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ABSOLUTE CONFIGURATION OF (−)-BIFLORA-4,10(19),15-TRIENE, A DITERPENE FROM A TERMITE SOLDIER, AS DETERMINED BY THE SYNTHESIS OF ITS (1*R*, 6*S*, 7*S*, 11*R*-(+)-ISOMER†

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Abstract—(1*R*, 6*S*, 7*S*, 11*R*)-(+)-Biflora-4, 10(19),15-triene was synthesized starting from (*R*)-(+)-citronellic acid. This enabled us to assign (1*S*, 6*R*, 7*R*, 11*S*)-stereochemistry to the naturally occurring (−)-enantiomer isolated from soldiers of the termite species *Cubitermes umbratus*.

(−)-Biflora-4,10(19),15-triene **1** is a diterpene isolated from the frontal gland secretion of a termite soldier, *Cubitermes umbratus* Williams.[1] By X-ray analysis of its derivative, its relative configurations were assigned as C-1(*R**), C-6(*S**), C-7(*S**) and C-11(*R**).[1] Its absolute stereochemistry, however, remained unknown. It sometimes happens that the absolute configuration of a terpene of insect origin is different from that of plant origin. For example, while methyl branching in acyclic terpenoids of plant origin often involves (*R*)-configuration, that in insect pheromone molecules is sometimes with (*S*)-configuration as in the case of the yellow scale pheromone.[2] We therefore became interested in clarifying the absolute stereochemistry of (−)-biflora-4,10(19),15-triene **1**. As its relative configurations are known, the problem can be solved by executing a chiral synthesis of either the natural product itself or its enantiomer starting from an optically active building block of known absolute configuration. Herein we describe the result of our work along this line culminating in a synthesis of (1*R*, 6*S*, 7*S*, 11*R*)-(+)-biflora-4,10(19), 15-triene **1c**. The present synthesis firmly establishes the absolute configurations of natural and levorotatory **1c** to be (1*S*, 6*R*, 7*R*, 11*S*).

As shown in the scheme, our synthesis started from (*R*)-(+)-citronellic acid **2** of 100% optical purity.[2] An intramolecular Diels–Alder reaction (**10**→**11**) was employed for the construction of the carbocycle as previously reported by Taber and Gunn in the synthesis of (±)-torreyol.[3]

(*R*)-(+)-Citronellic acid **2** was reduced with LAH to citronellol, which was oxidized with pyridinium chlorochromate (PCC)[4] to give (*R*)-(+)-citronellal **3**. Addition of its piperidine enamine to ethyl acrylate was followed by hydrolysis to give an aldehyde **4** in 75.1% yield. Reaction between **4** and a ylid derived from methallyltriphenylphosphonium chloride yielded an olefinic ester **5** (58.0%). This was reduced with LAH to give an alcohol **6** (98.9%), whose Moffatt oxidation[5] afforded an aldehyde **7** in 88.8% yield. Although the addition of CH$_2$=CHMgBr to **7** was unsuccessful, LiC≡CH in THF[6] smoothly added to **7** to give an acetylenic alcohol **8** (72.6%) as a diastereomeric mixture. This was hydrogenated over Pd–BaSO$_4$ in the presence of quinoline to give a tetraene alcohol **9** (86.5%), the key acyclic intermediate. Upon oxidation with Jones reagent, the acyclic precursor **9** cyclized spontaneously *via* **10** to give a stereoisomeric mixture of bicyclic ketones **11a** and **11b** (*ca* 1:1 ratio) in 73.6% yield.[1] The assigned structures of **11a** and **11b** were based on the final identification of **1c** as the antipode of the natural product. Oxidation of **9** under Brown's two-phase condition (Et$_2$O–H$_2$Cr$_2$O$_7$)[7] also gave a mixture of **11a** and **11b**, although in less satisfactory yield (50.4%). PCC oxidation also resulted in a poor yield (51.8%). These two isomers were separable by medium pressure LC and each of them was fully characterized. Treatment of the ketone mixture (**11a** + **11b**) with Ph$_3$P=CH$_2$ yielded a mixture of hydrocarbons **1a** and **1b**. These were separated by prep GLC to give pure **1a**, $[\alpha]_D^{17}$-26° (MeOH), and **1b**, $[\alpha]_D^{21}$ + 32° (MeOH). Both of them showed spectral properties different from those reported for the natural product.

In order to obtain the natural product itself or its enantiomer, isomerization of the *cis*-ketones **11a** and **11b** to thermodynamically more stable *trans*-ketones **11c** and **11d** was examined. A pure sample of **11a** obtained by LC separation was heated with NaOMe in MeOH to effect equilibration. The resultant mixture of **11a** and **11c** was treated with Ph$_3$P=CH$_2$ to give a mixture of **1a** and **1c**. These were separated by HPLC to give pure **1c**, $[\alpha]_D^{20.5}$+93° (MeOH). The overall yield of **1c** from **3** in 9 steps was 4.5%. Its ^{1}H-NMR and ^{13}C-NMR spectral data were identical with those reported for the natural product (see Experimental).[1] However, the sign of the optical rotation was opposite to that of the natural product, $[\alpha]_D$ − 92° (MeOH). As we started from (*R*)-(+)-citronellic acid **2**, our synthetic **1c** possesses (1*R*, 6*S*, 7*S*, 11*R*)-absolute stereochemistry. The antipodal natural product is therefore (1*S*, 6*R*, 7*R*, 11*S*)-biflora-4,10(19),15-triene **1c**. Similarly, equilibration of **11b** with NaOMe in MeOH was followed by the Wittig methylenation to give, after prep GLC separation, impure **1d** containing 21% of **1b**, $[\alpha]_D^{21.5}$ − 61° (MeOH).

In conclusion, four stereoisomers of biflora-4,10(19),15-triene **1a**, **1b**, **1c** and **1d** were synthesized starting from 100% optically pure (*R*)-(+)-citronellic

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†Diterpenoid Total Synthesis-22. Part 21, M. Shiozaki, K. Mori, T. Hiraoka and M. Matsui, *Tetrahedron* **30**, 2647 (1974).

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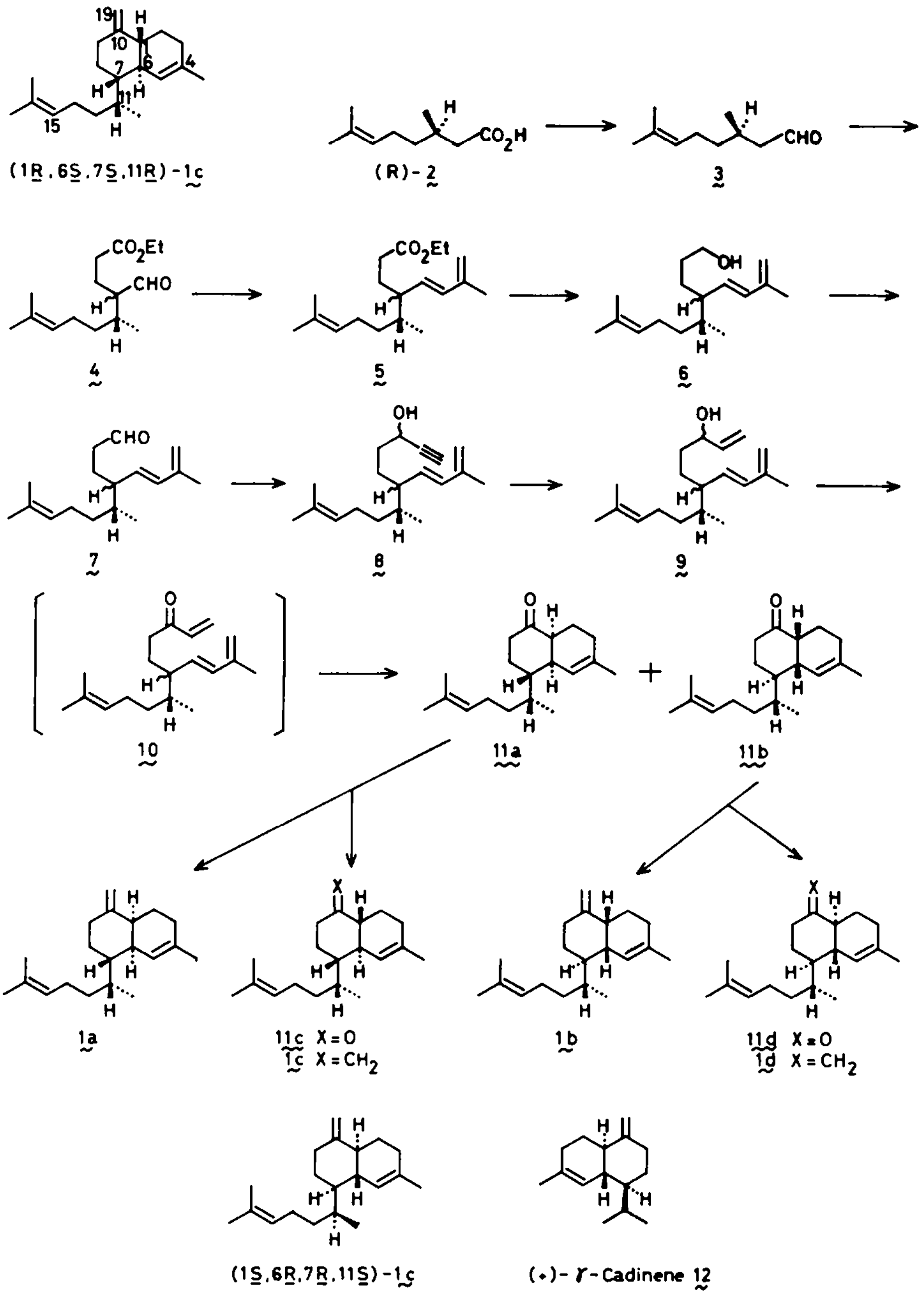

acid **2**. The assignment of (1*S*, 6*R*, 7*R*, 11*S*)-stereochemistry to the natural product isolated from the termite soldiers is of interest from the standpoint of biogenetic consideration. (+)-γ-Cadinene **12** is a sesquiterpene obtainable from higher plants. It is, however, a mirror image of the sesquiterpene part of the present termite diterpene (1*S*, 6*R*, 7*R*, 11*S*)-**1c**. In addition the configuration at C-11 of the natural **1c** is (*S*), while that of citronellol of plant origin is usually (*R*). The biosynthetic pathway in termite seems to generate terpenoids antipodal to those which are usually found in higher plants.

EXPERIMENTAL

All bps are uncorrected. IR spectra were measured as films on a Jasco A-102 spectrometer. NMR spectra were recorded at 60 MHz in $CDCl_3$ with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP-140 polarimeter. GLC analyses were performed on a Jeol JGC-20K or Yanaco GCG-550 F gas chromatographs.

(R)-(+)-*Citronellal* **3**

A soln of (*R*)-**2** (58.9 g) in dry ether (200 ml) was added dropwise during 45 min to a stirred and ice-cooled suspension of LAH (19.3 g) in dry ether (1600 ml) at 11 ~ 17°. The mixture was stirred for 5 h at room temp. Excess LAH was destroyed by the dropwise addition of water (21 ml) during 30 min with stirring and ice-cooling. 15% NaOH aq (62 ml) and water (21 ml) were added and the mixture was filtered. The filter cake was washed with THF (100 ml). The combined filtrate and washings were concentrated *in vacuo* to give a crude oil (69.2 g). This was dissolved in dry CH_2Cl_2 (350 ml) and added dropwise to a stirred and ice-cooled suspension of PCC (111.9 g) and anhyd NaOAc (28.4 g) in dry CH_2Cl_2 (350 ml). The mixture was stirred for 4 h at 10 ~ 30°. It was then diluted with ether (700 ml) and filtered through Florisil (200 g). The Florisil layer was washed with ether (350 ml). The combined filtrate and washings were concentrated *in vacuo*. The residue was distilled to give 34.1 g (63.9%) of **3**, b.p. 53 ~ 60°/2.0 mm, n_D^{25} 1.442; $[\alpha]_D^{26}$ + 17.9° (c=7.17, $CHCl_3$); ν_{max} 2720 (m), 1730 (s) cm^{-1}; δ 0.95 (3H, d, J=6 Hz), 1.61 (3H, s), 1.68 (3H, s), 1.1 ~ 2.4 (7H), 5.08 (1H, t, J=7 Hz), 9.75 (1H, t, J=4 Hz); GLC (Column, 20% PEG 20 M, 2 m × 3 mm at 100°; Carrier gas, N_2, 1.0 kg/cm^2) Rt 20.4 min (94.7%).

Ethyl (4RS, 5R)-(+)-5,9-*dimethyl-4-formyl-8-decenoate* **4**

A soln of **3** (31.0 g) and piperidine (35.6 g) in C_6H_6 (300 ml) was stirred and heated under reflux with continuous removal of water for 3 h. The soln was concentrated *in vacuo* to give 46.4 g of an enamine as an oil. This was dissolved in MeCN (300 ml). Ethyl acrylate (40.0 g) was added to the soln and the mixture was stirred and heated at 80 ~ 81° (inner temp) for 50 h. After cooling, AcOH (10 ml) and water (60 ml) were added and the mixture was heated at 75 ~ 76° (inner temp) for 2 h. After cooling, the mixture was washed with sat brine. The organic layer was concentrated *in vacuo*. The residue was shaken with ether (300 ml) and water (200 ml). The ether layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 38.2 g (75.1%) of **4**, b.p. 121 ~ 127°/0.7–0.9 mm, n_D^{25} 1.455; $[\alpha]_D^{20}$ + 12.9° (c=7.31, $CHCl_3$); ν_{max} 2720 (w), 1735 (s), 1180 (s) cm^{-1}; δ 0.87 (1.5H, d, J=6 Hz), 0.97 (1.5H, d, J=6 Hz), 1.22 (3H, t, J=7 Hz), 1.60 (3H, s), 1.67 (3H, s), 2.19 (2H, t, J=6 Hz), 1.1 ~ 2.5 (8H), 4.06 (2H, q, J=7 Hz), 5.04 (1H, t, J=7 Hz), 9.60 (1H, br. s); GLC (Column, 20% PEG 20M, 2 m × 3 mm at 210°; Carrier gas, N_2, 2.0 kg/cm^2) R_t 9.1 min (99.3% purity). Found: C, 70.46; H, 10.05. Calc for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30%.

Ethyl (4RS, 5R)-(−)-5,9-*dimethyl-4-(3′-methyl-1′,3′-butadienyl)-8-decenoate* **5**

A soln of $NaCH_2SOMe$ was prepared from 50% NaH [8.72 g, washed with n-hexane (50 ml × 3) to remove mineral oil] in dry DMSO (100 ml) by stirring and heating at 80° for 60 min. After cooling, a soln of methallyltriphenylphosphonium chloride (64.2 g) in dry DMSO (300 ml) was added dropwise during 10 min to the stirred soln at 22–30° to yield a red soln of the phosphorane. The mixture was stirred for 15 min at room temp. A soln of **4** (39.4 g) in dry DMSO (50 ml) was added during 15 min to the phosphorane with stirring at 20 ~ 25°. The stirring was continued for 80 min. The mixture was then poured into water (1000 ml) and extracted with n-hexane (500 ml). The hexane soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 26.3 g (58.0%) of **5**, b.p. 120 ~ 136°/0.4 mm, n_D^{23} 1.476; $[\alpha]_D^{24}$ − 13.4° (c=7.03, $CHCl_3$); ν_{max} 1740 (s), 1610 (w), 1160 (s), 970 (m), 885 (m) cm^{-1}; δ 0.85 (1.5H, d, J=6 Hz), 0.87 (1.5H, d, J=6 Hz), 1.21 (3H, t, J=7 Hz), 1.58 (3H, s), 1.66 (3H, s), 1.80 (3H, s), 2.10 (2H, t, J=6 Hz), 1.5 ~ 2.5 (8H), 4.05 (2H, q, J=7 Hz), 4.83 (2H, s), 5.0 ~ 6.2 (3H, m); GLC (Column, 20% PEG 20M, 2 m × 3 mm at 210°; Carrier gas, N_2, 2,0 kg/cm^2) R_t 8.3 min (100% purity). Found: C, 77.80; H, 11.21. Calc for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03%.

(4RS, 5R)-(−)-5,9-*Dimethyl-4-(3′-methyl-1′,3′-butadienyl)-8-decen-1-ol* **6**

A soln of **5** (17.65 g) in dry ether (150 ml) was added dropwise during 35 min to a stirred and ice-cooled suspension of LAH (3.44 g) in dry ether (150 ml) at 3 ~ 10° The stirring was continued for 30 min at room temp. The stirred mixture was then ice-cooled and the excess LAH was destroyed by the addition of water (3.5 ml), 15% NaOH aq (10.5 ml) and water (3.5 ml). The mixture was filtered and the filter cake was washed with THF. The combined filtrate and washings were concentrated *in vacuo*. The residual crude oil (17.71 g) was purified by chromatography over SiO_2 to give 15.0 g (98.9%) of **6**, b.p. 123°/0.5 mm, n_D^{25} 1.489; $[\alpha]_D^{25}$ − 15.0° (c=7.00, $CHCl_3$); ν_{max} 3350 (s), 1640 (w), 1610 (w), 1060 (s), 970 (s), 890 (s) cm^{-1}; δ 0.81 (1.5H, d, J=6 Hz), 0.85 (1.5H, d, J=6 Hz), 1.58 (3H, s), 1.66 (3H, s), 1.1 ~ 2.7 (10H), 3.53 (2H, br. s), 4.81 (2H, s), 5.04 (1H, t, J=7), 5.1 ~ 6.2 (2H, m); GLC (Column, 20% PEG 20M, 2 m × 3 mm at 210°; Carrier gas, N_2, 2.0 kg/cm^2) Rt 13.9 min (99.4% purity). Found: C, 81.30; H, 12.01. Calc for $C_{17}H_{30}O$: C, 81.54; H, 12.08%.

(4RS, 5R)-(−)-5,9-*Dimethyl-4-(3′-methyl-1′,3′-butadienyl)-8-decenal* **7**

DCC (19.8 g) was added during 5 min to a soln of **6** (5.0 g) in C_6H_6 (37 ml) and DMSO (30 ml) containing CF_3CO_2H (1.14 g) and C_5H_5N (1.58 g) at 5 ~ 10°. The mixture was stirred overnight at room temp and then diluted with ether (30 ml). A soln of $HO_2C{-}CO_2H \cdot 2H_2O$ (7.56 g) in MeOH (12 ml) was added dropwise during 20 min at 14 ~ 18°. The mixture was filtered and the filtrate was diluted with ether (400 ml). The ether soln was washed with $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 to give 4.41 g (88.8%) of **7**, b.p. 118°/1.1 mm, $n_D^{25.5}$ 1.484; $[\alpha]_D^{25.5}$ − 15.4° (c=6.85, $CHCl_3$); ν_{max} 2710 (m), 1725 (s), 1640 (w), 1610 (m), 970 (s), 890 (s) cm^{-1}; δ 0.83 (1.5H, d, J=6 Hz), 0.87 (1.5H, d, J=6 Hz), 1.57 (3H, s), 1.65 (3H, s), 1.78 (3H, s), 1.1 ~ 2.2 (8H), 2.35 (2H, t, J=7 Hz), 4.80 (2H, s), 5.01 (1H, t, J=7 Hz), 5.1 ~ 6.2 (2H, m), 9.65 (1H, br. s); GLC (Column, 20% PEG 20M, 2 m × 3 mm at 210°; Carrier gas, N_2, 2.0 kg/cm^2) Rt 6.4 min (99.1% purity). Found: C, 81.80; H, 11.39. Calc for $C_{17}H_{28}O$: C, 82.20; H, 11.36%.

(3RS, 6RS, 7R)-(−)-7,11-*Dimethyl-6-(3′-methyl-1′,3′-butadienyl)-10-dodecen-1-yn-3-ol* **8**

A soln of acetylene gas (> 715 ml) in dry THF (80 ml) was prepared by bubbling C_2H_2 (dried by passing through conc H_2SO_4 and soda lime) into THF at −65°. To this was added during 10 min n-BuLi in n-hexane (1.5N, 27.5 ml) with stirring at −55 ~ 68°. The stirring was continued for 8 min at −68°. A soln of **7** (6.6g) in dry THF (10 ml) was added during 6 min to the mixture at −57 ~ −67°. The mixture was stirred for 20 min at −67°. The cooling bath was then removed. The stirring was continued until the mixture was warmed up to room temp. Then water (14 ml) was added to the mixture. Excess water was removed by the addition of dry K_2CO_3. The mixture was extracted with ether (200 ml × 2). The ether soln was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 to give 5.30g (72.6%) of **8**, b.p. 126 ~ 145°/0.08 ~ 0.11 mm, n_D^{21} 1.496; $[\alpha]_D^{21}$ − 14.1° (c=5.07, $CHCl_3$); ν_{max} 3380 (s), 3320 (s), 1640 (w), 1610 (m), 1020 (s), 965 (s), 880 (s) cm^{-1}; δ 0.83 (1.5H, d, J=6 Hz), 0.87 (1.5H, d, J=6 Hz), 1.60 (3H, s), 1.68 (3H, s), 1.83 (3H, s), 1.1 ~ 2.4 (11H), 2.43 (1H, d, J=2 Hz), 4.32 (1H, br), 4.85 (2H, s), 5.07 (1H, t, J=7 Hz), 5.1 ~ 6.25 (2H, m). Found: C, 83.33; H, 11.12. Calc for $C_{19}H_{30}O$: C, 83.15; H, 11.02%.

(3RS, 6RS, 7R)-(−)-7,11-*Dimethyl-6-(3′-methyl-1′,3′-butadienyl)-1,10-dodecadien-3-ol* **9**

5% Pd–$BaSO_4$ (81 mg) and quinoline (81 mg) were added to a soln of **8** (1.61 g) in MeOH (100 ml). The mixture was stirred under H_2 for 4 h at 20 ~ 25°, filtered and concentrated *in vacuo*. The residue was acidified with 2N HCl (25 ml) and extracted with ether (100 ml). The ether soln was washed with brine, $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 to give 1.40 g (86.5%) of **9**, b.p. 134 ~ 136°/0.08 ~ 0.05 mm, n_D^{21} 1.494; $[\alpha]_D^{21.5}$ − 14.1° (c=1.71, $CHCl_3$); ν_{max} 3380 (s), 1640 (w), 1610 (m), 990 (m), 970 (s), 920 (s), 885 (s) cm^{-1}; δ 0.80 (1.5H, d, J=6 Hz), 0.85 (1.5H, d, J=6 Hz), 1.57 (3H, s), 1.66 (3H, s), 1.79 (3H, s), 1.0 ~ 2.2 (11H), 3.97 (1H, br. s), 4.77 (2H, s), 4.8 ~ 6.2 (6H, m).

Found: C, 82.64; H, 11.89. Calc for $C_{19}H_{32}O$: C, 82.54; H, 11.67%.

(1S, 6S, 7S, 11R)-(+)-19-*Norbiflora-4,15-dien-10-one* **11a** *and* (1R, 6R, 7R, 11R)-(−)-19-*norbiflora-4,15-dien-10-one* **11b**

Jones reagent (8N in CrO_3, 3.0 ml) was added during 1 min to a soln of **9** (1.39 g) in acetone (30 ml) with stirring and ice-cooling. After stirring for 10 min, MeOH (1 ml) was added to destroy the excess CrO_3. The mixture was diluted with water (50 ml) and extracted with ether (100 ml × 2). The ether soln was washed with $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 to give 1.02 g (73.6%) of a mixture of **11a** and **11b**. This could not be analyzed by GLC but its separation was possible by medium pressure LC employing a Merck Lobar column. Elution with C_6H_6–n-hexane (1:1) yielded **11b**, **11b** + **11a** and **11a** in a ratio of 15:70:15. **11a** showed the following properties: b.p. 152 ~ 160°/0.4 mm, $[\alpha]_D^{21.5}$ + 26.1° (c=0.145, $CHCl_3$); ν_{max} 1710 (s), 1670 (w) cm^{-1}; δ 0.86 (3H, d, J=6 Hz), 1.60 (3H, s), 1.66 (6H, s), 1.1 ~ 2.6 (16H, m), 5.07 (1H, t, J=7 Hz), 5.33 (1H, br. s); GLC (Column, 20% PEG 20M, 2 m × 3 mm at 220°; Carrier gas, N_2, 1.5 kg/cm^2) Rt 25.1 min (100% purity). Found: C, 82.65; H, 10.93. Calc for $C_{19}H_{30}O$: C, 83.15; H, 11.02%. **11b** showed the following properties: b.p. 152 ~ 158°/0.4 mm, $[\alpha]_D^{21.5}$ − 8.6° (c=0.20, $CHCl_3$); ν_{max} 1710 (s), 1670 (w) cm^{-1}; δ 0.99 (3H, d, J=6 Hz), 1.62 (6H, s), 1.68 (3H, s), 1.1 ~ 2.6 (16H, m), 5.11 (1H, t, J=7 Hz), 5.31 (1H, br. s); GLC (Column 20% PEG 20M, 2 m × 3 mm at 220°; Carrier gas, N_2, 1.5 kg/cm^2) Rt 23.6 min (99.9% purity). Found: C, 82.60; H, 11.00. Calc for $C_{19}H_{30}O$: C, 83.15; H, 11.02%. These two ketones were distinguishable by NMR comparison.

(1S, 6S, 7S, 11R)-(−)-*Biflora-4,10(19),15-triene* **1a** and (1R, 6R, 7R, 11R)-(+)-*biflora-4,10(19),15-triene* **1b**

A soln of n-BuLi in n-hexane (1.48N, 11.5 ml) was added dropwise during 7 min to a suspension of Ph_3PMeBr (6.33g) in dry THF (20 ml) with stirring and ice-cooling at 4 ~ 11°. The stirring was continued for 30 min under ice-cooling. A portion (7 ml) of this ylid soln was added to a stirred and ice-cooled soln of a mixture of **11a** and **11b** (550 mg) in dry THF (15 ml) at 5 ~ 7°. The mixture was stirred for 30 min at 21°. The reaction was quenched by the addition of water (2 ml). The mixture was concentrated *in vacuo*. The residue was dissolved in n-hexane. The hexane soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by prep TLC (n-hexane, R_f 0.45) to give 330 mg (60.6%) of a mixture of **1a** and **1b**. This was further purified by prep GLC (Hitachi K-53; Column, 10% PEG 20M, 2 m × 8 mm at 190°; Carrier gas, N_2, 1.0 kg/cm^2). **1a** showed the following properties: $[\alpha]_D^{17}$ − 26° (c=0.17, MeOH); ν_{max} 3080 (w), 2970 (s), 2925 (s), 2860 (s), 1665 (w), 1645 (m), 1445 (m), 1375 (m), 880 (s) cm^{-1}; ^{1}H-NMR δ (400 MHz, $CDCl_3$) 0.78 (3H, d, J=7 Hz), 0.96 ~ 1.07 (1H, m), 1.20 ~ 1.31 (2H, m), 1.38 ~ 1.45 (1H, m), 1.47 ~ 1.55 (1H, m), 1.58 ~ 1.64 (1H, m), 1.60 (3H, s), 1.67 (6H, s), 1.74 ~ 1.81 (1H, m), 1.86 ~ 2.21 (8H, m), 2.35 ~ 2.41 (1H, m), 4.58 (1H, t, J=2 Hz), 4.65 (1H, br. s), 5.09 (1H, tt, J_1=2, J_2=14 Hz), 5.53 (1H, d, J=5 Hz); ^{13}C-NMR δ (25 MHz, $CDCl_3$) 13.5, 17.6, 23.9, 25.4, 25.7, 26.2, 26.3, 30.9, 31.5, 31.7, 36.0, 39.4, 42.9, 43.7, 106.5, 124.4, 125.9, 130.9, 133.7, 154.3; GLC (Column, 20% PEG 20M, 2 m × 3 mm at 200°; Carrier gas, N_2, 1.0 kg/cm^2) Rt 17.4 min (100% purity); MS: *m/z* 272.2511 (Calc for $C_{20}H_{22}$: 272.2502). **1b** showed the following properties: $[\alpha]_D^{21}$ + 32° (c=0.11, MeOH); ν_{max} 3080 (w), 2970 (s), 2925 (s), 2860 (s), 1640 (m), 1375 (m), 880 (s) cm^{-1}; ^{1}H-NMR δ (400 MHz, $CDCl_3$) 0.92 (3H, d, J=7 Hz), 0.93 ~ 1.04 (2H, m), 1.88 ~ 1.96 (3H, m), 1.61 (3H, s), 1.66 (3H, s), 1.70 (3H, s), 1.65 ~ 2.20 (10H, m), 2.33 ~ 2.39 (1H, m), 4.58 (1H, t, J=2 Hz), 4.64 (1H, br. s), 5.12 (1H, tt, J_1=2, J_2=14 Hz), 5.51 (1H, d, J=5 Hz); GLC (Column, 20% PEG 20M, 2 m × 3 mm at 200°; Carrier gas, N_2, 1.6 kg/cm^2) Rt 11.9 min (96.8% purity); MS: *m/z* 272.2485; calc for $C_{20}H_{22}$: 272.2502.

Equilibration of **11a** *to a mixture of* **11a** *and* **11c**

A soln of **11a** (100 mg) in 2% NaOMe–MeOH (25 ml) was stirred and heated under reflux for 1.5 h. After cooling, the mixture was acidified with 2N HCl (12 ml) and concentrated *in vacuo*. The residue was diluted with water (100 ml) and extracted with ether (100 ml × 2). The ether soln was dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oil. This was purified by prep TLC ($CHCl_3$) to give 100 mg of a mixture of **11a** and **11c**, $[\alpha]_D^{21.5}$ + 51.4° (c=0.604, $CHCl_3$); GLC (Column, 20% PEG 20M, 2 m × 3 mm at 220°; Carrier gas, N_2, 1.8 kg/cm^2) Rt 23.5 min (43%, **11a**), 27.5 min (57%, **11c**).

(1R, 6S, 7S, 11R)-(+)(*Biflora-4,10(19),15-triene* **1c**

In the same manner as described for the preparation of a mixture of **1a** and **1b**, the Wittig methylenation of an equilibrated mixture of **11a** and **11c** (95 mg) yielded 68 mg (72%) of a mixture of **1a** and **1c**. These were separated by prep HPLC (Shimadzu LC-2; Column, Partisil-5, 25 cm × 4.6 mm; Solvent, n-hexane, 2.0 ml/min; Detector, SPD-1, 217 nm) Rt 10.6 min (**1a**), 14.0 min (**1c**). **1c** showed the following properties: $[\alpha]_D^{20.5}$ + 93° (c=0.20, MeOH); ν_{max} 3080 (w), 2970 (s), 2925 (s), 2860 (s), 1640 (m), 1445 (m), 1375 (m), 880 (s) cm^{-1}; ^{1}H-NMR δ (400 MHz, $CDCl_3$) 0.74 (3H, d, J=7 Hz), 1.08 ~ 1.20 (1H, m), 1.23 ~ 1.35 (3H, m), 1.43 ~ 1.54 (1H, m), 1.61 (3H, s), 1.69 (6H, s), 1.66 ~ 1.79 (3H, m), 1.91 ~ 2.18 (7H, m), 2.35 ~ 2.40 (1H, m), 4.54 (1H, br. s), 4.66 (1H, br. s), 5.12 (1H, tt, J_1=2, J_2=14 Hz), 5.53 (1H, s); ^{13}C-NMR (25 MHz, $CDCl_3$) 13.3, 17.7, 23.9, 25.7, 26.3, 26.9, 30.5, 31.2, 35.9, 36.4, 44.3, 44.9, 45.2, 103.2, 122.4, 124.9, 131.1, 134.7, 153.2; GLC (Column, 20% PEG 20M, 2 m × 3 mm at 200°; Carrier gas, N_2, 1.0 kg/cm^2) Rt 9.3 min (98.7%); MS: *m/z* 272.2525; calc for $C_{20}H_{22}$: 272.2502. The natural **1c** was reported to show the following properties:[1] $[\alpha]_D$ − 92° (c=0.13, MeOH); ^{1}H-NMR δ 0.75 (3H, d, J=7 Hz), 1.10 (1H, s), 1.12 ~ 1.44 (6H, m), 1.62 (3H, br. s), 1.70 (6H, br. s), 1.80 ~ 2.40 (9H, m), 4.57 (1H, s), 4.68 (1H, s), 5.15 (1H, br. t, J=6 Hz), 5.55 (1H, br. s); ^{13}C-NMR δ 13.2, 17.7, 23.9, 25.7, 26.3, 26.8, 30.5, 31.2, 35.9, 36.3, 44.2, 44.8, 45.1, 103.2, 122.4, 124.9, 131.1, 134.7, 153.3.

Equilibration of **11b** *to a mixture of* **11b** *and* **11d**

A soln of **11b** (194 mg) in 2% NaOMe–MeOH (50 ml) was stirred and heated under reflux for 2 h. Subsequent work-up as described for the preparation of **11c** yielded 184 mg (95%) of a mixture of **11b** and **11d**, $[\alpha]_D^{21.5}$ − 31° (c=0.59, $CHCl_3$); GLC (Column, 5% PEG 20M, 2 m × 3 mm at 210°; Carrier gas, N_2, 1.0 kg/cm^2) Rt 10.8 min (50.6%, **11b**), 11.9 min (48.2%, **11d**).

(1S, 6R, 7R, 11R)-(−)-*Biflora-4,10(19),15-triene* **1d**

In the same manner as described for the preparation of a mixture of **1a** and **1b**, the Wittig methylenation of an equilibrated mixture of **11b** and **11d** (175 mg) yielded 131 mg (75.4%) of a mixture of **1b** and **1d**. Separation of these two isomers was effected by prep GLC (Hitachi K-53; Column, 20% PEG 20M, 2 m × 8 mm at 190°; Carrier gas, N_2, 1.0 kg/cm^2) to give **1d** contaminated with **1b** (21%) and a trace amount of **1a** (1%), $[\alpha]_D^{21.5}$ − 61° (c=0.17, MeOH), ν_{max} 3080 (w), 2970 (s), 2925 (s), 2860 (s), 1640 (m), 1445 (m), 1375 (m), 880 (s) cm^{-1}; ^{1}H-NMR δ (60 MHz, $CDCl_3$) 0.92 (3H, d, J=7 Hz), 1.1 ~ 2.3 (16H, m), 1.60 (3H, s), 1.67 (6H, s), 4.55 (1H, s), 4.63 (1H, s), 4.9 ~ 5.25 (1H, m), 5.53 (1H, s); GLC (Column, 5% PEG 20M, 2 m × 3 mm at 200°; Carrier gas, N_2, 1.0 kg/cm^2) Rt 3.5 min (1%, **1a**), 3.8 min (21%, **1b**), 4.7 min (78%, **1d**).

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