mosphere. Water was added and the mixture was extracted with ether and washed twice with water. Flash chromatography (50% EtOAc/hexane) afforded 220 mg (99%) of unsaturated ester **11a** as a colorless oil: R_f 0.57 (50% EtOAc/hexane); IR (neat) 2226, 1741, 1724, 1657, 1438 cm^{-1}; GC/MS, *m/e* (relative intensity) 250 (74), 218 (29), 173 (24), 93 (70), 67 (100); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.79 (dd, J = 15.7, 8.2 Hz, 1 H), 5.92 (d, J = 15.7 Hz, 1 H), 5.15 (q, J = 5.2 Hz, 1 H), 3.74 (s, 3 H), 3.60 (m, 2 H), 2.75–1.50 (m, 10 H), 1.38–1.18 (m, 6 H), 1.19 (s, 3 H).

Keto Alcohol 12. To a solution of 100 mg (0.29 mmol) of ketone **11a** in 4 mL of THF was added a solution of 220 mg (0.87 mmol) of lithium hydridotri-*tert*-butoxyaluminate (Alfa) in 1.5 mL of THF dropwise at −75 °C over a period of 10 min under a nitrogen atmosphere. The reaction mixture was stirred at this temperature for 2.5 h and at 0 °C for 3 h. The mixture was poured into a cold dilute acetic acid extracted with ether and washed with saturated sodium bicarbonate and water. The organic portion was dried over $MgSO_4$ and concentrated in vacuo to give a mixture of diastereomeric alcohols **11b** [R_f 0.37, 0.29 (50% EtOAc/hexane)] in quantitative yield. The mixture of the crude alcohols in 2 mL of ether, 2 mL of methanol, and 0.5 mL of 5% HCl was stirred at room temperature for 50 min. The solution was extracted with ethyl acetate and concentrated in vacuo. To the residue was added 4 mL of absolute methanol and 150 mg of finely ground anhydrous potassium carbonate and the mixture was stirred at room temperature for 30 min. The mixture was taken up in ethyl acetate, washed successively with 5% HCl, saturated sodium bicarbonate solution, and brine, dried over $MgSO_4$, and concentrated in vacuo to give 64 mg (89%) of keto alcohol **12** as a colorless oil: R_f 0.23 (50% EtOAc/hexane); IR (neat) 3437 (br), 1728, 1716, 1650, 1456 cm^{-1}; GC/MS, *m/e* (relative intensity) 252 (M^+, 20), 193 (15), 180 (53), 149 (40), 113 (90), 81 (100); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.75 (dd, J = 15.6, 7.5 Hz, 1 H), 5.79 (d, J = 15.6 Hz, 1 H), 3.90 (br t, J = 8.7 Hz, 1 H), 3.71 (s, 3 H), 2.60–1.20 (m, 10 H), 0.76 (d, J = 0.5 Hz, 3 H), hydroxyl proton was not observed.

Ester 13. A solution of 62.0 mg (0.25 mmol) of unsaturated ester **12** and 10.0 mg of 10% Pd/C in 4 mL of ethyl acetate was stirred at room temperature under an atmosphere of hydrogen (1 atm) for 30 min. The reaction mixture was filtered through a Celite (10 g) pad with ethyl acetate and the filtrate through a Celite (10 g) pad with ethyl acetate and the filtrate was concentrated in vacuo to give 61.0 mg (98%) of pure ester **13** as a colorless oil: R_f 0.14 (50% EtOAc/hexane); IR (neat) 3460 (br), 1735, 1710, 1435 cm^{-1}; GC/MS, *m/e* (relative intensity) 254 (M^+, 13), 223 (11), 180 (100), 149 (36), 121 (44), 109 (31); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.86 (br t, J = 8.6 Hz, 1 H), 3.67 (s, 3 H), 2.50–1.30 (m, 14 H), 0.71 (s, 3 H), hydroxyl proton was not observed. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.86; H, 8.77.

Keto Acid 15. To a solution of 40.0 mg (0.16 mmol) of ester **13** and 44.0 mg (0.64 mmol) of imidazole in 1.5 mL of DMF was added a solution of *tert*-butyldimethysilyl chloride in 0.7 mL of DMF dropwise at room temperature under a nitrogen atmosphere over a period of 5 min. The solution was stirred for 17.5 h at this temperature and then poured into water. The solution was extracted 8 times with pentane, washed successively with 5% HCl saturated sodium bicarbonate, and brine. The pentane solution was dried over $MgSO_4$ and concentrated in vacuo to give 57.0 mg of silyl ether **14** as a colorless oil. An analytical sample was prepared by flash chromatography (20% EtOAc/hexane): R_f 0.48 (25% EtOAc/hexane); IR (neat) 1739, 1712, 1252 cm^{-1}; GC/MS(CI) *m/e* (relative intensity) 369 (M^+ + 1, 100), 353 (37), 337 (94); ^1H NMR ($CDCl_3$, 90 MHz) δ 3.77 (br t, J = 8.5 Hz, 1 H), 3.65 (s, 3 H), 2.50–1.30 (m, 14 H), 0.85 (s, 9 H), 0.67 (s, 3 H), 0.01 (s, 6 H).

The crude product was dissolved in 5 mL of methanol and was added to 0.5 mL of 5% aqueous potassium hydroxide solution at room temperature. The solution was stirred at this temperature for 4 h and then neutralized with 5% HCl. The reaction mixture was extracted 3 times with methylene chloride, dried over $MgSO_4$, and concentrated in vacuo to give 50.0 mg (91%) of acid **15** as a crystalline solid. Recrystallization gave material of mp 135–136 °C (cyclohexane; lit.[15] mp 118–120 °C, EtOAc); R_f 0.40 (50% EtOAc/hexane); IR ($CHCl_3$) 2957, 2929, 2856, 1706, 1470, 1420, 1137, 1096, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.78 (br t, J = 8.5 Hz, 1 H), 2.50–1.35 (m, 14 H), 0.86 (s, 9 H), 0.68 (s, 3 H), 0.00 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 210.9, 178.3, 80.1, 53.3, 48.4, 46.9, 46.2, 35.9, 31.1, 29.3, 25.8, 23.2, 18.0, 12.2, −4.5, −4.9.

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Registry No. (±)-**1**, 83747-57-3; (±)-**2**, 91202-50-5; (±)-**2** alcohol, 91202-51-6; (±)-**3**, 91202-52-7; (±)-**4a**, 91202-53-8; **4a** cyanohydrin, 91202-54-9; **4a** acetal cyanohydrin, 91202-55-0; (±)-**4b**, 91237-59-1; (±)-**5a**, 91237-60-4; (±)-**5b**, 91237-61-5; (±)-**6**, 91237-62-6; (±)-**7a**, 91202-56-1; **7b**, 91202-57-2; **7b** alcohol, 91202-58-3; (±)-**8a**, 91202-59-4; (±)-**8c**, 91202-60-7; **9a**, 91202-61-8; (±)-**9b**, 91202-62-9; **10**, 91202-63-0; **11a**, 91202-64-1; **11b**, 91202-65-2; (±)-**12**, 91202-66-3; (±)-**13**, 91202-67-4; (±)-**14**, 91202-68-5; (±)-**15**, 91237-63-7; (*E*)-2-butene-1,4-diol, 821-11-4; *tert*-butyldimethylsilyl chloride, 18162-48-6; (*E*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-buten-1-ol, 91202-69-6; (*E*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-buten-1-ol mesylate, 91202-70-9; (*E*)-1-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-butene, 91202-71-0; $MeO_2CCH{=}PPh_3$, 2605-67-6.

An Efficient Construction of Germacrane Skeleton via the Substituted (Phenylthio)acetonitriles: The Synthesis of (−)-Dihydrogermacrene D†

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An efficient cyclization procedure using intramolecular alkylation of a substituted acetonitrile was developed for the preparation of medium cyclic systems. A synthesis of (−)-dihydrogermacrene D, a sesquiterpene derivative with a 10-membered ring, was achieved via this route.

(−)-Germacrene D (**1**), one of typical germacrane sesquiterpenes which have been recognized as both biogenetic and synthetic precursors to a variety of sesquiterpene families,[1] was first isolated from *Pseudotsuga japnonica* by Hirose and co-workers in 1969.[2] Since then, this labile compound has been detected widely in plants, especially

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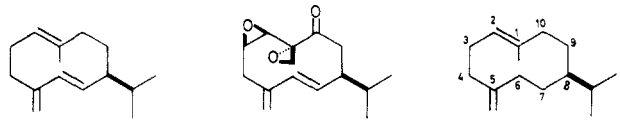
0022-3263/84/1949-3281$01.50/0

in Compositae. In 1975, Takahashi et al. discovered that **1** is active as a sex pheromone mimic against the American



1 **2** **3**

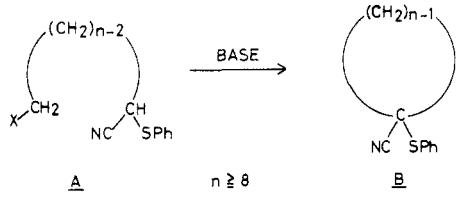
cockroach, *Periplaneta americana* L. (threshold, 10^{-1} mg).[3] The true pheromone, periplanone B (**2**) (threshold, 10^{-9} mg), identified by Persoons et al. in the next year,[4] also contains the same carbon skeleton as **1**. Because of its extreme instability, a synthesis of **1** has not yet been achieved. Dihydrogermacrene D (**3**) was obtained by hydrogenation of **1** during studies on the structural elucidation[1] and structure–pheromone activity relationship of **1**.[5]

In connection with our continuing interest on the synthesis of medium ring systems and optically active compounds with pheromone activity, syntheses of these analogues **1–3** have been investigated. Although several methods for the preparation of 10-membered rings and their utilization for syntheses of germacrene sesquiterpenes have been reported,[6] some of them are reversible processes and at equilibrium the six-membered ring form dominates.[6b-d,h,i,n] Procedures that overcome this difficulty have been reported recently.[6j-m,o,7]

We now describe an efficient cyclization procedure for cyclodecanes and its application to the synthesis of (−)-dihydrogermacrene D.[8]

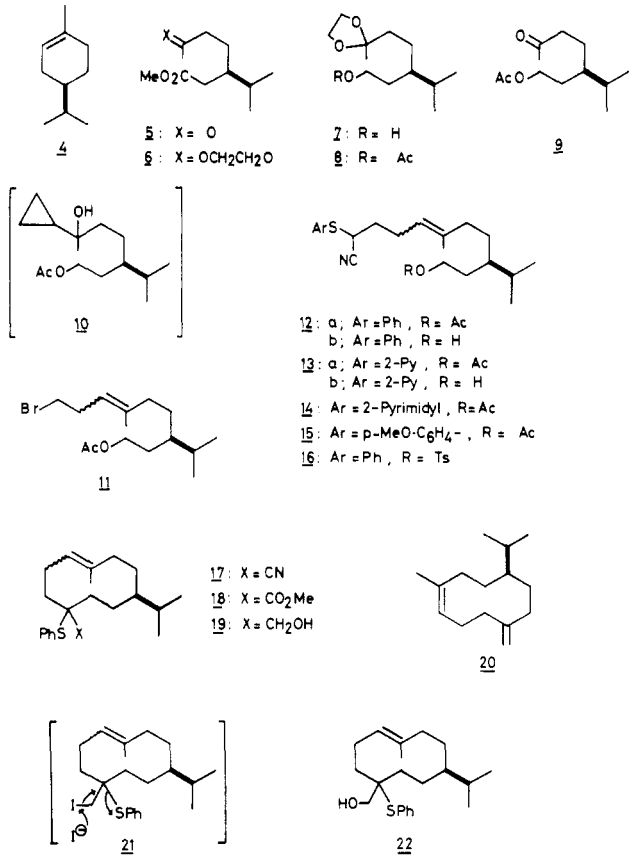
Discussion

Our synthetic planning was based on the intramolecular alkylation of the precursor A in which the methine proton is doubly activated by nitrile and phenylthio groups. In this procedure, cyclizations can be a ccomplished without high dilution techniques because product B does not contain any active hydrogen and the process is irreversible. In order to prove the efficiency of this method, we selected **3** as the first target molecule. (+)-Dihydrolimonene (**4**), easily available from (+)-limonene,[9] was employed as a chiral starting material.



A $n \geq 8$ **B**

Preparation of the Precursor for the Cyclization. Ozonolysis of **4** and oxidative workup with Jones' reagent followed by esterification with diazomethane provided keto ester **5** (77%) which was treated with ethylene glycol to give an acetal **6** in 98% yield. Reduction with $LiAlH_4$, acetylation, and subsequent hydrolysis with 35% HCl-O_4–THF (0 °C, 5 min) gave a keto acetate **9** in 95% yield. Selective addition of cyclopropylmagnesium bromide[10] to **9** at −5 to 0 °C was followed by the cleavage of the resulting cyclopropylcarbinol **10** with 47% HBr at 0 °C to give a mixture of acetoxy bromides **11** in 68% yield. Unfortunately, this Julia rearrangement[11] was not stereoselective as anticipated and the ratio of *E* and *Z* isomer had to be determined at a later stage, because the labile bromides **11** could not be analyzed by GC.



4 **5**: X = O; **6**: X = OCH_2CH_2O **7**: R = H; **8**: R = Ac **9** **10** **11**

12: a; Ar = Ph, R = Ac; b; Ar = Ph, R = H
13: a; Ar = 2-Py, R = Ac; b; Ar = 2-Py, R = H
14: Ar = 2-Pyrimidyl, R = Ac
15: Ar = p-MeO-C_6H_4-, R = Ac
16: Ar = Ph, R = Ts

17: X = CN; **18**: X = CO_2Me; **19**: X = CH_2OH **20** **21** **22**

Phase transfer catalyzed alkylation[12] of various (arylthio)acetonitriles ($ArSCH_2CN$, Ar = phenyl, 2-pyridyl, 2-pyrimidyl, and *p*-methoxyphenyl) with **11** was attempted to establish what kind of aryl group is the best substituent for the alkylation. Refluxing **11** and (arylthio)acetonitriles with base in benzene for 60 min gave alkylated products (**12a**, 71%; **13a**, 42%; **14**, 10%; **15**, trace). In the case of

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14 and 15, reaction was extremely slow and most of the starting material remained even after refluxing for 2 h. Accordingly, (phenylthio)acetonitrile was chosen as a candidate for the cyclization. Refluxing 11 with (phenylthio)acetonitrile (1.5 equiv) in the presence of 50% NaOH (2 equiv) and n-Bu_4NBr (0.5 equiv) in benzene for 75 min gave a mixture of **12a,b** which without separation was treated with 1% MeONa in dry methanol for 30 min to give hydroxy nitrile **12b** in 79–86% yield.[13] Tosylation of **12b** provided **16**, the precursor for the cyclization, in 81% yield.

Formation of Cyclodecene Ring and Transformation to (−)-Dihydrogermacrene D. Preliminary experiments indicated that DME and $NaN(SiMe_3)_2$ were the proper solvent and base for the key step. Cyclization was effected by addition of **16** in DME over 2 h to a solution of $NaN(SiMe_3)_2$ (2 equiv) in DME at reflux temperature to give cyclodecene derivative **17** in 80% yield. The concentration of tosylate **16** had to be kept below 0.033 M (1 g/60 mL) to give only the desired monomer; at concentrations higher than 0.05 M (1 g/40 mL) using $LiN(SiMe_3)_2$ as a base, however, the dimer became the main product. Thus, this method is very useful for preparative scale synthesis of 10-membered ring systems. Use of the procedure for syntheses of other medium cyclic and macrocyclic carbon skeletons will be discussed elsewhere.[14]

The remaining problems were conversion of the thiophenyl and cyano groups to an exocyclic methylene and the separation of E and Z isomers. Alkaline hydrolysis of the nitrile under strenuous conditions and successive treatment with diazomethane provided a methyl ester mixture **18** (71%) which was reduced with $LiAlH_4$ to give vicinal hydroxy sulfide **19** (88%). Mesylation of crude **19**, followed by treatment with excess sodium iodide in refluxing acetone in the presence of sodium bicarbonate gave directly a mixture of (−)-dihydrogermacrene D (**3**) and Z isomer **20** in 54% yield, presumably via reductive elimination of an intermediate iodo sulfide **21** with excess sodium iodide. A GC analysis revealed that the product was a mixture of **3** and **20** (57:43), whose separation by preparative GC afforded **1** (93% pure) and **20** (81% pure).

When mixture **19** was purified by chromatography (Lobar column–medium pressure), two fractions, I (76.5%) and II (23.5%), were obtained. Fraction I solidified in the refrigerator; the solid was recrystallized from n-pentane to give E isomer **22**, mp 87–88 °C, which was submitted to the sequence described above to give (−)-dihydrogermacrene D **3** (98% pure by GC analysis, $[\alpha]^{21}_D$ −42.7° (c 0.55, $CHCl_3$), whose spectral data were identical with those reported.[5] The E stereochemistry of the trisubstituted olefin unit in synthetic **3** and **22** was confirmed by ^1H NMR analysis at 400 MHz which showed no NOEs between C–H and C–Me protons.

In summary, intramolecular alkylation of ω-(tosyloxy)-α-(phenylthio)alkanenitrile under optimized condition provided an efficient formation of cyclodecenes and the synthesis of (−)-dihydrogermacrene D was achieved via this route.

Experimental Section

All boiling points and melting points are uncorrected. IR spectra were obtained with a Jasco A-102 spectrophotometer. ^1H NMR were measured with Hitachi R-24 (60 MHz) and JEOL FX-400 (400 MHz) spectrometers. All signals are in ppm downfield from Me_4Si used as internal standard. Unless otherwise noted, CCl_4 was used as solvent. MS and GC–MS were measured with a Hitachi RMU-6MG spectrometer with using a glass capillary column; PEG-20M, 0.25 mm × 50 m. Optical rotations were obtained with a Jasco DIP-140 polarimeter.

Methyl (*R*)-3-(1-Methylethyl)-6-oxoheptanoate (5). Ozone was bubbled into a solution of dihydrolimonene (**4**) (90% pure, 152 g, 1.1 mol) in acetone (760 mL) at −78 °C over 8 h. After removal of excess ozone with nitrogen, Jones' reagent (125 mL, 1 mol) was added to the resulting ozonide solution at −70 to −65 °C over 30 min. The mixture was stirred until the temperature was raised to −10 °C and MeOH (10 mL) was added to decompose excess reagent. After the reaction mixture was concentrated in vacuo, the residue was diluted with water and extracted with ether repeatedly. The extract was washed with cold 15% NaOH aqueous (100 mL × 5) and the aqueous layer was acidified with cold 4 N HCl, saturated with NaCl, and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The resulting crude acid was treated with excess CH_2N_2 for 5 min; the workup gave the crude ester which on distillation under reduced pressure gave **5** (154 g, 77%); bp 84–85 °C (0.65 mmHg); n^{24}_D 1.4382; R_f 0.34 (hexane/EtOAc 3/1); $[\alpha]^{24}_D$ + 2.33° (c 1.29, $CHCl_3$); IR (film) 1742, 1722, 1460, 1440, 1370, 1260, 1200, 1170 (sh), 1160, 1110, 1020 cm^{-1}; NMR 0.87 (6 H, d, J = 6.0 Hz), 1.25–2.05 (4 H, m), 2.08 (3 H, s), 2.10–2.60 (4 H, m), 3.64 (3 H, s). Anal. Found: C, 65.61; H, 9.97. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07.

Methyl (3*R*)-6,6-(Ethlenedioxy)-3-(1-methylethyl)heptanoate (6). A mixture of the keto ester **5** (140 g, 0.7 mol), ethylene glycol (47 g, 0.76 mol), and p-TsOH (1 g) in benzene (560 mL) was refluxed with a Dean-Stark water separator to remove water completely. After cooling, the reaction mixture was washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. Distillation under reduced pressure gave **6** (167.3 g, 98%); bp 97–98 °C (0.60 mmhg); n^{24}_D 1.4425; R_f 0.37 (hexane/EtOAc 3/1); $[\alpha]^{25}_D$ + 2.98° (c 1.02, $CHCl_3$); IR (film) 1742, 1460 (sh), 1440, 1380, 1338, 1255, 1220, 1170, 1120, 1055 (br), 950, 855 cm^{-1}; NMR 0.87 (6 H, d, J = 6.0 Hz), 1.23 (3 H, s), 1.20–2.00 (6 H, m), 2.05–2.35 (2 H, m), 3.63 (3 H, s), 3.88 (4 H, s). Anal. Found: C, 63.72; H, 9.90. Calcd for $C_{13}H_{24}O_4$: C, 63.90; H, 9.90.

(3*R*)-6,6-(Ethylenedioxy)-3-(1-methylethyl)-1-heptanol (7). A solution of the ester **6** (48.8 g, 0.2 mol) in dry ether (100 mL) was added dropwise to a suspension of $LiAlH_4$ (6.1 g, 0.15 mol) in dry ether (300 mL) at −5 to 0 °C over 60 min and the mixture was stirred for a further 60 min at 0–10 °C. Filtration after careful addition of water and aqueous NaOH, drying of the filtrate ($MgSO_4$), and concentration afforded crude alcohol **7** (43.6 g), which was directly used for the next step.

In another run, analytical sample was obtained by distillation. **7**: bp 119–120 °C (1.3 mmHg); n^{22}_D 1.4564; R_f 0.07 (hexane/EtOAc 3/1); $[\alpha]^{22}_D$ + 1.49° (c 1.06, $CHCl_3$); IR (film) 3430, 1465, 1378, 1255, 1220, 1090 (sh), 1050, 945, 860 cm^{-1}; NMR 0.86 (6 H, d, J = 6.0 Hz), 1.05–2.00 (8 H, m), 1.22 (3 H, s), 2.76 (1 H, br s, OH), 3.52 (2 H, br t, J = 6.0 Hz), 3.85 (4 H, s). Anal. Found: C, 66.45; H, 10.99. Calcd for $C_{12}H_{24}O_4$: C, 66.63; H, 11.18.

(*R*)-7-Acetoxy-5-(1-methylethyl)-2-heptanone (9). A mixture of the crude alcohol **7** (43.6 g) and Ac_2O (30 mL, 0.3 mol) in pyridine (150 mL) was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-concentrated HCl (2:1) and extracted quickly with ether. The extract was washed with cold 4 N HCl, water, aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to give a crude acetate **8**, which was submitted to the next step without purification. The crude acetal **8** (52 g) was dissolved in a mixture of THF–35% $HClO_4$ (1/1, 310 mL) at 0 °C and stirred vigorously for 5 min. The reaction mixture was poured into 25% aqueous Na_2CO_3 and ether carefully. The ether layer was separated and the aqueous layer was extracted with ether. The combined extract was washed with aqueous Na_2CO_3 and brine, dried ($MgSO_4$), and concentrated. The residue was distilled under reduced pressure to give **9** (40.7 g, 95%): bp 107–8 °C (1.5 mmHg); n^{22}_D 1.4936; R_f 0.32 (hexane/EtOAc $[\alpha]^{22}_D$ + 2.57° (c 1.11, $CHCl_3$); IR (film) 1738, 1715, 1465, 1420 (sh), 1385, 1365, 1240, 1162, 1030 cm^{-1}; NMR 0.86 (8 H, d, J = 6.0 Hz), 1.00 −1.95 (6 H, m,), 1.91 (3 H, s), 2.00 (3 H, s), 2.31 (2 H, br t, J = 7.0 Hz), 3.89 (2 H, t, J = 7.0 Hz). Anal.

(13) Efficient stirring was critical for high yield. Accordingly, the yield varied slightly depending on the reaction scale, the highest yield being obtained at a 500-mg scale. Preparative scale reactions (4–6 g) gave a 79–82% yield.

(14) Kitahara, T.; Hidaka, A.; Hatakeyama, H.; Mori, K., manuscript is in preparation.

Found: C, 66.52; H, 10.26. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35.

[3(*R*),6(*E*,*Z*)]-9-Bromo-6-methyl-3-(1-methylethyl)-6-nonenyl Acetate (11). Cyclopropylmagnesium bromide was prepared from bromocyclopropane (13.3 g, 0.11 mol) and Mg (2.88 g, 0.12 mol) in dry THF (110 mL) by Seyferth's procedure.[10] To a solution of the keto acetate **9** (15.0 g, 0.07 mol) in dry THF (45 mL) was added dropwise a solution of cyclopropylmagnesium bromide in THF over 20 min at −5 to 0 °C under argon and the mixture was stirred for an additional 20 min below 0 °C. The reaction mixture was poured into cold aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated to give crude cyclopropylcarbinol **10** (18 g): IR (film) 3380, 3090, 1740, 1240, 1035, 785, 760 cm^{-1}. To a solution of this in ether (72 mL) was added cold 47% aqueous HBr (36 mL) as rapidly as possible below 0 °C. The mixture was stirred for 10 min and added carefully to cold saturated aqueous Na_2CO_3. The ether layer was separated and the aqueous layer was extracted with ether. The combined extract was washed with 10% aqueous Na_2CO_3 and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (SiO_2, 250 g, hexane/EtOH 95/5–4/1) to give **11** (15.2 g, 68%) and starting material **9** (1.7 g). **11**: n^{24}_D 1.4769; R_f 0.68 (hexane/EtOAc 3/1); $[\alpha]^{24}_D$ −0.45° (*c* 0.82, hexane); IR (film) 1740, 1660, 1460 (br), 1385, 1370, 1265 (sh), 1240, 1030 (br) cm^{-1}; NMR 0.85 (6 H, d, J = 6.0 Hz), 1.00–2.30 (8 H, m), 1.60 (3 H, br s), 1.93 (3 H, s), 2.50 (2 H, br q, J = 7.0 Hz), 3.24 (2 H, t, J = 7.0 Hz), 3.94 (2 H, t, J = 7.0 Hz), 5.07 (1 H, br t, J = 7.0 Hz).

[2(*R*,*S*),5(*E*,*Z*),9*R*]-11-Hydroxy-6-methyl-9-(1-methylethyl)-2-(2-pyridylthio)-5-undecenenitrile (13b). A mixture of the bromide **11** (2.56 g, 8.0 mmol), (2-pyridylthio)acetonitrile (1.82 g, 12.0 mmol), 50% aqueous NaOH (w/w, 1.41 mL, 17.6 mmol), and *n*-Bu_4NBr (1.29 g, 4 mmol) in benzene (2 mL) was refluxed with vigorous stirring for 2 h. The reaction mixture was diluted with CH_2Cl_2, washed with water, dried ($MgSO_4$), and concentrated. The residue was dissolved in 1% MeONa/MeOH (30 mL) and stirred at room temperature for 20 min. The reaction mixture was neutralized with 10% HCl and concentrated in vacuo. The residue was dissolved in CH_2Cl_2, washed with water, dried ($MgSO_4$), and concentrated. The residual oil was chromatographed (SiO_2, 70 g, hexane/EtOAc 85/15–80/20) to give **13b** (1.17 g, 42%); R_f 0.17 (hexane/EtoAc 3/1); $[\alpha]^{24}_D$ + 3.35° (*c* 1.01, $CHCl_3$); IR (film) 3420, 3050, 2240, 1660, 1580, 1560, 1455, 1418, 1385, 1365, 1280, 1150, 1120, 1040, 985, 760, 720 cm^{-1}; NMR 0.83 (6 H, d, J = 6 Hz), 1.00–2.60 (12 H, m), 1.60 (3 H, br s), 2.57 (1 H, br s, OH), 3.46 (2 H, br t , J = 6.0 Hz), 4.70 (1 H, t, J = 7.0 Hz), 5.04 (1 H, br t), 6.67–7.60 (3 H, m), 8.30 (1 H, d-d, J = 6.0 and 1.0 Hz).

[2(*R*,*S*),5(*E*,*Z*),9*R*]-11-Hydroxy-6-methyl-9-(1-methylethyl)-2-(phenylthio)-5-undecenenitrile (12b). A mixture of the bromide **11** (4.78 g, 15 mmol), (phenylthio)acetonitrile (3.35 g, 22.5 mmol), 50% aqueous NaOH (1.8 mL, 22.5 mmol), and *n*-Bu_4NBr (1.93 g, 6 mmol) in benzene (2 mL) was refluxed with vigorous stirring for 40 min. To this was added an additional amount of *n*-Bu_4NBr (0.48 g, 1.5 mmol) and 50% aqueous NaOH (0.4 mL, 5 mmol) and the mixture was again refluxed with vigorous stirring for 30 min. The reaction mixture was diluted with ether, washed with water, dried ($MgSO_4$), and concentrated. This procedure was repeated again on the same scale; the combined residue (13.0 g) was dissolved in 1% MeONa/MeOH (65 mL) and the mixture was stirred at room temperature for 30 min. The reaction mixture was neutralized with 10% HCl and concentrated in vacuo. The residue was dissolved in ether, washed with water, dried ($MgSO_4$), and concentrated. The crude product was chromatographed (SiO_2, 100 g, hexane/EtOAc 90–10–85/15) to give **12b** (8.47 g, 82%): R_f 0.23 (hexane/EtOAc 3/1); $[\alpha]^{21.5}_D$ + 0.57° (*c* 2.13 $CHCl_3$); IR (film) 3400, 3050, 2230, 1580, 1480, 1440, 1380, 1360, 1050, 1020, 745, 690 cm^{-1}; NMR 0.83 (6 H, d, J = 6.0 Hz), 1.00–2.46 (13 H, m), 1.62 (3 H, br s), 3.44 (2 H, br t, J = 6.0 Hz), 3.57 (1 H, t, J = 7.0 Hz), 4.97 (1 H, br t), 7.00–7.70 (5 H, m); MS, m/z 346 (M^+ + 1), 331, 318, 313, 303, 285, 245, 237, 219, 203, 186, 149, 119, 110, 109, 97, 95, 85, 83 (100), 81, 71, 69, 57, 55, 43. Anal. Found: C, 72.67; H, 8.93; N, 4.12. Calcd for $C_{21}H_{31}NOS$: C, 73.00; H, 9.05; N, 4.05.

[2(*R*,*S*),5(*E*,*Z*),9*R*]-6-Methyl-9-(1-methylethyl)-2-(phenylthio)-11-[(*p*-tolylsulfonyl)oxy]-5-undecenenitrile (16). To a solution of the alcohol **12b** (7.94 g, 23 mmol) in dry pyridine (24 mL) was added *p*-TsCl (5.68 g, 29.9 mmol) at −5 to 0 °C and the mixture was stirred at 0 °C for 3 h. The reaction mixture was poured into cold 4 N HCl and extracted with ether. The extract was washed with 4 N HCl, water, aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (SiO_2, 90 g, hexane/EtOAc 9/1–4/1) to give **16** (9.3 g, 81%): R_f 0.30 (hexane/EtOAc 3/1); $[\alpha]^{21.5}_D$ −3.93° (*c* 1.07, $CHCl_3$); IR (film) 3060, 2230, 1600, 1590 (sh), 1460, 1440, 1380 (sh), 1360, 1190, 1175, 1100, 1020, 955, 900, 815, 750 cm^{-1}; NMR 0.79 (6 H, d, J = 6.0 Hz), 1.00–2.50 (12 H, m), 1.58 (3 H, br s), 2.39 (3 H, s), 3.55 (1 H, t, J = 7.0 Hz), 3.90 (2 H, br t, J = 6.0 Hz), 4.94 (1 H, br t), 7.00–7.60 (7 H, m), 7.61 (2 H, d, J = 8.0 Hz).

[1(*R*,*S*),4(*E*,*Z*),8*R*]-5-Methyl-8-(1-methylethyl)-1-(phenylthio)-4-cyclodecenecarbonitrile (17). To a stirred solution of $NaN(SiMe_3)_2$ (3.62 g, 20 mmol) in dry DME (140 mL) under reflux was added dropwise a solution of the tosylate **16** (4.99 g, 100 mmol) in dry DME (160 mL) over 2.5 h. The mixture was stirred under reflux for an additional 10 min and the cooled reaction mixture was quenched with aqueous NH_4Cl. DME was removed in vacuo and the residue was dissolved in ether, washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed (SiO_2, 250 g, hexane/EtOAc 97/3) to give **17** (2.62 g, 80%): R_f 0.69 (hexane/EtOAc 3/1); $[\alpha]^{21}_D$ −7.68° (*c* 1.22, $CHCl_3$); IR (film) 3080 (sh), 3060, 2230, 1665, 1585, 1575, 1480, 1470, 1455, 1440, 1385, 1370, 1120, 1070, 1025, 920, 815, 750, 705, 695 cm^{-1}; NMR 0.67–0.85 (6 H, m), 1.00–2.90 (14 H, m), 1.72 (3 H, br s), 4.80–5.70 (1 H, m), 7.10–7.73 (5 H, m); MS, m/z 327 (M^+), 312, 298, 294, 284, 250, 218, 204, 202, 190, 174, 162, 148, 135, 121, 109 (100), 108, 95, 83, 81, 69, 55, 43, 41. Anal. Found: C, 76.53; H, 8.95; N, 4.23. Calcd for $C_{21}H_{29}NS$: C, 77.02; H, 8.93; N, 4.28.

Methyl [1(*R*,*S*),4(*E*,*Z*),8*R*]-5-Methyl-8-(1-methylethyl)-1-(phenylthio)-4-cyclodecenecarboxylate (18). A mixture of **17** (2.29 g, 7.0 mmol) and aqueous KOH, prepared from 85% KOH (2.73 g, 42 mmol) and the minimum amount of water to dissolve the KOH, $MeOCH_2CH_2OH$ (12 mL), and $(CH_2OH)_2$ (12 mL), was heated at 170–175 °C for 48 h. The reaction mixture was diluted with water and extracted with ether. The ether layer was washed with 5% KOH. The combined aqueous layer was acidified with cold 4 N aqueous HCl (pH 3) and extracted with ether. The extract was washed with brine, dried, and then treated with excess CH_2N_2 for 5 min; the usual workup gave an oil which was chromatographed (SiO_2, 70 g, hexane/EtOAc 97/3) to give **18** (1.79 g, 71%): R_f 0.62 (hexane/EtOAc 3/1); $[\alpha]^{21.5}_D$ −18.1° (*c* 0.85 $CHCl_3$); IR (film) 3080 (sh), 3060, 1730, 1660, 1585, 1575, 1470 (sh), 1455, 1440, 1385, 1365, 1260, 1230 (sh), 1210, 1160, 1080, 1065, 1025, 750, 705, 690 cm^{-1}; NMR 0.81 (6 H, br, d, J = 6.0 Hz); 0.90–2.65 (14 H, m), 1.61 and 1.73 (total 3 H, each br s), 3.53 and 3.56 (total 3 H, each s), 4.55–5.85 (1 H, m), 7.10–7.45 (5 H, br s); MS, m/z 360 (M^+), 317, 301, 283, 251, 250, 219, 207, 191 (100), 175, 149, 147, 135, 123, 121, 109, 107, 95, 93, 83, 81, 79, 69, 67, 55, 43, 41. Anal. Found: C, 73.08; H, 8.90. Calcd for $C_{22}H_{32}O_2S$: C, 73.30; H, 8.95.

[1(*R*,*S*),4(*E*,*Z*),8*R*]-5-Methyl-8-(1-methylethyl)-1-(phenylthio)-4-cyclodecenemethanol (19). A solution of the ester **18** (1.44 g, 4.0 mmol) in dry ether (15 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (152 mg, 4.0 mmol) in dry ether (15 mL) over 30 min at −5 to 0 °C. The mixture was stirred for an additional 30 min and quenched with water and 10% aqueous NaOH. The precipitate was filtered and washed thoroughly with ether. The filtrate was dried ($MgSO_4$) and concentrated. The residue was passed through a short column (SiO_2, 15 g, hexane/EtOAc 4/1) to collect the alcohol fraction (giving a lengthy spot on TLC), **19** (1.17 g, 88%) [IR (film) 3430, 3070, 3050, 1580, 1570, 1465, 1435, 1380, 1195, 1050 (br), 1020, 780, 745, 700, 690 cm^{-1}], which was submitted to the next step without further purification.

(1*E*,8*S*)-1-Methyl-5-methylene-8-(1-methylethyl)-1-cyclodecene (3) and (1*Z*,8*S*)-1-Methyl-5-methylene-8-(1-methylethyl)-1-cyclodecene (20). To a solution of crude **19** (1.17 g) in pyridine (2 mL) was added slowly MsCl (460 mg, 4 mmol) at −5 to 0 °C and the mixture was stirred for 90 min at 0 °C. The reaction mixture was poured into cold aqueous HCl and extracted with ether. The extract was washed with cold 2 N HCl, water, aqueous $NaHCO_3$, and brine, dried, and concentrated. The residue was mixed with NaI (6.0 g, 40 mmol) and $NaHCO_3$ (840 mg, 10 mmol) in dry acetone (25 mL) and the

mixture was stirred under reflux for 15 h. After the solvent was removed in vacuo, the residue was diluted with water and extracted with pentane. The extract was washed with aqueous $Na_2S_2O_3$, water, and brine, dried, and concentrated. The residue was chromatographed (Al_2O_3, grade II, 50 g, pentane/ether 97.5/2.5) to give a mixture of **3** and **20** (392 mg, 54%). GC [PEG–20 M, 0.25 mm × 50 m glass capillary column, temp 70–220 °C, rate 3°C/min, N_2 pressure 1.2 Kg/cm^2] t_R: **20**, 24.11 min (38.0%); **3**, 24.47 min (49.9%). Preparative GC was performed with a Hitachi 163 gas chromatograph (PEG-20 M, 10 mm × 3 m stainless column) to give **3** (93% pure) and **20** (81% pure. **3**: $[\alpha]^{25}_D$ −41.0° (*c* 0.50, $CHCl_3$); IR (film) 3080, 1660 (sh), 1638, 1450 (br), 1382, 1365, 1185, 1165, 1110, 1090, 1025, 890, 880 (sh), 805 cm^{-1}; NMR (400 MHz) 0.78 (3 H, d, *J* = 7.8 Hz), 0.88 (3 H, d, *J* = 7.8 Hz), 0.96–1.09 (1 H, m), 1.09–1.20 (2 H, m), 1.21–1.32 (1 H, m), 1.34–1.42 (1 H, m), 1.55–1.64 (1 H, m), 1.64 (3 H, br s), 1.82–2.05 (4 H, m), 2.10–2.22 (2 H, m), 2.22–2.35 (2 H, m), 2.55–2.65 (trace, due to the methylene protons of *Z* isomer), 460 and 474 (trace, due to the exocyclic olefin protons of *Z* isomer), 4.81 (1 H, br s, hhw = 6.0 Hz), 4.84 (1 H, br s), hhw = 6.0 Hz), 6.37 (1 H, br t, *J* = 7.8 Hz), no NOE effect was observed between C_2–H and C_1–Me; GC–MS, *m/z* 206 (M^+), 191, 177, 163, 150, 135, 121, 109, 107, 95, 93, 81, 69, 67, 55, 43, 41 (100), 32. **20**: $[\alpha]^{21}_D$ −29.9° (*c* 0.26, $CHCl_3$); IR (film) 3090, 1660 (sh), 1638, 1455 (br), 1382, 1375 (sh), 1365, 1230, 1200, 1170, 1085, 1020, 925, 890, 840, 820, 740 cm^{-1}; NMR (400 MHz) 0.78 (3 H, d, *J* = 7.9 Hz), 0.85 (3 H, d, *J* = 7.9 Hz), 0.98–1.08 (1 H, m), 1.21–1.40 (2 H, m), 1.45–1.68 (3 H, m), 1.60 (3 H, br s), 1.75 (1 H, br d, *J* = 15.5 Hz), 1.96 (4 H, br d, *J* = 15.5 Hz), 2.10–12.35 (4 H, m), 2.52–2.68 (2 H, m), 4.60 (0.85 H, d, *J* = 2.9 Hz), 4.74 (0.85 H, d, *J* = 2.9 Hz), 4.81 and 4.84 (each 0.15 H, due to the exocyclic olefin protons of *E* isomer), 5.10 (0.85 H, d-d, *J* = 4.4 and 11.7 Hz), 5.37 (0.15 H, t, due to the trisubstituted olefin proton of *E* isomer), clear NOE effect was observed between C_2–H and C_1–Me; GC–MS, *m/z* 206 (M^+), 191, 177, 163, 150, 135, 121, 109, 107, 95, 93, 81, 69, 67, 55, 43, 41 (100), 32. Anal. Found: C, 86.58; H, 12.42. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70.

(4*E*,8*R*)-5-Methyl-8-(1-methylethyl)-1-(phenylthio)-4-cyclodecenemethanol (22). The alcoholic fraction **19** (1.1 g) obtained by the procedure described above was rechromatographed by using a Lobar column [prepacked column size C (37 nn × 440 mm), Si 60 (63–125 μm)] to give two fractions, F-I (706 mg) and F-II (217 mg). F-I solidified partly in the refrigerator; the solid was recrystallized from *n*-pentane to give pure *E* isomer **22** (419 mg): mp 87–88 °C; $[\alpha]^{25}_D$ −18.6° (*c* 0.5, $CHCl_3$); IR (nujol) 3530, 3060, 1570, 1220, 1185, 1165, 1075, 1050, 1010, 890, 870, 815, 755, 705, 695 cm^{-1}; NMR (400 MHz) 0.75 (3 H, d, *J* = 7.0 Hz), 0.81 (3 H, d, *J* = 7.0 Hz), 0.80–0.92 (2 H, m), 1.00–1.16 (1 H, m), 1.20–1.63 (9 H, m), 1.77 (3 H, s), 1.81–2.07 (3 H, m), 2.12–2.23 (1 H, m), 2.23–2.37 (1 H, m), 2.56 (1 H, m, OH), 3.20 (1 H, d-d, *J* = 3.0 and 11.0 Hz), 3.38 (1 H, br d-d, *J* = 8.0 and 11.0 Hz), 5.52 (1 H, br t, *J* = 7.0 Hz), 7.30–7.40 (3 H, m), 7.45–7.51 (2 H, m); MS, *m/z* 332 (M^+, 266, 255, 222, 191, 179, 163, 149, 135, 125, 123, 121, 109, 95, 93, 83, 79, 66, 54, 42 (100). Anal. Found: C, 75.57; H, 9.63. Calcd for $C_{21}H_{32}OS$: C, 75.86; H, 9.70.

(−)-Dihydrogermacrene D (3). Crystalline *E* alcohol **22** (348 mg, 1 mmol) was treated in the same manner as described already for the preparation of the mixture of **3** and **20** to give **3** (105 mg, 51%), which was purified with preparative GC. **3** (98% pure): $[\alpha]^{21}_D$ −42.7° (*c* 0.55, $CHCl_3$). IR and GC–MS spectra were completely identical with those described (vide supra). The NMR spectrum (400 MHz) was almost identical with that of **3** (93% pure) except that 98% pure **3** did not show any signals due to the contamination oof *Z* isomer **20**. Anal. Found: C, 87.05; H, 12.76. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70.

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Registry No. **3**, 64141-33-9; **4**, 1195-31-9; **5**, 91201-40-0; **6**, 91201-41-1; **7**, 91201-42-2; **8**, 91201-43-3; **9**, 91201-44-4; **10**, 91201-45-5; (*R*)-(*E*)-**11**, 91201-46-6; (*R*)-(*Z*)-**11**, 91201-52-4; **12b**, 91201-47-7; **13b**, 91201-48-8; **16**, 91208-70-7; **17**, 91201-49-9; **18**, 91201-50-2; **19**, 91201-51-3; **20**, 91278-65-8; bromocyclopropane, 4333-56-6; (2-pyridylthio)acetonitrile, 7521-19-9; (phenylthio)-acetonitrile, 5219-61-4.

Ionic Bicyclobutane as an Intermediate in the Reaction of PhS^- with 3-Halobicyclobutanecarbonitrile: Comparison between Thio- and Oxycarbenium Ions[1]

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The nucleophilic reaction of PhS^- with 3-chloro- and 3-bromobicyclobutanecarbonitrile (**2**–Cl (Br)) in MeOH and DME was investigated. The products in MeOH are the dithioketal **3** and the two cis–trans isomers of the thiooxoketal **4**. The identity of the element (Cl or Br) in **2** strongly affects the product ratio **3**/**4** but has no effect on the stereodistribution of the two isomers of **4**. It is shown that the mechanism of the reaction of PhS^- with **2** in MeOH is similar to that of an alkoxide reacting with the same substrate (path c, Scheme I). After the cleavage of the central bond by the nucleophile, the thio halo ether group on C-3 expels a halide anion to form thiocarbenium before the negatively charged carbon reacts further. Addition of MeOH or PhSH to the zwitterionic intermediate completes the reaction. In DME, the mechanism is altered and 3-(phenylthio)bicyclobutanecarbonitrile (**2**–SPh) is obtained (path a, Scheme I). By carrying out the reaction at varying concentrations of MeOH in DME it is shown that **2**–SPh is not obtained via a collapse of a zwitterionic intermediate but rather by a γ-elimination step (Scheme II). The γ-elimination mechanism prevails as long as the MeOH concentration in DME is kept below 2 M. Beyond this limit the change in medium polarity induces a gradual changeover in the mechanism and the proportion of the mixed ketal **4** is increased with the concentration of MeOH and follows a sigmoidic curve. A similar sigmoidic curve is obtained for the solubility of KBr in these solvent mixtures, supporting the assumption that the mechanistic changeover is caused by the change in the nature of the medium. Qualitative analysis shows that oxygen is superior to sulfur in enhancing the formation of an adjacent positive center.

Due to geometrical constraints, the internuclear distance between two nonbonded carbon atoms in cyclobutane is only 2.1 Å.[2a] One should therefore expect that the two nonbonded carbons will strongly interact with each other

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