Pheromone Synthesis, CC[‡]

Synthesis of (*S*)-9-Methylgermacrene-B, the Male-Produced Sex Pheromone of the Sandfly *Lutzomyia longipalpis* from Lapinha, Brazil, and Its (*R*)-Isomer

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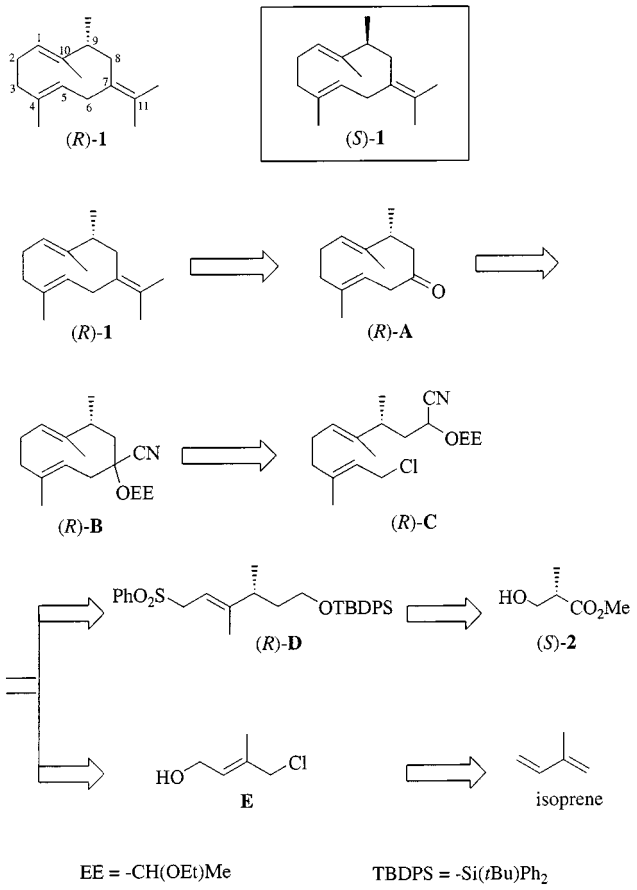
Both the enantiomers of 9-methylgermacrene-B (**1**) were synthesized from the enantiomers of methyl 3-hydroxy-2-methylpropanoate (**2**). The male-produced sex pheromone of the sandfly *Lutzomyia longipalpis* (the vector of the protozoan parasite *Leishmania chagasi*) from Lapinha, Brazil, was identified as (*S*)-**1** by GC comparison.

Introduction

The sandfly *Lutzomyia longipalpis* is the vector of the protozoan parasite *Leishmania chagasi*, the causative agent of visceral leishmainiasis in South and Central America.[1] In 1996 Hamilton et al. proposed 9-methylgermacrene-B (**1**) as the structure of the male-produced sex pheromone of *L. longipalpis* from Lapinha, Brazil.[2] In 1999, (±)-**1** was synthesized by us,[3] and was shown to be bioactive as the pheromone.[4] In continuation of that work, we report herein the synthesis of both the enantiomers of 9-methylgermacrene-B (**1**).

The present synthesis is the enantioselective version of our previous one to yield (±)-**1**.[3] Because there is only a single stereogenic center at C-9 of **1**, methyl (*S*)-3-hydroxy-2-methylpropanoate (**2**) can serve as the commercially available chiral building block for the synthesis of (*R*)-**1** as shown in Scheme 1. According to our published synthesis of (±)-**1**,[3] the immediate precursor to (*R*)-**1** is the ten-membered ring ketone (*R*)-**A**, which is the deprotected form of the ethoxyethyl (*EE*)-protected cyanohydrin (*R*)-**B**. This can be obtained by cyclization of the open-chain precursor (*R*)-**C** according to Takahashi's protocol.[5] The acyclic precursor (*R*)-**C** can be prepared from (*R*)-**D** and **E**, the former of which can be derived from (*S*)-**2**. The chloride **E** is a known compound obtainable from isoprene.[6]

The above plan has been successfully executed as detailed below, and the absolute configuration of the naturally occurring **1** is now established as *S* by its direct GC comparison with the synthetic enantiomers of **1**.



Scheme 1. Structures of the enantiomers of 9-methylgermacrene-B (**1**) and the retrosynthetic analysis of (*R*)-**1**

Results and Discussion

Scheme 2 summarizes the synthesis of the two building blocks **4** and (*R*)-**13**. Isoprene was converted into the chlorohydrin **3** (*E*/*Z* = > 99% as estimated by ^{1}H NMR spectroscopy) in 22% yield (2 steps) according to Ueda and co-workers.[6] The corresponding *tert*-butyldimethylsilyl (TBS) ether **4** served as one of the building blocks. The synthesis of the chiral and nonracemic building block (*R*)-**13** (= **D**) started from commercially available methyl (*S*)-3-hydroxy-2-methylpropanoate (**2**), which was converted into (*R*)-**5** by the method of Kakinuma and co-workers.[7] The free hydroxy group of (*R*)-**5** was protected as its *tert*-butyldiphenylsilyl (TBDPS) ether, and the resulting (*R*)-**6** was treated

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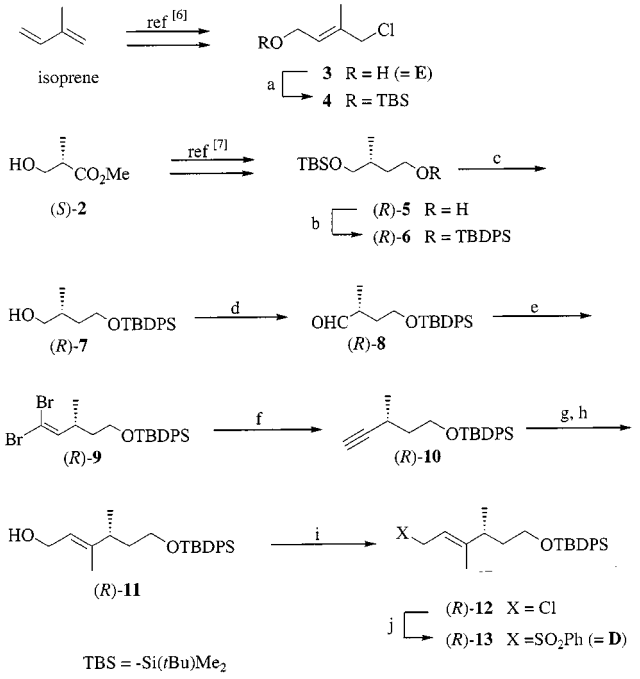
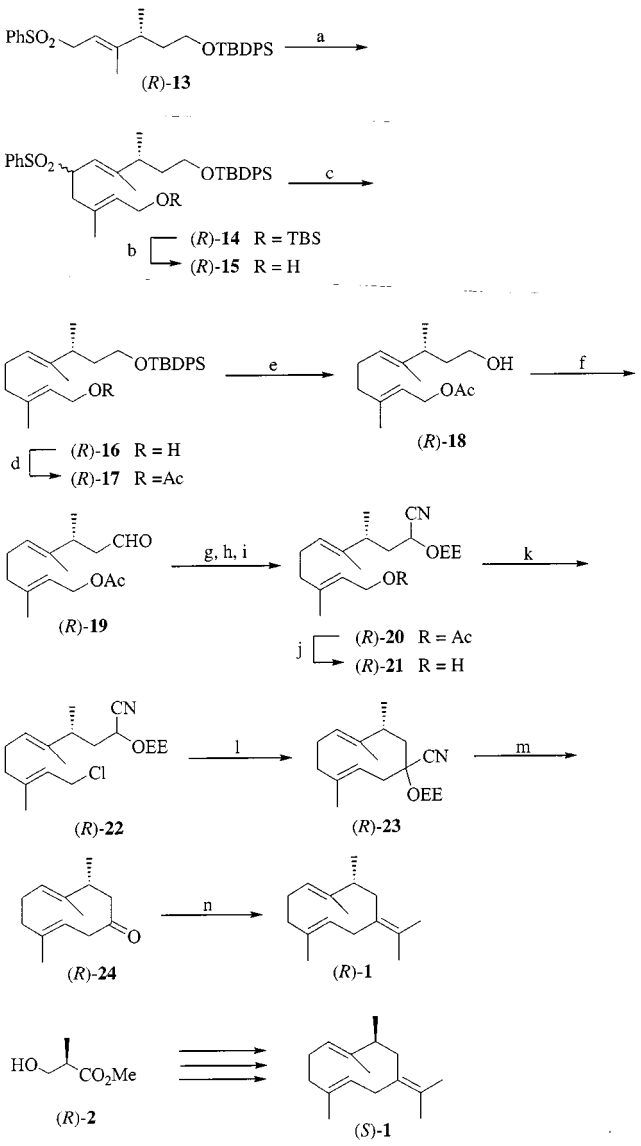
with aqueous acetic acid to remove the TBS protective group to give (*R*)-**7**. Swern oxidation of (*R*)-**7** furnished the aldehyde (*R*)-**8**, which was converted into the alkyne (*R*)-**10** via (*R*)-**9** according to Corey and Fuchs.[8] The alkyne (*R*)-**10** was subjected to the Wipf modification[9] of Negishi's zirconocene-catalyzed carboalumination reaction,[10] followed by quenching with formaldehyde to afford the alcohol (*R*)-**11**. Treatment of the corresponding chloride (*R*)-**12** with sodium phenylsulfinate gave the phenylsulfone (*R*)-**13**, the desired building block **D**. The overall yield of (*R*)-**13** was 16% based on (*S*)-**2** (14 steps).



Scheme 2. Synthesis of the two building blocks **4** and (*R*)-**13**; reagents: (a) TBSCl, imidazole, DMF (quant.); (b) TBDPSCl, imidazole, DMF (89%); (c) AcOH, THF, H_2O (84%); (d) $(COCl)_2$,DMSO, Et_3N, CH_2Cl_2; (e) PPh_3, CBr_4, CH_2Cl_2 [87% based on (*R*)-**7**]; (f) *n*BuLi, Et_2O (98%); (g) Me_3Al, Cp_2ZrCl_2, CH_2Cl_2, H_2O; (h) i) *n*BuLi, hexane; ii) $(CH_2O)_n$, THF (85%); (i) PPh_3, CCl_4; (j) $PhSO_2Na{\cdot}2H_2O$, DMF [76% based on (*R*)-**11**]

Coupling of the two building blocks **4** and (*R*)-**13** and conversion of the resulting product (*R*)-**14** to (*R*)-9-methylgermacrene-B (**1**) are summarized in Scheme 3. Alkylation of the carbanion derived from (*R*)-**13** with **4** yielded (*R*)-**14**, whose TBS protective group was removed with aqueous acetic acid to give (*R*)-**15**. The phenylsulfonyl group of (*R*)-**15** was reductively detached by treatment with lithium triethylhydroborate in the presence of a palladium catalyst[11] to give (*R*)-**16** without any appreciable migration of the adjacent double bond. After acetylation of the hydroxy group of (*R*)-**16**, the TBDPS protective group of the resultant (*R*)-**17** was removed with tetrabutylammonium fluoride to give the diol monoacetate (*R*)-**18**. This was oxidized with Dess–Martin periodinane[12] to furnish (*R*)-**19**. Treatment of (*R*)-**19** with trimethylsilyl cyanide (TMSCN) and potassium cyanide in the presence of 18-crown-6 afforded the corresponding TMS-protected cyanohydrin. Its TMS group was replaced by the EE group by successive treatments with fluoride anion followed by ethyl vinyl ether and *p*-toluenesulfonic acid to provide (*R*)-**20**. The acetyl group of (*R*)-**20** was then removed, and the resulting (*R*)-**21** was converted into the corresponding chloride (*R*)-**22**. Macrocyclization of (*R*)-**22** under the conditions of Takahashi et al.[5] gave the cyclodecadiene (*R*)-**23** in 47% yield. Deprotection of the EE group was followed by base treatment to effect retro-hydrocyanation, yielding the crystalline ketone (*R*)-**24**. Finally, the isopropylidene group was attached to (*R*)-**24** according to the method of Utimoto et al.[13] with samarium and chromium as the metals to yield (*R*)-9-methylgermacrene-B $\{[\alpha]_D^{18} = +61.4\ (CHCl_3)\}$. The overall yield of (*R*)-**1** was 6.94% based on (*R*)-**13** (14 steps) or 1.11% based on (*S*)-**2**



Scheme 3. Synthesis of the enantiomers of 9-methylgermacrene-B (**1**); reagents: (a) *n*BuLi, THF, HMPA, then **4** (88%); (b) AcOH, THF, H_2O (85%); (c) $LiBEt_3H$, $PdCl_2$(dppp), THF (82%); (d) Ac_2O, C_5H_5N. (98%); (e) nBu_4NF, THF (90%); (f) Dess–Martin periodinane, CH_2Cl_2 (85%); (g) TMSCN, KCN-18-crown-6; (h) $BnNMe_3F$, THF, H_2O; (i) $EtOCH{=}CH_2$, TsOH, C_6H_6 (quant.); (j) K_2CO_3, MeOH (89%); (k) MsCl, LiCl, DMF, *s*-collidine (95%); (l) NaHMDS, THF (47%); (m) PPTS, MeOH, then NaOHaq, Et_2O (57%); (n) CBr_2Me_2, Sm, SmI_2, $CrCl_3$, THF (60%)

(28 steps). Similarly (*R*)-**2** afforded (*S*)-**1** {$[\alpha]_D^{20}$ = –61.3 ($CHCl_3$)} in 1.34% overall yield based on (*R*)-**2** (28 steps). HPLC analysis of our synthetic (*R*)- and (*S*)-**1** revealed them to be of ca. 95% *ee*, and they showed antipodal CD spectra (see Experimental Section).

The enantiomers of **1** were sent to Prof. J. A. Pickett′s laboratory in the U. K. for comparison with the natural pheromone. GC comparison on a β-cyclodextrin-derived chiral stationary phase definitively proved the identity of (*S*)-**1** to be the naturally occurring pheromone of the male sandfly *Lutzomyia longipalpis* from Lapinha, Brazil. This comparison, and the bioassay of our synthetic samples, will be reported separately by Prof. Pickett.[4]

In conclusion, the unambiguous synthesis of (*R*)- and (*S*)-9-methylgermacrene-B made it possible to establish the absolute configuration of the sandfly pheromone as *S*.

Experimental Section

General: Boiling points and melting points: Uncorrected values. – IR: Jasco IRA-102. – ^{1}H NMR: Jeol JNM-EX 90A (90 MHz), Jeol JNM-LA 400 (400 MHz), Jeol JNM-LA 500 (500 MHz), (internal standard: TMS at δ_H = 0.00, $CHCl_3$ at δ_H = 7.26 or [D_6]DMSO at δ_H = 2.49). – ^{13}C NMR: Jeol JNM-LA 400 (100 MHz), ($CDCl_3$ at δ_C = 77.0 as an internal standard). – MS: Jeol JMS-SX 102A and Hitachi M-80B. – Optical rotation: Jasco DIP-1000. – M.p.: Yanaco MP-S3. – CD spectrum: Jasco J-725. – CC: Merck Kieselgel 60 Art 1.07734. – TLC: 0.25 mm Merck silica gel plates (60F-254).

(*E*)-4-(*tert*-Butyldimethylsilyloxy)-1-chloro-2-methyl-2-butene (4): To a solution of **3** (3.00 g, 24.9 mmol) in DMF (30 mL) were added imidazole (4.24 g, 62.3 mmol) and TBSCl (4.80 g, 31.8 mmol) at 0 °C and the mixture stirred for 30 min at room temperature. Water was added and the organic phase was separated. The aqueous phase was extracted with diethyl ether. The combined organic phase was washed with water and brine, dried with Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (70 g, hexane/ethyl acetate, 500:1) to give **4** (5.00 g, 97%) as a colorless oil, n_D^{24} = 1.4569. – IR (film): $\tilde{\nu}$ = 1665 cm^{-1} (w, C=C), 1260 (s, Si–CH_3), 1110 (s, Si–O). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.07 [s, 6 H, Si(CH_3)$_2$], 0.90 (s, 9 H, *t*Bu), 1.75 (s, 3 H, 2-CH_3), 4.01 (s, 2 H, 1-H), 4.22 (d, *J* = 6.1 Hz, 2 H, 4-H), 5.66 (tt, *J* = 0.7, 6.1 Hz, 1 H, 3-H). – $C_{11}H_{23}ClOSi$: calcd. 234.1207; found 234.1207 (HRMS).

1-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldiphenylsilyloxy)-2-methylbutane (6). – (a) (*R*)-Isomer: To a solution of (*R*)-**5** (18.2 g, 83.3 mmol) in DMF (200 mL) were added imidazole (14.2 g, 209 mmol) and TBDPSCl (25.0 mL, 91.9 mmol) at 0 °C, and the mixture stirred for 12 h at room temperature. Water was added and the organic phase was separated. The aqueous phase was extracted with hexane. The combined organic phase was washed with water, saturated aq. $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (600 g, hexane/ethyl acetate, 300:1) to give (*R*)-**6** (33.9 g, 89%) as a colorless oil, n_D^{22} = 1.5065. – $[\alpha]_D^{18}$ = +1.48 (*c* = 1.02, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 1590 cm^{-1} (w, aromatic), 1255 (s, Si–CH_3), 1110 (s, Si–O). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.03 [s, 6 H, Si(CH_3)$_2$], 0.82 (d, *J* = 7.0 Hz, 3 H, 2-CH_3), 0.87, 1.05 (each s, 18 H, *t*Bu), 1.15–1.90 (m, 3 H, 2-H, 3-H), 3.39 (d, *J* = 5.8 Hz, 1 H, 1-H_a), 3.41 (d, *J* = 5.8 Hz, 1 H, 1-H_b), 3.70 (t, *J* = 6.8 Hz, 2 H, 4-H), 7.40 (m, 6 H, *o,p*-aromatic-H), 7.70 (m, 4 H, *m*-aromatic-H). – $C_{27}H_{44}O_2Si_2$ (456.82): calcd. C 70.99, H 9.71; found C 70.87, H 9.57.

(b) (*S*)-Isomer: In the same manner as described above, (*S*)-**5** (31.5 g, 114 mmol) gave 65.2 g (99%) of (*S*)-**6**, whose spectral data were identical with those of (*R*)-**6**, n_D^{23} = 1.5085. – $[\alpha]_D^{18}$ = –1.43 (*c* = 1.02, $CHCl_3$). – $C_{27}H_{44}O_2Si_2$ (456.82): calcd. C 70.99, H 9.71; found C 71.14, H 9.58.

4-(*tert*-Butyldiphenylsilyloxy)-2-methyl-1-butanol (7). – (a) (*R*)-Isomer: A solution of (*R*)-**6** (33.5 g, 73.3 mmol) in AcOH/THF/H_2O (3:1:1, 300 mL) was stirred at room temperature for 36 h. The reaction mixture was diluted with diethyl ether and H_2O. The organic phase was separated, and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed with water, saturated aq. $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (400 g, hexane/ethyl acetate, 50:1) to give (*R*)-**7** (21.1 g, 84%) as a colorless oil, n_D^{23} = 1.5388. – $[\alpha]_D^{19}$ = +6.65 (*c* = 1.09, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3360 cm^{-1} (s, O–H), 1590 (m, aromatic), 1115 (s, Si–O). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 7.2 Hz, 3 H, 2-CH_3), 1.05 (s, 9 H, *t*Bu), 1.35–1.95 (m, 3 H, 2-H, 3-H), 2.42 (t, *J* = 5.8 Hz, 1 H, OH), 3.50 (t, *J* = 6.8 Hz, 2 H, 1-H), 3.75 (t, *J* = 6.8 Hz, 1 H, 4-H), 7.40 (m, 6 H, *o,p*-aromatic-H), 7.70 (m, 4 H, *m*-aromatic-H). – $C_{21}H_{30}O_2Si$ (342.55): calcd. C 73.63, H 8.83; found C 73.35, H 8.67.

(b) (*S*)-Isomer: In the same manner as described above, (*S*)-**6** (64.9 g, 142 mmol) gave 42.1 g (86%) of (*S*)-**7**, whose spectral data were identical with those of (*R*)-**7**, n_D^{23} = 1.5409. – $[\alpha]_D^{18}$ = –6.20 (*c* = 1.09, $CHCl_3$). – $C_{21}H_{30}O_2Si$ (342.55): calcd. C 73.63, H 8.83; found C 73.26, H 8.53.

4-(*tert*-Butyldiphenylsilyloxy)-2-methylbutanal (8). – (a) (*R*)-Isomer: To a solution of oxalyl chloride (6.66 mL, 76.3 mmol) in dry dichloromethane (50 mL) was added a solution of dimethyl sulfoxide (10.8 mL,152 mmol) in dry dichloromethane (50 mL) at –60 °C. After the mixture had been stirred for 15 min at this temperature, a solution of (*R*)-**7** (20.1 g, 58.7 mmol) in dry dichloromethane (100 mL) was added at –60 °C. Stirring was continued for 30 min at this temperature, and triethylamine (40.0 mL, 287 mmol) was added to the mixture that was subsequently warmed to 0 °C. The mixture was then poured into water and extracted several times with dichloromethane. The extracts were combined, washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure to give (*R*)-**8** (21.4 g, quant.) as a colorless oil. This was used for the next step without further purification, – IR (film): $\tilde{\nu}$ = 2720 cm^{-1} (m, CHO), 1730 (vs, C=O), 1590 (m, aromatic), 1110 (s, Si–O). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.04 (s, 9 H, *t*Bu), 1.08 (d, *J* = 7.2 Hz, 3 H, 2-CH_3), 1.40–2.20 (m, 2 H, 3-H), 2.40–2.70 (m, 1 H, 2-H), 3.75 (t, *J* = 6.1 Hz, 2 H, 4-H), 7.38 (m, 6 H, *o,p*-aromatic-H), 7.64 (m, 4 H, *m*-aromatic-H), 9.68 (d, *J* = 1.5 Hz, 1 H, CHO).

(b) (*S*)-Isomer: In the same manner as described above, (*S*)-**7** (18.6 g, 54.3 mmol) gave 19.8 g (quant.) of (*S*)-**8**, whose spectral data were identical with those of (*R*)-**8**.

1,1-Dibromo-5-(*tert*-butyldiphenylsilyloxy)-3-methyl-1-pentene (9). – (a) (*R*)-Isomer: To a solution of the crude (*R*)-**8** (21.4 g, ca. 62.8 mmol) in dichloromethane (200 mL) were slowly added triphenylphosphane (65.9 g, 251 mmol) and carbon tetrabromide (98%, 42.5 g, 126 mmol) at 0 °C under argon. The mixture was stirred for 1.5 h at room temperature. Water was added to it at 0 °C, the organic phase was separated, and the aqueous phase was

extracted with dichloromethane. The combined organic phase was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (400 g, hexane/ethyl acetate, 100:1) to give (*R*)-**9** [25.3 g, 87%, based on (*R*)-**7**] as a colorless oil, – $[\alpha]_D^{22}$ = –4.60 (*c* = 1.05, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 1620 cm^{-1} (w, C=C), 1590 (m, aromatic), 1110 (s, Si–O). – ^1H NMR (90 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 7.2 Hz, 3 H, 3-CH_3), 1.06 (s, 9 H, *t*Bu), 1.58 (q, *J* = 6.8 Hz, 2 H, 4-H), 2.56–2.89 (m, 1 H, 3-H), 3.65 (t, *J* = 6.8 Hz, 2 H, 5-H), 6.20 (d, *J* = 10.0 Hz, 1 H, 2-H), 7.40 (m, 6 H, *o,p*-aromatic-H), 7.68 (m, 4 H, *m*-aromatic-H). – $C_{22}H_{28}Br_2OSi$ (496.36): calcd. C 53.24, H 5.69; found C 53.26, H 5.62.

(b) (*S*)-Isomer: In the same manner as described above, (*S*)-**8** (19.8 g) gave 25.1 g [93% based on (*S*)-**7**] of (*S*)-**9**, whose spectral data were identical with those of (*R*)-**9**, – $[\alpha]_D^{20}$ = +4.61 (*c* = 1.10, $CHCl_3$). – $C_{22}H_{28}Br_2OSi$ (496.36): calcd. C 53.24, H 5.69; found C 53.22, H 5.66.

5-(*tert*-Butyldiphenylsilyloxy)-3-methylpentyne (10). – (a) (*R*)-Isomer: To a stirred solution of (*R*)-**9** (24.1 g, 48.6 mmol) in dry diethyl ether (250 mL) was added a solution of *n*-butyllithium (3.02 M in hexane, 40.2 mL, 121 mmol) at –78 °C under argon. After stirring for 1 h at –78 °C and an additional 1 h at 0 °C, water was added to the mixture, and it was stirred for 1 h. The organic phase was then separated, and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (300 g, hexane/ethyl acetate, 200:1) to give (*R*)-**10** (16.1 g, 98%) as a colorless oil, n_D^{24} = 1.5351. – $[\alpha]_D^{22}$ = –27.8 (*c* = 0.99, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3310 cm^{-1} (m, C≡C–H), 2130 (w, C≡C), 1590 (m, aromatic), 1115 (s, Si–O). – ^1H NMR (90 MHz, $CDCl_3$): δ = 1.03 (s, 9 H, *t*Bu), 1.10 (d, *J* = 7.0 Hz, 3 H, 3-CH_3), 1.68 (dq, *J* = 6.7, 7.0 Hz, 2 H, 4-H), 2.00 (d, *J* = 2.6 Hz, 1 H, 1-H), 2.55–2.90 (m, 1 H, 3-H), 3.78 (t, *J* = 6.7 Hz, 1 H, 5-H_a), 3.81 (t, *J* = 7.0 Hz, 1 H, 5-H_b), 7.38 (m, 6 H, *o,p*-aromatic-H), 7.68 (m, 4 H, *m*-aromatic-H). – $C_{22}H_{28}OSi$ (336.55): calcd. C 78.52, H 8.39; found C 78.19, H 8.67.

(b) (*S*)-Isomer: In the same manner as described above, (*S*)-**9** (4.23 g, 8.52 mmol) gave 2.81 g (98%) of (*S*)-**10**, whose spectral data were identical with those of (*R*)-**10**, n_D^{23} = 1.5356. – $[\alpha]_D^{20}$ = +28.5 (*c* = 1.05, $CHCl_3$). – $C_{22}H_{28}OSi$ (336.55): calcd. C 78.52, H 8.39; found C 78.20, H 8.50.

(*E*)-6-(*tert*-Butyldiphenylsilyloxy)-3,4-dimethyl-2-hexen-1-ol (11). – (a) (*R*)-Isomer: To a solution of trimethylaluminum (1.01 M in hexane, 220 mL, 222 mmol) and bis(cyclopentadienyl)zirconium dichloride (98%, 4.38 g, 14.7 mmol) in dry dichloromethane (100 mL) was slowly added water (2.00 mL, 111 mmol) at –23 °C with vigorous stirring under argon. After the mixture had been stirred for 30 min at this temperature, a solution of (*R*)-**10** (24.7 g, 74.0 mmol) in dry dichloromethane (200 mL) was added. The mixture was stirred for 2 h at –23 °C and concentrated under reduced pressure. The residue was extracted with dry hexane, and the extract was transferred into another flask under argon via a double-tipped needle. To this was added *n*-butyllithium (2.52 M in hexane, 29.4 mL, 74.1 mmol). THF (100 mL) was then added to dissolve the precipitate, and the resulting solution was added to paraformaldehyde (5.1 g, 170 mmol) under argon. This reaction mixture was stirred for 18 h at room temperature, and quenched with 1 M aq. HCl. The organic phase was separated and the aqueous phase extracted with diethyl ether. The combined organic phase was washed with water, saturated aq. $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (800 g, hexane/ethyl acetate, 200:1) to give (*R*)-**11** (23.8 g, 85%) as a colorless oil, n_D^{26} = 1.5402. – $[\alpha]_D^{18}$ = +3.05 (*c* = 1.03, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3340 cm^{-1} (s, O–H), 1665 (m, C=C), 1590 (m, aromatic), 1115 (s, Si–O). – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 7.0 Hz, 3 H, 4-CH_3), 1.04 (s, 9 H, *t*Bu), 1.25 (br s, 1 H, OH), 1.52 (ddq, *J* = 1.2, 7.0, 14.0 Hz, 1 H, 5-H_a), 1.54 (s, 3 H, 3-CH_3), 1.65 (ddq, *J* = 1.2, 7.0, 14.0 Hz, 1 H, 5-H_b), 2.34 (sextet, *J* = 7.0 Hz, 1 H, 4-H), 3.60 (dt, *J* = 1.8, 7.0 Hz, 2 H, 6-H), 4.10 (d, *J* = 6.8 Hz, 2 H, 1-H), 5.37 (dt, *J* = 1.2, 6.8 Hz, 1 H, 2-H), 7.36 (m, 6 H, *o,p*-aromatic-H), 7.66 (m, 4 H, *m*-aromatic-H). – $C_{24}H_{34}O_2Si$ (382.62): calcd. C 75.34, H 8.96; found C 75.61, H 8.80.

(b) (*S*)-Isomer: In the same manner as described above, (*S*)-**10** (11.7 g, 34.8 mmol) gave 10.6 g (80%) of (*S*)-**11**, whose spectral data were identical with those of (*R*)-**11**, n_D^{20} = 1.5408. – $[\alpha]_D^{18}$ = –3.22 (*c* = 1.10, $CHCl_3$). – $C_{24}H_{34}O_2Si$ (382.62): calcd. C 75.34, H 8.96; found C 75.43, H 8.87.

(*E*)-6-(*tert*-Butyldiphenylsilyloxy)-1-chloro-3,4-dimethyl-2-hexene (12). – (a) (*R*)-Isomer: To a solution of (*R*)-**11** (10.9 g, 28.5 mmol) in carbon tetrachloride (50 mL) was added triphenylphosphane (9.7 g, 37.0 mmol). After stirring for 6 h under reflux, the resulting mixture was cooled to room temperature, then diluted with cold pentane, and filtered through Celite. The filtrate was concentrated under reduced pressure to give (*R*)-**12** (12.3 g quant.) as a colorless oil. The obtained oil was used for the next step without further purification, – IR (film): $\tilde{\nu}$ = 1670 cm^{-1} (m, C=C), 1600 (m, aromatic), 1110 (s, Si–O). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 7.2 Hz, 3 H, 4-CH_3), 1.03 (s, 9 H, *t*Bu), 1.60 (s, 3 H, 3-CH_3), 1.45–1.75 (m, 2 H, 5-H), 2.40 (sextet, *J* = 7.2 Hz, 1 H, 4-H), 3.60 (t, *J* = 6.8 Hz, 2 H, 6-H), 4.05 (d, *J* = 7.2 Hz, 2 H, 1-H), 5.42 (br t, *J* = 7.2 Hz, 1 H, 2-H), 7.38 (m, 6 H, *o,p*-aromatic-H), 7.65 (m, 4 H, *m*-aromatic-H).

(b) (*S*)-Isomer: In the same manner as described above, (*S*)-**11** (12.6 g, 32.9 mmol) gave 16.6 g (quant.) of (*S*)-**12**, whose spectral data were identical with those of (*R*)-**12**.

(*E*)-6-(*tert*-Butyldiphenylsilyloxy)-3,4-dimethyl-1-phenylsulfonyl-2-hexene (13). – (a) (*R*)-Isomer: To a solution of the crude (*R*)-**12** (12.3 g, ca. 30.7 mmol) in DMF (100 mL) was added sodium benzenesulfinate dihydrate (8.50 g, 42.5 mmol). The mixture was stirred for 15 h at room temperature, then poured into water and extracted with ethyl acetate. The extracts and the organic layer were combined and washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (300 g, hexane/ethyl acetate, 40:1) to give (*R*)-**13** [11.0 g, 76% based on (*R*)-**11**] as a colorless oil, – $[\alpha]_D^{18}$ = –9.38 (*c* = 1.15, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 1665 cm^{-1} (m, C=C), 1595 (m, aromatic), 1310 (s, SO_2), 1150 (s, SO_2), 1110 (s, Si–O). – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 7.0 Hz, 3 H, 4-CH_3), 1.03 (s, 9 H, *t*Bu), 1.14 (s, 3 H, 3-CH_3), 1.43 (dq, *J* = 7.0, 14.0 Hz, 1 H, 5-H_a), 1.53 (dq, *J* = 7.0, 14.0 Hz, 1 H, 5-H_b), 2.31 (sextet, *J* = 7.0 Hz, 1 H, 4-H), 3.53 (dt, *J* = 7.0, 10.4 Hz, 1 H, 6-H_a), 3.54 (dt, *J* = 7.0, 10.4 Hz, 1 H, 6-H_b), 3.73 (dd, *J* = 7.8, 14.3 Hz, 1 H, 1-H_a), 3.77 (dd, *J* = 7.8, 14.3 Hz, 1 H, 1-H_b), 5.15 (t, *J* = 7.8 Hz, 1 H, 2-H), 7.36–7.48 (m, 8 H, Si-*o,p*-aromatic-H, *S*-*o*-aromatic-H), 7.57 (m, 1 H, *S*-*p*-aromatic-H), 7.64 (m, 4 H, Si-*m*-aromatic-H), 7.82 (m, 2 H, *S*-*m*-aromatic-H). – $C_{30}H_{38}O_3SSi$ (506.78): calcd. C 71.10, H 7.56; found C 71.18, H 7.41.

(b) (*S*)-Isomer: In the same manner as described above, (*S*)-**12** (16.6 g) gave 14.0 g [84% based on (*S*)-**11**] of (*S*)-**13**, whose spectral data were identical with those of (*R*)-**13**, – $[\alpha]_D^{20}$ = +8.81 (*c* = 1.02,

$CHCl_3$). – $C_{30}H_{38}O_3SSi$ (506.78): calcd. C 71.10, H 7.56; found C 70.92, H 7.31.

(2*E*,6*E*)-1-(*tert*-Butyldimethylsilyloxy)-10-(*tert*-butyldiphenylsilyloxy)-3,7,8-trimethyl-5-phenylsulfonyldeca-2,6-diene (14). – (a) (8*R*)-Isomer: To a solution of (*R*)-**13** (24.1 g, 47.6 mmol) in dry THF (250 mL) and HMPA (125 mL) was added a solution of *n*-butyllithium (1.57 M in hexane, 60.6 mL, 95.1 mmol) at –50 °C under argon, and the mixture was stirred at –50 °C for 30 min. Then a solution of **4** (12.5 g, 60.5 mmol) in dry THF (100 mL) was added dropwise, and stirring was maintained for 18 h at 4 °C. After the addition of water, the mixture was neutralized with acetic acid, and extracted with diethyl ether. The extracts and the organic layer were combined and washed with water, saturated aq. $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (500 g, hexane/ethyl acetate, 300:1) to give (*R*)-**14** (29.5 g, 88%) as a colorless oil, $[\alpha]_D^{18} = -8.63$ (*c* = 1.07, $CHCl_3$). – IR (film): $\tilde{\nu} = 1665\ cm^{-1}$ (m, C=C), 1590 (m, aromatic), 1305 (s, SO_2), 1255 (s, Si–CH_3), 1150 (s, SO_2), 1110 (s, Si–O). – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.01 [s, 6 H, $Si(CH_3)_2$], 0.78, 0.82 (each d, *J* = 7.0 Hz, 3 H, 8-CH_3), 0.86, 1.01, 1.03 (each s, 18 H, *t*Bu), 1.04, 1.10 (each s, 3 H, 7-CH_3), 1.30–1.37 (m, 1 H, 9-H_a), 1.42–1.52 (m, 1 H, 9-H_b), 1.48, 1.52 (each s, 3 H, 3-CH_3), 2.19–2.31 (m, 2 H, 4-H_a, 8-H), 2.90 (m, 1 H, 4-H_b), 3.45–3.55 (m, 2 H, 10-H), 3.82–4.12 (m, 3 H, 1-H, 5-H), 4.88, 4.92 (each d, *J* = 12.5 Hz, 1 H, 6-H), 5.26 (t, *J* = 7.2 Hz, 1 H, 2-H), 7.35–7.50 (m, 8 H, Si-*o,p*-aromatic-H, *S*-*o*-aromatic-H), 7.55 (m, 1 H, *S*-*p*-aromatic-H), 7.64 (m, 4 H, Si-*m*-aromatic-H), 7.80 (m, 2 H, *S*-*m*-aromatic-H). – $C_{41}H_{60}O_4SSi_2$ (705.16): calcd. C 69.84, H 8.58; found C 69.98, H 8.17.

(b) (8*S*)-Isomer: In the same manner as described above, (*S*)-**13** (693 mg, 1.37 mmol) gave 837 mg (87%) of (*S*)-**14**, whose spectral data were identical with those of (*R*)-**14**, – $[\alpha]_D^{27} = +8.00$ (*c* = 1.13, $CHCl_3$). – $C_{41}H_{60}O_4SSi_2$ (705.16): calcd. C 69.84, H 8.58; found C 69.81, H 8.24.

(2*E*,6*E*)-10-(*tert*-Butyldiphenylsilyloxy)-3,7,8-trimethyl-5-phenylsulfonyldeca-2,6-dien-1-ol (15). – (a) (8*R*)-Isomer: A solution of (*R*)-**14** (8.92 g, 12.6 mmol) in AcOH/THF/H_2O (3:1:1, 100 mL) was stirred at room temperature for 24 h. The mixture was diluted with diethyl ether and H_2O, the organic phase was separated, and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed with water, saturated aq. $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (150 g, hexane/ethyl acetate, 10:1) to give (*R*)-**15** (6.34 g, 85%) as a colorless oil, – $[\alpha]_D^{27} = -7.33$ (*c* = 1.07, $CHCl_3$). – IR (film): $\tilde{\nu} = 3530\ cm^{-1}$ (s, O–H), 1660 (m, C=C), 1590 (m, aromatic), 1305 (s, SO_2), 1145 (s, SO_2), 1110 (s, C–O). – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.76, 0.82 (each d, *J* = 7.0 Hz, 3 H, 8-CH_3), 0.97, 1.09 (each s, 3 H, 7-CH_3), 1.02, 1.04 (each s, 9 H, *t*Bu), 1.32–1.40 (m, 1 H, 9-H_a), 1.42–1.52 (m, 1 H, 9-H_b), 1.47, 1.56 (each s, 3 H, 3-CH_3), 2.20 (sextet, *J* = 7.0 Hz, 1 H, 8-H), 2.29 (dd, *J* = 11.3, 13.4 Hz, 1 H, 4-H_a), 2.91 (m, 1 H, 4-H_b), 3.40–3.54 (m, 2 H, 10-H), 3.81–3.93 (m, 2 H, 1-H_a, 5-H), 3.93–4.06 (m, 1 H, 1-H_b), 4.88, (m, 1 H, 6-H), 5.29, 5.34 (each t, *J* = 6.7 Hz, 1 H, 2-H), 7.35–7.52 (m, 9 H, Si-*o,p*-aromatic-H, *S*-*o,p*-aromatic-H), 7.52–7.70 (m, 4 H, Si-*m*-aromatic-H), 7.81 (m, 2 H, *S*-*m*-aromatic-H). – $C_{35}H_{46}NaO_4SSi$: calcd. 613.2784; found 613.2770 (HRMS).

(b) (8*S*)-Isomer: In the same manner as described above, (*S*)-**14** (24.7 g, 35.0 mmol) gave 16.7 g (81%) of (*S*)-**15**, whose spectral data were identical with those of (*R*)-**15**, – $[\alpha]_D^{20} = +7.67$ (*c* = 1.01, $CHCl_3$). – $C_{35}H_{46}NaO_4SSi$: calcd. 613.2784; found 613.2798 (HRMS).

(2*E*,6*E*)-10-(*tert*-Butyldiphenylsilyloxy)-3,7,8-trimethyldeca-2,6-dien-1-ol (16). – (a) (*R*)-Isomer: To a solution of (*R*)-**15** (5.74 g, 9.71 mmol) and palladium chloride-1,3-bis(diphenylphosphano)-propane complex (767 mg, 1.30 mmol) in dry THF (100 mL) was added a solution of lithium triethylhydroborate (1.0 M in THF, 29.0 mL, 29.0 mmol) at 0 °C under argon, and the mixture was stirred at 4 °C for 6 h. Then the mixture was diluted with 10% NaCN aqueous solution and extracted with diethyl ether. The extracts and the organic layer were combined, washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (80 g, hexane/ethyl acetate, 40:1) to give (*R*)-**16** (3.57 g, 82%) as a colorless oil, – $[\alpha]_D^{22} = +0.628$ (*c* = 1.00, $CHCl_3$). – IR (film): $\tilde{\nu} = 3345\ cm^{-1}$ (m, O–H), 1670 (m, C=C), 1590 (m, aromatic), 1110 (s, Si–O). – ^1H NMR (500 MHz, [D_6]DMSO): δ = 0.90 (d, *J* = 7.0 Hz, 3 H, 8-CH_3), 0.97 (s, 9 H, *t*Bu), 1.40 (s, 3 H, 7-CH_3), 1.48 (dq, *J* = 14.0, 7.0 Hz, 1 H, 9-H_a), 1.51–1.58 (m, 1 H, 9-H_b), 1.52 (s, 3 H, 3-CH_3), 1.84 (t, *J*= 7.0 Hz, 2 H, 4-H), 1.98 (q, *J* = 7.0 Hz, 2 H, 5-H), 2.25 (sextet, *J* = 7.0 Hz, 1 H, 8-H), 3.52 (dt, *J* = 7.0, 10.1 Hz, 1 H, 10-H_a), 3.56 (dt, *J* = 7.0, 10.1 Hz, 1 H, 10-H_b), 3.89 (t, *J* = 5.2 Hz, 2 H, 1-H), 4.39 (t, *J* = 5.2 Hz, 1 H, OH), 5.06 (t, *J* = 7.0 Hz, 1 H, 6-H), 5.21 (dt, *J* = 1.2, 5.2 Hz, 1 H, 2-H), 7.44 (m, 6 H, *o,p*-aromatic-H), 7.59 (m, 4 H, *m*-aromatic-H). – $C_{29}H_{42}O_2Si$ (450.74): calcd. C 77.28, H 9.39; found C 77.10, H 9.43.

(b) (*S*)-Isomer: In the same manner as described above, (*S*)-**15** (16.2 g, 27.4 mmol) gave 10.0 g (81%) of (*S*)-**16**, whose spectral data were identical with those of (*R*)-**16**, – $[\alpha]_D^{24} = -0.453$ (*c* = 1.06, $CHCl_3$). – $C_{29}H_{42}O_2Si$ (450.74): calcd. C 77.28, H 9.39; found C 77.61, H 9.45.

(2*E*,6*E*)-1-Acetoxy-10-(*tert*-butyldiphenylsilyloxy)-3,7,8-trimethyldeca-2,6-diene (17). – (a) (*R*)-Isomer: To a solution of (*R*)-**16** (10.1 g, 22.4 mmol) in pyridine (100 mL) was added acetic anhydride (10.6 mL, 112 mmol). The mixture was stirred for 20 h at room temperature, then poured into water, and extracted with diethyl ether. The extracts and the organic layer were combined, washed with water, saturated aq. $CuSO_4$, water, saturated aq. $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (200 g, hexane/ethyl acetate, 100:1) to give (*R*)-**17** (10.8 g, 98%) as a colorless oil, $n_D^{24} = 1.5295$. – $[\alpha]_D^{22} = +0.231$ (*c* = 1.09, $CHCl_3$). – IR (film): $\tilde{\nu} = 1745\ cm^{-1}$ (vs, C=O), 1670 (w, C=C), 1590 (w, aromatic), 1240 (s, OAc), 1115 (s, Si–O). – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 7.0 Hz, 3 H, 8-CH_3), 1.05 (s, 9 H, *t*Bu), 1.46 (s, 3 H, 7-CH_3), 1.52 (dq, *J* = 14.0, 7.0 Hz, 1 H, 9-H_a), 1.62 (dq, *J* = 14.0, 7.0 Hz, 1 H, 9-H_b), 1.69 (s, 3 H, 3-CH_3), 2.00 (t, *J*= 7.0 Hz, 2 H, 4-H), 2.05 (s, 3 H, Ac), 2.07 (dt, *J* = 6.7, 7.0 Hz, 2 H, 5-H), 2.28 (sextet, *J* = 7.0 Hz, 1 H, 8-H), 3.57 (dt, *J* = 7.0, 10.1 Hz, 1 H, 10-H_a), 3.60 (dt, *J* = 7.0, 10.1 Hz, 1 H, 10-H_b), 4.57 (d, *J* = 7.0 Hz, 2 H, 1-H), 5.08 (t, *J* = 6.7 Hz, 1 H, 6-H), 5.31 (t, *J* = 7.0 Hz, 1 H, 2-H), 7.35 (m, 6 H, *o,p*-aromatic-H), 7.66 (m, 4 H, *m*-aromatic-H). – $C_{31}H_{44}O_3Si$ (492.77): calcd. C 75.56, H 9.00; found C 75.35, H 8.73.

(b) (*S*)-Isomer: In the same manner as described above, (*S*)-**16** (9.18 g, 20.4 mmol) gave 9.52 g (95%) of (*S*)-**17**, whose spectral data were identical with those of (*R*)-**17**, $n_D^{25} = 1.5287$. – $[\alpha]_D^{26} = -0.375$ (*c* = 1.10, $CHCl_3$). – $C_{31}H_{44}O_3Si$ (492.77): calcd. C 75.56, H 9.00; found C 75.97, H 9.07.

(4*E*,8*E*)-10-Acetoxy-3,4,8-trimethyldeca-4,8-dien-1-ol (18). – (a) (*R*)-Isomer: To a solution of (*R*)-**17** (3.10 g, 6.29 mmol) in THF (30 mL) was added a solution of tetrabutylammonium fluoride (1.0 M in THF, 9.5 mL, 9.5 mmol). The mixture was stirred for 2 h at room temperature, then poured into water, and extracted with di-

ethyl ether. The extracts and the organic layer were combined, washed with water, saturated aq. $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (30 g, hexane/ethyl acetate, 20:1) to give (*R*)-**18** (1.44 g, 90%) as a colorless oil, n_D^{23} = 1.4790. – $[\alpha]_D^{23}$ = +2.65 (*c* = 1.02, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3450 cm^{-1} (s, O–H), 1740 (vs, C=O), 1670 (w, C=C), 1240 (s, OAc). – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 7.0 Hz, 3 H, 3-CH_3), 1.44 (br s, 1 H, OH), 1.52 (s, 3 H, 4-CH_3), 1.48–1.65 (m, 2 H, 2-H), 1.69 (s, 3 H, 8-CH_3), 2.04 (s, 3 H, Ac), 2.06 (t, *J*= 7.3 Hz, 2 H, 7-H), 2.10 (q, *J*= 7.3 Hz, 1 H, 6-H_a), 2.13 (q, *J*= 7.3 Hz, 1 H, 6-H_b), 2.26 (m, 1 H, 3-H), 3.56 (br t, *J* = 4.3 Hz, 2 H, 1-H), 4.58 (d, *J* = 7.0 Hz, 2 H, 10-H), 5.15 (t, *J* = 7.3 Hz, 1 H, 5-H), 5.31 (tt, *J* = 1.1, 7.0 Hz, 1 H, 9-H). – $C_{15}H_{26}O_3$ (254.37): calcd. C 70.83, H 10.30; found C 70.44, H 10.67.

(b) (*S*)-Isomer: In the same manner as described above, (*S*)-**17** (9.20 g, 18.7 mmol) gave 3.97 g (83%) of (*S*)-**18**, whose spectral data were identical with those of (*R*)-**18**, n_D^{23} = 1.4781. – $[\alpha]_D^{18}$ = –2.72 (*c* = 1.10, $CHCl_3$). – $C_{15}H_{26}O_3$ (254.37): calcd. C 70.83, H 10.30; found C 70.49, H 10.72.

(4*E*,8*E*)-10-Acetoxy-3,4,8-trimethyldeca-4,8-dienal (19). – (a) (*R*)-Isomer: To a stirred suspension of Dess–Martin periodinane (10.0 g, 23.6 mmol) in dry dichloromethane (200 mL) was added a solution of (*R*)-**18** (4.00 g, 15.7 mmol) in dry dichloromethane (50 mL). The reaction mixture was stirred for 2 h at room temperature, then poured into saturated aq. $Na_2S_2O_3$-$NaHCO_3$ (400 mL), and extracted with diethyl ether. The extracts and the organic layer were combined and washed with water, saturated aq. $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (60 g, hexane/ethyl acetate, 40:1) to give (*R*)-**19** (3.37 g, 85%) as a colorless oil, n_D^{24} = 1.4738. – $[\alpha]_D^{23}$ = –1.74 (*c* = 1.09, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 2740 cm^{-1} (m, CHO), 1740 (s, C=O), 1730 (s, C=O). – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 7.1 Hz, 3 H, 3-CH_3), 1.56 (s, 3 H, 4-CH_3), 1.67 (s, 3 H, 8-CH_3), 2.04 (s, 3 H, Ac), 2.05 (m, 2 H, 7-H), 2.10 (m, 2 H, 6-H), 2.31 (ddd, *J* = 2.4, 7.1, 16.0 Hz, 1 H, 2-H_a), 2.45 (ddd, *J* = 2.4, 7.6, 16.0 Hz, 1 H, 2-H_b), 2.70 (sextet, *J* = 7.1 Hz, 2 H, 3-H), 4.57 (d, *J* = 7.1 Hz, 2 H, 10-H), 5.17 (t, *J* = 6.8 Hz, 1 H, 5-H), 5.31 (qt, *J* = 0.7, 7.1 Hz, 1 H, 9-H), 9.65 (t, *J* = 2.5 Hz, 1 H, CHO). – $C_{15}H_{24}O_3$ (252.35): calcd. C 71.39, H 9.59; found C 71.27, H 9.77.

(b) (*S*)-Isomer: In the same manner as described above, (*S*)-**18** (3.31 g, 13.0 mmol) gave 2.87 g (87%) of (*S*)-**19**, whose spectral data were identical with those of (*R*)-**19**, n_D^{23} = 1.4738. – $[\alpha]_D^{20}$ = +1.87 (*c* = 1.06, $CHCl_3$). – $C_{15}H_{24}O_3$ (252.35): calcd. C 71.39, H 9.59; found C 71.26, H 9.82.

(5*E*,9*E*)-11-Acetoxy-2-(1′-ethoxyethoxy)-4,5,9-trimethyl-5,9-undecadienenitrile (20). – (a) (4*R*)-Isomer: To a mixture of (*R*)-**19** (1.06 g, 4.20 mmol) and TMSCN (5.0 mL, 37.5 mmol) was added a catalytic amount of KCN·18-crown-6 complex at 0 °C. The mixture was stirred for 12 h at 4 °C, diluted with THF/H_2O (5 mL/1 mL) and benzyltrimethylammonium fluoride (97%, 30 mg, 0.172 mmol) added in one portion. The resulting mixture was stirred for 1 h at room temperature, then poured into brine, and extracted with diethyl ether. The extract was dried with $MgSO_4$, and concentrated in vacuo. The residue was diluted with benzene (4 mL) and ethyl vinyl ether (3 mL, 31.4 mmol) was added. A catalytic amount (2 mg) of TsOH was added at 0 °C and the mixture was stirred for 4 h at 0 °C. The resulting solution was then poured into saturated aq. $NaHCO_3$, and extracted with diethyl ether. The extract was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (12 g, hexane/ethyl acetate, 40:1) to give (*R*)-**20** (1.51 g, quant.) as a colorless oil, n_D^{23} = 1.4648. – $[\alpha]_D^{24}$ = –6.74 (*c* = 1.09, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 1745 cm^{-1} (vs, C=O), 1670 (m, C=C). – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.012, 1.016, 1.029 and 1.031 (each d, 3 H, each *J* = 7.0 Hz, 4-CH_3), 1.190, 1.198, 1.204 and 1.228 (each t, 3 H, each *J* = 7.0 Hz, 2"-H), 1.324, 1.329, 1.337 and 1.356 (each d, 3 H, each *J* = 5.5 Hz, 2′-H), 1.51, 1.52 and 1.53 (each s, 3 H, 5-CH_3), 1.69 (s, 3 H, 9-CH_3), 1.75–1.93 (m, 2 H, 3-H), 2.04 (s, 3 H, Ac), 2.06 (br t, 2 H, *J* = 7.0 Hz, 8-H), 2.12 (br q, 2 H, *J* = 7.0 Hz, 7-H), 2.39 (m, 1 H, 4-H), 3.45–3.69 (m, 2 H, 1"-H), 4.04, 4.11, 4.29 and 4.33 (each dd, 1 H, *J* = 8.3, 6.1 and 9.2, 6.1 and 9.2, 6.1 and 8.5, 5.2 Hz, 2-H), 4.58 (d, 2 H, *J* = 7.0 Hz, 11-H), 4.47, 4.79, 4.87 and 4.88 (each q, 1 H, each *J* = 5.5 Hz, 1′-H), 5.14, 5.17 and 5.24 (each t, 1 H, each *J* = 6.5 Hz, 6-H), 5.33 (m, 1 H, 10-H). – $C_{20}H_{33}NO_4$ (351.49): calcd. C 68.34, H 9.46, N 3.99; found C 68.20, H 9.74, N 3.85.

(b) (4*S*)-Isomer: In the same manner as described above, (*S*)-**19** (2.69 g, 10.7 mmol) gave 3.53 g (94%) of (*S*)-**20**, whose spectral data were identical with those of (*R*)-**20**, n_D^{23} = 1.4641. – $[\alpha]_D^{20}$ = +7.14 (*c* = 1.05, $CHCl_3$). – $C_{20}H_{33}NO_4$ (351.49): calcd. C 68.34, H 9.46, N 3.99; found C 68.02, H 9.61, N 3.85.

(5*E*,9*E*)-2-(1′-Ethoxyethoxy)-11-hydroxy-4,5,9-trimethyl-5,9-undecadienenitrile (21). – (a) (4*R*)-Isomer: To a solution of (*R*)-**20** (3.26 g, 9.27 mmol) in MeOH (35 mL) was added potassium carbonate (1.36 g, 9.84 mmol). The mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with diethyl ether and H_2O, and the organic phase was separated. The aqueous phase was extracted with diethyl ether. The combined organic phase was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (60 g, hexane/ethyl acetate, 10:1) to give (*R*)-**21** (2.54 g, 89%) as a colorless oil, n_D^{23} = 1.4719. – $[\alpha]_D^{24}$ = +1.99 (*c* = 1.01, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3445 cm^{-1} (s, O–H), 1665 (w, C=C). – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.012, 1.017, 1.031 and 1.034 (each d, 3 H, each *J* = 7.1 Hz, 4-CH_3), 1.20, 1.21, 1.22 and 1.24 (each t, 3 H, each *J* = 7.1 Hz, 2"-H), 1.32, 1.33, 1.35 and 1.36 (each d, 3 H, each *J* = 5.5 Hz, 2′-H), 1.51, 1.52 and 1.53 (each s, 3 H, 9-CH_3), 1.67 (s, 3 H, 5-CH_3), 1.75–1.94 (m, 2 H, 3-H), 2.07 (m, 2 H, 8-H), 2.13 (m, 2 H, 7-H), 2.33–2.47 (m, 1 H, 4-H), 3.46–3.70 (m, 2 H, 1"-H), 4.07, 4.11, 4.29 and 4.35 (each dd, 1 H, *J* = 8.0, 6.4 and 9.5, 6.4 and 9.8, 6.4 and 8.6, 5.2 Hz, 2-H), 4.14 and 4.16 (each d, 2 H, *J* = 6.4 and 6.1 Hz, 11-H), 4.77, 4.81, 4.89 and 4.90 (each q, 1 H, each *J* = 5.5 Hz, 1′-H), 5.14, 5.19 and 5.27 (each t, 1 H, *J* = 6.5 Hz, 6-H), 5.40 (m, 1 H, 10-H). – $C_{18}H_{31}NO_3$ (309.45): calcd. C 69.86, H 10.10, N 4.53; found C 69.63, H 10.36, N 4.30.

(b) (4*S*)-Isomer: In the same manner as described above, (*S*)-**20** (3.06 g, 8.71 mmol) gave 2.31 g (86%) of (*S*)-**21**, whose spectral data were identical with those of (*R*)-**21**, n_D^{23} = 1.4721. – $[\alpha]_D^{20}$ = –2.15 (*c* = 1.02, $CHCl_3$). – $C_{18}H_{31}NO_3$ (309.45): calcd. C 69.86, H 10.10, N 4.53; found C 69.63, H 10.36, N 4.31.

(5*E*,9*E*)-11-Chloro-2-(1′-ethoxyethoxy)-4,5,9-trimethyl-5,9-undecadienenitrile (22). – (a) (4*R*)-Isomer: To a solution of (*R*)-**21** (1.15 g, 3.72 mmol) and *s*-collidine (1.23 mL, 9.31 mmol) in DMF (15 mL) at 0 °C was added LiCl (315 mg, 7.43 mmol) under argon. After stirring for 40 min at 0 °C, MsCl (0.576 mL, 7.44 mmol) was added dropwise. The resulting suspension was stirred for 1.5 h at 0 °C, then diluted with water, and extracted with diethyl ether. The extract was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was flash chromatographed on silica gel (10 g, hexane/ethyl acetate, 40:1) to give

(*R*)-**22** (1.16 g, 95%) as a colorless oil. This was used for the next step without further purification, – IR (film): $\tilde{\nu}$ = 1660 cm^{-1} (m, C=C). – ^1H NMR (90 MHz, $CDCl_3$): δ = 1.02, 1.03 (each d, *J* = 6.8 Hz, 3 H, 4-CH_3), 1.10–1.42 (m, 6 H, 2′-H, 2′′-H) 1.53 (s, 3 H, 5-CH_3), 1.73 (s, 3 H, 9-CH_3), 1.75–1.95 (m, 2 H, 3-H), 2.02–2.20 (m, 4 H, 7-H, 8-H), 2.22–2.60 (m, 1 H, 4-H), 3.30–3.80 (m, 2 H, 1′′-H), 3.96–4.44 (m, 1 H, 2-H), 4.09 (d, *J* = 7.9 Hz, 2 H, 11-H), 4.64–5.00 (m, 1 H, 1′-H), 5.00–5.58 (m, 2 H, 6-H, 10-H).

(b) (4*S*)-Isomer: In the same manner as described above, (*S*)-**21** (1.00 g, 3.23 mmol) gave 993 mg (94%) of (*S*)-**22**, whose spectral data were identical with those of (*R*)-**22**.

(4*E*,8*E*)-1-(1′-Ethoxyethoxy)-3,4,8-trimethyl-4,8-cyclodecadienecarbonitrile (23). – (a) (3*R*)-Isomer: A solution of (*R*)-**22** (1.15 g, 3.1 mmol) in THF (40 mL) was slowly added dropwise over 5 h to a solution of $NaN(SiMe_3)_2$ (1.0 M in THF, 17.5 mL, 17.5 mmol) in dry THF (165 mL) at reflux under argon. After stirring for 30 min at 70 °C, the resulting mixture was cooled to room temperature, then diluted with saturated aq. NH_4Cl, and extracted with diethyl ether. The extract was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (30 g, hexane/ethyl acetate, 100:1) to give (*R*)-**23** (485 mg, 47%) as a colorless oil, n_D^{24} = 1.4870. – $[\alpha]_D^{23}$ = –55.6 (*c* = 1.08, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 2220 cm^{-1} (w, C≡N), 1640 (m, C=C). – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.02, 1.03, 1.07 and 1.08 (each d, 3 H, each *J* = 7.0 Hz, 3-CH_3), 1.23 (m, 6 H, 4-CH_3, 2"-H), 1.38 (m, 3 H, 2′-H), 1.54 (br. s, 3 H, 8-CH_3), 1.70–2.20 (m, 6 H, 2-H, 6-H, 7-H), 2.45 (m, 1 H, 10-H_a), 2.58–2.81 (m, 1 H, 3-H), 2.90 (m, 1 H, 10-H_b), 3.50–3.70 (m, 2 H, 1"-H), 4.55 and 4.67 (m, 1 H, 9-H), 4.81 and 4.88 (m, 1 H, 5-H), 5.03 and 5.12 (m, 1 H, 1′-H). – $C_{18}H_{29}NO_2$ (291.43): calcd. C 74.18, H 10.03, N 4.81; found C 74.35, H 10.28, N 4.58.

(b) (3*S*)-Isomer: In the same manner as described above, (*S*)-**22** (965 mg, 2.94 mmol) gave 450 mg (53%) of (*S*)-**23**, whose spectral data were identical with those of (*R*)-**23**, n_D^{22} = 1.4874. – $[\alpha]_D^{18}$ = +59.0 (*c* = 1.10, $CHCl_3$). – $C_{18}H_{29}NO_2$ (291.43): calcd. C 74.18, H 10.03, N 4.81; found C 74.37, H 10.35, N 4.68.

(4*E*,8*E*)-3,4,8-Trimethyl-4,8-cyclodecadien-1-one (24). – (a) (*R*)-Isomer: To a solution of (*R*)-**23** (372 mg, 1.28 mmol) in MeOH (8 mL) was added a catalytic amount (2 mg) of PPTS. After stirring for 2 h at 40 °C, the resulting mixture was diluted with saturated aq. $NaHCO_3$ and extracted with diethyl ether. The extract was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was diluted with diethyl ether and the mixture was placed in a separating funnel and shaken vigorously for 5 min with 0.1 M aq. NaOH (5 mL). The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with 0.2 M aq. HCl, water, saturated aq. $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (4 g, pentane/diethyl ether, 50:1) to give (*R*)-**24** (140 mg, 57%) as needles, m.p. 56–60 °C. – $[\alpha]_D^{26}$ = +187 (*c* = 1.18, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 1690 cm^{-1} (vs, C=O), 1660 (m, C=C), 1425 (s, CH_2CO). – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.4 Hz, 3 H, 3-CH_3), 1.46 (s, 3 H, 8-CH_3), 1.56 (s, 3 H, 4-CH_3), 2.18 (m, 4 H, 2-H_a, 6-H_a, 7-H), 2.35 (m, 1 H, 6-H_b), 2.57 (m, 1 H, 3-H), 2.72 (m, 1 H, 2-H_b), 2.87 (m, 1 H, 10-H_a), 3.05 (dd, *J* = 12.8, 9.8 Hz, 1 H, 10-H_b), 4.96 (d, *J* = 10.7 Hz, 1 H, 5-H), 5.13 (m, 1 H, 9-H). – $C_{13}H_{20}O$ (192.30): calcd. C 81.20, H 10.48; found C 80.87, H 10.74.

(b) (*S*)-Isomer: In the same manner as described above, (*S*)-**23** (250 mg, 0.86 mmol) gave 83 mg (50%) of (*S*)-**24**, whose spectral data were identical with those of (*R*)-**24**, m.p. 59–62 °C. – $[\alpha]_D^{26}$ = –191 (*c* = 1.04, $CHCl_3$). – $C_{13}H_{20}O$ (192.30): calcd. C 81.20, H 10.48; found C 80.99, H 10.68.

(1*E*,5*E*)-1,5,10-Trimethyl-8-(1-methylethylidenyl)-1,5-cyclodecadiene (1), 9-Methylgermacrene-B. – (a) (*R*)-Isomer: To a mixture of Sm (159 mg, 1.06 mmol), SmI_2 (0.1 M, THF) (10.6 mL, 1.06 mmol) and anhydrous $CrCl_3$ (84 mg, 0.530 mmol) was added a mixture of (*R*)-**24** (102 mg, 0.53 mmol) and 2,2-dibromopropane (214 mg, 1.06 mmol) in THF (4 mL) at room temperature under argon. After stirring for 30 min at room temperature, the resulting mixture was diluted with pentane and filtered through a short silica gel (10 g) column. The filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (6 g, pentane) to give (*R*)-**1** (69 mg, 60%) as a colorless oil, n_D^{23} = 1.5150. – $[\alpha]_D^{18}$ = +61.4 (*c* = 0.50, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 2920 cm^{-1} (s), 1660 (w), 1450 (m), 1365 (m). – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (d, 3 H, *J* = 7.1 Hz, 9-CH_3), 1.43 (s, 3 H, 10-CH_3), 1.54 (s, 3 H, 4-CH_3), 1.68 and 1.70 (each s, 6 H, 11-CH_3), 1.94 (ddd, *J* = 11.9, 11.9, 5.2 Hz, 1 H, 8-H_a), 2.01 (m, 1 H, 2-H_a), 2.09 (m, 2 H, 9-H, 3-H_a), 2.31 (m, 4 H, 2-H_b, 3-H_b, 6-H_a, 8-H_b), 3.06 (d, *J* = 13.4 Hz, 1 H, 6-H_b), 4.39 (d, *J* = 11.2 Hz, 1 H, 5-H), 4.72 (dd, *J* = 12.2, 2.9 Hz, 1 H, 1-H). – ^{13}C NMR (100 MHz, $CHCl_3$): δ = 11.1, 16.4, 20.4, 20.7, 20.9, 25.3, 34.4, 38.9, 40.8, 46.3, 125.7, 127.0, 128.7, 130.9, 133.8, 140.2. – HPLC [column: Daicel Chiralcel OD (0.46 cm × 25 cm) and OD-H (0.46 cm × 25 cm) were combined], eluent: *n*-hexane, flow rate: 0.2 mL/min, temperature: 3 °C, detection: UV (210 nm)]: t_r = 43.0 min [(*R*)-**1** (97.7%)], t_r = 46.5 min [(*S*)-**1** (2.3%)]. The enantiomeric purity of (*R*)-**1** was therefore 95.4% *ee* – CD (*c* = 0.000504, hexane) Δε (λ, nm) = –33.4 (227), +53.3 (201). – $C_{16}H_{26}$ (218.38): calcd. C 88.00, H 12.00; found C 87.81, H 12.28.

(b) (*S*)-Isomer: In the same manner as described above, (*S*)-**24** (61 mg, 0.32 mmol) gave 45 mg (64%) of (*S*)-**1**, whose spectral data were identical with those of (*R*)-**24**, n_D^{23} = 1.5143. – $[\alpha]_D^{20}$ = –61.3 (*c* = 0.51, $CHCl_3$). – HPLC [column: Daicel Chiralcel OD and OD-H were combined]: t_r = 43.1 min [(*R*)-**1** (2.6%)], t_r = 46.3 min [(*S*)-**1** (97.4%)] [under the same conditions as described above]. The enantiomeric purity of (*S*)-**1** was therefore 94.8% *ee* – CD (*c* = 0.000687, hexane) Δε (λ, nm) = +31.3 (226), –48.5 (201). – $C_{16}H_{26}$ (218.38): calcd. C 88.00, H 12.00; found C 87.72, H 12.21.

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