Cyclic Alkenenitriles: Synthesis, Conjugate Addition, and Stereoselective Annulation

Fraser F. Fleming, Zhiyu Zhang, Qunzhao Wang, and Omar W. Steward.*

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Experimental¹

General methylthiomethylation procedure.² An Ac₂O solution of the TMS cyanohydrin (4.6-1.1 mmol) was added to a room temperature, Ac₂O-DMSO solution (12 – 24 mM, 1:2), prepared 6 h in advance, followed by additional DMSO to maintain a 1:2 solvent ratio. After 40 h aqueous, 3M NaOH (26 mL) was added, and the reaction mixture extracted with hexane. The combined extracts were washed successively with 1M NaOH and water, dried (Na₂SO₄), and concentrated to afford a crude product that was then purified by radial chromatography.

1-(Methylthiomethoxy)cyclohex-2-enecarbonitrile (6a): Performing the general procedure with **5a**³ (330 mg, 3.47mmol) provided, after purification by radial chromatography (1:19 EtOAc/hexanes), 250 mg (70%) of **6a** as an oil: IR (film) 3037, 1646 cm⁻¹; ¹H NMR d 1.74-1.88 (m, 2H), 2.04-2.29 (m, 4H), 2.23 (s, 3H), 4.75 (s, 2H), 5.85(d, 1H, *J*=9.9 Hz), 6.12 (dt,1H, *J*=10, 3.7 Hz); ¹³C NMR d 14.6, 17.8, 24.5, 33.4, 70.5, 70.8, 119.8, 123.6, 135.1.

1-(Chloromethoxy)cyclohex-2-enecarbonitrile (11a): Neat thionyl chloride (12 μL, 0.15 mmol) was added to a room temperature CH₂Cl₂ solution (2 mL) of **6a** (31 mg, 0.145 mmol). After 10 min the solvent was removed to afford **11a** as an oil that was used without purification: IR: 1652, 1096 cm⁻¹; ¹H NMR d 1.78-1.95 (m, 2H), 2.02-2.14 (m, 4H), 5.65 (s, 2H), 5.87-5.95 (m, 1H), 6.18-6.26 (m, 1H); ¹³C NMR d 17.6, 24.3, 33.7, 72.3, 119.1, 122.6, 135.6.

1-(Cyanomethoxy)cyclohex-2-enecarbonitrile (vi): Standard⁴ cyanide displacement was performed on the crude chloride **11a** with TMSCN (0.3 mmol, 30mg), TBAF (0.3mmol, 0.3mL) in MeCN at 80°C for 5 min to afford a light yellow mixture that was concentrated under vacuum

to afford, after radial chromatography (3:17 EtOAc/Hexane), the dinitrile **vi** 48 mg (63%, from **6a**) as an oil: IR (film) 3039, 2234, 1646 cm^{-1} ; ^1H NMR d 1.72-1.91 (m, 2H), 2.09-2.19 (m, 4H), 4.41 (s, 3H), 5.75-5.84 (m, 1H), 6.19-6.27 (m, 1H); ^{13}C NMR d 17.4, 24.4, 32.7, 51.2, 72.3, 115.6, 118.4, 121.7, 137.3.

1-Cyano-3-methyl-1-trimethylsilyloxy-cyclopent-2-ene (5b): Following the standard cyanosilylation procedure,⁵ a CH_2Cl_2 solution (20 mL) of 3-methylcyclopent-2-en-1-one (0.49 mL, 4.32 mmol,) was added to dry ZnI_2 (850 mg, 2.6 mmol, dried at 120°C under high vacuum for 2 h) and the suspension cooled to 0°C . Stirring was continued until a homogenous solution was obtained and then neat Me_3SiCN (792 mg, 8mmol) was added. After 40 min Et_3N (2.5 mL) and Et_2O (50 mL) were added, and then the mixture was poured into water in a well ventilated fume hood. The reaction mixture was extracted with Et_2O and the combined extract was then washed with brine, dried (Na_2SO_4), and concentrated to afford a crude product that was purified by radial chromatography (1:49 EtOAc/hexanes) to afford 610 mg (62%) of **5b** as a colorless oil: IR (film) 3061, 2226, 1654 cm^{-1} ; ^1H NMR d 0.21 (s, 9H), 1.80 (s, 3H), 2.13-2.66 (m, 4H), 5.46 (s, 1H); ^{13}C NMR d 1.2, 16.6, 34.7, 41.3, 78.2, 121.8, 126.1, 149.0; MS: 195 (M^+).

1-(1,1-Dimethyl-1-silaethoxy)-3-methylcyclohex-2-enecarbonitrile (5c): Repeating the procedure for **5b** with ZnI_2 (530 mg, 1.63mmol), 3-methyl-cyclohexen-1-one (330 mg, 3.0 mmol), and Me_3SiCN (476 mg, 4.8 mmol) in CH_2Cl_2 (12 mL) afforded, after radial chromatography (1: 49 EtOAc/hexanes), 600 mg (95%) of **5c** as a colorless oil: IR (film) 2228, 1667 cm^{-1} ; ^1H NMR d 0.23 (s, 9H), 1.72 (s, 3H), 1.73-2.11 (m, 6H), 5.49 (s, 1H); ^{13}C NMR d 1.4, 18.6, 23.3, 29.3, 36.7, 67.4, 122.1, 122.2, 141.1.

1-(1,1-Dimethyl-1-silaethoxy)-3,5,5-trimethylcyclohex-2-enecarbonitrile (5d): Repeating the procedure for **5b** with ZnI₂ (477 mg, 1.50 mmol), 3,5,5-trimethylcyclohex-2-en-1-one (414 mg, 3.0 mmol), and Me₃SiCN (445 mg, 4.4 mmol) in CH₂Cl₂ (12 mL) afforded, after radial chromatography (1: 49 EtOAc/hexanes), 480 mg (68%) of **5d** as a colorless oil: IR (film) 2227, 1670 cm⁻¹; ¹H NMR d 0.25 (s, 9H), 1.00 (s, 3H), 1.06 (s, 3H), 1.74 (s, 3H), 1.78-1.88 (m, 3H), 2.01 (d, *J*=13.6 Hz, 1H), 5.48 (s, 1H); ¹³C NMR d 1.4, 23.6, 28.2, 29.3, 30.3, 43.5, 48.7, 67.1, 120.2, 122.1, 139.6; MS: 237 (M⁺).

3-Cyano-3-trimethylsilyloxy-4-cholestene⁶ (i): Repeating the procedure for **5b** with ZnI₂ (500 mg, 1.57 mmol), 4-cholesten-3-one (1.15 g, 3.0 mmol), and Me₃SiCN (445 mg, 4.50 mmol) in CH₂Cl₂ (12 mL) afforded, after radial chromatography (1: 49 EtOAc/hexanes), 1.08 g (75%) of **i** as a colorless oil: IR (film) 2225, 1655 cm⁻¹; ¹H NMR d 0.24 (s, 9H), 0.67 (s, 3H), 0.86 (d, *J*=6.6 Hz, 6H), 0.90 (d, *J*=6.5 Hz, 3H), 1.04 (s, 3H); 0.73-2.23 (m, 26H), 5.30 (s, 1H) ¹³C NMR d 1.4, 11.8, 18.3, 18.5, 20.8, 22.4, 22.7, 23.7, 24.0, 27.8, 28.0, 31.9, 32.4, 33.8, 34.1, 35.6, 36.0, 37.1, 39.4, 39.5, 42.3, 53.6, 55.7, 56.0, 68.4, 120.6, 121.4, 150.2; MS: 483 (M⁺).

3-Methyl-3-(methylthiomethoxy)cyclopent-1-enecarbonitrile (14b): Performing the DMSO-Ac₂O general procedure with **5b** (610 mg, 3.13 mmol) provided, after purification by radial chromatography (1:19 EtOAc/hexanes), 140 mg (24%) of **14b** as an oil: IR (film) 2222, 1733 cm⁻¹; ¹H NMR d 1.41 (s, 3H), 1.89-2.38 (m, 2H), 2.16 (s, 3H), 2.50-2.75 (m, 2H), 4.43 (ABq, *J*=16.3 Hz, 1H), 6.61 (s, 1H); ¹³C NMR d 14.3, 25.0, 33.1, 35.3, 68.6, 88.7, 115.9, 116.8, 150.9; MS 183 (M⁺).

3-Methyl-3-(1-methyl-1-thiavinyl-1-oxo)cyclohex-1-enecarbonitrile (14c): Performing the DMSO-Ac₂O general procedure with **5c** (370 mg, 1.77 mmol) provided, after purification by radial chromatography (1:19 EtOAc/hexanes), 210 mg (55 %) of **14c** as an oil: IR (film) 2220, 1632 cm⁻¹; ¹H NMR d 1.35 (s, 3H), 2.18 (s, 3H), 1.41-2.32 (m, 6H), 4.51 (ABq, $\nu = 13.7$, $J = 10.7$ Hz), 6.52 (s, 1H); ¹³C NMR d 14.4, 18.8, 25.5, 26.8, 33.1, 67.9, 73.4, 115.1, 118.6, 147.1.

3,5,5-Trimethyl-3-(methylthiomethoxy)cyclohex-1-enecarbonitrile (14d): Performing the general procedure with **5d** (440 mg, 1.85 mmol) provided, after purification by radial chromatography (1:19 EtOAc/hexanes), 176 mg (40%) of recovered **5d**, 82.5 mg (20 %) of **14d**, and 78 mg (18%) of **16d** as oils. For **14d**: IR (film) 2222 cm⁻¹; ¹H NMR d 0.99 (s, 3H), 1.05 (s, 3H), 1.35 (s, 3H), 1.20-2.09 (m, 4H), 4.49 (s, 2H), 6.55 (s, 1H); ¹³C NMR d 14.5, 26.2, 27.8, 29.9, 30.0, 40.4, 45.9, 67.4, 73.8, 113.6, 118.9, 145.2; MS 225 (M⁺). For **16d**: IR (film) 2222, 1748 cm⁻¹; ¹H NMR d 1.00 (s, 3H), 1.01 (s, 3H), 1.35 (s, 3H), 1.15 (ABq, $\Delta\nu = 123.8$ Hz, $J = 14.5$ Hz), 1.95-2.19 (m, 2H), 2.08 (s, 3H), 5.29-5.34 (m, 2H) 6.49 (s, 1H); ¹³C NMR d 21.2, 26.7, 27.6, 30.0, 30.1, 40.3, 46.7, 74.5, 83.5, 114.0, 118.8, 144.7, 170.2; HRMS(ESI) calcd for (M+Na⁺), C₁₃H₁₉NO₃Na⁺ 260.1257, found 260.1282.

3-Hydroxy-3-methylcyclopent-1-enecarbonitrile (1a): Standard mercury-assisted hydrolysis⁷ was performed by adding solid mercuric chloride (407 mg, 1.5 mmol) to an acetonitrile-water solution (4:1, 5 mL) of **14b** (180 mg, 0.98 mmol). After 8 h the reaction mixture was filtered through celite, washed with saturated, aqueous NH₄OAc and then the aqueous layer was re-extracted with ether. The combined extract was washed with brine, dried (Na₂SO₄), concentrated,

and purified by radial chromatography (3:7 EtOAc/hexanes) to afford 110 mg (90%) of **1a** as an oil: IR (film) 3445, 2230, 1645 cm^{-1} ; ^1H NMR d 1.44 (s, 3H), 1.58 (br s, 1H), 1.99-2.18 (m, 2H), 2.53-2.80 (m, 2H), 6.51 (t, $J = 2.0$ Hz, 1H); ^{13}C NMR d 26.6, 32.8, 39.0, 82.9, 115.3, 116.0, 152.9; MS: 124 ($\text{M}+\text{H}^+$).

3-Hydroxy-3-methylcyclohex-1-enecarbonitrile (1b): Repeating the procedure for **1a** with **14c** (190 mg, 0.97 mmol) afforded, after radial chromatography (3:7 EtOAc/hexanes), 110 mg (92%) of **1b** as an oil: IR (film) 3425, 2226, 1631 cm^{-1} ; ^1H NMR d 1.34 (s, 3H), 1.62-2.28 (m, 7H), 6.42 (s, 1H); ^{13}C NMR d 18.7, 26.6, 28.3, 36.1, 67.4, 113.1, 118.7, 148.8; MS 137 (M^+).

3-Hydroxy-3,5,5-trimethylcyclohex-1-enecarbonitrile (1c): Repeating the procedure for **1a** with **14d** (82.5 mg, 0.37 mmol) afforded, after radial chromatography (3:7 EtOAc/hexanes), 35 mg (59%) of **1c** as an oil: IR (film) 3439, 2223, 1636 cm^{-1} ; ^1H NMR d 1.01 (s, 3H), 1.06 (s, 3H), 1.33 (s, 3H), 1.53-1.73 (m, 2H), 1.95-2.08 (m, 2H), 6.43 (s, 1H); ^{13}C NMR d 27.1, 29.8, 30.2, 40.1, 49.0, 68.1, 111.7, 119.0, 147.4; MS 166 ($\text{M}+\text{H}$).

5(R)-Hydroxycholest-3-ene-3-carbonitrile (iii): Aqueous, 1M HCl (3 mL) was added to a methanolic solution (6 mL) of **i** (2.24 mmol, 1.08g) at room temperature. After 1 h the solution was concentrated and dried under high vacuum to afford spectrally pure **ii** as a powder: IR (KBr) 3401, 2224, 1654 cm^{-1} ; ^1H NMR d 0.67 (s, 3H), 0.85 (s, 3H), 0.87 (s, 3H), 0.90 (d, $J = 6.5$ Hz, 3H); 1.05 (s, 3H), 0.97-2.20 (m, 29H), 5.30 (s, 1H); ^{13}C NMR d 11.9, 18.5, 18.6, 21.0, 22.5, 22.8, 23.8, 24.1, 28.0, 28.2, 32.0, 32.5, 32.9, 34.1, 35.8, 36.1, 37.5, 39.5, 39.6, 42.4, 53.8, 55.8, 56.1, 67.4, 118.7, 121.7, 152.4. Solid TsOH.H₂O (32 mg, 0.17 mmol) was added to a room

temperature, CH₂Cl₂ solution (5 mL) of **ii** (70 mg, 0.17 mmol). After stirring at room temperature overnight, saturated, aqueous NH₄Cl was added, the mixture extracted with EtOAc, and the crude extracts concentrated and purified by radial chromatography (1:9 EtOAc/Hexanes) to afford 33.6 mg (48%) of recovered **ii**, 17.5 mg of **iii** (**25%**), 11.4 mg (18%) of **iv**, and 5.9 mg (9%) of **v**. For **iii**:⁸ IR (KBr) 3442, 2222, 1678 cm⁻¹; ¹H NMR d 0.59 (s, 3H), 0.85 (s, 3H), 0.87(s, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.98 (s, 3H), 1.02-2.02 (m, 29H), 6.34 (s, 1H); ¹³C NMR d 11.9, 15.9, 18.6, 22.3, 22.5, 22.8, 23.8, 24.1, 26.8, 28.0, 28.1, 28.7, 34.7, 35.0, 35.7, 36.1, 38.4, 39.5, 39.7, 42.4, 43.5, 56.0, 56.1, 71.3, 115.1, 118.8, 148.7; MS 411 M⁺; HRMS(ESI) calcd for (M+Na⁺), C₂₈H₄₅NNa⁺ 434.3393, found 434.3393 For (**iv**): IR (KBr) 2204, 1635 cm⁻¹; ¹H NMR d 0.70 (s, 3H), 0.85 (s, 3H), 0.87(s, 3H), 0.90 (d, *J* = 4 Hz, 3H); 0.92 (s, 3H), 0.96-2.32 (m, 29H), 5.78 (s, 1H), 6.64 (s, 1H); ¹³C NMR d 12.0, 18.7, 18.9, 20.9, 22.6, 22.8, 23.8, 24.1, 24.4, 28.0, 28.2, 31.6, 32.2, 32.8, 34.5, 35.8, 36.2, 39.5, 39.6, 42.5, 47.9, 56.1, 56.7, 106.5, 120.4, 132.9, 139.9, 143.4; HRMS(ESI) calcd for (M+Na⁺), C₂₈H₄₃NNa⁺ 416.3288, found 416.3254.

General annulation procedure: A THF solution of *t*-BuMgCl (1.2 equiv) was added to a -78 °C, THF solution (0.6 M) of the alkenenitrile. After 10 min, a THF solution of the chloroalkyl Grignard reagent (1.5 equiv) was added and, after 10 min, the solution was allowed to warm to room temperature over a 2 h period. Subsequent addition of saturated, aqueous NH₄Cl, extraction, and radial chromatography afforded the spectroscopically pure bicyclic nitrile.

(1*R,5*S**,6*S**)-6-Hydroxy-6-methyl-4-methylenebicyclo[3.3.0]octanecarbonitrile (18a):** The Grignard reagent **17a** was prepared by standard⁹ halogen-magnesium exchange as follows: A THF solution of *i*-PrMgCl (1.5 M, 0.20 mmol) was added to a -10 °C, THF solution (2 mL) of 1-

chloro-3-iodo-4-butene¹⁰ (0.17 mmol). After 1.5 h at -10 °C the solution was cooled to -78 °C followed by addition of a cold THF solution of the magnesium alkoxide prepared by deprotonation of nitrile **1a** (17 mg, 0.14 mmol) with 1.2 eq *t*-BuMgCl (1.2M) at -78 °C for 10 min. After 30 min at -78 °C a hexanes solution of *t*-BuLi (1.2 M, 0.40 mmol) was added. The resultant mixture was maintained at -78 °C for 30 min, the cooling bath was removed, and then the reaction allowed to warm to room temperature over a 2 h period. Subsequent addition of saturated NH₄Cl, extraction and radial chromatography (1:4 EtOAc/Hexane) afforded the product 13.1 mg as a white solid (62%) (m.p. 73-74 °C) IR (KBr) 3497, 3074, 2233, 1658 cm⁻¹; ¹H NMR d 0.94 (dd, *J*=18.6, 6.7 Hz, 1H), 1.12 (dd, *J*=20.3, 6.6 Hz, 1H), 1.42 (s, 3H), 1.87-2.50 (m, 7H), 3.06 (s, 1H), 4.98 (s, 1H), 5.17 (s, 1H); ¹³C NMR d 28.1, 34.5, 36.3, 37.2, 41.5, 47.5, 65.7, 80.0, 109.4, 126.0, 149.3; MS: 178 (M+H); HRMS(ESI) calcd for (M+Na⁺), C₁₁H₁₅NONa⁺ 200.1046, found 200.1055.

(1R*,6S*,7S*)-7-hydroxy-7-methyl-5-methylenebicyclo[4.3.0]nonanecarbonitrile (18b): The Grignard reagent **17b** was prepared by standard halogen-magnesiates¹¹ exchange as follows: A hexanes solution of *n*-BuLi (1.2 M, 0.29 mmol) was added to a room temperature, THF solution of *i*-PrMgCl (2.0 M, 0.14 mmol). After 0.5 h the mixture was cooled to -78 °C and a THF solution (1 mL) of 1-chloro-4-iodo-5-pentene¹⁰ (26 mg, 0.12 mmol) was added, maintaining the temperature at -78 °C for 1 h before using in the general procedure. Performing the general procedure with **1a** (15 mg, 0.12 mmol) and Grignard **17b** (0.12 mmol) afforded, after chromatography (1:4 EtOAc/Hexanes) 16 mg (68%) of **18b** as a white solid (m.p. 88-90 °C) IR (KBr) 3492, 3074, 2230, 1633 cm⁻¹; ¹H NMR d 1.34 (s, 3H), 1.20-2.30 (m, 11H), 2.53 (s, 1H), 4.83 (s, 1H), 5.08 (s, 1H); ¹³C NMR d 23.6, 28.3, 32.8, 32.9, 35.9, 39.5, 42.6, 60.5, 81.5, 115.3,

125.2, 142.3; MS 192 (M+H⁺); HRMS (ESI) calcd for (M+Na⁺), C₁₂H₁₇NONa⁺ 214.1202, found 244.1214.

(1R*,6S*,7S*)-7-Hydroxy-7-methylbicyclo[4.3.0]nonanecarbonitrile (18c) : Performing the general procedure with **1a** (14 mg, 0.11 mmol) and a THF solution of chlorobutylmagnesium bromide¹² afforded, after radial chromatography (1:4 EtOAc/hexanes), 11.0 mg (56%) of **18c** as a white solid (m.p. 94-95 °C): IR (KBr) 3502, 2233 cm⁻¹; ¹H NMR d 1.28 (s, 1H), 1.35 (s, 3H), 1.50-2.23 (m, 13H); ¹³C NMR d 20.7, 21.5, 21.8, 28.6, 32.5, 35.7, 40.1, 40.8, 51.6, 81.1, 126.0; MS 180 (M+H⁺); HRMS(ESI) calcd for (M+Na⁺), C₁₁H₁₇NONa⁺ 202.1202, found 202.1200.

(1S*,5S*,6S*)-5-hydroxy-5-methyl-7-methylenebicyclo[4.3.0]nonanecarbonitrile (18d): Performing the general procedure with **1b** (18mg, 0.13mmol) and Grignard **17a**, prepared as for **17b**¹¹ with 1-chloro-3-iodo-4-butene,¹⁰ afforded, after chromatography (1:4 EtOAc/Hexanes) 17.7 mg (65%) of **18d** as a white solid (m.p. 109-110 °C): IR (KBr) 3492, 3079, 2235, 1657 cm⁻¹; ¹H NMR d 1.30 (s, 1H), 0.88-2.09 (m, 11H), 2.21-2.82 (m, 3H), 5.19 (s, 1H), 5.23 (s, 1H); ¹³C NMR d 16.0, 30.2, 30.7, 32.8, 37.4, 42.9, 57.2, 70.2, 112.5, 126.0, 149.1; HRMS (ESI) calcd for (M+Na⁺), C₁₂H₁₇NONa⁺ 214.1202, found 244.1219.

(1R*,5S*,6S*)-5-hydroxy-5-methylbicyclo[4.4.0]decanecarbonitrile (18e): Performing the general procedure with **1b** (17 mg, 0.12 mmol) and chlorobutylmagnesium bromide¹² afforded, after chromatography (1:4 EtOAc/Hexanes) 15.3 mg (58%) of **18e** as a white solid (m.p. 101-103°C): IR (KBr) 3472, 2238 cm⁻¹; ¹H NMR d 1.15 (s, 1H), 1.48 (s, 3H), 1.22-1.98 (m, 14H),

2.12-2.17 (m, 1H); MS 194 ($M+H^+$); HRMS (ESI) calcd for ($M+Na^+$), $C_{12}H_{19}NONa^+$ 216.1359, found 216.1373.

(1*R, 6*S**, 7*S**)-7-Hydroxy-7-methyl-5-methylenebicyclo[4.4.0]decanecarbonitrile (18f):**

Performing the general procedure with **1b** (17 mg, 0.12 mmol) and Grignard **17b** (0.15, mmol), prepared as for **18b**, afforded, after radial chromatography (1:4 EtOAc/hexanes), 19.0 mg (75%) of **18f** as a white solid¹³ (m.p. 155-156 °C): IR (KBr) 3472, 3080, 2234, 1646 cm^{-1} ; ¹H NMR d 0.96 (s, 1H), 1.23 (s, 3H), 1.37-2.03 (m, 9H), 2.12-2.22 (m, 2H), 2.40-2.56 (m, 2H), 4.80 (s, 1H), 5.06 (s, 1H); ¹³C NMR d 16.7, 24.1, 28.9, 31.0, 31.8, 36.5, 40.4, 40.5, 54.5, 71.4, 115.5, 124.9, 144.4; MS 206 ($M+H^+$); HRMS (ESI) calcd for ($M+Na^+$), $C_{13}H_{19}NONa^+$ 228.1359, found 228.1353.

(1*R,5*S**,6*S**)-5-hydroxy-3,3,5-trimethylbicyclo[4.4.0]decanecarbonitrile (18g):** Performing the general procedure with **1c** (16.4 mg, 0.10 mmol) and chlorobutylmagnesium bromide¹² afforded, after chromatography (1:4 EtOAc/Hexanes) 12.0 mg (55%) of **18g** as a white solid (m.p. 118-119 °C): IR (KBr) 3489, 2228 cm^{-1} ; ¹H NMR d 1.12 (s, 3H), 1.14 (s, 3H), 1.51 (s, 3H), 0.93-1.98 (m, 13H), 2.22-2.30 (m, 1H); ¹³C NMR d 22.2, 22.5, 23.2, 31.0, 31.7, 31.9, 32.4, 35.1, 37.4, 44.0, 45.9, 50.1, 73.3, 126.9; HRMS (ESI) calcd for ($M+Na^+$), $C_{14}H_{23}NONa^+$ 244.1672, found 244.1683.

(1*R,5*S**,6*S**)-5-Hydroxybicyclo[4.4.0]decanecarbonitrile (18h).** Performing the general procedure with **1d**¹⁴ (45.3 mg, 0.37 mmol) and chlorobutylmagnesium bromide¹² (2.5 equiv) afforded, after radial chromatography (2:3 EtOAc/hexanes) 41.9 mg (64%) of **18h** as an oil:¹⁵ IR

(film) 3421, 2230 cm^{-1} ; ^1H NMR δ 1.19-2.10 (m, 16H), 4.13 (dt, $J = 11.7, 4.5$ Hz, 1H); ^{13}C NMR δ 18.7, 20.8, 21.4, 24.8, 26.7, 28.4, 36.1, 38.4, 44.5, 69.9, 124.9; MS m/e 180 ($M+1$).

(1*R,2*R**,3*R**)-2-(4-chlorobutyl)-3-hydroxy-3-methylcyclohexanecarbonitrile (26):**

Performing the general procedure with **1b** (120 mg, 0.88 mmol) and the Grignard prepared from 1-1-(2,2-dimethyl-1,1-diphenyl-1-silapropoxy)-4-chlorobutane¹⁶ (750 mg, 1.74 mmol) and magnesium metal (80 mg, 3.3 mmol), afforded, after radial chromatography (1:4 EtOAc/Hexane), 330 mg (84%) of (1*R**,2*S**,3*R**)-2-[4-(2,2-dimethyl-1,1-diphenyl-1-silapropoxy)butyl]-3-hydroxy-3-methylcyclohexanecarbonitrile (**vii**) as a white solid (m.p. 55-58 °C): IR (KBr) 3070, 2237 cm^{-1} ; ^1H NMR δ 1.06 (s, 9H), 1.24 (s, 3H), 1.30-1.72 (m, 13H), 2.09 (br d, $J=10.5$ Hz, 1H), 2.69 (td, $J=12, 3$ Hz, 1H), 3.70 (t, $J=5.5$ Hz, 2H), 7.35-7.47 (m, 6H), 7.62-7.76 (m, 4H); ^{13}C NMR δ 19.1, 20.2, 26.1, 26.8, 29.1, 29.4, 30.4, 31.5, 32.9, 39.7, 47.8, 63.5, 70.8, 122.8, 127.5, 129.4, 134.0, 135.5; HRMS(ESI) calcd for ($M+\text{Na}^+$), $\text{C}_{28}\text{H}_{39}\text{NO}_2\text{SiNa}^+$ 472.2642, found 472.2609. A THF solution of *n*-Bu₄NF (1 M, 1 mmol) was added to a room temperature, THF solution (20 mL) of **vii** (330 mg 0.74 mmol) and the reaction allowed to stir overnight. The resulted mixture was concentrated and purified by radial chromatography (2:3 EtOAc/Hexane) to afford 145 mg (93%) of (1*R**,2*S**,3*R**)-3-hydroxy-2-(4-hydroxybutyl)-3-methylcyclohexanecarbonitrile (**viii**) as an oil: IR (film) 3445, 2239 cm^{-1} ; ^1H NMR δ 1.27 (s, 3H), 1.29-1.79 (m, 13H), 2.09 (d, $J=10.8$ Hz, 1H), 2.73 (td, $J=12, 3$ Hz, 1H), 3.67 (t, $J=6.0$ Hz, 2H); ^{13}C NMR δ 20.0, 25.7, 28.7, 29.1, 30.2, 31.3, 32.6, 39.5, 47.7, 61.9, 70.5, 123.0; HRMS(ESI) calcd for ($M+\text{Na}^+$), $\text{C}_{12}\text{H}_{21}\text{NO}_2\text{Na}^+$ 234.1464, found 234.1456. Solid PPh₃ (360 mg, 1.38 mmol) and CCl₄ (636 mg, 4.14 mmol) were sequentially added to a room temperature, CH₂Cl₂ solution (10 mL) of **viii** (145 mg, 0.69mmol). After stirring overnight, the solvent was

removed and the crude product purified by radial chromatography (1:4 EtOAc/Hexane) to afford 150 mg (96%) of **26** as an oil: IR (film) 3491, 2237 cm^{-1} ; ^1H NMR d 1.04 (br s, 1H), 1.28 (s, 3H), 1.33-1.84 (m, 12H), 2.11 (br d, $J=11.2$ Hz, 1H), 2.72 (td, $J=12, 3$ Hz, 1H), 3.67 (t, $J=6.0$ Hz, 2H); ^{13}C NMR d 20.2, 26.9, 28.9, 29.1, 30.4, 31.4, 32.8, 39.8, 44.6, 47.7, 70.8, 122.8. MS: 230 (M+H); HRMS(ESI) calcd for (M+Na $^+$), $\text{C}_{12}\text{H}_{20}\text{ClNONa}^+$ 252.1126, found 252.1127.

(1*S,6*S**,5*R**)-5-hydroxy-5-methylbicyclo[4.4.0]decanecarbonitrile (27):** Addition of a toluene solution (2 mL) of **26** (15 mg, 65 μmol) to LiHMDS, prepared by addition of a hexanes solution of BuLi (1.6 M, 0.16 mmol) to a THF solution (2 mL) of 1,1,1,3,3,3-hexamethyldisilazane (0.04 mL, 0.164 mmol), was followed by heating to reflux. After 1 h the reaction was cooled, saturated, aqueous, NH_4Cl was added, and the organic phase separated. The aqueous phase was extracted with EtOAc, the extracts combined, dried (Na_2SO_4), concentrated and purified by radial chromatography (1:4 EtOAc/hexanes) to afford 8.1 mg (65%) of **27** as a white solid (m.p. 90-91 $^\circ\text{C}$): IR (KBr) 3499, 2229 cm^{-1} ; ^1H NMR d 1.19 (s, 3H), 1.10-2.17 (m, 16H); ^{13}C NMR d 18.8, 22.7, 23.0, 26.0, 28.8, 37.8, 39.0, 39.2, 40.2, 52.0, 70.4, 123.7; MS: 194 (M+H); HRMS (ESI) calcd for (M+Na $^+$), $\text{C}_{12}\text{H}_{19}\text{NONa}^+$ 216.1359, found 216.1370.

FFZY006.004
DATE 21-2-0
TIME 18:57

SOLVENT CDCl₃
SF 210.0
SI 4800.000
SI 16384
TD 16384
SH 4504.505
HZ/PT .550

PM 5.0
RD 2.500
RG 1.819
NS 8
TE 297

FW 5700
OZ 5684.205
DP 4L P0

LB 0.0
GB 0.0
CX 25.00
CY 0.0
F1 10.001P
F2 -1.98P
HZ/CN 122.444
PM/CN 3366.408
SR 3366.50

PPM

FFZY006.101
DATE 22-2-0
TIME 8:11

SOLVENT CDCl₃
SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SM 17857.143
HZ/PT 2.180
PM 4.0
RD 3.000
AQ .459
R6 200
NS 13513
TE 297
FM 22400
O2 4004.452
DP 20H BB
LB 0.0
GB 0.0
CX 25.00
CY 0.0
F1 220.004P
F2 -.004P
HZ/CM 664.150
PPM/CM 8.800
SR -1403.38

135.114

123.590

119.835

77.428

76.889

76.867

76.818

76.530

39.418

24.490

17.760

14.584

~~BRUKER~~

FFZY007.002
DATE 28-2-0
TIME 14:54

SOLVENT CDCl₃
SF 300.133
SY 210.0
O1 4800.000
SI 16384
TD 16384
SM 4504.505
HZ/PT .550

PM 5.0
RD 2.500
AQ 1.819
RG 4
NS 8
TE 297

FM 5700
O2 5684.205
DP 4L P0

LB 0.0
GB 0.0
CX 25.00
CY 0.0
F1 10.001P
F2 -1.98P
HZ/CM 122.444
PPM/CM .408
SR 3368.30

FFZY009.005
DATE 24-5-0

SF 300.133
SY 210.0
D1 4800.000
SI 16384
TD 16384
SM 4504.505
HZ/PT .550

PM 5.0
RD 2.500
AQ 1.819
RG 10
NS 8
TE 297

FW 5700
D2 5684.205
DP 4L P0

LB 0.0
GB 0.0
CX 20.50
CY 10.00
F1 10.001P
F2 -1.98P
HZ/CM 149.322
PPM/CM 498
SH 3367.75

FFZY009.103
DATE 21-5-0

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SM 17857.143
HZ/PT 2.180

PM 4.0
RD 3.000
AG 3.459
RG 200
NS 13833
TE 297

FW 22400
O2 4004.452
DP 20H BB

LB 0.0
GB 0.0
CX 20.50
CY 5.00
F1 220.004P
F2 .024P
HZ/CM 809.832
PPM/CM 10.731
SR -1401.20

FFZY044.001
DATE 19-6-1

SF	300.133
SY	210.0
Q1	4800.000
SI	8192
TD	8192
SW	4504.505
HZ/PT	1.100
PM	5.0
RD	2.500
AG	.909
RG	2
NS	8
TE	297
FW	5700
O2	5684.205
DP	4L P0
LB	0.0
GB	0.0
CX	25.00
CY	15.00
F1	9.999P
F2	-1.98P
HZ/CW	122.422
PPM/CW	.408
SR	3366.03

PPM

FFZY044.101
DATE 20-6-1

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SW 17857.143
HZ/PT 2.180
PM 4.0
RD 3.000
AQ .459
RG 200
NS 13227
TE 297
FW 22400
O2 4004.452
DP 20H BB
LB 0.0
GB 0.0
CX 25.00
CY 5.00
F1 220.004P
F2 .004P
HZ/CM 664.150
PPM/CM 8.800
SR -1405.56

148.951

126.134

121.831

78.245

77.437

77.200

77.020

76.598

41.358

34.717

16.604

1.270

FFZY012.001
DATE 3-7-0

SF	300.133
SY	210.0
O1	4800.000
SI	16384
TD	16384
SW	4504.505
HZ/PT	.550
PM	5.0
RD	2.500
RG	1.819
NS	2
TE	297
FM	5700
O2	5684.205
DP	4L PD
LB	0.0
GB	0.0
CX	20.50
CY	12.00
F1	10.001P
F2	-198P
HZ/CM	149.322
PPM/CM	498
SR	3367.75

FFZY012.101
DATE 2-7-0

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SW 17857.143
HZ/PT 2.180

PM 4.0
RD 3.000
RG .459
NS 200
TE 235
297

FW 22400
O2 4004.452
DP 20H BB

LB 0.0
GB 0.0
CX 20.50
CY .50
F1 220.004P
F2 -1.997P
HZ/CM 817.276
PPM/CM 10.829
SR -1401.20

FFZY068.001
DATE 18-3-2

SF 300.133
SY 210.0
O1 4800.000
S1 8192
TD 8192
SW 4504.505
HZ/PT 1.100

PW 5.0
RD 2.500
AQ .509
RG 2
NS 8
TE 297

FW 5700
O2 5684.205
DP 4L P0

LB 0.0
GB 0.0
CX 25.00
CY 15.00
F1 10.001P
F2 -.200P
HZ/CM 122.466
PPM/CM 408
SR 3367.75

PPM

FFZY068.101
DATE 18-3-2

SF 75.469
SY 75.0
O1 6147.202
S1 16384
TD 16384
SM 17857.143
HZ/PT 2.180

PM 4.0
RD 3.000
RG .459
NS 200
TE 166
TE 297

FW 22400
O2 4004.452
DP 20H B8

LB 0.0
GB 0.0
CX 25.00
CY 5.00
F1 220.004P
F2 - .004P
HZ/CW 664.150
PPM/CW 8.800
SR -1396.84

139.608

122.056
120.209

77.431
77.001
76.591

67.118

48.663

43.465

30.292
29.283
28.157

23.565

1.411

FFZY076.001
DATE 5-4-2

SF	300.133
SY	210.0
O1	4800.000
SI	8192
TD	8192
SM	4504.505
HZ/PT	1.100
PW	5.0
RD	2.500
AG	.909
RG	4
NS	8
TE	297
FW	5700
O2	5684.205
DP	4L P0
LB	0.0
GB	0.0
CX	25.00
CY	15.00
F1	10.004P
F2	.197P
HZ/CN	122.466
PPM/CN	.408
SR	3367.75

ppm

FFZY076.101
DATE 5-4-2

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SW 17857.143
HZ/PT 2.180

PM 4.0
RD 3.000
AQ .459
RG 200
NS 201
TE 297

FW 22400
O2 4004.452
DP 20H BB

LB 0.0
GB 0.0
CX 25.00
CY 6.00
F1 220.004P
F2 .024P
HZ/CM 664.062
PPM/CM 8.799
SR -1392.48

150.160

121.422
120.639

77.431
76.999
76.579
68.448

55.999
55.713
53.606
42.277
39.496
39.363
37.141
36.010
35.614
34.087
33.818
32.432
31.910
28.015
27.797
24.002
23.736
22.670
22.432
20.819
18.511
18.338
11.810
1.441

FFZY046.002
DATE 2-7-1

SF 300.133
SY 210.0
O1 4800.000
SI 8192
TD 8192
SW 4504.505
HZ/PT 1.100
PW 5.0
RD 2.500
AQ .909
RG 2
NS 8
TE 297
FW 5700
O2 5684.205
DP 4L P0
LB 0.0
GB 0.0
CX 25.00
CY 7.00
F1 10.001P
F2 .200P
HZ/CM 122.466
PPM/CM .408
SR 3368.92

PPM

FFZY046.101
DATE 2-7-1

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SW 17857 143
HZ/PT 2.180

PW 4.0
RD 3.000
RG 459
NS 200
TE 297

FW 22400
O2 4004.452
DP 20H BB

LB 0.0
GB 0.0
CX 25.00
CY 4.00
F1 220.004P
F2 -004P
HZ/CM 664.150
PPM/CM 8.800
SR -1405.56

150.856

116.830
115.850

88.671

77.578
77.145
76.726
68.567

35.263
33.097

24.955

14.295

FFZY013.101
DATE 9-7-0

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SH 17857.143
HZ/PT 2.180
PW 4.0
RD 3.000
AQ .459
RG 200
NS 18177
TE 297
FW 22400
O2 4004.452
DP 20H BB
LB 0.0
GB 0.0
CX 20.50
CY 5.00
F1 220.004P
F2 .024P
HZ/CM 809.832
PPM/CM 10.731
SR -1403.38

FFZY070.002
DATE 22-3-2

SF 300.133
SY 210.0
O1 4800.000
SI 8192
TD 8192
SW 4504.505
HZ/PT 1.100
PM 5.0
RD 2.500
AQ 1.909
RG 1
NS 8
TE 297
FW 5700
O2 5684.205
DP 4L P0
LB 0.0
GB 0.0
CX 25.00
CY 8.00
F1 9.999P
F2 -198P
HZ/CW 122.422
PPM/CW 408
SR 3368.15

PPM

FFZY070.101
DATE 23-3-2

SF	75.469
SY	75.0
O1	6147.202
SI	16384
TD	16384
SW	17857.143
HZ/PT	2.180
PW	4.0
RD	3.000
AG	.459
RG	200
NS	15711
TE	297
FW	22400
O2	4004.452
DP	20H BB
LB	0.0
GB	0.0
CX	25.00
CY	6.00
F1	220.004P
F2	.024P
HZ/CM	664.062
PPM/CM	8.799
SR	-1401.20

145.194

118.854

113.623

77.427

76.999

76.568

73.764

67.413

45.920

40.404

30.034

29.887

27.782

26.223

14.467

14d

FFZY079.001
DATE 19-4-2

SF 300.133
SY 210.0
O1 4900.000
SI 8192
TD 8192
SW 6024.096
HZ/PT 1.471

PM 5.0
RD 2.500
AQ .680
RG 10
NS 8
TE 297

FW 7600
O2 5664.205
DP 4L P0

LB 0.0
GB 0.0
CX 25.00
CY 10.00
F1 9.999P
F2 .198P
HZ/CM 122.423
PPM/CM 408
SR 3368.15

FFZY047.001
DATE 3-7-1

SF	300.133
SY	210.0
O1	4800.000
SI	8192
TD	8192
SW	4504.505
HZ/PT	1.100
PW	5.0
RD	2.500
AG	.909
RG	20
NS	8
TE	297
FW	5700
O2	5684.205
DP	4L P0
LB	0.0
GB	0.0
CX	25.00
CY	10.00
F1	9.999P
F2	.198P
HZ/CM	122.422
PPM/CM	408
SR	3364.85

PPM

FFZY047.101
DATE 1-3-96

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SW 17857 143
HZ/PT 2.180

PM 4.0
RD 3.000
RG .459
NS 200
TE 292
TE 297

FW 22400
O2 4004.452
DP 20H 88

LB 5.000
GB 0.0
CX 25.00
CY 2.50
F1 220.004P
F2 .004P
HZ/CM 664.150
PPM/CM 8.800
SR -1399.02

152.880

116.034
115.286

82.912

77.435
77.006
76.589

38.959

32.758

26.592

B
 J
 R
 FFZY023.001
 DATE 14-11-0
 SF 300.133
 SY 210.0
 O1 4800.000
 SI 8192
 TD 8192
 SM 4504.505
 HZ/PT 1.100
 PM 5.0
 RD 2.500
 AG .909
 RG 4
 NS 8
 TE 297
 FM 5700
 O2 5684.205
 DP 4L P0
 LB 0.0
 GB 0.0
 CX 20.50
 CY 10.00
 F1 10.001P
 F2 .200P
 HZ/CM 149.349
 PPM/CM .498
 SR 3367.75

FFZY023.102
DATE 25-11-0

SF 75.469
SY 75.0
O1 6.147.202
SI 16384
TD 16384
SW 17857.143
HZ/PT 2.180

PW 4.0
RD 3.000
AG .459
RG 200
NS 666
TE 297

FW 22400
O2 4004.452
DP 20H BB

LB 0.0
GB 0.0
CX 20.50
CY 2.00
F1 220.004P
F2 .024P
HZ/CM 809.832
PPM/CM 10.731
SR -1396.84

B
J
K
R

FFZY073.001
DATE 31-3-2

SF 300.133
SY 210.0
Q1 5500.000
SI 8192
TD 8192
SW 6024.096
HZ/PT 1.471

PW 5.0
RD 2.500
AQ 1.680
RG 4
NS 16
TE 297

FW 7600
O2 5684.205
DP 4L P0

LB 0.0
GB 0.0
CX 25.00
CY 8.00
F1 9.999P
F2 -1.98P
HZ/CM 122.423
PPM/CM 408
SR 3368.10

ppm

FFZY073.101
DATE 1-4-2

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SW 17857.143
HZ/PT 2.180

PW 4.0
RD 3.000
AQ .459
RG 200
NS 15343
TE 297

FW 22400
O2 4004.452
DP 20H BB

LB 0.0
GB 0.0
CX 25.00
CY 4.00
F1 220.004P
F2 -.004P
HZ/CM 664.150
PPM/CM 8.800
SR -1401.20

147.367

118.997

111.688

77.432

77.002

76.591

68.132

48.982

40.115

30.216

29.843

27.117

FFZY088.001
DATE 6-7-2

SF 300.133
SY 210.0
O1 4800.000
SI 8192
TD 8192
SW 4504.505
HZ/Pt 1.100
PM 5.0
RD 2.500
AQ 2.909
RG 2
NS 8
TE 297
FW 5700
O2 5684.205
DP 4L P0
LB 0.0
GB 0.0
CX 25.00
CY 6.50
F1 10.001P
F2 1.200P
HZ/CM 122.466
PPM/CM .408
SR 3367.75

PPM

FFZY08B-101
DATE 7-7-2

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SW 17857.143
HZ/PT 2.180

PM 4.0
RD 3.000
AQ .459
RG 200
NS 14861
TE 297

FW 22400
O2 4004.452
DP 20H BB

LB 0.0
GB 0.0
CX 25.00
CY 6.00
F1 220.004P
F2 .004P
HZ/CW 664.150
PPM/CW 8.800
SR -1403.38

148.690

118.796

115.127

77.432

77.000

76.574

71.280

56.059

55.973

43.470

42.426

39.674

39.451

38.355

36.074

35.697

35.018

34.653

28.677

28.124

27.956

26.800

24.114

23.768

22.758

22.526

22.323

18.599

15.940

11.896

FFZY080.001
DATE 19-5-2

SF 300.133
SY 210.0
O1 4600.000
SI 8192
TD 8192
SW 4504.505
HZ/PT 1.100
PW 5.0
RD 2.500
AQ .909
RG 2
NS 8
TE 297
FW 5700
O2 5684.205
DP 4L P0
LB 0.0
GB 0.0
CX 25.00
CY 6.50
F1 10.001P
F2 .200P
HZ/CM 122.466
PPM/CM .408
SR 3367.75

PPM

FFZY080.101
DATE 21-5-2

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SW 17857.143
HZ/PT 2.180
PM 4.0
RD 3.000
AQ .459
RG 200
NS 14674
TE 297
FW 22400
O2 4004.452
DP 20H BB
LB 0.0
GB 0.0
CX 25.00
CY 7.00
F1 220.004P
F2 -.004P
HZ/CM 664.150
PPM/CM 8.800
SR -1405.56

143.406

139.941

132.890

120.386

106.518

77.434

77.002

76.584

56.694

56.132

47.855

42.457

39.565

39.510

36.157

35.755

34.486

32.750

32.202

31.568

28.157

27.989

24.374

24.115

23.825

22.785

22.551

20.908

18.943

18.685

11.954

iv

FFZY056.001
DATE 11-11-1

SF 300.133
SY 210.0
O1 4800.000
SI 8192
TD 8192
SW 4504.505
HZ/PT 1.100
PM 5.0
RD 2.500
AQ .509
RG 4
NS 8
TE 297
FW 5700
O2 5684.205
DP 4L P0
LB 0.0
GB 0.0
CX 25.00
CY 8.00
F1 9.999P
F2 .198P
HZ/CM 122.422
PPM/CM .408
SR 3367.05

PPM

FFZY056.101
DATE 12-11-1

SF 75.469
SY 75.0
O1 6147.202
S1 16384
TD 16384
SW 17857.143
HZ/PT 2.180

PM 4.0
RD 3.000
AQ .459
RG 200
NS 15616
TE 297

FW 22400
O2 4004.452
DP 20H BB

LB 0.0
GB 0.0
CX 25.00
CY 8.00
F1 220.004P
F2 -.004P
HZ/CM 664.150
PPM/CM 8.800
SR -1405.56

149.325

125.980

109.436

80.004

77.431

76.999

76.575

65.676

47.537

41.501

37.196

36.331

34.482

28.129

~~BIOX-R~~

FFZY052.001
DATE 25-7-1

SF 300.133
SY 210.0
Q1 4800.000
S1 8192
TD 8192
SW 4504.505
HZ/PT 1.100
PW 5.0
RD 2.500
AQ 1.909
RG 4
NS 8
TE 297
FW 5700
O2 5684.205
DP 4L P0
LB 0.0
GB 0.0
CX 25.00
CY 12.00
F1 10.001P
F2 -200P
HZ/CM 122.466
PPM/CM 408
SR 3367.75

PPM

FFZY052.101
DATE 28-7-1

SF 75.469
SY 75.0
O1 6147.202
S1 16384
TD 16384
SW 17857.143
HZ/PT 2.180

PW 4.0
RD 3.000
AQ .459
RG 200
NS 14217
TE 297

FW 22400
O2 4004.452
DP 204 BB

LB 0.0
GB 0.0
CX 25.00
CY 5.00
F1 220.004P
F2 - .004P
HZ/CM 664.150
PPM/CM 8.800
SR -1403.38

142.280

125.177

115.273

81.506
77.410
76.999
76.569

60.481

42.630
39.486
35.872
32.862
32.781
28.332
23.602

FFZY050.001
DATE 6-7-1

SF 300.133
SY 210.0
O1 4800.000
SI 8192
TD 8192
SW 4504.505
HZ/PT 1.100
PM 5.0
RD 2.500
AQ .909
RG 4
NS 8
TE 297
FW 5700
O2 5684.205
D0 4L P0
LB 0.0
GB 0.0
CX 25.00
CY 10.00
F1 9.999P
F2 -.198P
HZ/CW 122.422
PPM/CW .408
SR 3364.85

ppm

FFZY050.101
DATE 7-7-1

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SM 17857.143
HZ/PT 2.180
PW 4.0
RD 3.000
AQ 459
RG 200
NS 12853
TE 297
FW 22400
O2 4004.452
DP 20H BB
LB 0.0
GB 0.0
CX 25.00
CY 6.00
F1 220.004P
F2 024P
HZ/CM 664.062
PPM/CM 8.799
SR -1403.38

125.990

81.069
77.407
76.990
76.566

51.612

40.754
40.147
35.668
32.515
28.594
21.776
21.545
20.658

FFZY043.001
DATE 27-5-1

SF 300.133
SY 210.0
O1 4800.000
SI 8192
TD 8192
SW 4504.505
HZ/PT 1.100
PW 5.0
RD 2.500
AG .909
RG 4
NS 8
TE 297
FW 5700
O2 5684.205
DP 4L P0
LB 0.0
GB 0.0
CX 25.00
CY 10.00
F1 10.004P
F2 .197P
HZ/CM 122.456
PPM/CM .408
SR 3366.65

PPM

FFZY043.101
DATE 28-5-1

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SM 17857.143
HZ/PT 2.180

PM 4.0
RD 3.000
RG 200.459
NS 14824
TE 297

FW 22400
O2 4004.452
DP 20H BB

LB 0.0
GB 0.0
CX 25.00
CY 4.00
F1 220.004P
F2 -004P
HZ/CM 664.150
PPM/CM 8.800
SR -1405.56

149.063

125.958

112.525

77.571
77.435
77.230
77.146
77.014
76.772
76.595
76.459
70.156

57.220

42.918

37.430

32.837

30.670

30.210

16.028

18d

FFZY030.001
DATE 4-2-1

SF	300.133
SY	210.0
O1	4800.000
SI	8192
TD	8192
SW	4504.505
HZ/Pt	1.100
PW	5.0
RD	2.500
AG	.909
RG	4
NS	8
TE	297
FW	5700
O2	5684.205
DP	4L P0
LB	0.0
GB	0.0
CX	20.50
CY	12.00
F1	10.001P
F2	-200P
HZ/CM	149.349
PPM/CM	.498
SR	3367.75

~~BULKY~~ R

FFZY039.002
DATE 19-4-1

SF 300.133
SY 210.0
O1 4800.000
SI 8192
TD 8192
SW 4504.505
HZ/PT 1.100

PW 5.0
RD 2.500
RG 2.909
NS 8
TE 297

FW 5700
O2 5684.205
DP 4L P0

LB 0.0
GB 0.0
CX 25.00
CY 12.00
F1 10.001P
F2 2.200P
HZ/CW 122.466
PPM/CW .408
SR 3367.75

PPM

FFZY039.101
DATE 13-4-1

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SM 17857.143
HZ/PT 2.180

PM 4.0
RD 3.000
AQ 459
RG 200
NS 1246
TE 297

FW 22400
O2 4004.452
DP 20H BB

LB 0.0
GB 0.0
CX 25.00
CY 4.00
F1 220.004P
F2 -004P
HZ/CM 664.150
PPM/CM 8.800
SR -1403.38

144.443

124.921

115.465

77.428
76.999
76.582
71.420

54.493

40.515
40.412
36.530
31.769
31.038
28.875
24.138

16.689

~~BLOCKER~~

FFZY081.002
DATE 18-8-2

SF 300.133
SY 210.0
O1 4800.000
SI 8192
TD 8192
SW 4504.505
HZ/Pt 1.100
PW 5.0
RD 2.500
AQ .909
RG 4
NS 8
TE 297
FW 5700
O2 5684.205
DP 4L P0
LB 0.0
GB 0.0
CX 25.00
CY 6.50
F1 10.001P
F2 200P
HZ/CM 122.466
PPM/CM .408
SR 3367.75

PPM

FFZY084.101
DATE 20-5-2

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SM 17857.143
HZ/PT 2.180
PM 4.0
RD 3.000
AQ .459
RG 200
NS 12392
TE 297
FW 22400
O2 4004.452
DP 20H BB
LB 0.0
GB 0.0
CX 25.00
CY 10.00
F1 220.004P
F2 .024P
HZ/CM 664.062
PPM/CM 8.799
SR -1405.56

126.941

18g

77.434
77.002
76.590
73.334

50.112

45.864
44.045
37.431
35.060
32.376
31.914
31.744
30.959
23.248
22.526
22.237

B
 FFGMA007.271
 DATE 27-7-0
 SF 300.133
 SY 210.0
 O1 4800.000
 SI 16384
 TD 16384
 SM 4504.505
 HZ/PT .550
 PM 5.0
 RD 2.500
 AG 1.819
 RG 2
 NS 8
 TE 297
 FM 5700
 O2 5684.205
 DP 4L P0
 LB 0.0
 GB 0.0
 CX 20.50
 CY 10.00
 F1 10.001P
 F2 .198P
 HZ/CM 149.322
 PPM/CM .498
 SR 3367.75

 FFOH4007.281
 DATE 28-7-0
 SF 75.0 75.469
 O1 6147.202
 SI 16384
 TD 16384
 SM 17857.143
 HZ/p1 2.180
 PW 4.0
 RD 3.000
 AG 3.459
 RG 200
 NS 12002
 TE 297
 FW 22400
 O2 4004.452
 DP 20H 86
 LB 0.0
 GB 0.100
 CX 20.50
 CY 10.00
 F1 220.004P
 F2 -0.04P
 HZ/CN 809.939
 PPM/CN 10.732
 SR -1405.56

FFZY045.001
DATE 3-7-1

SF 300.133
SY 210.0
O1 4800.000
SI 8192
TD 8192
SW 4504.505
HZ/PT 1.100
PW 5.0
RD 2.500
AG .909
RG 2
NS 8
TE 297
FM 5700
O2 5684.205
DP 4L P0
LB 0.0
GB 0.0
CX 25.00
CY 15.00
F1 10.003P
F2 1.198P
HZ/CM 122.466
PPM/CM .408
SR 3371.45

FFZY048.002
DATE 5-7-1

SF	300.133
SY	210.0
O1	4800.000
SI	8192
TD	8192
SW	4504.505
HZ/PT	1.100
PM	5.0
RD	2.500
RG	.909
NS	4
TE	8
TE	297
FW	5700
O2	5684.205
DP	4L P0
LB	0.0
GB	0.0
CX	25.00
CY	10.00
F1	9.999P
F2	-198P
HZ/CM	122.422
PPM/CM	.408
SR	3365.95

PPM

FFZY048.101
DATE 5-7-1

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SW 17857.143
HZ/PT 2.180

PM 4.0
RD 3.000
AG .459
RG 200
NS 168
TE 297

FW 22400
O2 4004.452
DP 20H BB

LB 0.0
GB 0.0
CX 25.00
CY 2.00
F1 220.004P
F2 -.004P
HZ/CM 664.150
PPM/CM 8.800
SR -1392.48

123.013

77.432
77.005
76.572
70.503

61.867

47.737

39.482

32.637

31.260

30.239

29.120

28.708

25.703

20.014

viii

FFZY051.004
DATE 23-7-1

SF 300.133
SY 210.0
O1 4800.000
SI 8192
TD 8192
SW 4804.505
HZ/PT 1.100
PW 5.0
RD 2.500
AG 2.909
RG 8
NS 8
TE 297
FW 5700
O2 5684.205
DP 4L P0
LB 0.0
GB 0.0
CX 25.00
CY 10.00
F1 9.999P
F2 -1.198P
HZ/CM 122.422
PPM/CM .408
SR 3365.95

PPM

FFZY051.101
DATE 23-7-1

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SW 17857.143
HZ/PT 2.180
PM 4.0
RD 3.000
AQ .459
RG 200
NS 805
TE 297
FM 22400
O2 4004.452
DP 20H BB
LB 0.0
GB 0.0
CX 25.00
CY 3.00
F1 220.033P
F2 .053P
HZ/CM 664.082
PPM/CM 8.799
SR -1401.20

122.756

77.407
76.998
76.566

70.760

47.710
44.630

39.796

32.776

31.422

30.411

29.053

28.879

26.889

20.155

FFZY053.003
DATE 5-12-1

SF 300.133
SY 210.0
O1 4800.000
SI 8192
TD 8192
SW 4504.505
HZ/PT 1.100

PW 5.0
RD 2.500
AQ .909
RG 1
NS 8
TE 297

FW 5700
O2 5684.205
DP 4L P0

LB 0.0
GB 0.0
CX 25.00
CY 6.00
F1 10.0031P
F2 -.197P
HZ/CM 122.422
PPM/CM .408
SR 3367.75

PPM

FFZY053.102
DATE 5-12-1

SE 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SM 17857.143
HZ/PI 2.180
PM 4.0
RD 3.000
AQ .459
RG 200
NS 11801
TE 297
FM 22400
O2 4004.452
DP 20H BB
LB 0.0
GB 0.0
CX 25.00
CY 5.00
F1 220.033P
F2 .053P
HZ/CM 664.062
PPM/CM 8.799
SR -1403.38

123.738

77.718
77.436
77.180
77.009
76.910
76.762
76.595
70.359

51.960

40.233
39.220
39.025
37.751

28.783
26.024
22.969
22.707
18.633

References

- ¹ For general experimental procedures see: Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305. The high-resolution mass spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center.
- ² Okada, Y.; Wang, J. D.; Yamamoto, T.; Mu, Y. Yokoi, T. *J. Chem. Soc., Perkin Trans. I* **1996**, 2139-2143.
- ³ Wada, M.; Takahashi, T.; Domae, T.; Fukuma, T.; Miyoshi, N.; Smith, K. *Tetrahedron Asymm.* **1997**, *8*, 3939.
- ⁴ Soli, E.D.; Manoso, A. S.; Patterson, M. C.; Deshong, D.; Favor, D. A.; Hirschmann, R; Smith, III, A.B. *J. Org. Chem.* **1999**, *64*, 3171-3177.
- ⁵ Higuchi, K.; Onaka, M.; Izumi, Y.; *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2016-2032.
- ⁶ 3-Cyano-3-trimethylsilyloxy-4-cholestene was previously synthesized and partial ¹H NMR data reported: Agami, C.; Fadlallah, M. *Tetrahedron* **1983**, *39*, 777.
- ⁷ Corey, E. J.; Book, M. G. *Tetrahedron Lett.* **1975**, *16*, 3256-3270.
- ⁸ Alkenenitrile **ii** was previously synthesized although no spectral data was reported.^a The stereochemical assignment rests on the extreme sensitivity of the steroidal A-B ring junction to ¹³C NMR chemical shifts^b that allow a correlation of the alkenenitrile ¹³C chemical shifts of **ii** with the *cis*- and *trans*-decalin nitriles **viii** and **ix**^c and the diagnostic^d C-19 methyl shift of **ii** 15.9 with that of *trans*-fused steroids (15.8-16.1). (a) Harusawa, S.; Miki, M.; Yoneda, R.; Kurihara, T. *Chem. Pharm. Bull.* **1985**, *33*, 2164. (b) Gough, J. L.; Guthrie, J. P.; Stothers, J. B. *J. Chem. Soc. Chem. Commun.* **1972**, 979. (c) Boyer, F.-

D.; Ducrot, P.-H. *Synthesis* **2000**, 1868. (d) Ayer, W. A.; Browne, L. M.; Fung, S.; Stothers, J. B. *Can. J. Chem.* **1976**, *54*, 3272.

- ⁹ Delacroix, T.; Bérillon, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 8108-8110.
- ¹⁰ Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett*, **1990**, *11*, 675.
- ¹¹ Kitagawa, K.; Inoue, A.; Shinkubo, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2481-2483.
- ¹² Bernady, K. F.; Poletto, J. F.; Nocera, J.; Mirando, P.; Schaub, R. E.; Weiss, M. J. *J. Org. Chem.* **1980**, *45*, 4702.
- ¹³ X-ray crystallography of **18f** (CCDC# 213775) confirmed the stereochemical assignment. The supplementary crystallographic data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44 1223 336033; or deposit@ccdc.cam.ac.uk.).

- ¹⁴ Fleming, F. F.; Wang, Q.; Steward, O. W. *J. Org. Chem.* **2001**, *66*, 2171.
- ¹⁵ Conversion of **18h** to the corresponding xanthate affords a crystalline *cis*-decalin whose structure was determined by x-ray crystallography, thereby confirming the *cis*-stereochemistry shown: Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 2885.
- ¹⁶ Prepared by silylation of 4-chlorobutanol: US patent 5665829.