Cyclic 5-7 Membered Oxonitriles: Divergent Stereoselectivity in Grignard Addition Alkylations

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General Procedure for Oxonitrile Synthesis: Two individual watchglasses having a thin (< 3mm) layer of powdered chromium trioxide (12 equiv) or 2, 3-dimethylpyrazole (12 equiv) were dried overnight (> 16 h) in a vacuum desiccator (< 5mm/Hg) containing P₂O₅. Dry 2, 3-dimethylpyrazole was added to a magnetically stirred, -20 °C, CH₂Cl₂ solution (1.2 M) of dry CrO₃. After stirring at -20 °C for 15 min, neat nitrile (1 equiv) was added. The mixture was stirred between -10 °C to -12 °C for 3 h and then the temperature raised to 0 °C. Aqueous NaOH (5M) was then added and stirring continued at 0 °C for 1 h. The crude reaction mixture was then refrigerated (-10 °C) overnight causing the aqueous phase to freeze and the organic phase to be removed by decanting. The aqueous phase was further extracted twice with CH₂Cl₂, the organic extracts were then combined, and the resulting organic material was then washed sequentially with HCl, H₂O and brine. The organic extract was dried (Na₂SO₄) and then concentrated to give a dark yellow oil that was purified by radial chromatography to afford pure oxonitrile.

3-Oxocyclopent-1-enecarbonitrile (1a): The standard procedure was employed with cyclopentenecarbonitrile (2.79 g, 0.03 mol), 2, 3-dimethylpyrazole (34.8 g, 0.36 mol), and CrO₃ (36 g, 0.36 mol) to afford, after radial chromatography (1 : 10 EtOAc/hexanes), 1.03 g (32%) of **1a**. IR (film) 3090, 2238, 1721 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.53-2.57 (m, 2H), 2.91-2.93 (m, 2H), 6.78 (s, 1H); ¹³C NMR (300 MHz, CDCl₃): δ 30.0, 33.9, 114.7, 142.9, 143.3, 206.0.

(E)-3-Oxocyclohept-1-enecarbonitrile (1c): The standard procedure was employed with cyclohexenecarbonitrile¹ (1.21 g, 0.01 mol), 2, 3-dimethylpyrazole (11.6 g, 0.12 mol), and CrO₃ (12 g, 0.12 mol) to afford, after radial chromatography (1 : 7 EtOAc/hexanes), 0.5 g (37%) of **1c**. IR (film): 2222, 1679 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.84-1.97 (m, 4H), 2.65-2.72 (m, 4H), 6.58 (s, 1H); ¹³C NMR (500 MHz, CDCl₃): δ 21.1, 25.3, 32.1, 42.9, 118.9, 127.3, 142.7, 201.1.

General Grignard Addition-Acylation Procedure with Oxonitrile 1a: A THF solution of MeMgCl (2.5 equiv) was added to a -78 °C THF solution (0.1M) of oxonitrile **1a**, and the resulting solution was stirred at -78 °C for 1 h and then warmed to room temperature. After 0.5 h, the solution was cooled to 0 °C and the electrophile (2-10 equiv) was then added neat. After 1 h, saturated aqueous NH₄Cl was added and the resulting mixture was extracted with EtOAc. The extracts were combined, washed with brine and dried (NaSO₄). Concentration and purification of the crude product by radial chromatography afforded the pure nitrile.

¹ Prepared from cycloheptanone by cyanation and dehydration: Pawlak, J. L.; Berchtold, G. A. *J. Org. Chem.* **1988**, 53, 4063.

(1S, 2S, 3R)-3-Hydroxy-1, 2, 3-trimethylcyclopentanecarbonitrile (14a) and **(1R, 2S, 3R)-3-Hydroxy-1, 2, 3-trimethylcyclopentanecarbonitrile (14g)**: The standard procedure was employed with oxonitrile **1a** (30 mg, 0.28 mmol), MeMgCl (2.5 M, 0.28 mL), and MeI (0.18 mL, 2.8 mmol) to afford, after radial chromatography (1 : 20 EtOAc/hexanes), 16.1 mg (38%) of **14a** and 4.7 mg (11%) of **14g**. For **14a**: IR (film) 3478, 2234 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 1.16 (d, J = 7.4 Hz, 3H), 1.28 (s, 3H), 1.40-1.49 (m, 5H), 1.65-1.72 (m, 1H), 1.82-1.88 (m, 1H), 1.91-1.99 (m, 1H), 2.40-2.48 (m, 1H); ^{13}C NMR (500 MHz, CDCl_3): δ 8.7, 25.6, 26.5, 36.6, 39.5, 41.8, 53.9, 80.1, 124.5; HRMS (ESI), m/z calculated for $(\text{M}+\text{H})^+$ ($\text{C}_9\text{H}_{15}\text{NOH}^+$): 154.1240, found 154.1232. For **14g**: IR (film) 3487, 2235 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 1.06 (d, J = 7.3 Hz, 3H), 1.10 (s, 1H), 1.31 (s, 3H), 1.37 (s, 3H), 1.86-1.97 (m, 3H), 2.06 (q, J = 7.3 Hz, 1H), 2.22-2.30 (m, 1H); ^{13}C NMR (500 MHz, CDCl_3): δ 7.5, 21.4, 27.4, 37.2, 39.4, 39.7, 51.7, 79.9, 126.7.

(1R, 2S, 3S)-3-Cyano-1, 2, 3-trimethylcyclopentyl 4-nitrobenzoate (14i): A 0 °C THF solution (0.05 M) of **14a** (42 mg, 0.27 mmol) was successively treated with MeMgCl (2.5 M, 0.12 mL) and p-nitrobenzoyl chloride (78 mg, 0.42 mmol). After 2 h, saturated aqueous NaHCO_3 was added, and the resulting mixture was extracted with EtOAc. The extracts were combined, washed with brine and dried (NaSO_4). Concentration and purification of the crude product by radial chromatography afforded 49.1 mg (59%) of **14i** as a crystalline solid (mp 121-122°C) whose structure was determined by X-ray crystallography. IR (film) 3118, 2234, 1716, 1523 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 1.39 (d, J = 6.8 Hz, 3H), 1.51 (s, 3H), 1.63 (q, J = 6.8 Hz, 1H), 1.71 (s, 3H), 1.76-1.84 (m, 1H), 2.01-2.10 (m, 1H), 2.32-2.40 (m, 1H), 2.78-2.86 (m, 1H), 8.25-

8.31 (m, 4H); ^{13}C NMR (500 MHz, CDCl_3): δ 9.2, 22.2, 25.5, 35.5, 36.6, 41.8, 56.2, 91.1, 123.5, 124.0 128.1, 130.8, 136.6, 163.8.

(1R, 2S, 3R)-Methyl 1-cyano-3-(methoxycarbonyloxy)-2, 3-dimethylcyclopentanecarboxylate (14b): The standard procedure was employed with oxonitrile **1a** (26.8 mg, 0.25 mmol), MeMgCl (2.5 M, 0.25 mL), and methyl cyanoformate (0.04 mL, 0.5 mmol) which was added at -78°C , to afford, after radial chromatography (1 : 5 EtOAc/hexanes), 35.1 mg (55%) of **14b** as a crystalline solid (mp $112\text{--}113^\circ\text{C}$) whose structure was determined by X-ray crystallography. IR (film) 2243, 1747, 1732 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 1.28 (d, $J = 7.3\text{ Hz}$, 3H), 1.60 (s, 3H), 1.90–2.01 (m, 1H), 2.30 (q, $J = 7.3\text{ Hz}$, 1H), 2.37–2.43 (m, 3H), 2.78–2.87 (m, 1H), 3.75 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (300 MHz, CDCl_3): δ 9.5, 21.0, 34.5, 35.8, 51.9, 53.4, 53.8, 54.4, 90.2, 118.4, 153.8, 170.2; MS (EI) m/z 255 (M^+).

(1R, 2S, 3R)-1-Allyl-3-hydroxy-2, 3-dimethylcyclopentanecarbonitrile (14c): The standard procedure was employed with oxonitrile **1a** (30 mg, 0.28 mmol), MeMgCl (2.5 M, 0.28 mL), and allyl bromide (0.1 mL, 1.16 mmol) to afford, after radial chromatography (1 : 10 EtOAc/hexanes), 25.6 mg (51%) of **14c** as an oil. IR (film) 3499, 2233, 1644 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 1.16 (d, $J = 7.4\text{ Hz}$, 3H), 1.28 (s, 3H), 1.52–1.59 (m, 1H), 1.70–1.95 (m, 3H), 2.19–2.28 (m, 1H), 2.33–2.39 (m, 1H), 2.46–2.52 (m, 1H), 5.17–5.23 (m, 2H), 5.81–5.95 (m, 1H); ^{13}C NMR (300 MHz, CDCl_3): δ 9.3, 26.1, 34.0, 39.4, 43.1, 46.0, 51.9, 80.0, 119.6, 123.5, 132.4; MS (EI) m/z 180 ($\text{M}+1$) $^+$.

(1S, 2S, 3S)-3-Allyl-3-cyano-1, 2-dimethylcyclopentyl 4-nitrobenzoate (14j): A 0°C THF solution (0.05 M) of **14c** (22.7 mg, 0.13 mmol) was successively treated with MeMgCl (2.5 M,

0.06 mL) and p-nitrobenzoyl chloride (48 mg, 0.26 mmol). After 2 h, saturated aqueous NaHCO₃ was added, and the resulting mixture was extracted with EtOAc. The extracts were combined, washed with brine and dried (NaSO₄). Concentration and purification of the crude product by radial chromatography afforded 22.2 mg (52%) of **14j** as a crystalline solid (mp 115-116°C) whose structure was determined by X-ray crystallography. IR (film) 3080, 2232, 1721 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.38 (d, *J* = 7.4 Hz, 3H), 1.69-1.75 (m, 4H), 1.87-1.97 (m, 2H), 2.21-2.33 (m, 2H), 2.58-2.62 (m, 1H), 2.80-2.87 (m, 1H), 5.23-5.27 (m, 2H), 5.86-5.94 (m, 1H), 8.27 (s, 4H); ¹³C NMR (500 MHz, CDCl₃): δ 9.7, 21.8, 33.9, 35.2, 42.9, 45.8, 54.1, 91.3, 120.2, 123.1, 123.5, 130.8, 131.8, 136.5, 163.8.

(1R, 2S, 3R)-3-Hydroxy-2, 3-dimethyl-1-pivaloylcyclopentanecarbonitrile (14d): The standard procedure was employed with oxonitrile **1a** (29 mg, 0.27 mmol), MeMgCl (2.5 M, 0.27 mL), and pivaloyl chloride (0.1 mL, 0.81 mmol) to afford, after radial chromatography (1 : 4 EtOAc/hexanes), 28.3 mg (47%) of **14d** as an oil. IR (film) 3507, 2236, 1698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.12 (d, *J* = 7.3 Hz, 3H), 1.33 (s, 3H), 1.40 (s, 9H), 1.84-2.04 (m, 4H), 2.45-2.62 (m, 2H); ¹³C NMR (300 MHz, CDCl₃): δ 9.4, 25.8, 26.8, 36.6, 40.2, 45.9, 50.9, 54.7, 80.0, 122.0, 208.3; MS (EI) *m/z* 224 (*M*+1)⁺.

(1R, 2S, 3S)-3-Cyano-1, 2-dimethyl-3-pivaloylcyclopentyl 4-nitrobenzoate (14k): A 0°C THF solution (0.05 M) of **14d** (47 mg, 0.21 mmol) was successively treated with MeMgCl (2.5M, 0.1 mL) and p-nitrobenzoyl chloride (78 mg, 0.42 mmol). After 2 h, saturated aqueous NaHCO₃ was added, and the resulting mixture was extracted with EtOAc. The extracts were combined, washed with brine and dried (NaSO₄). Concentration and purification of the crude product by radial chromatography afforded 27.8 mg (56%) of **14k** as a crystalline solid (mp 141-

142.5°C) whose structure was determined by X-ray crystallography. (IR (film) 3113, 2234, 1709, 1607 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.32 (d, *J* = 7.3 Hz, 3H), 1.41 (s, 9H), 1.76 (s, 3H), 1.95-2.11 (m, 2H), 2.30-2.48 (m, 1H), 2.79 (q, *J* = 7.3 Hz, 1H), 2.89-3.02 (m, 1H), 8.29 (s, 4H); ¹³C NMR (300 MHz, CDCl₃): δ 9.8, 21.5, 26.8, 35.9, 36.4, 46.0, 52.9, 54.3, 91.1, 121.8, 123.5, 130.9, 136.4, 150.5, 163.7, 207.4.

(1R, 2S, 3R)-1-(2, 2-Diethylbutanoyl)-3-hydroxy-2, 3-dimethylcyclopentanecarbonitrile (14e): The standard procedure was employed with oxonitrile **1a** (24.6 mg, 0.2 mmol), MeMgCl (2.5 M, 0.2 mL), and 2, 2-diethylbutanoyl chloride² (97.5 mg, 0.6 mmol) to afford, after radial chromatography (1 : 6 EtOAc/hexanes), 25.7 mg (49%) of **14e** as an oil. IR (film) 3500, 2234, 1698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.78 (t, *J* = 7.4 Hz, 9H), 1.33 (d, *J* = 7.4 Hz, 3H), 1.33 (s, 3H), 1.57 (br s, 1H), 1.65-1.83 (m, 3H), 1.85-2.07 (m, 6H), 2.35-2.51 (m, 1H), 2.56 (q, *J* = 7.4 Hz, 1H); ¹³C NMR (300 MHz, CDCl₃): δ 8.5, 9.6, 25.0, 25.8, 37.0, 40.2, 51.4, 54.7, 57.7, 80.2, 122.2, 207.7; HRMS (ESI), *m/z* calculated for (M+Na)⁺ (C₁₆H₂₇NO₂Na⁺): 288.1964, found 288.1940.

(1S, 2S, 3R)-3-hydroxy-1-(1-hydroxycyclohexyl)-2, 3-dimethylcyclopentanecarbonitrile (14f) and (1R, 2S, 3R)-3-hydroxy-1-(1-hydroxycyclohexyl)-2, 3-dimethylcyclopentanecarbonitrile (14h): The standard procedure was employed with oxonitrile **1a** (30 mg, 0.28 mmol), MeMgCl (2.5 M, 0.28 mL), and cyclohexanone (0.2 mL, 1.93 mmol) which was added at -78 °C to afford, after radial chromatography (1 : 5 and 1 : 4 EtOAc/hexanes), 25.7 mg (39%) of **14f** and 14.4 mg (22%) of **14h**, as an oil in each case. For

² Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010.

14f: IR (film) 3307, 2227 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 1.29 (s, 3H), 1.31 (d, $J = 10.3$ Hz, 3H), 1.44-1.59 (m, 12H), 2.06-2.41 (m, 3H), 2.80-3.65 (m, 2H); ^{13}C NMR (300 MHz, CDCl_3): δ 10.9, 21.7, 24.6, 24.9, 32.2, 33.8, 34.4, 39.6, 52.5, 55.5, 75.5, 79.5, 125.8. For **14h:** IR (film) 3452, 2234 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 1.24 (d, $J = 7.3$ Hz, 3H), 1.28 (s, 3H), 1.52-1.86 (m, 14H), 1.98-2.05 (m, 1H), 2.10-2.14 (m, 1H), 2.23-2.34 (m, 1H); ^{13}C NMR (300 MHz, CDCl_3): δ 11.9, 21.5, 25.1, 25.5, 31.4, 32.8, 32.9, 40.1, 45.9, 56.0, 74.9, 80.7, 123.4; MS (EI) m/z 238 ($M+1$) $^+$.

General Grignard Addition-Acylation Procedure with Oxonitrile 1c: A THF solution of MeMgCl (2.5-6 equiv) was added to a -78 $^\circ\text{C}$ THF solution (0.1 M) of oxonitrile **1c**, and the resulting solution was stirred at -78 $^\circ\text{C}$ for 1 h and then warmed to room temperature. After 1.5 h, the electrophile (2.5-6equiv) was added neat either at room temperature or with prior cooling to -78 $^\circ\text{C}$. Subsequent addition of saturated NH_4Cl and extraction with EtOAc afforded a crude product that was washed with brine and dried (MgSO_4), concentrated, and purified by radial chromatography to afford the pure product.

(1S, 2R, 3S)-3-Hydroxy-1, 2, 3-trimethylcycloheptanecarbonitrile (15a): The standard procedure was employed with oxonitrile **1c** (54 mg, 0.4 mmol), MeMgCl (2.5 M, 0.4 mL), and methyl iodide (0.25 mL, 4 mmol) to afford, after radial chromatography (1 : 6 EtOAc/hexanes), 36 mg (50%) of **15a** as a crystalline solid (m.p. 70-71 $^\circ\text{C}$) whose structure was determined by X-ray crystallography. IR (film) 3501, 2229 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 1.23 (d, $J = 7.3$ Hz, 3H), 1.30 (s, 3H), 1.43 (s, 3H), 1.52-1.61 (m, 1H), 1.66-1.85 (m, 6H), 1.94-2.06 (m, 3H); ^{13}C NMR (500 MHz, CDCl_3): δ 13.3, 21.9, 22.3, 23.2, 32.3, 38.1, 41.0, 41.7, 46.4, 75.3, 127.0; HRMS (ESI), m/z calculated for ($M+\text{Na}$) $^+$ ($\text{C}_{11}\text{H}_{19}\text{NONa}^+$): 204.1357, found 204.1364.

(1S, 6S, 9R, Z)-Methyl 8-(methoxycarbonylimino)-6, 9-dimethyl-7-oxabicyclo[4. 2. 1]nonane-1-carboxylate (15b): The standard procedure was employed with oxonitrile **1c** (81 mg, 0.6 mmol), MeMgCl (2.5 M, 0.6 mL), and methyl cyanoformate (0.24 mL, 3 mmol) to afford, after radial chromatography (1 : 4 EtOAc/hexanes), 40.3 mg (24%) of **15b** as an oil. IR (film) 2552, 1744, 1437 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.00 (d, *J* = 7.4 Hz, 3H), 1.38 (s, 3H), 1.56-1.85 (m, 6H), 1.96-2.06 (m, 1H), 2.33 (br s, 1H), 2.58 (q, *J* = 7.4 Hz, 1H), 3.74 (s, 1H), 3.76 (s, 1H); ¹³C NMR (500 MHz, CDCl₃): δ 14.2, 23.4, 23.5, 24.4, 37.1, 41.5, 43.2, 52.1, 53.1, 62.1, 91.4, 161.2, 170.4; MS (EI) *m/z* 284 (M+1)⁺.

N-((Z)-1-((2R, 3S)-3-Hydroxy-2, 3-dimethylcycloheptylidene)ethyl)pivalamide (15c): The standard procedure was employed with oxonitrile **1c** (33.8 mg, 0.25 mmol), MeMgCl (2.5 M, 0.6 mL), and pivaloyl chloride (0.18 mL, 1.5 mmol) to afford, after radial chromatography (2 : 5 EtOAc/hexanes), 18.7 mg (28%) of **15c** as an oil. IR (film) 3446, 3310, 1638 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.11 (d, *J* = 7.4 Hz, 3H), 1.24 (s, 9H), 1.27 (s, 3H), 1.32 (br s, 1H), 1.35-1.46 (m, 2H), 1.50-1.57 (m, 1H), 1.69-1.83 (m, 3H), 1.95 (s, 3H), 2.18-2.24 (m, 2H), 2.66 (q, *J* = 7.3 Hz, 1H), 6.61 (s, 1H); ¹³C NMR (500 MHz, CDCl₃): δ 14.2, 17.2, 23.3, 26.8, 27.0, 27.7, 30.6, 39.0, 39.5, 45.2, 74.2, 126.0, 134.8, 176.6; MS (EI) *m/z* 268 (M+1)⁺.

General Procedure for the Addition-Alkylation with Stereochemical Inversion: A THF solution of MeMgCl (1.05-1.1 equiv) was added to a -15 °C THF solution (0.1 M) of the oxonitrile **1b**. After 2h, a second Grignard reagent (1.2-1.5 equiv), if different from MeMgCl, was added and the solution was then allowed to warm to room temperature. After 2h, the solution was transferred by syringe to a 0 °C THF solution (0.3 M) of cis-cyclohexane-1, 2-diol

(3 equiv) to which n-BuLi (3.3 equiv) had been added. The resulting solution was cooled to -78°C and after 0.5h, the electrophile (3.0-10 equiv) was added neat. After 1h, the solution was allowed to warm to room temperature, and after 16h, saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The extracts were combined, washed with brine and dried (NaSO_4). Concentration and purification of the crude product by radial chromatography afforded the pure nitrile.

(1R, 2R, 3S)-3-hydroxy-1,2,3-trimethylcyclohexanecarbonitrile (5d) and **(1S, 2R, 3S)-3-hydroxy-1,2,3-trimethylcyclohexanecarbonitrile (5a)**: The standard procedure was employed with **1b** (30.3 mg, 0.25 mmol), MeMgCl (2.5 M, 0.25 mL), cis-cyclohexane-1, 2-diol (88 mg, 0.75 mmol), n-BuLi (2.57 M, 0.64 mL), and methyl iodide (0.25 mL, 4.0 mmol) to afford, after radial chromatography (1:100 and 1:50 MeOH/ CH_2Cl_2), 23 mg (55%) of **5d** as a white solid (m.p. $53-54^{\circ}\text{C}$) and 7mg (17%) of **5a** as a white crystalline solid (m.p. $100-103^{\circ}\text{C}$). The spectral data of both **5d** and **5a** was identical to those of the material previously isolated and the structure of **5a** (218678) had been confirmed before by X-ray crystallography.³

(1R, 2R, 3S)-1-allyl-3-hydroxy-2,3-dimethylcyclohexanecarbonitrile (5c) and **(1S, 2R, 3S)-1-allyl-3-hydroxy-2,3-dimethylcyclohexanecarbonitrile (5e)**: The standard procedure was employed with **1b** (30.3 mg, 0.25 mmol), MeMgCl (2.5 M, 0.25 mL), cis-cyclohexane-1, 2-diol (88 mg, 0.75 mmol), n-BuLi (2.57 M, 0.64 mL), and allyl bromide (0.2 mL, 2.3 mmol) to afford, after radial chromatography (1 : 100 and 4 : 100 $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$), 4.3 mg (9%) of **5c** as a crystalline solid (m.p. $73-74^{\circ}\text{C}$) and 33.8 mg (70%) of **5e** as an oil. The spectral data of both **5c**

³ Fraser, F. F.; Zhang, Z.; Wei, G.; Steward, O. W. *J. Org. Chem.* **2006**, *71*, 1430.

and **5e** was identical to those of the material previously isolated and the structure of **5c** (242092) had been confirmed before by X-ray crystallography.³

(1R, 2R, 3S)-3-hydroxy-2, 3-dimethyl-1-propylcyclohexanecarbonitrile (5f) and **(1S, 2R, 3S)-3-hydroxy-2,3-dimethyl-1-propylcyclohexanecarbonitrile (5j)**: The standard procedure was employed with **1b** (30.3 mg, 0.25 mmol), MeMgCl (2.5 M, 0.25 mL), cis-cyclohexane-1, 2-diol (88 mg, 0.75 mmol), n-BuLi (2.57 M, 0.64 mL), and propyl iodide (0.38 mL, 0.88 mmol) to afford, after radial chromatography (1 : 6 and 1 : 5 EtOAc/hexanes), 32.4 mg (63%) of **5f** as an oil and 5.5 mg (10%) of **5j** as a crystalline solid (m.p. 125-126 °C). The spectral data of both **5f** and **5j** was identical to those of the material previously isolated and the structure of **5j** (242090) had been confirmed before by X-ray crystallography.³

(1S, 2R, 3S)-1-(But-3-enyl)-3-hydroxy-2, 3-dimethylcyclohexanecarbonitrile (5g) and **(1R, 2R, 3S)-1-(But-3-enyl)-3-hydroxy-2,3-dimethylcyclohexanecarbonitrile (5k)**: The standard procedure was employed with **1b** (30.3 mg, 0.25 mmol), MeMgCl (2.5 M, 0.25 mL), cis-cyclohexane-1, 2-diol (88 mg, 0.75 mmol), n-BuLi (2.57 M, 0.64 mL), and 4-iodobut-1-ene (455 mg, 2.5 mmol) to afford, after radial chromatography (1 : 10 and 1 : 7 EtOAc/hexanes), 29.9 mg (58%) of **5g** as an oil and 5.8 mg (11%) of **5k** as a crystalline solid (m.p. 78-80 °C). The spectral data of both **5g** and **5k** was identical to those of the material previously isolated and the structure of **5k** (281464) had been confirmed before by X-ray crystallography.³

(1R, 2R, 3S)-3-Hydroxy-1, 3-dimethyl-2-vinylcyclohexanecarbonitrile (5h) and **(1S, 2R, 3S)-3-Hydroxy-1, 3-dimethyl-2-vinylcyclohexanecarbonitrile (5l)**: The standard procedure

was employed with **1b** (217.8 mg, 1.8 mmol), MeMgCl (2.5 M, 0.76 mL), vinylmagnesium bromide (0.7 M, 3.9 mL), cis-cyclohexane-1, 2-diol (634 mg, 5.4 mmol), n-BuLi (2.57 M, 2.31 mL), and methyl iodide (1 mL, 16 mmol) to afford, after radial chromatography (1 : 20 EtOAc/CH₂Cl₂), 182.3 mg (57%) of **5h** and 50.6 mg (16%) of **5l**, as an oil in each case. For **5h**: IR (film) 3524, 3072, 2233, 1639 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.17 (s, 3H), 1.20-1.51 (m, 6H), 1.58-1.71 (m, 2H), 1.84 (d, *J* = 11 Hz, 1H), 1.95-2.16 (m, 2H), 5.10-5.19 (m, 1H), 5.38 (dd, *J* = 10.3, 2.9 Hz, 1H), 5.92-6.08 (m, 1H); ¹³C NMR (300 MHz, CDCl₃): δ 18.7, 27.5, 29.88, 34.7, 38.0, 39.3, 58.9, 70.3, 121.0, 124.0, 133.8; MS (EI) *m/z* 180 (M+1)⁺. For **5l**: IR (film) 3473, 3074, 2238, 1632 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.09 (s, 1H), 1.22 (s, 3H), 1.38-1.74 (m, 6H), 1.77-2.06 (m, 3H), 2.15 (d, *J* = 10.2 Hz, 1H), 5.29-5.54 (m, 2H), 5.86-6.02 (m, 1H); ¹³C NMR (300 MHz, CDCl₃): δ 16.92, 19.6, 30.7, 36.8, 37.7, 39.2, 55.3, 70.6, 121.2, 125.6, 133.0; MS (EI) *m/z* 180 (M+1)⁺.

(1S, 2R, 3S)-1-(Cyclopropylmethyl)-3-hydroxy-2, 3-dimethylcyclohexanecarbonitrile (5i) and **(1R, 2R, 3S)-1-(Cyclopropylmethyl)-3-hydroxy-2, 3-dimethylcyclohexane-carbonitrile (5m)**: The standard procedure was employed with **1b** (18.2 mg, 0.15 mmol) and MeMgCl (2.5 M, 0.15 mL), cis-cyclohexane-1, 2-diol (53 mg, 0.45 mmol), n-BuLi (2.57 M, 0.38 mL), and cyclopropylmethyl iodide (262 mg, 1.43 mmol) to afford, after radial chromatography (1 : 10 and 1 : 6 EtOAc/hexanes), 7.8 mg (25%) of **5i** as an oil, 3.5 mg (11%) of **5m** as a crystalline solid (m.p. 70-72 °C), 4.8 mg (16%) of **5g** as an oil, and 1.9 mg (6%) of **5k** as a crystalline solid. The spectral data of **5g**, **5k**, **5i**, and **5m** was identical to those of the material previously isolated and the structure of **5m** (281463) had been confirmed before by X-ray crystallography.³

2-Bromo-3-oxocyclohex-1-ene-1-carbonitrile (23): A 1 mL CH₂Cl₂ solution of the bromine (240 mg, 1.5 mmol) was added to a 0 °C, 4 mL CH₂Cl₂ solution of **1b** (181 mg, 1.5 mmol). After 1.5 h at 0 °C, Et₃N (0.32 mL, 2.25 mmol) was added dropwise. The solution was stirred at room temperature for 1.5 h and was washed with 3% HCl twice and saturated brine once and dried (MgSO₄). Concentration and radial chromatography (stepped gradient 1:9, 3:17, 1:4, 1:3 EtOAc/Hexanes) to afford **23** (210 mg, 70%) as a light yellow oil. IR (film) 2221, 1706, 1692 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.10-2.18 (m, 2H), 2.62-2.70 (m, 4H); ¹³C NMR (300 MHz, CDCl₃): δ 21.9, 30.6, 37.4, 116.2, 131.1, 134.6, 188.7; HRMS (EI) calcd for (M⁺), C₇H₆BrNO⁺ 198.9627, found 198.9633.

3-Hydroxy-2, 3-dimethylcyclohex-1-ene-1-carbonitrile (26): A THF solution of MeMgCl (3 M, 3 mmol) was added to a -78 °C THF solution of **23** (0.1 M). After 1 h at -78 °C and 2.5 h at room temperature, MeI was added neat and the resulting solution was stirred overnight. Saturated aqueous NH₄Cl was added and the resultant mixture was extracted with EtOAc. The extracts were combined, washed with brine, and dried (NaSO₄). Concentration and purification of the crude product by radial chromatography (stepped gradient 1:4, 3:7 EtOAc/hexanes) furnished 46 mg (51%) of **26** as a wax solid. IR (film) 3438, 2213, 1646 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.31 (s, 3H), 1.60-1.75 (m, 4H), 2.06 (s, 3H), 2.20-2.22 (m, 2H); ¹³C NMR (300 MHz, CDCl₃): δ 16.7, 19.0, 26.9, 27.8, 38.2, 70.0, 108.7, 118.7, 156.0.

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Bruker 75MHz
¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

Varian 500MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Varian 125MHz
¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

Varian 500MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Varian 125MHz
¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

Varian 500MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Varian 125MHz

^{13}C NMR

CDCl_3 (solvent)

CDCl_3 (77.0, internal standard)

Varian 500MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Varian 125MHz

^{13}C NMR

CDCl_3 (solvent)

CDCl_3 (77.0, internal standard)

Bruker 300MHz

¹H NMR

CDCl₃ (solvent)

CDCl₃ (7.26, internal standard)

Bruker 75MHz

^{13}C NMR

CDCl_3 (solvent)

CDCl_3 (77.0, internal standard)

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Bruker 75MHz
 ^{13}C NMR

CDCl_3 (solvent)

CDCl_3 (77.0, internal standard)

Varian 500MHz

¹H NMR

CDCl₃ (solvent)

CDCl₃ (7.26, internal standard)

Varian 125MHz
¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Bruker 75MHz

^{13}C NMR

CDCl_3 (solvent)

CDCl_3 (77.0, internal standard)

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Bruker 75MHz

^{13}C NMR

CDCl_3 (solvent)

CDCl_3 (77.0, internal standard)

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Bruker 75MHz

^{13}C NMR

CDCl_3 (solvent)

CDCl_3 (77.0, internal standard)

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Bruker 75MHz
¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Bruker 75MHz

^{13}C NMR

CDCl_3 (solvent)

CDCl_3 (77.0, internal standard)

Varian 500MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Varian 125MHz
¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

Varian 500MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Varian 125MHz
¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

Varian 500MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Varian 125MHz

^{13}C NMR

CDCl_3 (solvent)

CDCl_3 (77.0, internal standard)

Bruker 300MHz

¹H NMR

CDCl₃ (solvent)

CDCl₃ (7.26, internal standard)

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
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	9.999P
F2	-1.98P
HZ/CM	122.422
PPM/CM	.408
SR	3367.05

Bruker 75MHz

¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

F .001
DATE 15-1-2
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 80
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 -1388.12

Bruker 300MHz

¹H NMR

CDCl₃ (solvent)

CDCl₃ (7.26, internal standard)

FFZY101.001
DATE 24-11-2
SF 300.134
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 4
NS 8
TE 297
FW 7600
O2 5684.205
DP 4L P0
LB 0.0
GB 0.0
CX 25.00
CY 12.00
F1 9.999P
F2 .198P
HZ/CM 122.423
PPM/CM .408
SR 3368.15

Bruker 75MHz
¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

Bruker 300MHz

¹H NMR

CDCl₃ (solvent)

CDCl₃ (7.26, internal standard)

FFZY091.001
DATE 28-8-2

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

PD 5.0
RD 2.500
AQ .909
RG 4
NS 9
TE 297

FW 5700
O2 5684.205
DP 4L P0

LB 0.0
GB 0.0
CX 25.00
CY 9.00
F1 10.001P
F2 -.200P
HZ/CM 122.466
PPM/CM .408
SR 3367.75

Bruker 75MHz

¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

FFZY091.101
DATE 29-8-2

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
AG	.459
RG	200
NS	13548
TE	297
FW	22400
O2	4004.452
DP	20H BB
LB	0.0
GB	0.0
CX	25.00
CY	6.50
F1	220.004P
F2	.024P
HZ/CM	664.062
PPM/CM	8.799
SR	-1403.38

PPM

133.843

124.832

119.141

77.430

77.000

76.569

71.222

45.025

41.647

39.888

33.157

32.981

30.613

16.316

10.597

Bruker 300MHz

¹H NMR

CDCl₃ (solvent)

CDCl₃ (7.26, internal standard)

FFZY092.001
DATE 29-8-2

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
AG	.909
RG	4
NS	11
TE	297
FW	5700
O2	5684.205
DP	4L P0
LB	0.0
GB	0.0
CX	25.00
CY	12.00
F1	10.003P
F2	-197P
HZ/CM	122.422
PPM/CM	.408
SR	3367.75

Bruker 75MHz

¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

¹³C NMR

CDCl₃ (77.0, internal standard)

FEZ	Y30	101
DATE	16-11-3	
SY	75.0	75.475
S1	6147	.202
SI	16384	
TD	16384	
SW	17857	.143
HZ/P1	2.180	
PM	4.0	
AD	3.000	
RG	.459	
NS	296	
TE	297	
FM	22400	
D2	4004	.452
DP	2014	BB
LB	0.0	
GB	0.0	
CX	25.00	
CY	3.00	
F1	220	.014P
F2	.024P	
HZ/CM	664	150
PRM/CM	8	800
SR	-1396.	.84

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Bruker 75MHz

¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

FFGM1213.114
DATE 9-1-0

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 42081
TE 297

FW 22400
O2 4004.452
DP 20H BB

LB 0.0
GB 0.0
CX 25.00
CY 0.0
F1 220.033P
F2 .024P
HZ/CM 664.150
PPM/CM 8.800
SR -1403.38

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Bruker 75MHz
¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

U1	D14/.cvc
SI	16384
TD	16384
SW	17857.143
HZ/PT	2.180
PW	4.0
RO	3.000
AG	.459
RG	200
NS	15768
TE	297
FW	22400
O2	4004.452
DP	20H 88
LB	0.0
GB	0.0
CX	25.00
CY	7.50
F1	220.014P
F2	.024P
HZ/CM	664.150
PPM/CM	8.800
SR	-1401.20

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Bruker 75MHz
¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

FFGW0129.115
DATE 25-2-0

~~BRUKER~~

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 1.459
RG 200
NS 23196
TE 297

FW 22400
O2 4004.452
DP 20H B8

LB 0.0
GB 0.0
CX 25.00
CY 0.0
F1 220.033P
F2 220.024P
HZ/CM 664.150
PPM/CM 8.800
SR -1403.38

137.138

123.186

115.446

77.429

76.998

76.568

70.991

46.124

40.633

39.865

38.265

34.858

29.660

28.214

18.596

9.786

Bruker 300MHz

¹H NMR

CDCl₃ (solvent)

CDCl₃ (7.26, internal standard)

Bruker 75MHz

^{13}C NMR

CDCl_3 (solvent)

CDCl_3 (77.0, internal standard)

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Bruker 75MHz

^{13}C NMR

CDCl_3 (solvent)

CDCl_3 (77.0, internal standard)

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Bruker 75MHz

^{13}C NMR

CDCl_3 (solvent)

CDCl_3 (77.0, internal standard)

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Bruker 75MHz

¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

SI	75.0	/C, 403
SI	6147.202	
SI	16384	
TD	16384	
SW	17857.143	
HZ/PT	2.180	
PM	4.0	
RD	3.000	
AG	.459	
RG	200	
NS	16669	
TE	297	
FW	22400	
O2	4004.452	
DP	20H 8B	
LB	0.0	
GB	0.0	
CX	25.00	
CY	0.0	
F1	220.033P	
F2	.024P	
HZ/CM	664.150	
PPM/CM	8.800	
SR	-1405.56

Bruker 300MHz

¹H NMR

CDCl₃ (solvent)

CDCl₃ (7.26, internal standard)

SF	300.133
SY	210.0
O1	4900.000
SI	8192
TD	8192
SW	8928.571
HZ/PT	2.180
PW	5.0
RD	2.500
AG	.459
RG	2
NS	8
TE	297
FW	11200
O2	5684.205
DP	4L P0
LB	0.0
GB	0.0
CX	25.00
CY	12.50
F1	10.001P
F2	-196P
HZ/CM	122.419
PPM/CM	.408
SR	3354.50

Bruker 75MHz

¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

134.585
131.149
116.190
77.406
76.994
76.562
37.430
30.584
21.862

SF 75.475
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 629
TE 297
FW 22400
O2 4004.452
DP 20H BB
LB 0.0
GB 0.0
CX 25.00
CY 3.00
F1 220.014P
F2 .024P
HZ/CM 664.150
PPM/CM 8.800
SR -1394.66

Bruker 300MHz

^1H NMR

CDCl_3 (solvent)

CDCl_3 (7.26, internal standard)

Bruker 75MHz

¹³C NMR

CDCl₃ (solvent)

CDCl₃ (77.0, internal standard)

FFZY131.101
DATE 18-11-3
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 15115
TE 297
FW 22400
D2 4004.452
DP 20H BB
LB 0.0
GB 0.0
CX 25.00
CY 15.00
F1 220.033P
F2 024P
HZ/CM 664.150
PPM/CM 8.800
SR -1403.38