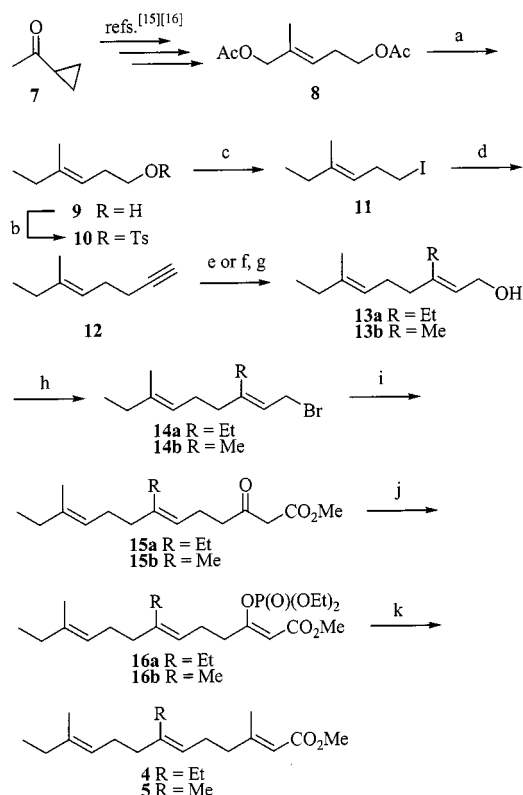




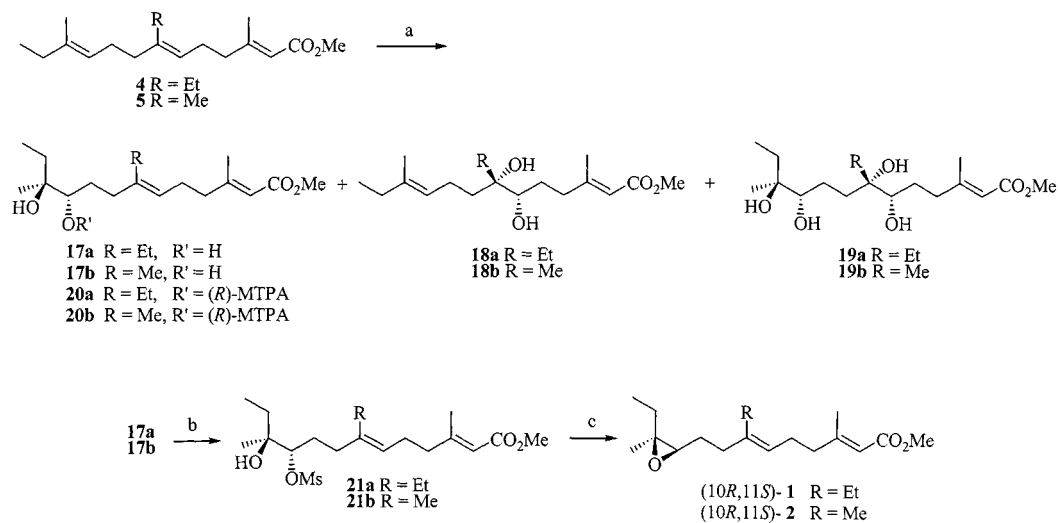
Scheme 2. Syntheses of triene esters **4** and **5**; reagents: (a) MeMgBr, Li₂CuCl₄, THF (83%); (b) TsCl, C₅H₅N, CH₂Cl₂; (c) NaI, Me₂CO (92%, 2 steps); (d) HC≡CLi·H₂N(CH₂)₂NH₂, DMSO (50%); (e) Et₃Al, Cp₂ZrCl₂, H₂O, CH₂Cl₂ for **13a**; (f) Me₃Al, Cp₂ZrCl₂, H₂O, CH₂Cl₂ for **13b**; (g) *n*BuLi, (CH₂O)_{*n*}, hexane, THF (31% for **13a** and 70% for **13b**); (h) PBr₃, Et₂O; (i) MeCOCH₂CO₂Me, NaH, *n*BuLi, THF (83% for **15a**, 77% for **15b**); (j) NaH, (EtO)₂P(O)Cl, THF; (k) Me₂CuLi, Et₂O (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- $\alpha^{\text{®}}$, MeSO₂NH₂, *t*BuOH, H₂O (65% for **17a** and 35% for **17b**); (b) Ms₂O, Et₃N, CH₂Cl₂; (c) K₂CO₃, 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. – ¹H NMR: Jeol JNM-EX 90A (90 MHz), Jeol JNM-LA400 (400 MHz), and Jeol JNM-LA500 (500 MHz) (TMS at $\delta = 0.00$ or CHCl₃ at $\delta = 7.26$ as an internal standard). – ¹³C NMR: Jeol JNM-LA400 (100 MHz) and Jeol JNM-LA500 (126 MHz) (CDCl₃ at $\delta = 77.0$ 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.

(3E)-4-Methylhex-3-en-1-ol (9): A solution of Li₂CuCl₄ (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 NH₄Cl solution was then added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried with MgSO₄, 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). – ¹H NMR (90 MHz, CDCl₃): $\delta = 1.00$ (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]

(3E)-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 CH₂Cl₂ (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 CH₂Cl₂. It was extracted with diethyl ether, and the ether solution was washed with 1 M HCl, water, and brine, dried with MgSO₄, 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, SO₂), 1180 (s, SO₂). – ¹H NMR (90 MHz, CDCl₃): $\delta = 0.94$ (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-CH₃), 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).

(3E)-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 Na₂S₂O₃ and brine, dried with MgSO₄, 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). – ¹H NMR (400 MHz, CDCl₃): $\delta = 1.00$ (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 ¹H NMR spectroscopic data are identical with those reported for **11**.^[19] – HR-MS [C₇H₁₃I]: calcd. 224.0062; found 224.0068.

(5E)-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 NaHCO₃ and brine, dried with MgSO₄, 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, $\equiv$ C–H), 2120 (m, C $\equiv$ C), 1670 (w, C=C). – ¹H NMR (400 MHz, CDCl₃): $\delta = 0.99$ (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 [C₉H₁₄]: calcd. 122.1095; found 122.1093.

(2E,6E)-3-Ethyl-7-methylnona-2,6-dien-1-ol (13a): Water (443 μ L, 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 triethylaluminum (0.92 M in hexane, 53 mL, 49 mmol) in dry CH₂Cl₂ (20 mL). After stirring for 30 min at –23 °C, a solution of **12** (2.00 g, 16.4 mmol) in dry CH₂Cl₂ (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 NaHCO₃ and brine, dried with MgSO₄, 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). – ¹H NMR (500 MHz, CDCl₃): $\delta = 0.98$ (t, $J = 7.4$ Hz, 3 H, CH₂CH₃), 0.99 (t, $J = 7.6$ Hz, 3 H, CH₂CH₃), 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-CH₂CH₃), 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). – C₁₂H₂₂O (182.3): calcd. C 79.06, H 12.16; found C 78.94, H 12.24.

(2E,6E)-3,7-Dimethylnona-2,6-dien-1-ol (13b): Water (773 μ L, 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**. $n_D^{20} = 1.4710$. – IR (film): $\tilde{\nu}_{\text{max}} = 3350\text{ cm}^{-1}$ (br. s, O–H), 1670 (w, C=C), 1000 (s, C–O). – ^1H NMR (500 MHz, CDCl_3): $\delta = 0.98$ (t, $J = 7.5\text{ Hz}$, 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, $J = 7.5\text{ Hz}$, 2 H, 8-H), 2.04 (br. t, $J = 7.4\text{ Hz}$, 2 H, 4-H), 2.12 (q like, $J = 7.0\text{ Hz}$, 2 H, 5-H), 4.15 (d, $J = 7.1\text{ Hz}$, 2 H, 1-H), 5.09 (br. t, 1 H, 6-H), 5.42 (t, $J = 7.1\text{ Hz}$, 1 H, 2-H). These IR and ^1H NMR spectroscopic data are identical with those reported for **13b**.^[22] – $\text{C}_{11}\text{H}_{20}\text{O}$ (168.2): calcd. C 78.51, H 11.98; found C 78.51, H 12.05.

(2E,6E)-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): $\tilde{\nu}_{\text{max}} = 1640\text{ cm}^{-1}$ (w, C=C), 1200 (m). – ^1H NMR (90 MHz, CDCl_3): $\delta = 0.98$ (t, $J = 7.7\text{ Hz}$, 3 H, 9-H), 1.04 (t, $J = 7.6\text{ Hz}$, 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, $J = 8.6\text{ Hz}$, 2 H, 1-H), 5.09 (m, 1 H, 6-H), 5.49 (t, $J = 8.6\text{ Hz}$, 1 H, 2-H).

(2E,6E)-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): $\tilde{\nu}_{\text{max}} = 1660\text{ cm}^{-1}$ (m, C=C), 1200 (m). – ^1H NMR (90 MHz, CDCl_3): $\delta = 0.98$ (t, $J = 7.4\text{ Hz}$, 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, $J = 8.4\text{ Hz}$, 2 H, 1-H), 5.09 (br. s, 1 H, 6-H), 5.53 (br. t, $J = 8.4\text{ Hz}$, 1 H, 2-H).

Methyl (6E,10E)-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): $\tilde{\nu}_{\text{max}} = 1760\text{ cm}^{-1}$ (s, C=O), 1720 (s, C=O), 1660 (m, C=O), 1640 (m, C=C). – ^1H NMR (400 MHz, CDCl_3): $\delta = 0.95$

(t, $J = 7.6\text{ Hz}$, 3 H, CH_2CH_3), 0.97 (t, $J = 7.4\text{ Hz}$, 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, $J = 7.4\text{ Hz}$, 2 H, 5-H), 2.56 (t, $J = 7.4\text{ Hz}$, 2 H, 4-H), 3.45 (s, 2 H, 2-H), 3.74 (s, 3 H, CO_2Me), 5.02 (t, $J = 7.2\text{ Hz}$, 1 H, 6-H), 5.08 (br. t, $J = 6.7\text{ Hz}$, 1 H, 10-H). Some peaks considered to belong to the enol form could also be observed [$\delta = 12.01$ (s, 0.07 H, O–H), 3.72 (s, 0.21 H, CO_2Me)]. – $\text{C}_{17}\text{H}_{28}\text{O}_3$ (280.4): calcd. C 72.82, H 10.06; found C 72.85, H 10.34.

Methyl (6E,10E)-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): $\tilde{\nu}_{\text{max}} = 1760\text{ cm}^{-1}$ (s, C=O), 1725 (s, C=O), 1660 (w, C=O), 1640 (m, C=C). – ^1H NMR (500 MHz, CDCl_3): $\delta = 0.97$ (t, $J = 7.5\text{ Hz}$, 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, $J = 7.3\text{ Hz}$, 2 H, 5-H), 2.56 (t, $J = 7.3\text{ Hz}$, 2 H, 4-H), 3.44 (s, 2 H, 2-H), 3.74 (s, 3 H, CO_2Me), 5.07 (br. t, $J = 7.3\text{ Hz}$, 2 H, 6, 10-H). Some peaks considered to belong to the enol form could also be observed [$\delta = 12.01$ (s, 0.06 H, O–H), 3.72 (s, 0.18 H, CO_2Me)]. – $\text{C}_{16}\text{H}_{26}\text{O}_3$ (266.4): calcd. C 72.14, H 9.84; found C 72.17, H 10.10.

Methyl (2E,6E,10E)-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 $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$ (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 carried 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): $\tilde{\nu}_{\text{max}} = 1720\text{ cm}^{-1}$ (s, C=O), 1645 (m, C=C). – ^1H NMR (500 MHz, CDCl_3): $\delta = 0.96$ (t, $J = 7.6\text{ Hz}$, 3 H, CH_2CH_3), 0.98 (t, $J = 7.4\text{ Hz}$, 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, $J = 1.3\text{ Hz}$, 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, $J = 6.3\text{ Hz}$, 1 H, 6-H or 10-H), 5.09 (br. t, $J = 6.8\text{ Hz}$, 1 H, 6-H or 10-H), 5.67 (br. s, 1 H, 2-H). – $\text{C}_{18}\text{H}_{30}\text{O}_2$ (278.4): calcd. C 77.65, H 10.86; found C 77.67, H 11.13.

Methyl (2E,6E,10E)-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): $\tilde{\nu}_{\text{max}} = 1720\text{ cm}^{-1}$ (s, C=O), 1650 (m, C=C). – ^1H NMR (500 MHz, CDCl_3): $\delta = 0.97$ (t, $J = 7.5\text{ Hz}$, 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, $J = 1.2\text{ Hz}$, 3 H, 3-Me), 2.13–2.20 (m, 4 H, two of 4-, 5-, 8-, 9-, 12-H), 3.68 (s, 3 H,

CO₂Me), 5.06–5.11 (m, 2 H, 6-, 10-H), 5.67 (br. s, 1 H, 2-H). – C₁₇H₂₈O₂ (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- $\alpha^{\text{®}}$ [14] (4.53 g) and MeSO₂NH₂ (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, Na₂S₂O₃·5H₂O (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 MgSO₄, 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**: $n_D^{25} = 1.4875$. – $[\alpha]_D^{25} = -17.2$ ($c = 1.00$, MeOH) {ref.^[8] $[\alpha]_D^{25} = -17$ ($c = 0.99$, MeOH)}. – IR (film): $\tilde{\nu}_{\text{max}} = 3450 \text{ cm}^{-1}$ (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, CDCl₃): $\delta = 0.93$ (t, $J = 7.6 \text{ Hz}$, 3 H, 13-H), 0.97 (t, $J = 7.6 \text{ Hz}$, 3 H, 7-CH₂CH₃), 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-CH₂CH₃), 2.16 (d, $J = 1.0 \text{ Hz}$, 3 H, 3-Me), 2.13–2.32 (m, 4 H, two of 4-, 5-, 8-H and 7-CH₂CH₃), 3.39 (dd, $J = 10.4, 1.8 \text{ Hz}$, 1 H, 10-H), 3.69 (s, 3 H, CO₂Me), 5.09 (br. t, $J = 7.0 \text{ Hz}$, 1 H, 6-H), 5.67 (s, 1 H, 2-H). – C₁₈H₃₂O₄ (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): $\tilde{\nu}_{\text{max}} = 3480 \text{ cm}^{-1}$ (br. s, O–H), 1720 (s, C=O), 1640 (s, C=C). – ¹H NMR (500 MHz, CDCl₃): $\delta = 0.90$ (t, $J = 7.6 \text{ Hz}$, 3 H, 7-CH₂CH₃), 0.97 (t, $J = 7.5 \text{ Hz}$, 3 H, 13-H), 1.37–1.45 (m, 1 H, one proton of 5-, 8-H or 7-CH₂CH₃), 1.61 (s, 3 H, 11-Me), 1.48–1.68 (m, 5 H, five protons of 5-, 8-H and 7-CH₂CH₃), 1.86 (br. s, 2 H, O–H), 1.95–2.10 (m, 4 H, 9-, 12-H), 2.18 (d, $J = 1.2 \text{ Hz}$, 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, $J = 10.6, 2.0 \text{ Hz}$, 1 H, 6-H), 3.68 (s, 3 H, CO₂Me), 5.11 (br. t, $J = 7.0 \text{ Hz}$, 1 H, 10-H), 5.72 (br. s, 1 H, 2-H). – C₁₈H₃₂O₄ (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): $\tilde{\nu}_{\text{max}} = 3330 \text{ cm}^{-1}$ (br. s, O–H), 1730 (s, C=O), 1650 (s, C=C). – ¹H NMR (500 MHz, CDCl₃): $\delta = 0.88$ (t, $J = 7.5 \text{ Hz}$, 3 H, 7-CH₂CH₃), 0.94 (t, $J = 7.6 \text{ Hz}$, 3 H, 13-H), 1.10 (s, 3 H, 11-Me), 1.34–1.83 (m, 10 H, 5-, 8-, 9-, 12-H, 7-CH₂CH₃), 2.18 (d, $J = 1.0 \text{ Hz}$, 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, $J = 10.5, 2.0 \text{ Hz}$, 1 H, 10-H), 3.45 (dd, $J = 10.5, 2.0 \text{ Hz}$, 1 H, 6-H), 3.69 (s, 3 H, CO₂Me), 5.72 (br. s, 1 H, 2-H). – C₁₈H₃₄O₆ (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): $\tilde{\nu}_{\text{max}} = 3450 \text{ cm}^{-1}$ (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, CDCl₃): $\delta = 0.92$ (t, $J = 7.5 \text{ Hz}$, 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, $J = 0.9 \text{ Hz}$, 3 H, 3-Me), 2.03–2.27 (m, 6 H, 4-, 5-, 8-H), 3.37 (dd, $J = 10.7, 1.8 \text{ Hz}$, 1 H, 10-H), 3.67 (s, 3 H, CO₂Me), 5.14 (br. s, 1 H, 6-H), 5.66 (s, 1 H, 2-H). – C₁₇H₃₀O₄ (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): $\tilde{\nu}_{\text{max}} = 3500 \text{ cm}^{-1}$ (br. s, O–H), 1730 (s, C=O), 1660 (s, C=C). – ¹H NMR (500 MHz, CDCl₃): $\delta = 0.97$ (t, $J = 7.5 \text{ Hz}$, 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, $J = 10.7, 1.8 \text{ Hz}$, 1 H, 6-H), 3.68 (s, 3 H, CO₂Me), 5.11 (t, $J = 6.1 \text{ Hz}$, 1 H, 10-H), 5.71 (s, 1 H, 2-H). – C₁₇H₃₀O₄ (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): $\tilde{\nu}_{\text{max}} = 3330 \text{ cm}^{-1}$ (br. s, O–H), 1720 (s, C=O), 1650 (m, C=C). – ¹H NMR (500 MHz, CDCl₃): $\delta = 0.94$ (t, $J = 7.5 \text{ Hz}$, 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, $J = 1.2 \text{ Hz}$, 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, $J = 10.7, 1.8 \text{ Hz}$, 1 H, 6-H or 10-H), 3.41 (dd, $J = 10.4, 1.8 \text{ Hz}$, 1 H, 6-H or 10-H), 3.69 (s, 3 H, CO₂Me), 5.72 (s, 1 H, 2-H). – C₁₇H₃₂O₆ (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**: $t_R = 11.1 \text{ min}$ (2.3%); (10*R*,11*R*)-**20a**: $t_R = 12.6 \text{ min}$ (97.7%). – **17b**: 92% *ee*; (10*S*,11*S*)-**20b**: $t_R = 12.4 \text{ min}$ (3.9%); (10*R*,11*R*)-**20b**: $t_R = 14.1 \text{ min}$ (96.1%).

Methyl (2*E*,6*E*,10*R*,11*S*)-10,11-Epoxy-7-ethyl-3,11-dimethyltrideca-2,6-dienoate (1): Ms₂O (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 CH₂Cl₂ (3 mL) and Et₃N (246 μ L, 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 NaHCO₃ and brine, and concentrated in vacuo to give 287 mg of crude **21a**. This was dissolved in MeOH (15 mL), and K₂CO₃ (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] $[\alpha]_D^{25} = +14.5$ ($c = 0.78$, MeOH)}. – IR (film): $\tilde{\nu}_{\text{max}} = 3000 \text{ cm}^{-1}$ (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, CDCl₃): $\delta = 0.96$ (t, $J = 7.6 \text{ Hz}$, 3 H, CH₂CH₃), 1.00 (t, $J = 7.6 \text{ Hz}$, 3 H, CH₂CH₃), 1.27 (s, 3 H, 11-Me), 1.42–1.69 (m, 4 H, 9, 12-H), 2.16 (d, $J = 1.0 \text{ Hz}$, 3 H, 3-Me), 1.99–2.23 (m, 8 H, 4-, 5-, 8-H, 7-CH₂CH₃), 2.71 (dd, $J = 6.7, 5.5 \text{ Hz}$, 1 H, 10-H), 3.68 (s, 3 H, CO₂Me), 5.08 (br. t, $J = 5.9 \text{ Hz}$, 1 H, 6-H), 5.66 (s, 1 H, 2-H). – ¹³C NMR (126 MHz, CDCl₃): $\delta = 9.7, 13.2, 18.9, 21.6, 23.1, 25.6, 25.8, 27.3, 33.3, 41.2, 50.8, 61.8, 64.7, 115.3, 122.9, 141.3, 160.0, 167.2$. These ¹H and ¹³C NMR spectroscopic data are identical with those re-

ported for **1**.^[8] – C₁₈H₃₀O₃ (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 (2E,6E,10R,11S)-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): $\tilde{\nu}_{\max} = 3000\text{ cm}^{-1}$ (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). – ¹H NMR (400 MHz, CDCl₃): $\delta = 0.99$ (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, CO₂Me), 5.13 (br. s, 1 H, 6-H), 5.66 (br. s, 1 H, 2-H). These ¹H NMR spectroscopic data are identical with those reported for **2**.^[8,10] – ¹³C NMR (100 MHz, CDCl₃): $\delta = 9.6, 16.0, 18.7, 21.5, 25.7, 25.8, 27.0, 36.4, 40.8, 50.7, 61.7, 64.5, 115.2, 123.4, 135.3, 159.9, 167.2$. These ¹³C NMR spectroscopic data are identical with those reported for **2**.^[8] – C₁₇H₂₈O₃ (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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