New Enantioselective Synthesis of (10*R*,11*S*)-(+)-Juvenile Hormones I and II[‡]

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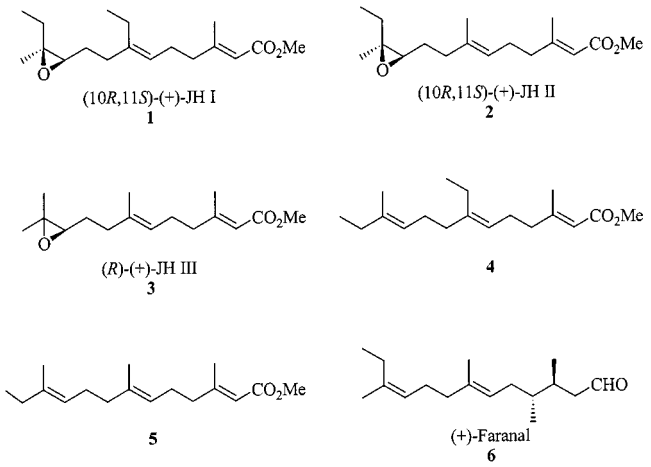
The (10*R*,11*S*)-(+)-juvenile hormones I (**1**) and II (**2**) were synthesized by Sharpless asymmetric dihydroxylations of methyl (2*E*,6*E*,10*E*)-7-ethyl-3,11-dimethyl-2,6,10-tridecatrienoate (**4**) and methyl (2*E*,6*E*,10*E*)-3,7,11-trimethyl-2,6,10-tridecatrienoate (**5**), respectively, as the key steps.

Since the isolation and identification, in the late 1960s, of insect juvenile hormones I [(+)-JH I (**1**)][1] and II [(+)-JH II (**2**)][2] secreted by the moth *Hyalophora cecropia*, the chemistry and biology of JHs has attracted the attention of many scientists. The synthesis of enantiomerically pure (+)-JH I and (+)-JH II remained a difficult task, as reviewed previously.[3−6] Indeed, it was only in 1990 that (+)-JH I (**1**) was shown to be 12,000 times more active than (−)-JH I, when bioassayed by topical application against allatectomized fourth instar larvae of the silkworm moth, *Bombyx mori*.[7] The enantiomers of **1** used for the bioassay were prepared by Mori and Fujiwhara, employing yeast reduction as the key asymmetric process.[8,9] There are two known syntheses of (+)-JH II (**2**): one by Mori and Fujiwhara,[8] and the other by Kosugi et al.[10] Both of them, however, suffer from multi-step conversion into **2** after introduction of the two chiral centers into the intermediates.



Scheme 1. Structures of insect juvenile hormones and related compounds

The widely used asymmetric Sharpless processes − epoxidation (AE) and dihydroxylation (AD) − are very versatile and efficient reactions for utilization in the synthesis of JHs in substantial quantities. AE was employed by Prestwich and Wawrzeńczyk[11] to prepare (+)-JH I (**1**, 95% *ee*), while AD was applied to the synthesis of (+)-JH III (**3**, 92% *ee*) by Crispino and Sharpless.[12] An advantage of the AD approach is the introduction of the two hydroxy groups at C-10 and C-11 at a late stage in the synthesis, eliminating the need for a cumbersome protection-deprotection of the diol system during the course of the synthesis. To synthesize (+)-JH I (**1**) and II (**2**) employing AD, however, triene esters **4** and **5** must be prepared efficiently. Because we had already developed this capability, largely in the course of the synthesis of (+)-faranal (**6**), the trail pheromone of the Pharaoh's ant,[13] we started our endeavor to synthesize (+)-JH I (**1**) and II (**2**) employing AD.

Scheme 2 summarizes our synthesis of triene esters **4** and **5**, the substrates for Sharpless AD.[14] Commercially available cyclopropyl methyl ketone (**7**) was converted into the known diacetate **8**[15] by Julia cleavage[16] of cyclopropylmethylcarbinol, followed by transformations including selenium dioxide oxidation of a terminal methyl group.[15] Treatment of **8** with methylmagnesium bromide in the presence of dilithium tetrachlorocuprate under Schlosser conditions[17] gave the known alcohol **9**.[18] Tosylation of **9** to give **10** was followed by Finkelstein reaction to convert **10** to the known iodide **11**.[19] Alkylation of acetylene as its lithium salt−ethylenediamine complex with **11** furnished **12** in a moderate yield of 50%. Negishi's zirconocene-catalyzed carboalumination[20] of **12** with triethylaluminium in the presence of a small amount of water in dichloromethane[21] was followed by treatment with *n*-butyllithium and paraformaldehyde to give **13a** in 31% yield. The observed low yield must have been due to the bulkiness of the ethyl group, because the yield of the lower homologue **13b**[22] was 70% when the same process was executed employing trimethylaluminium. The alcohols **13a** and **13b** were then converted into the corresponding bromides **14a** and **14b** by treatment with phosphorus tribromide.

Further transformations leading to the triene esters **4** and **5** were executed according to the method developed by Sum and Weiler,[23] which had been successfully used in our pre-

[‡] Synthesis of Compounds with Juvenile Hormone Activity, XXXII. − Part XXXI: H. Watanabe, H. Shimizu, K. Mori, *Synthesis* **1994**, 1249−1254.

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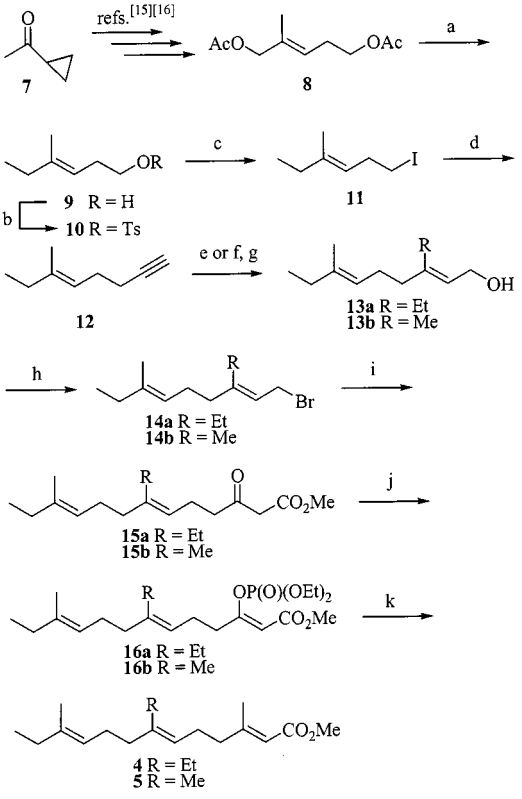
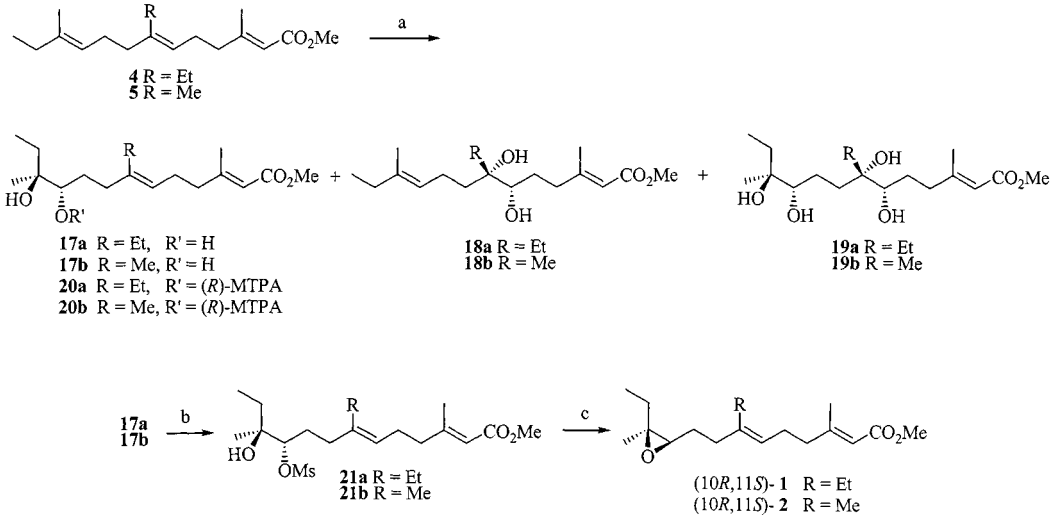


Scheme 2. Syntheses of triene esters **4** and **5**; reagents: (a) MeMgBr, Li_2CuCl_4, THF (83%); (b) TsCl, C_5H_5N, CH_2Cl_2; (c) NaI, Me_2CO (92%, 2 steps); (d) $HC{\equiv}CLi{\cdot}H_2N(CH_2)_2NH_2$, DMSO (50%); (e) Et_3Al, Cp_2ZrCl_2, H_2O, CH_2Cl_2 for **13a**; (f) Me_3Al, Cp_2ZrCl_2, H_2O, CH_2Cl_2 for **13b**; (g) *n*BuLi, $(CH_2O)_n$, hexane, THF (31% for **13a** and 70% for **13b**); (h) PBr_3, Et_2O; (i) $MeCOCH_2CO_2Me$, NaH, *n*BuLi, THF (83% for **15a**, 77% for **15b**); (j) NaH, $(EtO)_2P(O)Cl$, THF; (k) Me_2CuLi, Et_2O (60% for **4** and 66% for **5**, 2 steps)

vious JH synthesis.[8] Accordingly, the dianion derived from methyl acetoacetate was alkylated with **14a** or **14b** to give β-oxo ester **15a** or **15b** in 83 and 77% yield, respectively. Phosphorylation of **15a** and **15b** as their enol forms furnished **16a** and **16b**, which were separately treated with lithium dimethylcuprate to afford the desired triene esters **4** and **5**. The overall yields of **4** and **5** were 1.8% and 4.1%, respectively, on the basis of **7** (15 steps).

The remaining steps to (+)-JH I (**1**) and (+)-JH II (**2**) are summarized in Scheme 3. In the key AD steps, we essentially followed the procedure as reported by Crispino and Sharpless[12] in their JH III synthesis. Asymmetric dihydroxylation of **4** in the presence of 1,4-bis(dihydroquininephthalazine) [$(DHQ)_2$-PHAL] was achieved by using commercially available AD-mix-α® to give, after chromatographic separation, the desired (10*S*,11*S*)-diol **17a** (46%), (6*S*,7*S*)-diol **18a** (7%), and crystalline (6*S*,7*S*,10*S*,11*S*)-tetrol **19a** (15%). The diol **17a** was shown to be of 95% *ee* as estimated by the HPLC analysis of the corresponding (*R*)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester, **20a**). Similarly, triene ester **5** furnished **17b** (27%), **18b** (5%), and crystalline **19b** (38%) upon AD with AD-mix-α®. In the case of **5**, the double bond at C-6 with a methyl group at C-7 was dihydroxylated almost as rapidly as the terminal double bond at C-10, and therefore the tetrol **19b** was the major product. The enantiomeric purity of **17b** as determined by the HPLC analysis of **20b** was an *ee* of 92%, a value slightly lower than that for **17a**.

Finally, the diols **17a** and **17b** were converted into (10*R*,11*S*)-(+)-JH I (**1**) and (10*R*,11*S*)-(+)-JH II (**2**), respectively, via the corresponding monomesylates **21a** and **21b** according to the reported procedure.[8] Physical and spectral properties of **1** and **2**, including specific rotations, were in good accord with the data previously published.[8,10] The enantiomeric purity of **2** was about 93% *ee* as estimated by HPLC analysis on Chiralcel OB-H®, while that of **1** could not be estimated by HPLC analysis due to lack of separation of its enantiomers on the same column. The enantiomeric purity of **1** was assumed to be about 95% *ee*, reflecting that of the starting diol **17a**.



Scheme 3. Synthesis of (10*R*,11*S*)-(+)-JH I (**1**) and (10*R*,11*S*)-(+)-JH II (**2**); reagents: (a) AD-mix-α®, $MeSO_2NH_2$, *t*BuOH, H_2O (65% for **17a** and 35% for **17b**); (b) Ms_2O, Et_3N, CH_2Cl_2; (c) K_2CO_3, MeOH (91% for **1** and 84% for **2**, 2 steps)

In conclusion, the naturally occurring (+)-enantiomers of JH I (**1**, 95% *ee*) and JH II (**2**, 92−93% *ee*) were synthesized by employing Sharpless asymmetric dihydroxylation as the key step. The overall yields of **1** and **2** were 1.0% and 1.2%, respectively, from **7** (18 steps). Our previous syntheses of **1** and **2** gave them in 0.34% and 0.13% overall yields (21 steps), respectively, from commercially available 2-methylcyclohexane-1,3-dione, although enantiomerically pure **1** and **2** (ca. 100% *ee*) could be secured.[8] These results therefore substantially improved the overall yields and slightly shortened the synthetic routes. Both Kosugi[10] and Prestwich[11] reported their works as preliminary communications, and exact overall yields of their syntheses could not be calculated. The present synthesis, however, is still not efficient enough, due partly to the poor regioselectivity at the key AD step, and further improvement in the efficiency of JH synthesis to provide quantities of JHs sufficient for biological studies is still awaited.

Experimental Section

Boiling points and melting points: uncorrected values. − IR: Jasco A-102. − ^{1}H NMR: Jeol JNM-EX 90A (90 MHz), Jeol JNM-LA400 (400 MHz), and Jeol JNM-LA500 (500 MHz) (TMS at δ = 0.00 or $CHCl_3$ at δ = 7.26 as an internal standard). − ^{13}C NMR: Jeol JNM-LA400 (100 MHz) and Jeol JNM-LA500 (126 MHz) ($CDCl_3$ at δ = 77.0 as an internal standard). − Optical rotation: Jasco DIP-1000. − MS: Jeol JMS-AX505HA. − Column chromatography: Merck Kieselgel 60 Art 1.07734. − TLC: 0.25 mm Merck silica gel plates (60F−254). −MPLC: Pegasil Prepsil-5020−12B.

(3*E*)-4-Methylhex-3-en-1-ol (9): A solution of Li_2CuCl_4 (0.75 M in THF, 2.0 mL, 1.5 mmol) was added at −10 °C under argon to a stirred and cooled solution of **8**[15] (6.80 g, 34.0 mmol) in dry THF (40 mL). To this was added dropwise a solution of MeMgBr (0.95 M in THF, 143 mL, 136 mmol). The mixture was allowed to warm to room temperature and stirred for 1 h. A saturated aqueous NH_4Cl solution was then added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was distilled to give 3.24 g (83%) of **9**; b.p. 82−84 °C/23 Torr. − n_D^{23} = 1.4484. − IR (film): $\tilde{\nu}_{max}$ = 3350 cm^{-1} (br. s, O−H), 1675 (w, C=C), 1050 (s, C−O). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.4 Hz, 3 H, 6-H), 1.49 (s, 1 H, O−H), 1.65 (s, 3 H, 4-Me), 1.86−2.43 (m, 4 H, 2-, 5-H), 3.62 (t, *J* = 6.7 Hz, 2 H, 1-H), 5.12 (br. t, *J* = 7.3 Hz, 1 H, 3-H). These data are identical with those reported for **9**.[18]

(3*E*)-4-Methylhex-3-enyl Tosylate (10): TsCl (68.8 g, 361 mmol) was added portionwise at 0 °C to a stirred and cooled solution of **9** (31.5 g, 274 mmol) in CH_2Cl_2 (300 mL) and pyridine (44 mL, 545 mmol). After stirring for 7 h at 0 °C, the mixture was quenched with water and concentrated in vacuo to remove CH_2Cl_2. It was extracted with diethyl ether, and the ether solution was washed with 1 M HCl, water, and brine, dried with $MgSO_4$, and concentrated in vacuo to give 62.3 g (quant.) of crude **10**. This was employed in the next step without further purification. − IR (film): $\tilde{\nu}_{max}$ = 1670 cm^{-1} (w, C=C), 1600 (m, Ar), 1500 (w, Ar), 1360 (s, SO_2), 1180 (s, SO_2). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.4 Hz, 3 H, 6-H), 1.55 (s, 3 H, 4-Me), 1.95 (q, *J* = 7.4 Hz, 2 H, 5-H), 2.15−2.50 (m, 2 H, 2-H), 2.45 (s, 3 H, Ar-CH_3), 3.99 (t, *J* = 7.1 Hz, 2 H, 1-H), 4.96 (t, *J* = 7.1 Hz, 1 H, 3-H), 7.33 (d, *J* = 8.3 Hz, 2 H, Ar), 7.79 (d, *J* = 8.3 Hz, 2 H, Ar).

(3*E*)-1-Iodo-4-methylhex-3-ene (11): NaI (61.6 g, 411 mmol) was added to a stirred solution of crude **10** (62.3 g, 274 mmol) in dry acetone (600 mL), and the mixture was stirred and refluxed for 3 h. It was cooled to room temperature, quenched with water, and extracted with pentane. The pentane extract was washed with saturated aqueous $Na_2S_2O_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (pentane) to give 56.6 g (92% from **9**) of **11**. − n_D^{23} = 1.5169. − IR (film): $\tilde{\nu}_{max}$ = 1670 cm^{-1} (w, C=C). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.2 Hz, 3 H, 6-H), 1.61 (s, 3 H, 4-Me), 2.00 (q, *J* = 7.2 Hz, 2 H, 5-H), 2.58 (q, *J* = 7.2 Hz, 2 H, 2-H), 3.11 (t, *J* = 7.2 Hz, 2 H, 1-H), 5.09 (t, *J* = 7.2 Hz, 1 H, 3-H). These ^{1}H NMR spectroscopic data are identical with those reported for **11**.[19] − HR-MS [$C_7H_{13}I$]: calcd. 224.0062; found 224.0068.

(5*E*)-6-Methyloct-5-en-1-yne (12): A solution of **11** (55.6 g, 248 mmol) in dry DMSO (100 mL) was added dropwise under argon to a stirred and cooled (10 °C) suspension of lithium acetylide−ethylenediamine complex (27.4 g, 297 mmol) in dry DMSO (200 mL). The mixture was stirred for 1 h at 10 °C and quenched with water. To this was added 1 M HCl, and the mixture was extracted with pentane. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated under atmospheric pressure with a Vigreux column. The residue was distilled to give 15.1 g (50%) of **12**; b.p. 76−79 °C/80 Torr. − n_D^{28} = 1.4450. − IR (film): $\tilde{\nu}_{max}$ = 3310 cm^{-1} (s, ≡C−H), 2120 (m, C≡C), 1670 (w, C=C). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.4 Hz, 3 H, 8-H), 1.62 (s, 3 H, 6-Me), 1.94 (t, *J* = 2.6 Hz, 1 H, 1-H), 2.00 (q, *J* = 7.4, 2 H, 7-H), 2.17−2.29 (m, 4 H, 3-, 4-H), 5.17 (m, 1 H, 5-H). − HR-MS [C_9H_{14}]: calcd. 122.1095; found 122.1093.

(2*E*,6*E*)-3-Ethyl-7-methylnona-2,6-dien-1-ol (13a): Water (443 μL, 24.6 mmol) was slowly added at −23 °C under argon, with vigorous stirring, to a stirred and cooled solution of bis(cyclopentadienyl)zirconium dichloride (1.05 g, 3.52 mmol) and triethylaluminium (0.92 M in hexane, 53 mL, 49 mmol) in dry CH_2Cl_2 (20 mL). After stirring for 30 min at −23 °C, a solution of **12** (2.00 g, 16.4 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to the reaction mixture. It was then stirred for 2 h at −23 °C and concentrated under reduced pressure. The organic compounds were dissolved by addition of dry hexane (20 mL), and the hexane solution was transferred into another flask through a cannula. To this was added *n*-butyllithium (1.60 M in hexane, 10.3 mL, 16.4 mmol). After dissolving the precipitate by addition of THF (20 mL), paraformaldehyde (984 mg, 32.8 mmol) was added to the mixture. It was stirred for 14 h at room temperature, and quenched with MeOH. To this was added 1 M HCl, and the mixture was filtered through a pad of Celite. The filtrate was extracted with diethyl ether, and the ether solution was washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate, 10:1) to give 923 mg (31%) of **13a**. − n_D^{28} = 1.4740. − IR (film): $\tilde{\nu}_{max}$ = 3330 cm^{-1} (br. s, O−H), 1670 (w, C=C), 1010 (s, C−O). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 0.99 (t, *J* = 7.6 Hz, 3 H, CH_2CH_3), 1.28 (br. s, 1 H, O−H), 1.60 (s, 3 H, 7-Me), 1.95−2.15 (m, 8 H, 4-, 5-, 8-H, 3-CH_2CH_3), 4.16 (d, *J* = 7.0 Hz, 2 H, 1-H), 5.11 (br. t, *J* = 6.7 Hz, 1 H, 6-H), 5.38 (t, *J* = 7.0 Hz, 1 H, 2-H). − $C_{12}H_{22}O$ (182.3): calcd. C 79.06, H 12.16; found C 78.94, H 12.24.

(2*E*,6*E*)-3,7-Dimethylnona-2,6-dien-1-ol (13b): Water (773 μL, 42.9 mmol) was slowly added at −23 °C under argon, with vigorous stirring, to a stirred and cooled solution of bis(cyclopentadienyl)zirconium dichloride (1.84 g, 6.17 mmol) and trimethylalu-

minium (1.0 M in hexane, 86 mL, 86 mmol) in dry CH_2Cl_2 (50 mL). After stirring for 30 min at −23 °C, a solution of **12** (3.50 g, 28.6 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise to the reaction mixture. It was then stirred for 30 min at −23 °C and concentrated under reduced pressure. The organic compounds were dissolved by addition of dry hexane (30 mL), and the hexane solution was transferred into another flask through a cannula. To this was added *n*-butyllithium (1.60 M in hexane, 17.9 mL, 28.6 mmol). After dissolving the precipitate by addition of THF (30 mL), paraformaldehyde (1.71 g, 57.2 mmol) was added to the mixture. It was stirred for 1 h at room temperature, and quenched with MeOH. To this was added 1 M HCl, and the mixture was concentrated in vacuo. The residue was extracted with diethyl ether. The ether solution was washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate, 10:1) to give 3.35 g (70%) of **13b**. − n_D^{26} = 1.4710. − IR (film): $\tilde{\nu}_{max}$ = 3350 cm^{-1} (br. s, O−H), 1670 (w, C=C), 1000 (s, C−O). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.5 Hz, 3 H, 9-H), 1.30 (br. s, 1 H, O−H), 1.60 (s, 3 H, 7-Me), 1.68 (s, 3 H, 3-Me), 1.98 (q, *J* = 7.5 Hz, 2 H, 8-H), 2.04 (br. t, *J* = 7.4 Hz, 2 H, 4-H), 2.12 (q like, *J* = 7.0 Hz, 2 H, 5-H), 4.15 (d, *J* = 7.1 Hz, 2 H, 1-H), 5.09 (br. t, 1 H, 6-H), 5.42 (t, *J* = 7.1 Hz, 1 H, 2-H). These IR and ^1H NMR spectroscopic data are identical with those reported for **13b**.[22] − $C_{11}H_{20}O$ (168.2): calcd. C 78.51, H 11.98; found C 78.51, H 12.05.

(2*E*,6*E*)-1-Bromo-3-ethyl-7-methylnona-2,6-diene (14a): Phosphorus tribromide (765 μL, 4.20 mmol) was added to a stirred and cooled solution of **13a** (2.19 g, 12.0 mmol) in dry diethyl ether (25 mL) at −40 °C under argon. The mixture was allowed to warm to −30 °C, stirring for 20 min, and quenched with MeOH. It was diluted with water and extracted with diethyl ether. The ether solution was washed with saturated aqueous $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated in vacuo to give 2.68 g (91%) of crude **14a**. It was employed in the next step without further purification. − IR (film): $\tilde{\nu}_{max}$ = 1640 cm^{-1} (w, C=C), 1200 (m). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.7 Hz, 3 H, 9-H), 1.04 (t, *J* = 7.6 Hz, 3 H, 3-CH_2CH_3), 1.60 (s, 3 H, 7-Me), 1.80−2.33 (m, 8 H, 4-, 5-, 8-H, 3-CH_2CH_3), 4.04 (d, *J* = 8.6 Hz, 2 H, 1-H), 5.09 (m, 1 H, 6-H), 5.49 (t, *J* = 8.6 Hz, 1 H, 2-H).

(2*E*,6*E*)-1-Bromo-3,7-dimethylnona-2,6-diene (14b): In the same manner as described above, **13b** (3.32 g, 19.7 mmol) was converted into **14b** (4.60 g, quant.). − IR (film): $\tilde{\nu}_{max}$ = 1660 cm^{-1} (m, C=C), 1200 (m). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.4 Hz, 3 H, 9-H), 1.60 (s, 3 H, 7-Me), 1.72 (s, 3 H, 3-Me) 1.80−2.20 (m, 6 H, 4-, 5-, 8-H), 4.02 (d, *J* = 8.4 Hz, 2 H, 1-H), 5.09 (br. s, 1 H, 6-H), 5.53 (br. t, *J* = 8.4 Hz, 1 H, 2-H).

Methyl (6*E*,10*E*)-7-Ethyl-11-methyl-3-oxotrideca-6,10-dienoate (15a): A solution of methyl acetoacetate (1.81 g, 15.6 mmol) in dry THF (15 mL) was added dropwise at 0 °C under argon to a stirred and cooled suspension of NaH (60% dispersion in mineral oil, 686 mg, 17.1 mmol) in dry THF (20 mL). The mixture was stirred for 15 min at 0 °C, and *n*-butyllithium (1.59 M in hexane, 9.81 mL, 15.6 mmol) was added to it. After stirring for 40 min, a solution of **14a** (2.68 g, 10.9 mmol) in dry THF (15 mL) was added dropwise, and the mixture was stirred for 1 h at 0 °C. The reaction mixture was then quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The ether solution was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate, 30:1) to give 2.60 g (77% from **13a**) of **15a**. − n_D^{27} = 1.4704. − IR (film): $\tilde{\nu}_{max}$ = 1760 cm^{-1} (s, C=O), 1720 (s, C=O), 1660 (m, C=O), 1640 (m, C=C). − ^1H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.6 Hz, 3 H, CH_2CH_3), 0.97 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.59 (s, 3 H, 11-Me), 1.93−2.09 (m, 8 H, 8-, 9-, 12-H, 7-CH_2CH_3), 2.30 (q like, *J* = 7.4 Hz, 2 H, 5-H), 2.56 (t, *J* = 7.4 Hz, 2 H, 4-H), 3.45 (s, 2 H, 2-H), 3.74 (s, 3 H, CO_2Me), 5.02 (t, *J* = 7.2 Hz, 1 H, 6-H), 5.08 (br. t, *J* = 6.7 Hz, 1 H, 10-H). Some peaks considered to belong to the enol form could also be observed [δ = 12.01 (s, 0.07 H, O−H), 3.72 (s, 0.21 H, CO_2Me)]. − $C_{17}H_{28}O_3$ (280.4): calcd. C 72.82, H 10.06; found C 72.85, H 10.34.

Methyl (6*E*,10*E*)-7,11-Dimethyl-3-oxotrideca-6,10-dienoate (15b): In the same manner as described above, **14b** (4.60 g, 19.7 mmol) was converted into **15b** (4.37 g, 83% from **13b**). − n_D^{24} = 1.4745. − IR (film): $\tilde{\nu}_{max}$ = 1760 cm^{-1} (s, C=O), 1725 (s, C=O), 1660 (w, C=O), 1640 (m, C=C). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.5 Hz, 3 H, 13-H), 1.59 (s, 3 H, 11-Me), 1.61 (s, 3 H, 7-Me), 1.94−2.01 (m, 4 H, two of 8-, 9-, 12-H), 2.03−2.09 (m, 2 H, one of 8-, 9-, 12-H), 2.29 (q like, *J* = 7.3 Hz, 2 H, 5-H), 2.56 (t, *J* = 7.3 Hz, 2 H, 4-H), 3.44 (s, 2 H, 2-H), 3.74 (s, 3 H, CO_2Me), 5.07 (br. t, *J* = 7.3 Hz, 2 H, 6, 10-H). Some peaks considered to belong to the enol form could also be observed [δ = 12.01 (s, 0.06 H, O−H), 3.72 (s, 0.18 H, CO_2Me)]. − $C_{16}H_{26}O_3$ (266.4): calcd. C 72.14, H 9.84; found C 72.17, H 10.10.

Methyl (2*E*,6*E*,10*E*)-7-Ethyl-3,11-dimethyltrideca-2,6,10-trienoate (4): A solution of **15a** (2.07 g, 7.38 mmol) in dry THF (20 mL) was added dropwise at 0 °C under argon to a stirred and cooled suspension of NaH (60% dispersion in mineral oil, 429 mg, 11.1 mmol) in dry THF (8 mL). The mixture was stirred at 0 °C for 15 min, and $(EtO)_2P(O)Cl$ (1.60 mL, 1.92 g, 11.1 mmol) was added dropwise at 0 °C. After stirring for 1.5 h, the mixture was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The ether solution was washed with saturated aqueous $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated in vacuo to give 3.16 g of crude phosphoric ester **16a**. This was dissolved in dry diethyl ether (30 mL), and this ethereal solution was added dropwise to a solution of Me_2CuLi (0.50 M, 43 mL, 22 mmol), prepared according to the reported procedure,[23] at −70 °C under argon. After stirring for 2 h at −70 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl. The stirring was continued for an additional 5 min, and the mixture was filtered through a pad of Celite. The filtrate was extracted with diethyl ether, and the ether solution was washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate, 100:1) to give 1.71 g (83% from **15a**) of **4**. Further purification was curried out by MPLC (hexane/ethyl acetate, 100:1) to give pure **4** (1.24 g, 60% from **15a**). − n_D^{27} = 1.4821. − IR (film): $\tilde{\nu}_{max}$ = 1720 cm^{-1} (s, C=O), 1645 (m, C=C). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.6 Hz, 3 H, CH_2CH_3), 0.98 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.59 (s, 3 H, 11-Me), 1.94−2.09 (m, 8 H, four of 4-, 5-, 8-, 9-, 12-H and 7-CH_2CH_3), 2.17 (d, *J* = 1.3 Hz, 3 H, 3-Me), 2.13−2.22 (m, 4 H, two of 4-, 5-, 8-, 9-, 12-H and 7-CH_2CH_3), 3.68 (s, 3 H, CO_2Me), 5.05 (br. t, *J* = 6.3 Hz, 1 H, 6-H or 10-H), 5.09 (br. t, *J* = 6.8 Hz, 1 H, 6-H or 10-H), 5.67 (br. s, 1 H, 2-H). − $C_{18}H_{30}O_2$ (278.4): calcd. C 77.65, H 10.86; found C 77.67, H 11.13.

Methyl (2*E*,6*E*,10*E*)-3,7,11-Trimethyltrideca-2,6,10-trienoate (5): In the same manner as described above, **15b** (660 mg, 2.48 mmol) was converted into **5** (434 mg, 66% from **15b**). − n_D^{26} = 1.4825. − IR (film): $\tilde{\nu}_{max}$ = 1720 cm^{-1} (s, C=O), 1650 (m, C=C). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.5 Hz, 3 H, 13-H), 1.59 (s, 3 H, 7-Me or 11-Me), 1.60 (s, 3 H, 7-Me or 11-Me), 1.94−2.10 (m, 6 H, three of 4-, 5-, 8-, 9-, 12-H), 2.16 (d, *J* = 1.2 Hz, 3 H, 3-Me), 2.13−2.20 (m, 4 H, two of 4-, 5-, 8-, 9-, 12-H), 3.68 (s, 3 H,

CO_2Me), 5.06−5.11 (m, 2 H, 6-, 10-H), 5.67 (br. s, 1 H, 2-H). − $C_{17}H_{28}O_2$ (264.4): calcd. C 77.22, H 10.67; found C 77.21, H 10.96.

Methyl (2*E*,6*E*,10*S*,11*S*)-7-Ethyl-10,11-dihydroxy-3,11-dimethyltrideca-2,6-dienoate (17a): AD-mix-α® [14] (4.53 g) and $MeSO_2NH_2$ (307 mg, 3.23 mmol) were added to a stirred and cooled solution of **4** (900 mg, 3.23 mmol) in *t*BuOH (22.5 mL) and water (22.5 mL). After stirring for 24 h at 0° C, $Na_2S_2O_3{\cdot}5H_2O$ (4.5 g, 18 mmol) was added to the mixture, which was allowed to warm to room temperature, with stirring, over 1 h. The mixture was extracted with ethyl acetate, and the organic layer was washed with 1 M KOH and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate, 1:1) to give recovered **4** (267 mg, 30%) and a mixture of **17a** and **18a** (540 mg, 54%). Further elution with ethyl acetate gave 165 mg (15%) of tetrol **19a**. The mixture of **17a** and **18a** was rechromatographed on silica gel (hexane/ethyl acetate, 1:1) to give pure **17a** [467 mg, 46% (65% based on the consumed **4**)] and 70 mg (7%) of 6,7-diol **18a**. The tetrol **19a** was recrystallized from benzene to give 142 mg (12%) of colorless fluffy crystals. − **17a**: n_D^{28} = 1.4875. − $[\alpha]_D^{27}$ = −17.2 (*c* = 1.00, MeOH) {ref.[8] $[\alpha]_D^{25}$ = −17 (*c* = 0.99, MeOH)}. − IR (film): $\tilde{\nu}_{max}$ = 3450 cm^{-1} (br. s, O−H), 1720 (s, C=O), 1645 (s, C=C). These IR data are identical with those reported for **17a**.[8] − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.6 Hz, 3 H, 13-H), 0.97 (t, *J* = 7.6 Hz, 3 H, 7-CH_2CH_3), 1.08 (s, 3 H, 11-Me), 1.35−1.58 (m, 4 H, 9-, 12-H), 1.75 (br. s, 2 H, O−H), 1.95−2.10 (m, 4 H, two of 4-, 5-, 8-H and 7-CH_2CH_3), 2.16 (d, *J* = 1.0 Hz, 3 H, 3-Me), 2.13−2.32 (m, 4 H, two of 4-, 5-, 8-H and 7-CH_2CH_2), 3.39 (dd, *J* = 10.4, 1.8 Hz, 1 H, 10-H), 3.69 (s, 3 H, CO_2Me), 5.09 (br. t, *J* = 7.0 Hz, 1 H, 6-H), 5.67 (s, 1 H, 2-H). − $C_{18}H_{32}O_4$ (312.4): calcd. C 69.19, H 10.32; found C 69.17, H 10.61. − **18a**: n_D^{26} = 1.4929. − $[\alpha]_D^{27}$ = −21.1 (*c* = 1.00, MeOH). − IR (film): $\tilde{\nu}_{max}$ = 3480 cm^{-1} (br. s, O−H), 1720 (s, C=O), 1640 (s, C=C). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.6 Hz, 3 H, 7-CH_2CH_3), 0.97 (t, *J* = 7.5 Hz, 3 H, 13-H), 1.37−1.45 (m, 1 H, one proton of 5-, 8-H or 7-CH_2CH_3), 1.61 (s, 3 H, 11-Me), 1.48−1.68, (m, 5 H, five protons of 5-, 8-H and 7-CH_2CH_3), 1.86 (br. s, 2 H, O−H), 1.95−2.10 (m, 4 H, 9-, 12-H), 2.18 (d, *J* = 1.2 Hz, 3 H, 3-Me), 2.14−2.24 (m, 1 H, 4-H), 2.42−2.49 (m, 1 H, 4-H), 3.48 (dd, *J* = 10.6, 2.0 Hz, 1 H, 6-H), 3.68 (s, 3 H, CO_2Me), 5.11 (br. t, *J* = 7.0 Hz, 1 H, 10-H), 5.72 (br. s, 1 H, 2-H). − $C_{18}H_{32}O_4$ (312.4): calcd. C 69.19, H 10.32; found C 68.86, H 10.34. − **19a**: m.p. 123−124 °C. − $[\alpha]_D^{27}$ = −44.6 (*c* = 1.01, MeOH). − IR (film): $\tilde{\nu}_{max}$ = 3330 cm^{-1} (br. s, O−H), 1730 (s, C=O), 1650 (s, C=C). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.5 Hz, 3 H, 7-CH_2CH_3), 0.94 (t, *J* = 7.6 Hz, 3 H, 13-H), 1.10, (s, 3 H, 11-Me), 1.34−1.83 (m, 10 H, 5-, 8-, 9-, 12-H, 7-CH_2CH_3), 2.18 (d, *J* = 1.0 Hz, 3 H, 3-Me), 2.19 (br. s, 4 H, O−H), 2.14−2.26 (m, 1 H, 4-H), 2.41−2.48 (m, 1 H, 4-H), 3.41 (dd, *J* = 10.5, 2.0 Hz, 1 H, 10-H), 3.45 (dd, *J* = 10.5, 2.0 Hz, 1 H, 6-H), 3.69 (s, 3 H, CO_2Me), 5.72 (br. s, 1 H, 2-H). − $C_{18}H_{34}O_6$ (346.5): calcd. C 62.40, H 9.89; found C 62.39, H 10.18.

Methyl (2*E*,6*E*,10*S*,11*S*)-10,11-Dihydroxy-3,7,11-trimethyltrideca-2,6-dienoate (17b): In the same manner as described above, recovered **5** (143 mg, 24%), a mixture of **17b** and **18b** (252 mg, 35%) and tetraol **19b** (286 mg, 38%) were obtained from 588 mg (2.22 mmol) of **5**. The mixture of **17b** and **18b** was rechromatographed on silica gel (hexane/ethyl acetate, 1:1) to give pure **17b** [176 mg, 27% (35% based on the consumed **5**)] and 35 mg (5%) of 6,7-diol **18b**. Recrystallization of **19b** from benzene gave 217 mg (29%) of colorless fluffy crystals. − **17b**: n_D^{26} = 1.4919. − $[\alpha]_D^{28}$ = −21.9 (*c* = 1.00, MeOH) {ref.[8] $[\alpha]_D^{24}$ = −20 (*c* = 0.96, MeOH)}. − IR (film): $\tilde{\nu}_{max}$ = 3450 cm^{-1} (br. s, O−H), 1720 (s, C=O), 1650 (s, C=C). These IR data are identical with those reported for **17b**.[8] − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.5 Hz, 3 H, 13-H), 1.08 (s, 3 H, 11-Me), 1.35−1.58 (m, 4 H, 9-, 12-H), 1.61, (s, 3 H, 7-Me), 1.99 (br. s, 2 H, O−H), 2.15 (d, *J* = 0.9 Hz, 3 H, 3-Me), 2.03−2.27 (m, 6 H, 4-, 5-, 8-H), 3.37 (dd, *J* = 10.7, 1.8 Hz, 1 H, 10-H), 3.67 (s, 3 H, CO_2Me), 5.14 (br. s, 1 H, 6-H), 5.66 (s, 1 H, 2-H). − $C_{17}H_{30}O_4$ (298.4): calcd. C 68.42, H 10.13; found C 68.63, H 10.34. − **18b**: n_D^{26} = 1.4920. − $[\alpha]_D^{25}$ = −25 (*c* = 0.40, MeOH). − IR (film): $\tilde{\nu}_{max}$ = 3500 cm^{-1} (br. s, O−H), 1730 (s, C=O), 1660 (s, C=C). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.5 Hz, 3 H, 13-H), 1.12, (s, 3 H, 7-Me), 1.61 (s, 3 H, 11-Me), 1.43−1.68, (m, 4 H, 5-, 8-H), 2.03 (br. s, 2 H, O−H), 1.95−2.23 (m, 5 H, 4-, 9-, 12-H), 2.17 (s, 3 H, 3-Me), 2.42−2.48 (m, 1 H, 4-H), 3.38 (dd, *J* = 10.7, 1.8 Hz, 1 H, 6-H), 3.68 (s, 3 H, CO_2Me), 5.11 (t, *J* = 6.1 Hz, 1 H, 10-H), 5.71 (s, 1 H, 2-H). − $C_{17}H_{30}O_4$ (298.4): calcd. C 68.42, H 10.13; found C 68.08, H 10.05. − **19b**: m.p. 102−103 °C. − $[\alpha]_D^{28}$ = −49.0 (*c* = 1.02, MeOH). − IR (film): $\tilde{\nu}_{max}$ = 3330 cm^{-1} (br. s, O−H), 1720 (s, C=O), 1650 (m, C=C). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.5 Hz, 3 H, 13-H), 1.11, (s, 3 H, 7-Me or 11-Me), 1.12, (s, 3 H, 7-Me or 11-Me), 1.43−1.75 (m, 12 H, 5-, 8-, 9-, 12-H, O−H), 2.18 (d, *J* = 1.2 Hz, 3 H, 3-Me), 2.17−2.26 (m, 1 H, 4-H), 2.42−2.49 (m, 1 H, 4-H), 3.37 (dd, *J* = 10.7, 1.8 Hz, 1 H, 6-H or 10-H), 3.41 (dd, *J* = 10.4, 1.8 Hz, 1 H, 6-H or 10-H), 3.69 (s, 3 H, CO_2Me), 5.72 (s, 1 H, 2-H). − $C_{17}H_{32}O_6$ (332.4): calcd. C 61.42, H 9.70; found C 61.37, H 9.87.

Determination of the Enantiomeric Purities of 17a and 17b: The *ee* values of **17a** and **17b** were determined by HPLC analysis of the corresponding (*R*)-MTPA esters **20a** and **20b** (column: Pegasil Silica 60−5, 4.6 mm × 25 cm; solvent: hexane/THF, 7:1; flow rate: 1.0 mL/min; detection: 254 nm). −**17a**: 95% *ee*; (10*S*,11*S*)-**20a**: t_R = 11.1 min (2.3%); (10*R*,11*R*)-**20a**: t_R = 12.6 min (97.7%). − **17b**: 92% *ee*; (10*S*,11*S*)-**20b**: t_R = 12.4 min (3.9%); (10*R*,11*R*)-**20b**: t_R = 14.1 min (96.1%).

Methyl (2*E*,6*E*,10*R*,11*S*)-10,11-Epoxy-7-ethyl-3,11-dimethyltrideca-2,6-dienoate (1): Ms_2O (167 mg, 0.96 mmol) was added at 0° C to a stirred and cooled solution of **17a** (250 mg, 0.80 mmol) in dry CH_2Cl_2 (3 mL) and Et_3N (246 μL, 1.76 mmol). After having been stirred for 2 h at 0 ° C, the mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and concentrated in vacuo to give 287 mg of crude **21a**. This was dissolved in MeOH (15 mL), and K_2CO_3 (166 mg, 1.20 mmol) was added to it at room temperature. After stirring for 30 min, the mixture was quenched with water and concentrated to remove MeOH. The residue was extracted with ethyl acetate, and the extract was washed with brine and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate, 10:1) to give 175 mg (91% based on the consumed **17a**) of **1**. Further elution (hexane/ethyl acetate, 1:1) afforded 39 mg of the recovered **17a**. − **1**: n_D^{26} = 1.4769. − $[\alpha]_D^{27}$ = +12.7 (*c* = 1.01, MeOH) {ref.[8] $[\alpha]_D^{22.5}$ = +14.5 (*c* = 0.78, MeOH)}. − IR (film): $\tilde{\nu}_{max}$ = 3000 cm^{-1} (s, C−H), 2900 (m, C−H), 1720 (s, C=O), 1650 (m, C=C), 1435 (m), 1380 (m), 1360 (m), 1280 (w), 1220 (s, C−O−C), 1150 (s, C−O−C), 1060 (w), 1030 (w), 880 (m). − ^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.6 Hz, 3 H, CH_2CH_3), 1.00 (t, *J* = 7.6 Hz, 3 H, CH_2CH_3), 1.27, (s, 3 H, 11-Me), 1.42−1.69, (m, 4 H, 9, 12-H), 2.16 (d, *J* = 1.0 Hz, 3 H, 3-Me), 1.99−2.23 (m, 8 H, 4-, 5-, 8-H, 7-CH_2CH_3), 2.71 (dd, *J* = 6.7, 5.5 Hz, 1 H, 10-H), 3.68 (s, 3 H, CO_2Me), 5.08 (br. t, *J* = 5.9 Hz, 1 H, 6-H), 5.66 (s, 1 H, 2-H). − ^{13}C NMR (126 MHz, $CDCl_3$): δ = 9.7, 13.2, 18.9, 21.6, 23.1, 25.6, 25.8, 27.3, 33.3, 41.2, 50.8, 61.8, 64.7, 115.3, 122.9, 141.3, 160.0, 167.2. These ^1H and ^{13}C NMR spectroscopic data are identical with those re-

ported for **1**.[8] − $C_{18}H_{30}O_3$ (294.4): calcd. C 73.43, H 10.27; found C 73.41, H 10.37. − The enantiomeric excess of **1** was assumed to be the same as that of **17a**, although the HPLC analysis of **1**, employing a variety of chiral stationary phases, afforded only one peak.

Methyl (2*E*,6*E*,10*R*,11*S*)-10,11-Epoxy-3,7,11-trimethyltrideca-2,6-dienoate (2): In the same manner as described above, compound **2** (104 mg, 84% based on consumed **17b**) and recovered **17b** (81 mg) were obtained from **17b** (213 mg, 0.71 mmol). − **2**: n_D^{24} = 1.4782. − $[\alpha]_D^{28}$ = +14.2 (*c* = 1.01, MeOH) {ref.[8] $[\alpha]_D^{24.5}$ = +17.6 (*c* = 0.590, MeOH), ref.[10] $[\alpha]_D^{23}$ = +15.1 (*c* = 1.47, MeOH)}. − IR (film): $\tilde{\nu}_{max}$ = 3000 cm^{-1} (s, C−H), 2900 (s, C−H), 1725 (s, C=O), 1650 (m, C=C), 1440 (s), 1380 (m), 1360 (m), 1220 (s, C−O−C), 1160 (s, C−O−C), 880 (m), 870 (m). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.6 Hz, 3 H, 13-H) 1.26, (s, 3 H, 11-Me), 1.41−1.70, (m, 4 H, 9-, 12-H), 1.62, (s, 3 H, 7-Me), 2.16 (d, *J* = 1.2 Hz, 3 H, 3-Me), 2.03−2.22 (m, 6 H, 4-, 5-, 8-H), 2.70 (dd, *J* = 6.8, 5.6 Hz, 1 H, 10-H), 3.68 (s, 3 H, CO_2Me), 5.13 (br. s, 1 H, 6-H), 5.66 (br. s, 1 H, 2-H). These ^{1}H NMR spectroscopic data are identical with those reported for **2**.[8,10] − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.6, 16.0, 18.7, 21.5, 25.7, 25.8, 27.0, 36.4, 40.8, 50.7, 61.7, 64.5, 115.2, 123.4, 135.3, 159.9, 167.2. These ^{13}C NMR spectroscopic data are identical with those reported for **2**.[8] − $C_{17}H_{28}O_3$ (280.4): calcd. C 72.82, H 10.06; found C 72.72, H 10.12.

Determination of the Enantiomeric Purity of 2: The *ee* value of **2** was determined as 93% by HPLC analysis (column: Chiralcel OB-H®, 4.6 mm × 25 cm; solvent: hexane/*i*PrOH, 120:1; flow rate: 0.3 mL/min; detection: 230 nm); (+)-**2**: t_R = 28.1 min (96.6%); (−)-**2**: t_R = 30.3 min (3.4%).

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