รายงานวิจัยฉบับสมบูรณ์

โครงการ การศึกษาแนวทางการสังเคราะห์กรดโปรโตคอนสติพาติก กรดอัลโร-เพอร์ทูซาริก กรดอัลโร-ไดไฮโดรเพอร์ทูซาริก และอนุพันธ์

โดย ผู้ช่วยศาสตราจารย์ ดร. พุฒินันท์ มีเผ่าพันธ์

กรกฎาคม 2552

สัญญาเลขที่ MRG4780117

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ภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยเชียงใหม่

สนับสนุนโดยสำนักงานคณะกรรมการการอุดมศึกษา
และสำนักงานกองทุนสนุบสนุนการวิจัย

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Puttinan Meepowpan

บทคัดย่อ

รหัสโครงการ : MRG4780117

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ชื่อนักวิจัย : ผู้ช่วยศาสตราจารย์ ดร. พุฒินันท์ มีเผ่าพันธ์
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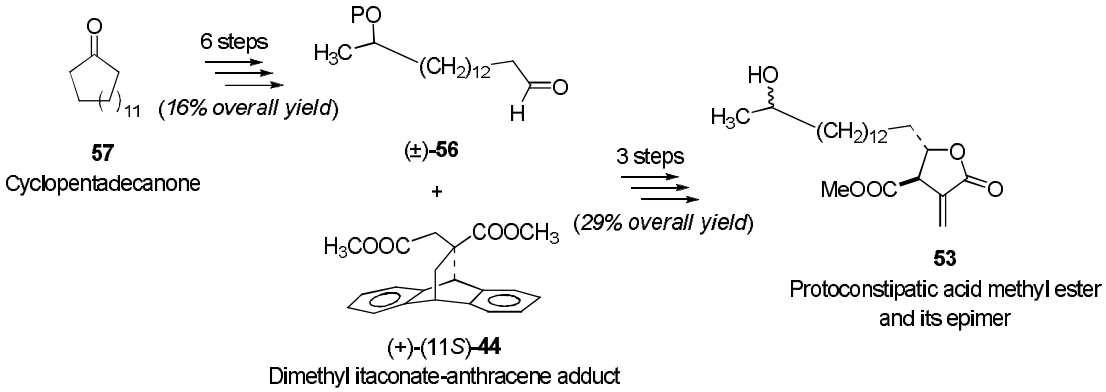
ระยะเวลาโครงการ : 2 ปี (1 กรกฎาคม 2547 ถึง 30 มิถุนายน 2549)

กรดโปรโตคอนสติพาติกเมทิลเอสเทอร์ (53) และเอพิเมอร์ สามารถสังเคราะห์ได้จากไดเมทิลอิทาโคเนต-แอนทราซีนแอดดัค ในรูปของอิแนนทิโอเมอร์ [(+)-(11*S*)-44] เป็นโครงสร้างหลัก ทำปฏิกิริยากับไครัลอีเทอร์อัลดีไฮด์ (±)-56 ผ่านปฏิกิริยาแทนเดมอัลดอล-แลคโทไนเซชัน ไอโซเมอไรเซชัน และไพโรไลซีส ตามลำดับ ในเปอร์เซ็นต์ผลผลิตรวม 29%

ารเริ่มต้นอีกตัวที่สำคัญ ไครัลอีเทอร์อัลดีไฮด์ (±)-56 เตรียมสำเร็จได้โดยใช้วิธีการสังเคราะห์ที่เหมาะสม ประกอบด้วยเมทิเลชันของไซโคลเพนตะเดคะโนน (57) ปฏิกิริยาเบเยอร์-วิลิเกอร์ออกซิเดชัน ทรานสเมทิเลชัน การป้องกันของแอลกอฮอล์ รีดักชัน และสเวิร์นออกซิเดชัน ตามลำดับ ในเปอร์เซ็นต์ผลผลิตรวม 16%



คำหลัก : ไซโคลเพนตะเดคะโนน, ไดเมทิลอิทาโคเนต-แอนทราซีนแอดดัค, อัลดอล-แลคโทไนเซชัน, กรดโปรโตคอนสติพาติก

ABSTRACT

Project Code : MRG4780117

Project Title : Towards to the synthesis of protoconstipatic acid, *allo*-pertusaric acid, *allo*-dihydropertusaric acid and their derivatives

Investigator : Asst. Prof. Dr. Puttinan Meepowpan
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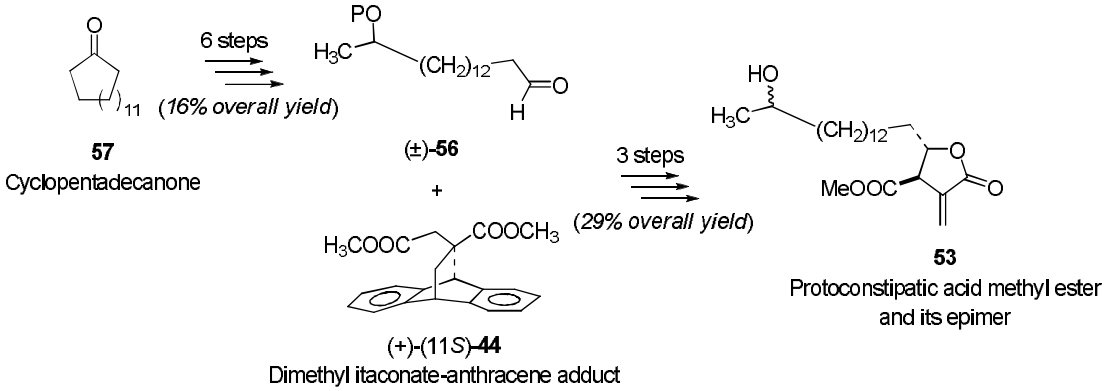
Project Period : 2 Years (1 July 2004 to 30 June 2006)

The protoconstipatic acid methyl ester (53) and its epimer can be synthesized from the readily available dimethyl itaconate-anthracene adduct in enantiomerically pure forms, [(+)-(11*S*)-44], as building blocks, reacted with the chiral ether aldehyde (±)-56 via tandem aldol-lactonization, isomerization and pyrolysis respectively in 29% overall yield. The other important starting material, the chiral ether aldehyde (±)-56 was achieved using the practically synthetic methodology including methylation of cyclopentadecanone (57), Baeyer-Villiger oxidation, transmethylation, protection of alcohol, reduction and Swern oxidation respectively in 16% overall yield.



Keywords : cyclopentadecanone, dimethyl itaconate-anthracene adduct, aldol-lactonization, protoconstipatic acid

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ABBREVIATIONS AND SYMBOLS

AIBN	2,2'-azobisisobutyronitrile
Api	apiose
Ara	arabinose
BnBr	benzyl bromide
n-BuLi	*n*-butyllithium
calc.	calculated
cat.	catalyst
m-CPBA	*m*-chloroperbenzoic acid
conc.	concentration
DABCO	1,4-diazabicyclo[2.2.2]octane
DHP	3,4-dihydro-2*H*-pyran
DMAP	4-(*N*,*N*-dimethyl)pyridine
DMF	*N*,*N*-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulphoxide
d	doublet (spectral)
ddd	double of double doublets (spectral)
ESI-MS	electrospray ionization mass spectrometry
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate
equiv	equivalent
FVP	flash vacuum pyrolysis
FT-IR	fourier-transform infrared
Glu	glucose
g	gram
HMPA	hexamethyphosphoric triamide
HRMS	high resolution mass spectrometer
Hz	hertz
h	hour (s)
IR	infrared radiation

LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
lit.	literature
Me	methyl
MHz	megahertz
M-K10	montmorillonite K10
m	multiplet (spectral)
min	minute (s)
ml	millilitre
mmol	milimole
mol	mole
m.p.	melting point
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromte
PLC	preparative layer chromatography
ppm	parts per million (in NMR)
Rha	rhamnose
rt	room temperature (◦C)
s	singlet (spectral)
TBAF	tetrabutylammonium fluoride
TBDSCl	*t*-butyldiphenylsilyl chloride
TBS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	tetramethylsilane
TsCl	tosyl chloride
t	triplet (spectral)
Xyl	xylose
δ	chemical shift (ppm)
◦C	degrees celcius
%	percent
$[\alpha]$	specific optically rotation
ν	wave number (cm^{-1})

CHAPTER 1
INTRODUCTION

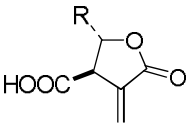
1.1 The α-methylene- and α-methyl-γ-butyrolactones

Paraconic acids, a class of trisubstituted γ-butyrolactones, are most widely present as the basic skeletal unit of biologically active natural products.[1-3] A characteristic feature of this class is functionalised at the γ-carbon atom (C_4) with carboxylic group, which is accompanied by an alkyl chain at C_5 that ranges in length from five to fifteen carbons, in some cases the C_5-alkyl chain is oxidized at one or more positions. Importantly, the α-carbon atom (C_3) is invariably substituted with either a methylene (1) or methyl (2) group, which plays a significant role in determining the physiological properties (Figure 1).

1 **2**

R = alkyl chain that ranges in length from 5-15 carbon atoms

Figure 1 α-Methylene- and α-methyl-γ-butyrolactones



3

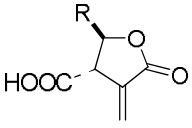
a : R = *n*-C_5H_{11} ; Methylenolactocin[8]
(isolated from the culture filtrate of *Penicillium sp.*)

b : R = *n*-$C_{11}H_{23}$; Nephosterinic acid[1]
(isolated from *Centraria endocrocea*)

c : R = *n*-$C_{13}H_{27}$; Protolichesterinic acid[8,9,10]
(isolated from several species of moss *Cetraria islandica* Laurr. and *Parmelia nepalensis* Tayl.)

(*S*)

d : R = $CH_3CH(OH)(CH_2)_{13}$; Protoconstipatic acid[11,12,13]
(isolated from *Acarospora gobiensis, Cladonia furcata, Lecanora frucata, P. tinctina, Peltigera canina, Xanthopamelia camtschadalis* and *X. tinctina*)



4

a : R = *n*-C_8H_{17} ; C75[14]

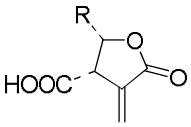
(*R*)

b : R = $CH_3CH(OH)(CH_2)_{13}$; Murolic acid[11,12]
(isolated from *Acarospora gobiensis, Rhizoplaca peltata* and *Xanthoria elegans*)

Figure 2 *trans*-α-Methylene-γ-butyrolactones

Chiral hydroxy esters are important versatile building blocks in asymmetric synthesis. For instance, γ- and δ-hydroxy acid derivatives can be easily transformed

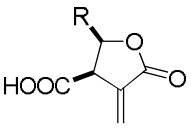
into the corresponding lactones which are present in variety of natural products. In addition, lactones are important building blocks for the synthesis of natural products such as alkaloids and terpenoids and continue to attract considerable attention due to their interesting pharmacological activities.[4] Disubstituted α-methylene-γ-butyrolactones are noted for their biological activities, *e.g.* antibacterial, antifungal, antitumor, and in certain cases, growth regulating agents.[5,6,7] The example of γ-butyrolactones 3–9 are depicted in Figures 2-4.[1,5,6,8-15]



5

a : R = *n*-$C_{13}H_{27}$; *allo*-Protolichesterinic acid[1]
(isolated from *Cetraria ericetorum and C. islandica*)

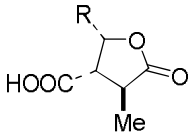
b : R = $CH_3CO(CH_2)_{13}$; *allo*-Pertusaric acid[5]
(*R*)
c : R = $CH_3CH(OH)(CH_2)_{13}$; *allo*-Murolic acid[11,12]
(isolated from *Leptogium saturnium, Parmelia camtschadalis* and *Xanthoria elegans*)
(*S*)
d : R = $CH_3CH(OH)(CH_2)_{13}$; *allo*-Dihydropertusaric acid[1]



6

R = $C_{12}H_{25}$; *allo*-Protolichesterolic acid[6]

Figure 3 *cis*-α-Methylene-γ-butyrolactones

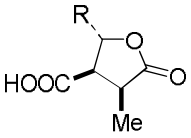


7

a : R = *n*-C_5H_{11} ; Phaseolinic acid[8]
(metabolite of a fungus, *Macrophomina phaseolina*)

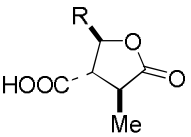
b : R = *n*-$C_{13}H_{27}$; Nephromopsinic acid[1]
(isolated from *Nephromopsis stracheyi, Cetraria strocheyi, ecocarpisma* Hue and lichen)

c : R = $CH_3CO(CH_2)_{13}$; Pertusarinic acid[15]
(isolated from *Punctelia microsticta*)



8

R = n-$C_{13}H_{27}$; Dihydroprotolichesterinic acid[15]
(isolated from *Pertusaria albescens*)



9

a : R = *n*-$C_{11}H_{23}$; Nephrosteranic acid[1]
(isolated from *Nephromopsis endocrocea* and lichen)

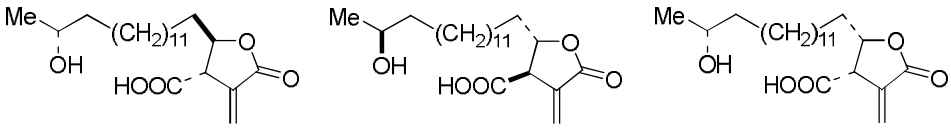
b : R = n-$C_{27}H_{55}$; Roccellaric acid[1]
(isolated by Hesse from the chilenic lichen species Roccellaria mollis (HAMPE)ZAHLBR)

c : R = $CH_3CH(OH)(CH_2)_{13}$; Neodihydromurolic acid[1]
(isolated from *L. muralis, L. melanopthalma* and *L. rubina*)

Figure 4 α-Methyl-γ-butyrolactones

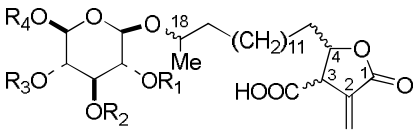
1.2 Literature reviews

Rezanka and Guschina[11,12,16] succeeded to isolate glycoside compounds from an extract of Central Asian lichens as shown in Table 1. New glycosides bearing murolic acid (4b), protoconstipatic acid (3d) and *allo*-murolic acid (5c) (Figure 5), as the aglycones and the oligosaccharide moiety lingked at C-18 made up of five sugars (xylose, rhamnose, glucose, arabinose and apiose) 10a–q and 11a–j, are as shown in Figure 6.



4b **3d** **5c**

Figure 5 Murolic acid, protoconstipatic acid and *allo*-murolic acid



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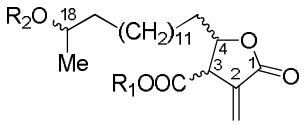


11

a $R_1 = R_2 = R_3 = R_4 = H$ 3*S*, 4*R*, 18*R*

b $R_1 = R_2 = R_3 = R_4 = H$ 3*S*, 4*S*, 18*S*

c $R_1 = R_2 = R_3 = H$, R_4 = Xyl 3*S*, 4*S*, 18*R*

d $R_1 = R_2 = R_3 = H$, R_4 = Rha 3*S*, 4*S*, 18*R*

e $R_1 = R_2 = R_4 = H$, R_3 = Rha 3*S*, 4*R*, 18*R*

f $R_1 = R_2 = R_3 = H$, R_4 = Ara 3*S*, 4*S*, 18*R*

g $R_1 = R_2 = R_3 = H$, R_4 = Api 3*S*, 4*S*, 18*R*

h $R_1 = R_2 = R_4 = H$, R_3 = Api 3*S*, 4*S*, 18*R*

i R_1 = Api, $R_2 = R_3 = R_4 = H$ 3*S*, 4*S*, 18*R*

j R_1 = Glc, $R_2 = R_3 = R_4 = H$ 3*S*, 4*S*, 18*R*

k $R_1 = R_3 = R_4 = H$, R_2 = Glc 3*S*, 4*S*, 18*R*

l $R_1 = R_2 = R_3 = H$, R_4 = Glc 3*R*, 4*S*, 18*S*

m $R_1 = R_2$ = Glc, $R_3 = R_4 = H$ 3*S*, 4*S*, 18*R*

n $R_1 = R_4$ = Glc, $R_2 = R_3 = H$ 3*S*, 4*S*, 18*R*

o R_1 = Glc"2-1Glc"', $R_2 = R_3 = R_4 = H$ 3*S*, 4*S*, 18*R*

p $R_2 = R_4$ = Glc, $R_1 = R_3 = H$ 3*S*, 4*R*, 18*R*

q R_1 = Glc"6-1Glc"", R_2 = Glc, $R_3 = R_4 = H$ 3*R*, 4*S*, 18*S*

a $R_1 = R_2 = H$ 2*R*, 3*S*, 4*S*, 18*R*

b $R_1 = R_2 = H$ 2*S*, 3*R*, 4*S*, 18*S*

c $R_1 = R_2 = H$ 2*R*, 3*R*, 4*S*, 18*S*

d R_1 = Rha, $R_2 = H$ 2*R*, 3*S*, 4*S*, 18*R*

e R1 = Glc, $R_2 = H$ 2*S*, 3*R*, 4*S*, 18*S*

f R_1 = Glc, $R_2 = H$ 2*R*, 3*R*, 4*S*, 18*S*

g R_1 = Rha, R_2 = Glc 2*R*, 3*S*, 4*S*, 18*R*

h R_1 = Glc, R_2 = Xyl 2*S*, 3*R*, 4*S*, 18*S*

i R_1 = Glc, R_2 = Rha 2*R*, 3*R*, 4*S*, 18*S*

j R_1 = Glc, R_2 = Glc 2*R*, 3*R*, 4*S*, 18*S*

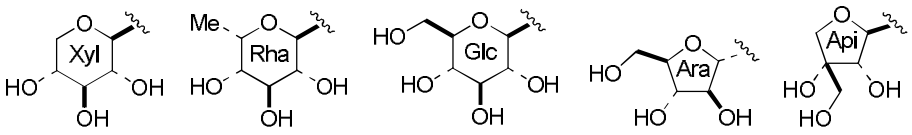


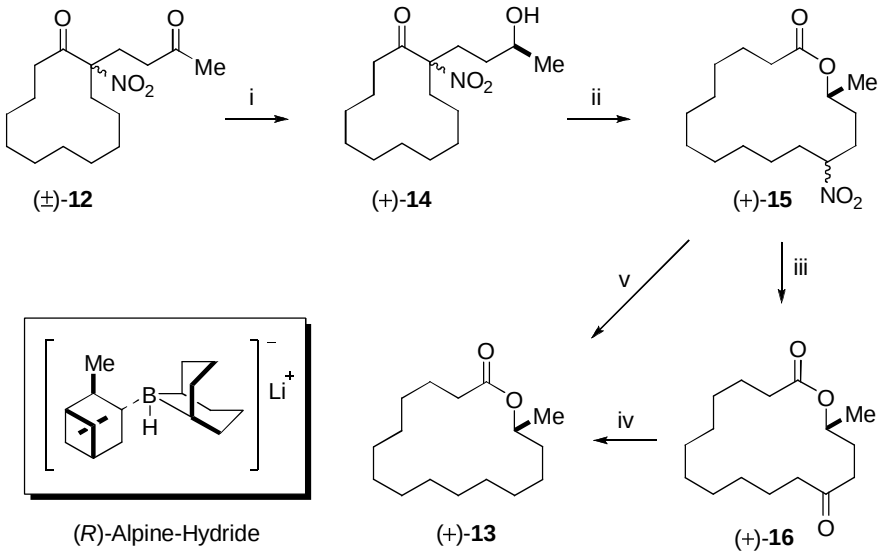
Figure 6 New glycoside compounds

Table 1 Occurrence of acids and their derivatives from lichens of Tian Shan mountains

Name of lichen	Name of compounds																													
	4	**3**	**5**	**10**																	**11**									
	b	**d**	**c**	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**	**m**	**n**	**o**	**p**	**q**	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**
Acarospora gobiensis	/	/	-	/	-	-	-	-	-	-	-	/	-	-	-	-	-	-	-	/	/	/	-	/	-	-	-	-	-	-
Cladonia furcata	-	/	-	-	/	-	-	/	/	-	/	-	/	-	-	/	/	-	/	-	-	/	-	-	/	-	-	/	/	-
Lecanora fructulosa	-	/	-	-	/	-	-	/	/	-	/	-	/	-	-	/	/	-	/	-	-	/	-	-	/	-	-	/	/	-
Leptogium saturnium	-	-	/	-	-	/	/	-	-	/	-	-	-	/	/	-	-	/	-	-	-	-	/	-	-	/	/	-	-	/
Parmelia camtschadalis	-	-	/	-	-	-	-	-	-	-	-	-	-	/	/	-	-	/	-	-	-	-	-	-	-	-	-	-	-	-
P. tinctina	-	-	-	-	-	-	-	-	-	-	-	-	/	-	-	/	/	-	/	-	-	-	-	-	-	-	-	-	-	-
Peltigera canina	-	-	/	-	-	/	/	-	-	-	-	-	/	-	-	/	/	-	/	-	-	-	/	-	-	/	/	-	-	/
Rhizoplaca peltata	/	-	-	-	-	-	-	-	-	/	-	-	-	-	-	-	-	-	-	/	-	/	-	-	/	-	-	/	/	-
Xanthoparmelia camtschadalis	-	/	-	-	/	-	-	/	/	-	/	-	-	-	-	-	-	-	-	-	-	/	-	-	/	-	-	/	/	-
X. tinctina	-	/	-	-	/	-	-	/	/	-	/	-	-	-	-	-	-	-	-	-	/	-	-	/	-	-	-	-	-	-
Xanthoria elegans	/	-	-	/	-	-	-	-	-	-	-	/	-	/	/	-	-	/	-	-	/	-	-	/	-	-	-	-	/	-

Note - ; *Not found,* / ; *Found*

In 1989, Stanchev and Hesse[17] reported the reduction of the carbonyl group in the side chain of 4-(1-nitro-2-oxocyclododecyl)butan-2-one [(±)-12] with organoboron complexs to give 15-hexadecanolide (13). The synthetic routes and conditions were as detailed in Scheme 1 and Table 2 respectively.



Scheme 1 Synthesis of 15-hexadecanolide (13) from 4-(1-nitro-2-oxocyclododecyl) butan-2-one [(±)-12]

Table 2 Chemical yields and enantiomeric excess of compound 15

Entry[a]	Reducing agents	Product	Yields (%)[b]	ee form $[\alpha]_D^c$	ee from ^{1}H NMR[d]	Configuration At C(15)
1	$NaBH_4$	(±)-15	88	-	-	-
2	(*S*)-Alpine-Hydride	(+)-15	82	15	15.5	(*S*)
3	(*R*)-Alpine-Hydride	(–)-15	72	24	18.8	(*R*)

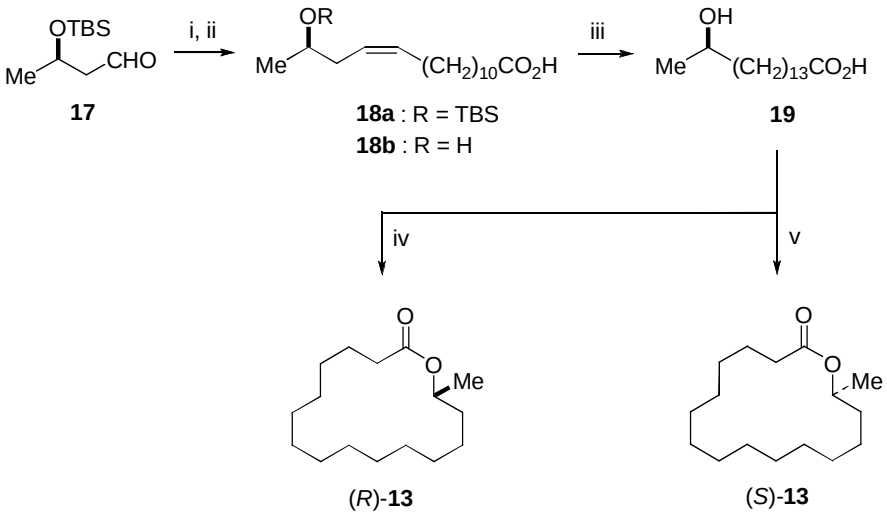
[a]) 1 : (i) $NaBH_4$, MeOH, 4 h, 0 °C, 91%; (ii) Bu_4NF, THF, 15 min, 20 °C, 97%.
2 : (i) and (ii) (*S*)-Alpine-Hydride, THF, 2 h, –78 °C, $HOCH_2CH_2NH_2$, 1 h, 20 °C, 82%
(iii) NaOMe, MeOH, 15 min, 20 °C, NaOAc, $TiCl_3$, 1.5 h, 20 °C, 85%;
(iv) NH_2NHTs, MeOH, 1 h, reflux, $(Ph_3P)_2CuBH_4$, $CHCl_3$, 4 h, reflux, 78%.
3 : (i) and (ii) (*R*)-Alpine-Hydride, THF, 2 h, –78 °C, $HOCH_2CH_2NH_2$, 1 h, 20 °C, 72 %
(v) Bu_3SnH, AIBN, toluene, 40 min, reflux, 47%.

[b]) In some experiments, the reaction product 14 was accompanied by the rearrangement product 15. To compare chemical yields, all pure products and product mixtures were rearranged to 15.

[c]) Because of its diastereomeric nature, (+)-15 was converted to (+)-13; thus, the ee values refer to (+)-13. The %-ee values were determined by comparison of the $[\alpha]_D$ values of the product and those of (–)-13.

[d]) The enantiomeric purities of 13 were determined by ^{1}H NMR measurements (400 MHz, $CDCl_3$) of the CH_3-C(15) signal, using [Eu(hfc)$_3$] as chiral shift reagent.

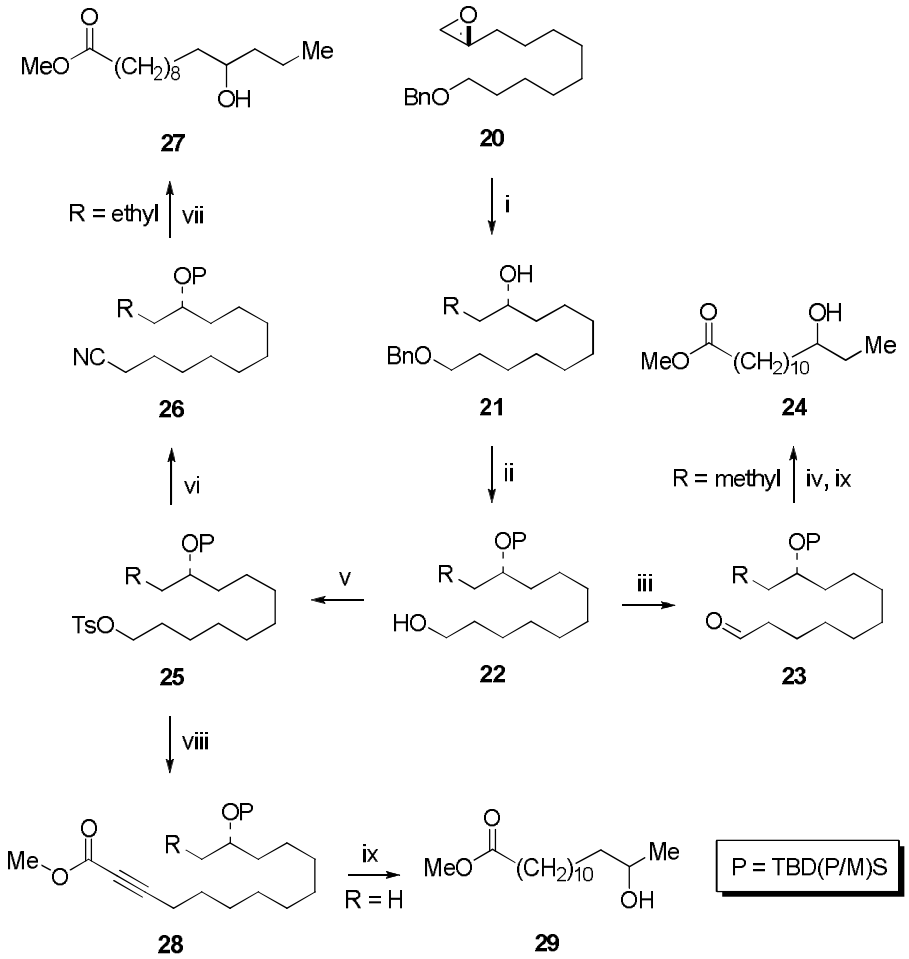
In 1998, Kuwahara *et al*.[18] synthesized 15-methylcyclopentadecalactone or 15-hexadecanolide (13), a sex pheromone component of the stink bug, *Piezodorus hybneri* by using the Yamaguchi or Mitsunobu macrolactonization reaction (Scheme 2).



Reagents and conditions: (i) $Ph_3PCH(CH_2)_{10}CO_2K$, THF-HMPA; (ii) HF, CH_3CN, 46%; (iii) H_2, Pd-C, EtOH; (iv) 2,4,6-trichlorobenzoyl chloride, DMAP, toluene; (v) Ph_3P, diethyl azodicarboxylate, ether.

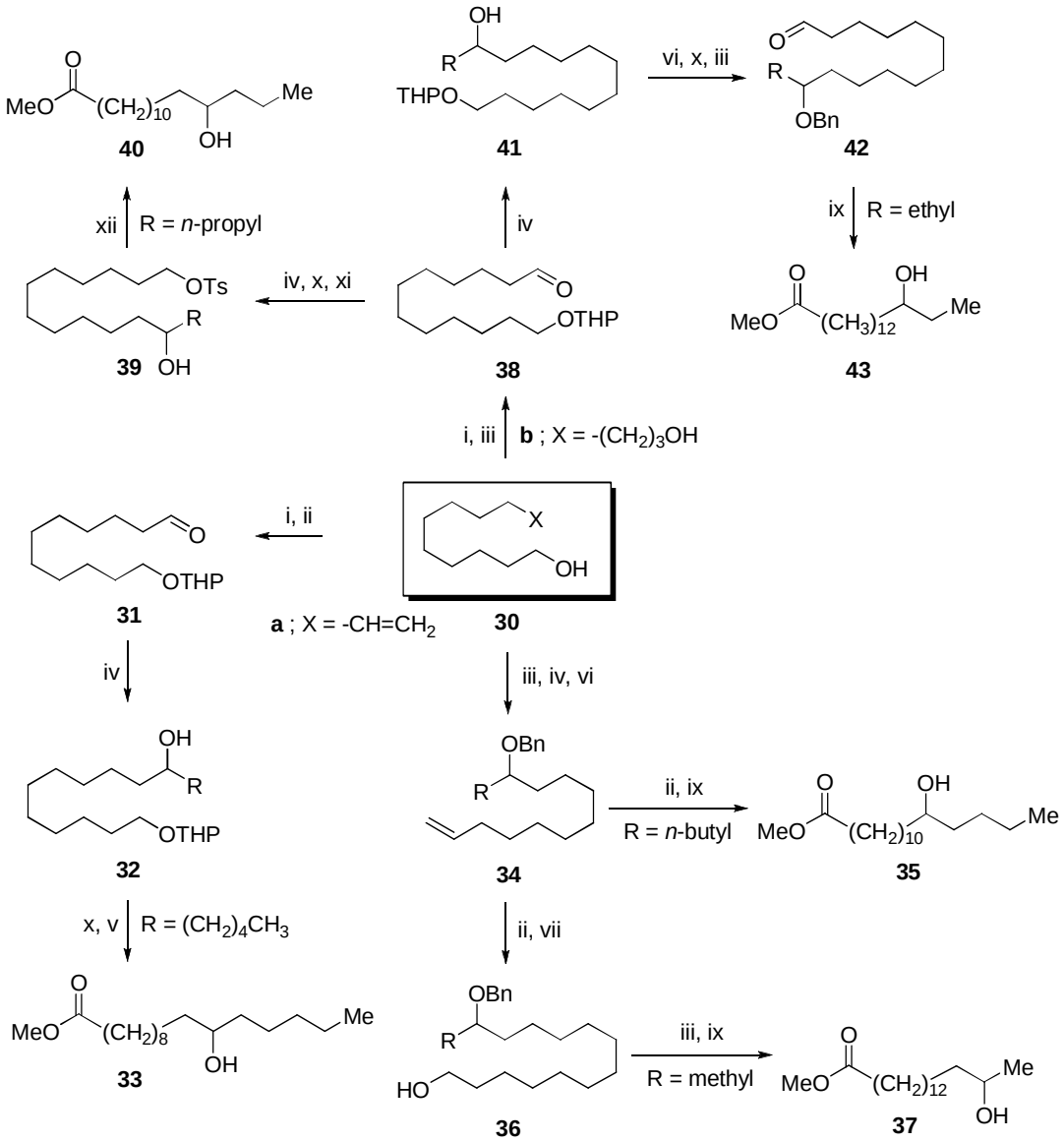
Scheme 2 Syntheses of (*R*)- and (*S*)-15-hexadecanolides (13)

Cryle, Matovic and Voss (2003)[19] reported the synthesis of 11-, 12-, and 13-hydroxy C_{14} fatty acids ester from epoxide 20 and 11- to 15-hydroxy C_{16} fatty acids ester from terminally difunctionalized compounds, undec-10-en-1-ol (30a) and 1,12-dodecandiol (30b) (Schemes 3 and 4).



Reagents and conditions: (i) LAH, THF, 0 °C, 90%, or RMgX, THF, –10 °C, 79%; (ii) (a) TBD(P/M)SCl, imidazole, MeCN, (b) H_2, Pd-C, hexane, 80%; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, TEA, –78 °C, 75%; (iv) Ph_3PCHCO_2Me, CH_2Cl_2, Δ, 94%; (v) TsCl, DABCO, CH_2Cl_2, 92%; (vi) NaCN, DMF, Δ, 80%; (vii) (a) HCl-MeOH, 59%; (viii) Propiolic acid, *n*-BuLi, HMPA, THF, 0 °C, 71%; (ix) (a) H_2, Pd-C, hexane, (b) TBAF, THF, 0 °C, 74%.

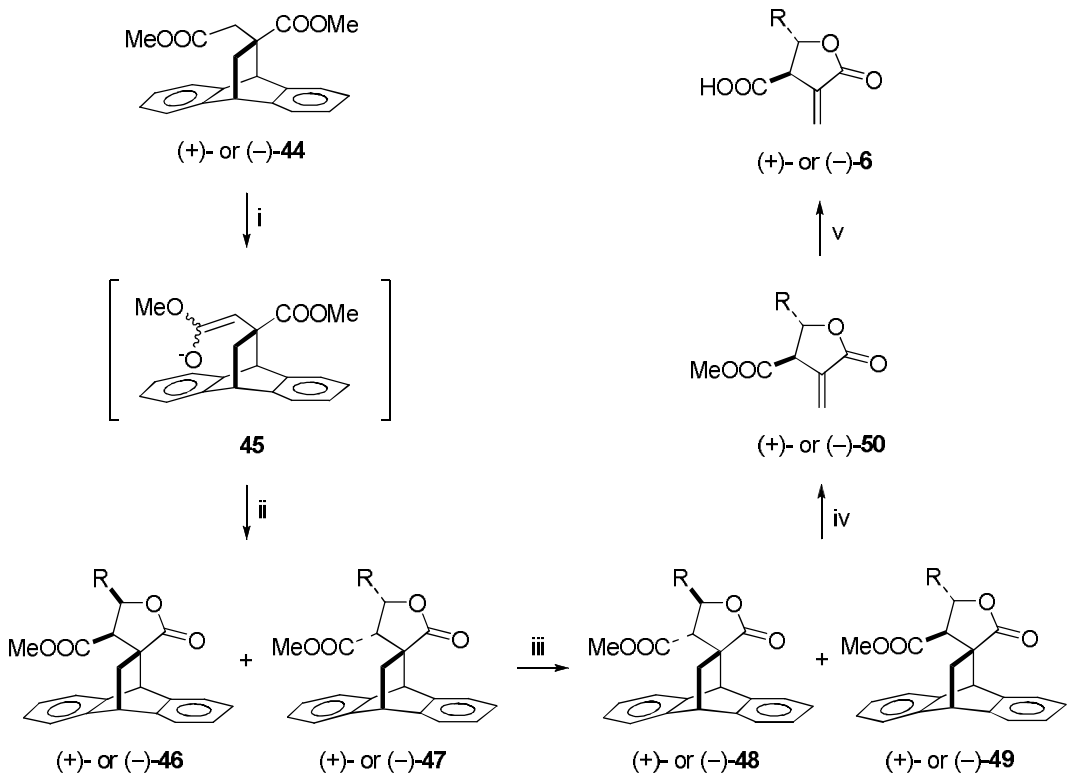
Scheme 3 Syntheses of 11-, 12-, and 13-hydroxy C_{14} fatty acids ester



Reagents and conditions: (i) dihydropyran, H^+, CH_2Cl_2, 68%; (ii) (a) BH_3.DMS, CH_2Cl_2, H_2O_2, Δ, (b) PCC, NaOAc, CH_2Cl_2, 67%; (iii) PCC, CH_2Cl_2, 90%; (iv) RMgBr, Et_2O, –40 °C, 70%; (v) (a) CrO_3-H_2SO_4, acetone, (b) CH_2N_2, Et_2O, (c) $NaBH_4$, MeOH, 0 °C, 45%; (vi) NaH, BnBr, *n*-$Bu_4N^+I^-$, THF, 94%; (vii) (a) Ph_3PCHCO_2Me, CH_2Cl_2, Δ, (b) LAH, THF, 0 °C, 63%; (viii) O_3, CH_2Cl_2, –78 °C, DMSO, 100%; (ix) (a) Ph_3PCHCO_2Me, CH_2Cl_2, Δ, (b) H_2, Pd-C, hexane, 64%; (x) H^+, MeOH, 94%; (xi) TsCl, pyridine, 0 °C, 67%; (xii) (a) NaCN, DMF, Δ, (b) HCl-MeOH, 57%.

Scheme 4 Syntheses of 11- to 15-hydroxy C_{16} fatty acids ester

Kongsaeree *et al.* (2001)[20] reported that both enantiomers of methylenolactocin (6a), nephrosterinic acid (6b) and protolichesterinic acid (6c) were synthesized *via* tandem aldol-lactonization reactions of aldehydes and the optically active dimethyl itaconate-anthracene adduct (44) (Scheme 5).

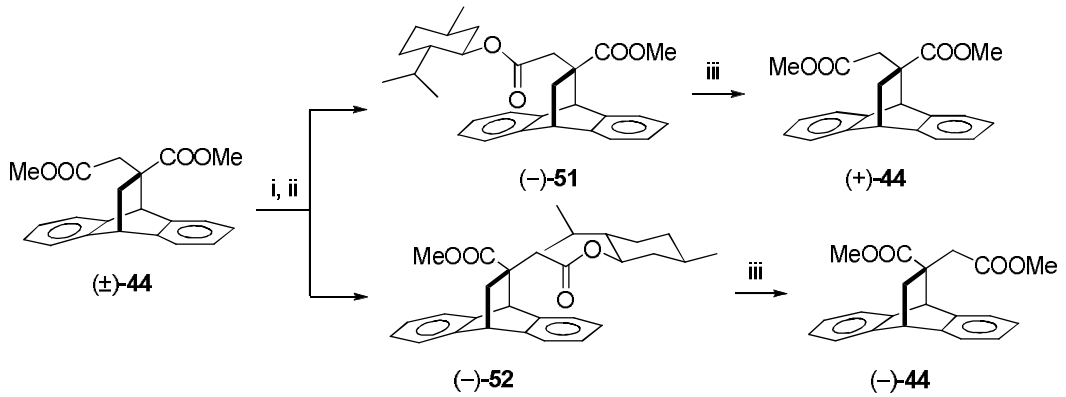


R = **a**: *n*-C_5H_{11} ; **b**: *n*-$C_{11}H_{23}$ and **c**: *n*-$C_{13}H_{27}$

Reagents and conditions: (i) (a) 1.2 equiv LDA, THF, –78 to 0 °C 2 h; (ii) (a) 1.2 equiv RCHO, 0 °C to rt 3 h, (b) aq. NH_4Cl, 30% HCl; (iii) 0.5 equiv NaOMe, THF:MeOH (2:1), rt 6 days; (iv) FVP; (v) 2-butanone, 6 N HCl, reflux 2 h.

Scheme 5 Syntheses of methylenolactocin (6a), nephrosterinic acid (6b) and protolichesterinic acid (6c)

Scheme 6 presented synthetic route for separation of optically active dimethyl itaconate-anthracene adducts (44) employing (–)-menthol as a chiral auxillary agent.

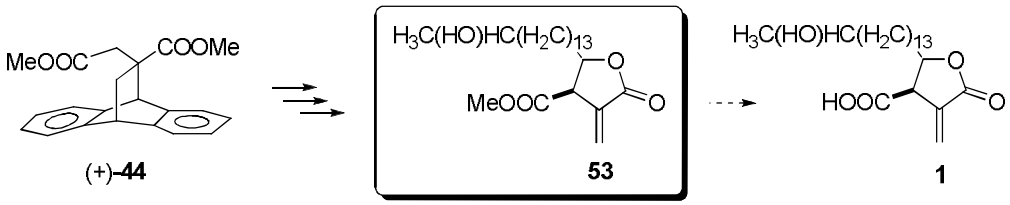


Reagents and conditions: (i) 1.3 equiv. KOH, MeOH:H_2O (2:1), reflux 2 h, 97%; (ii) (a) 5.0 equiv. $SOCl_2$, DMF (cat.), N_2, reflux 2 h, (b) 1.3 equiv. (–)-(1*R*,2*S*,5*R*)-menthol, 1.3 equiv. NEt_3, benzene, reflux 2 h [(–)-51, 34%; (–)-52, 34%]; (iii) excess anhydrous MeOH, H_2SO_4 (cat.), reflux 6 days [(+)-44, 95%; (–)-44, 89%].

Scheme 6 Separation of optically active dimethyl itaconate-anthracene adducts

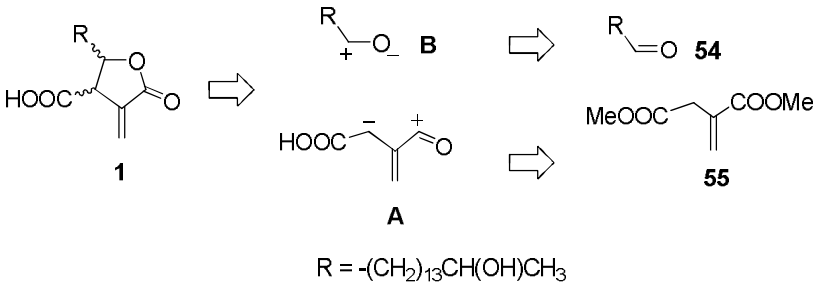
1.3 Principle and research objectives

The synthesis of γ-butyrolactones derivatives has attached considerable attention over the years because of their wide occurrence in bioactive natural product.[21] In this thesis, we are interested in synthetic methodology of protoconstipatic acid methyl ester and its epimer employing the readily available dimethyl itaconate-anthracene adduct in enantiomerically pure forms, [(+)-(11S)-44], as building blocks (Scheme 7).



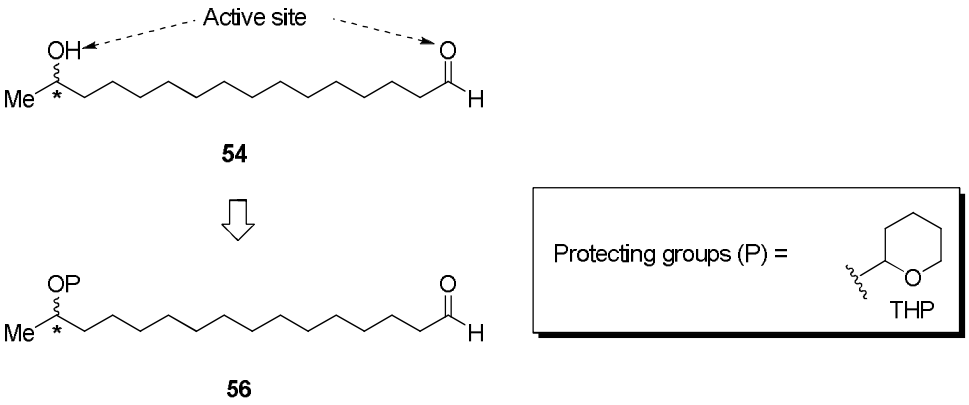
Scheme 7 Synthesis of protoconstipatic acid methyl ester and its epimer (53)

From considerably method for retrosynthesis of α-methylene-γ-butyrolactones 1, it was found that compound 1 can be disconnected to synthon A: dimethyl itaconate (55) and synthon B: aldehyde 54 (Scheme 8). It is well-known that dimethyl itaconate anion was quickly polymerized and therefore, it is necessary to protect the reactive double bond of dimethyl itaconate (55) in the form of anthracene adduct 44 which could be obtained by the Diels-Alder reaction.



Scheme 8 Retrosynthesis of α-methylene-γ-butyrolactones 1

The hydroxyl group in 15-Hydroxypentanaldehyde (54) bearing two active difunctional groupswas converted to the corresponding chiral ether group 56 for the next reaction as shown in Scheme 9.



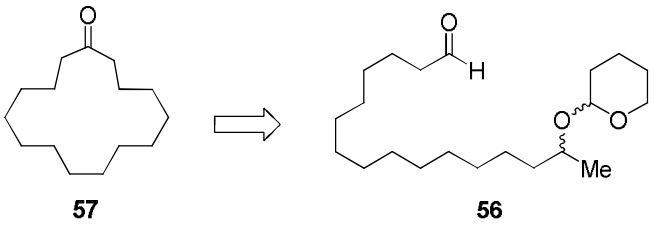
Scheme 9 Protecting of hydroxy group with 3,4-dihydro-2*H*-pyran

In this thesis, we have focused on

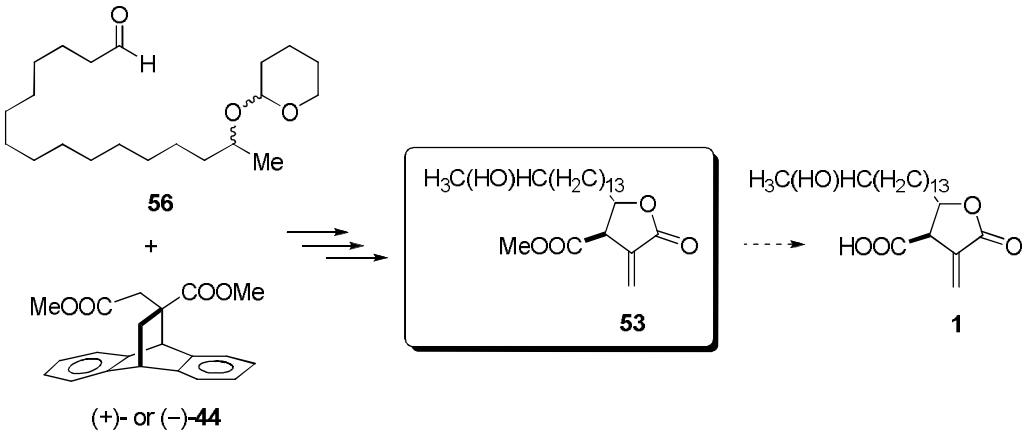
1) synthesis of the chiral ether aldehyde 56 from cyclopentadecanone (57) as shown in Scheme 10

2) synthesis of dimethyl itaconate-anthracene adduct in optically active form [(+)-44]

3) synthesis of protoconstipatic acid methyl ester (53) employing the reaction of pure dimethyl itaconate-anthracene adduct [(+)-44] with the chiral ether aldehyde 56 as shown in Scheme 11.



Scheme 10 Synthesis of the chiral ether aldehyde 56 from cyclopentadecanone (57)



Scheme 11 Synthesis of protoconstipatic acid methyl ester (53) and its epimer

CHAPTER 2
EXPERIMENTAL

2.1 Chemicals, apparatus and instruments

2.1.1 Chemicals

The chemicals used in this research project were as listed in Table 3.

Table 3 Chemicals used in this research

Chemical	Molecular	Molecular weight	Grade	Supplier
Acetone*	C_3H_6O	58.08	commercial	-
Ammonium chloride	NH_4Cl	53.49	≥ 99.0%	Scharlau
Anthracene	$C_{14}H_{10}$	178.24	≥ 95%	Fluka
Benzophenone	$C_{13}H_{10}O$	182.22	≥ 99.0%	Fluka
n-Butyllithium**	C_4H_9Li	64.06	-	Acros
Calcium hydride	CaH_2	42.10	≥ 97.0%	Fluka
Celite 545	-	-	-	Fluka
Chloroform***	$CHCl_3$	119.38	99.8%	Ajex
Chloroform-d_1	$CDCl_3$	120.38	≥ 99.8%	Wilmad
3-Chloroperbenzoic acid	$C_7H_5ClO_3$	172.57	-	Fluka
Cyclopentadecanone	$C_{15}H_{28}O$	224.39	≥ 97.0%	Fluka
Dichloromethane*	CH_2Cl_2	84.93	commercial	-
3,4-Dihydro-2*H*-pyran	C_5H_8O	84.12	97%	Fluka
N,*N*-dimethyl formamide***	C_3H_7NO	73.09	99.8%	CarloErba
Dimethyl itaconate	$C_7H_{10}O_4$	158.16	≥ 97.0%	Fluka
Dimethyl sulphoxide****	C_2H_6OS	78.13	99.5%	Lab-Scan
Ethyl acetate*	$C_4H_8O_2$	88.11	commercial	-
Hexane*	C_6H_{14}	86.18	commercial	-
Iodine	I_2	126.90	≥ 99.8%	AJAX
Iodomethane	CH_3I	141.94	≥ 99.5%	Fluka
Lithium aluminium hydride	$LiAlH_4$	37.95	≥ 95%	Acros

Table 3 Chemicals used in this research (continued)

Chemical	Molecular	Molecular weight	Grade	Supplier
Magnesium sulphate anhydrous	$MgSO_4$	120.37	$\geq$ 98.0%	Fluka
(–)-Menthol	$C_{10}H_{20}O$	156.27	$\geq$ 99%	Fluka
Methanol*	CH_4O	32.04	commercial	-
Montmorillonite K10	-	-	-	Fluka
Oxalyl chloride*	$C_2O_2Cl_2$	126.93	96%	Fluka
Silica gel 60, GE0030	-	-	-	Scharlau
Silica gel 60 PF_{254}	-	-	-	Merck
Sodium bicarbonate	$NaHCO_3$	84.01	99 - 101%	BDH
Sodium hydride	NaH	24.00	Moistened with oil, 55 - 60%	Fluka
Sodium metal	Na	22.99	-	May & Baker Ltd
Sulfuric acid	H_2SO_4	98.08	96%	CarloErba
Thionyl chloride	$SOCl_2$	117.90		BDH
Tetrahydrofuran*****	C_4H_8O	72.11	$\geq$ 99.5 %	Merck
Triethylamine***	$C_6H_{15}N$	101.19	$\geq$ 99%	BDH
Xylene*	C_8H_{10}	C_8H_{10}	-	Fluka

Note * Simple distillation

** Molarity of *n*-butyllithium was determined by titration according to the 2,5-dimethoxybenzyl alcohol method

*** Refluxed over CaH_2 for 1 h followed by simple distillation

**** Distilled under reduce pressure

***** Distilled from sodium / benzophenone under nitrogen atmosphere

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2.1.2 Apparatus and instruments

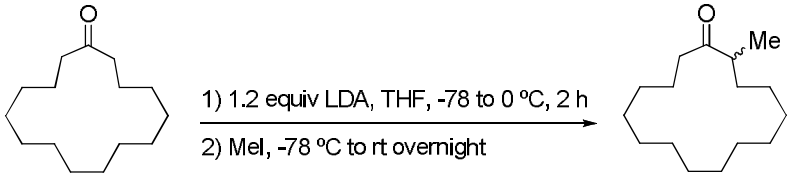
The apparatus and instruments used were as listed in Table 4.

Table 4 Apparatus and instruments used in this research

Apparatus and instruments	Company	Model
High vacuum pump	Edwards	Edwards 18
Infrared spectrometer (FT-IR)	Bruker	Tensor 27
Mass spectrometer (HRMS)	Waters	Micromass-Q-Tof-2^{Tm}
Melting point apparatus	SANYO	Gallenkamp
Nuclear magnetic resonance spectrometer	Bruker	-
Rotary evaporator	Büchi	R-200
UV-lamp 254	-	-
Weighing balance (2 and 4 positions)	Mettler Toledo	PG802-S and AB204-S

2.2 Synthesis of 15-(tetrahydro-2*H*-pyran-2-yloxy)hexadecanal [(±)-56]

2.2.1 2-Methylcyclopentadecanone [(±)-58]



57 **(±)-58**

To a 250 ml round-bottomed flask equipped with a magnetic stirrer was fitted with a three-way stopcock with a septum cap and nitrogen inlet was added THF (40 ml) and dry diisopropylamine (9.1 ml, 64.33 mmol) *via* syringes. The mixture was cooled down to –78 °C followed by addition of *n*-butyllithium (38.3 ml, 1.4 N in hexane, 53.61 mmol). The resulting solution was left stirring at 0 °C for 1 h. Then, a solution of cyclopentadecanone (57) (10.0246 g, 44.68 mmol) in THF (40 ml) was introduced to the LDA solution at –78 °C. After stirring at 0 °C for 2 h, the reaction mixture was cooled to –78 °C and iodomethane (27.87 ml, 446.76 mmol) was added. The reaction mixture was left stirring at room temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride solution at 0 °C followed by extraction several times with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered, and evaporated to dryness.

The crude product was purified by flash column chromatography on silica gel with elution of EtOAc : hexane = 0.3 : 9.7 to give α-methyl ketone (±)-58, *2-methylcyclopentadecanone* in 91% yield (9.6922 g) and 100% conversion from the starting material.

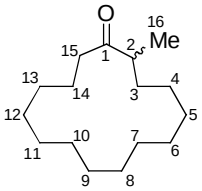


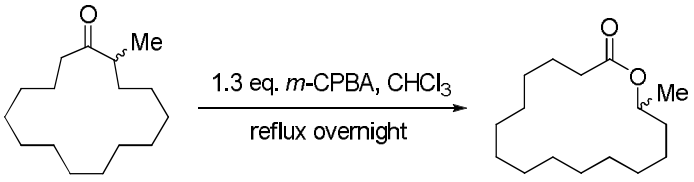
Table 5 Data of compound (±)-58

Physical property : Colorless oil	
IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
2855, 2926	-CH_2-, -CH_3 stretching
1698	C=O stretching of ketone
1450	-CH_2-, -CH_3 bending
1368	-CH_3 bending

Table 5 Data of compound (±)-58 (continued)

^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
1.04	3H, *d* (*J* = 6.9 Hz), CH_3-16
1.17-1.78	24H, *m*, CH_2-3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
2.43	2H, *m*, CH_2-15
2.60	1H, *m*, CH-2
^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of carbon
16.72	CH_3-16
22.74, 26.12, 26.27, 26.29, 26.34, 26.46, 26.63, 26.91, 27.29, 27.47, 33.04	CH_2-3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
40.50	CH_2-15
45.98	CH-2
215.20	C=O-1
Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{16}H_{30}O$	238.2297 (M^+)
Lock mass of $C_{12}H_{14}N_4O_4SNa$	333.0633 $(M+Na)^+$
Calc. for $C_{16}H_{30}ONa$	261.2194 $(M+Na)^+$
Found for $C_{16}H_{30}ONa$	261.2192 $(M+Na)^+$

2.2.2 15-Methylhexadecalactone [(±)-13]



(±)-**58** (±)-**13**

A mixture of compound (±)-58 (3.3410 g, 14.01 mmol) and *m*-chloroperbenzoic acid (4.4906 g, 18.22 mol) in anhydrous chloroform (40 ml) was heated to reflux overnight. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate solution at 0 ◦C and the crude mixture was extracted several times with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered, and evaporated to dryness.

The crude product was purified by flash column chromatography on silica gel using EtOAc : hexane = 0.5 : 9.5 as eluent to give the lactone (±)-13, *15-methylhexadecalactone* in 88% yield (2.3811 g) and 76% conversion from the starting material.

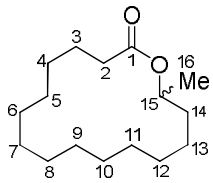


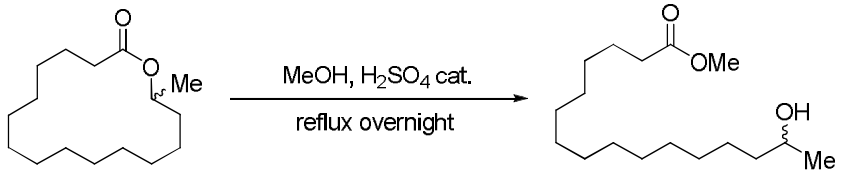
Table 6 Data of compound (±)-13

Physical property : Colorless oil	
IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
2849, 2932	$-CH_2-$, $-CH_3$ stretching
1737	C=O stretching of lactone
1462	$-CH_2-$, $-CH_3$ bending
1242	C-O stretching of lactone
^1H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
1.21	3H, *d* (*J* = 6.3 Hz), CH_3-16
1.23-1.77	24H, *m*, CH_2-3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
2.29	2H, *m*, CH_2-2
4.95	1H, *m*, CH-15
20.36	CH_3-16
24.28, 25.01, 25.62, 25.66, 25.98, 26.20, 26.60, 27.22, 27.46, 27.75, 34.83	CH_2-3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
35.86	CH_2-2
70.65	CH-15
173.76	C=O-1

Table 6 Data of compound (±)-13 (continued)

Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{16}H_{30}O_2$	254.2246 (M^+)
Lock mass of $C_{12}H_{14}N_4O_4SNa$	333.0633 $(M+Na)^+$
Calc. for $C_{16}H_{31}O_2$	255.2324 $(M + H)^+$
Found for $C_{16}H_{31}O_2$	255.2325 $(M + H)^+$

2.2.3 Methyl 15-hydroxyhexadecanoate [(±)-59]



(±)-13 (±)-59

A mixture of compound (±)-13 (0.5100 g, 2.00 mmol) and conc. sulfuric acid (2 ml) in anhydrous methanol (40 ml) was heated to reflux overnight. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate solution at 0°C and the crude mixture was extracted several times with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered, and evaporated to dryness.

The crude product was purified by flash column chromatography on silica gel using EtOAc : hexane = 0.5 : 9.5 as eluent to give hydroxyl ester (±)-59, *methyl 15-hydroxyhexadecanoate* in 90% yield (0.4102 g) and 79% conversion from the starting material.

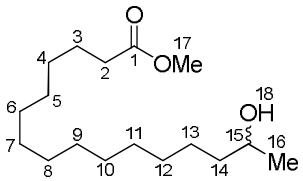


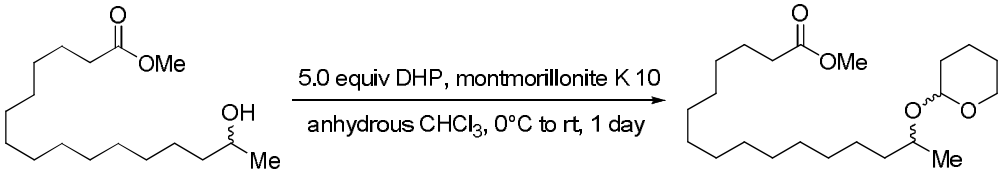
Table 7 Data of compound (±)-59

Physical properties : White crystals, m.p. 57.9-58.3 ◦C (EtoAc/Hexane)	
IR spectroscopy (KBr-pellet)	
Frequency (ν, cm^{-1})	Type of vibration
3154-3676	O-H stretching of hydroxyl
2851, 2917	$-CH_2-$, $-CH_3$ stretching
1740	C=O stretching of ester
1462	$-CH_2-$, $-CH_3$ bending

Table 7 Data of compound (±)-59 (continued)

IR spectroscopy (KBr-pellet)	
Frequency (ν, cm^{-1})	Type of vibration
1390	-CH_3 bending
1203	C-O stretching of ester
1110	C-O stretching of 2 ◦alcohol
^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
1.18	3H, *d* (*J* = 6.2 Hz), CH_3-16
1.21-1.66	24H, *m*, CH_2-3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
2.29	2H, *t* (*J* = 7.6 Hz), CH_2-2
3.66	3H, *s*, $COOCH_3$-17
3.78	1H, *m*, CH-15
23.47	CH_3-16
24.97, 25.75, 29.13, 29.23, 29.41, 29.56, 29.59, 29.62, 34.10	CH_2-3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
39.36	CH_2-2
51.42	CH_3-17
68.18	CH-15
174.35	C=O-1
Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{17}H_{34}O_3$	286.2508 (M^+)
Lock mass of $C_{12}H_{14}N_4O_4SNa$	333.0633 $(M+Na)^+$
Calc. for $C_{17}H_{34}O_3Na$	309.2406 $(M+Na)^+$
Found for $C_{17}H_{34}O_3Na$	309.2408 $(M+Na)^+$

2.2.4 Methyl 15-(tetrahydro-2*H*-pyran-2-yloxy)hexadecanoate [(±)-60]



(±)-**59** (±)-**60**

Montmorillonite K10 was added into a solution of (±)-59 (4.5536 g, 15.90 mmol), in anhydrous chloroform (200 ml) followed by 3,4-dihydro-2*H*-pyran (DHP) (7.0378 g, 79.48 mmol) at 0 ◦C over 15 min. The reaction mixture was stirred at room temperature for 1 day and then passed through Celite 545, washed with CH_2Cl_2. The organic phase was evaporated to dryness.

The crude product was purified by flash column chromatography on silica gel using EtOAc : hexane = 0.3 : 9.7 as eluent to give protected hydroxyl ester (±)-60, *methyl 15-(tetrahydro-2H-pyran-2-yloxy)hexadecanoate* in 87% yield (5.1072 g) and 100% conversion from the starting material.

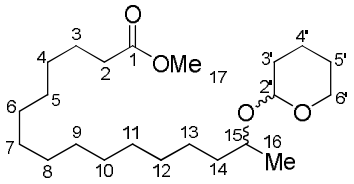


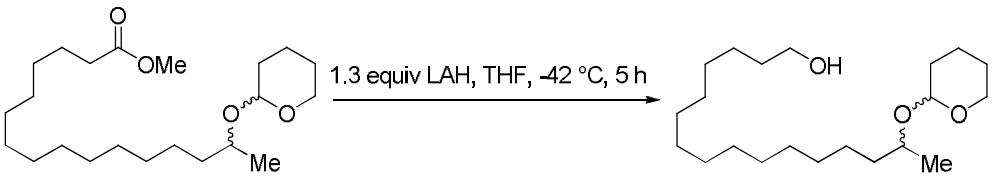
Table 8 Data of compound (±)-60

Physical property : Colorless oil	
IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
2855, 2932	$-CH_2-$, $-CH_3$ stretching
1748	C=O stretching of ester
1462	$-CH_2-$, $-CH_3$ bending
1368	$-CH_3$ bending
1077, 1203	C-O stretching of ether
1170	C-O stretching of ester
^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
1.09, 1.18 (strong peak), 1.21	3H, *d* (*J* = 6.2, 6.2, 6.1 Hz), CH_3-16
1.22-1.92	30H, *m*, CH_2-3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 3', 4', 5'
2.30	2H, *t* (*J* = 7.6 Hz), CH_2-2
3.44-3.59, 3.68-4.47	3H, *m*, CH-15, CH_2-6'
3.66	3H, *s*, $COOCH_3$-17
4.54-4.98	1H, *m*, CH-2'

Table 8 Data of compound (±)-60 (continued)

^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of carbon
23.60	CH_3-16
25.09, 25.72, 25.90, 26.02, 29.30, 29.41, 29.59, 29.77, 29.90, 29.92, 30.36, 31.41, 34.31, 36.72, 37.77	CH_2-3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 3', 4', 5'
39.59	CH_2-2
51.73	CH_3-17
62.79	CH_2-6'
68.59	CH-15
98.58	CH-2'
174.30	C=O-1
Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{22}H_{42}O_4$	370.3083 (M^+)
Lock mass of $C_{12}H_{14}N_4O_4SNa$	333.0633 $(M+Na)^+$
Calc. for $C_{22}H_{42}O_4Na$	393.2981 $(M+Na)^+$
Found for $C_{22}H_{42}O_4Na$	393.2980 $(M+Na)^+$

2.2.5 15-(Tetrahydro-2*H*-pyran-2-yloxy)hexadecan-1-ol [(±)-61]



(±)-**60** (±)-**61**

Lithium aluminium hydride (0.4307g, 10.78 mmol) in a 250 ml round-bottomed flask equipped with a magnetic stirrer and fitted with a three-way stopcock with a septum cap and nitrogen inlet was added THF (120 ml). To a stirred –42 °C solution, a solution of (±)-60 (2.9989 g, 8.09 mmol) in THF (120 ml) was added and left stirring at –42 °C for an additional 5 h. The reaction mixture was quenched with aqueous acetone (200 ml) at –78 °C followed by water and then the reaction was neutralized with dilute HCl and then passed through Celite 545, washed with CH_2Cl_2. The crude mixture was extracted several times with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered, and evaporated to dryness.

The crude product was purified by flash column chromatography on silica gel using EtOAc : hexane = 0.5 : 9.5 as eluent to give protected hydroxyl alcohol (±)-61, *15-(tetrahydro-2H-pyran-2-yloxy)hexadecan-1-ol* in 79% yield (1.4495 g), and 69% conversion from the starting material.

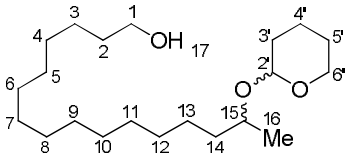


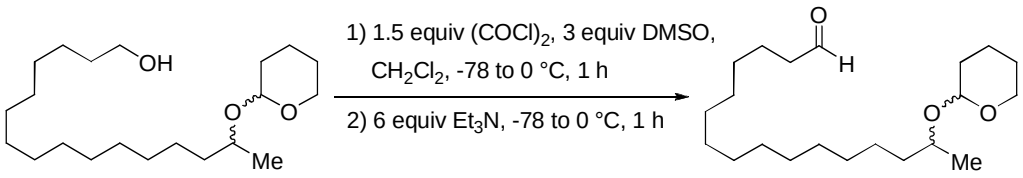
Table 9 Data of compound (±)-61

Physical property : Colorless oil	
IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
3069-3686	O-H stretching of hydroxyl
2849, 2921	$-CH_2-$, $-CH_3$ stretching
1462	$-CH_2-$, $-CH_3$ bending
1368	$-CH_3$ bending
1198	C-O stretching of ester
1082, 1132	C-O stretching of ether
1022	C-O stretching of 1°alcohol
^1H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
1.09, 1.18 (strong peak), 1.21	3H, *d* (*J* = 6.1, 6.2, 6.3 Hz), CH_3-16
1.23-1.90	32H, *m*, CH_2-2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 3', 4', 5'
3.33-3.60, 3.67-3.95	3H, *m*, CH-15, CH_2-6'
3.63	2H, *t* (*J* = 6.6 Hz), CH_2-1
4.54-4.73	1H, *m*, CH-2'
^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of carbon
23.47	CH_3-16
25.49, 25.57, 25.72, 25.76, 26.22, 29.40, 29.47, 29.60, 29.62, 29.74, 30.77, 32.79, 39.36, 67.70	CH_2-2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 3', 4', 5'
62.33	CH_2-6'
63.08	CH_2-1

Table 9 Data of compound (±)-61 (continued)

^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of carbon
68.19	CH-15
98.83	CH-2'
Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{21}H_{42}O_3$	342.3134 (M^+)
Lock mass of $C_{12}H_{14}N_4O_4SNa$	333.0633 $(M+Na)^+$
Calc. for $C_{21}H_{42}O_3Na$	365.3032 $(M+Na)^+$
Found for $C_{21}H_{42}O_3Na$	365.3032 $(M+Na)^+$

2.2.6 15-(Tetrahydro-2*H*-pyran-2-yloxy)hexadecanal [(±)-56]



(±)-**61** (±)-**56**

To a 250 ml, three necks, round-bottomed flask equipped with a magnetic stirrer and a dropping funnel was charged with dry CH_2Cl_2 (50 ml) under nitrogen atmosphere. To a stirred –78 °C solution, a solution of oxalyl chloride (2.3292 g, 17.62 mmol) in dry CH_2Cl_2 (50 ml) was added followed by a solution of dimethyl sulfoxide (2.7676 g, 35.24 mmol) in dry CH_2Cl_2 (20 ml) over 30 min. A solution of (±)-61 (4.0243 g, 11.75 mmol) in dry CH_2Cl_2 (30 ml) was added dropwise. After stirring at –78 °C for an additional 30 min, triethylamine (9.9 ml, 70.49 mmol) was added and the reaction mixture was left stirring at 0 °C for 1 h. The reaction mixture was quenched with 1 M HCl (100 ml) at 5-10 °C, passed through Celite 545, washed with CH_2Cl_2 and then extracted several times with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered, and evaporated to dryness.

The crude product was purified by flash column chromatography on silica gel using EtOAc : hexane = 0.5 : 9.5 as eluent to give the mixture of chiral ether aldehyde (±)-56, *15-(tetrahydro-2H-pyran-2-yloxy)hexadecanal* in 90% yield (3.1511 g), and 88% conversion from the starting material.

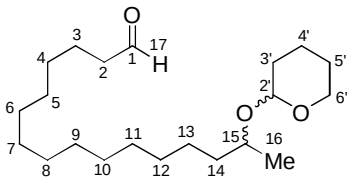


Table 10 Data of compound (±)-56

Physical property : Colorless oil	
IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
2855, 2932	-CH_2-, -CH_3 stretching
2723	C-H stretching of aldehyde
1731	C=O stretching of aldehyde
1461	-CH_2-, -CH_3 bending
1379	-CH_3 bending
1081, 1125	C-O stretching of ether
^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
1.10 (strong peak), 1.21	3H, *d* (*J* = 6.1, 6.3 Hz), CH_3-16
1.23-1.90	30H, *m*, CH_2-3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 3', 4', 5'
2.42	2H, *t* (*J* = 7.4 Hz), CH_2-2
3.42-3.98	3H, *m*, CH-15, CH_2-6'
4.60-4.74	1H, *m*, CH-2'
9.76	1H, *t* (*J* = 1.9 Hz), CHO-1
^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of carbon
21.56	CH_3-16
22.06, 25.46, 25.51, 25.57, 25.75, 25.86, 26.22, 29.14, 29.33, 29.40, 29.60, 29.74, 31.21, 36.50, 37.55	CH_2-3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 3', 4',5'
39.35	CH_2-2
62.82	CH_2-6'
71.14	CH-15
98.57	CH-2'
202.93	C=O-1

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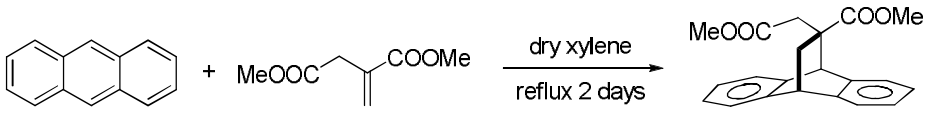
Table 10 Data of compound (±)-56 (continued)

Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{21}H_{40}O_3$	340.2977 (M^+)
Lock mass of $C_{12}H_{14}N_4O_4SNa$	333.0633 $(M+Na)^+$
Calc. for $C_{21}H_{40}O_3Na$	363.2875 $(M+Na)^+$
Found for $C_{21}H_{40}O_3Na$	363.2875 $(M+Na)^+$

2.3 Synthesis of (11*S*)-11-Carbomethoxy-11-methoxyacetyl-9,10-dihydro-9,10 ethanoanthracenes [(+)-(11*S*)-44 and (–)-(11*R*)-44]

2.3.1 11-Carbomethoxy-11-methoxyacetyl-9,10-dihydro-9,10-ethano anthracene [(±)-44]



62 **55** (±)-**44**

A mixture of anthracene (62) (1.0193 g, 5.43 mmol) and dimethyl itaconate (55) (0.5905 g, 3.62 mmol) in dry xylene (80 ml) was heated under reflux for 2 days. The crude reaction mixture was evaporated to reduced pressure to dryness and chromatographed by silica gel column. The column was eluted with hexane until no an anthracene (62) was detected, and then stripped with 30% dichloromethane in hexane. Solvent was removed under reduced pressure and the almost pure product was crystallized from a dichloromethane/hexane mixture to give the adduct (±)-44, *11-carbomethoxy-11-methoxyacetyl-9,10-dihydro-9,10-ethanoanthracene* in 98% yield (1.1939 g) and 100% conversion from the starting material.

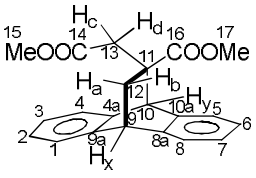


Table 11 Data of compound (±)-44

Physical properties : White crystals, m.p. 154.6-155.3 °C (CH_2Cl_2/Hexane) [lit.[1] m.p. 154-155 °C (CH_2Cl_2/Hexane)]

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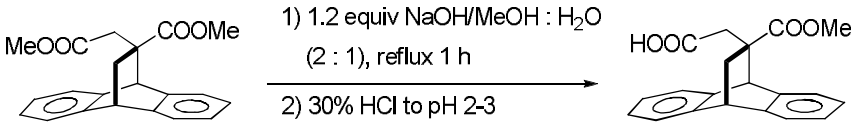
Table 11 Data of compound (±)-44 (continued)

IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
3031	C-H stretching
2949, 2981	$-CH_2-$, $-CH_3$ stretching
1741	C=O stretching of ester
1466	C=C stretching of aromatic
1427	$-CH_2-$, $-CH_3$ bending
1345	$-CH_3$ bending
1163	C-O stretching of ester
^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
1.45, 2.81, 4.32	3H, *ABX* system (*J* = 13.0, 3.0, 2.4 Hz), H_a, H_b, H_x
1.96	1H, *d* (*J* = 16.1 Hz), H_c
2.92	1H, *d* (*J* = 16.1 Hz), H_d
3.47	3H, *s*, $COOCH_3$-17
3.67	3H, s, $COOCH_3$-15
4.36	1H, s, H_y
7.03-7.32	8H, *m*, Ar-H
^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of carbon
36.66	CH_2-12
44.02	CH-9
44.29	CH_2-13
50.25	C_q-11
51.57	CH_3-17
52.13	CH_3-15
52.74	CH-10
123.25, 123.51, 124.19, 125.69, 126.43, 126.59, 139.57, 140.05, 142.79, 143.60	C aromatic-1, 2, 3, 4, 5, 6, 7, 8, 4a, 8a, 9a, 10a
171.44	C=O-14
174.80	C=O-16

Table 11 Data of compound (±)-44 (continued)

Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{21}H_{20}O_4$	336.1362 (M^+)
Lock mass of $C_{12}H_{14}N_4O_4SNa$	333.0633 $(M+Na)^+$
Calc. for $C_{21}H_{20}O_4Na$	359.1259 $(M+Na)^+$
Found for $C_{21}H_{20}O_4Na$	359.1259 $(M+Na)^+$

2.3.2 (±)-11-Carbomethoxy-11-carboxylmethyl-9,10-dihydro-9,10-ethanoanthracene [(±)-63]



(±)-**44** (±)-**63**

A solution of NaOH (0.1459 g, 3.61 mmol) in H_2O (20 ml) was added to a solution of adduct ((±)-44) (1.0121 g, 3.01 mmol) in MeOH (40 ml) and heated to reflux for 1 h. The mixture was acidified with 30% HCl (pH 2-3) followed by extraction several times with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness. Crystallization from the mixture of CH_2Cl_2 and hexane afforded the monoacid (±)-63, *(±)-11-carbomethoxy-11-carboxylmethyl-9,10-dihydro-9,10-ethanoanthracene* in 97% yield (0.9408 g) and 100% conversion from the starting material.

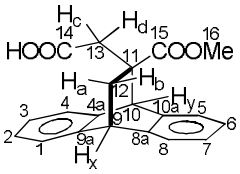


Table 12 Data of compound (±)-63

Physical properties : White crystals, m.p. 202.7-204.2 °C (CH_2Cl_2/Hexane) [lit.[1] m.p. 207-208 °C (CH_2Cl_2/Hexane)]	
IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
3130-3380	O-H stretching of acid
3026	C-H stretching
2850, 2949	$-CH_2-$, $-CH_3$ stretching
1743	C=O stretching of acid

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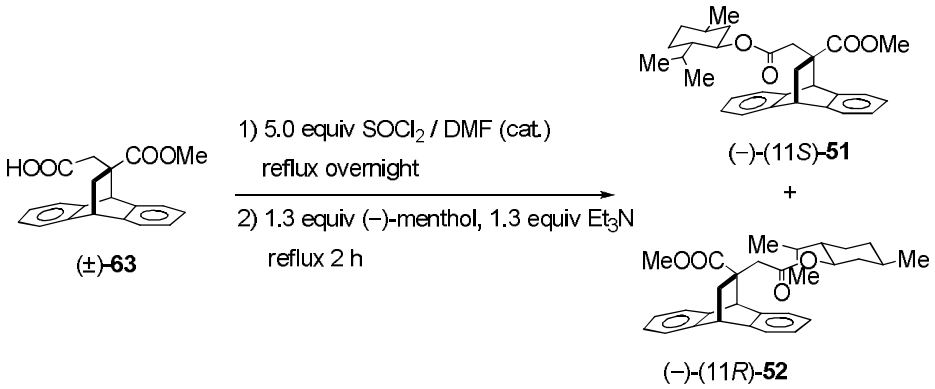
Table 12 Data of compound (±)-63 (continued)

IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
1710	C=O stretching of ester
1451	C=C stretching of aromatic
1434	$-CH_2-$, $-CH_3$ bending
1308	$-CH_3$ bending
1193	C-O stretching of ester
^1H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
1.48, 2.78, 4.30	3H, *ABX* system (J = 13.1, 3.0, 2.4 Hz), H_a, H_b, H_x
1.97	1H, *d* (J = 16.6 Hz), H_c
2.96	1H, *d* (J = 16.6 Hz), H_d
3.45	3H, s, $COOCH_3$-16
4.34	1H, s, H_y
7.03-7.30	8H, *m*, ArH-1, 2, 3, 4, 5, 6, 7, 8
^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of carbon
36.74	CH_2-12
44.02	CH-9
44.14	CH_2-13
50.01	C_q-11
52.23	CH_3-16
52.81	CH-10
123.33, 123.56, 124.20, 124.98, 125.72, 125.75, 125.78, 126.52, 126.72, 139.45, 139.93, 142.76, 143.56	C aromatic-1, 2, 3, 4, 5, 6, 7, 8, 4a, 8a, 9a, 10a
174.68	C=O-15
176.62	C=O-14

Table 12 Data of compound (±)-63 (continued)

Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{20}H_{18}O_4$	322.1205 (M^+)
Lock mass of $C_{12}H_{14}N_4O_4SNa$	333.0633 $(M+Na)^+$
Calc. for $C_{20}H_{18}O_4Na$	345.1103 $(M+Na)^+$
Found for $C_{20}H_{18}O_4Na$	345.1103 $(M+Na)^+$

2.3.3 (–)-11-Carbomethoxy-11-[(–)-menthoxyacetyl]-9,10-dihydro-9,10-ethanoanthracenes [(–)-(11*S*)-51 and (–)-(11*R*)-52]



A mixture of the monoacid (±)-63 (42.27 g, 0.13 mol), thionyl chloride (47.81 ml, 0.66 mol) and dimethyl formamide (as catalyst) was heated to reflux overnight. The solvent was removed under reduced pressure to dryness. A mixture of the crude acid chloride, triethylamine (21.93 ml, 0.16 mol), and (–)-menthol (40.98 g, 0.26 mol) in THF (150 ml) was heated to reflux for 2 h.

The reaction mixture was passed through Celite 545, diluted with H_2O and extracted with CH_2Cl_2. The combined extracts were washed with H_2O, saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel using EtOAc : hexane = 1.0 : 9.0 as eluent to give two diastereoisomers, (–)-(11*S*)-51 in 34% yield (41.09 g) and (–)-(11*R*)-52 in 34% yield (41.05 g) and 100% conversion from the starting material.

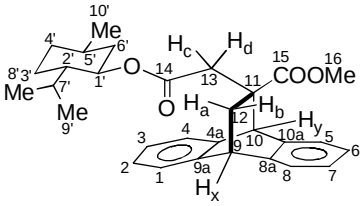


Table 13 Data of compound (–)-(11*S*)-51

Physical properties : White powder, m.p. 185.1-186.9 °C (CH_2Cl_2/Hexane) [lit.[1] m.p. 185-187 °C (CH_2Cl_2/Hexane)], $[\alpha]_D^{30}$ = –108.95° (*c* = 1.285, $CHCl_3$)	
IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
3001	C-H stretching
2863, 2951	-CH_2-, -CH_3 stretching
1727	C=O stretching of ester
1462	C=C stretching of aromatic
1362	-CH_3 bending
1175	C-O stretching of ester
^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
0.69	3H, *d* (*J* = 7.0 Hz), CH_3-10'
0.85	3H, *d* (*J* = 3.6 Hz), CH_3-8'
0.86	3H, *d* (*J* = 4.1 Hz), CH_3-9'
0.73-1.89	9H, *m*, H menthyl-2', 3', 4', 5', 6', 7'
1.47, 2.81, 4.31	3H, *ABX* system (*J* = 13.0, 3.0, 2.4 Hz), H_a, H_b, H_x
1.93	1H, *d* (*J* = 16.2 Hz), H_c
2.91	1H, *d* (*J* = 16.2 Hz), H_d
4.34	1H, *s*, H_y
4.59	1H, *ddd* (*J* = 10.9, 10.9, 4.4 Hz), H-1'
7.02-7.32	8H, *m*, ArH-1, 2, 3, 4, 5, 6, 7, 8
^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of carbon
16.05, 20.76, 21.94, 25.97, 31.32, 46.81	CH_3 menthyl-8', 9', 10', CH menthyl-2', 5', 7'
23.16, 34.12, 44.98	CH_2 menthyl-3', 4', 6'
37.00	CH_2-12
40.82	CH_2-13
44.15	CH-9
50.23	C_q-11

Table 13 Data of compound (–)-(11*S*)-51 (continued)

^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of carbon
52.05	CH_3-16
52.97	CH-10
74.60	CH-1'
118.58, 120.37, 123.32, 123.54, 124.21, 125.71, 126.45, 126.58, 139.75, 140.17, 142.82, 143.69	C aromatic-1, 2, 3, 4, 5, 6, 7, 8, 4a, 8a, 9a, 10a
170.64	C=O-14
174.74	C=O-15
Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{30}H_{36}O_4$	460.2614 (M^+)
Lock mass of $C_{32}H_{41}NO_2$	472.3215 (M^+)
Calc. for $C_{30}H_{36}O_4Na$	483.2511 $(M+Na)^+$
Found for $C_{30}H_{36}O_4Na$	483.2511 $(M+Na)^+$

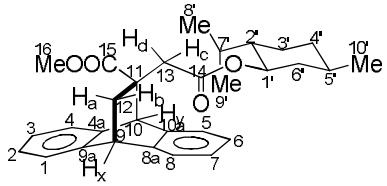


Table 14 Data of compound (–)-(11*R*)-52

Physical properties : White crystals, m.p. 101.3-102.8 °C (CH_2Cl_2/Hexane) [lit.[1] m.p. 101-103 °C (methanol)], $[\alpha]_D^{30}$ = –51.38° (c = 1.195, $CHCl_3$)	
IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
3073	C-H stretching
2858, 2957	-CH_2-, -CH_3 stretching
1716	C=O stretching of ester
1451	C=C stretching of aromatic
1363	-CH_3 bending

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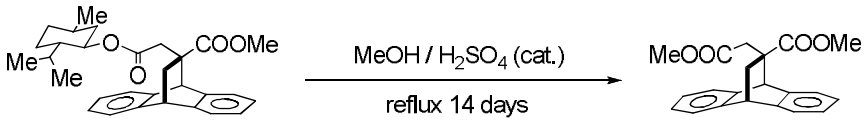
Table 14 Data of compound (–)-(11*R*)-52 (continued)

IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
1181	C-O stretching of ester
^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
0.66	3H, *d* (*J* = 7.0 Hz), CH_3-10'
0.82	3H, *d* (*J* = 7.0 Hz), CH_3-8'
0.86	3H, *d* (*J* = 6.5 Hz), CH_3-9'
0.74-1.90	9H, *m*, H menthyl-2', 3', 4', 5', 6', 7'
1.44, 2.80, 4.31	3H, *ABX* system (*J* = 13.0, 3.0, 2.4 Hz), H_a, H_b, H_x
1.93	1H, *d* (*J* = 15.8 Hz), H_c
2.95	1H, *d* (*J* = 15.8 Hz), H_d
4.34	1H, s, H_y
4.58	1H, *ddd* (*J* = 10.9, 10.9, 4.4 Hz), H-1'
7.02-7.32	8H, *m*, ArH-1, 2, 3, 4, 5, 6, 7, 8
^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of carbon
15.93, 20.77, 21.94, 25.83, 31.29, 46.75	CH_3 menthyl-8', 9', 10', CH menthyl-2', 5', 7'
23.05, 34.09, 44.87	CH_2 menthyl-3', 4', 6'
36.60	CH_2-12
40.62	CH_2-13
44.08	CH-9
50.39	C_q-11
52.01	CH_3-16
52.97	CH-10
74.62	CH-1'
123.27, 123.57, 124.15, 124.98, 125.71, 125.75, 126.45, 126.61, 139.58, 140.19, 142.76, 143.73	C aromatic-1, 2, 3, 4, 5, 6, 7, 8, 4a, 8a, 9a, 10a
170.43	C=O-14
174.71	C=O-15

Table 14 Data of compound (–)-(11*R*)-52 (continued)

Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{30}H_{36}O_4$	460.2614 (M^+)
Lock mass of $C_{32}H_{41}NO_2$	472.3215 (M^+)
Calc. for $C_{30}H_{36}O_4Na$	483.2511 $(M+Na)^+$
Found for $C_{30}H_{36}O_4Na$	483.2511 $(M+Na)^+$

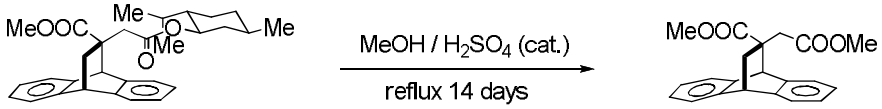
2.3.4 (11*S*)-11-Carbomethoxy-11-methoxyacetyl-9,10-dihydro-9,10-ethanoanthracene [(+)-(11*S*)-44]



(–)-(11*S*)-**51** (+)-(11*S*)-**44**

To a solution of (–)-(11*S*)-51 (21.67g, 47.05 mmol) in anhydrous MeOH (1500 ml) was added conc. H_2SO_4 (35 ml, catalyst) and the reaction mixture was heated to reflux for 14 days. The reaction mixture was evaporated to remove MeOH. The residue was diluted with H_2O, neutralized with aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was crystallized from EtOAc/hexane to give optically active adduct (+)-(11*S*)-43 in 95% yield (>99% e.e., 15.03 g), and 100% conversion from the starting material, as white crystals ; m.p. 154.6-155.3 ◦C (EtOAc/hexane), [lit.[1] m.p. 154-155 ◦C (EtOAc/hexane)]; $[\alpha]_D^{29}$ = +38.67◦ (*c* = 1.055, $CHCl_3$). IR, ^1H, ^{13}C NMR and mass are identical to previously reported data (Table 11).

2.3.5 (11*R*)-11-Carbomethoxy-11-methoxyacetyl-9,10-dihydro-9,10-ethanoanthracene [(–)-(11*R*)-44]



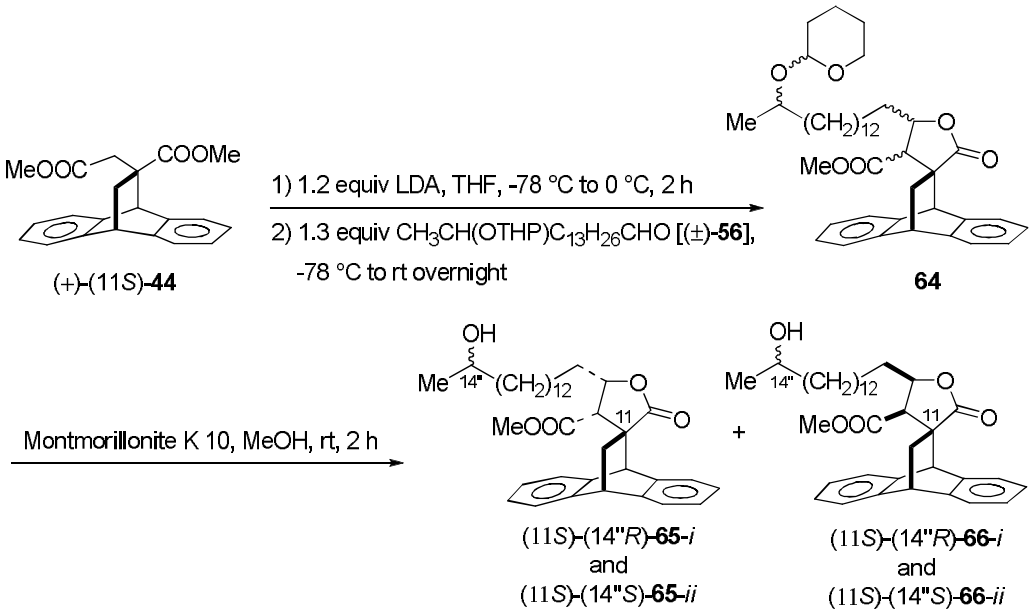
(–)-(11*R*)-**52** (–)-(11*R*)-**44**

The procedure was carried out as described previously, using adduct (–)-(11*R*)-52 (1.0542 g, 2.28 mmol) as the starting material. The adduct (–)-(11*R*)-44 was obtained in 89% yield (0.6624 g), >99% e.e., and 96% conversion from the starting material, as white crystals ; m.p. 154.6-155.3 ◦C (EtOAc/Hexane), [lit.[1] m.p. 154-155 ◦C

(EtOAc/hexane)] ; $[\alpha]_D^{29}$ = –38.98° (*c* = 1.175, $CHCl_3$). IR, ^1H, ^{13}C NMR and mass are identical to previously reported data (shown in Table 11).

2.4 Synthesis of methyl tetrahydro-4-methylene-5-oxo-2-(14-hydroxypentadecanyl)-3-furancarboxylates [(14"*R*)-53-*i* and (14"*S*)-53-*ii*]

2.4.1 Tetrahydro-4'-carbomethoxy-5'-(14"-hydroxypentadecanyl)-2'-furanone-3'–spiro-11-9,10-ethanthracenes [(11*S*)-(14"*R*)-65-*i*, (11*S*)-(14"*S*)-65-*ii*, (11*S*)-(14"*R*)-66-*i* and (11*S*)-(14"*S*)-66-*ii*]



To a 250 ml round-bottomed flask equipped with a magnetic stirrer was fitted with a three-way stopcock with a septum cap and nitrogen inlet was added THF (70 ml) and dry diisopropylamine (1.3 ml, 9.11 mmol) *via* syringes. The mixture was cooled down to –78 °C, *n*-butyllithium (5.4 ml, 1.4 N in hexane, 7.59 mmol) was added and the mixture left stirring at 0 °C for 1 h. A solution of adduct [(+)-(11*S*)-44] (2.1284 g, 6.33 mmol) in THF (20 ml) was introduced to the LDA solution at –78 °C, then stirred at 0°C for 2 h. To a stirred –78 °C solution, a solution of (±)-56 (2.8012 g, 8.22 mmol) was added and the reaction mixture was left stirring at room temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride solution at 0°C followed by extraction with CH_2Cl_2. The dichloromethane solution was washed with H_2O, dried over $MgSO_4$, filtered, and evaporated to dryness.

The crude product (64) and montmorillonite K10 (as a catalyst) in MeOH (50 ml) was stirred at room temperature for 2 h, then passed through Celite 545 and evaporated to dryness. The crude product was purified by preparative thin layer

chromatography (PLC) using EtOAc : hexane = 2.0 : 8.0 as developing solvent to give a mixture of *tetrahydro-4'-carbomethoxy-5'-(14"-hydroxypentadecanyl)-2'-furanone-3'-spiro-11-9,10-ethan-thracenes* [(11*S*)-(14"*R*)-65-*i*, (11*S*)-(14"*S*)-65-*ii*] and [(11*S*)-(14"*R*)-66-*i*, (11*S*)-(14"*S*)-66-*ii*)] in 64% (2.2708 g) and 15% (0.5322 g) yield respectively, and 100% conversion from the starting material.

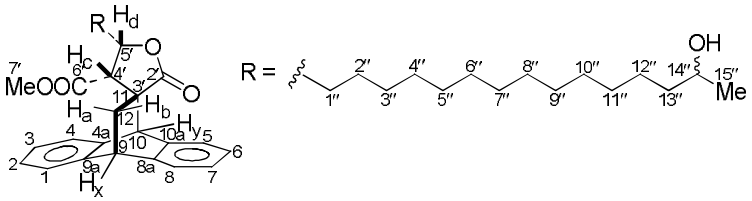


Table 15 Data of compounds (11*S*)-(14"*R*)-65-*i* and (11*S*)-(14"*S*)-65-*ii*

Physical properties : White crystals, m.p. 125.1-126.9 °C (EtOAc/Hexane)	
IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
3094-3732	O-H stretching
3028	C-H stretching
2852, 2929	$-CH_2-$, $-CH_3$ stretching
1780	C=O stretching of ester
1468	C=C stretching of aromatic
1429	$-CH_2-$, $-CH_3$ bending
1204	$-CH_3$ bending
1165	C-O stretching of ester
1104	O-H stretching of 2° alcohol
^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
1.17	3H, *d* (*J* = 6.2 Hz), CH_3-15"
1.20-1.71	26H, *m*, CH_2-1", 2", 3", 4", 5", 6", 7", 8", 9", 10", 11", 12", 13"
1.99, 2.09, 4.39	3H, *ABX* system (*J* = 12.4, 3.2, 2.2 Hz), H_a, H_b, H_x
2.24	1H, *d* (*J* = 5.1 Hz), H_c
3.37	1H, *m*, CH-14"
3.82	3H, s, $COOCH_3$-7'
4.30	1H, *m*, H_d
4.64	1H, *s*, H_y

Table 15 Data of compounds (11*S*)-(14"*R*)-65-*i* and (11*S*)-(14"*S*)-65-*ii* (continued)

^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
7.00-7.52	8H, *m*, ArH-1, 2, 3, 4, 5, 6, 7, 8, 4a, 8a, 9a, 10a
^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (ν, ppm)	Type of carbon
23.43	CH_3-15"
25.68, 25.72, 29.21, 29.26, 29.38, 29.50, 29.55, 29.59, 30.95, 39.30	CH_2-1", 2", 3", 4", 5", 6", 7", 8", 9", 10", 11", 12", 13"
40.66	CH_2-12
43.70	CH-9
46.80	CH-10
50.64	Cq-3'
51.65	CH_3-7'
58.19	CH-4'
68.15	CH-14"
76.41	CH-5'
122.32, 123.91, 124.28, 125.89, 126.13, 126.68, 127.36, 139.46, 140.77, 142.09, 143.29	C aromatic-1, 2, 3, 4, 5, 6, 7, 8, 4a, 8a, 9a, 10a
170.34	C=O-6'
176.95	C=O-2'
Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{36}H_{48}O_5$	560.3502 (M^+)
Lock mass of $C_{28}H_{37}N_5O_7$	556.2771 (M^+)
Calc. for $C_{36}H_{48}O_5Na$	583.3399 $(M+Na)^+$
Found for $C_{36}H_{48}O_5Na$	583.3414 $(M+Na)^+$

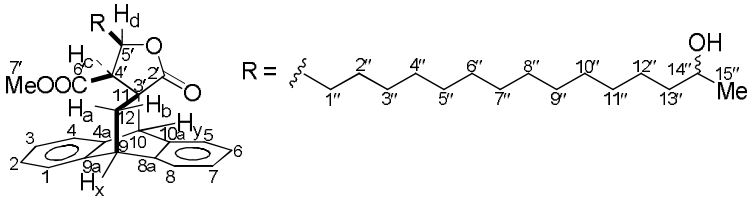


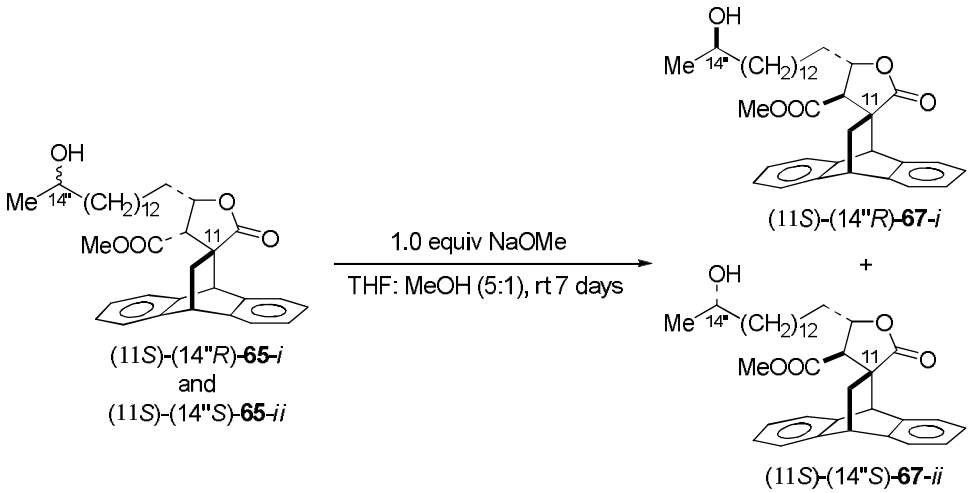
Table 16 Data of compounds (11*S*)-(14"*R*)-66-*i* and (11*S*)-(14"*S*)-66-*ii*

Physical properties : White crystals, m.p. 57.8-59.2 ◦C (EtOAc/Hexane)	
IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
3113-3730	O-H stretching
3025	C-H stretching
2849, 2932	-CH_2-, -CH_3 stretching
1780	C=O stretching of ester
1466	C=C stretching of aromatic
1429	-CH_2-, -CH_3 bending
1209	-CH_3 bending
1179	C-O stretching of ester
1110	O-H stretching of 2° alcohol
^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
1.19	3H, *d* (*J* = 6.2 Hz), CH_3-15"
1.21-1.70	26H, *m*, CH_2-1", 2", 3", 4", 5", 6", 7", 8", 9", 10", 11", 12", 13"
1.44, 2.41, 4.35	3H, *ABX* system (*J* = 13.1, 2.7, 2.6 Hz), H_a, H_b, H_x
2.85	1H, *d* (*J* = 5.5 Hz), H_c
3.59	3H, *s*, $COOCH_3$-7'
3.79	1H, *m*, CH-14"
4.33	1H, *s*, H_y
4.86	1H, *m*, H_d
7.05-7.35	8H, *m*, ArH-1, 2, 3, 4, 5, 6, 7, 8, 4a, 8a, 9a, 10a
^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of carbon
23.43	CH_3-15"
25.68, 25.72, 29.21, 29.26, 29.38, 29.50, 29.55, 29.59, 30.95, 39.30	CH_2-1", 2", 3", 4", 5", 6", 7", 8", 9", 10", 11", 12", 13"
43.70	CH-9
46.80	CH-10

Table 16 Data of compounds (11*S*)-(14"*R*)-66-*i* and (11*S*)-(14"*S*)-66-*ii* (continued)

^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of carbon
50.64	Cq-3'
51.65	CH_3-7'
58.19	CH-4'
68.15	CH-14"
76.41	CH-5'
122.32, 123.91, 124.28, 125.89, 126.13, 126.68, 127.36, 139.46, 140.77, 142.09, 143.29	C aromatic-1, 2, 3, 4, 5, 6, 7, 8, 4a, 8a, 9a, 10a
170.34	C=O-6'
176.95	C=O-2'
Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{36}H_{48}O_5$	560.3502 (M^+)
Lock mass of $C_{28}H_{37}N_5O_7Na$	578.2591 $(M+Na)^+$
Calc. for $C_{36}H_{48}O_5Na$	583.3399 $(M+Na)^+$
Found for $C_{36}H_{48}O_5Na$	583.3401 $(M+Na)^+$

2.4.2 Tetrahydro-4'-carbomethoxy-5'-(14"-hydroxypentadecanyl) -2'-furanone-3'-spiro-11-9,10-dihydro-9,10-ethanoanthracenes [(11*S*)-(14"*R*)-67-*i* and (11*S*)-(14"*R*)-67-*ii*]



(11*S*)-(14"*R*)-**65**-*i* and (11*S*)-(14"*S*)-**65**-*ii*

(11*S*)-(14"*R*)-**67**-*i*

(11*S*)-(14"*S*)-**67**-*ii*

To a solution mixture of the *cis*-adduct (11*S*)-(14"*R*)-65-*i* and (11*S*)-(14"*S*)-65-*ii* (0.2938 g, 0.52 mmol) in THF (50 ml) : MeOH (10 ml) was added sodium methoxide

solution (0.52 mmol, 0.21 N in anhydrous MeOH, 2.5 ml,) at 0 ◦C and the reaction mixture was left stirring at room temperature for 7 days. The reaction mixture was quenched with saturated NH_4Cl solution and extracted several times with CH_2Cl_2. The combined organic layer was washed with H_2O, saturated NaCl solution, then dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by preparative thin layer chromatography (PLC) using EtOAc : hexane = 2.0 : 8.0 as developing solvent to provide the mixture of *trans*-isomer (11*S*)-(14"*R*)-67-*i* and (11*S*)-(14"*S*)-67-*ii* in 91% yield (0.1530 g), and 57% conversion from the starting material.

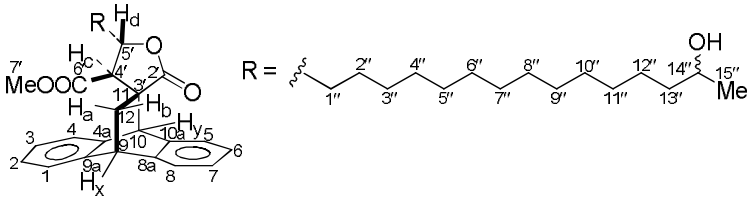


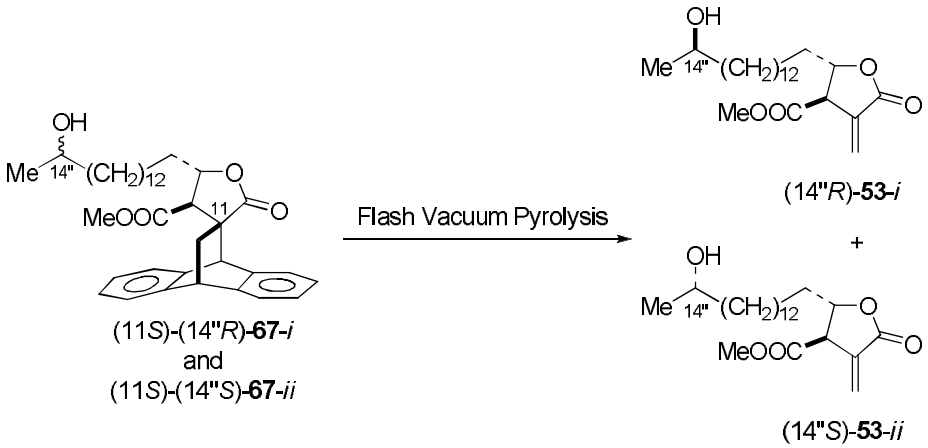
Table 17 Data of compounds (11*S*)-(14"*R*)-67-*i* and (11*S*)-(14"*S*)-67-*ii*

Physical properties : White crystals, m.p. 89.8-91.2 ◦C (EtOAc/Hexane)	
IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
3080-3752	O-H stretching
3025	C-H stretching
2849, 2926	-CH_2-, -CH_3 stretching
1769	C=O stretching of ester
1467	C=C stretching of aromatic
1429	-CH_2-, -CH_3 bending
1209	-CH_3 bending
1158	C-O stretching of ester
1115	O-H stretching of 2° alcohol
^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
1.18	3H, *d* (*J* = 6.2 Hz), CH_3-15"
1.20-1.85	26H, *m*, CH_2-1", 2", 3", 4", 5", 6", 7", 8", 9", 10", 11", 12", 13"
1.95, 2.55, 4.34	3H, *ABX* system (*J* = 13.0, 3.3, 2.2 Hz), H_a, H_b, H_x
2.90	1H, *d* (*J* = 7.8 Hz), H_c
3.21	3H, *s*, $COOCH_3$-7'

Table 17 Data of compounds (11*S*)-(14"*R*)-67-*i* and (11*S*)-(14"*S*)-67-*ii* (continued)

^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
3.78	1H, *m*, CH-14"
4.26	1H, s, H_y
4.35	1H, *m*, H_d
7.07-7.36	8H, *m*, ArH-1, 2, 3, 4, 5, 6, 7, 8, 4a, 8a, 9a, 10a
^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of carbon
23.45	CH_3-15"
25.29, 25.74, 29.22, 29.35, 29.43, 29.56, 29.59, 34.94, 39.33	CH_2-1", 2", 3", 4", 5", 6", 7", 8", 9", 10", 11", 12", 13"
35.06	CH_2-12
43.76	CH-9
51.29	Cq-3'
51.93	CH_3-7'
53.06	CH-10
56.73	CH-4'
68.17	CH-14"
78.68	CH-5'
122.56, 124.03, 125.60, 125.75, 126.24, 126.39, 126.84, 139.28, 139.42, 143.22, 143.54	C aromatic-1, 2, 3, 4, 5, 6, 7, 8, 4a, 8a, 9a, 10a
170.65	C=O-6'
177.04	C=O-2'
Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{36}H_{48}O_5$	560.3502 (M^+)
Lock mass of $C_{28}H_{37}N_5O_7Na$	578.2591 $(M+Na)^+$
Calc. for $C_{36}H_{48}O_5Na$	583.3399 $(M+Na)^+$
Found for $C_{36}H_{48}O_5Na$	583.3401 $(M+Na)^+$

2.4.3 Methyl tetrahydro-4-methylene-5-oxo-2-(14-hydroxypentadecanyl)-3-furancarboxylates [(14"*R*)-53-*i* and (14"*S*)-53-*ii*]



The mixture of (11*S*)-(14"*R*)-67-*i* and (11*S*)-(14"*S*)-67-*ii* (0.1404 g, 0.25 mmol) was placed in a 10 ml round-bottomed flask of the modified flash vacuum pyrolysis apparatus (sinter glass column, Figure 13 in Chapter 3) and the system was subjected to high vacuum. The mixture of (11*S*)-(14"*R*)-67-*i* and (11*S*)-(14"*S*)-67-*ii* was carefully pyrolyzed with free flame and the vapor was trapped in the sinter glass column. The crude product was digested with cooled hexane to precipitate out the mixture of anthracene and the adduct (11*S*)-(14"*R*)-67-*i* and (11*S*)-(14"*S*)-67-*ii*. The filtrate was evaporated and the residue was crystallized from cooled hexane to give the mixture of *trans*-isomer (14"*R*)-53-*i* and (14"*S*)-53-*ii* in 88% yield (0.0844 g), and 100% conversion from the starting material.

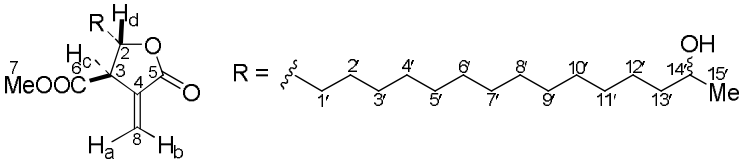


Table 18 Data of compounds (14"*R*)-53-*i* and (14"*S*)-53-*ii*

Physical properties : White crystals, m.p. 61.7-62.8 ◦C (Hexane)	
IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
2992-3757	O-H stretching
2855, 2915	$-CH_2-$, $-CH_3$ stretching
1736	C=O stretching of ester
1462	$-CH_2-$, $-CH_3$ bending
1346	$-CH_3$ bending

Table 18 Data of compounds (14"*R*)-53-*i* and (14"*S*)-53-*ii* (continued)

IR spectroscopy (evaporated thin film)	
Frequency (ν, cm^{-1})	Type of vibration
1176	C-O stretching of ester
1121	O-H stretching of 2° alcohol
873	C=C bending of alkene
^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of proton
1.18	3H, *d* (*J* = 6.2 Hz), CH_3-15'
1.21-1.79	26H, *m*, CH_2-1', 2', 3', 4', 5', 6', 7', 8', 9', 10', 11', 12', 13'
3.57	1H, *m*, H_c
3.78	1H, *m*, CH-14'
3.80	3H, s, $COOCH_3$-7
4.80	1H, *m*, H_d
5.92	1H, *d* (*J* = 2.7 Hz), H_a
6.41	1H, *d* (*J* = 3.1 Hz), H_b
^{13}C NMR spectroscopy (100 MHz) in $CDCl_3$	
Chemical shift (δ, ppm)	Type of carbon
23.60	CH_3-15'
24.89, 25.90, 29.33, 29.54, 29.62, 29.74, 29.76, 30.74, 30.97, 35.94, 39.58	CH_2-1', 2', 3', 4', 5', 6', 7', 8', 9', 10', 11', 12', 13'
50.09	CH-3
53.26	CH_3-7
68.60	CH-14
79.50	CH-2
125.93	CH_2-8
133.83	C=C-4
169.33	C=O-5
170.74	C=O-6
Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{22}H_{38}O_5$	382.2719 (M^+)
Lock mass of $C_{12}H_{14}N_4O_4SNa$	333.0633 $(M+Na)^+$

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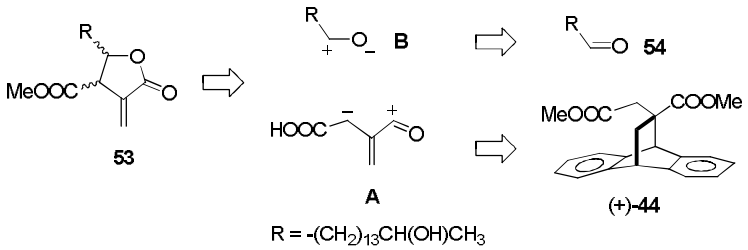
Table 18 Data of compounds (14"*R*)-53-*i* and (14"*S*)-53-*ii* (continued)

Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{22}H_{38}O_5Na$	405.2617 $(M+Na)^+$
Found for $C_{22}H_{38}O_5Na$	405.2618 $(M+Na)^+$

CHAPTER 3
RESULTS AND DISCUSSION

3.1 Retrosynthetic analysis in total synthesis of α-methylene-γ-butyrolactone

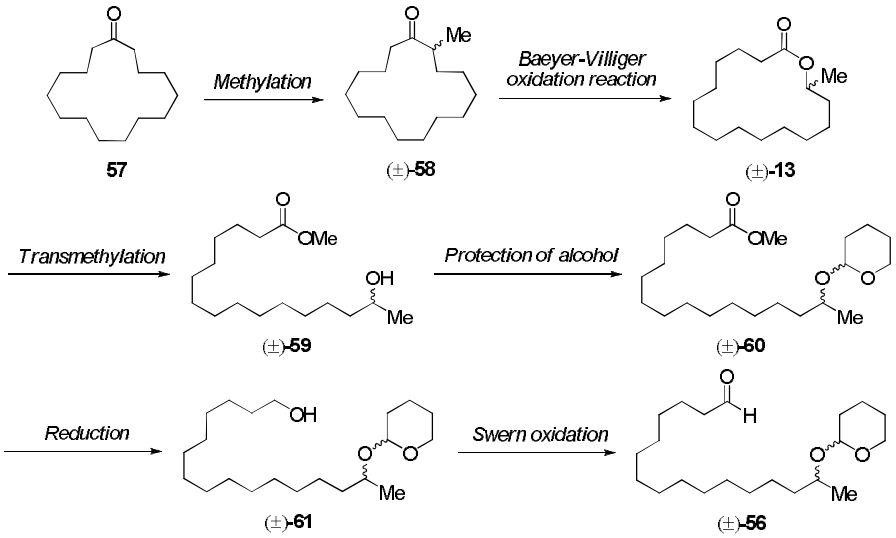
The retrosynthetic analysis of protoconstipatic acid methyl eater (53) and its epimer could be derived from dimethyl itaconate-anthracene adduct (44) and 15-hydroxylaldehyde (54) *via* tandem aldol-lactonization reaction (Scheme 12).



Scheme 12 Retrosynthesis of protoconstipatic acid methyl ester (53) and its epimer

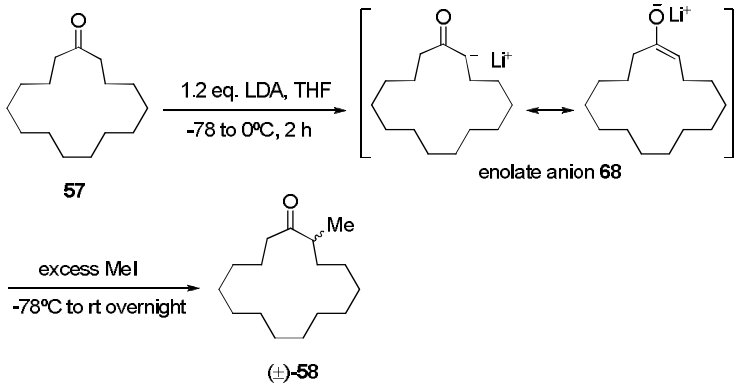
3.2 Synthesis of 15-(tetrahydro-2*H*-pyran-2-yloxy)hexadecanal [(±)-56]

Chiral ether aldehyde (±)-56, 15-(tetrahydro-2*H*-pyran-2-yloxy)hexadecanal, could be synthesized from cyclopentadecanone (57) *via* methylation, Baeyer-Villiger reaction, transmethylation, protection of alcohol group, reduction, and Swern oxidation,, respectively (Scheme 13).



Scheme 13 The synthetic plane of the chiral ether aldehyde (±)-56 from cyclopentadecanone (57)

Cyclopentadecanone (57), commercially available compound, was chosen as starting material for synthesis of 15-(tetrahydro-2*H*-pyran-2-yloxy)hexadecanal [(±)-56]. Upon treatment of 57 with LDA (1.2 equiv) in THF at 0 ◦C generated the enolate anion 68. An alkylation of 68 with MeI (10 equiv) at –78 ◦C followed by stirring at room temperature afforded the desired compound 58. Quenching with aqueous saturated ammonium chloride solution, extraction, and evaporation gave the crude product. Purification by flash column chromatography (silica gel) using EtOAc : hexane = 0.3 : 9.7 as eluent afforded compound (±)-58 in 91% yield (Scheme 14).

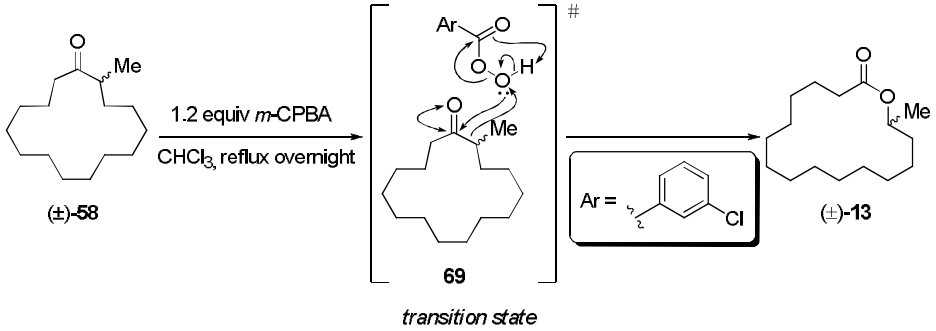


Scheme 14 Methylation reaction of cyclopentadecanone (57)

Compound (±)-58 was assessable by ^{1}H NMR technique. ^{1}H NMR data: methyl group appeared doublets δ at 1.04 ppm (J = 6.9 Hz) and the proton at 2-position appeared multiplets δ at 2.60 ppm. ESI-MS data revealed 261.2192 m/z $(M+Na)^+$ of $C_{16}H_{30}ONa$.

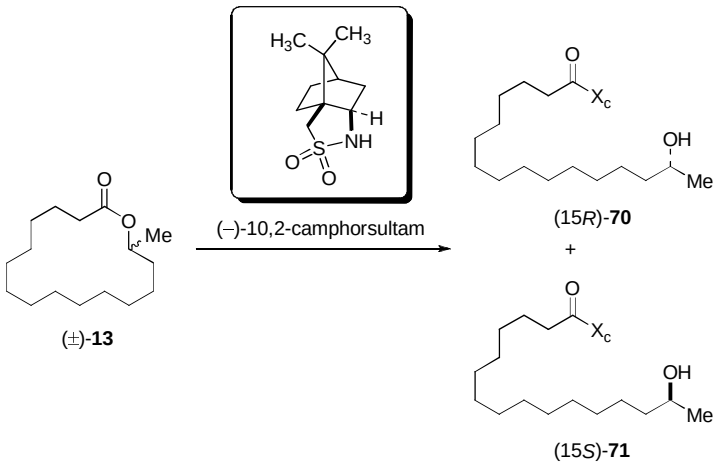
2-Methylcyclopentadecanone [(±)-58] was subsequently converted to 15-hexadecanolide [(±)-13], a sex pheromone component of the stink bug, *Piezodorus hybneri*, employing Baeyer-Villiger reaction. Oxidation of (±)-58 with *m*-CPBA in $CHCl_3$ followed by refluxing for overnight and work-up with aqueous sodium bicarbonate solution resulted in the crude lactone. The crude lactone was purified by flash column chromatography (silica gel) using EtOAc : hexane = 0.5 : 9.5 as eluent to give the lactone (±)-13. It was assessable by ^{1}H NMR technique ^{1}H NMR data: methyl group of (±)-13 appeared doublets δ at 1.21 ppm (J = 6.3 Hz) and the proton at 15-position appeared multiplets δ at 4.95 ppm. ESI-MS data revealed 255.2325 m/z $(M+H)^+$ of $C_{16}H_{31}O_2$.

Due to electron rich of the secondary carbon at 2-position, and decreasing the sterically hindrance between methyl group and a part of *m*-CPBA, the transition state 69 of Baeyer-Villiger rearrangement, the migration reaction occurred only at C-2 to give lactone (±)-13 (Scheme 15).



Scheme 15 Regioselective oxidation by Baeyer-Villiger reaction

Next step of our synthesis, we focused on separation of two enantiomerically pure compounds. In our initial approach (route 1), an reaction of 15-hexadecanolide ((±)-13) and (–)-10,2-camphorsultam as a chiral auxiliary was carried out in various conditions to afford enantiomerically pure (15*R*)-70 and (15*S*)-71 as outlined in Scheme 16 and Table 19.

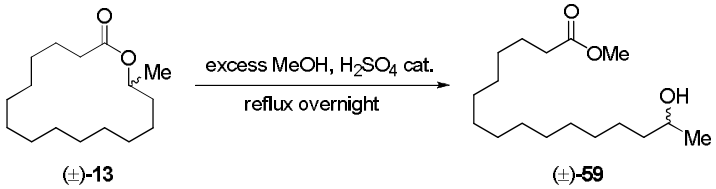


Scheme 16 Reaction of (±)-13 with (–)-10,2-camphorsultam as a chiral auxiliary

Table 19 Conditions for reaction of compound (±)-13 and (–)-10,2-camphorsultam

Entry	Conditions	Results
1	1.2 equiv (–)-10,2-camphorsultam, 1.1 equiv $AlCl_3$, toluene, reflux	Recover of starting material
2	1.2 equiv (–)-10,2-camphorsultam, toluene, reflux	Recover of starting material
3	1.2 equiv (–)-10,2-camphorsultam, conc. H_2SO_4, toluene, reflux	Recover of starting material
4	1.2 equiv (–)-10,2-camphorsultam, toluene, microwave	Recover of starting material

Unfortunately, the desired product was not successively synthesized employing the above conditions as expected. The reason is depend on the steric hindrance of (–)-10,2-camphorsultam towards lactone 13, and the less active carbonyl group of 13. Therefore, we investigated the second approach (Route 2) by employing transmethylation reaction of 15-hexadecanolide [(±)-13] and the desired product was successively prepared as shown in Scheme 17. Refluxing in MeOH with a catalytic amount of conc. H_2SO, and purification by flash column chromatography (silica gel) using EtOAc : hexane = 0.5 : 9.5 as eluent afforded the racemic methyl 15-hydroxyhexadecanoate [(±)-59].



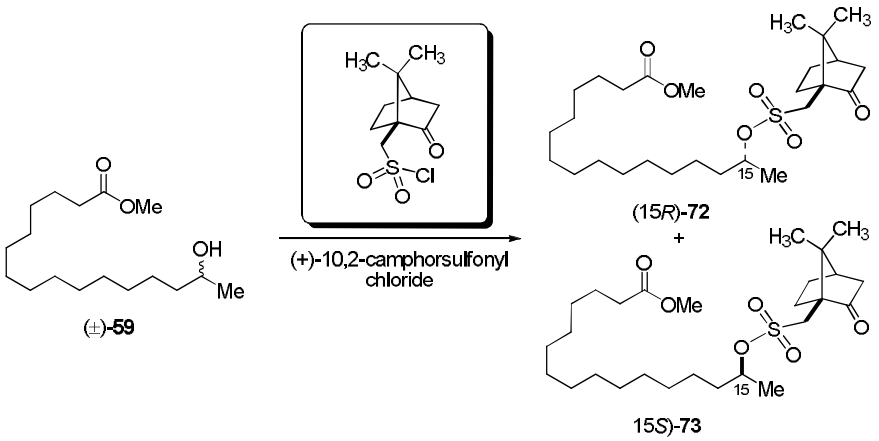
(±)-13 (±)-59

Scheme 17 Transmethylation of 15-hexadecanolide [(±)-13] with MeOH

^{1}H NMR data of the racemic methyl 15-hydroxyhexadecanoate ((±)-59) : methyl group of (±)-59 appeared doublets δ at 1.18 ppm (J = 6.2 Hz), the proton at 15-position appeared multiplets δ at 3.78 ppm and the methyl ester at 17-position appeared singlet δ at 3.66 ppm. IR data revealed broad peak of O-H stretching of hydroxyl at 3776-3154 cm^{-1} and ESI-MS data revealed 309.2408 m/z $(M+Na)^+$ of $C_{17}H_{34}O_3Na$.

To further separation two pure forms [(±)-59], (+)-camphor-10-sulfonyl chloride was examined in this step. A reaction of methyl 15-hydroxyhexadecanoate [(±)-59] and

(+)-camphor-10-sulfonyl chloride (a chiral auxiliary) was carried out in various conditions to afford enantiomerically pure (15*R*)-72 and (15*S*)-73 as illustrated in Scheme 18 and Table 20. Treatment of (±)-59 with 1.3 equiv (+)-camphor-10-sulfonyl chloride and 3.0 equiv NaH in DMF (entry 1) didn't give the desired product as planned. Only mixture compounds were detected in Entries 2 and 3 employing Et_3N and LDA as base. Purification was not successively separated to afford pure compounds.

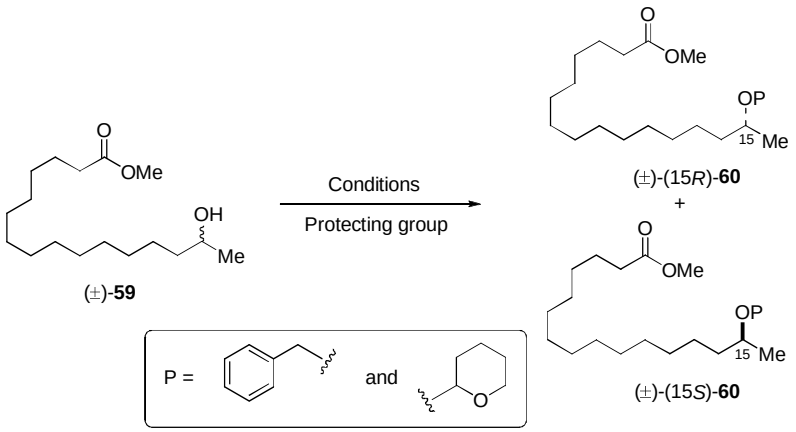


Scheme 18 Reaction of (±)-59 with (+)-camphor-10-sulfonyl chloride as a chiral auxiliary

Table 20 Conditions for reaction of compound (±)-59 with (+)-camphor-10-sulfonyl chloride

Entry	Conditions	Results
1	1.3 equiv (+)-camphor-10-sulfonyl chloride, 3.0 equiv NaH, DMF, THF, 0 °C to rt overnight	Recover of starting material
2	2.0 equiv (+)-camphor-10-sulfonyl chloride, 3.0 equiv Et_3N, THF, 0 °C, then reflux overnight	Complex mixture
3	1.3 equiv (+)-camphor-10-sulfonyl chloride, 1.2 equiv LDA, THF, –78 - 0 °C and then rt overnight	Complex mixture

As shown in Scheme 19, preparartion of chiral ether (±)-59 with benzyl bromide, and 3,4-dihydro-2*H*-pyran (DHP) was carried out in various conditions as summarized in Table 2.

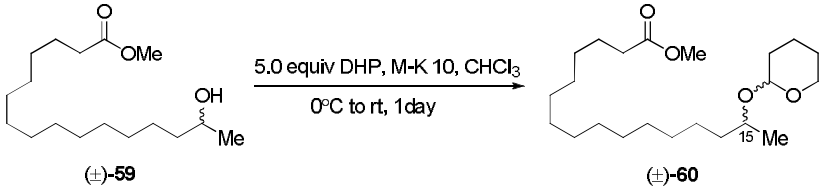


Scheme 19 Another synthetic route for protection of active alcohol (±)-59

Table 21 Conditions for protection of methyl 15-hydroxyhexadecanoate [(±)-59]

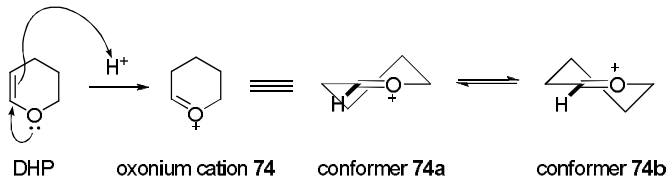
Entry	Conditions	Results
1	1.3 equiv benzyl bromide, 3.0 equiv NaH, DMF, 0 ◦C to rt, overnight	Recover of starting material
2	3.0 equiv benzyl bromide, 3.0 equiv NaH, THF, 0 ◦C to rt, overnight	Recover of starting material
3	3.0 equiv benzyl bromide, 3.0 equiv NaH, DMF, THF, 0 ◦C to rt, overnight	Recover of starting material
4	5.0 equiv DHP, montmorillonite K10, $CHCl_3$, 0 ◦C to rt overnight	87%

Benzylation reaction under the above conditions didn't give the desired products as expected (Entries 1-3). Of the synthetic routes designed to protect of alcohol group of (±)-59 in this thesis, only ether product was successively prepared according to from 3,4-dihydro-2*H*-pyran method in Entry 4. Upon treatment of (±)-59 with 3,4-dihydro-2*H*-pyran (5.0 equiv) with a catalytic amount of montmorillonite K10 (mind acid catalyst) in $CHCl_3$ afforded the racemic (±)-60 in 87% depicted in Entry 4.

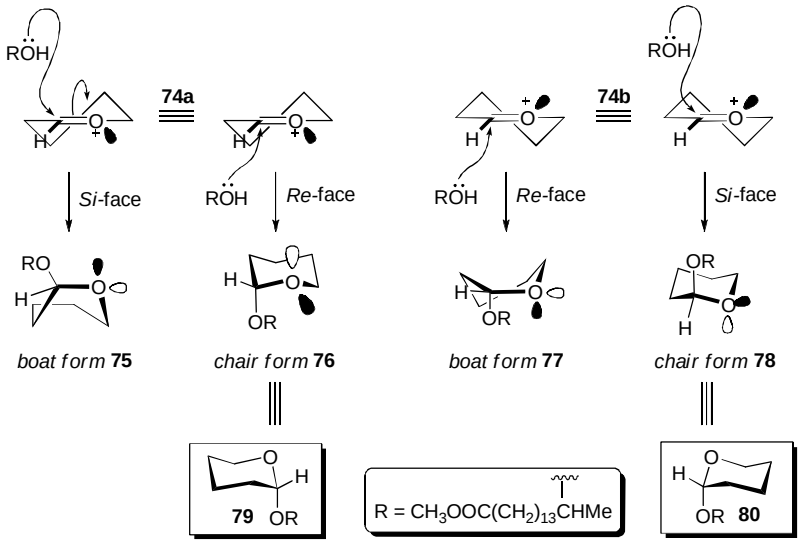


Scheme 20 Protection of alcohol group by DHP and M-K10

As shown in Scheme 21, DHP was activated with montmorillonite K10 to give the corresponding oxonium cation (74) which occurred in two conformers, 74a and 74b. Hydroxyl group as nucleophile attacked at carbon of oxonium 74a[21] in *Si*-face and *Re*-face to provide boat conformer 75 and chair conformer 76, respectively, which chair conformer 76 was more stable than 75. This could be explained in terms of the favorable chair-like transition state 74 where upon all large substituents occupied the less sterically demanding equatorial orientations. In the same style, the hydroxyl group attacked at carbon of oxonium 74b in *Si*-face to give more stable conformer 78 as shown in Scheme 22.

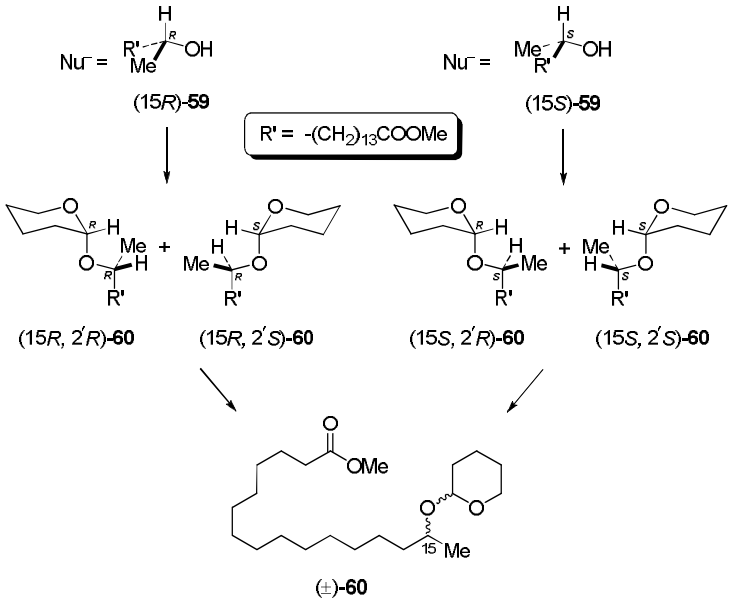


Scheme 21 Mechanism of 3,4-dihydro-2*H*-pyran with montmorillonite K10



Scheme 22 Possible pathway of nucleophileic attack towards oxoniun ion 74a and 74b

As shown in Scheme 23, reaction of (15*R*)-59 with DHP gave the protected (15*R*,2'*R*)-60 and (15*R*,2'*S*)-60 as diastereomers. The diastereomers (15*S*,2'*R*)-60 and (15*S*,2'*S*)-60 were prepared from (15*S*)-59 in the same reaction as illustrated in Scheme 23.



Scheme 23 Conformers of compound (±)-60

Compound (±)-60 was confirmed by spectroscopic techniques. ^{1}H NMR data : methyl group appeared doublets δ at 1.09, 1.18 (major), 1.21ppm (J = 6.1, 6.2, 6.2 Hz), the H-2' appeared multiplets δ at 4.54-4.98 ppm and the methyl ester at 17-position appeared singlet δ at 3.66 ppm (Figure 7). IR data displayed broad peak of C-O stretching of ether at 1077, 1203 cm^{-1} and ESI-MS data revealed 393.2980 m/z $(M+Na)^{+}$ of $C_{22}H_{42}O_4Na$.

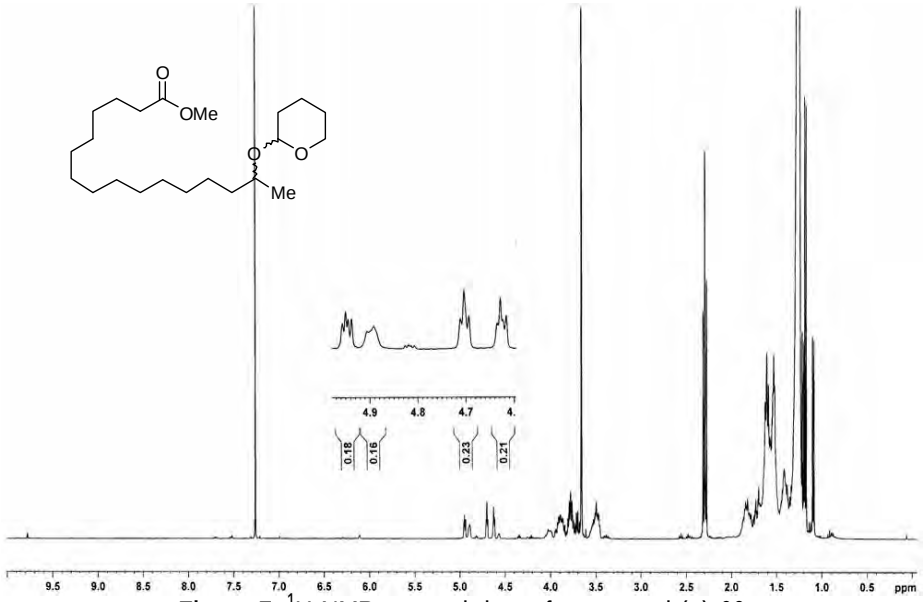
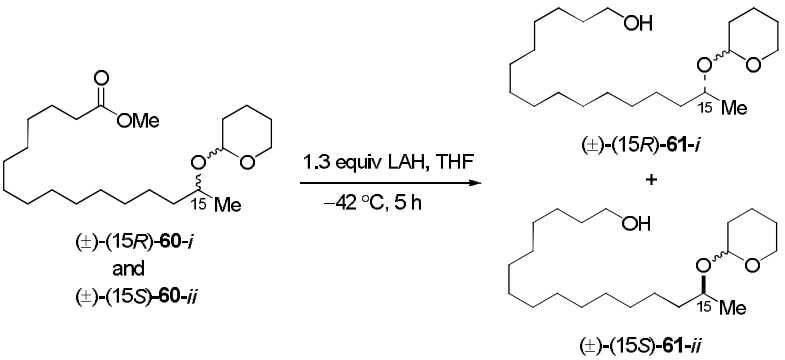


Figure 7 ^{1}H NMR spectral data of compound (±)-60

Subsequently, Reduction of methyl ester of (±)-60 with lithium aluminium hydride in THF at –42 °C for 5 h gave both diastereomers of (±)-61 in 79% yield (Scheme 24).



(±)-(15*R*)-**60**-*i*
and
(±)-(15*S*)-**60**-*ii*

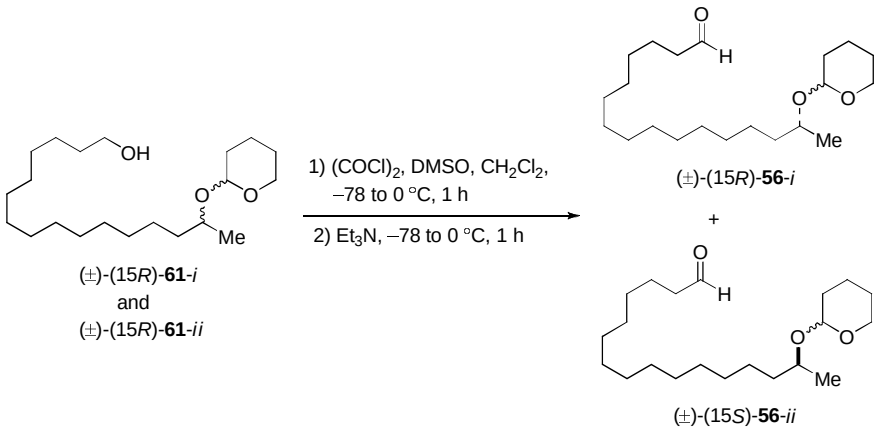
(±)-(15*R*)-**61**-*i*

(±)-(15*S*)-**61**-*ii*

Scheme 24 Reduction of compound (±)-60 with lithium aluminium hydride

^{1}H NMR spectral data of compound (±)-61 revealed that H-2' of tetrahydropyran ring appeared multiplets δ at 4.54-4.73 ppm and H-1 appeared triplets δ at 3.63 ppm (J = 6.6 Hz). Significantly, the singlet peak of methoxy group disappeared in (±)-61. IR data shown broad peak of O-H stretching of hydroxyl at 3069-3686 cm^{-1}, and ESI-MS data revealed that shown in 365.3032 m/z $(M+Na)^+$ of $C_{21}H_{42}O_3Na$.

For next step, Swern oxidation of alcohol (±)-61 with oxalyl chloride / DMSO / triethylamine afforded the corresponding aldehyde (±)-56 (Scheme 25).



(±)-(15*R*)-**61**-*i*
and
(±)-(15*R*)-**61**-*ii*

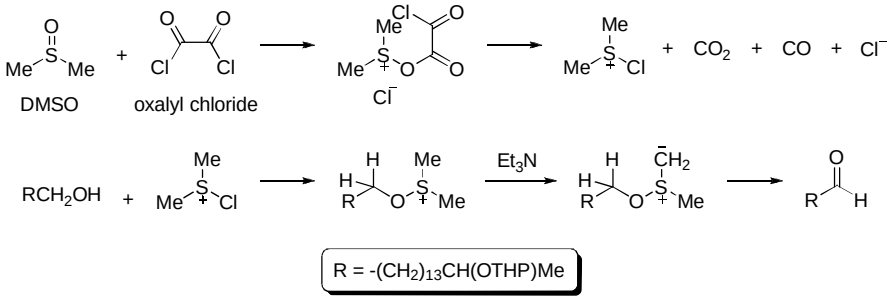
(±)-(15*R*)-**56**-*i*

(±)-(15*S*)-**56**-*ii*

Scheme 25 Swern oxidation of compound (±)-61

^{1}H NMR spectral data of aldehyde (±)-56 revealed an additional aldehyde proton at 9.76 ppm (triplets, J = 1.9 Hz) and H-2' of tetrahydropyran ring appeared

multiplets δ at 4.60-4.74 ppm. IR data displayed absent of the broad peak of O-H, and ESI-MS data revealed in 363.2875 m/z $(M+Na)^+$ of $C_{21}H_{40}O_3Na$. The mechanism of Swern oxidation shown in Scheme 26.

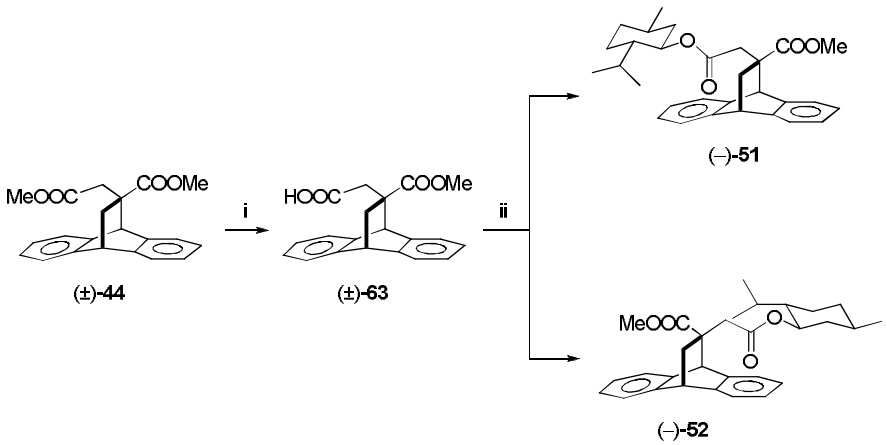


Scheme 26 Mechanism of Swern oxidation

3.3 Synthesis of methyl tetrahydro-4-methylene-5-oxo-2-(14-hydroxypentadecanyl)-3-furancarboxylates [(14''*R*)-53-*i* and (14''*S*)-53-*ii*]

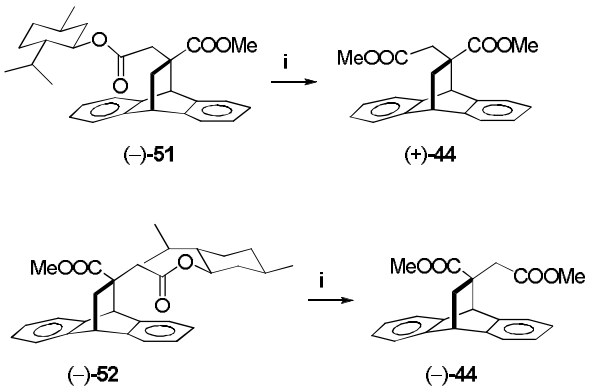
Our synthetic method for enantiomerically pure protoconstipatic acid methyl ester focused on enantiomerically pure itaconate adduct 44 as building block. The optically active adducts, (11*S*)-44 and (11*R*)-44, were successively prepared followed by separation of the mixture of diastereoisomers [(11*S*)-51 and (11*R*)-52] according to the standard procedure as shown in Scheme 27. Refluxing racemic 44 with sodium hydroxide (1.2 equiv) in methanol : water (2 : 1) for 1 h gave the hydrolysed mono acid adducts [(±)-63], in 97% yield after crystallization from ethyl acetate/hexane. The mono acid (±)-63 was converted to the corresponding acid chloride by refluxing in thionyl chloride (5.0 equiv) with a catalytic amount of dimethyl formamide for overnight. Then, the crude acid chloride was treated with (–)-(1*R*,3*R*,4*S*)-menthol (1.3 equiv) and triethylamine (1.3 equiv). The crude product was subjected to column chromatographic separation (silica gel, ethyl acetate : hexane = 1.0 : 9.0 as eluent) to afford (–)-(11*S*)-51 (34%, $[\alpha]_D^{30}$ = –108.95°, *c* = 1.285, in $CHCl_3$) and (–)-(11*R*)-52 (34%, $[\alpha]_D^{30}$ = –51.38°, *c* = 1.195, in $CHCl_3$) (Scheme 27). The absolute configuration of (–)-(11*S*)-51 and (–)-(11*R*)-52 were confirmed by X-ray crystallographic analysis.[1,20] IR, ^1H, ^{13}C NMR and mass are identical to previously reported data.[1,20]

Hence enantiomerically pure dimethyl itaconate-anthracene adducts, (+)-44 and (–)-44 were obtained by transmethylation of (–)-(11*S*)-51 and (–)-(11*R*)-52 by refluxing in anhydrous methanol with a catalytic amount of conc. sulfuric acid (Scheme 28). IR, ^1H, ^{13}C NMR and mass are identical to previously reported data.[1,20]



Reagents and conditions: (i) 1.2 equiv NaOH, MeOH:H_2O (2:1), reflux 1 h, 97%; (ii) (a) 5.0 equiv $SOCl_2$, DMF (cat.), N_2, reflux overnight, (b) 1.3 equiv (–)-(1*R*,2*S*,5*R*)-menthol, 1.3 equiv Et_3N, reflux 2 h [(–)-51, 34%; (–)-52, 34%].

Scheme 27 Separation of optically active dimethyl itaconate-anthracene adducts



Reagents and conditions: (i) excess anhydrous MeOH, H_2SO_4 (cat.), reflux 14 days [(+)-44, 95%; (–)-44, 89%].

Scheme 28 Transmethylation of compounds (–)-51 and (–)-52

The synthetic pathway of protoconstipatic acid methyl ester 53 involved aldol-lactonization reactions of the dimethyl itaconate-anthracene adduct [(+)-(11*S*)-44] with aldehyde (±)-56, followed by isomerization and flash vacuum pyrolysis (retro Diels-Alder reaction), respectively (Scheme 29).

จัดรูปแบบ: แบบอักษร: เอียง, แบบอักษรภาษาไทยและภาษาอื่นๆ: เอียง

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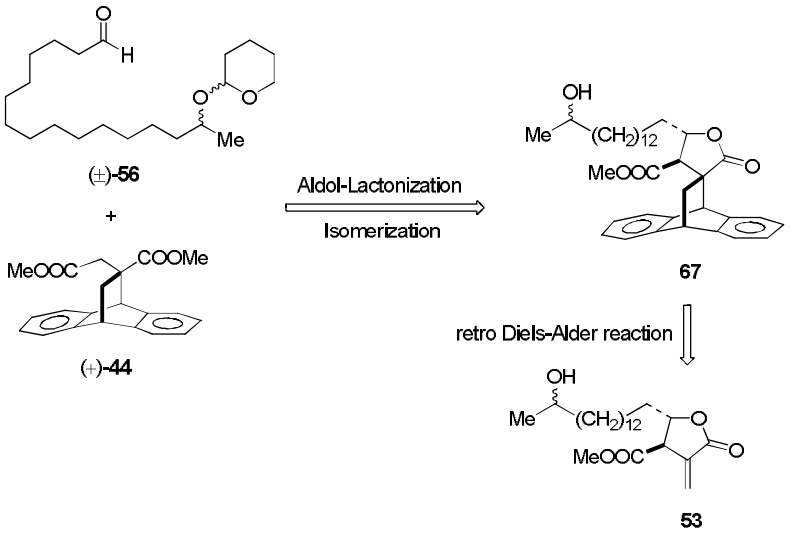
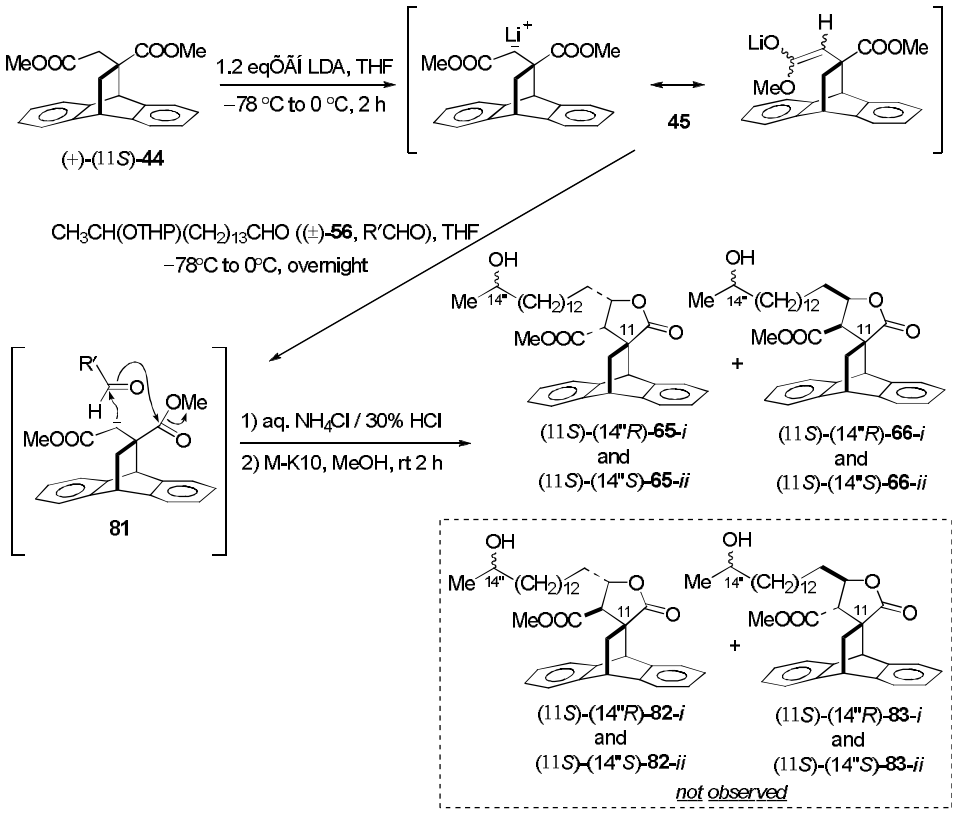


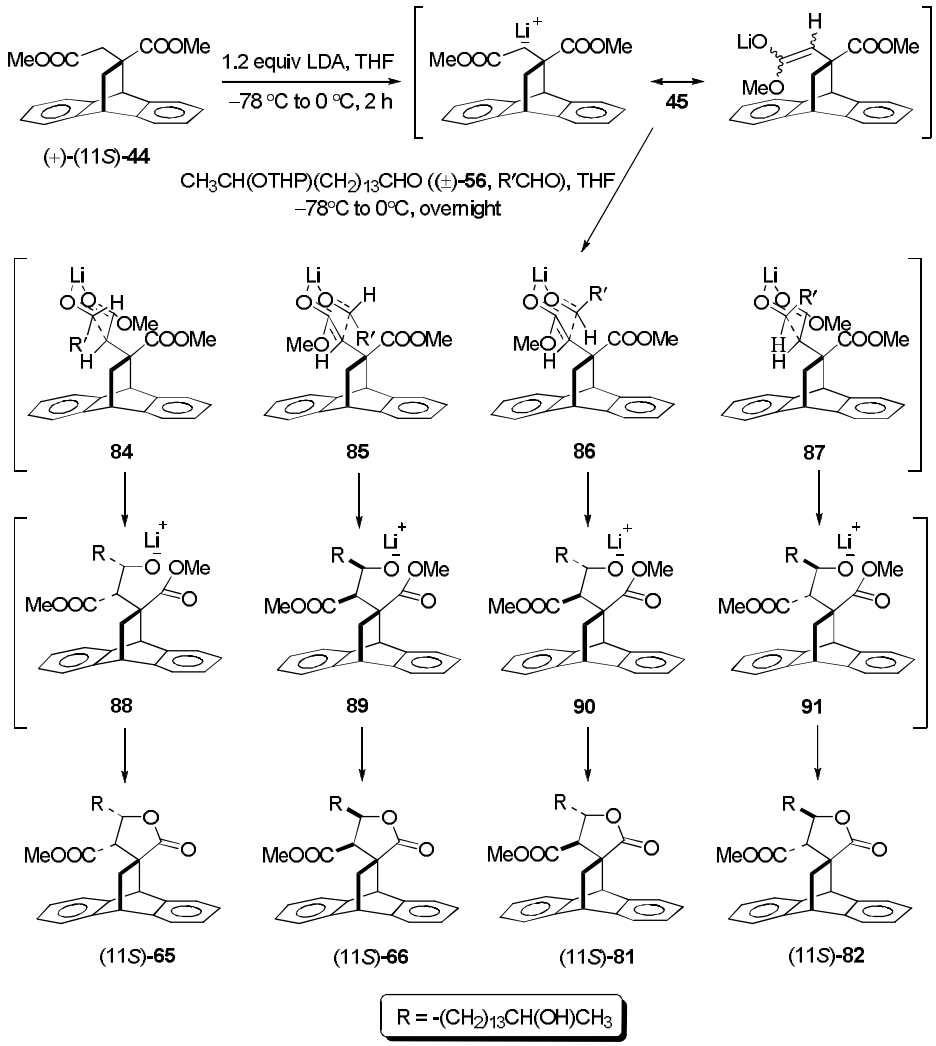
Scheme 29 Retrosynthesis of compound 53

Anion 45 was formed by treatment dimethyl itaconate-anthracene adduct (+)-(11S)-44 with LDA (1.2 equiv) in THF at 0°C, followed by alkylation with aldehyde (±)-56 at –78 °C. After stirring at room temperature overnight, standard work up with aqueous saturated ammonium chloride solution and deprotection with montmorillonite K10 in methanol afforded a mixture of diastereoisomers (Scheme 30). Purification by preparative thin layer chromatographic afforded the pure diastereoisomer as (11S)-65 (64%) and (11S)-66 (15%).



Scheme 30 Tandem aldol-lactonization reactions and deprotection

Our result showed that the *cis*-isomer (11*S*)-65 was the major product and *cis*-isomer (11*S*)-66 as minor product. However, separation by chromatography indicated that no *trans*-isomers (11*S*)-82 and (11*S*)-83 occurred from the tandem aldol-lactonization reactions between the anion (+)-(11*S*)-44 and aldehyde (±)-56. The reasonable result is based on the favorable chair-like transition state 84 where upon all large substituents occupied the less sterically demanding equatorial orientations. In addition, the similar transition state (85) was also favorable as compared to 86 and 87, hence the product (66) from 85 was also observed and separated (Scheme 31).



Scheme 31 Influence of chair form in transition state and size of substituent

The relative stereochemistry of products (65 and 66) was assigned by ^{1}H NMR and compared with the related compounds of previously publications of Lertvorachon *et al.*[22] in 1998 and Kongsaeree *et al.*[20] in 2001.

The relative stereochemistry assigned by ^{1}H NMR of *cis*-isomer (11*S*)-65 revealed that proton of H_c appeared doublets δ at 2.24 ppm (J = 5.1 Hz) and multiplets δ at 4.30 ppm for H_d (Figure 8). IR spectral data shown broad peak of O-H stretching of hydroxyl at 3094-3732 cm^{-1}, and ESI-MS data revealed in 583.3414 m/z $(M+Na)^+$ of $C_{36}H_{48}O_5Na$.

The relative stereochemistry of *cis*-isomer (11*S*)-66 assigned by ^{1}H NMR technique showed that proton of H_c appeared doublets δ at 2.85 ppm (J = 5.5 Hz) and

multiplets δ at 4.86 ppm for H_d (Figure 9). IR spectral data shown broad peak of O-H stretching of hydroxyl at 3730-3113 cm^{-1} and ESI-MS data revealed in 583.3401 m/z $(M+Na)^+$ of $C_{36}H_{48}O_5Na$.

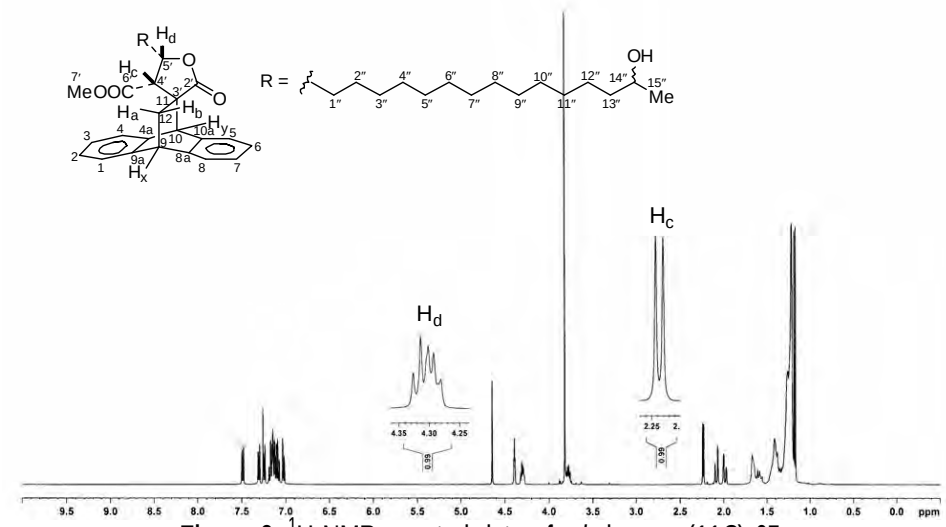


Figure 8 ^{1}H NMR spectral data of *cis*-isomer (11*S*)-65

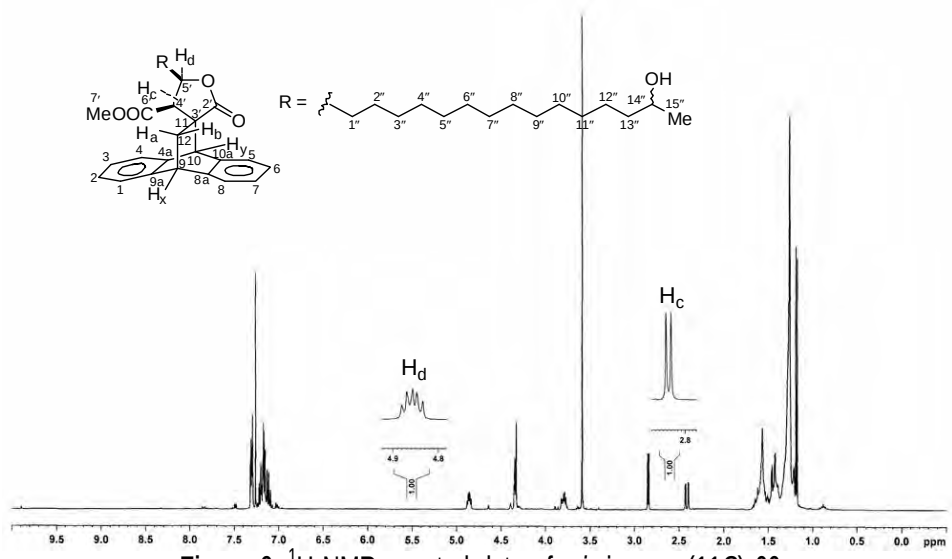
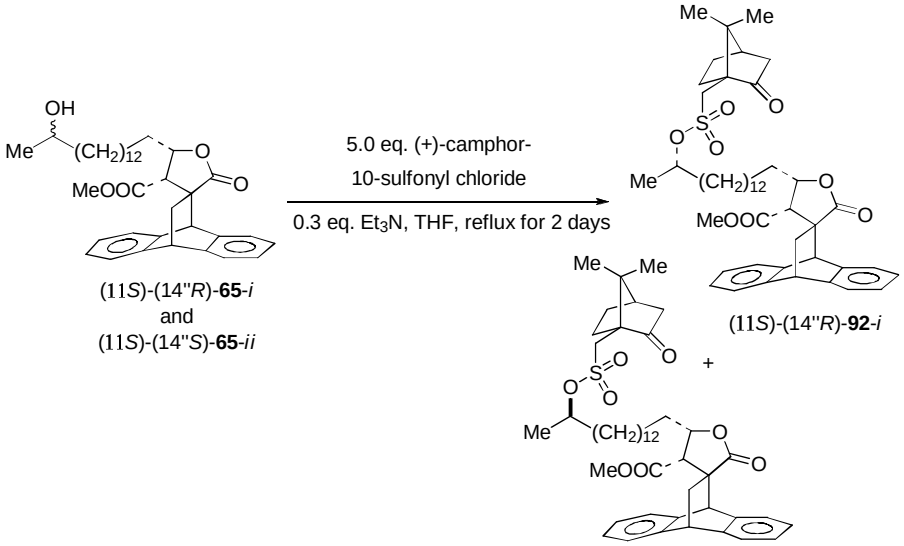


Figure 9 ^{1}H NMR spectral data of *cis*-isomer (11*S*)-66

We attempted to separate a mixture of diastereomers (11*S*)-(14"*R*)-65-*i* and (11*S*)-(14"*R*)-65-*ii* by treatment with (+)-camphor-10-sulfonyl chloride (5 eq , a chiral auxiliary) and triethylamine (3 equiv) in THF, followed by refluxing for 2 days. Upon standard aqueous saturated ammonium chloride work-up and purification, a mixture of

(11*S*)-(14"*R*)-92-*i* and (11*S*)-(14"*S*)-92-*ii* was separated in ratio 1:1 (Scheme 32). ^{1}H NMR spectral data of a mixture products showed doublets δ at 3.59 and 3.57 ppm (J = 15.0 and 15.0 Hz) of two H_a proton and two H_b proton appeared doublets δ at 2.99 and 2.97 ppm (J = 15.0 and 15.0 Hz (Figure 10).



Scheme 32 Separation of diastereoisomer of *cis*-isomer (11*S*)-(14"*R*)-65-*i* and (11*S*)-(14"*S*)-65-*ii* by (+)-camphor-10-sulfonyl chloride in THF

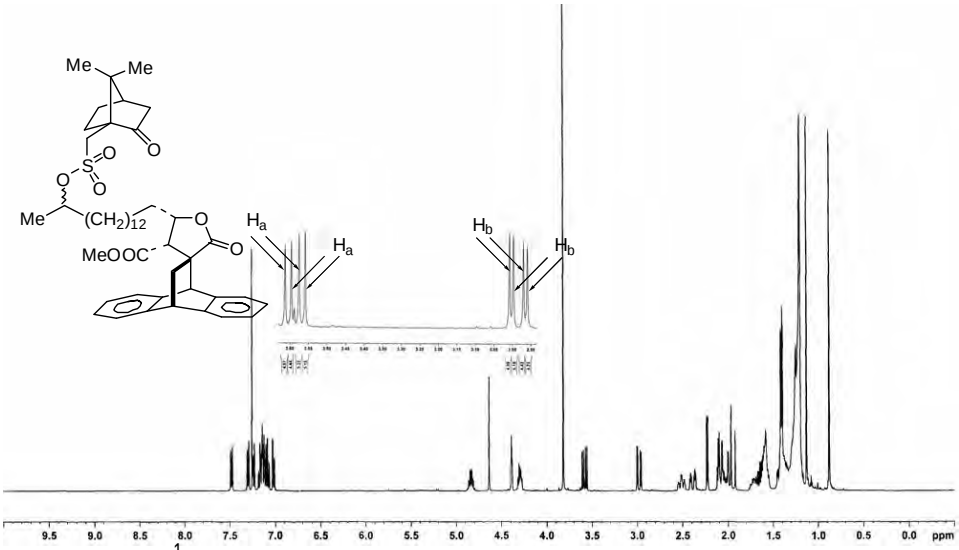
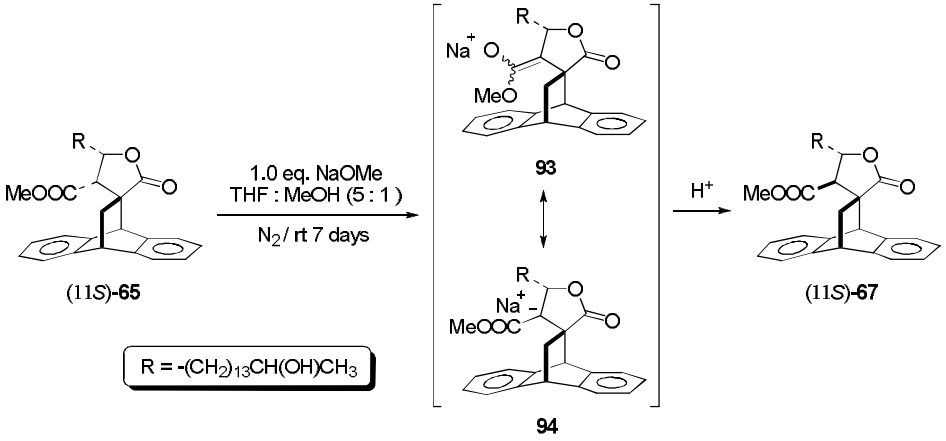


Figure 10 ^{1}H NMR spectral data of the mixture of compounds (11*S*)-(14"*R*)-92-*i* and (11*S*)-(14"*S*)-92-*ii*

The *cis*- → *trans*- isomerization reaction could be affected by treatment of (11*S*)-65 with sodium methoxide (1.0 equiv) in a mixture solution of THF and methanol (5 : 1), and then left stirring at room temperature for 7 days. Standard aqueous saturated ammonium chloride work-up followed by preparative thin layer chromatographic separation (silica gel, EtOAc : hexane = 2.0 : 8.0 as eluent) gave the diastereomeric *trans*-spiro-lactone (11*S*)-67 in 91% yield and the recovered *cis*-isomer 57% (Scheme 33).



Scheme 33 *cis*- → *trans*- Isomerization of (11*S*)-65

The conversion of *cis*- → *trans*- isomerization of (11*S*)-65 was confirmed by ^{1}H NMR spectral data : the proton of H_c appeared doublets δ at 2.90 ppm (J = 7.8 Hz) and multiplets δ at 4.35 ppm of H_d proton (Figure 11). IR spectral data shown broad peak of O-H stretching of hydroxyl at 3752-3080 cm^{-1}, and ESI-MS data revealed in 583.3401 m/z $(M+Na)^+$ of $C_{36}H_{48}O_5Na$.

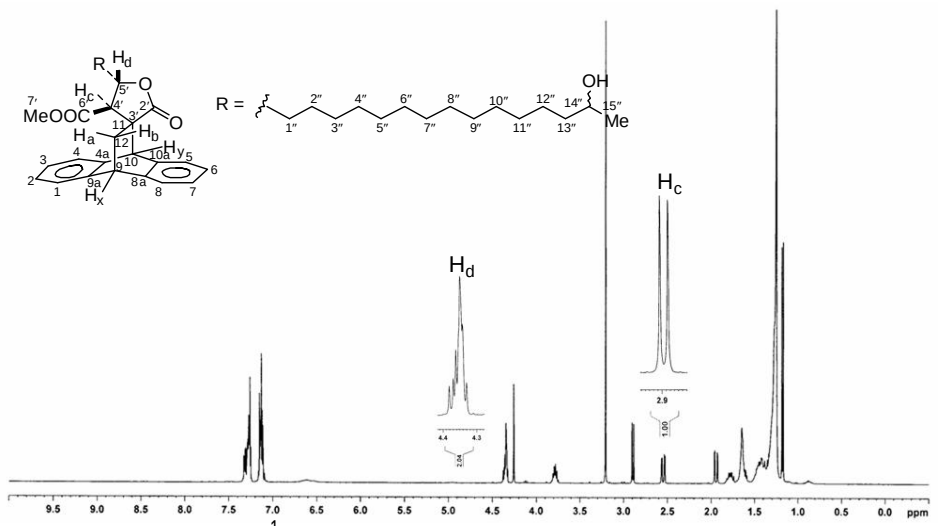


Figure 11 ^{1}H NMR spectral data of *trans*-isomer (11*S*)-67

The conversion of *cis*- → *trans*- isomerization of (11*S*)-65 depended on the size chain of alkyl groups. It was found that the longer, hence sterically more hindered, alkyl chains provided better yields of the *trans*-isomers ((11*S*)-67), an indication that the reactions were thermodynamically controlled (Figure 12).

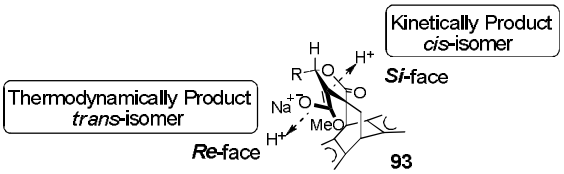


Figure 12 Intermediate of isomerization process of compound (11*S*)-65

The retro Diels-Alder reaction of *trans*-isomers (11*S*)-67, affected by the standard flash vacuum pyrolysis using apparatus as shown in Figure 13, provided a mixture of *exo*-53 and *endo*-96 double bond lactones in 88% and 17% yields, respectively (Scheme 34), as shown by the ^{1}H NMR spectrum of the crude pyrolysate. It was observed that the *endo*-96 was formed by isomerization of the *exo*-lactone 53 during pyrolysis.

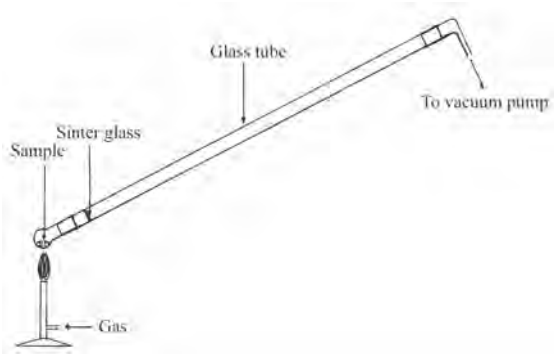
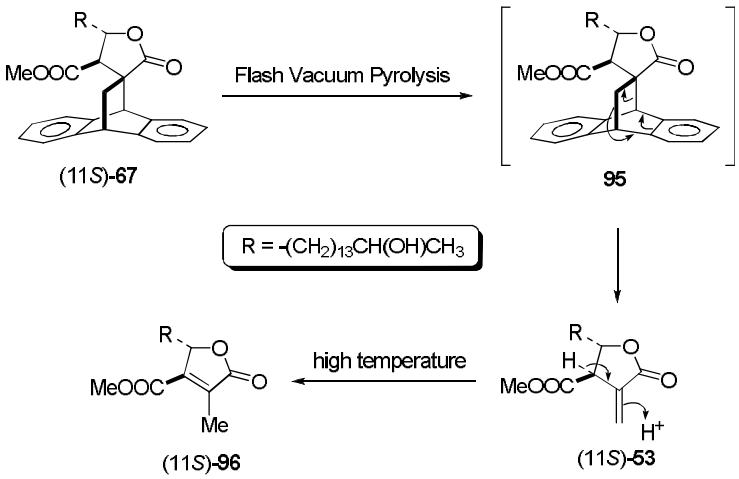


Figure 13 Modified flash vacuum pyrolysis apparatus



Scheme 34 Retro Diels-Alder reaction of *trans*-isomers (11S)-67

Moreover, it was later realized that high temperature made to *exo*- → *endo*-isomerization readily took place at room temperature. Attempts purification by crystallization in cool hexane from *endo*-product, the pure *exo*-53 products was obtained. The *exo*-53 products were characterized by NMR technique, the *exo*-methylene group of 53 appeared as two doublets δ at 5.92 (J = 2.7 Hz) and 6.41 ppm (J = 3.0 Hz), H_a and H_b respectively (Figure 14). IR data shown broad peak of O-H stretching of hydroxyl at 3757-2992 cm^{-1}, and ESI-MS data revealed that shown in 405.2618 m/z $(M+Na)^+$ of $C_{22}H_{38}O_5Na$.

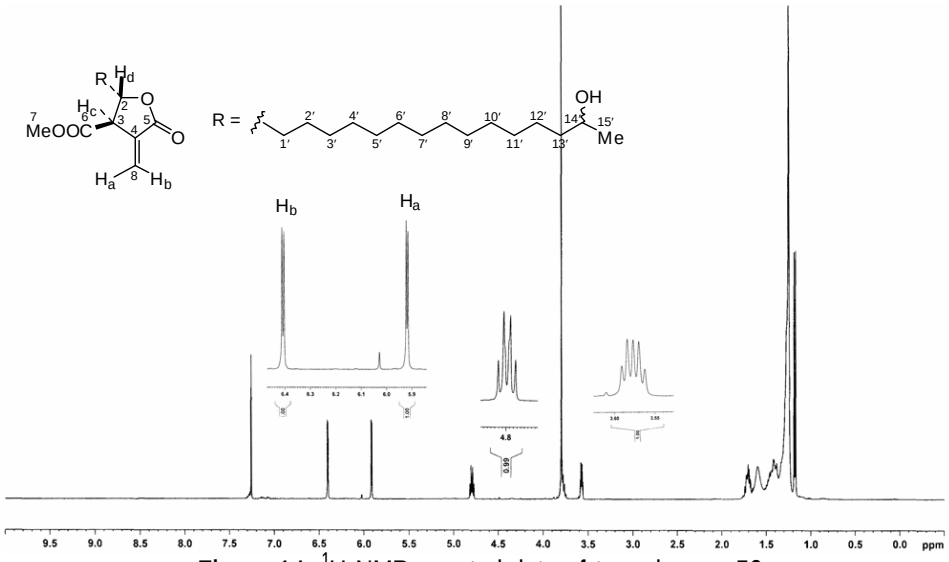
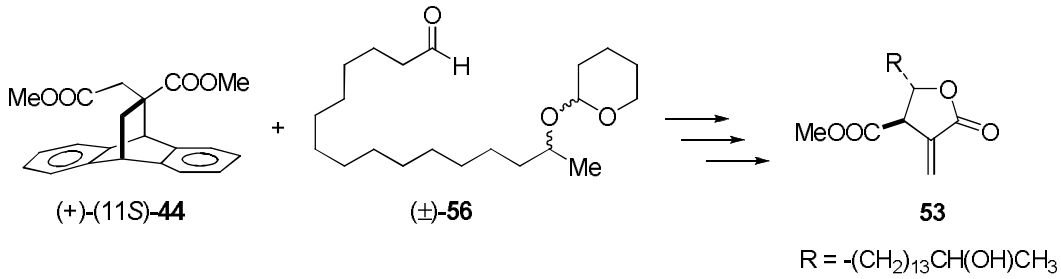


Figure 14 ^{1}H NMR spectral data of *trans*-isomer 53

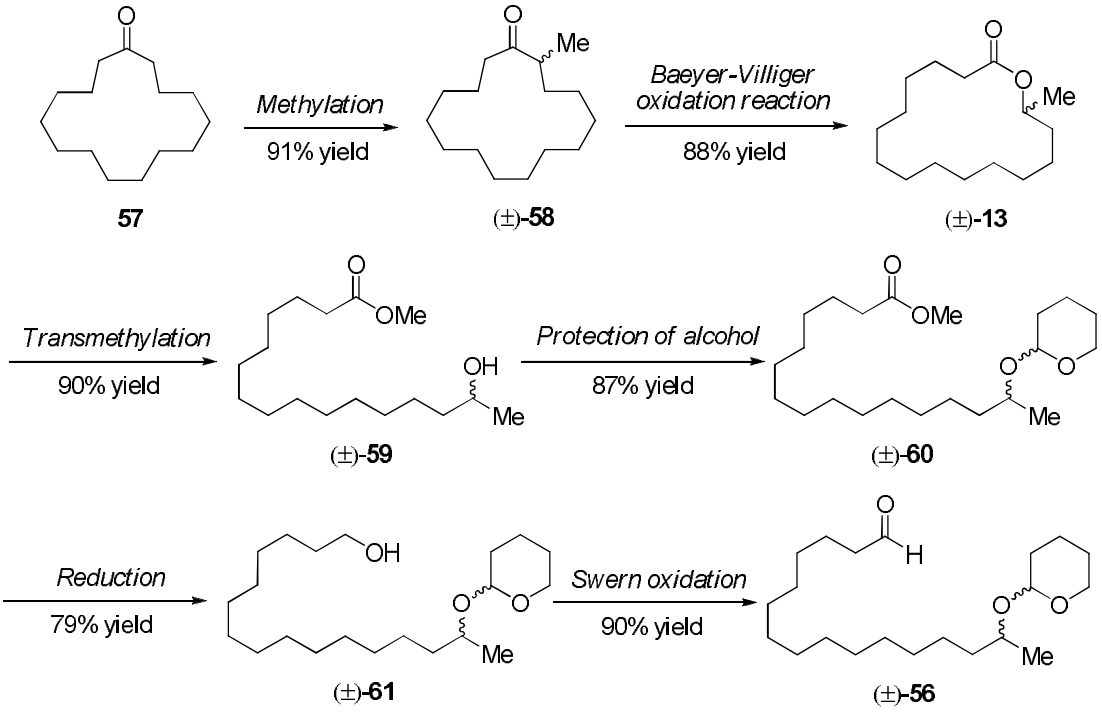
CHAPTER 4
CONCLUSION

The retrosynthesis revealed that diastereoisomer of protoconstipatic acid methyl ester (53) and its epimer were achieved by reaction of optically active dimemthyl itaconate-anthracene adducts [(+)-(11*S*)-44] with the chiral ether aldehyde (±)-56 as shown in Scheme 35.



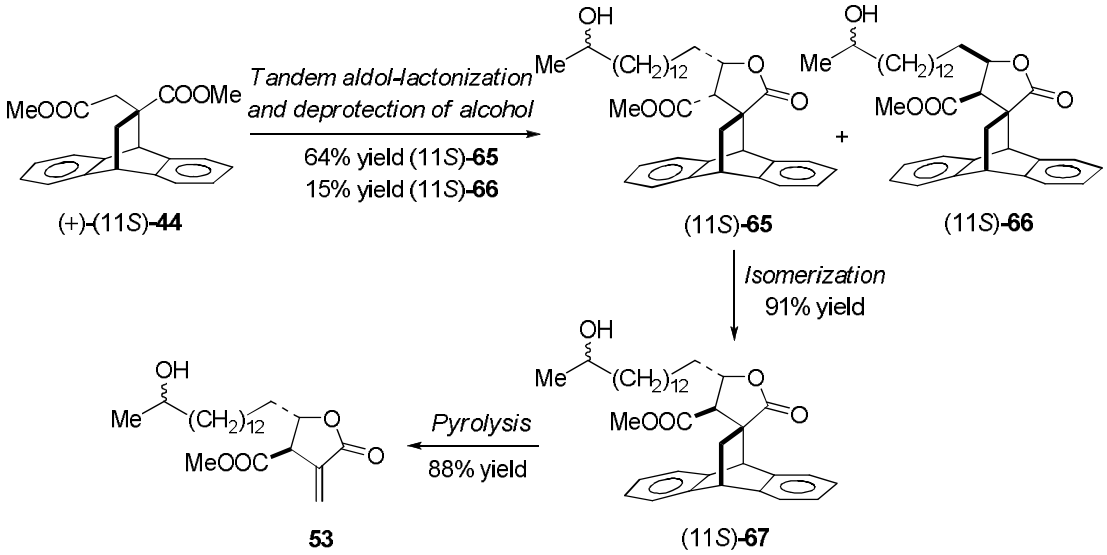
Scheme 35 Synthetic of protoconstipatic acid methyl ester (53) and its epimer

Our synthetic route of racemic aldehyde (±)-56 consisted of six crucial steps : by i) methylation, ii) Baeyer-Villiger reaction, iii) transmethylation, iv) protection of optically active alcohol, v) reduction, and vi) Swern oxidation as depicted in Scheme 36. The synthetic approach proves to be simple and efficient methodology because of its shorter steps, inexpensive, and very good in overall yields.



Scheme 36 The reaction and yields for synthesis to chiral ether aldehyde (±)-56

The synthetic strategy of protoconstipatic acid methyl ester (53) consisted of three curcial steps : i) tandem aldol-lactonization of the anion derived from dimethyl itaconate-anthracene adduct with aldehyde, ii) isomerization, and iii) flash vacuum pyrolysis of the lactone adduct *via* retro Diels-Alder reaction as depicted in Scheme 37. Protoconstipatic acid methyl ester (53) was successively synthesized with moderate yield. However, compound 53 was partially decomposed during the pyrolysis step.



Scheme 37 The reaction and yields for synthesis to protoconstipatic acid methyl ester (53) and its epimer

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OUTPUT

1. International Publication

   Rattana Jongkol, Ruangrat Choommongkol, Bongkoch Tarnchompoo, Piyarat Nimmanpipug and Puttinan Meepowpan, "Syntheses of methylenolactocin and nephrosterinic acid *via* diastereoselective acylation and chemoselective reduction–lactonization", *Tetrahedron* 2009, *65*, 6382–6389. (Impact factor = 2.869)

2. National Conference

   Piyanan Tangvenichcharoensuk, Winita Punyodom, Robert Molloy and Puttinan Meepowpan, "Synthesis and microstructural chracterisation of poly(ε-caprolactone) homopolymers with different molecular architectures", The International Congress for Innovation in Chemistry (PERCH CONGRESS IV), 8–11 May 2005, Pattaya, Chonburi, Thailand (2005).

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adduct *via* tandem Michael addition–ring closure (MIRC)", The 31st Congress on Science and Technology of Thailand (STT 2005), 18–20 October 2005 at Technopolis, Suranaree University of Technology, Nakhon Ratchasima (2005).

Boontharika Thapsukhon, Winita Punyodom, Robert Molloy, Puttinan Meepowpan, Taweechai Amornsakchai, "Synthesis and characterization of linear, branched and star-shaped biodegradable polyesters for use in biomedical applications", the 31st Congress on Science and Technology of Thailand (STT 2005), 18–20 October 2005 at Technopolis, Suranaree University of Technology, Nakhon Ratchasima (2005).

Puttinan Meepowpan, Anuruk Chailungka and Yodhathai Thebtaranonth, "Total synthesis of (±)-protoconstipatic acid via tandem aldol–lactonization," นักวิจัยรุ่นใหม่ ...พบ .... เมธีวิจัยอาวุโส สกว / สำนักงานกองทุนสนับสนุนการวิจัย, 12–14 ตุลาคม 2549 ณ โรงแรมรีเจนต์ อ.ชะอำ จ.ชลบุรี (2006).

Winita Punyodom, Robert Molloy, Puttinan Meepowpan and Taweechai Amornsakchai, "Controlled ring-opening polymerisation of cyclic esters", นักวิจัยรุ่นใหม่ ...พบ .... เมธีวิจัยอาวุโส สกว / สำนักงานกองทุนสนับสนุนการวิจัย, 12–14 ตุลาคม 2549 ณ โรงแรมรีเจนต์ อ.ชะอำ จ.ชลบุรี (2006).

3. Usefulness of the research

Despite the progress of science during the past four centuries did not lose their actuality. Knowledge about the etiology of diseases is still limited and for many life-threatening illnesses no effective treatments exist. Nature always has been a valuable source of drugs and despite the unprecedented opportunities afforded by medicinal chemistry, continues to deliver lead compounds. Traditionally, research on natural sources was focused on plants and microorganisms. However, the natural products from natural sources are less quantity for treatment many patients in the world.

Therefore, the objectives in this work, I interested in toward studies and synthesis of α-methylene-γ-butyrolactones *e.g.* protoconstipatic acid, *allo*-pertusaric acid, *allo*-dihydropertusaric acid and their derivatives which is a basic structure unit in a wide range of important naturally occurring compound. These compound exhibit interesting biological activities such as antibacterial, antifungal, antitumor, and in certain cases, growth regulating agents. Development of this synthetic approach

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proves to be short, simple and efficient methodology with high specific Baeyer-Villiger reaction and tandem aldol–lactonization reactions, which may be usefulness for drugs development in the future.

Finally, this grant supported B.S. and M.S. researches in title of “Synthesis of protoconstipatic acid methyl ester and its epimer”.

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APPENDIX I
REPRINT PAPER

Rattana Jongkol, Ruangrat Choommongkol, Bongkoch Tarnchompoo,
Piyarat Nimmanpipug and Puttinan Meepowpan

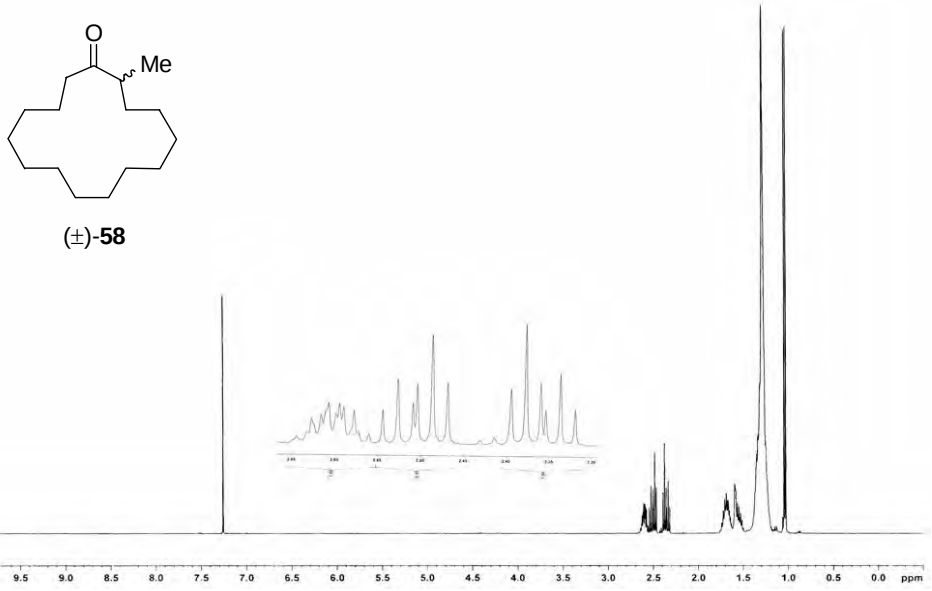
in title

"Syntheses of methylenolactocin and nephrosterinic acid via diastereoselective acylation and chemoselective reduction lactonization"

Tetrahedron 2009, *65*, 6382–6389.
(Impact factor = 2.869)

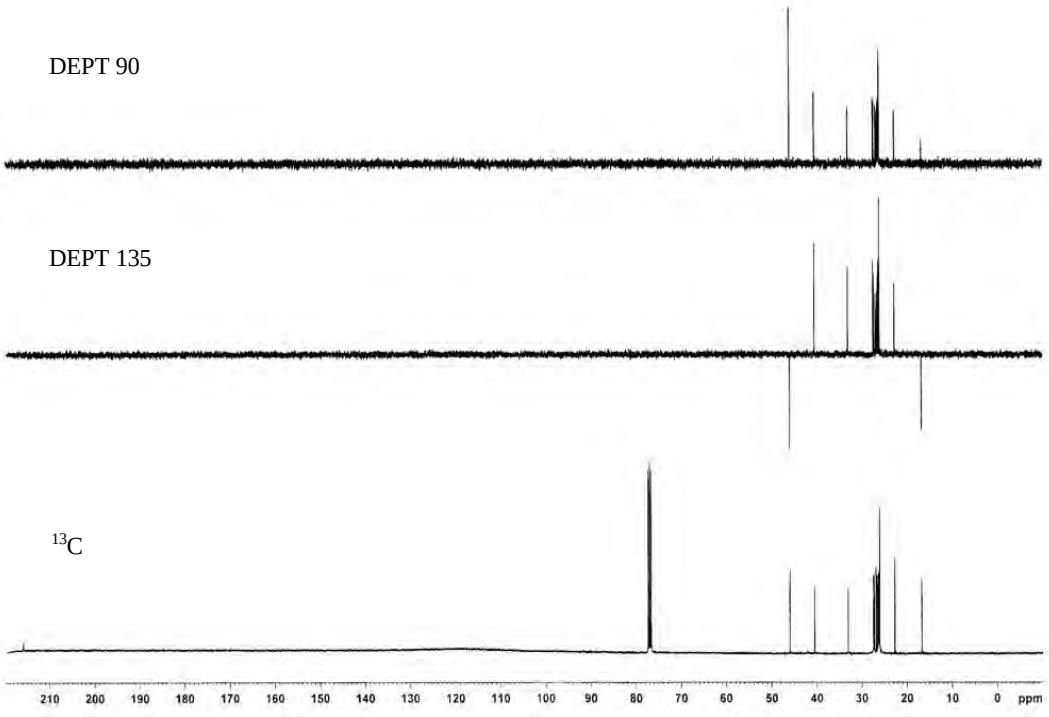
APPENDIX II
(^{1}H, and ^{13}C NMR)

^{1}H NMR in $CDCl_3$

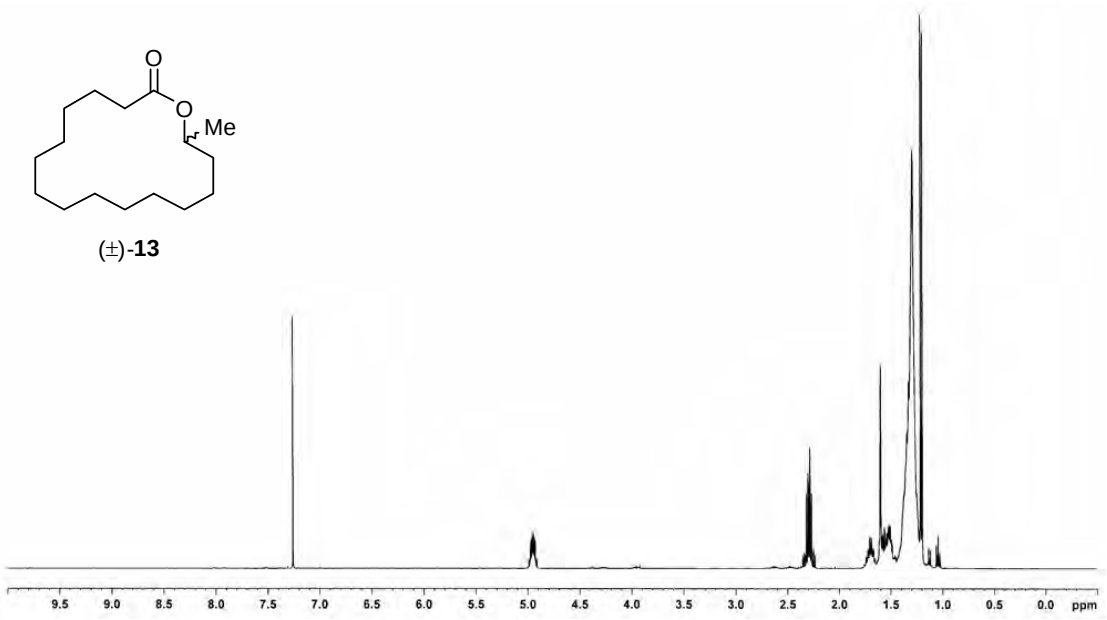


(±)-**58**

^{13}C NMR in $CDCl_3$

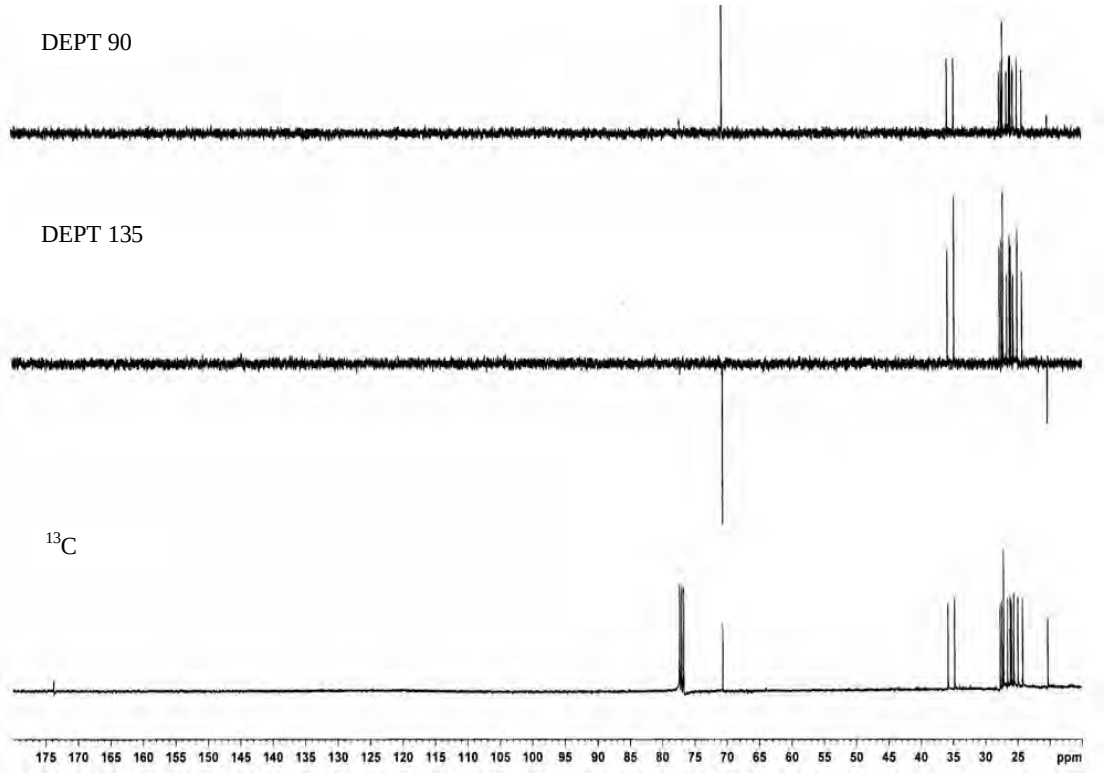


^{1}H NMR in $CDCl_3$

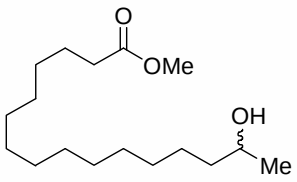


(±)-**13**

^{13}C NMR in $CDCl_3$

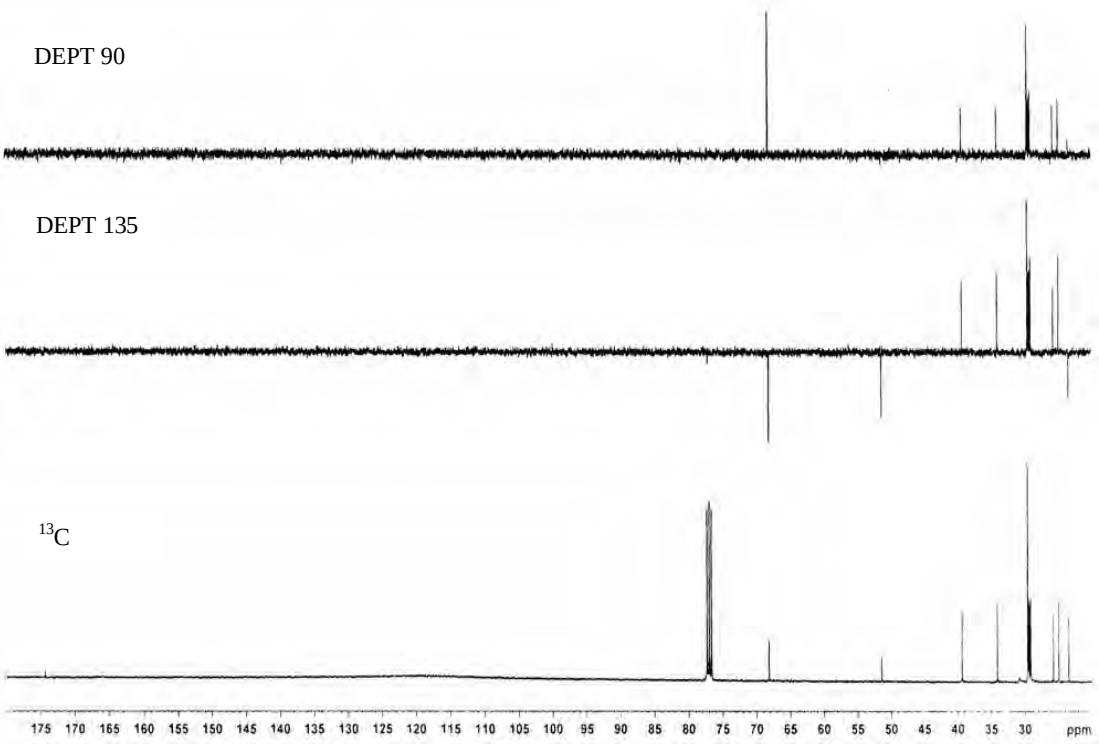


^{1}H NMR in $CDCl_3$

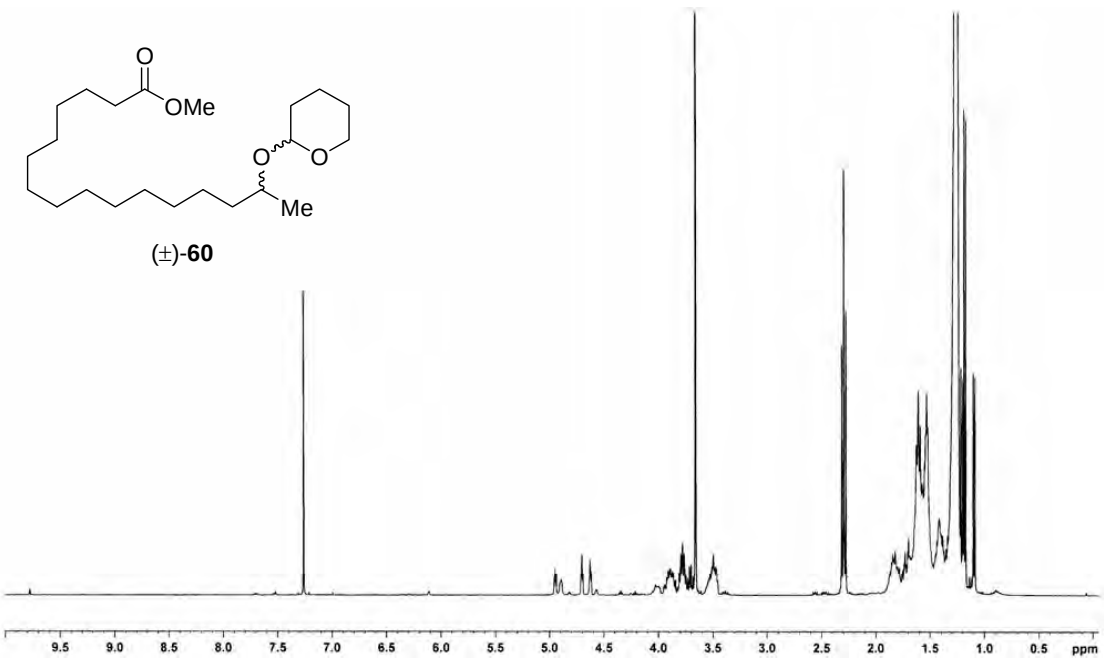


(±)-**59**

^{13}C NMR in $CDCl_3$

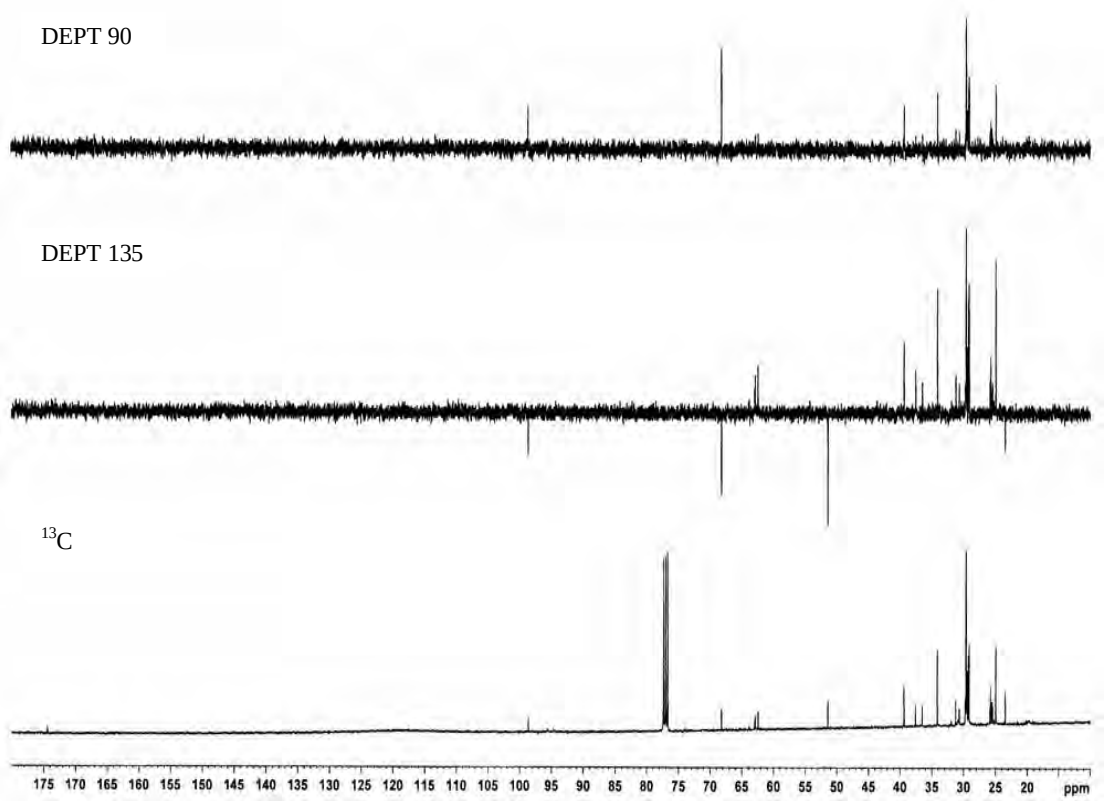


^{1}H NMR in $CDCl_3$

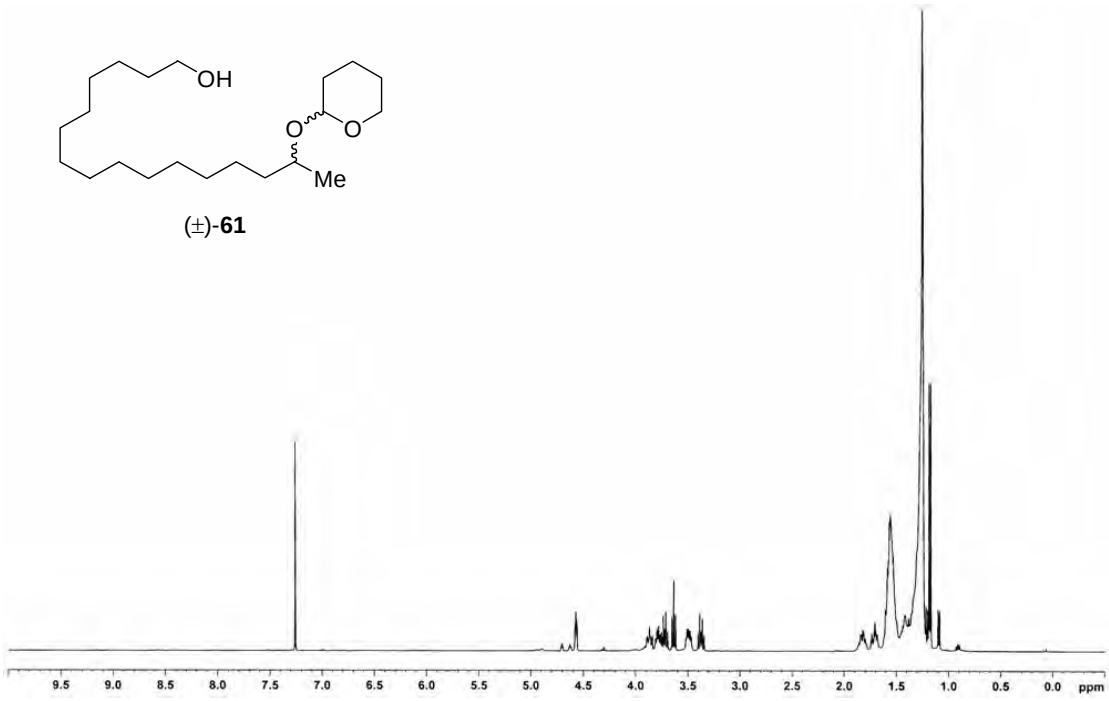


(±)-**60**

^{13}C NMR in $CDCl_3$

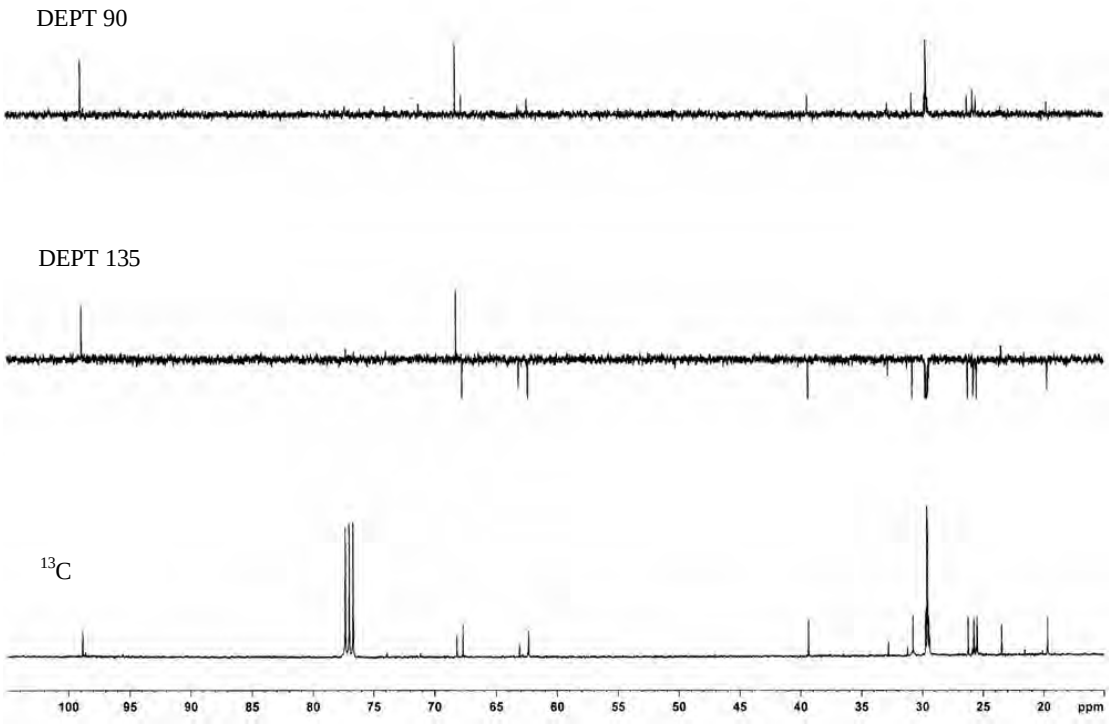


^{1}H NMR in $CDCl_3$

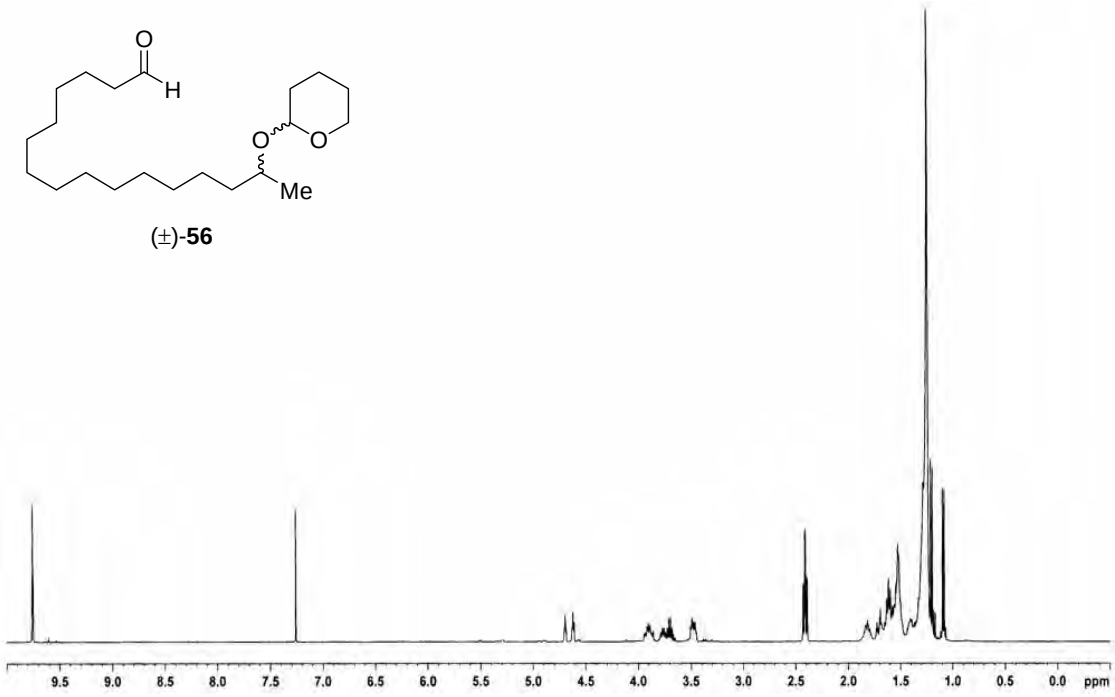


(±)-**61**

^{13}C NMR in $CDCl_3$

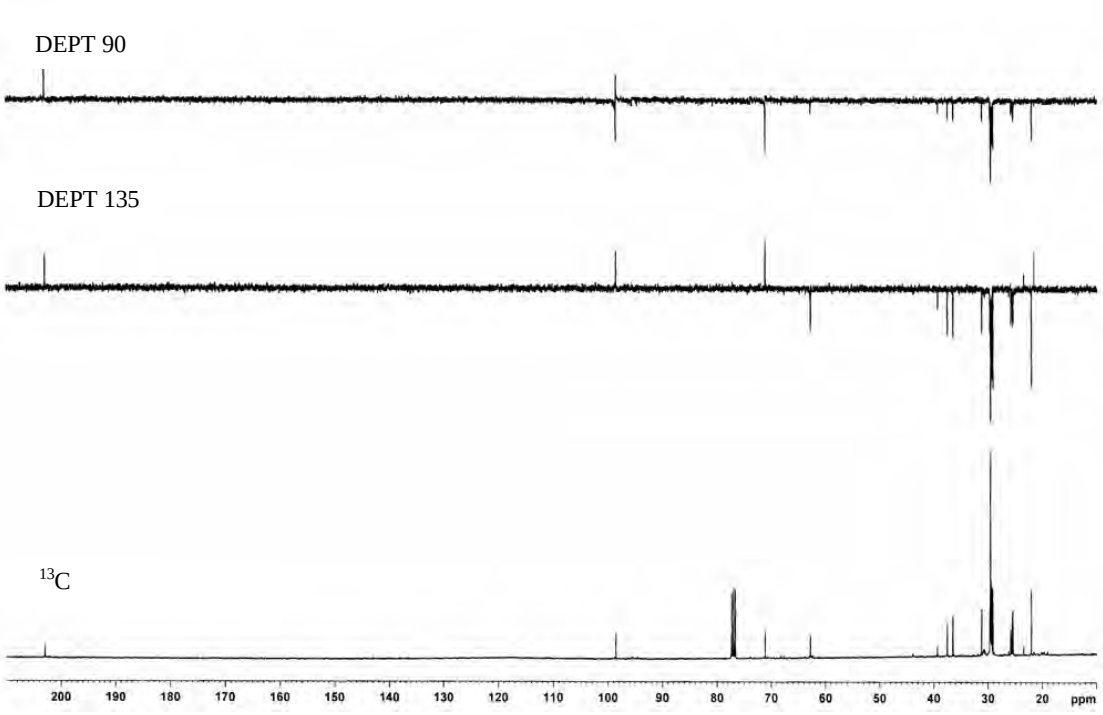


^{1}H NMR in $CDCl_3$

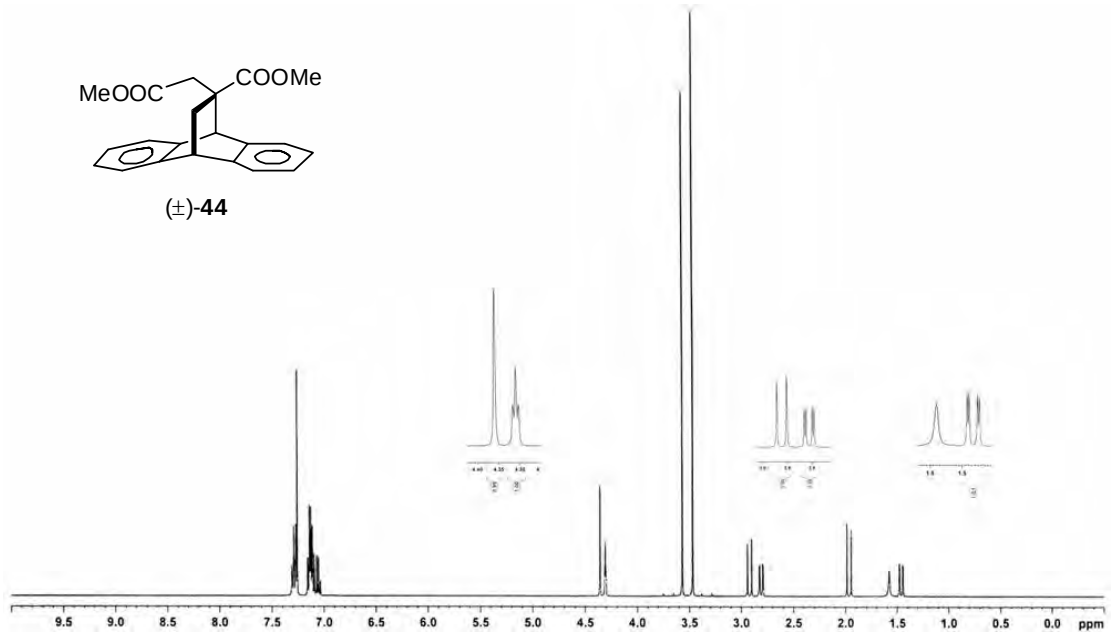


(±)-**56**

^{13}C NMR in $CDCl_3$

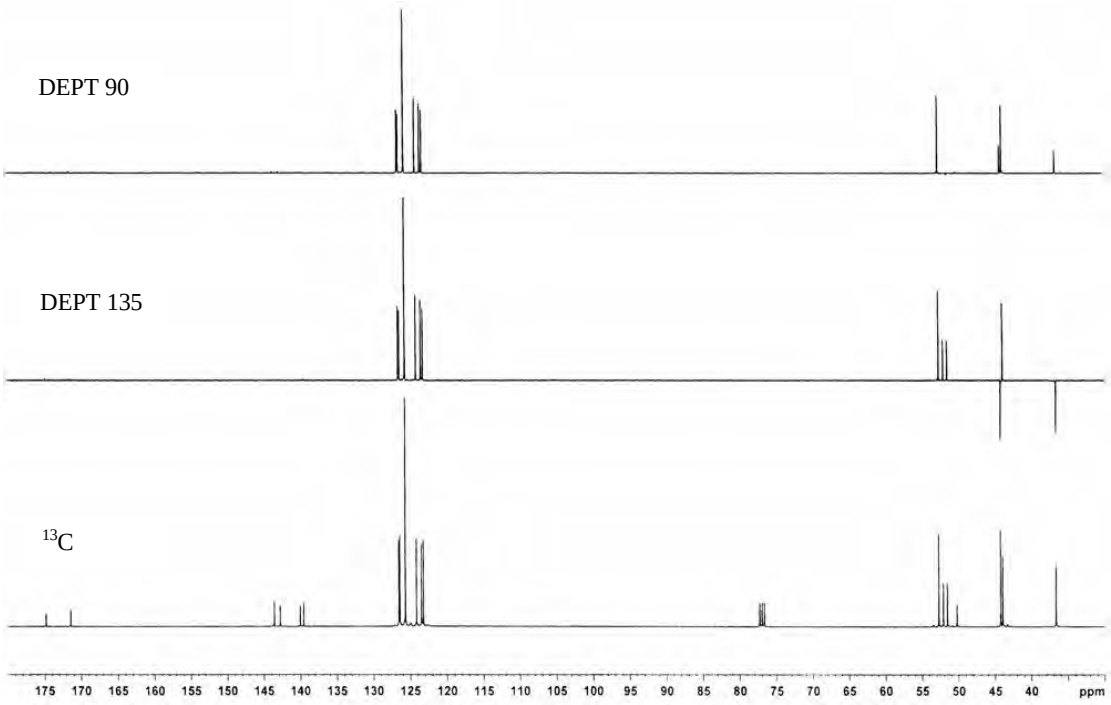


^{1}H NMR in $CDCl_3$



(±)-**44**

^{13}C NMR in $CDCl_3$



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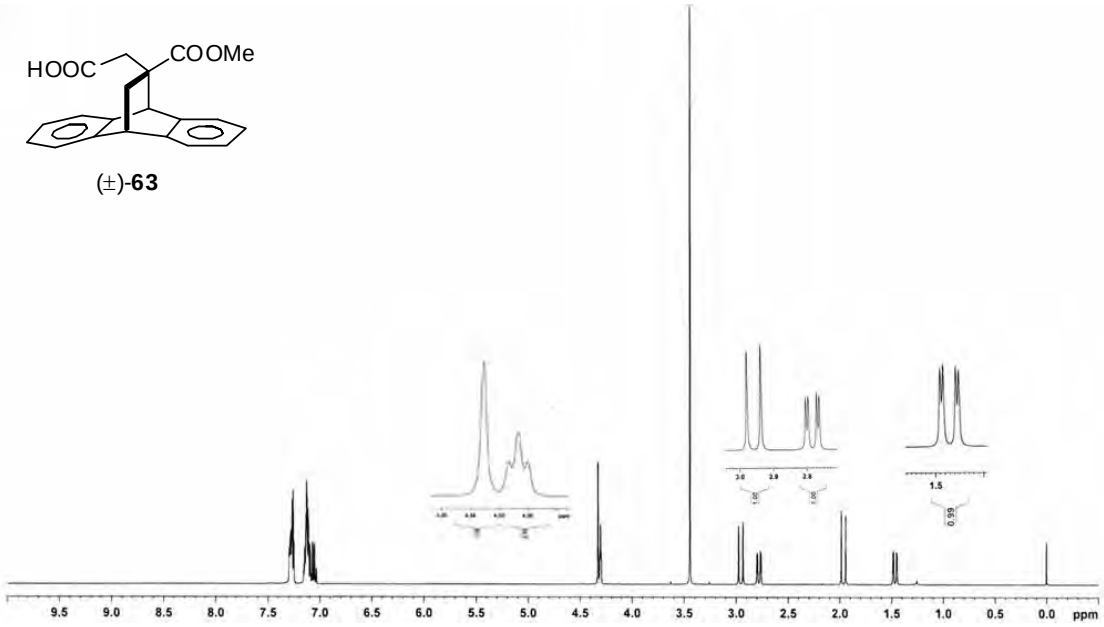
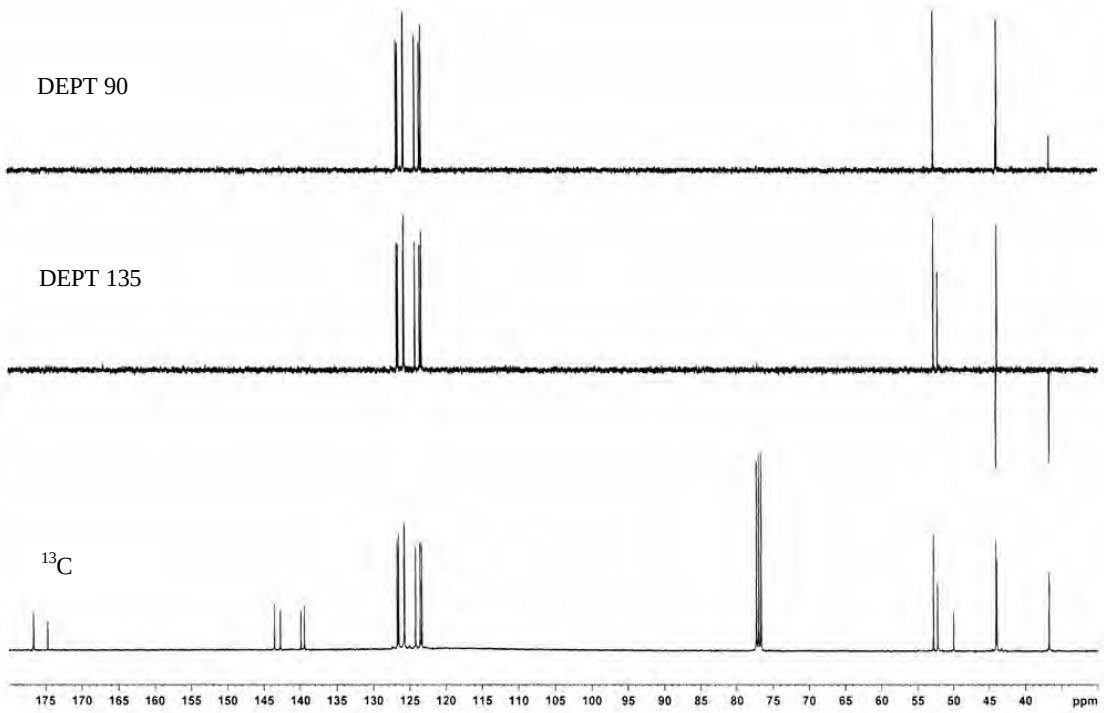


^{13}C NMR in $CDCl_3$



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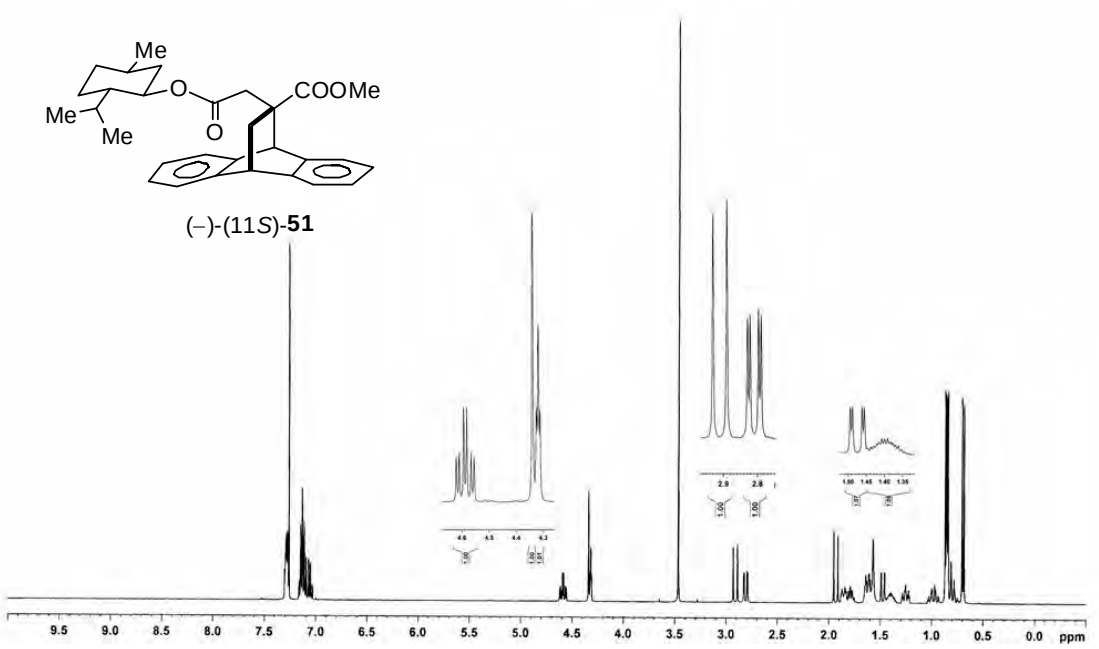
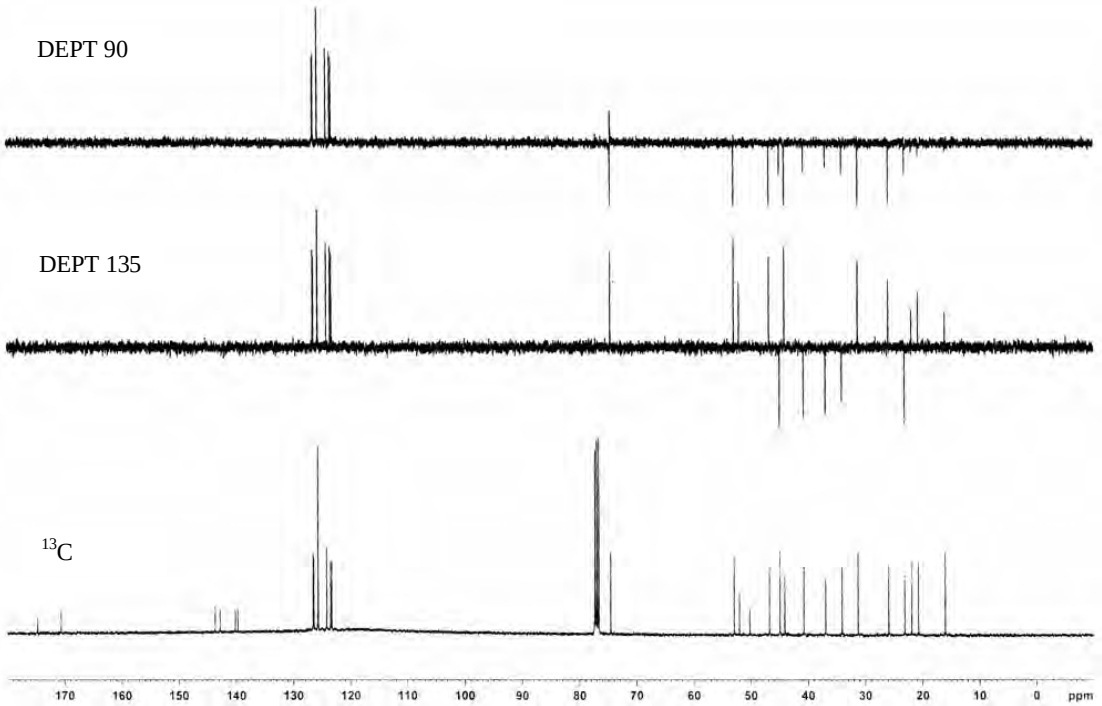


(–)-(11*S*)-**51**

^{13}C NMR in $CDCl_3$



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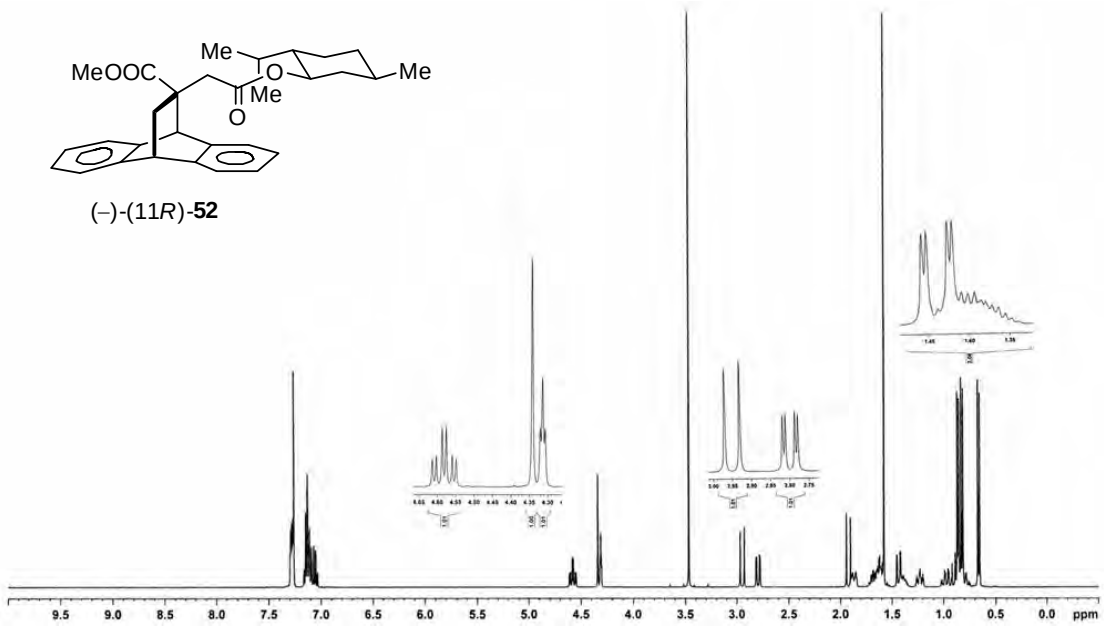
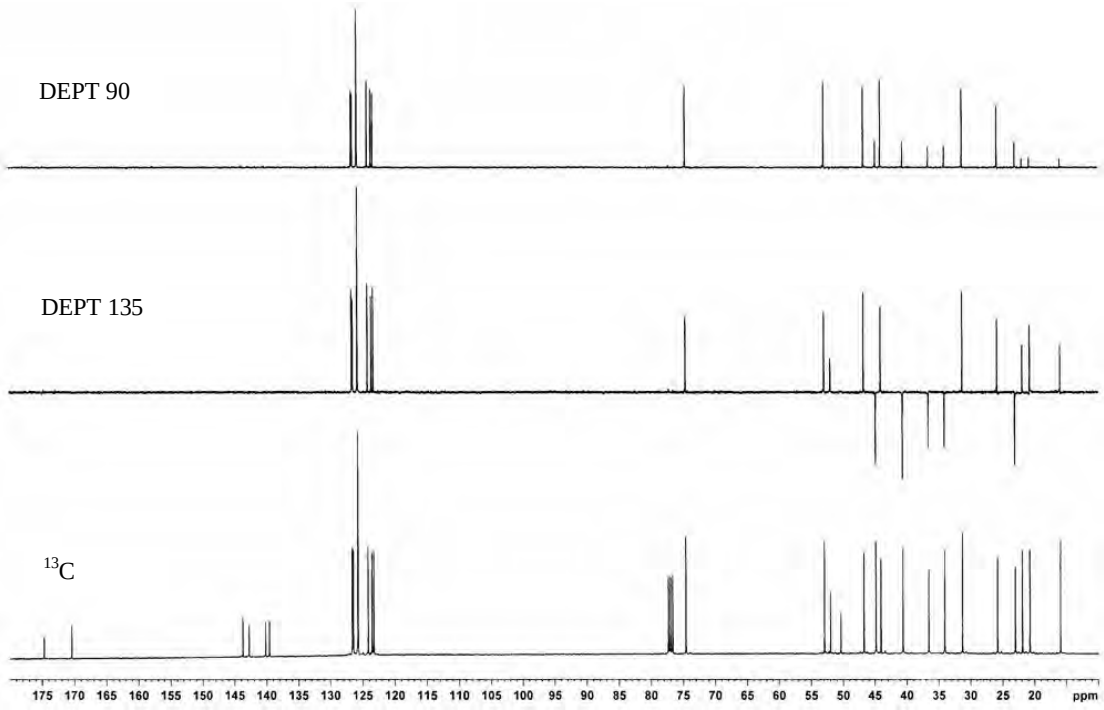


(–)-(11*R*)-**52**

^{13}C NMR in $CDCl_3$



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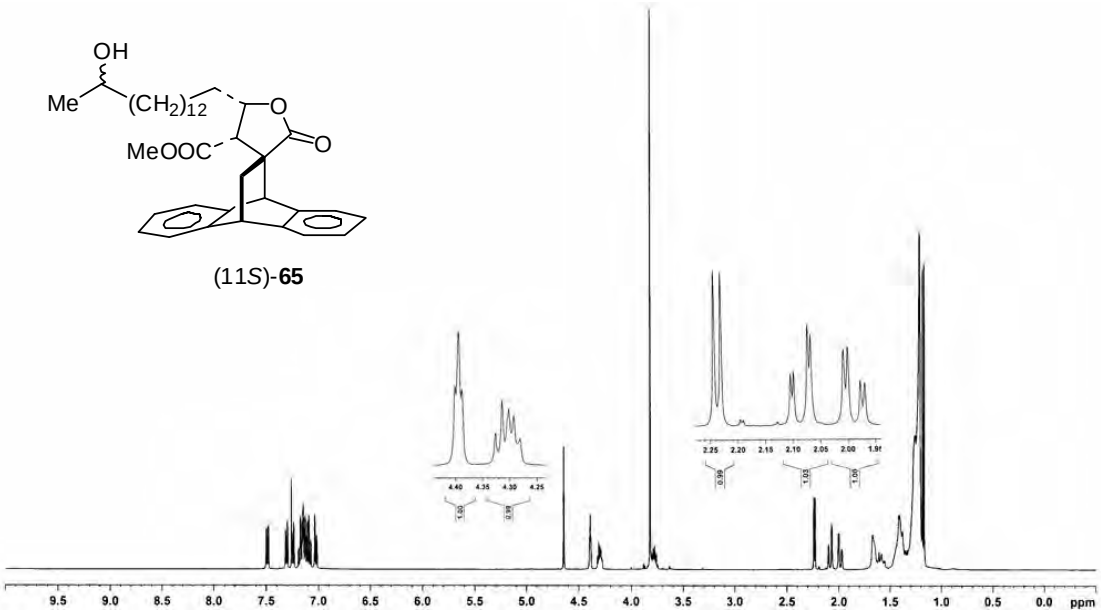
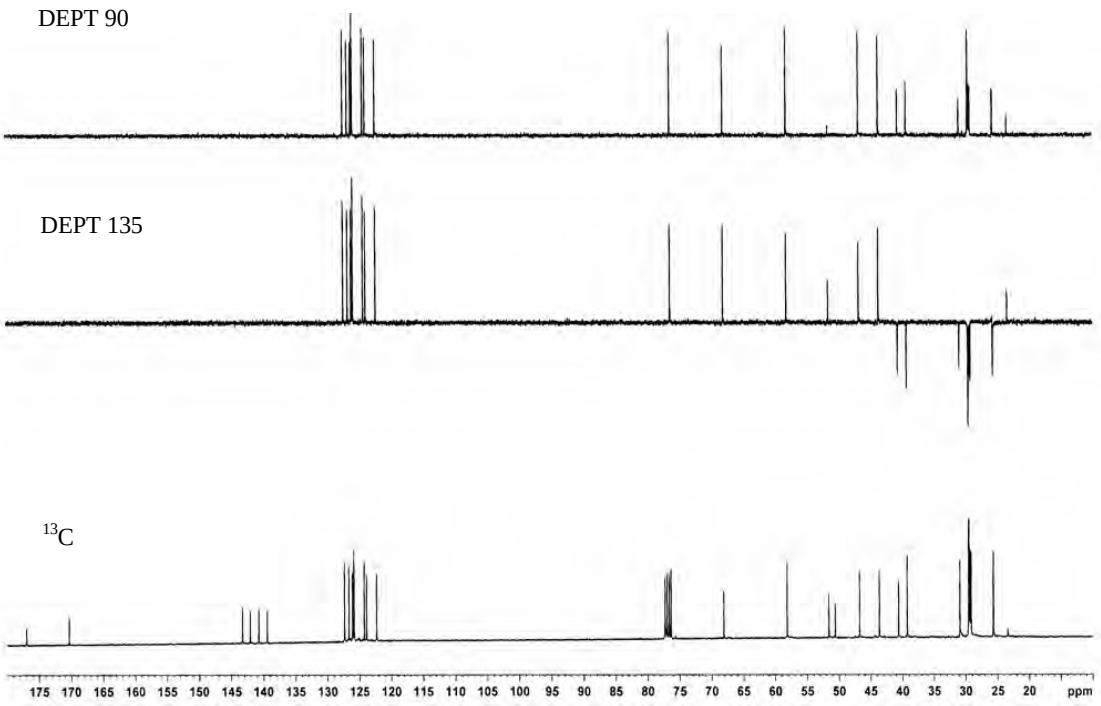


(11*S*)-**65**

^{13}C NMR in $CDCl_3$



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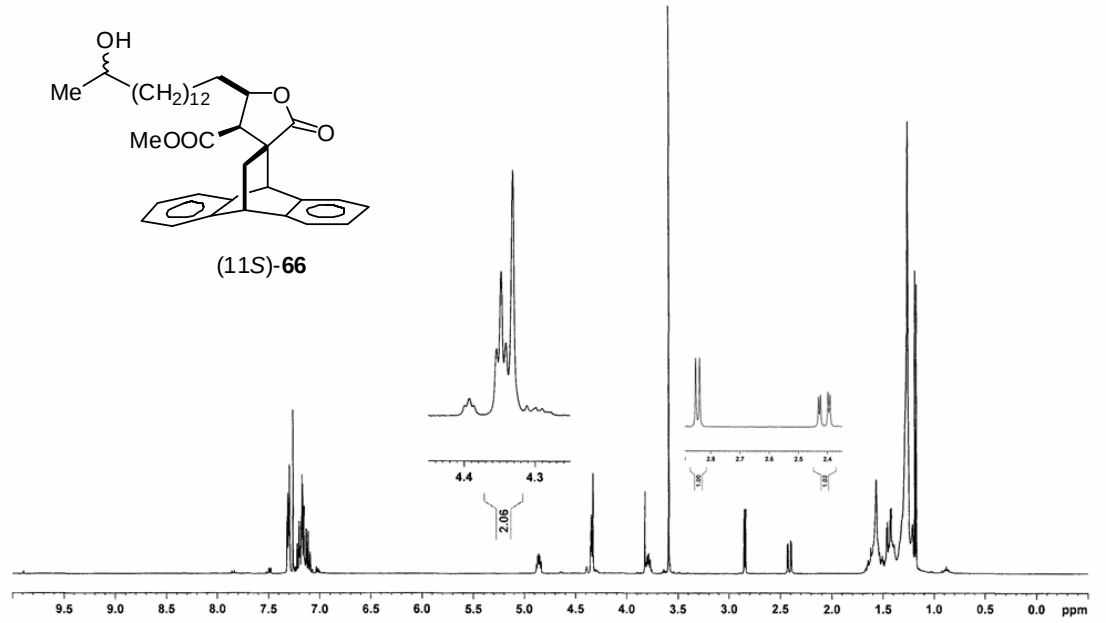
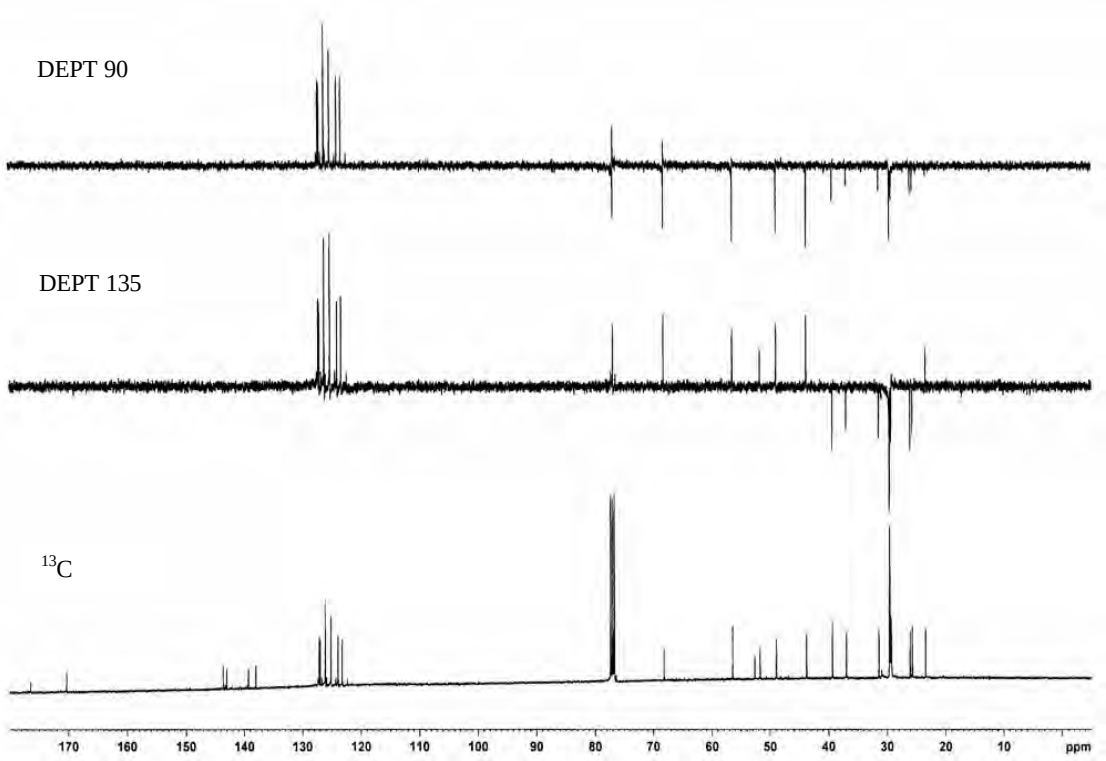


(11*S*)-**66**

^{13}C NMR in $CDCl_3$



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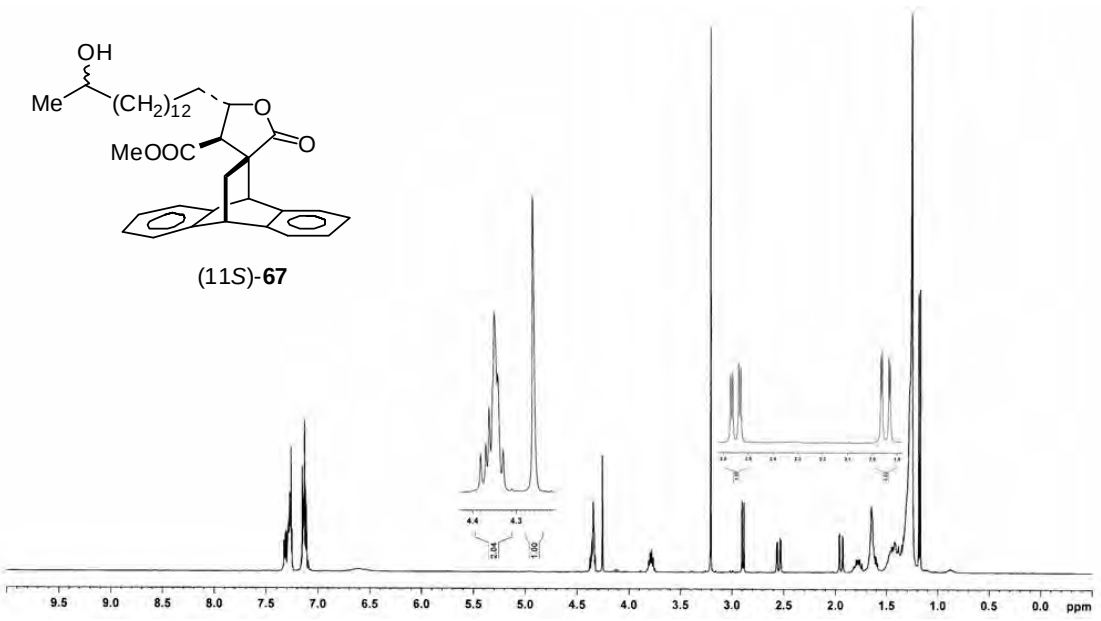
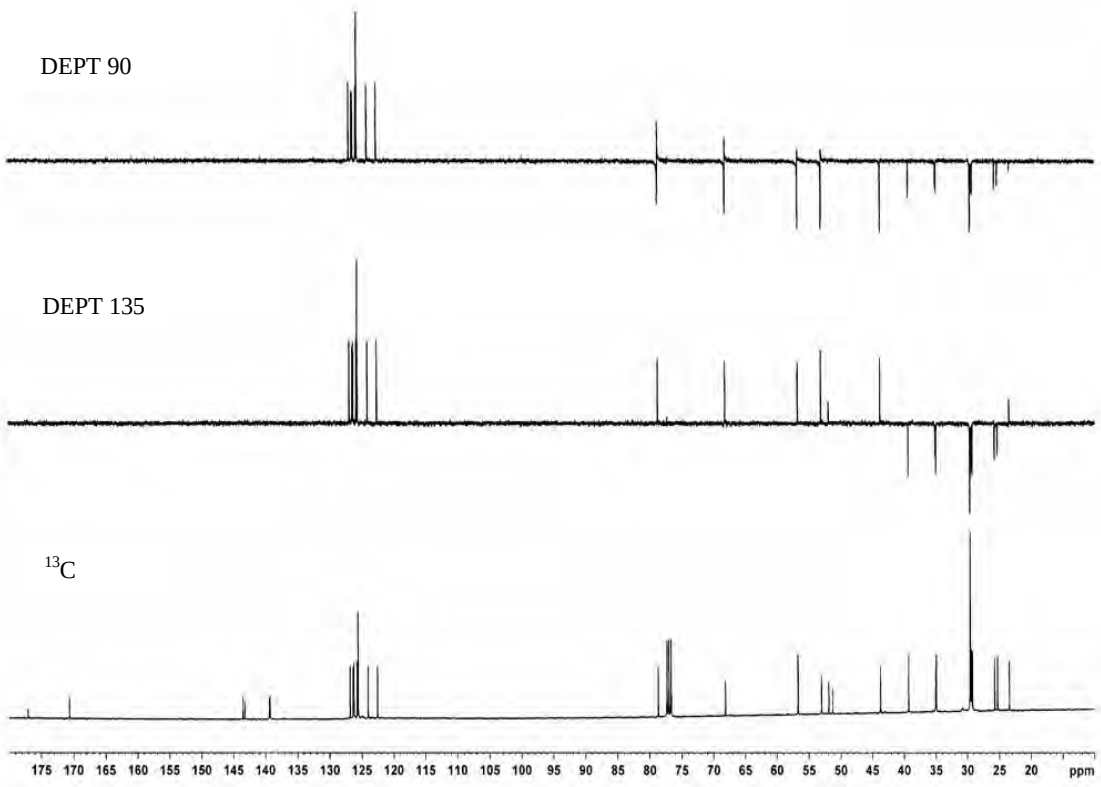


(11*S*)-**67**

^{13}C NMR in $CDCl_3$



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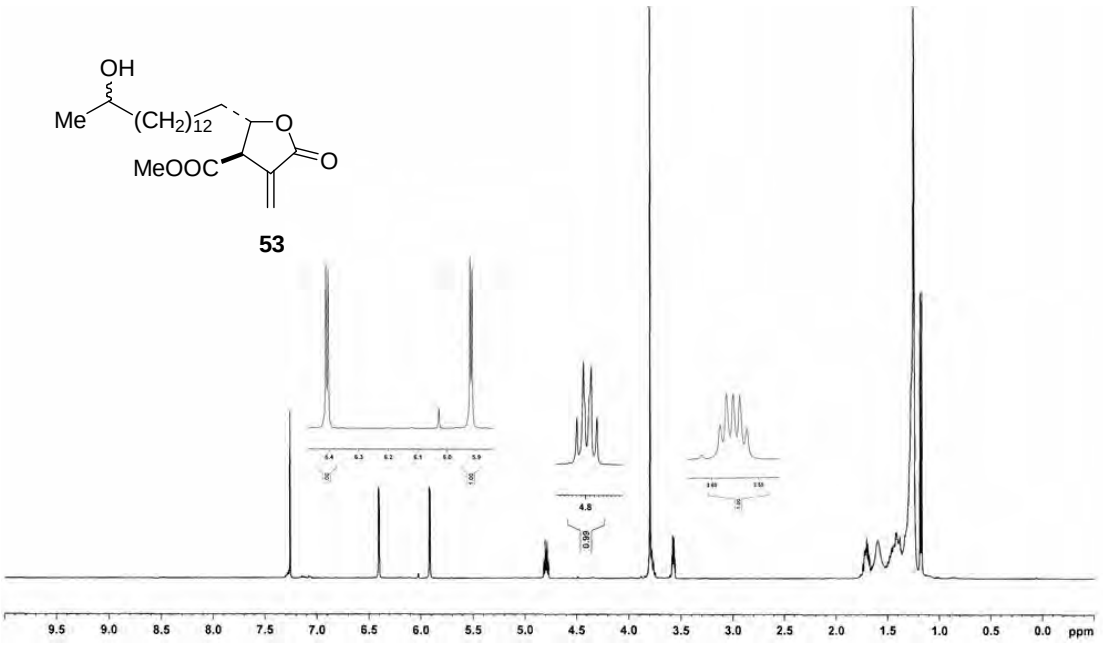

^{13}C NMR in $CDCl_3$