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SYNTHESIS OF BOTH THE ENANTIOMERS OF JUVENILE HORMONE III†

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Abstract -- Both the enantiomers (~100 % e.e.) of juvenile hormone III [methyl (2E, 6E)-10,11-epoxy-3,7,11-trimethyl-2,6-dodecadienoate, JH III] were synthesized employing (S)-3-hydroxy-2,2-dimethylcyclohexanone as a single chiral source.

Röller's discovery of juvenile hormone I (JH I) in 1967 was an epock-making event not only in insect endocrinology but also in natural products chemistry.[1] Since then four other juvenile hormones as shown in Fig.1 (JH II, JH III, JH 0 and 4-Me JH I) were isolated and identified by American chemists.[2] JH III 1, which was first isolated from organ cultures of corpora allata of the tobacco hornworm moth (Manduca sexta Johannson),[3] was later found in at least one stage of development in nearly all insects surveyed to date.[2] JH III must therefore be a ubiquitous juvenile hormone in the insect kingdom. Very recently, (±)-JH III and methyl farnesoate were detected even in a crustacean, adult spider crabs (Libinia emarginata Leach).[4]

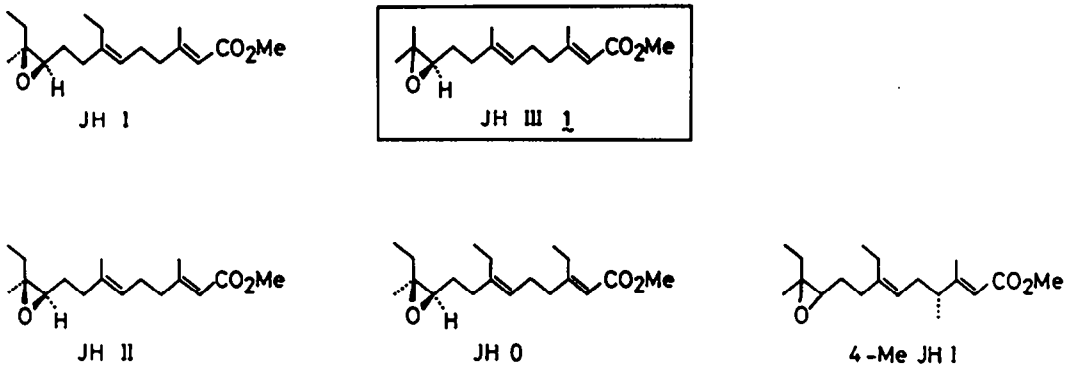

Fig.1. Structures of juvenile hormones.

A number of syntheses of JH III were accomplished including three chiral syntheses.[5-8] Indeed (±)-JH III had been synthesized by Bowers et al.[9] even before the discovery of (R)-(+)-JH III as the naturally occurring hormone. Chiral synthesis of JH III, however, was a difficult task, and the existing three syntheses afforded the enantio-

†Synthesis of compounds with juvenile hormone activity — 25. Part 24, N. Nakagawa, K. J. Kramer and K. Mori, Agric. Biol. Chem. 45, 2381 (1981). The present paper is dedicated to Prof. Masanao Matsui, the University of Tokyo, on the occasion of his 70th birthday. The experimental part of this work was taken from the forthcoming doctoral dissertation of H. M. (March, 1989).

mers of JH III of obscure optical purity.[6~8] This was due to the lack of an appropriate method for directly analyzing the enantiomeric excess (e.e.) of JH III at the time when the published chiral syntheses were achieved. The obscure optical purity of the enantiomers of JH III as prepared by Marumo et al.[6,7] and by Schooley et al.[8] prevented them from drawing a clear-cut conclusion concerning the bioactivities of the JH enantiomers. In fact, Schooley et al. stated that the activity observed for the unnatural (S)-JH III might be due to its contamination with the natural (R)-enantiomer.[8] To draw a definite conclusion on the relationship between absolute configuration of JH III and its bioactivity, it is of utmost importance to develop a new chiral synthesis of the pure enantiomers of JH III. Their enantiomeric purity may now be estimated with accuracy by employing one of the various modern methods for determining the optical purity of chiral organic compounds.[10] Herein is described our synthesis of the pure enantiomers of JH III starting from a chiral building block of microbial origin.

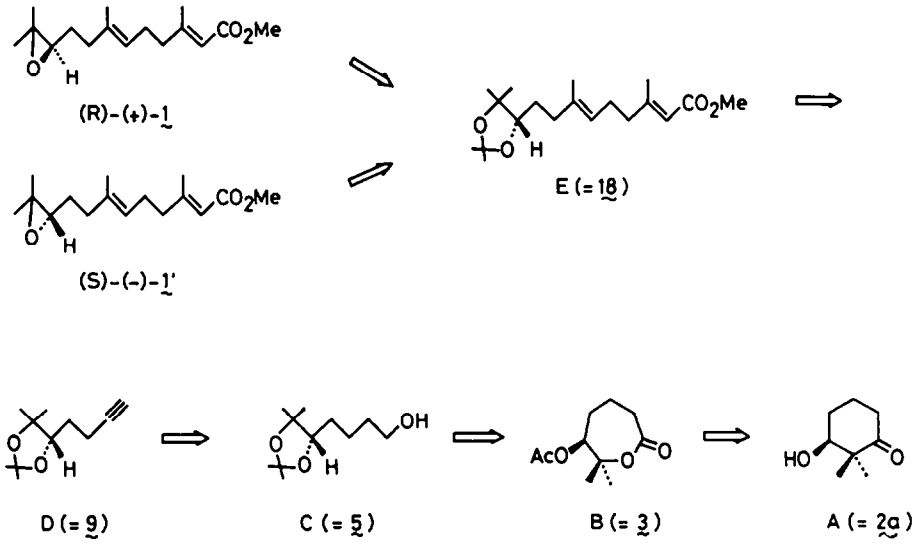

Fig. 2. Synthetic plan for JH III enantiomers.

Our synthetic plan is shown in Fig.2. (S)-3-Hydroxy-2,2-dimethylcyclohexanone **A** is employed as the starting material. This ketol **A** is readily available in high optical purity by a microbial process, and has been utilized by us in synthesizing various cyclic terpenes.[11] The ketol **A** is to be converted to ε-lactone **B** by Baeyer-Villiger oxidation. This pivotal step enables the derivation of acyclic epoxy terpenes including JH III from the cyclic ketol **A**. The key-intermediate **D** can be prepared from **B** via **C** by ring opening of **B**. Carbon-chain elongation of **D** affords diene ester **E**. Finally epoxide formation with inversion or retention of configuration at C-10 of **E** affords both the enantiomers of JH III (**1** and **1'**).

The first phase of our work was the synthesis of alkyne **9** (=**D**) as shown in Fig.3. Reduction of 2,2-dimethylcyclohexane-1,3-dione with baker's yeast gave **2a**, whose optical purity was estimated to be 98.4 % e.e. by the HPLC analysis of the corresponding (R)-α-methoxy-α-trifluoromethylphenylacetate[12] (MTPA ester) **2c**. After acetylating the OH group, the resulting **2b** was submitted to Baeyer-Villiger oxidation with MCPBA in the presence of $NaHCO_3$ to give ε-lactone **3** in 92 % yield. The crystalline nature of **3** enabled its optical enrichment by recrystallization. The purified lactone **3**, m.p. 51~52°C, $[\alpha]_D^{24}$ +24.7° ($CHCl_3$), was reduced with LAH to give triol **4a** quantitatively. Its optical purity was

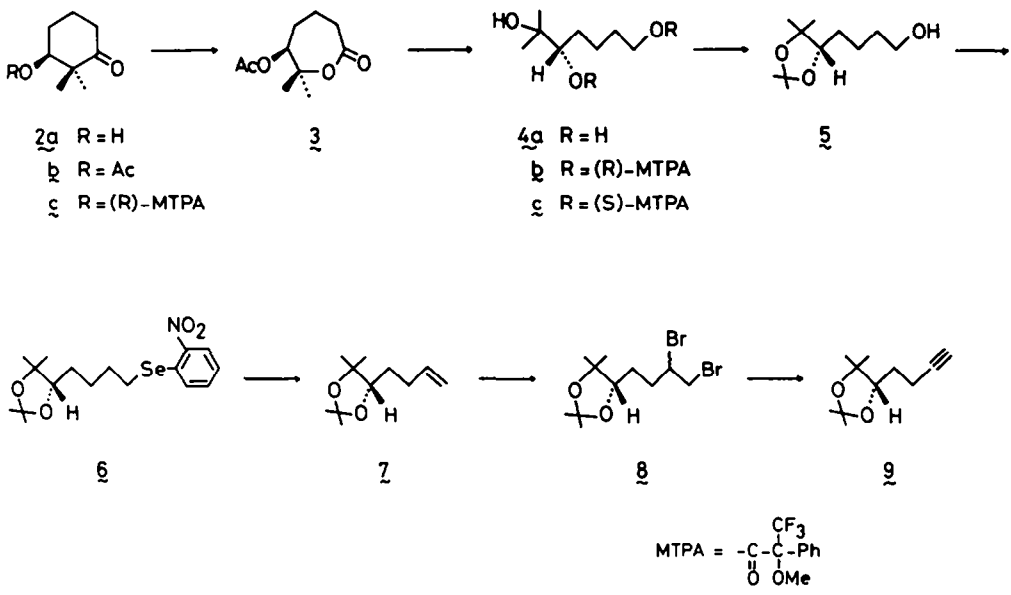

Fig.3. Synthesis of alkyne **9**.

proved to be ~100 % e.e. by the HPLC analysis of the corresponding (R)- and (S)-bis-MTPA esters **4b** and **4c**. After protecting the vic-diol portion of **4a** as an acetonide, the resulting **5** was converted quantitatively to **6** by treatment with o-$(O_2N)C_6H_4SeCN$ and $(n\text{-}Bu)_3P$ in THF.[13] The selenide **6** was oxidized with H_2O_2 in THF to give olefin **7** in 81 % yield. Bromination of **7** with $C_5H_5NHBr_3$ in THF furnished **8**, which was dehydrobrominated with excess $NaNH_2$ in liq NH_3 to give the desired alkyne **9** (=D) in 63 % yield from **7**.

The second stage of the synthesis as shown in Fig.4 was the carbon-chain elongation starting from **9**. We first tried haloboration reaction as developed by Suzuki et al.[14] However, all our attempts were in vain perhaps because of the Lewis acid nature of B-iodo-9-BBN, which interacted with the oxygen function of **9**. We therefore abandoned this approach, and adopted the method developed by Mukaiyama et al.[15] Thus **9** was methoxycarbonylated by treatment with n-BuLi and $ClCO_2Me$ in THF to give **10** in 85.2 % yield. The Michael addition of PhSH to **10** was effected with PhSNa in MeOH furnishing **11** and **12** as an isomeric mixture in 90.2 % yield. These two isomers were readily separable by SiO_2 chromatography and obtained in a ratio of 84:16. The geometries of **11** and **12** were assigned by considering the chemical shift of the olefinic proton α to the $-CO_2Me$ group. In the ^1H NMR spectrum of the major isomer **11**, the signal due to the olefinic proton was observed at δ 5.84. In the case of the minor isomer **12**, on the other hand, that signal was observed at δ 5.08. The desired (Z)-isomer **11** was treated with MeMgBr in the presence of CuI in THF at -65°C to give **13** stereoselectively in 71.3 % yield. The purity of **13** was confirmed to be 100 % as checked by GLC and ^{13}C NMR. Reduction of **13** with LAH furnished allylic alcohol **14** in 90 % yield. This was converted to the corresponding bromide **15** by the method of Stork et al.[16]

The third phase of the synthesis was the conversion of **15** to the diene ester **18** (=E). According to the procedure reported by Weiler et al.,[17,18] alkylation of the dianion of $MeCOCH_2CO_2Me$ with **15** yielded β-keto ester **16**. This was then converted to the corresponding enol phosphate **17** by treatment with NaH followed by the addition of $(EtO)_2POCl$. Subsequent reaction of **17** with Me_2CuLi in ether at -65°C generated the diene ester (2E,6E)-**18** in 40 % yield with 91 % stereoselectivity at C-2 as checked by GLC. This was further purified by SiO_2 chromatography (Merck Lobar® column) to give >97.5 % pure **18**,

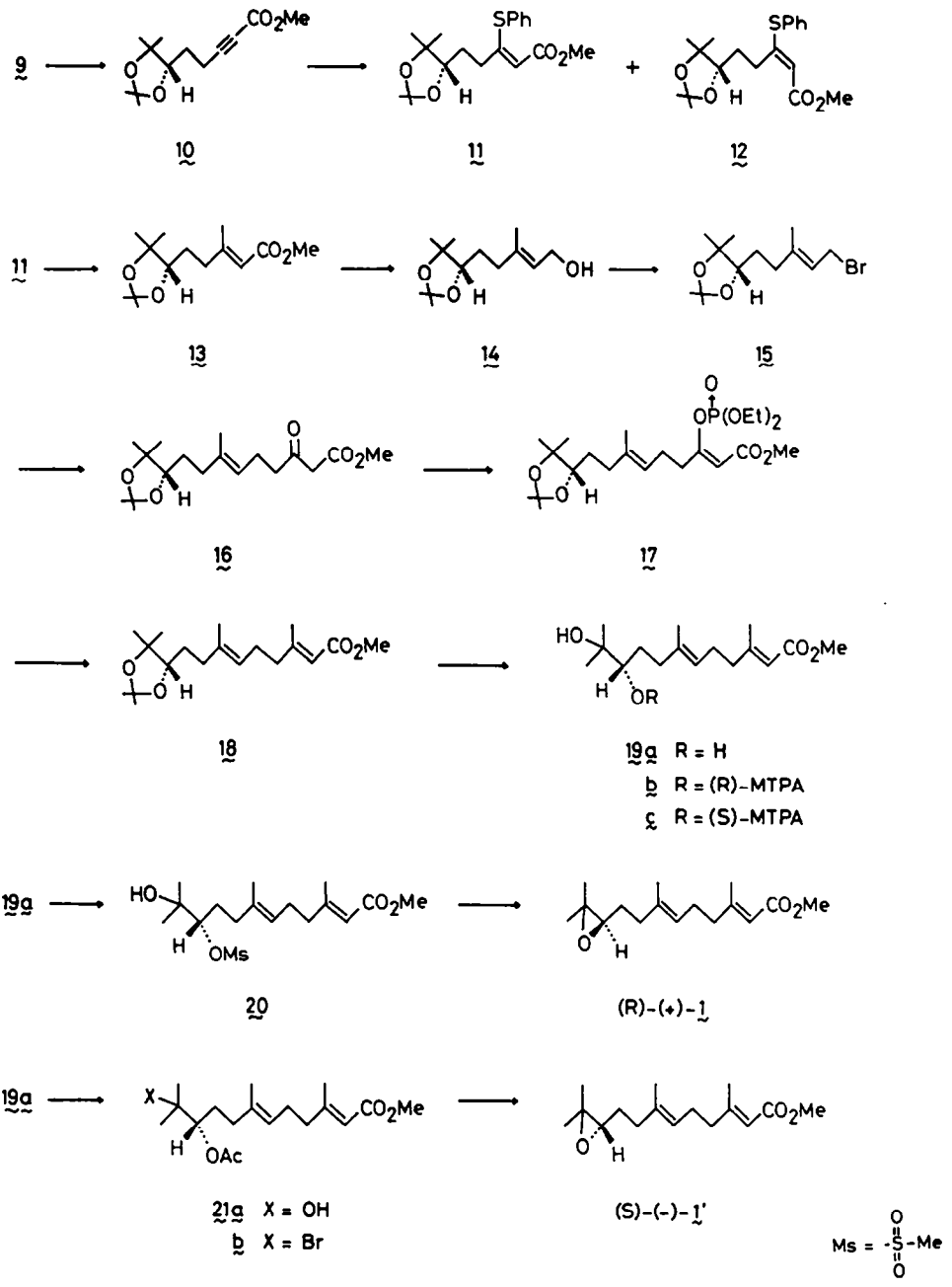

Fig.4. Synthesis of both the enantiomers of JH III.

$[\alpha]_D^{24}$ -2.5° (MeOH). Only the purified **18** was employed for the next step.

The final task was the epoxy-ring formation leading to JH III. Hydrolysis of acetonide was carried out by treatment of **18** with 75 % AcOH at 50°C to give diol **19a**, $[\alpha]_D^{24}$ -18.9° (MeOH) [lit[7] for its antipode: $[\alpha]_D$ +17.8° (MeOH)], in 98 % yield. Its optical purity was formed to be ~100 % e.e. by the HPLC analysis of the corresponding (R)- and (S)-MTPA esters **19b** and **19c**. Mesylation of **19a** with methanesulfonic anhydride (Ms_2O) in the presence of Et_3N in CH_2Cl_2 gave monomesylate **20**. Use of Ms_2O instead of the conventional MsCl in C_5H_5N was essential to avoiding the possible racemization in the course of conversion of **19a** to (R)-**1**. If we employ MsCl in C_5H_5N for mesylation, the generated **20** may suffer the S_N2 attack with Cl^- in the reaction mixture. This of course

causes the inversion of configuration at C-10. Accordingly, **20** may become contaminated with a trace amount of the (R)-chloride, resulting in the formation of optically impure (R)-**1** in the next step. Finally the monomesylate **20** was treated with NaOMe in MeOH to effect epoxide formation giving (R)-(+)-JH III **1**, $[\alpha]_D^{23}$ +6.71° (MeOH) [lit[7] $[\alpha]_D$ +5.75° (MeOH)], in 79.3 % yield from **19a**. The overall yield of (R)-(+)-**1** from **2a** was 3.6 % in 19 steps.

The synthesis of unnatural (S)-(-)-JH III **1'** was also achieved by the following sequence.[cf.6] Thus, acetylation of **19a** with Ac_2O in C_5H_5N furnished **21a**, which was brominated with PBr_3 in ether to give acetoxybromide **21b** in 60 % yield from **19a**. This was treated with NaOMe in MeOH to give (S)-(-)-**1'**, $[\alpha]_D^{23}$ -6.55° (MeOH) [lit[7] $[\alpha]_D$ -5.44° (MeOH)], in 83.1 % yield. The overall yield of (S)-(-)-**1'** from **2a** was 2.3 % in 20 steps.

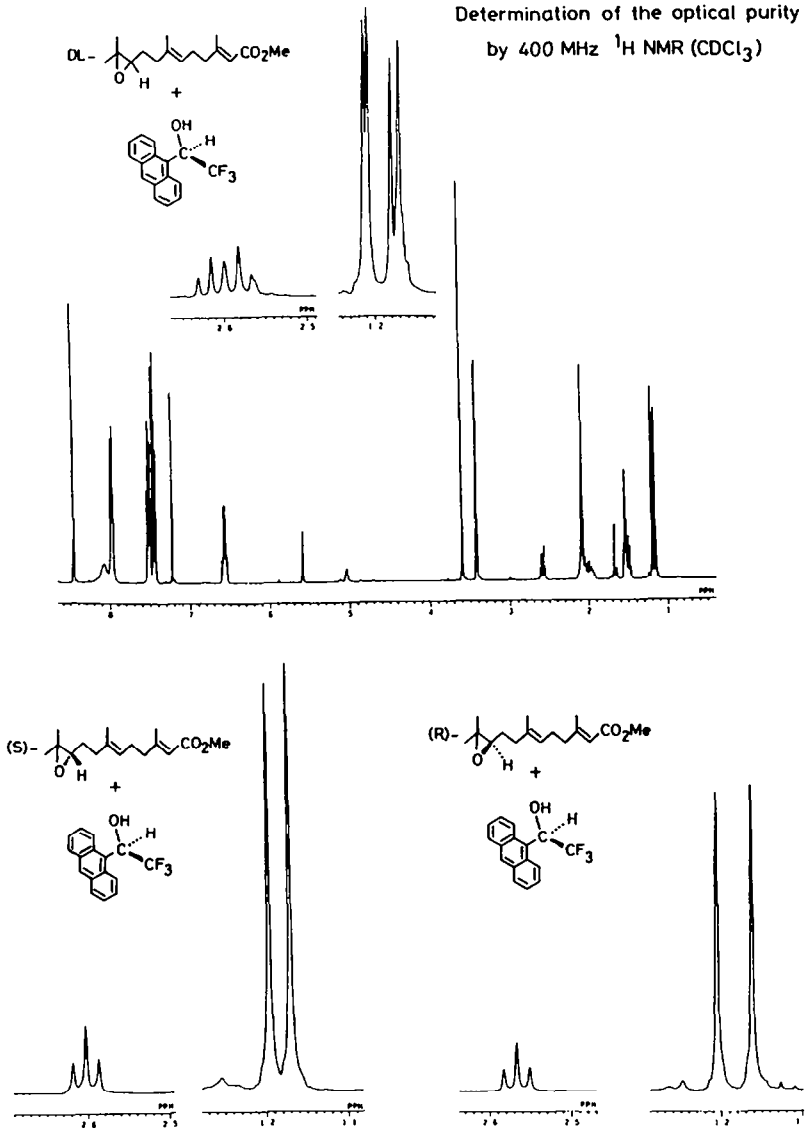

Fig.5.

With both the enantiomers of JH III (**1** and **1'**) available, we proceeded to the determination of the optical purity of our **1** and **1'**. Because two functional groups (epoxide and ester) exist separately each other at both the end of the molecule and are not reac-

tive ones such as OH group, there was no authentic method for determining the optical purity of JH. We therefore examined several methods such as HPLC analysis on chiral stationary phases or NMR analysis using chiral shift reagents. The only successful method was the use of the chiral solvating reagent developed by Pirkle et al.[19] The NMR non-equivalence induced by (R)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol upon its addition to (R)-**1** or (S)-**1'** was sufficiently large at 400 MHz as shown in Fig.5. The ^{1}H NMR spectrum of (±)-**1** measured at 400 MHz in $CDCl_3$ showed the splitting of the triplet due to the proton at C-10 of (±)-**1** into a pair of two triplets ($\Delta\delta$=0.035 ppm). With this procedure, we estimated the optical putity of our **1** and **1'** to be ~100 % e.e. as can be seen from Fig.5.

In conclusion, we completed a chiral synthesis of the pure enantiomers of JH III. The present work proved the utility of ketol **2a** not only in chiral syntheses of cyclic terpenes but also in those of acyclic terpenes such as JH III. The biological study on our **1** and **1'** is now under way in Prof. T. Ohtaki's laboratory in Kanagawa. It should be added that a chiral synthesis of the natural enantiomer of JH II was also completed using a similar biochemical reaction.[20]

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as nujol mulls for solids on a Jasco IRA-102 spectrometer. NMR spectra were recorded with TMS as an internal standard at 60 MHz on a Hitachi R-24A spectrometer or at 100 MHz on a JEOL JNM FX-100 spectrometer or at 400 MHz on a JEOL JNM FX-400 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV. Fuji Davison 820 MH gel was used for SiO_2 column chromatography.

(S)-(+)-3-Acetoxy-2,2-dimethylcyclohexanone **2b**. Ac_2O (20 ml, 211 mmol) was added to a stirred and cooled soln of **2a** (15.0 g, 105.5 mmol) in dry C_5H_5N (60 ml) and the mixture was stirred overnight at room temp. It was then poured into ice-water (~500 ml) and extracted with ether. The ether soln was washed with 3 N HCl aq, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 19.3 g (quantitative) of **2b** as a colorless oil, b.p. 75~77°C/2 Torr; n_D^{24} 1.4517; $[\alpha]_D^{24}$ +10.4° (c=1.36, $CHCl_3$), [lit[21] $[\alpha]_D^{20}$ +8.62° (c=0.58, $CHCl_3$)]; νmax 1740 (s), 1715 (s), 1385 (m), 1365 (s), 1235 (s), 1045 (s), 990 (s) cm^{-1}; δ (CCl_4) 1.01 (3H, s), 1.10 (3H, s), 1.53~2.17 (4H, m), 1.98 (3H, s), 2.17~2.60 (2H, m), 4.75~4.93 (1H, m). These IR and NMR spectra were identical with those reported previously.[21]

(S)-(+)-5-Acetoxy-6-methyl-6-heptanolide **3**. A soln of **2b** (13.5 g, 73.3 mmol) in dry CH_2Cl_2 (60 ml) was added dropwise to a mixture of 80 % MCPBA (23.7 g, 110 mmol) and $NaHCO_3$ (9.46 g) in dry CH_2Cl_2 (120 ml) and the mixture was stirred overnight at room temp. It was then filtered through a pad of Celite and the filter-cake was washed with ether. The combined filtrate and washings were washed with 10 % $NaHSO_3$ soln, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (17.3 g) was chromatographed over SiO_2 (140 g). Elution with C_6H_6-EtOAc (10:1) gave 13.4 g (92 %) of **3** as crystals. This was recrystallized from (i-Pr)$_2$O-n-hexane-C_6H_6 (36:25:5) to give 7.9 g of pure **3** as colorless needles, m.p. 51~52°C; $[\alpha]_D^{24}$ +24.7° (c=1.58, $CHCl_3$); νmax (KBr) 1740 (s), 1710 (s), 1290 (s), 1250 (s), 1230 (s), 1200 (s), 1115 (s), 1040 (s) cm^{-1}; δ (CCl_4) 1.37 (3H, s), 1.45 (3H, s), 1.50~2.35 (4H, m), 2.07 (3H, s), 2.43~2.72 (2H, m), 4.83 (1H, dd, J= 3 and 5 Hz); MS: m/z 201 (M^++1, 2.5 %), 188 (5 %), 160 (6.9 %), 145 (24.1 %), 117 (18.7 %), 99 (100 %), 71 (36.5 %), 59 (78.3 %); HRMS: (Found: m/z 201.1128 (M^++1, $C_{10}H_{17}O_4$). Calc for $C_{10}H_{17}O_4$: 201.1127).

(S)-6-Methylheptane-1,5,6-triol **4a**. A soln of **3** (12.3 g, 61.6 mmol) in dry THF (130 ml) was added dropwise to a stirred and ice-cooled suspension of LAH (4.67 g, 123 mmol) in dry THF (200 ml). After the addition was complete, the mixture was stirred for 30 min at 0°C, for 1 h at room temp and for 30 min under reflux. It was then cooled to 0°C and water (4.7 ml), 10 % NaOH aq (4.7 ml) and water (14 ml) were added to decompose the excess LAH. The mixture was stirred for 2 h at room temp and filtered through a pad of Celite. The filter-cake was washed with ether and THF. The combined filtrate and washings were dried (Na_2SO_4) and concentrated in vacuo to give 10.2 g of **4a** as a colorless oil, νmax 3400 (vs), 1165 (m), 1060 (s) cm^{-1}. This was employed for the next step immediately without purification.

Determination of the optical purity of **4a**. According to the reported procedure[12], (R)- and (S)-bis-MTPA esters **4b** and **4c** were prepared from **4a**. HPLC analysis (Column, Nucleosil® 50-5, 25 cm x 4mm; Eluent, n-hexane-THF=8:1, 1.4 ml/min; Detected at UV 254 nm) Co-injection of **4b** and **4c**: Rt 34.5 and 39.7 min; (R)-bis-MTPA ester **4b**: Rt 38.3 min (single peak). Therefore the optical purity of **4a** was determined to be ~100 % e.e.

(S)-(-)-5,6-Isopropylidenedioxy-6-methyl-1-heptanol **5**. p-TsOH was added to a soln of **4a** (10.2 g, 61.6 mmol) and $(MeO)_2CMe_2$ (12.8 g, 123 mmol) in acetone (200 ml) and the mixture was stirred for 30 min at room temp. The solvent was removed by evaporation and the residue was treated with water. The mixture was stirred for 20 min at room temp and extracted with ether. The ether soln was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 12.3 g (99 % from **3**) of **5** as a colorless oil, b.p. 82~85°C/0.2 Torr; n_D^{24} 1.4377; $[\alpha]_D^{24}$ -6.45° (c=1.1, MeOH); νmax 3440 (s), 1380 (sh), 1370 (s), 1240 (s), 1220 (s), 1200 (s), 1120 (s), 1065 (m), 1040 (m), 1015 (s), 915 (m) cm^{-1}; δ (CCl_4) 1.00 (3H, s), 1.14 (3H, s), 1.22 (3H, s), 1.30 (3H, s), 1.35~2.10 (6H, m), 2.29 (1H, br.s, OH), 3.22~3.75 (3H, m). (Found: C, 65.10; H, 10.83. Calc for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96 %).

(S)-2,3-Isopropylidenedioxy-2-methyl-7-o-nitrophenylselenoheptane 6. To a stirred soln of 5 (11.37 g, 56.2 mmol) and o-nitrophenyl selenocyanate (15.3 g, 67.44 mmol) in dry THF was added dropwise (n-Bu)$_3$P (13.65 g, 67.44 mmol) under Ar at room temp. The mixture was stirred for 3.5 h at room temp and the solvent was removed by evaporation. The residue (~42 g) was chromatographed over SiO_2 (300 g). Elution of C_6H_6–ether (50:1~40:1) gave 21.9 g (quantitative) of 6 as a low-melting yellow solid. This was employed for the next step without further purification.

(S)-(+)-2,3-Isopropylidenedioxy-2-methyl-6-heptene 7. To a stirred and ice-cooled soln of 6 (20.0 g, 51.8 mmol) in THF (250 ml) was added dropwise 35 % H_2O_2 aq (44 g, 450 mmol) over 16 min. The mixture was stirred for 1 h at -5°C and for 1.5 h at room temp. It was then poured into 8 % Na_2CO_3 soln (400 ml) and the organic layer was separated. The aq layer was extracted with n-pentane. The combined organic soln was washed with 5 % NaOH aq, water and brine, dried (K_2CO_3) and concentrated under atm press with a Vigreaux column. The residue was filtered through a column of neutral Al_2O_3 (grade 4, 150 g). Elution with n-pentane–ether (20:1) gave 7.7 g (81 %) of 7 as a volatile oil. A small portion of it was distilled to give an analytical sample, b.p. 95~96°C/35 Torr; n_D^{24} 1.4215; $[\alpha]_D^{24}$ +2.84° (c=0.985, n-pentane); νmax 3080 (w), 1640 (m), 1370 (s), 1215 (s), 1200 (s), 1115 (s), 1000 (s), 910 (s), 855 (m) cm^{-1}; δ (CCl_4) 1.00 (3H, s), 1.15 (3H, s), 1.21 (3H, s), 1.30 (3H, s), 1.30~1.90 (2H, m), 1.90~2.48 (2H, m), 3.54 (1H, dd, J= 4 and 9 Hz), 4.74~5.16 (2H, m), 5.42~6.15 (1H, m); HRMS (Found: m/z 169.1217 (M^+–CH_3, $C_{10}H_{17}O_2$). Calc for $C_{10}H_{17}O_2$: 169.1229).

(3S,6RS)-6,7-Dibromo-2,3-isopropylidenedioxy-2-methylheptane 8. $C_5H_5NHBr_3$ (9.6 g, 30 mmol) was added to a stirred and ice-cooled soln of 7 (4.6 g, 25 mmol) in THF (50 ml). The mixture was stirred for 30 min at 0°C and for 2.5 h at room temp. It was then poured into 4 % $NaHSO_3$ soln (60 ml) and the organic layer was separated. The aq layer was extracted with n-pentane. The combined organic soln was washed with water and brine, dried (K_2CO_3 and $MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (80 g) to give 7.5 g (87 %) of 8 as a colorless oil, νmax 1380 (sh), 1370 (s), 1235 (s), 1220 (s), 1200 (s), 1120 (s), 1005 (s), 915 (m), 855 (m) cm^{-1}; δ (CCl_4) 1.06 (3H, s), 1.21(3H, s), 1.26 (3H, s), 1.33 (3H, s), 1.40~2.30 (4H, m), 3.40~4.30 (4H, m). This was employed for the next step without further purification.

(S)-(-)-2,3-Isopropylidenedioxy-2-methyl-6-heptyne 9. To a stirred and cooled suspension of $NaNH_2$ [prepared from 7.0 g (304 mmol) of Na metal] in liq. NH_3 (250 ml) was added dropwise a soln of 8 (7.5 g, 22 mmol) in dry ether (40 ml) over 40 min at -50°C. The mixture was stirred for 30 min at -50°C and for 3.5 h at -27°C. The reaction was quenched by the addition of solid NH_4Cl (5 g) at -27°C and NH_3 was evaporated at room temp. The residue was diluted with sat NH_4Cl soln and extracted with a mixture of n-pentane–ether (1:1). The extract was washed with water and brine, dried (K_2CO_3 and $MgSO_4$) and concentraed under atm press with a Vigreaux column to give 2.9 g (72 %) of 9 as a volatile oil. A small portion of it was distilled to give an analytical sample, b.p. 101~102°C/57 Torr; n_D^{22} 1.4320; $[\alpha]_D^{22}$ -33.1° (c=1.49, n-pentane); νmax 3300 (s), 2120 (w), 1370 (s), 1215 (s), 1200 (s), 1115 (s), 1065 (s), 1000 (s) cm^{-1}; δ (CCl_4) 1.02 (3H, s), 1.19 (3H, s), 1.25 (3H, s), 1.30 (3H, s), 1.40~1.90 (3H, m), 2.10~2.50 (2H, m), 3.65 (1H, dd, J=4 and 9 Hz); HRMS (Found: m/z 182.1329 (M^+). Calc for $C_{11}H_{18}O_2$: 182.1307).

Methyl (S)-(-)-6,7-isopropylidenedioxy-7-methyl-2-octynoate 10. To a stirred soln of 9 (2.8 g, 15.4 mmol) in dry THF (65 ml) was added dropwise n-BuLi in n-hexane (1.50 N, 11.2 ml, 17 mmol) at -3~0°C under Ar. After stirring for 45 min at -5°C, the mixture was cooled to -60°C and a soln of $ClCO_2Me$ (2.9 g, 31 mmol) in dry THF (10 ml) was added dropwise. The mixture was stirred for 1 h at -60°C and overnight at room temp. It was then poured into sat NH_4Cl soln (~60 ml) and the organic layer was separated. The aq layer was extracted with ether. The combined organic soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (4.2 g) was chromatographed over SiO_2 (50 g) to give 3.2 g (85 %) of 10 as a colorless oil. An analytical sample was obtained by distillation, b.p. 91~93°C/26 Torr; n_D^{23} 1.4505; $[\alpha]_D^{23}$ -45.7° (c=1.045, MeOH); νmax 2240 (s), 1720 (s), 1380 (sh), 1370 (s), 1255 (s), 1120 (s), 1075 (s), 1005 (s) cm^{-1}; δ (CCl_4) 1.02 (3H, s), 1.20 (3H, s), 1.26 (3H, s), 1.30 (3H, s), 1.35~1.90 (2H, m), 2.28~2.65 (2H, m), 3.66 (3H, s), 3.46~3.75 (1H, m). (Found: C, 64.66; H, 8.24. Calc for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39 %).

Methyl (2Z,6S)-(+)-6,7-isopropylidenedioxy-7-methyl-3-phenylthio-2-octenoate 11 and its (2E,6S)-(+)-isomer 12. NaOH (500 mg, 12.7 mmol) was added to a stirred soln of C_6H_5SH (1.40 g, 12.7 mmol) in MeOH (18 ml) and the mixture was stirred for 30 min at room temp. To this was added a soln of 10 (2.55 g, 10.6 mmol) in MeOH (10 ml) and the stirring was continued for 4 h at room temp. AcOH aq (containing 760 mg of AcOH) was addd to quench the reaction. The reaction mixture was diluted with brine and extracted with ether. The ether soln was washed with 4 % NaOH aq, water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (3.7 g) was chromatographed twice over SiO_2 (70 g). Elution with n-hexane–ether (100:1~40:1) gave 470 mg (12.6 %) of (2E,6S)-12 as a viscous oil, TLC [SiO_2, Merck Art 5715; developed with n-hexane–ether (2:1)] Rf 0.46; n_D^{24} 1.5290; $[\alpha]_D^{24}$ +29.2° (c=1.15, MeOH); νmax 3080 (w), 1710 (s), 1600 (s), 1380 (sh), 1370 (s), 1340 (s), 1320 (m), 1215 (s), 1190 (s), 1170 (s), 1115 (s), 1005 (s), 850 (m), 750 (s) cm^{-1}; δ (CCl_4) 1.07 (3H, s), 1.21 (3H, s), 1.26 (3H, s), 1.35 (3H, s), 1.45~2.00 (2H, m), 1.65~3.30 (2H, m), 3.52 (3H, s), 3.69 (1H, dd, J=6 and 8 Hz), 5.08 (1H, s), 7.47 (5H, s). (Found: C, 64.98; H, 7.30. Calc for $C_{19}H_{26}O_4S$: C, 65.12; H, 7.48 %). Further elution with n-hexane–ether (30:1~10:1) gave 2.90 g (78 %) of (2Z,6S)-11 as a viscous oil, TLC [SiO_2, Merck Art 5715; developed with n-hexane–ether (2:1)] Rf 0.34; n_D^{24} 1.5304; $[\alpha]_D^{24}$ +12.9° (c=0.865, MeOH); νmax 3070 (w), 1710 (s), 1585 (s), 1380 (sh), 1370 (s), 1200 (vs), 1120 (s), 1020 (s), 1005 (s), 755 (m), 710 (m), 695 (m) cm^{-1}; δ (CCl_4) 0.87 (3H, s), 1.00 (3H, s), 1.11 (3H, s), 1.21 (3H, s), 1.05~1.60 (2H, m), 2.01~2.56 (2H, m), 3.14 (1H, dd, J=5 and 8 Hz), 3.55 and 3.65 (0.5H+2.5H = 3H, each s), 5.84 (1H, s), 7.20~7.70 (5H, m). (Found: C, 64.91; H, 7.44. Calc for $C_{19}H_{26}O_4S$: C, 65.12; H, 7.48 %).

Methyl (2E,6S)-(-)-6,7-isopropylidenedioxy-3,7-dimethyl-2-octenoate 13. MeMgBr in dry THF (2.52 N, 14.5 ml, 36.7 mmol) was added dropwise to a stirred and cooled suspension of CuI (2.79 g, 14.7 mmol, dried in vacuo for 3 h at room temp) in dry THF (80 ml) at -63°C under Ar. The mixture was stirred for 15 min at -65°C and to this was added dropwise a soln of 11 (2.57 g, 7.33 mmol) in dry THF (15 ml) below -60°C. After stirring for 3 h at -65°C, the mixture was poured into sat NH_4Cl soln (~100 ml) and stirred for 15 min at room temp. The organic layer was separeted and the aq layer was extracted with ether. The combined organic soln was washed with sat NH_4Cl soln, water, 4 % NaOH aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (1.9 g) was chromatographed over SiO_2 (40 g) to give 1.34 g (71.3 %) of 13 as an oil, n_D^{24} 1.4530; $[\alpha]_D^{24}$ -10.1° (c=1.07, MeOH); νmax 1720 (s), 1650 (s), 1380 (sh), 1370 (s), 1220 (s), 1150 (s), 1115 (s), 1005 (s), 915 (m), 860 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.12 (3H, s), 1.27 (3H, s), 1.34 (3H, s), 1.43 (3H, s), 1.46~1.77 (2H, m), 2.19 (3H, d, J=1.3 Hz), 2.23~2.48 (2H, m), 3.66 (1H, dd, J=4 and 9 Hz), 3.71 (3H, s), 5.72 (1H, tq, J=1.3 and 1.3 Hz); ^{13}C NMR δ (25 MHz, $CDCl_3$) 18.87, 22.96, 26.00, 26.88, 27.26, 28.55, 38.06, 50.81, 80.06, 82.55, 106.71, 115.48, 159.27, 167.08; GLC (Column: 5 % PEG, 1.5 m x 4 mm; Carrier gas: N_2, 1 kg/cm^2; Column temp: 100°C+5°C/min) Rt 9.4 min (100 %). (Found: C,

65.35; H, 9.14. Calc for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44 %).

(2E,6S)-(-)-6,7-Isopropylidenedioxy-3,7-dimethyl-2-octen-1-ol **14**. To a stirred and cooled suspension of LAH (150 mg, 3.95 mmol) in dry ether (24 ml) was added dropwise a soln of **13** (1.26 g, 4.92 mmol) in dry ether (6 ml) over 15 min at 0°C. After stirring for 3 h at 0°C, the reaction was quenched by the addition of water (0.15 ml), 10 % NaOH aq (0.15 ml) and water (0.45 ml). The mixture was stirred for 40 min at room temp and filtered through a pad of Celite. The filter-cake was washed with ether and THF. The combined filtrate and washings were dried ($MgSO_4$) and concentrated in vacuo. The residue (1.2 g) was chromatographed over SiO_2 (18 g) followed by distillation to give 1.01 g (90.0 %) of **14** as a colorless oil, b.p. 114~116°C/0.7 Torr; n_D^{24} 1.4555; $[\alpha]_D^{24}$ -3.92° (c=0.79, MeOH); νmax 3430 (s), 1665 (w), 1380 (sh), 1370 (s), 1230 (s), 1215 (s), 1200 (s), 1115 (s), 1000 (s), 910 (m), 850 (m) cm^{-1}; δ (CCl_4) 1.02 (3H, s), 1.18 (3H, s), 1.24 (3H, s), 1.32 (3H, s), 1.40~1.87 (2H, m), 1.67 (3H, s), 1.87~2.48 (2H, m), 2.09 (1H, s, OH), 3.54 (1H, dd, J=5 and 8 Hz), 4.01 (2H, d, J=7 Hz), 5.40 (1H, deformed t, J=7 Hz); GLC (Column: 5 % PEG, 1.5 m x 4 mm; Carrier gas: N_2, 1 kg/cm^2; Column temp: 80°C+10°C/min) Rt 8.8 min (100 %). (Found: C, 68.17; H, 10.51. Calc for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59 %).

(2E,6S)-6,7-Isopropylidenedioxy-3,7-dimethyl-2-octenyl bromide **15**. n-BuLi in n-hexane (1.50 N, 1.8 ml, 2.7 mmol) was added dropwise under Ar to a stirred and cooled soln of **14** (620 mg, 2.72 mmol) and Ph_3CH (3 mg) in dry ether (3 ml) and dry HMPA (3 ml) until the characteristic red color persisted. After stirring for 5 min at 0°C, a soln of p-TsCl (620 mg, 3.26 mmol) in dry ether (3 ml) was added dropwise and the mixture was stirred for 45 min at 0°C. Then anhydrous LiBr (1.18 g, 13.6 mmol) was added portionwise to the mixture and it was stirred overnight at room temp. The mixture was poured into sat $NaHCO_3$ soln (10 ml) and extracted with ether. The ether soln was washed with water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 860 mg (quantitative) of **15** as an oil, νmax 1655 (m), 1380 (s,sh), 1370 (s), 1230 (s), 1215 (s), 1200 (s), 1115 (s), 1005 (s), 915 (m), 855 (m) cm^{-1}; δ (CCl_4) 1.00 (3H, s), 1.15 (3H, s), 1.21 (3H, s), 1.30 (3H, s), 1.36~1.96 (2H, m), 1.70 (3H, s), 1.96~2.37 (2H, m), 3.48 (1H, dd, J=4 and 8 Hz), 3.87 and 3.93 (2H, each d, J=7 Hz), 5.20~5.70 (1H, m). Signal at δ 3.93 was due to the corresponding chloride (about 30 %). This was employed for the next step immediately without purification.

Methyl (6E,10S)-10,11-isopropylidenedioxy-7,11-dimethyl-3-oxo-6-dodecenoate **16**. To a stirred and cooled suspension of NaH (140 mg, 3.51 mmol, 60 % dispersion in mineral oil) in dry THF (6 ml) was added dropwise a soln of methyl acetoacetate (370 mg, 3.19 mmol) in dry THF (2 ml) at 0°C under Ar. The mixture was stirred for 15 min at -2°C and n-BuLi in n-hexane (1.57 N, 2.02 ml, 3.17 mmol) was added dropwise below 0°C. The mixture was stirred for 20 min at -2°C and a soln of **15** (860 mg, crude, 2.7 mmol) in dry THF (4 ml) was added dropwise below 0°C. After stirring for 2.5 h at 0°C, the mixture was poured into sat NH_4Cl soln (20 ml). The organic layer was separated and the aq layer was extracted with ether. The combined organic soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 960 mg (quantitative) of **16** as an oil, νmax 1750 (s), 1720 (s), 1655 (m), 1630 (m), 1380 (sh), 1370 (s), 1235 (s), 1215 (s), 1200 (s), 1115 (s), 1000 (s), 910 (m), 855 (m) cm^{-1}. **16** was unstable against SiO_2 chromatogreaphy and therefore employed for the next step without purification.

Methyl (2Z,6E,10S)-3-(diethylphosphoryloxy)-10,11-isopropylidenedioxy-7,11-dimethyl-2,6-dodecadienoate **17**. To a stirred and cooled suspension of NaH (140 mg, 3.51 mmol, 60 % dispersion in mineral oil) in dry THF (4 ml) was added dropwise a soln of **16** (960 mg, crude, 2.7 mmol) in dry THF (5 ml) at 0°C under Ar. The mixture was stirred for 15 min at 0°C and $(EtO)_2P(O)Cl$ (630 mg, 3.65 mmol) was added dropwise at 0°C. After stirring for 1.25 h at room temp, the mixture was poured into sat NH_4Cl soln (10 ml) and extracted with ether. The ether soln was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 1.15 g (92 %) of **17** as a viscous oil, νmax 1735 (s), 1665 (s), 1380 (sh), 1370 (s), 1280 (s), 1210 (s), 1030 (vs) cm^{-1}. This was employed for the next step immediately without purification.

Methyl (2E,6E,10S)-(-)-10,11-isopropylidenedioxy-3,7,11-trimethyl-2,6-dodecadienoate **18**. A soln of Me_2CuLi was prepared by the dropwise addition of MeLi in dry ether (0.80 N, 20.3 ml, 16.2 mmol) to a stirred and cooled suspension of CuI (1.55 g, 8.14 mmol, dried in vacuo for 3 h at room temp) in dry ether (16 ml) at -8~0°C under Ar. This was cooled to -65°C and a soln of **17** (1.15 g, crude, 2.5 mmol) in dry ether (10 ml) was added dropwise below -60°C. The mixture was stirred for 1 h at -65°C and then poured into ice-sat NH_4Cl soln (~80 ml). After stirring for 30 min at room temp, the organic layer was separated and the aq layer was extracted with ether. The combined organic soln was washed with sat NH_4Cl soln, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (870 mg) was chromatographed over SiO_2 (20 g) to give 350 mg (40 % from bromide **15**) of **18** as an oil, GLC (Column: OV-17, 1 m x 4mm; Carrier gas: N_2, 1 kg/cm^2; Column temp: 120°C+10°C/min) Rt 6.0 min (5.5 %), 6.3 min (91 %) and 6.9 min (3.5 %). This was further chromatographed over Merck Lobar® column (Grosse B). Elution with n-hexane-ether (20:1) gave 167.5 mg (19 %) of **18**, whose GLC purity was >97 % (Analyzed under the same condition as described above, Rt 6.3 min). Only this sample was employed for the next step, n_D^{24} 1.4688; $[\alpha]_D^{24}$ -2.5° (c=0.68, MeOH); νmax 1720 (s), 1645 (s), 1380 (s,sh), 1370 (s), 1220 (s), 1145 (s), 1000 (m), 855 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.11 (3H, s), 1.25 (3H, s), 1.33 (3H, s), 1.43 (3H, s), 1.46~1.70 (2H, m), 1.63 (3H, d, J=1.3 Hz), 1.90~2.40 (6H, m), 2.18 (3H, d, J=1.3 Hz), 3.65 (1H, dd, J=4 and 9 Hz), 3.69 (3H, s), 5.01~5.25 (1H, m), 5.67 (1H, br.s); ^{13}C NMR δ (25 MHz, $CDCl_3$) 16.06, 18.81, 22.93, 25.89, 26.06, 26.85, 27.79, 28.58, 36.68, 40.86, 50.75, 80.06, 82.81, 106.47, 115.31, 123.35, 135.55, 159.86, 167.17. (Found: C, 69.97; H, 9.95. Calc for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94 %).

Methyl (2E,6E,10S)-(-)-10,11-dihydroxy-3,7,11-trimethyl-2,6-dodecadienoate **19a**. A soln of **18** (111 mg, 0.342 mmol) in 75 % AcOH aq (4 ml) was stirred and heated for 2 h at 50°C. After cooling in an ice-bath, the mixture was diluted with EtOAc and NaOH aq (2 g of NaOH in 10 ml of water) was added dropwise to neutralize AcOH. The mixture was diluted with brine and extracted with EtOAc. The EtOAc soln was washed with sat $NaHCO_3$ soln and brine, dried (Na_2SO_4) and concentrated in vacuo to give 95.4 mg (98 %) of **19** as a viscous oil, $[\alpha]_D^{24}$ -18.9° (c=1.24, MeOH), [lit[7] $[\alpha]_D$ +17.8° (c=1.8, MeOH), for (R)-isomer]; νmax 3450 (m), 1720 (s), 1645 (m), 1380 (m), 1225 (s), 1145 (s), 1070 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.17 (3H, s), 1.21 (3H, s), 1.29~1.70 (4H, m), 1.63 (3H, s), 1.90~2.30 (6H, m), 2.17 (3H, d, J=1.3 Hz), 3.22~3.43 (1H, m), 3.70 (3H, s), 5.03~5.27 (1H, m), 5.68 (1H, br.s). This was employed for the next step without purification.

Determination of the optical purity of **19a**. According to the reported procedure[12], (R)- and (S)-MTPA esters **19b** and **19c** were prepared from **19a**. HPLC analysis (Column, Nucleosil® 50-5, 25 cm x 4mm; Eluant, n-hexane-THF=6:1, 1.0 ml/min; Detected at UV 254 nm) Co-injection of **19a** and **19b**: Rt 13.6 and 15.0 min; (R)-MTPA ester **19b**: Rt 15.0 min (single peak). Therefore the optical purity of **19a** was determined to be ~100 % e.e.

Methyl (2E,6E,10S)-11-hydroxy-10-mesyloxy-3,7,11-trimethyl-2,6-dodecadienoate **20**. $(MeSO_2)_2O$ (60.0 mg, 0.344 mmol) was added to a stirred and cooled soln of **19a** (90.1 mg, 0.316 mmol) and Et_3N (70 mg, 0.692 mmol) in dry CH_2Cl_2 (3 ml) at 0°C. After stirring for 1 h at 0°C, the mixture was poured into ice-water and extracted with EtOAc. The EtOAc soln was washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give 115 mg (quantitative) of **20** as an oil, νmax 3530 (m), 1720 (s), 1645 (m), 1350 (s), 1330 (s), 1215 (s), 1170 (s), 1145 (s), 915 (s) cm^{-1}. This was employed for the next step immediately without purification.

Methyl (2E,6E,10R)-(+)-10,11-epoxy-3,7,11-trimethyl-2,6-dodecadienoate [(R)-(+)-JH III] **1**. To a stirred and cooled soln of **20** (115 mg, crude, 0.32 mmol) in MeOH (3 ml) was added dropwise a soln of NaOMe (28 mg, 0.52 mmol) in MeOH (1 ml) at 0°C and the mixture was stirred for 15 min at 0°C. It was then poured into brine (10 ml) and extracted with ether. The ether soln was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by preparative TLC (Merck Art 5717; Eluent, n-hexane-ether=120:80) to give 66.8 mg (79.4 % from **19a**) of **1** as a colorless oil, n_D^{24} 1.4736; $[\alpha]_D^{24}$ +6.71° (c=0.57, MeOH), [lit[7] $[\alpha]_D$ +5.75° (c=0.4, MeOH)]; νmax 3030 (w.sh), 2960 (m), 2940 (m), 2860 (m.sh), 1720 (s), 1650 (m), 1470 (w.sh), 1460 (m.sh), 1435 (m), 1385 (m.sh), 1380 (m), 1370 (w), 1325 (w), 1275 (w), 1250 (w.sh), 1225 (s), 1150 (s), 1060 (w), 900 (w), 860 (w), 820 (w), 730 (w), 680 (w) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.27 (3H, s), 1.32 (3H, s), 1.35~1.74 (2H, m), 1.63 (3H, s), 1.98~2.27 (6H, m), 2.18 (3H, d, J=1.3 Hz), 2.70 (1H, t, J=6 Hz), 3.70 (3H, s), 5.03~5.27 (1H, m), 5.68 (1H, br.s); ^{13}C NMR δ (25 MHz, $CDCl_3$) 16.03, 18.75, 18.81, 24.86, 25.95, 27.47, 36.33, 40.83, 50.75, 58.27, 64.09, 115.34, 123.50, 135.32, 159.86, 167.20; (Found: C, 71.64; H, 9.88. Calc for $C_{16}H_{26}O_3$: C, 72.13; H, 9.84 %).

Methyl (2E,6E,10S)-10-acetoxy-11-hydroxy-3,7,11-trimethyl-2,6-dodecadienoate **21a**. Ac_2O (0.3 ml, 3.2 mmol) was added to a stirred and ice-cooled soln of **19a** (39 mg, 0.137 mmol) in dry C_5H_5N (0.9 ml) and the mixture was stirred overnight at room temp. It was then poured into ice-water and extracted with ether. The ether soln was washed with sat $CuSO_4$ soln, water, sat $NaHCO_3$ soln and brine, dried (Na_2SO_4) and concentrated in vacuo to give 50.8 mg (quantitative) of **21a** as an oil, νmax 3410 (m), 1740 (s.sh), 1720 (s), 1645 (m), 1370 (s), 1230 (s), 1145 (s), 1050 (m), 1025 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.20 (6H, s), 1.61 (3H, s), 1.63~1.80 (3H, m), 2.11 (3H, s), 2.18 (3H, d, J=1.3 Hz), 1.88~2.25 (6H, m), 3.70 (3H, s), 4.77 (1H, dd, J=6 and 8 Hz), 4.97~5.20 (1H, m), 5.68 (1H, br.s). This was employed for the next step without purification.

Methyl (2E,6E,10S)-10-acetoxy-11-bromo-3,7,11-trimethyl-2,6-dodecadienoate **21b**. PBr_3 (7 drops) was slowly added dropwise to a stirred and cooled soln of **21a** (50.8 mg, crude, 0.14 mmol) in dry ether (5 ml) and the mixture was stirred for 1.5 h at 0°C and for 1 h at room temp. It was then poured into sat $NaHCO_3$ soln (10 ml) and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 33 mg (60 % from **19a**) of **21b** as an oil, νmax 1740 (s), 1720 (s), 1650 (m), 1380 (sh), 1370 (m), 1240 (s), 1150 (s), 1020 (m) cm^{-1}. This was employed for the next step without purification.

Methyl (2E,6E,10S)-(-)-10,11-epoxy-3,7,11-trimethyl-2,6-dodecadienoate [(S)-(-)-JH III] **1'**. To a stirred and cooled soln of **21b** (33 mg, 0.082 mmol) in MeOH (3 ml) was added dropwise a soln of NaOMe (8.4 mg, 0.156 mmol) in MeOH (1 ml) at 0°C and the mixture was stirred for 1 h at 0°C and for 36 h at room temp. It was then poured into brine (10 ml) and extracted with ether. The ether soln was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by preparative TLC (Merck Art 5717; Eluent, n-hexane-ether=120:80) to give 18.2 mg (83.1 %) of **1'** as a colorless oil, n_D^{23} 1.4744; $[\alpha]_D^{23}$ -6.55° (c=0.25, MeOH), [lit[7] $[\alpha]_D$ -5.44° (c=0.7, MeOH)]; The IR and NMR spectra of **1'** were idential with those of **1**. (Found: C, 71.75; H, 9.88. Calc for $C_{16}H_{26}O_3$: C, 72.13; H, 9.84 %).

Determination of the optical purities of (R)-(+)-1 and (S)-(-)-1'. The optical purities of (R)-(+)-1 and (S)-(-)-**1'** were estimated by 400 MHz ^1H-NMR in the presence of (R)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral solvating reagent.[19] δ [6.3 mg of (R)-(+)-1 and 26.3 mg of the chiral solvating reagent in $CDCl_3$ (0.35 ml)] 2.567 (t, C-10 proton); [6.7 mg of (S)-(-)-**1'** and 27.8 mg of the chiral solvating reagent in $CDCl_3$ (0.35 ml)] 2.602 (t, C-10 proton). The signals derived from the antipode were not observed. Therefore the optical purities of (R)-(+)-1 and (S)-(-)-**1'** were both ~100 % e.e.

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