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

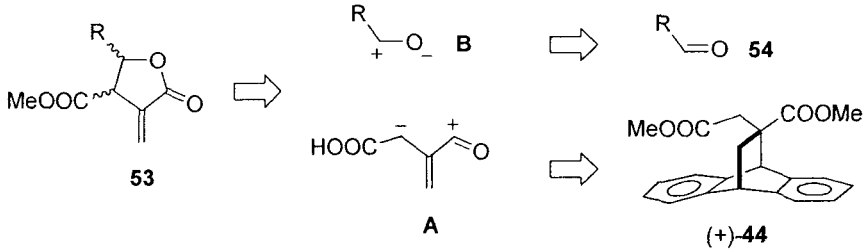
Mass spectrometry (ESI-MS)	
Molecular weight	m/z
Calc. for $C_{22}H_{38}O_5Na$	405.2617 $(M+Na)^+$
Found for $C_{22}H_{38}O_5Na$	405.2618 $(M+Na)^+$

CHAPTER 3

RESULTS AND DISCUSSION

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

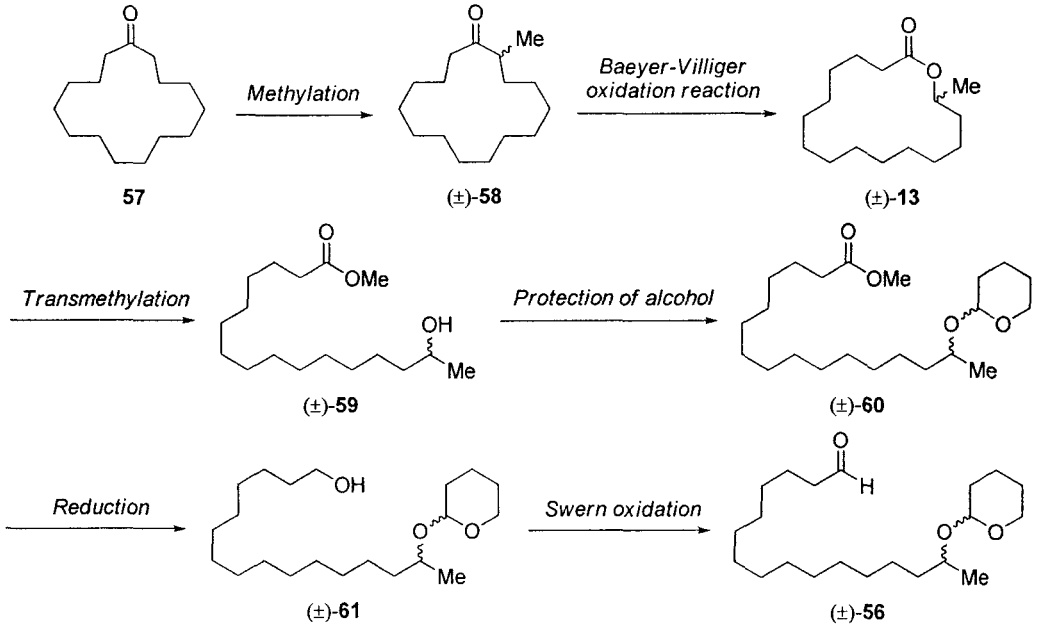
The retrosynthetic analysis of protoconstipatic acid methyl eater (**53**) and its epimer could be derived from dimethyl itaconate-anthracene adduct (**44**) and 15-hydroxylaldehyde (**54**) *via* tandem aldol-lactonization reaction (Scheme 12).



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

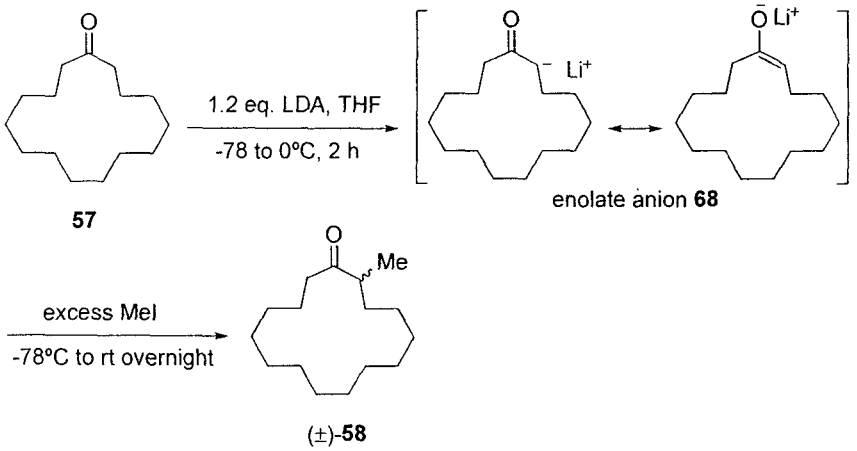
3.2 Synthesis of 15-(tetrahydro-2*H*-pyran-2-yloxy)hexadecanal [(±)-56]

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).

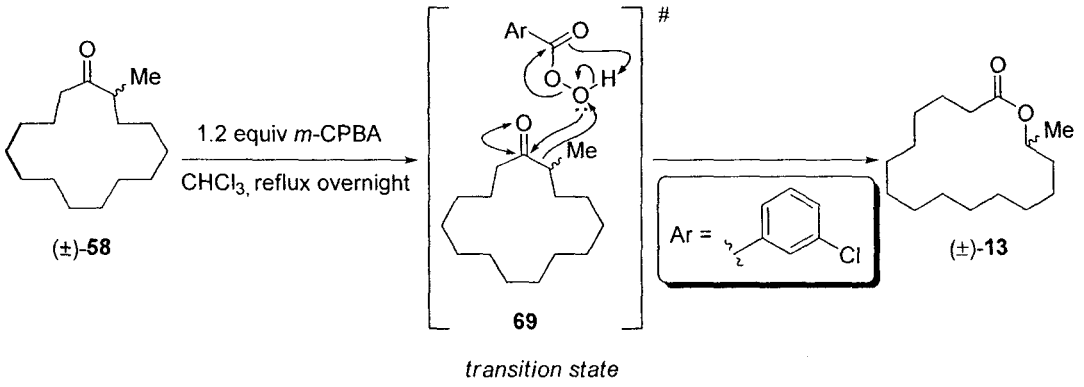


Scheme 14 Methylation reaction of cyclopentadecanone (**57**)

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 $C_{16}H_{30}ONa$.

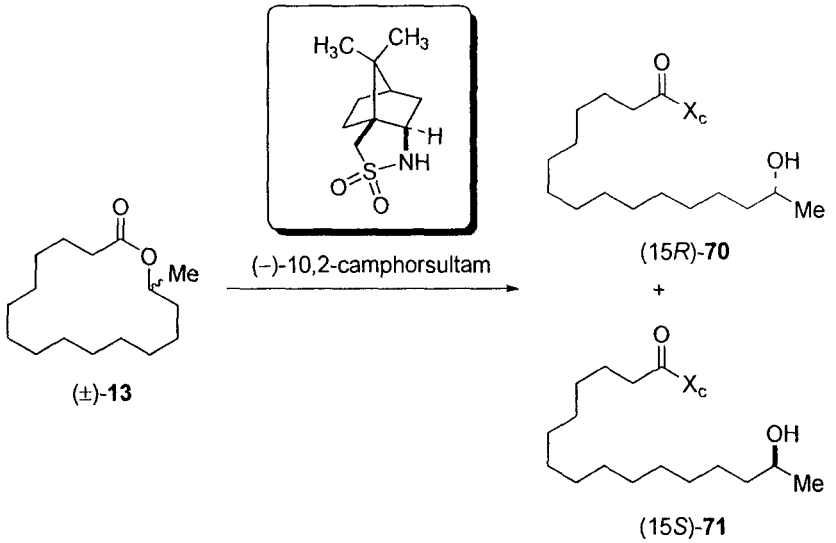
2-Methylcyclopentadecanone [(±)-**58**] was subsequently converted to 15-hexadecanolide [(±)-**13**], a sex pheromone component of the stink bug, *Piezodorus hybneri*, employing Baeyer-Villiger reaction. Oxidation of (±)-**58** with *m*-CPBA in $CHCl_3$ followed by refluxing for overnight and work-up 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.

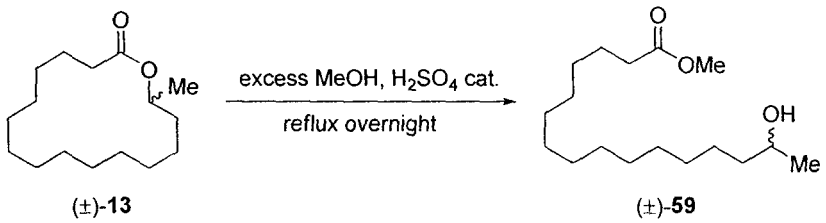


Scheme 16 Reaction of (±)-**13** with (−)-10,2-camphorsultam as a chiral auxiliary

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**].



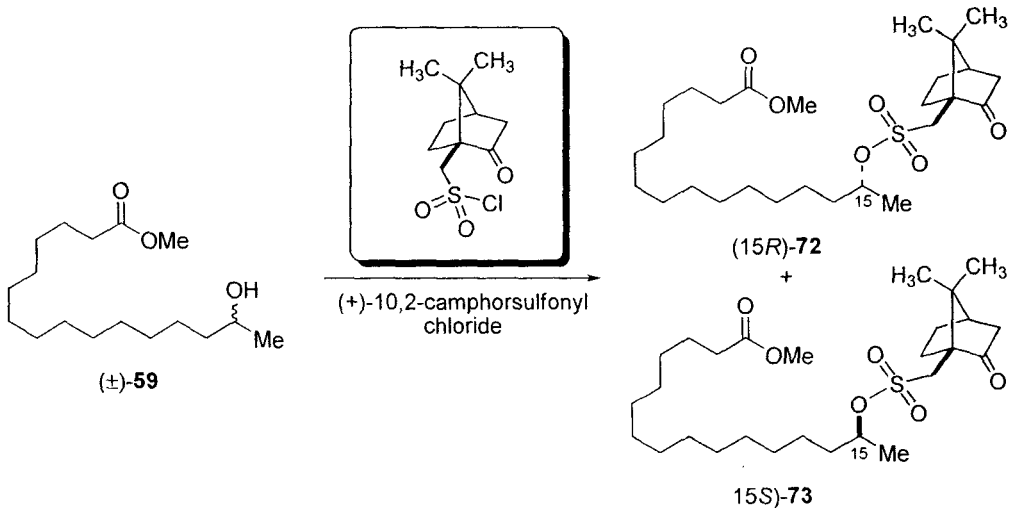
(±)-**13** (±)-**59**

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.

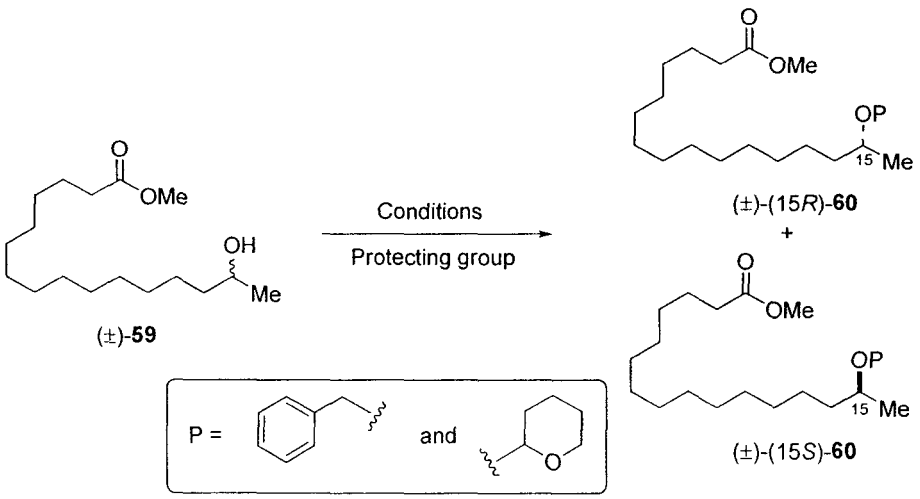


Scheme 18 Reaction of (±)-**59** with (+)-camphor-10-sulfonyl chloride as a chiral auxiliary

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.

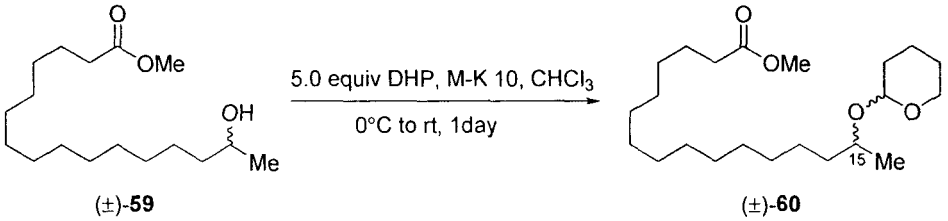


Scheme 19 Another synthetic route for protection of active alcohol (±)-**59**

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

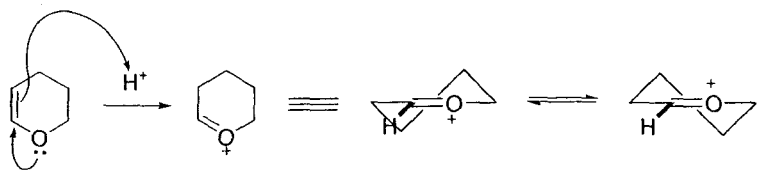
Entry	Conditions	Results
1	1.3 equiv benzyl bromide, 3.0 equiv NaH, DMF, 0 °C to rt, overnight	Recover of starting material
2	3.0 equiv benzyl bromide, 3.0 equiv NaH, THF, 0 °C to rt, overnight	Recover of starting material
3	3.0 equiv benzyl bromide, 3.0 equiv NaH, DMF, THF, 0 °C to rt, overnight	Recover 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.

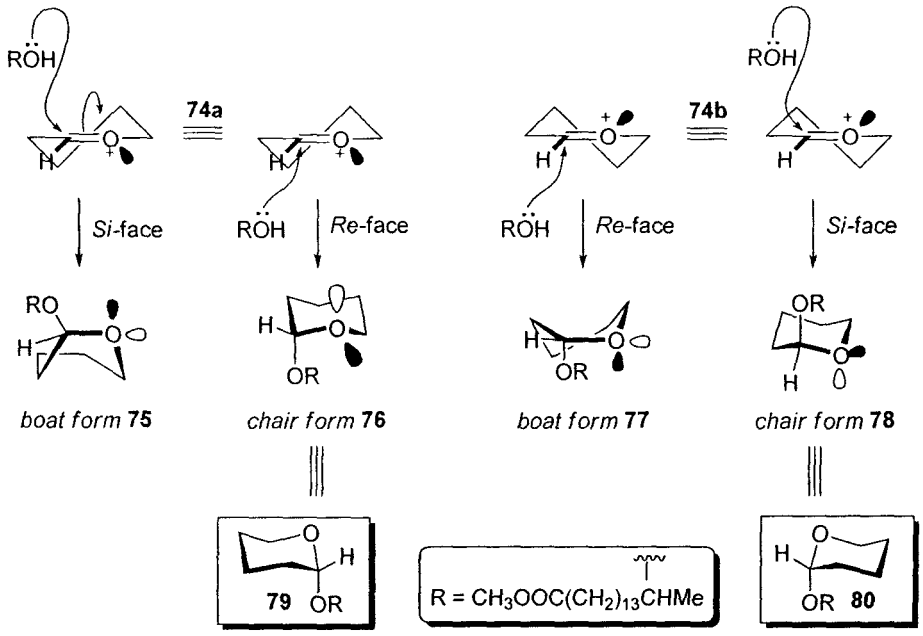


Scheme 20 Protection of alcohol group by DHP and M-K10

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.

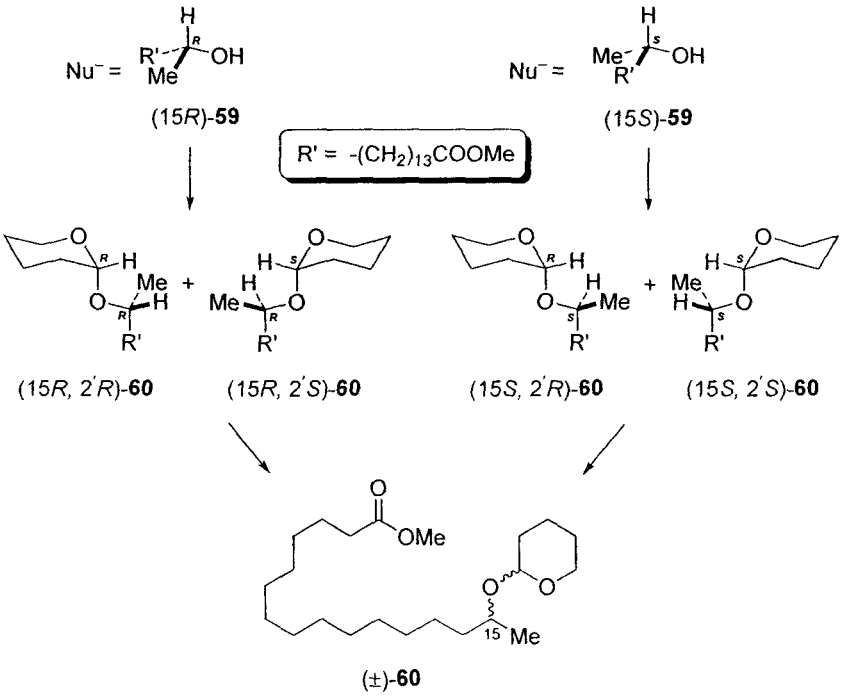


Scheme 21 Mechanism of 3,4-dihydro-2*H*-pyran with montmorillonite K10



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 $C_{22}H_{42}O_4Na$.

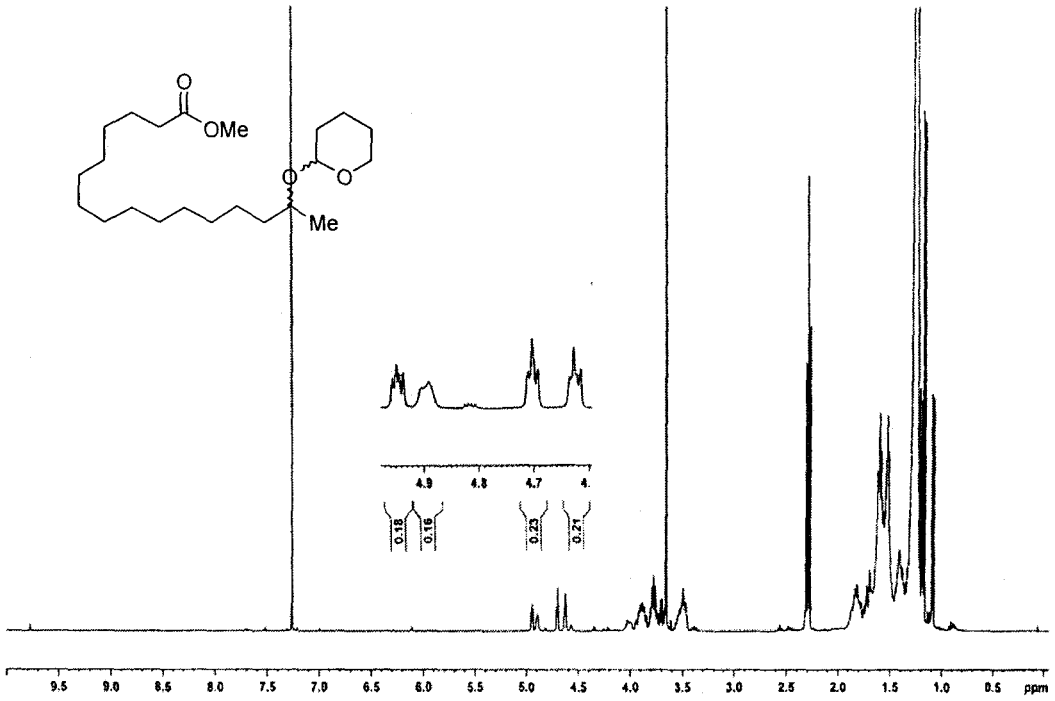
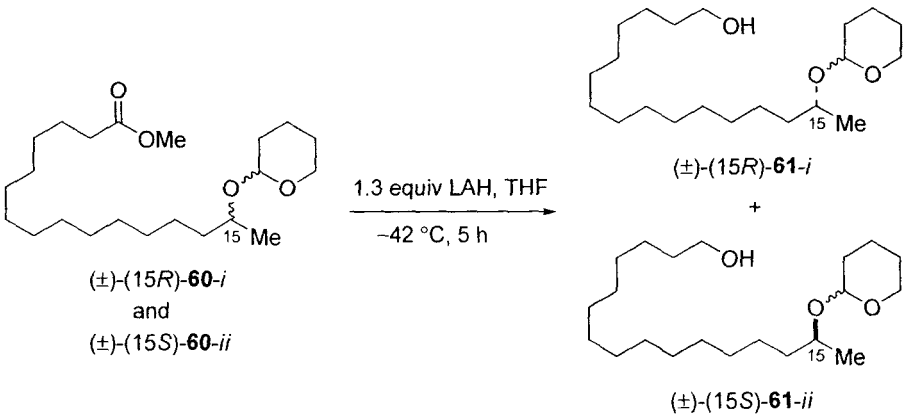


Figure 7 ^{1}H NMR spectral data of compound (±)-**60**

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*

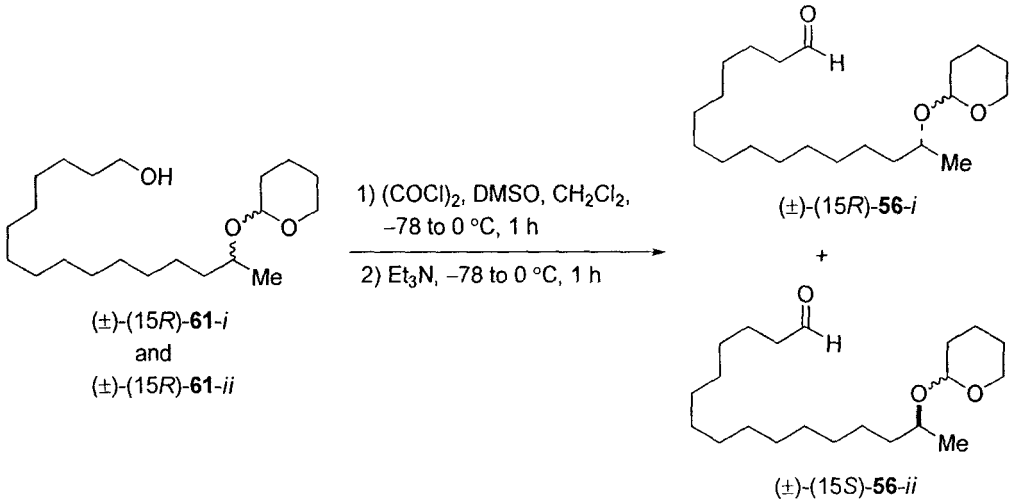
(±)-(15*R*)-**61**-*i*

(±)-(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 affored the corresponding aldehyde (±)-**56** (Scheme 25).



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

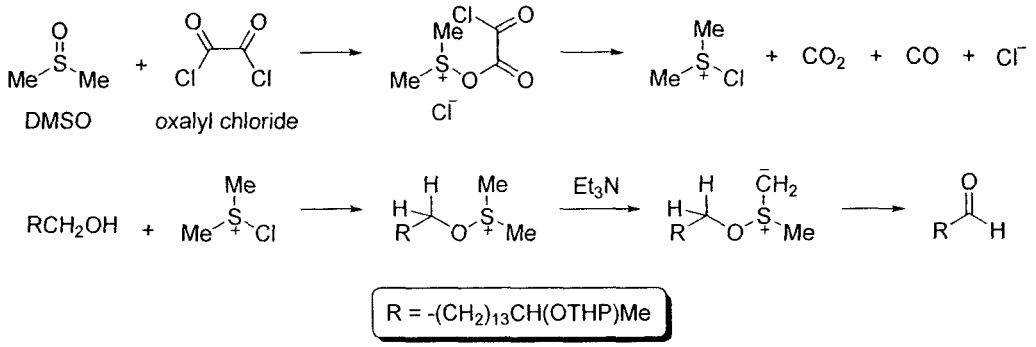
(±)-(15*R*)-**56**-*i*

(±)-(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.

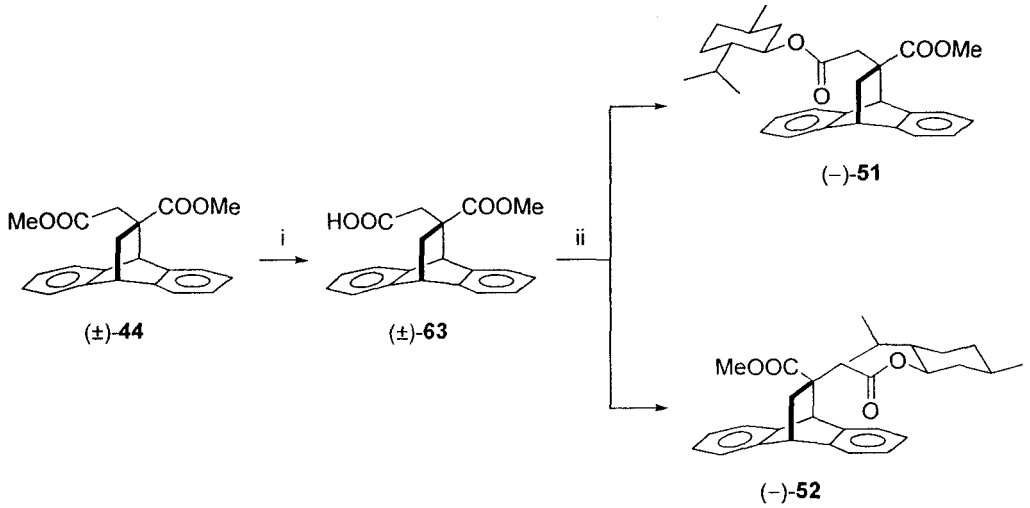


Scheme 26 Mechanism of Swern oxidation

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

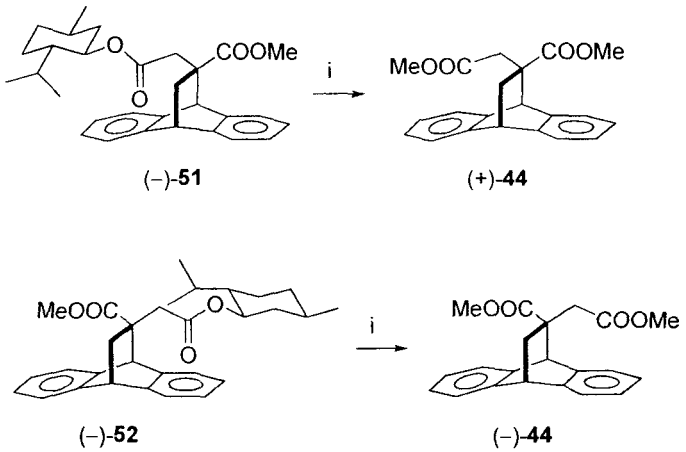
Our synthetic method for enantiomerically pure protoconstipatic acid methyl ester focused on enantiomerically pure itaconate adduct **44** as building block. The optically active adducts, (11*S*)-**44** and (11*R*)-**44,** were successively prepared followed by separation of the mixture of diastereoisomers [(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%].

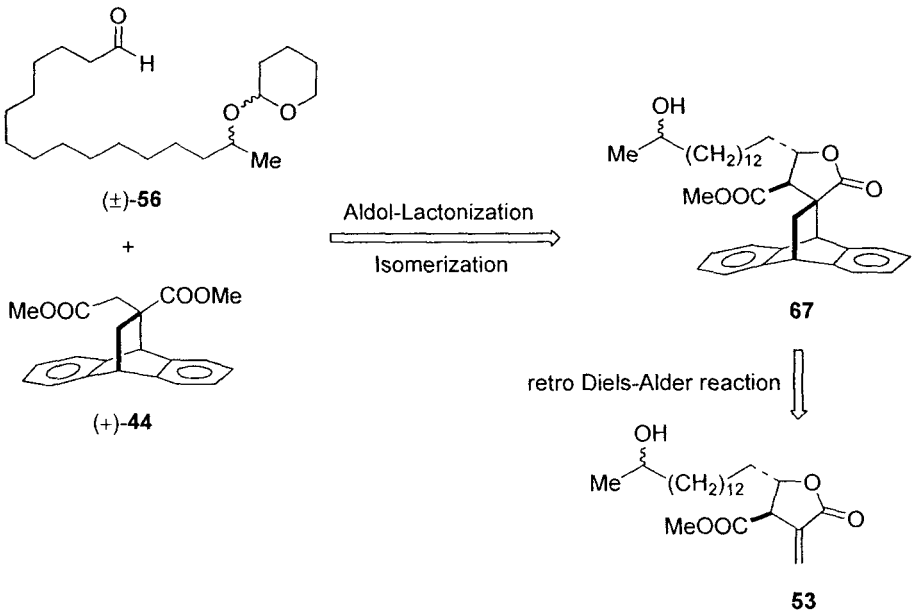
Scheme 27 Separation of optically active dimethyl itaconate-anthracene adducts



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

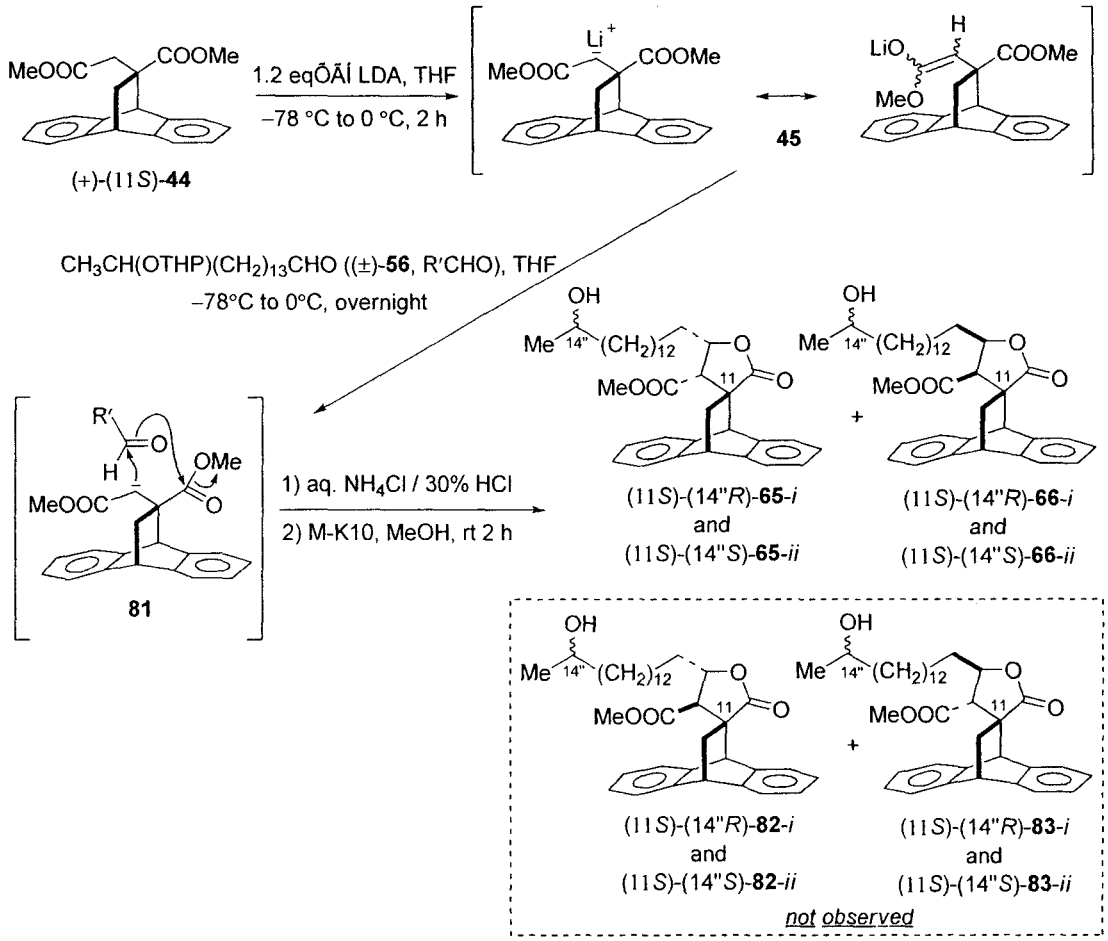
Scheme 28 Transmethylation of compounds (−)-**51** and (−)-**52**

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).



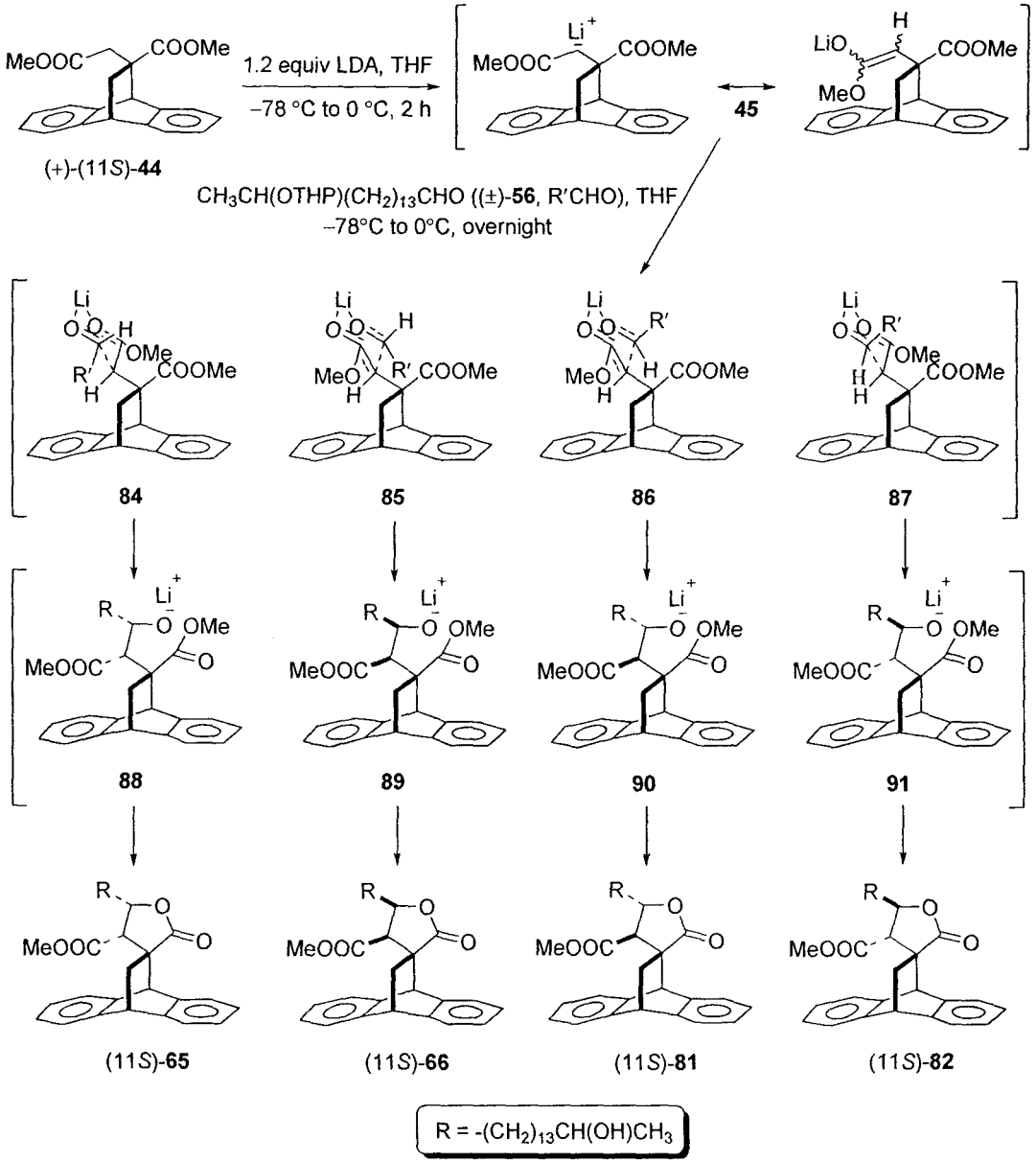
Scheme 29 Retrosynthesis of compound **53**

Anion **45** was formed by treatment dimethyl itaconate-anthracene adduct (+)-(11*S*)-**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 (11*S*)-**65** (64%) and (11*S*)-**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 $C_{36}H_{48}O_5Na$.

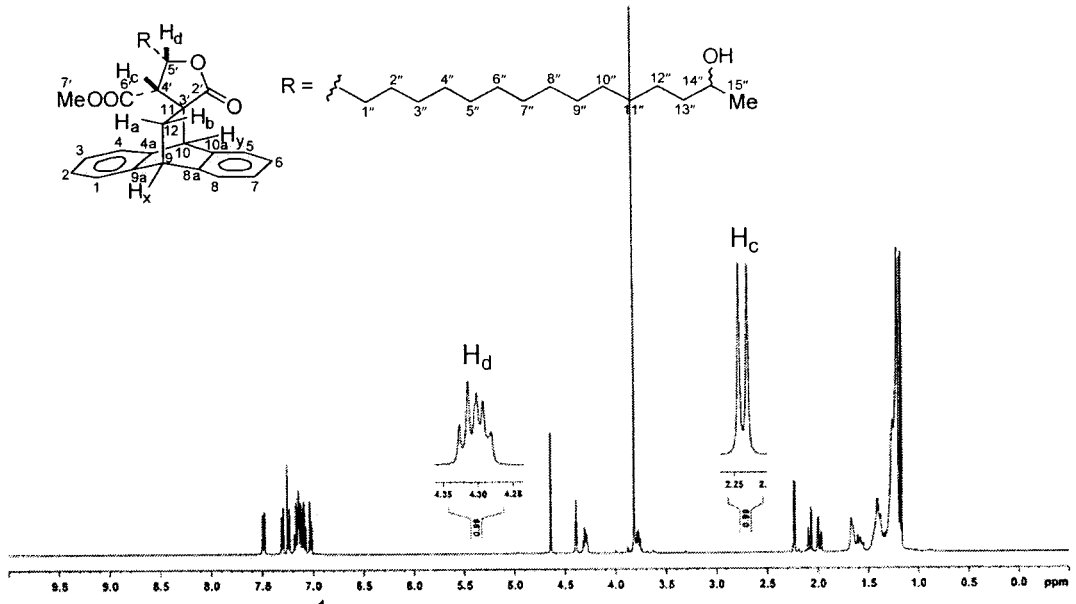


Figure 8 ^{1}H NMR spectral data of *cis*-isomer (11*S*)-**65**

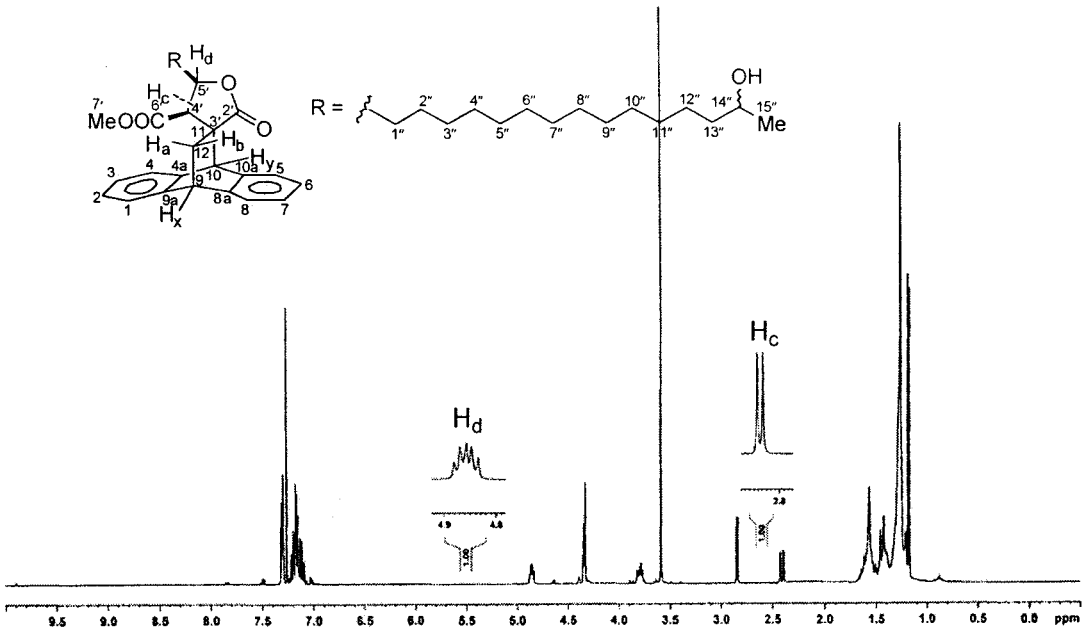
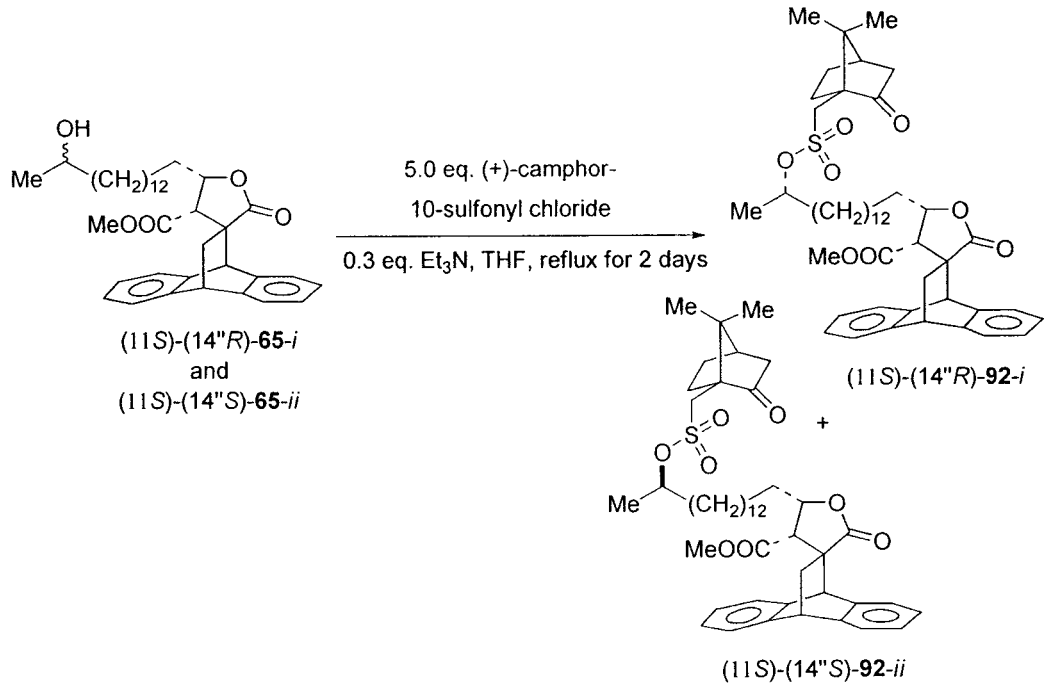


Figure 9 ^{1}H NMR spectral data of *cis*-isomer (11*S*)-**66**

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

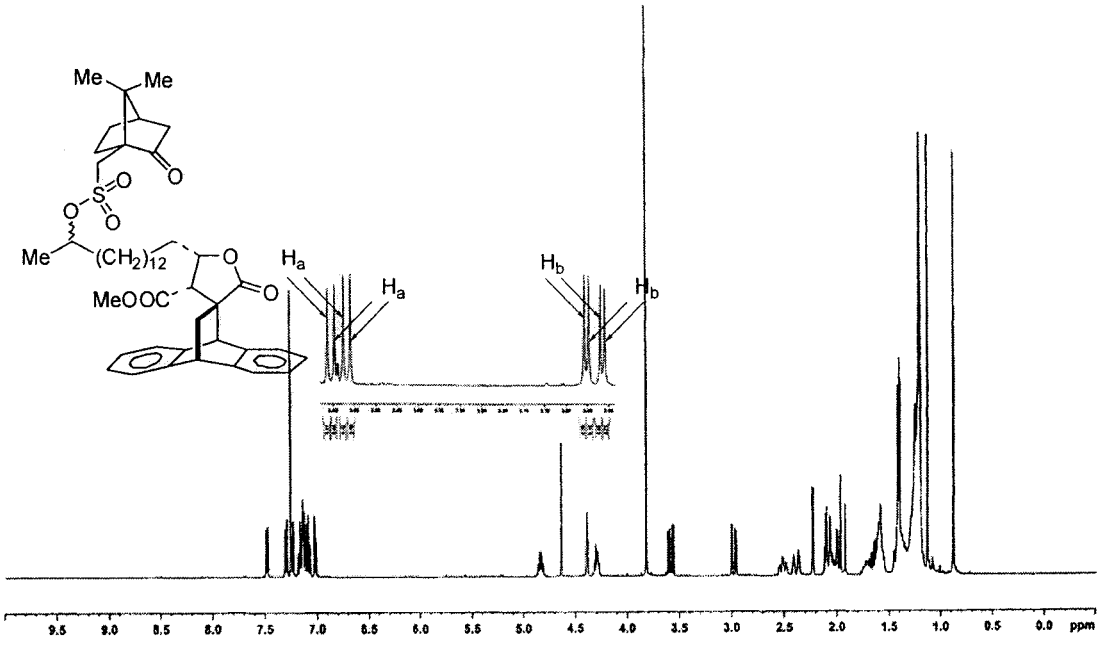
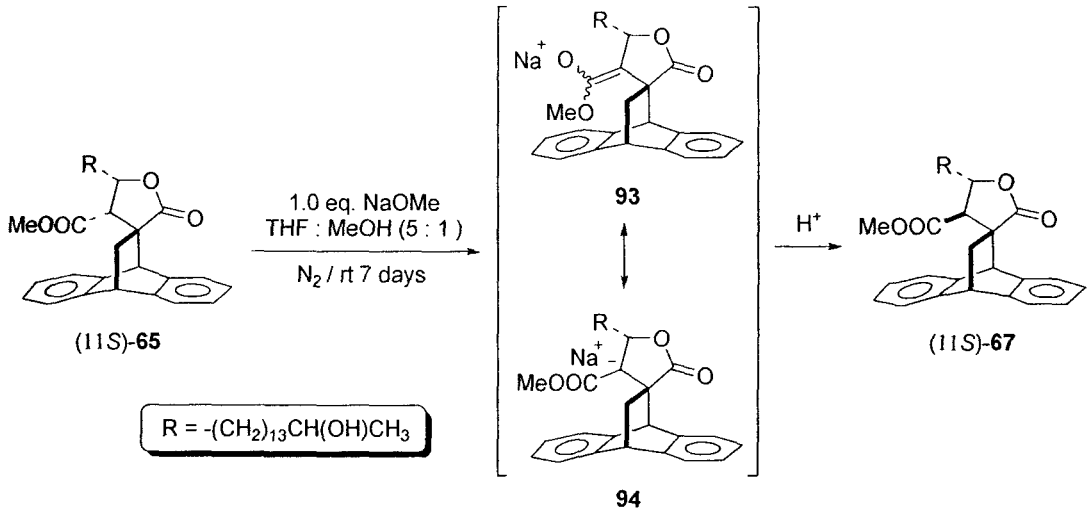


Figure 10 ^{1}H NMR spectral data of the mixture of compounds (11*S*)-(14"*R*)-**92**-*i* and (11*S*)-(14"*S*)-**92**-*ii*

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 $C_{36}H_{48}O_5Na$.

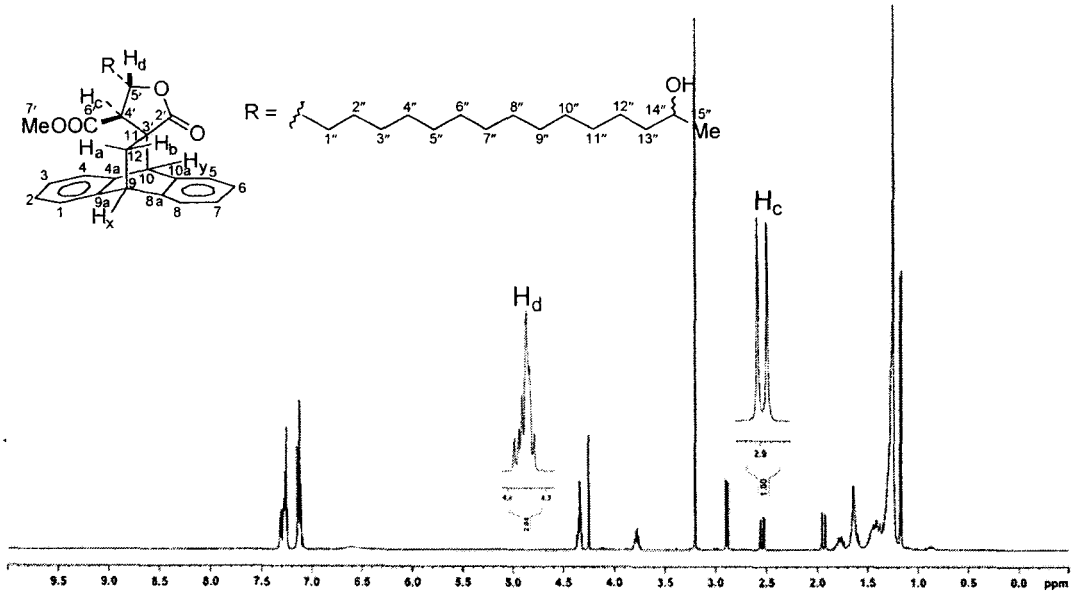


Figure 11 ^{1}H NMR spectral data of *trans*-isomer (11*S*)-**67**

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).

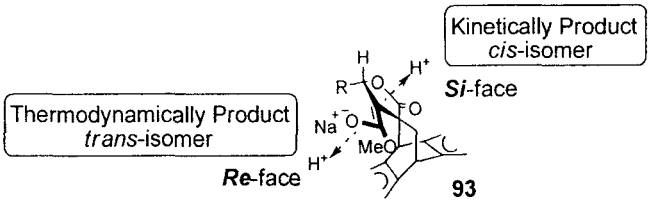


Figure 12 Intermediate of isomerization process of compound (11*S*)-**65**

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.

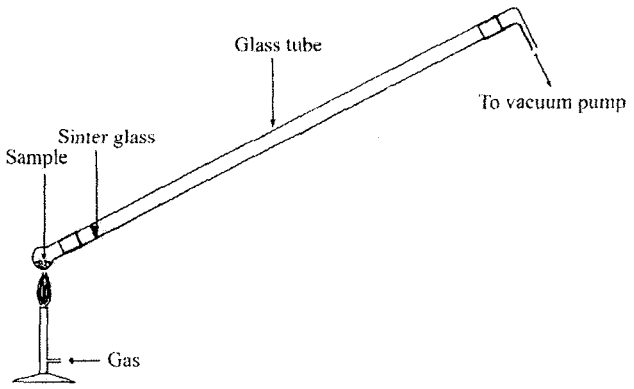
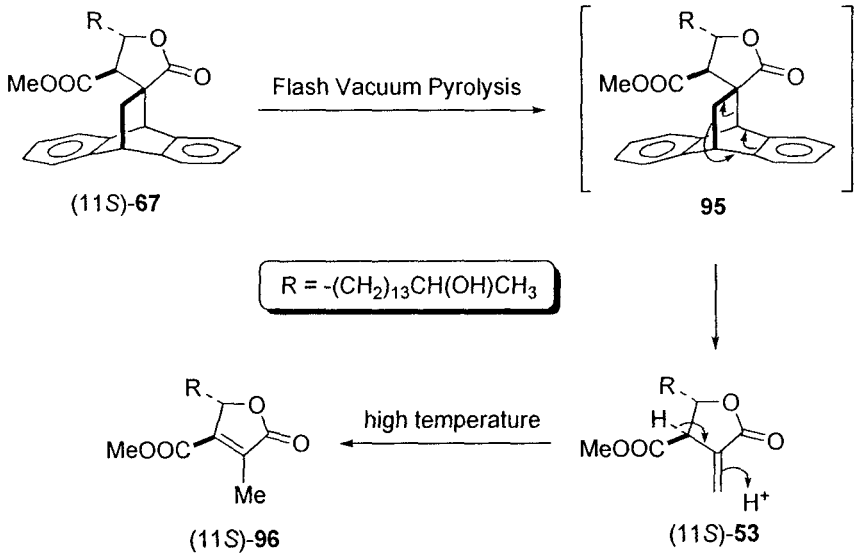


Figure 13 Modified flash vacuum pyrolysis apparatus



Scheme 34 Retro Diels-Alder reaction of *trans*-isomers (11*S*)-**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 $C_{22}H_{38}O_5Na$.

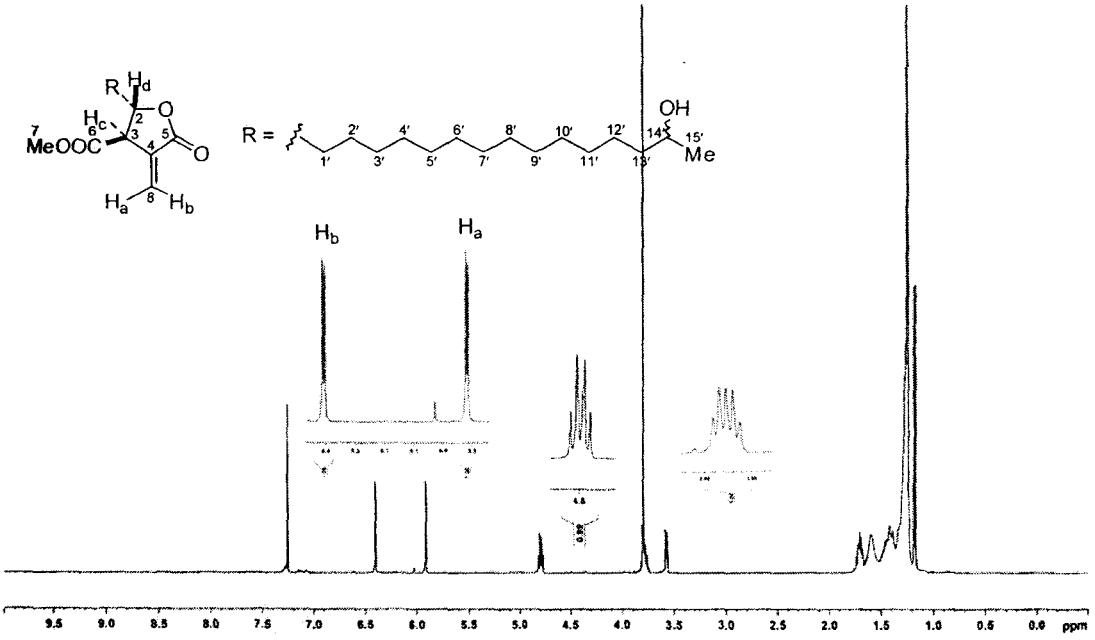
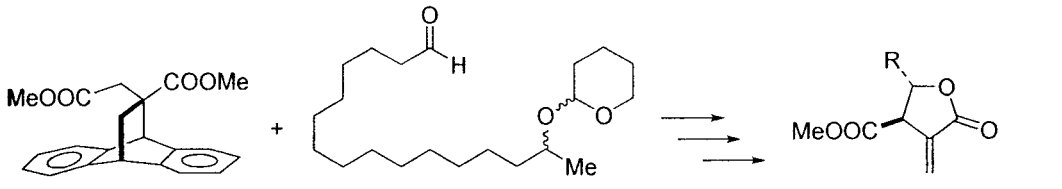


Figure 14 ^{1}H NMR spectral data of *trans*-isomer **53**

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.

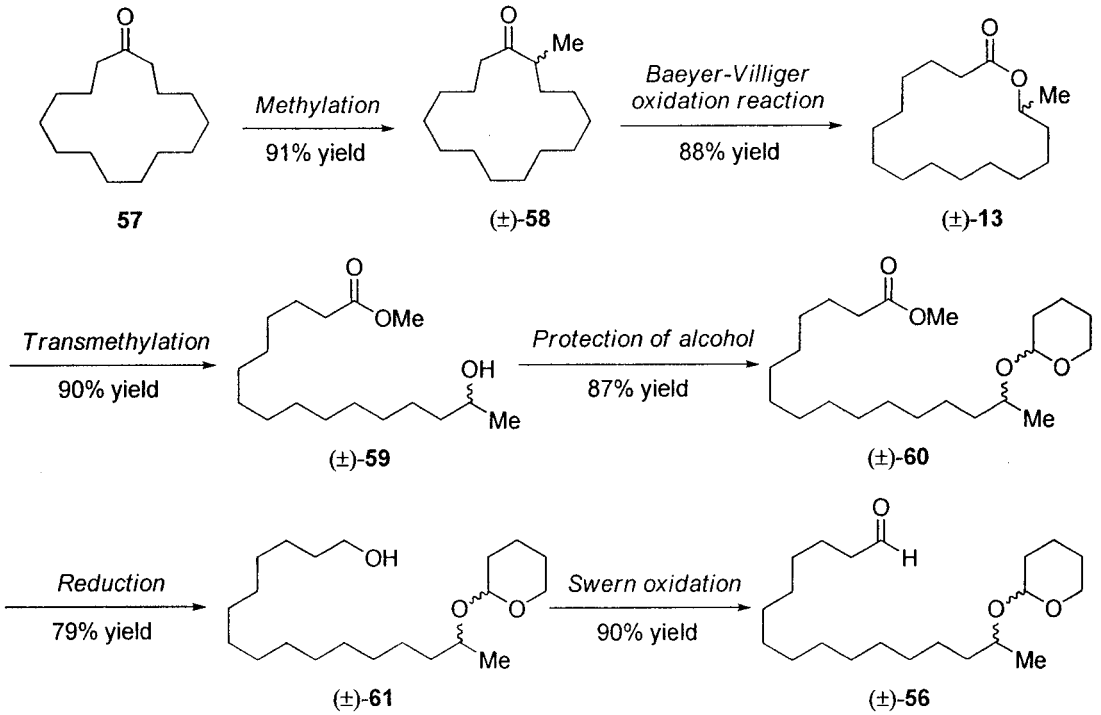


(+)-(11*S*)-**44** (±)-**56** **53**

R = $-(CH_2)_{13}CH(OH)CH_3$

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.



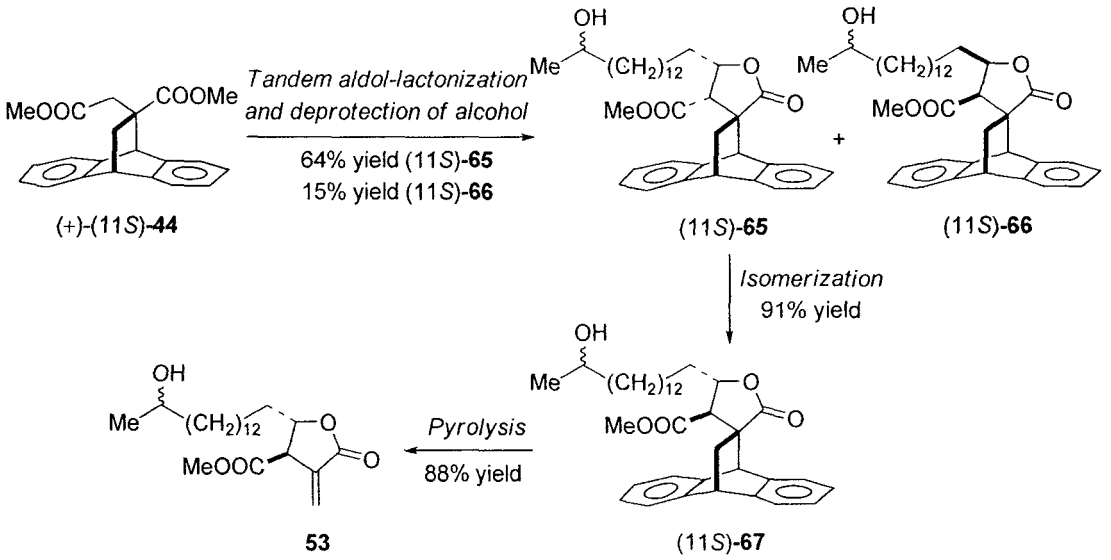
57 (±)-**58** (±)-**13**

(±)-**59** (±)-**60**

(±)-**61** (±)-**56**

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).

Puttinan Meepowpan, Anuruk Chailungka and Yodhathai Thebtaranonth, "Total synthesis of (±)-protoconstipatic acid *via* tandem aldol–lactonization," นักวิจัยรุ่นใหม่ ...พบ .... เมธีวิจัยอาวุโส สกว / สำนักงานกองทุนสนับสนุนการวิจัย, 13–15 ตุลาคม 2548 ณ โรงแรมรีเจนต์ อ.ชะอำ จ.ชลบุรี (2005).

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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

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".

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.

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

Rattana Jongkol [a], Ruangrat Choommongkol [a], Bongkoch Tarnchompoo [b], Piyarat Nimmanpipug [a], Puttinan Meepowpan [a,*]

[a] Department of Chemistry and Center for Innovation in Chemistry, Faculty of Science, Chiang Mai University, 239 Huay Kaew Road, Chiang Mai 50200, Thailand
[b] National Center for Genetic Engineering and Biotechnology (BIOTEC), 113 Thailand Science Park, Phahonyothin Road, Klong 1, Klong Luang, Pathumthani 12120, Thailand

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ABSTRACT

The syntheses of methylenolactocin, nephrosterinic acid and their derivatives can be achieved by using the efficient diastereoselective acylation of dimethyl itaconate–anthracene adduct followed by tandem chemoselective reduction–lactonization.

1. Introduction

The paraconic acids are a group of highly substituted γ-butyrolactones isolated from different species of moss, lichens, fungi and cultures of *Penicillium* sp.[1,2] Among them, methylenolactocin,[3,4] nephrosterinic acid,[5,6] and protolichesterinic acid,[7,8] are noted for their biological activities, being antibacterial agents,[9a–l] antifungal,[9b] antitumor,[9h] anti-inflammatory[9m] and displaying inhibitory activity on 12(*S*)-HETE production in human platelets[9n] while some of these compounds also display growth-regulating effects.[9o] Due to their important potential pharmacological applications,[10] several formal and total syntheses of members of this class of metabolite have attracted widespread attention.

Previous work has reported the total syntheses of methylenolactocin, nephrosterinic acid and protolichesterinic acid in both racemic and enantiomerically pure forms employing the versatile starting material, dimethyl itaconate–anthracene adduct (**1**)[11] via tandem aldol–lactonization reactions, isomerization of the C-4′ configuration followed by flash vacuum pyrolysis and hydrolysis of the ester group (Scheme 1).[4n,r]

This present work aims at controlling the stereochemistries at C-4′ and C-5′ using diastereoselective acylation and tandem chemoselective reduction–lactonization as key steps. The process is outlined in Scheme 2.

2. Results and discussion

In a typical diastereoselective acylation using alkanoyl chloride; *n*-heptanoyl chloride (**10b**) was added to the lithium ester enolate **9** at −78 °C for 15 min and the mixture stirred at 0 °C for 1 h. The crude product was subjected to column chromatography (silica gel, using EtOAc/hexane=0.5:9.5 as eluent) to yield **7b** in 63% yield and the minor product, **8b**, in 4% yield after crystallization from ethyl acetate/hexane. The relative stereochemistries at the α-position of the β-ketodiester adducts **7b** and **8b** were determined by NOE experiments (Fig. 1). In the case of compound **7b**, the proton H_c (δ appeared at 3.03 ppm) showed greater interaction with H_b than H_y; thus the orientation of H_c is on the upper face as shown. Conversely, the orientation of proton H_c (δ appeared at 3.43 ppm) of compound **8b** is on the opposite face. However, the NOE results could not unequivocally confirm the orientations of the COOMe and n-$C_7H_{15}CO$ groups.

These NOE results were compared with geometry optimizations of compounds **7b** and **8b** carried out using Gaussian 03 Programs[12,13] at the B3LYP/6-31G level of Density Functional Theory (DFT). The optimized structures are shown in Figure 2. From these calculations, compound **8b** is thermodynamically more stable than compound **7b** with a lower energy of 3.96 kcal/mol. The **7b** model showed that the distance from H_c to H_a, H_b, and H_y are 2.41, 3.10, and 3.89 Å respectively. In comparison, H_c is displaced from H_a, H_b, and H_y at distance of 3.70, 4.10, and 2.51 Å respectively in the minimized structure of **8b**. Results from the computational calculation are in agreement with the NOE results.

* Corresponding author. Tel.: +66 53 943 341 5x317; fax: +66 53 892 277.
E-mail address: puttinan@chiangmai.ac.th (P. Meepowpan).

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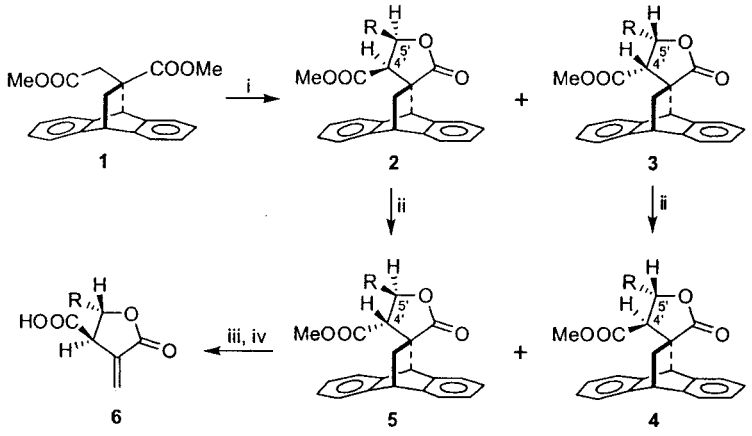
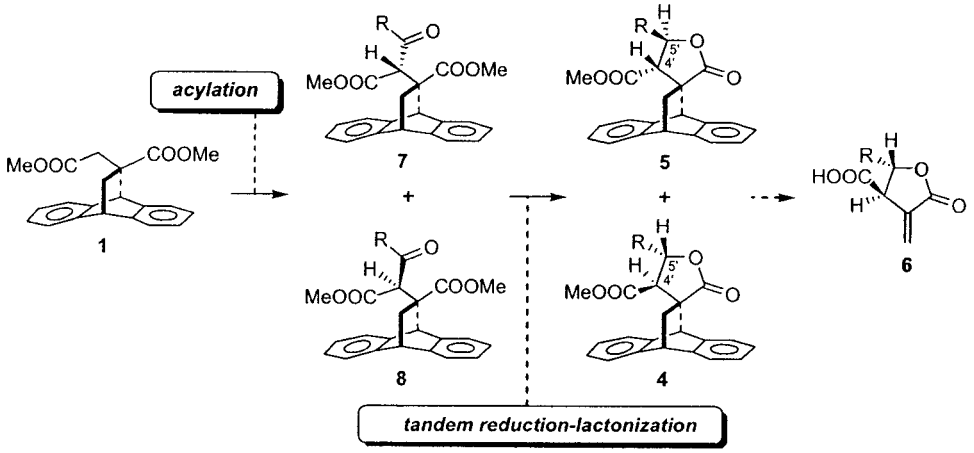


6; **R** = *n*-C_5H_{11} (Methylenolactocin); *n*-$C_{11}H_{23}$ (Nephrosterinic acid) and *n*-$C_{13}H_{27}$ (Protolichesterinic acid)

Scheme 1. Total syntheses of methylenolactocin, nephrosterinic acid and protolichesterinic acid. Reagents and conditions: (i) a. 1.2 equiv LDA, THF, −78 °C to 0 °C, 2 h, b. 1.2 equiv RCHO, 0 °C to rt, 3 h, c. aq NH_4Cl, 30% HCl; (ii) 0.5 equiv NaOMe, THF/MeOH (2:1), rt, 6 days; (iii) FVP; (iv) 2-butanone, 6 N HCl, reflux, 2 h.



Scheme 2. Synthetic pathway of *trans*-**6** via acylation and tandem reduction–lactonization reactions.

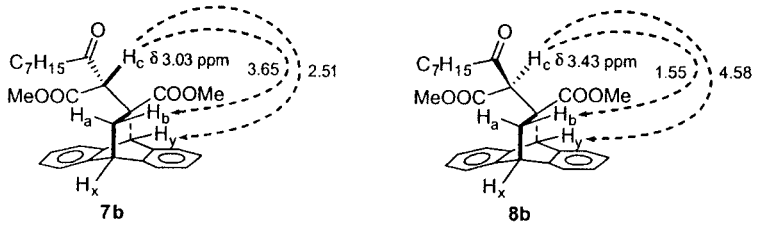


Figure 1. NOE results of β-ketodiester adducts **7b** and **8b**.

The stereochemical outcome of the acylation reaction can be explained by the chair-like transition states: **A** and **B** (Scheme 3). The transition structure **A** would lead to the major product **7b**. In contrast, the transition structure **B** would lead to the formation of the minor product **8b**. The latter is less favorable due to the large steric repulsion between the Cl atom and the anthracene ring.[4n]

Under similar reaction conditions, the lithium ester enolate **9** was allowed to react with various alkanoyl chlorides (**10a–e**), e.g., R=*n*-C_5H_{11}; *n*-C_9H_{19}; *n*-$C_{11}H_{23}$ and C_6H_5, to yield **7a–e** as the major products and **8a–e** as the minor products, respectively as detailed in Table 1.

It is possible that the β-ketodiester adducts **8** might be the result of isomerization of **7** under acylation conditions. To prove this hypothesis, three extra reaction conditions were carried out and results are as follows: treatment of the lithium ester enolate **9** with benzoyl chloride (**10e**) at −78 °C for 15 min and quickly quenching with saturated $NaHCO_3$ gave only recovered **1** in 98% yield. Secondly, the reaction mixture of the lithium ester enolate **9** and **10e** at −78 °C was left stirring at 0 °C for 15 min to also yield the recovered **1**. Lastly, addition of **10e** to the lithium ester enolate **9** at 0 °C for 15 min provided the β-ketodiester adducts **7e** and **8e**

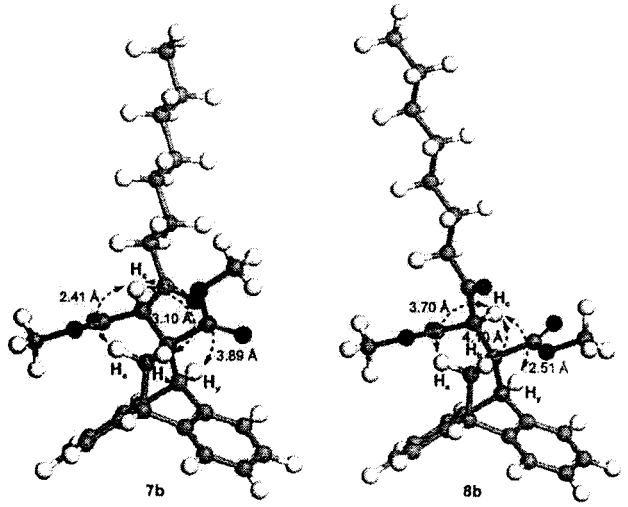
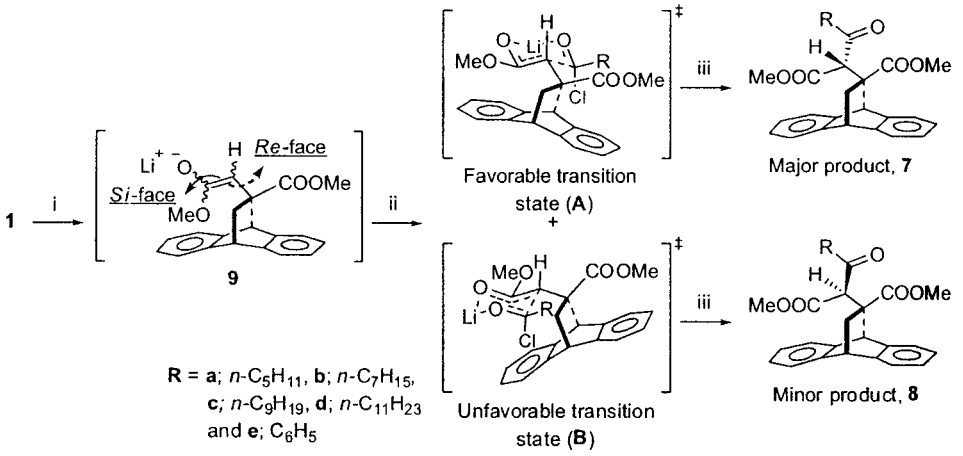


Figure 2. Structures of **7b** and **8b** from Gaussian 03 Programs at the B3LYP/6-31G level of DFT.

Having efficiently prepared the β-ketodiester adducts **7**, attention was turned to their chemoselective reduction to obtain spirolactones **5**.[14] Initially, we began by optimizing reaction conditions of the diastereoslective reduction of the model compound, the β-ketodiester adduct **7e**, using various amounts of $NaBH_4$ (1, 3, 5 and 10 equiv) in THF/MeOH (1:3) (Table 2). Results showed that the use of 5 equiv of $NaBH_4$ (Entry 3) gave high yields of spiro-lactones **3e** and **5e**, respectively (17 and 61% yields).

The structure of compounds *cis*-**3e** and *trans*-**5e** were determined from their ^1H NMR, ^{13}C NMR, IR and mass spectroscopic data.[4n] In the ^1H NMR spectrum of *cis*-**3e**, the protons H_c and H_d appeared at 2.54 and 5.51 ppm with a coupling constant *J* of 5.6 Hz while the same protons in *trans*-**5e** appeared at 3.05 and 6.05 ppm with a coupling constant *J* of 10.2 Hz. By observations from NOE experiments of compound *cis*-**3e** and *trans*-**5e**, the relative stereochemistries of these compounds were finally confirmed (Fig. 3). Irradiation of the proton H_d of *cis*-**3e** gave only a NOE effect on the proton H_c; thus the orientation of proton H_d is on the upper face and *syn*- with proton H_c. Furthermore, irradiation of proton H_d of *trans*-**5e** caused only NOE effect on the proton H_y, while irradiation of the proton H_c gave only NOE effects on the proton H_b; thus the orientation of proton H_d is at the lower face and *anti*- to proton H_c.



Scheme 3. A plausible reaction mechanism of diastereoselective acylation of the adduct **1** with acid chloride. Reagents and conditions: (i) 1.2 equiv **LDA**, THF, −78 °C to 0 °C, 2 h; (ii) 1.2 equiv RCOCl (**10**), −78 °C to 0 °C, 1 h; (iii) saturated $NaHCO_3$.

in 75 and 18% yields respectively. The above results clearly indicated that no isomerization took place under acylation conditions. It should be added that upon treatment of the β-ketodiester adduct **7e** with LDA (1.2 equiv) under acylation conditions employed the isomerized products **8e** was obtained in 12% yield (87% unchanged material).

Table 1
Diastereoselective acylation reactions of adduct **1** with various alkanoyl chlorides (**10a–e**)

Entry	RCOCl (**10**)	Yield[a,b] (%)		Diastereomeric ratio[b] of **7**/**8**
		7	**8**	
1	**10a**: n-$C_5H_{11}COCl$	58	4	94:6
2	**10b**: n-$C_7H_{15}COCl$	63	4	94:6
3	**10c**: n-$C_9H_{19}COCl$	53	6	90:10
4	**10d**: n-$C_{11}H_{23}COCl$	49	11	82:18
5	**10e**: C_6H_5COCl	73	19	79:21

[a] Compounds **7a–e** and **8a–e** were fully characterized by ^1H NMR, ^{13}C NMR, IR and HRMS (ESI).

[b] Yields and diastereomeric ratios of acylation products (**7a–e** and **8a–e**) were determined by ^1H NMR analysis.

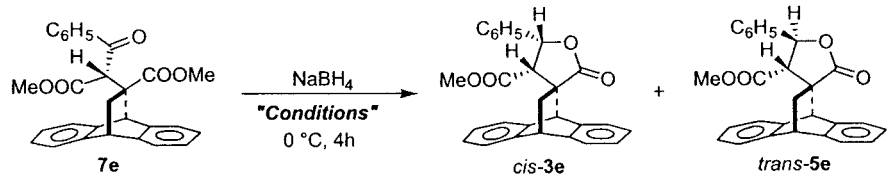
These results strongly confirm the orientation of the α-proton of β-ketodiester adduct **7e** is upper face and can be considered to be representative of **7a–d**. In addition, the β-ketodiester adducts **8e** was also obtained (colourless oil, 19%). $NaBH_4$ reduction of **8e** furnished the spiro-lactone *cis*-**2e** (white solid, mp 204.9–206.0 °C (CH_2Cl_2/hexane), 44% yield) as the only product isolated. The stereochemistry of *cis*-**2e** was fully confirmed by NOE experiments (Fig. 4).

In order to increase the diastereoselectivity of the reduction product (hence the final product), we decided to perform the $NaBH_4$ reduction in wet-THF system as previously reported by several groups.[15,16] Results are presented in Table 3 which demonstrates that the highest diastereoselectivity of **7e** were achieved by using $NaBH_4$ (5 equiv) in THF/H_2O (8:1) at 0 °C for 4 h (Entry 5).

These conditions were therefore employed for the reduction reactions of compounds **7a–d** and the results are shown in Table 4.

We have indepently demonstrated that the trans-products obtained were not the results of base induced isomerization of the carbon-bearing the ester functionality (C-4′). Thus treatment of *cis*-**3e**, obtained earlier, with $NaBH_4$ or NaOMe in MeOH or MeOH/THF provided only the recovered starting material.

Table 2
Reduction of β-ketodiester adduct **7e** with various amounts of $NaBH_4$ in THF/MeOH



Entry	Equiv of $NaBH_4$	Conditions	Yield[a] (%)		Diastereomeric ratio of *trans*-**5e**/*cis*-**3e**	% Conversion
			cis-**3e**	*trans*-**5e**		
1	1	THF/MeOH (1:3)	22	58	73:27	54
2	3	THF/MeOH (1:3)	22	60	73:27	100
3	5	THF/MeOH (1:3)	17	61	78:22	100
4	10	THF/MeOH (1:3)	18	35	66:34	100

[a] Yields of isolated compounds.

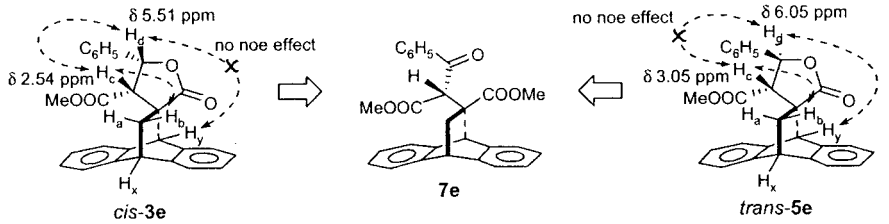


Figure 3. NOE results of spiro-lactones (*cis*-**3e** and *trans*-**5e**).

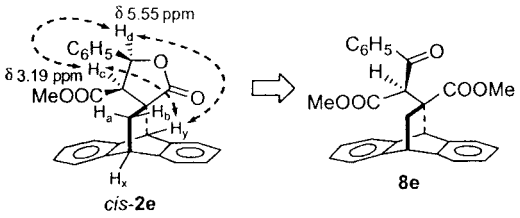


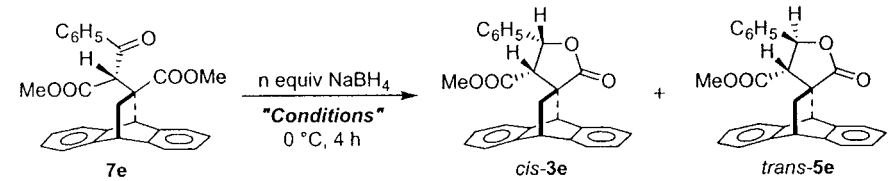
Figure 4. NOE results of spiro-lactone (*cis*-**2e**).

A plausible reaction mechanism is depicted in Scheme 4 which involves the Felkin–Anh model (**C**). The reduction of β-ketodiester **7** with $NaBH_4$ in a wet-THF system proceeds via the Felkin–Anh face to give the alkoxide **11** which, upon workup, furnished the final *trans*-**5**. trans-Products (**5a–e**) can be transformed to natural products, e.g., methylenolactocin (R=*n*-C_5H_{11}) and nephrosterinic acid (R=*n*-$C_{11}H_{23}$), and unnatural products (R=*n*-C_7H_{15}, *n*-C_9H_{19} and C_6H_5) by flash vacuum pyrolysis and hydrolysis, respectively.[4n]

3. Conclusion

Synthetic methodology for methylenolactocin, nephrosterinic acid and their derivatives using diastereoselective acylation and tandem chemoselective reduction–lactonization as key steps has been developed. The approach is short, practical, efficient with high stereoselectivity and can be applied to both alkyl and aryl groups. The methodology is very useful for enantiomeric synthesis of compounds in this class.

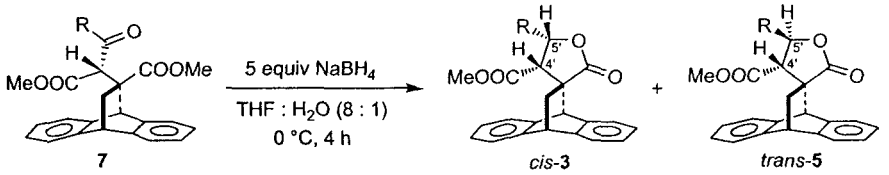
Table 3
Reduction of β-ketodiester adducts **7e** with various amounts of $NaBH_4$ in wet-THF systems



Entry	Equiv of $NaBH_4$	Conditions	Yield[a] (%)		Diastereomeric ratio of *trans*-**5e**/*cis*-**3e**	% Conversion
			cis-**3e**	*trans*-**5e**		
1	5.0	THF/H_2O (2:1)	15	80	84:16	100
2	5.0	THF/H_2O (4:1)	7	72	91:9	100
3	1.5	THF/H_2O (8:1)	1	53	98:2	77
4	3.0	THF/H_2O (8:1)	4	65	94:6	98
5	5.0	THF/H_2O (8:1)	2	70	97:3	100
6	7.0	THF/H_2O (8:1)	3	77	96:4	99
7	5.0	THF/H_2O (16:1)	5	92	95:5	67

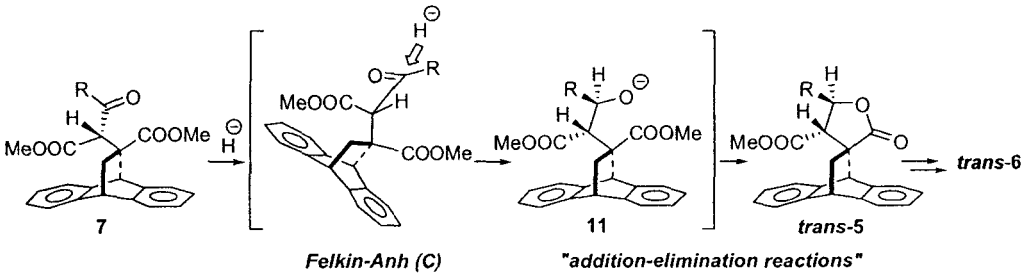
[a] Yields of isolated compounds.

Table 4
Reduction of β-ketodiester adducts (**7a–e**) with 5 equiv of $NaBH_4$ in THF/H_2O (8:1)



Entry	R	Yield[a] (%)		Diastereomeric ratio of *trans*-**5e**/*cis*-**3e**	% Conversion
		cis-**3e**	*trans*-**5e**		
1	**7a**: n-C_5H_{11}	6	70	92:8	84
2	**7b**: n-C_7H_{15}	19	78	80:20	81
3	**7c**: n-C_9H_{19}	4	90	96:4	76
4	**7d**: n-$C_{11}H_{23}$	8	89	92:8	81
5	**7e**: C_6H_5	2	70	97:3	100

[a] Yields of isolated compounds.



R = **a**; n-C_5H_{11}, **b**; n-C_7H_{15}, **c**; n-C_9H_{19}, **d**; n-$C_{11}H_{23}$ and **e**; C_6H_5

Scheme 4. *Tandem chemoselective reduction–lactonization reactions with $NaBH_4$ via the attachment of hydride (H^-) and β-ketodiester adducts (**7a–e**).*

4. Experimental section

4.1. General methods

All reactions were carried out under nitrogen or argon. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were determined by using a Gallenkamp Electrothermal apparatus and were uncorrected. The ^1H and ^{13}C NMR spectra were recorded on Bruker DRX 400 MHz spectrometers and chemical shifts were given in ppm downfield from tetramethylsilane (TMS). All NMR spectra were measured in $CDCl_3$ and chemical shifts were reported as δ-values in parts per million (ppm) relative to residue $CHCl_3$ as internal reference (^1H: δ 7.26, ^{13}C: δ 77.00) and coupling constants (*J* values) were reported in hertz (Hz). Peak multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), dt (doublet of triplets), ddd (doublet of doublet of doublets) and m (multiplet). Infrared spectra were taken with a FT-IR model TENSER 27 (Bruker) spectrometer and absorption frequencies were reported in reciprocal centimeters (cm^{-1}). Mass spectra (electrospray ionization mode, ESI-MS) were measured on a micromass Q-TOF-2™ (Waters) spectrometer. Flash column chromatography was performed employing Merck silica gel 60 and Merck silica gel 60H. Preparative thin layer chromatography (PLC) plates were carried out using Merck silica gel 60 PF_{254}. Analytical thin layer chromatography was performed with Merck silica gel 60 F_{254} aluminum plates. Solvents were dried over CaH_2 and distilled before used. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone ketyl under nitrogen. Diisopropylamine was distilled over CaH_2 and stored under nitrogen. *n*-Butyllithium was purchased from Fluka and Across as solution in hexane and titrated periodically according to the 2,5-dimethoxybenzyl alcohol method. Acid chlorides were freshly distilled under reduce pressure.

4.2. Chemistry

*4.2.1. General procedure for the synthesis of 11-carbomethoxy-11-(1′-alkanoyl or 1′-benzoyl-1′-carbomethoxymethyl)-9,10-dihydro-9,10-ethanoanthracenes (**7a–e** and **8a–e**)*

To a 100 mL round-bottomed flask equipped with a magnetic stirrer bar, fitted with a three-way stopcock and nitrogen inlet. *n*-Butyllithium (1.30 mL, 1.80 mmol, 1.4 M in hexane) was added to a stirring solution of diisopropylamine (0.30 mL, 2.16 mmol) in THF (5 mL) at −78 °C, then stirred at 0 °C for 1 h. To the LDA solution, dimethyl itaconate–anthracene adduct (**1**) (504.6 mg, 1.50 mmol) in THF (10 mL) was added at −78 °C and stirred at 0 °C for 2 h. At −78 °C, alkanoyl or benzoyl chloride (**10**) (1.80 mmol) was added to the reaction mixture and left stirring at 0 °C for 1 h. The resulting mixture was quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×15 mL). The combined organic layer were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc/hexane=1:9 as eluent) followed by preparative thin layer chromatography (EtOAc/hexane=1:9 as developing solvent) gave the β-ketodiester adducts **7** and **8**.

*4.2.1.1. 11-Carbomethoxy-11-(1′-hexanoyl-1′-carbomethoxymethyl)-9,10-dihydro-9,10-ethanoanthracenes (**7a** and **8a**).* Compound **7a** (58%): white solid; mp 198–199 °C (CH_2Cl_2/hexane); R_f (10% EtOAc/hexane) 0.25; ν_{max} (KBr) 2956, 2868, 1745, 1468, 1241 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, t, *J*=7.2 Hz, *Me*), 0.98, 2.86, 4.26 (3H, ABX system, *J*=13.2, 3.1, 2.3 Hz, CH_2, ArC*H*), 1.04–1.50 (6H, m, CH_2),

2.05 (1H, dt, J=17.8, 7.2 Hz, CHCO), 2.42 (1H, dt, J=17.8, 7.6 Hz, CHCO), 3.03 (1H, s, COCHCOOMe), 3.35 (3H, s, COOMe), 3.84 (3H, s, COOMe), 5.01 (1H, s, ArCH), 7.02–7.66 (8H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 13.8, 22.3, 22.8, 30.9, 37.8, 43.9, 44.1, 50.2, 52.1, 52.4, 53.7, 64.2, 122.9, 123.5, 124.4, 125.8, 126.6, 126.7, 139.5, 143.2, 143.9, 168.5, 173.9, 204.5; HRMS (ESI) m/z: $(M+Na)^+$, found 457.1990. $C_{27}H_{30}O_5Na$ requires 457.1991.

Compound **8a** (4%): colourless oil; R_f (10% EtOAc/hexane) 0.27; ν_{max} (liquid film) 2952, 2864, 1756, 1719, 1460, 1242 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, J=6.9 Hz, Me), 1.69, 2.83, 4.28 (3H, ABX system, J=13.2, 3.2, 2.3 Hz, CH_2, ArCH), 1.12–1.70 (6H, m, CH_2), 2.23 (1H, ddd, J=17.6, 8.3, 6.2 Hz, CHCO), 2.48 (1H, ddd, J=17.6, 8.4, 6.6 Hz, CHCO), 3.34 (3H, s, COOMe), 3.39 (1H, s, COCHCOOMe), 3.48 (3H, s, COOMe), 4.70 (1H, s, ArCH), 6.99–7.53 (8H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 13.9, 22.5, 23.1, 31.1, 35.1, 41.4, 44.0, 51.0, 52.1, 52.2, 54.6, 65.3, 123.0, 123.6, 124.2, 125.4, 125.7, 126.5, 126.6, 127.0, 139.0, 140.0, 143.5, 144.5, 169.7, 174.1, 203.5; HRMS (ESI) m/z: $(M+Na)^+$, found 457.1991. $C_{27}H_{30}O_5Na$ requires 457.1991.

*4.2.1.2. 11-Carbomethoxy-11-(1′-octanoyl-1′-carbomethoxymethyl)-9,10-dihydro-9,10-ethanoanthracenes (**7b** and **8b**).* Compound **7b** (63%): white solid; mp 200–202 °C (CH_2Cl_2/hexane); R_f (10% EtOAc/hexane) 0.23; ν_{max} (KBr) 2940, 2850, 1720, 1741, 1712, 1450, 1250 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J=7.1 Hz, Me), 0.98, 2.86, 4.26 (3H, ABX system, J=13.2, 3.1, 2.3 Hz, CH_2, ArCH), 1.06–1.48 (10H, m, CH_2), 2.05 (1H, dt, J=17.7, 7.2 Hz, CHCO), 2.42 (1H, dt, J=17.7, 7.6 Hz, CHCO), 3.03 (1H, s, COCHCOOMe), 3.36 (3H, s, COOMe), 3.85 (3H, s, COOMe), 5.01 (1H, s, ArCH), 7.01–7.64 (8H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 14.0, 22.6, 23.2, 28.7, 28.9, 31.6, 37.8, 43.9, 44.2, 50.2, 52.1, 52.4, 53.8, 64.2, 122.9, 123.5, 124.4, 125.8, 126.6, 126.7, 139.5, 143.2, 143.9, 168.5, 173.9, 204.5; HRMS (ESI) m/z: $(M+Na)^+$, found 485.2305. $C_{29}H_{34}O_5Na$ requires 485.2304.

Compound **8b** (4%): colourless oil; R_f (10% EtOAc/hexane) 0.34; ν_{max} (liquid film) 2929, 2849, 1748, 1719, 1460, 1247 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, J=7.1 Hz, Me), 1.05–1.65 (10H, m, CH_2), 1.69, 2.83, 4.28 (3H, ABX system, J=13.2, 3.1, 2.2 Hz, CH_2, ArCH), 2.23 (1H, ddd, J=17.6, 8.4, 6.2 Hz, CHCO), 2.47 (1H, ddd, J=17.6, 8.6, 6.3 Hz, CHCO), 3.34 (3H, s, COOMe), 3.42 (1H, s, COCHCOOMe), 3.48 (3H, s, COOMe), 4.70 (1H, s, ArCH), 7.00–7.53 (8H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 14.1, 22.7, 23.4, 29.0, 29.3, 29.4, 29.5, 29.7, 31.9, 35.2, 41.5, 44.0, 51.0, 52.2, 54.6, 65.3, 123.0, 123.6, 124.2, 125.4, 125.7, 126.5, 126.6, 127.0, 139.0, 140.1, 143.5, 144.5, 169.7, 174.1, 203.5; (ESI) m/z: $(M+Na)^+$, found 485.2304. $C_{29}H_{34}O_5Na$ requires 485.2304.

*4.2.1.3. 11-Carbomethoxy-11-(1′-decanoyl-1′-carbomethoxymethyl)-9,10-dihydro-9,10-ethanoanthracenes (**7c** and **8c**).* Compound **7c** (53%): colourless oil; R_f (10% EtOAc/hexane) 0.30; ν_{max} (liquid film) 2930, 2870, 1748, 1720, 1450, 1240 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J=7.1 Hz, Me), 0.99, 2.86, 4.26 (3H, ABX system, J=13.2, 3.1, 2.3 Hz, CH_2, ArCH), 1.06–1.48 (14H, m, CH_2), 2.04 (1H, dt, J=17.6, 7.2 Hz, CHCO), 2.42 (1H, dt, J=17.6, 7.6 Hz, CHCO), 3.03 (1H, s, COCHCOOMe), 3.36 (3H, s, COOMe), 3.84 (3H, s, COOMe), 5.01 (1H, s, ArCH), 7.00–7.66 (8H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 14.1, 22.6, 23.2, 28.7, 29.2, 29.3, 31.8, 37.8, 43.9, 44.2, 50.1, 52.1, 52.4, 53.7, 64.2, 122.9, 123.5, 124.4, 125.8, 126.6, 126.7, 139.5, 143.2, 143.9, 168.5, 173.9, 204.5; HRMS (ESI) m/z: $(M+Na)^+$, found 513.2617. $C_{31}H_{38}O_5Na$ requires 513.2617.

Compound **8c** (6%): colourless oil; R_f (10% EtOAc/hexane) 0.36; ν_{max} (liquid film) 2926, 2855, 1740, 1720, 1460, 1244 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, J=7.1 Hz, Me), 1.05–1.75 (14H, m, CH_2), 1.79, 2.83, 4.28 (3H, ABX system, J=13.2, 3.2, 2.3 Hz, CH_2, ArCH), 2.23 (1H, ddd, J=17.6, 8.4, 6.1 Hz, CHCO), 2.47 (1H, ddd, J=17.6, 8.6, 6.3 Hz, CHCO), 3.34 (3H, s, COOMe), 3.42 (1H, s, COCHCOOMe), 3.48 (3H, s, COOMe), 4.70 (1H, s, ArCH), 7.00–7.52 (8H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 14.1, 22.7, 23.4, 29.0, 29.3, 29.4, 29.7, 31.9, 35.1, 41.5, 44.0, 51.0, 52.1, 52.2, 54.6, 65.3, 123.0, 123.6, 124.2, 125.4, 125.7, 126.5, 126.6, 127.0, 139.0, 140.0, 143.5, 144.5, 169.7, 174.1, 203.5; HRMS (ESI) m/z: $(M+Na)^+$, found 513.2617. $C_{31}H_{38}O_5Na$ requires 513.2617.

*4.2.1.4. 11-Carbomethoxy-11-(1′-dodecanoyl-1′-carbomethoxymethyl)-9,10-dihydro-9,10-ethanoanthracenes (**7d** and **8d**).* Compound **7d** (49%): colourless oil; R_f (10% EtOAc/hexane) 0.33; ν_{max} (liquid film) 2931, 2858, 1748, 1720, 1458, 1236 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (t, J=7.1 Hz, Me), 0.98, 2.86, 4.26 (3H, ABX system, J=13.2, 3.1, 2.3 Hz, CH_2, ArCH), 1.07–1.48 (18H, m, CH_2), 2.04 (1H, dt, J=17.7, 7.2 Hz, CHCO), 2.42 (1H, dt, J=17.7, 7.6 Hz, CHCO), 3.03 (1H, s, COCHCOOMe), 3.36 (3H, s, COOMe), 3.88 (3H, s, COOMe), 5.01 (1H, s, ArCH), 7.00–7.66 (8H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 14.1, 22.7, 23.2, 28.8, 29.3, 29.4, 29.6, 31.9, 37.8, 43.9, 44.2, 50.2, 52.1, 52.4, 53.8, 64.2, 122.9, 123.5, 124.4, 125.8, 126.6, 126.7, 139.5, 143.2, 143.9, 168.5, 174.0, 204.5; HRMS (ESI) m/z: $(M+H)^+$, found 519.3115. $C_{33}H_{43}O_5$ requires 519.3110.

Compound **8d** (11%): colourless oil; R_f (10% EtOAc/hexane) 0.39; ν_{max} (liquid film) 2925, 2853, 1756, 1720, 1460, 1246 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, J=7.0 Hz, Me), 1.10–1.42 (18H, m, CH_2), 1.68, 2.82, 4.28 (3H, ABX system, J=13.2, 3.2, 2.3 Hz, CH_2, ArCH), 2.22 (1H, ddd, J=17.6, 8.5, 6.0 Hz, CHCO), 2.46 (1H, ddd, J=17.6, 8.6, 6.3 Hz, CHCO), 3.33 (3H, s, COOMe), 3.42 (1H, s, COCHCOOMe), 3.47 (3H, s, COOMe), 4.69 (1H, s, ArCH), 6.97–7.52 (8H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 14.1, 22.7, 23.4, 28.9, 29.3, 29.5, 29.6, 31.9, 35.1, 41.5, 44.0, 51.0, 52.1, 52.2, 54.6, 65.2, 123.0, 123.6, 124.2, 125.4, 125.6, 126.5, 126.6, 127.0, 138.9, 140.0, 143.5, 144.5, 169.7, 174.1, 203.5; HRMS (ESI) m/z: $(M+Na)^+$, found 541.2930. $C_{33}H_{42}O_5Na$ requires 541.2930.

*4.2.1.5. 11-Carbomethoxy-11-(1′-benzoyl-1′-carbomethoxymethyl)-9,10-dihydro-9,10-ethanoanthracenes (**7e** and **8e**).* Compound **7e** (73%): white solid; mp 188–190 °C (CH_2Cl_2/hexane); R_f (10% EtOAc/hexane) 0.10; ν_{max} (KBr) 2947, 1740, 1606, 1438, 1234 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.05, 2.96, 4.25 (3H, ABX system, J=13.3, 3.1, 2.3 Hz, CH_2, ArCH), 3.42 (3H, s, COOMe), 3.74 (3H, s, COOMe), 3.91 (1H, s, COCHCOOMe), 5.12 (1H, s, ArCH), 7.03–7.76 (13H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 37.9, 43.9, 50.3, 52.2, 52.5, 54.3, 59.8, 123.0, 123.6, 124.4, 125.8, 126.6, 126.9, 128.0, 128.7, 133.5, 136.6, 139.5, 143.3, 143.9, 168.5, 174.1, 194.0; HRMS (ESI) m/z: $(M+Na)^+$, found 463.1521. $C_{28}H_{24}O_5Na$ requires 463.1521.

Compound **8e** (19%): colourless oil; R_f (10% EtOAc/hexane) 0.13; ν_{max} (liquid film) 2950, 1737, 1691, 1597, 1448, 1232 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.51, 2.94, 4.36 (3H, ABX system, J=13.7, 2.9, 2.8 Hz, CH_2, ArCH), 3.17 (3H, s, COOMe), 3.31 (3H, s, COOMe), 4.60 (1H, s, COCHCOOMe), 4.87 (1H, s, ArCH), 6.94–7.87 (13H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 33.3, 44.2, 52.2, 53.9, 61.4, 123.4, 123.5, 124.5, 124.9, 125.5, 126.3, 126.6, 126.7, 128.3, 128.6, 133.4, 136.2, 138.7, 140.7, 143.9, 144.9, 167.8, 174.5, 194.1; HRMS (ESI) m/z: $(M+Na)^+$, found 463.1522. $C_{28}H_{24}O_5Na$ requires 463.1521.

*4.2.2. General procedure for the synthesis of tetrahydro-4′-carbomethoxy-5′-(alkyl or phenyl)-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes (cis-**3a–e** and trans-**5a–e**) by using $NaBH_4$ in wet-THF system*

To a cooled (0 °C) solution of β-ketodiester adduct (**7**) (0.23 mmol) in THF (4 mL) and H_2O (0.5 mL) was added $NaBH_4$ (1.20 mmol, 5.0 equiv). The reaction mixture was stirred at 0 °C for 4 h and then quenched by dropwise addition of acetone (1 mL). After that the resulting solution was extracted with CH_2Cl_2 (3×15 mL) and the combined organic portions were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc/hexane=1:9 as eluent) followed by preparative thin layer chromatography (EtOAc/hexane=1:9 as developing solvent) obtained *cis*-**3** as the minor product and *trans*-**5** as the major product.

*4.2.2.1. Tetrahydro-4′-carbomethoxy-5′-pentyl-2′-furanone-3′-spiro-11-9, 10-dihydro-9,10-ethanoanthracenes (cis-**3a** and trans-**5a**).* Compound *cis*-**3a** (6%): white solid; mp 211.1–212.2 °C (CH_2Cl_2/hexane) [lit.[4n] mp 210–212 °C (CH_2Cl_2/hexane)]; R_f (10% EtOAc/hexane) 0.17; ν_{max} (KBr) 2946, 2865, 1785, 1734, 1464, 1204, 1163 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J*=6.8 Hz, *Me*), 1.17–1.64 (8H, m, CH_2), 1.99, 2.09, 4.39 (3H, ABX system, *J*=12.4, 3.2, 2.2 Hz, CH_2, ArC*H*), 2.24 (1H, d, *J*=5.2 Hz, *CH*COOMe), 3.83 (3H, s, COO*Me*), 4.31 (1H, dt, *J*=8.3, 5.2 Hz, *CH*O), 4.64 (1H, s, ArC*H*), 7.00–7.51 (8H, m, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 13.8, 22.3, 25.4, 30.9, 31.4, 40.7, 43.7, 46.8, 50.6, 51.6, 58.2, 76.4, 122.3, 123.9, 124.3, 125.9, 126.1, 126. 7, 127.4, 139.5, 140.8, 142.1, 143.3, 170.3, 176.9; HRMS (ESI) *m/z*: $(M+H)^+$, found 405.2064. $C_{26}H_{29}O_4$ requires 405.2066.

Compound *trans*-**5a** (70%): white solid; mp 117.5–118.9 °C (CH_2Cl_2/hexane) [lit.[4n] mp 118–119 °C (hexane)]; R_f (10% EtOAc/hexane) 0.30; ν_{max} (KBr) 2946, 2870, 1780, 1449, 1212, 1164 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J*=6.8 Hz, *Me*), 1.24–1.73 (8H, m, CH_2), 2.09, 2.48, 4.36 (3H, ABX system, *J*=12.5, 3.1, 2.4 Hz, CH_2, ArC*H*), 2.75 (1H, d, *J*=10.4 Hz, *CH*COOMe), 3.00 (3H, s, COO*Me*), 4.50 (1H, s, ArC*H*), 5.02 (1H, ddd, *J*=10.4, 8.3, 3.0 Hz, *CH*O), 7.04–7.31 (8H, m, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 13.9, 22.4, 25.3, 31.4, 34.2, 37.1, 43.8, 46.7, 51.1, 51.7, 56.1, 77.5, 123.1, 123.4, 124.6, 125.1, 125.8, 126.5, 126.6, 127.5, 137.9, 140.0, 143.3, 145.4, 168.6, 176.3; HRMS (ESI) *m/z*: $(M+Na)^+$, found 427.1891. $C_{26}H_{28}O_4Na$ requires 427.1885.

*4.2.2.2. Tetrahydro-4′-carbomethoxy-5′-heptyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes (cis-**3b** and trans-**5b**).* Compound *cis*-**3b** (19%): white solid; mp 131.0–132.2 °C (CH_2Cl_2/hexane); R_f (10% EtOAc/hexane) 0.15; ν_{max} (KBr) 2930, 2857, 1782, 1730, 1460, 1210, 1172 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J*=6.7 Hz, *Me*), 1.16–1.64 (12H, m, CH_2), 1.98, 2.08, 4.39 (3H, ABX system, *J*=12.4, 3.2, 2.2 Hz, CH_2, ArC*H*), 2.23 (1H, d, *J*=5.1 Hz, *CH*COOMe), 3.82 (3H, s, COO*Me*), 4.31 (1H, dt, *J*=8.3, 5.1 Hz, *CH*O), 4.64 (1H, s, ArC*H*), 7.00–7.52 (8H, m, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 14.0, 22.5, 25.7, 28.9, 29.2, 31.0, 31.6, 40.7, 43.7, 46.8, 50.6, 51.6, 58.2, 76.4, 122.3, 123.9, 124.3, 125.9, 126.1, 126.7, 127.4, 139.5, 140.8, 142.1, 143.3, 170.3, 176.9; HRMS (ESI) *m/z*: $(M+Na)^+$, found 455.2198. $C_{28}H_{32}O_4Na$ requires 455.2198.

Compound *trans*-**5b** (78%): white solid; mp 112.4–113.4 °C (CH_2Cl_2/hexane); R_f (10% EtOAc/hexane) 0.18; ν_{max} (KBr) 2941, 2850, 1775, 1734, 1459, 1208, 1169 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J*=7.1 Hz, *Me*), 1.21–1.73 (12H, m, CH_2), 2.10, 2.49, 4.37 (3H, ABX system, *J*=12.5, 3.0, 2.4 Hz, CH_2, ArC*H*), 2.76 (1H, d, *J*=10.4 Hz, *CH*COOMe), 3.01 (3H, s, COO*Me*), 4.51 (1H, s, ArC*H*), 5.03 (1H, ddd, *J*=10.4, 8.3, 3.0 Hz, *CH*O), 7.05–7.33 (8H, m, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 14.0, 22.6, 25.7, 29.0, 29.2, 31.7, 34.2, 37.2, 43.8, 46.7, 51.1, 51.6, 56.1, 77.5, 123.1, 123.4, 124.7, 125.1, 125.9, 126.5, 126.6, 127.5, 137.9, 140.0, 143.3, 145.4, 168.6, 176.3; HRMS (ESI) *m/z*: $(M+H)^+$, found 433.2379. $C_{28}H_{33}O_4$ requires 433.2379.

*4.2.2.3. Tetrahydro-4′-carbomethoxy-5′-nonyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes (cis-**3c** and trans-**5c**).* Compound *cis*-**3c** (4%): white solid; mp 120–121.1 °C (CH_2Cl_2/hexane); R_f (10% EtOAc/hexane) 0.19; ν_{max} (KBr) 2929, 2857, 1782, 1734, 1460, 1204, 1173 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J*=6.7 Hz, *Me*), 1.15–1.68 (16H, m, CH_2), 1.99, 2.09, 4.40 (3H, ABX system, *J*=12.4, 3.1, 2.1 Hz, CH_2, ArC*H*), 2.24 (1H, d, *J*=5.1 Hz, *CH*COOMe), 3.83 (3H, s, COO*Me*), 4.31 (H, dt, *J*=8.2, 5.1 Hz, *CH*O), 4.65 (1H, s, ArC*H*), 7.01–7.53 (8H, m, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 14.1, 22.6, 25.7, 28.9, 29.2, 29.3, 29.4, 31.0, 31.6, 40.7, 43.7, 46.8, 50.7, 51.6, 58.2, 76.4, 122.3, 123.9, 124.3, 125.9, 126.1, 126.7, 127.4, 139.5, 140.8, 142.1, 143.3, 170.3, 176.9; HRMS (ESI) *m/z*: $(M+Na)^+$, found 483.2508. $C_{30}H_{36}O_4Na$ requires 483.2511.

Compound *trans*-**5c** (90%): white solid; mp 115.5–115.6 °C (CH_2Cl_2/hexane); R_f (10% EtOAc/hexane) 0.23; ν_{max} (KBr) 2941, 2850, 1780, 1734, 1454, 1204, 1159 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J*=7.1 Hz, *Me*), 1.22–1.71 (16H, m, CH_2), 2.09, 2.48, 4.36 (3H, ABX system, *J*=12.5, 3.0, 2.4 Hz, CH_2, ArC*H*), 2.75 (1H, d, *J*=10.4 Hz, *CH*COOMe), 3.00 (3H, s, COO*Me*), 4.49 (1H, s, ArC*H*), 5.01 (1H, ddd, *J*=10.4, 8.3, 3.0 Hz, *CH*O), 7.04–7.31 (8H, m, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 14.1, 22.6, 25.7, 29.2, 29.3, 29.4, 31.8, 34.2, 37.2, 43.8, 46.7, 51.1, 51.7, 56.1, 77.5, 123.1, 123.4, 124.6, 125.1, 125.9, 126.5, 126.6, 127.5, 137.9, 140.0, 143.3, 145.4, 168.6, 176.3; HRMS (ESI) *m/z*: $(M+Na)^+$, found 483.2511. $C_{30}H_{36}O_4Na$ requires 483.2511.

*4.2.2.4. Tetrahydro-4′-carbomethoxy-5′-undecyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes (cis-**3d** and trans-**5d**).* Compound *cis*-**3d** (8%): white solid; mp 160–161 °C (CH_2Cl_2/hexane) [lit.[4n] mp 159–160 °C (CH_2Cl_2/hexane)]; R_f (10% EtOAc/hexane) 0.22; ν_{max} (KBr) 2926, 2854, 1770, 1729, 1454, 1223, 1164 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J*=7.0 Hz, *Me*), 1.17–1.64 (20H, m, CH_2), 1.99, 2.09, 4.39 (3H, ABX system, *J*=12.4, 3.2, 2.2 Hz, CH_2, ArC*H*), 2.23 (1H, d, *J*=5.1 Hz, *CH*COOMe), 3.82 (3H, s, COO*Me*), 4.30 (1H, dt, *J*=8.3, 5.1 Hz, *CH*O), 4.64 (1H, s, ArC*H*), 7.00–7.51 (8H, m, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 14.1, 22.6, 25.7, 29.2, 29.3, 29.4, 29.6, 31.0, 31.9, 40.7, 43.7, 46.8, 50.7, 51.7, 58.2, 76.6, 122.3, 123.9, 124.3, 125.9, 126.2, 126.7, 127.4, 139.5, 140.8, 142.1, 143.3, 170.3, 176.9; HRMS (ESI) *m/z*: $(M+H)^+$, found 489.3008. $C_{32}H_{41}O_4$ requires 489.3005.

Compound *trans*-**5d** (89%): white solid; mp 78.9–79.1 °C (CH_2Cl_2/hexane) [lit.[4n] mp 78–79 °C (hexane)]; R_f (10% EtOAc/hexane) 0.31; ν_{max} (KBr) 2926, 2870, 1785, 1734, 1469, 1212, 1164 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J*=7.1 Hz, *Me*), 1.21–1.71 (20H, m, CH_2), 2.09, 2.48, 4.36 (3H, ABX system, *J*=12.5, 3.0, 2.4 Hz, CH_2, ArC*H*), 2.75 (1H, d, *J*=10.4 Hz, *CH*COOMe), 2.99 (3H s, COO*Me*), 4.50 (1H, s, ArC*H*), 5.01 (1H, ddd, *J*=10.4, 8.4, 3.0 Hz, *CH*O), 7.05–7.30 (8H, m, ArH, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 14.1, 22.7, 25.7, 29.3, 29.4, 29.5, 29.6, 31.9, 34.3, 37.2, 43.9, 46.7, 51.2, 51.8, 56.2, 77.6, 123.1, 123.4, 124.7, 125.1, 125.9, 126.5, 126.6, 127.6, 137.9, 140.0, 143.3, 145.5, 168.7, 176.4; HRMS (ESI): $(M+H)^+$, found 489.3006. $C_{32}H_{41}O_4$ requires 489.3005.

*4.2.2.5. Tetrahydro-4′-carbomethoxy-5′-phenyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes (cis-**3e** and trans-**5e**).* Compound *cis*-**3e** (2%): white solid; mp 220–221 °C (CH_2Cl_2/hexane); R_f (10% EtOAc/hexane) 0.09; ν_{max} (KBr) 2951, 1795, 1734, 1454, 1208, 1143 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.20, 2.26, 4.49 (3H, ABX system, *J*=12.4, 3.1, 2.3 Hz, CH_2, ArC*H*), 2.54 (1H, d, *J*=5.6 Hz, *CH*COOMe), 3.28 (3H, s, COO*Me*), 4.77 (1H, s, ArC*H*), 5.51 (1H, d, *J*=5.6 Hz, *CH*O), 6.97–7.56 (13H, m, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 40.8, 43.8, 46.9, 50.9, 51.4, 61.0, 76.9, 124.0, 124.4, 125.4, 126.0, 126.3, 126.8, 127.5, 128.2, 128.5, 139.3, 140.7, 142.0, 169.3, 176.7; HRMS (ESI): $(M+H)^+$, found 411.1594. $C_{27}H_{23}O_4$ requires 411.1596.

Compound *trans*-**5e** (70%): white solid; mp 228.9–229.9 °C (CH_2Cl_2/hexane); R_f (10% EtOAc/hexane) 0.12; ν_{max} (KBr) 2951, 2870, 1774, 1734, 1459, 1205, 1161 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.11, 2.55, 4.38 (3H, ABX system, *J*=12.5, 3.0, 2.4 Hz, CH_2, ArC*H*), 2.96 (3H, s, COO*Me*), 3.05 (1H, d, *J*=10.2 Hz, *CH*COOMe), 4.66 (1H, s, ArC*H*), 6.05 (1H, d, *J*=10.2 Hz, *CH*O), 7.05–7.44 (13H, m, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 37.4, 43.8, 46.7, 51.5, 51.8, 59.0, 78.4, 123.2, 123.4, 124.8, 125.2, 126.0, 126.3, 126.6, 126.7, 127.6, 128.6, 128.9, 137.2, 137.8, 139.9, 143.3, 168.1, 176.0; HRMS (ESI): $(M+H)^+$, found 411.1595. $C_{27}H_{23}O_4$ requires 411.1596.

4.3. Computational procedure

The calculations were carried out in a Pentium IV-based PC computer. Density functional calculations were performed with the Gaussian 03 program[12] (Revision C.02, Gaussian, Inc., Wallingford CT) at the B3LYP/6-31G level. The three-dimensional molecular graphics of the energetically optimized **7b** and **8b** were produced from the GaussView program, version 3.09.[13]

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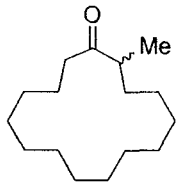
APPENDIX II

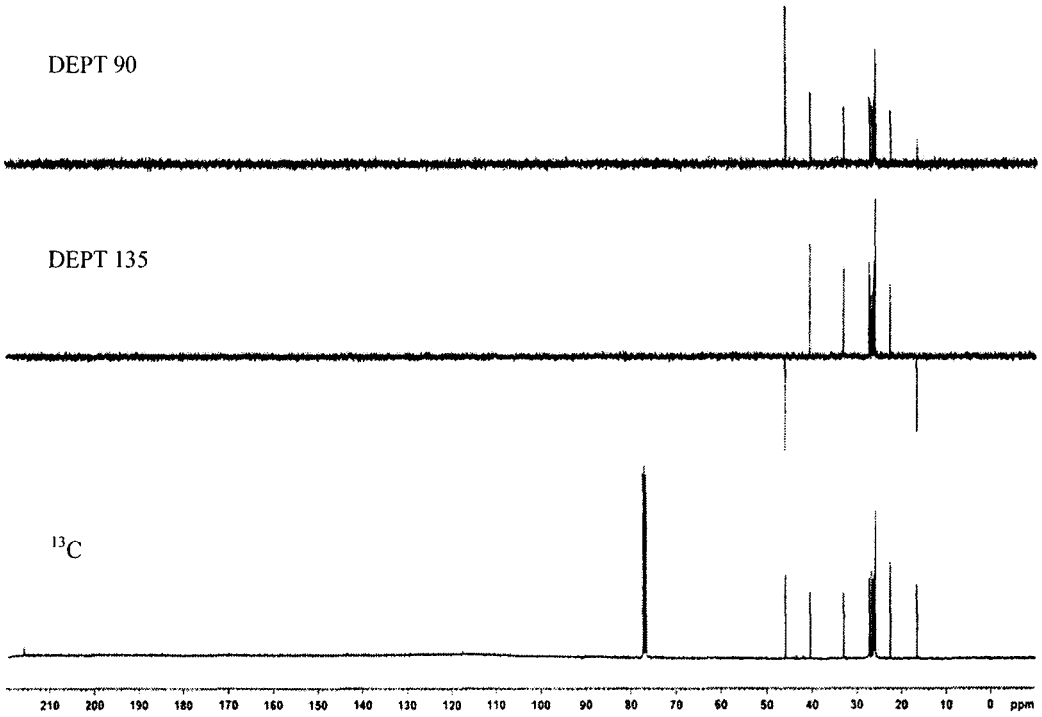
(^{1}H, and ^{13}C NMR)

^{1}H NMR in $CDCl_3$



(±)-**58**

^{13}C NMR in $CDCl_3$



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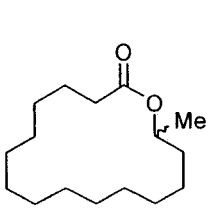
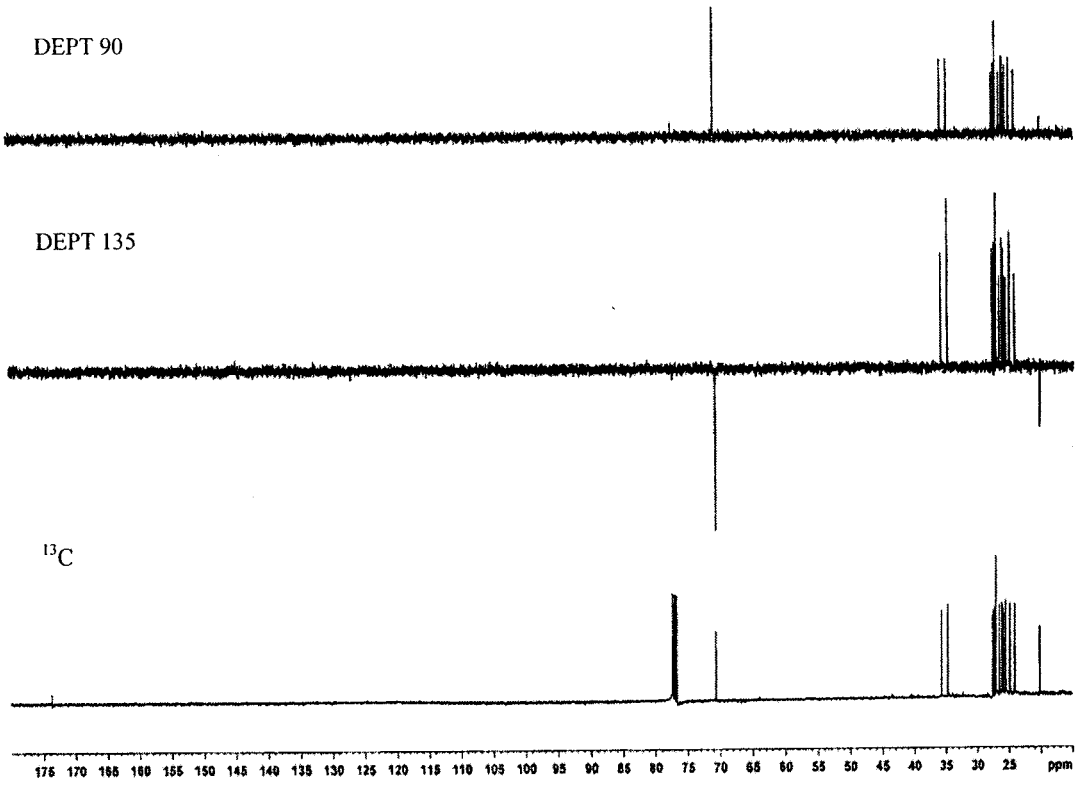


(±)-**13**

^{13}C NMR in $CDCl_3$



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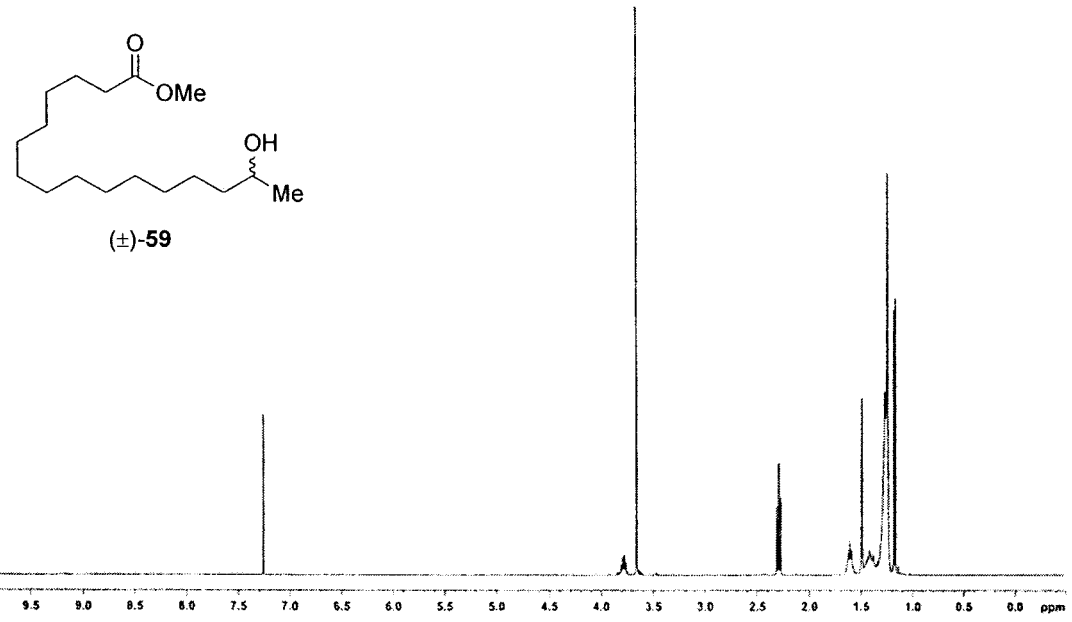
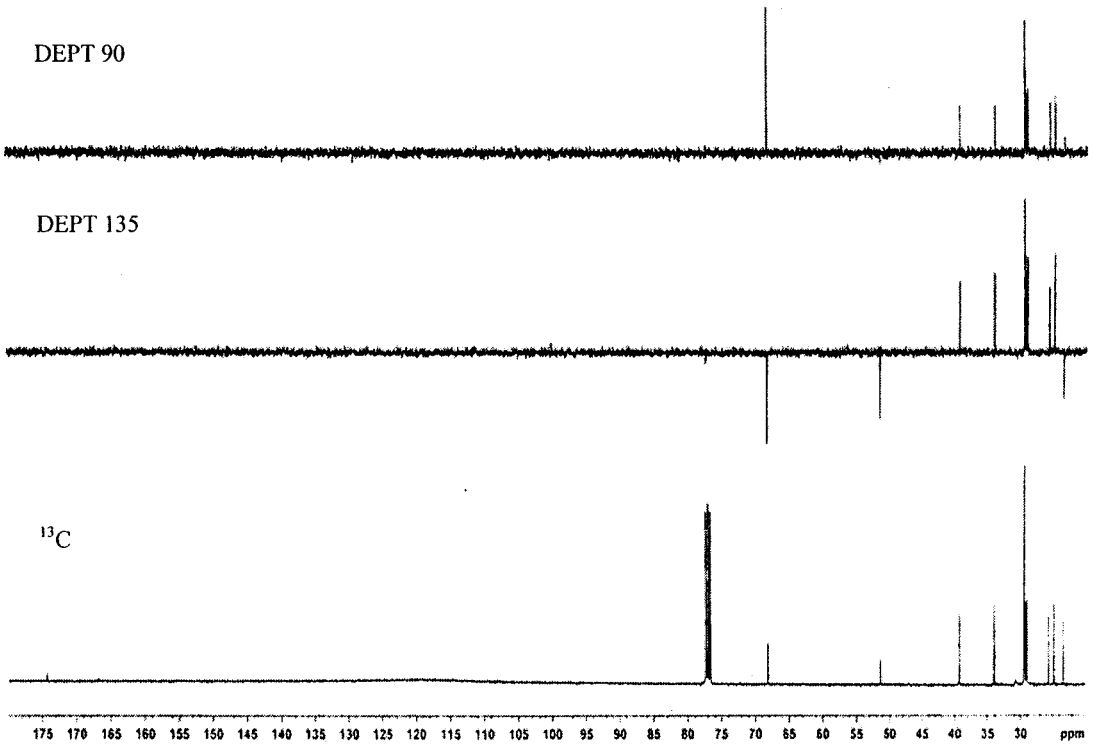
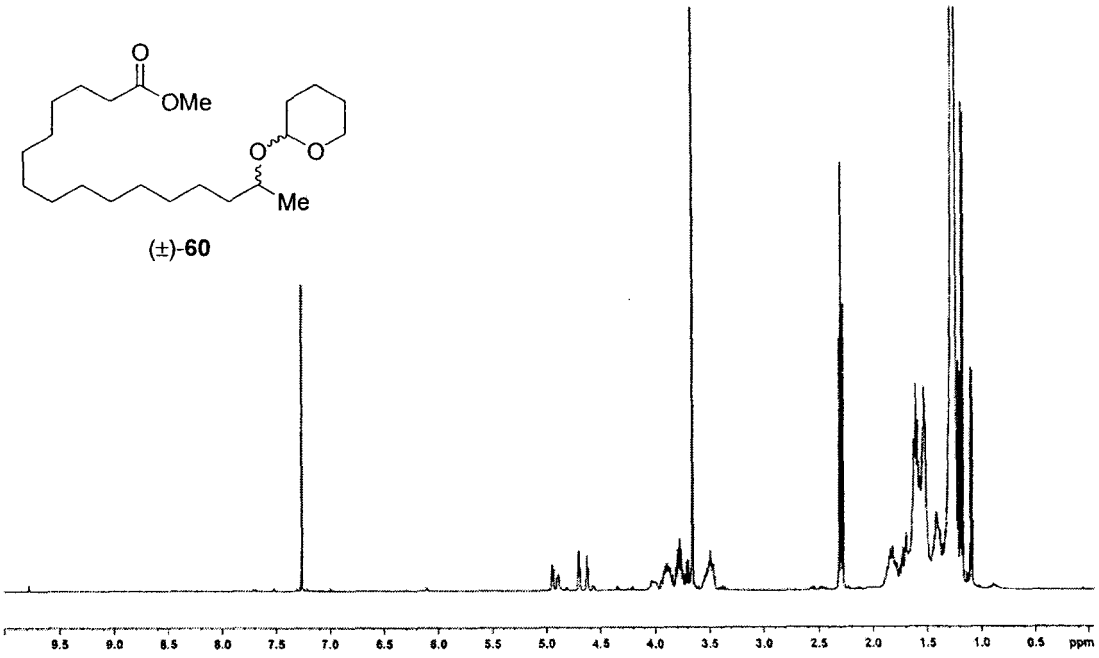


(±)-**59**

^{13}C NMR in $CDCl_3$

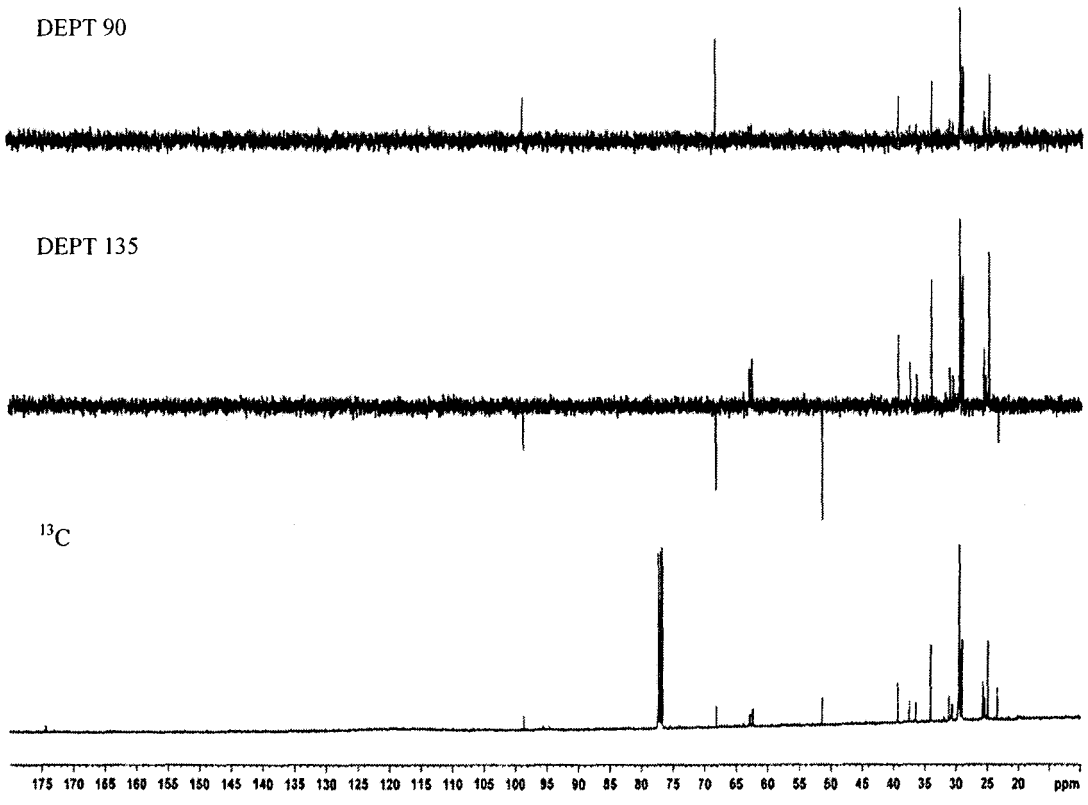


^{1}H NMR in $CDCl_3$

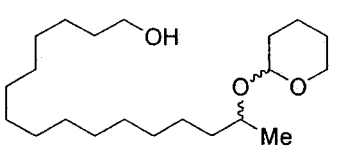


(±)-**60**

^{13}C NMR in $CDCl_3$



^{1}H NMR in $CDCl_3$



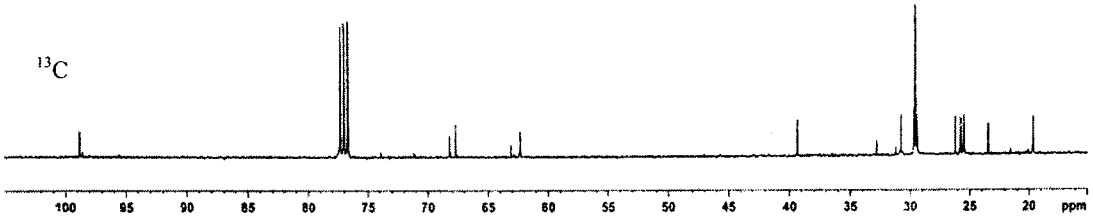
(±)-**61**

^{13}C NMR in $CDCl_3$

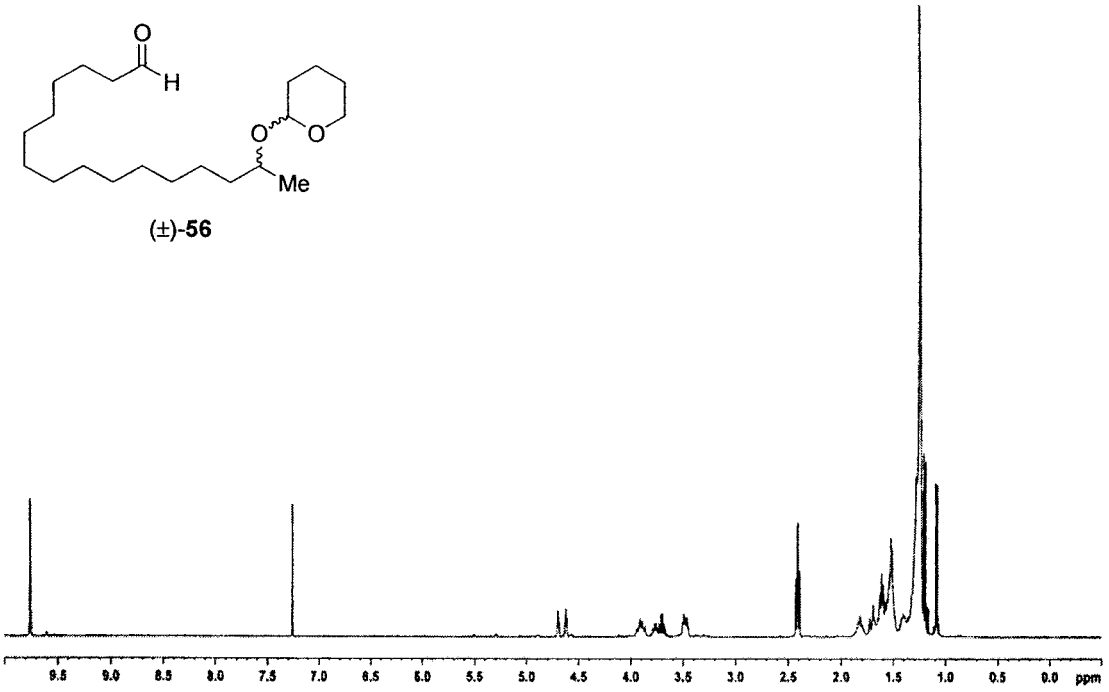
DEPT 90

DEPT 135

^{13}C

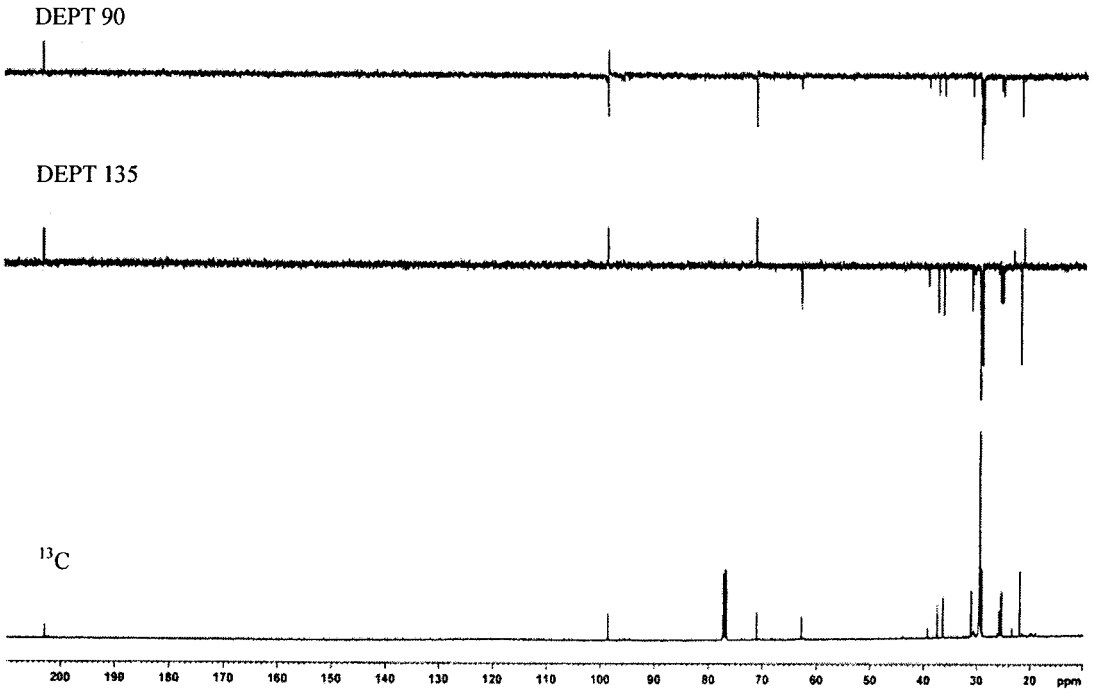


^{1}H NMR in $CDCl_3$

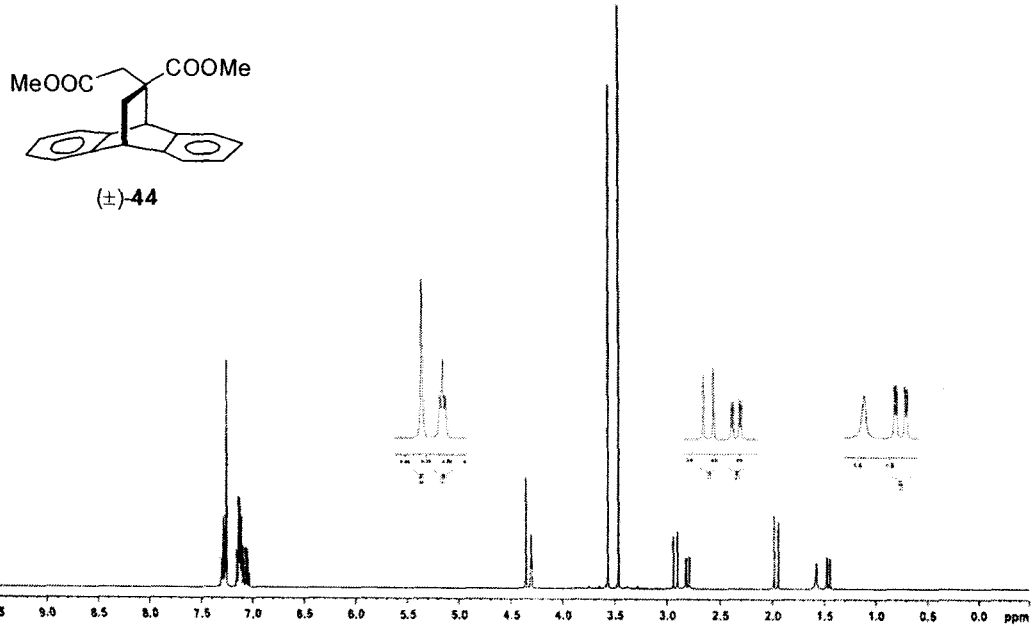


(±)-**56**

^{13}C NMR in $CDCl_3$

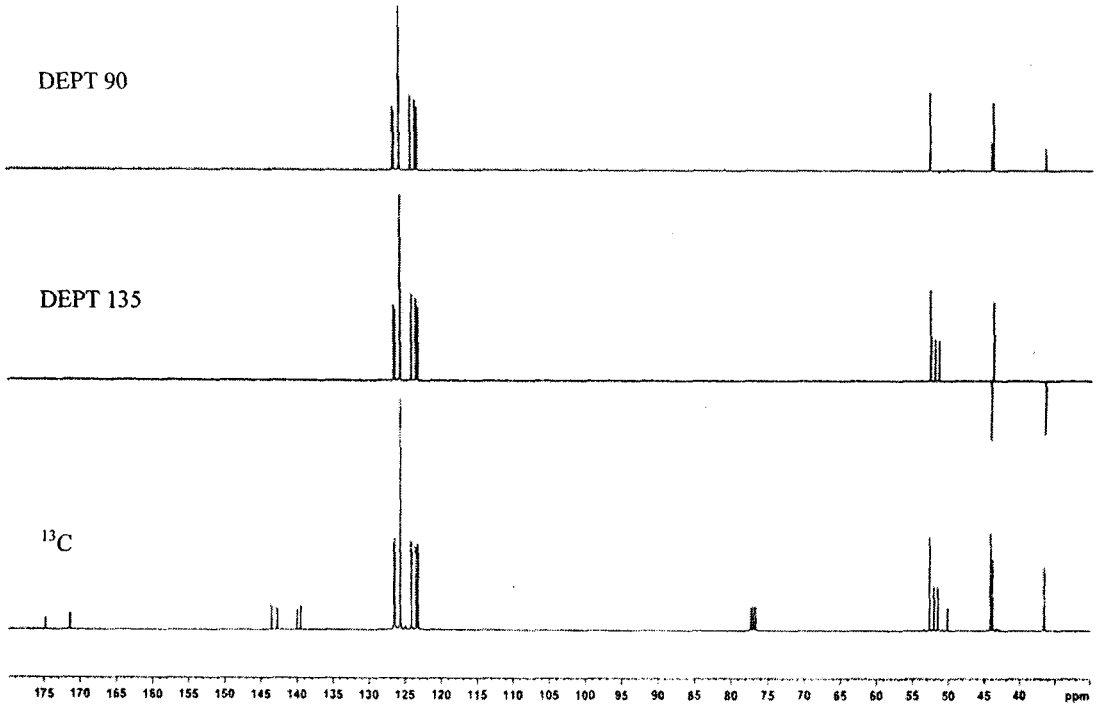


^{1}H NMR in $CDCl_3$



(±)-**44**

^{13}C NMR in $CDCl_3$



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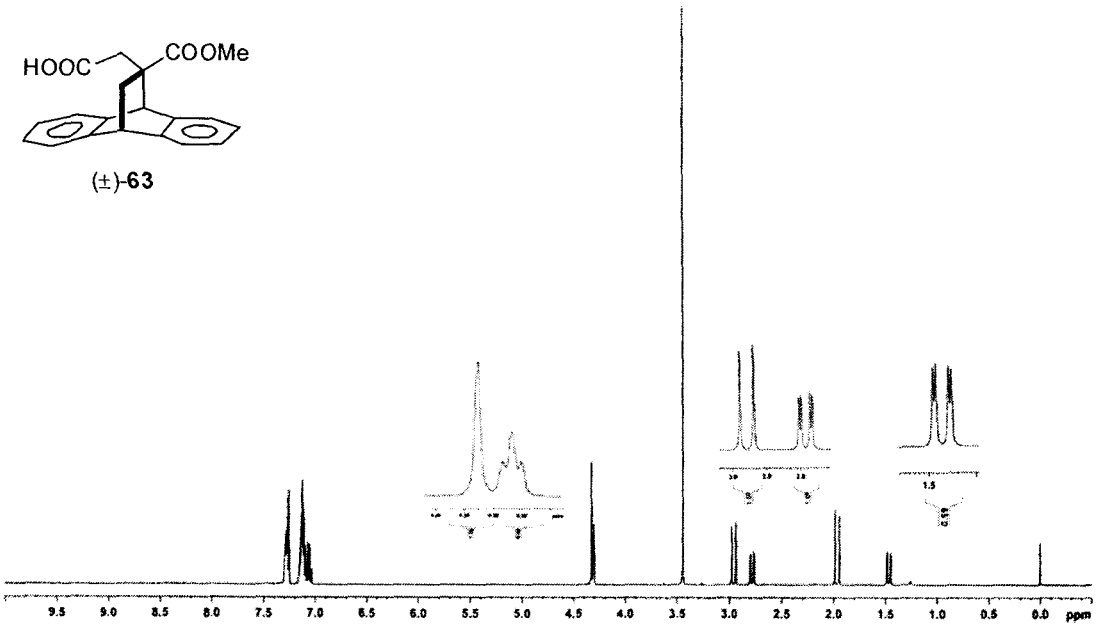

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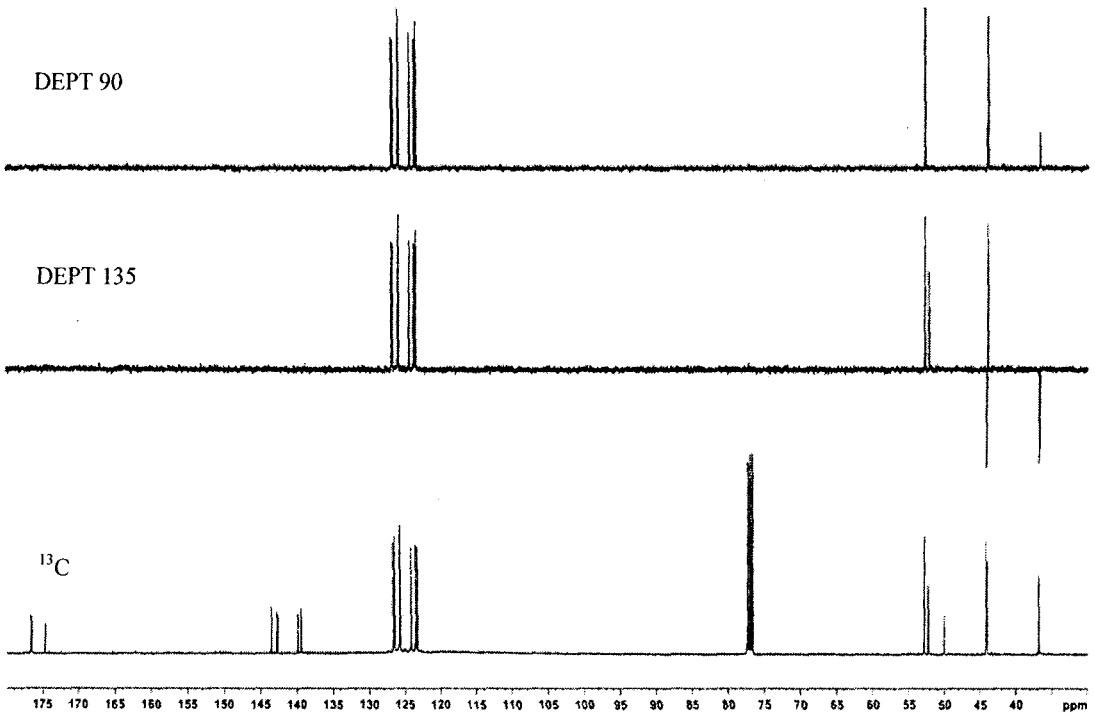

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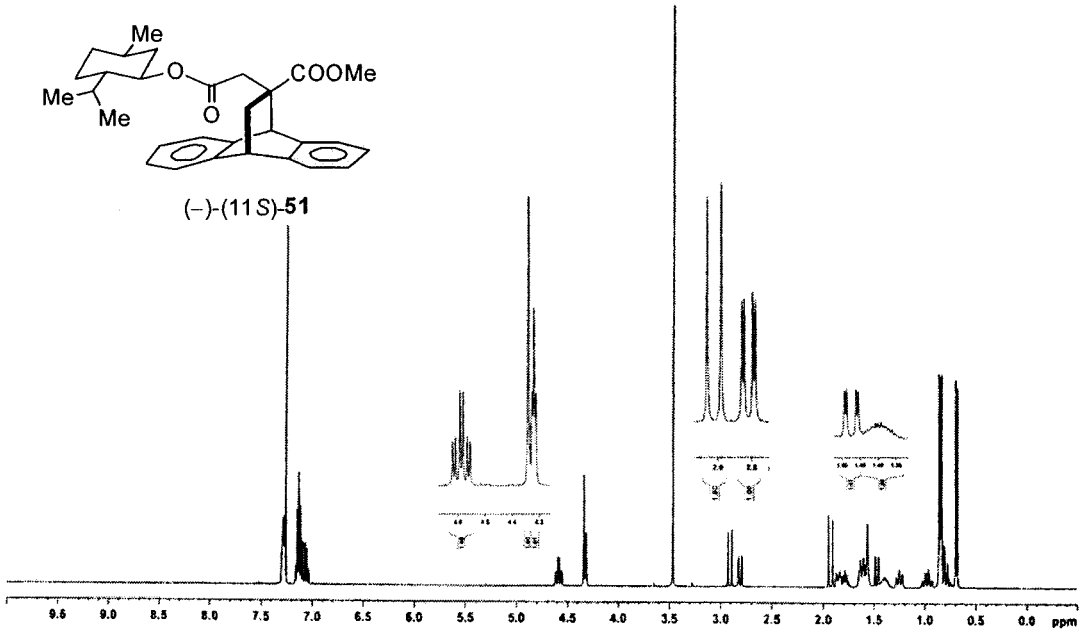

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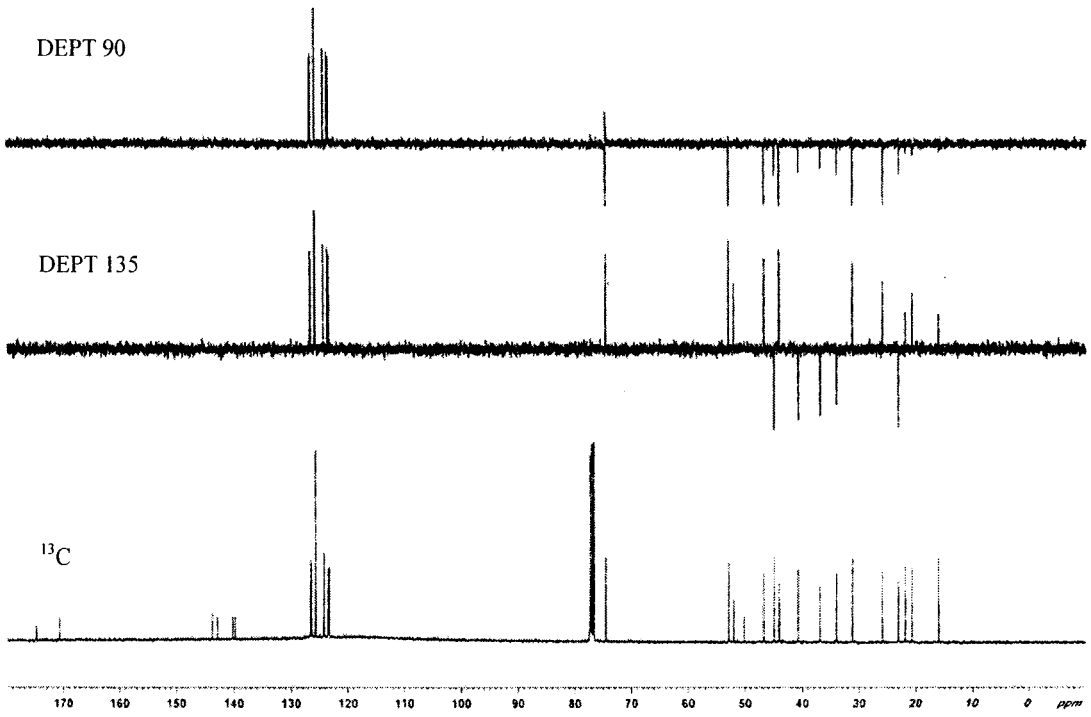

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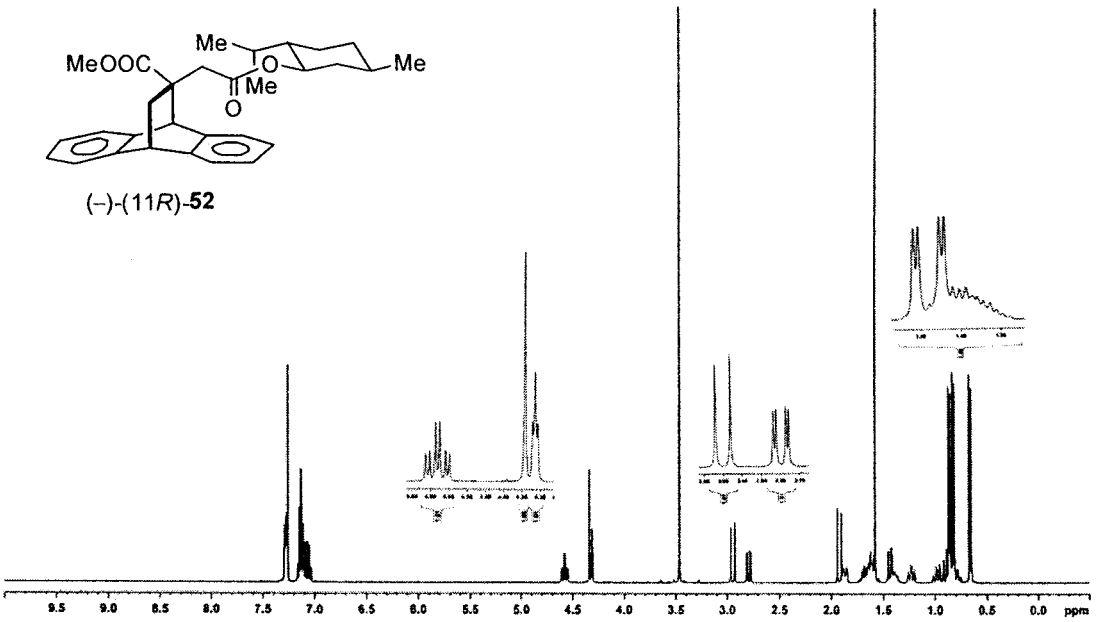
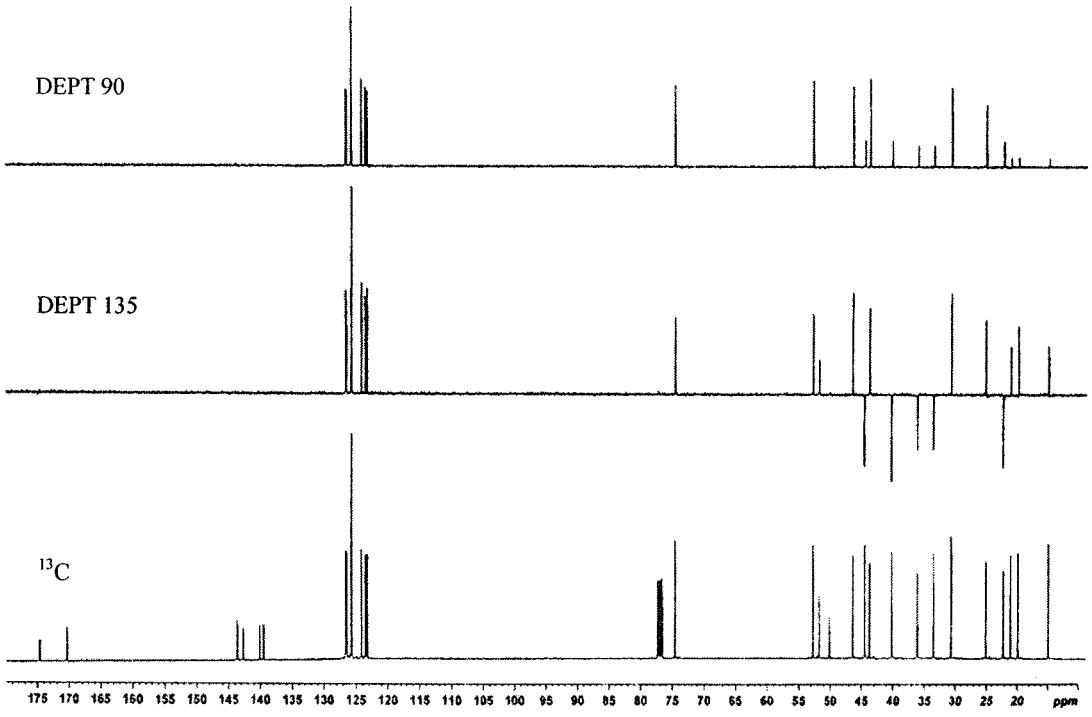
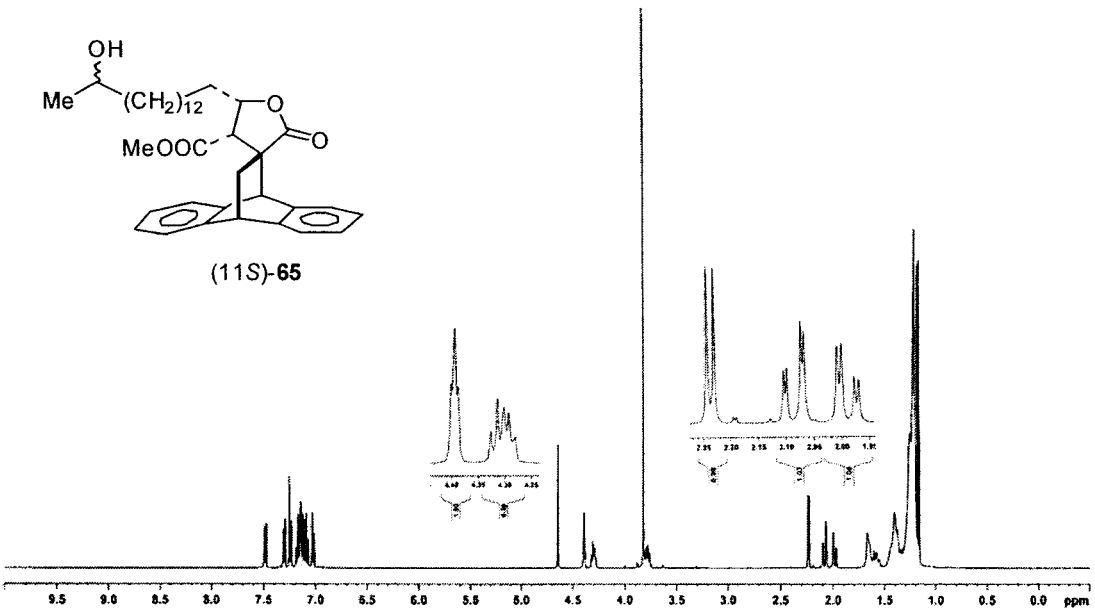


(–)-(11*R*)-**52**

^{13}C NMR in $CDCl_3$



^{1}H NMR in $CDCl_3$



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

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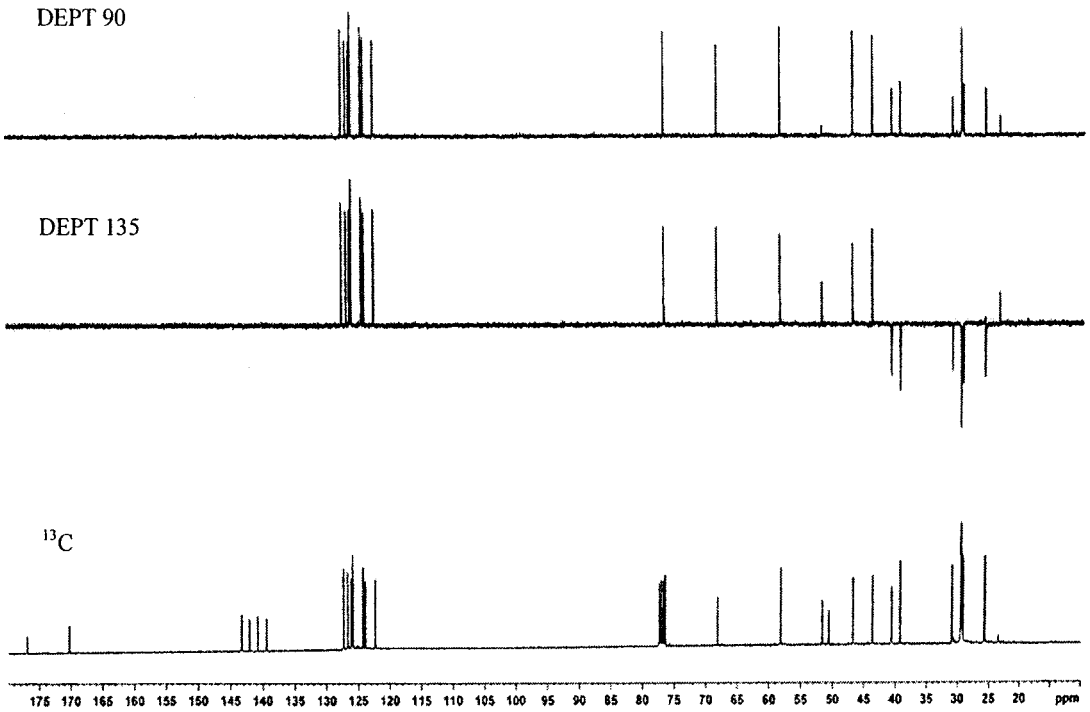

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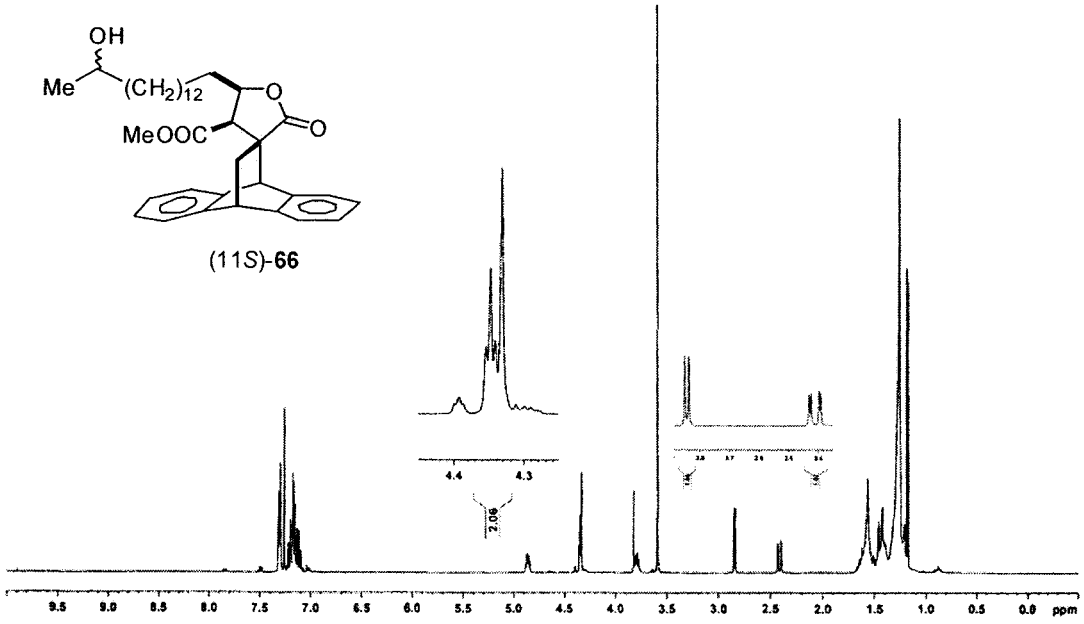

(11*S*)-**66**

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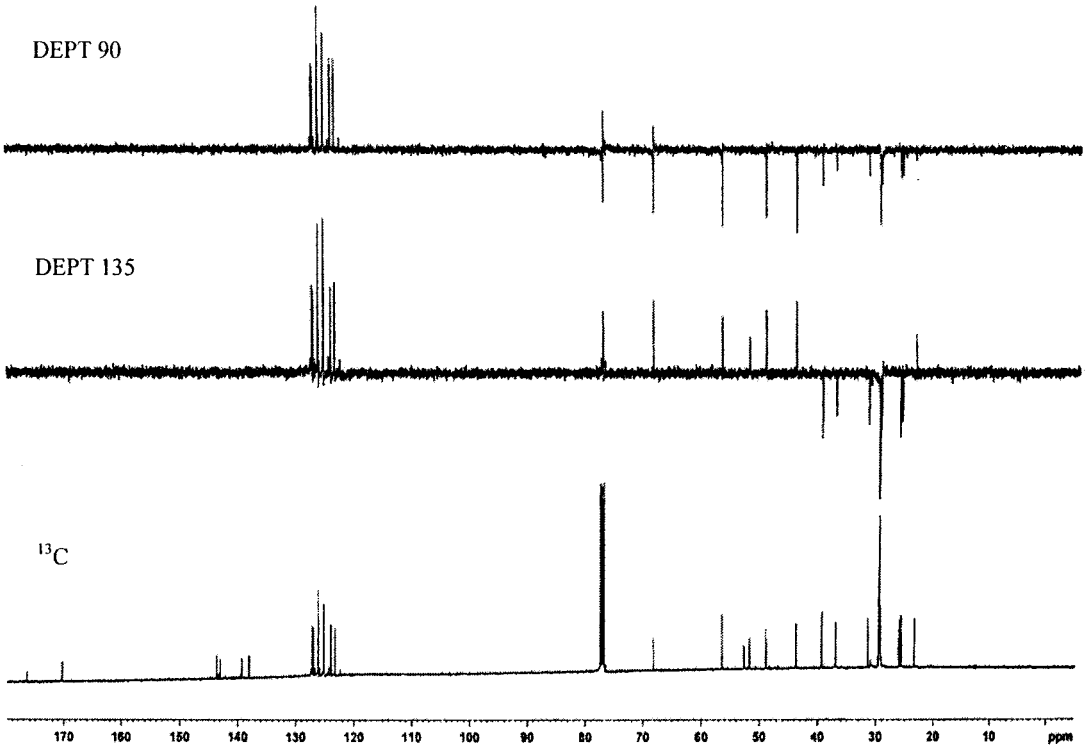

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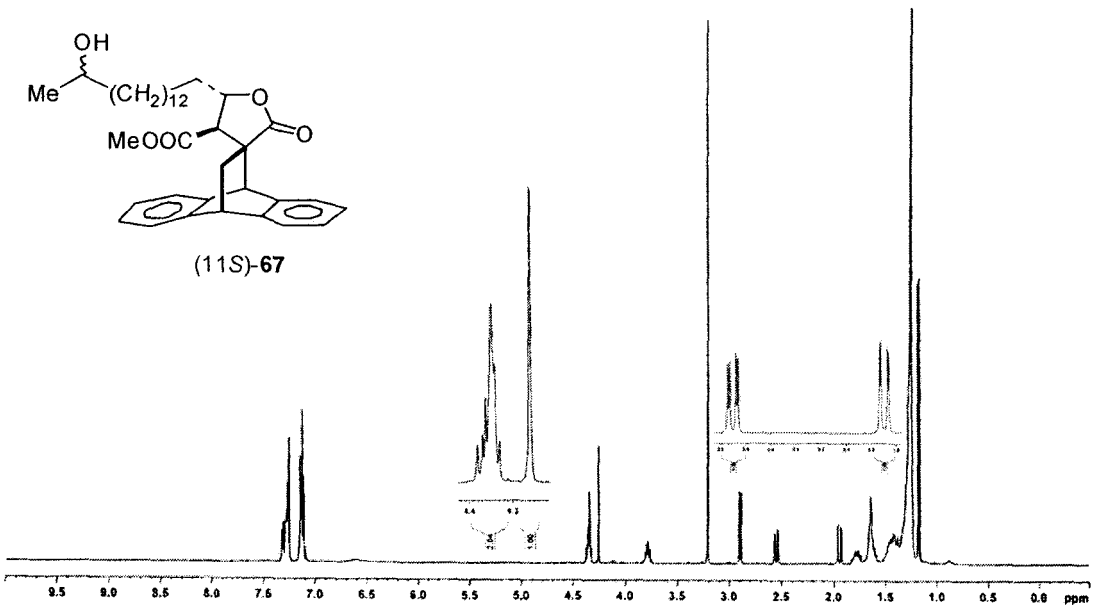
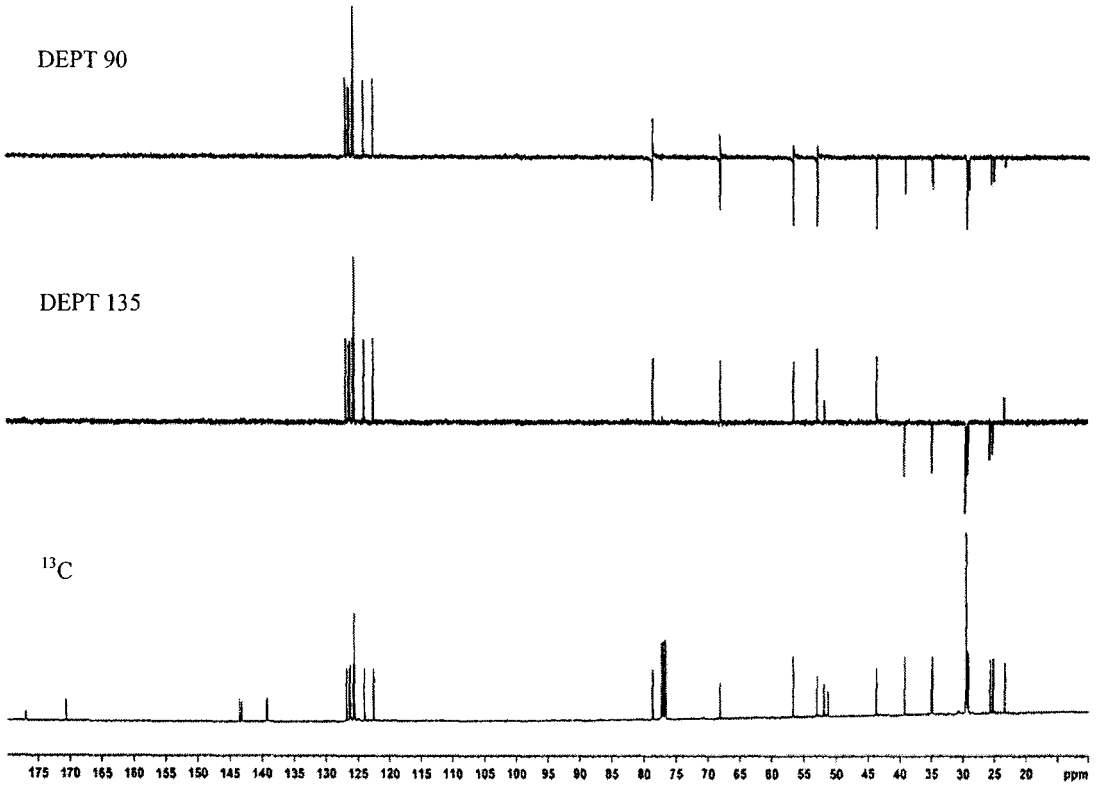
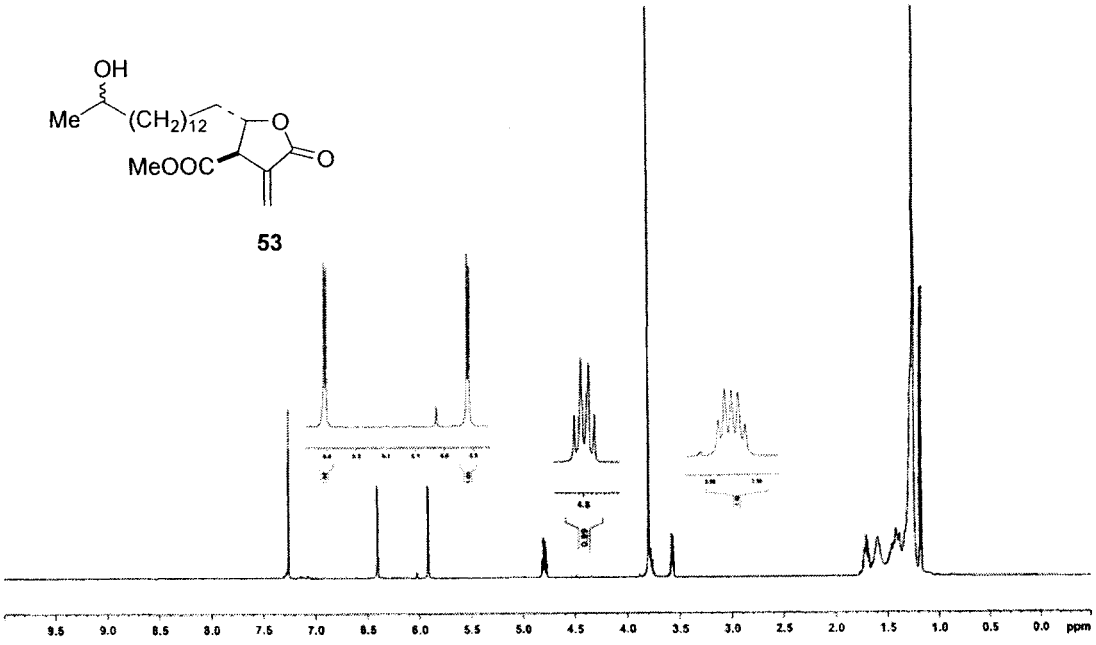


(11*S*)-**67**

^{13}C NMR in $CDCl_3$



^{1}H NMR in $CDCl_3$



^{13}C NMR in $CDCl_3$