Syntheses of Dechlorogreensporones A and D

Laksamee Jeanmard

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Science in Organic Chemistry

Prince of Songkla University

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Major Program	Organic Chemistry

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This is to certify that the work here submitted is the result of the candidate's own investigations. Due acknowledgement has been made of any assistance received.

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I hereby certify that this work has not been accepted in substance for any degree, and is not being currently submitted in candidature for any degree.

……...…..Signature
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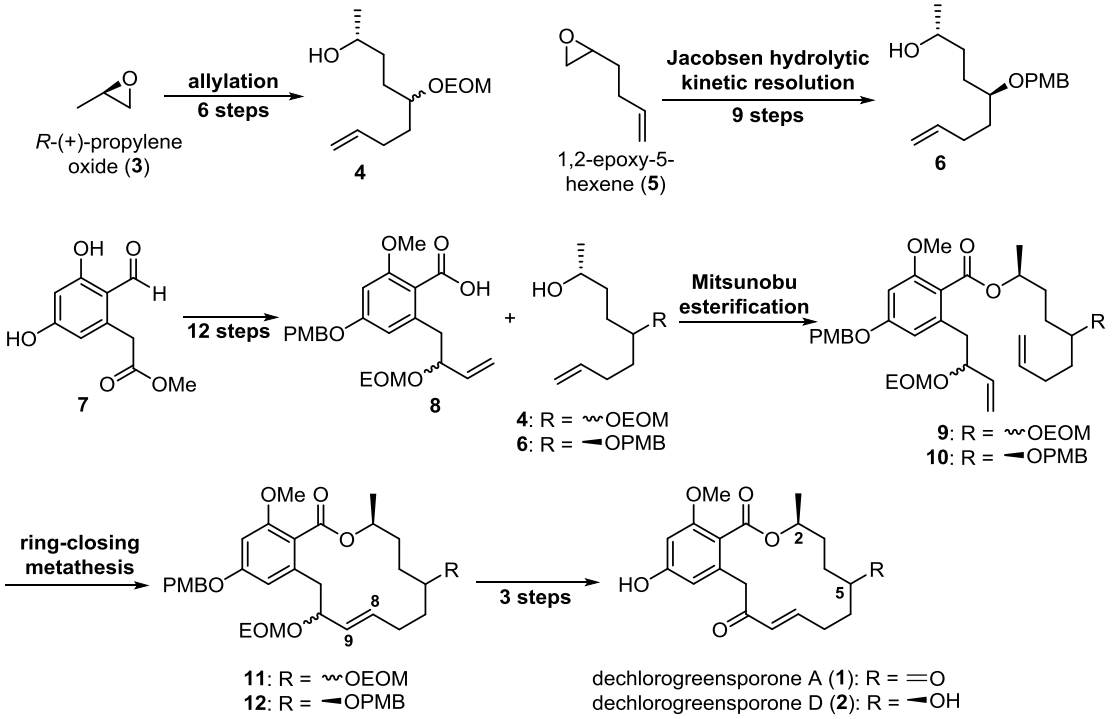
Candidate

ชื่อวิทยานิพนธ์ การสังเคราะห์ dechlorogreensporone A และ dechlorogreensporone D
ผู้เขียน นางสาวลักษมี เจียรมาศ
สาขาวิชา เคมีอินทรีย์
ปีการศึกษา 2560

บทคัดย่อ

Dechlorogreensporone A (**1**) และ dechlorogreensporone D (**2**) เป็นสารผลิตภัณฑ์ธรรมชาติชนิดใหม่ในกลุ่ม β-resorcylic acid lactones วง 14 เหลี่ยมซึ่งแยกได้พร้อมกับสารกลุ่มเดียวกันชนิดใหม่อีก 12 สาร จากเชื้อราน้ำจืด *Halenospora* sp. มีต้นกำเนิดบริเวณธารน้ำของรัฐ North Carolina ประเทศสหรัฐอเมริกา โดย Oberlies และคณะในปี ค.ศ. 2014 โครงสร้างที่สำคัญของสารทั้งสองประกอบด้วย β-resorcylic acid lactone วง 14 เหลี่ยมซึ่งมีหมู่ (*E*)-enone ที่คาร์บอนตำแหน่ง 8 ถึง 10 และมีไครัลคาร์บอนที่ตำแหน่ง 2 โดยโครงสร้างของสาร **1** มีหมู่คีโตนที่ตำแหน่ง 5 ในขณะที่สาร **2** มีหมู่แอลกอฮอล์ที่มีสเตอริโอเคมีสัมบูรณ์แบบ *S* สารผลิตภัณฑ์ธรรมชาติทั้งสองแสดงฤทธิ์ยับยั้งเซลล์มะเร็งผิวหนังชนิด MDA-MB-435 ด้วยค่า IC_{50} เท่ากับ 14.1 และ 11.2 μM ตามลำดับ และแสดงฤทธิ์ยับยั้งเซลล์มะเร็งลำไส้ใหญ่ชนิด HT-29 ด้วยค่า IC_{50} เท่ากับ >20 และ 25.4 μM ตามลำดับ งานวิจัยนี้เป็นการสังเคราะห์สาร **1** และ **2** เพื่อยืนยันสเตอริโอเคมีสัมบูรณ์ของสารผลิตภัณฑ์ธรรมชาติและเพื่อนำไปทดสอบฤทธิ์ยับยั้งเซลล์มะเร็งชนิดอื่นเพิ่มเติม ปฏิกิริยาหลักสำคัญที่ใช้ในการสังเคราะห์คือ ring-closing metathesis ของ diene **9** หรือ **10** เพื่อปิดวง macrolactone 14 เหลี่ยมและสร้างพันธะคู่ที่ตำแหน่งคาร์บอน 8 และ 9 แบบ *trans* และ Mitsunobu esterification ระหว่าง alcohol **4** หรือ **6** และ benzoic acid **8** เพื่อสร้างพันธะ ester ของ diene **9** หรือ **10** สำหรับ alcohol **4** สามารถเตรียมได้ใน 6 ขั้นตอนผ่านปฏิกิริยาหลัก allylation โดยใช้ *R*-(+)-propylene oxide (**3**) เป็นสารตั้งต้น และ alcohol **6** สามารถเตรียมได้ใน 9 ขั้นตอนโดยใช้ 1,2-epoxy-5-hexene (**5**) เป็นสารตั้งต้นและใช้ปฏิกิริยา Jacobsen hydrolytic kinetic resolution เป็นปฏิกิริยาหลักในการสร้างไครัลคาร์บอนตำแหน่งที่ 5 การสังเคราะห์อนุพันธ์ benzoic acid **8** ทำได้ใน 12 ขั้นตอนโดยใช้ methyl 2-(2-formyl-3,5-dihydroxyphenyl) acetate (**7**) เป็นสารตั้งต้น การสังเคราะห์สาร **1** และ **2** เสร็จสมบูรณ์ใน 17 ขั้นตอนของเส้นทางที่ยาวที่สุดแบบเส้นตรง ซึ่งใช้ 23 ขั้นตอนทั้งหมดในการสังเคราะห์สาร **1** และมีร้อยละผลิตภัณฑ์โดยรวมเป็น 2.8 และใช้ 26 ขั้นตอนทั้งหมดในการสังเคราะห์สาร **2** โดยมีร้อยละผลิตภัณฑ์โดยรวมเป็น 5.4 จากการวิเคราะห์ข้อมูล ^{1}H

และ ^{13}C NMR ค่ามวลของสารแบบความละเอียดสูง ค่าการหมุนระนาบแสงโพราไลซ์ของสารสังเคราะห์ **1** และ **2** เทียบกับสารผลิตภัณฑ์ธรรมชาติพบว่ามีค่าใกล้เคียงกัน ดังนั้นจึงสามารถยืนยันสเตอริโอเคมีสัมบูรณ์ของสารผลิตภัณฑ์ธรรมชาติทั้งสองได้ จากการทดสอบฤทธิ์ความเป็นพิษต่อเซลล์มะเร็งในมนุษย์ทั้งหมด 7 ชนิด พบว่าสารทั้งสองแสดงฤทธิ์ยับยั้งเซลล์มะเร็งในมนุษย์ทั้ง 7 ชนิดด้วยค่า IC_{50} ในช่วง 6.66−17.25 μM นอกจากนี้ยังพบว่าสาร **2** แสดงฤทธิ์ยับยั้งเซลล์มะเร็งที่ทดสอบทั้งหมดในระดับที่ดีกว่าสาร **1** อย่างไรก็ตามสาร **1** แสดงความเป็นพิษต่อ Vero cells น้อยกว่าสาร **2** ประมาณ 5 เท่า

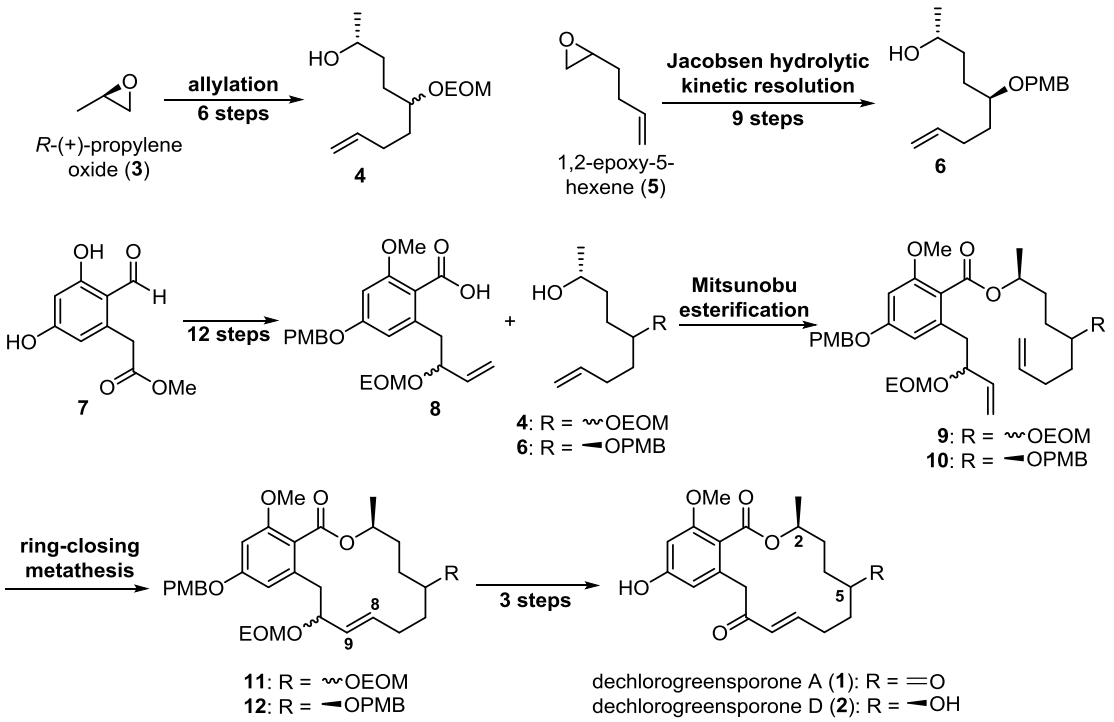


Thesis Title Syntheses of Dechlorogreensporones A and D
Author Miss Laksamee Jeanmard
Major Program Organic Chemistry
Academic Year 2017

ABSTRACT

Dechlorogreensporones A (**1**) and D (**2**) are new 14-membered β-resorcylic acid lactones (RALs), which were isolated, along with other 12 new RALs from a culture of a fresh water fungus *Halenospora* sp. originating from a stream in North Carolina, USA by Oberlies and co-workers in 2014. The structures of compounds **1** and **2** contain a 14-membered β-resorcylic acid lactone with an (*E*)-enone at C8–C10 and a stereogenic center at the 2-position. The only structural difference is that **1** consists of a keto group at the 5-position, while **2** bears an alcohol stereogenic center. These isolated natural products **1** and **2** displayed cytotoxicity against the MDA-MB-435 melanoma cancer cell line with IC_{50} values of 14.1 and 11.2 μM, respectively. They also displayed cytotoxicity against the HT-29 colon cancer cell line with IC_{50} values of >20 and 25.4 μM, respectively. This work involves the syntheses of **1** and **2** in order to confirm the assigned absolute configuration of these natural products and to further evaluate cytotoxic activity against other cancer cell lines. The key strategies include ring-closing metathesis of diene precursor **9** or **10** to assemble the 14-membered macrolactone and to also construct the *E*-double bond at C8–C9, and Mitsunobu esterification between alcohol intermediate **4** or **6** and benzoic acid derivative **8** to form the ester bond of diene **9** or **10**. Alcohol intermediate **4** was prepared in 6 steps via allylation of *R*-(+)-propylene oxide (**3**), while alcohol intermediate **6** was synthesized from 1,2-epoxy-5-hexene (**5**) in 9 steps using Jacobsen hydrolytic kinetic resolution (HKR) to generate the stereogenic center at the 5-position. The synthesis of benzoic acid **8** was accomplished in 12 steps from methyl 2-(2-formyl-3,5-dihydroxyphenyl)acetate (**7**). The syntheses of dechlorogreen-sporones A (**1**) and D (**2**) have been completed via a longest linear 17 steps from known phenol **7**. The synthesis of **1** has been accomplished in 23 total steps in 2.8%

overall yield, while the synthesis of **2** has been achieved in 26 total steps in 5.4% overall yield. The ^{1}H and ^{13}C NMR spectroscopic data, HRMS data and specific rotation of synthetic compounds **1** and **2** were in excellent agreement with those reported for the natural products, which confirmed the assigned absolute configurations of the natural products. Synthetic compounds **1** and **2** were found to exhibit the cytotoxic activity against seven cancer cell lines with the IC_{50} range of 6.66−17.25 μM. Moreover, dechlorogreensporone D (**2**) displayed more potent antiproliferative activity against these seven cancer cell lines compared to dechlorogreensporone A (**1**). Nevertheless, **1** was approximately 5-fold less cytotoxic to Vero cells compared to **2**.



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Laksamee Jeanmard

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LIST OF ABBREVIATIONS AND SYMBOLS

[α]	=	specific rotation
Ac	=	acetyl
Acetone-d_6	=	hexadeuteroacetone
Ac_2O	=	acetic anhydride
aq	=	aqueous
br	=	broad (spectral)
brsm	=	based on recovered starting material
ºC	=	degrees Celsius
c	=	concentration
cat	=	catalytic
cm^{-1}	=	wavenumber(s)
$CDCl_3$	=	deuterochloroform
m-CPBA	=	*meta*-chloroperoxybenzoic acid
δ	=	chemical shift in parts per million downfield from tetramethylsilane
d	=	doublet (spectral)
DIAD	=	diisopropyl azodicarboxylate
DMAP	=	4-(*N*,*N*-dimethylamino)pyridine
DMF	=	dimethylformamide
DMSO	=	dimethyl sulfoxide
DMSO-d_6	=	hexadeuterodimethyl sulfoxide
ee	=	enantiomeric excess
equiv	=	equivalent
ESI	=	electrospray ionization
Et	=	ethyl
FT	=	Fourier transform
g	=	gram(s)
h	=	hour(s)
HPLC	=	high-performance liquid chromatography

LIST OF ABBREVIATIONS AND SYMBOLS (Continued)

HRMS	=	high-resolution mass spectrometry
Hz	=	hertz
IBX	=	2-iodoxybenzoic acid
IR	=	infrared
J	=	coupling constant (in NMR spectrometry)
L	=	liter(s)
µ	=	micro
m	=	multiplet (spectral); meter(s); milli
M	=	molar (moles per liter)
Me	=	methyl
MHz	=	megahertz
min	=	minute(s)
mol	=	mole
mol %	=	mole percent
mp	=	melting point
MTPA	=	methoxy trifluoromethyl phenyl acetate
m/*z*	=	mass-to-charge ratio
nm	=	nanometer(s)
NMR	=	nuclear magnetic resonance
Ph	=	phenyl
ppm	=	part(s) per million
*i*Pr	=	isopropyl
q	=	quartet (spectral)
qn	=	quintet (spectral)
R_f	=	retention factor (in chromatography)
rt	=	room temperature
s	=	singlet (spectral)
sext	=	sextet (spectral)

LIST OF ABBREVIATIONS AND SYMBOLS (Continued)

TEMPO	=	2,2,6,6-tetramethylpiperidin-1-oxyl
TBS	=	*tert*-butyldimethylsilyl
TBDPS	=	*tert*-butyldiphenylsilyl
TBAF	=	tetrabutylammonium fluoride
TLC	=	thin-layer chromatography
wt	=	weight

LIST OF PUBLICATION

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CHAPTER 1

INTRODUCTION

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INTRODUCTION

1.1 Introduction

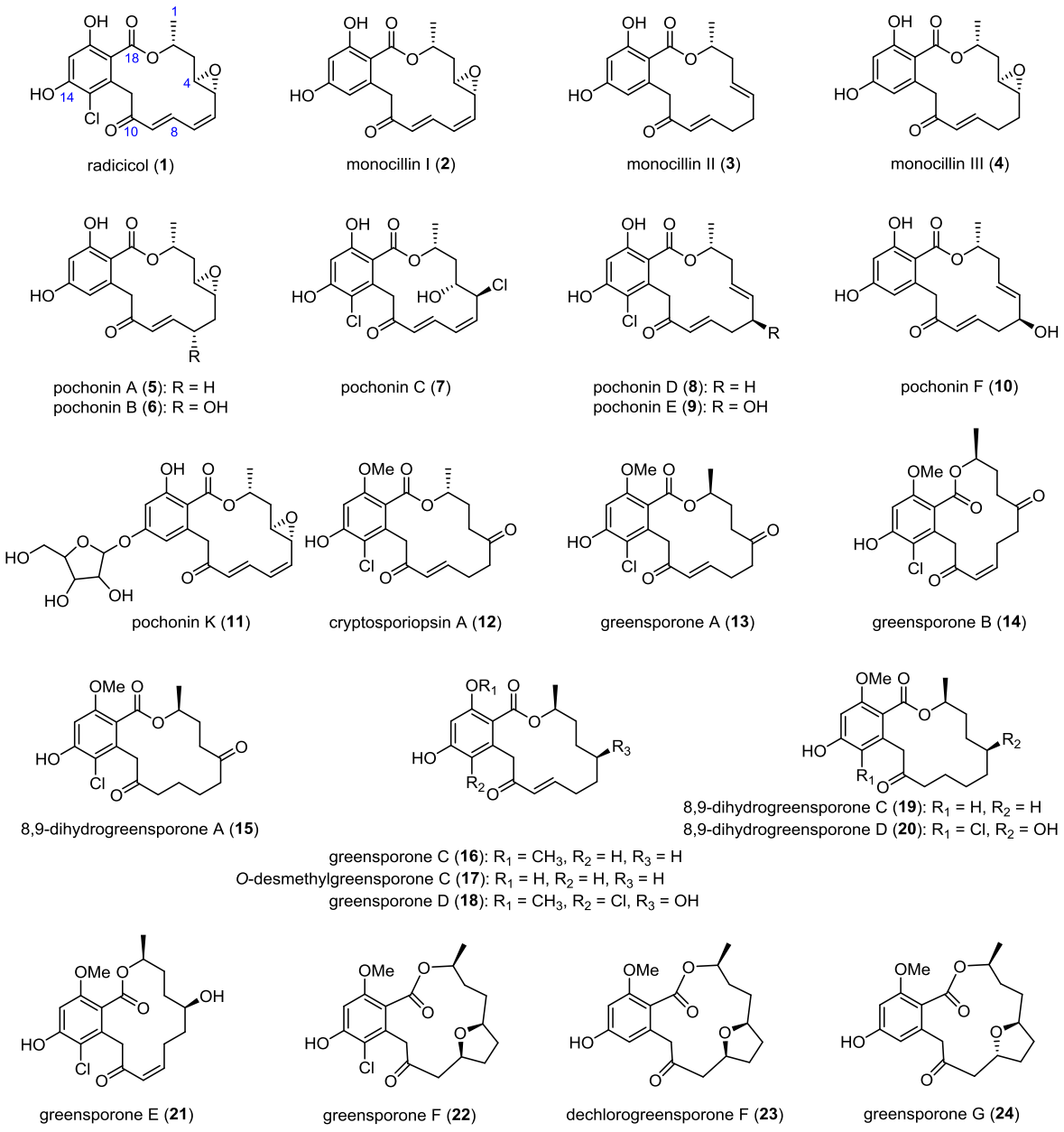
The well-known resorcylic acid lactones (RALs) are a group of fungal polyketide metabolites bearing a 14-membered macrocyclic ring fused to a β-resorcylic acid residue with a stereochemically pure methyl substituent at the 2-position. Since radicicol (**1**), the first discovered RAL, was isolated from the fungus *Monosporium bonorden* (*Monocillium nordinii*) in 1953 (Delmotte and Delmotte-Plaquee, 1953), a number of 14-membered RALs with remarkable biological activities have been isolated from a variety of different fungal strains. A subclass of RALs consisting of an α,β-unsaturated ketone at the 8-10 positions, is a group of minor examples of radicicol analogues. This group of compounds possesses diverse interesting biological activities. Herein, the structures, biological activities and synthetic approaches of radicicol and selected examples of its analogues will be reviewed.

Examples of RALs containing an α,β-unsaturated ketone at the 8-10 positions are shown in **Figure 1**. Firstly, radicicol (**1**) was originally found to exhibit a mild sedative activity along with moderate antibiotic activity (Delmotte and Delmotte-Plaquee, 1964), and was later found to show highly potent inhibition of the molecular chaperone heat shock protein 90 (HSP-90) with an IC_{50} value of 20 nM (Schulte *et al*., 1998 and Sharma *et al*., 1998) as well as antifungal activity against *Mucor flavas* IFO 9560 with an MIC value of 0.39 μg/mL (Fujita *et al*., 1999). Moreover, compound **1** showed moderate antiviral activity against Herpes Simplex Virus 1 (HSV 1) with IC_{50} value of 0.2–0.8 μM (Hellwig *et al*., 2003) and it also exhibited low potency in reactivating latent HIV-1 with an EC_{50} value of 9.1 μM (Tenny *et al*., 2014). After the isolation of compound **1**, a series of its analogues have been reported. In 1980, the monocillin series were first isolated from the same fungus (*Monocillium nordinii*) by Ayer et al. The metabolites included the known compound

1 and five new compounds namely monocillins I-V. The monocillin family exhibited various biological activities. For example, monocillin I (**2**) showed active antifungal activity against pine stem rusts and a wide variety of other fungi, including *Ceratocystisulmi*, the cause of Dutch elm disease (Ayer *et al*., 1980). Monocillins II (**3**) and III (**4**) displayed antiviral activity against the parasitic protozoan *Eimeria tenella* (Hellwig *et al*., 2003). In addition, compound **4** showed moderate antiviral activity against HSV 1 with an IC_{50} value of 0.4 µM (Hellwig *et al*., 2003). After the report of the monocillins, the major metabolites of this subclass of RALs, the pochonin family was isolated by Hellwig and co-workers in 2003. Pochonins A-F (**5**-**10**) were first isolated, along with radicicol, tetrahydromonorden and pseurotin A, from the culture of the clavicipitaceous hyphomycete fungus *Pochonia chlamydosporia* var. *catenulate* strain P 0297. Compounds **5**-**7**, **9** and **10** exhibited weak inhibition of HSV 1 replication with IC_{50} values of 2, 10, 6, 1.5 and 2 µM, respectively. Pochonins A (**5**) and F (**10**) also showed antiviral activity against the parasitic protozoan *Eimeria tenella* (Hellwig *et al*., 2003). Additionally, pochonin D (**8**) exhibited a good inhibitory activity against HSP-90 expression with an IC_{50} value of 80 nM (Moulin *et al*., 2005). A few years later, six new radicicol analogues of the pochonin series were isolated by Shinonaga and co-workers in 2009. Pochonin K (**11**) was identified, along with five pochonins without an α,β-unsaturated ketone at the 8-10 positions from the same fungus (*P. chlamydosporia*). Compound **11** displayed inhibitory activity on moderate wingless-type mouse mammary tumor virus integration site family, member 5A (WNT-5A) with an IC_{50} value of 8.57 µM. Three years after isolation of the pochonin series, the new radicicol derivative of this subclass of RALs containing a β-resorcylic acid monomethyl ether was identified by Laatsch and co-workers in 2012. Cryptosporiopsin A (**12**) was first isolated, along with hydroxypropan-2′,3′-diol orsellinate, two pentapeptides and (−)-phyllostine, from a culture of an endophytic fungus *Cryptosporiopsis* sp. strain CAFT122-1, which was derived from leaves, branches and stems of *Zanthoxylum leprieurii* (Rutaceae). Compound **12** displayed motility inhibitory and lytic activities against zoospores of the grapevine downy mildew pathogen *Plasmopara viticola* (MIC = 10–25 µg/mL) and showed potent inhibitory activity against mycelial growth of phytopathogens, *Pythium ultimum*, *Aphanomyces cochlioides* and a basidiomycetous fungus

Rhizoctoniasolani. Compound **12** also exhibited weak cytotoxic activity against brine shrimp larvae (Talontsi *et al*., 2012). Another group of this subclass of RALs is the greensporones reported by Oberlies and co-workers in 2014. Fourteen new RALs consisting of β-resorcylic acid monomethyl ethers were isolated from a culture of a freshwater aquatic fungus *Halenospora* sp. originating from a stream in North Carolina, USA. Greensporone A (**13**), greensporone C (**16**) and *O*-desmethylgreen sporone C (**17**) showed cytotoxicity against the MDA-MB-435 (melanoma) cancer cell line with IC_{50} values of 14.1, 2.9 and 14.5 µM, respectively. In addition, compounds **13**, **16** and **17** also displayed cytotoxicity against the HT-29 (colon) cancer cell line with IC_{50} values of >20, 7.5 and 13.8 µM, respectively (El-Elimat *et al*., 2014).

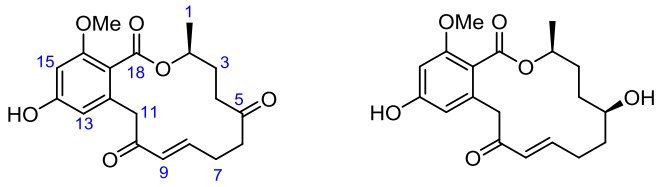
Figure 1 Structures of radicicol and examples of its natural analogues



Dechlorogreensporones A (**25**) and D (**26**) are new 14-membered β-resorcylic macrolides of the greensporones series. These compounds contain β-resorcylic acid monomethyl ether and (*E*)-enone functionalities at the 8-10 positions. Although the structures of dechlorogreensporones A and D possess the same absolute configuration at the 2-position, the only structural difference is that **25** consists of a keto group at the 5-position, while **26** contains an alcohol stereogenic center. The absolute configuration of a chiral carbon at the 2-position in both **25** and **26** and other

analogues was assigned to be *S* via an X-ray diffraction analysis of the bromobenzoyl derivative of 8,9-dihydrogreensporone C (**19**). The absolute configuration of C-5 chiral carbon in macrolide **26** and other co-metabolites possessing chiral center at the 5-position was proposed to be *S* by Mosher ester analysis. In addition, compounds **25** and **26** were evaluated for cytotoxic activities against two human cancer cell lines. These compounds exhibited cytotoxicity against the MDA-MB-435 melanoma cancer cell line with IC_{50} values of 14.1 and 11.2 μM, respectively. They also displayed cytotoxicity against the HT-29 colon cancer cell line with IC_{50} values of >20 and 25.4 μM, respectively (El-Elimat *et al*., 2014).

Figure 2 Structures of dechlorogreensporones A (**25**) and D (**26**)



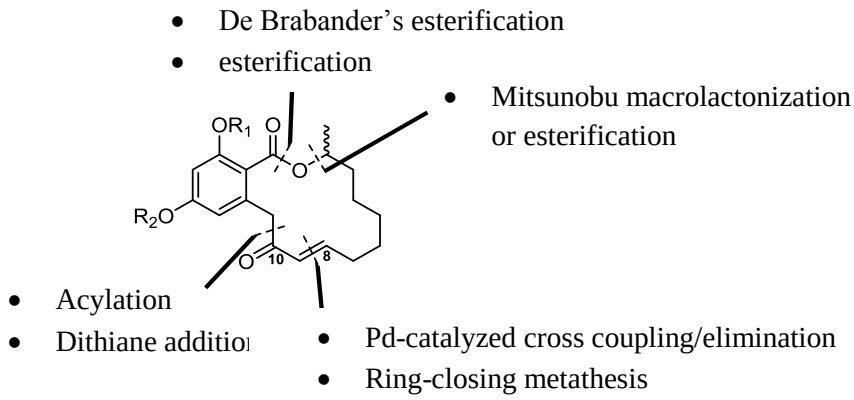
dechlorogreensporone A (**25**) dechlorogreensporone D (**26**)

Owing to promising biological activities of this subclass of RALs and our ongoing program for anticancer drug discovery, we have been focusing on a synthetic program of such compounds and are interested in synthesizing compounds **25** and **26** in order to confirm the assigned absolute configurations of these natural products and to further evaluate cytotoxic activity against other cancer cell lines.

In consequence of their several and impressive biological profiles and structural features, there has been growing interest on the synthetic programs of 14-membered β-resorcylic macrolide analogues by many synthetic organic research groups. In this section, the literature precedents on the syntheses of radicicol analogues having the 14-membered ring lactone core with an α,β-unsaturated ketone at C8–C10 similar to target natural products **25** and **26** will be reviewed. Previous reports on the syntheses of radicicol derivatives utilized the key bond formations to construct the (*E*)-enone and to form C10–C11 bond via dithiane addition and acylation as well as to form C8–C9 bond via Pd-catalyzed cross coupling/elimination and ring closing-metathesis. In addition, Mitsunobu macrolactonization and ring-closing metathesis were used to assemble the macrocycles, while the formations of

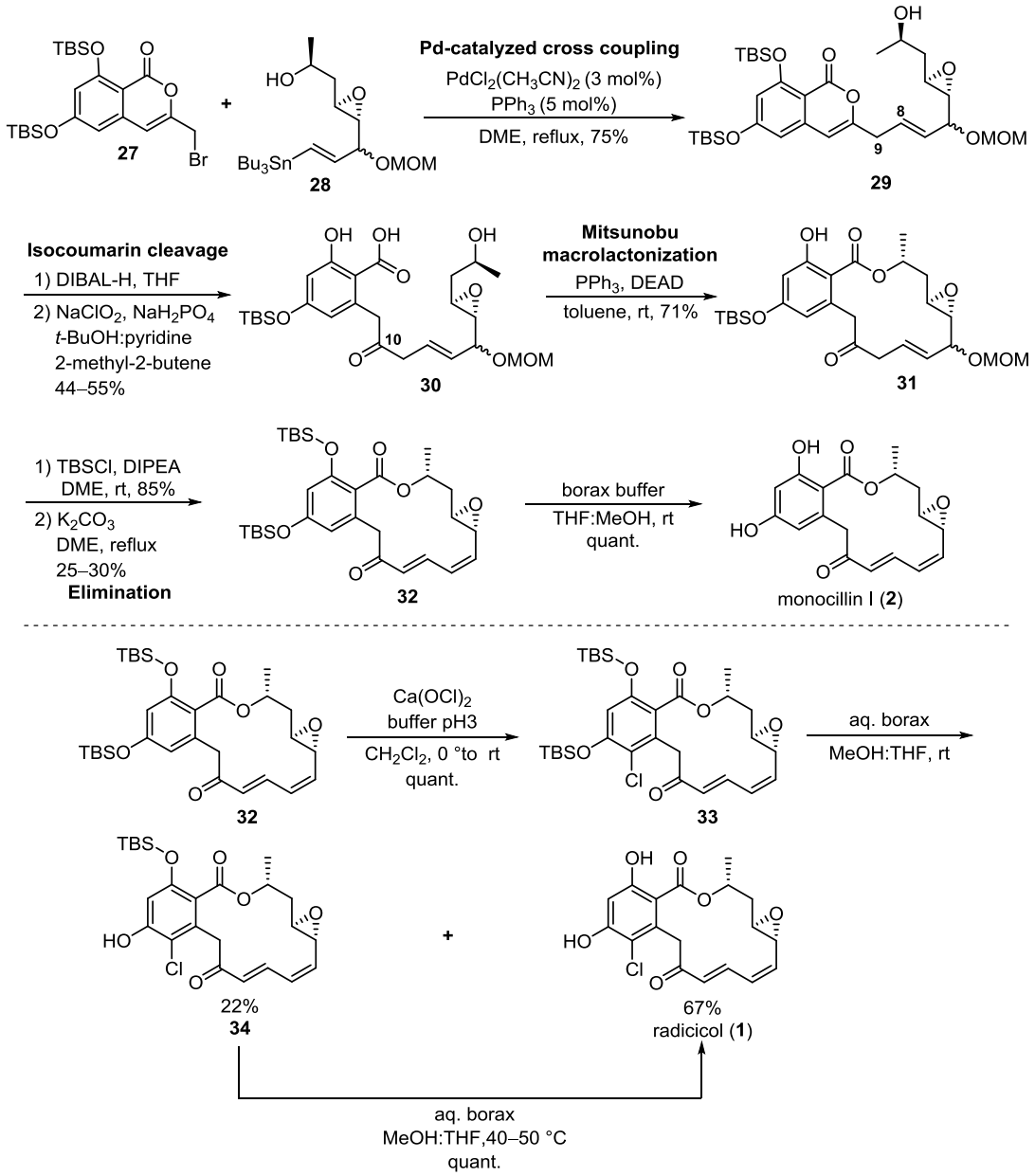
ester bonds were achieved by esterification as well as Mitsunobu and De Brabander's esterification (**Figure 3**).

Figure 3 Key bond disconnections in previous syntheses of radicicol and its analogues



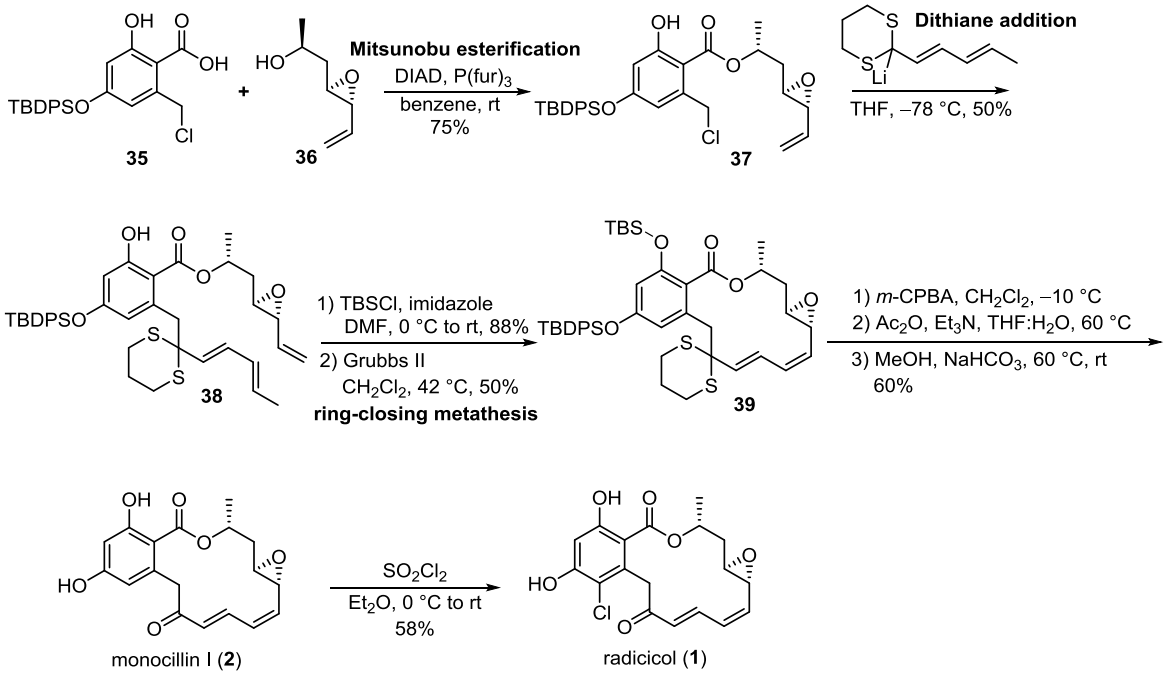
Firstly, the selected examples for the syntheses of radicicol analogues focusing on the C8–C9 formation via Pd-catalyzed cross coupling/elimination will be presented. In 1992, Lett and co-workers reported the first total synthesis of compounds **1** and **2**, which is shown in **Scheme 1**. The cross coupling between coumarin derivative **27** and stannane **28** in the presence of $PdCl_2(CH_3CN)_2$ catalyst and PPh_3 ligand constructed C8–C9 bond to provide isocoumarin **29** in 75% yield. The isocoumarin cleavage under DIBAL-H reduction, followed Pinnick oxidation produced keto acid **30**. The macrocyclic precursor **30** was subjected to Mitsunobu macrolactonization to furnish macrolide **31** in 71% yield. Subsequent protection of phenol **31** with TBS group, followed by elimination formed an (*E*)-double bond at C8–C9 and also established a conjugated (*Z*)-double bond at C6–C7 under basic conditions to give lactone **32**, which was subjected to desilylation using borax buffer to afford monocillin I (**2**) in quantitative yield. Radicicol (**1**) was obtained in 3 steps from macrolide intermediate **32** under regioselective aromatic chlorination using $Ca(OCl)_2$ and double deprotection of the silyl groups.

Scheme 1 Lett's synthesis of radicicol (**1**) and monocillin I (**2**)



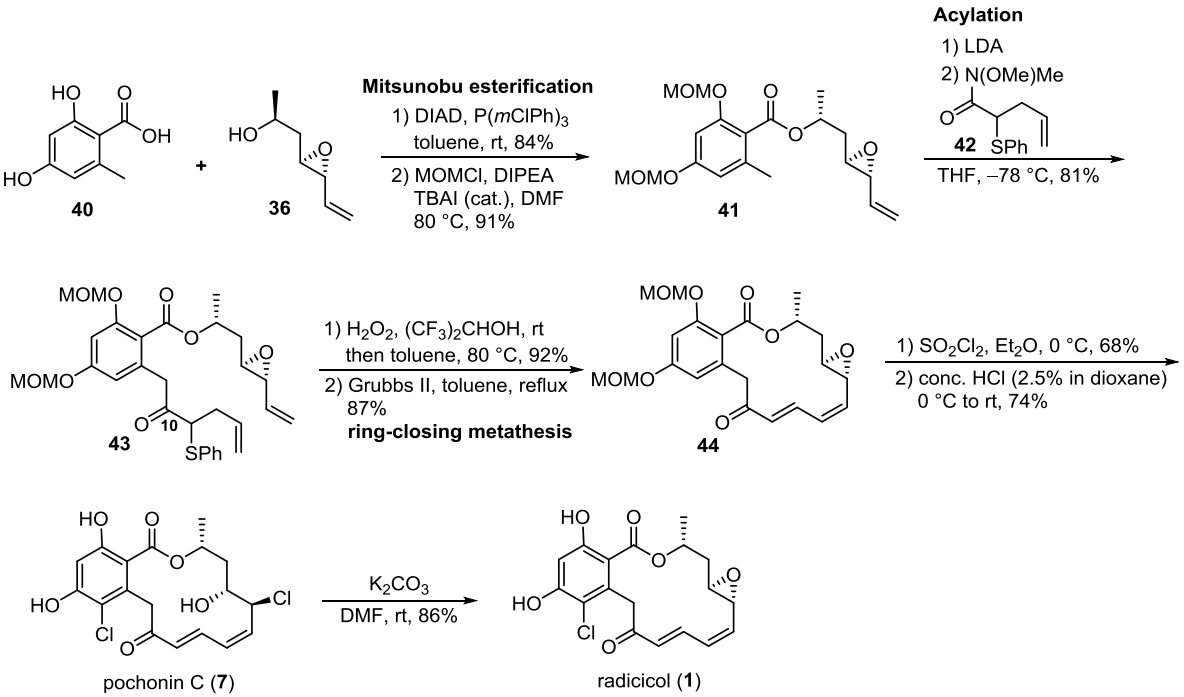
Dithiane addition is another successful approach for the formation of (*E*)-enone at the 8-10 positions of this class of compounds as shown in the example of the synthesis of **1** and **2** by the Danishefsky group in 2001. Moreover, this synthesis utilized ring-closing metathesis to construct the macrolactone ring (**Scheme 2**). The ester bond of **37** was constructed from benzoic acid **35** and alcohol **36** under Mitsunobu esterification conditions to give ester **37** in 75% yield. Subsequent alkylation of **37** with lithiated dienyl dithiane afforded the metathesis precursor **38** in 50% yield. Protection of phenol **38** with TBS group, followed by ring-closing metathesis to construct macrolactone ring using the second-generation Grubbs catalyst furnished macrolide **39** in 50% yield with excellent (*Z*)-selectivity. Conversion of the dithiane moiety of **39** to the α,β-unsaturated ketone via an oxidation with *m*-CPBA/Pummerer rearrangement with desilylation, followed by global deprotection with hydrolysis provided **2** in 60% yield. Finally, a regioselective chlorination of **2** using SO_2Cl_2 gave the desired radicicol (**1**) in 58% yield.

Scheme 2 Danishefsky's synthesis of radicicol (**1**) and monocillin I (**2**)



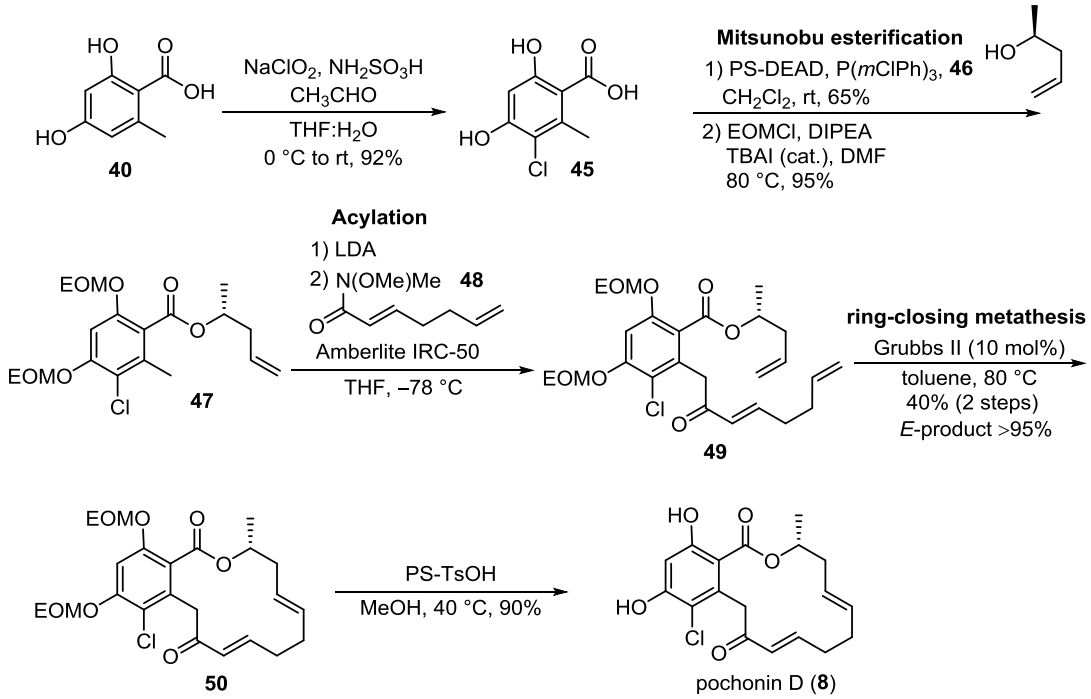
In addition, acylation is another method to construct C10–C11 bond and to also produce ketone at the 10-position, which has been popularly utilized in the synthesis of pochonin natural product series. In 2004, Winssinger and co-workers reported the synthesis of pochonin C (**7**) as illustrated in **Scheme 3**. Mitsunobu coupling between 2-hydroxytoluic acid (**40**) and alcohol **36** gave the corresponding ester product, which was subjected to MOM protection to provide ester **41** in 91% yield. Addition of lithiated **41** to Weinreb amide **42** at −78 °C produced diene **43** containing the ketone functionality at C-10 in 81% yield. Oxidation/elimination of the thioether **43** followed by ring-closing metathesis to assemble the macrolide using second-generation Grubbs catalyst in refluxing toluene yielded the desired macrolactone **44** in good yield. Chlorination of the aryl ring, followed by ring opening of epoxide and global deprotection in acidic conditions furnished pochonin C (**7**) in 74% yield. Treatment of compound **7** with K_2CO_3 led to oxirane formation thus yielding radicicol (**1**) in 86% yield.

Scheme 3 Winssinger's synthesis of pochonin C (**7**)



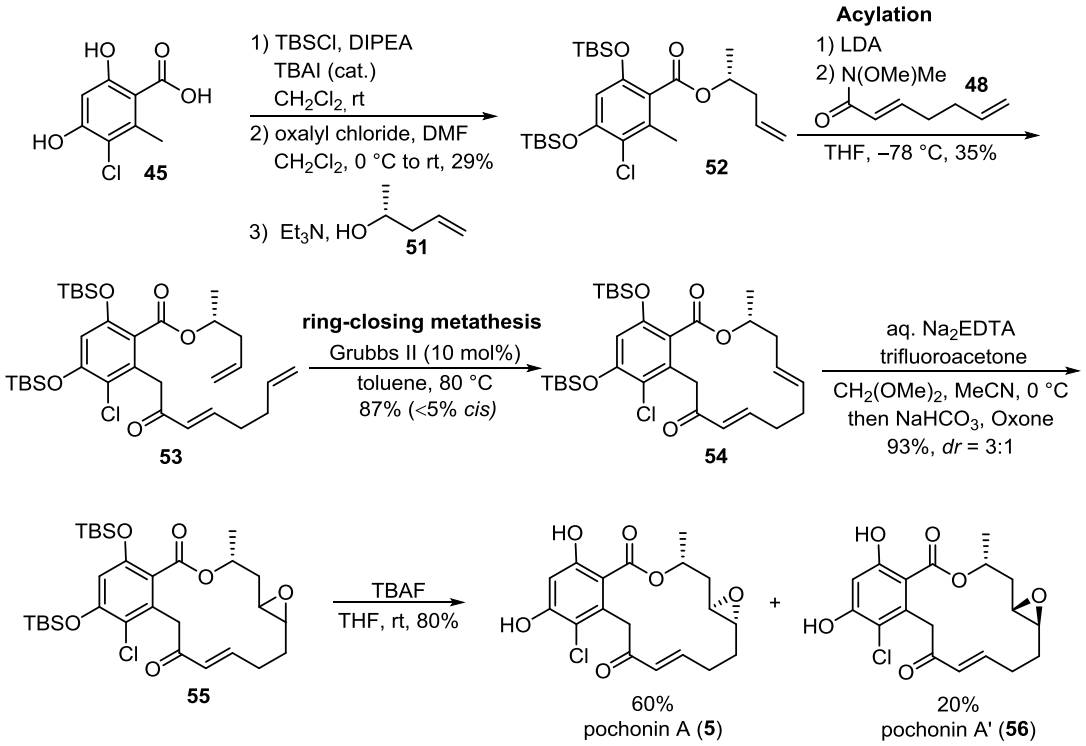
One year after the report on a synthesis of pochonin C (**7**), the Winssinger group also reported the synthesis of pochonin D (**8**) (**Scheme 4**), followed by the synthesis of pochonin A (**5**) (**Scheme 5**), which exploited the same key strategies. The synthesis of compound **8** started with regioselective aromatic chlorination of 2-hydroxytoluic acid (**40**) to give chlorohydroxytoluic acid **45** in 92% yield. Compound **45** was subjected to esterification with (*S*)-4-penten-2-ol (**46**) under Mitsunobu conditions to form the corresponding ester product, which was directed to protection of phenol with EOM groups to provide ester **47** in 95% yield. Acylation of **47** with Weinreb amide **48** furnished the RCM precursor **49**, which was assembled in the presence of second-generation Grubbs catalyst in toluene at 80 °C to give macrolide **50** with >95% of (*E*)-product in 40% yield over 2 steps. Removal of the EOM groups using sulfonic acid resin yielded pochonin D (**8**) in 90% yield.

Scheme 4 Winssinger's synthesis of pochonin D (**8**)



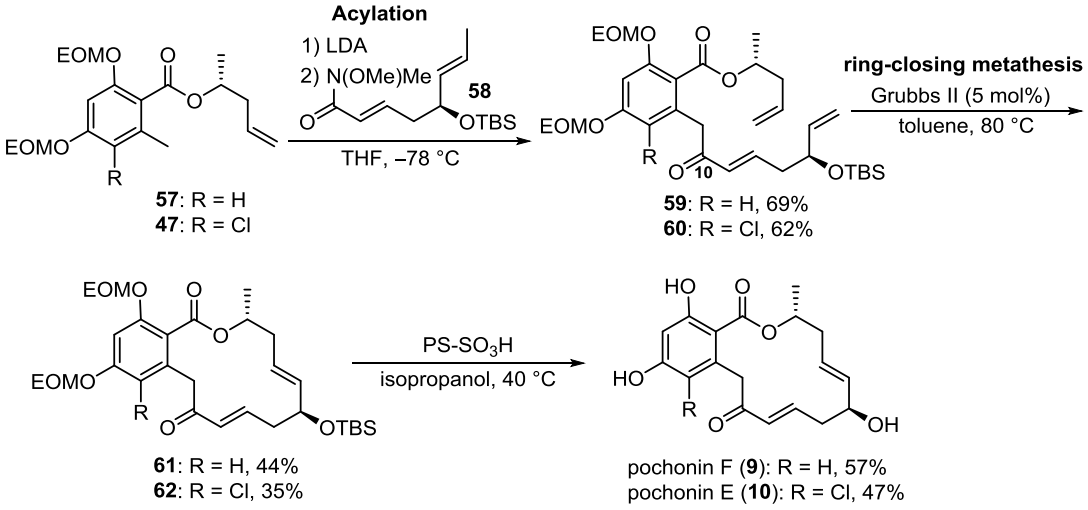
The synthesis of pochonin A (**5**) started with persilylation of benzoic acid **45**, followed by conversion of the silyl ester to the acyl chloride, which was subjected to esterification with (*R*)-4-penten-2-ol (**51**) to furnish ester **52** in 29% yield over 2 steps. Addition of lithiated **52** to Weinreb amide **48** at −78 °C produced diene **53** containing the α,β-unsaturated ketone at the 8-10 positions in 35% yield. Diene RCM precursor **53** was cyclized using 10 mol% of second-generation Grubbs catalyst to construct macrolide **54** in 87% yield with high (*E*)-selectivity (>95%) of the resultant alkene. Epoxidation of **54** using methyl(trifluoromethyl) dioxirane generated in situ, followed by deprotection of TBS groups yielded **5** and its diastereomer **56** in 80% yield after chromatographic separation.

Scheme 5 Winssinger's synthesis of pochonin A (**5**)



In 2012, the syntheses of pochonins E (**9**) and F (**10**) were presented by Winssinger and co-workers, which employed the key synthetic protocol similar to their other syntheses of the pochonin series (**Scheme 6**). The formation of ketone moiety at C-10 of compounds **59** and **60** utilized the key acylation of Weinreb amide **58** to provide dienes **59** and **60** in 69% and 62% yield, respectively. Diene RCM precursors **59** and **60** were subjected to macrocyclization using 5 mol% of second-generation Grubbs catalyst to form 14-membered macrolactone skeleton **61** in 44% yield and 35% yield for **62**. The global deprotection of all protecting groups using sulfonic acid resin furnished **9** and **10** in 57% and 47% yield, respectively.

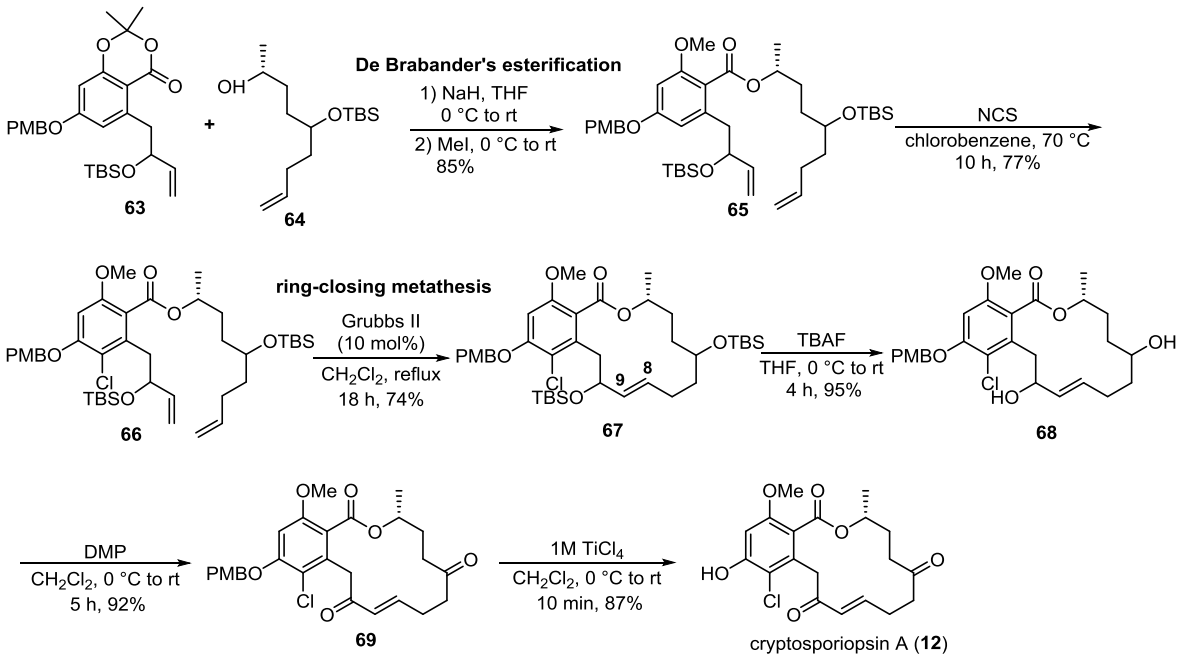
Scheme 6 Winssinger's synthesis of pochonins E (**9**) and F (**10**)



In addition to the accomplishment of the (*E*)-enone functionality at the 8-10 positions of these compounds by aforementioned strategies, the ring-closing metathesis reaction has been successfully demonstrated to construct the macrolactone core and also to establish *E*-double bond at C8–C9. The first example using ring-closing metathesis to form C8–C9 bond was reported on the total synthesis of cryptosporiopsin A (**12**) by Thirupathi and Mohapatra in 2014 as shown in **Scheme 7**. The ester bond formation of **65** was carried out via De Brabander's esterification of 1,3-benzodioxin derivative **63** and alcohol **64** using NaH in THF, followed by methylation with iodomethane to give ester product **65** in 85% yield. Diene RCM precursor **66** was obtained from regioselective chlorination of **65** using

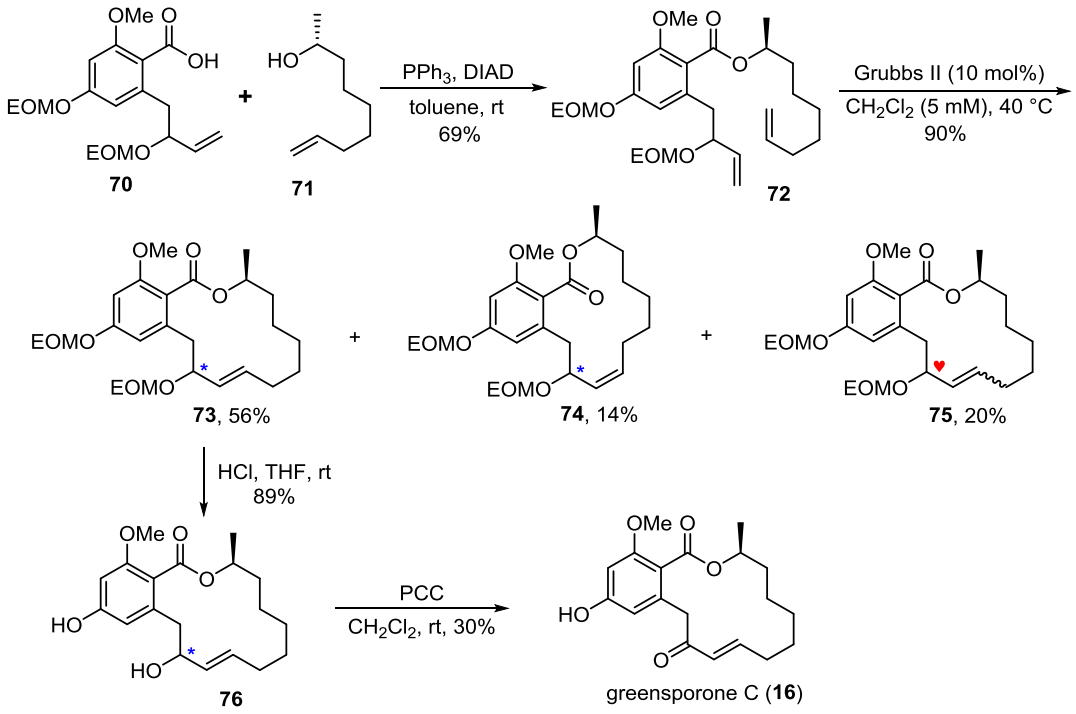
N-chlorosuccinamide in 77% yield. Assembly of 14-membered macrolactone proceeded smoothly under ring-closing metathesis conditions using 10 mol% of second-generation Grubbs catalyst to afford highly selective *E*-olefin of **67** as a 1:1:1:1 diastereomeric mixture in 74% yield. Removal of the silyl groups using TBAF and oxidation of secondary alcohols to ketones was completed by Dess–Martin periodinane to furnish compound **69** in 92% yield as a single isomer. Treatment of the compound **69** with $TiCl_4$ in CH_2Cl_2 yielded **12** in 87% yield.

Scheme 7 Thirupathi and Mohapatra's synthesis of cryptosporiopsin A (**12**)



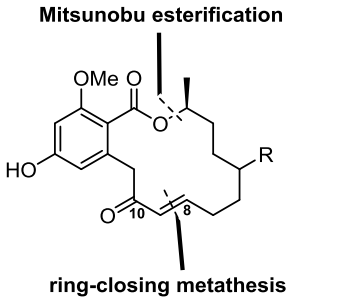
Another example of utilization of ring-closing metathesis to assemble the macrolactone core and to generate the *E*-double bond at C8–C9 was reported on the total synthesis of greensporone C (**16**) by Tadpetch et al. in 2017 (**Scheme 8**). The ester bond was formed by Mitsunobu esterification conditions between benzoic acid fragment **70** and (*R*)-non-8-en-2-ol (**71**) to give ester **72** in 69% yield. Subsequent ring-closing metathesis of diene precursor **72** in the presence of 10 mol% of second-generation Grubbs catalyst in refluxing CH_2Cl_2 provided macrolactone (*E*)-**73**, macrolactone (*Z*)-**74** and inseparable diastereomers of the (*E*)- and (*Z*)-macrocyclic adducts **75** in 56%, 14% and 20% yield, respectively. Removal of both EOM protecting groups of **73** using HCl in THF furnished diol **76** in 89% yield. Finally, oxidation of the resultant allylic alcohol **76** using pyridinium chlorochromate (PCC) gave **16** in 30% yield.

Scheme 8 Tadpetch's synthesis of greensporone C (**16**)



All of the synthetic protocols for the syntheses of radicicol analogues mentioned above indicate that Mitsunobu esterification is a popular and reliable method to form the ester functionality, while ring-closing metathesis is one of the good approaches to construct the macrolactone core and to also generate the *E*-double bond at the C8–C9 with high *E*-selectivity and excellent yield. Inspired by these reports, our synthetic approach toward dechlorogreensporones A (**25**) and D (**26**) would utilize key ring-closing metathesis to assemble the macrocycle and to also establish the (*E*) geometry, while ester functional group would be constructed from Mitsunobu esterification (**Scheme 9**).

Scheme 9 Proposed key synthetic features of dechlorogreensporones A (**25**) and D (**26**)



dechlorogreensporone A (**25**): R = ═O
dechlorogreensporone D (**26**): R = ━OH

1.2 Objectives

1. To synthesize dechlorogreensporones A (**25**) and D (**26**)

2. To prove the proposed absolute configuration of the natural products

CHAPTER 2

SYNTHESES OF DECHLOROGREENSPORONES A AND D

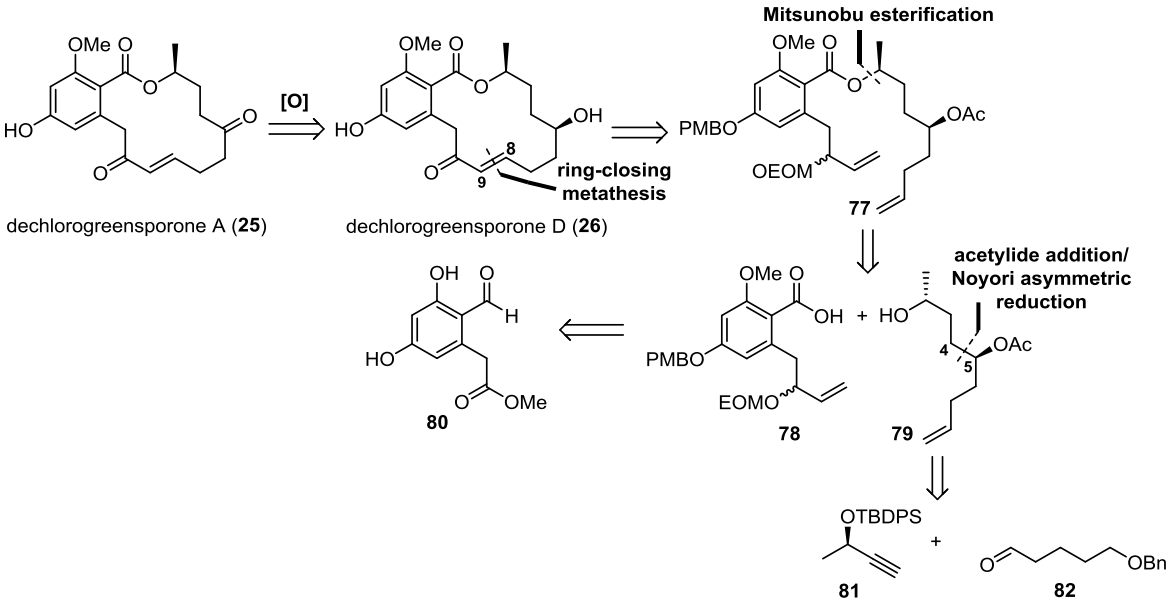
CHAPTER 2

SYNTHESES OF DECHLOROGREENSPORONES A AND D

2.1 Results and Discussion

Since dechlorogreensporone A (**25**) is structurally very similar to previously reported natural product cryptosporiopsin A (**12**) (Talontsi *et al*., 2012), we chose to utilize similar key bond disconnection to Mohapatra and Thirupathi's protocol (Mohapatra and Thirupathi, 2014) and our previous report (Tadpetch *et al*., 2017) for the retrosynthetic analysis of **25** and **26** as illustrated in **Scheme 10**. We planned to construct the 14-memberd macrocyclic core and the *E*-double bond at C8–C9 by ring-closing metathesis (RCM), and to form the ester functional group via Mitsunobu esterification. We envisioned that dechlorogreensporone A (**25**) would be obtained from oxidation of dechlorogreensporone D (**26**). Compound **26** would be assembled from diene precursor **77** by RCM. Diene **77** would then be united by Mitsunobu esterification of benzoic acid **78** and alcohol **79**. The benzoic acid fragment **78** would be obtained from known phenol **80**, while chiral alcohol intermediate **79** would be prepared from (*R*)-3-[(*tert*-butyldiphenylsilyl)oxy]-1-butyne (**81**) and 5-(benzyloxy)pentanal (**82**) via acetylide addition (Singh and Argade, 2010). The resulting racemic alcohol from acetylide addition would be oxidized to the corresponding ketone (Newton *et al*., 2014), which would then be reduced to the (*S*)-propargylic alcohol via Noyori asymmetric reduction (Sabitha *et al*., 2012).

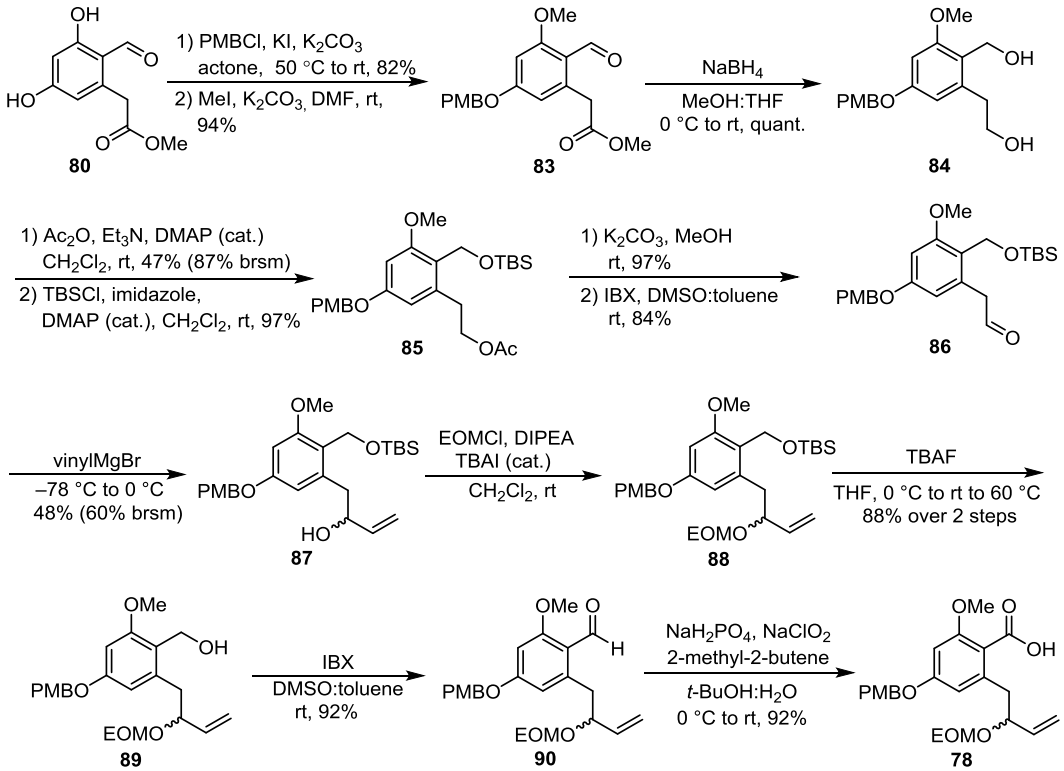
Scheme 10 Retrosynthetic analysis of dechlorogreensporones A (**25**) and D (**26**)



We started with the synthesis of requisite benzoic acid fragment **78** from known phenol **80** (von Delius *et al*., 2012), which required the different protecting groups on phenol moieties (**Scheme 11**). The 4-methoxybenzyl ether (PMB) group would be used as a protecting group on the benzoic acid fragment since it could be selectively removed in the presence of the methoxy group on β-resorcylic acid moiety (Mohapatra and Thirupathi, 2014). The selective protection of non-chelated phenol moiety of **80** with PMB group (Cai *et al*., 2015) using 1.1 equivalents of PMBCl, K_2CO_3 and KI in acetone at 50 ^oC provided PMB ether, which was subjected to methylation of the remaining phenol moiety with iodomethane and K_2CO_3 in DMF to give methyl ether **83** in 94% yield. Following our previously reported protocol (Tadpetch *et al*., 2017), both aldehyde and ester functional groups of compound **83** were reduced using 3.0 equivalents of $NaBH_4$ to give diol **84** in quantitative yield without purification. To achieve the requisite aldehyde **86**, selective acetylation of primary alcohol in the presence of benzylic alcohol of diol **84** was accomplished by treatment with acetic anhydride (1.0 equiv) and Et_3N (1.0 equiv) in the presence of catalytic DMAP to give monoacetate in 87% based on the recovered diol. Subsequent protection of the benzylic alcohol with TBS group using TBSCl, imidazole and DMAP in CH_2Cl_2 provided silyl ether **85** in 97% yield. Removal of the

acetyl group of **85** employing methanolysis (K_2CO_3 in MeOH) yielded the primary alcohol, which was oxidized by IBX to give the corresponding aldehyde **86** in 84% yield. Addition of vinylmagnesium bromide to aldehyde **86** in dry THF at −78 ^oC afforded racemic allylic alcohol **87** in 60% yield based on recovered aldehyde. The newly generated alcohol chiral center would finally be oxidized to a ketone therefore the stereoselectivity of this step was insignificant. Protection of allylic alcohol using a large excess (8.0 equivalents) of EOMCl in the presence of catalytic tetrabutylammonium iodide (TBAI) gave the corresponding EOM ether, which was immediately used in the next step with no chromatographic purification. Removal of the TBS protecting group was completed using TBAF in THF at 60 ^oC to furnish benzylic alcohol **89** in 88% yield over 2 steps. Finally, benzylic alcohol **89** was then converted to benzoic acid **78** via IBX oxidation of benzaldehyde derivative **90**, followed by Pinnick oxidation to deliver the desired benzoic acid **78** in 92% yield.

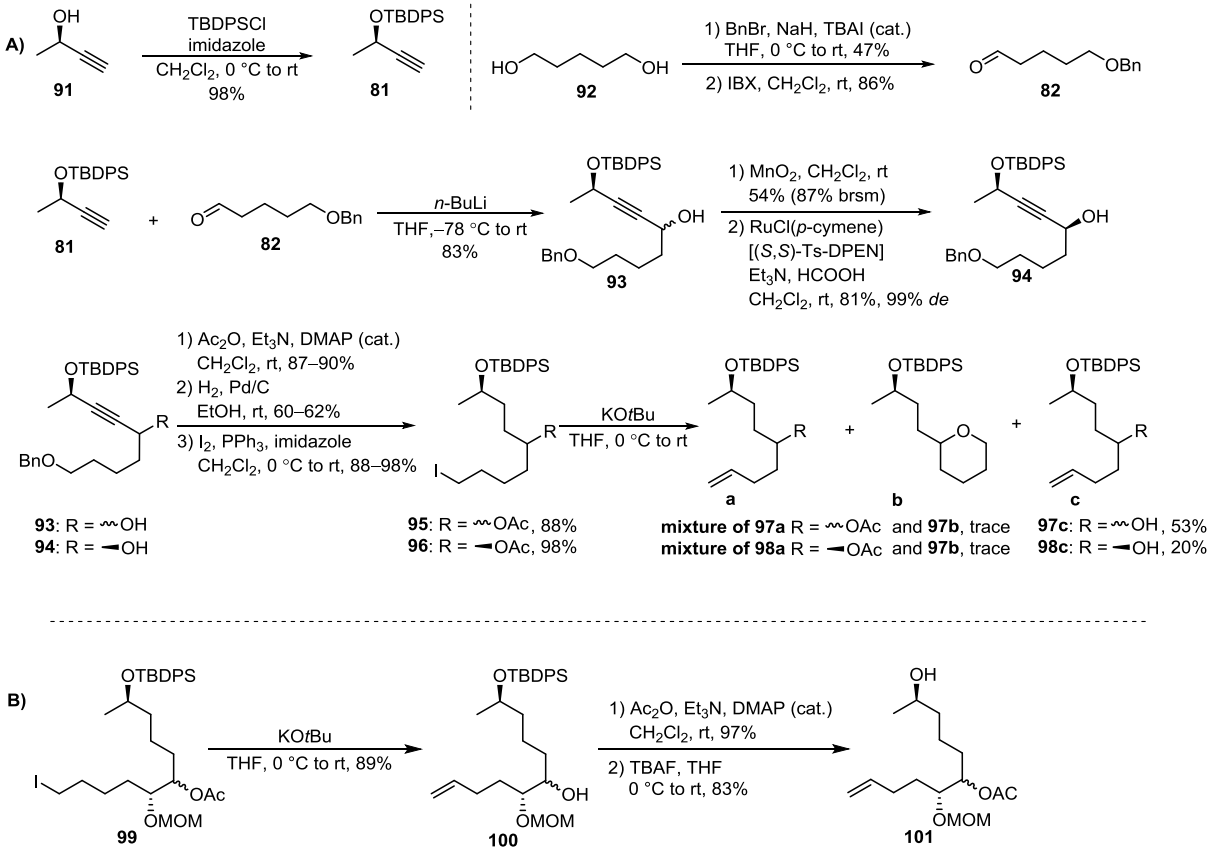
Scheme 11 Synthesis of benzoic acid fragment **78**



To achieve the chiral alcohol **79**, we began with preparation of key fragments alkyne **81** and 5-(benzyloxy)pentanal (**82**). Alkyne **81** was prepared from silylation of commercially available (*R*)-3-butyn-2-ol (**91**) (Kiyotsuka *et al*., 2009). Aldehyde **82** was synthesized from 1,5-pentanediol (**92**) in 2 steps via monobenzylation using BnBr and NaH in the presence of TBAI, followed by IBX oxidation (Reddy *et al*., 2015). With both alkyne **81** and aldehyde **82** in hand, the formation of alcohol intermediate **79** was undertaken via key acetylide addition to construct C4–C5 bond of the core structure (**Scheme 12A**). The acetylide anion generated *in situ* from deprotonation of terminal alkyne **81** with *n*-BuLi was treated with aldehyde **82** to give propargylic alcohol **93** as a mixture of diastereomers in 83% yield (Singh and Argade, 2010). Oxidation of propargylic alcohol **93** using a large excess of manganese dioxide (MnO_2) (Newton *et al*., 2014), followed by Noyori asymmetric reduction in the presence of catalytic RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN] yielded (*S*)-propargylic alcohol **94** in 81% yield (Sabitha *et al*., 2012) and 99% *de* (determined by chiral HPLC). To test the viability of proposed synthesis of chiral alcohol **79** and to save the precious chiral alcohol **94**, we continued on the next steps with racemic propargylic alcohol **93**. Compound **93** was then protected with Ac_2O to furnish acetate ester. Reduction of alkyne and simultaneous removal of the benzyl group of acetate ester under hydrogenolysis conditions using H_2 and Pd/C (12 mol%) in EtOH afforded the corresponding primary alcohol. Subsequent iodination of primary alcohol using I_2, PPh_3 and imidazole provided iodide **95** in 88% yield, which was subjected to elimination with KO*t*Bu in THF at 0 ºC. Excess (3.5 equivalents) KO*t*Bu was required to ensure complete consumption of starting iodide **95**, however, the acetyl protecting group was removed in this step to provide alcohol **97c** in 53% yield and trace amount of the inseparable mixture of alkene **97a** and tetrahydropyran **97b**. Unexpected formation of tetrahydropyran **97b** and alcohol **97c** was attributed to competitions between hydrolysis of acetyl group/intramolecular S_N2 and elimination of iodide/hydrolysis of acetyl group under these conditions. It should be noted that the results from these conditions contrasted with our previous work (Thiraporn *et al*., 2017). Elimination of alkyl iodide **99** containing 11 carbon atoms under the same conditions provided the desired alkene **100** with complete loss of acetyl group in 89% yield. The resulting alcohol product **100** from hydrolysis of acetate was reprotected

with acetyl group, followed by desilylation to give the desired chiral alcohol **101** as shown in **Scheme 12B** (Thiraporn *et al*., 2017). Our results of elimination of racemic iodide **95** were confirmed with elimination of chiral iodide **96** under the same conditions. Disappointingly, alcohol **98c** was obtained in much lower (20% yield) and trace amount of the inseparable mixture of alkene **98a** and tetrahydropyran **98b** was also observed. Even though alcohols **97c** and **98c** could be used in the next step following this synthetic route, these compounds were obtained in quite low yield particularly the requisite chiral alcohol **98c**.

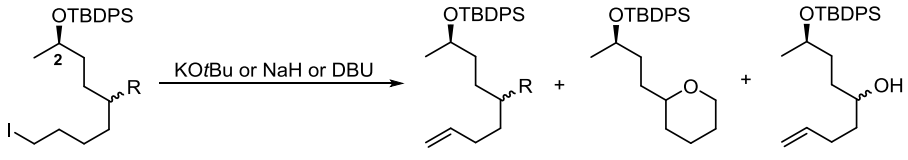
Scheme 12 A) Attempted synthesis of chiral alcohol **79** B) Thiraporn's synthesis of chiral alcohol **101**



Since the acetyl protecting group chosen was easily hydrolyzed under basic conditions, the elimination step was then attempted with different protecting groups i.e. benzoyl (Bz), ethoxymethyl (EOM), triisopropylsilyl (TIPS) and *tert*-butyldi phenylsilyl (TBDPS) ether groups (**Table 1**). The iodide starting materials **102**−**105** were prepared in the same fashion starting from racemic propargylic alcohol **93**. Similarly, when the iodide **102** containing benzoyl protecting group was treated with 3.5 equivalents of KO*t*Bu in THF at 0 ºC, 44% yield of alcohol **97c** was obtained along with trace amount of the mixture of alkene **102a** and tetrahydropyran **97b** (entry 2). The results from elimination of these iodide starting materials consisting of ester protecting groups (OAc and OBz) with KO*t*Bu suggested that these conditions led to facile hydrolysis of ester protecting groups and competitive tetrahydropyran formation. Moreover, the mixture of alkene product and unexpected tetrahydropyran was inseparable. Due to unsuccessful elimination of iodides **95** and **102** containing ester protecting groups, alkoxyether and silyl protecting groups were chosen since these protecting groups could not be hydrolyzed under these conditions. The iodide compound **103** with EOM protecting group was then treated under the same conditions (entry 3). Disappointingly, no desired product was obtained from this reaction and the starting material was recovered. Next, iodides with silyl protecting groups (TIPS and TBDPS) were then chosen since the selective deprotection of silyl group in the final step was possible. We expected that the selective removal of TIPS and TBDPS protecting groups at the 2-position in the final step would be easier than the TBDPS group at the 5-position due to the steric hindrance of alkyl sidechain (Williams *et al*., 2001). The iodide compounds with silyl protecting groups **104** and **105** were employed under the similar conditions using 3.0 equivalents of KO*t*Bu in THF at 0 ºC. Gratifyingly, the desired alkene products **104a** and **105a** were obtained in 41% and 53% yield, respectively (entries 4−5). Although the elimination of iodide compounds with silyl protecting groups **104** and **105** successfully gave the desired alkene products in moderate yields, selective deprotection of TBDPS groups at the 2-position of **104** and **105** in the presence of TIPS and TBDPS groups at the 5-position was unsuccessful. It was observed that the TIPS group was easier to remove by fluoride source (TBAF) than the TBDPS group due to the steric hindrance of silyl group to provide secondary alcohol at the 5-positon as a product. Attempts to

selectively deprotect the TBDPS group at the 2-position in the presence of the same group at the 5-position was again unsuccessful. A mixture of undesired secondary alcohol at the 5-position and diol was obtained. Owing to the failure of all cases, we decided to modify the conditions toward elimination of iodide compounds **95** and **103** with another bases such as NaH and DBU (entries 6−8) (Martinez *et al*., 1992, Barluenga *et al*., 1997, Khan *et al*., 2009 and Kitagaki *et al*., 2010). For iodide **95**, trace amount of the desired alkene product **97a** was observed under elimination conditions using NaH in DMF or DBU in benzene (entries 6 and 8). Unfortunately, iodide **103** containing EOM protecting group was recovered upon attempted elimination under the conditions of NaH in DMF (entry 7).

Table 1 Screening for elimination of iodide compounds



95: R = OAc
102: R = OBz
103: R = OEOM
104: R = OTIPS
105: R = OTBDPS

97a: R = OAc
102a: R = OBz
103a: R = OEOM
104a: R = OTIPS
105a: R = OTBDPS

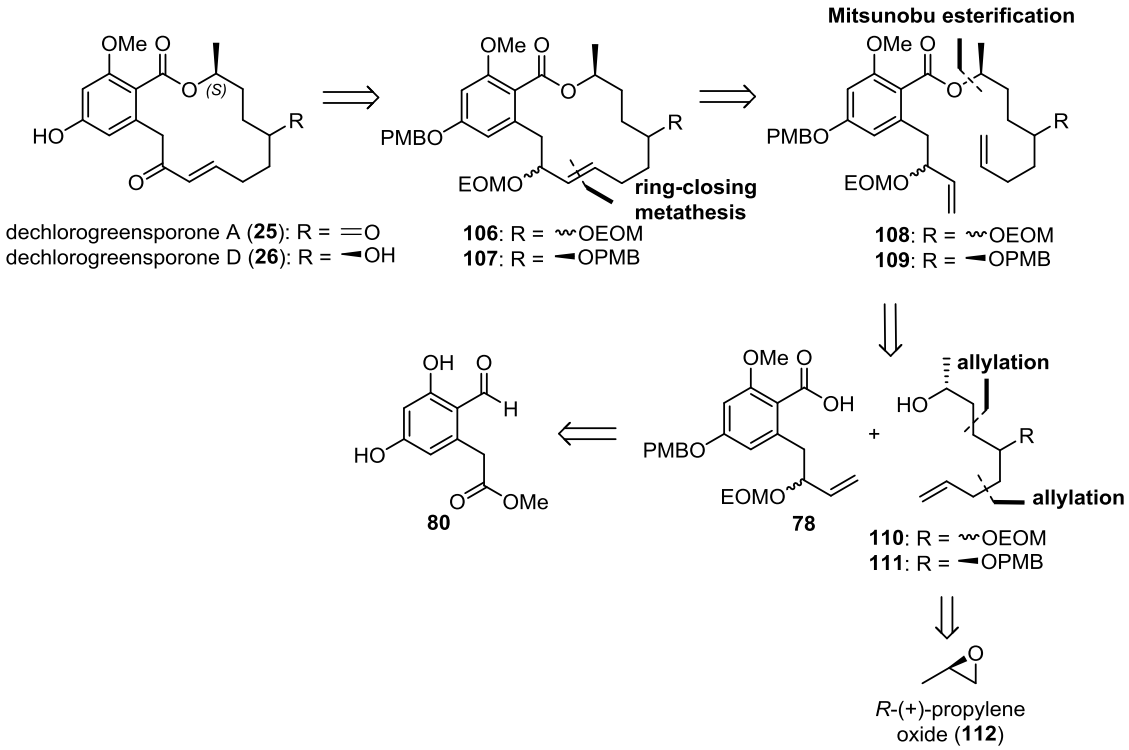
97b

97c

Entry	**R**	**Base (equiv)**	**Conditions**	**Results**
1	OAc	KO*t*Bu (3.5 equiv)	THF, 0 °C to rt, 3 h	trace mixture of **97a** and **97b** 53% yield for **97c**
2	OBz			trace mixture of **102a**, **97b** 44% yield for **97c**
3	OEOM			no reaction
4	OTIPS	KO*t*Bu (3.0 equiv)		41% for **104a**
5	OTBDPS			53% for **105a**
6	OAc	NaH (3.0 equiv)	DMF, 0 °C to rt, 3 h	trace amount of **97a**
7	OEOM			no reaction
8	OAc	DBU (4.0 equiv)	benzene, 0 °C to 85 °C, 3 h	trace amount of **97a**

Owing to unsuccessful formation of terminal alkene of alcohol key fragment **79**, revision of retrosynthesis of key chiral alcohol fragment for Mitsunobu esterification was necessitated and will be discussed, which also led to the revised retrosynthetic strategy of dechlorogreensporones A (**25**) and D (**26**). The revised retrosynthetic approach of target molecules **25** and **26** still used the same key bond disconnections via ring-closing metathesis and Mitsunobu esterification (**Scheme 13**). Structurally, dechlorogreensporones A (**25**) and D (**26**) only differ by the functional groups at the 5-position therefore these compounds could be prepared from the same intermediate. Target **26** challenges its synthesis due to the presence of the alcohol stereogenic center at the 5-position. Consequently, the synthesis of the alcohol fragments **110** and **111** required two different approaches with suitable protecting groups. Dechlorogreensporones A (**25**) or D (**26**) would be obtained from macrolactones **106** or **107**, respectively. Compounds **106** or **107** would be prepared from RCM precursors **108** or **109**, respectively via ring-closing metathesis. The diene RCM precursors **108** or **109** would be united by Mitsunobu esterification between the benzoic acid fragment **78** and alcohol intermediate **110** or **111**. Our next task is to synthesize both alcohols **110** and **111**, which would be prepared in the same fashion starting from *R*-(+)-propylene oxide (**112**) via double allylation. In addition, asymmetric carbon at the 5-position of chiral alcohol **111** would be installed via Jacobsen hydrolytic kinetic resolution (O'Brien *et al*., 2005).

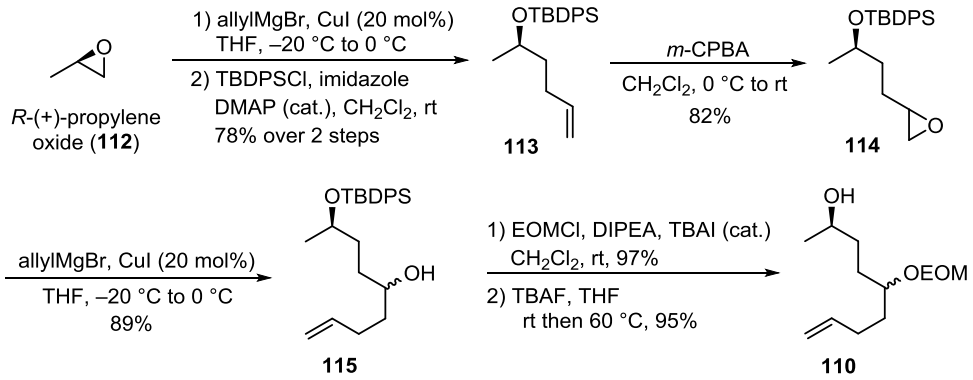
Scheme 13 Revised retrosynthetic analysis of dechlorogreensporones A (**25**) and D (**26**)



The revised synthesis of alcohol **110** for the synthesis of dechlorogreensporone A (**25**) was completed in 6 steps from commercially available *R*-(+)-propylene oxide (**112**) (>99% *ee*) as shown in **Scheme 14**. Following the procedure disclosed by Xie and co-workers, regioselective ring opening of **112** by allylmagnesium bromide in the presence of catalytic CuI (20 mol%) provided the corresponding chiral secondary alcohol, which was immediately protected with TBDPS group using TBDPSCl and imidazole in the presence of catalytic DMAP to give TBDPS ether **113** in 78% yield over 2 steps. The racemic alcohol **115** was obtained from **113** in 2 steps via an epoxidation with *m*-CPBA to provide racemic epoxide **114**, which was then subjected to another regioselective ring opening by allylmagnesium bromide to give racemic alcohol **115** in 89% yield (Wang *et al*., 2016). The stereoselectivity of this step was inconsequential since the newly generated alcohol chiral center would eventually be oxidized to a ketone. The secondary alcohol of **115** was protected with ethoxymethyl (EOM) group using excess EOMCl in the presence of catalytic TBAI to furnish EOM ether, which after

removal of TBDPS protecting group with TBAF in THF at 60 °C delivered the desired alcohol **110** in 95% yield. The absolute configuration of the alcohol stereogenic center at the 2-position was determined to be *R* based on Mosher's method.

Scheme 14 Synthesis of alcohol **110**



With both benzoic acid derivative **78** and alcohol intermediate **110** in hand, we continued to complete the synthesis of dechlorogreensporone A (**Scheme 15**). Union of the two key fragments **78** and **110** under Mitsunobu esterification conditions using diisopropyl azodicarboxylate (DIAD) and PPh_3 in toluene at room temperature gave the ester RCM diene precursor **108** in 72% yield. This Mitsunobu esterification step should also provide the correct stereochemistry of the C-2 stereogenic center of the natural product. Owing to successful use of this catalyst on *E*-selective RCM for this type of substrate as reported by Thirupathi and Mohapatra (Thirupathi and Mohapatra, 2014) and our group (Tadpetch *et al*., 2017), the key ring-closing metathesis of diene **108** was originally attempted with second-generation Grubbs catalyst. However, the second-generation Grubbs catalyst proved to be less reactive and led to incomplete consumption of the starting diene **108**. Fortunately, RCM of diene precursor **108** proceeded to completion within 3.5 h by using 10 mol% of second-generation Hoveyda-Grubbs catalyst in toluene at high dilution (5 mM) at 85 °C to give the desired macrocycle **106** in 59% yield as an inseparable mixture of diastereomers. The separation of these diastereomeric products was unnecessary because they would finally be oxidized into the same diketo product in the penultimate step. It should be noted that the geometry of the C8–C9 olefin could not

be determined by NMR spectroscopy at this stage. The diastereomeric mixture of **106** was then carried on to the removal of both EOM protecting groups under acidic conditions using 4M HCl in THF at room temperature to furnish diol **116** in 57% yield as a mixture of diastereomers. Subsequent oxidation of both hydroxyl groups of diol **116** using a large excess Dess-Martin periodinane in CH_2Cl_2 delivered diketone **117** in 62% yield. The geometry of the resulting C8–C9 olefin of macrocyclic products from RCM was confirmed to be *trans* in this step based on the coupling constant of 15.6 Hz between H-8 and H-9. Finally, deprotection of PMB group of diketone **117** with 1M titanium tetrachloride in CH_2Cl_2 at 0 °C (Thirupathi and Mohapatra, 2014) smoothly provided dechlorogreensporone A (**25**) in 79% yield. The ^{1}H and ^{13}C NMR spectroscopic data as well as HRMS data of synthetic dechlorogreensporone A (**25**) were nearly identical to those reported for natural **25** (**Table 2**). Additionally, the specific rotation of synthetic **25** ($[\alpha]_D^{26.4}$ = +66.0, *c* 0.10, MeOH) was in excellent agreement with the reported value for natural **25** ($[\alpha]_D^{20}$ = +56.0, *c* 0.10, MeOH) (El-Elimat *et al*., 2014). Thus, our synthesis confirmed the absolute configuration of the natural product dechlorogreensporone A determined by Oberlies and co-workers.

Scheme 15 Completion of the synthesis of dechlorogreensporone A (**25**)

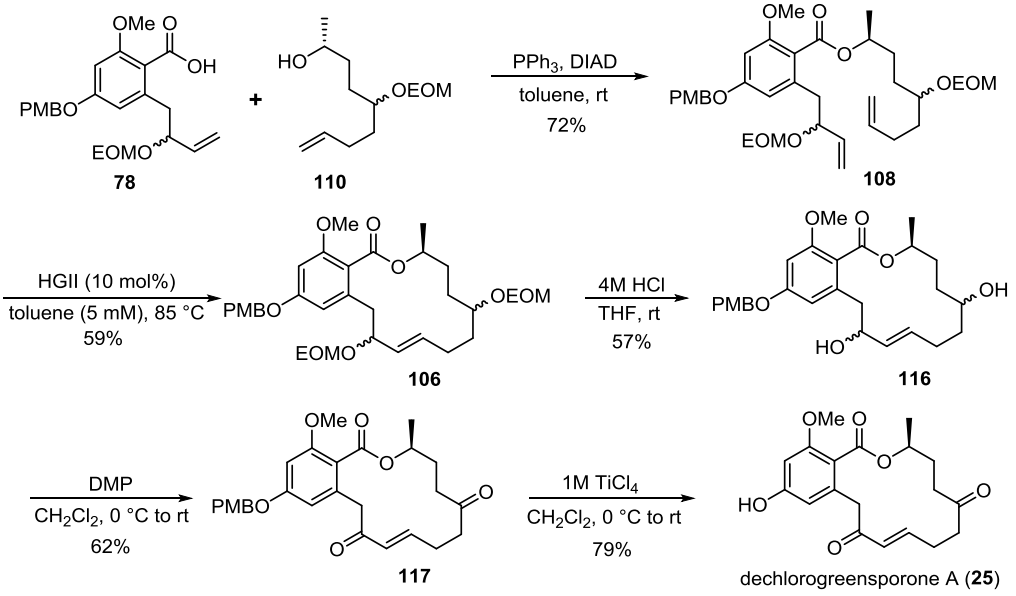


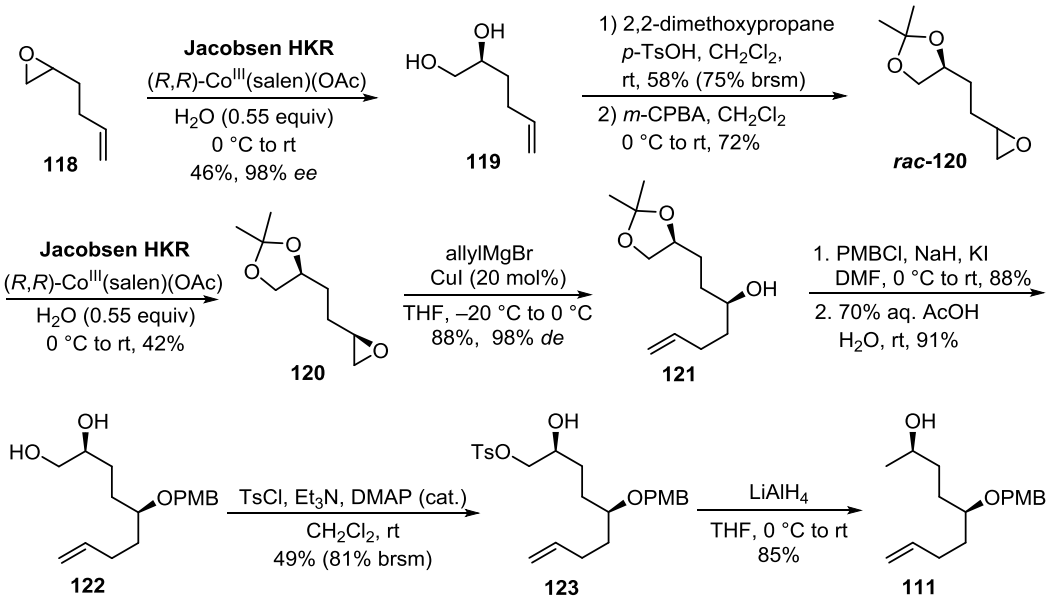
Table 2 Comparison of ^{1}H and ^{13}C NMR data in $CDCl_3$ for natural and synthetic **25**

Position	**^{1}H NMR** (δ and *J* in Hz)		**^{13}C NMR** (δ)	
	Natural (500 MHz)	Synthetic (300 MHz)	Natural (125 MHz)	Synthetic (75 MHz)
1	1.36, d (6.3)	1.37, d (6.0)	20.5	20.5
2	5.18, m	5.21–5.16, m	71.2	71.4
3	1.76, m	1.84–1.72, m	28.5	28.4
	2.01, m	2.19–1.96, m		
4	2.43, m	2.73–2.40, m	39.4	39.4
	2.67, m			
5	-	-	209.9	210.1
6	2.47, m	2.73–2.40, m	40.5	40.6
	2.53, m			
7	2.47, m		28.6	28.7
	2.56, m			
8	6.79, m	6.82–6.75, m	147.1	147.5
9	6.04, d (16.0)	6.05, d (15.6)	130.7	130.6
10	-	-	198.0	198.6
11	3.33, d (14.3)	3.35, d (14.1)	43.7	44.1
	4.31, d (14.3)	4.29, d (14.1)		
12	-	-	135.0	134.9
13	6.44, d (2.3)	6.43, d (2.1)	109.6	109.8
14	-	-	158.4	159.1
14-OH	6.33, br s	-	-	-
15	6.31, d (2.3)	6.30, d (2.1)	98.5	98.9
16	-	-	159.5	159.6
17	-	-	116.1	115.7
18	-	-	168.1	168.4
19	3.74, s	3.72, s	56.0	56.0

After completion of the synthesis of dechlorogreensporone A (**25**), our next goal was toward the synthesis of dechlorogreensporone D (**26**), which would be conducted through the same synthetic approach. The synthesis of chiral alcohol **111** would require the Jacobsen hydrolytic kinetic resolution of racemic epoxide intermediate **114** to install the C-5 stereogenic center (O'Brien *et al*., 2005). Disappointingly, the generation of the chiral epoxide by Jacobsen hydrolytic kinetic resolution of epoxide **114** was unsuccessful. The epoxide starting material was recovered and no desired chiral products were observed. Therefore, the revised synthesis of chiral alcohol **111** is needed, which required a different starting material. The revised synthesis of chiral alcohol **111** was achieved in 9 steps from commercially available 1,2-epoxy-5-hexene (**118**) as illustrated in **Scheme 16**. Following the protocol by the Jacobsen group, hydrolytic kinetic resolution of racemic **118** using Jacobsen's (*R*,*R*)-Co(III)(salen)(OAc) catalyst furnished (*S*)-diol **119** in 46% yield and 98% *ee* (Schaus *et al*., 2002). The enantiomeric excess was determined by chiral HPLC on the corresponding monobenzoate of **119**. Diol **119** was treated with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid to give the corresponding acetonide in 75% yield based on the recovered diol **119** (Morin and Rychnovsky, 2005). The acetonide was then subjected to epoxidation with *m*-CPBA to deliver racemic epoxide ***rac*-120** in 72% yield (Sharma *et al*., 2009). Racemic epoxide ***rac*-120** was converted to chiral alcohol **121** in 2 steps via a second hydrolytic kinetic resolution using (*R*,*R*)-Co(III)(salen)(OAc) as a catalyst to give (*R*)-epoxide **120** in 42% yield (Sharma *et al*., 2009 and Prataparedy *et al*., 2017). Subsequent regioselective ring-opening of chiral epoxide **120** by allylmagnesium bromide in the presence of catalytic CuI (20 mol%) smoothly gave chiral alcohol **121** in 88% yield and 98% *de*. The diastereomeric excess was determined on the monobenzoate derivative of **121** by chiral HPLC. The absolute configuration of the stereogenic center at the 5-position was confirmed to be *S* based on Mosher's method. The PMB protecting group was chosen for this chiral alcohol for the purpose of global deprotection in the final step. Protection of (*S*)-alcohol **121** with excess (5 equivalents) of both PMBCl and KI gave PMB ether in 88% yield. The acetonide was then converted to chiral alcohol **111** in 3 steps via removal of the acetonide protecting group with 70% AcOH gave diol **122** in 91% yield. Subsequent monotosylation using

TsCl and Et_3N in the presence of catalytic DMAP in CH_2Cl_2, followed by reduction using $LiAlH_4$ in THF yielded the requisite chiral alcohol **111** in 85% yield (Prataparedy *et al*., 2017). The absolute configuration of the alcohol stereogenic center at the 2-position was confirmed to be *R* via Mosher ester analysis.

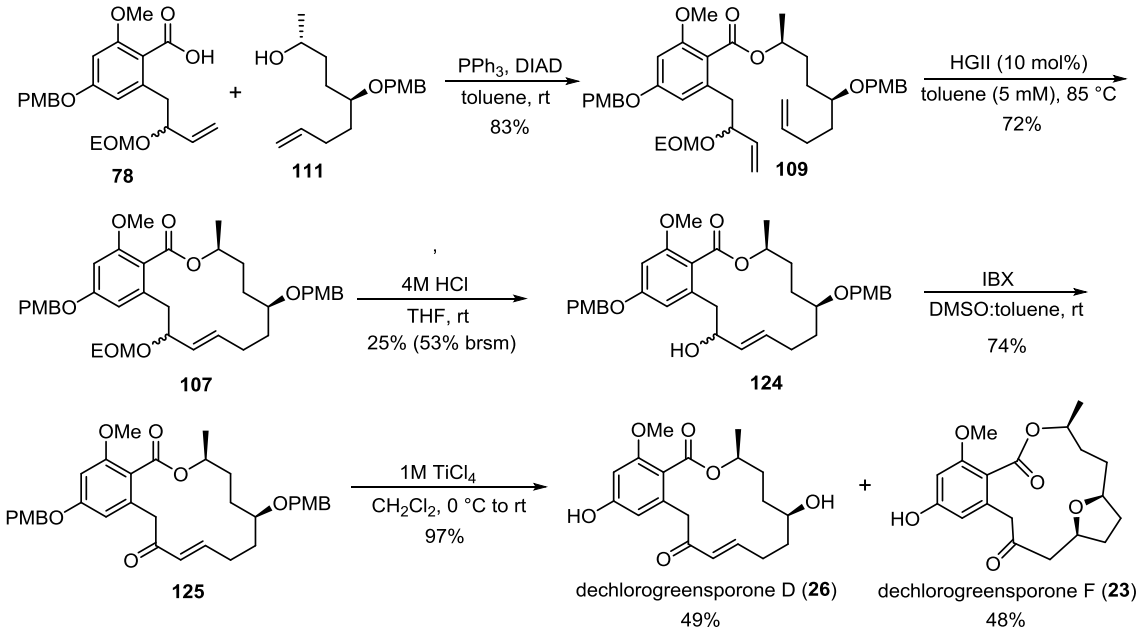
Scheme 16 Synthesis of chiral alcohol **111**



Having successfully synthesized chiral alcohol **111**, our final task was completion of the synthesis of dechlorogreensporone D (**26**), which was accomplished under the same synthetic route for **25** (**Scheme 17**). Mitsunobu esterification between benzoic acid **78** and alcohol intermediate **111** under the same conditions using DIAD and PPh_3 in toluene generated ester moiety of diene RCM precursor **109** in 83% yield. Ring-closing metathesis of diene **109** using second-generation Hoveyda-Grubbs catalyst (10 mol%) in toluene (5 mM) at 85 °C yielded macrocycle **107** in 72% yield as an inseparable mixture of diastereomers. The geometry of the newly formed C8–C9 olefin could be determined at a later stage of the synthesis. Careful removal of the EOM group under acidic conditions using 4M HCl solution in THF at room temperature for 4 h in order to prevent overdeprotection of the PMB groups provided macrolactone **124** in 53% yield based on recovered EOM ether. At this stage, the (*E*)-geometry of the C8−C9 double bond was assigned on the basis of the observation of a 15.9 Hz coupling constant between H-8 and H-9. Allylic alcohol **124** was oxidized

using excess IBX in a mixture of toluene and DMSO to afford macrocyclic enone **125** in 74% yield. Finally, global deprotection of both PMB protecting groups of **125** using 6.0 equivalents of 1M $TiCl_4$ in CH_2Cl_2 at 0 °C produced dechlorogreensporone D (**26**) in 49% yield along with unexpected analogue dechlorogreensporone F (**23**) in 48% yield. Unsurprisingly, byproduct **23** was obtained from the facile intramolecular cycloetherification of the desired target **26**, which was proposed by Oberlies and co-workers (El-Elimat *et al*., 2014) as shown in **Scheme 18**. The ^{1}H and ^{13}C NMR spectroscopic and HRMS data as well as analytical properties of synthetic dechlorogreenspones D (**26**) and F (**23**) were identical to those reported for the natural products **26** and **23** (**Table 3**). The specific rotation of synthetic **26** was observed as $[\alpha]_D^{26.8}$ = +64.60 (*c* 0.27, MeOH), which was in accordance with that of natural **26** ($[\alpha]_D^{20}$ = +116.0, *c* 0.27, MeOH), yet in a lower magnitude (El-Elimat *et al*., 2014). In addition, the specific rotation of synthetic **23** was obtained as $[\alpha]_D^{27.3}$ = –38.48 (*c* 0.11, MeOH), which was also nearly identical to the reported value for natural **23** ($[\alpha]_D^{20}$ = –31.0, *c* 0.11, MeOH). Our synthesis hence verified the absolute configuration of the natural product dechlorogreensporones D and F assigned by Oberlies group.

Scheme 17 Completion of the synthesis of dechlorogreensporone D (**26**)



Scheme 18 Proposed mechanism for the intramolecular cycloetherification of *ε*–hydroxy–*α*,*β*–unsaturated ketones by Oberlies and co-workers

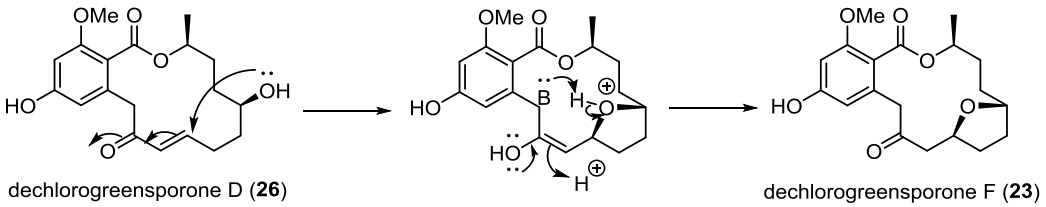


Table 3 Comparison of ^{1}H and ^{13}C NMR data in DMSO-d_6 for natural and synthetic **26**

Position	^{1}H NMR (δ and *J* in Hz)		^{13}C NMR (δ)	
	Natural (500 MHz)	Synthetic (300 MHz)	Natural (125 MHz)	Synthetic (75 MHz)
1	1.21, d (5.7)	1.23, d (5.7)	20.1	20.2
2	4.91, m	4.94–4.87, m	69.3	69.4
3	1.51, m	1.54–1.40, m	30.2	30.3
	1.76, m	1.79–1.68, m		
4	1.06, m	1.19–1.10, m	29.2	29.2
	1.52, m	1.54–1.40, m		
5	3.35, m	3.42–3.36, m	66.1	66.2
5-OH	4.48, br s	4.54, br s		
6	1.41, m	1.54–1.40, m	34.6	34.6
	1.68, m	1.79–1.68, m		
7	2.15, m	2.20–2.08, m	28.2	28.3
8	6.64, ddd (16.0, 8.0, 7.5)	6.68, dt (15.9, 7.5)	148.2	148.3
9	5.95, d (16.0)	5.98, d (15.9)	128.4	128.5
10	-	-	195.9	196.0
11	3.36, d (16.0)	3.42 –3.36, m	44.6	44.6
	4.03, d (16.0)	4.06, d (15.6)		
12	-	-	135.6	135.6
13	6.25, d (2.3)	6.29, s	109.7	109.7
14	-	-	159.8	159.8
14-OH	9.98, br s	10.0, br s	-	-
15	6.35, d (2.3)	6.39, s	98.5	98.5
16	-	-	159.2	159.2
17	-	-	114.1	114.2
18	-	-	167.3	167.3
19	3.68, s	3.72, s	55.9	55.9

Table 4 Comparison of ^{1}H and ^{13}C NMR data in $CDCl_3$ for natural and synthetic **23**

Position	^{1}H NMR (δ and *J* in Hz)		^{13}C NMR (δ)	
	Natural (500 MHz)	Synthetic (300 MHz)	Natural (125 MHz)	Synthetic (75 MHz)
1	1.32, d (6.3)	1.31, d (6.6)	20.9	20.8
2	5.26, m	5.28–5.25, m	72.7	72.6
3	1.83, m	2.02–1.43, m	33.0	32.9
4	1.51, m 1.96, m		31.3	31.2
5	3.81, m	3.89–3.79, m	79.5	79.3
6	1.50, m	2.02–1.43, m	33.5	33.5
7	1.65, m 1.94, m		30.5	30.4
8	4.14, m	4.22–4.14, m	76.1	76.0
9	2.55, dd (13.2, 8.0) 2.62, dd (13.2, 3.4)	2.56, dd (13.8, 8.1) 2.65, dd (13.8, 3.9)	47.9	47.8
10	-	-	207.7	208.6
11	3.90, d (17.2) 3.99, d (17.2)	3.92, d (17.1) 4.01, d (17.1)	49.0	49.1
12	-	-	134.2	133.8
13	6.25, d (2.3)	6.24, d (1.8)	109.2	109.4
14	-	-	157.7	158.4
14-OH	5.62, br s	-	-	-
15	6.34, d (2.3)	6.32, d (1.8)	98.3	98.5
16	-	-	159.0	159.0
17	-	-	117.3	116.5
18	-	-	167.7	167.9
19	3.77, s	3.73, s	56.0	55.8

The synthetic dechlorogreensporones A (**25**) and D (**26**) were assessed for their cytotoxic activity by MTT assay against seven human cancer cell lines consisting of two breast adenocarcinoma (MDA-MB-231 and MCF-7), one colorectal carcinoma (HCT116), one hepatoma (HepG2) and three cervical carcinoma (C33A, HeLa and SiHa) cells, as well as one monkey kidney non-cancerous cell line by the

laboratory of Dr. Panata Iawsipo, Burapha University (**Table 5**). It was observed that both compounds could inhibit all cancer cell lines with the IC_{50} ranges of 6.94–17.25 μM for compound **25** and 6.66–11.84 μM for compound **26**, yet in lower extent compared to a standard drug doxorubicin (**Table 5**). However, synthetic compounds **25** and **26** exhibited more potent cytotoxic activity against five cancer cell lines including MDA-MB-231, MCF-7, HCT116, HepG2 and SiHa than a standard drug cisplatin. Moreover, our results also showed that dechlorogreensporone D (**26**) displayed higher cytotoxic activity against most cancer cell lines than the ketone analogue **25**, which was consistent with the report by the Oberlies group (El-Elimat *et al*., 2014). Nevertheless, dechlorogreensporone A (**25**) was approximately 5-fold less cytotoxic to Vero cells compared to **26**.

Table 5 Cytotoxic activity of synthetic dechlorogreensporones A (**25**) and D (**26**) against seven human cancer cell lines and Vero cells

cell lines	**cytotoxicity, IC_{50} (μM)**			
	25	**26**	**cisplatin**	**doxorubicin**
MDA-MB-231	9.28 ± 0.13	6.97 ± 1.73	25.25	0.51
MCF-7	17.25 ± 0.71	11.84 ± 0.05	35.5	0.29
HCT116	7.53 ± 0.13	6.97 ± 0.05	35	0.81
HepG2	13.81 ± 0.27	7.88 ± 0.88	26	0.65
C33A	10.06 ± 0.53	10.41 ± 0.13	4.72	0.19
HeLa	15.5 ± 0	7.88 ± 1.06	8.98	0.16
SiHa	6.94 ± 1.06	6.66 ± 1.02	12.18	0.18
Vero	46.00 ± 3.18	10.13 ± 0.88	17.75	>1

2.2 Conclusion

In conclusion, we completed the first total syntheses of dechlorogreensporones A (**25**) and D (**26**) in a longest linear sequence of 17 steps from known phenol **78**. The synthesis of **25** has been accomplished in 23 total steps in 2.8% overall yield, while the synthesis of **26** has been achieved in 26 total steps in 5.4% overall yield The key strategies of our syntheses include allylation of *R*-(+)-propylene epoxide to generate the C-2 stereogenic center for **25**, Jacobsen hydrolytic kinetic resolution to install the C-2 and C-5 stereogenic centers for **26**, Mitsunobu esterification to generate ester functional group and ring-closing metathesis to assemble macrocycle and to also set up the (*E*)-olefin geometry at C8−C9. Our syntheses also verified the 2*S* absolute configuration of natural dechlorogreensporone A, and the 2*S* and 5*S* absolute configurations of natural dechlorogreensporone D proposed by the Oberlies group. Synthetic compounds **25** and **26** were found to display cytotoxic activity against seven human cancer cell lines with the IC_{50} range of 6.66−17.25 μM. Moreover, dechlorogreensporone D (**26**) exhibited more potent antiproliferative activity against these seven cancer cell lines compared to dechlorogreensporone A (**25**). Nevertheless, dechlorogreensporone A (**25**) was approximately 5-fold less cytotoxic to Vero cells compared to **26**.

CHAPTER 3

EXPERIMENTAL

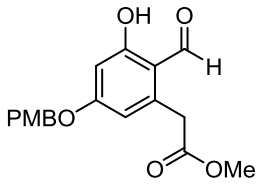
CHAPTER 3

EXPERIMENTAL

3.1 General Information

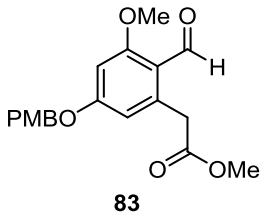
Unless otherwise stated, all reactions were performed under argon or nitgrogen atmosphere in oven- or flamed-dried glassware. Solvents were used as received from suppliers or distilled prior to use using standard procedures. All other reagents were obtained from commercial sources and used without further purification. Column chromatography was performed on SiliaFlash® G60 Silica (60-200 μm, Silicycle) or Silica gel 60 (0.063-0.200 mm, Merck). Thin-layer chromatography (TLC) was performed on Silica gel 60 F254 (Merck). ^{1}H, ^{13}C and 2D NMR spectroscopic data were recorded on a 300 MHz Bruker FTNMR UltraShield spectrometer. ^{1}H NMR spectra are reported in ppm on the δ scale and referenced to the internal tetramethylsilane. The data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, br = broad, app = apparent), coupling constant(s) in hertz (Hz), and integration. Infrared (IR) spectra were recorded on a Perkin Elmer 783 FTS165 FT-IR spectrometer. High-resolution mass spectra were obtained on a liquid chromatograph-mass spectrometer (2690, LCT, Waters, Micromass) and on a SpiralTOFTM MALDI TOF Mass Spectrometer Revolutionary (Scientific and Technological Research Equipment Centre; STREC, Chulalongkorn University). The optical rotations were recorded on a JASCO P-2000 polarimeter. Melting points were measured using an Electrothermal IA9300 melting point apparatus and are uncorrected. Enantiopurity was determined using HPLC on an Agilent series 1200 equipped with a diode array UV detector using either CHIRALCEL® OD-H column (15 cm) or CHIRALPAK® AS-H column (15 cm) and a guard column (1 cm).

3.2 Experimentals and Characterization Data



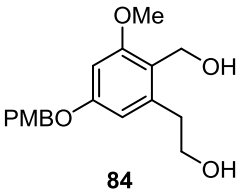
80a

PMB ether 80a. To a solution of phenol **80** (2.102 g, 10.0 mmol) in acetone (33 mL) were added KI (1.826 g, 11.0 mmol, 1.1 equiv), K_2CO_3 (1.520 g, 11.0 mmol, 1.1 equiv), followed by 4-methoxybenzyl chloride (1.50 mL, 11.0 mmol, 1.1 equiv) dropwise. The reaction mixture was heated at 60 °C for 4 h, after which the solvent was removed. The resultant residue was added H_2O (30 mL) and diluted with EtOAc (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3x30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by column chromatography (CH_2Cl_2) to give PMB ether **80a** as a light yellow solid (2.715 g, 82%): R_f = 0.47 (40% EtOAc/hexanes); mp 99.4–102.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.51 (s, 1H), 10.04 (s, 1H), 7.33 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.43 (d, J = 4.2 Hz, 2H), 5.00 (s, 2H), 3.83 (s, 2H), 3.82 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 170.7, 166.6, 165.6, 159.8, 139.2, 129.4, 127.5, 114.2, 113.0, 112.1, 100.9, 70.2, 55.3, 52.5, 37.6; IR (thin film) 3235, 3004, 2954, 2839, 1734, 1624, 1250 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{18}H_{18}NaO_6$ $(M+Na)^+$ 353.0996, found 353.0990.



83

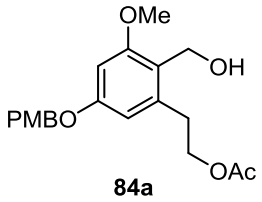
Methyl ether 83. To a solution of phenol **80a** (1.43 g, 4.33 mmol) in 15 mL of DMF at room temperature was added potassium carbonate (1.50 g, 10.9 mmol, 2.5 equiv), followed by iodomethane (410 µL, 6.59 mmol, 1.5 equiv). The mixture was stirred at ambient temperature for 1 h. H_2O (20 mL) was then added and the mixture was diluted with 20 mL of EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were washed with H_2O (2x20 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude residue by silica gel column chromatography (20–40% EtOAc/hexanes) yielded methyl ether **83** as a white solid (1.40 g, 94%): R_f = 0.36 (40% EtOAc/hexanes); mp 122.5–123.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.41 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.49 (d, *J* = 2.1 Hz, 1H), 6.40 (d, *J* = 2.1 Hz, 1H), 5.02 (s, 2H), 3.93 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 171.6, 165.3, 164.1, 159.8, 139.1, 129.5, 127.8, 117.1, 114.2, 110.7, 97.9, 70.1, 55.8, 55.3, 51.9, 40.5; IR (thin film) 3011, 2951, 2840, 1734, 1670, 1586, 1252 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}NaO_6$ $(M+Na)^+$ 367.1158, found 367.1157.



84

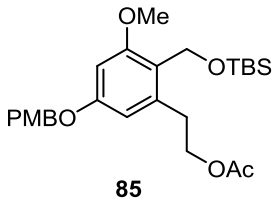
Diol 84. To a solution of ester **83** (632.9 mg, 1.84 mmol) in 10 mL of MeOH:THF (1:1) at 0 °C was added $NaBH_4$ (209.3 mg, 5.53 mmol, 3.0 equiv) slowly. The reaction mixture was stirred from 0 °C to room temperature for 1 h. The mixture was then quenched with saturated aqueous NH_4Cl (10 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (4x15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and

concentrated *in vacuo* to give the crude product as a white solid which was directly used for the next step without purification (610.4 mg, quant.): R_f = 0.16 (60% EtOAc/hexanes); mp 131.5–133.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.44 (s, 2H), 4.97 (s, 2H), 4.66 (s, 2H), 3.82 (s, 3H), 3.81 (t, *J* = 6.3 Hz, 2H), 3.80 (s, 3H), 2.90 (t, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 159.1, 140.8, 129.4, 129.3, 128.8, 120.9, 114.0, 107.0, 97.5, 69.8, 63.1, 55.6, 55.3, 55.0, 35.9; IR (thin film) 3305, 2941, 2875, 1588, 1456, 1239 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}NaO_5$ $(M+Na)^+$ 341.1365, found 341.1353.



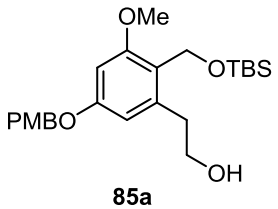
84a

Acetate 84a. To a solution of diol **84** (683.7 mg, 2.15 mmol) in CH_2Cl_2 (21 mL) were added DMAP (80.7 mg, 0.66 mmol, 0.3 equiv) and triethylamine (300 µL, 2.15 mmol, 1.0 equiv), followed by acetic anhydride (210 µL, 2.24 mmol, 1.0 equiv) dropwise. The reaction mixture was stirred under N_2 at room temperature for 1 h. The mixture was then quenched with saturated aqueous NH_4Cl (20 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by column chromatography (20–60% EtOAc/hexanes) to provide acetate **84a** as a light yellow oil (365.3 mg, 47%, 87% brsm) and 312.2 mg of recovered **84**: R_f = 0.18 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.45 (d, *J* = 2.1 Hz, 1H), 6.43 (d, *J* = 2.1 Hz, 1H), 4.97 (s, 2H), 4.69 (s, 2H), 4.25 (t, *J* = 7.2 Hz, 2H), 3.82 (s, 6H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 159.5, 159.4, 159.3, 138.5, 129.3, 128.8, 120.7, 114.1, 107.3, 97.9, 69.9, 65.1, 56.4, 55.6, 55.3, 32.5, 21.0; IR (thin film) 3588, 2937, 2839, 1733, 1516, 1247, 1034 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}NaO_6$ $(M+Na)^+$ 383.1471, found 383.1478.



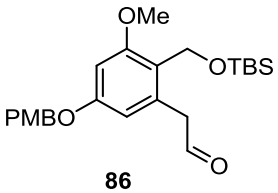
85

Silyl ether 85. To a solution of benzylic alcohol **84a** (506.4 mg, 1.41 mmol) in 7 mL of CH_2Cl_2 were added DMAP (58.2 mg, 0.47 mmol, 0.33 equiv) and imidazole (202.3 mg, 2.97 mmol, 2.1 equiv), followed by *tert*-butyldimethylsilyl chloride (358.1 mg, 2.38 mmol, 1.7 equiv). The reaction mixture was stirred at room temperature overnight before being quenched with H_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography (10% EtOAc/hexanes) provided silyl ether **85** as a light yellow oil (650.4 mg, 97%): R_f = 0.47 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.47 (d, *J* = 2.1 Hz, 1H), 6.42 (d, *J* = 2.1 Hz, 1H), 4.97 (s, 2H), 4.75 (s, 2H), 4.31 (t, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.05 (t, *J* = 7.2 Hz, 2H), 2.05 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 159.5, 159.3, 158.7, 140.0, 129.3, 129.0, 120.7, 114.1, 107.5, 97.8, 69.9, 65.2, 55.8, 55.5, 55.3, 32.3, 26.0, 21.0, 18.4, –5.3; IR (thin film) 2953, 2857, 1736, 1602, 1246, 1048 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{38}NaO_6Si$ $(M+Na)^+$ 497.2335, found 497.2333.



85a

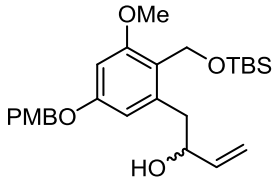
Alcohol 85a. To a solution of acetate **85** (714.2 mg, 1.50 mmol) in MeOH (28 mL) at room temperature was added K_2CO_3 (415.7 mg, 3.01 mmol, 2.0 equiv). The mixture was stirred at ambient temperature for 1 h, after which the solvent was removed. The resultant residue was added H_2O (30 mL) and diluted with EtOAc (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3x30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc/hexanes) to give alcohol **85a** as a light yellow oil (629.3 mg, 97%): R_f = 0.24 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 4.97 (s, 2H), 4.76 (s, 2H), 3.86–3.78 (m, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 2.95 (t, *J* = 6.0 Hz, 2H), 0.93 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 159.6, 158.7, 141.9, 129.4, 128.9, 120.4, 114.1, 107.1, 97.5, 69.8, 63.6, 55.7, 55.4, 55.3, 36.3, 26.0, 18.5, –5.3; IR (thin film) 3421, 2931, 2858, 1602, 1457, 1049, 833 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{24}H_{36}KO_5Si$ $(M+K)^+$ 471.1969, found 471.1972.



86

Aldehyde 86. To a solution of alcohol **85a** (629.3 mg, 1.45 mmol) in 9 mL of DMSO:toluene (1:1) was added IBX (1.02 g, 3.64 mmol, 2.5 equiv) in one portion. The reaction mixture was then stirred at room temperature for 2 h. The mixture was quenched with H_2O (10 mL) after which it was filtered to remove white solid and washed with EtOAc (30 mL). The organic layer was separated and the aqueous layer

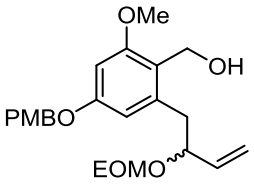
was extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude residue by silica gel column chromatography (5–10% EtOAc/hexanes) afforded aldehyde **86** as a light yellow oil (525.0 mg, 84%): R_f = 0.50 (20% EtOAc /hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.49 (d, *J* = 2.1 Hz, 1H), 6.43 (d, *J* = 2.1 Hz, 1H), 4.98 (s, 2H), 4.74 (s, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.78 (s, 2H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3, 159.6, 159.5, 158.6, 134.9, 129.4, 128.7, 121.3, 114.1, 108.1, 98.4, 69.9, 55.9, 55.6, 55.3, 48.1, 26.0, 18.4, –5.3; IR (thin film) 2933, 2858, 1723, 1600, 1454, 1045, 838 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{34}NaO_5Si$ $(M+ Na)^+$ 453.2073, found 453.2070.



87

Allylic alcohol 87. To a solution of aldehyde **86** (461.8 mg, 1.07 mmol) in dry THF (6 mL) at –78 °C was added vinylMgBr (1.0 M in THF, 1.8 mL, 1.80 mmol, 1.7 equiv) dropwise. The reaction mixture was stirred under a nitrogen atmosphere at –78 °C for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (5–10% EtOAc/hexanes) to give allylic alcohol **87** as a light yellow oil (235.1 mg, 48%, 60% based on 96.2 mg of recovered **86**): R_f = 0.38 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.49 (d, *J* = 2.1 Hz, 1H), 6.43 (d, *J* = 2.1 Hz, 1H), 5.99 (ddd, *J* = 16.8, 10.5, 5.4 Hz, 1H), 5.34 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.12 (dd, *J* = 10.5, 1.2 Hz, 1H), 4.98 (s, 2H), 4.91 (d, *J* = 10.8 Hz, 1H), 4.61 (d, *J* = 10.8 Hz, 1H), 4.38–4.30 (m, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 2.96 (dd, *J* = 13.8, 3.6 Hz, 1H), 2.84 (dd, *J* = 13.8, 9.0 Hz, 1H), 0.94 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 159.6, 158.7, 141.6, 140.9, 129.4, 128.9, 120.3, 114.0, 113.8, 107.4, 97.6, 73.3, 69.8, 55.7, 55.4, 55.3, 41.0, 26.1, 18.6, –5.2, –5.3; IR (thin film) 3420, 2931, 2857, 1521, 1251, 1148, 1036 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{26}H_{38}NaO_5Si$ $(M+Na)^+$ 481.2386, found 481.2375.

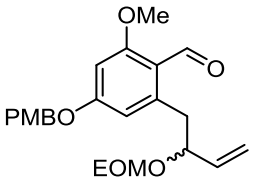


89

Benzylic alcohol 89. To a solution of allylic alcohol **87** (106.7 mg, 0.23 mmol) in 6 mL of CH_2Cl_2 were added *N*,*N*-diisopropylethylamine (320 μL, 1.88 mmol, 8.17 equiv) and tetrabutylammonium iodide (19.2 mg, 0.05 mmol, 0.22 equiv), followed by chloromethyl ethyl ether (175 μL, 1.88 mmol, 8.17 equiv). The reaction mixture was stirred under N_2 at room temperature overnight. The reaction mixture was then quenched with saturated aqueous NH_4Cl (6 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude allylic alcohol product as an orange oil which was directly used for the next step without purification.

To a solution of the above crude product in anhydrous THF (4 mL) at 0 °C was slowly added TBAF (1.0 M in THF, 0.8 mL, 0.80 mmol, 3.48 equiv). The reaction mixture was stirred from 0 °C to room temperature and heated at 60 °C for 3 h before being cooled to room temperature. H_2O (5 mL) was then added and the mixture was diluted with EtOAc (5 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc/hexanes) to give benzylic alcohol **89** as a colorless oil (82.0 mg, 88%): R_f = 0.33 (40% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.47 (d, *J* = 2.1 Hz, 1H), 6.43 (d, *J* = 2.1 Hz, 1H), 5.78 (ddd, *J* = 17.4, 10.5, 7.2 Hz, 1H), 5.30

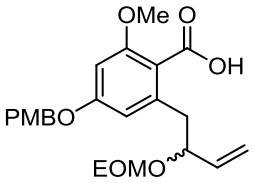
(d, *J* = 17.4 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.97 (s, 2H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 7.2 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 7.2 Hz, 1H), 4.30–4.23 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.18–3.08 (m, 1H), 3.04–2.94 (m, 2H), 2.82 (dd, *J* = 14.1, 3.9 Hz, 1H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 159.2, 159.1, 139.5, 137.4, 129.3, 128.9, 121.6, 117.6, 114.0, 107.3, 97.7, 91.9, 77.9, 69.9, 63.2, 55.7, 55.3, 39.0, 14.8; IR (thin film) 3464, 2934, 2884, 1605, 1517, 1250, 1147, 1033 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{23}H_{30}NaO_6$ $(M+Na)^+$ 425.1935, found 425.1926.



90

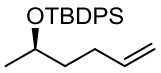
Benzaldehyde 90. To a solution of benzylic alcohol **89** (82.0 mg, 0.20 mmol) in 3.2 mL of DMSO:toluene (1:1) was added IBX (150.5 mg, 0.54 mmol, 2.65 equiv). The reaction mixture was stirred under N_2 at room temperature for 3 h. The mixture was then quenched with H_2O (5 mL), which resulted in the formation of white precitate. The white precipitate was filtered off through Celite. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc/hexanes) to provide benzaldehyde **90** as a light yellow oil (74.7 mg, 92%): R_f = 0.52 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.46 (d, *J* = 2.1 Hz, 1H), 6.42 (d, *J* = 2.1 Hz, 1H), 5.80 (ddd, *J* = 17.1, 10.5, 6.9 Hz, 1H), 5.21 (d, *J* = 17.1 Hz, 1H), 5.13 (d, *J* = 10.5 Hz, 1H), 5.03 (s, 2H), 4.59 (d, *J* = 6.9 Hz, 1H), 4.49 (d, *J* = 6.9 Hz, 1H), 4.28 (ddd, *J* = 8.1, 6.9, 4.5 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.36 (dd, *J* = 12.6, 4.5 Hz, 1H), 3.26 (qd, *J* = 7.2, 1.8 Hz, 2H), 3.02 (dd, *J* = 12.6, 8.1 Hz, 1H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2, 165.3, 163.4, 159.7, 144.6, 138.2, 129.3, 128.0, 117.1, 116.3, 114.1, 110.8, 97.3, 92.4, 77.3, 70.0, 62.8, 55.8, 55.3, 40.8,

14.9; IR (thin film) 2973, 2934, 2879, 1674, 1598, 1251, 1150 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{23}H_{28}NaO_6$ $(M+Na)^+$ 423.1784, found 423.1796.



78

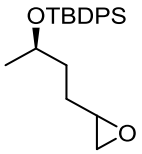
Benzoic acid 78. To a solution of benzaldehyde **90** (189.3 mg, 0.47 mmol) in *t*-BuOH (6.3 mL) at 0 °C were added 2-methyl-2-butene (500 µL, 4.69 mmol, 10.0 equiv) and sodium phosphate monobasic (341.6 mg, 2.85 mmol, 6.0 equiv), followed by a solution of sodium chlorite (72.2 mg, 0.80 mmol, 1.7 equiv) in H_2O (3 mL). The reaction mixture was stirred from 0 °C to room temperature for 3 h after which it was diluted with EtOAc (5 mL) and neutralized with 1M HCl (2.5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4x10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude residue by silica gel column chromatography (20–40% EtOAc/hexanes) afforded benzoic acid **78** as a yellow oil (182.5 mg, 92%): R_f = 0.19 (60% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.52 (d, *J* = 2.1 Hz, 1H), 6.47 (d, *J* = 2.1 Hz, 1H), 5.77 (ddd, *J* = 17.4, 10.2, 7.2 Hz, 1H), 5.27 (d, *J* = 17.4 Hz, 1H), 5.21 (d, *J* = 10.2 Hz, 1H), 5.01 (s, 2H), 4.63 (d, *J* = 7.2 Hz, 1H), 4.50 (d, *J* = 7.2 Hz, 1H), 4.35 (ddd, *J* = 8.7, 7.2, 4.8 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.23 (q, *J* = 7.2 Hz, 2H), 3.08 (dd, *J* = 13.5, 4.8 Hz, 1H), 2.99 (dd, *J* = 13.5, 8.7 Hz, 1H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 161.0, 159.7, 159.1, 141.0, 137.3, 129.3, 128.3, 117.5, 115.2, 114.1, 109.4, 98.2, 92.3, 78.0, 70.0, 63.2, 56.3, 55.3, 40.6, 14.8; IR (thin film) 3200, 3064, 2936, 1700, 1604, 1251, 1162 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{23}H_{28}NaO_7$ $(M+ Na)^+$ 439.1727, found 423.1713.



113

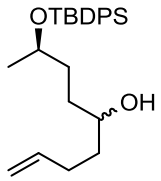
(*R*)-*tert*-Butyl(hex-5-en-2-yloxy)diphenylsilane (113). To a suspension of CuI (470.2 mg, 2.47 mmol, 0.20 equiv) in anhydrous THF (4 mL) at –20 °C was added allylMgBr (1.0 M in EtO_2, 30.0 mL, 30.0 mmol, 2.4 equiv) dropwise. The resultant dark brown suspension was stirred under an argon atmosphere at –20 °C for 20 min before a solution of *R*-(+)-propylene oxide (**112**) (730.6 mg, 12.5 mmol) in anhydrous THF (24 mL) was slowly added. The dark brown mixture was stirred at –20 °C for 2 h before it was quenched with saturated aqueous NH_4Cl (30 mL) and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the crude product which was directly used for the next step without purification.

To a solution of the above crude product in CH_2Cl_2 (30 mL) were added DMAP (320.7 mg, 2.63 mmol, 0.20 equiv), imidazole (1.72 g, 25.3 mmol, 2.00 equiv), followed by TBDPSCl (3.9 mL, 15.0 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature overnight before being quenched with H_2O (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude residue by silica gel column chromatography (2–5% EtOAc/hexanes) afforded the title compound as a colorless oil (3.3185 g, 78%): R_f = 0.72 (10% EtOAc/hexanes); $[\alpha]_D^{25.5}$ = +1.13 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.5, 1.5 Hz, 4H), 7.42–7.31 (m, 6H), 5.69 (ddt, *J* = 17.1, 10.5, 6.3 Hz, 1H), 4.92 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.87 (dd, *J* = 10.5, 1.8 Hz, 1H), 3.87 (sext, *J* = 6.0 Hz, 1H), 2.06 (q, *J* = 7.5 Hz, 2H), 1.64–1.43 (m, 2H), 1.07–1.05 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 136.0, 135.7, 135.0, 134.6, 129.7, 129.6, 129.5, 127.7, 127.6, 127.5, 114.3, 69.2, 38.7, 29.7, 27.2, 23.3, 19.4; IR (thin film) 3072, 2963, 2932, 2859, 1684, 1522, 1111 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{30}NaOSi$ $(M+Na)^+$ 361.1964, found 361.1966.



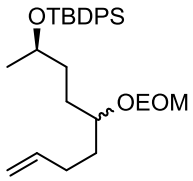
114

***tert*-Butyl(((2*R*)-4-(oxiran-2-yl)butan-2-yl)oxy)diphenylsilane (114).** To a solution of alkene **113** (3.3185 g, 9.80 mmol) in 40 mL of CH_2Cl_2 at 0 °C was added *m*-CPBA (70%, 4.8336 g, 19.6 mmol, 2.0 equiv) in one portion. The reaction mixture was stirred under an atmosphere of argon from 0 °C to room temperature for 3 h, then washed with saturated aqueous $NaHCO_3$ (3x30 mL) and extracted with CH_2Cl_2 (2x30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude residue by silica gel column chromatography (5–10% EtOAc/hexanes) afforded the racemic epoxide **114** as a pale oil (2.8562 g, 82%): R_f = 0.47 (10% EtOAc/hexanes); $[\alpha]_D^{24.8}$ = +2.87 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.2, 0.9 Hz, 4H), 7.44–7.35 (m, 6H), 3.94–3.84 (m, 1H), 2.79–2.77 (m, 1H), 2.68 (t, *J* = 4.5 Hz, 1H), 2.40–2.38 (m, 1H), 1.60–1.54 (m, 4H), 1.07–1.05 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 134.7, 134.4, 129.6, 129.5, 127.7, 127.6, 127.5, 69.2, 68.9, 52.4, 52.3, 47.1, 35.4, 35.2, 28.4, 28.0, 27.0, 23.2, 23.1, 19.3; IR (thin film) 3070, 3048, 2958, 2859, 1700, 1458, 1111 cm^{-1}; HRM (MALDI-TOF) *m/z* calcd for $C_{22}H_{30}NaO_2Si$ $(M+Na)^+$ 377.1913, found 377.1909.



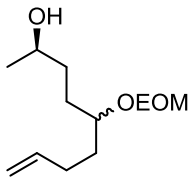
115

(*8R*)-8-((*tert*-Butyldiphenylsilyl)oxy)non-1-en-5-ol (115). To a suspension of CuI (214.4 mg, 1.12 mmol, 0.2 equiv) in anhydrous THF (3 mL) at –20 °C was added allylMgBr (1.0 M in Et_2O, 14.0 mL, 14.0 mmol, 2.5 equiv) dropwise. The resultant dark brown suspension was stirred under an argon atmosphere from –30 °C to –20 °C for 15 min before a solution of racemic epoxide **114** (1.971 g, 5.56 mmol) in anhydrous THF (12 mL) was slowly added. The dark brown mixture was stirred at –20 °C for 1.5 h before it was quenched with saturated aqueous NH_4Cl (20 mL) and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc/hexanes) to give the title compound as a light yellow oil (1.953 g, 89%): R_f = 0.45 (20% EtOAc/hexanes); $[\alpha]_D^{25.5}$ = +0.60 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.67 (m, 4H), 7.44–7.34 (m, 6H), 5.82 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.02 (dt, *J* = 17.1, 1.8 Hz, 1H), 4.96 (dd, *J* = 10.2, 1.2 Hz, 1H), 3.91–3.86 (m, 1H), 3.52–3.50 (m, 1H), 2.23–2.01 (m, 2H), 1.57–1.43 (m, 6H), 1.09–1.06 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 135.9, 134.8, 134.6, 134.5, 134.4, 129.6, 129.5, 127.7, 127.6, 127.5, 114.7, 114.6, 71.5, 71.3, 69.6, 69.4, 36.5, 36.4, 35.5, 34.9, 32.9, 32.6, 30.0, 27.1, 23.0, 22.9, 19.3; IR (thin film) 3366, 3072, 2932, 2859, 1683, 1458, 1111 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{36}NaO_2Si$ $(M+Na)^+$ 419.2382, found 419.2384.



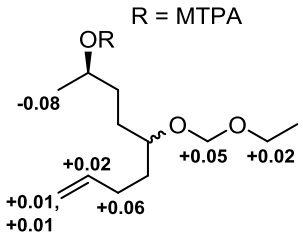
115a

Silyl ether 115a. To a solution of alcohol **115** (412.8 mg, 1.04 mmol) in CH_2Cl_2 (5.2 mL) at 0 °C were added *N*,*N*-diisopropylethylamine (710 μL, 4.17 mmol, 4.0 equiv) and tetrabutylammonium iodide (80.1 mg, 0.22 mmol, 0.2 equiv), followed by chloromethyl ethyl ether (390 μL, 4.21 mmol, 4.0 equiv). The reaction mixture was stirred under argon from 0 °C to room temperature overnight. The reaction mixture was then quenched with saturated aqueous NH_4Cl (6 mL). The organic layer was separated and extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* Purification of the crude residue by silica gel column chromatography (5% EtOAc/hexanes) yielded silyl ether **115a** as a light yellow oil (459.4 mg, 97%): R_f = 0.64 (20% EtOdAc/hexanes); $[\alpha]_D^{25.5}$ = +2.63 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.66 (m, 4H), 7.44–7.33 (m, 6H), 5.80 (ddt, *J* = 17.1, 10.5, 6.6 Hz, 1H), 5.00 (dt, *J* = 17.1, 1.5 Hz, 1H), 4.95 (d, *J* = 10.5 Hz, 1H), 4.68–4.61 (m, 2H), 3.85 (sext, *J* = 5.7 Hz, 1H), 3.58 (qd, *J* = 7.2, 2.4 Hz, 2H), 3.53–3.49 (m, 1H), 2.12–2.04 (m, 2H), 1.58–1.39 (m, 6H), 1.18 (td, *J* = 7.2, 1.5 Hz, 3H), 1.08–1.05 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 135.9, 135.7, 134.8, 134.5, 129.5, 129.4, 127.5, 127.4, 114.5, 93.9, 93.8, 76.9, 76.7, 69.8, 69.5, 63.3, 34.9, 34.7, 33.5, 33.4, 29.8, 29.6, 29.5, 27.0, 26.9, 23.3, 23.2, 19.3, 15.1; IR (thin film) 3072, 3050, 2932, 2860, 1684, 1458, 1106 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{42}NaO_3Si$ $(M+Na)^+$ 477.2801, found 477.2809.



110

Alcohol 110. To a solution of silyl ether **115a** (1.575 g, 3.46 mmol) in anhydrous THF (13 mL) at 0 °C was slowly added TBAF (1.0 M in THF, 8.7 mL, 8.7 mmol, 2.5 equiv). The reaction mixture was stirred from 0 °C to room temperature and heated at 60 °C for 2 h before being cooled to room temperature. H_2O (20 mL) was then added and the mixture was diluted with EtOAc (10 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc/hexanes) to provide alcohol **110** as a colorless oil (713.1 mg, 95%): R_f = 0.15 (20% EtOAc/hexanes); $[\alpha]_D^{25.6}$ = –6.83 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 4.96 (d, *J* = 17.1 Hz, 1H), 4.89 (d, *J* = 10.2 Hz, 1H), 4.64 (s, 2H), 3.71 (sext, *J* = 5.7 Hz, 1H), 3.60–3.53 (m, 3H), 2.10–2.00 (m, 2H), 1.59–1.39 (m, 6H), 1.17–1.11 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 138.3, 114.6, 93.9, 93.8, 76.9, 76.7, 67.9, 67.7, 63.5, 63.4, 34.6, 34.5, 33.4, 33.3, 30.4, 30.1, 29.5, 23.5, 23.4, 15.0; IR (thin film) 3422, 3079, 2933, 1653, 1522, 1098, 1045 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{24}NaO_3Si$ $(M+Na)^+$ 239.1623, found 239.1622. The absolute configuration was confirmed to be *R* by Mosher's method using the corresponding (*S*)-MTPA and (*R*)-MTPA esters.

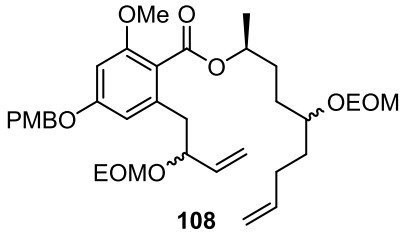


MTPA ester of (*R*)-110

(*S*)-MTPA ester of (*R*)-110. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.51 (m, 2H), 7.41–7.39 (m, 3H), 5.80 (ddt, *J* = 17.1, 10.5, 6.6 Hz, 1H), 5.18–5.10 (m, 1H), 5.01 (d, *J* = 17.1 Hz, 1H), 4.96 (d, *J* = 10.5 Hz, 1H), 4.67 (s, 2H), 3.60 (q, *J* = 7.2 Hz, 2H), 3.56–

3.54 (m, 4H), 2.08 (m, 2H), 1.84–1.39 (m, 6H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H).

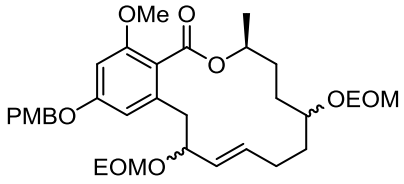
(*R*)-MTPA ester of (*R*)-110. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.52 (m, 2H), 7.40–7.38 (m, 3H), 5.78 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.19–5.10 (m, 1H), 5.00 (d, *J* = 17.1 Hz, 1H), 4.95 (d, *J* = 10.2 Hz, 1H), 4.62 (s, 2H), 3.58 (q, *J* = 7.2 Hz, 2H), 3.55–3.46 (m, 4H), 2.02 (m, 2H), 1.74–1.41 (m, 6H), 1.35 (d, *J* = 6.3 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H).



108

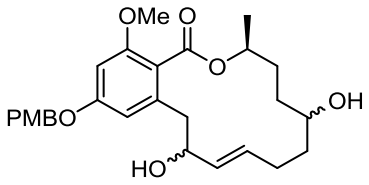
Ester diene 108. To a solution of benzoic acid **78** (245.3 mg, 0.59 mmol, 1.0 equiv) and (*R*)-alcohol **110** (122.3 mg, 0.57 mmol) in 5.9 mL of toluene at room temperature were added PPh_3 (314.9 mg, 1.20 mmol, 2.0 equiv), followed by diisopropyl azodicarboxylate (40% in toluene, 0.58 mL, 1.18 mmol, 2.0 equiv). The resultant yellow mixture was stirred at rt overnight before being concentrated *in vacuo*. Purification of the crude residue by column chromatography (5–10% EtOAc/hexanes) yielded ester diene **108** as a light yellow oil (259.1 mg, 72%): R_f = 0.63 (40% EtOAc/hexanes); $[\alpha]_D^{24.6}$ = +0.47 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.49 (s, 1H), 6.40 (s, 1H), 5.81 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.70 (ddd, *J* = 17.1, 9.9, 7.2 Hz, 1H), 5.21–5.12 (m, 3H), 5.04–4.93 (m, 4H), 4.69 (s, 2H), 4.61 (d, *J* = 6.6 Hz, 1H), 4.49 (d, *J* = 6.6 Hz, 1H), 4.29–4.23 (m, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.65–3.58 (m, 3H), 3.32 (qd, *J* = 6.9, 2.1 Hz, 2H), 2.95–2.73 (m, 2H), 2.16–2.07 (m, 2H), 1.70–1.57 (m, 6H), 1.36–1.30 (m, 3H), 1.12 (td, *J* = 6.9, 2.1 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 160.0, 159.5, 157.9, 138.5, 138.3, 138.2, 137.8, 129.2, 128.6, 117.9, 117.2, 117.1, 114.6, 114.0, 108.2, 97.8, 93.9, 92.3, 77.4, 77.3, 76.7, 76.5, 72.0, 71.7, 69.9, 63.3, 63.0, 55.7, 55.3, 39.7, 33.7, 33.6, 31.8, 31.5, 30.2, 30.1, 29.9, 29.8, 29.5,

29.4, 29.3, 21.9, 21.7, 20.2, 20.1, 15.1, 14.9; IR (thin film) 2977, 2935, 1717, 1517, 1250, 1159, 1107 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{35}H_{50}NaO_9$ $(M+Na)^+$ 637.3347, found 637.3341.



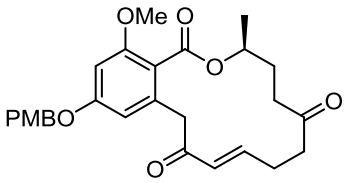
106

Macrolactone 106. A solution of diene **108** (131.5 mg, 0.214 mmol) in toluene (42 mL, 5 mM) was degassed with Ar for 10 min and second-generation Hoveyda Grubbs catalyst (13.4 mg, 0.021 mmol, 10 mol%) was added. The reaction mixture was heated at 85°C for 3.5 h, which the starting diene was completely consumed as judged by TLC. Solvent was then removed under reduced pressure. Purification of the crude residue by column chromatography (10–15% EtOAc/hexanes) yielded a mixture of macrolactone products as a light yellow oil (74.2 mg, 59%): R_f = 0.50 (40% EtOAc/hexanes); $[\alpha]_D^{25.3}$ = –5.26 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2H), 6.91 (dd, *J* = 8.4, 2.7 Hz, 2H), 6.81–6.58 (m, 1H), 6.41 (s, 1H), 5.66–5.54 (m, 1H), 5.29–5.04 (m, 2H), 4.98 (s, 2H), 4.75–4.58 (m, 4H), 4.29–4.17 (m, 1H), 3.80 (s, 3H), 3.77 (d, *J* = 2.1 Hz, 3H), 3.72–3.45 (m, 5H), 3.24–2.75 (m, 2H), 2.30–1.42 (m, 8H), 1.34 (t, *J* = 6.6 Hz, 3H), 1.30–1.14 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 167.9, 167.8, 160.3, 159.9, 159.5, 158.3, 158.2, 157.8, 157.7, 138.6, 138.4, 138.1, 137.9, 137.4, 136.7, 134.8, 134.6, 133.8, 130.7, 129.3, 129.2, 129.1, 129.0, 128.8, 128.6, 128.4, 118.1, 114.1, 114.0, 109.3, 108.4, 107.1, 107.0, 98.1, 98.0, 97.8, 94.2, 94.0, 93.8, 93.5, 93.0, 92.4, 91.9, 91.7, 91.4, 79.3, 78.2, 77.9, 76.0, 75.5, 74.3, 73.0, 72.3, 70.9, 69.9, 69.8, 63.4, 63.3, 63.2, 63.1, 62.8, 55.9, 55.8, 55.3, 39.2, 38.9, 38.2, 37.2, 33.2, 32.8, 32.6, 32.1, 32.0, 31.1, 30.9, 30.5, 29.1, 28.8, 28.3, 27.8, 23.7, 21.9, 21.7, 20.7, 20.2, 20.1, 15.2, 15.1, 14.8; IR (thin film) 2971, 2932, 1718, 1603, 1458, 1252, 1159 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{33}H_{46}NaO_9$ $(M+Na)^+$ 609.3034, found 609.3036.



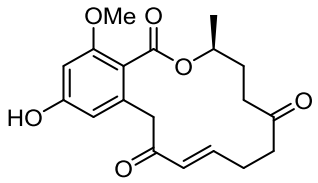
116

Diol 116. To a solution of EOM ether **106** (49.5 mg, 0.084 mmol) in THF (4.2 mL) at rt was added 2.4 mL of 4M HCl. The mixture was stirred at rt overnight, then which was quenched with saturated aqueous $NaHCO_3$ (5 mL) and diluted with EtOAc (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4x5 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography (40% EtOAc/hexanes) yielded diol **116** as a light yellow oil (22.5 mg, 57%): R_f = 0.34 (80% EtOAc/hexanes); $[\alpha]_D^{25.1}$ = –24.43 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 6.91 (dd, *J* = 8.4, 1.8 Hz, 2H), 6.75–6.52 (m, 1H), 6.43–6.40 (m, 1H), 5.60–5.51 (m, 1H), 5.38–5.02 (m, 2H), 4.98–4.97 (m, 2H), 4.46–4.34 (m, 1H), 3.81–3.75 (m, 6H), 3.72–3.57 (m, 1H), 3.21–2.74 (m, 2H), 2.17–1.54 (m, 8H), 1.36 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 167.9 160.8 160.3, 159.7, 158.9, 138.5, 138.0, 133.4, 133.0, 132.6, 132.2, 132.0, 131.6, 129.7, 129.5, 128.8, 128.6, 127.5, 118.1, 117.8, 114.2, 109.2, 108.4, 107.2, 106.9, 98.5, 98.1, 73.9, 73.8, 73.6, 73.2, 73.1, 72.9, 70.3, 70.1, 70.0, 69.8, 67.7, 67.5, 56.1, 55.5, 41.7, 41.4, 39.1, 38.5, 36.6, 36.4, 35.5, 35.3, 34.5, 32.2, 31.9, 30.7, 30.6, 29.4, 29.1, 28.5, 27.9, 21.1, 20.9, 20.4, 20.3; IR (thin film) 3447, 2933, 2858, 1700, 1603, 1251, 1161 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{27}H_{34}NaO_7$ $(M+Na)^+$ 493.2202, found 493.2211.



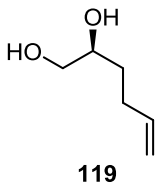
117

Diketone 117. To a solution of macrolactone diol **116** (112.2 mg, 0.24 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Dess-Martin periodinane (808.8 mg, 1.90 mmol, 8.0 equiv). The reaction mixture was stirred from 0 °C to room temperature for 4 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography (20–40% EtOAc/hexanes) provided the desired product as a light yellow oil (66.2 mg, 62%): R_f = 0.21 (40% EtOAc/hexanes); $[\alpha]_D^{25.3}$ = +2.80 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.78 (dt, *J* = 15.6, 6.3 Hz, 1H), 6.55 (d, *J* = 1.8 Hz, 1H), 6.43 (d, *J* = 1.8 Hz, 1H), 6.05 (d, *J* = 15.6 Hz, 1H), 5.18 (m, 1H), 4.98 (d, *J* = 2.4 Hz, 1H), 4.32 (d, *J* = 14.1 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.36 (d, *J* = 14.1 Hz, 1H), 2.73–2.38 (m, 6H), 2.07–1.97 (m, 1H), 1.82–1.68 (m, 1H), 1.37 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.5, 196.7, 167.9, 160.9, 159.7, 159.1, 146.1, 135.2, 130.6, 129.4, 128.4, 116.8, 114.1, 107.9, 99.0, 71.1, 70.0, 56.0, 55.3, 44.2, 40.5, 39.1, 28.6, 28.3, 20.3; IR (thin film) 3011, 2933, 2853, 1701, 1605, 1252, 1161 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{27}H_{30}NaO_7$ $(M+Na)^+$ 489.1884, found 489.1884.



25

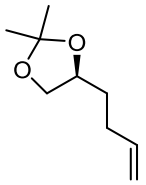
Dechlorogreensporone A (25). To a solution of macrolactone **117** (66.2 mg, 0.14 mmol) in 15 mL of CH_2Cl_2 at 0 °C was added $TiCl_4$ (1.0 M solution in CH_2Cl_2, 450 µL, 0.45 mmol, 3.2 equiv). The orange cloudy mixture was stirred from 0 °C to room temperature for 30 min, which was then quenched with saturated aqueous $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3x15 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (30–40% EtOAc/hexanes) to give dechlorogreensporone A (**25**) as a light yellow solid (38.4 mg, 79%): R_f = 0.37 (60% EtOAc /hexanes); mp 142.9–146.4 °C; $[\alpha]_D^{26.4}$ = +66.02 (*c* 0.10, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82–6.75 (m, 1H), 6.43 (d, *J* = 2.1 Hz, 1H), 6.30 (d, *J* = 2.1 Hz, 1H), 6.05 (d, *J* = 15.6 Hz, 1H), 5.21–5.16 (m, 1H), 4.29 (d, *J* = 14.1 Hz, 1H), 3.72 (s, 3H), 3.35 (d, *J* = 14.1 Hz, 1H), 2.73–2.40 (m, 6H), 2.19–1.96 (m, 1H), 1.84–1.72 (m, 2H), 1.37 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 198.6, 168.4, 159.6, 159.1, 147.5, 134.9, 130.6, 115.7, 109.8, 98.9, 71.4, 56.0, 44.1, 40.6, 39.4, 28.7, 28.4, 20.5; IR (thin film) 3367, 2930, 2855, 1699, 1610, 1458, 1273 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{19}H_{22}NaO_6$ $(M+Na)^+$ 369.1314, found 369.1322.



119

(*S*)-Hex-5-ene-1,2-diol (119). To a suspension of (*R*,*R*) cobalt(II) salen (150.0 mg, 0.25 mmol, 0.5 mol%) in THF (0.5 mL) was added AcOH (60 µL). The resultant mixture was stirred in open air at room temperature for 1 h. To this catalyst, racemic epoxide **118** (4.90 g, 49.9 mmol) was added in one portion and the stirred mixture was cooled in an ice-water bath. H_2O (500 µL, 27.5 mmol, 0.55 equiv) was slowly added

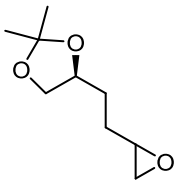
and the reaction mixture was stirred from 0 °C to room temperature for 15 h. Purification of the crude residue by silica gel column chromatography (20–100% EtOAc/hexanes) afforded the title compound as a light brown oil (2.69 g, 46%, 98% *ee*): R_f = 0.34 (80% EtOAc/hexanes); $[\alpha]_D^{25.1}$ = +1.33 (*c* 2.86, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.04 (dd, *J* = 17.1, 1.2 Hz, 1H), 4.98 (d, *J* = 10.2 Hz, 1H), 4.18 (brs, 1H), 3.69–3.59 (m, 2H), 3.41 (dd, *J* = 11.1, 7.8 Hz, 1H), 2.27–2.04 (m, 2H), 1.50 (q, *J* = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 115.0, 71.7, 66.5, 32.1, 29.7; IR (thin film) 3446, 2926, 2866, 1646, 1436, 1051 cm^{-1}. The spectral data of **119** matched those previously described (Shelke and Suryavanshi, 2016). The enantiomeric excess was determined on the corresponding benzoate, which was prepared by benzoylation with benzoyl chloride, from HPLC analysis using CHIRALPAK® AS-H column eluting with 2% isopropanol/hexanes (flow rate = 1.0 mL/min, pressure = 35.68 bar, temp = 24–25 °C, λ = 222 nm): retention time = 14.004 min, retention time of (*R*)-enantiomer = 17.516 min.



119a

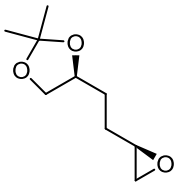
(*S*)-4-But-3-enyl-2,2-dimethyl[1,3]dioxolane (119a). To a solution of diol **119** (5.38 g, 46.3 mmol) in CH_2Cl_2 (90 mL) at room temperature were added 2,2-dimethoxypropane (11.5 mL, 93.9 mmol, 2.0 equiv) and *p*-toluenesulfonic acid (1.77 g, 9.30 mmol, 0.2 equiv). The mixture was stirred at ambient temperature overnight before being quenched with H_2O (40 mL) and saturated aqueous $NaHCO_3$ (40 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude residue by silica gel column chromatography (5–100% EtOAc/hexanes) provided the title compound as a light yellow oil (4.18 g, 58%, 75% based on 1.21 g of recovered **119**): R_f = 0.61 (20% EtOAc/hexanes); $[\alpha]_D^{25.0}$ = +9.30 (*c* 2.854, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.04 (dd, *J* = 17.1, 1.5 Hz, 1H),

4.98 (d, *J* = 10.2 Hz, 1H), 4.14–4.02 (m, 2H), 3.52 (app t, *J* = 7.2 Hz, 1H), 2.25–2.03 (m, 2H), 1.81–1.57 (m, 2H), 1.41 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 115.0, 108.7, 75.5, 69.4, 32.8, 29.9, 26.9, 25.7; IR (thin film) 2987, 2936, 2867, 1684, 1523, 1217, 1063 cm^{-1}. The spectral data of **119a** matched those previously described (Morin and Rychnovsky, 2015).



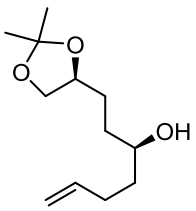
***rac*-120**

(*S*)-2,2-Dimethyl-4-(2-(oxiran-2-yl)ethyl)-1,3-dioxolane (*rac*-120). To a solution of alkene **119a** (4.89 g, 31.3 mmol) in CH_2Cl_2 (125 mL) at 0 °C was added *m*-CPBA (70%, 11.57 g, 46.9 mmol, 1.5 equiv) in one portion. The reaction mixture was stirred under an atmosphere of argon from 0 °C to room temperature overnight, then washed with saturated aqueous $NaHCO_3$ (3x60 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to give the title racemic epoxide as a light yellow oil (3.90 g, 72%): R_f = 0.33 (20% EtOAc/hexanes); $[\alpha]_D^{25.2}$ = +5.28 (*c* 2.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20–4.03 (m, 2H), 3.56–3.51 (m, 1H), 2.99–2.92 (m, 1H), 2.78–2.75 (m, 1H), 2.51–2.47 (m, 1H), 1.83–1.65 (m, 4H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.8, 75.6, 75.3, 69.3, 69.2, 52.0, 51.7, 47.0, 46.9, 30.0, 29.7, 29.0, 28.5, 26.9, 25.6; IR (thin film) 2986, 2935, 2870, 1698, 1522, 1216, 1062 cm^{-1}. The spectral data of ***rac*-120** matched those previously described (Sharma *et al*., 2009).



120

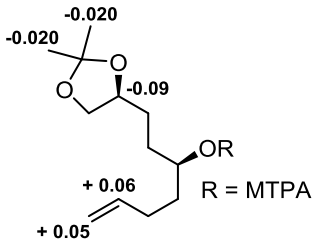
(*S*)-2,2-Dimethyl-4-(2-((*R*)-oxiran-2-yl)ethyl)-1,3-dioxolane (120). To a suspension of (*R*,*R*) cobalt(II) salen (12.2 mg, 0.02 mmol, 0.19 mol%) in toluene (1 mL) was added AcOH (20 µL). The resultant mixture was stirred in open air at room temperature for 1 h. The solvent was removed, and the brown residue was dried under vacuum. To this catalyst, racemic epoxide ***rac*-120** (1.80 g, 10.47 mmol) was added in one portion and the stirred mixture was cooled in an ice-water bath. H_2O (104 µL, 5.78 mmol, 0.55 equiv) was slowly added and the reaction mixture was stirred from 0 °C to room temperature for 15 h. The crude reaction mixture was purified by silica gel column chromatography (10–20–100% EtOAc/hexanes) to afford the (*R*)-epoxide **120** as a yellow oil (752.8 mg, 42%): R_f = 0.33 (20% EtOAc/hexanes); $[\alpha]_D^{25.2}$ = +8.66 (*c* 2.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16–4.04 (m, 2H), 3.56–3.52 (m, 1H), 2.96–2.92 (m, 1H), 2.78–2.75 (m, 1H), 2.50–2.48 (m, 1H), 1.81–1.70 (m, 3H), 1.55–1.47 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.9, 75.7, 69.4, 52.1, 47.1, 30.1, 29.0, 26.9, 25.7; IR (thin film) 2986, 2936, 2871, 1684, 1521, 1216, 1062 cm^{-1}. The spectral data of **120** matched those previously described (Prataparedy *et al*, 2017).



121

(*S*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)hept-6-en-3-ol (121). To a suspension of CuI (360.1 mg, 1.89 mmol, 0.2 equiv) in anhydrous THF (4 mL) at –20 °C was added allylMgBr (1.0 M in Et_2O, 23.5 mL, 23.5 mmol, 2.5 equiv) dropwise. The resultant dark brown suspension was stirred under an argon atmosphere at –20 °C for 15 min before a solution of (*R*)-epoxide **120** (1.62 g, 9.41mmol) in anhydrous THF (20 mL)

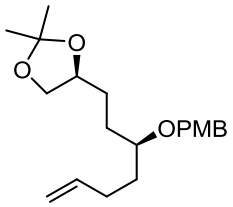
was slowly added. The dark brown mixture was stirred from –20 °C to 0 °C for 1.5 h before it was quenched with saturated aqueous NH_4Cl (50 mL) and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude residue by silica gel column chromatography (20% EtOAc/hexanes) afforded the title compound as a light yellow oil (1.77 g, 88%, 98% *de*): R_f = 0.15 (20% EtOAc/hexanes); $[\alpha]_D^{25.5}$ = +10.60 (*c* 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.05 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.97 (dd, *J* = 10.2, 0.9 Hz, 1H), 4.12–4.08 (m, 2H), 3.70–3.63 (m, 1H), 3.52 (dd, *J* = 7.5, 6.9 Hz, 1H), 2.28–2.07 (m, 2H), 1.74–1.43 (m, 6H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 114.8, 108.9, 76.2, 70.9, 69.5, 36.4, 33.6, 30.1, 29.5, 26.9, 25.7; IR (thin film) 3447, 2985, 2935, 2870, 1653, 1217, 1061 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{22}NaO_3$ $(M+Na)^+$ 237.1467, found 237.1466. The diastereomeric ratio was determined on the corresponding benzoate, which was prepared by benzoylation with benzoyl chloride, from HPLC analysis using CHIRALCEL® OD-H column eluting with 0.7% isopropanol/hexanes (flow rate = 0.8 mL/min, pressure = 25.75 bar, temp = 24–25 °C, λ = 226 nm): retention time = 6.036 min, retention time of minor = 5.711 min. The absolute configuration was determined to be *S* by Mosher's method using the corresponding (*S*)-MTPA and (*R*)-MTPA esters.



MTPA ester of (*S*)-121

(*S*)-MTPA ester of (*S*)-121. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.53 (m, 2H), 7.43–7.39 (m, 3H), 5.78 (ddt, *J* = 17.1, 10.5, 6.6 Hz, 1H), 5.16–5.08 (m, 1H), 5.01 (m, 2H), 3.97–3.91 (m, 2H), 3.56 (s, 3H), 3.38 (m, 1H), 2.12–2.05 (m, 2H), 1.87–1.40 (m, 6H), 1.37 (s, 3H), 1.32 (s, 3H).

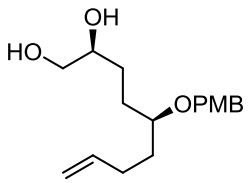
(*R*)-MTPA ester of (*S*)-121. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.53 (m, 2H), 7.42–7.39 (m, 3H), 5.72 (ddt, *J* = 17.4, 9.9, 6.6 Hz, 1H), 5.16–5.08 (m, 1H), 4.96 (m, 2H), 4.07–3.98 (m, 2H), 3.55 (s, 3H), 3.47 (m, 1H), 2.05–1.92 (m, 2H), 1.89–1.50 (m, 6H), 1.39 (s, 3H), 1.34 (s, 3H).



121a

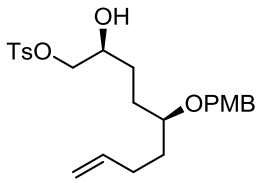
(*S*)-4-((*S*)-3-((4-Methoxybenzyl)oxy)hept-6-en-1-yl)-2,2-dimethyl-1,3-dioxolane (121a). To a solution of alcohol **121** (598.8 mg, 2.79 mmol) in DMF (11 mL) at 0 °C were added potassium iodide (2.32 g, 13.97 mmol, 5.0 equiv) and NaH (60% dispersion in mineral oil, 559.0 mg, 13.97 mmol, 5.0 equiv). The light yellow cloudy mixture was stirred at 0 °C under Ar for 30 min before 4-methoxybenzyl chloride (1.90 mL, 13.95 mmol, 5.0 equiv) was added dropwise. The reaction mixture was stirred from 0 °C to room temperature for 3 h. Next, H_2O (10 mL) was added and the mixture was diluted with 20 mL of EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were washed with H_2O (2x20 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude residue by silica gel column chromatography (5–10% EtOAc/hexanes) afforded the title compound as a colorless oil (826.6 mg, 88%): R_f = 0.42 (20% EtOAc/hexanes); $[\alpha]_D^{25.5}$ = +8.06 (*c* 1.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.81 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.01 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.95 (d, *J* = 10.2 Hz, 1H), 4.43 (s, 2H), 4.08–4.00 (m, 2H), 3.80 (s, 3H), 3.50 (t, *J* = 6.6 Hz, 1H), 3.41 (quint, *J* = 5.1 Hz, 1H), 2.18–2.09 (m, 2H), 1.73–1.49 (m, 6H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 138.6, 131.0, 129.3, 114.6, 113.8, 108.7, 77.8, 76.3, 70.6, 69.5, 55.3, 33.1, 30.0, 29.6, 29.4, 27.0, 25.7; IR (thin film) 2984,

2936, 2866, 1615, 1514, 1248, 1065 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{30}NaO_4$ $(M+Na)^+$ 357.2042, found 357.2043.



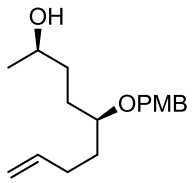
122

Diol 122. A solution of acetonide **121a** (901.3 mg, 2.69 mmol) in 70% AcOH (13.5 mL) was stirred at room temperature for 2 h, which was then quenched with saturated aqueous $NaHCO_3$ (20 mL) and diluted with EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4x20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (40–80% EtOAc/hexanes) to give diol **122** as a colorless oil (723.4 mg, 91%): R_f = 0.31 (80% EtOAc/hexanes); $[\alpha]_D^{24.5}$ = +0.37 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.80 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.01 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.96 (d, *J* = 10.2 Hz, 1H), 4.44 (s, 2H), 3.79 (s, 3H), 3.65–3.55 (m, 2H), 3.46–3.37 (m, 2H), 2.15–2.07 (m, 2H), 1.77–1.66 (m, 2H), 1.64–1.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 138.5, 130.5, 129.5, 114.7, 113.8, 78.1, 72.3, 70.7, 66.7, 55.3, 32.7, 29.7, 29.6, 28.8; IR (thin film) 3393, 2934, 2865, 1615, 1456, 1248, 1068 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{26}NaO_4$ $(M+Na)^+$ 317.1729, found 317.1719.



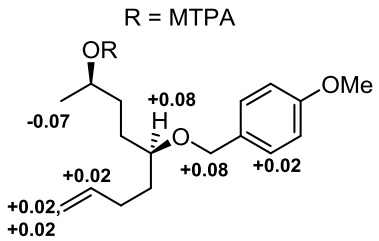
123

Tosylate 123. To a solution of diol **122** (86.1 mg, 0.29 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C were added DMAP (9.2 mg, 0.07 mmol, 0.26 equiv), and triethylamine (125 µL, 0.90 mmol, 3.0 equiv), followed by *p*-toluenesulfonyl chloride (73.2 mg, 0.38 mmol, 1.3 equiv). The reaction mixture was stirred under argon atmosphere from 0 °C to room temperature overnight. The mixture was then quenched with saturated aqueous NH_4Cl (5 mL) and diluted with CH_2Cl_2 (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude residue by silica gel column chromatography (10–80% EtOAc/hexanes) yielded tosylate **123** as a colorless oil (63.7 mg, 49%, 81% brsm) and 34.6 mg of recovered **122**: R_f = 0.41 (40% EtOAc/hexanes); $[\alpha]_D^{25.3}$ = –5.26 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.79 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.00 (dd, *J* = 16.8, 1.5 Hz, 1H), 4.96 (d, *J* = 10.2 Hz, 1H), 4.46–4.36 (m, 2H), 4.00–3.77 (m, 3H), 3.80 (s, 3H), 3.43–3.37 (m, 1H), 2.44 (s, 3H), 2.15–2.05 (m, 2H), 1.73–1.44 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 145.0, 138.4, 132.7, 130.4, 129.9, 129.5, 128.0, 114.7, 113.8, 77.8, 73.7, 70.6, 69.4, 55.3, 32.7, 29.5, 29.4, 28.5, 21.6; IR (thin film) 3446, 2935, 2863, 1647, 1515, 1362, 1248, 1177 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{32}KO_6S$ $(M+K)^+$ 487.1557, found 487.1555.



111

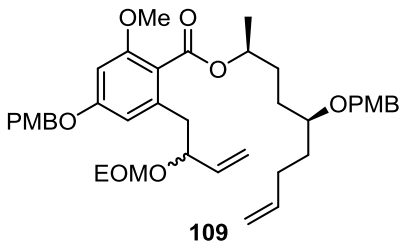
(2*R*,5*S*)-5-((4-Methoxybenzyl)oxy)non-8-en-2-ol (111). To a suspension of $LiAlH_4$ (47.1 mg, 1.24 mmol, 3.2 equiv) in anhydrous THF (1 mL) at 0 °C was added a solution of tosylate **123** (173.0 mg, 0.38 mmol) in anhydrous THF (7 mL). The reaction mixture was stirred from 0 °C to room temperature for 3 h and cooled back to 0 °C before which was quenched with saturated aqueous NH_4Cl (8 mL) and diluted with EtOAc (5 mL). The white cloudy mixture was filtered through Celite and washed with EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to provide the title compound as a colorless oil (91.7 mg, 85%): R_f = 0.12 (20% EtOAc/hexanes); $[\alpha]_D^{25.5}$ = –5.67 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.81 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.01 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.96 (dd, *J* = 10.2, 0.9 Hz, 1H), 4.45 (s, 2H), 3.80 (s, 3H), 3.79–3.74 (m, 1H), 3.44 (app quint, *J* = 5.4 Hz, 1H), 2.17–2.05 (m, 2H), 1.76–1.45 (m, 6H), 1.18 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 138.6, 130.7, 129.4, 114.6, 113.8, 78.1, 70.6, 68.0, 55.3, 34.8, 32.8, 29.9, 29.6, 23.5; IR (thin film) 3398, 2935, 2865, 1613, 1456, 1250, 1067 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{26}NaO_3$ $(M+Na)^+$ 301.1780, found 301.1789. The absolute configuration was confirmed to be *R* by Mosher's method using the corresponding (*S*)-MTPA and (*R*)-MTPA esters.



MTPA ester of (*R*)-111

(*S*)-MTPA ester of (*R*)-111. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.51 (m, 2H), 7.41–7.37 (m, 3H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.79 (ddt, *J* = 17.1, 10.2, 6.3 Hz, 1H), 5.13 (sext, *J* = 6.3 Hz, 1H), 5.00 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.96 (d, *J* = 10.2 Hz, 1H), 4.39 (m, 2H), 3.79 (s, 3H), 3.53 (s, 3H), 3.37 (m, 1H), 2.14–2.05 (m, 2H), 1.74–1.46 (m, 6H), 1.26 (d, *J* = 6.3 Hz, 3H).

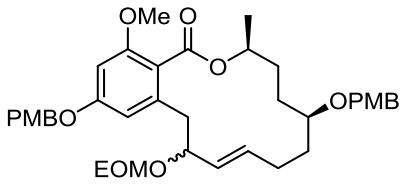
(*R*)-MTPA ester of (*R*)-111. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.53 (m, 2H), 7.39–7.37 (m, 3H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.77 (ddt, *J* = 17.1, 10.5, 6.6 Hz, 1H), 5.13 (sext, *J* = 6.3 Hz, 1H), 4.98 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.94 (d, *J* = 10.5 Hz, 1H), 4.31 (m, 2H), 3.80 (s, 3H), 3.57 (s, 3H), 3.29 (m, 1H), 2.09–1.96 (m, 2H), 1.69–1.38 (m, 6H), 1.34 (d, *J* = 6.0 Hz, 3H).



109

Ester diene 109. To a solution of benzoic acid **78** (272.5 mg, 0.65 mmol, 1.2 equiv) and (*R*)-alcohol **111** (148.1 mg, 0.53 mmol) in 6 mL of toluene at room temperature were added PPh_3 (351.9 mg, 1.34 mmol, 2.5 equiv), followed by diisopropyl azodicarboxylate (40% in toluene, 0.66 mL, 1.34 mmol, 2.5 equiv). The resultant yellow mixture was stirred at rt overnight before being concentrated *in vacuo*. Purification of the crude residue by column chromatography (5–10% EtOAc/hexanes) yielded ester diene **109** as a light yellow oil (297.8 mg, 83%): R_f = 0.55 (40% EtOAc/hexanes); $[\alpha]_D^{25.5}$ = –2.40 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36

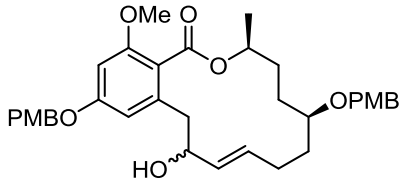
(d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.49 (s, 1H), 6.39 (s, 1H), 5.81 (ddt, *J* = 17.1, 10.2, 6.3 Hz, 1H), 5.69 (ddd, *J* = 17.4, 9.9, 7.2 Hz, 1H), 5.20–5.18 (m, 3H), 5.03–4.92 (m, 4H), 4.61 (d, *J* = 6.9 Hz, 1H), 4.45 (d, *J* = 6.9 Hz, 1H), 4.43 (s, 2H), 4.29–4.22 (m, 1H) 3.82 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 3.46–3.42 (m, 1H), 3.33 (qd, *J* = 7.2, 3.0 Hz, 2H), 2.95–2.75 (m, 2H), 2.16–2.07 (m, 2H), 1.78–1.60 (m, 6H), 1.34–1.31 (m, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 160.0, 159.6, 159.1, 158.0, 138.7, 138.3, 138.2, 137.8, 131.1, 129.3, 129.2, 128.7, 118.0, 117.0, 114.5, 114.1, 113.8, 108.4, 97.9, 92.4, 77.5, 77.4, 77.3, 71.7, 70.4, 69.9, 63.0, 55.8, 55.3, 39.7, 33.2, 31.5, 29.6, 29.4, 20.2, 20.1, 14.9; IR (thin film) 2933, 2862, 1716, 1516, 1250, 1159, 1034 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{40}H_{52}NaO_9$ $(M+Na)^+$ 699.3509, found 699.3533.



107

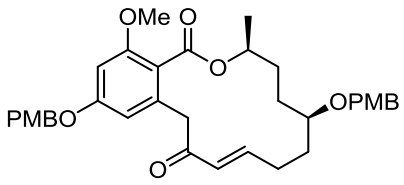
Macrolactone 107. To a solution of diene **109** (41.7 mg, 0.062 mmol) in toluene (12.3 mL, 5 mM) was degassed with Ar for 10 min and second-generation Hoveyda Grubbs catalyst (3.9 mg, 0.006 mmol, 10 mol%) was added. The reaction mixture was heated at 85 °C for 4 h, at which the starting diene was completely consumed as judged by TLC. Solvent was then removed under reduced pressure. Purification of the crude residue by column chromatography (10% EtOAc/ hexanes) yielded a mixture of macrolactone products as a light yellow oil (28.8 mg, 72%): R_f = 0.48 (40% EtOAc/hexanes); $[\alpha]_D^{24.7}$ = –2.53 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 4H), 7.26–7.21 (m, 4H), 6.92–6.86 (m, 8H), 6.79 (s, 1H), 6.59 (s, 1H), 6.39 (s, 2H), 5.66–5.46 (m, 2H), 5.36–5.13 (m, 2H), 5.13–4.90 (m, 6H), 4.76–4.71 (m, 2H), 4.68–4.60 (m, 2H), 4.53–4.46 (m, 2H), 4.38–4.25 (m, 4H), 3.79 (s, 6H), 3.74–3.62 (m, 8H), 3.62–3.47 (m, 2H), 3.46–3.21 (m, 2H), 3.21–3.07 (m, 1H), 3.01–2.95 (m, 2H), 2.85–2.64 (m, 1H), 2.51–1.41 (m, 16H), 1.40–1.29 (m, 6H), 1.25–1.18 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 167.9, 160.4, 159.9, 159.6, 159.2, 158.3, 138.6, 138.1, 134.8, 131.0, 129.3, 129.2, 128.7, 128.5, 118.2, 118.0, 114.0,

113.9, 109.2, 107.1, 98.0, 97.8, 93.1, 91.5, 77.4, 76.1, 76.0, 74.8, 70.8, 70.5, 70.2, 70.0, 63.4, 63.2, 55.9, 55.3, 39.9, 37.3, 31.5, 31.4, 30.7, 30.5, 28.8, 28.3, 28.2, 21.9, 21.7, 20.3, 20.2, 15.2; IR (thin film) 2933, 2875, 1716, 1603, 1516, 1250, 1160 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{38}H_{48}NaO_9$ $(M+Na)^+$ 671.3191, found 671.3157.



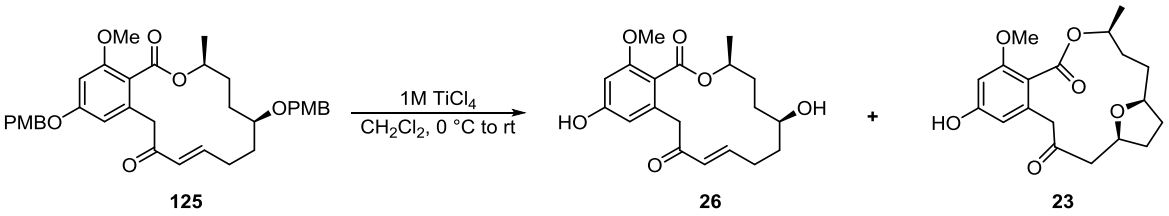
124

Allylic alcohol 124. To a solution of EOM ether **107** (148.8 mg, 0.23 mmol) in THF (11 mL) at rt was added 6.5 mL of 4M HCl. The mixture was stirred at rt for 4 h, which was then quenched with saturated aqueous $NaHCO_3$ (15 mL) and diluted with EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography (10–20% EtOAc/hexanes) yielded the desired product as a light yellow oil (34.2 mg, 25%, 53% based on 78.5 mg of recovered **107**): R_f = 0.27 (40% EtOAc/hexanes); $[\alpha]_D^{25.1}$ = –17.33 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 4H), 7.27–7.21 (m, 4H), 6.93–6.87 (m, 8H), 6.72 (s, 1H), 6.53 (s, 1H), 6.42–6.40 (m, 2H), 5.59–5.50 (m, 2H), 5.36 (dd, *J* = 15.3, 3.6 Hz, 1H), 5.26 (dd, *J* = 15.3, 8.4 Hz, 1H), 4.99 (s, 2H), 4.97 (s, 2H), 4.55–4.48 (m, 2H), 4.36–4.29 (m, 4H), 3.81 (s, 12H), 3.75 (s, 3H), 3.74 (s, 3H), 3.38–3.33 (m, 2H), 3.15 (dd, *J* = 14.4, 3.6 Hz, 1H), 3.03–2.94 (m, 2H), 2.81 (dd, *J* = 12.9, 9.6 Hz, 1H), 2.14–1.71 (m, 16H), 1.42–1.26 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 167.9, 160.5, 160.1, 159.6, 159.2, 158.7, 158.6, 138.2, 137.7, 132.9, 132.0, 131.6, 131.0, 129.4, 128.6, 128.5, 127.9, 118.1, 117.9, 114.1, 114.0, 113.9, 108.7, 106.9, 98.2, 98.0, 75.3, 75.1, 73.3, 73.0, 70.5, 70.3, 69.9, 69.8, 55.9, 55.3, 55.3, 41.4, 38.6, 31.5, 30.7, 30.6, 28.5, 28.4, 28.0, 27.8, 20.2; IR (thin film) 3447, 2933, 2860, 1701, 1605, 1249, 1161 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{35}H_{42}NaO_8$ $(M+Na)^+$ 613.2772, found 613.2753.

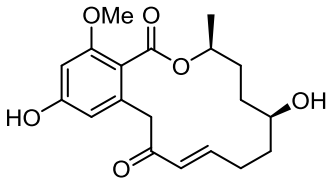


125

Macrolactone 125. To a solution of macrolactone **124** (75.0 mg, 0.127 mmol) in 3 mL of DMSO:toluene (1:1) was added IBX (178.1 mg, 0.636 mmol, 5.0 equiv). The reaction mixture was stirred at room temperature for 2 h before being added IBX (106.9 mg, 0.382 mmol, 3.0 equiv), and stirred at room temperature for 1 h. The reaction mixture was quenched with H_2O (3 mL), and diluted with EtOAc (3 mL). The mixture was filtered through a pad of Celite and washed with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography (20% EtOAc/hexanes) provided the desired product as a white solid (55.4 mg, 74%): R_f = 0.48 (40% EtOAc/hexanes); mp 141.3–144.5 °C; $[\alpha]_D^{24.5}$ = +10.6 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.72 (dt, *J* = 15.6, 7.8 Hz, 1H), 6.47 (s, 1H), 6.45 (s, 1H), 6.07 (d, *J* = 15.6 Hz, 1H), 4.96 (s, 2H), 4.90–4.85 (m, 1H), 4.51 (d, *J* = 11.1 Hz, 1H), 4.32 (d, *J* = 11.1 Hz, 1H), 4.27 (d, *J* = 15.6 Hz, 1H), 3.81 (s, 6H), 3.76 (s, 3H), 3.45 (d, *J* = 15.6 Hz, 1H), 3.37–3.31 (m, 1H), 2.29–2.22 (m, 2H), 1.82–1.35 (m, 6H), 1.29 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 167.7, 160.9, 159.6, 159.4, 159.3, 147.6, 135.8, 130.6, 129.5, 129.4, 129.2, 128.3, 116.8, 114.1, 113.9, 107.8, 98.9, 75.0, 70.5, 70.0, 56.0, 55.3, 45.7, 30.8, 30.4, 28.7, 27.9, 20.2; IR (thin film) 2926, 2856, 1700, 1521, 1251, 1162, 1034 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{35}H_{40}NaO_8$ $(M+Na)^+$ 611.2621, found 611.2640.

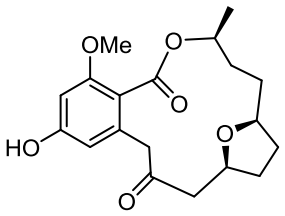


A solution of macrolactone **125** (55.4 mg, 0.094 mmol) in 9.4 mL of CH_2Cl_2 at 0 °C was added 1M $TiCl_4$ (565 µL, 0.565 mmol, 6.0 equiv). The orange cloudy mixture was stirred from 0 °C to room temperature for 30 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (20–30% EtOAc/hexanes) to yield a mixture of macrolactone products (31.7 mg, 97%) which consisted of dechlorogreensporone D (**26**) as a light yellow solid (16.1 mg, 49%) and dechlorogreensporone F (**23**) as a light yellow oil (15.6 mg, 48%).



26

Dechlorogreensporone D (26). 16.1 mg, 49%; R_f = 0.23 (60% EtOAc/hexanes); mp 182.7–185.8 °C; $[\alpha]_D^{26.8}$ = +64.60 (*c* 0.27, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.0 (br s, 1H), 6.68 (dt, *J* = 15.9, 7.5 Hz, 1H), 6.39 (s, 1H), 6.29 (s, 1H), 5.98 (d, *J* = 15.9 Hz, 1H), 4.94–4.87 (m, 1H), 4.54 (br s, 1H), 4.06 (d, *J* = 15.9 Hz, 1H), 3.72–3.62 (m, 4H), 3.42–3.36 (m, 1H), 2.20–2.08 (m, 2H), 1.79–1.40 (m, 5H), 1.23 (d, *J* = 5.7 Hz, 3H), 1.19–1.10 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 195.9, 167.3, 159.8, 159.2, 148.3, 135.6, 128.5, 114.2, 109.7, 98.5, 69.4, 66.2, 55.9, 44.6, 34.6, 30.3, 29.2, 28.3, 20.1; IR (thin film) 3446, 2926, 2857, 1695, 1685, 1523, 1089 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{19}H_{24}NaO_6$ $(M+Na)^+$ 371.1471, found 371.1478.



23

Dechlorogreensporone F (23). 15.6 mg, 48%; R_f = 0.33 (60% EtOAc/hexanes); $[\alpha]_D^{27.3}$ = –38.48 (*c* 0.11, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (d, *J* = 1.8 Hz, 1H), 6.24 (d, *J* = 1.8 Hz, 1H), 5.28–5.25 (m, 1H), 4.22–4.14 (m, 1H), 4.01 (d, *J* = 17.1 Hz, 1H), 3.92 (d, *J* = 17.1 Hz, 1H), 3.89–3.79 (m, 1H), 3.73 (s, 3H), 2.65 (dd, *J* = 13.8, 3.9 Hz, 1H), 2.56 (dd, *J* = 13.8, 8.1 Hz, 1H), 2.02–1.43 (m, 8H), 1.31 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 167.9, 159.0, 158.4, 133.8, 116.5, 109.4, 98.5, 79.3, 76.0, 72.6, 55.8, 49.1, 47.8, 33.5, 32.9, 31.2, 30.4, 20.8; IR (thin film) 3366, 2927, 2855, 1716, 1608, 1458, 1269 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{19}H_{24}NaO_6$ $(M+Na)^+$ 371.1471, found 371.1464.

CYTOTOXICITY ASSAY

Cytotoxic activity of synthetic **25** and **26** were evaluated against seven human cancer cell lines including two breast adenocarcinoma (MDA-MB-231 and MCF-7), one colorectal carcinoma (HCT116), one hepatoma (HepG2) and three cervical carcinoma (C33A, HeLa and SiHa) cells as well as one monkey kidney non-cancerous cell line by MTT assay using the general procedure previously described. Cancer cells were exposed to various concentrations of compounds **25** and **26** (0–25 μM; 0.2% (v/v) DMSO). Vero cells were exposed to 0–50 μM of **25** and **26**. Each experiment was performed in triplicate and was repeated three times. Data was expressed as IC_{50} values (the concentration needed for 50% cell growth inhibition) relative to the untreated cells (0.2% (v/v) DMSO) (means ± SD). Cisplatin (0–50 μM) and doxorubicin (0–1 μM) (Pfizer, Australia) were used as positive controls.

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APPENDIX

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Total synthesis and cytotoxic activity of dechlorogreensporones A and D

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ABSTRACT

The first and convergent total syntheses of polyketide natural products dechlorogreensporones A and D have been accomplished in 17 longest linear steps with 2.8% and 5.4% overall yields, respectively, starting from known methyl 2-(2-formyl-3,5-dihydroxyphenyl)acetate and commercially available *R*-(+)-propylene oxide and 1,2-epoxy-5-hexene. Our synthesis exploited key Mitsunobu esterification and (*E*)-selective ring-closing metathesis (RCM) to assemble the macrocycles as well as a Jacobsen hydrolytic kinetic resolution to install the stereogenic centers. Both synthetic compounds were found to display significant cytotoxic activity against seven human cancer cell lines with the IC_{50} ranges of 6.66–17.25 μM.

1. Introduction

The well-known 14-membered β-resorcylic acid lactones (RALs) are a group of fungal polyketide metabolites that possess a multitude of biological and pharmacological activities [1]. A subclass of RALs are those containing an α,β-unsaturated ketone at the 8–10 positions, which are derivatives of radicicol [2]. The major examples of this subclass of RALs are the pochonins [3] and the monocillins [4] (Fig. 1). This group of metabolites has been shown to exhibit various interesting biological activities e.g. antiviral activity against Herpes Simplex Virus 1 (HSV 1) [3a], antifungal activity (against *Mucorflavas* IFO 9560) [5], HSP-90 inhibitory activity [6], and latent HIV-1 reactivation activity [3c]. In consequence of their diverse and promising biological properties and structural features, this class of macrolides has been synthetic targets for many synthetic organic research groups worldwide [7]. Precedented strategies to construct the macrocyclic cores of RALs possessing similar core skeleton mainly relied on esterification reaction [7] and ring-closing metathesis [7c,f-k] (Fig. 2). Other key bond formations included Pd-catalyzed cross coupling/elimination [7a,b,d,e], substitution by dithiane anion [7c] and nucleophilic addition to Weinreb amide (acylation) [7f-i].

Dechlorogreensporones A (**5**) and D (**6**) are new 14-membered β-RALs, which were isolated, along with other 12 new RALs from a culture of a freshwater fungus *Halenospora* sp. by Oberlies and co-workers in 2014 (Fig. 3) [8]. Compounds **5** and **6** are radicicol analogues possessing a methoxy group at the 16-position, which represent rare examples of RALs containing β-resorcylic acid monomethyl ethers. Dechlorogreensporones A and D have the same planar structure which includes a stereogenic center at the 2-position. However, the minor structural difference is that **5** contains a keto group at the 5-position, whereas **6** bears an alcohol stereogenic center. In addition, dechlorogreensporone A (**5**) is structurally very similar to the previously reported natural product cryptosporiopsin A [9]. The absolute configuration of the C-2 asymmetric carbon in macrolactones **5** and **6** and other co-metabolites was proposed by the isolation group to be *S* by the evidence of X-ray diffraction analysis of the bromobenzoyl derivative of one of the metabolites in the series. The absolute configuration of the C-5 in **6** and co-metabolites containing C-5 alcohol stereogenic center was assigned to be *S* via a Mosher's ester method. Interestingly, the assigned C-2 absolute configuration of **5** and **6** and other analogues

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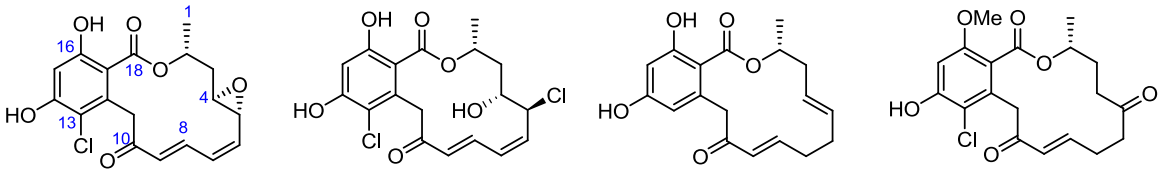

Fig. 1. Structures of radicicol and selected examples of its analogues.

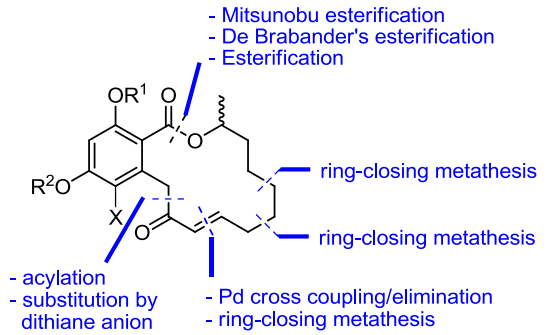

Fig. 2. Key bond formation strategies in previous syntheses of radicicol and its analogues.

in the series is opposite to that of cryptosporiopsin A, which was assigned by analogy to the known RAL pochonin D. Dechlorogreensporones A and D were tested for cytotoxic activities against two human cancer cell lines and were found to exhibit cytotoxicity against the MDA-MB-435 (melanoma) cancer cell line with IC_{50} values of 14.1 and 11.2 μM, respectively. They also exhibited cytotoxicity against the HT-29 (colon) cancer cell line with IC_{50} values of >20 and 25.4 μM, respectively. Due to promising biological activities of this subclass of RALs and our ongoing program for anticancer drug discovery, our research group has been focusing on a synthetic program of selected compounds of this class. Herein, we report the first total synthesis of both **5** and **6** as well as evaluation of their cytotoxic activity against seven human cancer cell lines.

2. Results and discussion

Our retrosynthetic approach toward dechlorogreensporones A (**5**) and D (**6**) would utilize similar disconnection strategy to Mohapatra and Thirupathi's [7j] and our previous report [7k] via ring-closing metathesis (RCM) as a key macrocyclization protocol and to concomitantly establish the (*E*) geometry of C8–C9 olefin. We would also rely on the Mitsunobu esterification to construct the ester functional group of the diene RCM precursor (Scheme 1). Although the targets **5** and **6** only differ by the functional groups at the 5-position and could be ideally synthesized from the same

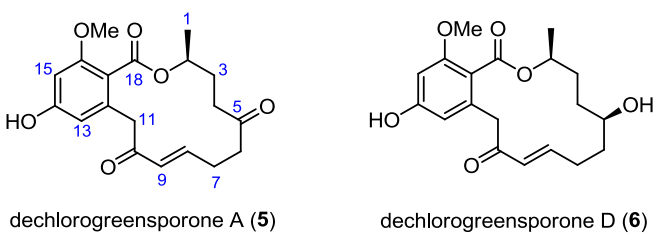

Fig. 3. Structures of dechlorogreensporones A (**5**) and D (**6**).

intermediate, the alcohol stereogenic center at the 5-position in **6** posed a challenge to the synthesis. Thus, we employed two different routes for the synthesis of the requisite alcohol fragments in conjunction with protecting group manipulation. The diene RCM precursor **9** (for **5**) or **10** (for **6**) would be assembled by Mitsunobu esterification between the common benzoic acid intermediate **11** and chiral alcohol intermediate **12** or **13**. The common benzoic acid intermediate **11** would be elaborated from the known phenol **14** using our previously described approach. The requisite chiral alcohol **12** for the synthesis of **5** would be obtained from *R*-(+)-propylene oxide (**15**) via double allylation, whereas enantioenriched alcohol **13** would be prepared from 1,2-epoxy-5-hexene (**16**) using Jacobsen hydrolytic kinetic resolution to construct both chiral centers [10].

Synthesis of benzoic acid **11** which was required as a Mitsunobu coupling partner for syntheses of both **5** and **6** commenced with selective protection of known phenol **14** [11] with 4-methoxybenzyl ether (PMB) group [12] to afford PMB ether **17** in 82% yield. Subsequent methylation of the remaining phenol moiety with iodomethane and K_2CO_3 in DMF furnished methyl ether **18** in 94% yield. Following our previously established sequence [7k], benzaldehyde **18** was further elaborated to the requisite benzoic acid **11** in 10 steps and 31% overall yield (Scheme 2).

Synthesis of alcohol **12** required for the synthesis of **5** was achieved in a concise sequence of 6 steps as illustrated in Scheme 3. Regioselective ring opening of commercially available *R*-(+)-propylene oxide (**16**) (>99% ee) by allylmagnesium bromide in the presence of catalytic CuI provided the corresponding chiral secondary alcohol [13], which was instantaneously protected with TBDPS group to afford TBDPS ether **19** in 78% yield over 2 steps. Subsequent epoxidation of alkene **19** with *m*-CPBA afforded racemic epoxide **20**, which was then subjected to another regioselective ring opening by allylmagnesium bromide to give racemic alcohol **21** in 89% yield [14]. Protection of the secondary alcohol of **21** with ethoxymethyl (EOM) group provided EOM ether, which after TBDPS deprotection with TBAF furnished the desired chiral alcohol **12** in 95% yield. The absolute configuration of the alcohol stereogenic center was confirmed to be *R* based on Mosher ester analysis.

Having successfully synthesized both key fragments **11** and **12**, we continued to complete the synthesis of dechlorogreensporone A (Scheme 4). Benzoic acid **11** was subjected to esterification with (*R*)-alcohol **12** under Mitsunobu conditions using diisopropyl azodicarboxylate (DIAD) and PPh_3 in toluene at room temperature to smoothly furnish the ester RCM diene precursor **9** in 72% yield. This step was expected to provide the correct stereochemistry of the C-2 stereogenic center. With diene **9** in hand, the stage was then set for the key ring-closing metathesis. We and the Mohapatra group have previously demonstrated that the second-generation Grubbs catalyst is a remarkable RCM catalyst for this type of substrate [7j,k]. However, in this case the second-generation Grubbs catalyst proved to be less reactive and led to incomplete consumption of the starting diene. To our delight, RCM of **9** using 10 mol% of second-

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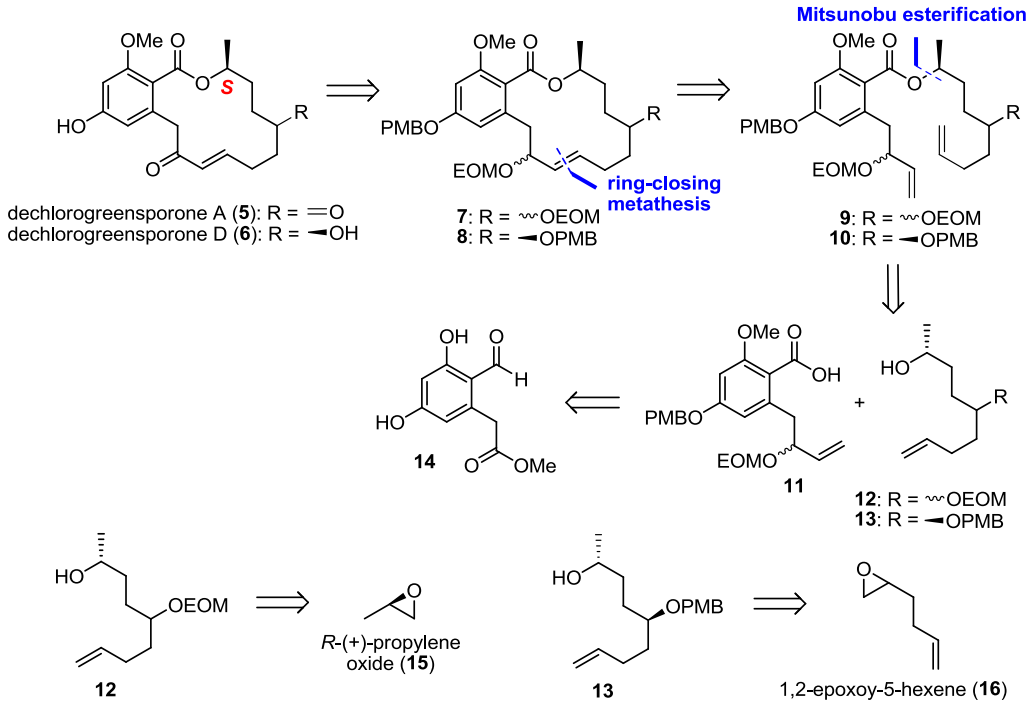
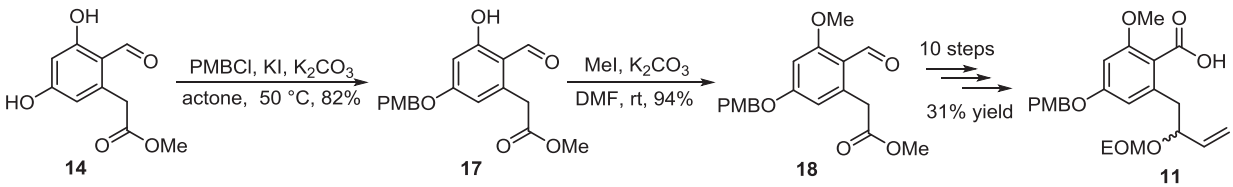
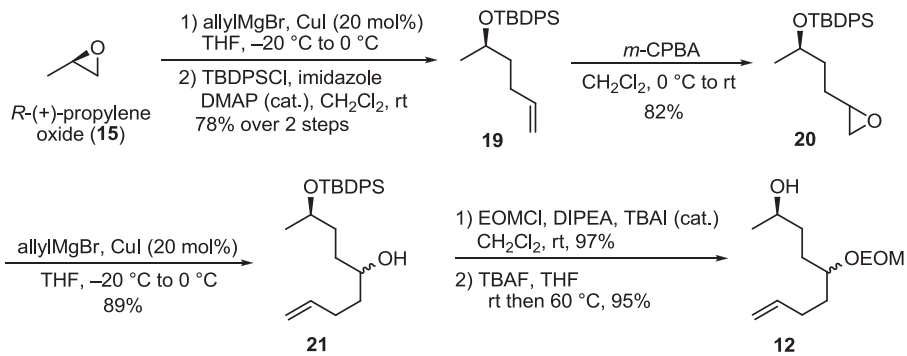


Scheme 1. Retrosynthesis of dechlorogreensporones A (**5**) and D (**6**).



Scheme 2. Synthesis of the common benzoic acid intermediate **11**.



Scheme 3. Synthesis of alcohol **12**.

generation Hoveyda-Grubbs catalyst in toluene at high dilution (5 mM) at 85 °C proceeded to completion within 3.5 h to afford RCM products **7** in 59% yield as an inseparable mixture of diastereomers. No attempts were made to separate these diastereomeric products because they would eventually be transformed into the same diketo product via oxidation in the penultimate step. It should be noted that the geometry of the resulting olefin at C8–C9 could not be determined by NMR spectroscopy at this stage. We then carried this diastereomeric mixture on to the next step, which was removal of both EOM protecting groups of **7** using 4 M HCl in THF at ambient temperature to furnish diol **22** in 57% yield as, again, a mixture of diastereomers. Both hydroxyl groups of **22** were then simultaneously oxidized using a large excess Dess-Martin periodinane in CH_2Cl_2 to furnish diketone **23** in 62% yield. The geometry of the C8–C9 olefin of the macrocyclic products from RCM could then be verified to be (*E*) in this step on the basis of the coupling constant of 15.6 Hz between H-8 and H-9. Finally, following Mohapatra's protocol [7j], treatment of **23** with 1 M titanium tetrachloride in

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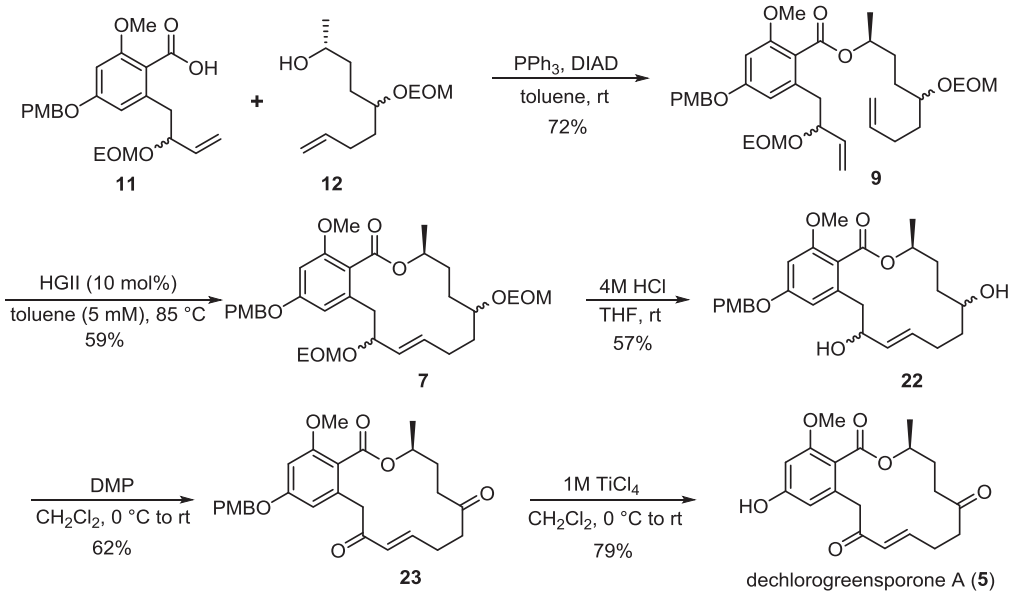
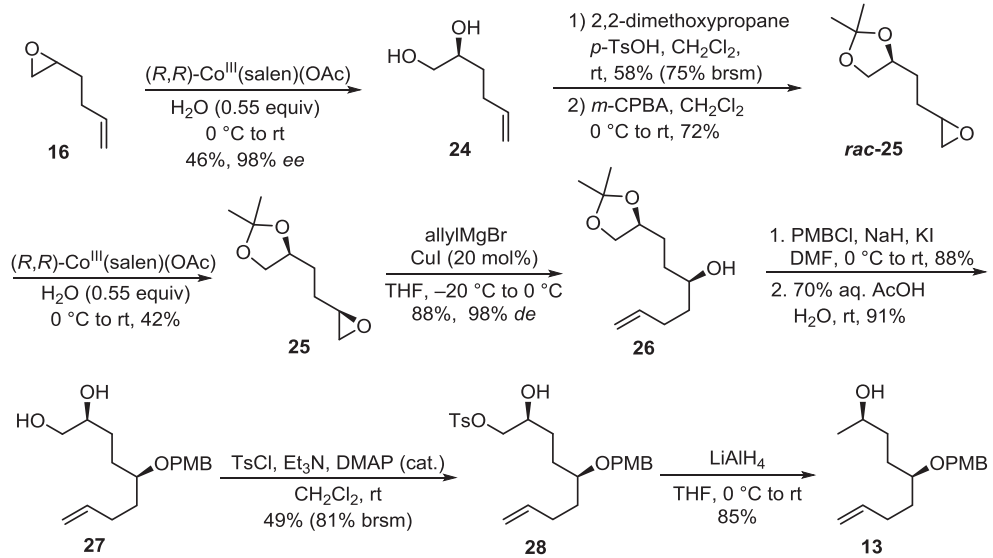


Scheme 4. Completion of the synthesis of dechlorogreensporone A (**5**).

CH_2Cl_2 at 0 °C furnished dechlorogreensporone A (**5**) in 79% yield. The ^1H and ^{13}C NMR spectroscopic and HRMS data of synthetic **5** were nearly identical to those reported for natural **5** (see Supplementary data). Additionally, the specific rotation of synthetic **5** ($[\alpha]_D^{26.4} = +66.02$ (*c* 0.10, MeOH)) was in excellent agreement with the reported value for natural **5** ($[\alpha]_D^{20} = +56.0$ (*c* 0.10, MeOH)) [8]. Our synthesis thus confirmed the absolute configuration of the natural product dechlorogreensporone A assigned by Oberlies and co-workers.

The synthesis of chiral alcohol **13** required for the synthesis of **6** is outlined in Scheme 5. Although we could in theory use the epoxide intermediate **20** for the synthesis of the desired chiral epoxide, the Jacobsen hydrolytic kinetic resolution of **20** was unsuccessful. Thus, we had to revise the synthesis of chiral alcohol **13** using a different starting material. Hydrolytic kinetic resolution of commercially available 1,2-epoxy-5-hexene (**16**) using Jacobsen's (*R*,*R*)-Co(III)(salen)(OAc) catalyst afforded (*S*)-diol **24** in 46% yield and 98% *ee* [10]. The enantiomeric excess of **24** was determined by chiral HPLC on the corresponding monobenzoate. Next, protection of diol **24** using 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid gave the corresponding acetonide in 75% yield based on the recovered diol **24** [15]. Subsequent epoxidation with *m*-CPBA furnished racemic epoxide ***rac*-25** in 72% yield [16]. Racemic epoxide **25** was then subjected to second hydrolytic kinetic resolution using (*R*,*R*)-Co(III)(salen)(OAc) as a catalyst to give (*R*)-epoxide **25** in 42% yield [16,17]. Regioselective ring-opening of epoxide **25** by allylmagnesium bromide in the presence of catalytic CuI yielded chiral alcohol **26** in 88% yield and 98% *de* (determined on the monobenzoate derivative by chiral HPLC). The absolute configuration of the newly generated alcohol stereogenic center was confirmed to be *S* based on Mosher ester analysis. We chose a PMB protecting group for this chiral alcohol for the purpose of



Scheme 5. Synthesis of chiral alcohol **13**.

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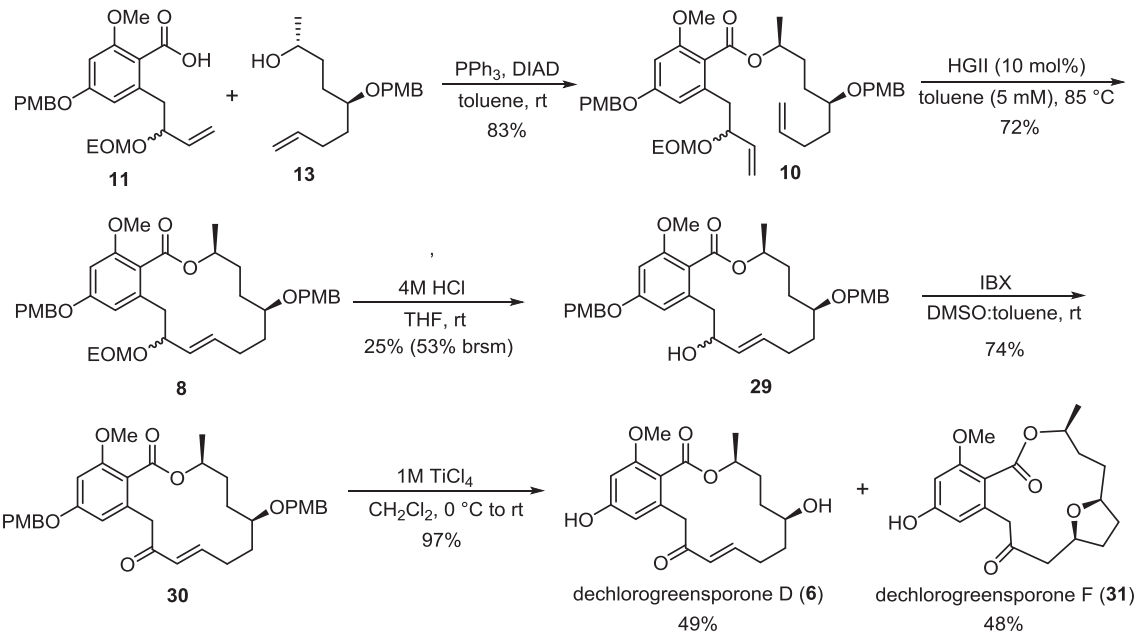
global deprotection in the final step. (*S*)-Alcohol **26** on protection using excess of both PMBCl and KI gave the corresponding PMB ether in 88% yield. The next task was to convert to the protected diol moiety to the chiral secondary alcohol which was accomplished in 3 steps. Removal of the acetonide protecting group with 70% AcOH smoothly gave diol **27** in 91% yield. Diol **27** on further monotosylation employing TsCl and Et_3N in the presence of catalytic DMAP in CH_2Cl_2, followed by reduction using $LiAlH_4$ in THF yielded the requisite (*R*)-alcohol **13** in 85% yield [17]. The absolute configuration of the alcohol stereogenic center was confirmed to be *R* via Mosher ester analysis.

With the requisite chiral alcohol **13** in hand, completion of the synthesis of dechlorogreensporone D (**6**) was achieved via the same synthetic approach as that of **5** (Scheme 6). Mitsunobu coupling of benzoic acid **11** and (*R*)-alcohol **13** under the same conditions previously described smoothly gave ester diene **10** in 83% yield. Ring-closing metathesis of diene **10** using second-generation Hoveyda-Grubbs catalyst (10 mol%) in toluene (5 mM) at 85 °C furnished macrocyclic product **8** in 72% yield as an inseparable mixture of diastereomers. The slightly higher yield of the RCM of **10** compared to **9** was ascribed to the better compatibility of the PMB protecting group under these RCM conditions. Similar to previous observation, the geometry of the newly formed C8–C9 olefin could be determined at a later stage of the synthesis. We proceeded to remove the EOM protecting group using 4 M HCl solution in THF at room temperature for 4 h to give **29** in 53% yield based on recovered starting EOM ether. Careful monitoring must be done in this step to prevent overdeprotection of the PMB groups. At this stage, the *trans* geometry of the double bond of **29** was confirmed based on the coupling constant (15.3 Hz) between H-8 and H-9. Oxidation of allylic alcohol **29** was achieved using excess 2-iodoxybenzoic acid (IBX) in a mixture of toluene and DMSO to afford macrocyclic enone **30** in 74% yield. Finally, both PMB protecting groups of **30** were removed using 6 equivalents of 1 M $TiCl_4$ in CH_2Cl_2 at 0 °C to deliver the requisite dechlorogreensporone D (**6**) in 49% yield along with unexpected analogue dechlorogreensporone F (**31**) in 48% yield. Byproduct **31** was a proposed artifact from a facile intramolecular cycloetherification of the parent **6** during the purification process by the Oberlies group. The spectroscopic and analytical properties of **6** and **31** (^1H and ^{13}C NMR, and HRMS) were identical to those of reported for the natural products **6** and **31** (see Supplementary data). The specific rotation of synthetic **6** was observed as $[\alpha]_D^{26.8} = +64.60$ (*c* 0.27, MeOH), which was in accordance with that of natural **6** ($[\alpha]_D^{20} = +116.0$ (*c* 0.27, MeOH)), yet in a lower magnitude [8]. In addition, the specific rotation of synthetic **31** was obtained as $[\alpha]_D^{27.3} = -38.48$ (*c* 0.11, MeOH), which was nearly identical to the reported value for natural **31** ($[\alpha]_D^{20} = -31.0$ (*c* 0.11, MeOH)) [8].

Synthetic compounds **5** and **6** were assessed for their cytotoxic activity by MTT assay against seven human cancer cell lines including two breast adenocarcinoma (MDA-MB-231 and MCF-7), one colorectal carcinoma (HCT116), one hepatoma (HepG2) and three cervical carcinoma (C33A, HeLa and SiHa) cells as well as one monkey kidney non-cancerous (Vero) cell line (Table 1) [18]. It was observed that both compounds could inhibit the proliferation of all cancer cell lines with the IC_{50} ranges of 6.94–17.25 μM for compound **5** and 6.66–11.84 μM for compound **6**, although in a significantly lower extent compared to a standard drug doxorubicin. Interestingly, however, both **5** and **6** showed more potent cytotoxic activity than a standard drug cisplatin against five cancer cell lines (MDA-MB-231, MCF-7, HCT116, HepG2 and SiHa) tested. Our results also revealed that dechlorogreensporone D (**6**) showed higher antiproliferative effect against most cancer cell lines tested than the

Table 1
Cytotoxic activity of synthetic **5** and **6** against seven cancer cell lines and Vero cells.

cell lines	cytotoxicity, IC_{50} (μM)			
	5	**6**	cisplatin	doxorubicin
MDA-MB-231	9.28 ± 0.13	6.97 ± 1.73	25.25	0.51
MCF-7	17.25 ± 0.71	11.84 ± 0.05	35.5	0.29
HCT116	7.53 ± 0.13	6.97 ± 0.05	35	0.81
HepG2	13.81 ± 0.27	7.88 ± 0.88	26	0.65
C33A	10.06 ± 0.53	10.41 ± 0.13	4.72	0.19
HeLa	15.5 ± 0	7.88 ± 1.06	8.98	0.16
SiHa	6.94 ± 1.06	6.66 ± 1.02	12.18	0.18
Vero	46.00 ± 3.18	10.13 ± 0.88	17.75	>1



Scheme 6. Completion of the synthesis of dechlorogreensporone D (**6**).

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ketone analogue **5**. This observation was consistent with the report by the Oberlies group [8]. Nevertheless, **5** was approximately 5-fold less cytotoxic to Vero cells compared to **6**.

3. Conclusion

In conclusion, the first and convergent total syntheses of dechlorogreensporones A (**5**) and D (**6**) have been accomplished via a longest linear sequence of 17 steps in 2.8% and 5.4% overall yields, respectively, from known phenol **14** and commercially available *R*-(+)-propylene oxide and 1,2-epoxy-5-hexene. Our approach exploited key Mitsunobu esterification and ring-closing metathesis to assemble the macrocycles and construct the (*E*)-olefin. Jacobsen hydrolytic kinetic resolution was also utilized to install the C-2 and C-5 stereogenic centers. Our syntheses verified the absolute stereochemistry of the natural products proposed by the Oberlies group. Synthetic compounds **5** and **6** were found to display significant cytotoxic activity against seven human cancer cell lines with the IC_{50} ranges of 6.66–17.25 μM. In addition, dechlorogreensporone D (**6**) showed more potent antiproliferative activity compared to dechlorogreensprone A (**5**), although **5** was approximately 5-fold less cytotoxic to Vero cells compared to **6**.

4. Experimental

4.1. General

All reactions were performed under argon or nitrogen atmosphere in oven- or flamed-dried glassware unless otherwise noted. Solvents were used as received from suppliers or distilled prior to use using standard procedures. All other reagents were obtained from commercial sources and used without further purification. Column chromatography was performed on SiliaFlash® G60 Silica (60–200 μm, Silicycle) or Silica gel 60 (0.063–0.200 mm, Merck). Thin-layer chromatography (TLC) was performed on Silica gel 60 F_{254} (Merck). ^{1}H, ^{13}C and 2D NMR spectroscopic data were recorded on a 300 MHz Bruker FTNMR UltraShield spectrometer. ^{1}H NMR spectra are reported in ppm on the δ scale and referenced to the internal tetramethylsilane. The data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, br = broad, app = apparent), coupling constant(s) in hertz (Hz), and integration. Infrared (IR) spectra were recorded on a Perkin Elmer 783 FTS165 FT-IR spectrometer. High-resolution mass spectra were obtained on a liquid chromatograph-mass spectrometer (2690, LCT, Waters, Micromass) and on a SpiralTOF™ MALDI TOF Mass Spectrometer Revolutionary (Scientific and Technological Research Equipment Centre; STREC, Chulalongkorn University). The optical rotations were recorded on a JASCO P-2000 polarimeter. Melting points were measured using an Electrothermal IA9300 melting point apparatus and are uncorrected. Enantiopurity was determined using HPLC on an Agilent series 1200 equipped with a diode array UV detector using either CHIRALCEL® OD-H column (15 cm) or CHIRALPAK® AS-H column (15 cm) and a guard column (1 cm).

4.2. Synthesis of diene RCM precursor **9**

To a solution of benzoic acid **11** (245.3 mg, 0.59 mmol, 1.0 equiv) and (*R*)-alcohol **12** (122.3 mg, 0.57 mmol) in 5.9 mL of toluene at room temperature were added PPh_3 (314.9 mg, 1.20 mmol, 2.0 equiv), followed by diisopropyl azodicarboxylate (40% in toluene, 0.58 mL, 1.18 mmol, 2.0 equiv). The resultant yellow mixture was stirred at rt overnight before being concentrated *in vacuo*. Purification of the crude residue by column chromatography (5–10% EtOAc/hexanes) yielded ester diene **9** as a light yellow oil (259.1 mg, 72%): R_f = 0.63 (40% EtOAc/hexanes); $[\alpha]_D^{24.6}$ = +0.47 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.49 (s, 1H), 6.40 (s, 1H), 5.81 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.70 (ddd, *J* = 17.1, 9.9, 7.2 Hz, 1H), 5.21–5.12 (m, 3H), 5.04–4.93 (m, 4H), 4.69 (s, 2H), 4.61 (d, *J* = 6.6 Hz, 1H), 4.49 (d, *J* = 6.6 Hz, 1H), 4.29–4.23 (m, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.65–3.58 (m, 3H), 3.32 (qd, *J* = 6.9, 2.1 Hz, 2H), 2.95–2.73 (m, 2H), 2.16–2.07 (m, 2H), 1.70–1.57 (m, 6H), 1.36–1.30 (m, 3H), 1.12 (td, *J* = 6.9, 2.1 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 160.0, 159.5, 157.9, 138.5, 138.3, 138.2, 137.8, 129.2, 128.6, 117.9, 117.2, 117.1, 114.6, 114.0, 108.2, 97.8, 93.9, 92.3, 77.4, 77.3, 76.7, 76.5, 72.0, 71.7, 69.9, 63.3, 63.0, 55.7, 55.3, 39.7, 33.7, 33.6, 31.8, 31.5, 30.2, 30.1, 29.9, 29.8, 29.5, 29.4, 29.3, 21.9, 21.7, 20.2, 20.1, 15.1, 14.9; IR (thin film) 2977, 2935, 1717, 1517, 1250, 1159, 1107 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{35}H_{50}NaO_9$ $(M + Na)^+$ 637.3347, found 637.3341.

4.3. RCM of **9** to afford macrolactones **7**

A solution of diene **9** (131.5 mg, 0.214 mmol) in toluene (42 mL, 5 mM) was degassed with Ar for 10 min and second-generation Hoveyda Grubbs catalyst (13.4 mg, 0.021 mmol, 10 mol%) was added. The reaction mixture was heated at 85 °C for 3.5 h, which the starting diene was completely consumed as judged by TLC. Solvent was then removed under reduced pressure. Purification of the crude residue by column chromatography (10–15% EtOAc/hexanes) yielded a mixture of macrolactone products **7** as a light yellow oil (74.2 mg, 59%): R_f = 0.50 (40% EtOAc/hexanes); $[\alpha]_D^{25.3}$ = −5.26 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2H), 6.91 (dd, *J* = 8.4, 2.7 Hz, 2H), 6.81–6.58 (m, 1H), 6.41 (s, 1H), 5.66–5.54 (m, 1H), 5.29–5.04 (m, 2H), 4.98 (s, 2H), 4.75–4.58 (m, 4H), 4.29–4.17 (m, 1H), 3.80 (s, 3H), 3.77 (d, *J* = 2.1 Hz, 3H), 3.72–3.45 (m, 5H), 3.24–2.75 (m, 2H), 2.30–1.42 (m, 8H), 1.34 (t, *J* = 6.6 Hz, 3H), 1.30–1.14 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 167.9, 167.8, 160.3, 159.9, 159.5, 158.3, 158.2, 157.8, 157.7, 138.6, 138.4, 138.1, 137.9, 137.4, 136.7, 134.8, 134.6, 133.8, 130.7, 129.3, 129.2, 129.1, 129.0, 128.8, 128.6, 128.4, 118.1, 114.1, 114.0, 109.3, 108.4, 107.1, 107.0, 98.1, 98.0, 97.8, 94.2, 94.0, 93.8, 93.5, 93.0, 92.4, 91.9, 91.7, 91.4, 79.3, 78.2, 77.9, 76.0, 75.5, 74.3, 73.0, 72.3, 70.9, 69.9, 69.8, 63.4, 63.3, 63.2, 63.1, 62.8, 55.9, 55.8, 55.3, 39.2, 38.9, 38.2, 37.2, 33.2, 32.8, 32.6, 32.1, 32.0, 31.1, 30.9, 30.5, 29.1, 28.8, 28.3, 27.8, 23.7, 21.9, 21.7, 20.7, 20.2, 20.1, 15.2, 15.1, 14.8; IR (thin film) 2971, 2932, 1718, 1603, 1458, 1252, 1159 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{33}H_{46}NaO_9$ $(M + Na)^+$ 609.3034, found 609.3036.

4.4. Removal of EOM protecting groups of **7** to give diol **22**

To a solution of EOM ether **7** (49.5 mg, 0.084 mmol) in THF (4.2 mL) at rt was added 2.4 mL of 4 M HCl. The mixture was stirred at rt overnight, then which was quenched with saturated aqueous $NaHCO_3$ (5 mL) and diluted with EtOAc (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography (40% EtOAc/hexanes) yielded diol **22** as a light yellow oil (22.5 mg, 57%): R_f = 0.34 (80% EtOAc/hexanes); $[\alpha]_D^{25.1}$ = −24.43 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 6.91 (dd, *J* = 8.4, 1.8 Hz, 2H), 6.75–6.52 (m, 1H), 6.43–6.40 (m, 1H), 5.60–5.51 (m, 1H), 5.38–5.02 (m, 2H), 4.98–4.97 (m, 2H), 4.46–4.34 (m, 1H), 3.81–3.75 (m, 6H), 3.72–3.57 (m, 1H), 3.21–2.74 (m, 2H), 2.17–1.54 (m, 8H), 1.36 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 167.9, 160.8, 160.3, 159.7, 158.9, 138.5, 138.0, 133.4, 133.0, 132.6, 132.2, 132.0, 131.6, 129.7, 129.5, 128.8, 128.6, 127.5, 118.1, 117.8, 114.2, 109.2, 108.4, 107.2, 106.9, 98.5, 98.1, 73.9, 73.8, 73.6, 73.2, 73.1, 72.9,

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70.3, 70.1, 70.0, 69.8, 67.7, 67.5, 56.1, 55.5, 41.7, 41.4, 39.1, 38.5, 36.6, 36.4, 35.5, 35.3, 34.5, 32.2, 31.9, 30.7, 30.6, 29.4, 29.1, 28.5, 27.9, 21.1, 20.9, 20.4, 20.3; IR (thin film) 3447, 2933, 2858, 1700, 1603, 1251, 1161 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{27}H_{34}NaO_7$ $(M + Na)^+$ 493.2202, found 493.2211.

4.5. Oxidation of diol **22** to give diketone **23**

To a solution of macrolactone diol **22** (112.2 mg, 0.24 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Dess-Martin periodinane (808.8 mg, 1.90 mmol, 8.0 equiv). The reaction mixture was stirred from 0 °C to room temperature for 4 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography (20–40% EtOAc/hexanes) provided diketone **23** as a light yellow oil (66.2 mg, 62%): $R_f = 0.21$ (40% EtOAc/hexanes); $[\alpha]_D^{25.3} = +2.80$ (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 6.78 (dt, $J = 15.6$, 6.3 Hz, 1H), 6.55 (d, $J = 1.8$ Hz, 1H), 6.43 (d, $J = 1.8$ Hz, 1H), 6.05 (d, $J = 15.6$ Hz, 1H), 5.18 (m, 1H), 4.98 (d, $J = 2.4$ Hz, 1H), 4.32 (d, $J = 14.1$ Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.36 (d, $J = 14.1$ Hz, 1H), 2.73–2.38 (m, 6H), 2.07–1.97 (m, 1H), 1.82–1.68 (m, 1H), 1.37 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.5, 196.7, 167.9, 160.9, 159.7, 159.1, 146.1, 135.2, 130.6, 129.4, 128.4, 116.8, 114.1, 107.9, 99.0, 71.1, 70.0, 56.0, 55.3, 44.2, 40.5, 39.1, 28.6, 28.3, 20.3; IR (thin film) 3011, 2933, 2853, 1701, 1605, 1252, 1161 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{27}H_{30}NaO_7$ $(M + Na)^+$ 489.1884, found 489.1884.

4.6. Deprotection of PMB group of **23** to furnish dechlorogreensporone A (**5**)

To a solution of macrolactone **23** (66.2 mg, 0.14 mmol) in 15 mL of CH_2Cl_2 at 0 °C was added $TiCl_4$ (1.0 M solution in CH_2Cl_2, 450 μL, 0.140 mmol, 3.2 equiv). The brick orange cloudy mixture was stirred from 0 °C to room temperature for 30 min, which was then quenched with saturated aqueous $NaHCO_3$ (20 mL) and the orange color dissipated. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (30–40% EtOAc/hexanes) to give dechlorogreensporone A (**5**) as a light yellow solid (38.4 mg, 79%): $R_f = 0.37$ (60% EtOAc/hexanes); mp 142.9–146.4 °C; $[\alpha]_D^{26.4} = +66.02$ (*c* 0.10, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 6.82–6.75 (m, 1H), 6.43 (d, $J = 2.1$ Hz, 1H), 6.30 (d, $J = 2.1$ Hz, 1H), 6.05 (d, $J = 15.6$ Hz, 1H), 5.21–5.16 (m, 1H), 4.29 (d, $J = 14.1$ Hz, 1H), 3.72 (s, 3H), 3.35 (d, $J = 14.1$ Hz, 1H), 2.73–2.40 (m, 6H), 2.19–1.96 (m, 1H), 1.84–1.72 (m, 2H), 1.37 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 198.6, 168.4, 159.6, 159.1, 147.5, 134.9, 130.6, 115.7, 109.8, 98.9, 71.4, 56.0, 44.1, 40.6, 39.4, 28.7, 28.4, 20.5; IR (thin film) 3367, 2930, 2855, 1699, 1610, 1458, 1273 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{19}H_{22}NaO_6$ $(M + Na)^+$ 369.1314, found 369.1322.

4.7. Synthesis of diene RCM precursor **10**

To a solution of benzoic acid **11** (272.5 mg, 0.65 mmol, 1.2 equiv) and (*R*)-alcohol **13** (148.1 mg, 0.53 mmol) in 6 mL of toluene at room temperature were added PPh_3 (351.9 mg, 1.34 mmol, 2.5 equiv), followed by diisopropyl azodicarboxylate (40% in toluene, 0.66 mL, 1.34 mmol, 2.5 equiv). The resultant yellow mixture was stirred at rt overnight before being concentrated *in vacuo*. Purification of the crude residue by column chromatography (5–10% EtOAc/hexanes) yielded ester diene **10** as a light yellow oil (297.8 mg, 83%): $R_f = 0.55$ (40% EtOAc/hexanes); $[\alpha]_D^{25.5} = -2.40$ (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, $J = 8.7$ Hz, 2H), 7.26 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 6.49 (s, 1H), 6.39 (s, 1H), 5.81 (ddt, $J = 17.1$, 10.2, 6.3 Hz, 1H), 5.69 (ddd, $J = 17.4$, 9.9, 7.2 Hz, 1H), 5.20–5.18 (m, 3H), 5.03–4.92 (m, 4H), 4.61 (d, $J = 6.9$ Hz, 1H), 4.45 (d, $J = 6.9$ Hz, 1H), 4.43 (s, 2H), 4.29–4.22 (m, 1H) 3.82 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 3.46–3.42 (m, 1H), 3.33 (qd, $J = 7.2$, 3.0 Hz, 2H), 2.95–2.75 (m, 2H), 2.16–2.07 (m, 2H), 1.78–1.60 (m, 6H), 1.34–1.31 (m, 3H), 1.05 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 160.0, 159.6, 159.1, 158.0, 138.7, 138.3, 138.2, 137.8, 131.1, 129.3, 129.2, 128.7, 118.0, 117.0, 114.5, 114.1, 113.8, 108.4, 97.9, 92.4, 77.5, 77.4, 77.3, 71.7, 70.4, 69.9, 63.0, 55.8, 55.3, 39.7, 33.2, 31.5, 29.6, 29.4, 20.2, 20.1, 14.9; IR (thin film) 2933, 2862, 1716, 1516, 1250, 1159, 1034 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{40}H_{52}NaO_9$ $(M + Na)^+$ 699.3509, found 699.3533.

4.8. RCM of **10** to afford macrolactones **8**

To a solution of diene **10** (41.7 mg, 0.061 mmol) in toluene (12.3 mL, 5 mM) was degassed with Ar for 10 min and second-generation Hoveyda Grubbs catalyst (3.9 mg, 0.006 mmol, 10 mol %) was added. The reaction mixture was heated at 85 °C for 4 h, at which the starting diene was completely consumed as judged by TLC. Solvent was then removed under reduced pressure. Purification of the crude residue by column chromatography (10% EtOAc/hexanes) yielded a mixture of macrolactone products **8** as a light yellow oil (28.8 mg, 72%): $R_f = 0.48$ (40% EtOAc/hexanes); $[\alpha]_D^{24.7} = -2.53$ (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, $J = 8.4$ Hz, 4H), 7.26–7.21 (m, 4H), 6.92–6.86 (m, 8H), 6.79 (s, 1H), 6.59 (s, 1H), 6.39 (s, 2H), 5.66–5.46 (m, 2H), 5.36–5.13 (m, 2H), 5.13–4.90 (m, 6H), 4.76–4.71 (m, 2H), 4.68–4.60 (m, 2H), 4.53–4.46 (m, 2H), 4.38–4.25 (m, 4H), 3.79 (s, 6H), 3.74–3.62 (m, 8H), 3.62–3.47 (m, 2H), 3.46–3.21 (m, 2H), 3.21–3.07 (m, 1H), 3.01–2.95 (m, 2H), 2.85–2.64 (m, 1H), 2.51–1.41 (m, 16H), 1.40–1.29 (m, 6H), 1.25–1.18 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 167.9, 160.4, 159.9, 159.6, 159.2, 158.3, 138.6, 138.1, 134.8, 131.0, 129.3, 129.2, 128.7, 128.5, 118.2, 118.0, 114.0, 113.9, 109.2, 107.1, 98.0, 97.8, 93.1, 91.5, 77.4, 76.1, 76.0, 74.8, 70.8, 70.5, 70.2, 70.0, 63.4, 63.2, 55.9, 55.3, 39.9, 37.3, 31.5, 31.4, 30.7, 30.5, 28.8, 28.3, 28.2, 21.9, 21.7, 20.3, 20.2, 15.2; IR (thin film) 2933, 2875, 1716, 1603, 1516, 1250, 1160 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{38}H_{48}NaO_9$ $(M + Na)^+$ 671.3191, found 671.3157.

4.9. Removal of EOM protecting group of **8** to give allylic alcohol **29**

To a solution of EOM ether **8** (148.8 mg, 0.23 mmol) in THF (11 mL) at rt was added 6.5 mL of 4 M HCl. The mixture was stirred at rt for 4 h, which was then quenched with saturated aqueous $NaHCO_3$ (15 mL) and diluted with EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography (10–20% EtOAc/hexanes) yielded the desired allylic alcohol **29** as a light yellow oil (34.2 mg, 25%, 53% based on 78.5 mg of recovered **8**): $R_f = 0.27$ (40% EtOAc/hexanes); $[\alpha]_D^{25.1} = -17.33$ (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, $J = 8.4$ Hz, 4H), 7.27–7.21 (m, 4H), 6.93–6.87 (m, 8H), 6.72 (s, 1H), 6.53 (s, 1H), 6.42–6.40 (m, 2H), 5.59–5.50 (m, 2H), 5.36 (dd, $J = 15.3$, 3.6 Hz, 1H), 5.26 (dd, $J = 15.3$, 8.4 Hz, 1H), 4.99 (s, 2H), 4.97 (s, 2H), 4.55–4.48 (m, 2H), 4.36–4.29 (m, 4H), 3.81 (s, 12H), 3.75 (s, 3H), 3.74 (s, 3H), 3.38–3.33 (m, 2H), 3.15 (dd, $J = 14.4$, 3.6 Hz, 1H), 3.03–2.94 (m, 2H), 2.81 (dd, $J = 12.9$, 9.6 Hz, 1H), 2.14–1.71 (m, 16H), 1.42–1.26 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 167.9, 160.5, 160.1, 159.6, 159.2, 158.7, 158.6,

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138.2, 137.7, 132.9, 132.0, 131.6, 131.0, 129.4, 128.6, 128.5, 127.9, 118.1, 117.9, 114.1, 114.0, 113.9, 108.7, 106.9, 98.2, 98.0, 75.3, 75.1, 73.3, 73.0, 70.5, 70.3, 69.9, 69.8, 55.9, 55.3, 55.3, 41.4, 38.6, 31.5, 30.7, 30.6, 28.5, 28.4, 28.0, 27.8, 20.2; IR (thin film) 3447, 2933, 2860, 1701, 1605, 1249, 1161 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{35}H_{42}NaO_8$ $(M + Na)^+$ 613.2772, found 613.2753.

4.10. Oxidation of allylic alcohol **29** to give ketone **30**

To a solution of **29** (75.0 mg, 0.127 mmol) in 3 mL of DMSO:toluene (1:1) was added IBX (178.1 mg, 0.636 mmol, 5.0 equiv). The reaction mixture was stirred at room temperature for 2 h before being added IBX (106.9 mg, 0.382 mmol, 3.0 equiv), and stirred at room temperature for 1 h. The reaction mixture was quenched with H_2O (3 mL), and diluted with EtOAc (3 mL). The mixture was filtered through a pad of Celite and washed with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography (20% EtOAc/hexanes) provided ketone **30** as a white solid (55.4 mg, 74%): $R_f = 0.48$ (40% EtOAc/hexanes); mp 141.3–144.5 °C; $[\alpha]_D^{24.5} = +10.6$ (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 8.4$ Hz, 2H), 6.91 (d, $J = 8.4$ Hz, 2H), 6.89 (d, $J = 8.4$ Hz, 2H), 6.72 (dt, $J = 15.6$, 7.8 Hz, 1H), 6.47 (s, 1H), 6.45 (s, 1H), 6.07 (d, $J = 15.6$ Hz, 1H), 4.96 (s, 2H), 4.90–4.85 (m, 1H), 4.51 (d, $J = 11.1$ Hz, 1H), 4.32 (d, $J = 11.1$ Hz, 1H), 4.27 (d, $J = 15.6$ Hz, 1H), 3.81 (s, 6H), 3.76 (s, 3H), 3.45 (d, $J = 15.6$ Hz, 1H), 3.37–3.31 (m, 1H), 2.29–2.22 (m, 2H), 1.82–1.35 (m, 6H), 1.29 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 167.7, 160.9, 159.6, 159.4, 159.3, 147.6, 135.8, 130.6, 129.5, 129.4, 129.2, 128.3, 116.8, 114.1, 113.9, 107.8, 98.9, 75.0, 70.5, 70.0, 56.0, 55.3, 45.7, 30.8, 30.4, 28.7, 27.9, 20.2; IR (thin film) 2926, 2856, 1700, 1521, 1251, 1162, 1034 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{35}H_{40}NaO_8$ $(M + Na)^+$ 611.2621, found 611.2640.

4.11. Deprotection of PMB groups of **30** to furnish dechlorogreensporone D (**6**)

A solution of macrolactone **30** (55.4 mg, 0.094 mmol) in 9.5 mL of CH_2Cl_2 at 0 °C was added 1.0 M $TiCl_4$ (565 μL, 0.565 mmol, 6.0 equiv). The brick orange cloudy mixture was stirred from 0 °C to room temperature for 30 min, which was then quenched with saturated aqueous $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (20–30% EtOAc/hexanes) to yield dechlorogreensporone D (**6**) as a light yellow solid (16.1 mg, 49%) and dechlorogreensporone F (**31**) as a light yellow oil (15.6 mg, 48%).

*Dechlorogreensporone D (**6**).* 16.1 mg, 49%; $R_f = 0.23$ (60% EtOAc/hexanes); mp 182.7–185.8 °C; $[\alpha]_D^{26.8} = +64.60$ (*c* 0.27, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 10.0 (br s, 1H), 6.68 (dt, $J = 15.9$, 7.5 Hz, 1H), 6.39 (s, 1H), 6.29 (s, 1H), 5.98 (d, $J = 15.9$ Hz, 1H), 4.94–4.87 (m, 1H), 4.54 (br s, 1H), 4.06 (d, $J = 15.9$ Hz, 1H), 3.72–3.62 (m, 4H), 3.42–3.36 (m, 1H), 2.20–2.08 (m, 2H), 1.79–1.40 (m, 5H), 1.23 (d, $J = 5.7$ Hz, 3H), 1.19–1.10 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 196.0, 167.3, 159.8, 159.2, 148.3, 135.6, 128.5, 114.2, 109.7, 98.5, 69.4, 66.2, 55.9, 44.6, 34.6, 30.3, 29.2, 28.3, 20.2; IR (thin film) 3446, 2926, 2857, 1695, 1685, 1523, 1089 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{19}H_{24}NaO_6$ $(M + Na)^+$ 371.1471, found 371.1478.

*Dechlorogreensporone F (**31**).* 15.6 mg, 48%; $R_f = 0.33$ (60% EtOAc/hexanes); $[\alpha]_D^{27.3} = -38.48$ (*c* 0.11, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 6.32 (d, $J = 1.8$ Hz, 1H), 6.24 (d, $J = 1.8$ Hz, 1H), 5.28–5.25 (m, 1H), 4.22–4.14 (m, 1H), 4.01 (d, $J = 17.1$ Hz, 1H), 3.92 (d, $J = 17.1$ Hz, 1H), 3.89–3.79 (m, 1H), 3.73 (s, 3H), 2.65 (dd, $J = 13.8$, 3.9 Hz, 1H), 2.56 (dd, $J = 13.8$, 8.1 Hz, 1H), 2.02–1.43 (m, 8H), 1.31 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 167.9, 159.0, 158.4, 133.8, 116.5, 109.4, 98.5, 79.3, 76.0, 72.6, 55.8, 49.1, 47.8, 33.5, 32.9, 31.2, 30.4, 20.8; IR (thin film) 3366, 2927, 2855, 1716, 1608, 1458, 1269 cm^{-1}; HRMS (MALDI-TOF) *m/z* calcd for $C_{19}H_{24}NaO_6$ $(M + Na)^+$ 371.1471, found 371.1464.

4.12. Cytotoxicity assay

Cytotoxic activity of synthetic **5** and **6** were evaluated against seven human cancer cell lines including two breast adenocarcinoma (MDA-MB-231 and MCF-7), one colorectal carcinoma (HCT116), one hepatoma (HepG2) and three cervical carcinoma (C33A, HeLa and SiHa) cells as well as one monkey kidney non-cancerous (Vero) cell line by MTT assay using the general procedure previously described [18]. Cancer cells were exposed to various concentrations of compounds **5** and **6** (0–25 μM; 0.2% (v/v) DMSO). Vero cells were exposed to 0–50 μM of **5** and **6**. Each experiment was performed in triplicate and was repeated three times. Data was expressed as IC_{50}values (the concentration needed for 50% cell growth inhibition) relative to the untreated cells (0.2% (v/v) DMSO) (means ± SD). Cisplatin (0–50 μM) and doxorubicin (0–1 μM) (Pfizer, Australia) were used as positive controls.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.07.025.

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^{1}H and ^{13}C NMR Spectra

Figure 4 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of PMB ether **80a**

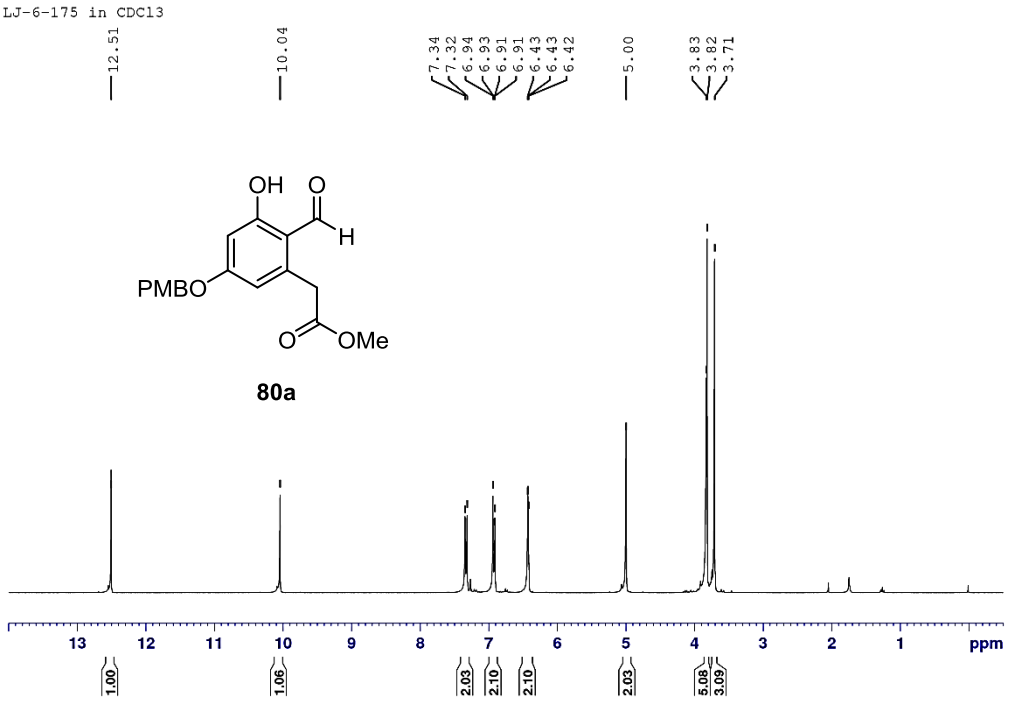


Figure 5 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of PMB ether **80a**

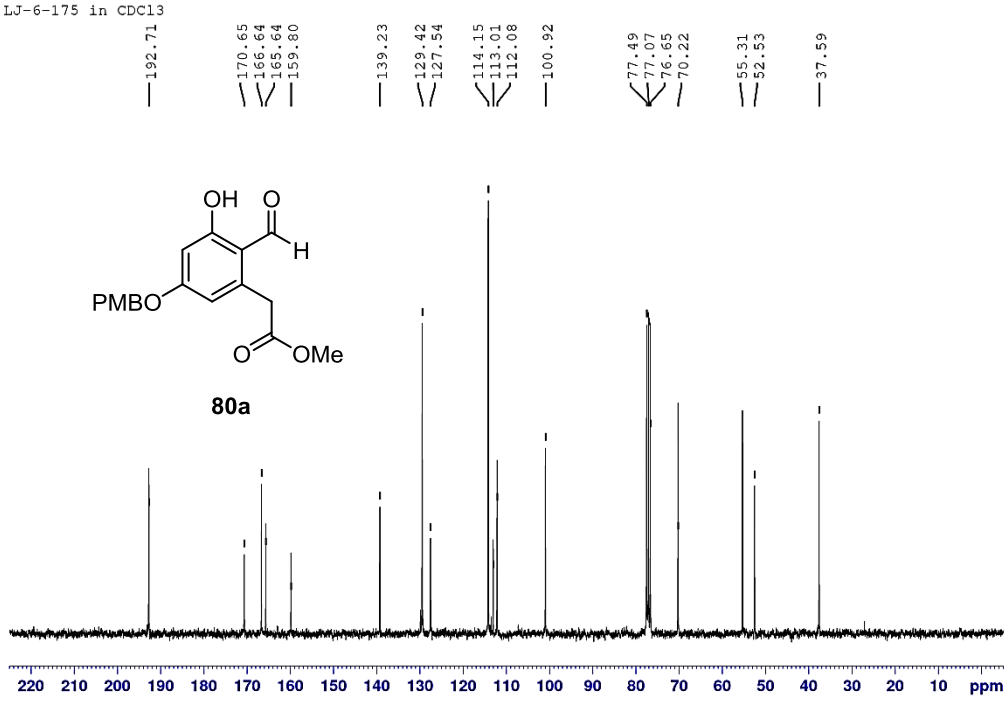


Figure 6 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of methyl ether **83**

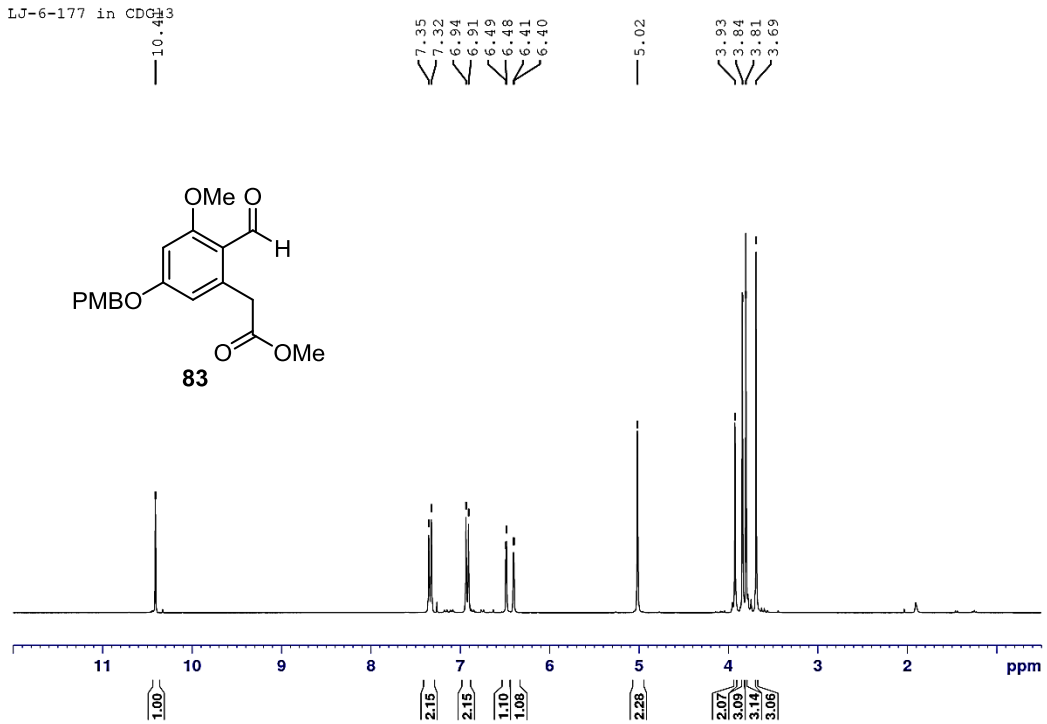


Figure 7 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of methyl ether **83**

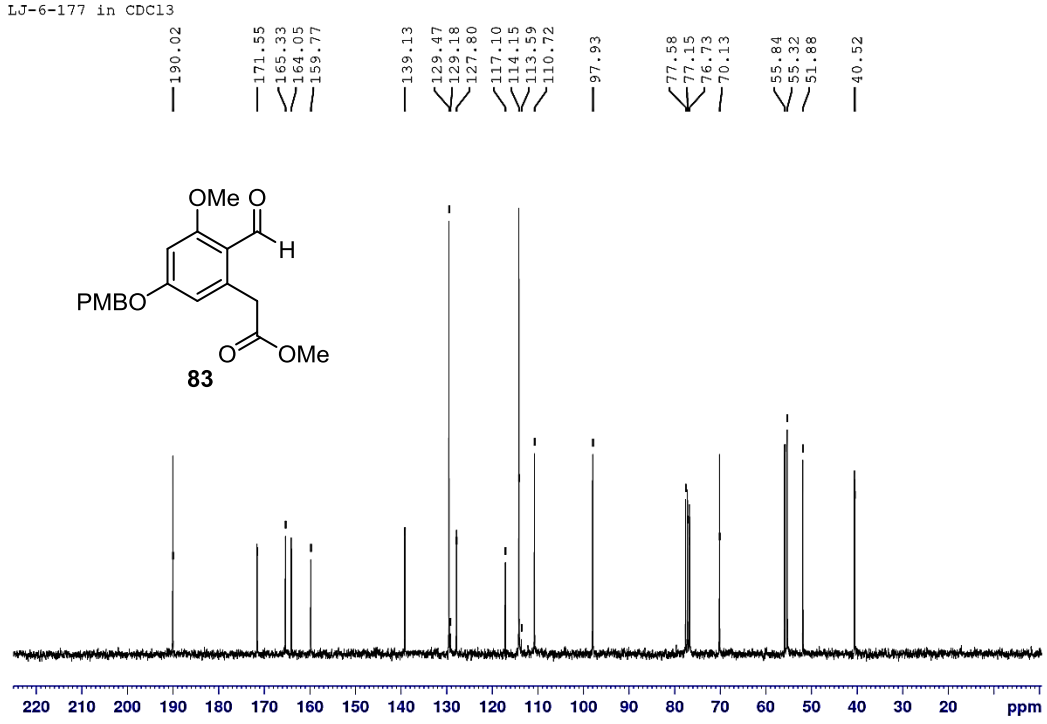


Figure 8 ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) spectrum of diol **84**

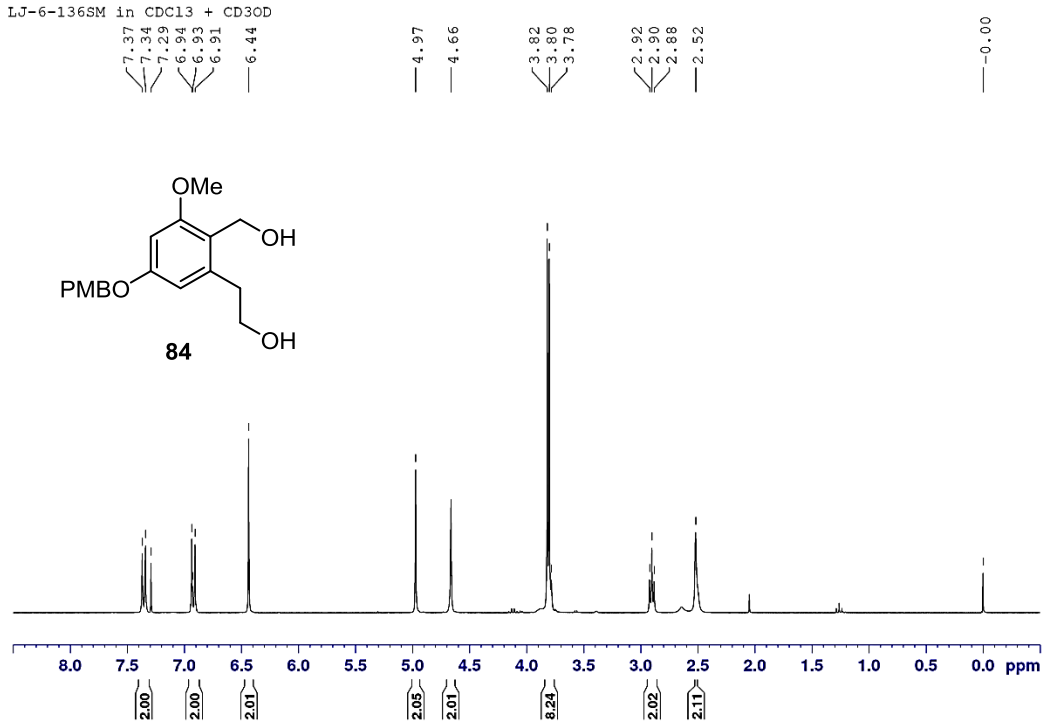


Figure 9 ^{13}C NMR (75 MHz, $CDCl_3$+CD_3OD) spectrum of diol **84**

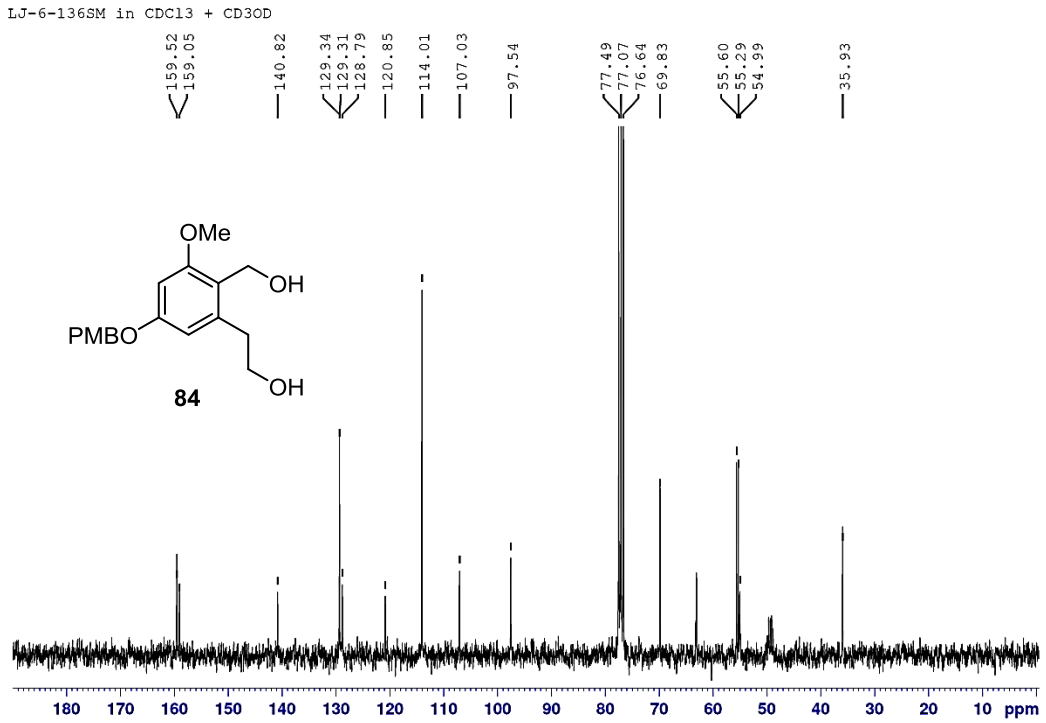


Figure 10 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of acetate **84a**

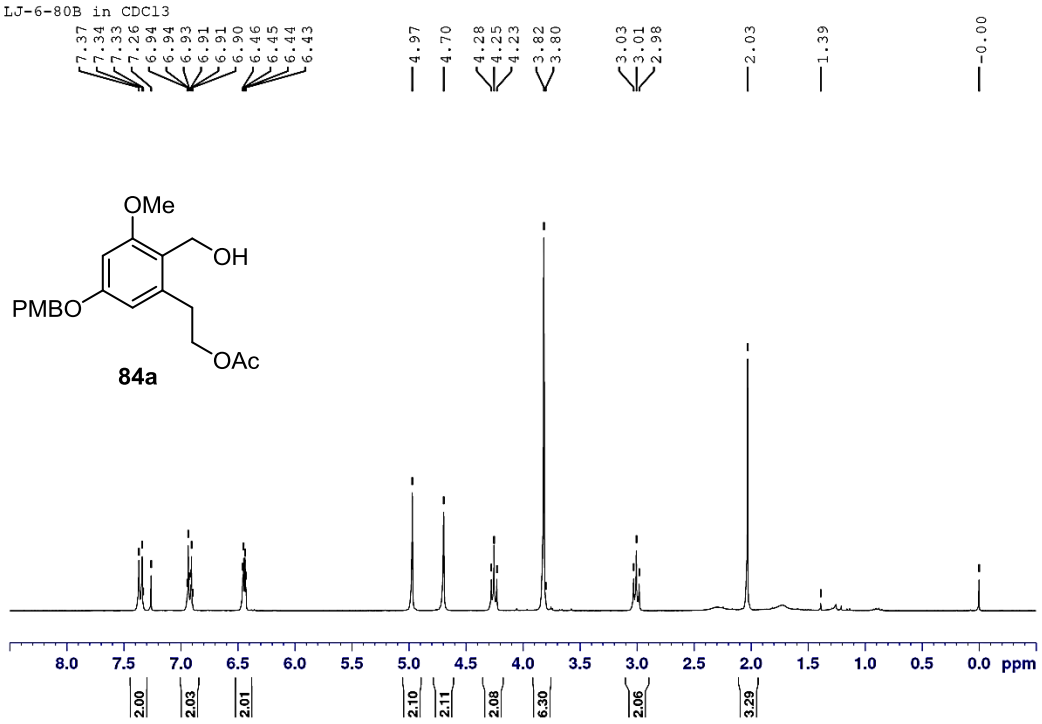


Figure 11 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of acetate **84a**

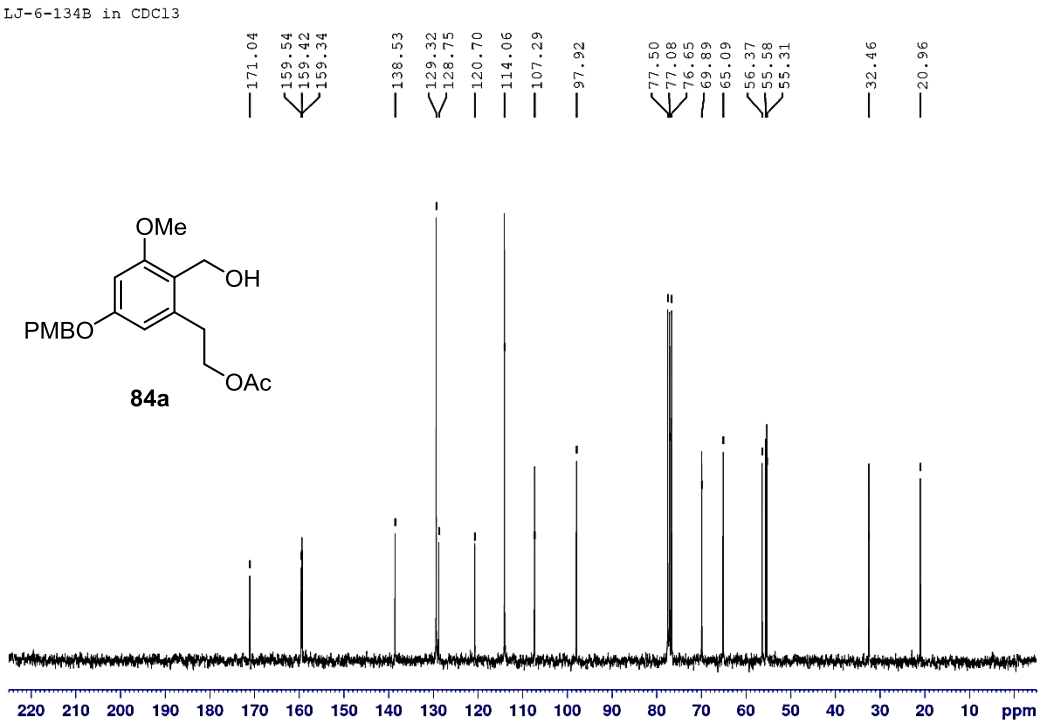


Figure 12 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of silyl ether **85**

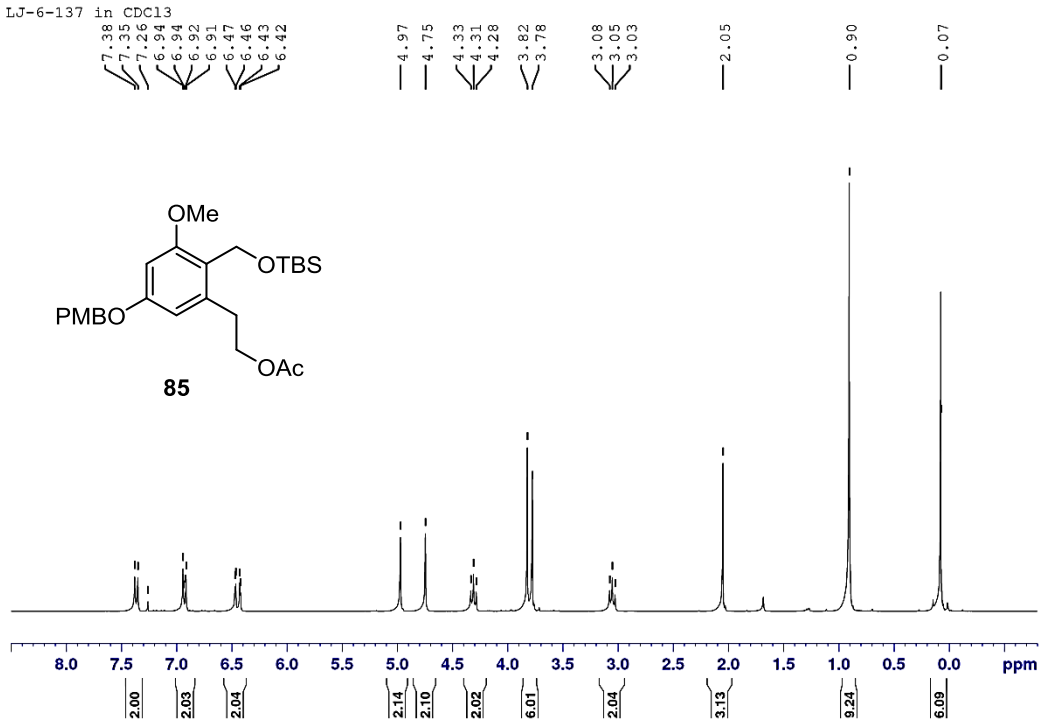


Figure 13 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of silyl ether **85**

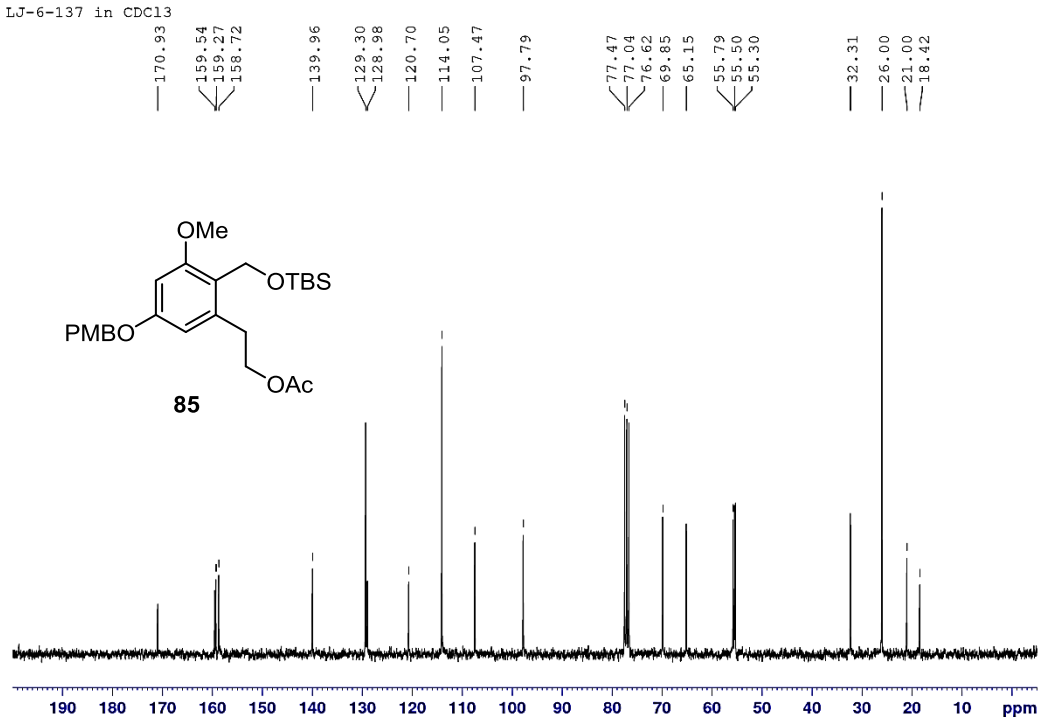


Figure 14 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of alcohol **85a**

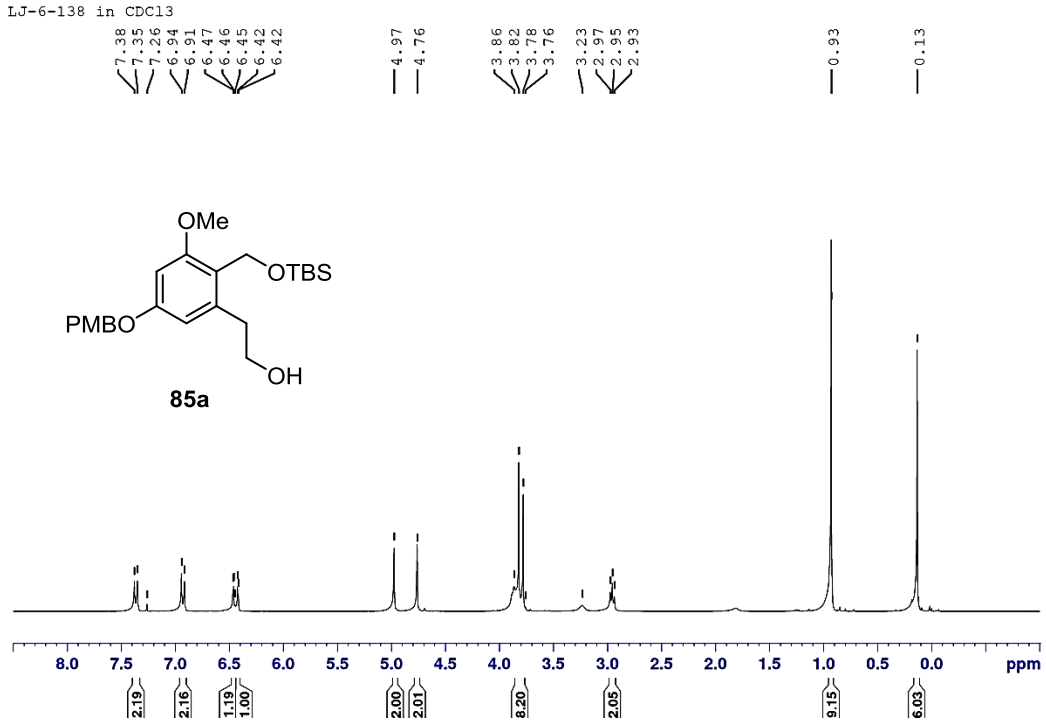


Figure 15 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of alcohol **85a**

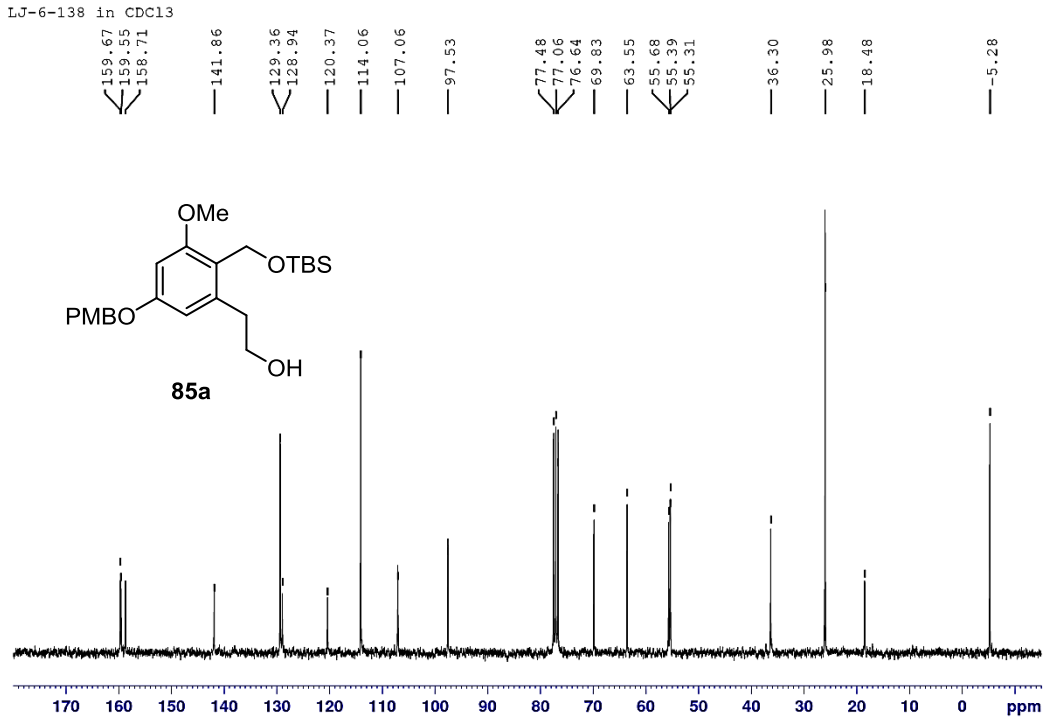


Figure 16 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of aldehyde **86**

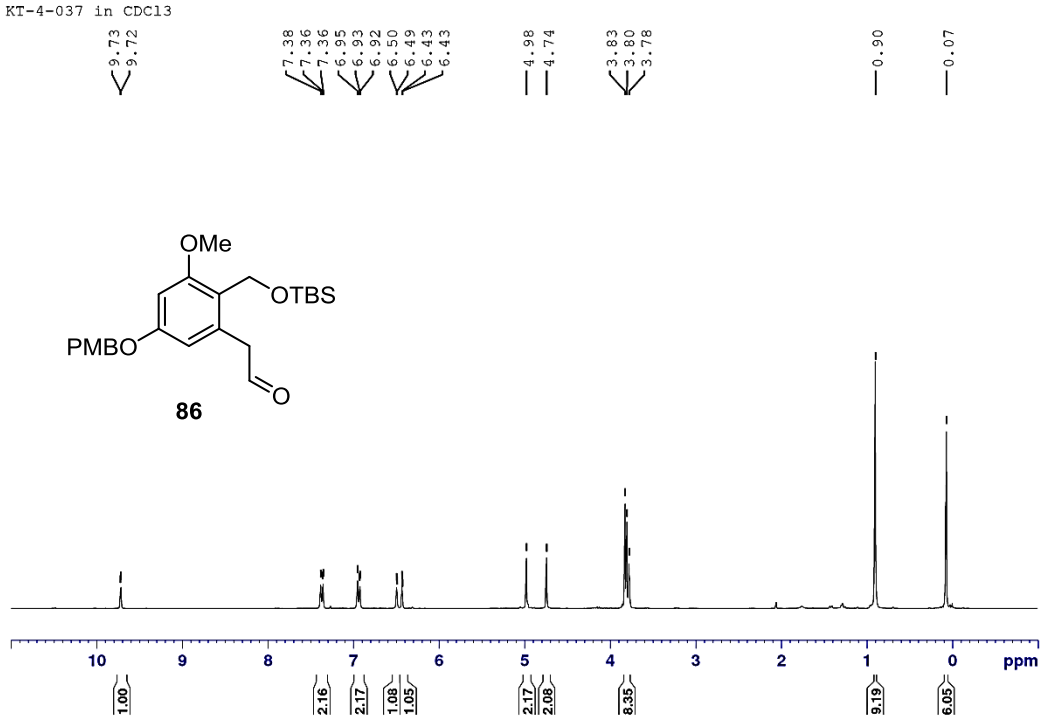


Figure 17 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of aldehyde **86**

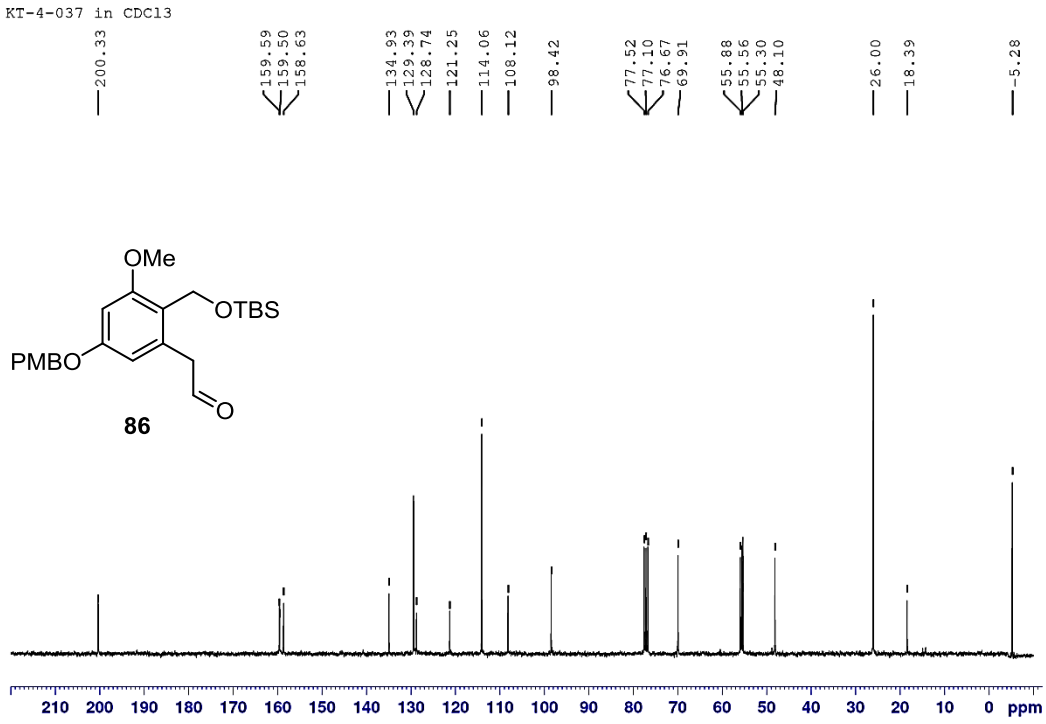


Figure 18 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of allylic alcohol **87**

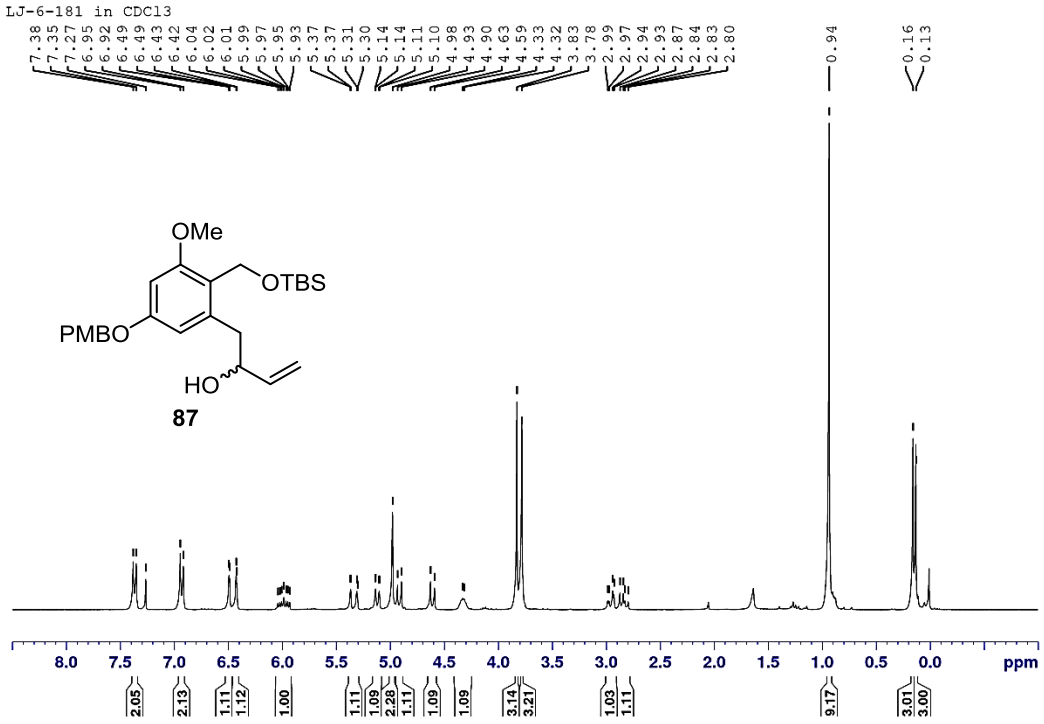


Figure 19 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of allylic alcohol **87**

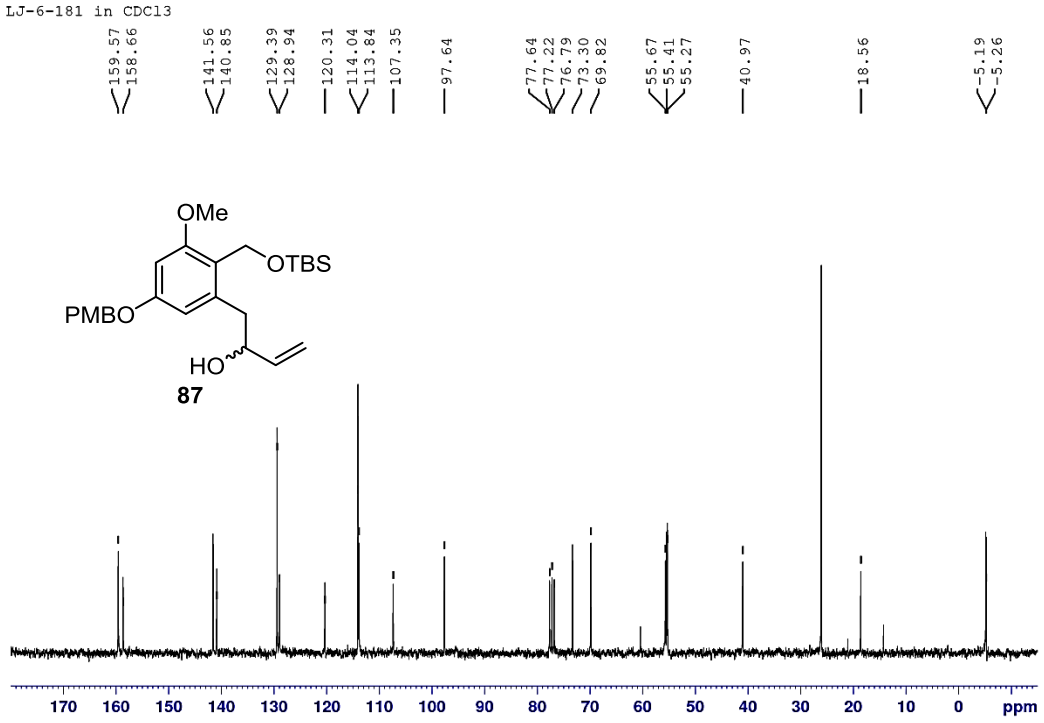


Figure 20 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of benzylic alcohol **89**

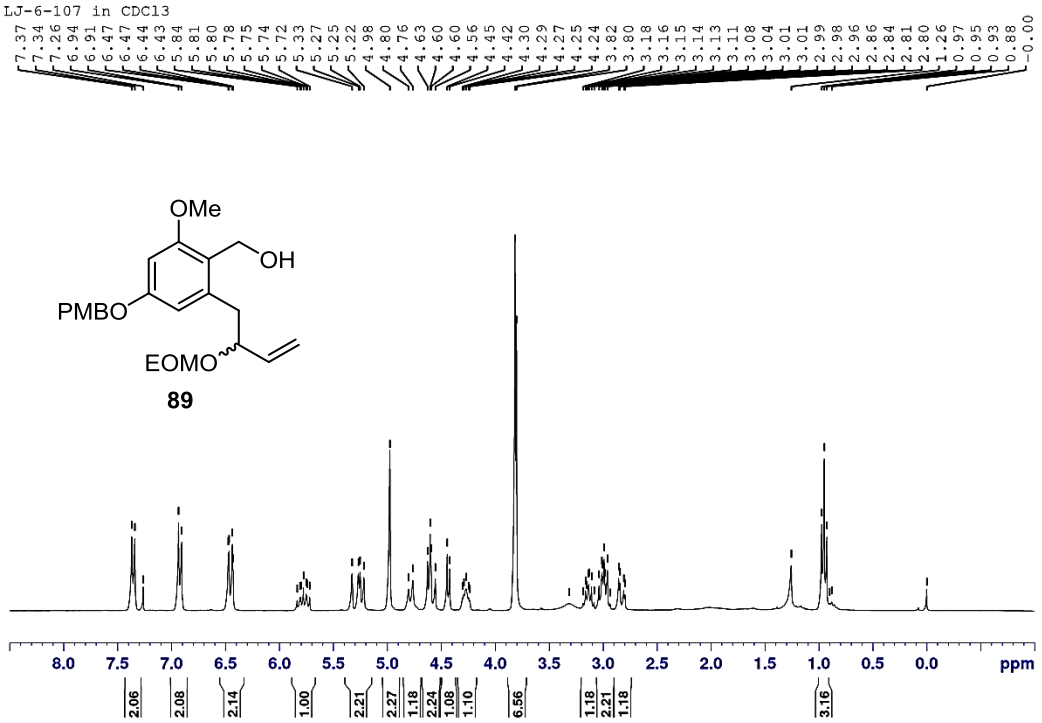


Figure 21 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of benzylic alcohol **89**

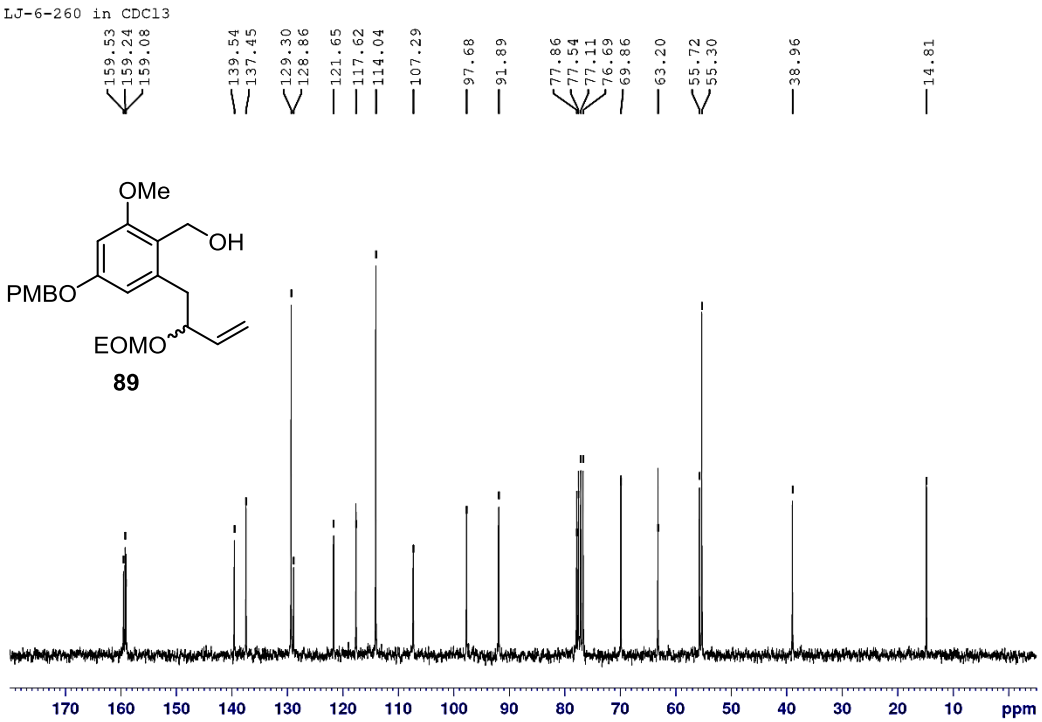


Figure 22 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of benzaldehyde **90**

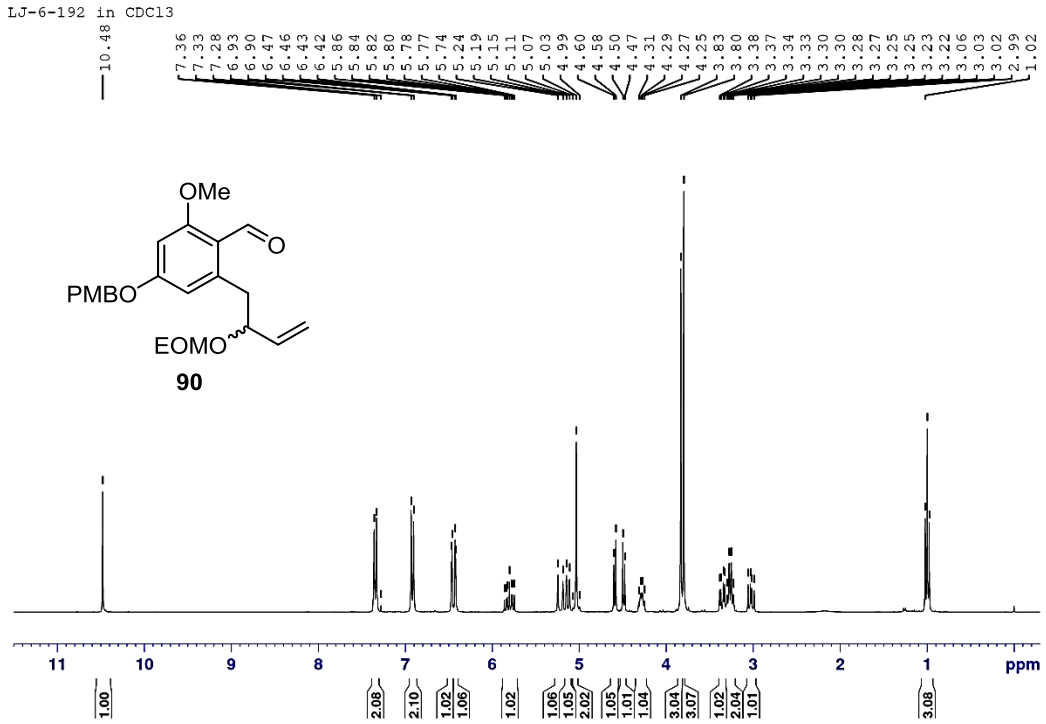


Figure 23 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of benzaldehyde **90**

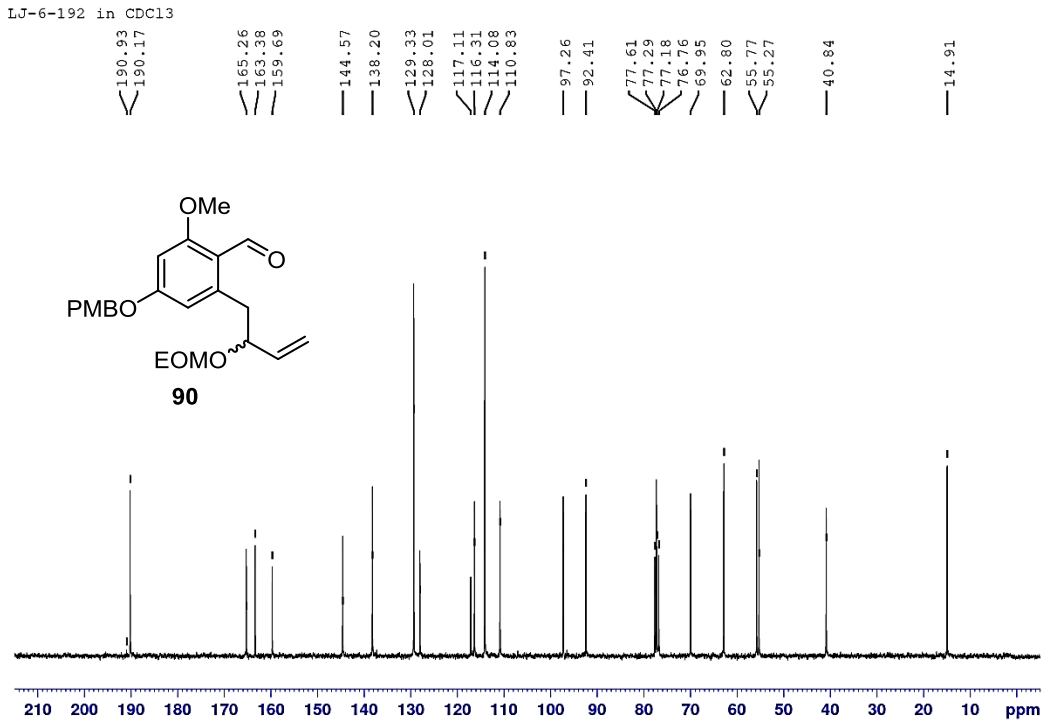


Figure 24 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of benzoic acid **78**

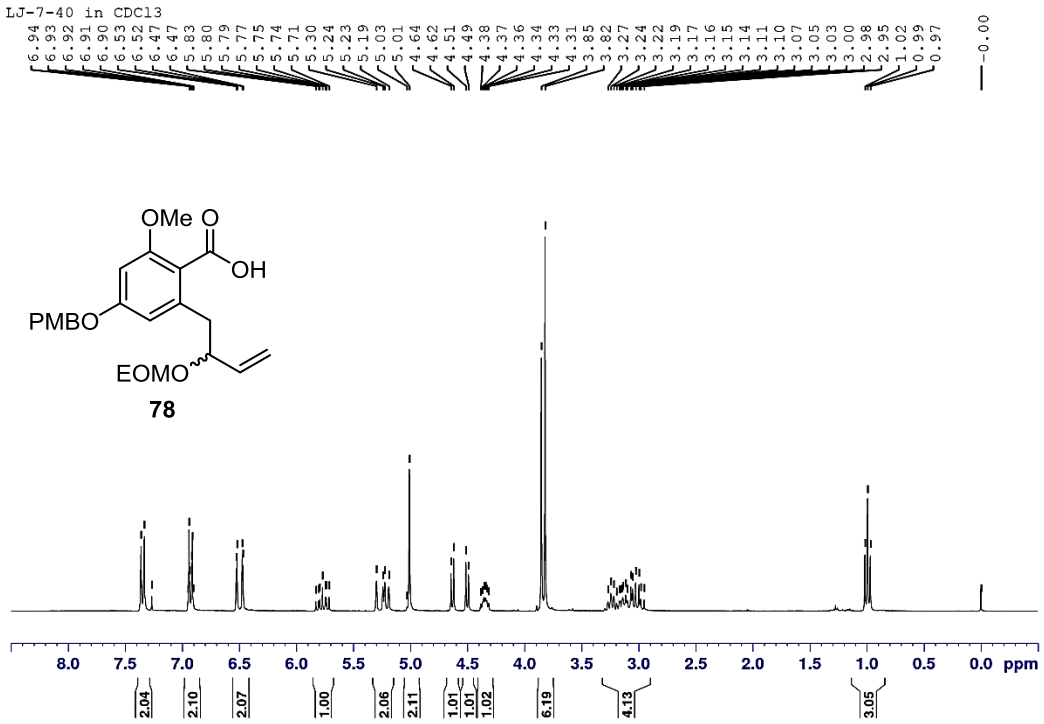


Figure 25 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of benzoic acid **78**

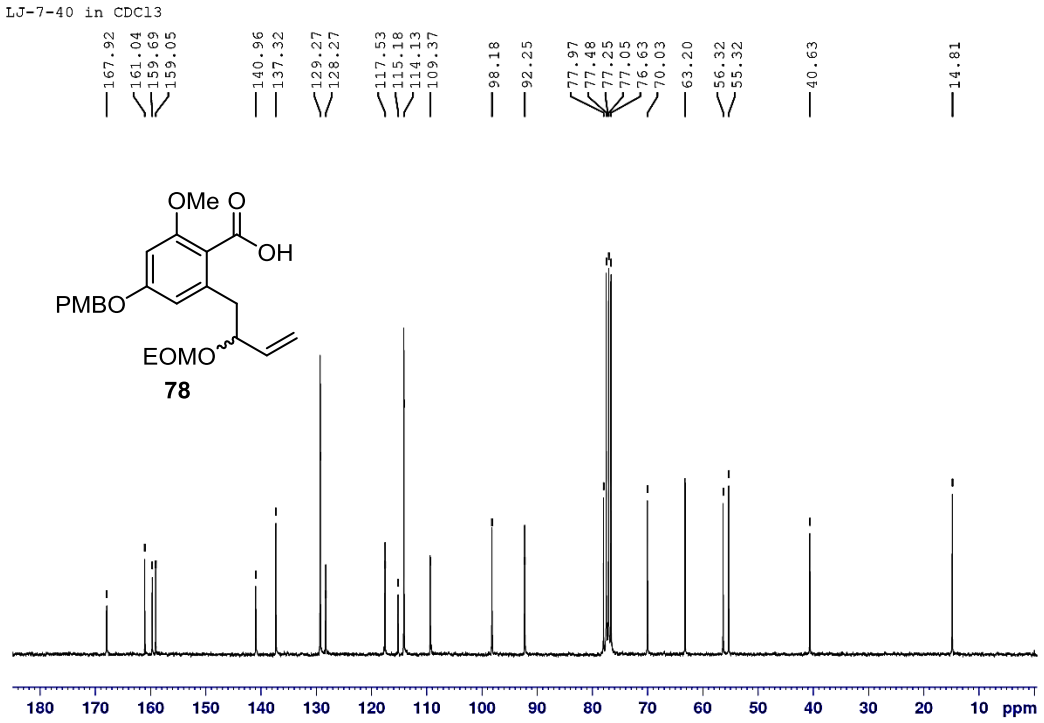


Figure 26 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of silyl ether **113**

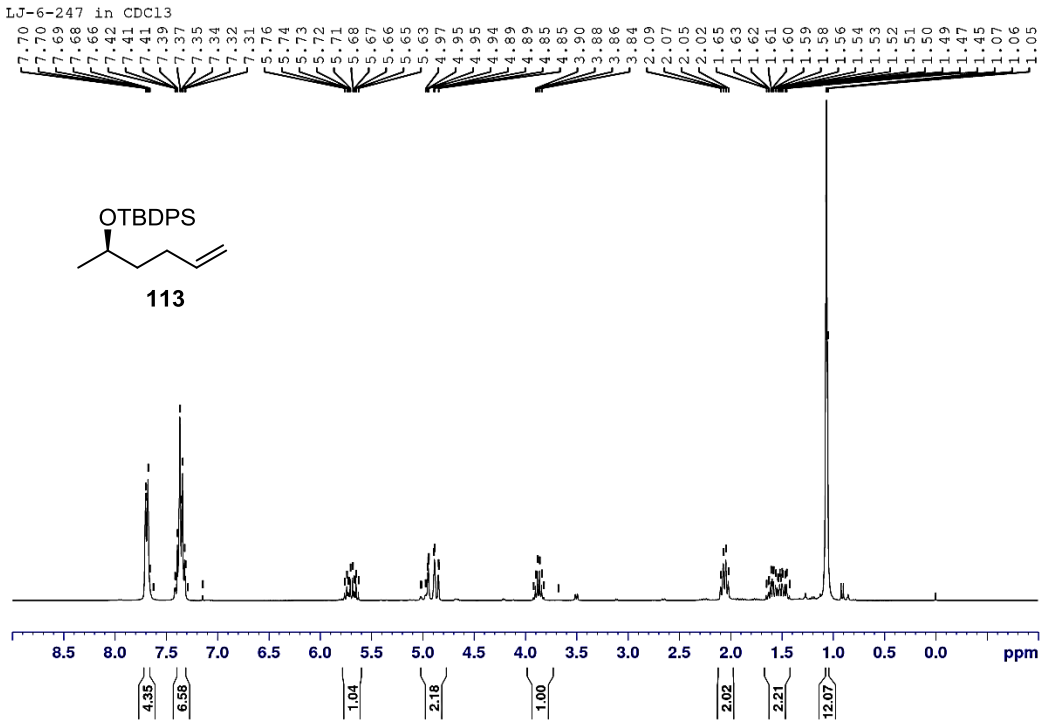


Figure 27 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of silyl ether **113**

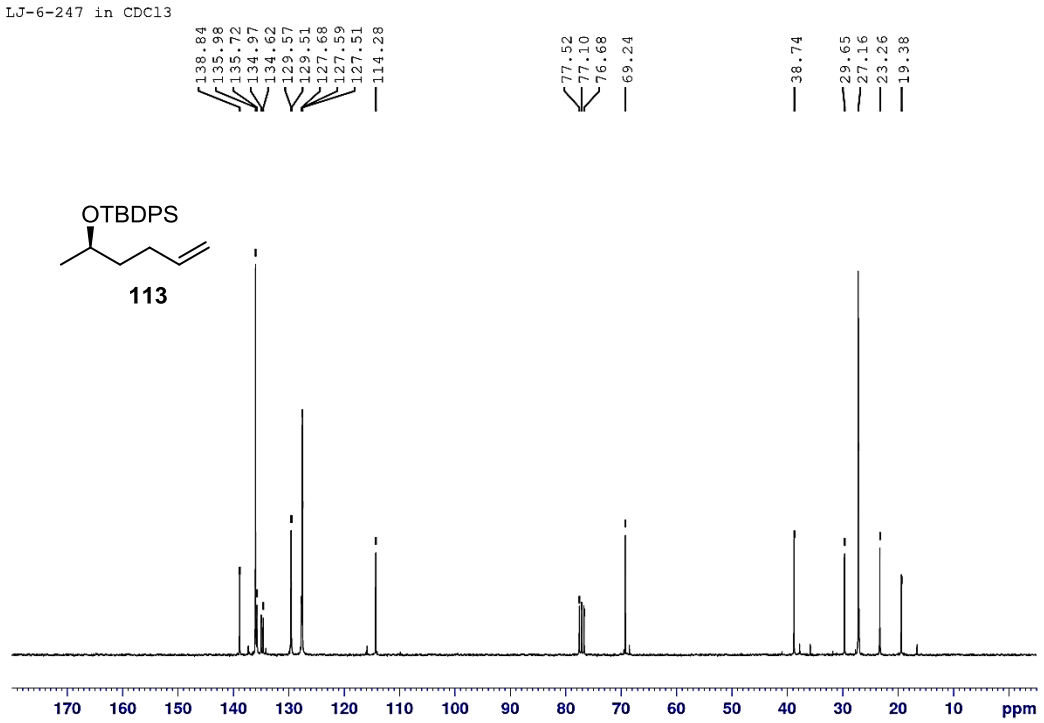


Figure 28 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of epoxide **114**

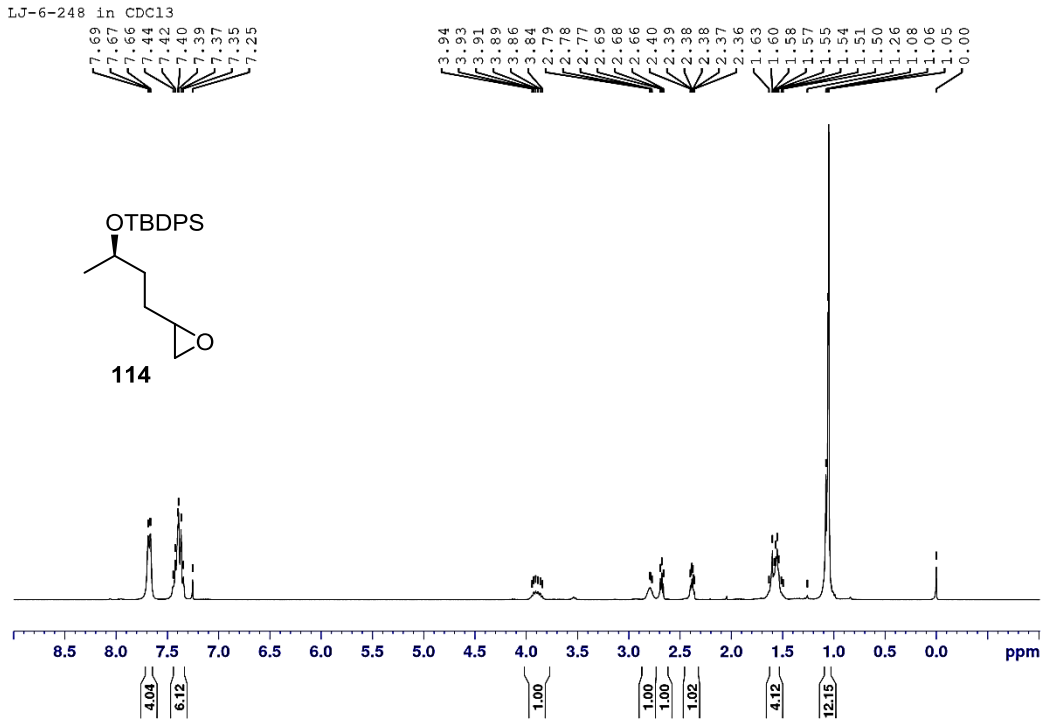


Figure 29 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of epoxide **114**

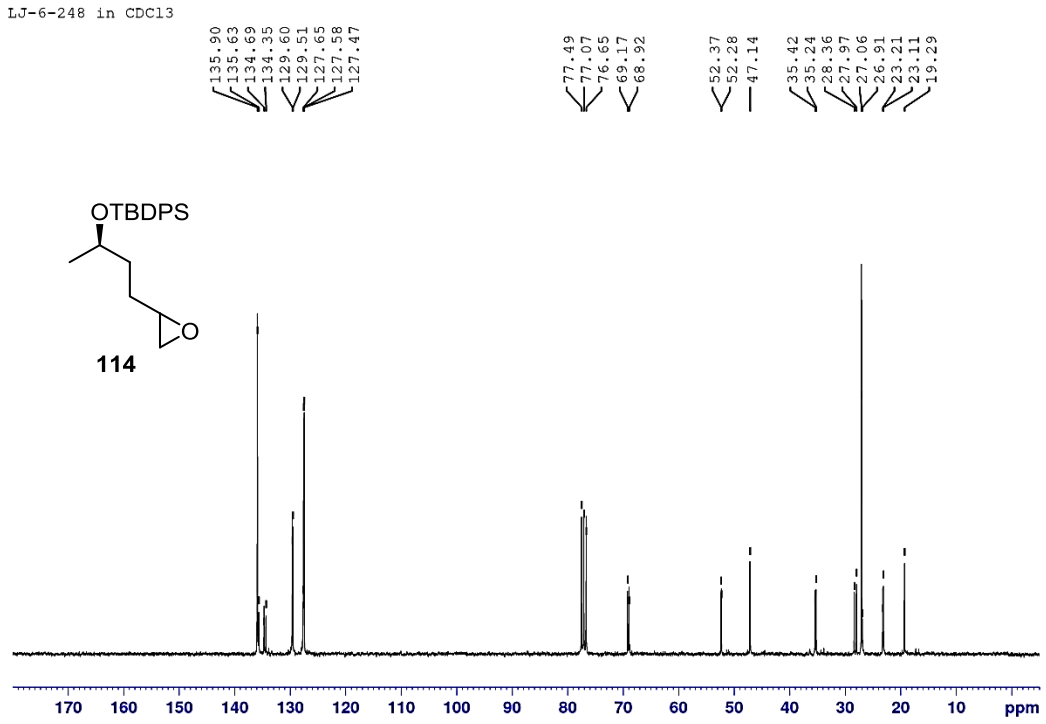


Figure 30 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of alcohol **115**

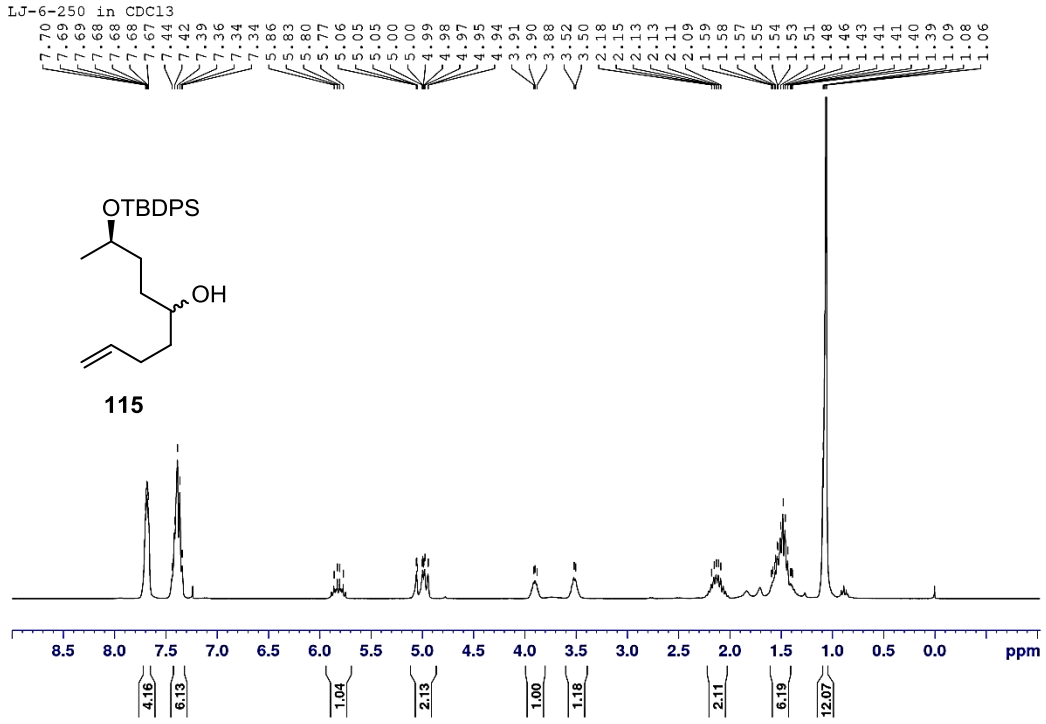


Figure 31 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of alcohol **115**

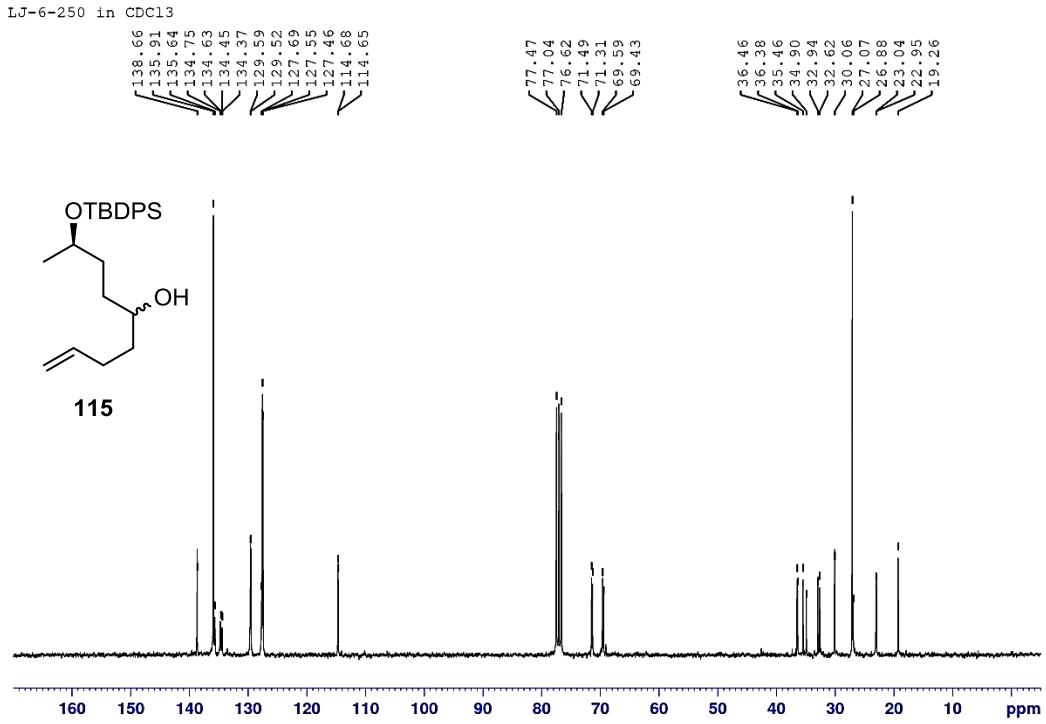


Figure 32 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of silyl ether **115a**

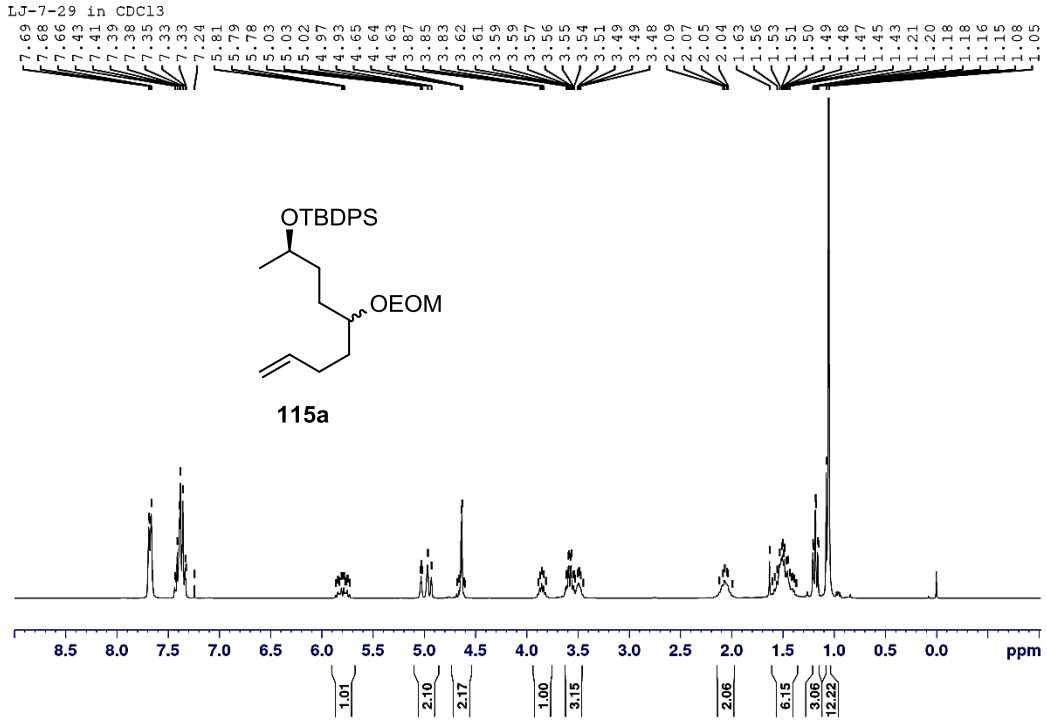


Figure 33 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of silyl ether **115a**

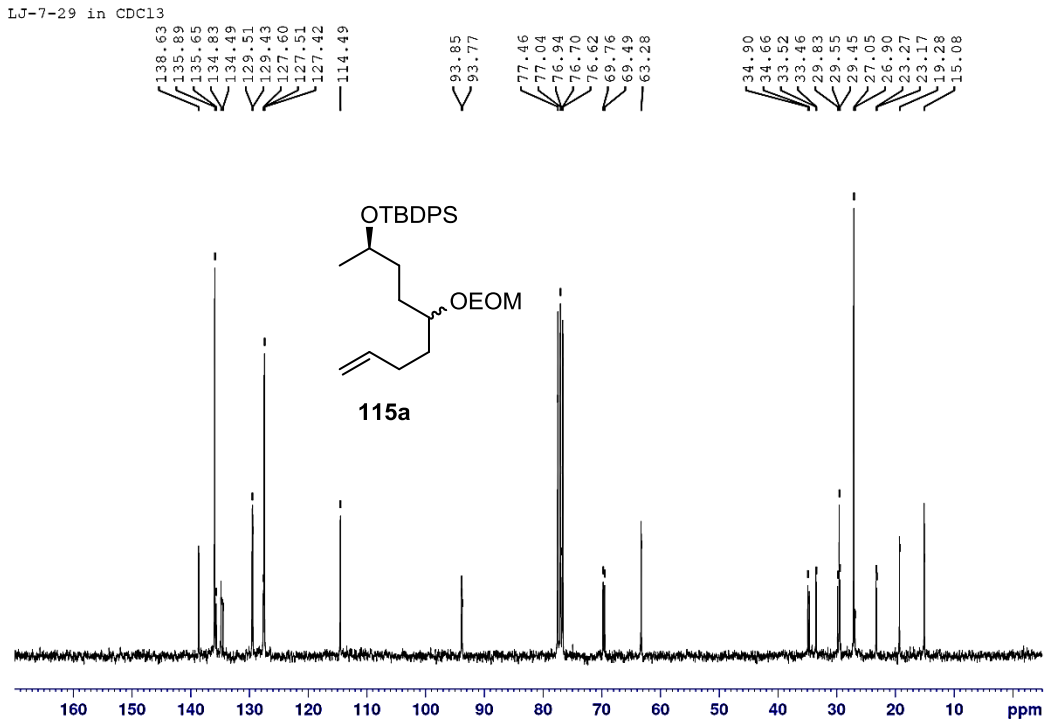


Figure 34 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of alcohol **110**

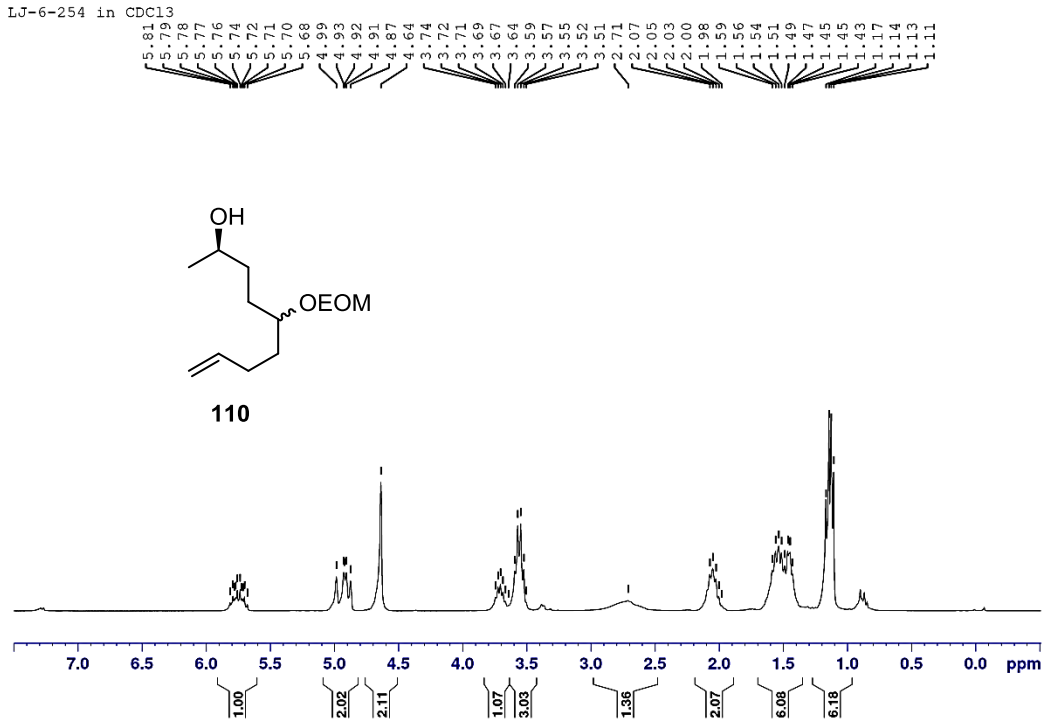


Figure 35 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of alcohol **110**

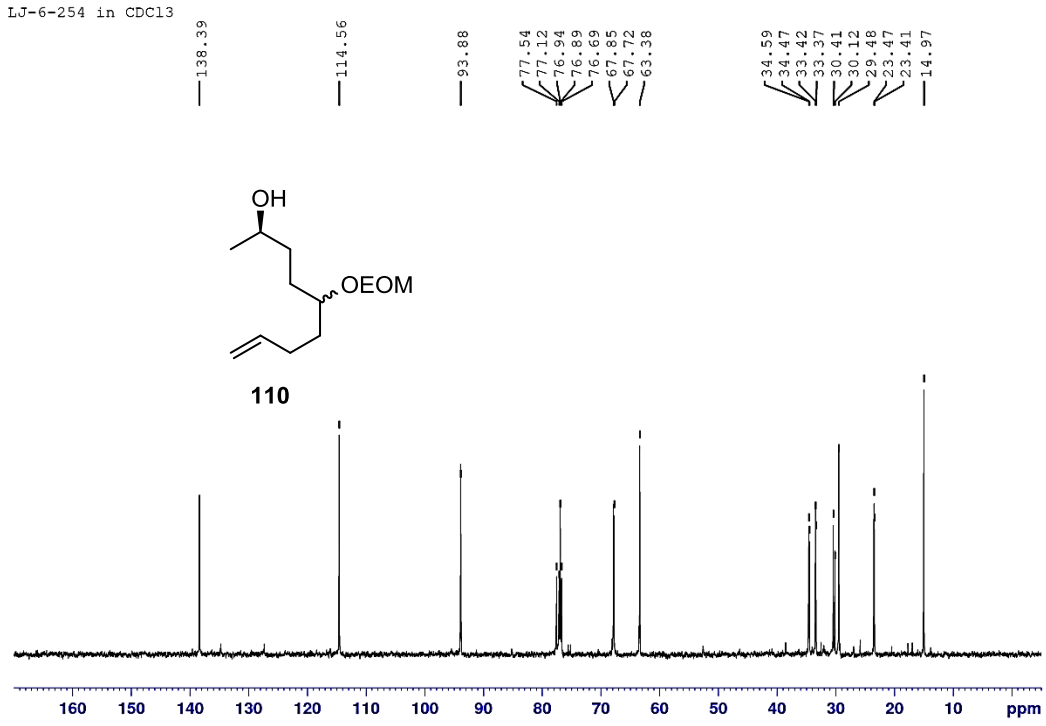


Figure 36 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of ester diene **108**

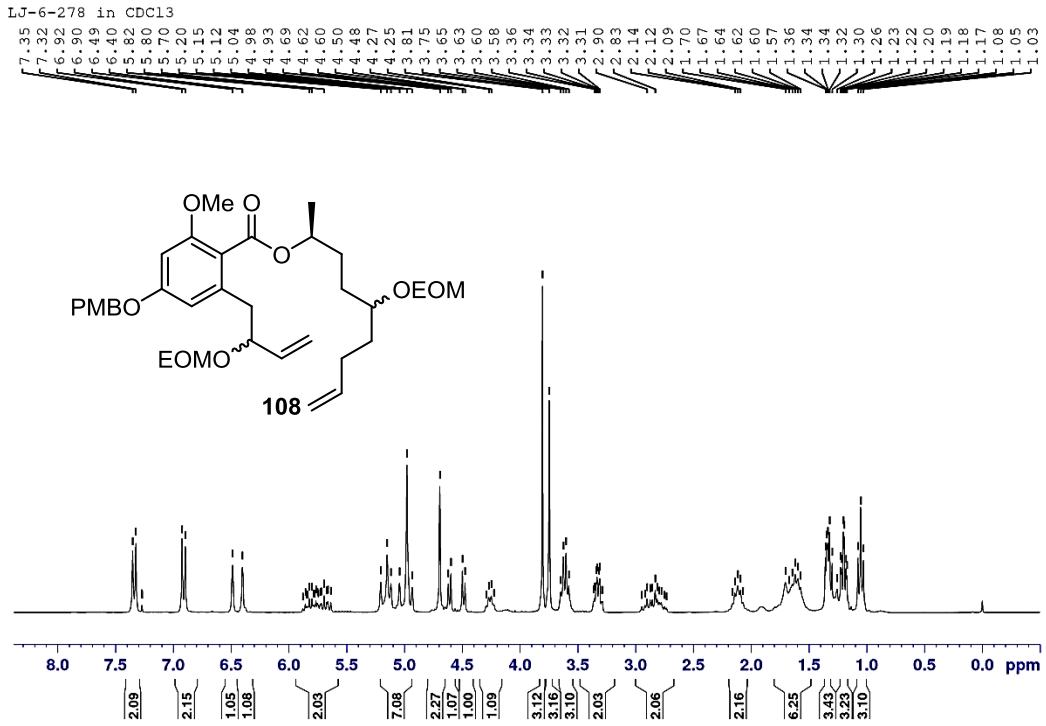


Figure 37 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of ester diene **108**

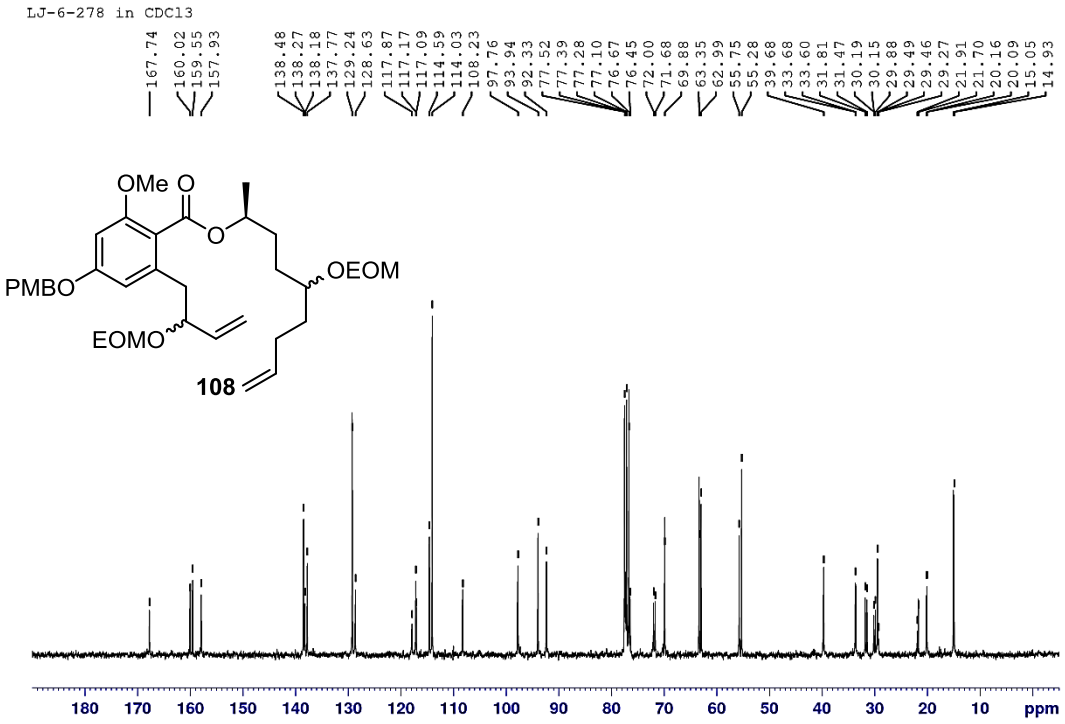


Figure 38 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of macrolactone **106**

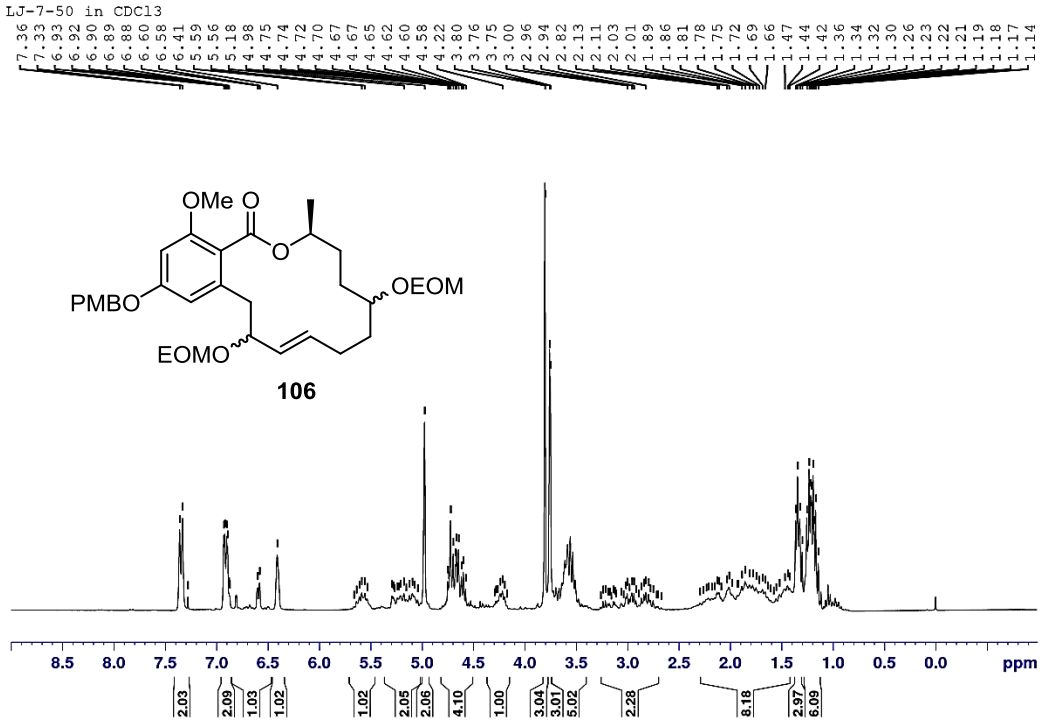


Figure 39 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of macrolactone **106**

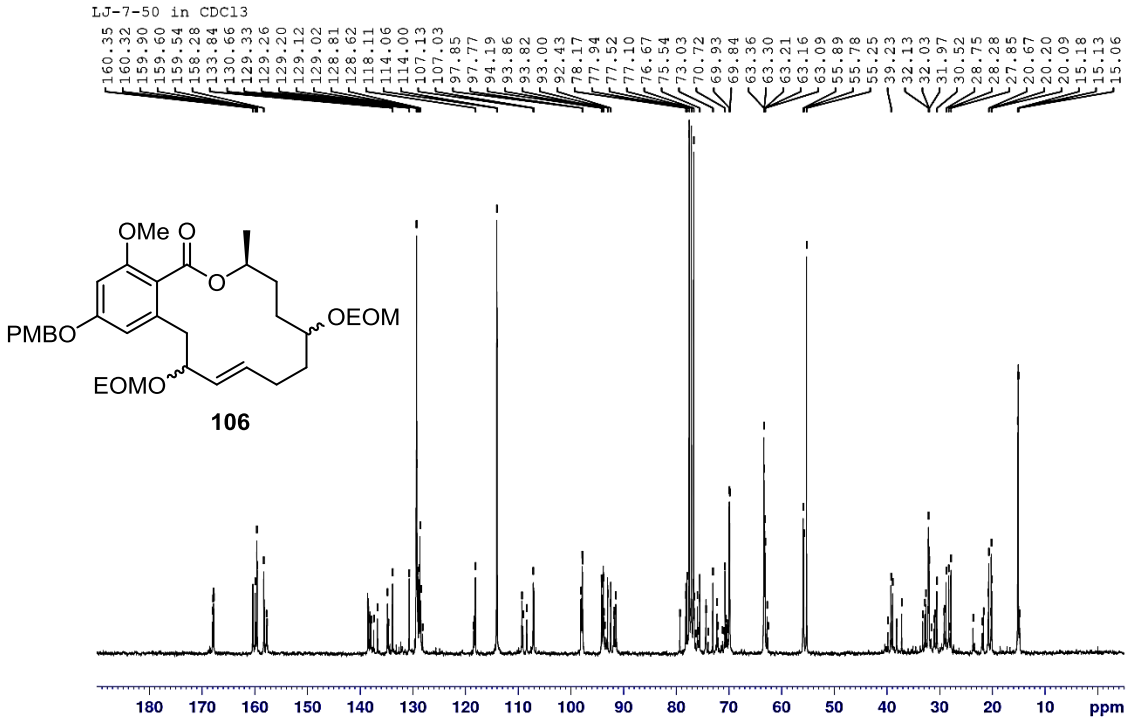


Figure 40 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of diol **116**

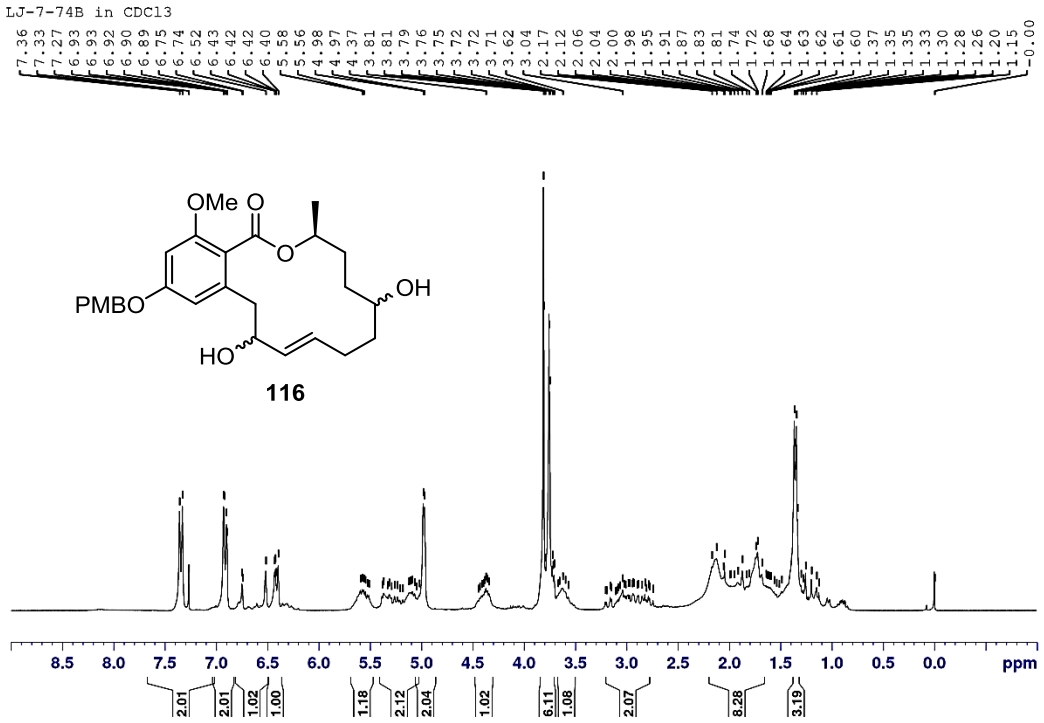


Figure 41 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of diol **116**

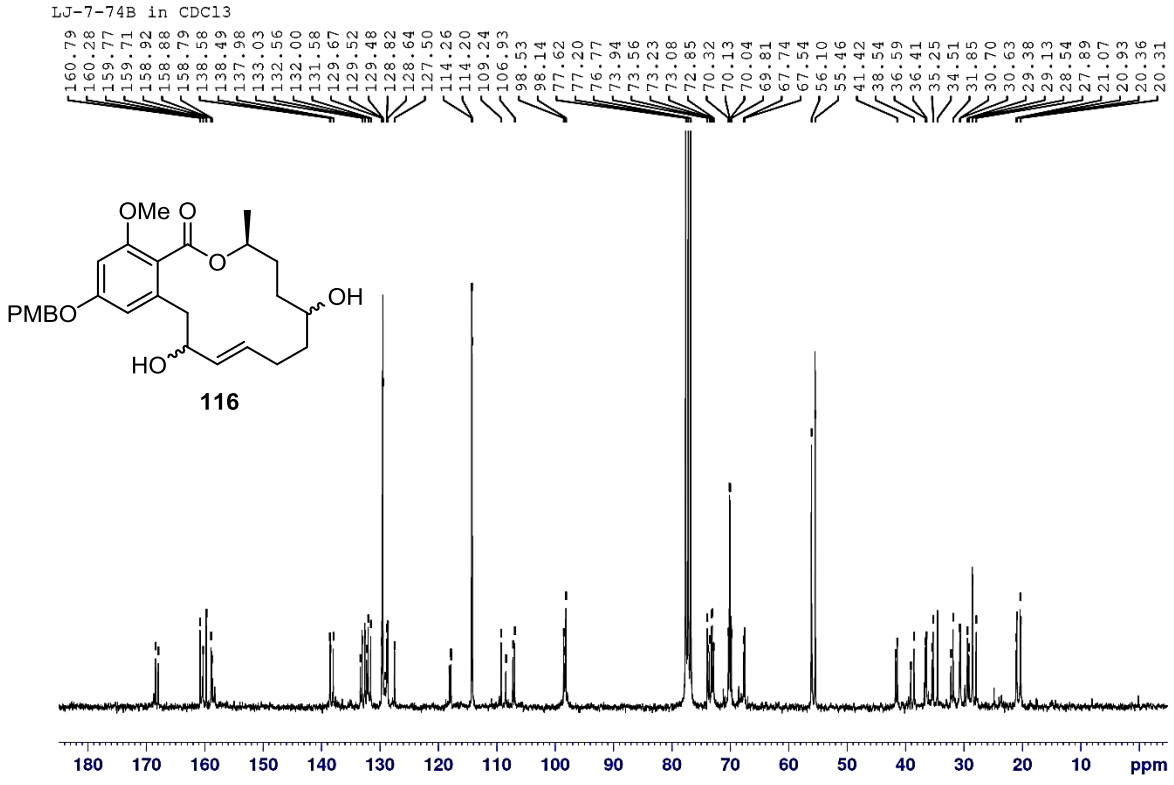


Figure 42 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of diketone **117**

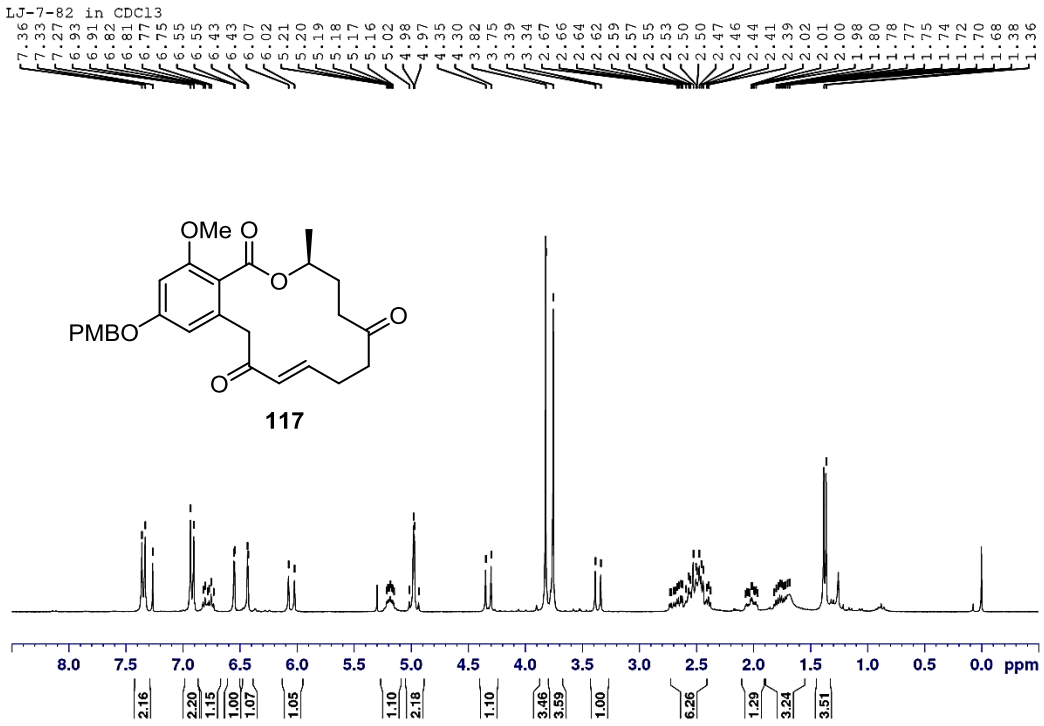


Figure 43 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of diketone **117**

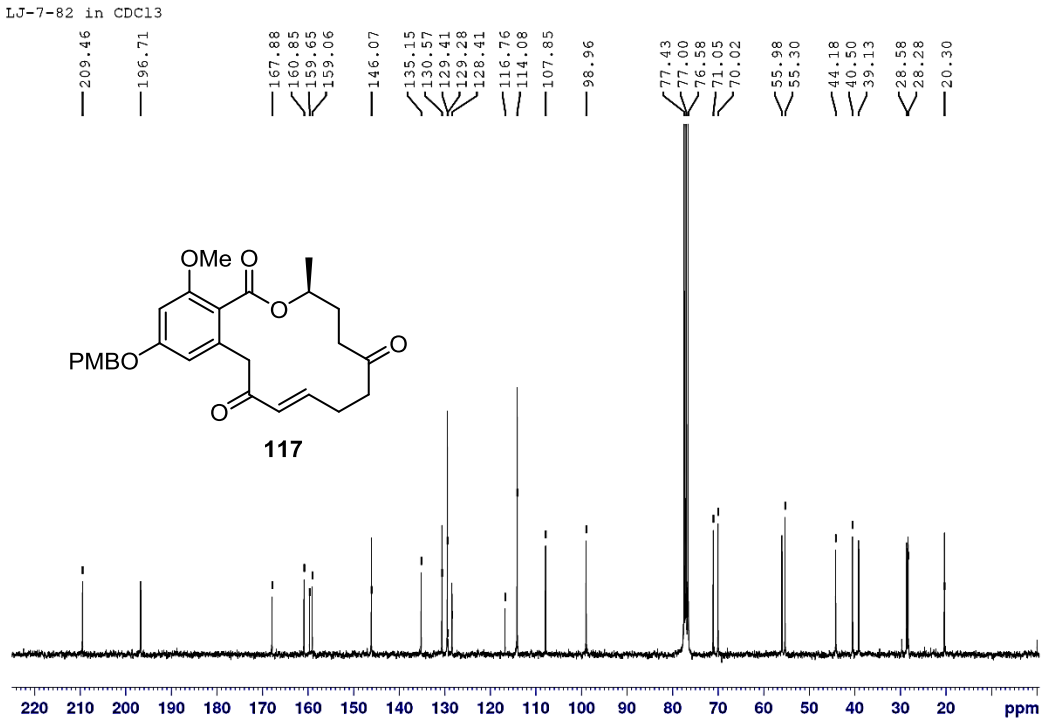


Figure 44 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of dechlorogreensporone A (**25**)

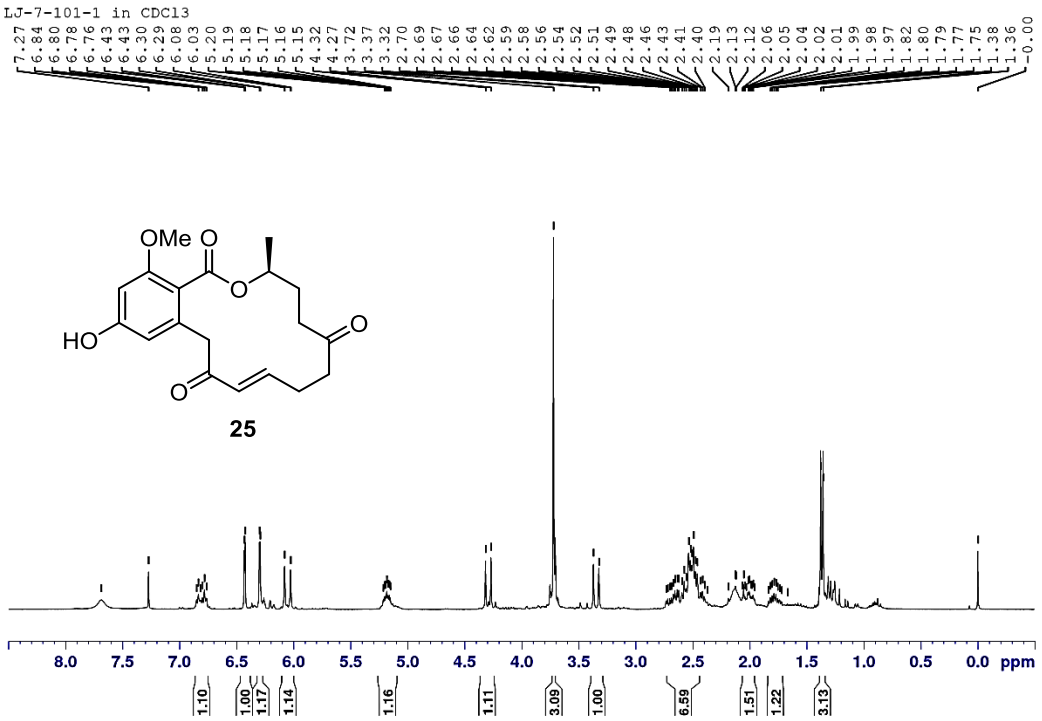


Figure 45 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of dechlorogreensporone A (**25**)

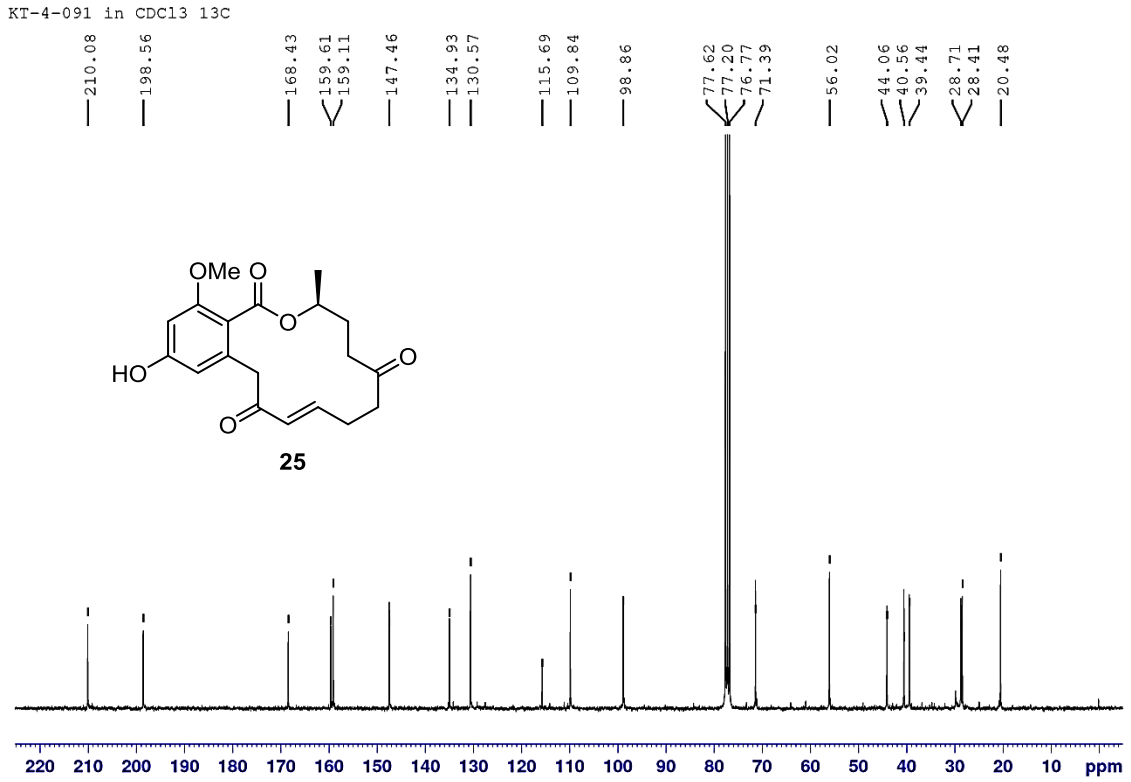


Figure 46 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of diol **119**

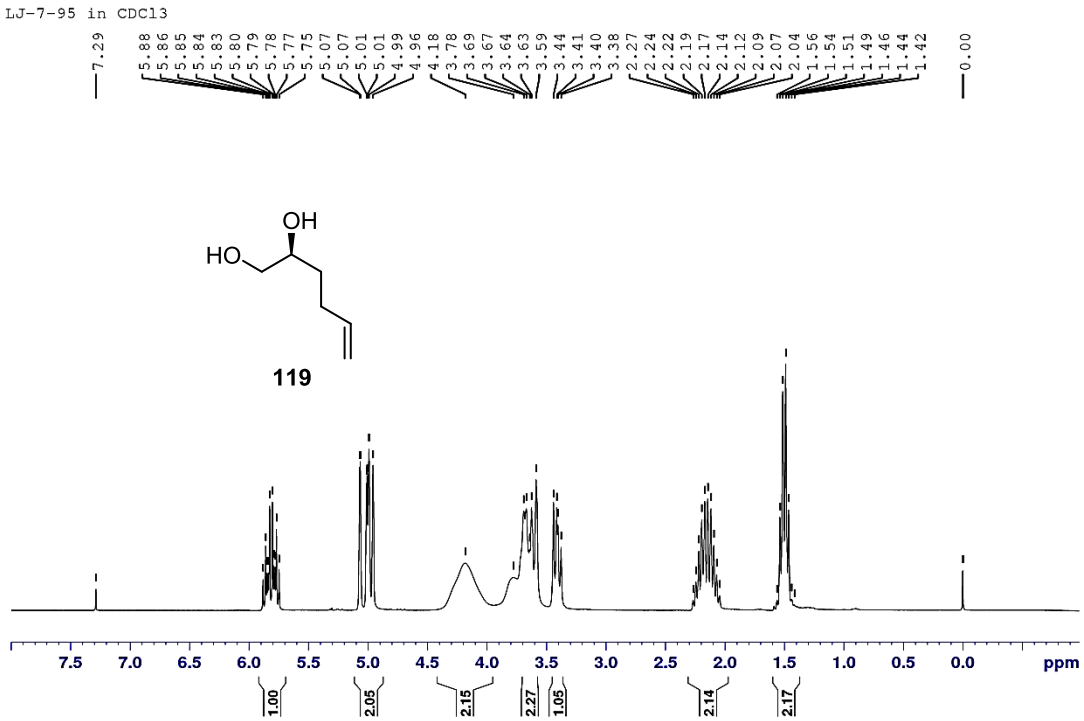


Figure 47 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of diol **119**

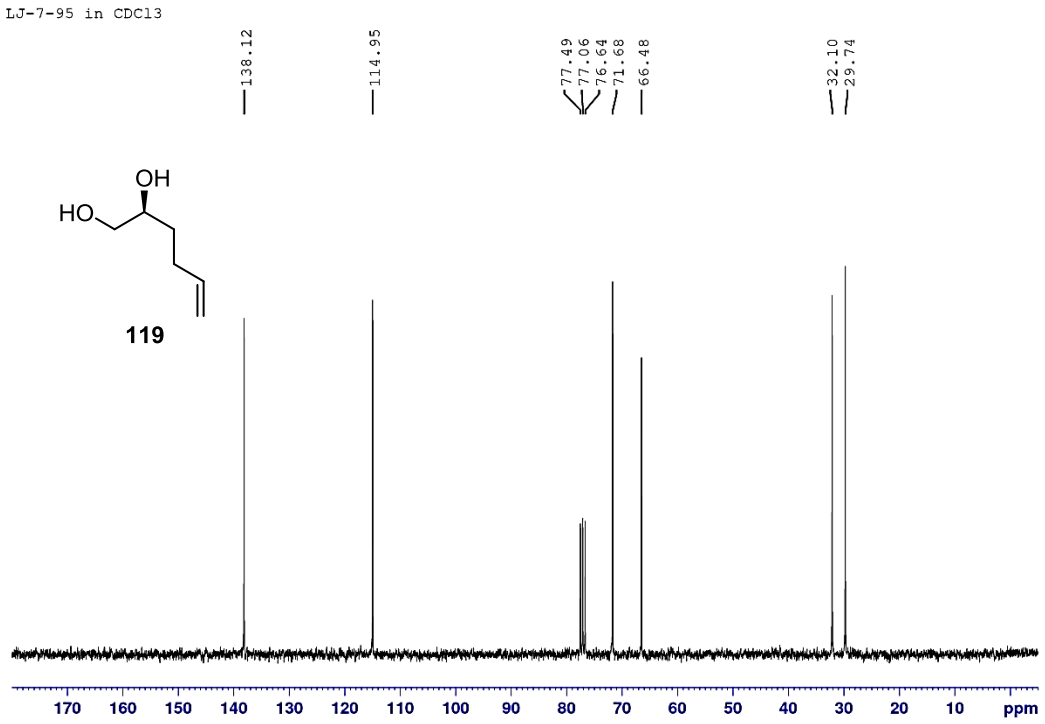


Figure 48 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of acetonide **119a**

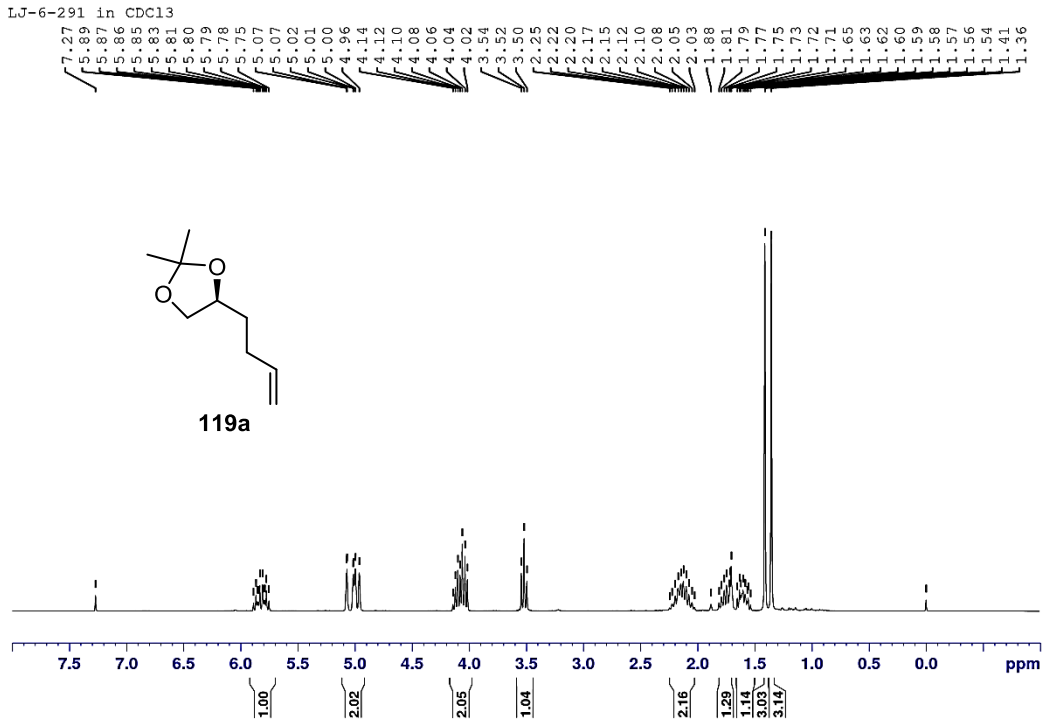


Figure 49 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of acetonide **119a**

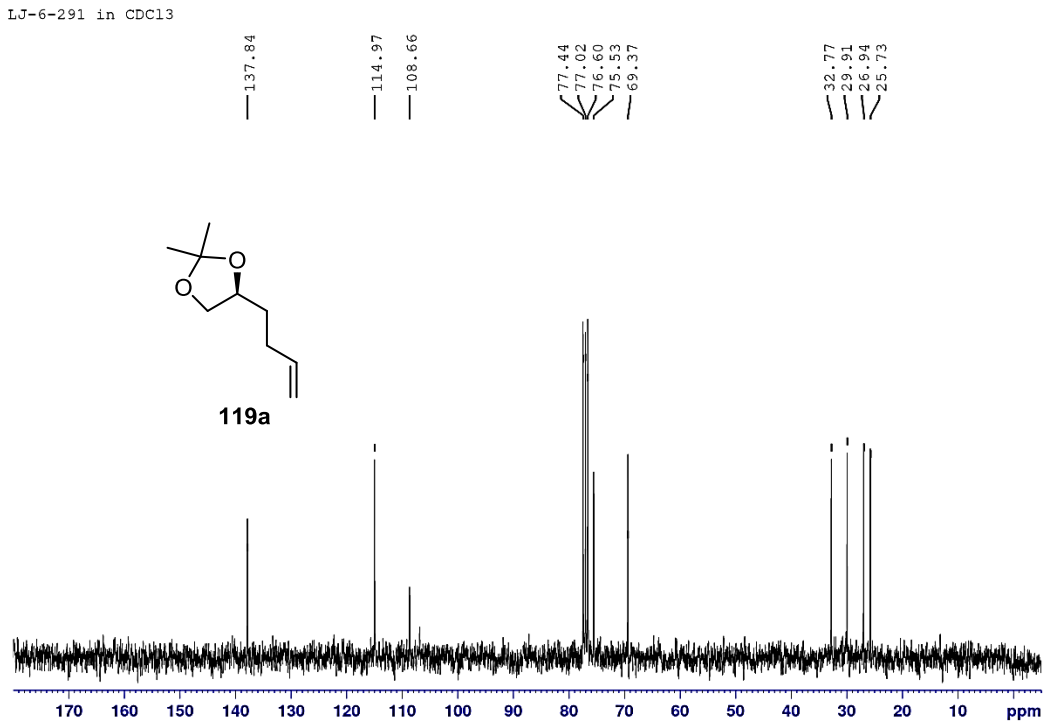


Figure 50 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of epoxide ***rac*-120**

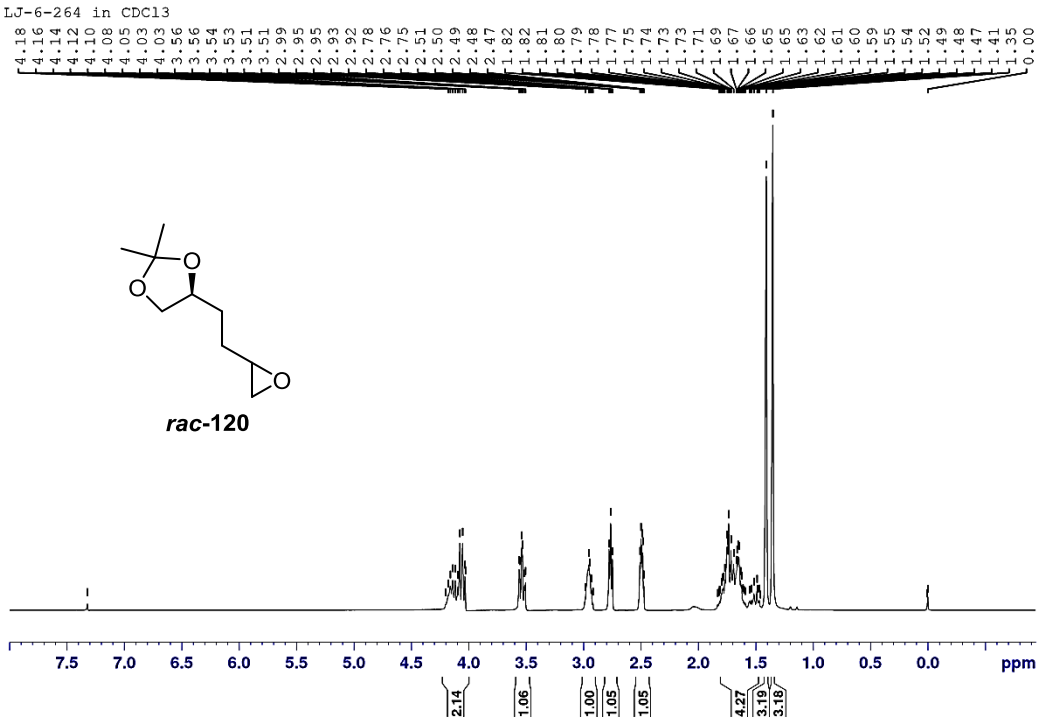


Figure 51 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of epoxide ***rac*-120**

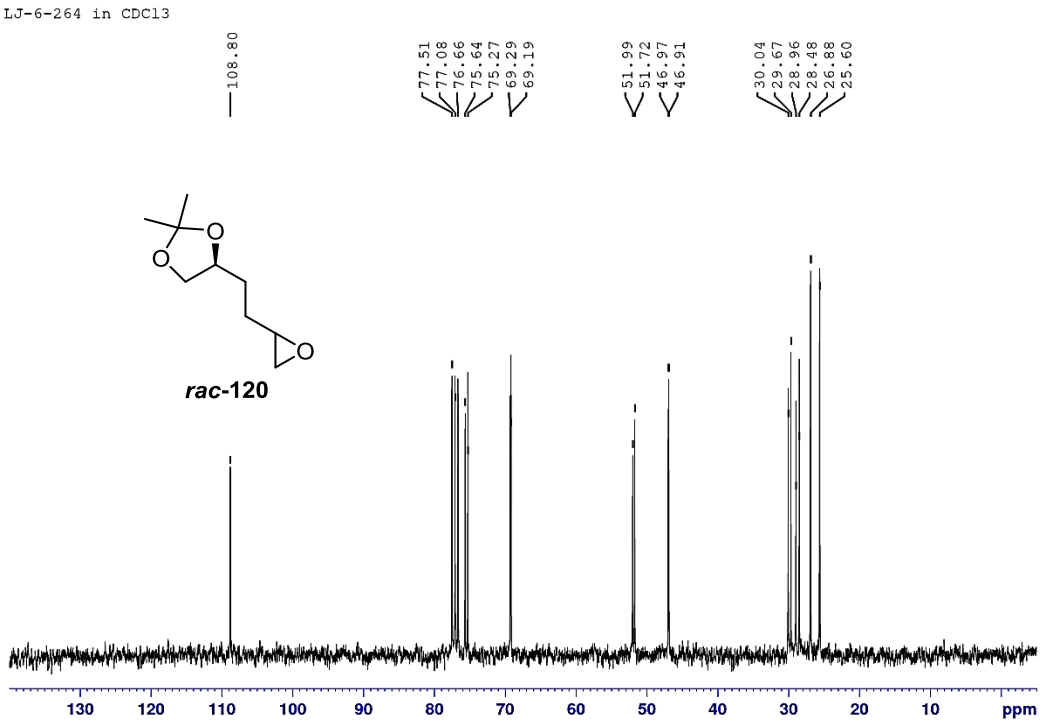


Figure 52 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of epoxide **120**

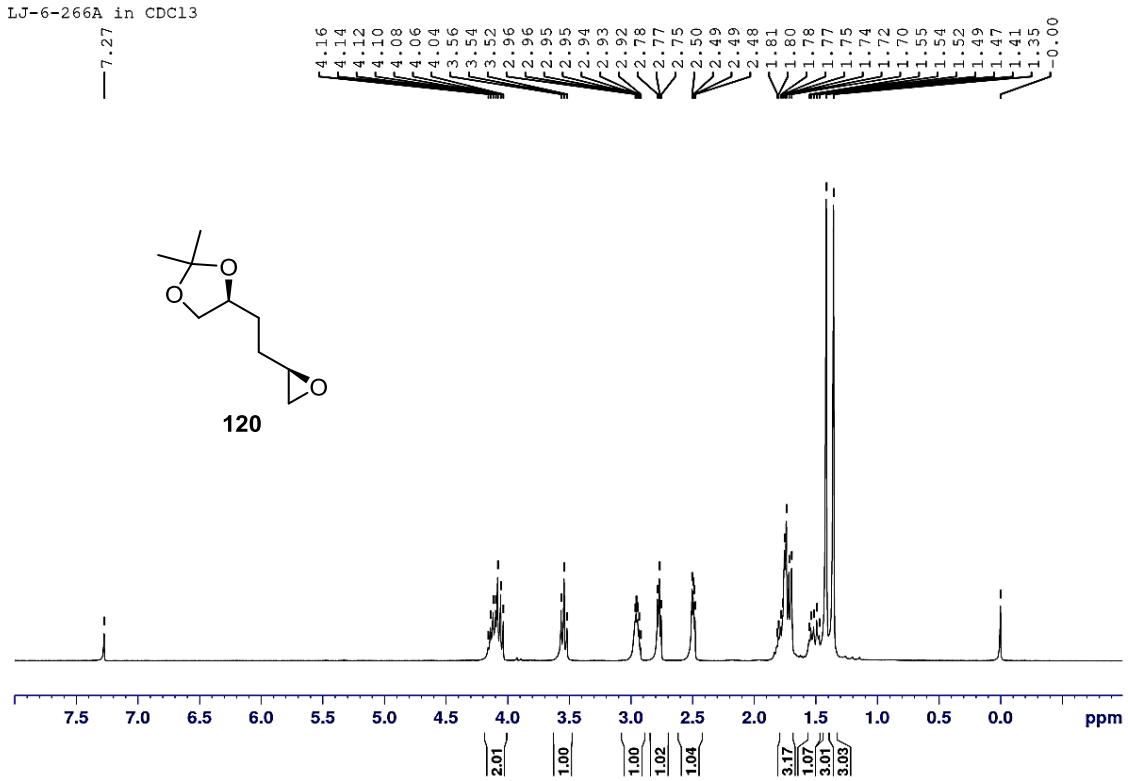


Figure 53 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of epoxide **120**

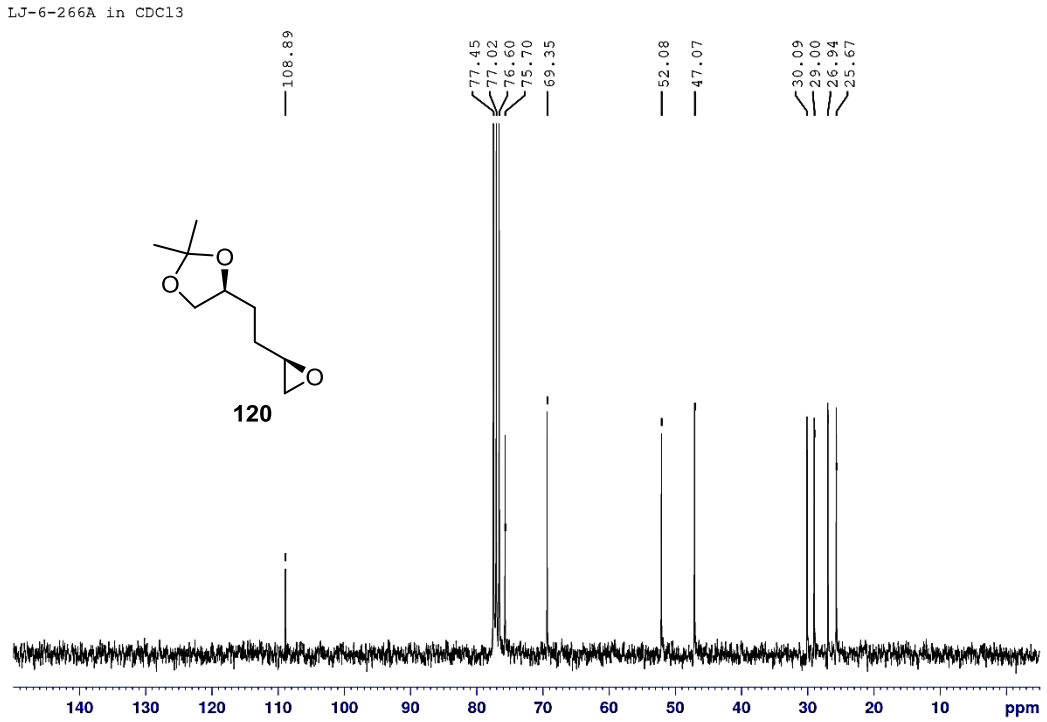


Figure 54 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of alcohol **121**

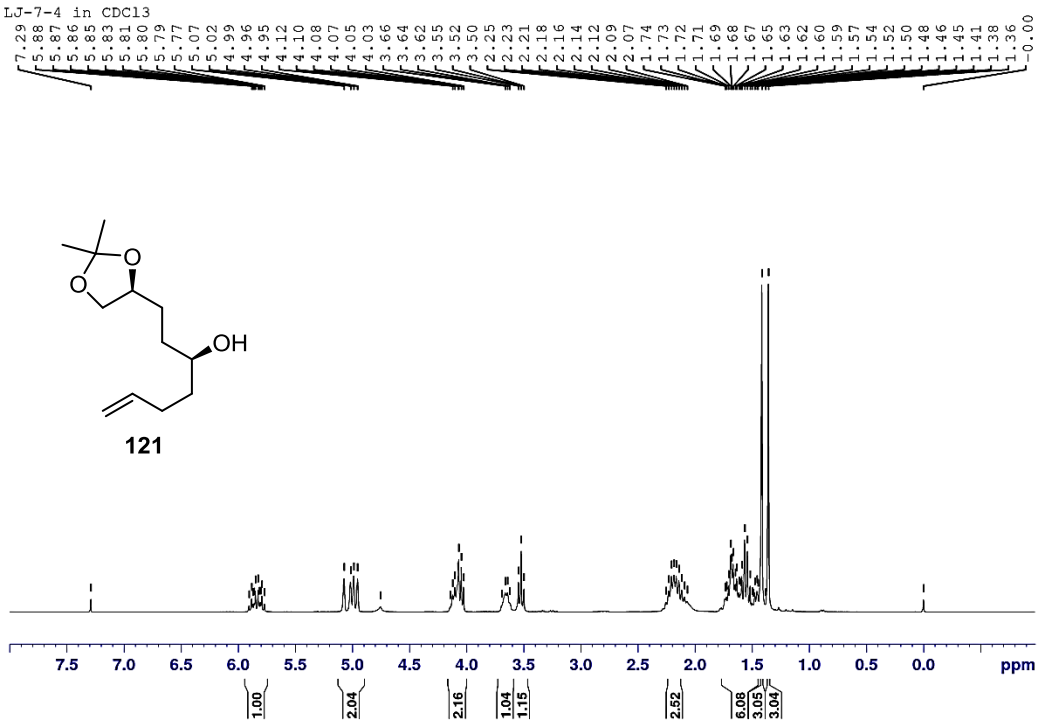


Figure 55 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of alcohol **121**

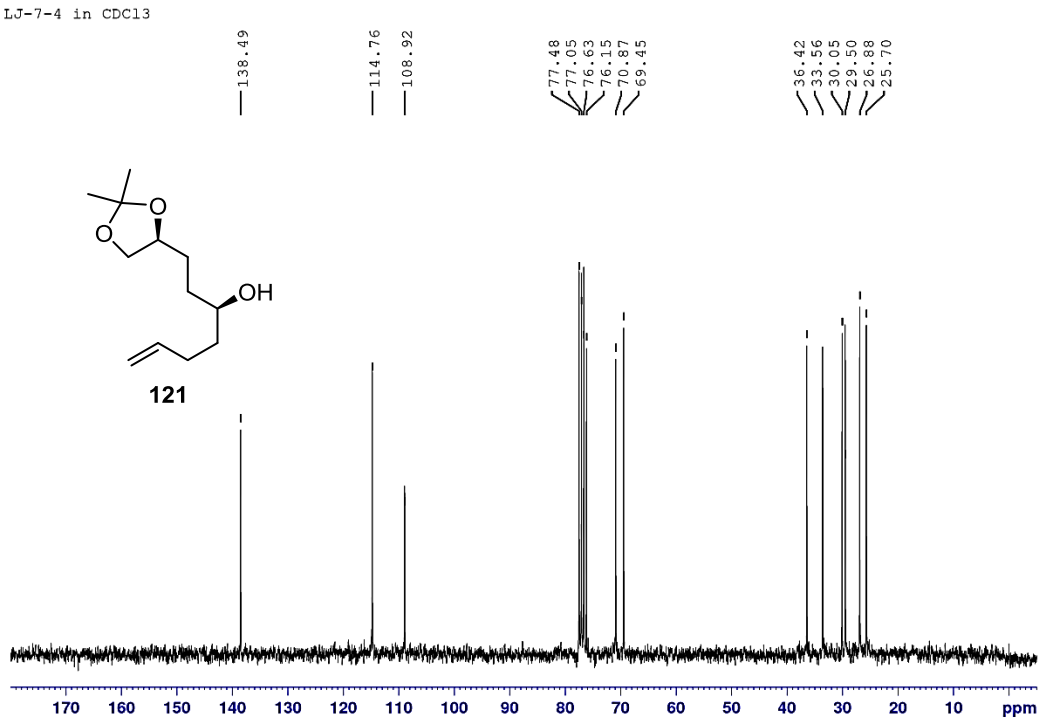


Figure 56 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of PMB ether **121a**

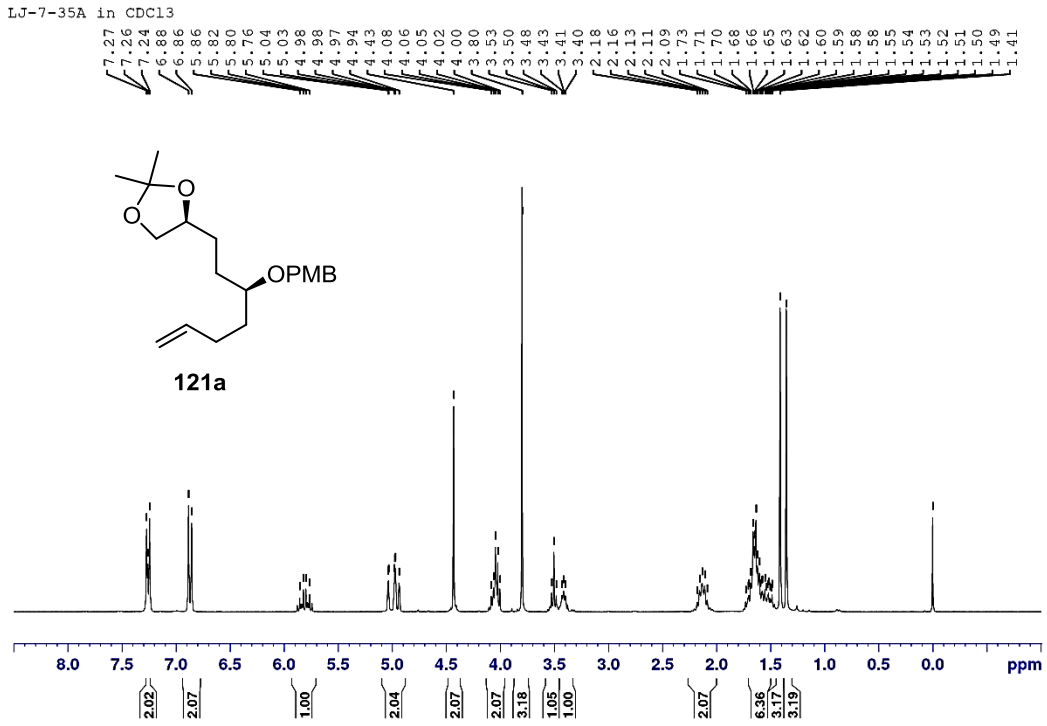


Figure 57 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of PMB ether **121a**

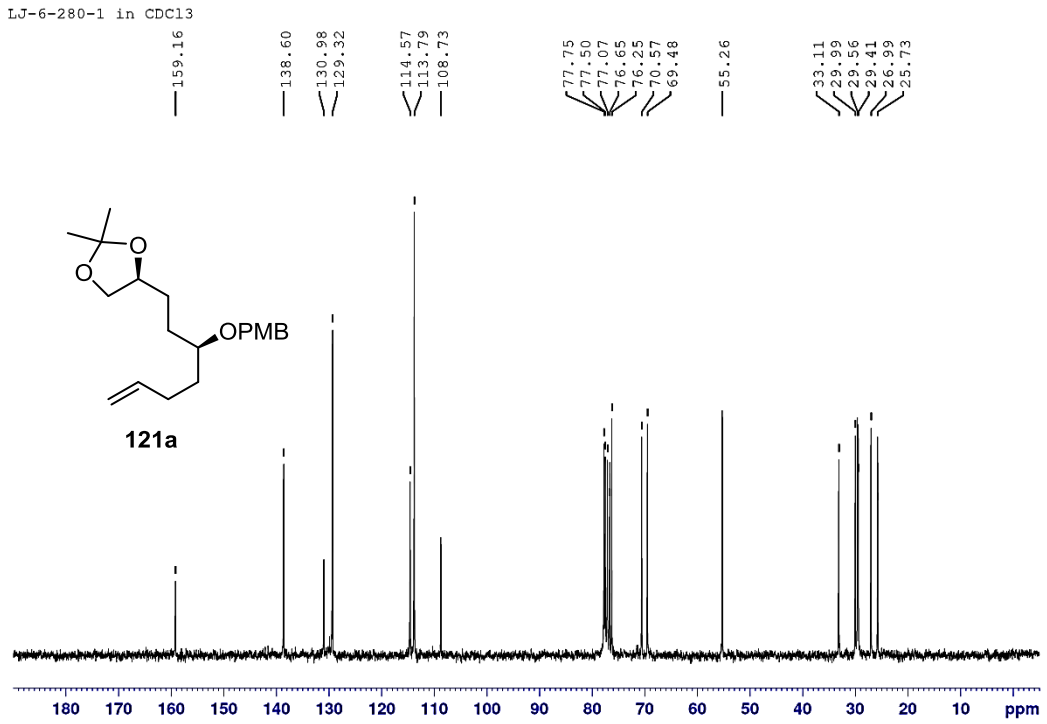


Figure 58 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of diol **122**

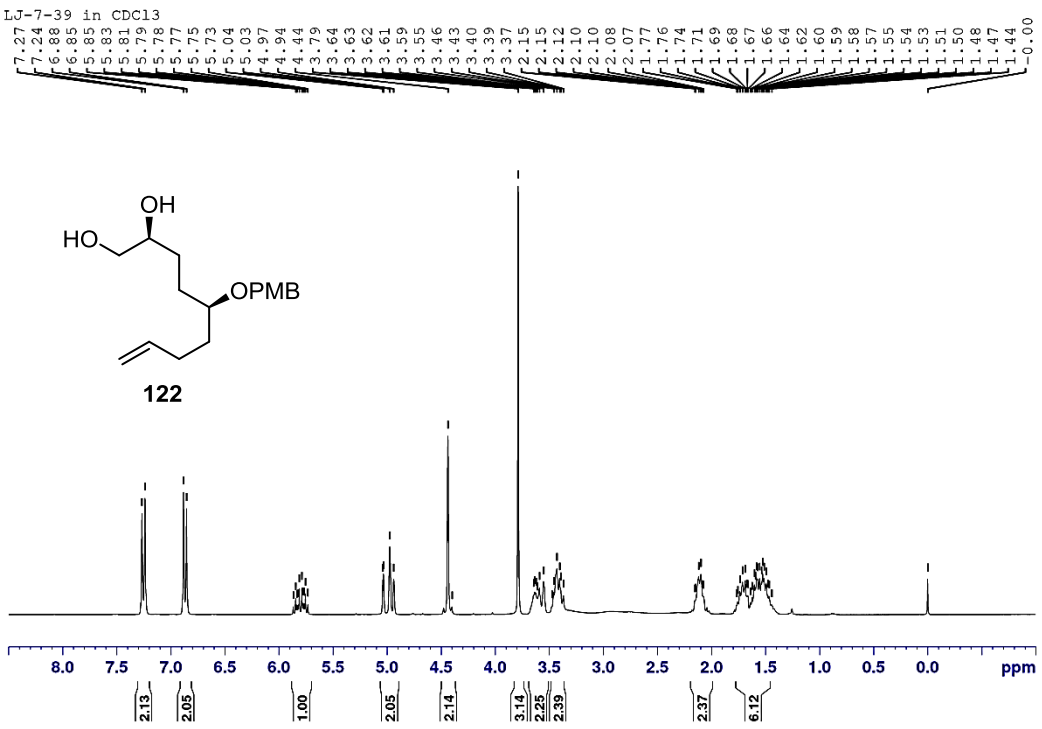


Figure 59 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of diol **122**

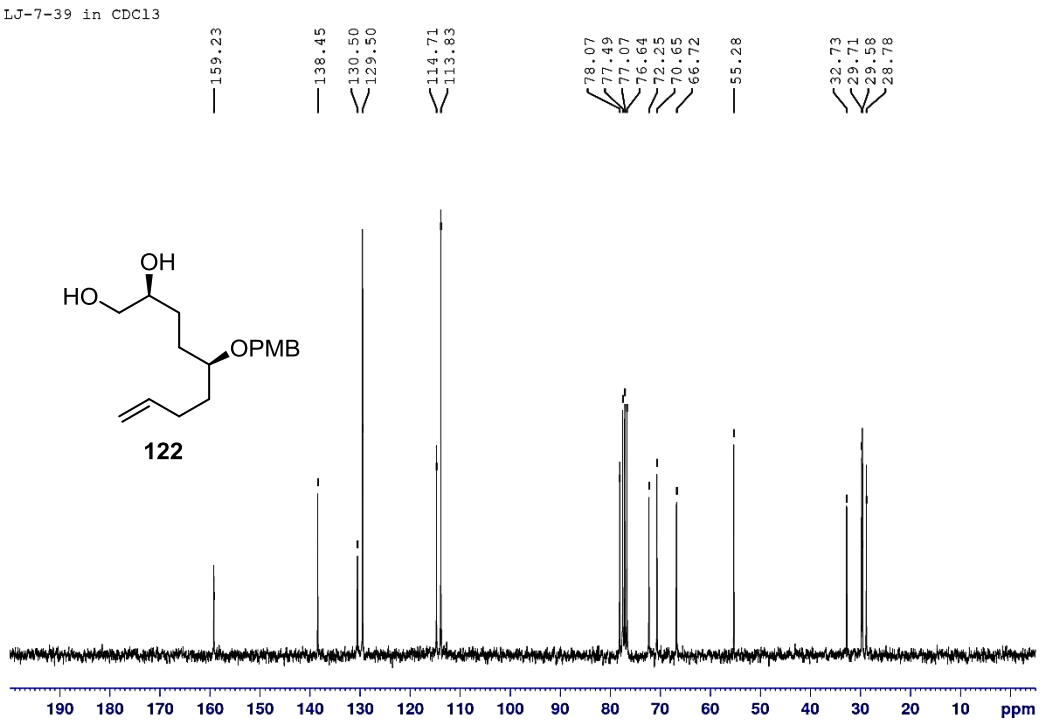


Figure 60 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of tosylate **123**

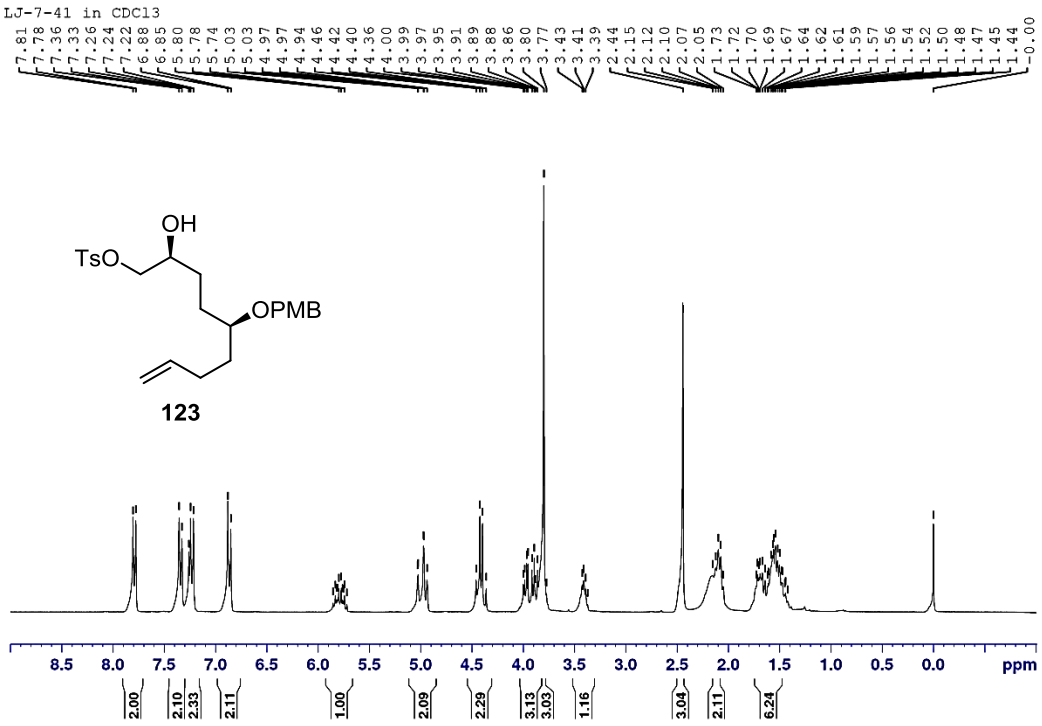


Figure 61 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of tosylate **123**

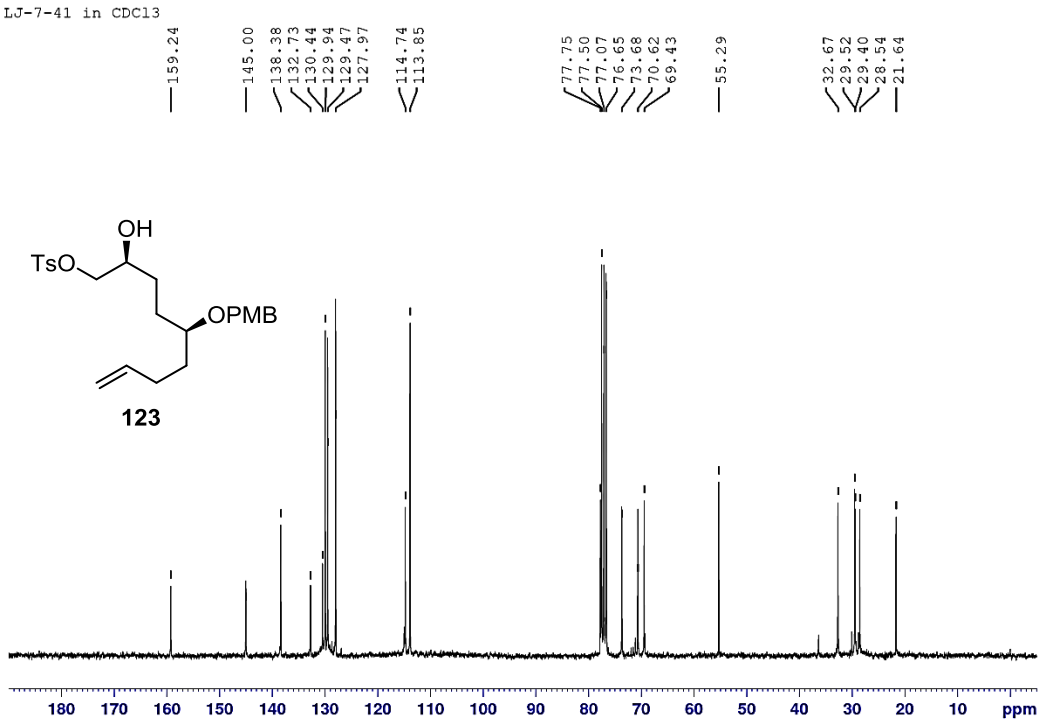


Figure 62 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of alcohol **111**

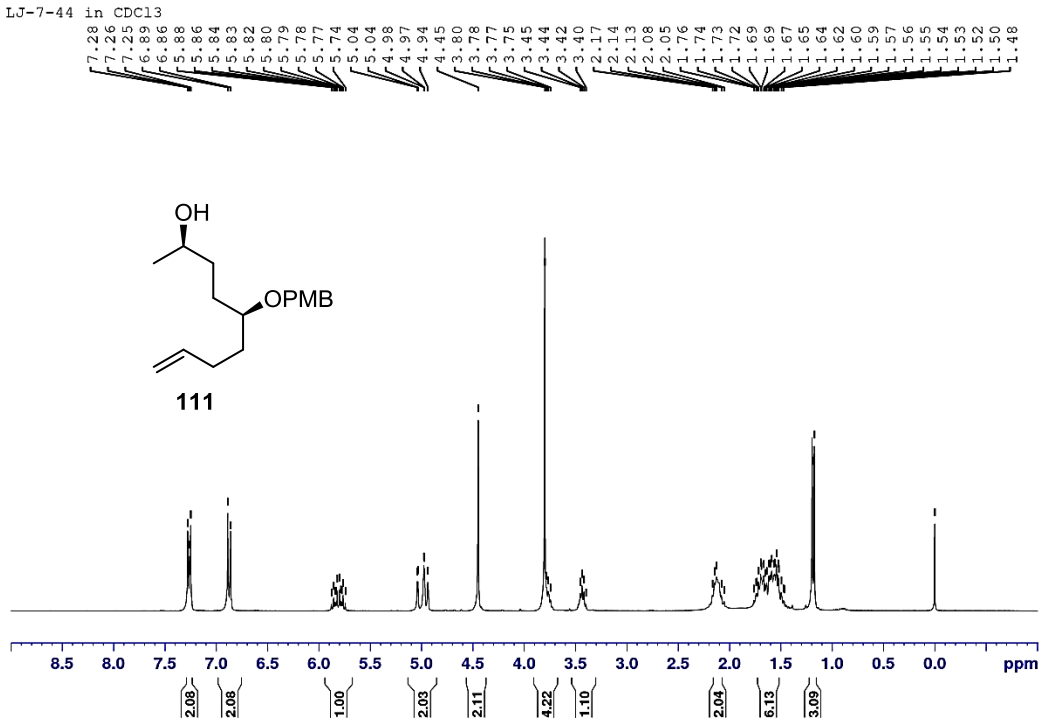


Figure 63 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of alcohol **111**

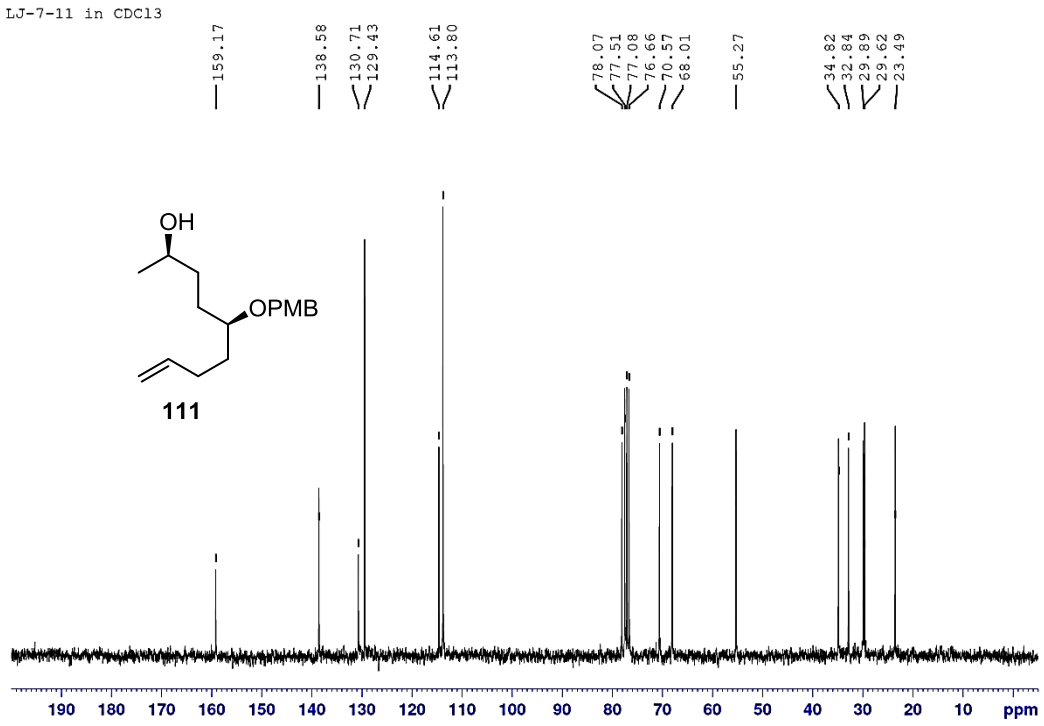


Figure 64 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum ester diene **109**

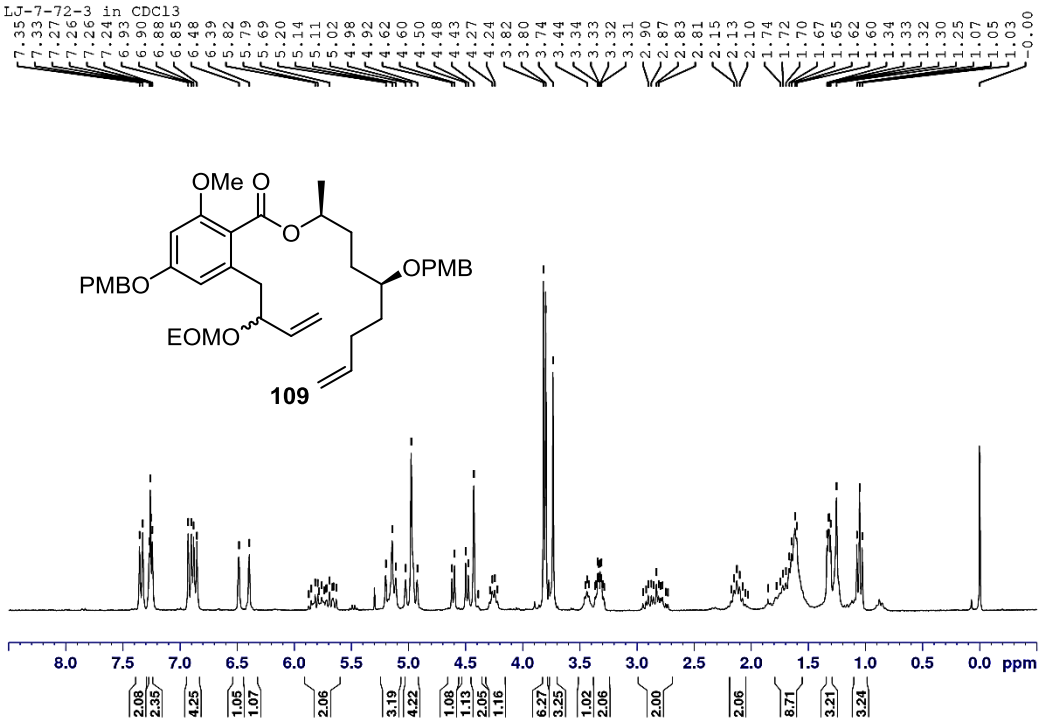


Figure 65 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of ester diene **109**

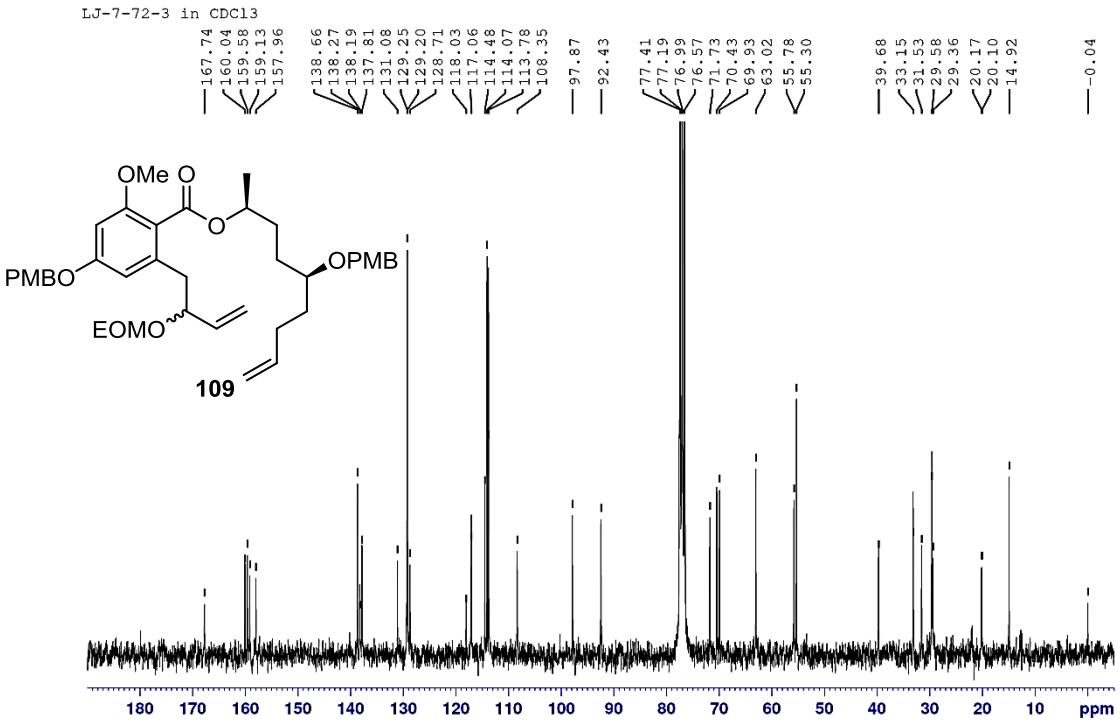


Figure 66 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of macrolactone **107**

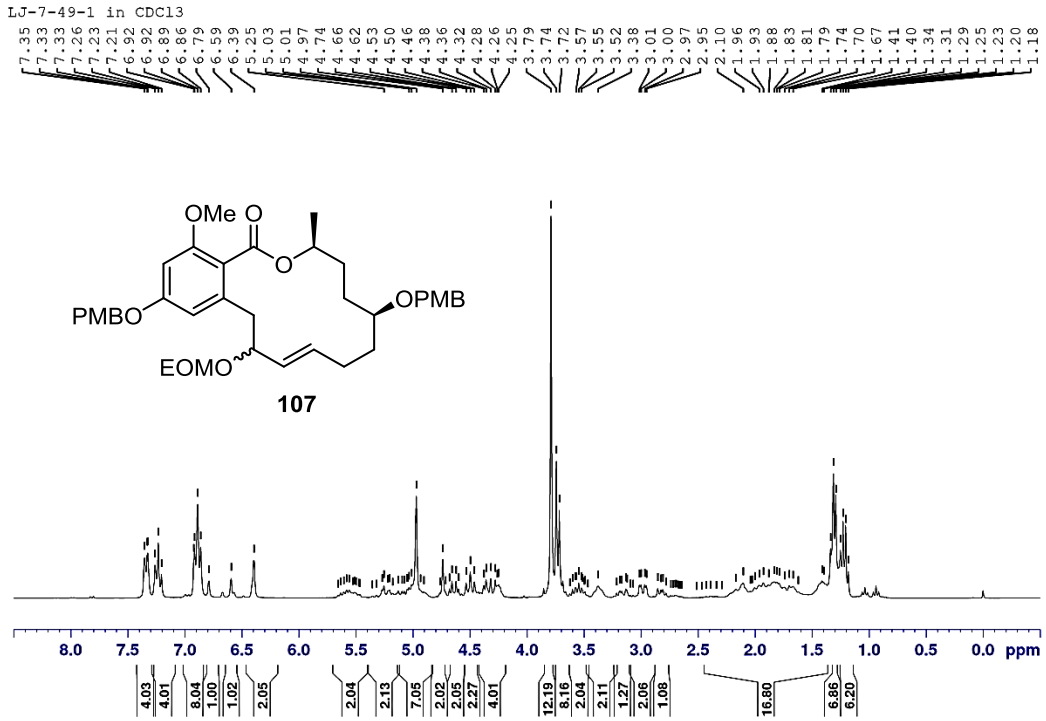


Figure 67 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of macrolactone **107**

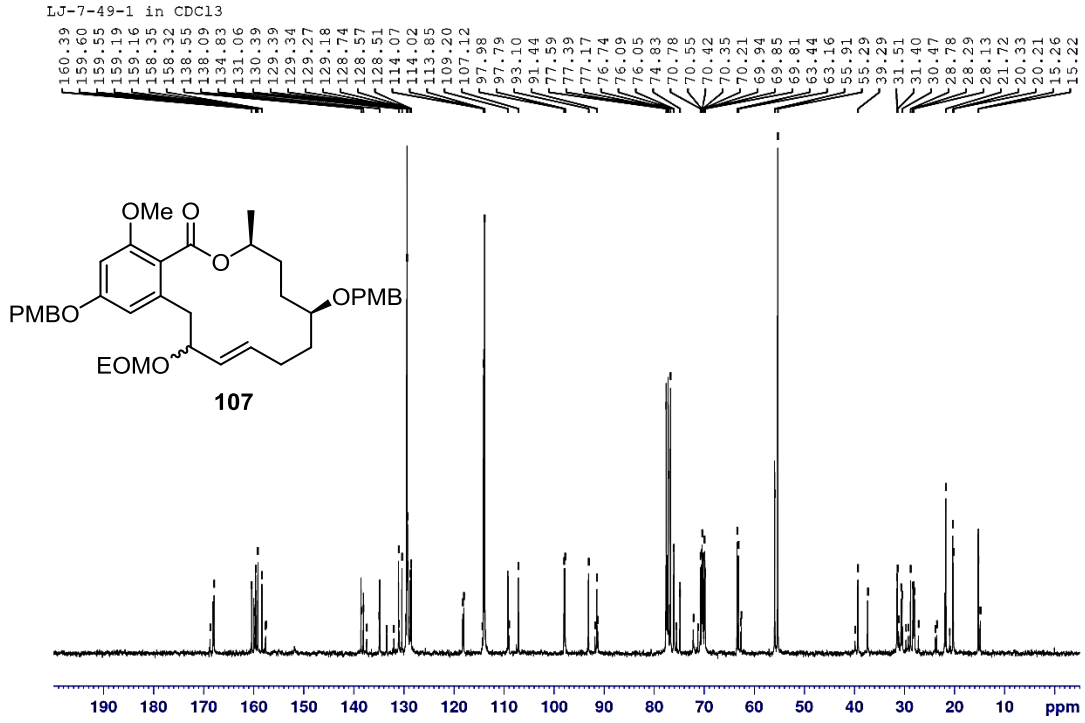


Figure 68 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of allylic alcohol **124**

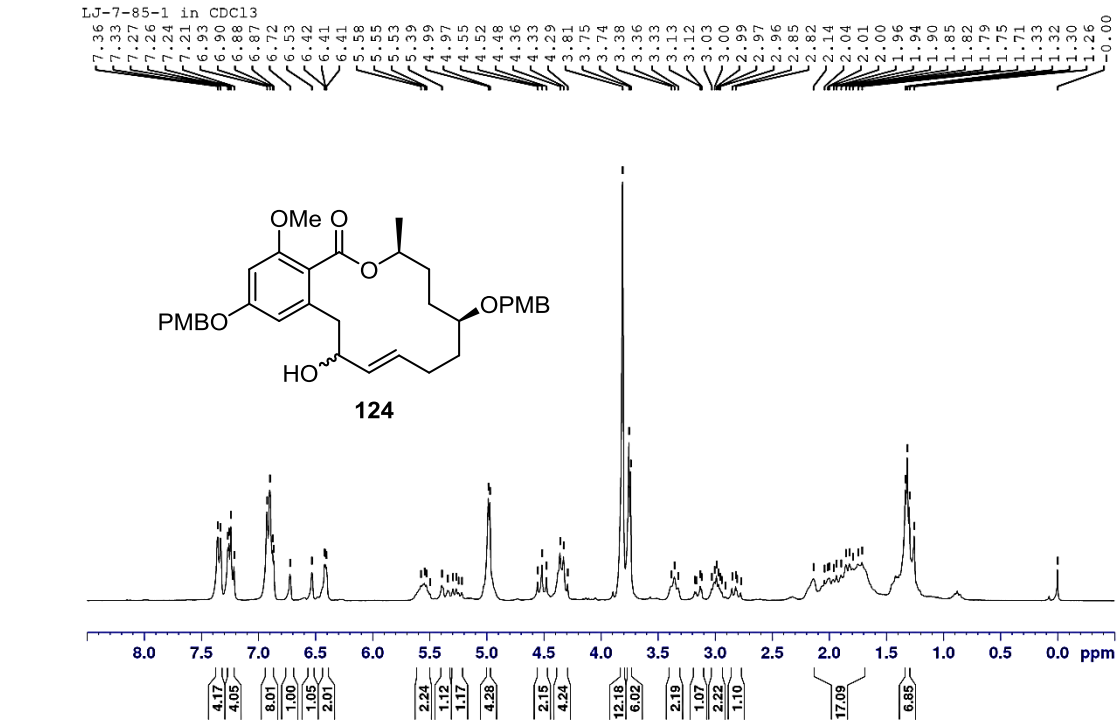


Figure 69 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of allylic alcohol **124**

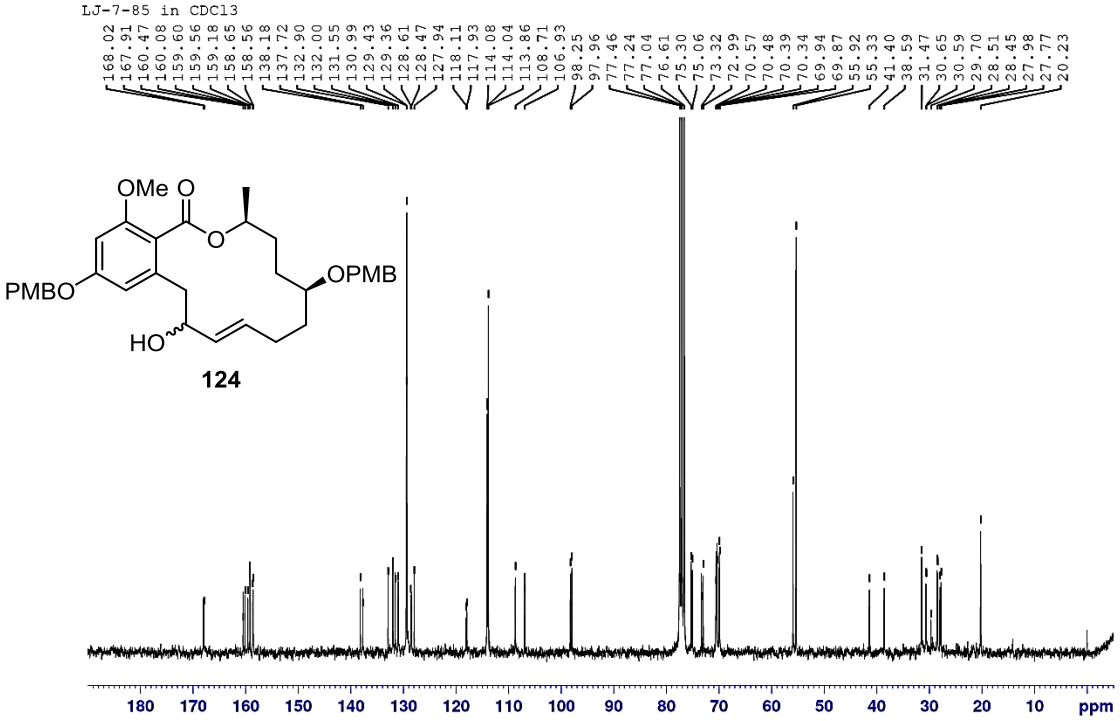


Figure 70 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of ketone **125**

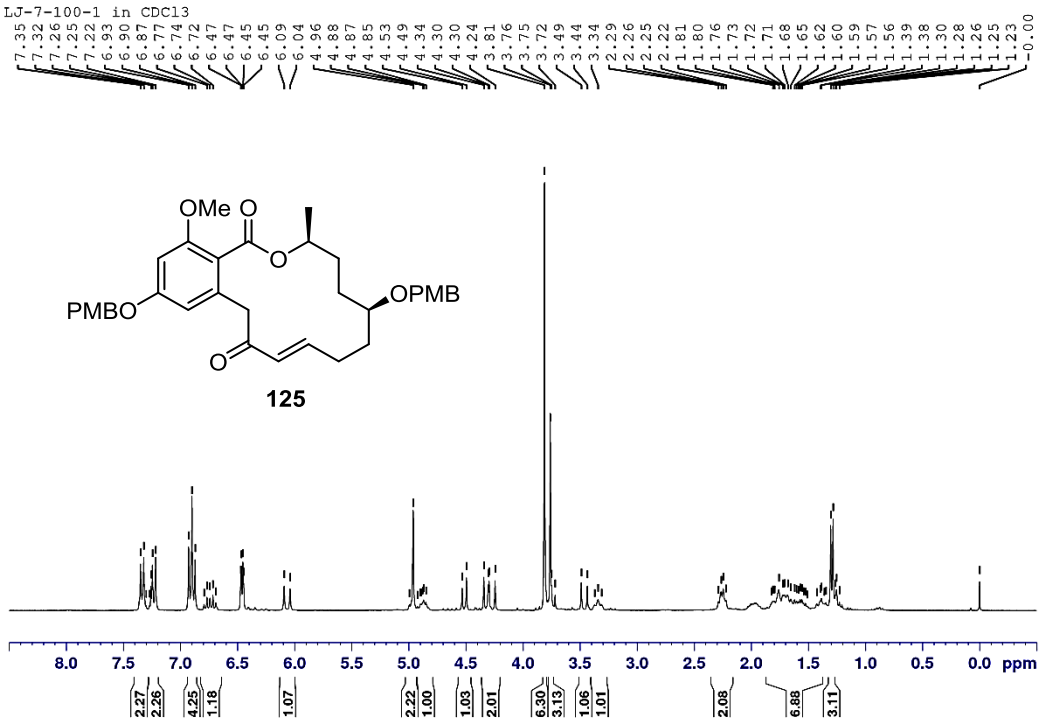


Figure 71 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of ketone **125**

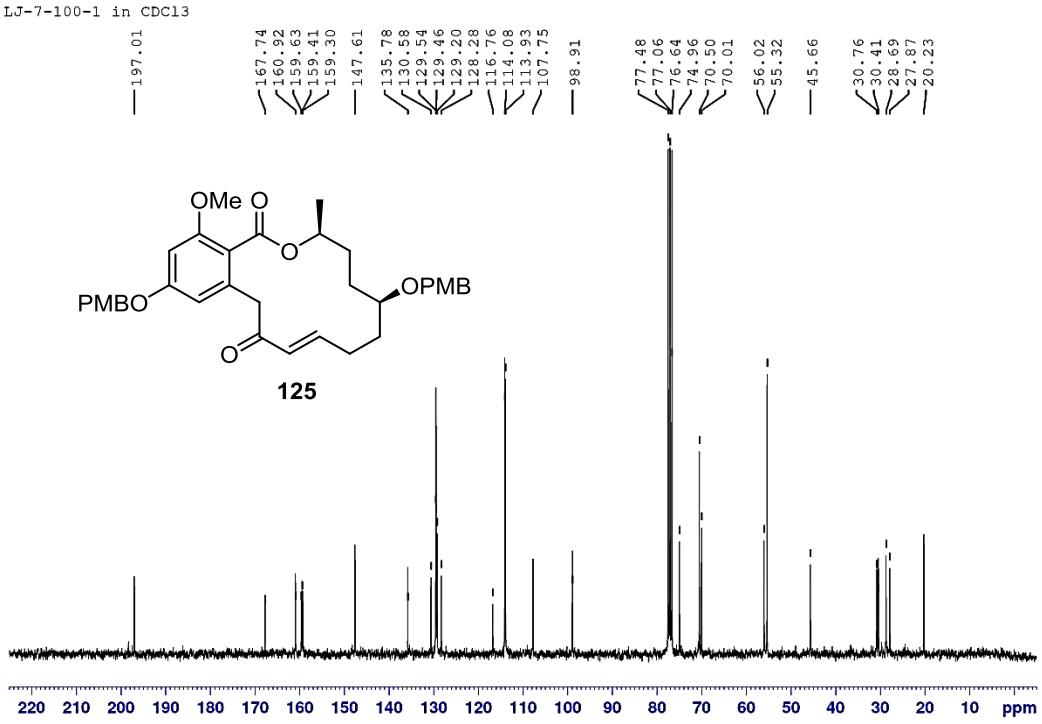


Figure 72 ^{1}H NMR (300 MHz, DMSO-d_6) spectrum of dechlorogreensporone D (**26**)

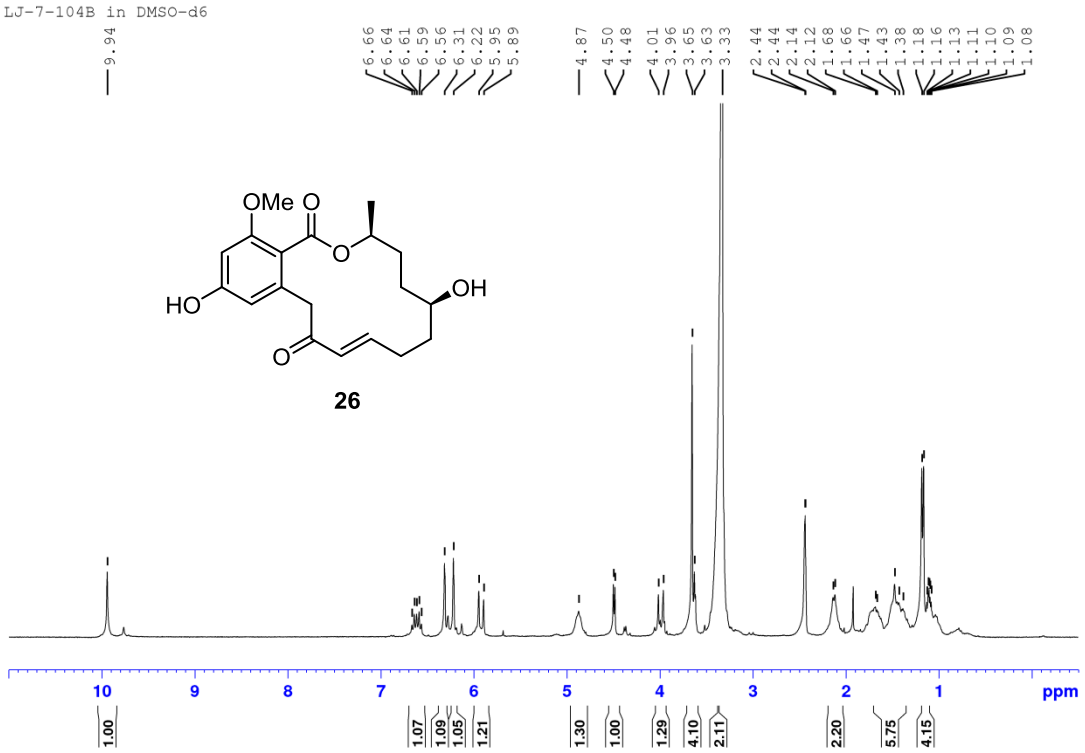


Figure 73 ^{13}C NMR (75 MHz, DMSO-d_6) spectrum of dechlorogreensporone D (**26**)

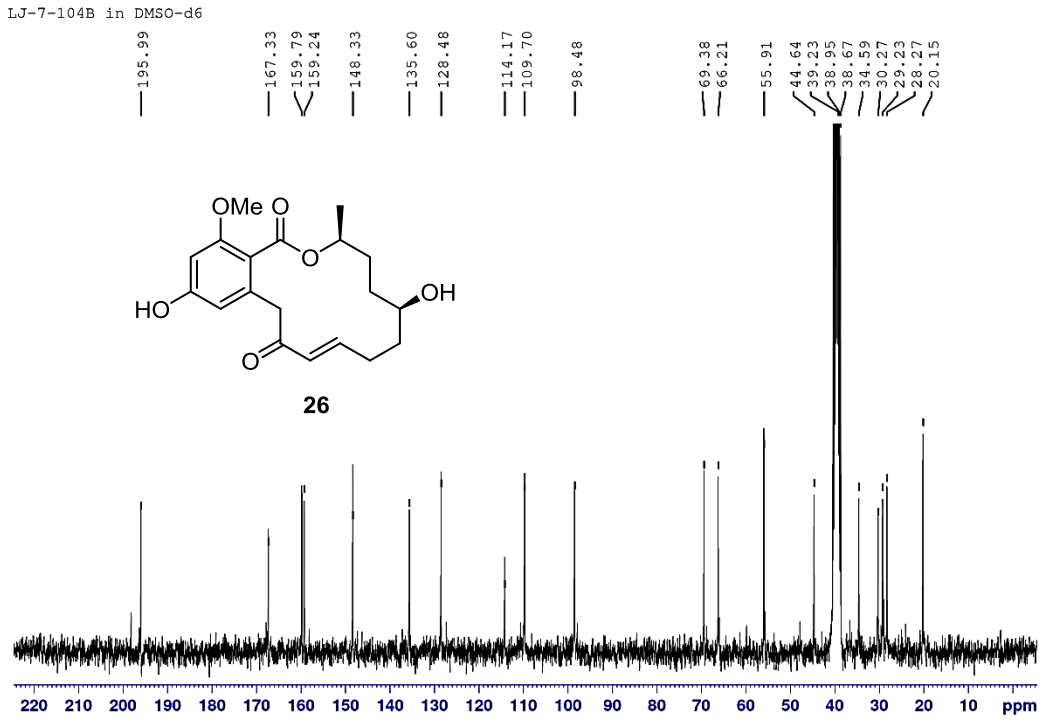


Figure 74 ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of dechlorogreensporone F (**23**)

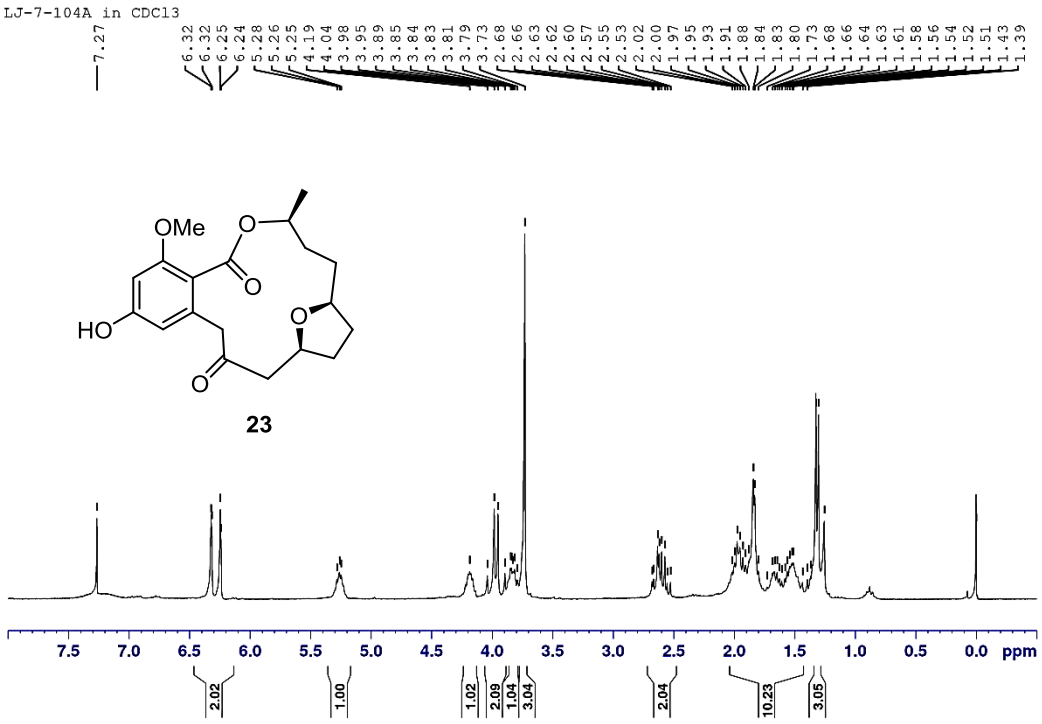
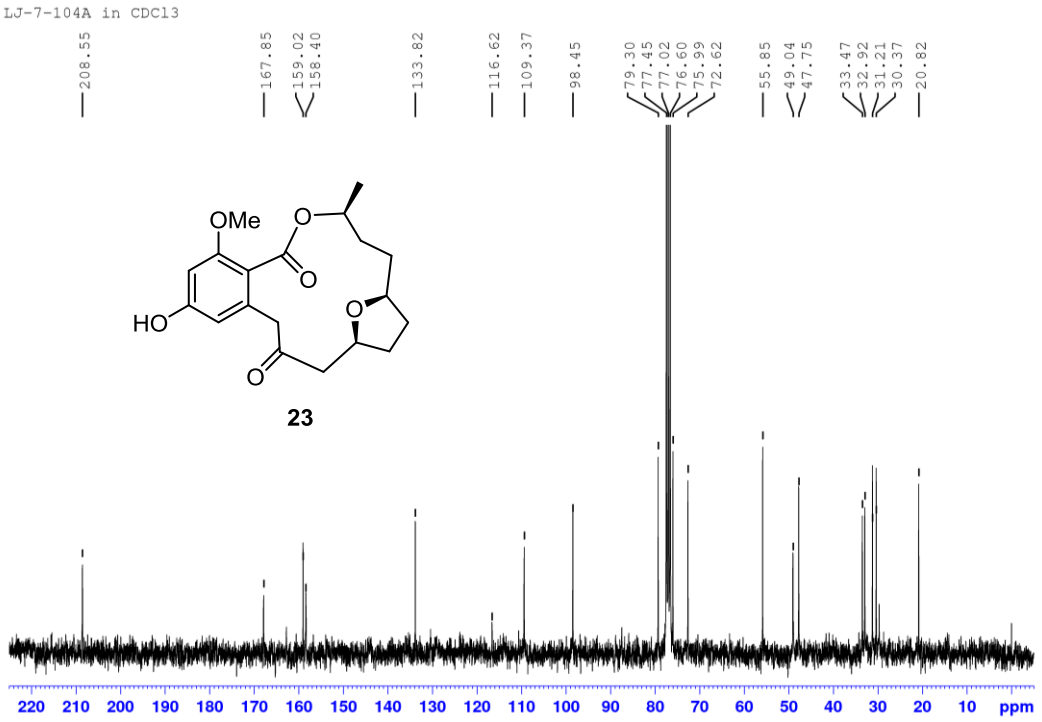
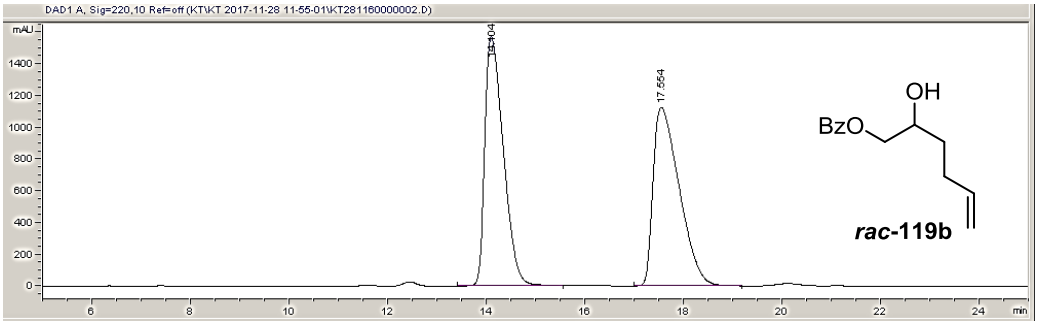


Figure 75 ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of dechlorogreensporone F (**23**)



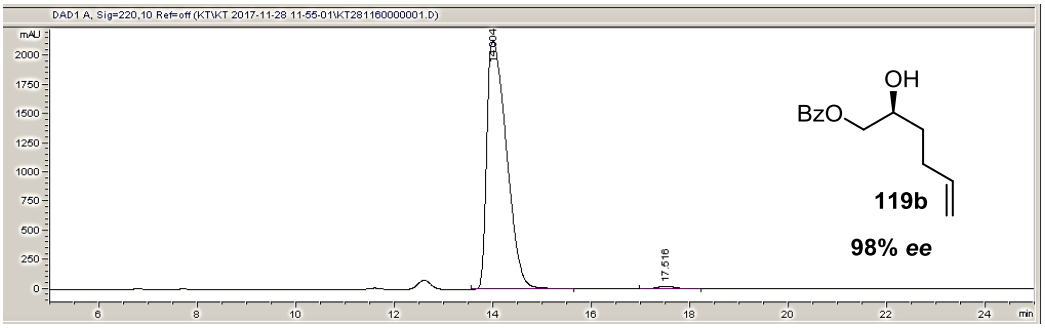
HPLC traces

Figure 76 Chromatogram of racemic benzoate ***rac*-119b**



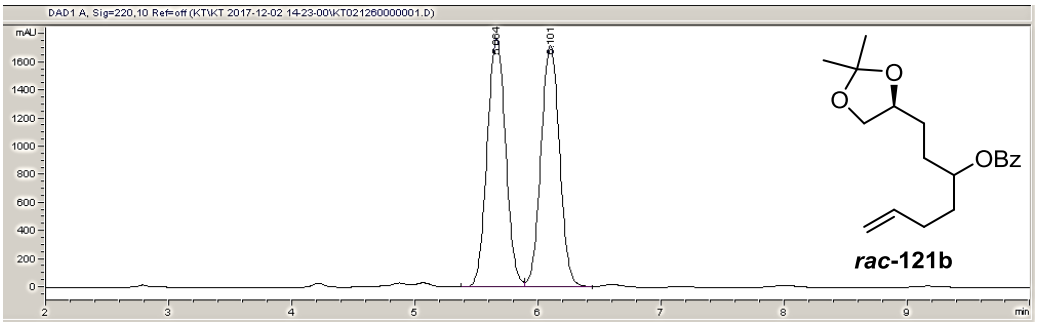
#	Time	Area	Height	Width	Area%	Symmetry
1	14.104	41042.1	1570.6	0.4069	49.716	0.495
2	17.554	41510.2	1123.5	0.579	50.284	0.427

Figure 77 Chromatogram of chiral benzoate **119b**



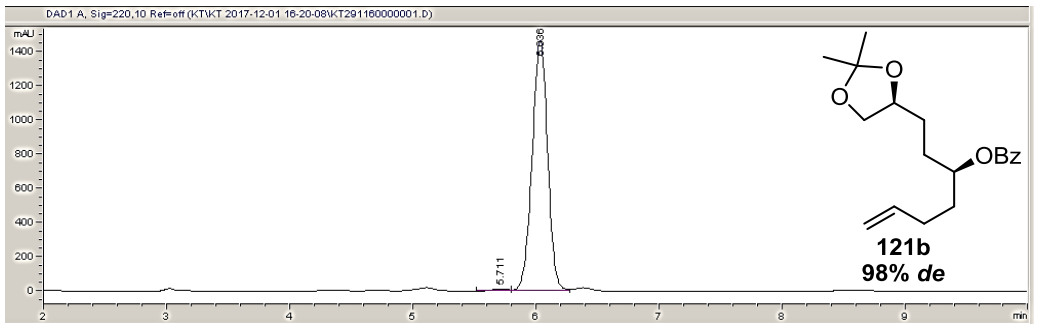
#	Time	Area	Height	Width	Area%	Symmetry
1	14.004	59410.5	2124.6	0.4482	98.935	0.421
2	17.516	639.4	23.8	0.4209	1.065	0.886

Figure 78 Chromatogram of racemic benzoate ***rac*-121b**



#	Time	Area	Height	Width	Area%	Symmetry
1	5.664	18627	1764.3	0.1672	50.710	0.973
2	6.101	18105.1	1716.9	0.165	49.290	0.968

Figure 79 Chromatogram of chiral benzoate **121b**



#	Time	Area	Height	Width	Area%	Symmetry
1	5.711	117.5	12.9	0.1426	0.903	1.062
2	6.036	12899	1466.6	0.1366	99.097	1.068

VITAE

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Bachelor of Science (1^{st} Hons.) (Chemistry)	Prince of Songkla University	2014

Scholarship Award during Enrolment

Development and Promotion of Science and Technology Talents Project (DPST)

List of Publications

Jeanmard, L.; Iawsipo, P.; Panprasert, J.; Rukachaisirikul, V.; Tadpetch, K. 2018. Total Synthesis and Cytotoxic Activity of Dechlororeensporones A and D. Tetrahedron. DOI: 10.1016/j.tet.2018.07.025

Tadpetch, K.; Jeanmard, L.; Rukachaisirikul, V. 2017. Total Synthesis of Greensporone C. Tetrahedron Lett. 58, 3453−3456.

Tadpetch, K.; Jeanmard, L.; Rukachaisirikul, V. 2015. Total Synthesis of the Proposed Structure of Pestalotioprolide A. Tetrahedron Asymmetry. 26, 918−923.

Tadpetch, K.; Chukong, C.; Jeanmard, L.; Thiraporn, A.; Rukachaisirikul, V.; Phongpaichit, S.; Sakayaroj, J. 2015. Cytotoxic Naphthoquinone and a New Succinate Ester from the Soil Fungus *Fusarium Solani* PSU-RSPG227. Phytochemistry Lett. 11, 106−110.