Termination of Mn(III)-Based Oxidative Cyclizations by Trapping with Azide

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Methyl 2-(1-Azido-propyl)-6-oxocyclohexanecarboxylate (10). A solution of methyl 3-oxo-7Z-decenoate (**9**)⁶ (300 mg, 1.5 mmol), Mn(OAc)₃·2H₂O (1.07 g, 4.0 mmol), and NaN₃ (490 mg, 7.5 mmol) in 18 mL of degassed MeOH was stirred in a 50-55 °C oil bath for 20 h, at which time the dark brown solution had turned colorless with a white precipitate. The mixture was cooled, diluted with H₂O, and extracted with CH₂Cl₂. The combined organic fractions were washed with a 10% sodium bisulfite solution and brine, dried (MgSO₄) and concentrated to give 368 mg of crude **10** as a 3:2 mixture of diastereomers. Attempted purification by flash chromatography on deactivated silica gel (deactivated with MeOH; 99:1 hexanes/EtOAc) provided 227 mg (63% yield) of a 1:1:1 inseparable mixture of both diastereomers of enol **11** and the major diastereomer of ketone **10**.

Partial data for the major diastereomer of **10** were determined from the mixture: ¹H NMR 3.801 (s, 3), 3.55 (d, 1, *J* = 11.6), 3.16-3.24 (m, 1), 1.04 (t, 3, *J* = 7.7).

Partial data for the minor diastereomer of **10**: ¹H NMR 3.78 (s, 3), 3.32 (d, 1, *J* = 11.0), 1.03 (t, 3, *J* = 7.7).

Partial data for the major isomer of **11** were determined from the mixture: ¹H NMR 3.804 (s, 3), 3.28-3.36 (m, 1), 2.88-2.94 (m, 1), 1.00 (t, 3, *J* = 7.3).

Partial data for the minor isomer of **11** were determined from the mixture: 3.79 (s, 3), 3.46-3.54 (m, 1), 2.75-2.82 (m, 1), 1.03 (t, 3, *J* = 7.3).

Ethyl *rel*-(1*R*,2*R*)-2-[(1*S* and 1*R*)-1-Azidopropyl]-1-methyl-6-oxocyclohexanecarboxylate (8a and 8b). A solution of ethyl 2-methyl-3-oxo-7Z-decenoate (**3**)⁶ (300 mg, 1.32 mmol), Mn(OAc)₃·2H₂O (885 mg, 3.3 mmol) and NaN₃ (430 mg, 6.6 mmol) in 15 mL of degassed MeOH was stirred in a 50-55 °C oil bath for 36 h. Work up as described above gave 320 mg of crude **8** as a 3:1 mixture of diastereomers. Flash chromatography on silica

gel (99:1 hexanes/EtOAc) gave 144 mg (41%) of **8a**, followed by 55 mg (16%) of a 1:1 mixture of **8a** and **8b**, and 25 mg (7%) of a > 9:1 mixture of **8b** and **8a** (64% total yield).

Data for **8a**: ^1H NMR 4.11-4.21 (m, 2), 3.58-3.64 (m, 1), 2.69 (ddd, 1, $J = 14.0, 14.0, 6.1$), 2.48 (br d, 1, $J = 14.0$), 2.05-2.15 (m, 1), 1.40-1.98 (m, 6), 1.48 (s, 3), 1.27 (t, 3, $J = 7.3$), 1.04 (t, 3, $J = 7.3$); ^{13}C NMR 206.7, 171.2, 65.8, 61.3, 59.7, 52.4, 39.4, 25.1, 24.4, 24.1, 19.6, 13.8, 11.3; IR (neat) 2097, 1718; HRMS (DCI/ NH_3) Calcd for $\text{C}_{13}\text{H}_{22}\text{N}_3\text{O}_3$ (MH^+) 268.1661, found 268.1662.

Data for **8b** obtained from the >9:1 mixture: ^1H NMR 4.10-4.28 (m, 2), 3.59 (br t, 1, $J = 7.0$), 2.97 (td, 1, $J = 14.6, 6.7$), 2.48 (br d, 1, $J = 14.7$), 2.00-2.18 (m, 2), 1.52-1.86 (m, 5), 1.38 (s, 3), 1.31 (t, 3, $J = 7.1$), 1.04 (t, 3, $J = 7.7$); ^{13}C NMR 207.9, 170.7, 63.8, 61.7, 59.3, 52.4, 40.0, 27.8, 24.1, 21.3, 19.0, 13.9, 11.2; IR (neat) 2095, 1727, 1702.

***rel*-(3*S* and 3*R*, 3*aR*, 7*aR*)-3-Ethyl-7*a*-methyl-hexahydro-isoindole-1,7-dione (12*a* and 12*b*).** A solution of crude **8a** and **8b** (640 mg, starting from 2.5 mmol of **3**) in 25 mL of EtOH containing 10% Pd on activated carbon (240 mg) was hydrogenated (50 PSI) at room temperature in a Parr shaker for 6 h. The mixture was filtered through Celite and concentrated to give 410 mg of the crude product as a mixture of diastereomers. Flash chromatography on silica gel (99:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) gave 33 mg (7%) of **12b**, followed by 57 mg (12%) of a 3:1 mixture of **12a** and **12b**, and 158 mg (32%) of **12a** (51% yield from **3**).

Data for **12a**: mp 135-136 °C; ^1H NMR 7.14 (br s, 1, NH), 3.25-3.33 (m, 1), 1.4-2.6 (m, 9), 1.42 (s, 3), 0.99 (t, 3, $J = 7.7$); ^{13}C NMR 209.3, 175.4, 57.9, 56.7, 50.8, 37.9, 27.8, 23.6, 22.4, 20.2, 10.4; IR (KBr) 1723, 1685; HRMS (EI) Calcd for $\text{C}_{11}\text{H}_{17}\text{N}_1\text{O}_2$ (M^+) 195.1259, found 195.1258.

Data for **12b**: mp 124-126 °C; ^1H NMR 6.95 (br s, 1, NH), 3.64-3.72 (m, 1), 1.5-2.5 (m, 9), 1.37 (s, 3), 0.99 (t, 3, $J = 7.5$); ^{13}C NMR 207.1, 176.5, 58.6, 57.1, 48.9, 40.4, 23.5, 22.8, 22.4, 17.3, 10.8; IR (KBr) 1716, 1679; HRMS (EI) Calcd for $\text{C}_{11}\text{H}_{17}\text{N}_1\text{O}_2$ (M^+) 195.1259, found 195.1267.

Ethyl *rel*-(1*R*,5*S*)- and *rel*-(1*R*,5*R*)-5-Azido-1,5-dimethyl-2-oxocyclohexanecarboxylate (14a and 14b). A solution of ethyl 2,6-dimethyl-3-oxo-6-heptenoate (**13**)⁸ (530 mg, 2.67 mmol), $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (1.8 g, 6.7 mmol) and NaN_3 (864 mg, 13.3 mmol) in 30 mL of degassed MeOH was stirred in a 50-55 °C oil bath for 36 h. Workup as described above gave 704 mg of crude **14** as a 3.3:1 mixture of diastereomers. Flash chromatography on silica gel (39:1 hexanes/EtOAc) yielded 361 mg (57%) of **14a**, followed by 42 mg (7%) of a 2:1 mixture of **14b** and **14a**, and 84 mg (13%) of pure **14b** (77% total yield).

Data for **14a**: ^1H NMR 4.13-4.27 (m, 2), 2.64 (d, 1, $J = 14.6$), 2.59-2.68 (m, 1), 2.52 (ddd, 1, $J = 16.2, 6.4, 6.4$), 1.99 (apparent t, 2, $J = 7.0$), 1.87 (d, 1, $J = 14.6$), 1.47 (s, 3), 1.44 (s, 3), 1.28 (t, 3, $J = 7.3$); ^{13}C NMR 207.0, 172.8, 61.7, 59.6, 54.9, 45.5, 35.6, 35.1, 24.9, 22.1, 13.9; IR (neat) 2101, 1733, 1715; HRMS (DCI/ NH_3) Calcd for $\text{C}_{11}\text{H}_{18}\text{N}_3\text{O}_3$ (MH^+) 240.1348, found 240.1340.

Data for **14b**: ^1H NMR 4.09-4.35 (m, 2), 3.02 (ddd, 1, $J = 14.6, 14.6, 6.1$), 2.75 (dd, 1, $J = 14.6, 3.6$), 2.34 (br d, 1, $J = 14.6$), 1.96-2.06 (m, 1), 1.75 (ddd, 1, $J = 14.6, 14.0, 4.2$), 1.62 (d, 1, $J = 14.6$), 1.41 (s, 3), 1.29 (t, 3, $J = 7.3$), 1.27 (s, 3); ^{13}C NMR 207.2, 173.0, 61.6, 60.0, 53.6, 47.6, 37.9, 36.2, 25.4, 21.8, 13.8; IR (neat) 2107, 1718; HRMS (DCI/ NH_3) Calcd for $\text{C}_{11}\text{H}_{18}\text{N}_3\text{O}_3$ (MH^+) 240.1348, found 240.1347.

Methyl 5-Azido-2-hydroxy-5-methyl-1-cyclohexenecarboxylate (16). A solution of methyl 6-methyl-3-oxo-6-heptenoate (**15**)⁹ (200 mg, 1.17 mmol), Mn(OAc)₃·2H₂O (785 mg, 2.9 mmol) and NaN₃ (380 mg, 5.9 mmol) in 10 mL of degassed MeOH was stirred in a 50-55 °C oil bath for 3 h. Workup as described above gave 210 mg of crude **16**. Flash chromatography on silica gel (10:1 hexanes/EtOAc) gave 75 mg (30% yield, 43% based on recovered **15**) of **16** followed by 60 mg (30%) of recovered **15**: ¹H NMR 12.14 (s, 1, OH), 3.76 (s, 3), 2.44-2.56 (m, 1), 2.47 (d, 1, *J* = 16.4), 2.24-2.34 (m, 1), 2.27 (d, 1, *J* = 16.4), 1.81-1.88 (m, 1), 1.62-1.72 (m, 1), 1.40 (s, 3); ¹³C NMR 172.3, 171.1, 94.4, 59.2, 51.5, 33.6, 32.0, 26.2, 25.3; IR (neat) 2094, 1662, 1618; HRMS (DCI/NH₃) Calcd for C₉H₁₄N₃O₃ (MH⁺) 212.1035, found 212.1035.

Diethyl 2-Azidomethyl-cyclopentane-1,1-dicarboxylate (18). A solution of diethyl 4-pentenyl-malonate (**17**)¹⁰ (200 mg, 0.87 mmol), Mn(OAc)₃·2H₂O (590 mg, 2.2 mmol) and NaN₃ (286 mg, 4.4 mmol) in 12 mL of degassed MeOH was stirred in a 50-55 °C oil bath for 40 h. Workup as described above gave 230 mg of crude **18** and **19**. Flash chromatography on silica gel (20:1 hexanes/EtOAc) gave 204 mg (87% yield) of a 9:1 mixture of **18** and **19**:

Data for **18** were determined from the mixture: ¹H NMR 4.12-4.28 (m, 4), 3.62 (dd, 1, *J* = 4.9, 12.2), 3.23 (dd, 1, *J* = 8.5, 12.2), 2.72-2.82 (m, 1), 2.36-2.46 (m, 1), 2.00-2.14 (m, 2), 1.80-1.90 (m, 1), 1.48-1.68 (m, 2), 1.23 (m, 6); ¹³C NMR 171.6, 170.5, 61.9, 61.34, 61.32, 52.8, 45.7, 34.5, 29.4, 22.5, 13.93, 13.90; IR (neat) 2099, 1734; HRMS (DCI/NH₃) Calcd for C₁₂H₂₀N₃O₄ (MH⁺) 270.1454, found 270.1452.

Partial data for **19** were determined from the mixture: ¹H NMR 3.52-3.64 (m, 1), 2.55 (br d, 1, *J* = 14.4), 2.19 (br d, 1, *J* = 13.4); ¹³C NMR 61.5, 56.7, 35.7, 30.4, 30.2, 20.5.

Ethyl 3-Oxohexahydro-cyclopenta[c]pyrrole-3a-carboxylate (20). A solution of crude **18** and **19** (545 mg, prepared from 2.19 mmol of **17**) in 22 mL of EtOH containing 10%

palladium on activated carbon (212 mg) was hydrogenated (50 PSI) at room temperature in a Parr shaker for 8 h. Workup as described above gave 430 mg of crude **20**. Flash chromatography on silica gel (39:1 hexanes/EtOAc) gave 215 mg (42% yield for 2 steps) of pure **20**: mp 74-75 °C; ^1H NMR 6.70 (br d, 1, NH), 4.14-4.26 (m, 2), 3.70 (dd, 1, $J = 7.9, 9.2$), 3.06 (d, 1, $J = 9.7$), 2.82-3.01 (m, 1), 2.26-2.37 (m, 1), 2.11-2.20 (m, 1), 1.96-2.08 (m, 1), 1.50-1.80 (m, 3), 1.27 (t, 3, $J = 7.1$); ^{13}C NMR 176.8, 171.6, 62.5, 61.1, 47.1, 43.9, 34.5, 32.9, 25.6, 13.8; IR (KBr) 1740, 1684; HRMS (EI) Calcd for $\text{C}_{10}\text{H}_{15}\text{N}_1\text{O}_3$ (M^+) 197.1052, found 197.1048.

Methyl *rel*-(1*R*,5*S*)- and *rel*-(1*R*,5*R*)-1-Allyl-5-azido-5-methyl-2-oxocyclohexanecarboxylate (24a and 24b) and Methyl *exo*- and *endo*-6-Azidomethyl-5-methyl-2-oxobicyclo[3.2.1]octane-1-carboxylate (25a and 25b). A solution of methyl 2-allyl-6-methyl-3-oxo-6-heptenoate (**21**)¹¹ (222 mg, 1.05 mmol), $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (670 mg, 2.5 mmol), and NaN_3 (341 mg, 5.25 mmol) in 12 mL of degassed MeOH was stirred at 25 °C for 4 d. Workup as described above gave 276 mg of crude **24** and **25** as a 4:1.5 and 2:1 mixture of diastereomers, respectively. Flash chromatography on silica gel (50:1 to 20:1 hexanes/EtOAc) gave 23 mg (8%) of **24b**, followed by 13 mg (5%) of a 2:1 mixture of **24b** and **24a**, 71 mg (26%) of pure **24a**, 19 mg (7%) of **25b**, 14 mg (5%) of a 3:1 mixture of **25a** and **25b**, and 35 mg (12%) of pure **25a** (63% total yield).

Data for **24a**: ^1H NMR 5.64-5.78 (m, 1), 5.06-5.14 (m, 2), 3.71 (s, 3), 2.63 (ddd, 1, $J = 14, 14, 6.5$), 2.44-2.58 (m, 4), 1.92-1.98 (m, 3), 1.44 (s, 3); ^{13}C NMR 206.0, 172.0, 132.8, 119.4, 59.7, 58.7, 52.6, 42.8, 39.4, 35.5, 35.4, 24.9; IR (neat) 2103, 1713; HRMS (DCI/ NH_3) Calcd for $\text{C}_{12}\text{H}_{18}\text{N}_1\text{O}_3$ ($\text{MH}^+ - \text{N}_2$) 224.1287, found 224.1283.

Data for **24b**: ^1H NMR 5.74-5.86 (m, 1), 5.00-5.10 (m, 2), 3.75 (s, 3), 2.99 (ddd, 1, $J = 14.3, 14.3, 6.1$), 2.63 (dd, 1, $J = 4.2, 14.6$), 2.28-2.48 (m, 3), 1.96-2.06 (m, 1), 1.71 (dt, 1, $J = 4.3,$

14.0), 1.70 (d, 1, $J = 14.6$), 1.41 (s, 3); ^{13}C NMR 206.5, 172.2, 133.2, 118.8, 60.1, 57.5, 52.5, 45.3, 39.8, 37.9, 36.6, 25.5; IR (neat) 2106, 1718; HRMS (DCI/ NH_3) Calcd for $\text{C}_{12}\text{H}_{21}\text{N}_4\text{O}_3$ (MNH_4^+) 269.1614, found 269.1621.

Data for **25a**: mp 79-81 °C; ^1H NMR 3.75 (s, 3), 3.55 (dd, 1, $J = 5.5, 12.2$), 3.28 (dd, 1, $J = 7.9, 12.2$), 2.51-2.64 (m, 1), 2.33-2.44 (m, 2), 2.12-2.24 (m, 1), 2.14 (dd, 1, $J = 3.6, 12.5$), 2.03 (dd, 1, $J = 5.5, 14.6$), 1.93 (d, 1, $J = 12.8$), 1.74-1.84 (m, 1), 1.68 (dt, 1, $J = 6.7, 12.8$), 1.13 (s, 3); ^{13}C NMR 207.7, 171.7, 63.7, 54.8, 52.2, 45.1, 43.0, 41.4, 40.6, 37.2, 34.6, 21.2; IR (KBr) 2093, 1738, 1701; HRMS (DCI/ NH_3) Calcd for $\text{C}_{12}\text{H}_{18}\text{N}_3\text{O}_3$ (MH^+) 252.1348, found 252.1336.

Data for **25b**: mp 65-66 °C; ^1H NMR 3.74 (s, 3), 3.53 (dd, 1, $J = 6.1, 12.2$), 3.40 (dd, 1, $J = 8.5, 12.2$), 2.54-2.66 (m, 2), 2.38 (dd, 1, $J = 8.0, 17.1$), 2.20-2.30 (m, 1), 2.16 (dd, 1, $J = 12.3, 3.5$), 2.05 (d, 1, $J = 12.3$), 1.80-1.90 (m, 2), 1.60-1.74 (m, 1), 1.18 (s, 3); ^{13}C NMR 207.2, 171.8, 62.9, 52.2, 52.1, 48.4, 46.2, 41.8, 36.0, 34.5, 33.0, 24.7; IR (KBr) 2099, 1732, 1701; HRMS (DCI/ NH_3) Calcd for $\text{C}_{12}\text{H}_{21}\text{N}_4\text{O}_3$ (MNH_4^+) 269.1614, found 269.1604.

Methyl (1 α ,2 α ,5 β)-2-(1-Azido-propyl)-8-oxobicyclo[3.2.1]octane-1-carboxylate (28 and 29). A solution of methyl 3-(3*Z*-hexenyl)-2-oxo-cyclopentanecarboxylate (**26**)⁶ (93 mg, 0.41 mmol), $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (268 mg, 1.0 mmol), and NaN_3 (130 mg, 2.0 mmol) in 6 mL of HOAc was stirred at 25 °C for 2 d. The mixture was diluted with water and extracted with CH_2Cl_2 . The combined organic fractions were washed with 10% sodium bisulfite solution, saturated sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated to give 94 mg of a 3:2:2 mixture of **28**, **29**, and **30**, respectively. Flash chromatography on silica gel (20:1 hexanes/EtOAc) gave 42 mg of an inseparable 3:2 mixture of **28** and **30**, followed by 20 mg (18% yield) of pure **29**.

Data for **28** were obtained from the mixture: ^1H NMR 3.79 (s, 3), 3.39 (ddd, 1, $J = 8.3$, 6.1, 2.2), 2.40-2.70 (m, 3), 1.80-2.10 (m, 5), 1.52-1.74 (m, 4), 1.01 (t, 3, $J = 7.7$); ^{13}C NMR 213.5, 170.3, 66.4, 62.2, 52.3, 49.3, 45.0, 33.2, 27.0, 21.62, 21.60, 17.6, 11.0.

Data for **29**: ^1H NMR 3.81 (s, 3), 3.16 (ddd, 1, $J = 8.8$, 8.8, 3.2), 2.60-2.74 (m, 2), 2.43-2.49 (m, 1), 2.00-2.11 (m, 2), 1.90-1.97 (m, 2), 1.50-1.86 (m, 5), 1.03 (t, 3, $J = 7.3$); ^{13}C NMR 213.6, 170.4, 66.3, 60.4, 52.3, 50.4, 44.4, 33.3, 25.6, 22.8, 21.5, 21.1, 10.6; IR (neat) 2102, 1730, 1718; HRMS (DCI/ NH_3) Calcd for $\text{C}_{13}\text{H}_{20}\text{N}_3\text{O}_3$ (MH^+) 266.1505, found 266.1511.

Ethyl (1 α ,2 α ,5 β)-2-(Propyl)-8-oxobicyclo[3.2.1]octane-1-carboxylate (30). A solution of crude **27**, prepared as described⁶ from **26** (54 mg, 0.24 mmol), in 2 mL of CH_2Cl_2 containing 10% palladium on activate carbon (20 mg) was hydrogenated (15 PSI) for 2 h. The mixture was filtered and concentrated to yield 32 mg of crude **30**. Flash chromatography on silica gel (20:1 hexanes/EtOAc) gave 15 mg (30% yield) of pure **30**: ^1H NMR 3.77 (s, 3), 2.50-2.56 (m, 2), 1.98-2.08 (m, 2), 1.82-1.94 (m, 3), 1.59-1.69 (m, 1), 1.34-1.48 (m, 2), 1.08-1.30 (m, 4), 0.88 (t, 3, $J = 7.1$); ^{13}C NMR 214.8, 170.6, 62.8, 52.1, 47.6, 45.0, 34.5, 34.2, 23.8, 21.4, 21.2, 20.3, 14.1; IR (neat) 1755, 1728; HRMS (DCI/ NH_3) Calcd for $\text{C}_{13}\text{H}_{21}\text{O}_3$ (MH^+) 225.1491, found 225.1478.

Ethyl 2-Azido-2-methylacetoacetate (32). A solution of ethyl 2-methylacetoacetate (**31**) (180 mg, 1.2 mmol), $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (750 mg, 2.8 mmol) and NaN_3 (406 mg, 6.2 mmol) in 10 mL of degassed MeOH was stirred in a 50-55 °C oil bath for 3 h. Workup as described above gave 190 mg of crude **32**. Flash chromatography on silica gel (20:1 hexanes/EtOAc) gave 130 mg (56% yield) of pure **32** with ^1H and ^{13}C NMR spectral data identical to those previously reported.¹⁴

Methyl 1-Azido-2-oxocycloheptanecarboxylate (34). A solution of methyl 2-oxo-1-cycloheptanecarboxylate (**33**) (287 mg, 1.68 mmol), $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (1.13 g, 4.2 mmol) and NaN_3 (546 mg, 8.4 mmol) in 15 mL of degassed MeOH was stirred in a 50-55 °C oil bath for 6 h. Workup as described above gave 298 mg of crude **34**. Flash chromatography on silica gel (10:1 hexanes/EtOAc) gave 206 mg (58% yield) of pure **34** with ^1H and ^{13}C NMR spectral data identical to those previously reported.¹³

NOEs in **14a** and **14b**

W coupling between H's
at δ 2.0 and H at δ 2.75

Calculated Conformational Preferences for **14a** and **14b**

$$\Delta G^0 = \Delta G_{\text{CO}_2\text{Et}} + \Delta G_{\text{Me}} - \Delta G_{\text{N}_3} - \Delta G_{\text{Me}}$$

$$= -1.15 - 1.74 + 0.54 + 1.74 = -0.61 \text{ kcal/mol}$$

$$\Delta G^0 = \Delta G_{\text{Me}} + \Delta G_{\text{Me}} - \Delta G_{\text{CO}_2\text{Et}} - \Delta G_{\text{N}_3}$$

$$= -1.74 - 1.74 + 1.15 + 0.54 = -1.79 \text{ kcal/mol}$$

Energies from: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons, Inc.: New York, 1994; pp 696-697.

Assignment of the ^{13}C NMR spectra of **25a** and **25b** showing the effect of the CH_2N_3 group on the adjacent carbons due to the γ -guache butane effect.

25a **25b**