Pheromone Synthesis, CXCVI[+]

Synthesis of Germacrene-B and Its Extension to the Synthesis of (±)-9-Methylgermacrene-B, the Racemate of the Male-Produced Sex Pheromone of the Sandfly *Lutzomyia longipalpis* from Lapinha, Brazil

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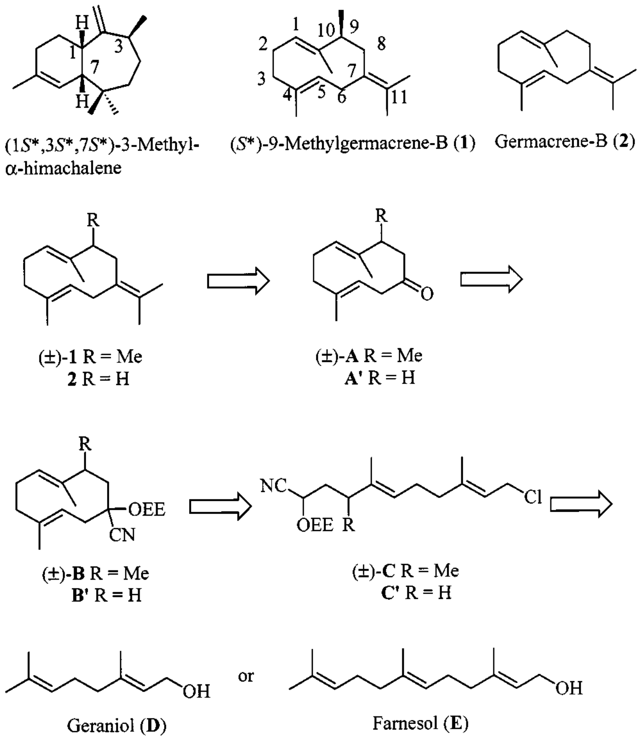
Both germacrene-B (**2**) and 9-methylgermacrene-B [(±)-**1**] were synthesized by employing cyclization reactions [**8** → **9** and (±)-**20** → (±)-**21**] as the key steps. The latter [(±)-**1**] was shown to be the racemate of the male-produced sex pheromone of the sandfly *Lutzomyia longipalpis* from Lapinha, Brazil.

Introduction

The sandfly *Lutzomyia longipalpis* is the vector of the protozoan parasite *Leishmania chagasi*, the causative agent of leishmaniasis in the New World.[1] *L. longipalpis* is known to exist as a species complex. GC analysis of pheromone gland extracts prepared from male *L. longipalpis* from a wide geographic range in South America indicated that there could be up to six different populations of this sandfly.[2] In 1996, 3-methyl-α-himachalene (Scheme 1) was proposed as one of the pheromones of the sandfly.[3] We synthesized it as the racemate, and showed it to be bioactive as the male-produced pheromone of *L. longipalpis* from Jacobina, Brazil.[4][5] In continuation of that work, we now report the synthesis of (±)-9-methylgermacrene-B [(*E*,*E*)-1,5,10-trimethyl-8-(1-methylethylidenyl)-1,5-cyclodecadiene (**1**)], which was proposed as the structure of the male-produced sex pheromone of *L. longipalpis* from Lapinha, Brazil.[6]

The purpose of our work is to confirm the structure proposed for the pheromone, and also to determine its absolute configuration. It is therefore necessary to develop a synthetic route which may be modified for the later enantioselective synthesis. To be sure about the feasibility of our plan, we decided to synthesize achiral germacrene-B (**2**) first. After some preliminary work we adopted the synthetic plan common to (±)-**1** and **2** as shown in Scheme 1. The immediate precursors to the target molecules (±)-**1** and **2** are the ten-membered ring ketones (±)-**A** and **A′**, which are the deprotected forms of the protected cyanohydrins (±)-**B** and **B′**. These can be obtained by cyclization of the open-chain precursors (±)-**C** and **C′** according to the procedure of Takahashi et al.[7] These acyclic precursors may be prepared from geraniol (**D**) and farnesol (**E**), respectively.



Scheme 1. Structures of 9-methylgermacrene-B and germacrene-B, and their retrosynthetic analysis

The above plan was realized as detailed below, and the structure of the sandfly pheromone was confirmed to be **1** as reported in the preliminary communication.[8]

Results and Discussion

Synthesis of Germacrene-B (2)

Germacrene-B [(*E*,*E*)-germacra-1(10),4,7(11)-triene (**2**)] was originally prepared from germacrone [(*E*,*E*)-germacra-1(10),4,7(11)-trien-8-one] by removing its oxygen func-

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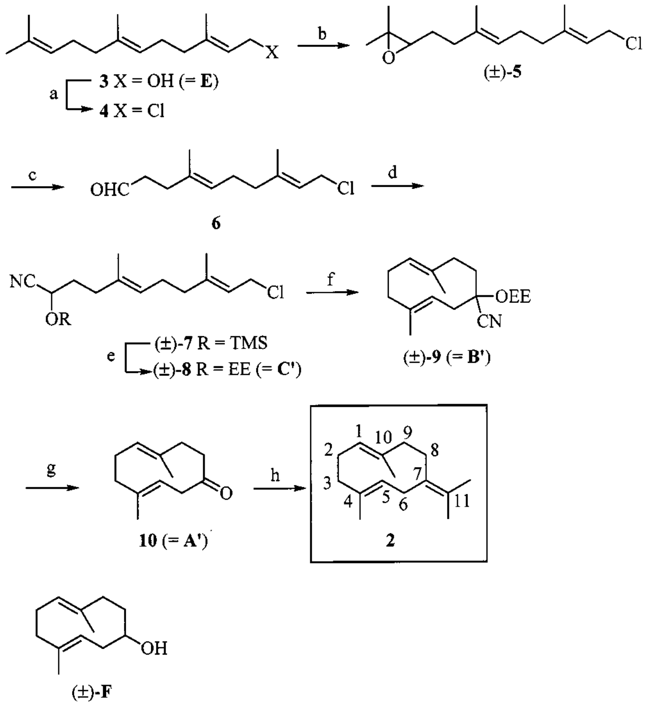
tion.[9] It was named germacrene-B,[10] and found in the cold-pressed peel oil of *Citrus junos.*[11] Its structure was firmly established as **2** by X-ray-crystallographic analysis of its silver nitrate adduct.[12] Germacrene-B was recently isolated from commercial Mexican lime oil from Key lime, *Citrus aurantifolia*.[13] In 1997, de Groot and his co-workers synthesized **2** by the enolate-assisted 1,4-fragmentation of suitably functionalized decalin-1-carboxaldehyde.[14] We preferred the cyclization strategy as discussed in Scheme 1 to the fragmentation strategy, considering its applicability to the synthesis of the target pheromone (±)-**1** itself.



Scheme 2. Synthesis of germacrene-B; reagents: (a) CCl_4, Ph_3P, reflux; (b) MCPBA, CH_2Cl_2 (61%, 2 steps); (c) $HIO_4 \cdot 2\ H_2O$, THF, Et_2O (72%); (d) TMSCN, KCN·18-crown-6; (e) (i) $PhCH_2NMe_3F$, THF, H_2O, (ii) $CH_2{=}CHOEt$, *p*-TsOH, C_6H_6 (91% based on **6**); (f) NaHMDS, THF (48%); (g) (i) PPTS, MeOH, (ii) NaOH, H_2O, Et_2O (61%); (h) Me_2CBr_2, Sm, SmI_2, $CrCl_3$, THF (82%)

Scheme 2 summarizes our synthesis of germacrene-B (**2**). Conversion of (*E*,*E*)-farnesol (**3** = **E**) to the key precursor (±)-**8** (= **C**′) for cyclization required five steps. Treatment of **3** with triphenylphosphane in refluxing carbon tetrachloride yielded farnesyl chloride (**4**). This was epoxidized with *m*-chloroperbenzoic acid (MCPBA) to give the epoxide (±)-**5**. Periodic acid dihydrate cleaved (±)-**5** to furnish the aldehyde **6**, which was treated with trimethylsilyl (TMS) cyanide and potassium cyanide. The resulting TMS-protected cyanohydrin (±)-**7** was then deprotected with benzyltrimethylammonium fluoride to give the corresponding cyanohydrin, whose hydroxy group was immediately protected as the ethoxyethyl (EE) ether to afford (±)-**8** (= **C**′), the precursor for cyclization.

In accordance with Takahashi′s procedure,[7] (±)-**8** was treated with sodium hexamethyldisilazide (NaHMDS) in THF under high-dilution conditions (ca. 0.05 M) by slowly adding (±)-**8** to the base giving the cyclization product (±)-**9** in 48% yield. Removal of the EE protective group of (±)-**9** with pyridinium *p*-toluenesulfonate (PPTS) in methanol was followed by base treatment to reverse the cyanohydrin formation, giving (*E*,*E*)-4,8-dimethylcyclodeca-3,7-dien-1-one (**10**). Prior to this successful synthesis of **10**, various different attempts were made to effect the cyclization. Treatment of the chloroaldehyde **6** with samarium(II) iodide[15] or indium[16] could not bring about the cyclization. Attempted cyclization of the epoxy sulfide [(±)-**5**, SPh instead of Cl] with base[17] was not successful either.

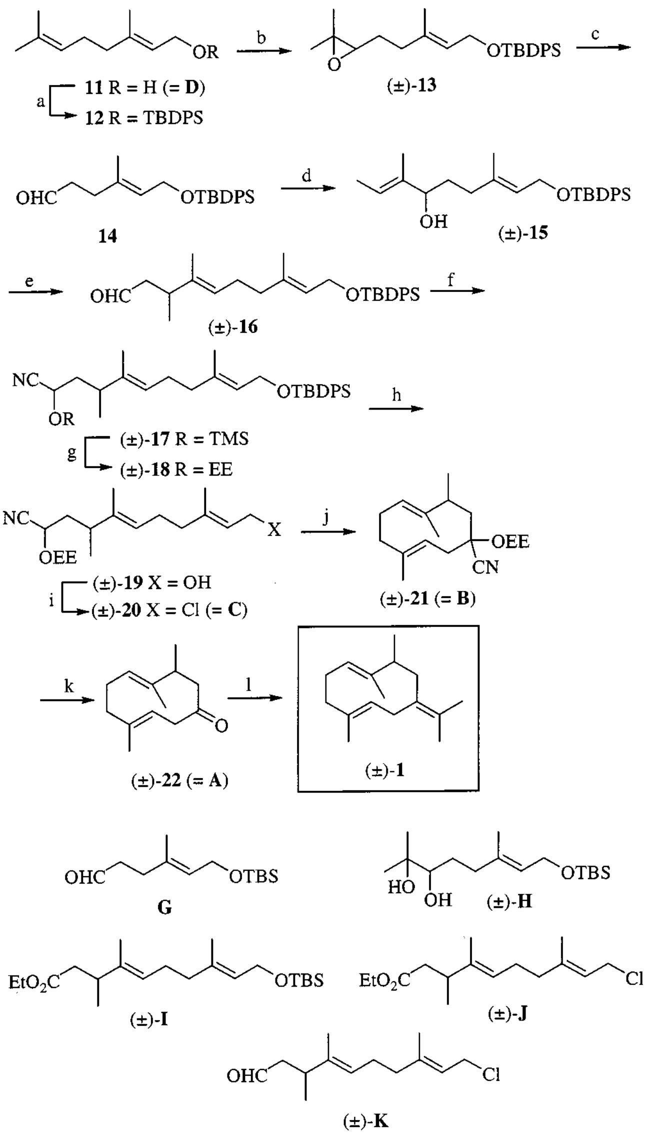
The final isopropylidenation could not be achieved by the conventional Wittig reaction, which caused double bond migration. After several attempts, Utimoto′s recent protocol[18] using samarium and chromium was found to be the method of choice to afford germacrene-B (**2**). Its ^{1}H-NMR spectrum is identical with the published spectrum of the naturally occurring germacrene-B isolated from *Citus aurantifolia*.[13] The overall yield of **2** was 9.6% in 7 steps from farnesol (**3**). This model experiment paved the way to the successful synthesis of (±)-9-methylgermacrene-B.

Synthesis of (±)-9-Methylgermacrene-B [(±)-1]

As shown in Scheme 3, the key precursor (±)-**20** for the cyclization was prepared from geraniol (**11**). The same strategy as for the synthesis of germacrene-B (**2**) was employed with some adaptations to streamline the synthesis.

Conversion of geraniol (**11**) into the aldehyde **14** was executed by a four-step procedure. After protecting the hydroxy group of geraniol (**11**) as the *tert*-butyldiphenylsilyl (TBDPS) ether, the resulting compound **12** was epoxidized with MCPBA to give epoxide (±)-**13**. Cleavage of the epoxide with periodic acid dihydrate furnished **14** in 77% overall yield. When this sequence of reactions was carried out employing the cheaper *tert*-butyldimethylsilyl (TBS) ether as the protective group, the yield of the cleavage reaction to give **G** dropped drastically to 30−40% due to the unwanted acid-catalyzed deprotection of the TBS group. Another attempt to obtain the diol (±)-**H** by dihydroxylation of geraniol TBS ether with osmium tetroxide afforded the desired (±)-**H** only in the modest yield of 31%. We were therefore forced to use the expensive TBDPS ether **12** as our intermediate.

The next stage was the chain extension of **14** to give the aldehyde (±)-**16**. Firstly, (*E*)-2-bromo-2-butene [(*E*)/(*Z*) = 98:2] was secured by careful fractional distillation of the (*E*)/(*Z*) mixture, and lithiated by treatment with *tert*-butyllithium in THF. The generated lithio derivative reacted with **14** to give the allylic alcohol (±)-**15** [(*E*)/(*Z*) = 98:2]. If the corresponding Grignard reagent in THF was employed instead of the lithio derivative, (±)-**15** was obtained as a mixture of geometrical isomers at the newly generated double bond [(*E*)/(*Z*) = 85:15]. The allylic alcohol (±)-**15** was treated with ethyl vinyl ether in the presence of mercury(II) acetate to give the corresponding vinyl ether, whose thermal



Scheme 3. Synthesis of 9-methylgermacrene-B; reagents: (a) TBDPSCl, imidazole, DMF (quant.); (b) MCPBA, $CHCl_3$ (89%); (c) $HIO_4 \cdot 2\,H_2O$, THF, Et_2O (86%); (d) (*E*)-2-bromo-2-butene, *t*BuLi, THF (67%); (e) $CH_2{=}CHOEt$, $Hg(OAc)_2$, *o*-xylene, 140°C (75%); (f) TMSCN, KCN·18-crown-6; (g) (i) $PhCH_2NMe_3F$, THF, H_2O, (ii) $CH_2{=}CHOEt$, *p*-TsOH, C_6H_6 [96% based on (±)-**16**]; (h) nBu_4NF, THF (quant.); (i) MsCl, LiCl, *s*-collidine, DMF (95%); (j) NaHMDS, THF (58%); (k) (i) PPTS, MeOH, (ii) NaOH, H_2O, Et_2O (70%); (l) Me_2CBr_2, Sm, SmI_2, $CrCl_3$, THF (82%)

rearrangement furnished the aldehyde (±)-**16** [(*E*)/(*Z*) = 98–99:1–2]. In the early stage of our work, we prepared the aldehyde as the TBS ether [(±)-**16**, TBS instead of TBDPS] in the following manner. Application of the Johnson ester Claisen rearrangement[19] to the allylic alcohol (±)-**15** (TBS instead of TBDPS) furnished (±)-**I**, whose reduction with lithium aluminum hydride (LAH), followed by oxidation with pyridinium chlorochromate (PCC) gave the desired aldehyde (±)-**16** (TBS instead of TBDPS). The overall yield, however, was only 36% in contrast to 75% in the case of the direct conversion [(±)-**15** → (±)-**16**]. We therefore adopted the more efficient direct conversion.

Treatment of the aldehyde (±)-**16** with TMSCN and KCN yielded (±)-**17**, which was then converted into the corresponding EE ether (±)-**18**. The alcohol (±)-**19**, obtained by deprotection of the TBDPS protecting group of (±)-**18** with tetrabutylammonium fluoride, was treated with methanesulfonyl (Ms) chloride, lithium chloride and *s*-collidine in DMF to afford the chloride (±)-**20** (= **C**). Cyclization of (±)-**20** to give (±)-**21** (= **B**) was achieved in 58% yield in the same manner as for the synthesis of (±)-**9**. Conversion of (±)-**21** to (±)-**22** (= **A**) was followed by the final step of isopropylidenation to give (±)-9-methylgermacrene-B [(±)-**1**]. The overall yield of (±)-**1** was 12% based on geraniol (**11**, 11 steps). An alternative route for the synthesis of (±)-**21** (= **B**) via (±)-**J** and (±)-**K** was originally explored as in the case for the synthesis of germacrene-B. Due to the instability of the allylic chlorides (±)-**J** and (±)-**K**, the overall yield by this route was 13% of (±)-**21** after cyclization [5 steps based on (±)-**15**] in contrast to 40% by the route finally adopted.

Our synthetic (±)-9-methylgermacrene-B (**1**) shows MS and ^{1}H-NMR spectra identical to those of the natural pheromone.[6] The identity was further confirmed by direct GC comparison with the natural product, and (±)-**1** was indeed bioactive. A summary of this comparison and a bioassay is in press as a joint preliminary communication with Pickett and his co-workers.[8]

In conclusion, our synthesis of (±)-9-methylgermacrene-B has definitely established the gross structure of the male-produced sex pheromone of *Lutzomyia longipalpis* from Lapinha, Brazil, as **1**. Synthesis of both the enantiomers of **1** is now in progress so as to determine the absolute configuration of the pheromone.

Experimental Section

General: Boiling points: Uncorrected values. – IR: Jasco IRA-102 and Hitachi Perkin–Elmer 1640. – ^{1}H NMR: Jeol JNM-EX 90A (90 MHz), Jeol JNM-EX 270L (270 MHz), Bruker DPX 300 (300 MHz), Jeol JNM-LA 400 (400 MHz), Jeol JNM-LA 500 (500 MHz), (TMS at $\delta_H = 0.00$ or $CHCl_3$ at $\delta_H = 7.26$ as an internal standard). – ^{13}C NMR: Jeol JNM-LA 500 (126 MHz), ($CDCl_3$ at $\delta_C = 77.0$ as an internal standard). – MS: Jeol JMS-SX 102A and Hitachi M-80B. – CC: Merck Kieselgel 60 Art 1.07734. – TLC: 0.25 mm Merck silica gel plates (60F-254).

(*E*,*E*)-1-Chloro-3,7,11-trimethyl-2,6,10-dodecatriene (4): To a solution of farnesol (3.00 g, 13.5 mmol) in CCl_4 (12 mL) was added Ph_3P (3.84 g, 14.6 mmol). The mixture was stirred under reflux for 1 h and then cooled to room temperature. The resulting mixture was diluted with hexane and filtered through Celite, then the filter cake was washed with hexane. The combined filtrate and washings were concentrated under reduced pressure to give crude **4** (3.40 g, quant.) as a colorless oil. This was directly used for the next step. – $n_D^{24} = 1.4975$. – IR (film): $\tilde{\nu} = 1665$ cm^{-1} (w, C=C), 1650 (w, C=C). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.60, 1.68, 1.72, 1.74 (each br. s, 12 H, 3-, 7-, 11-Me), 1.80–2.20 (m, 8 H, 4-, 5-, 8-, 9-H), 4.10 (d, 2 H, *J* = 5.4 Hz, 1-H), 4.9–5.2 (m, 2 H, 6-, 10-H), 5.45 (br. t, 2 H, *J* = 8.2 Hz, 12-H). – $C_{15}H_{25}Cl$: calcd. 240.1644; found 240.1639 (HRMS).

(*E*,*E*)-1-Chloro-10,11-epoxy-3,7,11-trimethyl-2,6-dodecadiene [(±)-5]: To a solution of **4** (3.40 g, 13.5 mmol) in CH_2Cl_2 (100 mL) at 0°C was added MCPBA (70%, 4.00 g, 16.3 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred for 1 h at 0°C and then diluted with saturated aq. $NaHCO_3$. It was extracted with diethyl ether, and the combined ethereal extracts were washed with water, saturated aq. $NaHCO_3$, brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (60 g, hexane/ethyl acetate, 80:1) to give recovered **12** (0.50 g, 2.1 mmol) and (±)-**5** (1.88 g, 51% 2 steps) as a colorless oil. − n_D^{24} = 1.4850. − IR (film): $\tilde{\nu}$ = 1665 cm^{-1} (w, C=C), 1660 (w, C=C). − ^1H NMR (90 MHz, $CDCl_3$): δ = 1.25, 1.30 (each s, 6 H, 11-Me), 1.61 (s, 3 H, 7-Me), 1.74 (s, 3 H, 3-Me), 1.93−2.22 (m, 8 H, 4-, 5-, 8-, 9-H), 2.71 (t, 1 H, *J* = 5.4 Hz, 10-H), 4.09 (d, 2 H, *J* = 7.7 Hz, 1-H), 4.9−5.6 (m, 2 H, 2-, 6-H). − $C_{15}H_{25}ClO$: calcd. 256.1594; found 256.1587 (HRMS).

(*E*,*E*)-10-Chloro-4,8-dimethyl-4,8-decadienal (6): To a solution of $HIO_4 \cdot 2\,H_2O$ (1.22 g, 5.36 mmol) in THF (50 mL) at 0°C was added (±)-**5** (1.25 g, 4.87 mmol) in diethyl ether (25 mL). The mixture was stirred for 1 h at 0°C and then diluted with saturated aq. $NaHCO_3$. After stirring for 15 min, the resulting mixture was filtered through Celite, and the filter cake was washed with diethyl ether. The combined filtrate and washings were extracted with diethyl ether. The extract was washed with water, saturated aq. $NaHCO_3$, brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (20 g, hexane/ethyl acetate, 50:1) to give **6** (756 mg, 72%) as a colorless oil. − n_D^{24} = 1.4862. − IR (film): $\tilde{\nu}$ = 1725 cm^{-1} (s, C=O), 1655 (w, C=C). − ^1H NMR (90 MHz, $CDCl_3$): δ = 1.61 (br. t, 3 H, 4-Me), 1.72 (br. t, 3 H, 8-Me), 1.8−2.7 (m, 8 H, 2-, 3-, 6-, 7-H), 4.09 (d, 2 H, *J* = 7.9 Hz, 10-H), 4.9−5.2 (m, 1 H, 5-H), 5.43 (br. t, 1 H, *J* = 7.9 Hz, 10-H), 9.75 (t, 1 H, *J* = 1.8 Hz, CHO). − $C_{12}H_{19}ClO$: calcd. 214.1124; found 214.1124 (HRMS).

(*E*,*E*)-10-Chloro-1-cyano-1-(1′-ethoxyethoxy)-4,8-decadiene [(±)-8]: To a mixture of **6** (2.90 g, 13.5 mmol) and TMSCN (8 mL) at 0°C was added a catalytic amount of KCN·18-crown-6 complex. The mixture was stirred for 12 h at 4°C. The mixture was diluted with THF/H_2O (10 mL/2 mL) and then a catalytic amount of benzyltrimethylammonium fluoride was added in one portion. The resulting mixture was stirred for 2 h at room temperature, then poured into brine and extracted with diethyl ether. The extract was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was diluted with benzene (5 mL) and to it was added ethyl vinyl ether (10 mL). A catalytic amount of *p*-TsOH was added at 0°C and the mixture was stirred for 3 h at 0°C. The resulting mixture was 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 (20 g, hexane/ethyl acetate, 60:1) to give (±)-**8** (3.86 g, 91%) as a colorless oil. − n_D^{24} = 1.4722. − IR (film): $\tilde{\nu}$ = 2250 cm^{-1} (w, C≡N), 1660 (w, C=C). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.8−1.5 (m, 8 H, 2-, 2′-, 2′′-H), 1.5−1.8 (m, 6 H, 4-, 8-Me), 1.8−2.4 (m, 6 H, 3-, 6-, 7-H), 3.3−3.9 (m, 2 H, 1′-H), 4.08 (d, 2 H, *J* = 5.4 Hz, 10-H), 4.1−4.5 (m, 1 H, 1-H), 4.7−5.2 (m, 1 H, 1′-H), 5.0−5.6 (m, 2 H, 5-, 9-H).

(*E*,*E*)-1-Cyano-1-(1′-ethoxyethoxy)-4,8-dimethyl-3,7-cyclodecadiene [(±)-9]: To a solution of $NaN(SiMe_3)_2$ (1.0 M in THF, 90.0 mL, 90.0 mmol) in dry THF (850 mL) was added (±)-**8** (5.90 g, 18.0 mmol) in THF (200 mL) dropwise over 8 h at 70°C under Ar. 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 brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (100 g, hexane/ethyl acetate, 100:1) to give (±)-**9** (2.52 g, 48%) as a colorless oil. − n_D^{25} = 1.4616. − IR (film): $\tilde{\nu}$ = 2230 cm^{-1} (w, C≡N), 1670 (w, C=C). − ^1H NMR (90 MHz, $CDCl_3$): δ = 1.00−2.90 (m, 22 H, 2-, 5-, 6-, 10-, 2′-, 2″-H, 4-, 8-Me), 3.40−3.80 (m, 2 H, 1″-H), 4.60−5.10 (m, 2 H, 3-, 7-H), 5.13 (q, *J* = 5.4 Hz, 1 H, 1′-H). − $C_{17}H_{27}O_2N$: calcd. 277.2042; found 277.2055 (HRMS).

(*E*,*E*)-4,8-Dimethyl-3,7-cyclodecadien-1-one (10): To a solution of (±)-**9** (69 mg, 0.25 mmol) in MeOH (5 mL) was added a catalytic amount of PPTS. After stirring for 6 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 under reduced pressure. The residue was diluted with diethyl ether and the mixture was placed in a separatory funnel and shaken vigorously for 3 min with 0.1 M NaOH. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with 0.2 N aq. HCl, water, saturated aq. $NaHCO_3$, brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (2 g, pentane/diethyl ether, 50:1) to give **10** (27 mg, 61%) as a colorless oil. − n_D^{25} = 1.5105. − IR (film): $\tilde{\nu}$ = 1705 cm^{-1} (s, C=O), 1665 (w, C=C). − ^1H NMR (270 MHz, $CDCl_3$): δ = 1.52 and 1.59 (each s, 6 H, 4-, 8-Me), 2.00−2.80 (m, 8 H, 5-, 6-, 9-, 10-H), 2.91 (dd, 1 H, *J* = 6.4 Hz, 12.4 Hz, 2-H), 3.00−3.60 (m, 1 H, 2-H), 4.60−5.10 (m, 2 H, 3-, 7-H). − $C_{12}H_{18}O$: calcd. 178.1356; found 178.1366 (HRMS). − $C_{12}H_{18}O$ (178.3): calcd. C 80.85, H 10.18; found C 80.45, H 10.54.

(*E*,*E*)-Germacra-1(10),4,7(11)-triene (Germacrene-B, 2): To a mixture of Sm (102 mg, 0.68 mmol), SmI_2 (0.1 M, THF) (0.68 mL, 0.068 mmol) and anhydrous $CrCl_3$ (54 mg, 0.34 mmol) was added a mixture of **10** (60 mg, 0.34 mmol) and 2,2-dibromopropane (136 mg, 0.68 mmol) in THF (2 mL) at room temperature under Ar. After stirring for 30 min at room temperature, the resulting mixture was diluted with pentane and filtered through a short silica-gel column. The filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (1 g, pentane) to give **2** (56 mg, 82%) as a colorless oil. − n_D^{25} = 1.5171. − IR (film): $\tilde{\nu}$ = 2920 cm^{-1} (s), 1660 (w, C=C), 1440 (m), 1385 (m), 855(m). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51, 1.54, 1.70, 1.72 (each s, 12 H, 4-, 10-, 11-Me), 1.8−2.6 (m, 9 H, 2-, 3-, 8-, 9-H, 6-H_a), 1.8−3.0 (m, 1 H, 6-H_b), 4.45−4.65 and 4.65−4.90 (each m, 2 H, 1-, 5-H). − $C_{15}H_{24}$: calcd. 204.1874; found 204.1875 (HRMS).

(*E*,*E*)-1-*tert*-Butyldiphenylsilyloxy-3,7-dimethyl-2,6-octadiene (12): To a solution of geraniol (**11**) (10.1 g, 65.5 mmol) and imidazole (9.50 g, 140 mmol) in DMF (60 mL) at 0°C was added TBDPSCl (18.7 mL, 71.9 mmol). The mixture was stirred for 1 h at room temperature and then quenched with water. It was extracted with diethyl ether. The extract was washed with water, saturated aq. $NaHCO_3$, brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by distillation to give **12** (25.7 g, quant.) as a colorless oil. − B.p. 193−195°C/1.5 Torr. − n_D^{25} = 1.5172. − IR (film): $\tilde{\nu}$ = 1665 cm^{-1} (w, C=C), 1590 (w, aromatic), 1260 (m), 1110 (s, Si−O). − ^1H NMR (90 MHz, $CDCl_3$): δ = 1.05 (s, 9 H, *t*Bu), 1.44 (s, 3 H, 3-Me), 1.61 and 1.68 (each s, 6 H, 7-Me, 8-H), 2.00 (br. s, 4 H, 4-, 5-H), 4.23 (d, 2 H, *J* = 6.4 Hz, 1-H), 5.11 (m, 1 H, 6-H), 5.38 (t, 1 H, *J* = 6.4 Hz, 2-H), 7.28 (m, 6 H, *m*,*p*-aromatic H), 7.66 and 7.70 (each d, 4 H, *J* = 6.8 and 7.0 Hz, *o*-aromatic H). − $C_{26}H_{36}OSi$ (392.7): calcd. C 79.53, H 9.24; found C 79.13, H 9.10.

(*E*)-1-*tert*-Butyldiphenylsilyloxy-3,7-dimethyl-6,7-epoxy-2-octene [(±)-13]: To a solution of **12** (19.5 g, 49.9 mmol) in $CHCl_3$ (300 mL) at 0°C, MCPBA (70%) (13.5 g, 54.8 mmol) was added in one portion. The mixture was stirred for 30 min at 0°C and then diluted with saturated aq. $NaHCO_3$. It was extracted with $CHCl_3$. The extract was washed with water, saturated aq. $NaHCO_3$, brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (300 g, hexane/ethyl acetate, 80:1) to give recovered **12** (3.30 g, 17%), and (±)-**13** (15.1 g, 89% based on the consumed **12**) as a colorless oil. − n_D^{25} = 1.5169. − IR (film): $\tilde{\nu}$ = 1665 cm^{-1} (w, C=C), 1590 (w, aromatic), 1250 (m), 1110 (s, Si−O). − ^1H NMR (90 MHz, $CDCl_3$): δ = 1.05 (s, 9 H, *t*Bu), 1.26 and 1.31 (each s, 6 H, 7-Me, 8-H), 1.47 (s, 3 H, 3-Me), 1.64 (dd, 2 H, *J* = 9.0, 6.1 Hz, 5-H), 2.12 (m, 2 H, 4-H), 2.71 (t, 2 H, *J* = 7.7 Hz, 1-H), 4.22 (d, 2 H, *J* = 6.2 Hz, 1-H), 5.41 (t, 1 H, *J* = 6.4 Hz, 2-H), 7.38 (m, 6 H, *m*,*p*-aromatic H), 7.68 and 7.72 (each d, 4 H, *J* = 7.3 and 6.0 Hz, *o*-aromatic H). − $C_{26}H_{36}O_2Si$ (392.7): calcd. C 76.42, H 8.88; found C 76.59, H 8.80.

(*E*)-6-*tert*-Butyldiphenylsilyloxy-4-methyl-4-hexenal (14): A solution of (±)-**13** (15.1 g, 37.2 mmol) in diethyl ether (50 mL) was added to a solution of $HIO_4 \cdot 2\ H_2O$ (10.1 g, 23.1 mmol) in THF (300 mL) at 0°C. The mixture was stirred for 30 min at 0°C and then diluted with saturated aq. $NaHCO_3$. After stirring for 15 min, the resulting mixture was filtered through Celite, and the filter cake was washed with diethyl ether. The combined filtrate and washings were extracted with diethyl ether. The extract was washed with water, saturated aq. $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (250 g, hexane/ethyl acetate, 50:1) to give **14** (11.7 g, 86%) as a colorless oil. − n_D^{25} = 1.5170. − IR (film): $\tilde{\nu}$ = 1725 cm^{-1} (s, C=O), 1665 (w, C=C), 1590 (w, aromatic), 1260 (m), 1115 (s, Si−O). − ^1H NMR (90 MHz, $CDCl_3$): δ = 1.04 (s, 9 H, *t*Bu), 1.44 (s, 3 H, 4-Me), 2.40 (m, 4 H, 2, 3-H), 4.20 (d, 2 H, *J* = 6.0 Hz, 6-H), 5.37 (t, 1 H, *J* = 6.0 Hz, 5-H), 7.40 (m, 6 H, *m*,*p*-aromatic H), 7.67 and 7.70 (each d, 4 H, *J* = 7.3 and 5.7 Hz, *o*-aromatic H), 9.75 (t, 1 H, *J* = 1.7 Hz, CHO). − $C_{23}H_{30}O_2Si$ (366.6): calcd. C 75.36, H 8.25; found C 75.36, H 8.13.

(*E*,*E*)-9-*tert*-Butyldiphenylsilyloxy-3,7-dimethyl-2,7-nonadien-4-ol [(±)-15]: To a solution of (*E*)-2-bromo-2-butene (4.24 mL, 41.8 mmol) in dry THF (100 mL) at −78°C was added *t*BuLi (1.48 M, pentane, 56.4 mL, 83.5 mmol) under Ar. The reaction mixture was stirred for 2 h at −78°C and then a solution of **14** (7.26 g, 20.9 mmol) in dry THF (40 mL) was added to it. After stirring for 1 h at −78°C, the reaction mixture was quenched with saturated aq. NH_4Cl. It was extracted with diethyl ether. The extract was washed with water, saturated aq. $NaHCO_3$, brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (150 g, hexane/ethyl acetate, 20:1) to give (±)-**15** (5.60 g, 67%) as a colorless oil. − n_D^{25} = 1.5171. − IR (film): $\tilde{\nu}$ = 3360 cm^{-1} (s, O−H), 1665 (w, C=C), 1590 (w, aromatic), 1260 (m), 1115 (s, Si−O). − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.04 (s, 9 H, *t*Bu), 1.32 (d, 1 H, *J* = 3.7 Hz, OH), 1.46 (s, 3 H, 7-Me), 1.55 (m, 1 H, 5-H_a), 1.61 (dd, 3 H, *J* = 7.0, 1.5 Hz, 1-H), 1.69 (dd, 3 H, *J* = 1.5, 1.5 Hz, 3-Me), 1.72 (m, 1 H, 5-H_b), 1.94 (ddd, 1 H, *J* = 14.0, 9.8 5.8 Hz, 6-H_a), 2.02 (ddd, 1 H, *J* = 14.0, 10.2, 6.2 Hz, 6-H_b), 4.22 (d, 2 H, *J* = 6.2 Hz, 9-H), 4.57 (ddd, 1 H, *J* = 7.3, 7.3, 4.2, 4-H), 5.34 (q, 1 H, *J* = 7.0 Hz, 2-H), 5.41 (t, 1 H, *J* = 6.2 Hz, 8-H), 7.39 (m, 6 H, *m*,*p*-aromatic H), 7.68 and 7.69 (each d, 4 H, *J* = 8.0 and 8.0 Hz, *o*-aromatic H). − $C_{27}H_{38}O_2Si$ (422.7): calcd. C 76.72, H 9.06; found C 76.74, H 8.92.

(*E*,*E*)-10-*tert*-Butyldiphenylsilyloxy-3,4,8-trimethyl-4,8-decadienal [(±)-16]: To a solution of (±)-**15** (265 mg, 23.1 mmol) in ethyl vinyl ether (2 mL) at room temperature was added $Hg(OAc)_2$ (30 mg, 94 μmol). The mixture was stirred for 1 d at room temperature and then *o*-xylene (2 mL) was added. The mixture was heated at 140°C for 1 h while removing ethyl vinyl ether by distillation. After cooling, the reaction mixture was filtered through Celite, and the filter cake was washed with diethyl ether. The combined filtrate and washings were concentrated under reduced pressure. The residue was chromatographed on silica gel (5 g, hexane/ethyl acetate, 50:1) to give recovered (±)-**15** (23 mg, 9%), and (±)-**16** [194 mg, 75% based on the consumed (±)-**15**] as a colorless oil. − n_D^{24} = 1.5172. − IR (film): $\tilde{\nu}$ = 1725 cm^{-1} (s, C=O), 1665 (w, C=C), 1590 (w, aromatic), 1260 (m), 1115 (s, Si−O). − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.05 (s, 9 H, *t*Bu), 1.05 (dd, 3 H, *J* = 8.5, 1.2 Hz, 3-Me), 1.44 (s, 3 H, 8-Me), 1.58 (s, 3 H, 4-Me), 1.98 (dd, 2 H, *J* = 8.0, 7.0 Hz, 7-H), 2.07 (dd, 2 H, *J* = 8.0, 7.0 Hz, 6-H), 2.30 (dddd, 1 H, *J* = 15.8, 8.8, 2.5, 1.3 Hz, 2-H_a), 2.45 (dddd, 1 H, *J* = 15.8, 7.3, 2.5, 1.3 Hz, 2-H_b), 2.69 (sext, 1 H, *J* = 7.0 Hz, 3-H), 4.21 (d, 2 H, *J* = 6.2 Hz, 10-H), 5.20 (t, 1 H, *J* = 7.0 Hz, 5-H), 5.37 (tt, 1 H, *J* = 6.3, 1.2 Hz, 9-H), 7.38 (m, 6 H, *m*,*p*-aromatic H), 7.68 (m, 4 H, *o*-aromatic H), 9.65 (dd, 1 H, *J* = 2.5, 1.3 Hz, CHO). − $C_{29}H_{40}O_2Si$ (448.7): calcd. C 77.63, H 8.99; found C 77.50, H 9.16.

(*E*,*E*)-11-*tert*-Butyldiphenylsilyloxy-2-(1-ethoxyethoxy)-4,5,9-trimethyl-5,9-undecadienenitrile [(±)-18]: To a mixture of (±)-**16** (720 mg, 1.60 mmol) and TMSCN (993 mg, 10.0 mmol) at room temperature was added a catalytic amount of KCN·18-crown-6 complex. The mixture was stirred for 2 h at room temperature, diluted with THF/H_2O (4 mL/1 mL) and a catalytic amount of benzyltrimethylammonium fluoride was added in one portion. The resulting mixture was stirred for 2 h at room temperature, then poured into brine and extracted with diethyl ether. The extract was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was diluted with benzene (1 mL) and ethyl vinyl ether (2 mL) was added. A catalytic amount of *p*-TsOH was added at 0°C and the mixture was stirred for a further 2 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 (20 g, hexane/ethyl acetate, 60:1) to give (±)-**18** (850 mg, 96%) as a colorless oil. − n_D^{24} = 1.5160. − IR (film): $\tilde{\nu}$ = 1665 cm^{-1} (w, C=C), 1590 (w, aromatic), 1260 (m), 1110 (s, Si−O). − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.05 (m, 12 H, 4-Me, *t*Bu), 1.20 and 1.21 and 1.22 and 1.24 (each t, 3 H, each *J* = 7.3 Hz, 2″-H), 1.33 and 1.34 and 1.36 (each d, 3 H, each *J* = 5.5 Hz, 2′-H), 1.45 (s, 3 H, 9-Me), 1.536 and 1.539 and 1.542 and 1.543 (each s, 3 H, 5-Me), 1.84 (m, 2 H, 3-H), 2.00 (m, 2 H, 8-H), 2.07 (m, 2 H, 7-H), 2.41 (m, 1 H, 4-H), 3.45−3.71 (m, 2 H, 1″-H), 4.05 and 4.12 and 4.31 and 4.33 (each dd, 1 H, *J* = 8.0, 6.1 and 8.9, 6.1 and 8.9, 6.1 and 8.6, 5.2 Hz, 2-H), 4.22 (d, 2 H, *J* = 6.1 Hz, 11-H), 4.74 and 4.80 and 4.88 (each q, 1 H, each *J* = 5.5 Hz, 1′-H), 5.17 and 5.20 and 5.27 (each t, 1 H, each *J* = 6.7 Hz, 6-H), 5.38 (m, 1 H, 10-H), 7.39 (m, 6 H, *m*,*p*-aromatic H), 7.691 and 7.692 (each d, 4 H, *J* = 7.3 and 6.7 Hz, *o*-aromatic H). − $C_{34}H_{49}NO_3Si$ (547.9): calcd. C 74.54, H 9.02, N 2.56; found C 74.43, H 8.90, N 2.55.

(*E*,*E*)-2-(1-Ethoxyethoxy)-11-hydroxy-4,5,9-trimethyl-5,9-undecadienenitrile [(±)-19]: To a solution of (±)-**18** (1.57 g, 2.87 mmol) in THF (5 mL) at 0°C was added TBAF (1.0 M in THF, 4.30 mL, 4.30 mmol). The mixture was stirred for 1 h at room temperature and then diluted with water and extracted with diethyl ether. The extract was washed with water, saturated aq. $NaHCO_3$, brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (20 g, hexane/ethyl acetate, 50:1) to give (±)-**19** (833 mg, quant.) as a colorless oil. − n_D^{24} = 1.4731. − IR (film): $\tilde{\nu}$ = 3420 cm^{-1} (s, OH), 2250 (w, C≡N), 1665 (w, C=C). − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.022

and 1.027 and 1.040 and 1.043 (each d, 3 H, each $J = 7.1$ Hz, 4-Me), 1.20 and 1.21 and 1.22 and 1.24 (each t, 3 H, each $J = 7.1$ Hz, 2″-H), 1.32 and 1.33 and 1.35 and 1.36 (each d, 3 H, each $J = 5.5$ Hz, 2′-H), 1.53 (s, 3 H, 9-Me), 1.67 (s, 3 H, 5-Me), 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 and 4.11 and 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 and 4.81 and 4.89 and 4.90 (each q, 1 H, each $J = 5.5$ Hz, 1′-H), 5.14 and 5.19 and 5.27 (each t, 1 H, $J = 6.5$ Hz, 6-H), 5.40 (m, 1 H, 10-H). − $C_{18}H_{31}NO_3$ (309.4): calcd. C 69.86, H 10.10, N 4.53; found C 69.77, H 10.32, N 4.24.

(*E*,*E*)-11-Chloro-2-(1-ethoxyethoxy)-4,5,9-trimethyl-5,9-undecadienenitrile [(±)-20]: To a solution of (±)-**19** (148 mg, 0.478 mmol) and *s*-collidine (158 µL, 1.20 mmol) in DMF (2 mL) at 0°C was added LiCl (40 mg, 0.96 mmol) under Ar. After stirring for 30 min at 0°C, MsCl (74 µL, 0.96 mmol) was added dropwise. The resulting suspension was stirred for 2 h at 0°C, and then diluted with water 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 (5 g, hexane/ethyl acetate, 25:1) to give (±)-**20** (150 mg, 95%) as a colorless oil. − $n_D^{24} = 1.4758$. − IR (film): $\tilde{\nu} = 1660$ cm^{-1} (w, C=C). − ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.02$ and 1.03 and 1.04 (each d, 3 H, each $J = 6.0$ Hz, 4-Me), 1.20 and 1.21 and 1.22 and 1.24 (each t, 3 H, each $J = 7.1$ Hz, 2″-H), 1.33 and 1.34 and 1.35 and 1.36 (each d, 3 H, each $J = 5.3$ Hz, 2′-H), 1.52 and 1.53 and 1.54 and 1.56 (each s, 3 H, 9-Me), 1.73 (s, 3 H, 5-Me), 1.84 (m, 2 H, 3-H), 2.12 (m, 4 H, 7, 8-H), 2.38 (m, 1 H, 4-H), 3.47−3.70 (m, 2 H, 1″-H), 4.06 and 4.29 and 4.33 (each dd, 1 H, $J = 7.8$, 5.9 and 9.0, 5.8 and 8.5, 5.4 Hz, 2-H), 4.100 and 4.106 (each d, 2 H, $J = 7.8$ and 7.7 Hz, 11-H), 4.75 and 4.80 and 4.89 and 4.90 (each q, 1 H, each $J = 5.3$ Hz, 1′-H), 5.14 and 5.17 and 5.24 (each t, 1 H, each $J = 5.9$ Hz, 6-H), 5.44 (m, 1 H, 10-H). − $C_{18}H_{30}ClNO_2$: calcd. 327.1965; found 327.1963 (HRMS).

(*E*,*E*)-1-(1-Ethoxyethoxy)-3,4,8-trimethyl-4,8-cyclodecadiene-1-carbonitrile [(±)-21]: A solution of (±)-**20** (734 mg, 2.52 mmol) in THF (40 mL) was slowly added dropwise over 6 h to a solution of $NaN(SiMe_3)_2$ (1.0 M in THF, 11.0 mL, 11.0 mmol) in dry THF (100 mL) at 70°C under Ar. After stirring for 30 min at 70°C, the resulting mixture was cooled to room temperature, and was then diluted with saturated aq. NH_4Cl 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 (15 g, hexane/ethyl acetate, 100:1) to give (±)-**21** (381 mg, 58%) as a colorless oil. − $n_D^{24} = 1.4877$. − IR (film): $\tilde{\nu} = 2220$ cm^{-1} (w, C≡N), 1640 (m, C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.02$ and 1.03 and 1.08 (each d, 3 H, each $J = 7.0$ Hz, 3-Me), 1.23 (m, 6 H, 4-Me, 2″-H), 1.38 (m, 3 H, 2′-H), 1.54 (br. s, 3 H, 8-Me), 1.70−2.20 (m, 6 H, 2, 6, 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). − $C_{18}H_{29}NO_2$ (291.4): calcd. C 74.18, H 10.03, N 4.81; found C 74.16, H 10.41, N 4.73.

(*E*,*E*)-3,4,8-Trimethyl-4,8-cyclodecadien-1-one [(±)-22]: To a solution of (±)-**21** (47 mg, 0.16 mmol) in MeOH (1 mL) was added a catalytic amount of PPTS. After stirring for 2.5 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 under reduced pressure. The residue was diluted with diethyl ether and the mixture was placed in a separatory funnel and shaken vigorously for 5 min with 1% NaOH. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with 0.2 N aq. HCl, water, saturated aq. $NaHCO_3$, brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (2 g, pentane/ethyl ether, 50:1) to give (±)-**22** (21 mg, 70%) as a colorless oil. − $n_D^{24} = 1.5059$. − IR (film): $\tilde{\nu} = 1710$ cm^{-1} (s, C=O), 1660 (m, C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.07$ (d, $J = 6.4$ Hz, 3 H, 3-Me), 1.46 (s, 3 H, 8-Me), 1.56 (s, 3 H, 4-Me), 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, 1 H, $J = 12.8$, 9.8 Hz, 10-H$_b$), 4.96 (d, 1 H, $J = 10.7$ Hz, 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 80.85, H 10.85.

(*E*,*E*)-1,5,10-Trimethyl-8-(1-methylethylidenyl)-1,5-cyclodecadiene [9-Methylgermacrene-B, (±)-1]: To a mixture of Sm (140 mg, 0.931 mmol), SmI_2 (0.1 M, THF) (2.5 mL, 0.25 mmol) and anhydrous $CrCl_3$ (15 mg, 95 µmol) was added a mixture of (±)-**22** (55 mg, 0.29 mmol) and 2,2-dibromopropane (170 mg, 0.845 mmol) in THF (2 mL) at room temperature under Ar. After stirring for 30 min at room temperature, the resulting mixture was diluted with pentane and filtered through a short silica-gel column. The filterate was concentrated under reduced pressure. The residue was chromatographed on silica gel (1 g, pentane) to give (±)-**1** (55 mg, 82%) as a colorless oil. − $n_D^{24} = 1.5150$. − IR (film): $\tilde{\nu} = 2920$ cm^{-1} (s), 1660 (w), 1450 (m), 1365 (m). − ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.03$ (d, 3 H, $J = 7.0$ Hz, 9-Me), 1.44 (s, 3 H, 10-Me), 1.54 (s, 3 H, 4-Me), 1.68 and 1.70 (each s, 6 H, 11-Me), 1.94 (ddd, 1 H, $J = 11.9$, 11.9, 5.2 Hz, 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, 1 H, $J = 13.8$ Hz, 6-H$_b$), 4.39 (d, 1 H, $J = 11.0$ Hz, 5-H), 4.72 (dd, 1 H, $J = 12.2$, 3.1, 1-H). − ^{13}C NMR (126 MHz, $CHCl_3$): $\delta = 11.1$, 16.4, 20.44, 20.74, 20.90, 25.3, 34.4, 39.0, 40.8, 46.3, 125.7, 127.0, 128.2, 130.9, 133.8, 140.2. − $C_{16}H_{26}$ (218.4): calcd. C 88.00, H 12.00; found C 87.70, H 12.27.

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