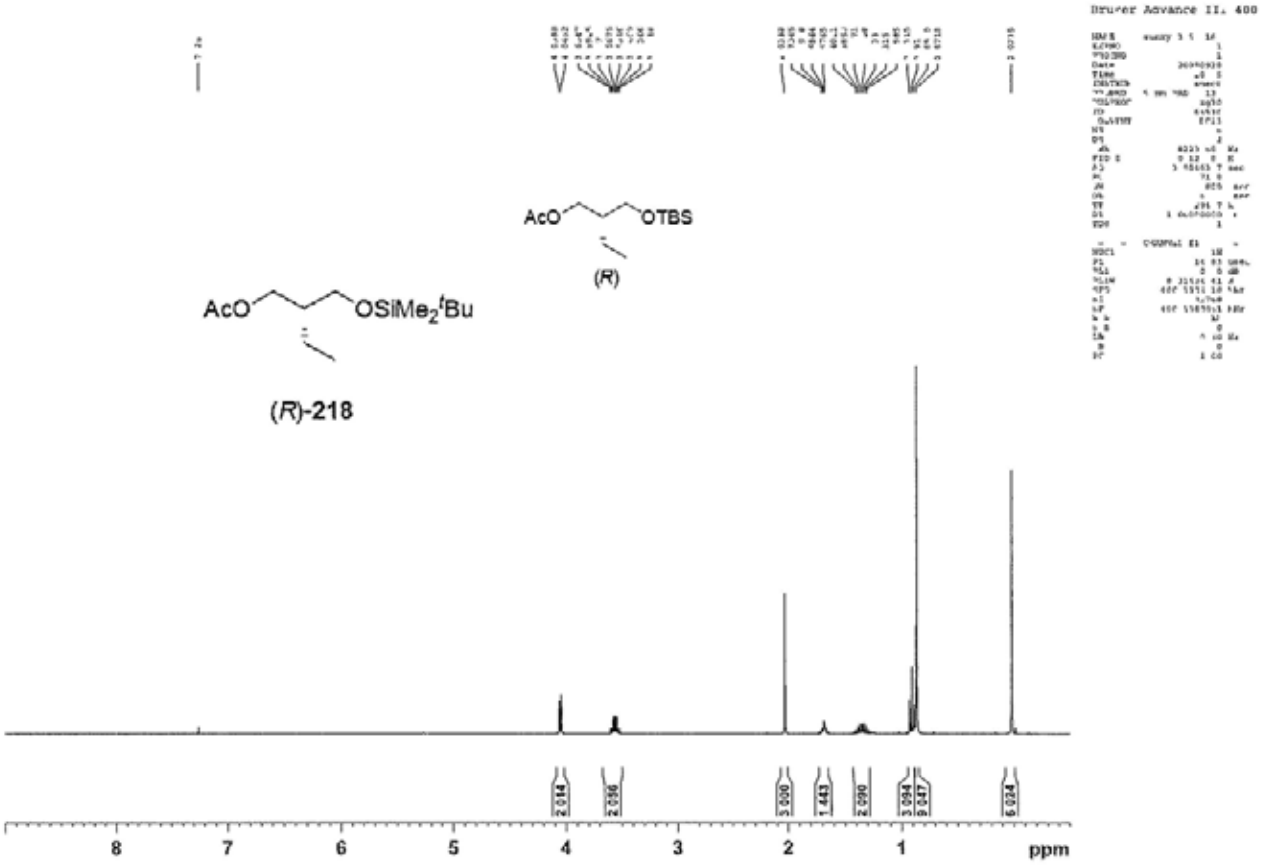


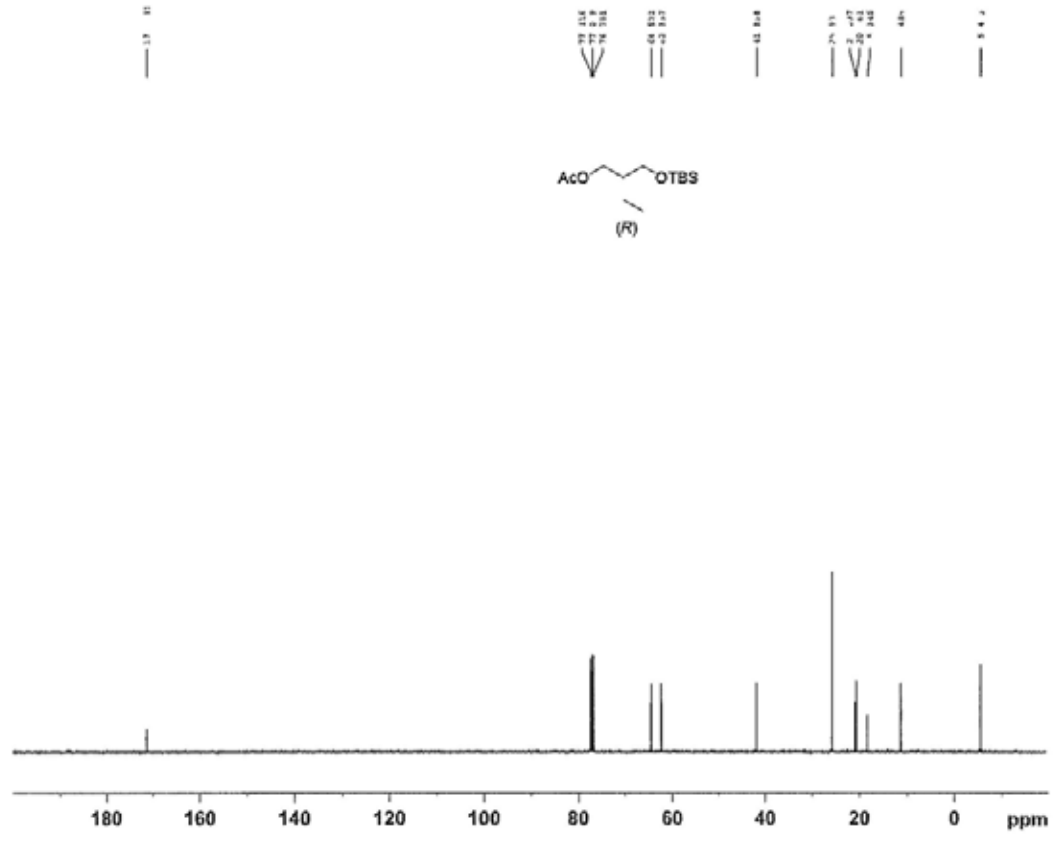

Bruker Advance III 400
tBuMe2SiO
169
ppm

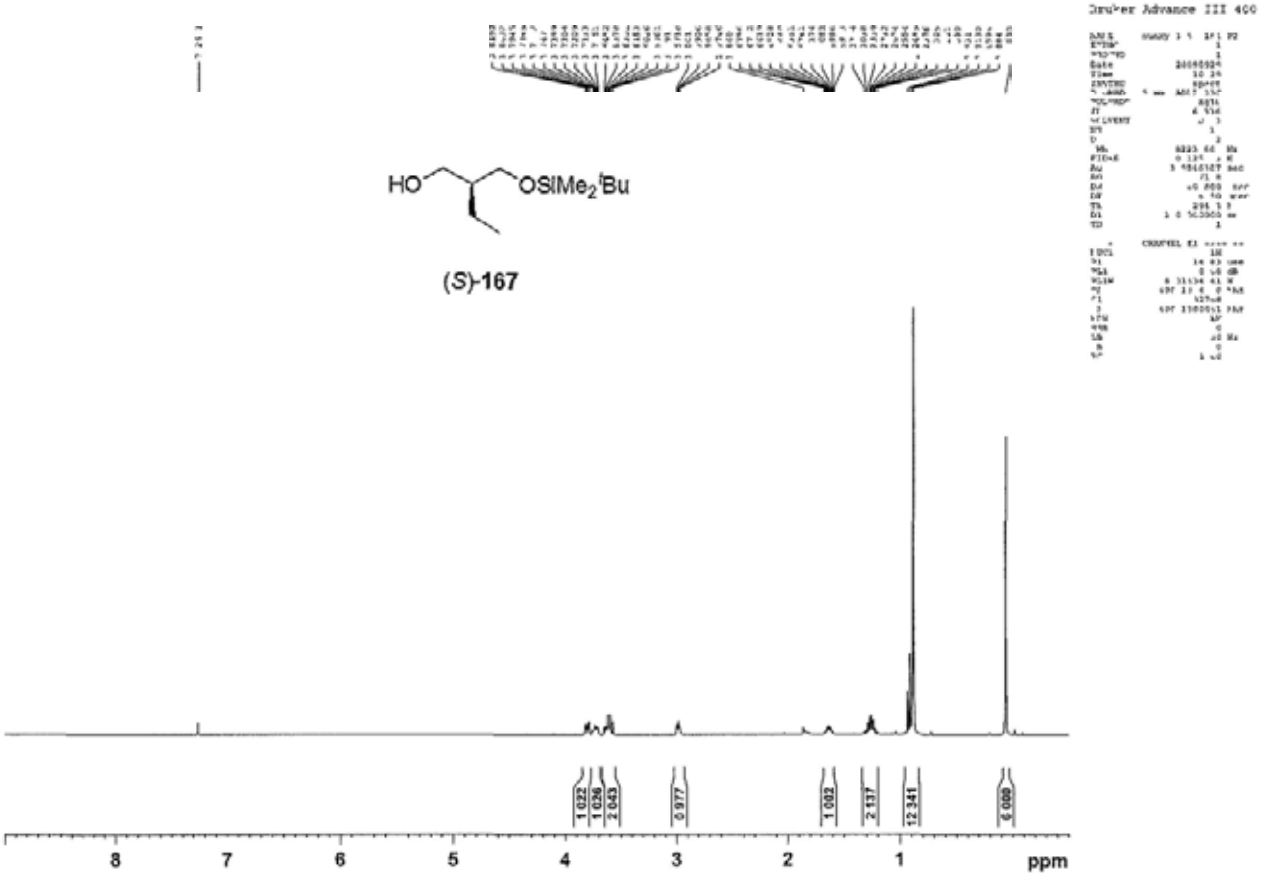

Bruker Advance III 400
ppm

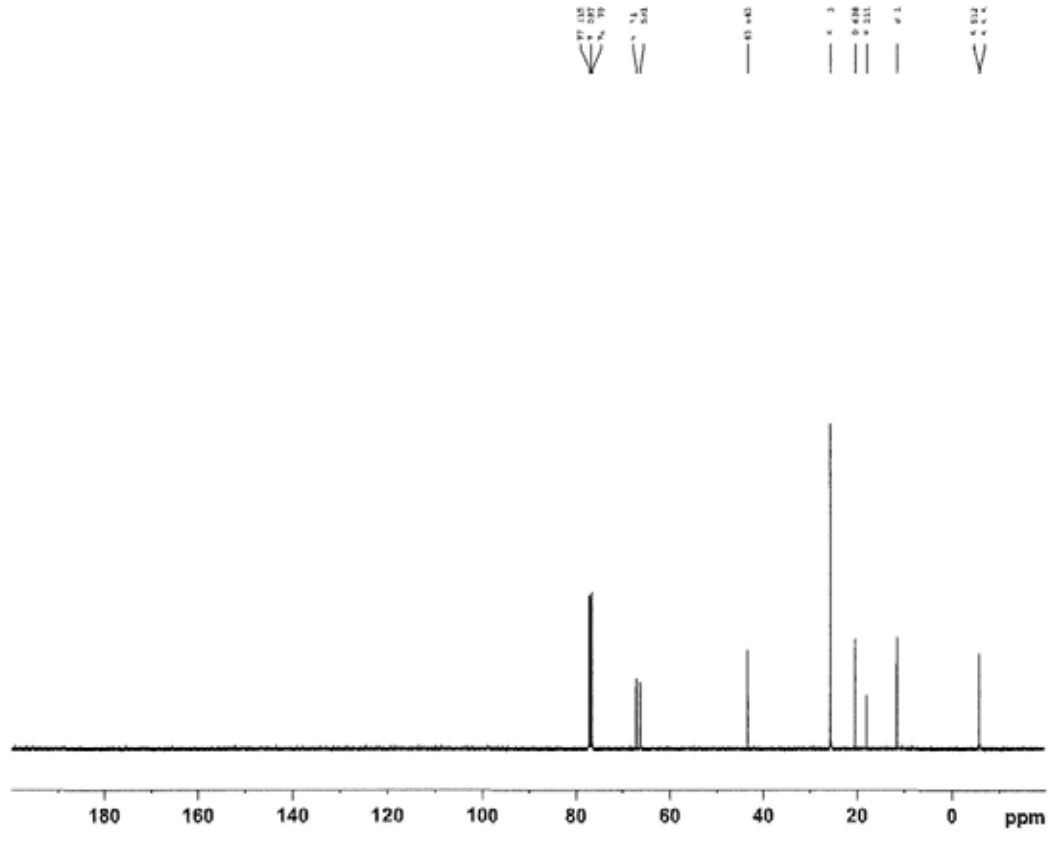

Bruker Advance III 400
HO
170
ppm

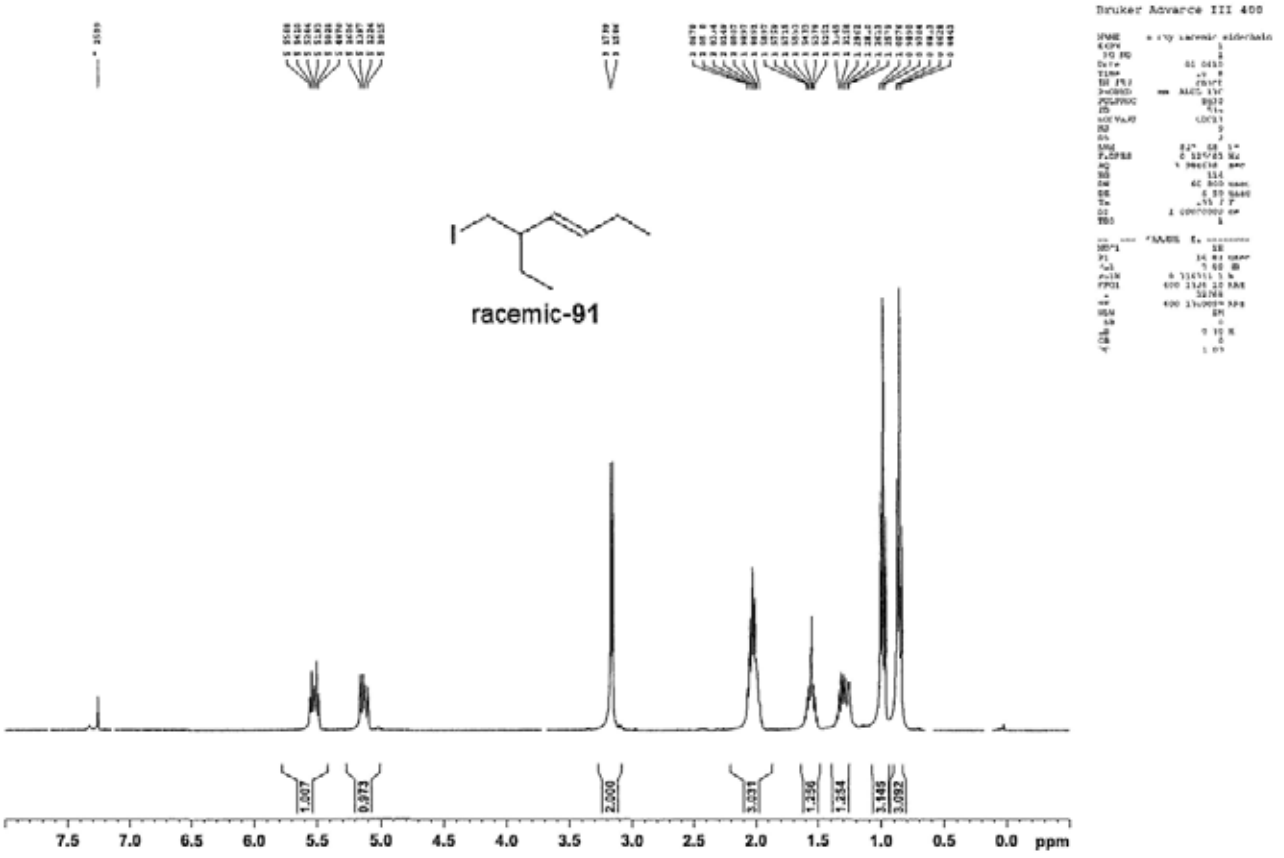

Bruker Advance III 400
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

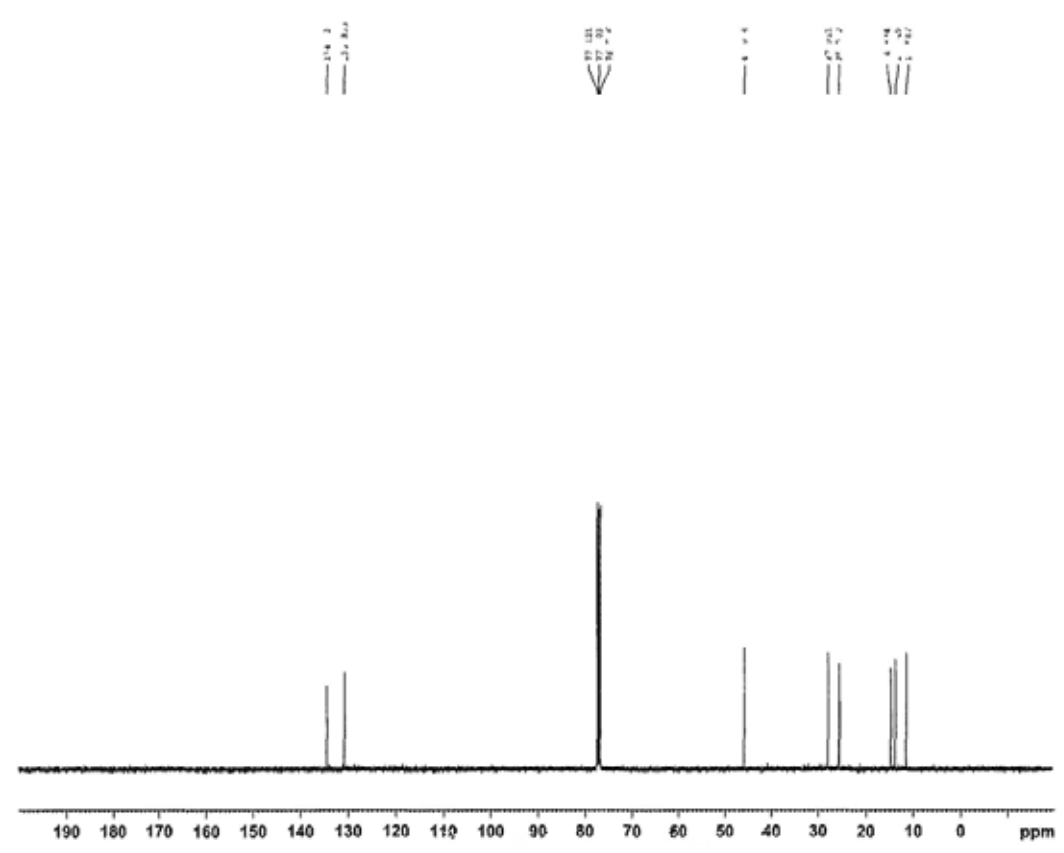

AcO
OTBS
(R)
AcO
OSiMe2tBu
(R)-218
2.014
2.036
3.000
1.443
2.090
3.094
9.047
6.024
8
7
6
5
4
3
2
1
ppm

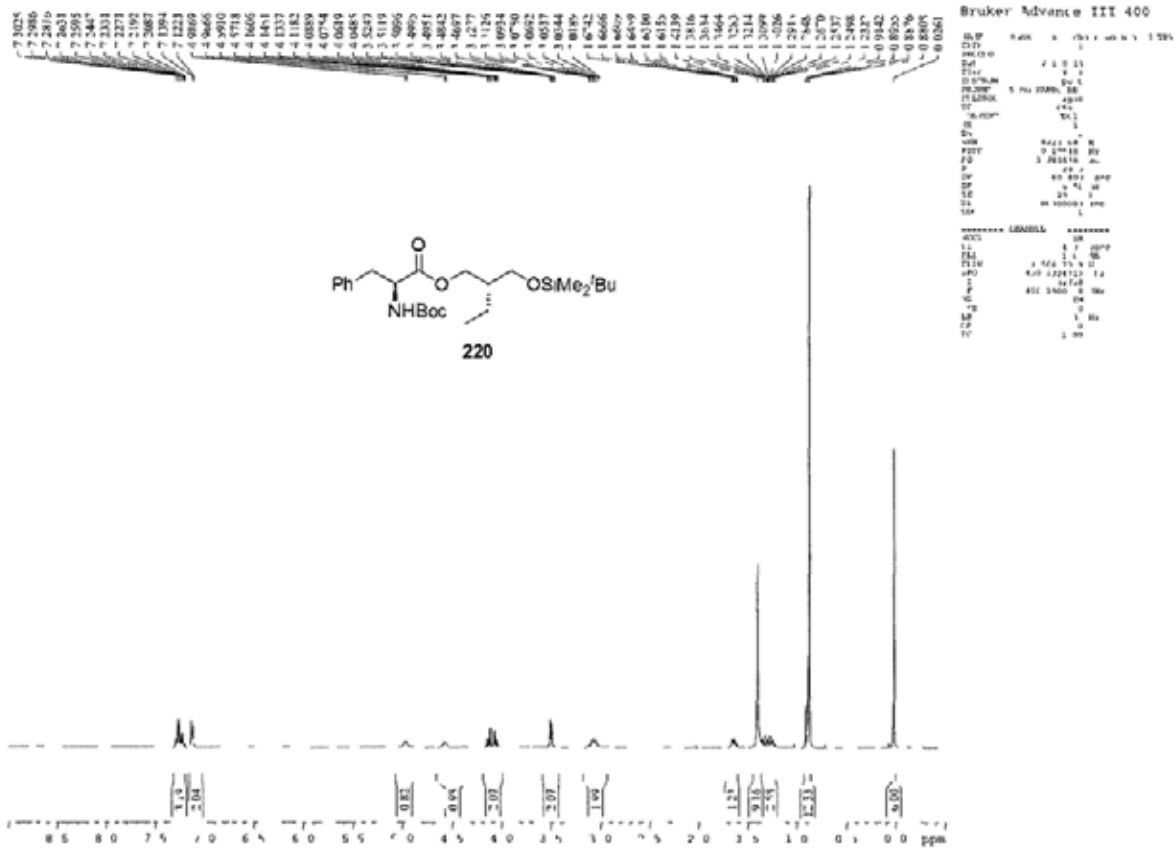

AcO
OTBS
(R)
180
160
140
120
100
80
60
40
20
0
ppm

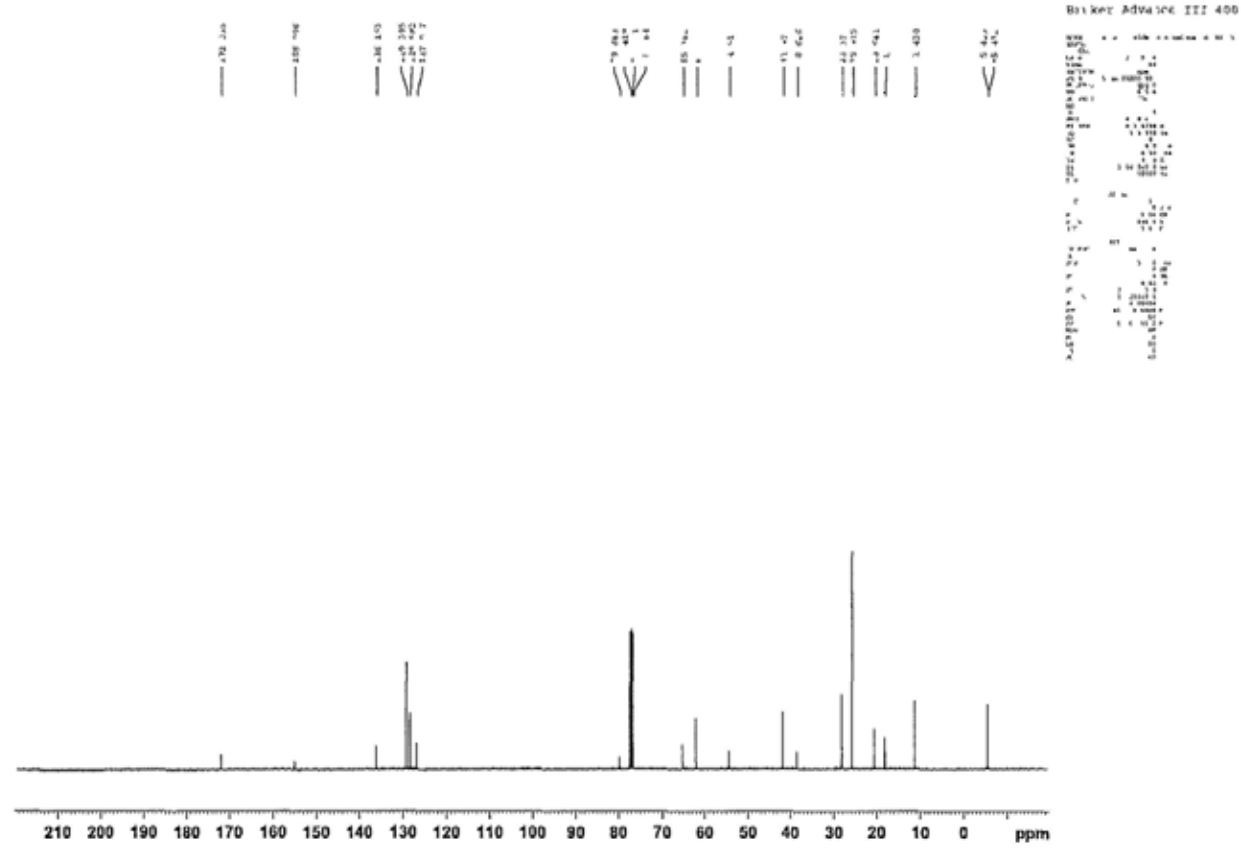

HO
OSiMe2tBu
(S)-167
1.022
1.036
2.043
3.977
1.002
2.137
12.341
6.000
8
7
6
5
4
3
2
1
ppm

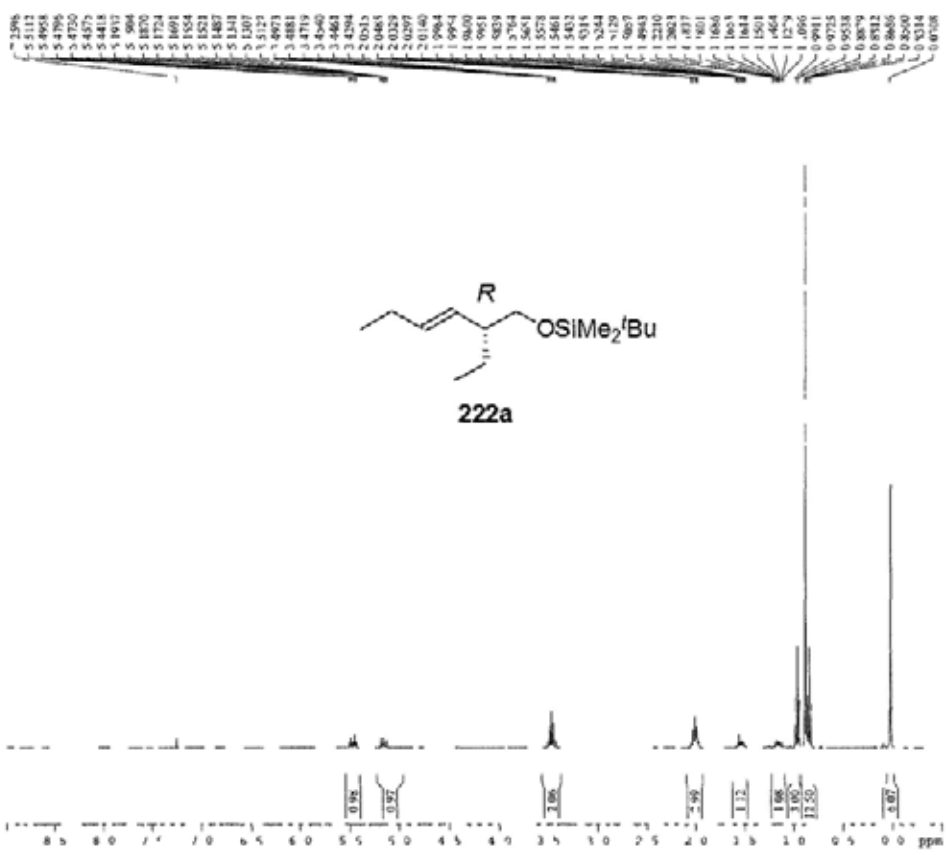

180
160
140
120
100
80
60
40
20
0
ppm

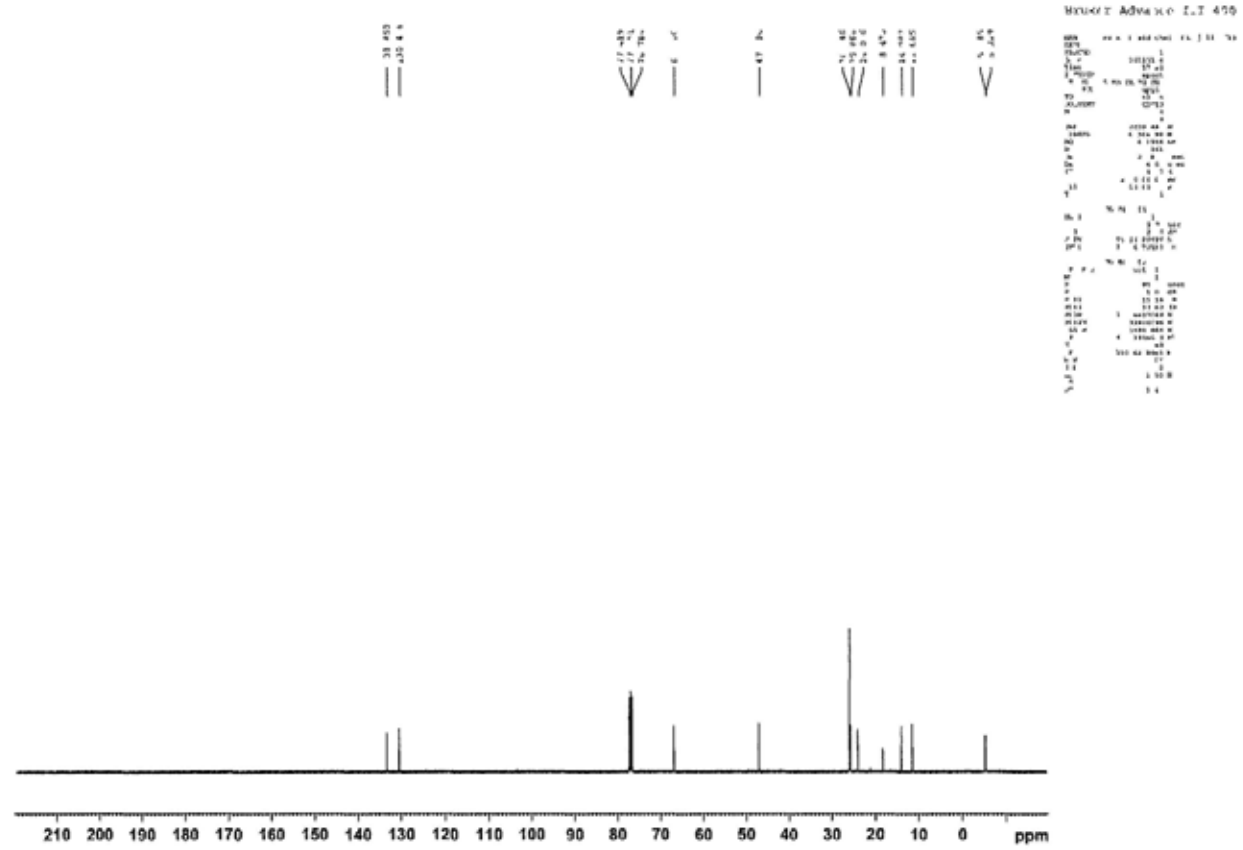

racemic-91
1.007
0.973
2.000
3.031
1.256
1.254
3.145
3.092
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

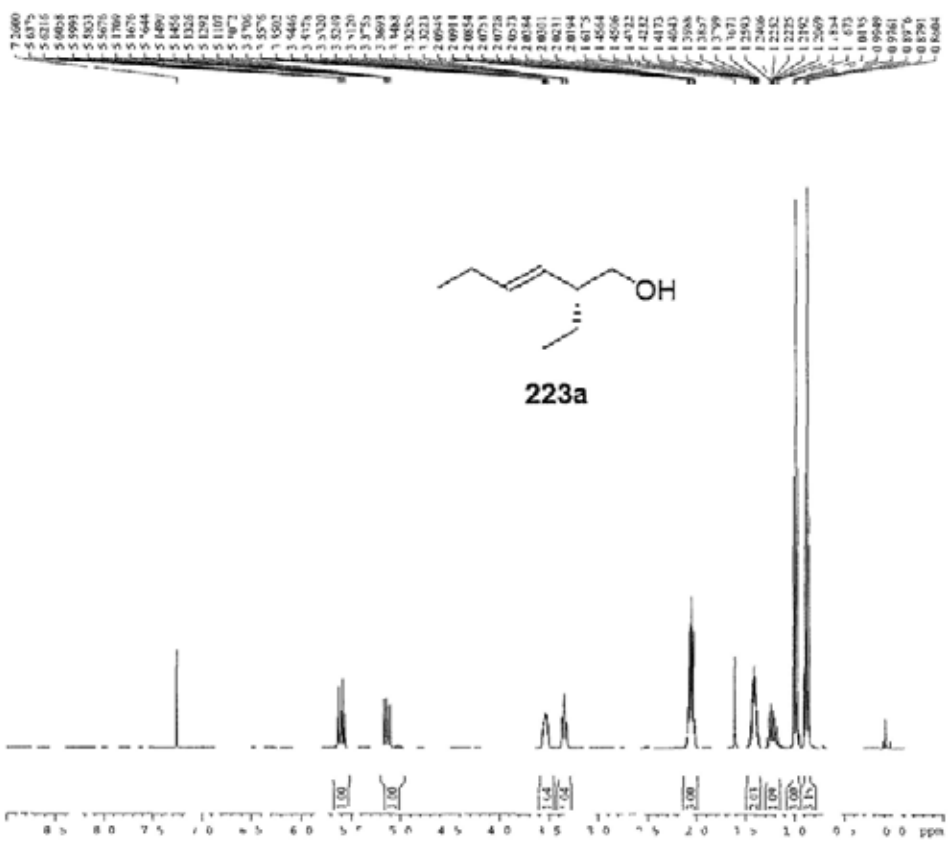

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

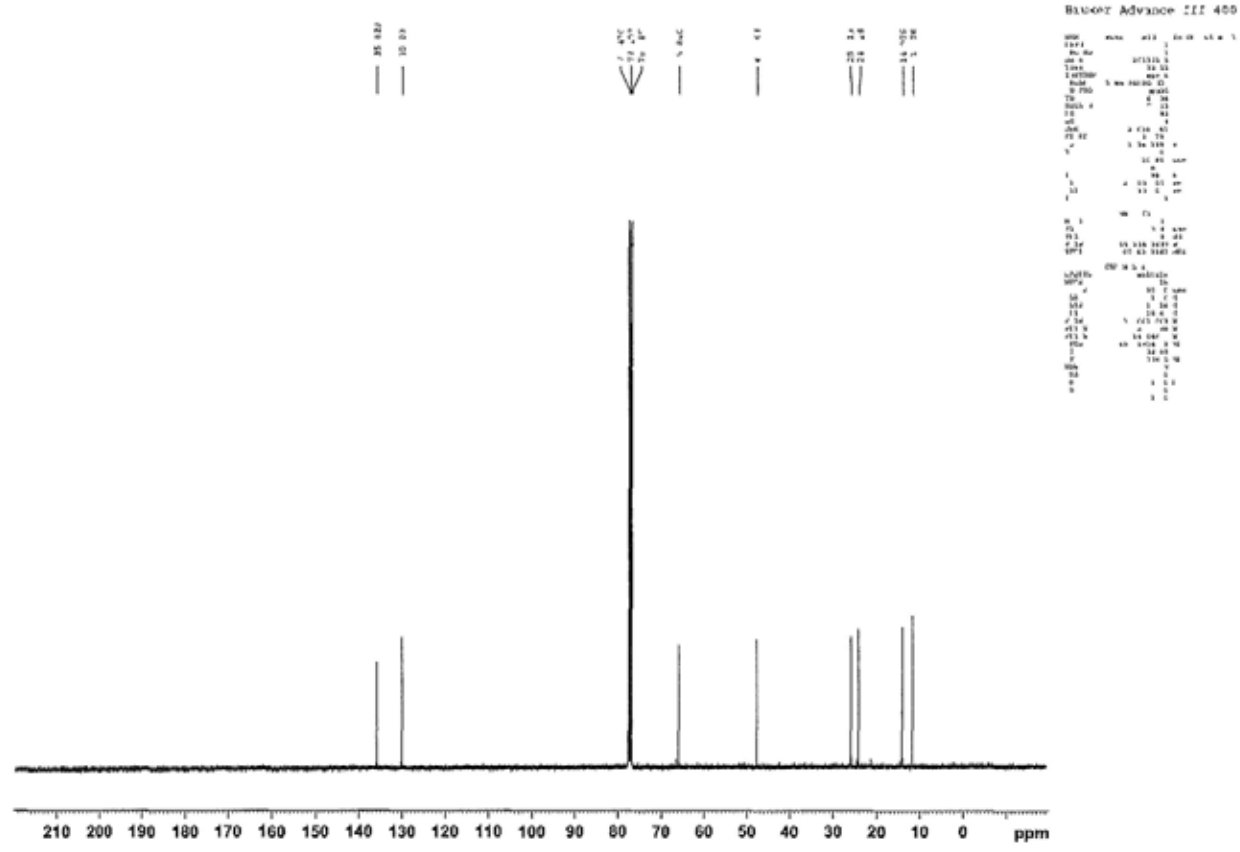

Bruker Advance III 400
Ph
NHBoc
OSiMe2tBu
220
ppm

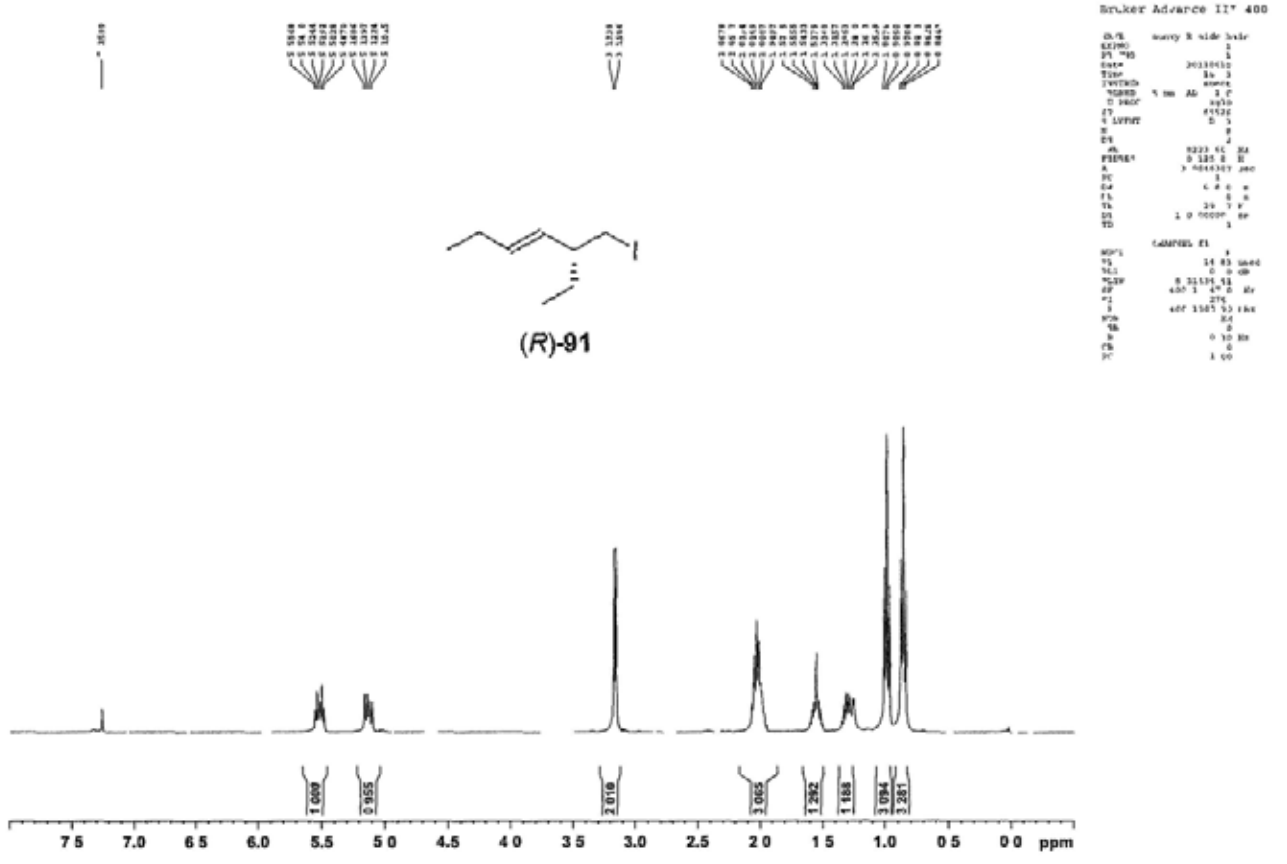

Bruker Advance III 400
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

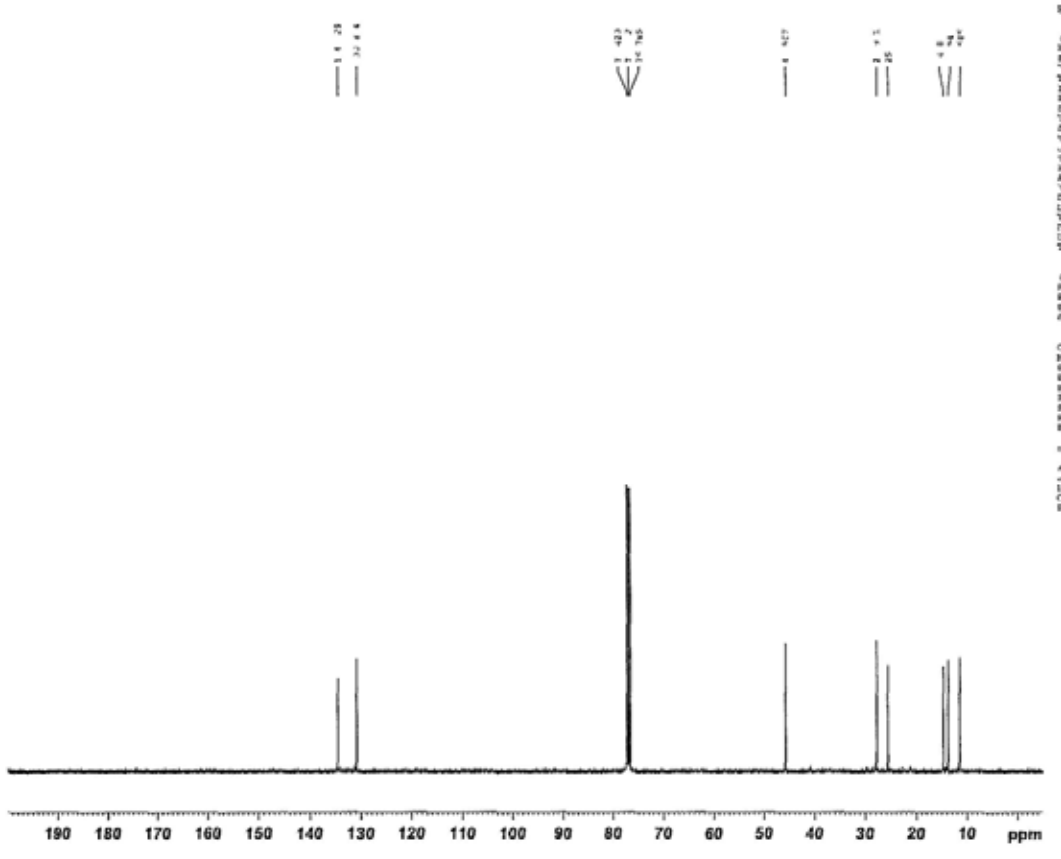

Bruker Advance III 400
R
OSiMe2tBu
222a
0.95
0.97
3.06
2.99
1.12
1.66
3.00
12.50
4.07
85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 05 00 ppm

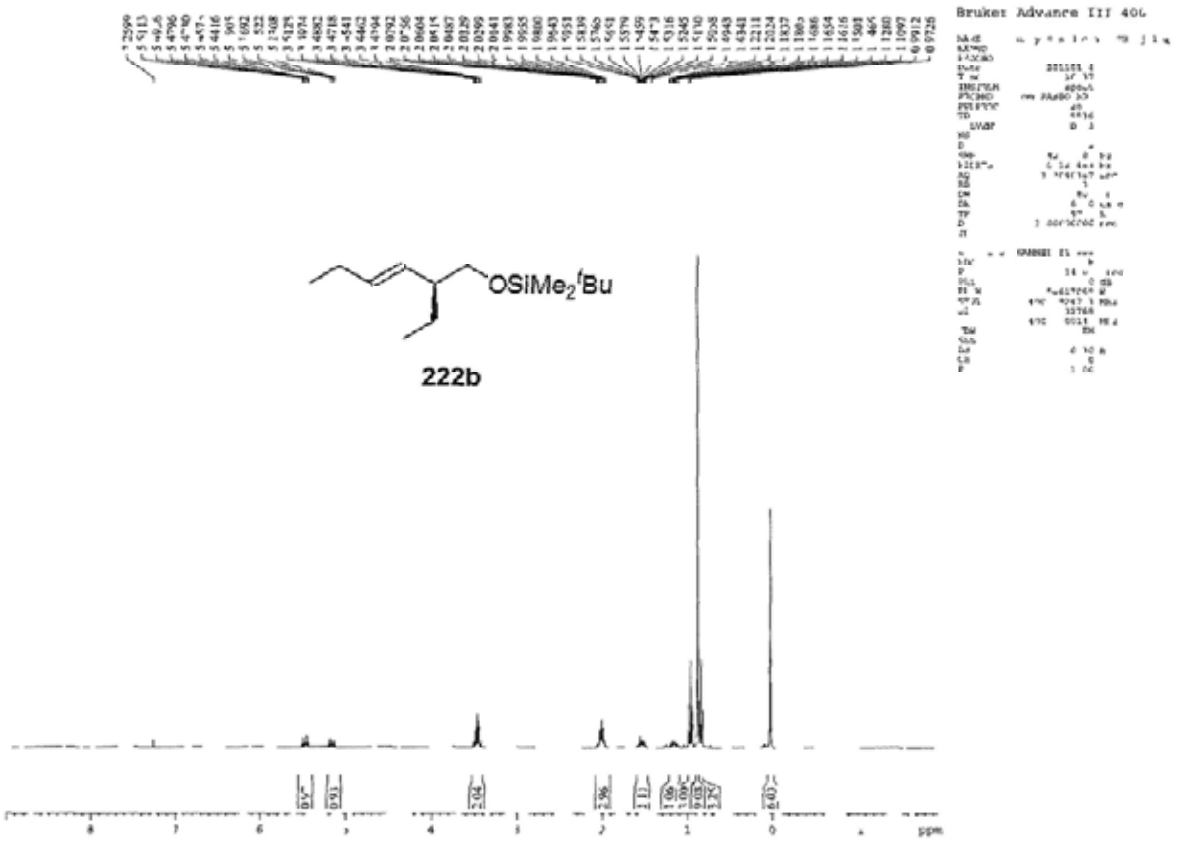

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

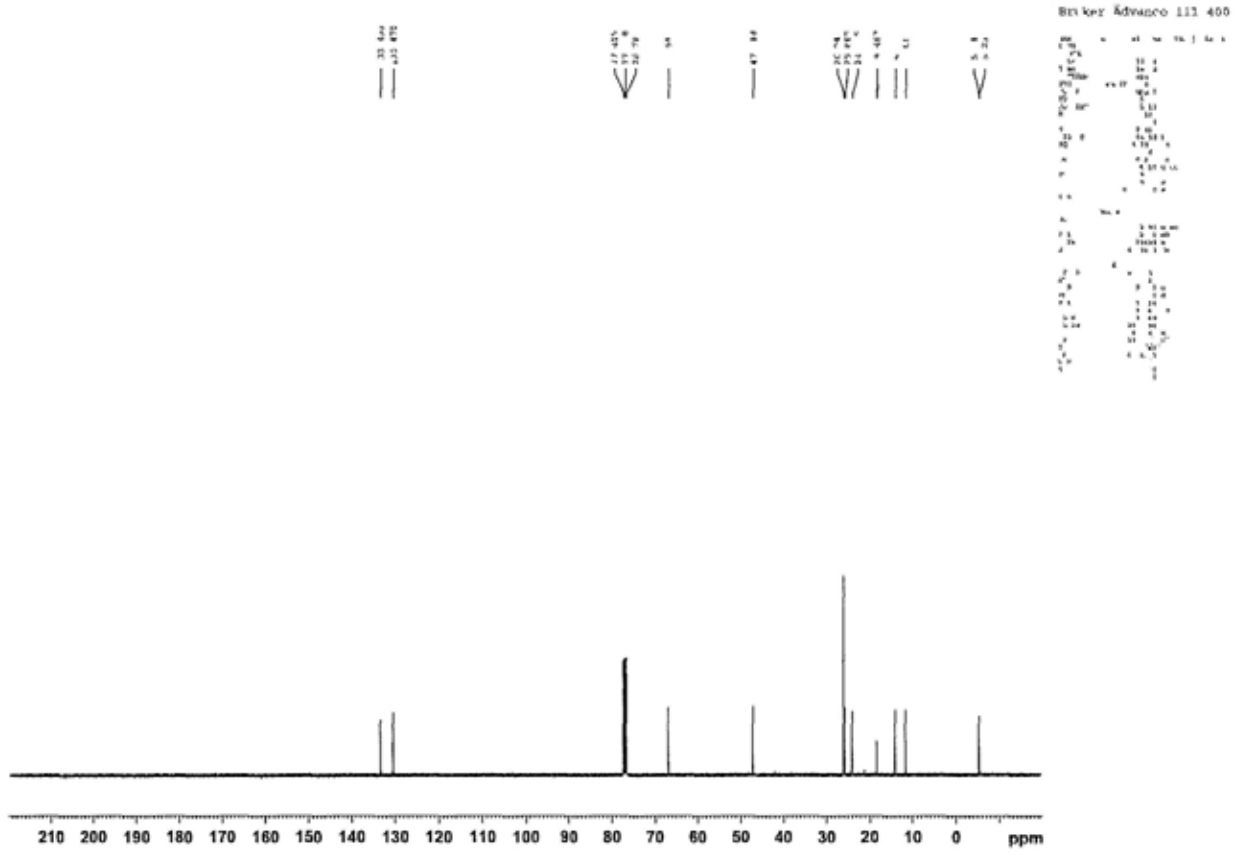

Bruker Advance III 400
OH
223a
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

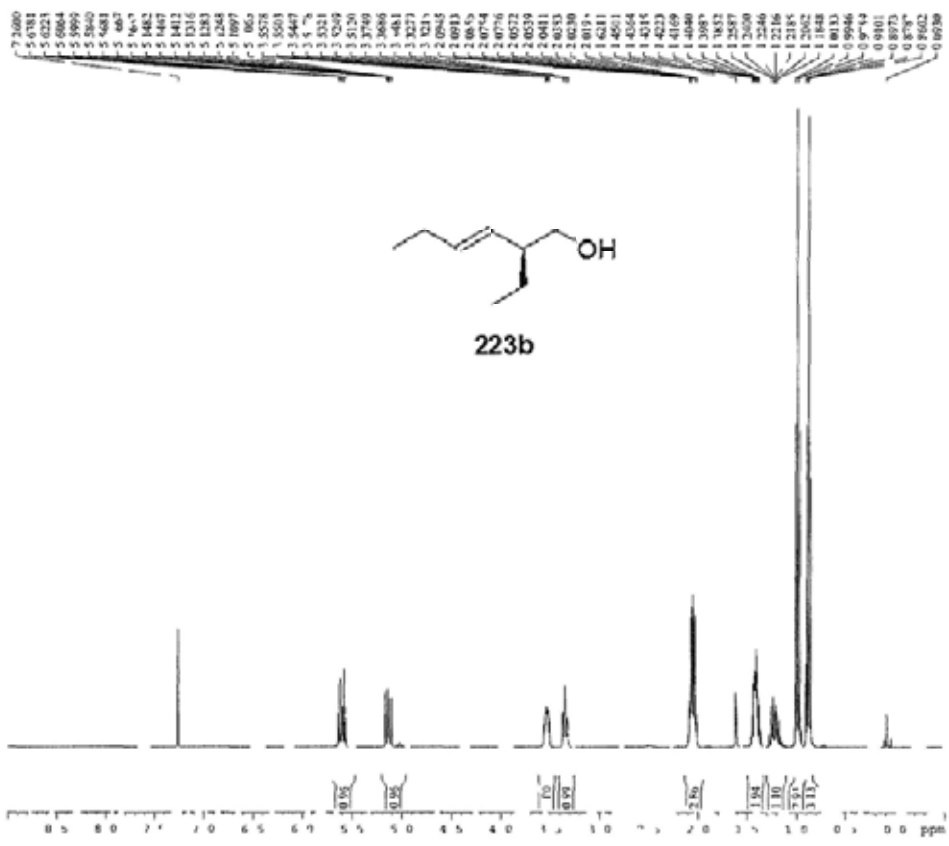

Bruker Advance III 400
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

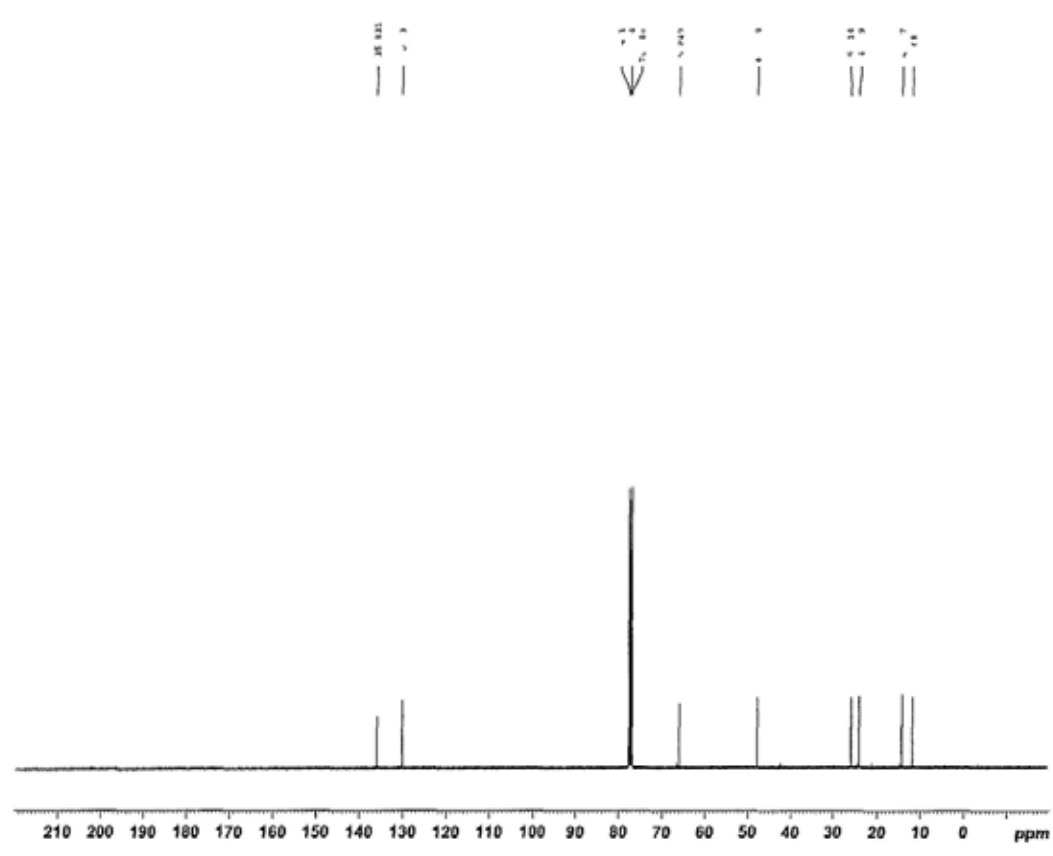

(R)-91
1.000
0.955
2.010
3.065
1.262
1.168
3.094
3.281
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

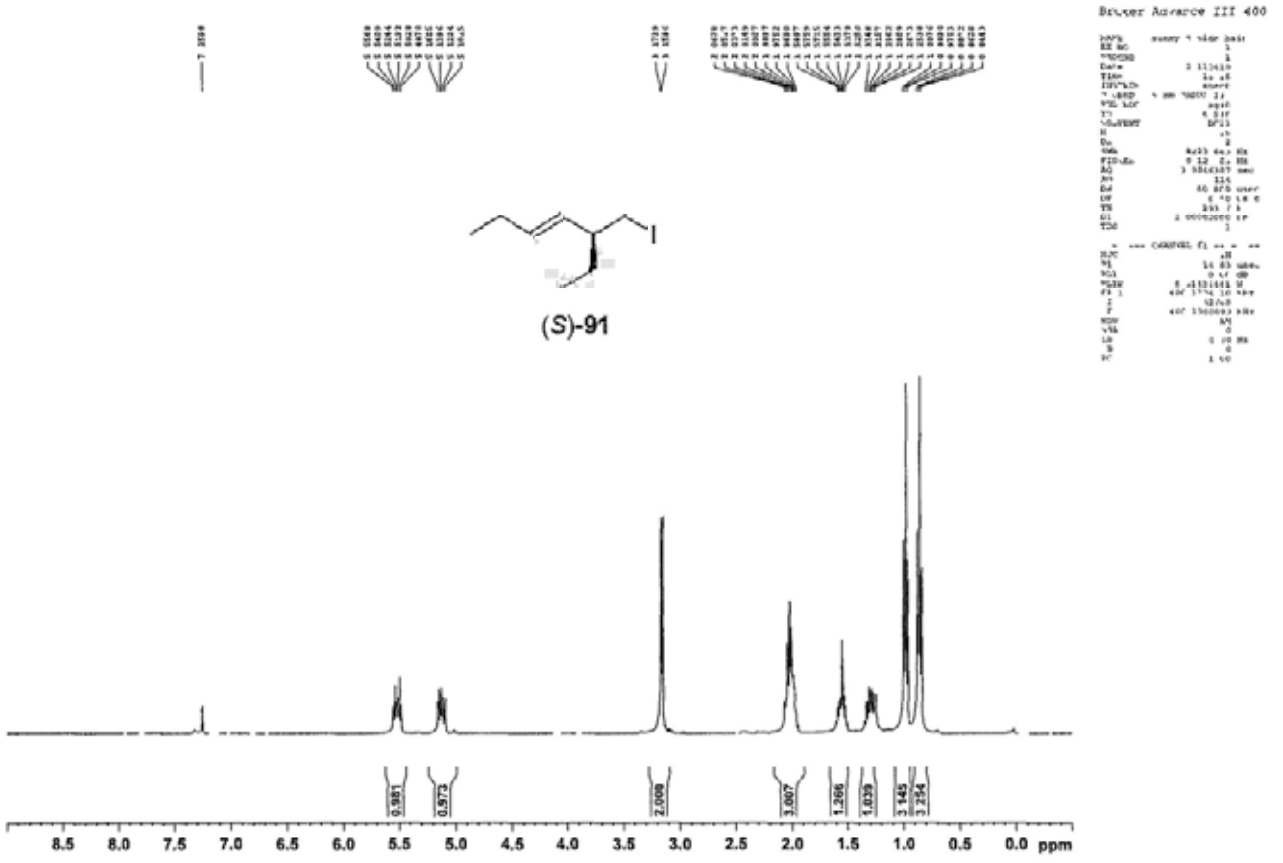

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

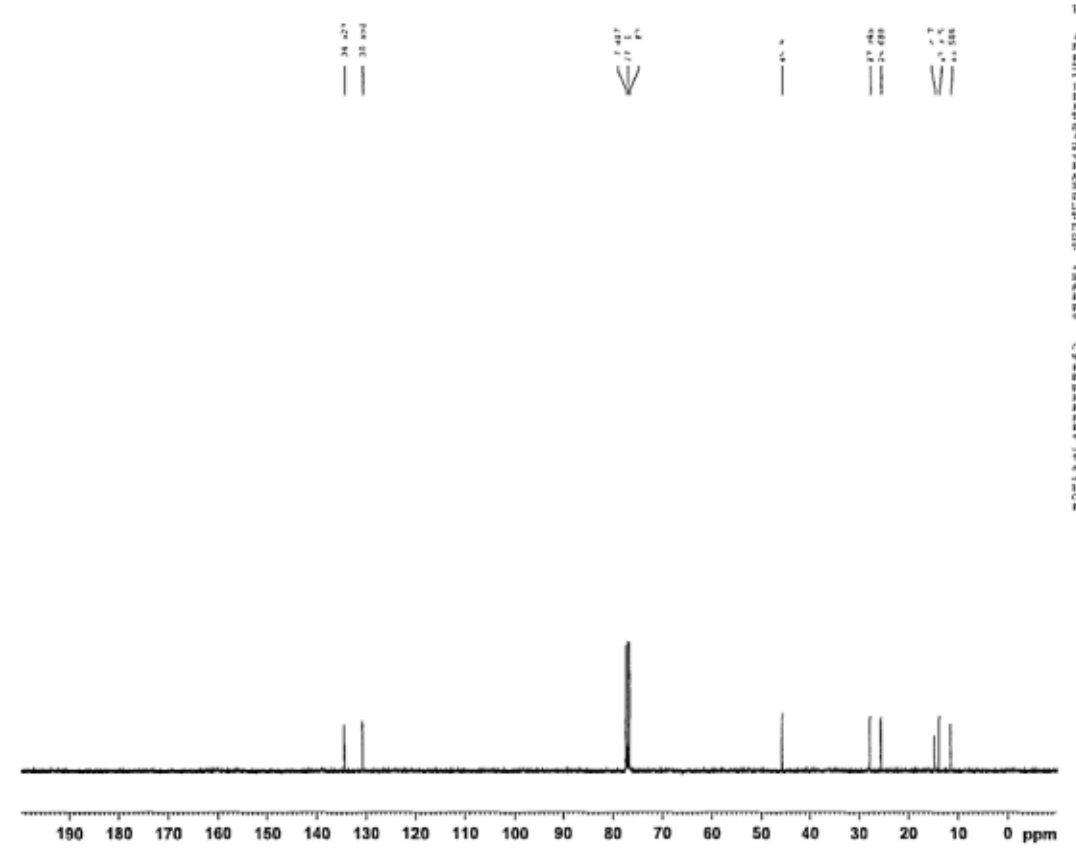

OSiMe2tBu
222b
ppm

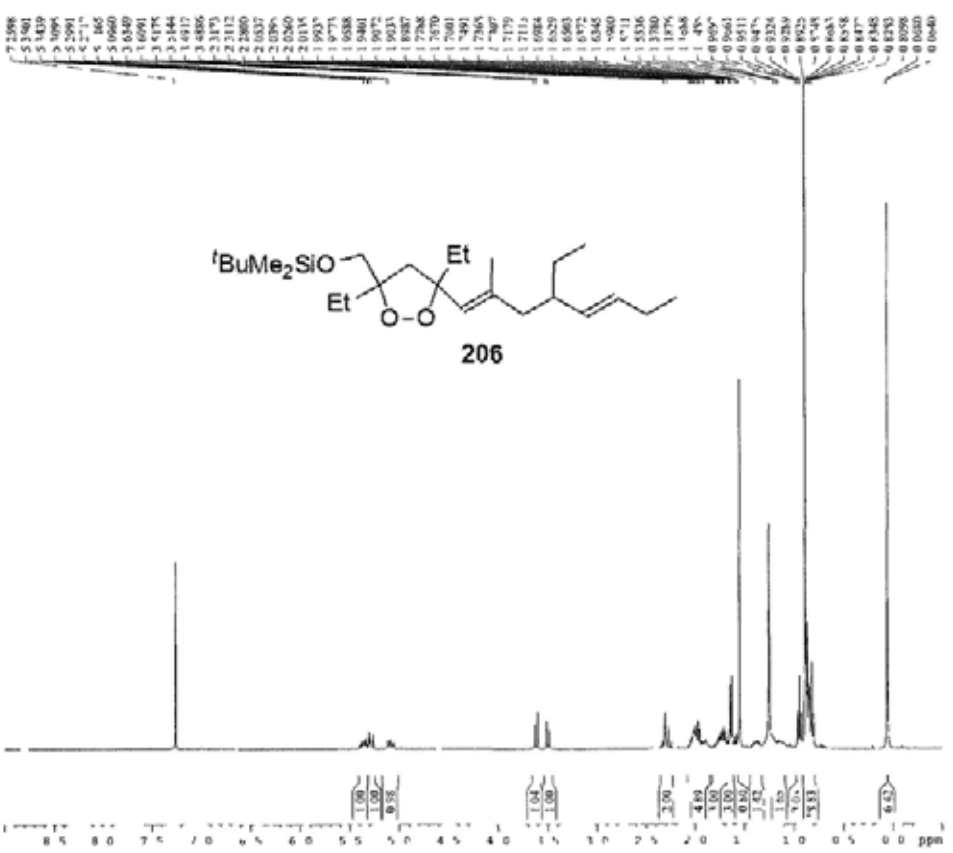

ppm

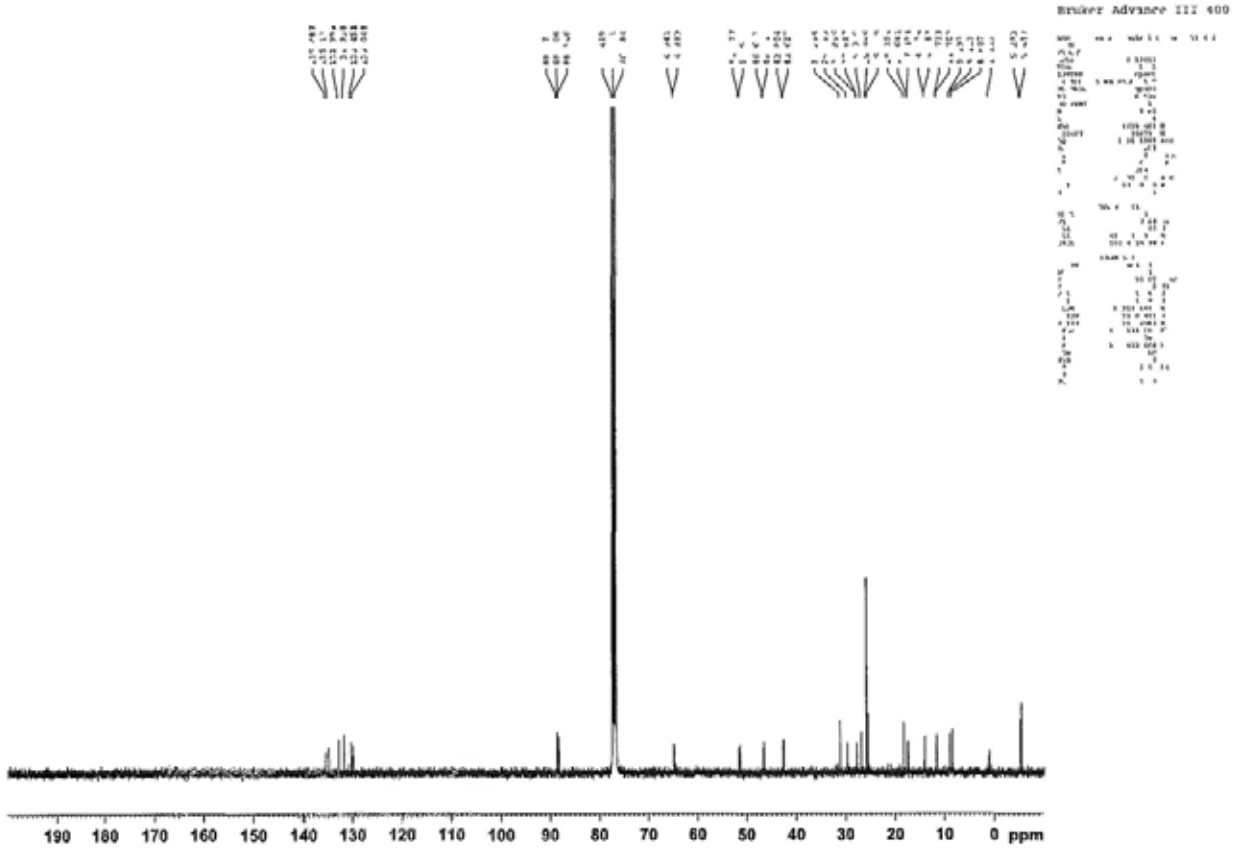

Bruker Advance III 400
OH
223b
ppm

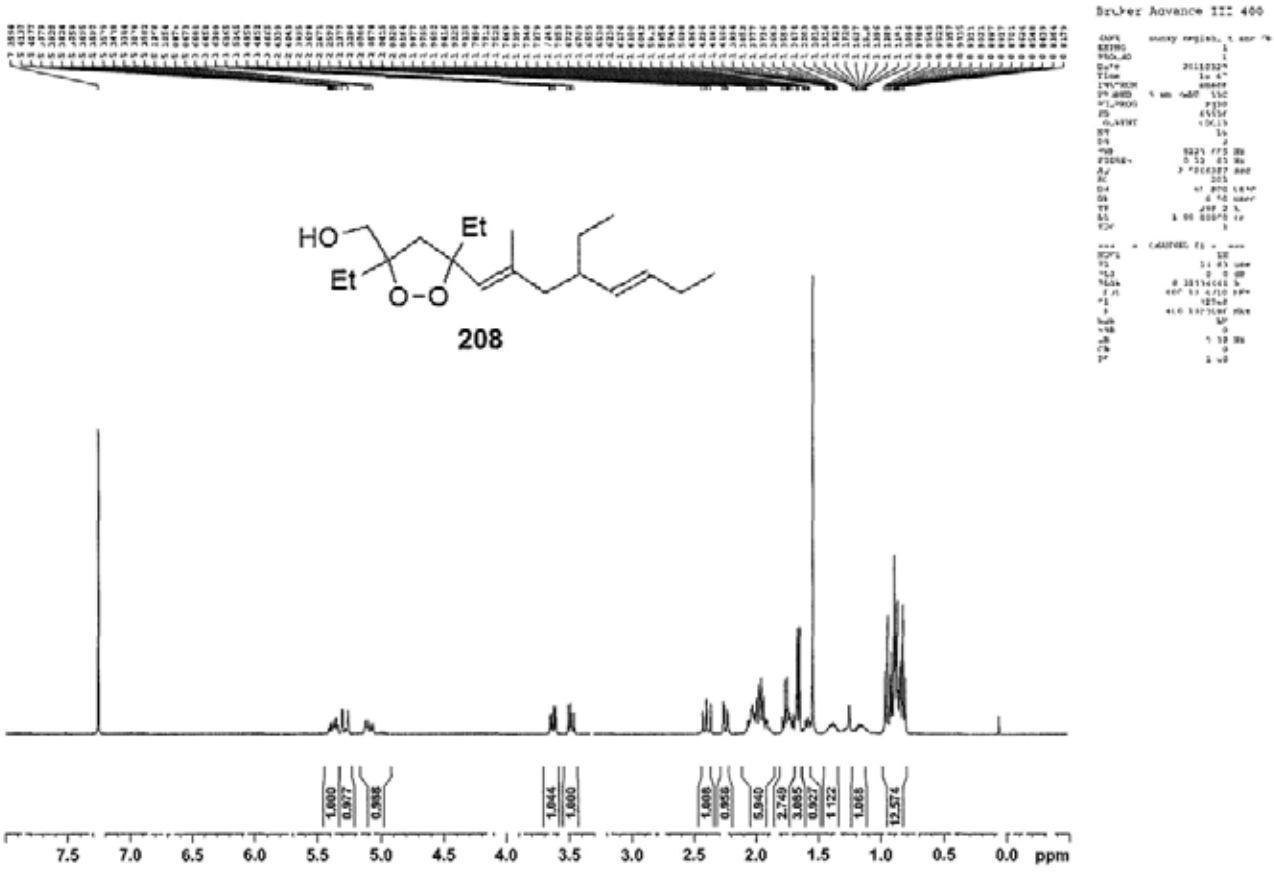

Bruker Advance III 400
ppm

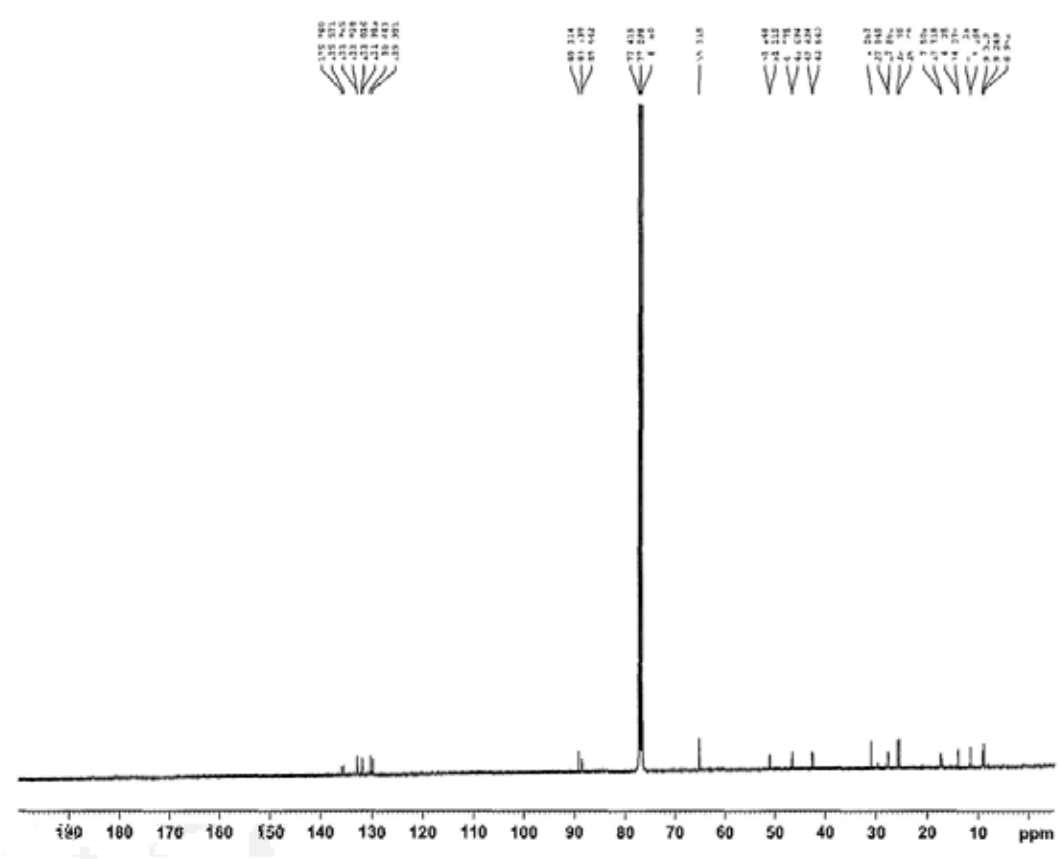

(S)-91
0.981
0.973
2.000
3.007
1.266
1.039
3.145
3.254
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

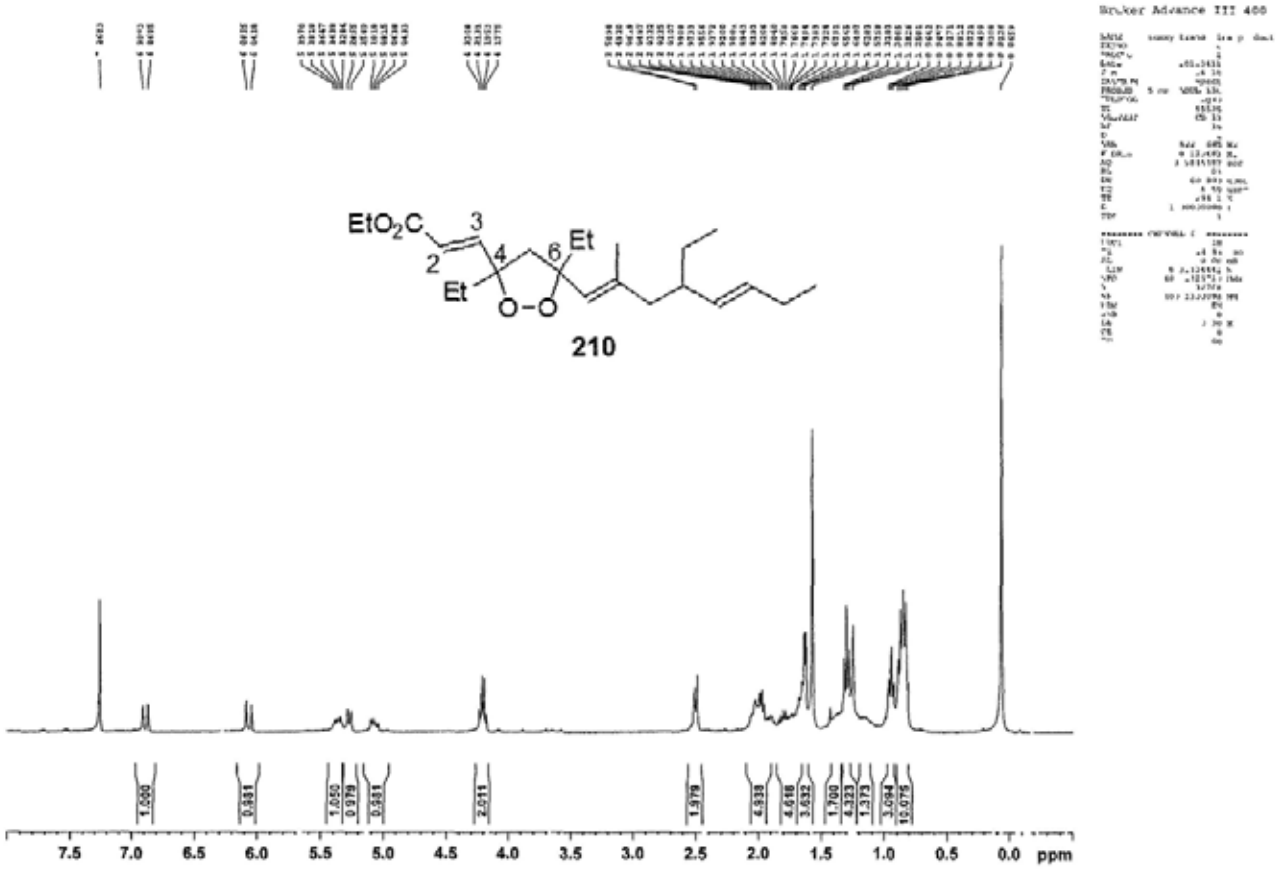

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

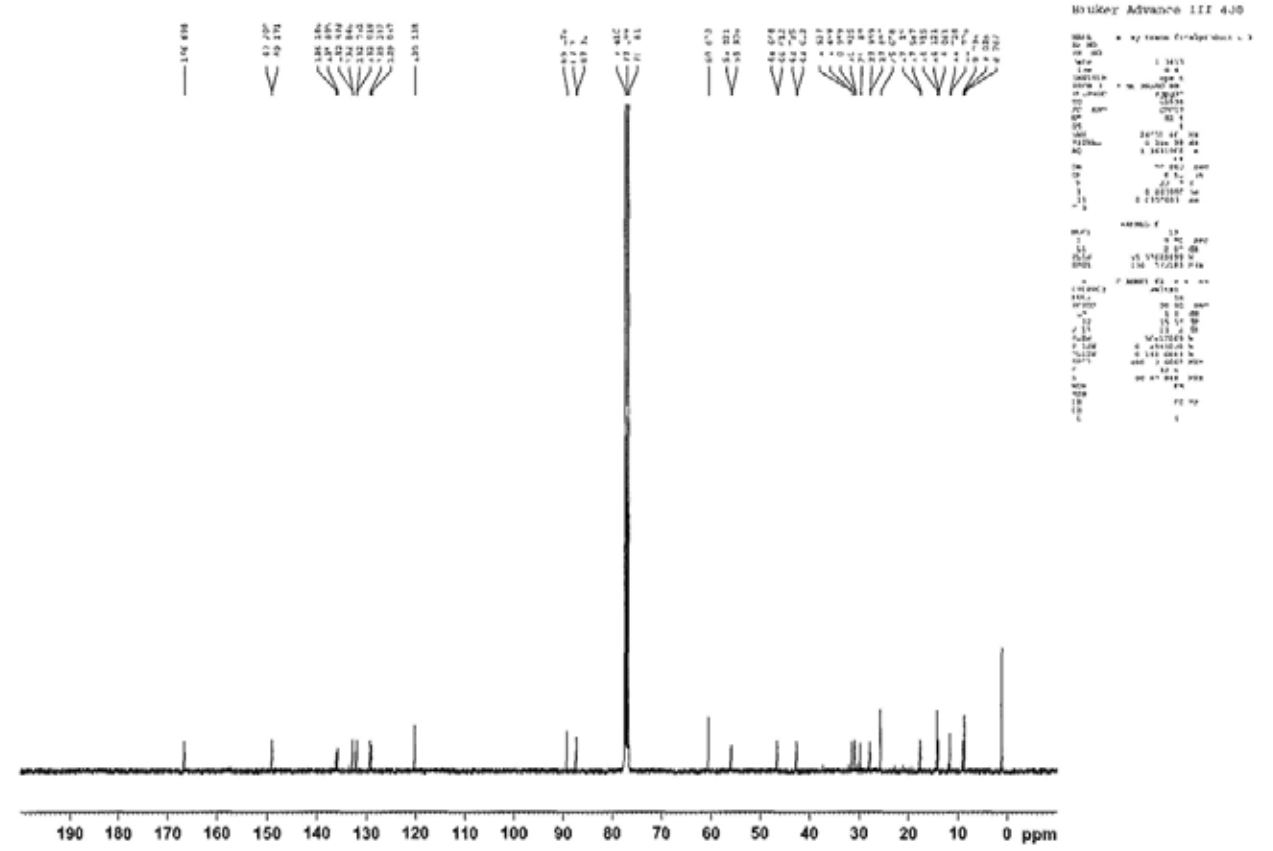

Bruker Advance III 400
tBuMe2SiO
Et
Et
O-O
206
ppm

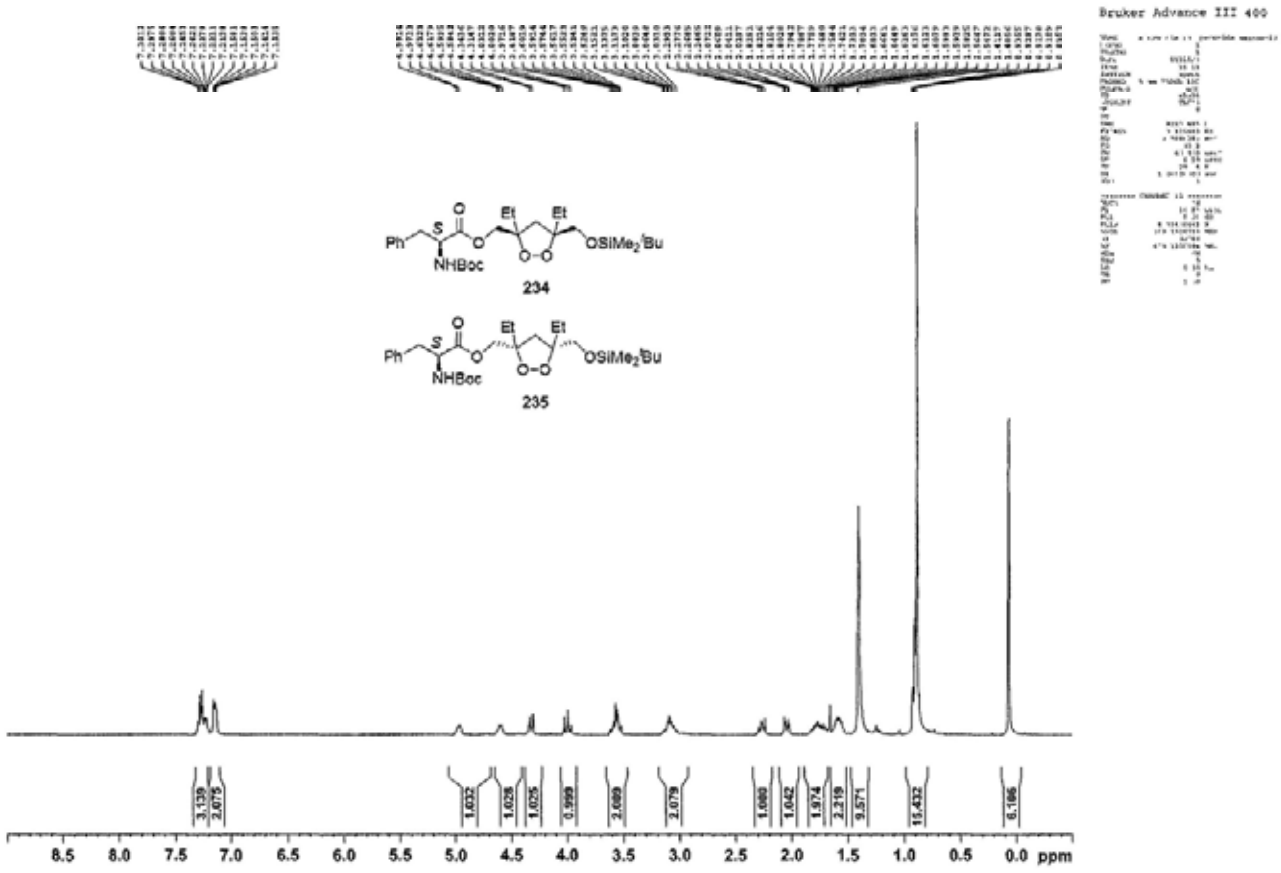

Bruker Advance III 400
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

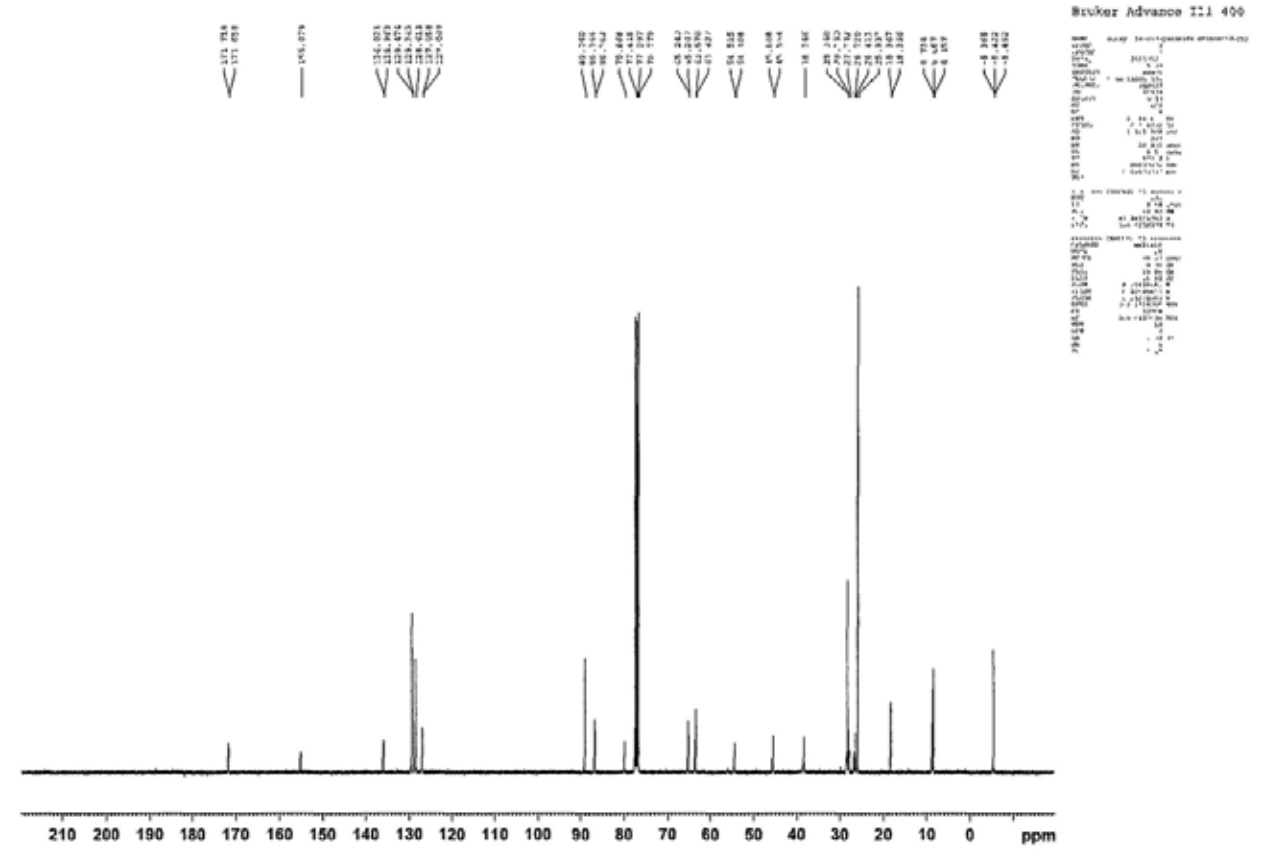

HO
Et
Et
O-O
208
1.000
0.977
0.988
1.044
1.000
1.008
0.956
5.940
2.749
3.085
0.927
4.122
1.065
12.574
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

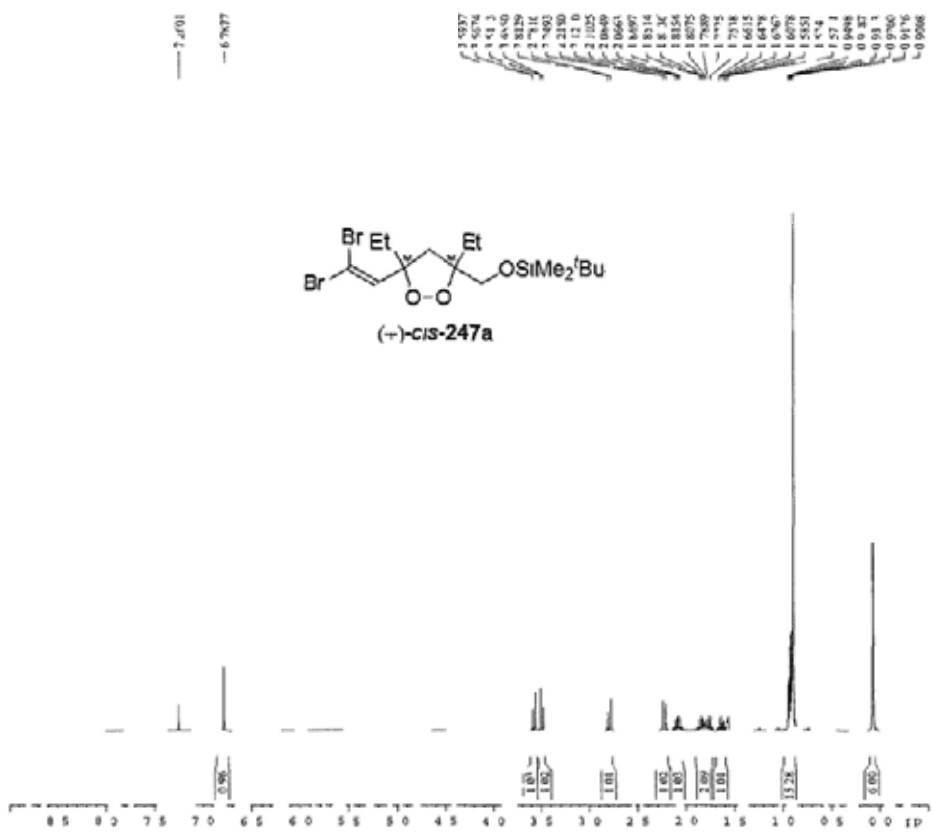

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Bruker Advance III 400
EtO2C
3
2
4
6
Et
Et
O-O
210
1.000
0.881
1.050
0.979
0.881
2.011
1.979
4.838
4.618
3.832
1.700
4.323
1.373
3.084
10.076
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

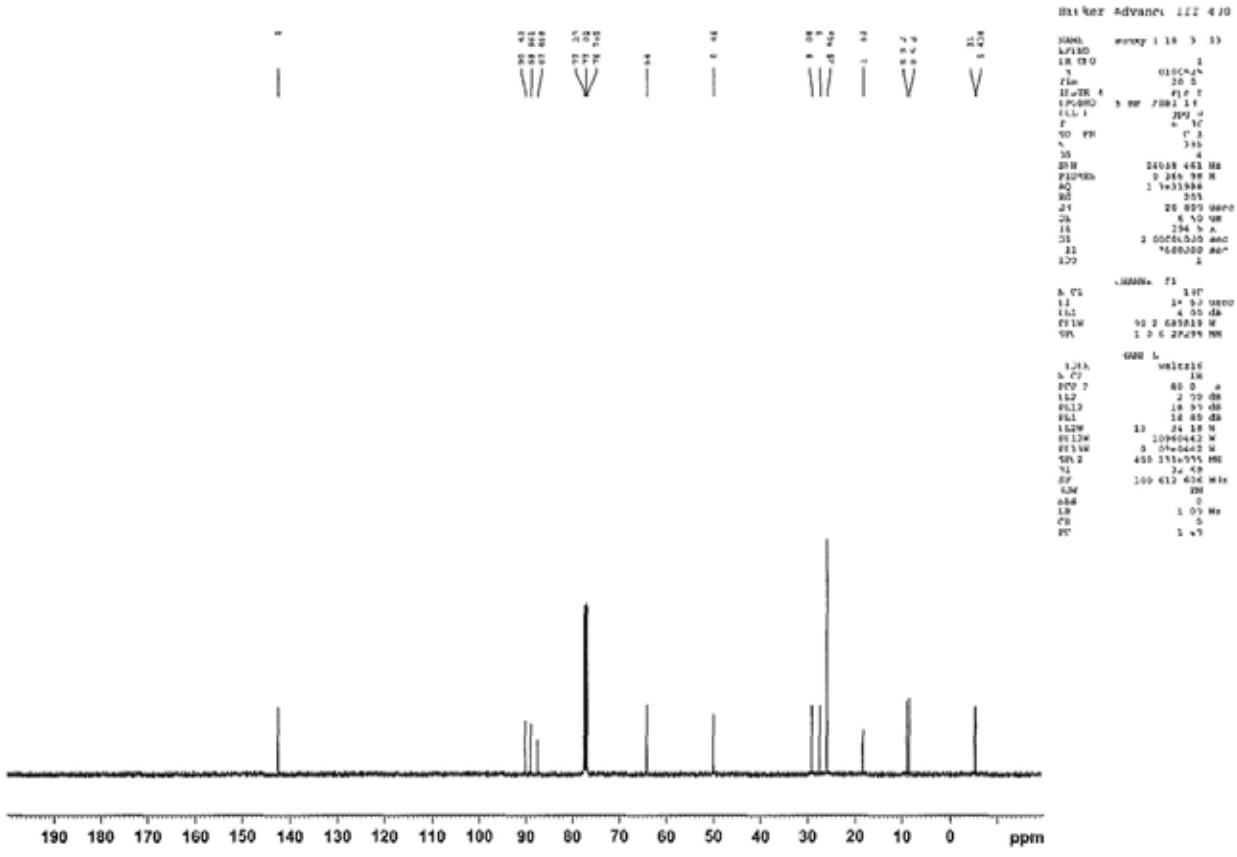

Bruker Advance III 400
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

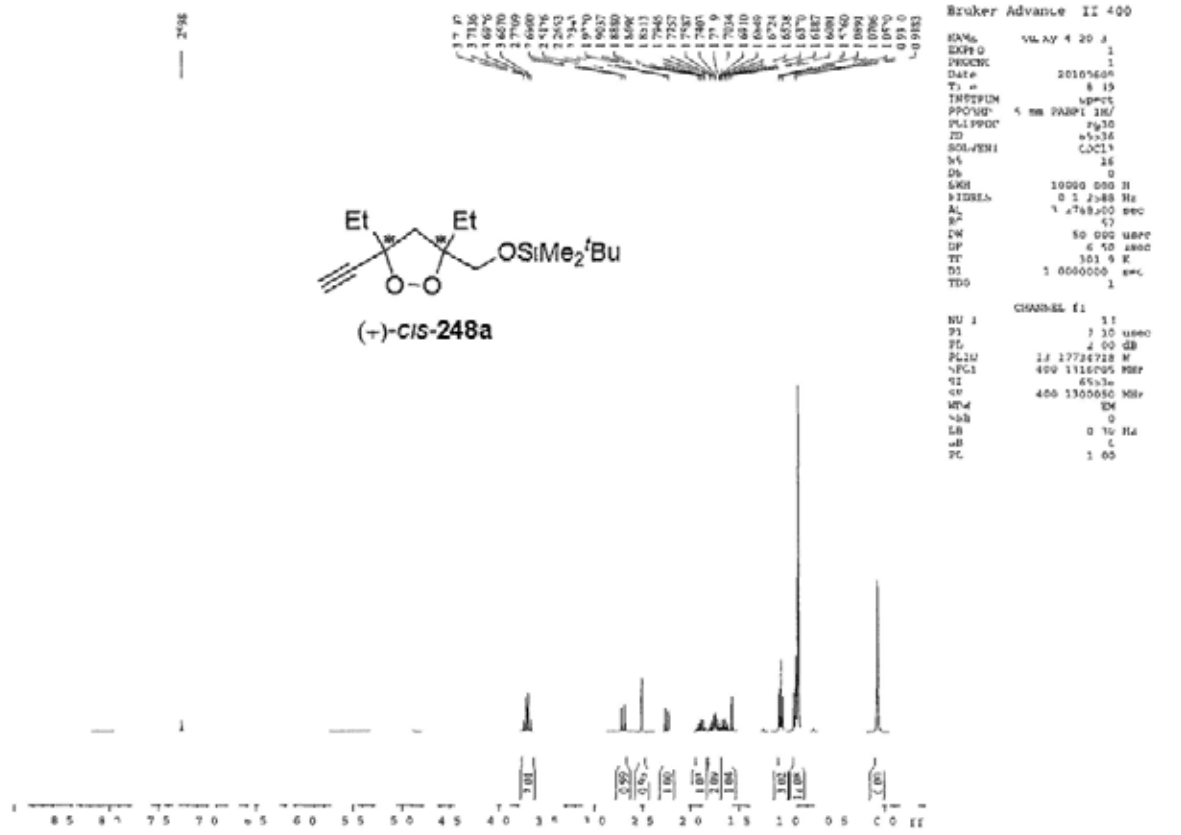

Bruker Advance III 400
Ph
S
NHBoc
Et
Et
OSiMe2tBu
234
235
3.139
2.075
1.632
1.628
1.625
0.999
2.089
2.079
1.080
1.042
1.974
2.219
9.571
15.432
6.166
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

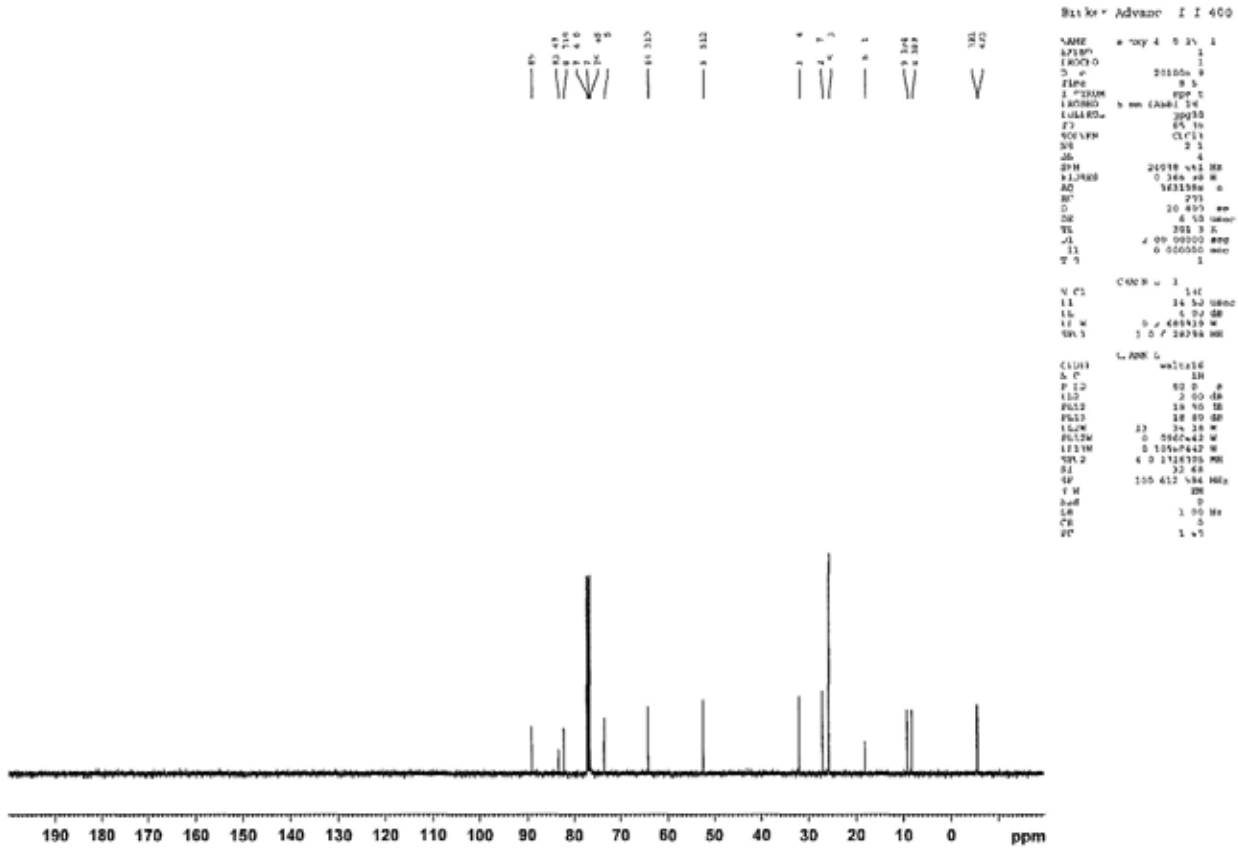

Bruker Advance III 400
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

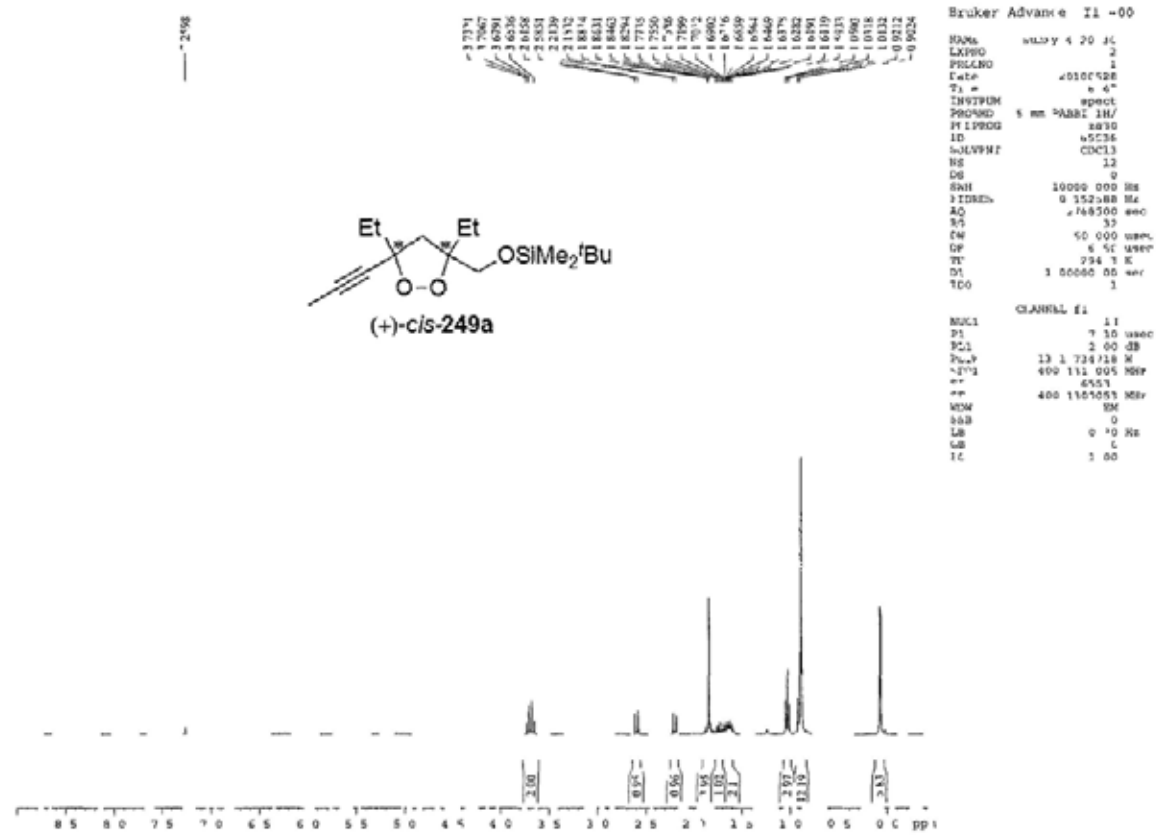


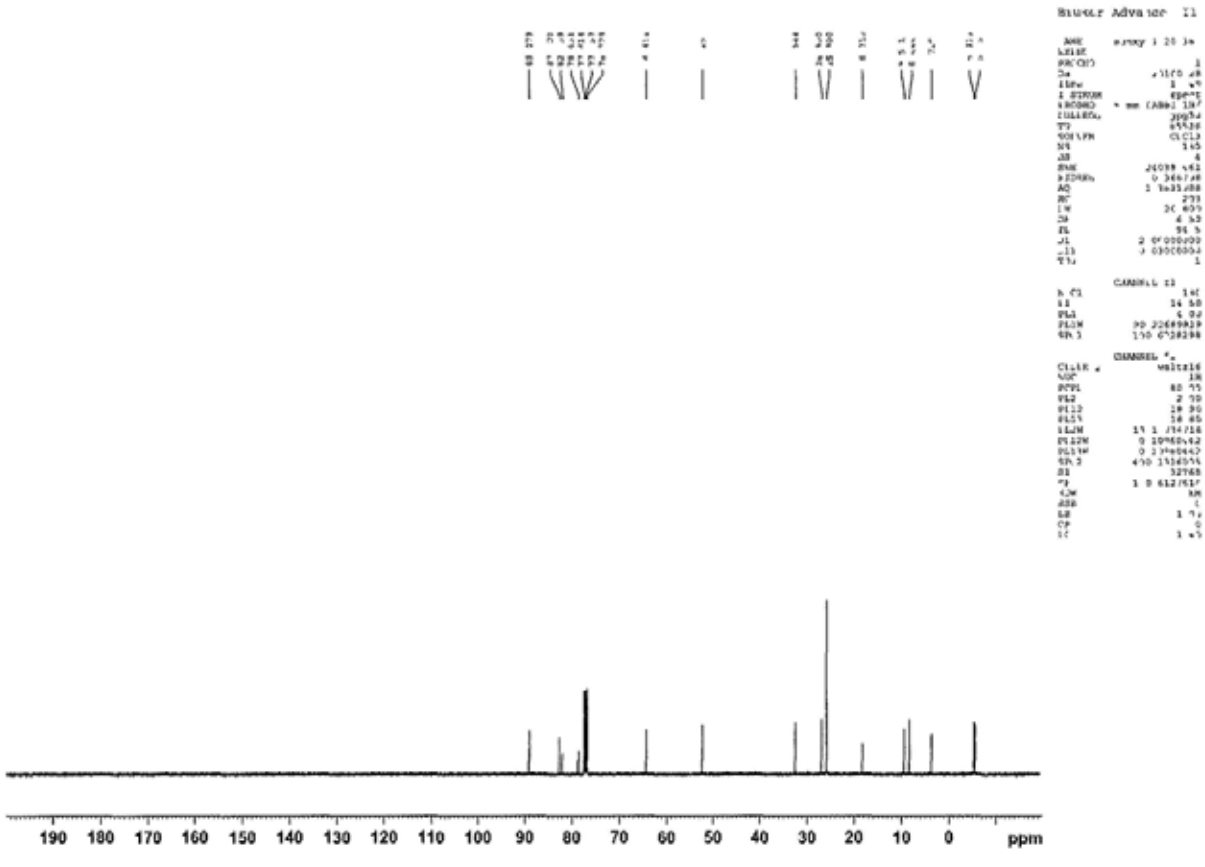
(+)-*cis*-247a

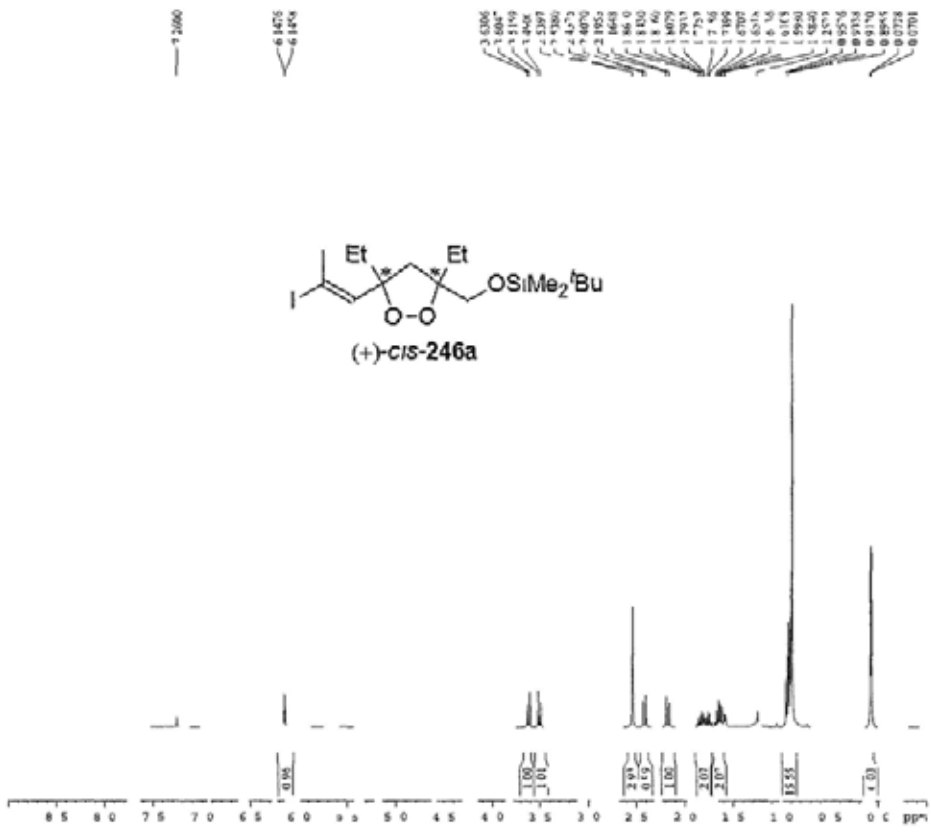


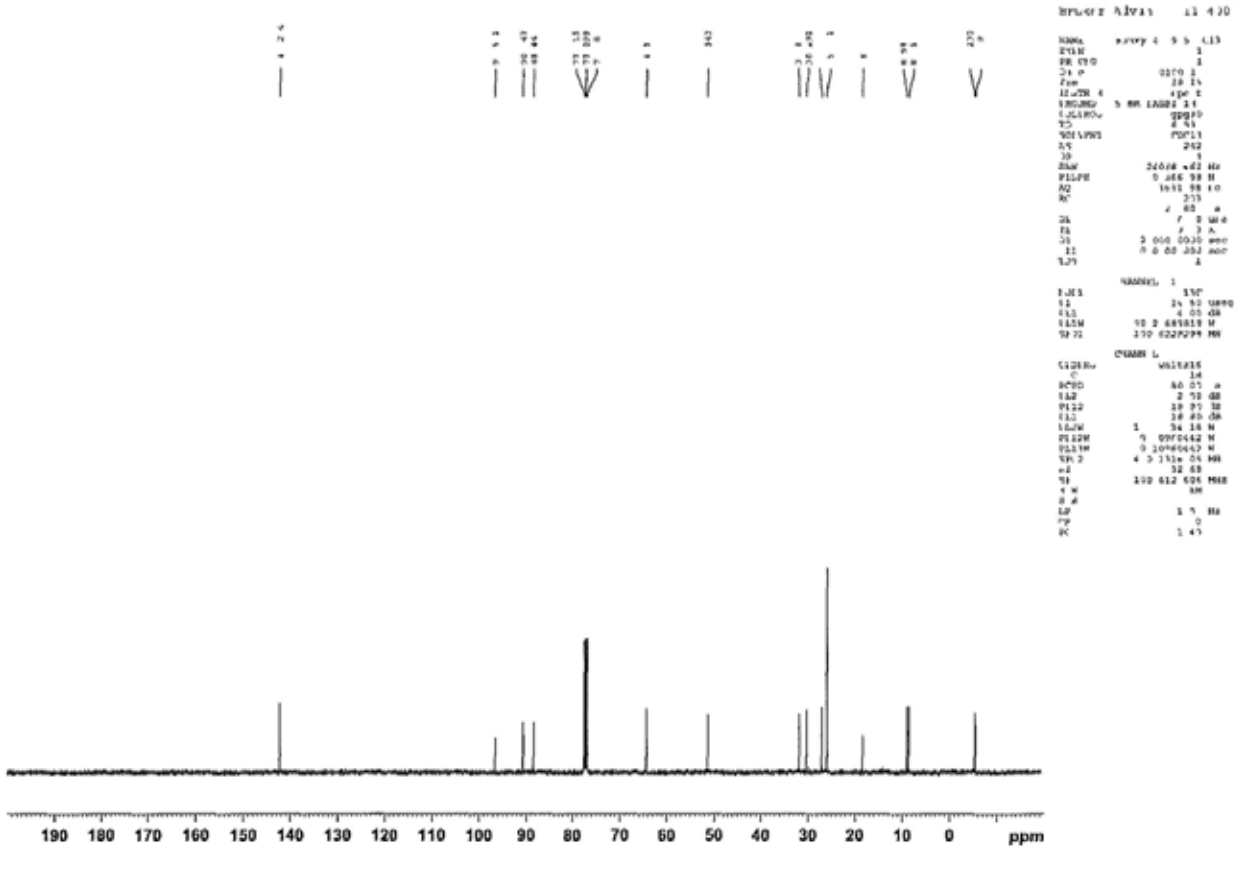

Et
Et
OSiMe2tBu
(+)-cis-248a

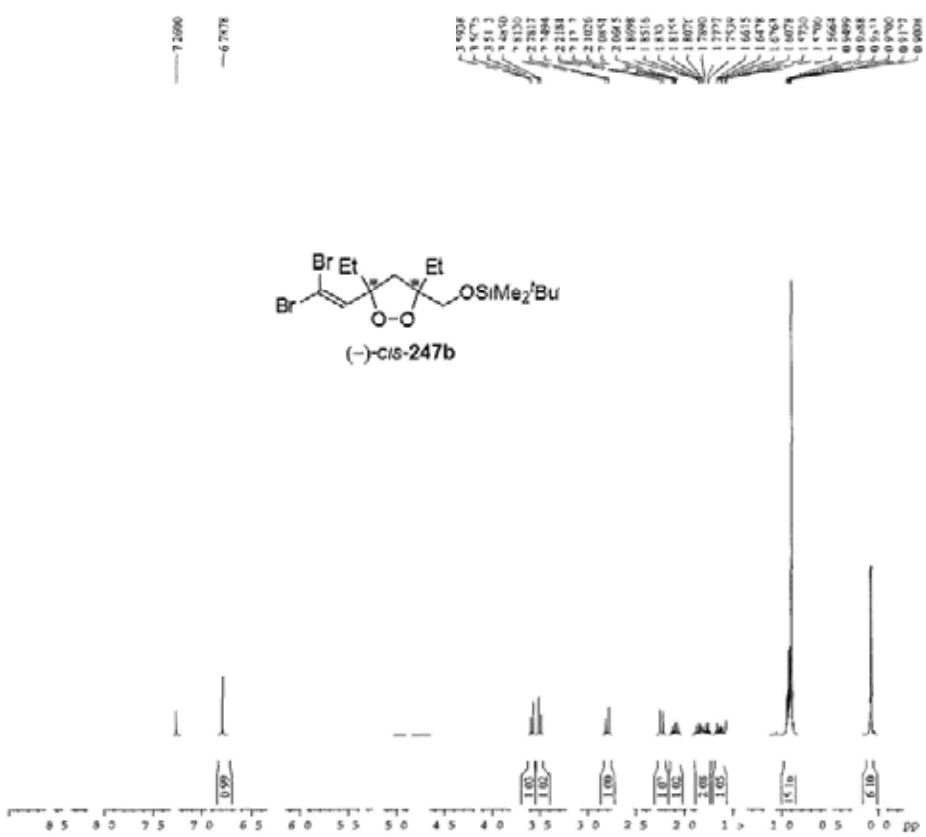

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

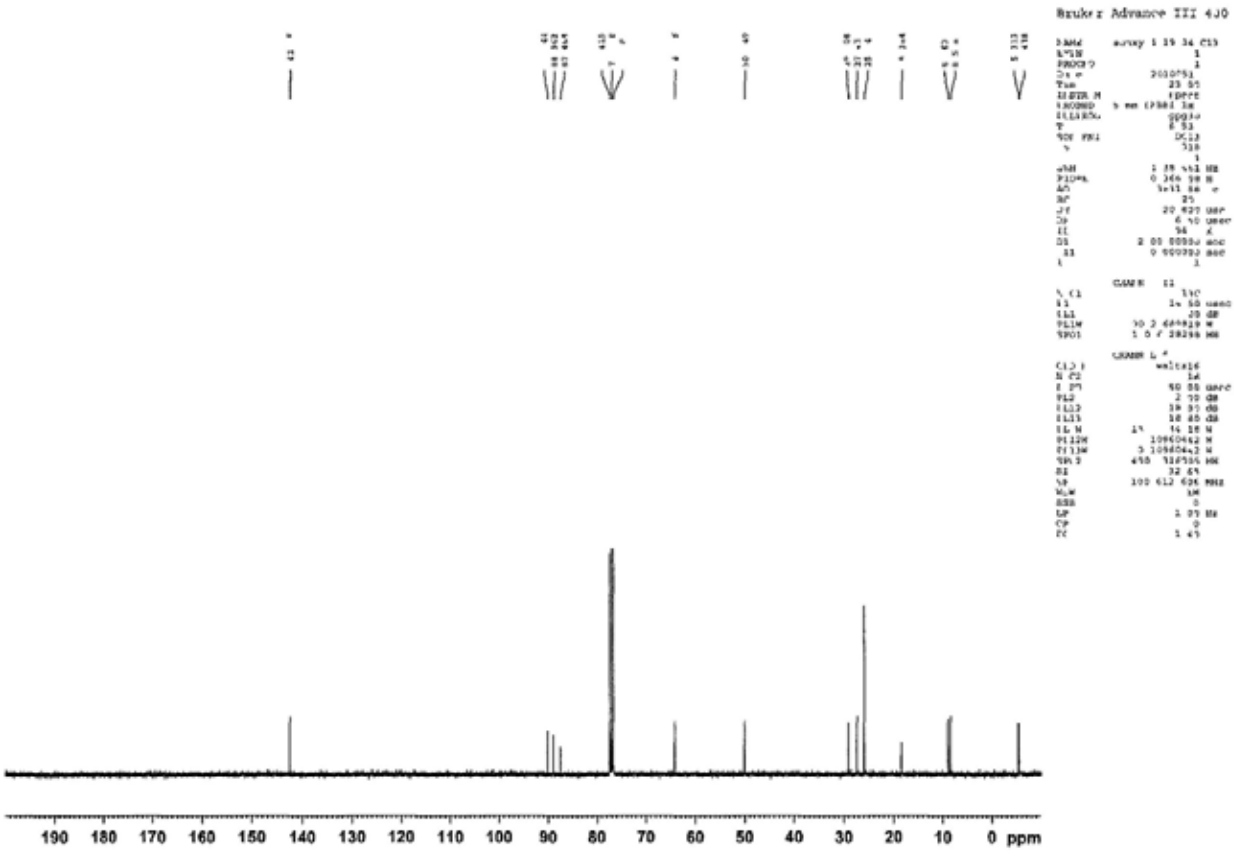

Et
Et
OSiMe2tBu
O
O
(+)-cis-249a

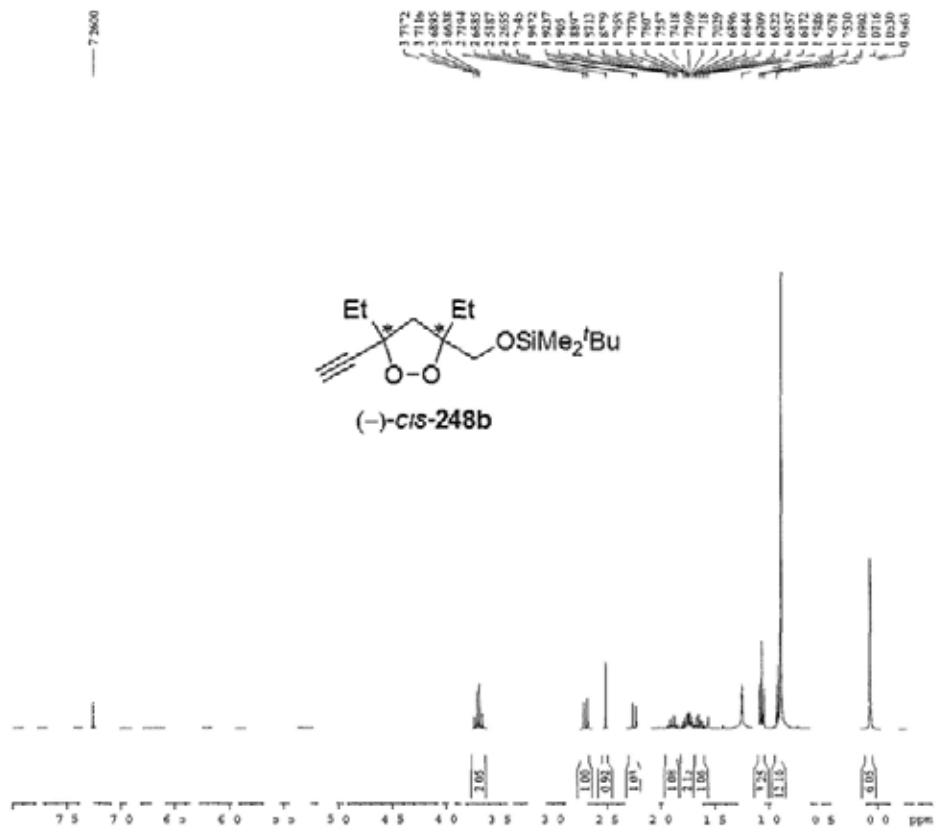


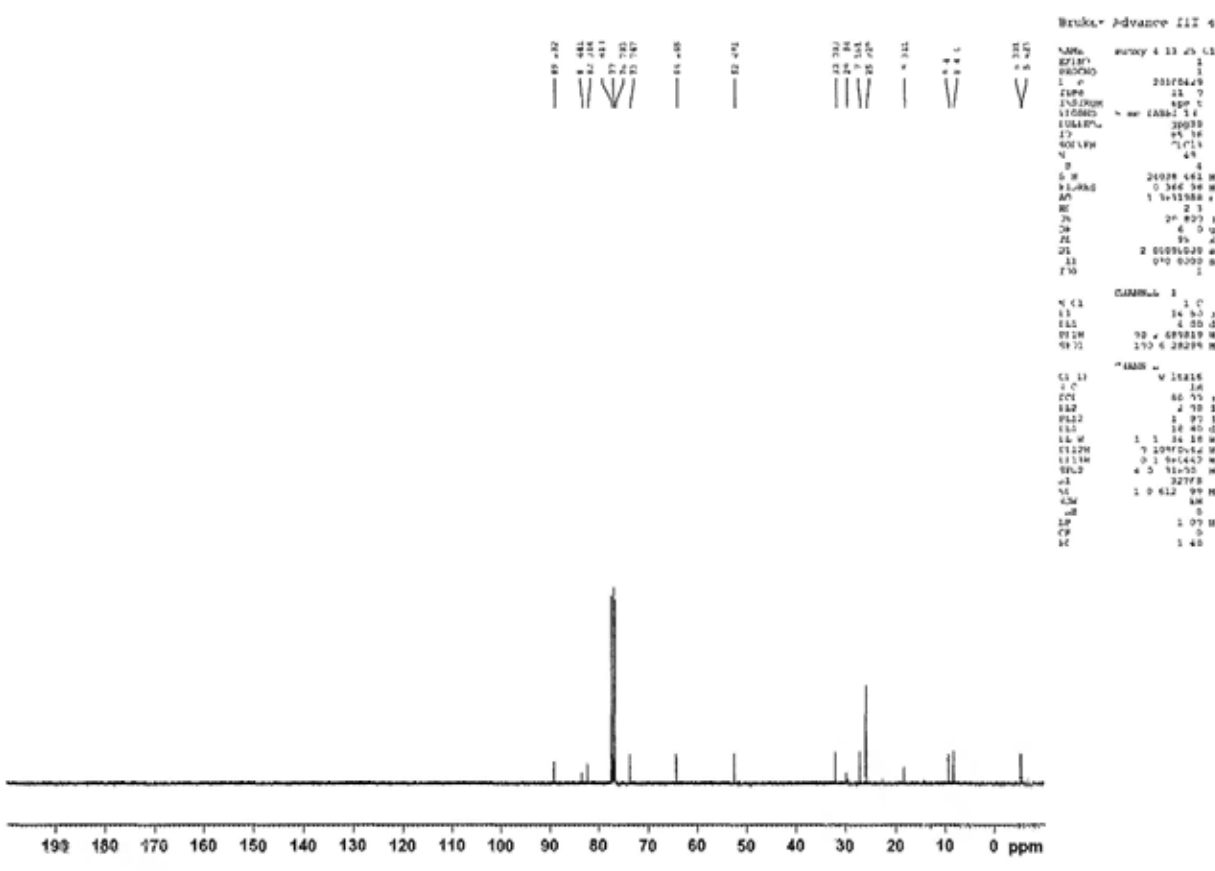

Et
Et
I
OSiMe2tBu
O–O
(+)-cis-246a

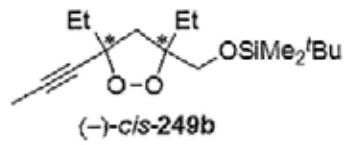



Br
Et
Et
Br
OSiMe2tBu
O–O
(–)-cis-247b

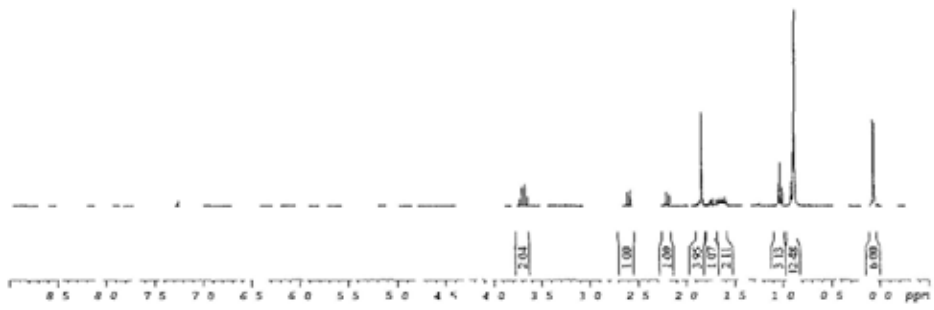


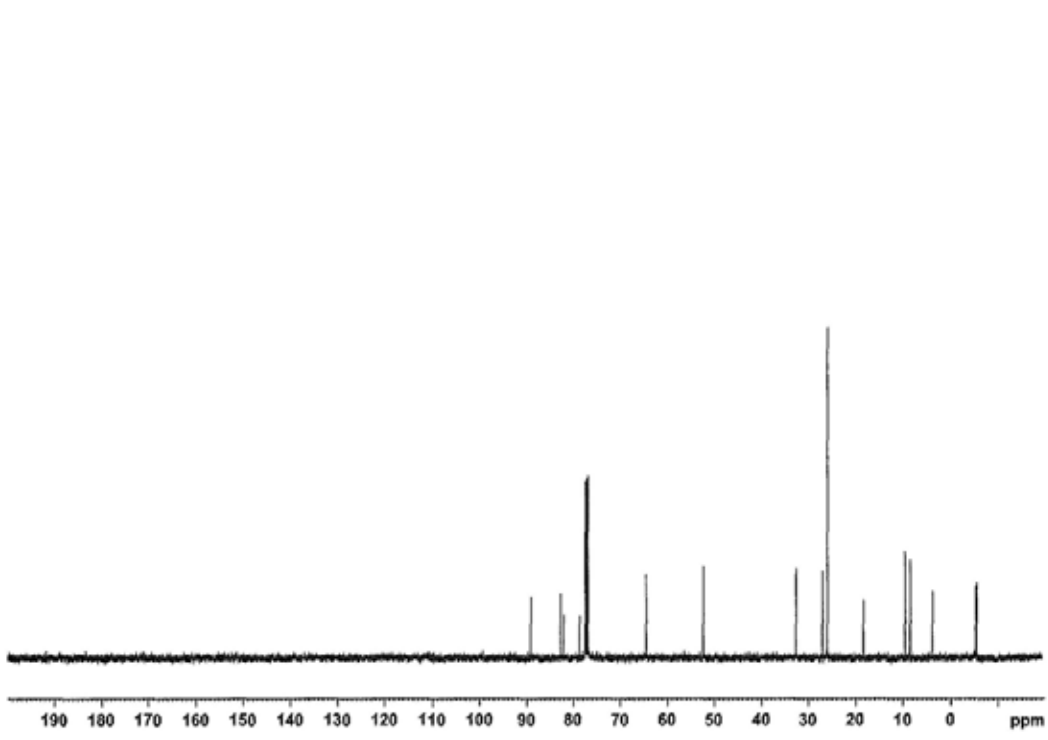

Et
Et
OSiMe2tBu
O–O
(–)-cis-248b

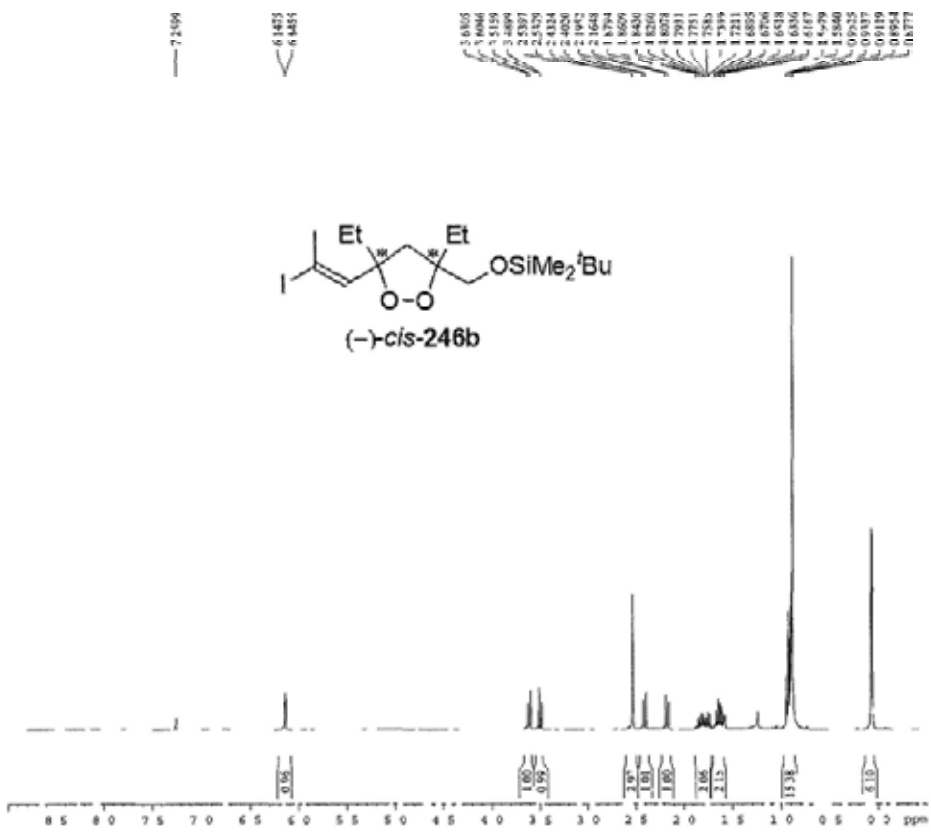


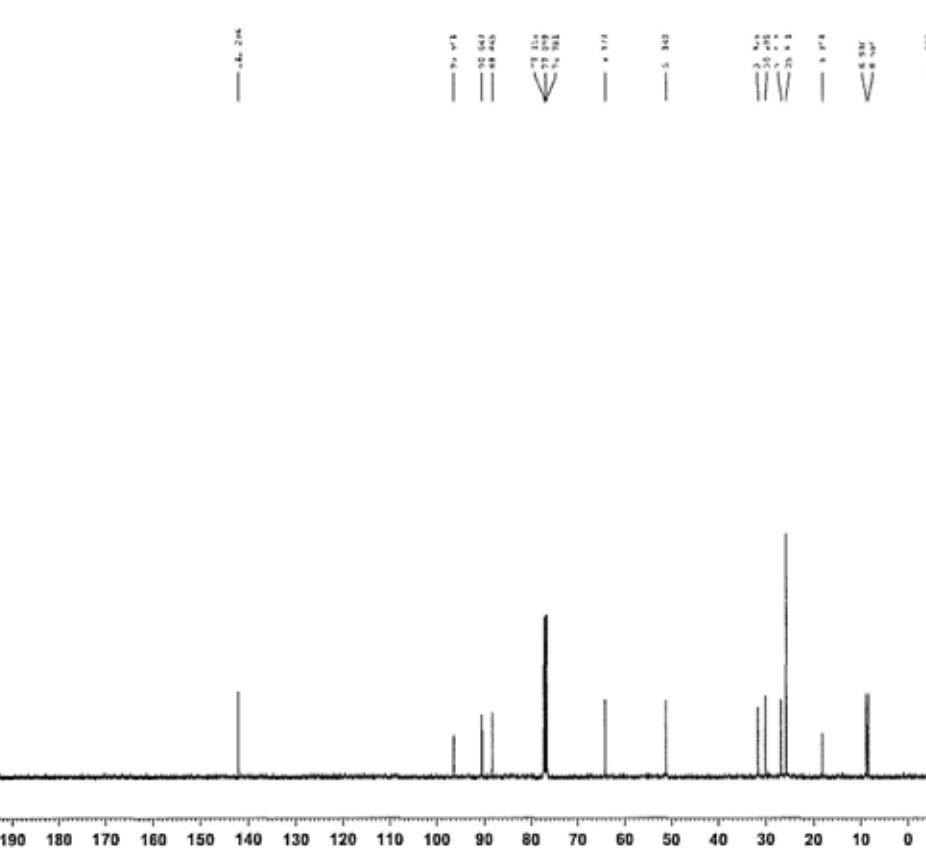

Et
Et
OSiMe2tBu
O–O

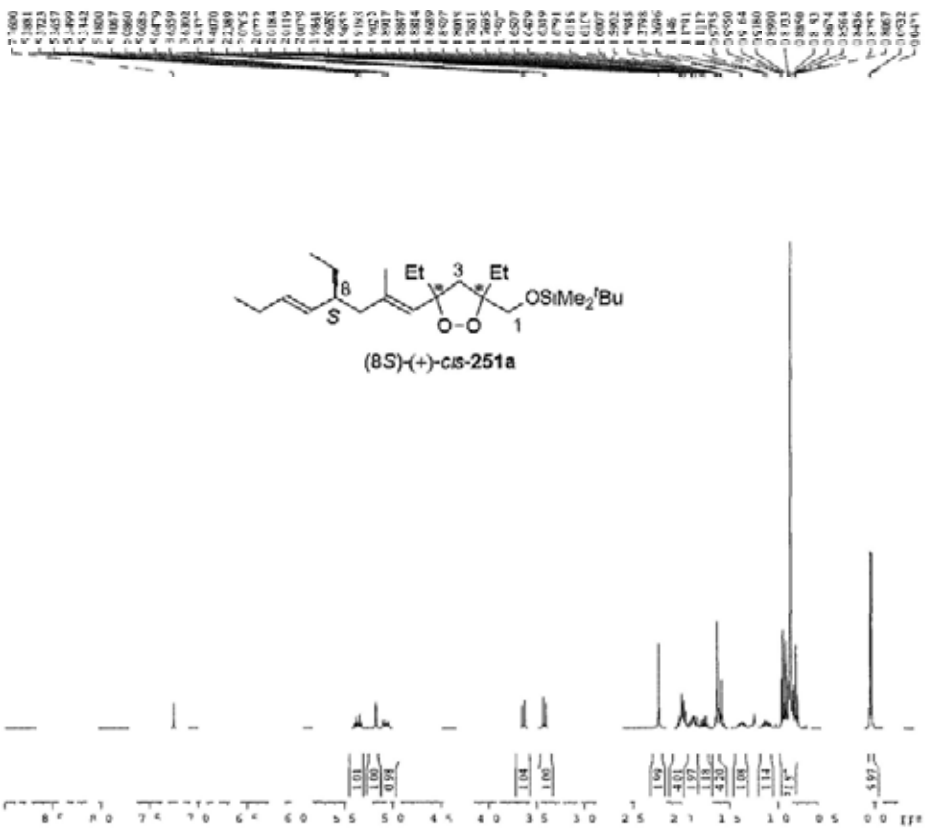
(–)-*cis*-**249b**


2.04
1.00
1.09
3.95
1.05
2.11
3.15
12.86
6.00
ppm

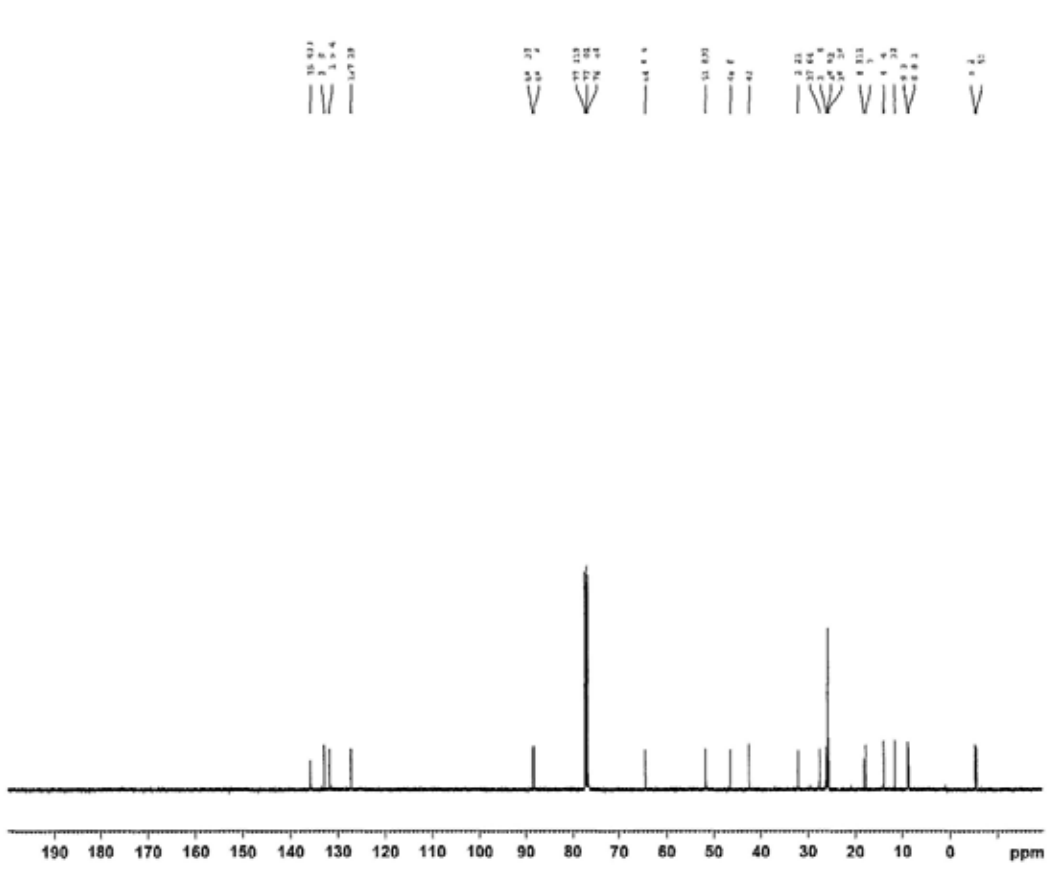

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

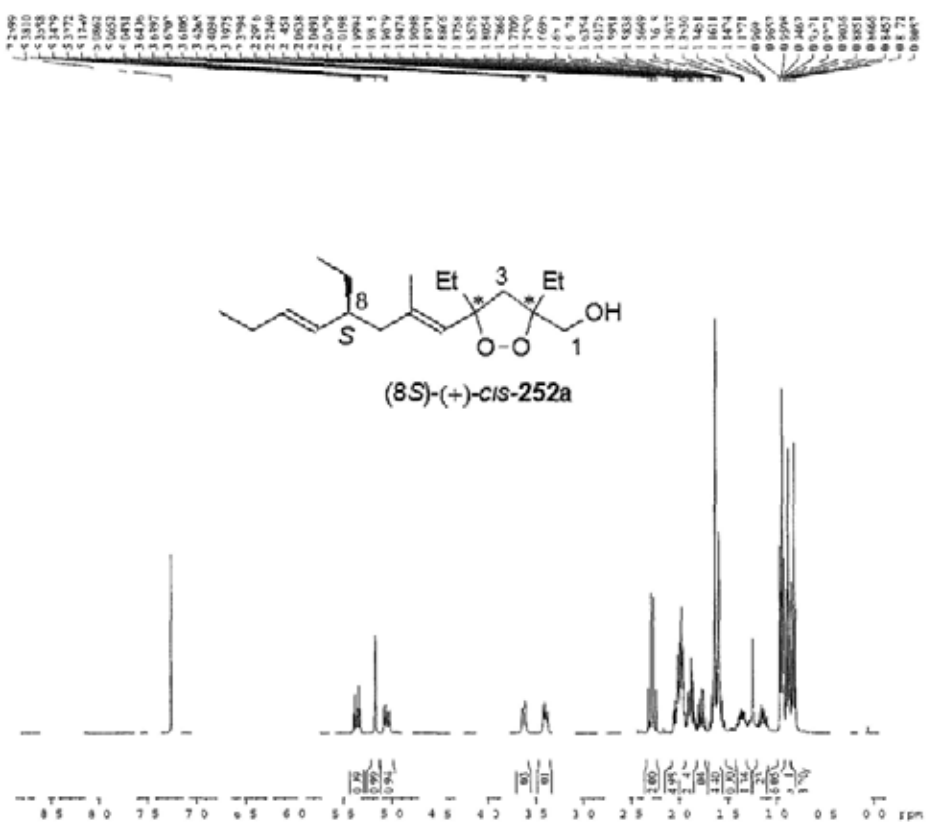

Et
Et
OSiMe2tBu
I
O-O
(−)-cis-246b

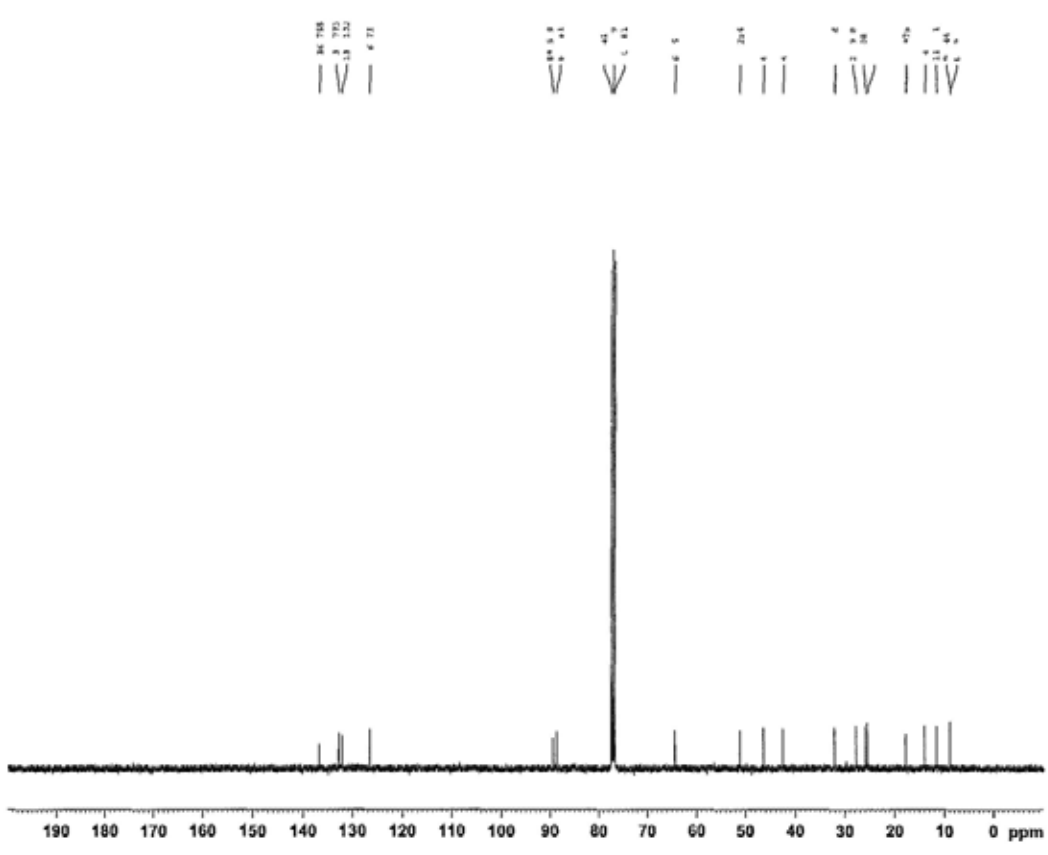


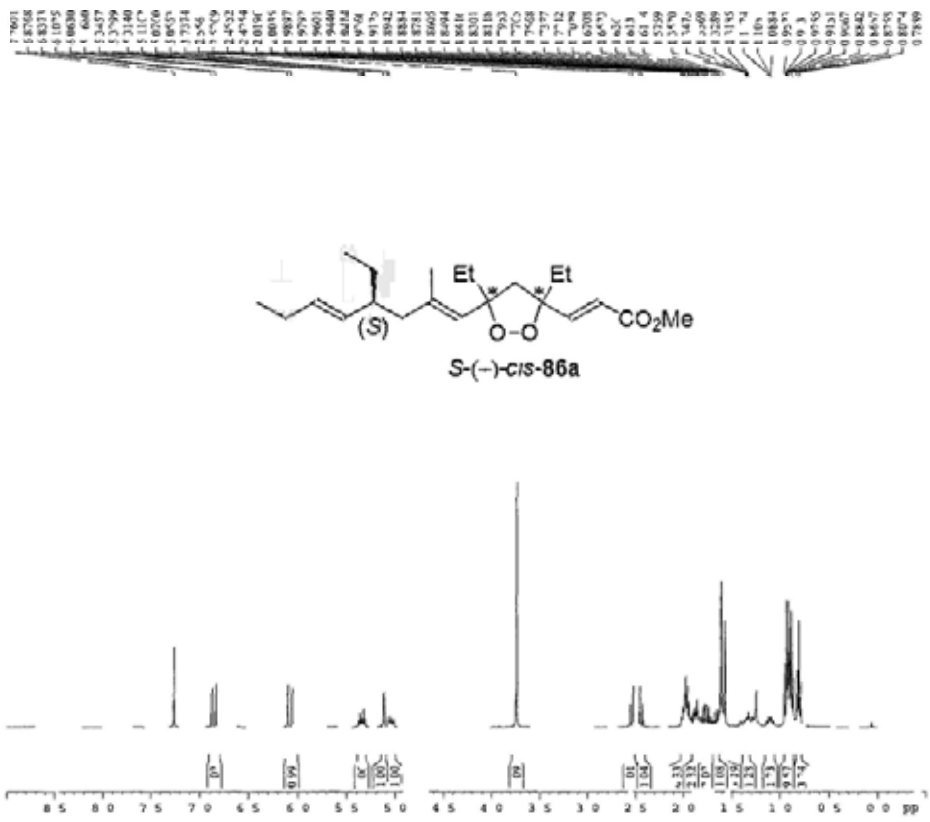


(8*S*)-(+)-*cis*-**251a**

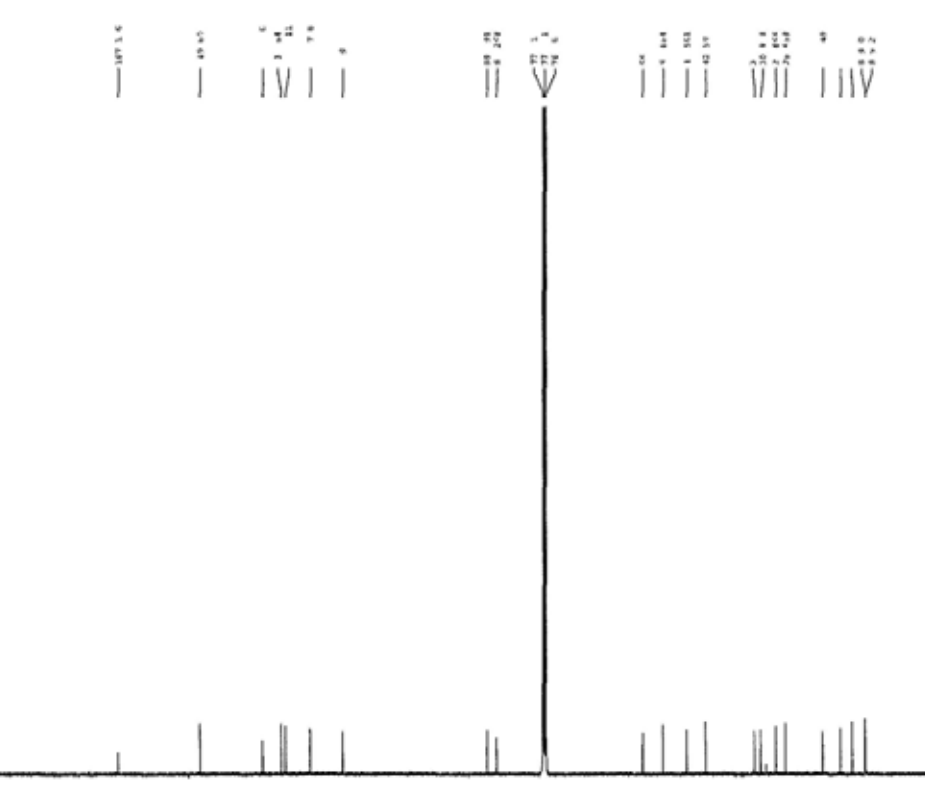


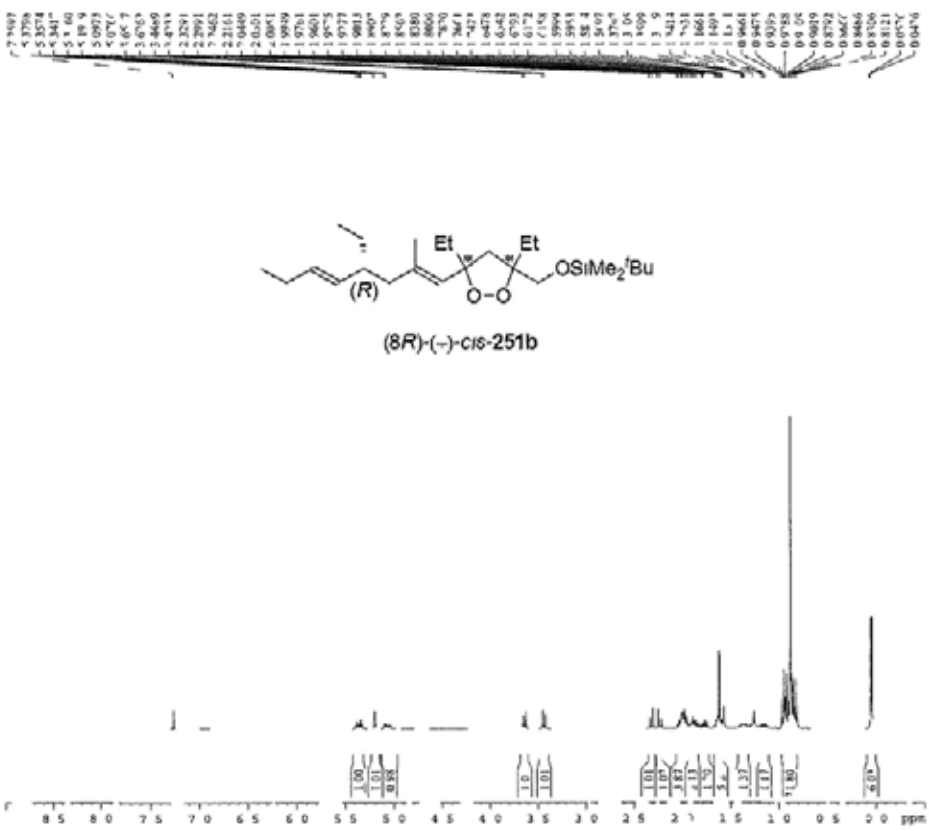

Et
3
Et
8
S
OH
O
O
1
(8S)-(+)-cis-252a



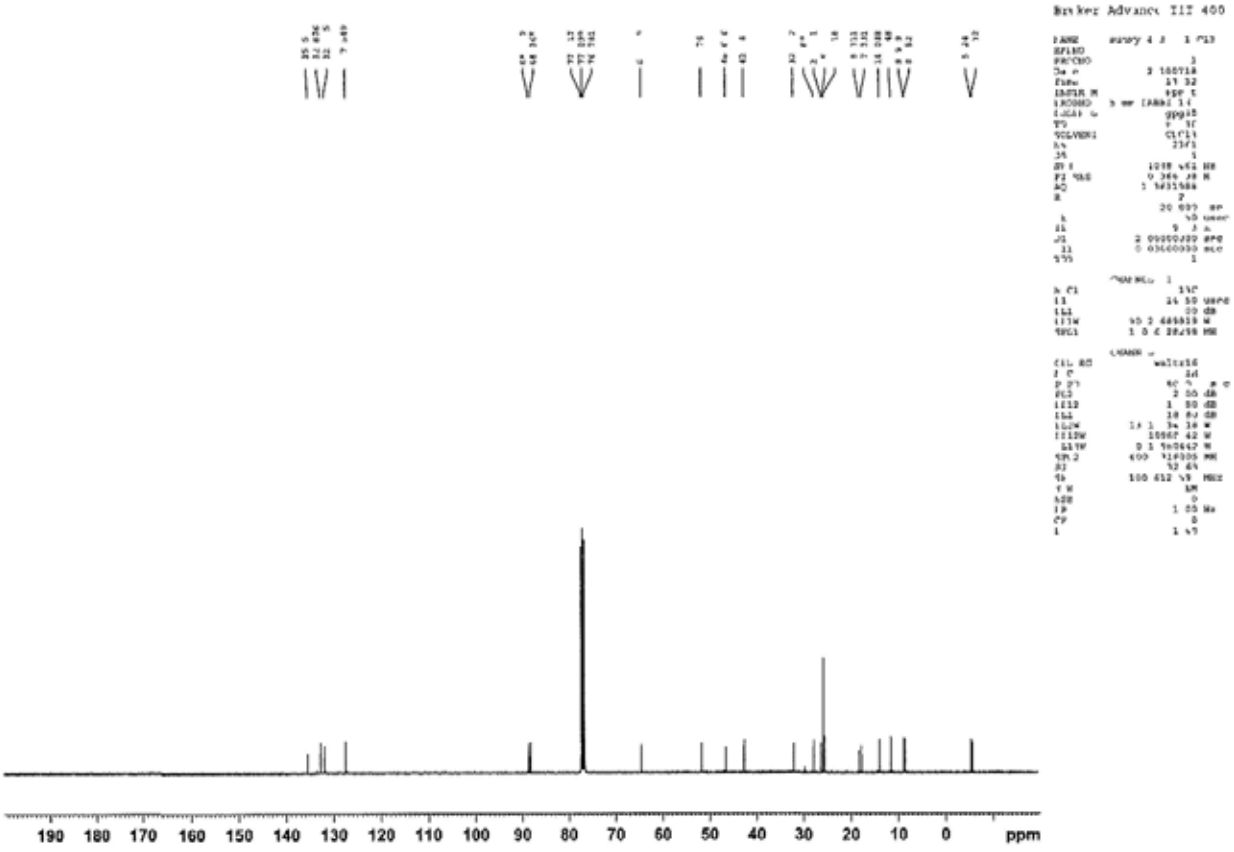


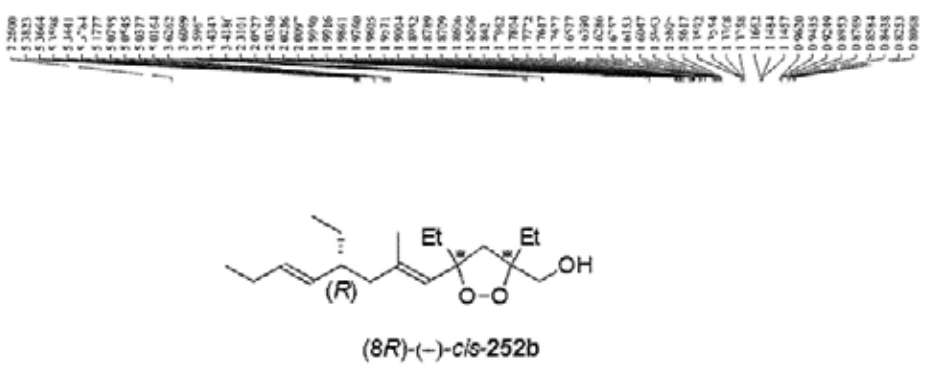
S-(−)-*cis*-**86a**



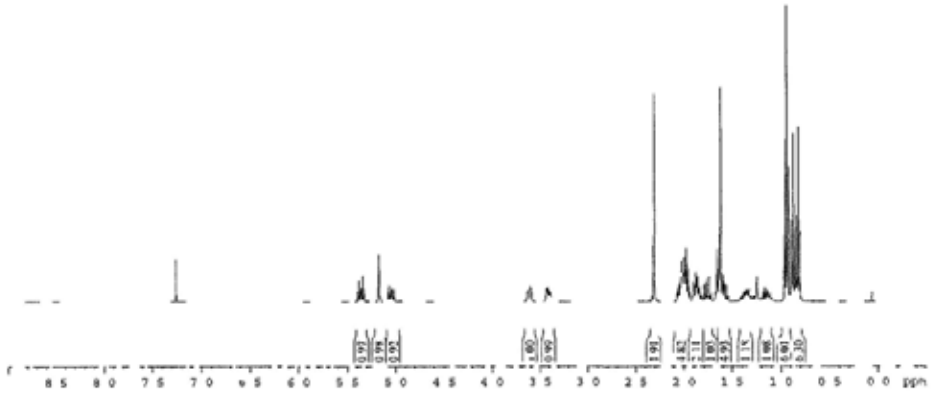

Et
Et
OSiMe2tBu
(R)
O-O
Bruker Advance II 400
ppm

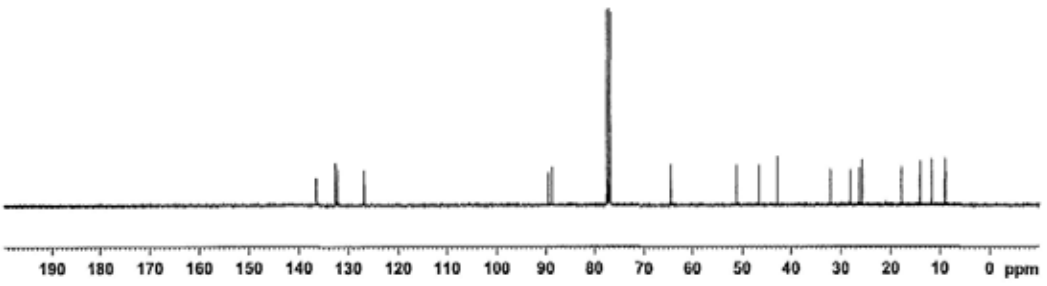
(8*R*)-(−)-*cis*-**251b**

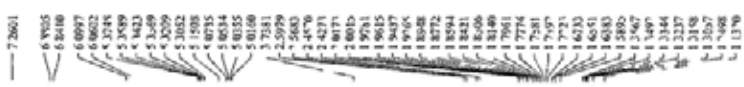

Bruker Advance III 400
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

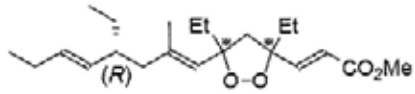

Et
Et
OH
(R)
O-O

(8*R*)-(−)-*cis*-252b

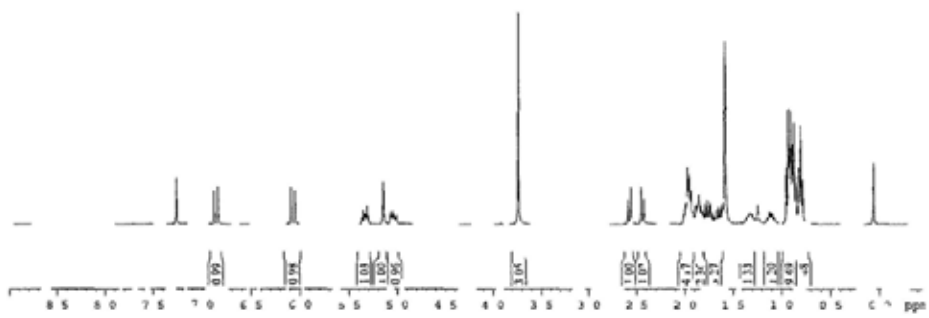

85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 05 00 ppm

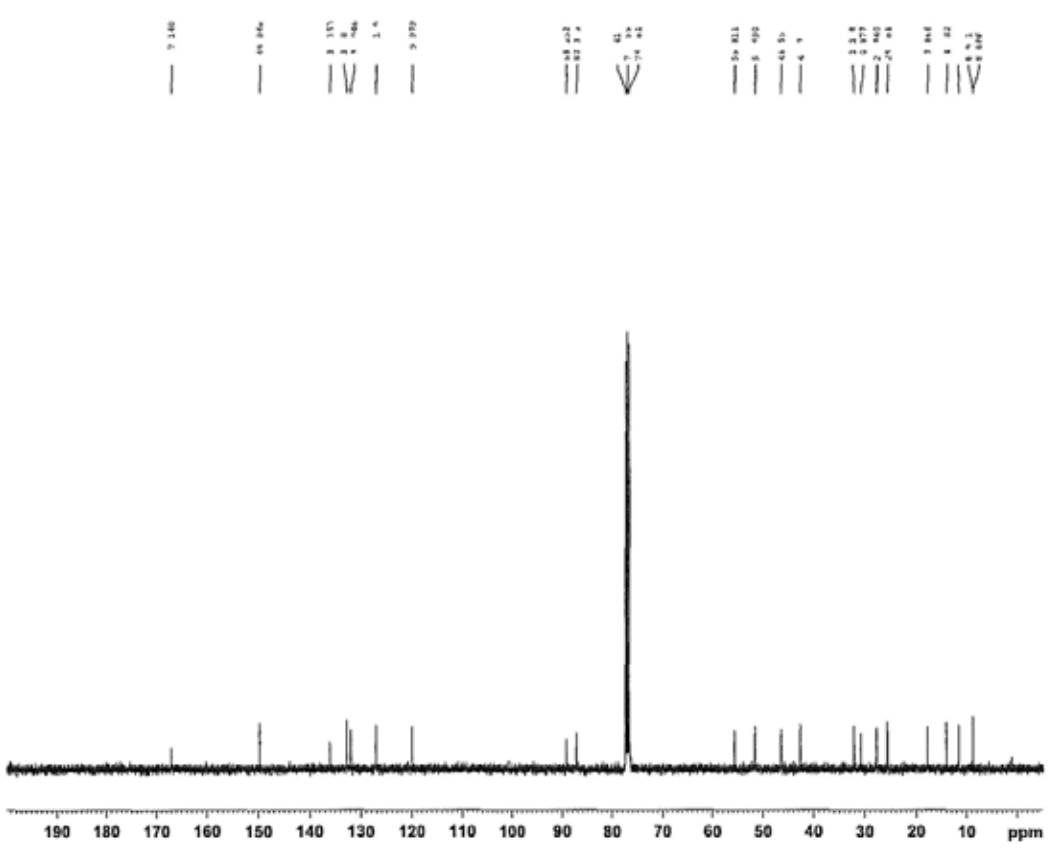

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

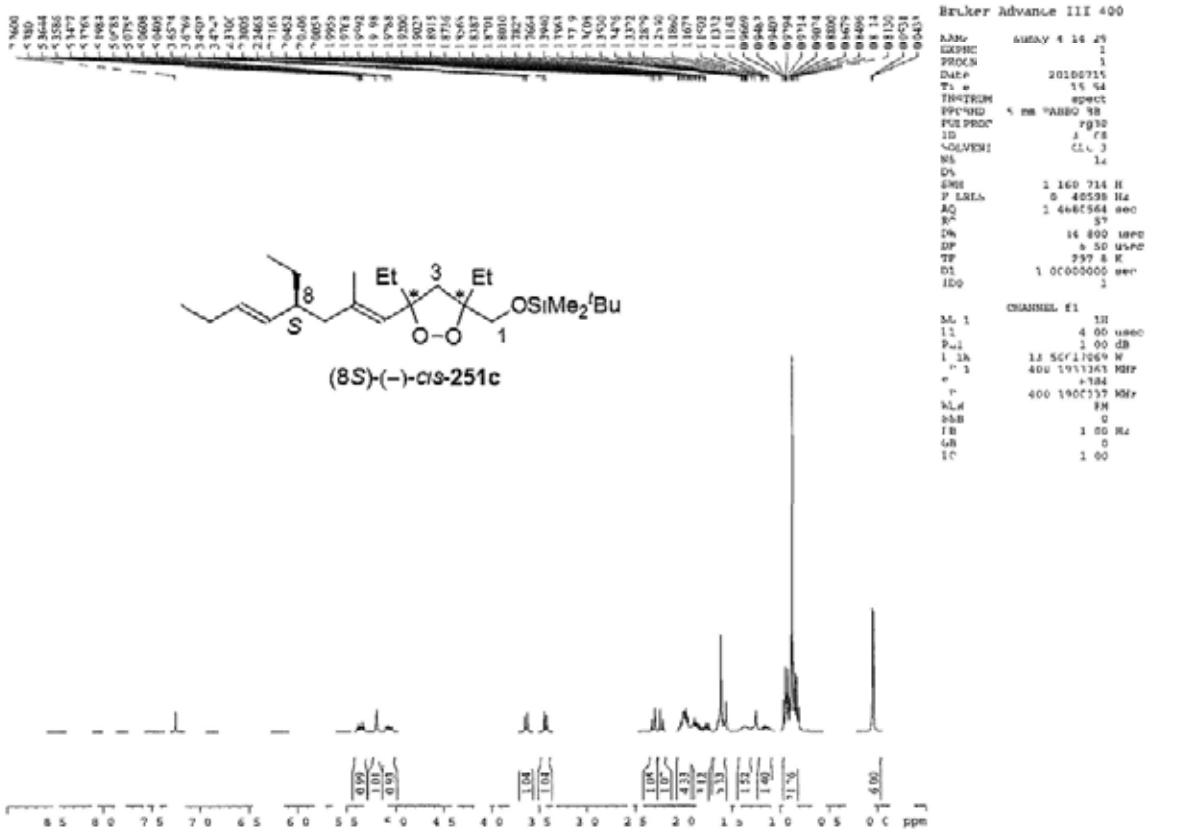


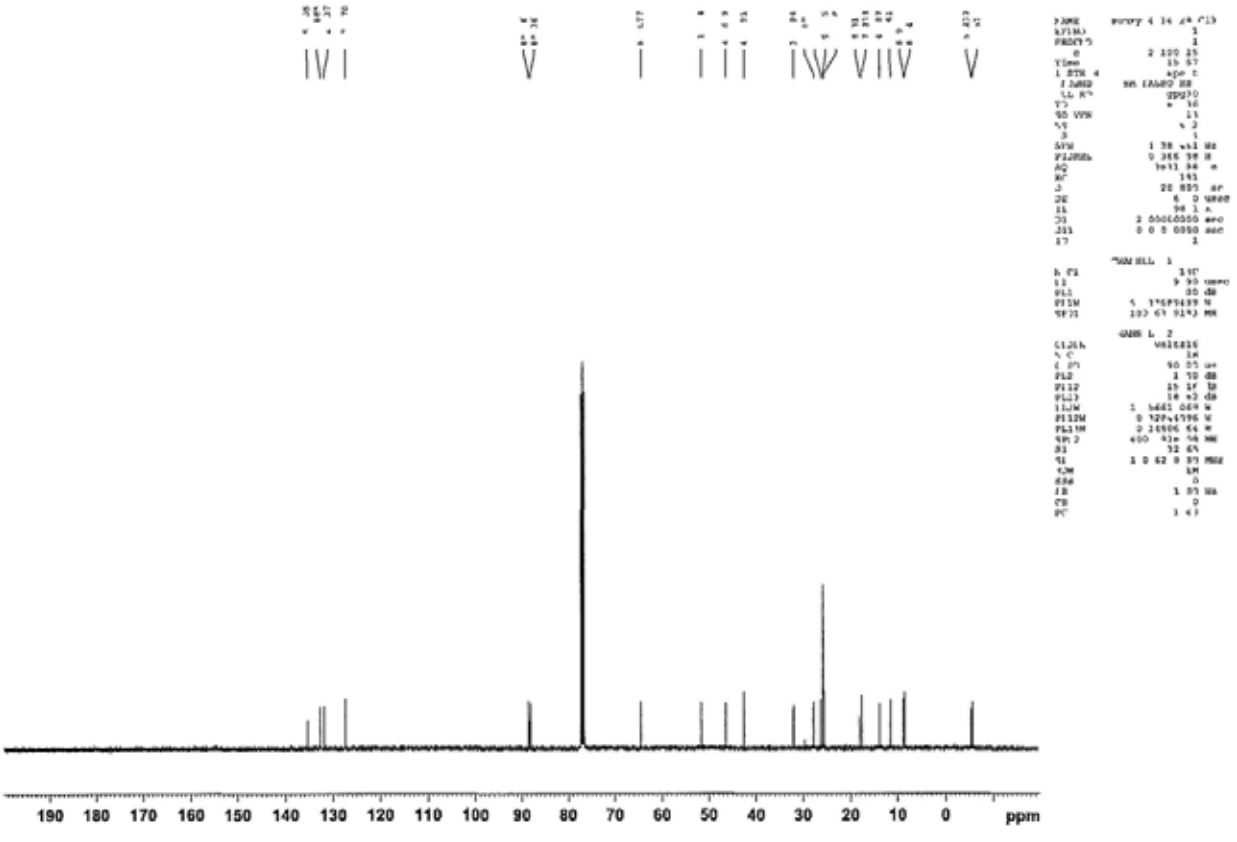


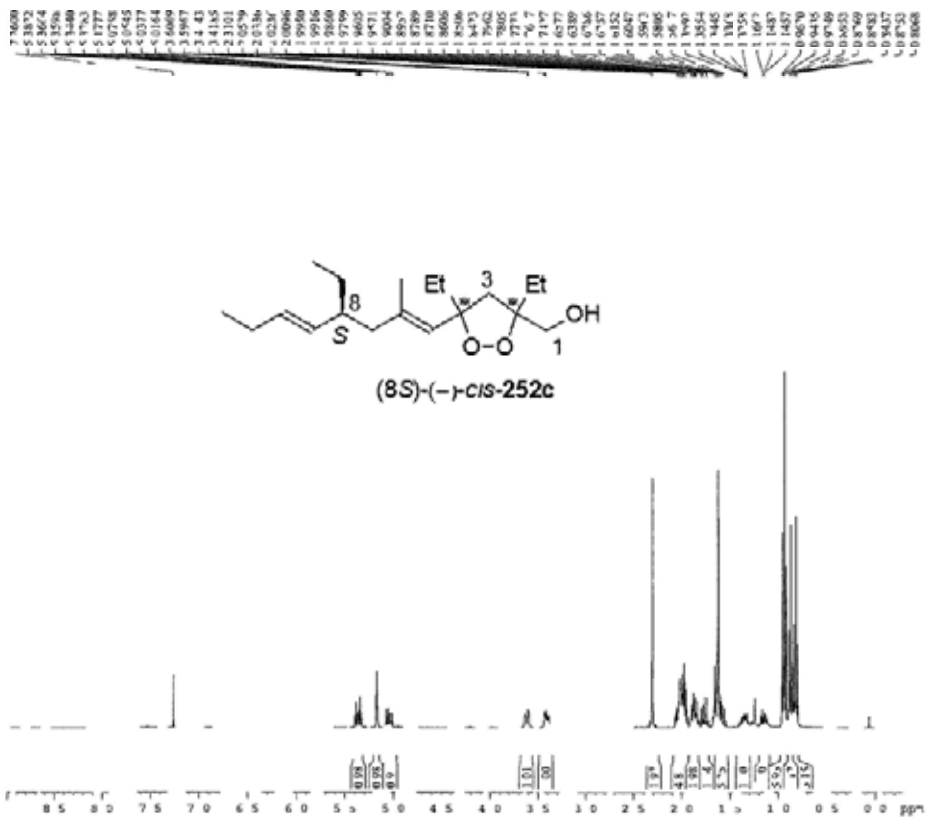
R-(+)-*cis*-**66b**



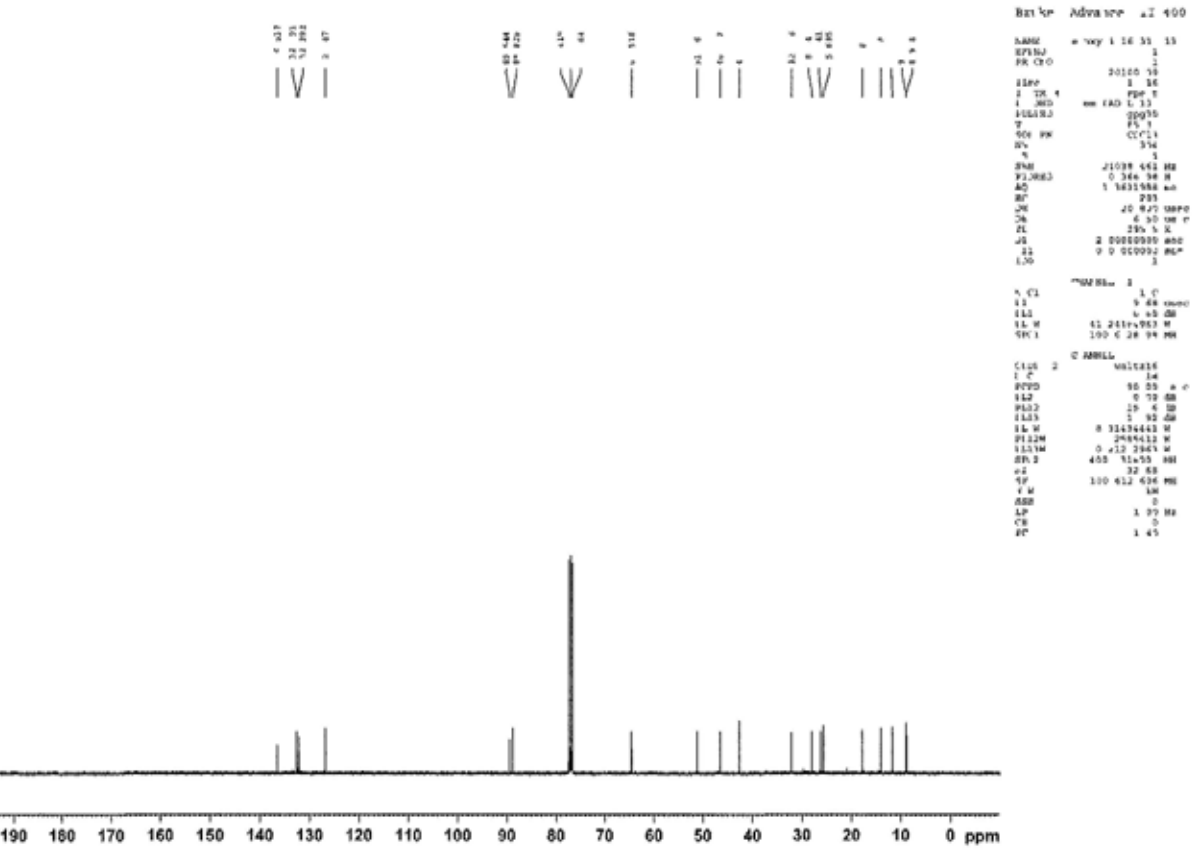


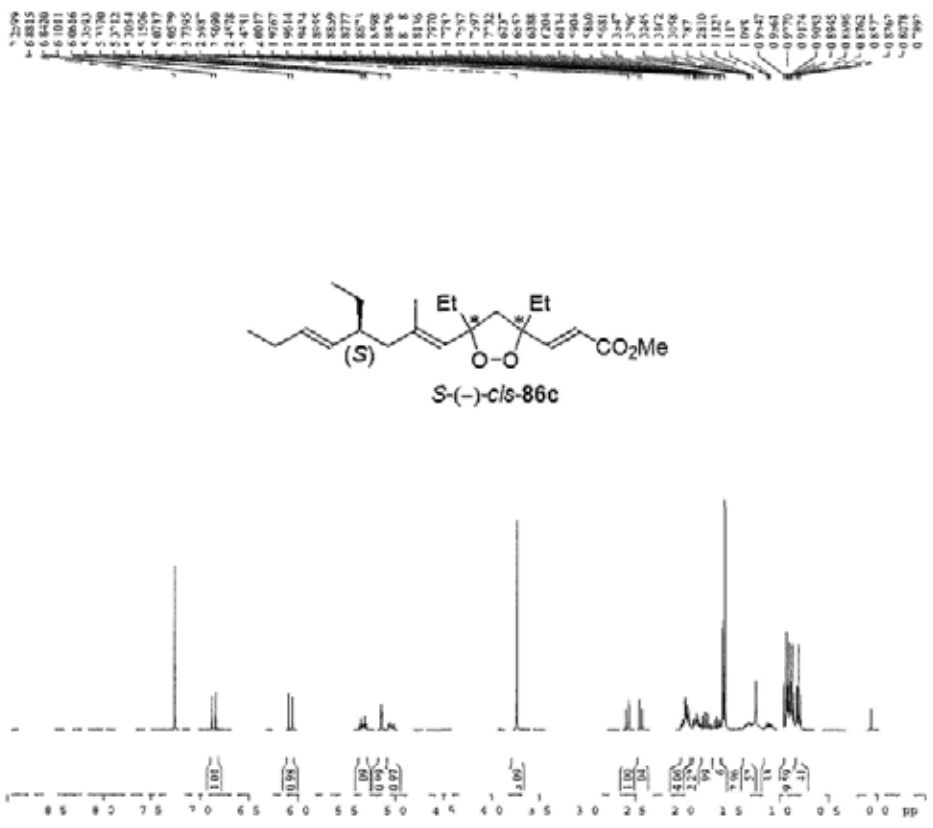

Et
3
Et
8
S
OSiMe2tBu
O–O
1
(8S)-(–)-cis-251c
Bruker Advance III 400
ppm


Bruker Advance III 400
ppm

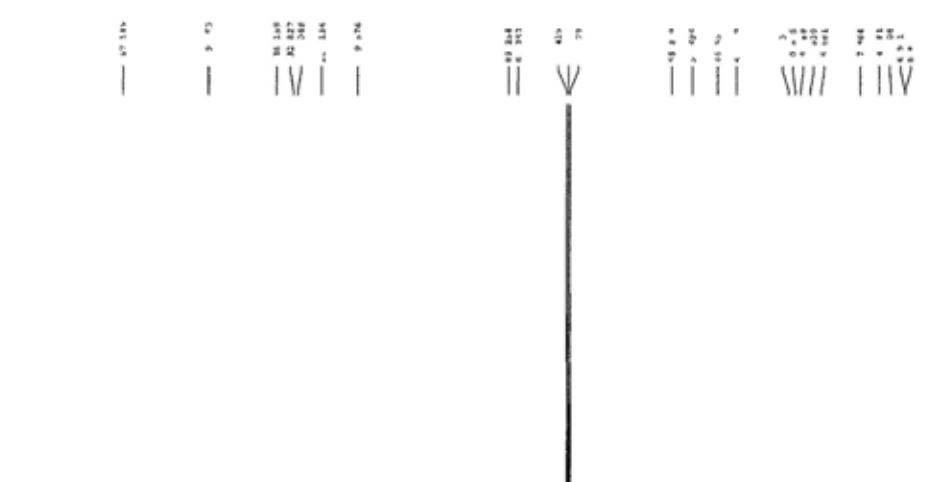


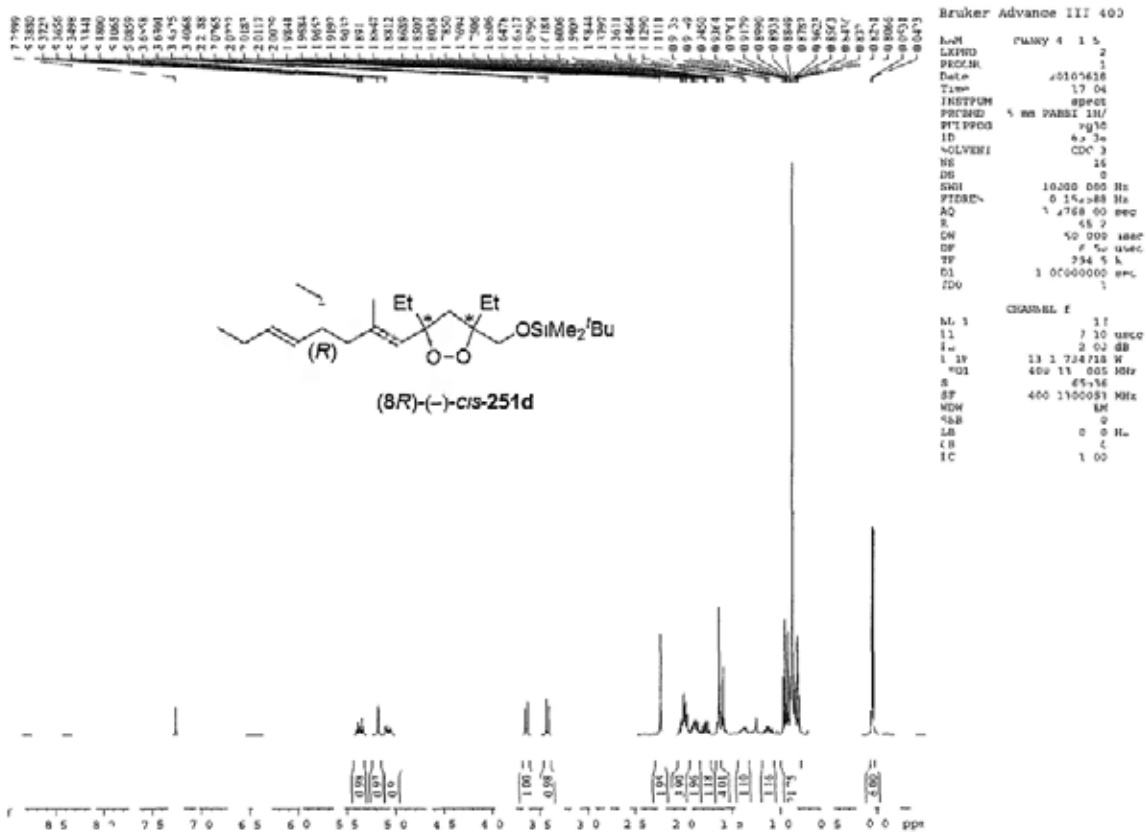
(8*S*)-(−)-*cis*-252c



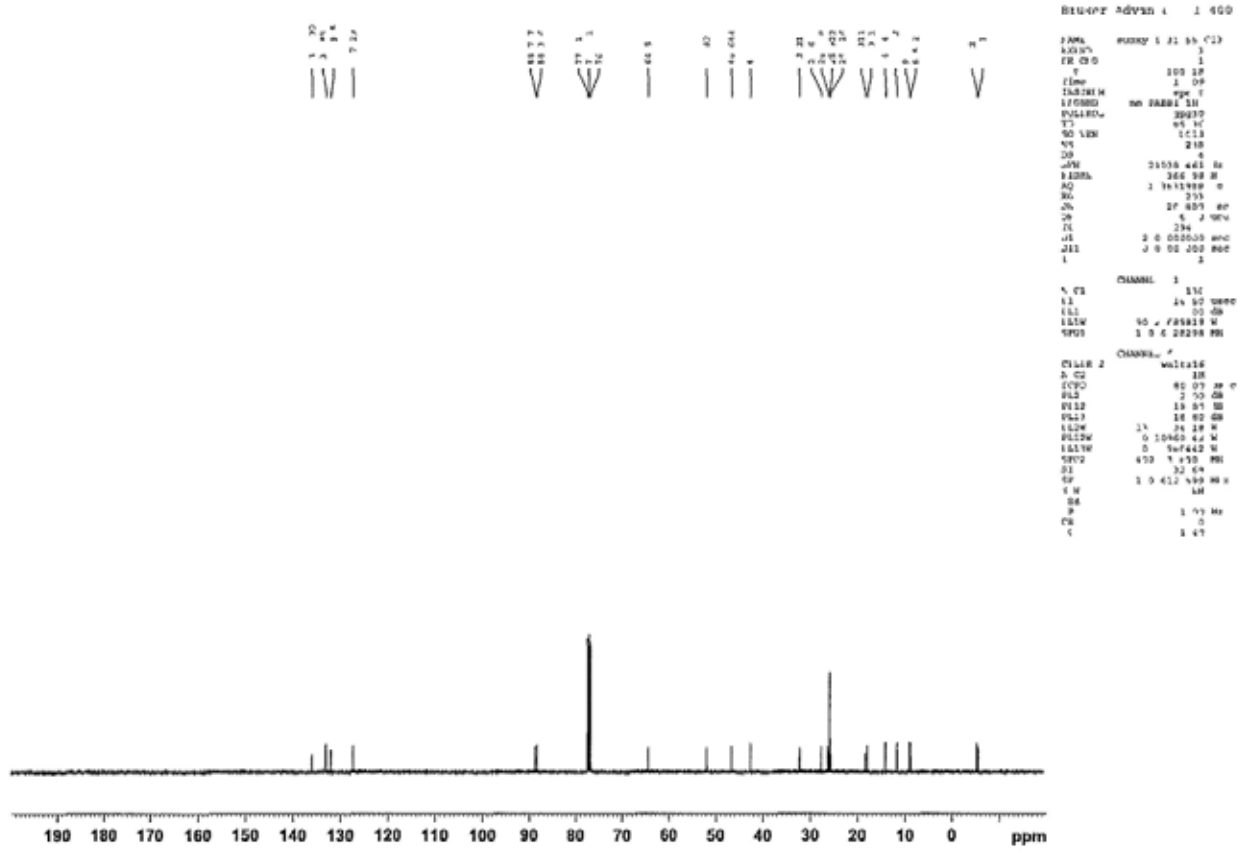


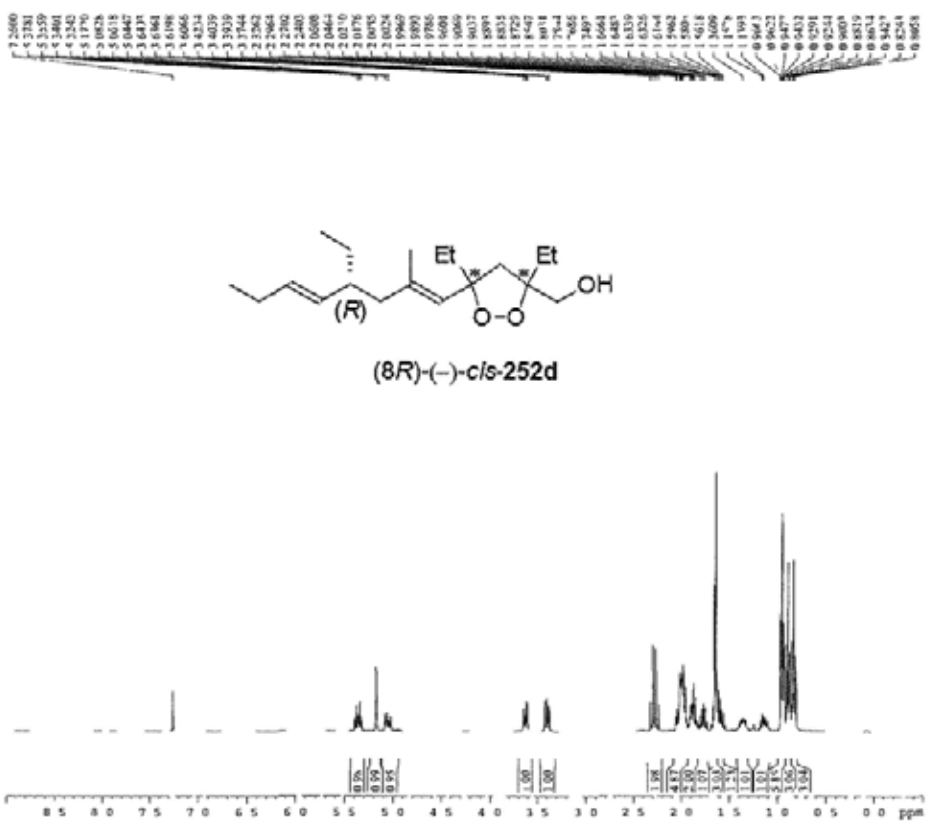
S-(−)-*cis*-86c



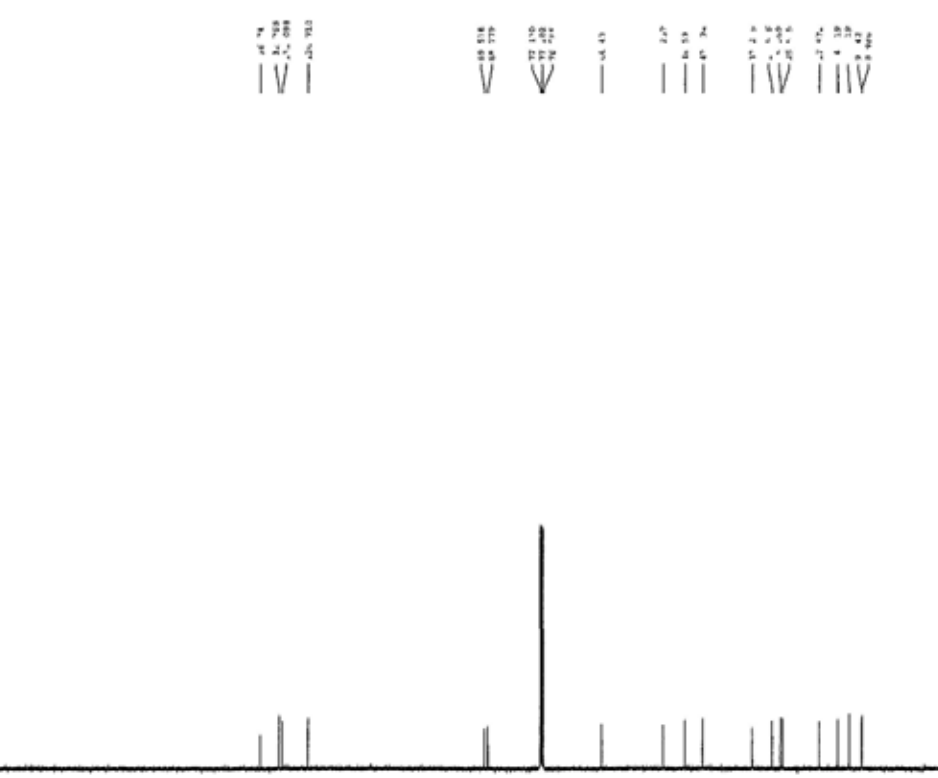

Et
Et
OSiMe2tBu
(R)
O–O
ppm

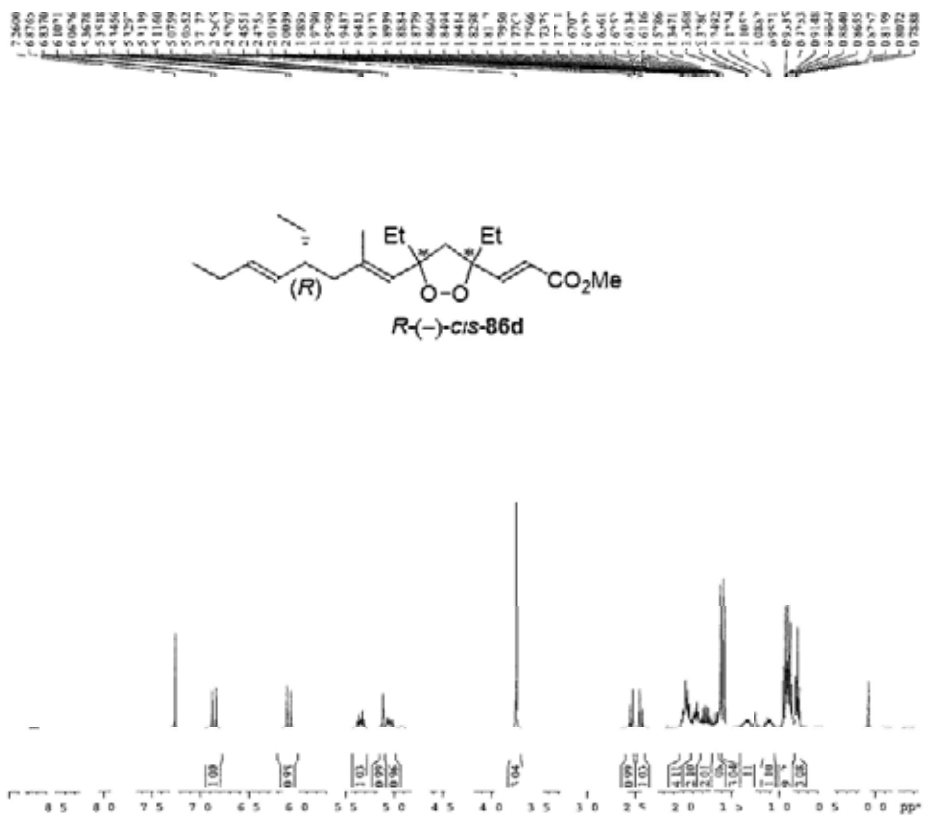
(8*R*)-(–)-*cis*-**251d**


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

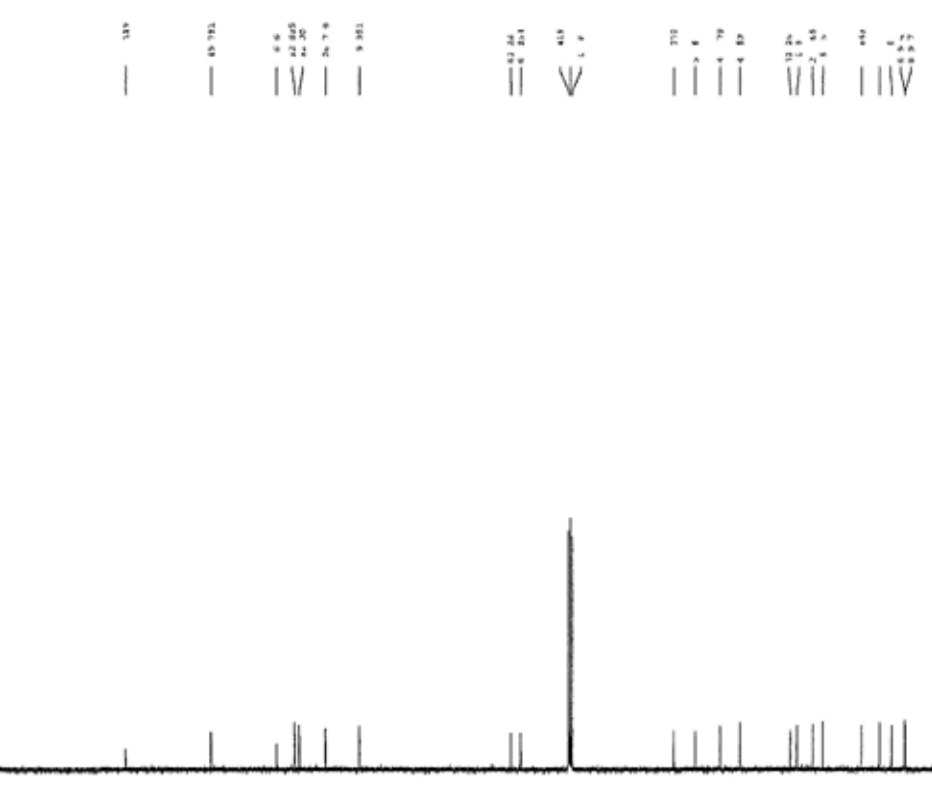


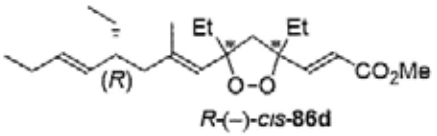
(8*R*)-(−)-*cis*-**252d**



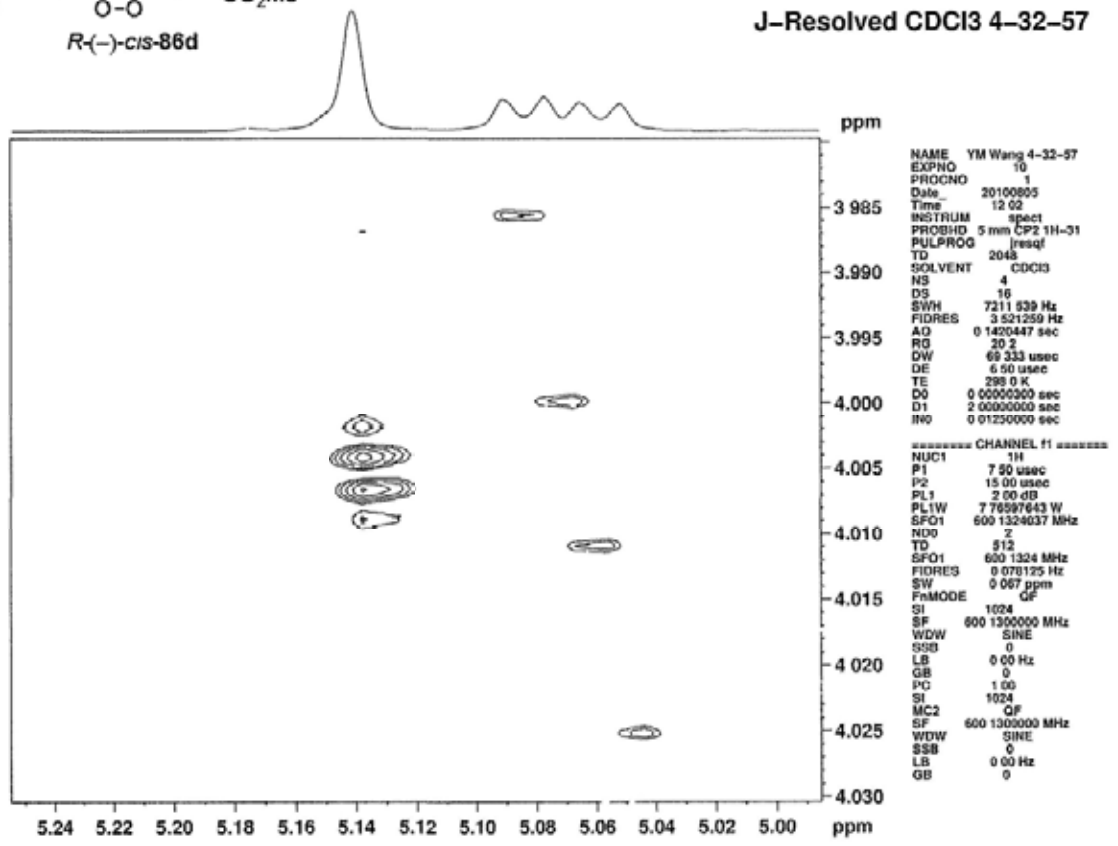


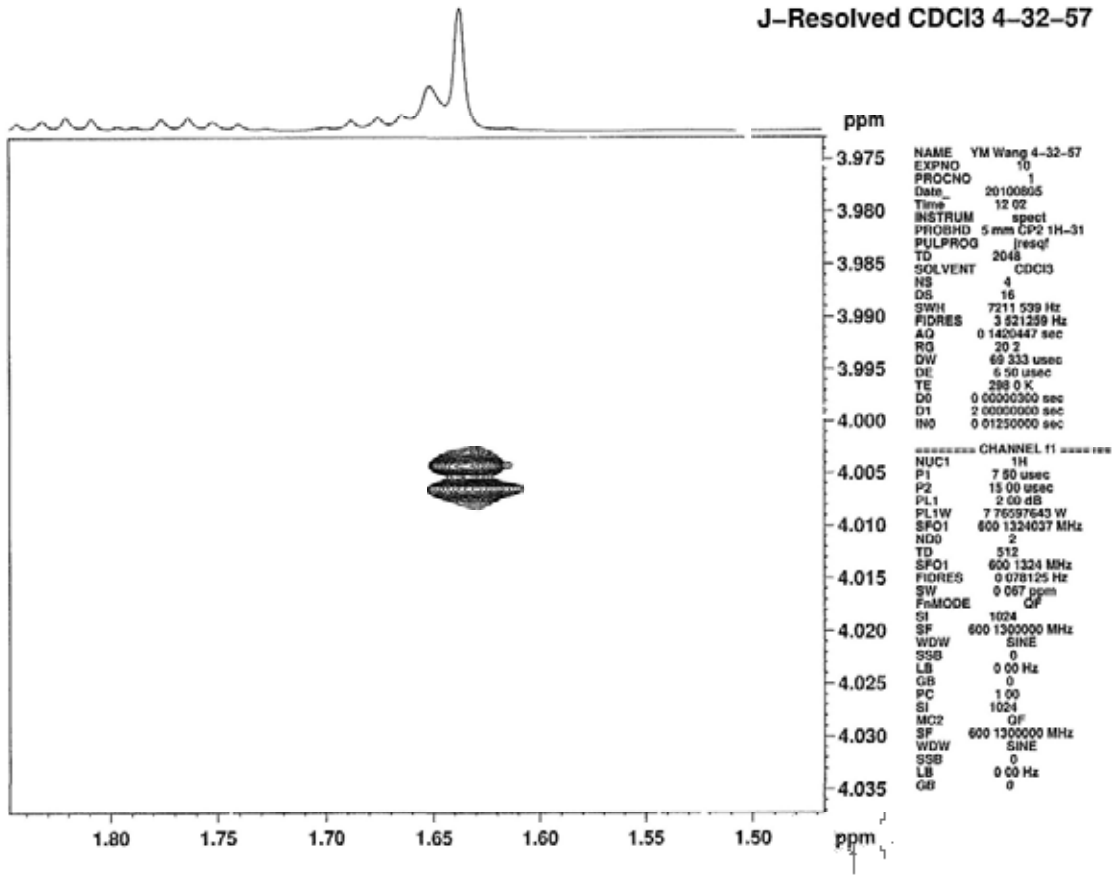
R-(–)-*cis*-**86d**

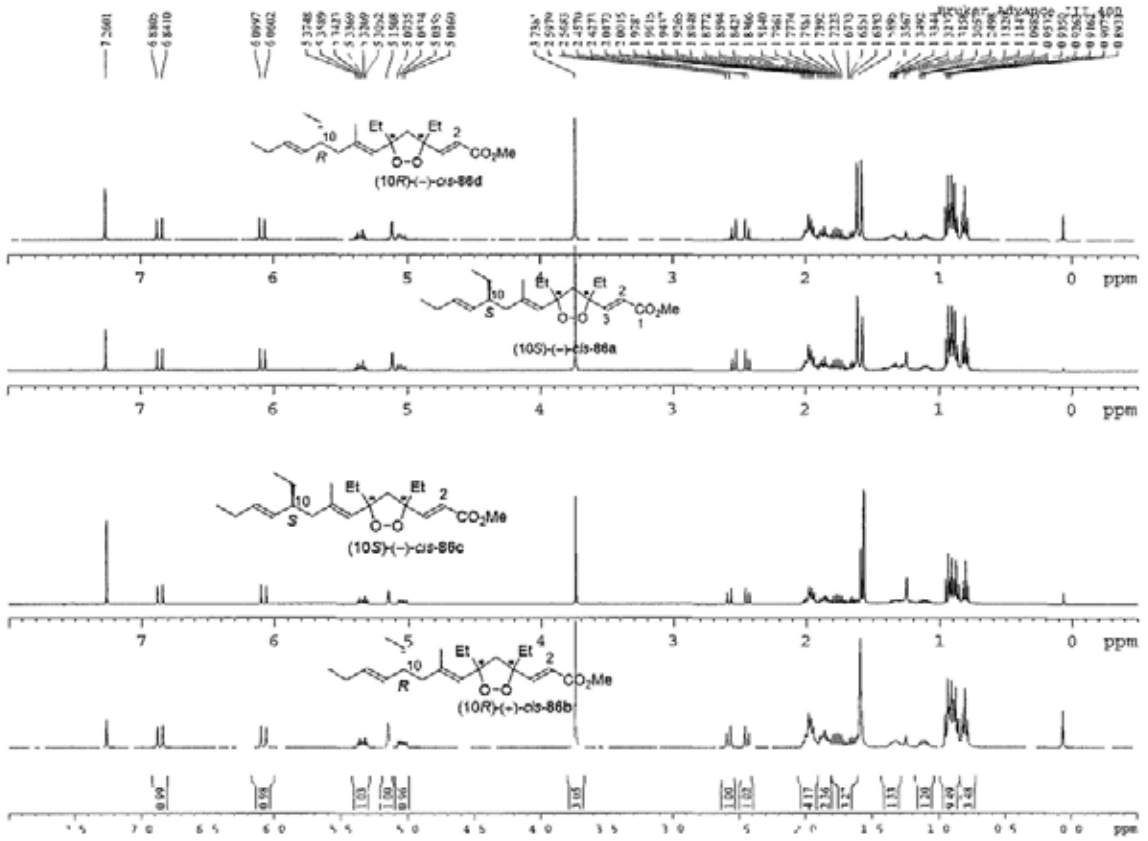


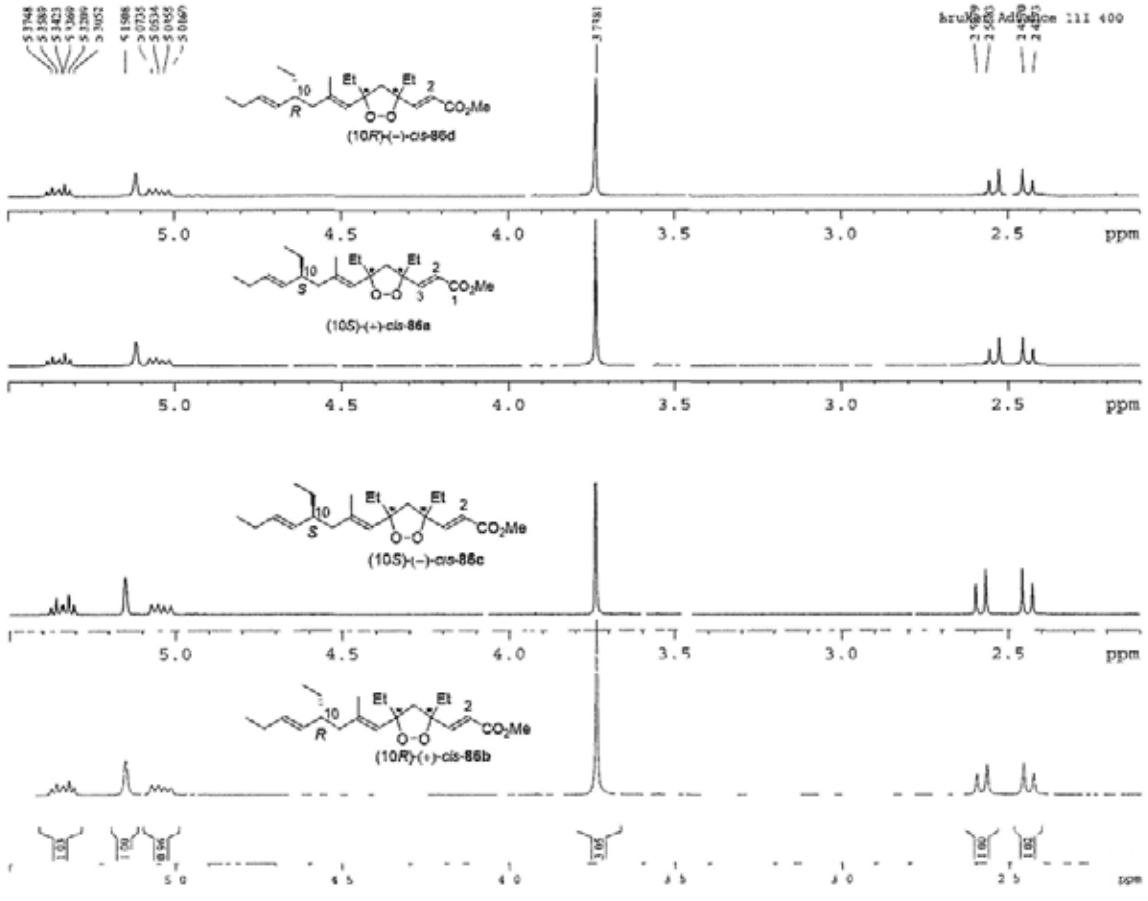

Et
Et
(R)
O-O
CO2Me

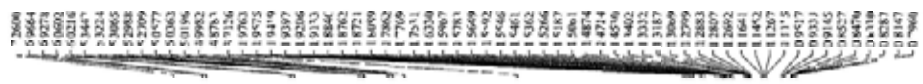
R-(−)-*cis*-**86d**

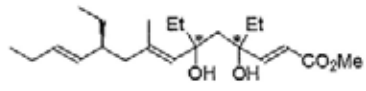

J-Resolved CDCl3 4-32-57
ppm
3.985
3.990
3.995
4.000
4.005
4.010
4.015
4.020
4.025
4.030
5.24 5.22 5.20 5.18 5.16 5.14 5.12 5.10 5.08 5.06 5.04 5.02 5.00 ppm
NAME YM Wang 4-32-57
EXPNO 10
PROCNO 1
Date_ 20100805
Time 12 02
INSTRUM spect
PROBHD 5 mm CP2 1H-31
PULPROG |resqf
TD 2048
SOLVENT CDCl3
NS 4
DS 16
SWH 7211 539 Hz
FIDRES 3 521259 Hz
AQ 0 1420447 sec
RG 20 2
DW 69 333 usec
DE 6 50 usec
TE 298 0 K
D0 0 00000300 sec
D1 2 00000000 sec
IN0 0 01250000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7 50 usec
P2 15 00 usec
PL1 2 00 dB
PL1W 7 76597643 W
SFO1 600 1324037 MHz
ND0 2
TD 512
SFO1 600 1324 MHz
FIDRES 0 078125 Hz
SW 0 067 ppm
FnMODE QF
SI 1024
SF 600 1300000 MHz
WDW SINE
SSB 0
LB 0 00 Hz
GB 0
PC 1 00
SI 1024
MC2 QF
SF 600 1300000 MHz
WDW SINE
SSB 0
LB 0 00 Hz
GB 0


J-Resolved CDCl3 4-32-57
ppm
3.975
3.980
3.985
3.990
3.995
4.000
4.005
4.010
4.015
4.020
4.025
4.030
4.035
1.80 1.75 1.70 1.65 1.60 1.55 1.50 ppm
NAME YM Wang 4-32-57
EXPNO 10
PROCNO 1
Date_ 20100805
Time 12 02
INSTRUM spect
PROBHD 5 mm CP2 1H-31
PULPROG |resqf
TD 2048
SOLVENT CDCl3
NS 4
DS 16
SWH 7211 539 Hz
FIDRES 3 521259 Hz
AQ 0 1420447 sec
RG 20 2
DW 69 333 usec
DE 6 50 usec
TE 298 0 K
D0 0 00000300 sec
D1 2 00000000 sec
IN0 0 01250000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7 50 usec
P2 15 00 usec
PL1 2 00 dB
PL1W 7 76597643 W
SFO1 600 1324037 MHz
ND0 2
TD 512
SFO1 600 1324 MHz
FIDRES 0 078125 Hz
SW 0 067 ppm
FnMODE QF
SI 1024
SF 600 1300000 MHz
WDW SINE
SSB 0
LB 0 00 Hz
GB 0
PC 1 00
SI 1024
MC2 QF
SF 600 1300000 MHz
WDW SINE
SSB 0
LB 0 00 Hz
GB 0

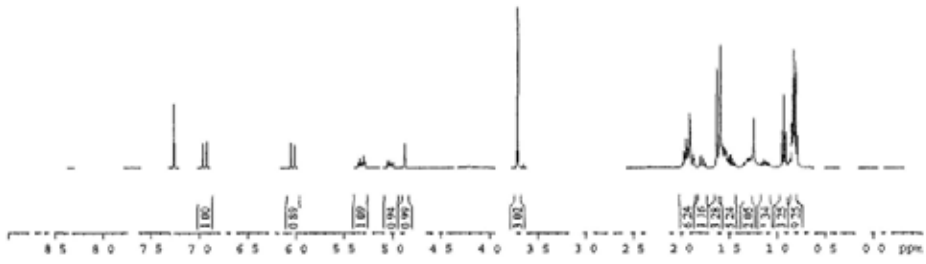

(10R)-(−)-cis-86d
(10S)-(−)-cis-86a
(10S)-(−)-cis-86c
(10R)-(+)-cis-86b
ppm

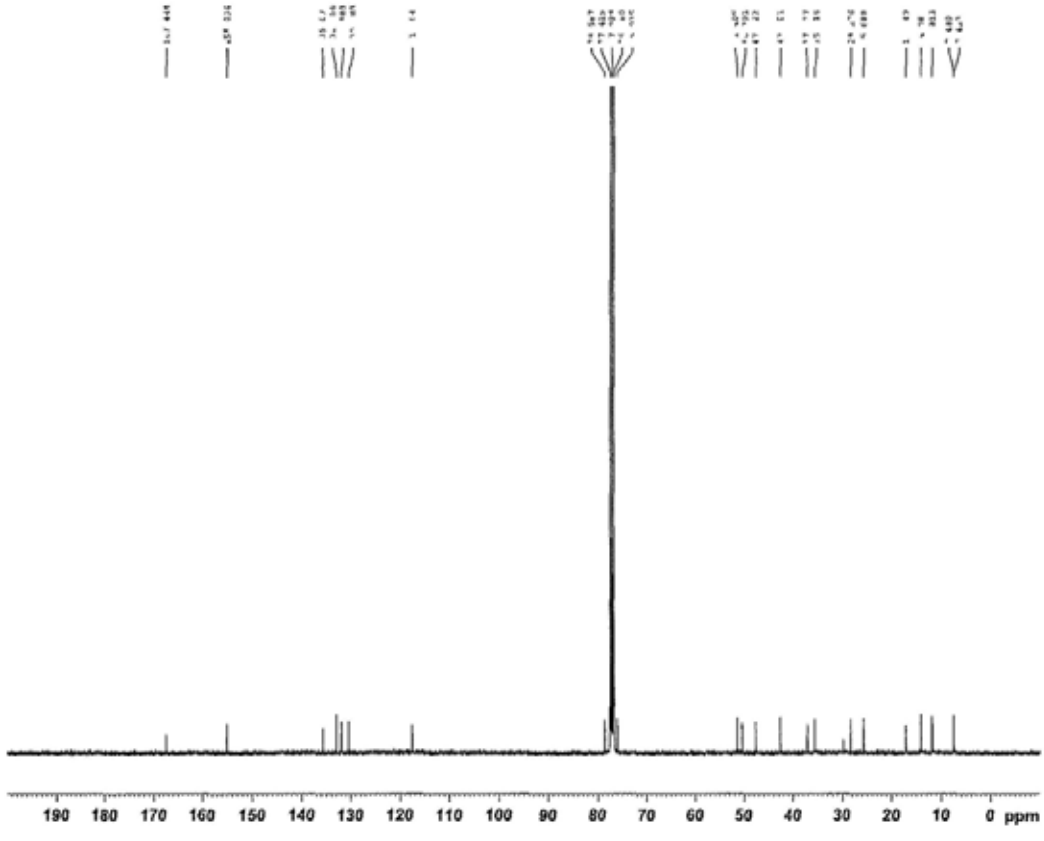

(10R)-(−)-cis-86d
(10S)-(+)-cis-86a
(10S)-(−)-cis-86c
(10R)-(+)-cis-86b
ppm

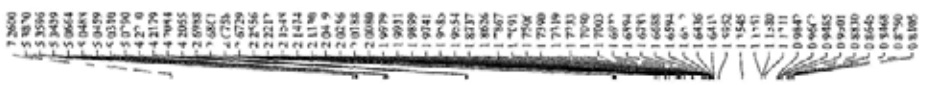


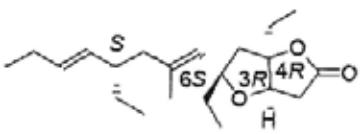

Et
Et
OH
OH
CO2Me

S-(+)-*cis*-268a

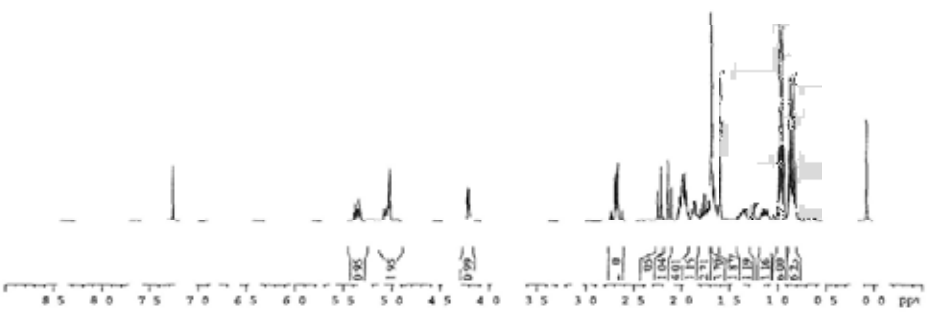

85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 05 00 ppm

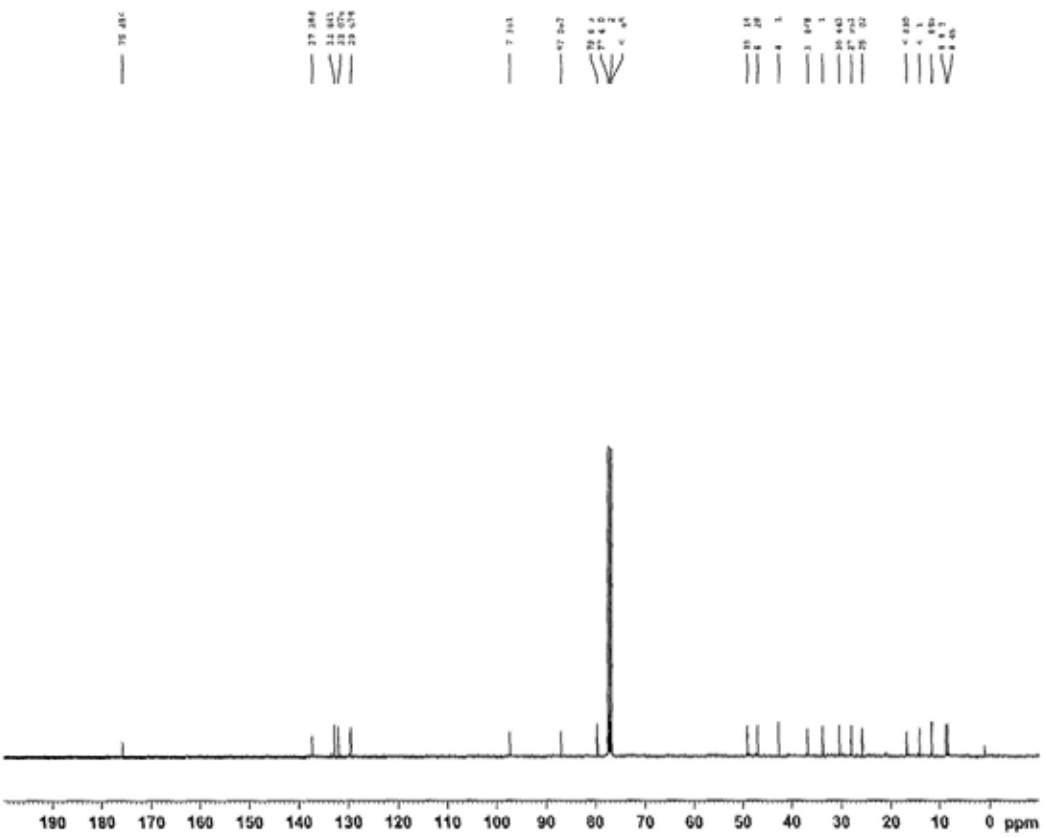

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

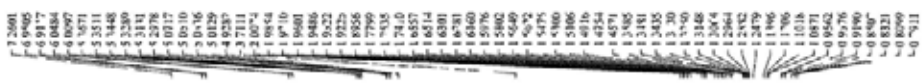


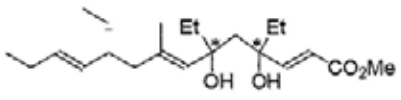


(3*R*,4*R*,6*S*,10*S*)-***ent*-87a**

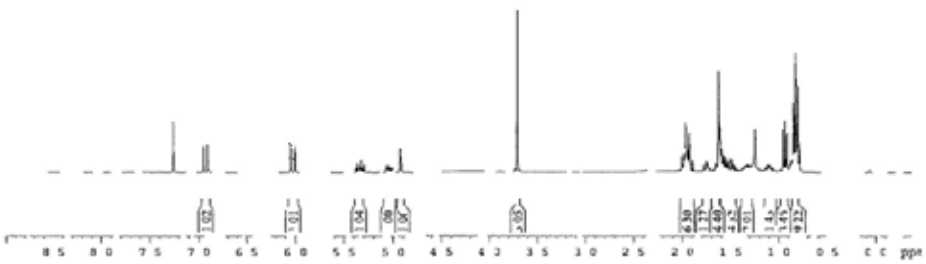


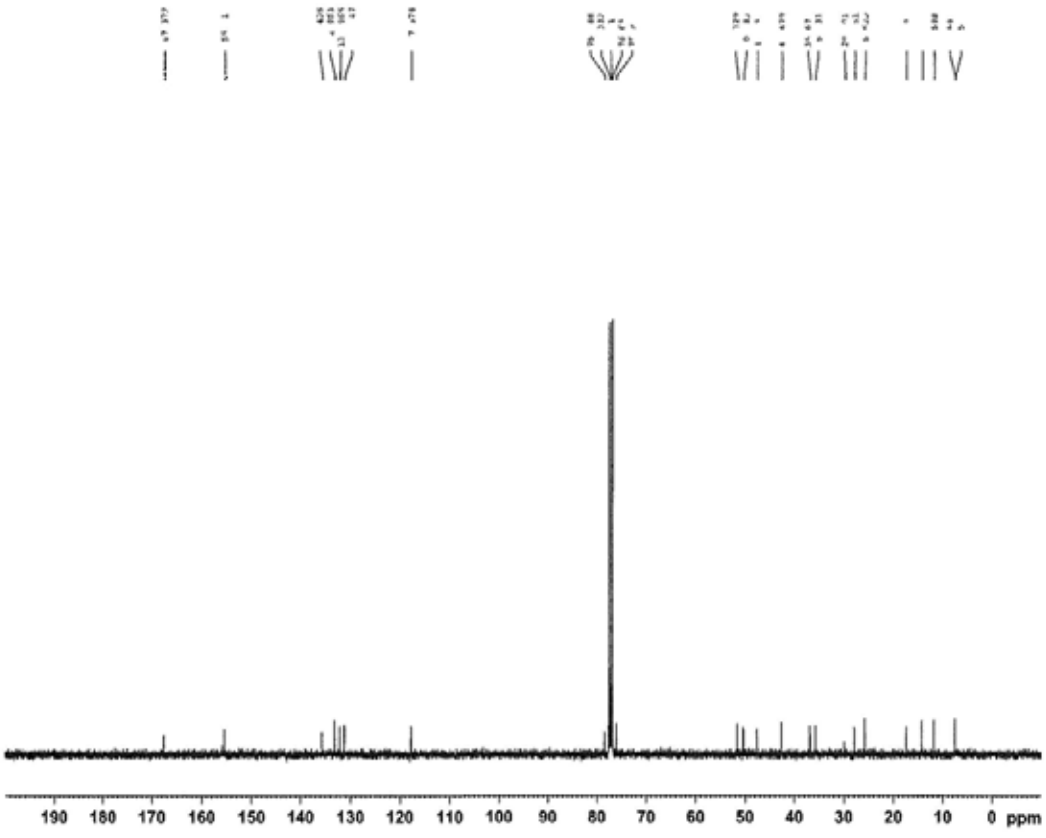


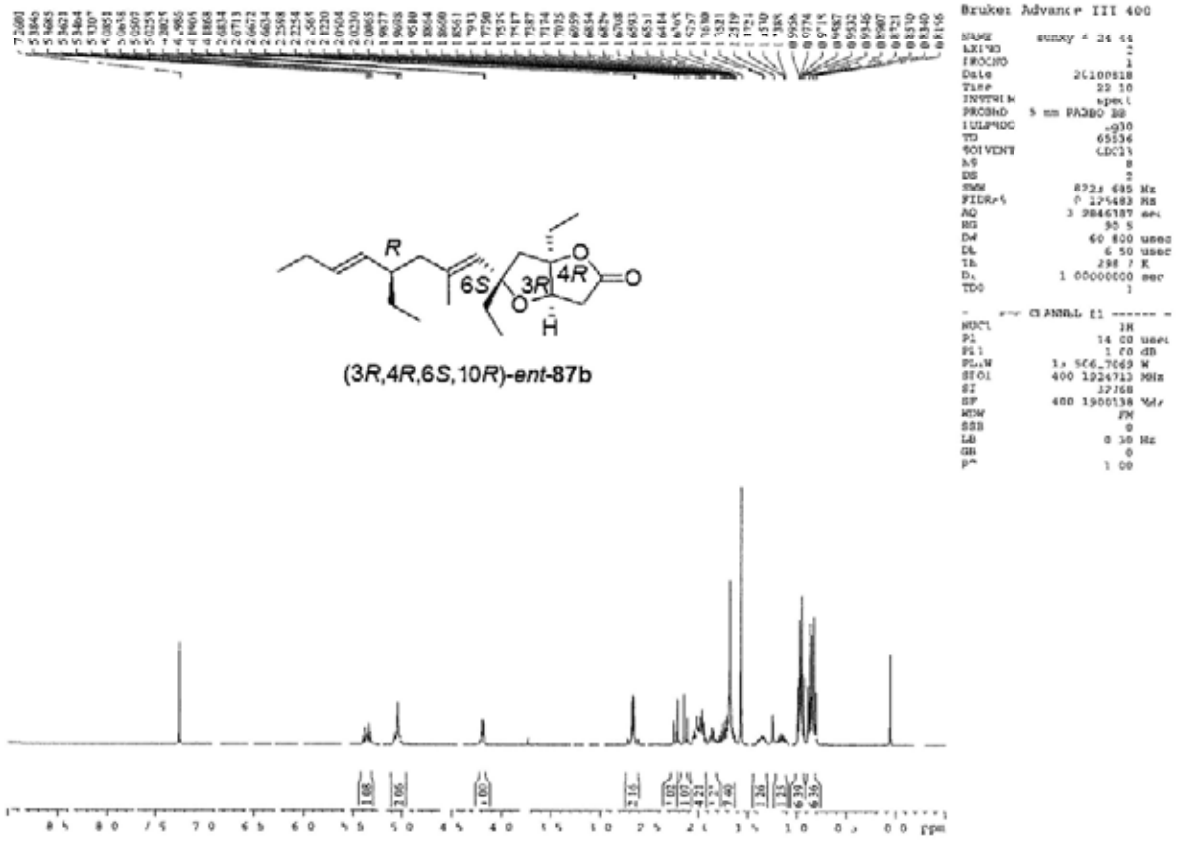




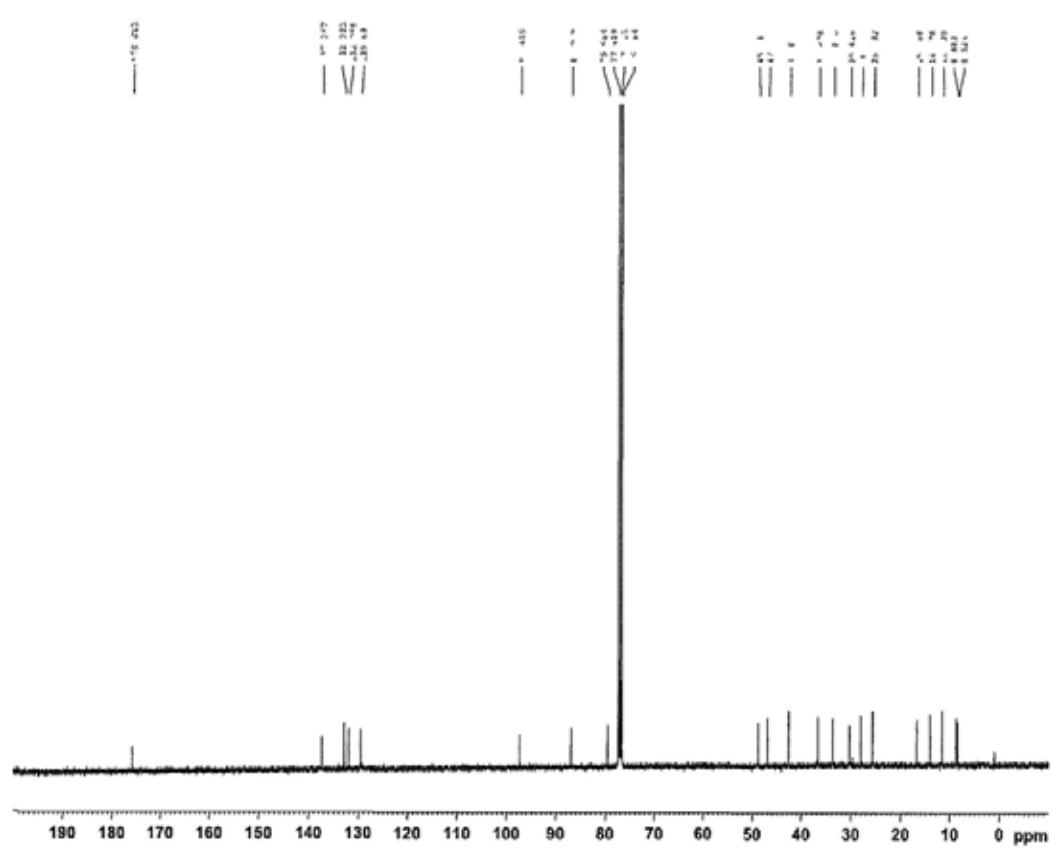
R-(+)-*cis*-268b

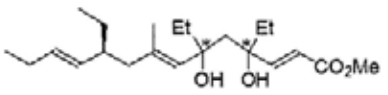




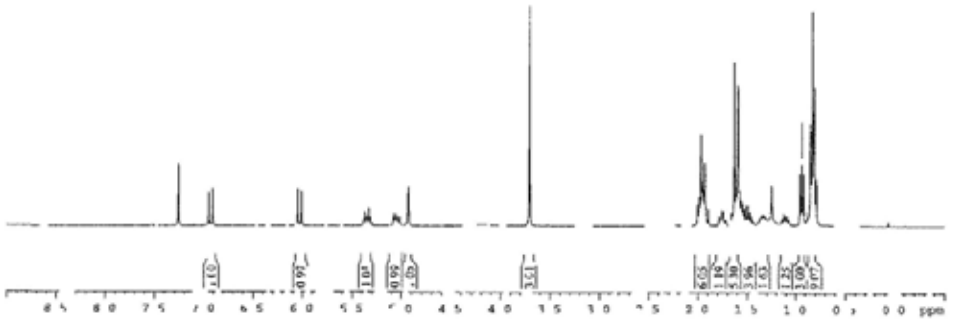


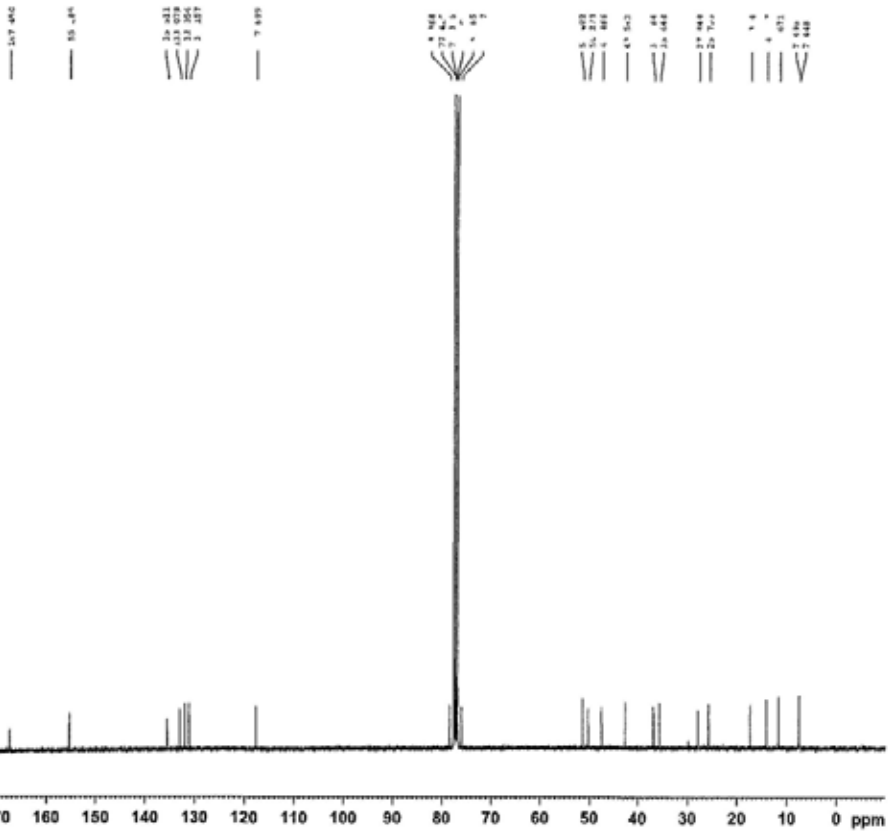
(3*R*,4*R*,6*S*,10*R*)-*ent*-87b

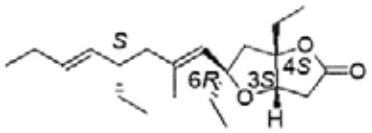




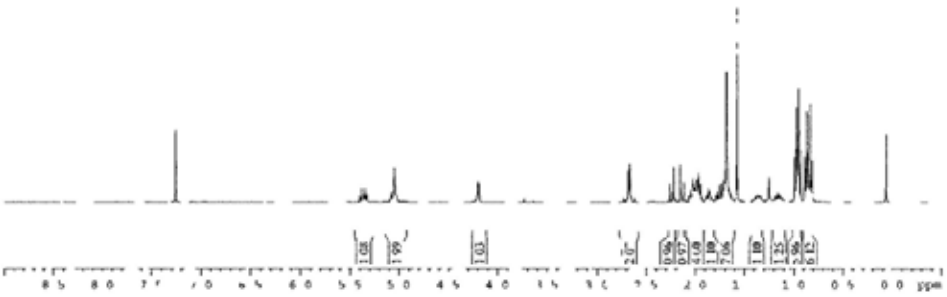
S-(−)-*cis*-268c

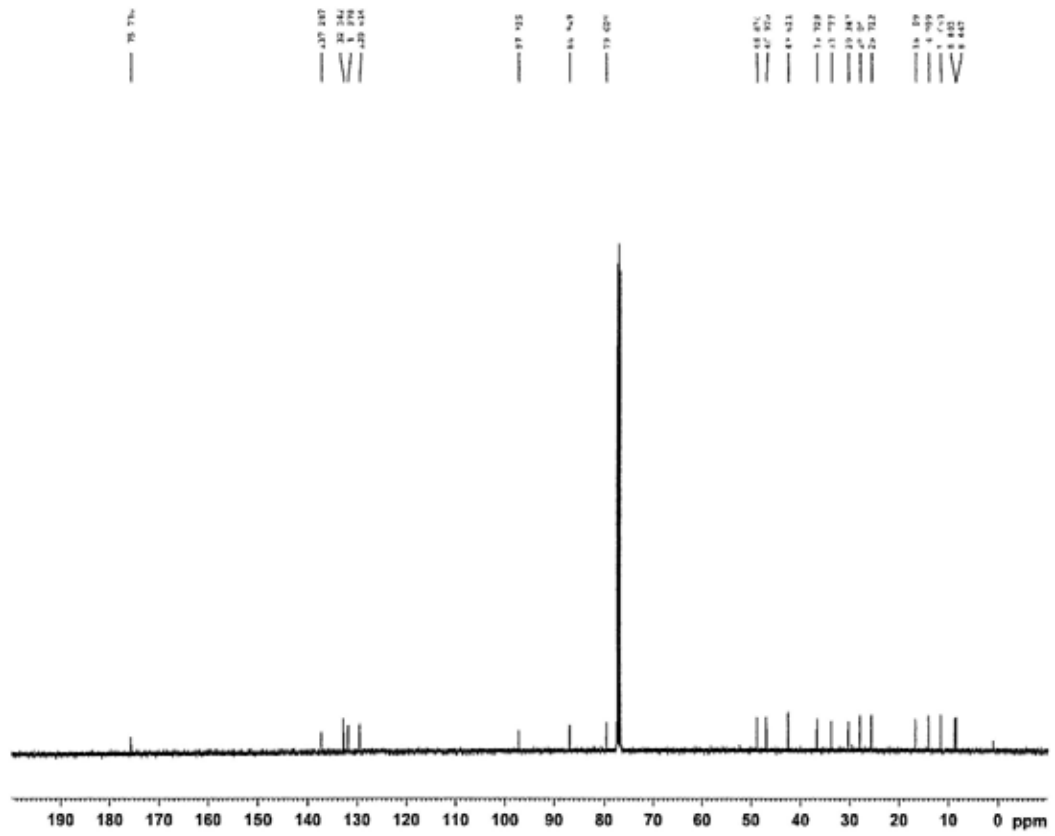


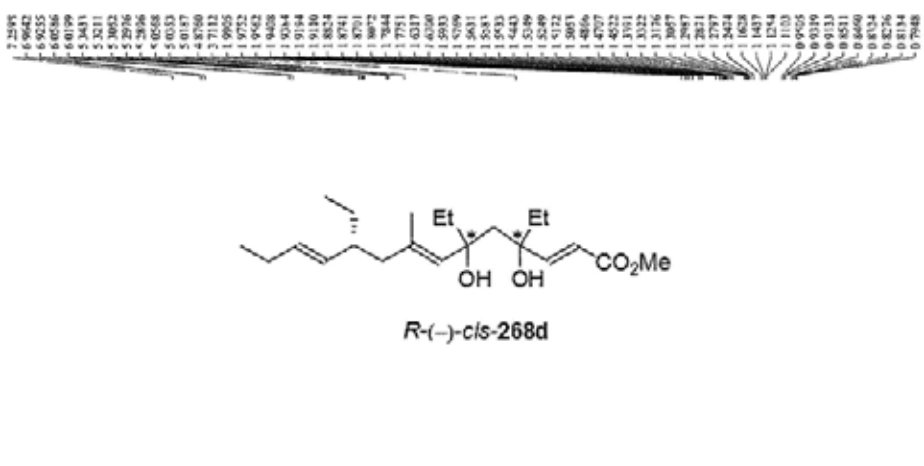




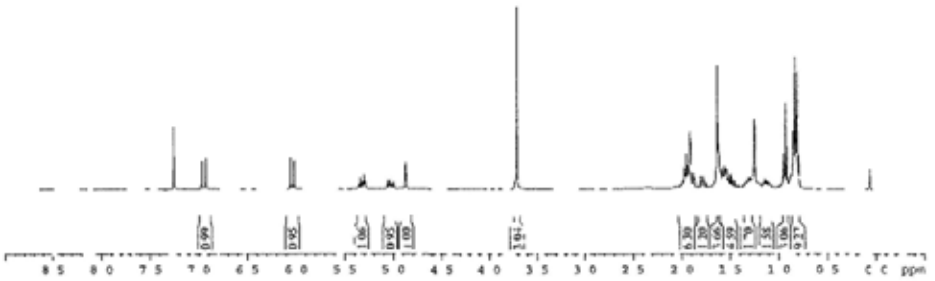
(3*S*,4*S*,6*R*.10*S*)-87b

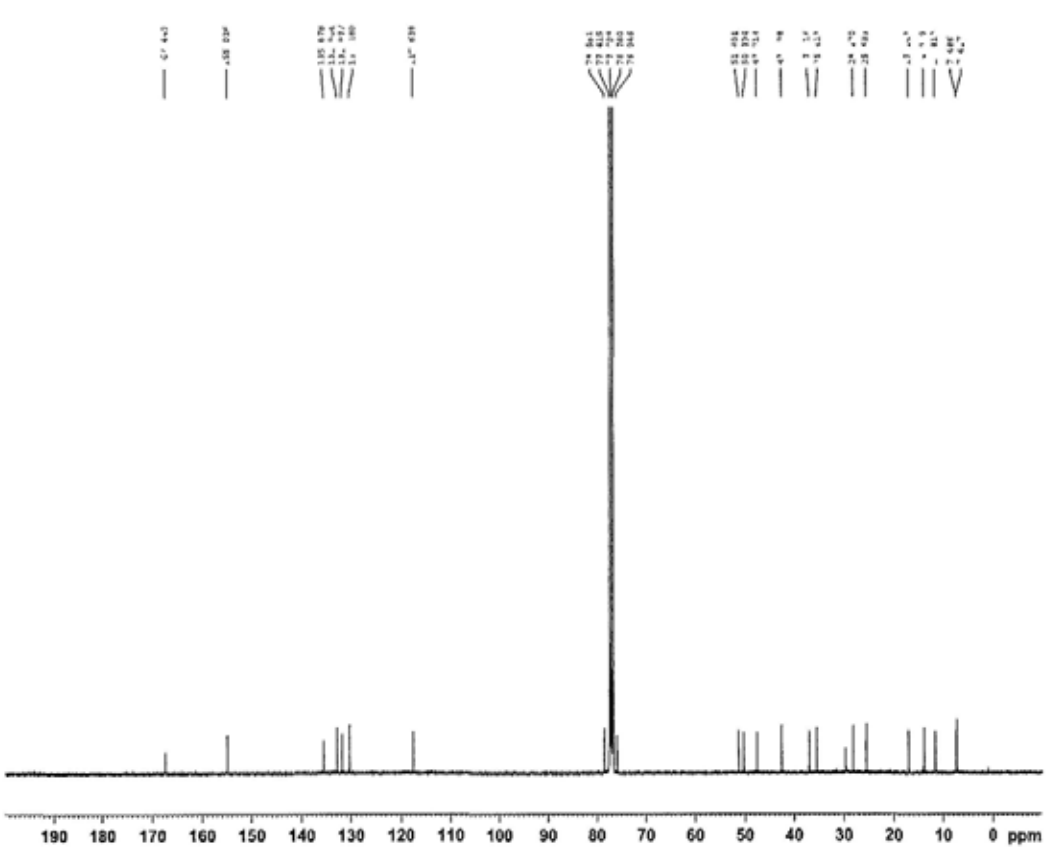


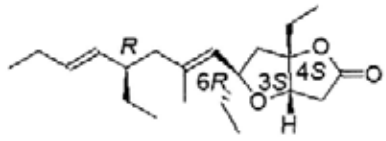




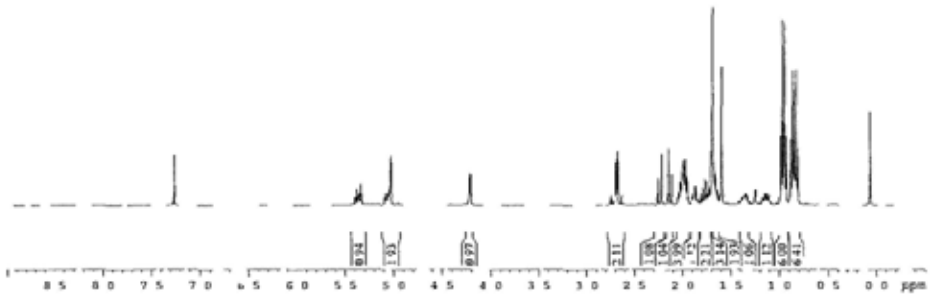
R-(–)-*cis*-**268d**

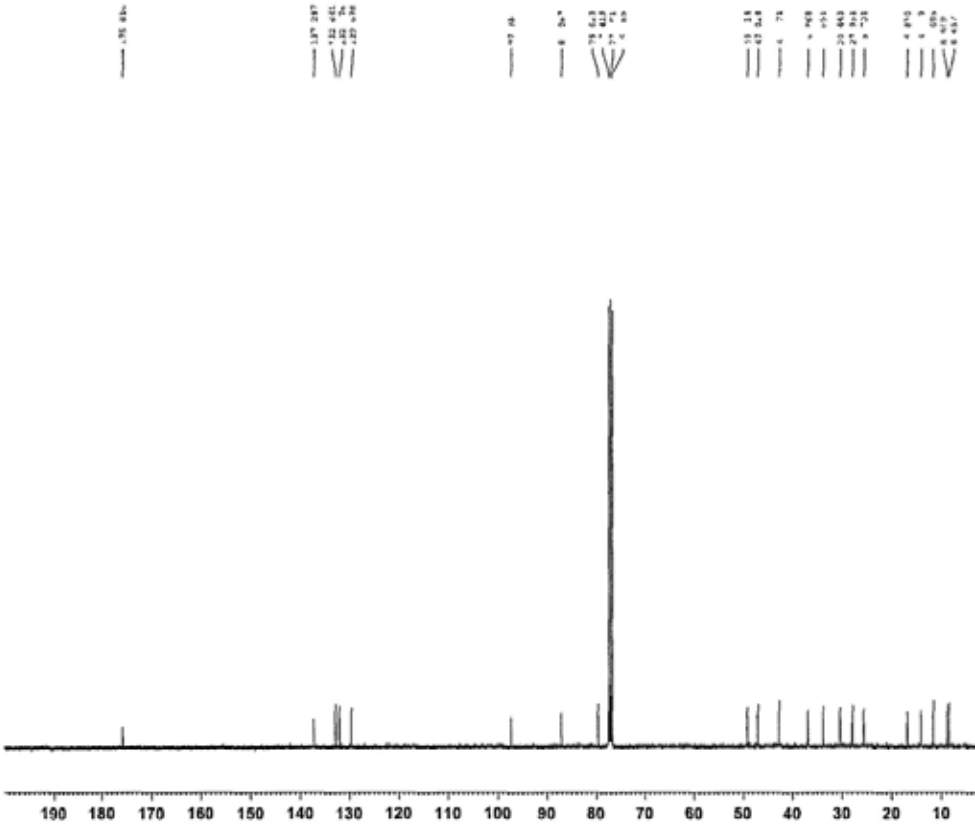


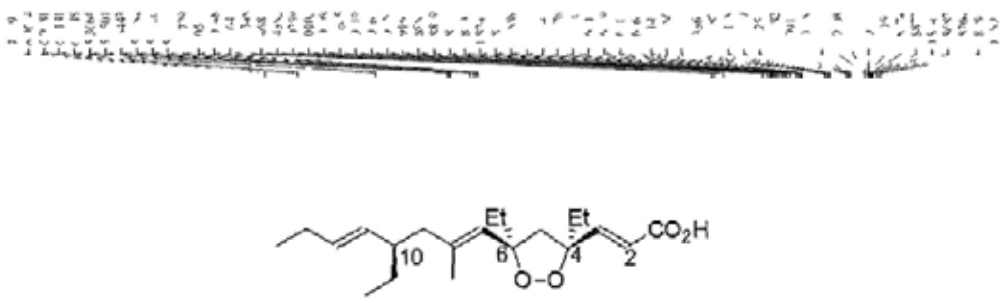




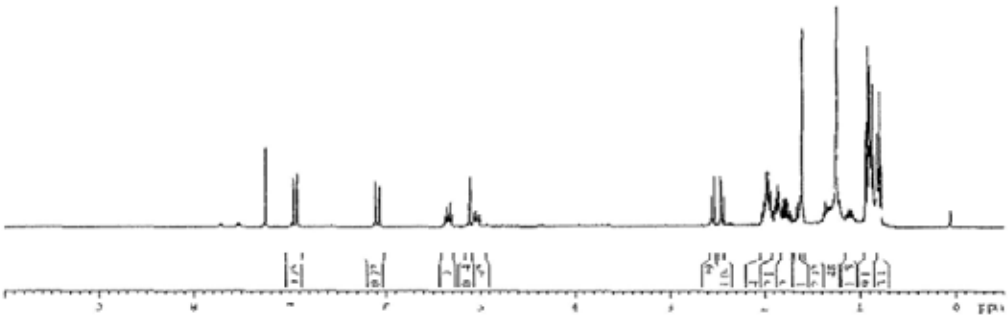
(3*S*,4*S*,6*R*,10*R*)-Plakortone B (**87a**)

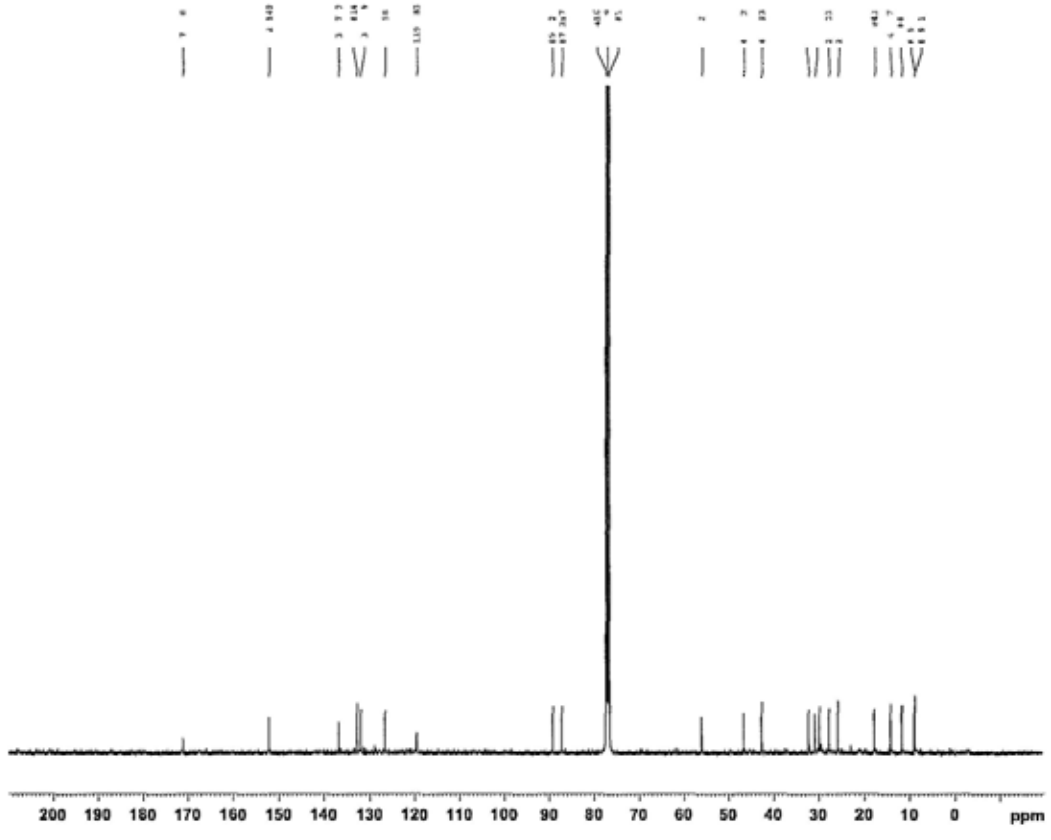






(4*S*,6*R*,10*R*)-Plakortide E (85a)

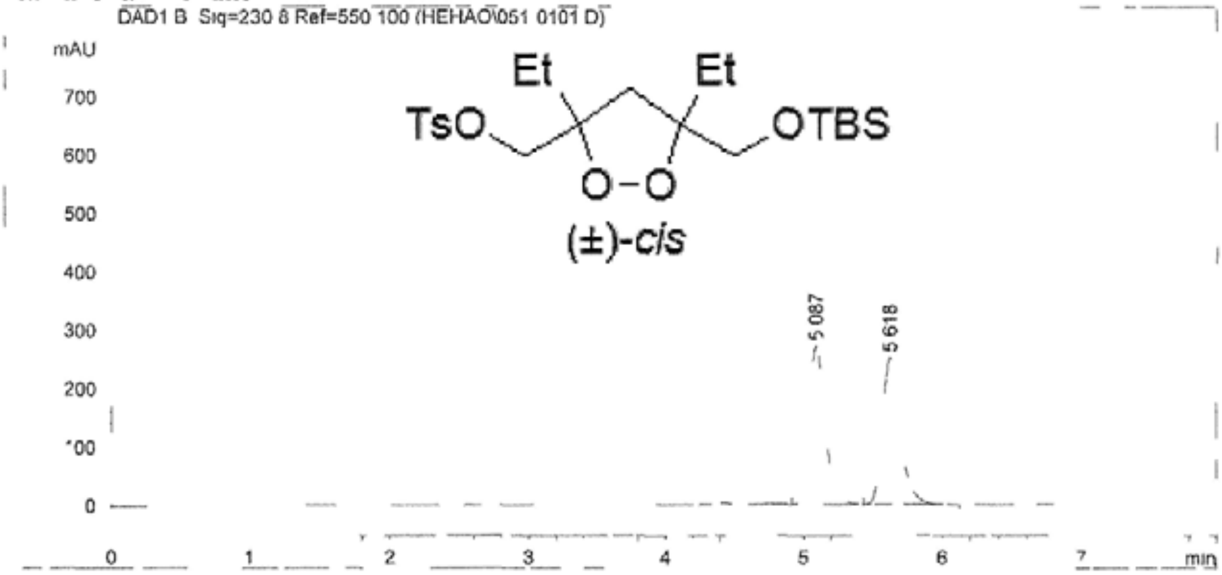




Data File C:\HPCHEM\1\DATA\HEHAO\051-0101.D   Sample Name: cis TO-OTs rac

MP 95 Hexane 5 IPA   Flow 1.0ml/min
column ~~[illegible]~~ \-H
CHIRALPAK

Injection Date : 3/1/04 2:52:44 PM   Seq. Line :
Sample Name : ts TO-cis_rac   Location : Vial 1
Acq. Operator : gr   Inj : 1
Acq. Instrument : Instrument 1   Inj Volume : 20 µl
Acq. Method : C:\HPCHEM\1\METHODS\SAM-2012.M
Last changed : 3/1/04 1:36:35 PM by gr
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\SAM-2012.M
Last changed : 1/29/04 2:13:30 PM by SAM
(modified after loading)
Enantioselective HPLC Method
Channel A:
Channel B: hexane



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=230,8 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.087	VV	0.2498	2249.16224	271.1382	49.9087
2	5.618	VB	0.1368	2257.39478	251.2930	50.0913

Totals : 4506.56201 522.49167

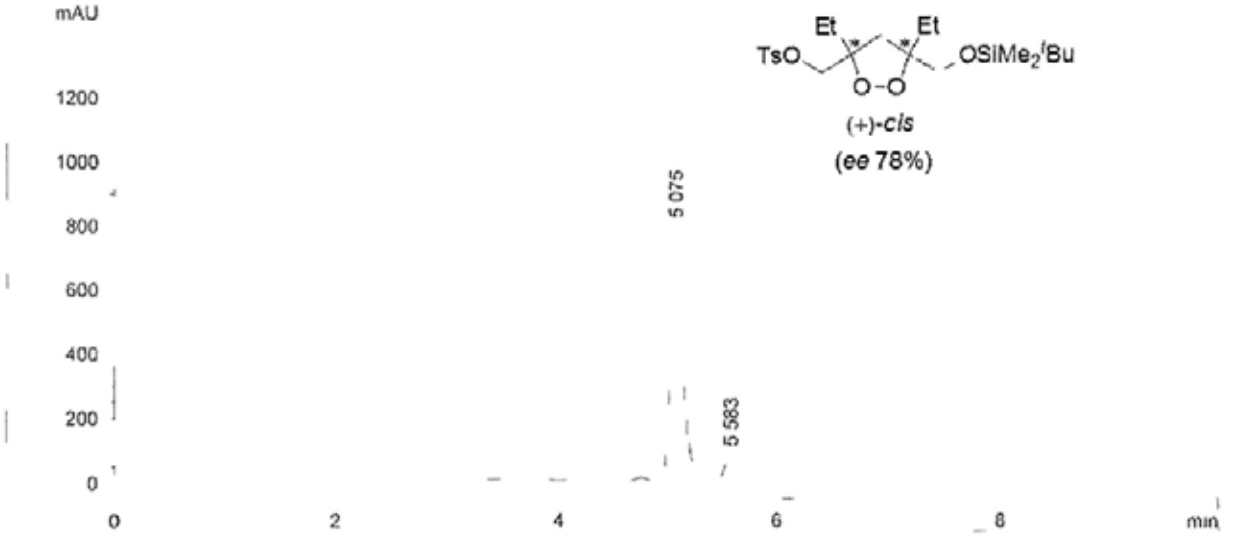
Results obtained with enhanced integrator!

*** End of Report ***

sunxy-3-132

CHIRALPAK

DAD1 B, Sig=230,8 Ref=550,100 (HEHAO\021 0101.D)



(+)-*cis*

(*ee* 78%)

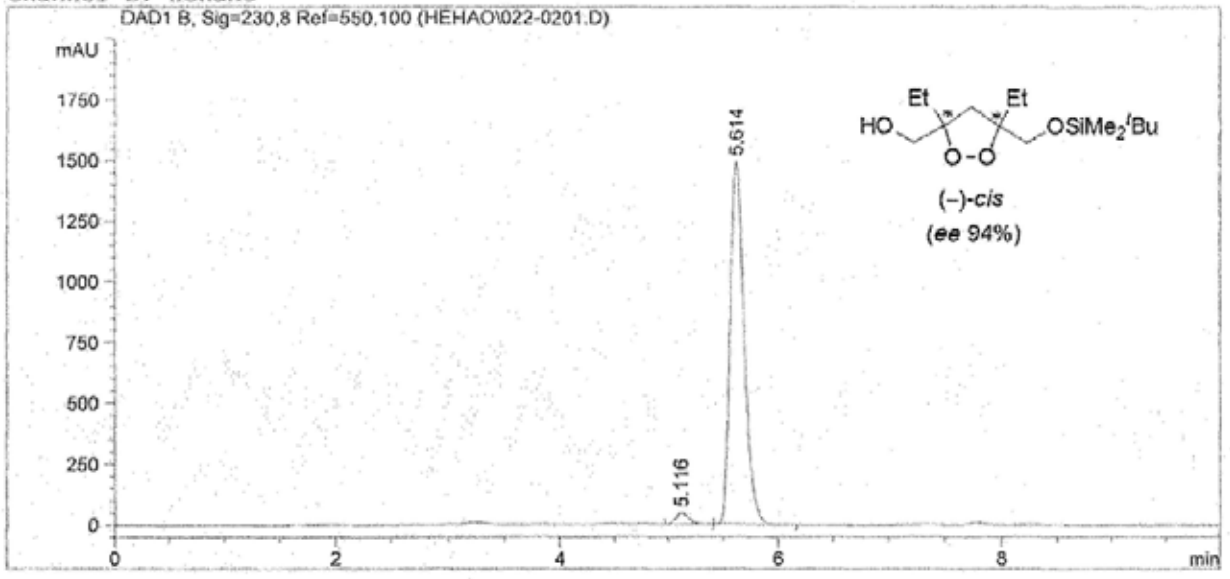
Signal
1.0000
1.0000

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.075	BV	0.1216	6089.63518	800.46634	49.1627
2	5.583	VB	0.1418	6297.18127	781.93552	50.8373
Total				12386.81645	1582.40186	

MP: 95% Hexane : 5% IPA Flow: 1.0ml/min
Column: CHIRALPAK AD-H

sunxy-3-135

Injection Date : 8/25/2009 2:05:46 PM Seq. Line : 2
Sample Name : XYSun_135 Location : Vial 22
Acq. Operator : SAM Inj : 1
Acq. Instrument : Instrument 1 Inj Volume : 20 µl
Acq. Method : I:\HPLC\METHODS\SAM-POT2.M
Last changed : 8/10/2009 12:50:39 PM by SAM
Analysis Method : I:\HPLC\METHODS\SAM-POT2.M
Last changed : 8/25/2009 2:24:42 PM by SAM
(modified after loading)
For XYSun Peroxide-OTs Product
Channel A: IPA
Channel B: Hexane



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=230,8 Ref=550,100

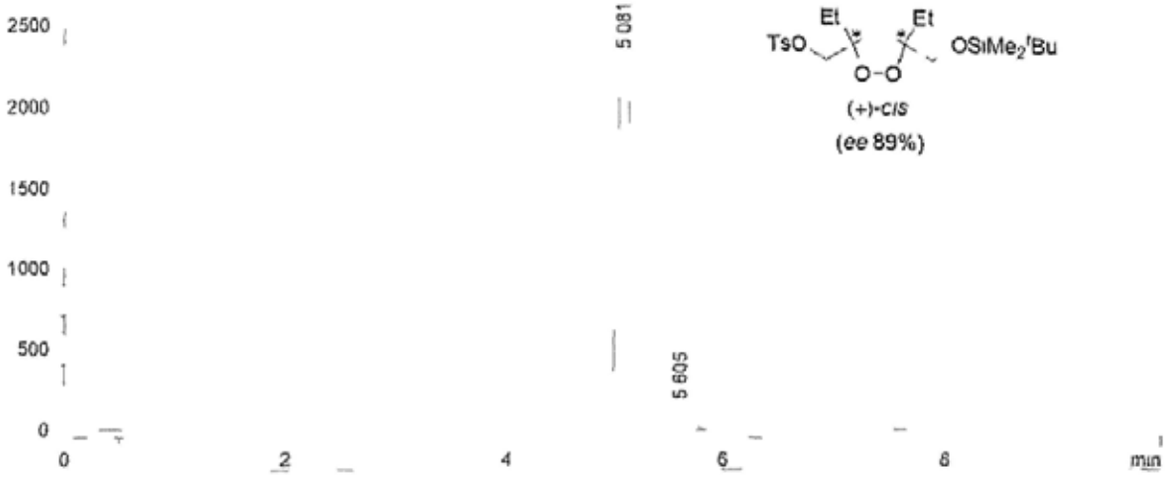
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.116	VP	0.1233	404.39487	49.52249	2.9286
2	5.614	VB	0.1366	1.34042e4	1495.09082	97.0714
Totals :				1.38086e4	1544.61331	

Results obtained with enhanced integrator!

*** End of Report ***

Sunxy-3-136

DAD1 B, Sig=230,8 Ref=550,100 (HEHAO\023-0301.D)



(+)-*cis*

(*ee* 89%)

Area Percent Report

XYS-rac-1
IPA: 5%, Hexanes: 95%
Column: CHIRALPAK AD-H

```
Injection Date  : 8/25/2010 1:21:30 PM
Sample Name     : XYS-rac-2                    Location : Vial 1
Acq. Operator   : SAM
                                               Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\1\METHODS\TERMS04.M
Last changed    : 8/25/2010 12:34:47 PM by SAM
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\TERMS04.M
Last changed    : 8/25/2010 1:37:29 PM by SAM
                  (modified after loading)
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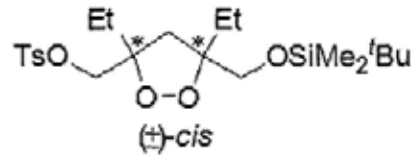
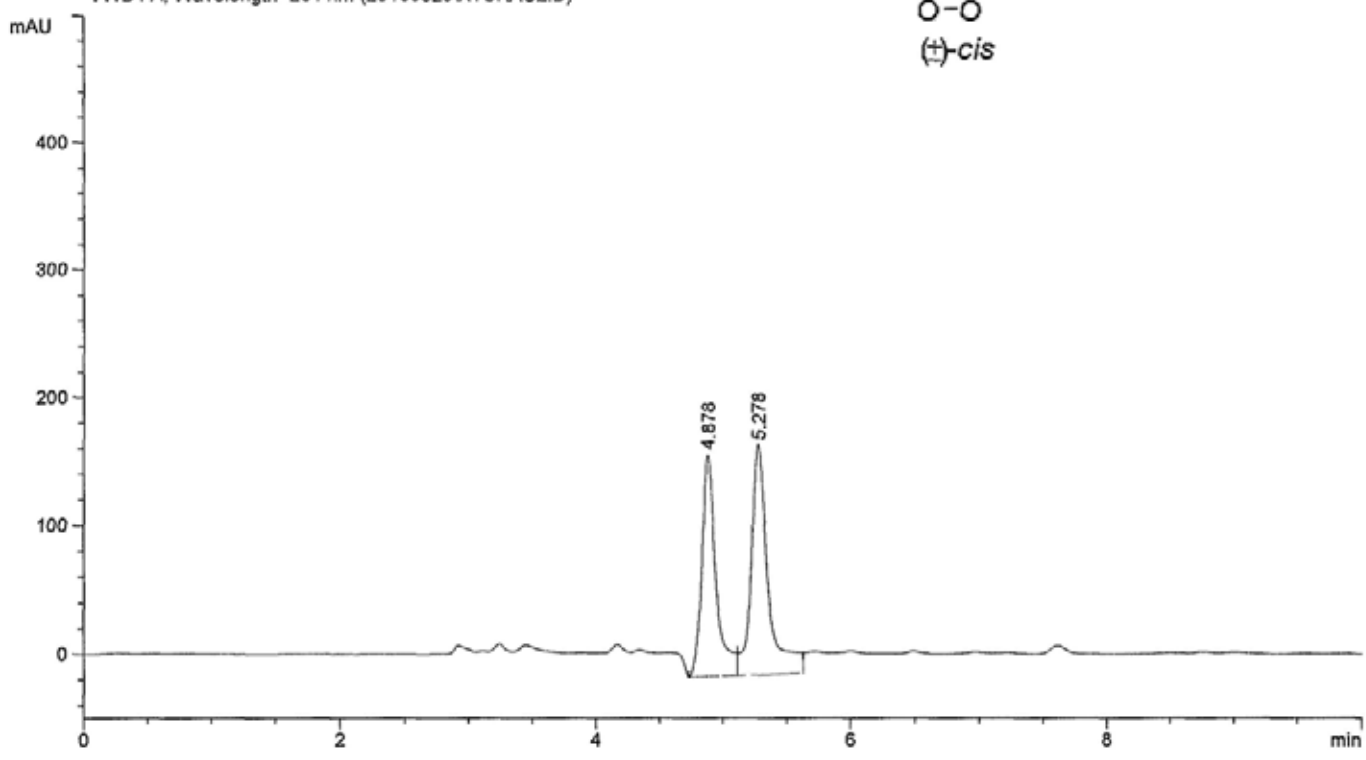




Area Percent Report

```
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
```

Signal 1: VWD1 A, Wavelength=254 nm

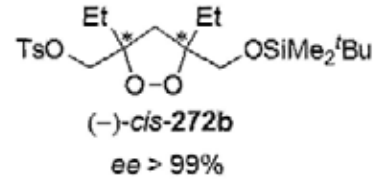
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	4.878	VV	0.1183	1362.06201	172.57300	45.0561
2	5.278	VV	0.1376	1660.97363	178.62419	54.9439
Totals :				3023.03564	351.19719	

Results obtained with enhanced integrator!

*** End of Report ***

XYS-4-40-79
IPA: 5%, Hexanes: 95%
Column: CHIRALPAK AD-H

```
Injection Date  : 8/25/2010 12:01:49 PM
Sample Name     : XYS-4-79                    Location : Vial 1
Acq. Operator   : SAM
                                              Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\1\METHODS\TERMS04.M
Last changed    : 8/25/2010 11:55:15 AM by CYW
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\TERMS04.M
Last changed    : 8/25/2010 12:34:47 PM by SAM
                  (modified after loading)
```



(−)-*cis*-272b
ee > 99%


```
                        Area Percent Report

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=230 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   5.438 VV    0.1676 1.11494e4  1025.61499 100.0000

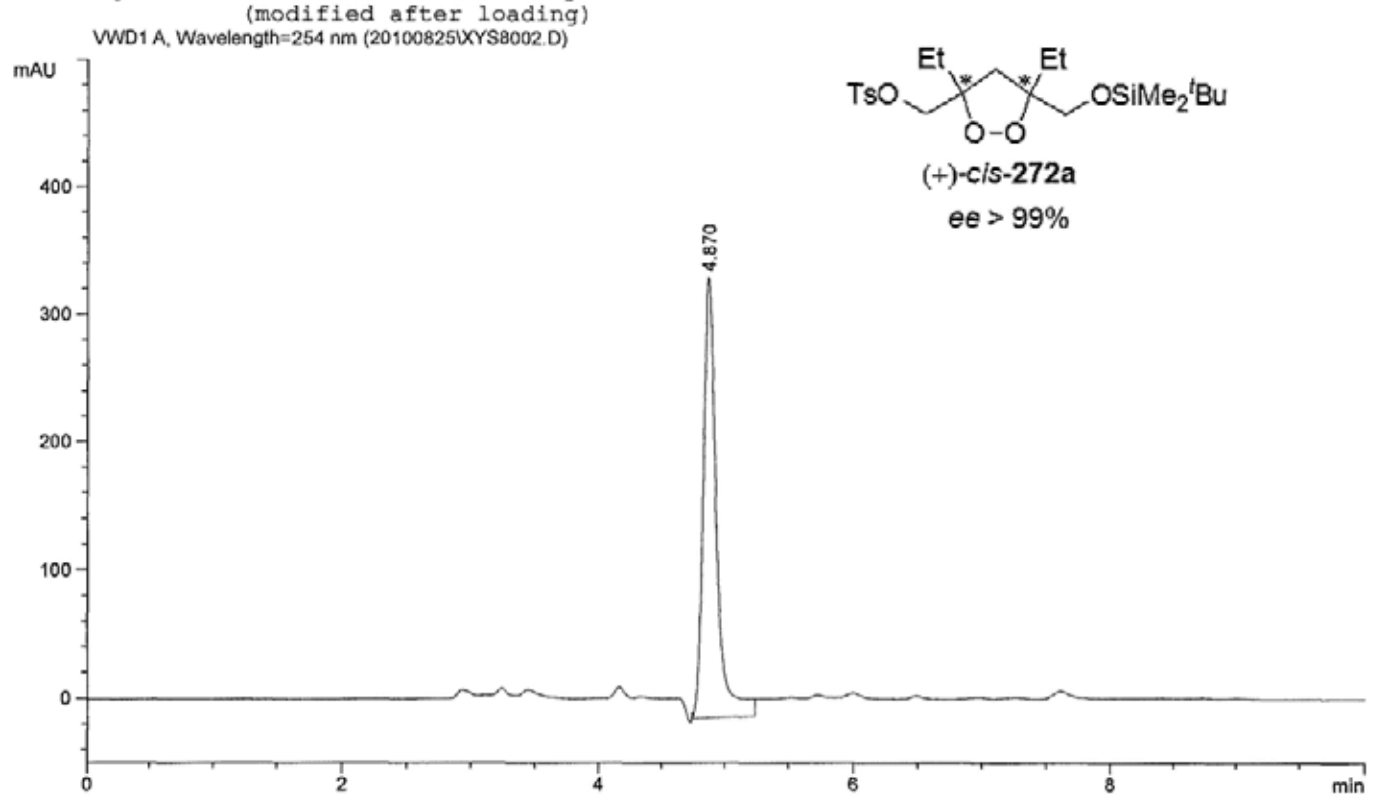
Totals :                  1.11494e4  1025.61499

 Results obtained with enhanced integrator!

                        *** End of Report ***
```

XYS-4-40-80
IPA: 5%, Hexanes: 95%
Column: CHIRALPAK AD-H

```
Injection Date   : 8/25/2010 12:51:32 PM
Sample Name      : XYS-4-80                          Location : Vial 1
Acq. Operator    : SAM
                                                     Inj Volume : 5 µl
Acq. Method      : C:\HPCHEM\1\METHODS\TERMS04.M
Last changed     : 8/25/2010 12:34:47 PM by SAM
                   (modified after loading)
Analysis Method  : C:\HPCHEM\1\METHODS\TERMS04.M
Last changed     : 8/25/2010 1:37:29 PM by SAM
                   (modified after loading)
```



Area Percent Report

```
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]     %
----|-------|----|-------|---------|---------|--------|
   1   4.870 PB    0.1113 2507.12842  343.81906 100.0000

Totals :                  2507.12842  343.81906

 Results obtained with enhanced integrator!
```

*** End of Report ***