First Synthesis of (+)-α- and (+)-γ-Polypodatetraenes

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First synthesis of (+)-α-polypodatetraene (1) and (+)-γ-polypodatetraene (2) was achieved from (+)-albicanol (6) and (−)-drimenol (8), respectively. The absolute structure of natural (+)-2 was established to be (5*S*,9*S*,10*S*)-polypoda-7,13(*E*),17(*E*),21-tetraene.

Key words (+)-α-polypodatetraene; (+)-γ-polypodatetraene; total synthesis

Polypodanes constitute a new class of bicyclic triterpenoids and their occurrence in nature is important for the mechanistic study of the biosynthesis of polycyclic triterpenoids. (+)-α-Polypodatetraene (**1**) and (+)-γ-polypodatetraene (**2**) are the first compound of this class and were isolated from the fresh leaves of *Polypodium fauriei* and *Lemmaphyllum microphyllum* for (**1**), and *Polystichum ovatopaleaceum* and *P. polyblephalum* for (**2**), respectively.[1] Their planar structures were established to be polypoda-8(26),13,17,21-tetraene (**1**) and polypoda-7,13,17,21-tetraene (**2**) by a careful analysis of ^{1}H-, ^{13}C-NMR, IR, and mass-spectral data.[1] The absolute structure of the natural (+)-α-polypodatetraene (+)-**1** is determined as depicted in **1** because the optical rotation shows opposite signs, $[\alpha]_D$ +27.4° for the natural (+)-**1** and $[\alpha]_D$ −18.9° for the synthetic *ent*-**1** derived from copalic acid (**3**).[2] On the other hand, the absolute structure of the natural (+)-γ-polypodatetraene (**2**) was assumed by comparison of optical rotation between **1**, **2** ($[\alpha]_D$ +8.7°) and α-onoceradiene (**4**) ($[\alpha]_D$ +22.4°), onocera-7,14(27)-diene (**5**) ($[\alpha]_D$ +15.0°).[1] Total synthesis of (±)-**1** was reported based on mercury(II)trifluoromethanesulphonate–amine complex-induced olefin cyclization,[3] while total synthesis of (+)-**1** and (+)-**2** was not reported so far. We previously reported that enantioselective acetylation of (±)-albicanol (**6**) in the presence of isopropenyl acetate using lipase PL-266 from *Alcaligenes* sp. gave (+)-albicanyl acetate (**7**) (>99% ee) and (−)-albicanol (**6**) (>99% ee). Reductive deprotection of acetyl group in (+)-**7** afforded the natural (+)-albicanol (**6**), which was treated with $BF_3 \cdot Et_2O$ to provide the natural (−)-drimenol (**8**).[4] In this paper, we describe the first synthesis of the natural (+)-α-polypodatetraene (**1**) from (+)-**6** and (+)-γ-polypodatetraene (**2**) from (−)-**8**, and the determination of the absolute structure of (+)-**2**.

Results and Discussion

Synthesis of (+)-α-Polypodatetraene (1) from (+)-Albicanol (6) The method of elongation of the carbon chain from the primary alcohol group of (+)-**6** was developed stepwise by the following synthetic sequence. Mesylation of (+)-**6** in pyridine gave the mesylate **9** (99%), which was treated with NaCN in dimethyl sulfoxide (DMSO) to afford the nitrile compound **10** (49%) along with diexo-olefin **11** (31%). Reduction of **10** with diisobutylaluminum hydride (DIBAL) in toluene furnished the aldehyde **12** in 89% yield, which was reduced with $NaBH_4$ to provide the alcohol **13** in quantitative yield. Bromination of **13** using carbon tetrabromide (CBr_4) and triphenylphosphine (Ph_3P) under neutral conditions gave the corresponding bromide **14**, which was treated with NaCN in DMSO to provide the nitrile **15** in 71% overall yield. Dibal-H reduction of **15** yielded an aldehyde **16** (82%), which was reacted with (carbethoxyethylidene)triphenylphosphorane to give selectively (*E*)-**17** in quantitative yield. Dibal-H reduction of (*E*)-**17** gave an allyl alcohol **18** in quantitative yield, which was treated with tosyl chloride to afford the allyl chloride **19** in 43% yield. The prepared **19** was immediately treated with sodium benzene sulfinate ($PhSO_2Na \cdot 2H_2O$) to provide the sulfone **20** in 93% yield. The sulfone **20** was treated with lithium diisopropylamide (LDA) to provide the corresponding carbanion, which was treated with *trans*-geranyl bromide to furnish the alkylated product **21** in 56% yield. Reductive elimination of phenylsulfonyl group in **21** using sodium-amalgam (5% Na–Hg) gave the synthetic (+)-**1** ($[\alpha]_D$ +29.6° (c=0.22, $CHCl_3$)) in 42% yield, which was consistent with the natural (+)-**1** ($[\alpha]_D$ +27.4° (c=0.4, $CHCl_3$)).[1]

Synthesis of (+)-γ-Polypodatetraene (2) from (−)-Drimenol (8) The elongation of the carbon chain from the primary alcohol group of the reported homodrimenol (**22**)[4] derived from (−)-drimenol (**8**) was achieved stepwise by the following synthetic sequence. Bromination of **22** using CBr_4 and Ph_3P under neutral condition gave the corresponding bromide **23**, which was treated with NaCN in DMSO to provide the nitrile **24** in 78% overall yield. Dibal-H reduction of **24** yielded an aldehyde **25** (84%), which was reacted with (carbethoxyethylidene)triphenylphosphorane to give selectively (*E*)-**26** in quantitative yield. Dibal-H reduction of (*E*)-**26** gave an allyl alcohol **27** in 89% yield, which was subjected to bromination under neutral conditions (CBr_4 and Ph_3P) to afford the allyl bromide **28** in 73% yield. The prepared **28** was immediately treated with sodium benzene sulfinate to provide the sulfone **29** in 79% yield. The sulfone **29** was treated with LDA to provide the corresponding carbanion, which was treated with *trans*-geranyl bromide to furnish the alkylated product **30** in 94% yield. Reductive elimination of **30** using [1,3-bis(diphenylphosphine)propane]-dichloropalladium (II) ($PdCl_2$(dppp))[5] gave the synthetic (+)-**2** ($[\alpha]_D$ +6.9° (c=1.17, $CHCl_3$)) in 59% yield, which was consistent with the natural (+)-**2** ($[\alpha]_D$ +8.7° (c=0.9, $CHCl_3$)).[1] This chiral synthesis of (+)-**2** indicates that the absolute configurations of the natural (+)-**2** are to be 5*S*, 9*S*, 10*S*.

In conclusion, first synthesis of (+)-α-polypodatetraene (**1**) and (+)-γ-polypodatetraene (**2**) was achieved from (+)-

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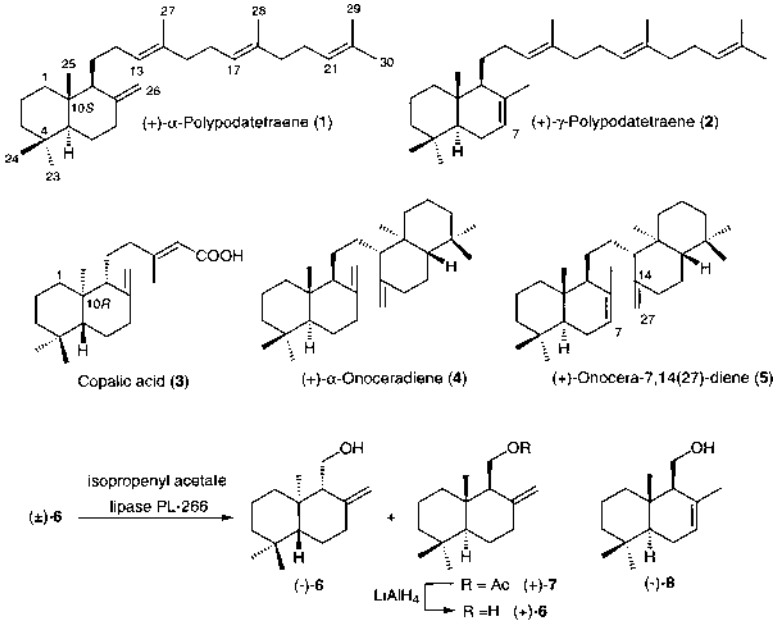

Chart 1

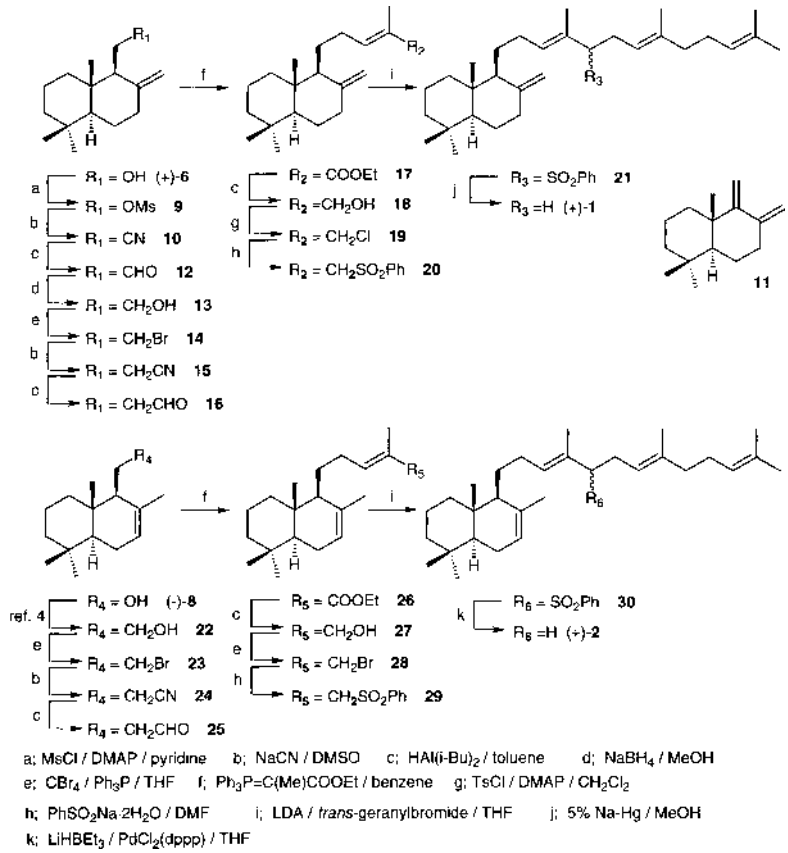

Chart 2

albicanol (**6**) and (−)-drimenol (**8**), respectively. The absolute structure of natural (+)-**2** was established to be (5*S*,9*S*,10*S*)-polypoda-7,13(*E*),17(*E*),21-tetraene.

Experimental

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by distortionless enhancement by polarization transfer (DEPT) pulse sequence. The fast atom bombardment mass spectra (FAB-MS) were obtained with JEOL JMS 600H spectrometer. IR spectra were recorded a JASCO FT/IR-300E spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

(1′*S*,4a′*S*,8a′*S*)-(+)-2-(1′,2′,3′,4′,4a′,5′,6′,7′,8′,8a′-Decahydro-5′,5′,8a′-trimethyl-2′-methylene-1′-naphtyl)-1-ethanol (13) 1) To a solution of (+)-albicanol (**6**) (3.01 g, 13.5 mmol) and 4-dimethylaminopyridine (DMAP) (0.161 g, 1.3 mmol) in pyridine (40 ml) was added MsCl (1.93 g, 16.8 mmol) and the whole mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (50 g, *n*-hexane : AcOEt=20 : 1) to give a colorless oil **9** (4.06 g, 99%). **9**: IR (neat): 1386, 1047 cm^{-1}; $[\alpha]_D^{30}$ +27.5° (*c*=0.91, $CHCl_3$); ^{1}H-NMR: δ: 0.74 (3H, s), 0.79 (3H, s), 0.86 (3H, s), 1.11 (1H, dd, *J*=2.5, 12.5 Hz), 1.14—1.42 (4H, m), 1.46—1.61 (2H, m), 1.66—1.75 (2H, m), 1.97—2.06 (1H, m), 2.10—2.15 (1H, m), 2.40 (1H, ddd, *J*=2, 4, 13 Hz), 2.96 (3H, s), 4.32 (1H, t, *J*=10 Hz), 4.47 (1H, dd, *J*=4, 10 Hz), 4.59 (1H, br s), 4.89 (1H, br s). ^{13}C-NMR: δ: 15.4 (q), 19.2 (t), 21.8 (q), 23.9 (t), 33.6 (s), 33.7 (q), 37.5 (t), 37.6 (q), 39.2 (t), 39.2 (s), 41.8 (t), 55.0 (d), 55.1 (d), 66.6 (t), 107.6 (t), 145.4 (s). *Anal.* Calcd for $C_{16}H_{28}O_3S$: C, 63.96; H, 9.39. Found: C,64.02; H, 9.41%.

2) A mixture of **9** (4.14 g, 13.8 mmol) and NaCN (3.41 g, 69.9 mmol) in DMSO (60 ml) was stirred for 12 h at 100 °C. The reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (60 g) to give a colorless oil **11** (0.889 g, 31%) from *n*-hexane eluate and a colorless oil **10** (1.573 g, 49%) from *n*-hexane : AcOEt=20 : 1 eluate. A part of **10** was recrystallized from *n*-hexane to give colorless plates. Compound **10**: mp 91 °C; $[\alpha]_D^{27}$ +41.8° (*c*=0.89, $CHCl_3$); IR (KBr): 2240 cm^{-1} (CN); ^{1}H-NMR: δ: 0.69 (3H, s), 0.82 (3H, s), 0.90 (3H, s), 1.13 (1H, dd, *J*=2.5, 12.5 Hz), 1.14—1.25 (2H, m), 1.33 (1H, dq, *J*=4, 12 Hz), 1.40—1.45 (1H, m), 1.50—1.62 (3H, m), 1.76 (1H, *J*=2, 13 Hz), 2.08 (1H, dt, *J*=5, 13 Hz), 2.17 (1H, dd, *J*=4, 11 Hz), 2.33 (1H, dd, *J*=11, 17 Hz), 2.45 (1H, ddd, *J*=2, 4, 13 Hz), 2.54 (1H, dd, *J*=4, 17 Hz), 4.62 (1H, br s), 4.96 (1H, br s). ^{13}C-NMR: δ: 13.7 (q), 13.9 (t), 19.1 (t), 21.7 (q), 23.7 (t), 33.5 (q and s), 37.2 (t), 39.1 (t), 39.3 (s), 41.7 (t), 53.2 (d), 55.0 (d), 107.8 (s), 120.3 (s), 146.3 (t). *Anal.* Calcd for $C_{16}H_{25}N$: C, 83.06; H, 10.89; N, 6.05. Found: C, 83.38; H, 10.85; N, 5.95%. FAB-MS *m*/*z*: 232 (M^++1). Compound **11**: IR (neat): 2928, 1632, 1460 cm^{-1}; $[\alpha]_D^{26}$ −186.6° (*c*=0.42, $CHCl_3$); ^{1}H-NMR: δ: 0.85 (3H, s), 0.86 (3H, s), 0.93 (3H, s), 1.11 (1H, dd, *J*=3, 12.5 Hz), 1.18 (1H, dt, *J*=4.5, 13.5 Hz), 1.38—1.57 (4H, m), 1.59—1.67 (2H, m), 1.75—1.78 (1H, m), 2.06—2.15 (1H, m), 2.45 (1H, ddd, *J*=2.5, 4.5, 13.5 Hz), 4.52 (1H, d, *J*=2 Hz), 4.63 (1H, t, *J*=2.5 Hz), 4.74 (1H, d, *J*=2 Hz), 4.78 (1H, t, *J*=2.5 Hz). ^{13}C-NMR: δ: 19.3 (t), 20.8 (q), 22.2 (q), 22.8 (t), 33.5 (q), 33.9 (s), 36.0 (t), 37.6 (t), 40.3 (s), 42.4 (t), 52.6 (d), 103.0 (t), 108.8 (t), 149.9 (s), 161.5 (s). *Anal.* Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 87.92; H, 11.52%. FAB-MS *m*/*z*: 205 (M^++1).

3) To a solution of **10** (1.573 g, 6.8 mmol) in toluene (20 ml) was added 1 M DIBAL in toluene (8.1 ml, 8.1 mmol) at −78°C, the whole was stirred for 30 min at the same temperature. After addition of acetone (5 ml), the reaction mixture was diluted with 2 M aqueous HCl and extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (30 g) to give a colorless oil **12** (1.433 g, 89%) from *n*-hexane : AcOEt=20 : 1 eluate. Compound **12**: IR (neat): 1725 cm^{-1}; $[\alpha]_D^{25}$ −18.1° (*c*=0.70, $CHCl_3$); ^{1}H-NMR: δ: 0.71 (3H, s), 0.82 (3H, s), 0.90 (3H, s), 1.09 (1H, dt, *J*=4.5, 13 Hz), 1.22 (1H, dd, *J*=2.5, 12.5 Hz), 1.17—1.24 (1H, m), 1.35 (1H, dq, *J*=4, 12.5 Hz), 1.40—1.45 (1H, m), 1.47—1.53 (3H, m), 1.74 (1H, dq, *J*=2.5, 13 Hz), 2.10 (1H, dt, *J*=5, 12 Hz), 2.34—2.37 (1H, m), 2.42 (1H, ddd, *J*=2.5, 4, 13 Hz), 2.43 (1H, ddd, *J*=1.5, 4.5, 16 Hz), 2.49 (1H, ddd, *J*=3, 10, 16 Hz), 9.64 (1H, dd, *J*=1.5, 3 Hz). ^{13}C-NMR: δ: 14.6 (q), 19.2 (t), 21.7 (q), 23.9 (t), 33.5 (q and s), 37.5 (t), 38.9 (s), 39.4 (t), 39.8 (t), 42.0 (t), 51.0 (d), 55.3 (d), 108.0 (t), 148.5 (s), 203.5 (d). *Anal.* Calcd for $C_{16}H_{26}O$: C, 81.98; H, 11.18. Found: C, 82.32; H, 11.28. FAB-MS *m*/*z*: 235 (M^++1).

4) To a solution of **12** (1.433 g, 6.1 mmol) in MeOH (30 ml) was added $NaBH_4$ (0.302 g, 8 mmol) at 0 °C, the whole was stirred for 30 min at the same temperature. After addition of acetone (5 ml), the reaction mixture was condensed to give a residue, which was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (30 g, *n*-hexane : AcOEt=5 : 1) to afford a colorless oil **13** (1.432 g, 99%). **13**: IR (neat): 3302 cm^{-1}; $[\alpha]_D^{24}$ +27.6° (*c*=1.14, $CHCl_3$); ^{1}H-NMR: δ: 0.65 (3H, s), 0.77 (3H, s), 0.84 (3H, s), 1.01 (1H, dt, *J*=4, 13 Hz), 1.09 (1H, dd, *J*=3, 13 Hz), 1.15 (1H, dt, *J*=4, 13 Hz), 1.24—1.39 (2H, m), 1.42—1.74 (8H, m), 1.96 (1H, dt, *J*=5, 13 Hz), 2.35 (1H, ddd, *J*=2.5, 4, 13 Hz), 3.44—3.51 (1H, m), 3.65—3.71 (1H, m), 4.50 (1H, br s), 4.79 (1H, br s). ^{13}C-NMR: δ: 14.6 (q), 19.5 (t), 21.8 (q), 24.5 (t), 27.1 (t), 33.6 (s), 33.7 (q), 38.3 (t), 39.1 (t), 39.4 (s), 42.2 (t), 52.8 (d), 55.5 (d), 62.5 (t), 106.2 (t), 148.6 (s). *Anal.* Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.02; H, 11.83%. FAB-MS *m*/*z*: 237 (M^++1).

(1′*S*,4a′*S*,8a′*S*)-(+)-3-(1′,2′,3′,4′,4a′,5′,6′,7′,8′,8a′-Decahydro-5′,5′,8a′-trimethyl-2′-methylene-1′-naphtyl)propionaldehyde (16) 1) To a solution of **13** (1.403 g, 5.9 mmol) in THF (30 ml) was added Ph_3P (5.463 g, 20.8 mmol) and CBr_4 (5.345 g, 16.1 mmol) and the whole was stirred for 15 min at room temperature. The reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (50 g, *n*-hexane) to give a colorless oil **14** (3.698 g). **14**: ^{1}H-NMR: δ: 0.67 (3H, s), 0.78 (3H, s), 0.86 (3H, s), 1.05 (1H, dt, *J*=4, 12 Hz), 1.11 (1H, dd, *J*=2.5, 12 Hz), 1.17 (1H, dt, *J*=4, 12 Hz), 1.30 (1H, ddd, *J*=4, 13, 20 Hz), 1.36—1.41 (1H, m), 1.45—1.62 (2H, m), 1.66—1.75 (2H, m), 1.78—1.82 (1H, m), 1.88—2.07 (3H, m), 2.38 (1H, ddd, *J*=2, 4, 13 Hz), 3.25 (1H, ddd, *J*=7.5, 8, 8.5 Hz), 3.51 (1H, ddd, *J*=4, 8, 8.5 Hz), 4.45 (1H, br s), 4.82 (1H, br s). ^{13}C-NMR: δ: 14.8 (q), 19.4 (t), 21.8 (q), 24.4 (t), 28.0 (t), 33.6 (s), 33.6 (q), 33.7 (t), 38.2 (t), 39.0 (t), 39.6 (s), 42.1 (t), 55.3 (d), 55.4 (d), 106.2 (t), 147.7 (s).

2) A mixture of **14** (3.698 g) and NaCN (4.53 g, 92.4 mmol) in DMSO (30 ml) was stirred for 0.5 h at 100 °C. The reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (50 g, *n*-hexane : AcOEt=20 : 1) to give a colorless oil **15** (1.035 g, 71% overall yield from **13**). Compound **15**: IR (KBr): 2263 cm^{-1}; $[\alpha]_D^{27}$ +37.5° (*c*=0.89, $CHCl_3$); ^{1}H-NMR: δ: 0.66 (3H, s), 0.72 (3H, s), 0.86 (3H, s), 1.04—1.21 (3H, m), 1.25—1.41 (2H, m), 1.46—1.58 (2H, m), 1.65—1.75 (4H, m), 1.84—2.02 (2H, m), 2.24 (1H, dt, *J*=7.5, 9 Hz), 2.38 (1H, ddd, *J*=2.5, 4, 13 Hz), 2.44 (1H, ddd, *J*=4, 8, 13 Hz), 4.39 (1H, br s), 4.85 (1H, br s). ^{13}C-NMR: δ: 14.6 (q), 16.3 (t), 19.4 (t), 20.4 (t), 21.8 (q), 24.5 (t), 33.6 (s), 33.6 (q), 38.1 (t), 39.0 (t), 39.8 (s), 42.0 (t), 55.3 (d), 55.8 (d), 106.2 (t), 120.2 (s), 147.1 (s). *Anal.* Calcd for $C_{17}H_{27}N$: C, 83.20; H, 11.09; N, 5.71. Found: C, 83.17; H, 11.30; N, 5.68%. FAB-MS *m*/*z*: 244 (M^+−1), 245 (M^+).

3) To a solution of **15** (1.016 g, 4.1 mmol) in toluene (15 ml) was added 1 M DIBAL in toluene (10 ml, 10 mmol) at −78 °C, the whole was stirred for 15 min at the same temperature. The reaction mixture was worked up by the same way as for the preparation of **12** to give a colorless oil **16** (0.842 g, 82%). Compound **16**: IR (neat): 1726 cm^{-1}; $[\alpha]_D^{26}$ +30.0° (*c*=0.66, $CHCl_3$); ^{1}H-NMR: δ: 0.67 (3H, s), 0.78 (3H, s), 0.84 (3H, s), 1.01—1.08 (2H, m), 1.15 (1H, dt, *J*=4, 13 Hz), 1.24—1.41 (2H, m), 1.44—1.61 (4H, m), 1.68—1.79 (2H, m), 1.84—1.97 (2H, m), 2.23—2.38 (2H, m), 2.52—2.60 (1H, m), 4.40 (1H, br s), 4.81 (1H, br s), 9.73 (1H, t, *J*=1.5 Hz). ^{13}C-NMR: δ: 14.4 (q), 16.0 (t), 19.5 (t), 21.8 (q), 24.5 (t), 33.6 (s), 33.7 (q), 38.3 (t), 39.1 (t), 39.9 (s), 42.2 (t), 43.3 (t), 55.5 (d), 56.3 (d), 106.4 (t), 147.8 (s), 202.5 (d). *Anal.* Calcd for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 81.98; H, 11.18%. FAB-MS *m*/*z*: 249 (M^++1).

(1′*S*,2*E*,4a′*S*,8a′*S*)-(+)-3-(1′,2′,3′,4′,4a′,5′,6′,7′,8′,8a′-Decahydro-5′,5′,8a′-trimethyl-2′-methylene-1′-naphtyl)-2-methyl-1-phenylsulfonyl-2-pentene (20) 1) To a solution of **16** (0.826 g, 3.3 mmol) in benzene (30 ml) was added Ph_3P=C(Me)COOEt (1.689 g, 4.6 mmol) and the whole was refluxed for 12 h with stirring. The reaction mixture was evaporated to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane : AcOEt=20 : 1) to give a colorless oil **17** (1.096 g, 99%). **17**: IR (neat): 1710 cm^{-1}; $[\alpha]_D^{27}$ +40.7° (*c*=0.67, $CHCl_3$); ^{1}H-NMR: δ: 0.64 (3H, s), 0.77 (3H, s), 0.84 (3H, s), 0.99 (1H, dt, *J*=4, 13 Hz), 1.06 (1H, dd, *J*=3, 13 Hz), 1.15 (1H, dt, *J*=4, 13 Hz), 1.22—1.63 (8H, m), 1.27 (3H, t, *J*=7 Hz), 1.68—1.73 (1H, m), 1.77 (3H, br s), 1.90—2.04 (2H, m), 2.22—2.31 (1H, m), 2.34—2.40 (1H, m), 4.16 (2H, q, *J*=7 Hz), 4.49 (1H, s), 4.82 (1H, s), 6.72 (1H, t, *J*=8 Hz). ^{13}C-NMR: δ: 12.5 (q), 14.5 (q), 14.6 (q), 19.5 (t), 21.9 (q), 22.8 (t), 24.6 (t), 27.8 (t), 33.7 (s), 33.7 (q), 38.4 (t), 39.2 (t), 39.8 (s), 42.2 (t), 55.5 (d), 56.5 (d), 60.4 (t), 106.2 (t), 127.5 (s), 142.5 (d), 148.2 (s), 168.1 (s). *Anal.* Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.51; H, 10.96%. FAB-MS *m*/*z*: 333 (M^++1).

2) To a solution of **17** (1.076 g, 3.2 mmol) in toluene (20 ml) was added 1 M DIBAL in toluene (5 ml, 5 mmol) at −78 °C, the whole was stirred for 30 min at the same temperature. The reaction mixture was worked up by the same way as for the preparation of **12** to give a colorless oil **18** (0.937 g, 99%). Compound **18**: IR (neat): 3314 cm^{-1}; $[\alpha]_D^{27}$ +6.8° (*c*=0.88, $CHCl_3$); ^{1}H-NMR: δ: 0.65 (3H, s), 0.77 (3H, s), 0.85 (3H, s), 0.98 (1H, dt, *J*=4, 13 Hz), 1.06 (1H, dd, *J*=3, 12 Hz), 1.15 (1H, dt, *J*=4, 13 Hz), 1.22—1.61 (8H, m), 1.61 (3H, br s), 1.68—1.74 (2H, m), 1.78—2.00 (2H, m), 2.09—2.18 (1H, m), 2.37 (1H, ddd, *J*=2, 3, 12 Hz), 3.98 (2H, br s), 4.51 (1H, br s),

4.81 (1H, br s), 5.37 (1H, dt, J=1, 7 Hz). ^{13}C-NMR: δ: 13.8 (q), 14.6 (q), 19.5 (t), 21.9 (q), 23.6 (t), 24.6 (t), 26.7 (t), 33.7 (s), 33.7 (q), 38.5 (t), 39.2 (t), 39.7 (s), 42.3 (t), 55.6 (d), 56.4 (d), 69.1 (t), 106.1 (t), 126.8 (d), 134.5 (s), 148.5 (s). *Anal.* Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.77; H, 11.91%. FAB-MS *m/z*: 291 (M^++1).

3) To a solution of **18** (0.836 g, 2.88 mmol) and DMAP (0.176 g, 1.44 mmol) in CH_2Cl_2 (20 ml) was added TsCl (0.659 g, 3.45 mmol) at 0 °C and the whole mixture was stirred for 7 h at room temperature. The reaction mixture was worked up by the same way as for the preparation of **14** to give a colorless oil **19** (0.382 g, 43%). Compound **19**: $[\alpha]_D^{24}$ +25.3° (c=0.56, $CHCl_3$); ^{1}H-NMR: δ: 0.64 (3H, s), 0.78 (3H, s), 0.84 (3H, s), 0.98 (1H, dt, J=4, 12.5 Hz), 1.06 (1H, dd, J=3, 12.5 Hz), 1.15 (1H, dt, J=4, 13 Hz), 1.24—1.60 (8H, m), 1.67 (3H, br s), 1.67—1.73 (1H, m), 1.80—1.99 (2H, m), 2.09—2.18 (1H, m), 2.37 (1H, ddd, J=2.5, 4.5, 13 Hz), 4.00 (2H, s), 4.40 (1H, br s), 4.81 (1H, br s), 5.49 (1H, t, J=7 Hz).

4) To a solution of **19** (0.138 g, 0.44 mmol) in dimethylformamide (DMF) (5 ml) was added $PhSO_2Na\cdot 2H_2O$ (0.84 g, 6.2 mmol) at room temperature and the whole was stirred for 2 h at 60 °C. The reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (15 g, *n*-hexane : AcOEt=20 : 1) to afford a colorless oil **20** (0.173 g, 93%). **20**: IR (neat): 1386, 1307 cm^{-1}; $[\alpha]_D^{27}$ +25.2° (c=0.94, $CHCl_3$); ^{1}H-NMR: δ: 0.61 (3H, s), 0.77 (3H, s), 0.84 (3H, s), 0.91 (1H, dt, J=4, 12.5 Hz), 1.02 (1H, dd, J=3, 12.5 Hz), 1.11—1.17 (2H, m), 1.21—1.71 (11H, m), 1.68 (3H, s), 1.90—2.35 (2H, m), 3.70 (2H, s), 4.36 (1H, br s), 4.77 (1H, br s), 5.02 (1H, t, J=6.5 Hz), 7.51 (2H, t, J=1.5 Hz), 7.61 (1H, t, J=1.5 Hz), 7.82 (2H, d, J=1.5 Hz). ^{13}C-NMR: δ: 14.6 (q), 16.8 (q), 19.5 (t), 21.8 (q), 23.1 (t), 24.5 (t), 27.5 (t), 33.7 (s), 33.7 (q), 38.4 (t), 39.2 (t), 39.7 (s), 42.2 (t), 55.5 (d), 56.3 (d), 66.3 (t), 106.0 (t), 122.9 (s), 128.4 (d), 128.4 (s), 128.7 (d), 133.3 (d), 136.9 (d), 148.3 (s). *Anal.* Calcd for $C_{26}H_{38}O_2S$: C, 75.31; H, 9.24. Found: C, 75.02; H, 9.01%.. FAB-MS *m/z*: 415 (M^++1).

(+)-α-Polypodatetraene (1) 1) *n*-Butyllithium (1.6 M *n*-BuLi in hexane, 0.5 ml, 0.8 mmol) was added to a stirred solution of diisopropylamine (0.077 g, 0.76 mmol) in tetrahydrofuran (THF) (2 ml) at −78 °C under an argon atmosphere and the mixture was stirred for 15 min at the same temperature. A solution of **20** (0.154 g, 0.37 mmol) in THF (2 ml) was added to the resulting LDA-THF solution and the whole mixture was stirred for 15 min at the same temperature. To the above reaction mixture was added a solution of *trans*-geranyl bromide (0.167 g, 0.77 mmol) in THF (2 ml) and the whole mixture was stirred for 15 min at −78 °C, for 1 h at −20 °C and for 1 h at room temperature. The reaction mixture was diluted with saturated brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Removal of the organic solvent gave an oily product, which was chromatographed on silica gel (15 g, *n*-hexane : AcOEt=20 : 1) to afford **21** as a homogeneous oil (0.115 g, 56%). FAB-MS *m/z*: 551 (M^++1).

2) A mixture of **21** (0.115 g, 0.21 mmol) and 5% Na–Hg (1.32 g, 0.3 mmol) in MeOH (20 ml) was refluxed for 12 h with stirring. The reaction mixture was evaporated to give a residue, which was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (15 g, *n*-hexane) to give a colorless oil (+)-**1** (0.036 g, 42%) as a colorless oi. Compound (+)-**1**: IR (neat): 3076, 1655 cm^{-1}; $[\alpha]_D^{26}$ +29.6° (c=0.22, $CHCl_3$); ^{1}H-NMR: δ: 0.64 (3H, s), 0.77 (3H, s), 0.85 (3H, s), 0.98 (1H, dt, J=4, 12.5 Hz), 1.06 (1H, dd, J=2.5, 12.5 Hz), 1.15 (1H, dt, J=4, 13 Hz), 1.23—1.84 (17H, m), 1.54 (3H, br s), 1.57 (6H, br s), 1.65 (3H, br s), 1.92—2.09 (2H, m), 2.33—2.49 (2H, m), 4.51 (1H, br s), 4.80 (1H, br s), 5.05—5.12 (3H, m). ^{13}C-NMR (BCM): δ: 14.5, 16.0, 16.0, 17.8, 19.6, 21.9, 23.8, 24.6, 25.7, 26.8, 26.8, 29.7, 33.6, 33.6, 38.5, 39.1, 39.6, 39.8, 39.8, 42.3, 55.6, 56.2, 106.1, 124.2, 124.4, 125.1, 131.1, 134.8, 134.8, 148.4. *Anal.* Calcd for $C_{30}H_{50}$: C, 87.73; H, 12.27. Found: C, 87.77; H, 12.01%. EI-MS *m/z*: 409 (M^+−1), 411 (M^++1).

(1′*S*,4a′*S*,8a′*S*)-(+)-3-(1′,4′,4a′,5′,6′,7′,8′,8a′-Octahydro-2′,5′,5′,8a′-tetramethyl-1′-naphtyl)propionaldehyde (25) 1) To a solution of **22** (1.234 g, 5.2 mmol) in THF (20 ml) was added Ph_3P (2.74 g, 10.4 mmol) and CBr_4 (3.45 g, 10.4 mmol) and the whole was stirred for 30 min at room temperature. The reaction mixture was worked up by the same way as for the preparation of **14** to give a colorless oil **23** (2.69 g). **23**: IR (neat): 2927 cm^{-1}; $[\alpha]_D^{25}$ +9.9° (c=0.78, $CHCl_3$); NMR: δ: 0.74 (3H, s), 0.86 (3H, s), 0.87 (3H, s), 1.01 (1H, dt, J=4, 13 Hz), 1.15 (1H, dt, J=4, 13 Hz), 1.18 (1H, dd, J=5, 12 Hz), 1.37—1.58 (4H, m), 1.66 (3H, br s), 1.70—1.89 (4H, m), 1.93—2.04 (2H, m), 3.34 (1H, q, J=8.5 Hz), 3.56 (1H, dt, J=4, 8.5 Hz), 5.42 (1H, br s). ^{13}C-NMR: δ: 13.8 (q), 18.8 (t), 22.0 (q), 22.2 (q), 23.9 (t), 31.4 (t), 33.1 (s), 33.2 (q), 34.5 (t), 36.7 (s), 39.3 (t), 42.3 (t), 50.1 (d), 54.0 (d), 123.2 (d), 133.4 (s). FAB-MS *m/z*: 299 (M^+−1), 297 (M^+−1).

2) A mixture of **23** (2.69 g) and NaCN (2.64 g, 53.9 mmol) in DMSO (25 ml) was stirred for 0.5 h at 100 °C. The reaction mixture was worked up by the same way as for the preparation of **15** to give a colorless oil **24** (1.004 g, 78% overall yield from **22**). Compound **24**: IR (neat): 2220 cm^{-1}; $[\alpha]_D^{24}$ −4.0° (c=0.8, $CHCl_3$); ^{1}H-NMR: δ: 0.74 (3H, s), 0.83 (3H, s), 0.86 (3H, s), 1.04 (1H, dt, J=4, 12.5 Hz), 1.16 (1H, dt, J=4, 12.5 Hz), 1.19 (1H, dd, J=5, 12 Hz), 1.37—1.58 (4H, m), 1.65 (3H, br s), 1.73 (1H, br s), 1.79—1.88 (3H, m), 1.93—2.02 (1H, m), 2.33 (1H, dt, J=8.5, 17 Hz), 2.50 (1H, ddd, J=5.5, 8.5, 17 Hz). ^{13}C-NMR: δ: 13.8 (q), 18.8 (t), 19.1 (t), 21.9 (q), 22.1 (q), 23.3 (t), 23.8 (t), 33.0 (s), 33.2 (q), 36.8 (s), 39.2 (t), 42.1 (t), 49.9 (d), 53.9 (d), 119.8 (s), 123.8 (d), 132.7 (s). FAB-MS *m/z*: 246 (M^++1).

3) To a solution of **24** (1.003 g, 4.1 mmol) in toluene (15 ml) was added 1 M DIBAL in toluene (11 ml, 11 mmol) at −78 °C, the whole was stirred for 1 h at the same temperature. The reaction mixture was worked up by the same way as for the preparation of **16** to give a colorless oil **25** (0.856 g, 84%). Compound **25**: IR (neat): 1730 cm^{-1}; $[\alpha]_D^{24}$ −0.4° (c=1.11, $CHCl_3$); ^{1}H-NMR: δ: 0.76 (3H, s), 0.82 (3H, s), 0.85 (3H, s), 0.92 (1H, dt, J=4, 13 Hz), 1.12 (1H, dt, J=4, 13 Hz), 1.14 (1H, dd, J=5, 12 Hz), 1.35—1.54 (4H, m), 1.63 (3H, br s), 1.78—1.99 (4H, m), 2.37—2.45 (1H, m), 2.62 (1H, dddd, J=1.5, 5, 10, 17 Hz), 5.40 (1H, br s), 9.72 (1H, t, J=1.5 Hz). ^{13}C-NMR: δ: 13.7 (q), 18.9 (t), 19.2 (t), 22.0 (q), 22.3 (q), 23.9 (t), 33.0 (s), 33.3 (q), 37.0 (s), 39.5 (t), 42.3 (t), 46.1 (t), 50.1 (d), 54.3 (d), 123.1 (d), 133.9 (s), 202.1 (d). FAB-MS *m/z*: 247 (M^+−1).

(1′*S*,2*E*,4a′*S*,8a′*S*)-(+)-5-(1′,4′,4a′,5′,6′,7′,8′,8a′-Octahydro-2′,5′,5′,8a′-tetramethyl-1′-naphtyl)-2-methyl-1-phenylsulfonyl-2-pentene (29) 1) To a solution of **25** (0.856 g, 3.4 mmol) in benzene (20 ml) was added Ph_3P=C(Me)COOEt (3.15 g, 9.7 mmol) and the whole was heated at 60 °C for 30 min with stirring. The reaction mixture was worked up by the same way as for the preparation of **17** to give a colorless oil **26** (1.135 g, 99%). **26**: IR (neat): 1711 cm^{-1}; $[\alpha]_D^{25}$ +13.5° (c=0.79, $CHCl_3$); ^{1}H-NMR: δ: 0.73 (3H, s), 0.84 (3H, s), 0.86 (3H, s), 0.94 (1H, dt, J=4, 13 Hz), 1.14 (1H, dt, J=4, 13 Hz), 1.16 (1H, dd, J=5, 12 Hz), 1.23—1.34 (1H, m), 1.27 (3H, t, J=7 Hz), 1.36—1.48 (3H, m), 1.49—1.59 (2H, m), 1.62 (1H, br s), 1.69 (3H, br s), 1.82 (3H, br s), 1.79—1.88 (2H, m), 1.91—1.99 (1H, m), 2.07—2.17 (1H, m), 2.29—2.38 (1H, m), 4.17 (2H, q, J=7 Hz), 5.38 (1H, br s), 6.74 (1H, t, J=8 Hz). ^{13}C-NMR: δ: 12.6 (q), 13.6 (q), 14.4 (q), 18.9 (t), 22.0 (q), 22.3 (q), 23.9 (t), 26.2 (t), 31.0 (t), 33.1 (s), 33.3 (q), 36.9 (s), 39.3 (t), 42.3 (t), 50.2 (d), 54.5 (d), 60.4 (t), 122.5 (d), 127.5 (s), 134.6 (s), 142.1 (d), 168.0 (s). *Anal.* Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.10; H, 10.93%. FAB-MS *m/z*: 333 (M^++1).

2) To a solution of **26** (1.151 g, 3.5 mmol) in toluene (15 ml) was added 1 M DIBAL in toluene (9 ml, 9 mmol) at −78 °C, the whole was stirred for 30 min at the same temperature. The reaction mixture was worked up by the same way as for the preparation of **18** to give a colorless oil **27** (0.894 g, 89%). Compound **27**: IR (neat): 3332 cm^{-1}; $[\alpha]_D^{22}$ +3.2° (c=0.81, $CHCl_3$); ^{1}H-NMR: δ: 0.74 (3H, s), 0.85 (3H, s), 0.87 (3H, s), 0.95 (1H, dt, J=4, 9 Hz), 1.15 (1H, dt, J=4, 9 Hz), 1.17 (1H, dd, J=5, 12 Hz), 1.20—1.28 (1H, m), 1.30 (1H, br s), 1.38—1.56 (4H, m), 1.63 (1H, br s), 1.68 (3H, br s), 1.71 (3H, br s), 1.80—1.90 (2H, m), 1.93—2.05 (2H, m), 2.18—2.27 (1H, m), 4.00 (2H, br s), 5.39 (1H, br s), 5.42 (1H, t, J=7 Hz). ^{13}C-NMR: δ: 14.0 (q), 14.3 (q), 19.3 (t), 22.3 (q), 22.6 (q), 24.3 (t), 27.4 (t), 30.4 (t), 33.4 (s), 33.6 (t), 37.2 (s), 39.6 (t), 42.7 (t), 50.5 (d), 54.8 (d), 69.3 (t), 122.5 (d), 126.8 (d), 134.8 (s), 135.4 (s). *Anal.* Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.43; H, 11.80%. FAB-MS *m/z*: 291 (M^++1).

3) To a solution of **27** (0.681 g, 2.3 mmol) in THF (20 ml) was added Ph_3P (1.34 g, 5.1 mmol) and CBr_4 (1.64 g, 4.9 mmol) and the whole was stirred for 1 h at room temperature. The reaction mixture was worked up by the same way as for the preparation of **23** to give a colorless oil **28** (0.606 g, 73%). Compound **28**: IR (neat): 2929 cm^{-1}; $[\alpha]_D^{22}$ +3.2° (c=0.81, $CHCl_3$); ^{1}H-NMR: δ: 0.72 (3H, s), 0.84 (3H, s), 0.86 (3H, s), 0.94 (1H, dt, J=4, 13 Hz), 1.10—1.27 (3H, m), 1.36—2.04 (9H, m), 1.68 (3H, br s), 1.75 (3H, br s), 2.15—2.25 (1H, m), 3.96 (2H, s), 5.38 (1H, br s), 5.59 (1H, t, J=7 Hz). ^{13}C-NMR: δ: 13.6 (q), 14.9 (q), 18.9 (t), 22.0 (q), 22.3 (q), 23.9 (t), 26.6 (t), 30.6 (t), 33.1 (s), 33.3 (q), 36.8 (s), 39.3 (t), 42.0 (t), 42.4 (t), 50.2 (d), 54.2 (d), 122.3 (d), 131.6 (d), 131.6 (s), 134.9 (s).

4) To a solution of **28** (0.578 g, 1.6 mmol) in DMF (20 ml) was added $PhSO_2Na\cdot 2H_2O$ (0.813 g, 4.1 mmol) at room temperature and the whole was stirred for 30 min at 60 °C. The reaction mixture was worked up by the same way as for the preparation of **20** to give a colorless oil **29** (0.539 g, 79%). Compound **29**: IR (neat): 1310, 1141 cm^{-1}; $[\alpha]_D^{23}$ +13.7° (c=1.51, $CHCl_3$); ^{1}H-NMR: δ: 0.70 (3H, s), 0.85 (3H, s), 0.87 (3H, s), 0.82—0.91 (1H, m), 0.94—1.20 (1H, m), 1.10—1.18 (1H, m), 1.13 (1H, dd, J=5, 12 Hz), 1.20—1.27 (1H, m), 1.37—1.54 (4H, m), 1.62 (3H, br s),1.69—1.75 (1H, m), 1.75

(3H, br s), 1.82—1.98 (3H, m), 2.15—2.30 (1H, m), 3.73 (2H, s), 5.04 (1H, t, J=7 Hz), 5.37 (1H, br s), 7.52 (2H, t, J=8 Hz), 7.62 (1H, t, J=8 Hz), 7.84 (2H, d, J=8 Hz). ^{13}C-NMR: δ: 13.4 (q), 16.6 (q), 18.7 (t), 21.8 (q), 22.0 (q), 23.7 (t), 26.3 (t), 30.5 (t), 32.9 (s), 33.1 (q), 36.6 (s), 39.1 (t), 42.2 (t), 49.4 (d), 54.2 (d), 66.1 (t), 122.2 (d), 122.8 (s), 128.2 (d), 128.5 (d), 133.1 (d), 134.5 (s), 136.3 (d), 138.0 (s). *Anal.* Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94%. Found: C, 81.27; H, 12.04%. FAB-MS m/z: 415 (M^++1).

(+)-γ-Polypodatetraene (2) 1) *n*-Butyllithium (1.6 M *n*-BuLi in hexane, 0.95 ml, 1.5 mmol) was added to a stirred solution of diisopropylamine (0.094 g, 0.9 mmol) in THF (3 ml) at −78 °C under an argon atmosphere and the mixture was stirred for 15 min at the same temperature. A solution of **29** (0.193 g, 0.5 mmol) in THF (1 ml) was added to the resulting LDA-THF solution and the whole mixture was stirred for 15 min at the same temperature. To the above reaction mixture was added a solution of *trans*-geranyl bromide (0.203 g, 0.9 mmol) in THF (1 ml) and the whole mixture was stirred for 30 min at −78 °C and for 2 h at −20 °C. The reaction mixture was worked up by the same way as for the preparation of **21** to give a colorless oil **30** (0.241 g, 94%).

2) To a solution of **30** (0.048 g, 0.1 mmol) and $PdCl_2$ (dppp) (20.6 mg, 0.05 mmol) in THF was added 1 M $LiHBEt_3$ in THF (0.54 ml, 0.54 mmol) and the whole mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with 2 M aqueous NaOH and extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (15 g, *n*-hexane) to give a colorless oil (+)-**2** (0.021 g, 59%) as a colorless oil. Compound (+)-**2**: IR (neat): 2921, 1448 cm^{-1}; $[\alpha]_D^{24}$ +6.9° (c=1.17, $CHCl_3$); ^{1}H-NMR: δ: 0.72 (3H, s), 0.83 (3H, s), 0.85 (3H, s), 0.94 (1H, dt, J=4, 13 Hz), 1.09—1.23 (3H, m), 1.31—1.70 (9H, m), 1.57 (6H, s), 1.59 (3H, s), 1.66 (3H, s), 1.79—1.88 (2H, m), 1.90—2.20 (10H, m), 2.67 (1H, t, J=7 Hz), 5.06—5.14 (2H, m), 5.36 (1H, br s). ^{13}C-NMR (BCM): δ: 13.6, 16.1, 16.3, 17.8, 19.0, 21.9, 22.3, 23.9, 25.8, 26.7, 26.9, 27.4, 30.3, 33.0, 33.3, 36.8, 39.3, 39.8, 39.8, 42.4, 50.2, 54.3, 121.9, 124.1, 124.3, 124.7, 131.1, 134.8, 134.8, 135.5. *Anal.* Calcd for $C_{30}H_{50}$: C, 87.73; H, 12.27. Found: C, 87.89; H, 12.35%. FAB-MS m/z: 409 (M^+−1).

References

1) Shiojima K., Arai Y., Masuda K., Kamada T., Ageta H., *Tetrahedron Lett.*, **24**, 5733—5736 (1983).
2) Imamura P. M., Pantarotto H., *Liebigs Ann.*, **1995**, 1891—1894 (1995).
3) Nishizawa M., Nishide H., Hayashi Y., *J. Chem. Soc., Chem. Commun.*, **1984**, 467—468 (1984).
4) Akita H., Nozawa M., Mitsuda A., Ohsawa H., *Tetrahedron: Asymmetry*, **11**, 1375—1388 (2000).
5) Mohri M., Kinoshita H., Inomata K., Kotake H., *Chem. Lett.*, **1985**, 451—454 (1985).