Aza-Cope Rearrangement–Mannich Cyclizations for the Formation of Complex Tricyclic Amines: Stereocontrolled Total Synthesis of (±)-Gelsemine

William G. Earley, Jon E. Jacobsen, Andrew Madin, G. Patrick Meier, Christopher J. O'Donnell, Taeboem Oh, David W. Old, Larry E. Overman,* and Matthew J. Sharp

Department of Chemistry, University of California, Irvine, 516 Rowland Hall, Irvine, California 92697-2025

Supporting Information

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A. The Final Route to Gelsemine

(1R*,2S*,4S*)-5-Methyl-1-triisopropylsiloxybicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester (50). *n*-Butyllithium (232 mL, 2.2 M in hexane, 511 mmol) was added dropwise over 10 min to a solution of diisopropylamine (67 mL, 511 mmol) in THF (850 mL) at 0 °C. After stirring 10 min this solution was cooled to –78 °C. A solution of **48** (50.2 g, 456 mmol) in THF (120 mL) was then added dropwise over 10 min to the LDA solution. After stirring for 10 min, triisopropylsilyl triflate (151 mL, 561 mmol) was added and the resultant solution was allowed to warm to rt over a period of 2 h. The solution was maintained at rt for 30 min and the excess triisopropylsilyl triflate was quenched with MeOH (10 mL). Hexanes (500 mL) and saturated aqueous NaHCO₃ (300 mL) were added and the layers were separated. The aqueous layer was extracted with hexanes (3 × 300 mL). The organic layers were dried (MgSO₄), filtered and concentrated. The crude residue was purified by distillation (125–150 °C, 6.5 mm of Hg) to afford 111 g (92%) of dienoxysilane **49** as a clear oil that was used immediately in the Diels–

Alder step. Diagnostic data: ^1H NMR (80 MHz, CDCl_3) δ 5.15 (br s, 1 H), 5.05 (s, 1 H), 2.27 (br s, 4 H), 1.77 (d, $J = 1.0$ Hz, 3 H), 1.17 (br s, 21 H).

Methyl acrylate (42.0 mL, 466 mmol) was added to a suspension of AlCl_3 (12.0 g, 105 mmol) in CH_2Cl_2 (2.9 L) at -78°C . The suspension was allowed to stir for 15 min and then a solution of diene **49** (117 g, 439 mmol) in CH_2Cl_2 (100 mL) was added dropwise through a cooled (-78°C), jacketed addition funnel. The reaction mixture was stirred at -78°C for 7 h and was then quenched with saturated aqueous NaHCO_3 (500 mL) and saturated aqueous Rochelle's salt (500 mL). The mixture was allowed to warm to rt and the phases were separated. The aqueous phase was extracted with hexanes (4×500 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated. The crude material was dissolved in hexanes (200 mL) and filtered through a plug of silica gel (10% Et_2O /hexanes wash) to afford 152 g (98%) of **50** as a mixture of *endo* and *exo* isomers (8:1 respectively by ^1H NMR analysis). An analytical sample of *endo*-**50** was prepared by chromatography (9:1 hexanes/ Et_2O): ^1H NMR (250 MHz, CDCl_3) δ 5.77 (s, 1 H), 3.59 (s, 3 H), 2.75 (dd, $J = 9.8, 5.9$ Hz, 1 H), 2.29 (br s, 1 H), 1.83 (d, $J = 1.5$ Hz, 3 H), 1.90–1.75 (m, 1 H), 1.8–1.2 (m, 5 H), 1.05 (br s, 18 H), 1.1–0.9 (m, 3 H); ^{13}C NMR (63 MHz, CDCl_3) δ 175.7, 140.1, 129.0, 77.5, 51.3, 51.0, 36.2, 35.1, 33.0, 25.2, 20.1, 17.9, 13.6; IR (CCl_4) 2943, 2865, 1736, 1199 cm^{-1} ; MS (CI) m/z 352.2440 (M, 352.2434 calcd for $\text{C}_{20}\text{H}_{36}\text{O}_3\text{Si}$) 321, 309. Anal. Calcd for $\text{C}_{20}\text{H}_{36}\text{O}_3\text{Si}$: C, 68.13; H, 10.29. Found: C, 68.39; H, 10.48.

(1R*,2S*,4S*)-5-Formyl-1-triisopropylsiloxybicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester (72). A solution of **50** (114 g, 324 mmol) and selenium dioxide (54.0 g, 487 mmol) in dioxane (1.08 L) was degassed by bubbling argon through it for 15 min. The solution was heated to reflux for 20 h, then concentrated. The residue was triturated with Et_2O and the solids were removed by filtration. The ether phases were concentrated and the residue was purified by chromatography (15% Et_2O /petroleum ether) affording 95.0 g (80%) of *endo*-**72** and 11.9 g (10%) of *exo*-**72**. Data for *endo*-**72**: ^1H NMR (500 MHz, CDCl_3) δ 9.47 (s, 1 H), 7.17 (s, 1 H), 3.60 (s, 3 H), 3.22 (br s, 1 H), 2.91 (dd, $J = 10.7, 6.6$ Hz, 1 H), 2.02 (ddd, $J = 13.0, 10.3, 2.9$ Hz, 1 H), 1.78 (td, $J = 10.7, 3.5$ Hz, 1 H), 1.75–1.65 (m, 1 H), 1.58 (td, $J = 11.7, 4.8$ Hz, 1

H), 1.48–1.32 (m, 2 H), 1.08 (br s, 21 H); ^{13}C NMR (125 MHz, CDCl_3) δ 188.9, 174.6, 156.2, 144.4, 51.6, 51.4, 34.4, 33.0, 25.5, 24.7, 18.2, 18.1, 17.7, 13.3; IR (film) 2540, 2860, 1740, 1685 cm^{-1} ; MS (EI) m/z 366.2227 (M, 366.2226 calcd for $\text{C}_{20}\text{H}_{34}\text{O}_4\text{Si}$), 323. Anal. Calcd for $\text{C}_{20}\text{H}_{34}\text{O}_4\text{Si}$: C, 65.53; H, 9.35. Found: C, 65.53; H, 9.48.

(1R*,2S*,4S*)-1-Triisopropylsiloxy-5-vinylbicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester (73). Methyltriphenylphosphonium bromide (120 g, 336 mmol) was flame dried under vacuum with vigorous shaking. It was allowed to cool under an argon atmosphere, and dry THF (1.0 L) was added. This solution was cooled to 0 °C and n-BuLi (31.2 mL, 10 M in hexanes, 312 mmol) was added. After 15 min this solution was cooled to –78 °C and a solution of aldehyde **72** (88.1 g, 240 mmol) in THF (200 mL) was added. After a period of 1.5 h at –78 °C, the solution was allowed to warm to rt over a period of 1.5 h. Acetone (25 mL) was added and after 15 min the reaction was quenched with saturated aqueous NaHCO_3 (800 mL). The reaction mixture was poured into petroleum ether (800 mL) and the phases were separated. The aqueous phase was extracted with petroleum ether (3 $\times$ 400 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (hexanes $\rightarrow$ 5% Et_2O /hexanes $\rightarrow$ 10% Et_2O /hexanes gradient) to afford 83.1 g (95%) of **73** as a yellow oil: ^1H NMR (500 MHz, CDCl_3) δ 6.36 (dd, J = 17.4, 10.6 Hz, 1 H), 6.09 (s, 1 H), 5.26 (d, J = 17.5 Hz, 1 H), 5.01 (d, J = 10.8 Hz, 1 H), 3.60 (s, 3 H), 2.92 (br s, 1 H), 2.84 (dd, J = 10.2, 6.2, Hz, 1 H), 1.95 (ddd, J = 15.3, 9.9, 2.9 Hz, 1 H), 1.7 (dt, J = 10.7, 3.2 Hz, 1 H), 1.69–1.65 (m, 1 H), 1.59–1.45 (m, 2 H), 1.48–1.35 (m, 1 H), 1.06 (br s, 21 H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.2, 141.5, 134.8, 134.7, 111.2, 51.3, 51.2, 35.8, 32.9, 27.8, 24.9, 18.3, 18.2, 17.7, 13.3; IR (film) 2950, 2870, 1740, 1590 cm^{-1} ; MS (EI) m/z 364.2445 (M, 364.2434 calcd for $\text{C}_{21}\text{H}_{36}\text{O}_3\text{Si}$), 321. Anal. Calcd for $\text{C}_{21}\text{H}_{36}\text{O}_3\text{Si}$: C, 69.18; H, 9.95. Found: C, 69.21; H, 10.13.

(1R*,2S*,4S*)-1-Triisopropylsiloxy-5-vinylbicyclo[2.2.2]oct-5-ene-2-carboxylic acid (74). A solution of 5 N KOH (146 mL, 730 mmol) was added to a solution of ester **73** (77.1 g, 212 mmol) in EtOH (1.1 L). The cloudy solution became clear when heated to reflux. After 6 h

at reflux the solution was allowed to cool to rt, concentrated to one-third its original volume and acidified with 6 N HCl (200 mL). The resulting mixture was extracted with CH₂Cl₂ (4 × 400 mL) and the combined organic phases were dried (Na₂SO₄), filtered and concentrated to a yellow solid. The crude solid was purified by chromatography (4:1 petroleum ether/Et₂O → 1:1 petroleum ether/Et₂O gradient) to afford 67.8 g (91%) of **74** as a colorless solid: mp 105–107 °C; ¹H NMR (250 MHz, CDCl₃) δ 6.27 (dd, *J* = 17.6, 10.8 Hz, 1 H), 6.03 (s, 1 H), 5.30 (d, *J* = 17.5 Hz, 1 H), 5.06 (d, *J* = 10.7 Hz, 1 H), 2.96 (s, 1 H), 2.76 (t, *J* = 7.3 Hz, 1 H), 1.95–1.91 (m, 2 H), 1.85–1.62 (m, 3 H), 1.50–1.35 (m, 1 H), 1.12 (br s, 21 H); ¹³C NMR (125 MHz, CDCl₃) δ 175.4, 143.8, 134.0, 131.9, 112.8, 77.8, 50.3, 34.3, 30.0, 27.8, 26.4, 18.2, 13.4; IR (film) 3500–2500, 2940, 2970, 1725 cm⁻¹; MS (EI) *m/z* 350.2285 (M, 350.2277 calcd for C₂₀H₃₄O₃Si). Anal. Calcd for C₂₀H₃₄O₃Si: C, 68.52; H, 9.78. Found C, 68.56; H, 9.82.

(1R*,2S*,4S*)-(1-Triisopropylsiloxy-5-vinylbicyclo[2.2.2]oct-5-en-2-yl)-carbamic acid 4-methoxybenzyl ester (75). Triethylamine (25.6 mL, 184 mmol) and diphenylphosphoryl azide (39.6 mL, 184 mmol) were added to a solution of **74** (58.5 g, 167 mmol) in toluene (834 mL). The resulting solution was heated at reflux for a period of 8 h. The reaction mixture was allowed to cool to rt and triethylamine (25.6 mL, 184 mmol) and 4-methoxybenzyl alcohol (87.4 mL, 701 mmol) were added. The reaction mixture was heated at reflux for a period of 12 h. The reaction mixture was allowed to cool to rt and then poured into H₂O (500 mL). Petroleum ether (250 mL) was added and the layers were separated. The aqueous layer was extracted with petroleum ether (3 × 250 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated. The crude residue was purified by chromatography (15% Et₂O/petroleum ether → 25% Et₂O/petroleum ether gradient) to afford 58.7 g (72%) of **75** as a yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.26 (d, *J* = 8.3 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 6.25 (dd, *J* = 17.5, 10.7 Hz, 1 H), 5.90 (s, 1 H), 5.28 (d, *J* = 17.5 Hz, 1 H), 5.03 (d, *J* = 10.7 Hz, 1 H), 4.99–4.94 (m, 2 H), 4.80 (br d, *J* = 6.7 Hz, 1 H), 3.90–3.83 (m, 1 H), 3.79 (s, 3 H), 2.84 (br s, 1 H), 2.25 (br t, *J* = 10.9 Hz, 1 H), 1.78–1.57 (m, 3 H), 1.39–1.31 (m, 1 H), 1.22–1.19 (m, 1 H), 1.05 (br s, 21 H); ¹³C NMR (125 MHz, CDCl₃) δ 159.4, 156.2, 144.4, 134.0, 132.7, 129.9, 128.8,

113.8, 112.4, 76.4, 66.1, 56.7, 55.2, 37.3, 32.9, 28.0, 26.0, 18.2, 13.2; IR (film) 3440 (br), 2944, 2866, 1726, 1514, 1246, 1221 cm^{-1} ; MS (FAB) m/z 486.3046 (MH, 486.3039 calcd for $\text{C}_{28}\text{H}_{43}\text{NO}_4\text{Si}$), 442, 364. Anal. Calcd for $\text{C}_{28}\text{H}_{43}\text{NO}_4\text{Si}$: C, 69.24; H, 8.92; N, 2.88. Found: C, 69.34; H, 8.95; N, 2.90.

(1R*,2S*,4S*)-(1-Triisopropylsiloxy-5-vinylbicyclo[2.2.2]oct-5-en-2-ylamino)-acetonitrile (76). Trifluoroacetic acid (46 mL, 604 mmol) was added to a solution of **75** (58.7 g, 121 mmol) and anisole (65.7 mL, 604 mmol) in CH_2Cl_2 (465 mL). After a period of 1.5 h at rt, the reaction mixture was cooled to 0 °C and 1 N KOH (600 mL) was slowly added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 300 mL). The combined organic extracts were dried (MgSO_4), filtered and concentrated. The resulting crude amine was dissolved in THF (465 mL) and pH 7 buffer (465 mL, 0.05 M, Fisher), and KCN (9.2 g, 141 mmol) was added. The resulting basic mixture was then carefully neutralized to pH 7 by the dropwise addition of 1 N HCl. Formalin (10.6 mL, 37% aqueous solution, 131 mmol) was then added and the resulting mixture stirred at rt for 24 h. The reaction mixture was then poured into 5 N KOH (600 mL), extracted with petroleum ether (2 $\times$ 200 mL) then Et_2O (2 $\times$ 200 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography (8:1 $\rightarrow$ 4:1 $\rightarrow$ 2:1 petroleum ether/ Et_2O gradient) to give 35.1 g (81%) of **76** as a colorless oil: ^1H NMR (250 MHz, CDCl_3) δ 6.30 (dd, J = 17.5, 10.7 Hz, 1 H), 5.98 (s, 1 H), 5.25 (d, J = 17.4 Hz, 1 H), 5.02 (d, J = 10.8 Hz, 1 H), 3.69 (d, J = 17.6 Hz, 1 H), 3.37 (d, J = 17.7 Hz, 1 H), 3.12 (dd, J = 8.6, 3.8 Hz, 1 H), 2.90 (br s, 1 H), 2.30 (br s, 1 H), 1.93 (ddd, J = 12.5, 8.4, 2.8 Hz, 1 H), 1.75–1.57 (m, 3 H), 1.42–1.38 (m, 1 H), 1.02–1.00 (br s, 22 H); ^{13}C NMR (75 MHz, CDCl_3) δ 142.2, 134.3, 133.5, 117.5, 111.9, 76.6, 61.9, 34.3, 33.7, 33.3, 27.7, 25.5, 18.4, 13.3; IR (film) 3330, 2940, 2860, 1585, 1460 cm^{-1} ; MS (EI) m/z 360.2614 (M, 360.2597 calcd for $\text{C}_{21}\text{H}_{36}\text{N}_2\text{OSi}$), 334. Anal. Calcd for $\text{C}_{21}\text{H}_{36}\text{N}_2\text{OSi}$: C, 69.94; H, 10.06; N, 7.77. Found: C, 69.71; H, 9.99; N, 7.58.

(1R*,2S*,4S*)-(1-Hydroxy-5-vinylbicyclo[2.2.2]oct-5-en-2-ylamino)-acetonitrile (77). Tetrabutylammonium flouride (136 mL, 1 M in THF, 136 mmol) was added to a solution of **76**

(35.1 g, 97.3 mmol) in THF (490 mL) at $-30\text{ }^{\circ}\text{C}$. The reaction mixture was allowed to warm to rt over a period of 4 h. The solution was poured into saturated aqueous NaHCO_3 (200 mL) and extracted with EtOAc ($3 \times 250\text{ mL}$). The combined organic phases were washed successively with saturated aqueous NaHCO_3 (200 mL), H_2O (200 mL) and brine (250 mL) then dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (1:1 petroleum ether/ $\text{Et}_2\text{O} \rightarrow \text{Et}_2\text{O} \rightarrow 30:1\text{ Et}_2\text{O}/\text{MeOH}$ gradient) to give 18.9 g (95%) of hydroxy amine **77** as a colorless solid. This solid was purified further by recrystallization from hexanes/EtOAc to give 17.9 g (90%) of **77** as clear prisms: mp $71\text{--}73\text{ }^{\circ}\text{C}$; ^1H NMR (250 MHz, CDCl_3) δ 6.20 (dd, $J = 17.5, 10.8\text{ Hz}$, 1 H), 5.85 (s, 1 H), 5.19 (d, $J = 17.5\text{ Hz}$, 1 H), 4.95 (d, $J = 10.8\text{ Hz}$, 1 H), 3.49 (AB_q , $J_{\text{AB}} = 17.4\text{ Hz}$, $\Delta\nu_{\text{AB}} = 29.0\text{ Hz}$, 2 H), 2.84 (br s, 2 H), 2.02 (ddd, $J = 12.9, 8.8, 2.7\text{ Hz}$, 1 H), 1.55 (ap d, $J = 8.9\text{ Hz}$, 2 H), 1.43 (dt, $J = 9.9, 2.4\text{ Hz}$, 1 H), 1.27 (m, 1 H), 1.06 (dq, $J = 13.1, 3.0\text{ Hz}$, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.4, 133.9, 132.4, 118.1, 112.1, 74.4, 62.3, 35.5, 35.1, 32.0, 28.2, 25.0; IR (film) 3426, 3330, 3095, 3040, 2950, 2870, 1630, 1590 cm^{-1} ; MS (EI) m/z 204.1261 (M, 204.1262 calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}$), 178. Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}$: C, 70.56; H, 7.89; N, 13.71. Found: C, 70.38; H, 7.95; N, 13.66.

(4aR*,8aS*)-7-Oxo-8a-vinyl-4a,5,6,7,8,8a-hexahydro-1H-isoquinoline-2-carboxylic acid methyl ester (79). A solution of **77** (3.0 g, 14.7 mmol) and 18-Crown-6 (9.6 g, 36.3 mmol) in THF (100 mL) was added to a slurry of KH [3.15 g, 78.6 mmol, prewashed with hexane and THF, then treated with a solution of iodine³ (0.147 mL, 0.5 M in THF, 70 μmol)] at rt. The resulting mixture was stirred at rt for a period of 1 h during which a red solution developed. The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of 2,6-di-*tert*-butyl-4-methylpyridine (15 g, 73 mmol) in THF (50 mL) was added followed by freshly distilled methyl chloroformate (4.8 mL, 62.3 mmol). The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for a period of 10 min and then allowed to warm to rt over 1.5 h. The reaction was slowly quenched with saturated aqueous NaHCO_3 (100 mL) and diluted with H_2O (100 mL) and hexanes (200 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 ($4 \times 100\text{ mL}$). The combined organic phases were concentrated and the crude residue was diluted with MeOH (72 mL). A 1 N KOH

solution (24 mL, 24 mmol) was added and the resulting heterogeneous solution was stirred at rt for 10 min. Brine (100 mL) was added, and the resulting mixture was extracted with CH₂Cl₂ (4 × 100 mL). The combined organic phases were dried (Na₂SO₄), filtered and concentrated. The resulting crude residue was purified by chromatography (4:1 → 1:1 → 2:3 petroleum ether/Et₂O gradient) to afford 2.8 g (81%) of octahydroisoquinoline **79** as a colorless oil which crystallized on standing and was 98% pure by capillary GC analysis: mp 48.5–51.5 °C; ¹H NMR (500 MHz, CDCl₃)⁶ δ 7.02 (d, *J* = 8.1 Hz), 6.88 (d, *J* = 8.1 Hz, 1 H), 5.63 (dd, *J* = 17.2, 10.9 Hz, 1 H), 5.62 (dd, *J* = 17.5, 10.8 Hz), 5.21 (d, *J* = 10.9 Hz, 1 H), 5.16 (d, *J* = 17.5 Hz, 1 H), 4.87 (d, *J* = 8.2 Hz), 4.77 (d, *J* = 8.3 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s), 3.66 (d, *J* = 13.1 Hz, 1 H), 3.50 (d, *J* = 13.0 Hz), 3.16 (d, *J* = 13.4 Hz), 3.13 (d, *J* = 13.1 Hz, 1 H), 2.46 (br s, 1 H), 2.42 (m, 1 H), 2.38–2.30 (m, 1 H), 2.28–2.22 (m, 1 H), 2.17–2.12 (m, 1 H), 2.08–2.00 (m, 1 H), 1.86–1.78 (m, 1 H); ¹³C NMR (125 MHz, CDCl₃, mixture of conformational isomers) δ 216, 210, 154.2, 153.8, 141.6, 141.5, 125.9, 125.6, 116.7, 116.7, 108.2, 107.9, 53.2, 53.1, 50.3, 49.9, 43.5, 43.4, 41.8, 36.5, 35.9, 35.7, 27.0, 26.9; IR (film) 1716, 1712, 1709, 1653 cm⁻¹; MS (EI) *m/z* 235.1213 (M, 235.1208 calcd for C₁₃H₁₇NO₃). Anal. Calcd for C₁₃H₁₇NO₃: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.44; H, 7.35; N, 5.84.

(1R*,2R*,6S*,7R*,8S*)-7-Bromo-3-oxo-1-vinyl-9-aza-tricyclo[4.4.0.0^{2,8}]decane-9-carboxylic acid methyl ester (18). Pentamethylpiperidine (7.8 mL, 43.0 mmol) and bromine (0.676 mL, 13.2 mmol) were added to a solution of octahydroisoquinoline **79** (2.7 g, 11.5 mmol) in CH₂Cl₂ (67.5 mL) at –78 °C. After 0.5 h at –78 °C the cold bath was removed and the solvent was removed *in vacuo*. The resulting solid residue was dissolved in trifluoroacetic acid (120 mL) and trifluoroacetic anhydride (1.2 mL) was added. The resulting red solution was heated at reflux for 14 h. The reaction was then allowed to cool to rt. The TFA was removed by concentration with toluene (2 × 250 mL). The residue was diluted with CH₂Cl₂ (100 mL) and saturated aqueous NaHCO₃ was added until bubbling ceased. The aqueous phase was extracted with CH₂Cl₂ (3 × 50 mL) and the combined organic phases were dried (K₂CO₃), filtered and concentrated. Purification of the residue by chromatography (1:1 petroleum ether/Et₂O) afforded 2.45 g (67%)

of tricyclic ketone **18** as a colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 5.95 (dd, $J = 17.5, 10.9$ Hz, 1 H), 5.93 (dd, $J = 17.5, 11.0$ Hz), 5.29 (d, $J = 10.9$ Hz, 1 H), 5.28 (d, $J = 11.0$ Hz), 5.12 (d, $J = 17.6$ Hz, 1 H), 5.11 (d, $J = 17.6$ Hz), 4.59 (t, $J = 2.5$ Hz), 4.46 (t, $J = 2.6$ Hz, 1 H), 4.21 (t, $J = 2.5$ Hz), 4.14 (t, $J = 2.6$ Hz, 1 H), 3.72 (s), 3.71 (s, 3 H), , 3.40 (s, 1 H), 3.39 (s), 3.34 (d, $J = 10.2$ Hz, 1 H), 2.95–2.93 (m, 1 H), 2.46 (br s, 1 H), 2.45 (br s), 2.42–2.3 (m, 3 H), 2.06–1.98 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3 , mixture of conformational isomers) δ 207.9, 207.8, 154.6, 154.3, 133.7, 133.5, 119.0, 118.2, 63.5, 63.2, 61.4, 61.1, 53.7, 52.5, 52.4, 52.2, 52.1, 50.6, 33.3, 23.2, 23.2; MS (EI) m/z 315.1275 (M, 315.0292 calcd for $\text{C}_{13}\text{H}_{16}^{81}\text{BrNO}_3$), 236. Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{BrNO}_3$: C, 49.70; H, 5.13; N, 4.46. Found: C, 50.16; H, 5.28; N, 4.20.

B. Preliminary Studies

(1R*,2S*,4S*)-1-Methoxy-5-vinylbicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester (25) and (1R*,2S*,4S*)-1-Methoxy-5-vinylbicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester (26) A degassed solution of diene **24**⁴ (5.00 g, 40.3 mmol), methyl acrylate (9.00 mL, 99.9 mmol) and dichloromaleic anhydride (3.0 mg, 18 μ mol) was heated at reflux for 42 h. The solution was cooled and concentrated (to remove excess dieneophile). The residue was purified by chromatography (10:1 hexane/EtOAc) affording 2.70 g (32%) of the *endo* isomer **25** and 1.05 g (12%) of the *exo* isomer **26**. Data for **25**:³ ¹H NMR (250 MHz, CDCl₃) δ 5.79 (br s, 1 H), 3.63 (s, 3 H), 3.34 (s, 3 H), 2.85 (dd, *J* = 9.8, 5.6 Hz, 1 H), 2.31 (br s, 1 H), 1.83 (d, *J* = 1.6 Hz, 3 H), 1.9–1.3 (m, 6 H); ¹³C NMR (63 MHz, CDCl₃) δ 175.4, 141.7, 124.7, 79.7, 51.7, 51.1, 47.3, 35.1, 32.5, 29.5, 24.7, 20.2; IR (CCl₄) 2936, 1738, 1431, 1195, 1155 cm⁻¹; MS (CI) *m/z* 211, 179, 145.

Data for **26**: ¹H NMR (250 MHz, CDCl₃) δ 5.99 (br s, 1 H), 3.71 (s, 3 H), 3.40 (s, 3 H), 2.72 (ddd, *J* = 11.4, 4.9, 2.0 Hz, 1 H), 2.31 (br s, 1 H), 1.80 (d, *J* = 1.7 Hz, 3 H), 2.1–1.3 (m, 6 H); ¹³C NMR (63 MHz, CDCl₃) δ 174.4, 142.4, 126.1, 79.5, 51.0, 50.6, 44.7, 34.8, 30.0, 26.1, 24.7, 19.7; IR (CCl₄) 2939, 1731, 1324, 1202, 1158 cm⁻¹; MS (EI) *m/z* 210, 182, 124, 123, 109.

(1R*,2S*,4S*)-1-Methoxy-5-vinylbicyclo[2.2.2]oct-5-ene-2-carboxylic acid (27). A solution of ester **25** (1.31 g, 6.24 mmol), MeOH (75 mL), water (25 mL) and KOH (1.15 g, 20.5 mmol) was heated at reflux for 16 h. The solution was cooled to rt and concentrated (removing the MeOH). The basic residue was extracted with petroleum ether (50 mL), acidified to pH 3 with 6 N HCl and then extracted with CH₂Cl₂ (3 $\times$ 80 mL). The organic layers were dried (MgSO₄), filtered and concentrated to give 1.07 g (88%) of acid **27** as a colorless solid. An analytical sample was prepared by recrystallizing a small amount of **27** twice from hot hexane: mp 119.5–121 $^{\circ}$ C; ¹H NMR (250 MHz, CDCl₃) δ 5.83 (br s, 1 H), 3.51 (s, 3 H), 2.71 (dd, *J* = 10.0, 3.9 Hz, 1 H), 2.40 (br s, 1 H), 2.08 (ddd, *J* = 13.2, 7.0, 3.6 Hz, 1 H), 1.81 (d, *J* = 1.7 Hz, 3 H), 1.9–1.3 (m, 5 H); ¹³C NMR (63 MHz, CDCl₃) δ 176.5, 143.8, 122.7, 80.0, 51.0, 47.4, 34.7, 30.0, 28.2, 25.3, 20.1; IR (CCl₄) 3055 (br), 2939, 1760, 1707, 1420, 1320, 1227, 1094 cm⁻¹; MS

(EI) m/z 196, 124, 123, 109, 91. Anal. Calcd for $C_{11}H_{16}NO_3$: C, 67.32; H, 8.22. Found: C, 67.23; H, 8.25.

(1R*,2S*,4S*)-(1-Methoxy-5-vinylbicyclo[2.2.2]oct-5-en-2-yl)-carbamic acid ethyl ester (28). A solution of acid **27** (1.0 g, 5.1 mmol), diisopropylethylamine (0.90 mL, 5.2 mmol) and acetone (3.1 mL) was added dropwise to a solution of freshly distilled ethyl chloroformate (0.49 mL, 5.1 mmol) in acetone (1.4 mL) over a period of 5 min at 0 °C. The solution was stirred for 40 min, and then a chilled (0 °C) solution of sodium azide (0.68 g, 10 mmol) and H_2O (1.4 mL) was added. After stirring for 2 h at 0 °C the solution was poured into ice water (20 mL) and was extracted with toluene (5×10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to a volume of 9.0 mL. This was added dropwise over a period of 5 min to a refluxing solution of toluene (5.0 mL), ethanol (0.36 mL, 6.1 mmol) and 4-*t*-butylcatechol (1 mg). Additional ethanol (~0.36 mL) was added after 0.5 h and 4.5 h. After 18 h the solution was cooled to rt and concentrated. The residue was purified by chromatography (8:1:0.1 hexane/EtOAc/ Et_3N) to give 0.66 g (54%) of carbamate **28** as a yellow oil: 1H NMR (250 MHz, $CDCl_3$) δ 5.60 (br s, 1 H), 4.71 (br s, 1 H), 4.04 (q, $J = 7.1$ Hz, 2 H), 3.96 (m, 1 H), 3.27 (s, 3 H), 2.24 (br s, 1 H), 2.14 (ap t, $J = 11.3$ Hz, 1 H), 1.78 (d, $J = 1.7$ Hz, 3 H), 1.8–1.3 (m, 5 H), 1.19 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 156.1, 143.7, 124.0, 78.3, 60.1, 51.0, 49.8, 37.2, 34.8, 26.7, 25.2, 19.6, 14.3; IR (CCl_4) 3444, 2936, 1715, 1491, 1219 cm^{-1} ; MS (CI) m/z 240.1589 (MH, 240.1633 calcd for $C_{13}H_{21}NO_3$), 151, 124.

(1R*,3R*,6R*,7S*)-7-Methoxy-10-methylene-4-aza-tricyclo[4.3.1.0^{3,7}]decane-4-carboxylic acid ethyl ester (32). Aluminium hydride (7.60 mL, 1.20 M in THF, 9.12 mmol) was added to a solution of carbamate **28** (228 mg, 0.954 mmol) and THF (0.5 mL) and the resultant solution was stirred for 18 h at rt. The excess AlH_3 was quenched with MeOH (5 mL) and the reaction mixture was diluted with Et_2O (20 mL) and 6 N NaOH (15 mL) was added. This heterogeneous mixture was stirred for 1 h and was then neutralized to pH 7 with 6 N HCl. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 $\times$). The combined organic phases were dried (K_2CO_3), filtered and concentrated to afford 163 mg (94%) of **29** as a

light yellow oil, which was homogeneous by tlc analysis and used immediately in the next step. Diagnostic data: ^1H NMR (250 MHz, CDCl_3) δ 5.76 (br s, 1 H), 3.33 (s, 3 H), 2.74 (ddd, $J = 8.4$, 3.4, 1.4 Hz, 1 H), 2.27 (s, 3 H), 2.25 (br s, 1 H), 1.80 (d, $J = 1.6$ Hz, 3 H), 1.9–1.7 (m, 2 H), 1.6–1.3 (m, 4 H), 1.16 (ap dq, $J = 12.6$, 3.2 Hz, 1 H); ^{13}C NMR (63 MHz, CDCl_3) δ 141.9, 124.0, 80.3, 62.7, 50.6, 35.3, 34.9, 33.7, 27.3, 25.3, 20.4; IR (CCl_4) 3340, 2931, 1440, 1090 cm^{-1} ; MS (CI) m/z 182.1540 (MH, 182.1564 calcd for $\text{C}_{11}\text{H}_{19}\text{NO}$), 151, 124.

A solution of amine **29** (48.4 mg, 0.267 mmol), paraformaldehyde (9.1 mg, 0.30 mmol), camphorsulfonic acid (60.5 mg, 0.261 mmol), sodium sulfate (50.0 mg, 0.352 mmol) and acetonitrile (1.50 mL) was heated at 100 °C in a sealed ampule under Ar for 24 h. The reaction mixture was allowed to cool to rt and was neutralized to pH 7 with 1 N KOH. The layers were separated and the aqueous layer was extracted with basic CHCl_3 (3 $\times$). The combined organic phases were dried (K_2CO_3), filtered and concentrated. Purification of the residue by chromatography (20:1:0.5 $\text{CHCl}_3/\text{MeOH}/\text{Et}_3\text{N}$) resulted in 40.1 mg (76%) of **32** as a yellow oil that contained ~8% of an unknown impurity: ^1H NMR (250 MHz, CDCl_3) δ 4.80 (ap t, $J = 1.4$ Hz, 1 H), 4.71 (ap t, $J = 1.4$ Hz, 1 H), 3.21 (s, 3 H), 2.97 (dd, $J = 8.1$, 4.7 Hz, 1 H), 2.91 (ap dt, $J = 6.1$, 1.8 Hz, 1 H), 2.77 (br dd, $J = 4.4$, 1.5 Hz, 1 H), 2.64 (d, $J = 8.1$ Hz, 1 H), 2.51 (s, 3 H), 2.18 (s, 1 H), 1.9–1.5 (m, 6 H); ^{13}C NMR (63 MHz, CDCl_3) δ 156.2, 106.7, 83.7, 64.8, 62.1, 49.3, 47.1, 43.2, 36.3, 33.6, 29.1, 20.2; IR (CCl_4) 2919, 1646, 1440, 1347, 1093 cm^{-1} ; MS (CI) m/z 194.1538 (MH, 194.1573 calcd for $\text{C}_{12}\text{H}_{19}\text{NO}$), 162, 124.

(1R*,2S*,4S*)-(1-Methoxy-bicyclo[2.2.2]oct-5-en-2-yl)-carbamic acid ethyl ester (34). A solution of acid **33**⁵ (0.93 g, 5.1 mmol), diisopropylethylamine (0.90 mL, 5.2 mmol) and acetone (3.1 mL) was added dropwise to a solution of ethyl chloroformate (0.49 mL, 5.1 mmol) in acetone (1.4 mL) over a period of 5 min at 0 °C. The solution was maintained at 0 °C for 40 min and then a chilled solution (0 °C) of sodium azide (0.68 g, 10 mmol) and water (1.4 mL) was added. The reaction mixture was stirred for 2 h at 0 °C and then poured into ice water (30 mL). The aqueous solution was extracted with toluene (5 $\times$ 10 mL) and the combined organic layers were dried (MgSO_4), filtered and concentrated to a volume of 10 mL. This azide solution

was added dropwise over a period of 5 min to a refluxing solution of toluene (5 mL), ethanol (0.36 mL, 6.2 mmol) and 4-*t*-butylcatechol (1 mg). Additional volumes of ethanol (0.36 mL) were added after 1 and 2 h. After 18 h, the solution was cooled to rt and concentrated. The residue was purified by chromatography (6:1:0.1 hexane/EtOAc/Et₃N) to give 0.65 g (57%) of **34** as a light yellow oil: ¹H NMR (250 MHz, CDCl₃) δ 6.34 (dd, *J* = 8.7, 6.5 Hz, 1 H), 6.03 (d, *J* = 8.6 Hz, 1 H), 4.69 (br s, 1 H), 4.08 (q, *J* = 7.1 Hz, 2 H), 4.15–3.95 (m, 1 H), 3.33 (s, 3 H), 2.60–2.45 (m, 1 H), 2.3–2.1 (m, 1 H), 1.8–1.3 (m, 5 H), 1.22 (t, *J* = 7.1 Hz, 3 H); ¹³C NMR (63 MHz, CDCl₃) δ 156.2, 134.8, 132.1, 78.0, 60.3, 50.5, 50.0, 37.7, 29.4, 25.7, 25.5, 14.4; IR (CCl₄) 3447, 2944, 1723, 1495, 1219 cm⁻¹; MS (CI) *m/z* 226.1442 (MH, 226.1445 calcd for C₁₂H₁₉NO₃), 137, 110. Anal. Calcd for C₁₂H₁₉NO₃: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.77; H, 8.38; N, 6.24.

(1R*,2S*,4S*)-[(1-Methoxy-bicyclo[2.2.2]oct-5-en-2-yl)-methylamino]-acetonitrile

(36). Aluminum hydride (22.0 mL, 1.16 M in THF, 25.5 mmol) was added to a solution of carbamate **34** (0.638 g, 2.82 mmol) in THF (2 mL) at rt. The resultant cloudy solution was stirred at rt for 20 h and then quenched by the dropwise addition of MeOH (5 mL). Et₂O (50 mL) and 6 N NaOH (40 mL) were added and the resultant solution stirred for 1 h. The solution was neutralized with 6 N HCl. The phases were separated and the aqueous phase was extracted with CHCl₃ (3 × 5 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated to give 410 mg (87%) of **35** as a light yellow oil, which was homogeneous by tlc and used immediately in the next step: ¹H NMR (250 MHz, CDCl₃) δ 6.26 (dd, *J* = 8.7, 6.3 Hz, 1 H), 6.15 (d, *J* = 8.7 Hz, 1 H), 3.35 (s, 3 H), 2.78 (dd, *J* = 8.3, 3.1 Hz, 1 H), 2.60–2.45 (m, 1 H), 2.29 (s, 3 H), 1.90–1.28 (m, 6 H), 1.18 (ap dq, *J* = 12.6, 3.0 Hz, 1 H); ¹³C NMR (63 MHz, CDCl₃) δ 132.7, 131.9, 79.6, 61.8, 50.3, 34.7, 33.3, 29.4, 26.0, 25.6; IR (CCl₄) 2940, 1463, 1346, 1104 cm⁻¹; MS (CI) *m/z* 168.1388 (MH, 168.1390 calcd for C₁₀H₁₇NO), 137, 110.

A solution of crude amine **35** (58.9 mg, 0.353 mmol), THF (10 mL) and water (1.0 mL) was neutralized with 1 N HCl. Potassium cyanide (27.6 mg, 0.424 mmol) and paraformaldehyde (21.2 mg, 0.706 mmol) were added and the resulting mixture was stirred for 24 h at rt. The

reaction mixture was diluted with CH_2Cl_2 (10 mL) and made basic (pH 10) with the addition of 5 N KOH. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$). The combined organic layers were dried (K_2CO_3), filtered and concentrated to afford 66.7 mg (92%) of **36** as a light yellow oil that was used immediately in the next step. Diagnostic data: ^1H NMR (250 MHz, CDCl_3) δ 6.3–6.1 (m, 2 H), 3.61 (AB_q , $J_{\text{AB}} = 17.1$ Hz, $\Delta\nu_{\text{AB}} = 18.8$ Hz, 2 H), 3.36 (s, 3 H), 3.12 (dd, $J = 9.3, 4.9$ Hz, 1 H), 2.6–2.5 (m, 1 H), 2.34 (s, 3 H), 1.95–1.80 (m, 1 H), 1.7–1.3 (m, 5 H); ^{13}C NMR (63 MHz, CDCl_3) δ 132.6, 131.9, 117.6, 80.2, 64.7, 50.7, 43.6, 38.9, 31.4, 29.7, 28.6, 24.8; IR (CCl_4) 2939, 1456, 1192, 1106 cm^{-1} ; MS (CI) m/z 207, 180, 110.

(1R*,3R*,6S*,7S*,10R*)-10-Formyloxy-7-methoxy-4-azatricyclo[4.3.1.0^{3,7}]decane-4-carboxylic acid ethyl ester (37). A solution of carbamate **34** (163 mg, 0.724 mmol), paraformaldehyde (28.7 mg, 0.957 mol) and formic acid (5.0 mL) was heated at 50 °C for 1.5 h. The resulting yellow solution was cooled to rt and concentrated. The crude residue was dissolved in Et_2O (10 mL) and made basic (pH 10) with the addition of 5 N KOH. The layers were separated and the aqueous layer was extracted with Et_2O (3 $\times$ 10 mL). The combined organic layers were dried (K_2CO_3), filtered and concentrated. Purification of the crude residue by chromatography (7:3 hexane/ EtOAc) gave 184 mg (90%) of **38** as a clear oil: ^1H NMR (250 MHz, CDCl_3)⁶ δ 7.99 (s), 7.96 (s, 1 H), 5.0–4.8 (m, 1 H), 4.25–4.00 (m, 3 H), 3.80 (dd, $J = 15.6, 10.7$ Hz, 1 H), 3.5–3.3 (m, 1 H), 3.26 (s), 3.25 (s, 3 H), 2.6–2.4 (m, 2 H), 2.4–1.8 (m, 5 H) 1.50–1.35 (m, 1 H), 1.26 (t, $J = 7.1$, Hz, 3 H), 1.23 (t, $J = 7.0$ Hz); ^{13}C NMR (63 MHz, CDCl_3 , mixture of conformational isomers) δ 160.5, 160.2, 155.1, 154.9, 90.4, 89.7, 72.6, 72.4, 60.7, 60.6, 58.7, 58.1, 51.5, 51.1, 47.4, 45.8, 44.9, 44.8, 42.9, 42.7, 32.2, 31.4, 26.7, 26.6, 24.9, 24.5, 14.9, 14.8; IR (CCl_4) 2951, 1702, 1421, 1167 cm^{-1} ; MS (CI) m/z 284.1490 (MH, 284.1517 calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_5$), 238.

(1R*,4S*,5R*)-5-Ethoxycarbonylamino-4-methoxybicyclo[2.2.2]oct-2-ene-2-carboxylic acid methyl ester (40). Selenium dioxide (0.696 g, 6.2 mmol) was added to a solution of methyl carbamate **28** (1.0 g, 4.18 mmol) in dioxane (20 mL) at rt. The resulting mixture was degassed by bubbling Argon through the solution for 15 min. The mixture was heated

at reflux for 2 h and then allowed to cool to rt and vacuum filtered (wash the filter cake with CH_2Cl_2 (10 mL). The reddish solution was concentrated and the residue was purified by chromatography (4:1 hexanes/EtOAc) to afford 0.95 g (89%) of aldehyde **38** as a colorless oil, which was used immediately in the following step Diagnostic data: ^1H NMR (250 MHz, CDCl_3) δ 9.46 (s, 1 H), 6.99 (s, 1 H) 4.61–4.58 (m, 1 H), 4.09 (q, $J = 7.1$ Hz, 2 H), 3.39 (s, 3 H), 3.19 (s, 1 H) 2.37–2.23 (m, 1 H), 1.95–1.82 (m, 1 H), 1.78–1.65 (m, 1 H), 1.50 dd, $J = 11.7, 3.5$, 1 H), 1.4–1.11 (m, 2 H), 1.23 (t, $J = 7.1$, 3 H); IR (film) 3360, 2970, 2890, 2850, 2770, 1729, 1717, 1694, 1684, 1630 cm^{-1} ; MS (CI) m/z 254, 236, 165.

A solution of NaO_2Cl (6.66 g, 74 mmol), H_2O (68 mL) and $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ (7.8 g, 567 mmol) was added to a solution of 2-methylbutene (42 mL), *tert*-butanol (171 mL), and a comparable sample of crude aldehyde **38** (2 g, 8.2 mmol). The resulting clear yellow solution was maintained at rt for 12 h. The solution was concentrated and poured into H_2O (50 mL). The mixture was then extracted with hexanes (10 mL). The aqueous layer was cooled (0 °C) and acidified with concentrated HCl to pH 3. The acidic solution was then extracted with CH_2Cl_2 (3 $\times$ 30 mL). The combined organic layers were dried (MgSO_4), filtered and concentration to afford 1.85 g (83%) of acid **39** as a colorless foam, which was used immediately in the next step. Diagnostic data: ^1H NMR (250 MHz, CDCl_3) δ 7.21 (s, 1 H), 4.74–4.70 (m, 1 H), 4.17–4.05 (m, 3 H), 3.38 (s, 3 H), 3.14 (br s, 1 H), 2.33–2.24 (m, 1 H) 1.86–1.64 (m, 3 H) 1.59–1.18 (m, 3 H), 1.22 (t, $J = 7.5$ Hz, 3 H); MS (EI) 269.1271 (M, 269.1263 calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_5$), MS (CI) m/z 270, 252, 224, 181, 154.

Potassium carbonate (1.87 g, 13.5 mmol) and methyl iodide (1.3 mL, 20.8 mmol) were added to a solution of carbamate **39** (2.8 g, 10.4 mmol) in acetone (50 mL) at rt. The mixture was degassed by bubbling Argon through the solution for 15 min and then stirred at rt for 25 h. The solution was concentrated and partitioned between H_2O (20 mL) and CH_2Cl_2 (25 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 25 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated. The residue was purified by chromatography (4:1 hexanes/EtOAc) to give 2.53 g (89%) of methyl ester **40** as a

colorless oil: ^1H NMR (250 MHz, CDCl_3) δ 7.05 (s, 1 H), 4.62 (d, $J = 5.2$ Hz, 1 H), 4.20–4.17 (m, 1 H), 4.07 (q, $J = 7.1$ Hz, 2 H), 3.72 (s, 3 H), 3.36 (s, 3 H), 3.13 (br s, 1 H), 2.37–2.20 (m, 1 H), 1.84–1.60 (m, 2 H), 1.55–1.15 (m, 6 H); IR (film) 3370, 2965, 2885, 1717, 1707, 1635, 1517 cm^{-1} ; MS (EI) 283.1414 (M, 283.1420 calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_5$), MS (CI) m/z 284, 238, 195, 168.

(1R*,2S*,4R*,7R*,8S*)-8-Methoxy-2-(2,2,2-trifluoroacetoxy)-5-azatricyclo[5.3.0.0.4,8]decane-1,5-dicarboxylic acid 5-ethyl ester 1-methyl ester (42). A solution of trifluoroacetic acid (5 mL), paraformaldehyde (0.190 g, 6.3 mmol) and ethylcarbamate **40** (0.60 g, 2.1 mmol) was purged with Ar, sealed in a glass ampule and the solution was then heated at 85 °C for 15 h. The solution was then cooled to rt, concentrated, then diluted with ice (4 g) and NaHCO_3 (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (MgSO_4), filtered and concentrated. The residue was purified by chromatography (3:1 hexane/EtOAc) to afford 432 mg (50%) of **42** as a colorless solid: mp 97.5–99 °C; ^1H NMR (250 MHz, CDCl_3) δ 5.35 (d, $J = 5.3$ Hz, 1 H), 4.23–4.18 (m, 1 H), 4.08 (q, $J = 7.2$ Hz, 2 H), 3.79 (ap d, $J = 11.2$ Hz, 1 H), 3.69 (s, 3 H), 3.47 (dd, $J = 11.2, 5.7$ Hz, 1 H), 3.28 (s, 3 H), 3.02 (ap d, $J = 5.7$ Hz, 1 H), 2.42 (dd, $J = 16.2, 3.2$ Hz, 1 H), 2.30–1.65 (m, 5 H), 1.24 (t, $J = 7.2$ Hz, 3 H); IR (CHCl_3) 2934, 1780, 1722, 1679, 1426, 1381, 1338, 1289, 1252, cm^{-1} ; MS (EI) 409.1367 (M, 409.1348 calcd for $\text{C}_{17}\text{H}_{22}\text{F}_3\text{NO}_7$); MS (CI) m/z 410, 296.

(1R*,2S*,4S*)-(5-Methyl-1-triisopropylsiloxybicyclo[2.2.2]oct-5-en-2-yl)-carbamic acid ethyl ester (52). A solution of pure endo-ester **50** (1.79 g, 5.09 mmol), EtOH (75 mL), water (21 mL) and KOH (1.25 g, 22.3 mmol) was heated at reflux for 22 h. The resultant solution was cooled to rt and concentrated. The basic residue was partitioned between petroleum ether (40 mL) and water (40 mL). The basic solution was then carefully acidified with 1 N HCl until pH 3 and then extracted with CHCl_3 (3×50 mL). The organic layers were dried (MgSO_4), filtered and concentrated to give 1.28 g (74%) of **52** as a light yellow solid which although slightly impure was sufficiently pure to be employed in the Curtius rearrangement step. Diagnostic data: mp 83–85 °C; ^1H NMR (250 MHz, CDCl_3) δ 5.75 (s, 1 H), 2.66 (dd, $J = 9.8, 4.2$ Hz, 1 H), 2.38 (br s, 1 H), 2.10–1.95 (m, 1 H), 1.78 (d, $J = 1.5$ Hz, 3 H), 1.9–1.5 (m, 4 H),

1.5–1.3 (m, 1 H), 1.11 (s, 18 H), 1.25–1.0 (m, 3 H); ^{13}C NMR (63 MHz, CDCl_3) δ 175.7, 143.4, 127.0, 78.2, 50.5, 35.0, 34.4, 29.8, 26.7, 20.1, 18.5, 13.7; IR (CCl_4) 3050 (br) 2929, 1761, 1708, 1321, 1229, 1187 cm^{-1} ; MS m/z 339, 321, 295.

Oxalyl chloride (0.180 mL, 2.06 mmol) was added to a solution of crude acid **51** (0.238 g, 0.702 mmol) in benzene (10.5 mL). The solution was stirred for 30 min and then concentrated. A solution of sodium azide (0.120 g, 1.85 mmol) and water (0.22 mL) was added to a solution of the crude acid chloride in acetone (1.10 mL) at 0 °C. After stirring for 30 min, this solution was quenched with ice water (5 mL) and extracted with benzene (4 $\times$ 5 mL). The combined organic layers were washed with brine, dried (MgSO_4) and heated to reflux for 12 h. The reaction mixture was cooled to rt and ethanol (1.1 mL, 18.8 mmol) was added. The resulting solution was heated at reflux for 15 h. The solution was cooled to rt, concentrated and the residue was purified by chromatography (10:1 hexane/EtOAc with 2% Et_3N) to give 183 mg (68%) of **51** as a light yellow oil: ^1H NMR (250 MHz, CDCl_3) δ 5.64 (s, 1 H), 4.76 (br s, 1 H), 4.2–3.9 (m, 2 H), 3.85–3.65 (m, 1 H), 2.30–2.05 (m, 2 H), 1.79 (d, J = 1.5 Hz, 3 H), 1.8–1.45 (m, 3 H), 1.21 (t, J = 7.0 Hz, 3 H), 1.06 (s, 18 H), 1.4–0.9 (m, 5 H); ^{13}C NMR (63 MHz, CDCl_3) δ 156.6, 143.5, 127.4, 76.4, 60.4, 56.6, 37.6, 35.2, 33.2, 26.1, 20.0, 18.4, 14.8, 13.5; IR (CCl_4) 3448, 2941, 1724, 1491, 1214 cm^{-1} ; MS (CI) m/z 382.2775 (MH, 382.2781 calcd for $\text{C}_{21}\text{H}_{39}\text{NO}_3\text{Si}$), 338, 293, 266. Anal. Calcd for $\text{C}_{21}\text{H}_{39}\text{NO}_3\text{Si}$: C, 66.09; H, 10.30. Found: C, 65.88; H, 10.48.

(1R*,2S*,4S*)-5-Methyl-1-triisopropylsiloxybicyclo[2.2.2]oct-5-en-2-ylamine (53).

Tetra-*n*-butylammonium fluoride (1.1 mL, 1 M in THF, 1.1 mmol) was added to a solution of carbamate **52** (380 mg, 0.997 mmol) in THF (12 mL). After stirring at rt for 30 min, the reaction mixture was poured into saturated aqueous NaHCO_3 (20 mL) and extracted with Et_2O (3 $\times$ 10 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated to give 390 mg of the crude alcohol. A solution of KOH (8.00 g, 143 mmol) in water (2 mL) was added to the crude alcohol dissolved in MeOH (21 mL). The mixture was heated at reflux for 20 h. The solution was cooled to rt and concentrated. The resulting crude residue was dissolved in Et_2O , neutralized with 1 M HCl to pH 7 and the layers were then separated. The aqueous phase was

extracted with CHCl_3 (3×10 mL) and the combined organic phases were dried (K_2CO_3), filtered and concentrated to give 97.3 mg (64%) of **53** as a yellow solid. Successive recrystallization from hot hexane gave an analytical sample: mp 84–84.5 °C; ^1H NMR (250 MHz, CDCl_3) δ 5.60 (q, $J = 1.4$ Hz, 1 H), 2.74 (ddd, $J = 9.0, 3.6, 1.3$ Hz, 1 H), 2.50–2.49 (m, 1 H), 2.10 (ddd, $J = 13.1, 9.1, 2.6$ Hz, 1 H), 1.81 (d, $J = 1.6$ Hz, 3 H), 1.7–1.3 (m, 7 H), 0.98 (ddd, $J = 13.2, 6.4, 3.0$ Hz, 1 H); ^{13}C NMR (63 MHz, CDCl_3) δ 142.8, 126.7, 75.3, 55.8, 38.5, 35.9, 32.5, 25.9, 19.9; IR (CCl_4) 3350 (br), 2932, 1441, 1175, 1077 cm^{-1} ; MS m/z 154, 137.

(1R*,2S*,4S*)-(1-Hydroxy-5-methylbicyclo[2.2.2]oct-5-en-2-ylamino)-acetonitrile

(54). A solution of amine **53** (550 mg, 3.59 mmol), THF (15 mL) and aqueous pH 7 buffer (15 mL, 0.5 M solution, Fisher) was acidified to pH 7 with 1 N HCl. KCN (258 mg, 3.96 mmol) and 37% formalin (0.291 mL, 3.88 mmol) were added to this solution and the resulting mixture was stirred for 16 h at rt. The reaction mixture was poured into 5 N KOH (30 mL) and extracted with CHCl_3 (3×25 mL). The combined organic phases were dried (K_2CO_3), filtered and concentrated. Purification of the crude residue by chromatography (20:1 $\text{CHCl}_3/\text{MeOH}$) afforded 580 mg (84%) of **54** as a light yellow oil, which solidified upon standing. An analytical sample was prepared by recrystallization from CH_2Cl_2 /hexane to give translucent crystals: mp 89–90 °C; ^1H NMR (250 MHz, CDCl_3) δ 5.62 (br s, 1 H), 3.57 (AB_q , $J_{\text{AB}} = 17.4$ Hz, $\Delta\nu_{\text{AB}} = 13.7$ Hz, 2 H), 2.80 (ddd, $J = 8.6, 3.4, 0.9$ Hz, 1 H), 3.3–2.5 (br s, 1 H), 2.32 (br s, 1 H), 2.07 (ddd, $J = 13.0, 8.7, 2.7$ Hz, 1 H), 1.79 (d, $J = 1.6$ Hz, 3 H), 1.9–1.1 (m, 6 H); ^{13}C NMR (63 MHz, CDCl_3) δ 142.7, 127.1, 118.5, 74.4, 62.3, 35.8, 35.4, 35.3, 32.4, 25.2, 19.9; IR (CCl_4) 3614, 3488, 2932, 1441, 1170 cm^{-1} ; MS (CI) m/z 193.1341 (MH, 193.1341 calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}$), 166, 137, 110.

(3R*,4aS*,8aS*)-8a-Methyl-7-oxodecahydro-isoquinoline-3-carbonitrile (58).

A solution of amine **54** (24.8 mg, 0.129 mmol) in THF (1.50 mL) was added dropwise over 2 min to a suspension of potassium hydride (129 mg of a 24.6% suspension in mineral oil washed with hexanes, 0.793 mmol) in THF (1.50 mL) at rt. The resulting mixture was stirred for 2.5 h at rt and then cooled to –78 °C. A solution of 1 N KCN (5.00 mL) and 10 N HCl (0.45 mL) was then added and the resultant solution allowed to warm to rt. After 1 h, the reaction mixture was

neutralized with 5 N KOH and CHCl_3 (10 mL) was added. The layers were separated and the aqueous layer was extracted with CHCl_3 (3×10 mL). The combined organic layers were dried ($\text{K}_2\text{CO}_3/\text{Na}_2\text{SO}_4$), filtered and concentrated. Purification of the residue by chromatography (15:1 $\text{CHCl}_3/\text{MeOH}$) resulted in 16.6 mg (67%) of **58** as a colorless crystalline solid. An analytical sample was prepared by recrystallizing a small amount from $\text{CH}_2\text{Cl}_2/\text{hexane}$: mp 128.5–129 °C; ^1H NMR (250 MHz, CDCl_3) δ 4.26 (dd, $J = 5.0, 2.2$ Hz, 1 H), 2.69 (AB_q , $J_{\text{AB}} = 12.3$ Hz, $\Delta\nu_{\text{AB}} = 104.9$ Hz, 2 H), 2.45 (AB_q , $J_{\text{AB}} = 14.6$ Hz, $\Delta\nu_{\text{AB}} = 307.8$ Hz, 2 H), 2.4–2.1 (m, 3 H), 2.0–1.6 (m, 5 H), 0.96 (d, $J = 0.8$ Hz, 3 H), ^{13}C NMR (63 MHz, CDCl_3) δ 211.9, 119.6, 53.4, 46.9, 46.7, 38.1, 36.2, 35.4, 29.2, 26.7, 25.0; IR (CCl_4) 3353, 1711, 1446, 1320, 1212 cm^{-1} ; MS (CI) m/z 193.1344 (MH, 193.1328 calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}$), 166.

(3R*,4aS*,8aS*)-2,8a-Dimethyl-7-oxodecahydroisoquinoline-3-carbonitrile (59). A solution of amine **58** (165 mg, 0.854 mmol), methyl methanesulfonate (0.51 mL, 6.0 mmol), diisopropylethylamine (0.17 mL, 0.98 mmol) in CHCl_3 (20 mL) was heated at reflux for 17 h. The solution was cooled to rt, combined with ether (50 mL) and 2 N NH_4OH (18 mL), and stirred for 1 h. The reaction mixture was made basic with 1 N KOH until pH 9 and CHCl_3 (10 mL) was added. The layers were separated and the aqueous layer was extracted with CHCl_3 (3×10 mL). The combined organic layers were dried ($\text{K}_2\text{CO}_3/\text{Na}_2\text{SO}_4$), filtered and concentrated. Purification of the residue by chromatography (15:1 $\text{CHCl}_3/\text{MeOH}$) resulted in 122 mg (69%) of **59** as a light yellow oil which crystallized upon standing. An analytical sample was prepared by recrystallizing a small amount of **59** from $\text{CH}_2\text{Cl}_2/\text{hexane}$: mp 120–122 °C; ^1H NMR (250 MHz, CDCl_3) δ 3.94 (br d, $J = 3.1$ Hz, 1 H), 2.41 (AB_q , $J_{\text{AB}} = 14.5$, $\Delta\nu_{\text{AB}} = 286.0$ Hz, 2 H), 2.35 (s, 3 H), 2.25 (AB_q , $J_{\text{AB}} = 12.5$ Hz, $\Delta\nu_{\text{AB}} = 2.7$ Hz, 2 H), 2.40–2.10 (m, 4 H), 1.8–1.65 (m, 3 H) 0.93 (s, 3 H), ^{13}C NMR (63 MHz, CDCl_3) δ 211.7, 116.2, 62.1, 55.0, 47.7, 44.0, 38.4, 36.3, 34.4, 29.6, 26.4, 25.1; IR (CCl_4) 2937, 1711, 1445, 1104 cm^{-1} ; MS (CI) m/z 207.1497 (MH, 207.1501 calcd for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}$), 180.

(1R*,2S*,6S*,8S*)-1,9-Dimethyl-9-azatricyclo[4.4.0.0^{2,8}]decan-3-one (61). A solution of ketone **59** (33 mg, 0.16 mmol), methanol (3.1 mL) and 37% HCl (0.10 mL) was heated at 85

°C for 15 h in a sealed ampule. After cooling to rt, the reaction mixture was made basic (pH 9) by the dropwise addition of 1 N KOH. CHCl₃ (5 mL) was added and the layers were separated. The aqueous layer was extracted with CHCl₃ (3 × 5 mL). The combined organic phases were dried (K₂CO₃), filtered and concentrated. Purification of the residue by chromatography (12:1 CHCl₃/MeOH) gave 11 mg (44%) of **61**, which was contaminated with ~15% of an unknown impurity: ¹H NMR (250 MHz, CDCl₃) δ 3.2–3.1 (m, 2 H), 2.55 (ap q, *J* = 1.8 Hz, 1 H), 2.52 (AB_q, *J*_{AB} = 10.1 Hz, Δ*v*_{AB} = 32.7 Hz, 2 H), 2.40–2.30 (m, 2 H), 2.34 (s, 3 H), 2.06 (ddd, *J* = 13.8, 8.2, 1.7 Hz, 1 H), 2.03–1.85 (m, 1 H), 1.75–1.65 (m, 1 H), 1.60 (ddd, *J* = 13.8, 4.1, 1.9 Hz, 1 H), 1.13 (s, 3 H); ¹³C NMR (63 MHz, CDCl₃) δ 212.5, 68.2, 66.2, 62.0, 50.6, 41.8, 39.5, 33.9, 31.6, 25.0, 15.6; IR (CCl₄) 2943, 1694, 1450, 1092 cm⁻¹; MS (EI) *m/z* 179, 108, 96.

4-Benzyloxy-Z-but-2-enoic acid methyl ester (62).⁷ 1,4-Buten-diol (23.0 mL, 0.279 mmol) was added to a suspension of KH (25 g of a 25% suspension in mineral oil washed with THF, 0.634 mmol) in THF (500 mL) at 0 °C. The reaction mixture was allowed to warm to rt and 14 h later the reaction was cooled to 0 °C and benzyl bromide (74.0 mL, 0.622 mmol) was added. The reaction mixture was allowed to warm to rt again. After a period of 14 h, isopropanol (30 mL) was carefully added. The reaction was quenched by the slow addition of 30% saturated ammonium chloride solution (100 mL). The layers were separated and the aqueous phase extracted (3 × 100 mL hexanes). The combined organic phases were dried (MgSO₄), filtered and concentrated to a yellow oil. Vacuum distillation (145–160 °C at 1.2–0.8 mm of Hg) gave a colorless oil in quantitative yield: ¹H NMR (CDCl₃, 250 MHz) δ 7.36 (s, 10 H), 5.81 (dd, *J* = 5.8, 3.6 Hz, 2 H), 4.51 (s, 4 H), 4.09 (d, *J* = 4.6 Hz, 4 H).

The alkene was dissolved in 4:1 MeOH/CH₂Cl₂ (50 mL) and cooled to –78 °C and ozone was bubbled through the solution for 30 h. Dimethylsulfide (250 mL) was carefully added and the mixture was allowed to warm to rt. After a period of 12 h at rt the solution was concentrated and distilled (80–85 °C at 1.2 mm) to obtain 56.1 g of colorless oil and an azeotrope fraction of aldehyde and DMSO. The contaminated fraction was filtered through silica gel to give an 87% overall yield of the aldehyde: ¹H NMR (CDCl₃, 250 MHz) δ 9.75 (s, 1 H), 7.48 (s, 5 H), 4.65 (s, 2

H), 4.12 (s, 2 H).

Trimethyl phosphonoacetate (65.0 mL, 0.40 mmol) was added to a suspension of NaH (18.5 g of a 50% suspension in mineral oil washed with THF, 0.38 mmol) in THF (1.4 L) at 0 °C. The solution effervesced and became a thick slurry. A solution of the aldehyde prepared above (50.0 g, 0.334 mmol) in THF (120 mL) was slowly added. The mixture was warmed to rt on complete addition of the aldehyde and after a period of 2.5 h, H₂O (300 mL) was added and the solution was diluted with hexanes (500 mL). The layers were separated and the aqueous phase was extracted with hexanes (4 × 300 mL). The combined organic phases were dried (Na₂SO₄), filtered and concentrated. Purification of the crude residue by chromatography (1:1 hexanes/Et₂O) gave 56.6 g (82%) of **62** as a colorless oil: ¹H NMR (CDCl₃, 250 MHz) δ 7.38 (s, 5 H), 7.00 (dt, *J* = 14.9, 3.9 Hz, 1 H), 6.15 (dt, *J* = 15.4, 2.4 Hz, 1 H), 4.56 (s, 2 H), 4.20 (dd, *J* = 5.6, 3.0 Hz, 2 H), 3.78 (s, 3 H); IR (film) 1724 cm⁻¹.

(1R*,2S*,3R*,4S*)-3-Benzoyloxymethyl-5-methyl-1-triisopropylsiloxy-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester (63). A solution of dienophile **62** (210 mg, 1.02 mmol) in CH₂Cl₂ (4.0 mL) was added to a stirred solution of aluminum chloride (200 mg, 1.5 mmol) in CH₂Cl₂ (5.5 mL) at -78 °C. After a period of 20 min, a solution of diene **49** (0.53 g, 2 mmol) in CH₂Cl₂ (0.5 mL) was added dropwise over 5 min. The reaction mixture was maintained at -78 °C for 15 h at which time saturated aqueous NaHCO₃ (10 mL) was added and the mixture was warmed to rt. The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were dried (Na₂SO₄), filtered and concentrated to an oil. Purification of the oil by chromatography (1:1 hexanes/Et₂O with 1% Et₃N) gave 340 mg (71%) of **63-endo** and **63-exo** as a slightly yellow oil. ¹H NMR integration of vinyl peaks of *endo*-**63** (δ 5.79, s) and *exo*-**63** (δ 5.87, s) gives a ratio of 7:1 for *endo:exo* products. Pure samples were prepared by flash chromatography. *Endo*-**63**: ¹H NMR (250 MHz, CDCl₃) δ 7.33 (m, 5 H), 5.79 (s, 1 H), 4.50 (AB_q, *J*_{AB} = 12.1 Hz, Δ*v*_{AB} = 13.0 Hz, 2 H), 3.59 (s, 3 H), 3.50 (dd, *J* = 9.4, 6.8 Hz, 1 H), 3.40 (t, *J* = 8.9 Hz, 1 H), 2.33 (br s, 1 H), 2.27 (d, *J* = 6.7 Hz, 1 H), 2.14 (qt, *J* = 8.2, 1.6 Hz, 1 H), 1.85 (d, *J* = 1.5 Hz, 3 H), 1.70 (dd, *J* = 9.8, 6.9, 2.6 Hz, 1

H), 1.55 (td, $J = 6.8, 4.2$ Hz, 1 H), 1.47 (td, $J = 11.0, 4.3$ Hz, 1 H), 1.26–1.24 (m, 1 H), 1.04 (br s, 21 H); IR (film) 2925, 2860, 1740 cm^{-1} ; MS (EI) m/z 472.2993 (M, 472.3009 calcd for $\text{C}_{28}\text{H}_{44}\text{O}_4\text{Si}$), 429. *Exo-63*: ^1H NMR (250 MHz, CDCl_3) δ 7.32 (m, 5 H), 5.87 (s, 1 H), 4.45 (AB_q, $J_{\text{AB}} = 12.1$ Hz, $\Delta\nu_{\text{AB}} = 11.7$ Hz, 2 H), 3.64 (s, 3 H), 3.10 (d, $J = 7.5$ Hz, 2 H), 2.39 (br s, 1 H), 2.33 (dq, $J = 10.9, 3.9$ Hz, 1 H), 2.07 (d, $J = 4.9$ Hz, 1 H), 1.80–1.78 (m, 1 H), 1.76 (d, $J = 1.6$ Hz, 3 H), 1.41–1.39 (m, 1 H), 1.27–1.25 (m, 2 H), 1.05 (br s, 21 H); IR (film) 2950, 2870, 1730 cm^{-1} ; MS (EI) m/z 472.3019 (M, 472.3009 calcd for $\text{C}_{28}\text{H}_{44}\text{O}_4\text{Si}$), 429.

(1R*,2S*,3R*,4S*)-3-Benzyloxymethyl-5-formyl-1-triisopropylsiloxy-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester (64). Argon was bubbled through a solution of **63** (321 mg, 0.678 mmol) and selenium dioxide (120 mg, 1.08 mmol) in dioxane (7.0 mL). The solution was heated to reflux for 6 h and then allowed to cool to rt. The solids were removed by filtration. The resulting orange solution was concentrated to a yellow oil which was purified by chromatography (hexanes $\rightarrow$ 4:1 $\rightarrow$ 1:1 hexanes/Et₂O gradient) to obtain 309 mg (94%) of **64** as a yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 9.48 (s, 1 H), 7.31 (s, 5 H), 7.17 (s, 1 H), 4.49 (AB_q, $J_{\text{AB}} = 12.1$ Hz, $\Delta\nu_{\text{AB}} = 13.6$ Hz, 2 H), 3.59 (s, 3 H), 3.54 (dd, $J = 9.5, 7.5$ Hz, 1 H), 3.48 (dd, $J = 9.5, 7.2$ Hz, 1 H), 3.24 (br s, 1 H), 2.52 (d, $J = 6.7$ Hz, 1 H), 1.99 (qt, $J = 6.9, 1.8$ Hz, 1 H), 1.84 (dddd, $J = 14.3, 9.6, 3.9, 1.9$ Hz, 1 H), 1.70 (td, $J = 10.7, 4.0$ Hz, 1 H), 1.57 (td, $J = 9.7, 4.3$ Hz, 1 H), 1.06 (br s, 22 H); ^{13}C NMR (75 MHz, CDCl_3) δ 188.3, 174.0, 156.1, 145.1, 138.1, 128.2, 127.4, 127.3, 77.7, 72.9, 71.5, 56.0, 51.5, 44.0, 34.4, 27.5, 20.0, 18.1, 13.2; IR (film) 2946, 2866, 1737, 1687 cm^{-1} ; MS (EI) m/z 486.2801 (M, 486.2801 calcd for $\text{C}_{28}\text{H}_{42}\text{O}_5\text{Si}$), 443.

(1R*,2S*,3R*,4S*)-3-Benzyloxymethyl-1-triisopropylsiloxy-5-vinylbicyclo[2.2.2]oct-5-ene-2-carboxylic acid (66). Methyltriphenylphosphonium bromide (380 mg, 1.06 mmol) was flame dried under vacuum and flushed with argon. The flask was cooled to rt and dissolved in THF (12 mL). This solution was cooled to 0 °C and *n*-BuLi (0.40 mL, 2.35 M in hexane, 0.94 mmol) was added dropwise. After a period of 15 min at 0 °C, the solution was cooled to –78 °C. A solution of aldehyde **64** (302 mg, 0.622 mmol) in THF (3 mL) was added dropwise to the

Wittig reagent. After a period of 2 h, the reaction mixture was warmed to 0 °C. After a period of 30 min at 0 °C the reaction was quenched by the dropwise addition of saturated aqueous NaHCO₃ (10 mL). The layers were separated and the aqueous phase was extracted with hexanes (3 × 10 mL). The combined organic phases were dried (Na₂SO₄), filtered and concentrated. Purification to the residue by chromatography (hexanes → 8:1 → 4:1 hexanes/Et₂O gradient) gave 216 mg (72%) of **65** as a colorless oil, which was used immediately in the next step. Diagnostic data: ¹H NMR (300 MHz, CDCl₃) δ 7.34 (br s, 5 H), 6.38 (dd, *J* = 17.5, 10.8 Hz, 1 H), 6.12 (s, 1 H), 5.30 (d, *J* = 17.5 Hz, 1 H), 5.04 (d, *J* = 10.8 Hz, 1 H), 4.53 (AB_q, *J*_{AB} = 12.1 Hz, Δ*v*_{AB} = 16.8 Hz, 2 H), 3.60 (s, 3 H), 3.56–3.50 (m, 2 H), 2.95 (br s, 1 H), 2.39 (d, *J* = 6.8 Hz, 1 H), 2.14 (qt, *J* = 7.4, 1.7 Hz, 1 H), 1.81 (dddd, *J* = 14.5, 9.7, 4.2, 2.3 Hz, 1 H), 1.66 (td, *J* = 11.2, 4.2 Hz, 1 H), 1.57 (td, *J* = 11.5, 4.6 Hz, 1 H), 1.07 (br s, 21 H), 1.01 (q, *J* = 4.6 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 174.3, 142.3, 138.4, 135.0, 134.3, 128.2, 127.4, 127.3, 111.5, 77.2, 72.8, 71.9, 56.0, 51.3, 43.0, 36.0, 29.5, 20.1, 18.2, 13.2; IR (film) 2945, 2866, 1741 cm⁻¹; MS (EI) *m/z* 484.3004 (M, 484.3009 calcd for C₂₉H₄₄O₄Si), 453, 441, 279, 107.

A solution of potassium hydroxide (5.00 g, 89.1 mmol) in H₂O (80 mL) was added to a solution of ester **65** (19.8 g, 40.9 mmol) in EtOH (260 mL). The solution was heated at reflux for 48 h. The flask was cooled to rt and concentrated to *ca* 80 mL. The flask was cooled to 0 °C and concentrated HCl (7.0 mL) was carefully added. The solution was extracted with CH₂Cl₂ (5 × 100 mL) and the combined organic phases were dried (Na₂SO₄), filtered and concentrated to obtain a yellow oil. Purification of this oil by chromatography (hexanes → hexanes/Et₂O gradient) gave 17.0 g (88%) of **66** as a colorless oil: ¹H NMR (250 MHz, CDCl₃) δ 7.36–7.29 (m, 5 H), 6.29 (dd, *J* = 17.5, 10.7 Hz, 1 H), 6.06 (s, 1 H), 5.33 (d, *J* = 17.5 Hz, 1 H), 5.07 (d, *J* = 10.8 Hz, 1 H), 4.56 (AB_q, *J*_{AB} = 12.1 Hz, Δ*v*_{AB} = 13.6 Hz, 2 H), 3.64 (dd, *J* = 9.5, 5.6 Hz, 1 H), 3.50 (t, *J* = 9.0 Hz, 1 H), 3.00 (s, 1 H), 2.38–2.32 (m, 1 H), 2.29 (d, *J* = 5.8 Hz, 1 H), 1.95–1.83 (m, 1 H), 1.76–1.58 (m, 2 H), 1.33–1.15 (m, 1 H), 1.10 (br s, 21 H); IR (film) 3400–2500, 1710, 1590 cm⁻¹; MS (EI) *m/z* 470.2828 (M, 470.2852 calcd for C₂₈H₄₂O₄Si).

(1R*,2S*,3R*,4S*)-3-Benzylloxymethyl-1-triisopropylsiloxy-5-vinylbicyclo[2.2.2]oct-

5-en-2-ylamine (67). Oxalyl chloride (70 μ L, 0.80 mmol) was added to a stirring solution of acid **66** (103 mg, 0.219 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C. The reaction was allowed to warm to rt during which time gas evolved. After a period of 1.5 h the solution was concentrated to an oil and dissolved in acetone (2.0 mL). This solution was cooled to 0 °C and a slurry of sodium azide (0.060 g, 0.923 mmol) in acetone/ H_2O (0.50 mL/0.15 mL) was added. The solution was maintained at 0 °C for a period of 20 min and was poured into ice-water (7 mL). This solution was extracted with cold toluene (4×6 mL) and the combined organic phase was dried (MgSO_4). The drying agent was removed by filtration and the solution was heated to reflux for 2.5 h. The solution was allowed to cool to rt and concentrated to give 88.3 mg (86.5%) of the corresponding isocyanate as a slightly yellow oil, which was used immediately. Diagnostic data ^1H NMR (250 MHz, CDCl_3) δ 7.36 (s, 5 H), 6.33 (dd, $J = 17.5, 10.8$ Hz, 1 H), 6.01 (s, 1 H), 5.32 (d, $J = 17.4$ Hz, 1 H), 5.09 (d, $J = 10.8$ Hz, 1 H), 4.57 (s, 2 H), 3.58 (dd, $J = 9.5, 6.7$ Hz, 1 H), 3.43 (t, $J = 8.9$ Hz, 1 H), 3.18 (dd, $J = 4.3, 1.2$ Hz, 1 H), 2.89 (br s, 1 H), 1.85–1.72 (m, 1 H), 1.67 (dd, $J = 15.2, 3.2$ Hz, 1 H), 1.60–1.52 (m, 2 H), 1.30–1.15 (m, 1 H), 1.10 (br s, 21 H); IR (film) 2940, 2461, 2225, 1605, 1460 cm^{-1} ; MS (EI) m/z 467.2863 (M, 467.2855 calcd for $\text{C}_{28}\text{H}_{41}\text{NO}_3\text{Si}$), 424.

A 1-liter round bottom was attached to a Büchi rotary evaporator and cooled using a dry ice-isopropanol bath. Isocyanate (3.01 g, 6.45 mmol, theoretical yield from the acid **66**) in 500 mL dioxane was added through the top inlet under vacuum, while the round bottom was rotating in the cold bath. Potassium hydroxide (5.00 g, 89.1 mmol) in H_2O (80 mL) was added in the same manner. The bath was allowed to warm to rt and 14 h later the volume was reduced to 1/4 the original volume. The solution was diluted with H_2O (50 mL) and hexanes (50 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (5×50 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated to obtain a slightly yellow oil. Purification of the residue by chromatography (1:1 hexane/ $\text{Et}_2\text{O} \rightarrow \text{Et}_2\text{O}$ gradient) afforded 1.93 g (68% from acid **66**) of **67** and some urea side product: ^1H NMR (250 MHz, CDCl_3) δ 7.36–7.34 (m, 5 H), 6.32 (dd, $J = 17.5, 10.8$ Hz, 1 H), 5.95 (s, 1 H), 5.32 (d, $J = 17.4$

Hz, 1 H), 5.04 (d, $J = 10.8$ Hz, 1 H), 4.56 (AB_q, $J_{AB} = 12.2$ Hz, $\Delta\nu_{AB} = 17.7$ Hz, 2 H), 3.72 (dd, $J = 9.5$, 5.7 Hz, 1 H), 3.44 (t, $J = 9.6$ Hz, 1 H), 2.95 (br s, 1 H), 2.29 (dd, $J = 4.5$, 1.1 Hz, 1 H), 1.79 (tq, $J = 9.8$, 3.2 Hz, 1 H), 1.56 (dq, $J = 11.8$, 3.5 Hz, 1 H), 1.45 (m, 1 H), 1.32–1.15 (m, 1 H), 1.08 (br s, 22 H); IR (film) 3370, 2950, 2860, 1585, 1465 cm⁻¹; MS (EI) m/z 441.3060 (M, 441.3063 calcd for C₂₇H₄₃NO₂Si), 398.

(1R*,2S*,3R*,4S*)-(3-Benzyloxymethyl-1-triisopropylsiloxy-5-vinyl-bicyclo[2.2.2]oct-5-en-2-ylamino)-acetonitrile (68). Chloroacetonitrile (0.15 mL, 2.4 mmol) was added to a solution of amine **67** (0.71 g, 1.6 mmol), diisopropylethylamine (0.60 mL, 3.4 mmol) and tetrabutylammonium iodide (12.0 mg, 32 μ mol) in THF (8.0 mL). The solution was heated at reflux for 25 h and cooled to rt. The solution was diluted with hexanes (30 mL), dried (Na₂SO₄), filtered and concentrated. Purification of the residue by chromatography (8:1 $\rightarrow$ 4:1 hexanes/Et₂O gradient) afforded 0.51 g (65%) of **68** as a yellow oil: ¹H NMR (250 MHz, CDCl₃) δ 7.44–7.42 (m, 5 H), 6.32 (dd, $J = 17.5$, 10.8 Hz, 1 H), 6.00 (s, 1 H), 5.27 (d, $J = 17.5$ Hz, 1 H), 5.04 (d, $J = 10.8$ Hz, 1 H), 4.60 (AB_q, $J_{AB} = 11.9$ Hz, $\Delta\nu_{AB} = 23.6$ Hz, 2 H), 3.64 (d, $J = 7.7$ Hz, 2 H), 3.54–3.46 (m, 2 H), 2.86 (br s, 1 H), 2.72 (d, $J = 3.3$ Hz, 1 H), 2.37 (ap t, $J = 7.6$ Hz, 1 H), 1.78–1.55 (m, 1 H), 1.66 (br s, 1 H), 1.63 (dd, $J = 4.7$, 3.7 Hz, 1 H), 1.53–1.42 (m, 1 H), 1.30–1.16 (m, 1 H), 1.11 (br s, 21 H); IR (film) 3330, 2940, 2860, 1585, 1460 cm⁻¹; MS (EI) m/z 480.3183 (M, 480.3172 calcd for C₂₉H₄₄N₂O₂Si), 454.

(1R*,5S*,6R*,7S*)-6-Benzyloxymethyl-8-vinyl-2-oxa-4-aza-tricyclo[5.2.2.0^{1,5}]-undec-8-ene-4-carboxylic acid methyl ester (71). Tetrabutylammonium fluoride (1.5 mL, 1 M in THF, 1.5 mmol) was added to a solution of silyl ether **68** (451 mg, 0.940 mmol) in THF (5.0 mL) at 0 °C. After a period of 40 min saturated aqueous NaHCO₃ (10 mL) and hexanes (10 mL) were added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (4 $\times$ 10 mL). The combined organic phases were dried (Na₂SO₄), filtered and concentrated. Purification of the residue by chromatography (hexanes $\rightarrow$ 8:1 $\rightarrow$ 4:1 $\rightarrow$ 1:1 hexanes/Et₂O $\rightarrow$ Et₂O gradient) gave 270 mg (91%) of **69** as a yellow oil, which was used immediately in the next step. Diagnostic data: ¹H NMR (250 MHz, CDCl₃) δ 7.39–7.36 (m, 5 H), 6.29 (dd, $J = 17.5$, 10.8 Hz,

1 H), 6.95 (s, 1 H), 5.29 (d, $J = 17.5$ Hz, 1 H), 4.53 (d, $J = 11.8$ Hz, 1 H), 4.58 (AB_q, $J_{AB} = 11.9$ Hz, $\Delta\nu_{AB} = 23.6$ Hz, 2 H), 3.62 (s, 2 H), 3.50 (m, 2 H), 2.87 (br s, 1 H), 2.50 (d, $J = 2.5$ Hz, 1 H), 1.75–1.62 (m, 1 H), 1.60–1.50 (m, 3 H), 1.22 (t, $J = 7.0$ Hz, 2 H); IR (film) 3450, 3330, 2950, 2865, 1595 cm^{-1} ; MS (EI) m/z 324.1833 (M, 324.1838 calcd for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$), 298.

A solution of cyanomethylamine **69** (39.9 mg, 0.123 mmol) in THF (1 mL) was added to a slurry of KH (50 mg, 35% in mineral oil washed with hexanes, 0.44 mmol) in THF (2 mL). After a period of 45 min, the flask was cooled to -78 °C and methylchloroformate (0.10 mL, 1.05 mmol) and pyridine (0.20 mL, 0.25 mmol) were added. The reaction mixture was warmed to rt and maintained at this temperature for 2 h. The reaction was quenched with saturated aqueous NaHCO_3 (5 mL) and the mixture was diluted with hexanes (5 mL) and the phases were separated. The aqueous phase was extracted CH_2Cl_2 (3×5 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification of the residue by chromatography (2:1 $\rightarrow$ 1:1 hexanes/ Et_2O gradient) gave 18.8 mg (43%) of **71** as a colorless oil: ^1H NMR ($\text{CD}_3\text{C}_6\text{D}_5$, 300 MHz, 80 °C) δ 7.45 (d, $J = 7.4$ Hz, 2 H), 7.34 (t, $J = 7.4$ Hz, 3 H), 6.32 (dd, $J = 17.5, 10.8$ Hz, 1 H), 5.94 (s, 1 H), 5.44 (d, $J = 17.4$ Hz, 1 H), 5.16 (d, $J = 3.5$ Hz, 1 H), 5.09 (d, $J = 10.8$ Hz, 1 H), 4.99 (d, $J = 4.0$ Hz, 1 H), 4.63 (AB_q, $J_{AB} = 12.2$ Hz, $\Delta\nu_{AB} = 18.2$ Hz, 2 H), 4.38 (br s, 1 H), 3.69–3.67 (m, 1 H), 3.53 (s, 3 H), 3.32 (s, 1 H), 2.94 (d, $J = 6.3$ Hz, 1 H), 2.24–2.21 (m, 1 H), 1.96–1.93 (m, 1 H), 1.77–1.74 (m, 2 H), 1.55–1.50 (m, 1 H). IR (film) 1710 cm^{-1} ; MS (EI) m/z 355, 264, 91.

(1) The procedure we employed to purify THF, Et_2O , CH_2Cl_2 , and toluene has been described: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520. Triethylamine, pyridine, and diisopropylethylamine were distilled from CaH_2 at atmospheric pressure. Other general experimental details have been described: Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241-11250. Full characterization data for oxindole acetal **82** is provided in the accompanying article.

(2) ^1H NMR spectra of compounds prepared during preliminary studies that were not characterized by elemental analysis. Some intermediates give highly complex NMR spectra as they are mixtures of 2–4 carbamate conformational isomers.

- (3) Macdonald, T. L.; Natalie, K. J., Jr.; Prasad, G.; Sawyer, J. S. *J. Org. Chem.* **1986**, *51*, 1124-1126.
- (4) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1977**, *42*, 1051.
- (5) a) Alfaro, I.; Ashton, W.; McManus, L. D.; Newstead, R. C.; Rabone, K. L.; Rogers, N. A. J.; Kernick, W. *Tetrahedron* **1970**, *26*, 201; b) The endo and exo isomers are misassigned in this paper, see Jacobsen, E. J. Ph.D. Dissertation, University of California, Irvine, 1983.
- (6) A mixture of conformation isomers. When signals for the two isomers are clearly separated and assignable, the absorption for the major isomer is noted in italics font and the total hydrogen count is specified with the signal of the major isomer.
- (7) For a more recent preparation see: Trost, B.M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819.

C. NMR Spectra of Selected Compounds.²

32

Exp. Number
Date

Number of Scans
Attenuation (dB)
Sweep Time
Sweep Rate
Receiver Gain (dB)
SFO
Prog. Offset (Hz)
Amplification (dB)
Receiver Noise (dB)

Peak Picked and Retained

Signal

Frequency

Frequency Offset (Hz)

Power (dBm)

Decoupling Mode

Reference

Operator
Date

32

36

Scan 1000
Exp. Number
Date

50

Number of Scans
Attenuation 0
Sweep Time
Sweep Width
Receiver Gain 0
Filter
Pulse Width 0
Attenuation 0
Receiver Gain 0

Peak Data and Histogram

Signal
Frequency
Frequency Offset 0.0
Phase 0.0
Display Mode

REMARKS

S29

37

Sample No. 37
 Run on Date 8/1
 Date 8/1
 Prep. Unit 37
 Attenuation 8
 Receiver Gain 8

Peak Prod. and Reference
 Signal Address
 Frequency
 Frequency Offset, Hz
 Power Level
 Decoupling Mode
 REMARKS

ES
 Date 8/1
 Unit 37

53

Sample Width _____
 Data Points (100) _____
 Input Filter _____
 Prog. Offset _____
 Stop Window _____
 Delay _____

53

Number of Scans _____
 Attenuation (dB) _____
 Sweep Time _____
 Sweep Rate _____
 Receiver Gain (dB) _____
 Filter _____
 Prog. Offset (dB) _____
 Attenuation (dB) _____
 Receiver Gain (dB) _____

Push Print out Reference

Signal _____ Address _____
 Frequency _____
 Frequency Offset (dB) _____
 Power Level _____
 Decoding Mode _____
 REMARKS

S32

54

Exp. No.
Date
Page
Exp. No.
Date
Page

54
Number of Scans
Acquisition
Sweep Rate
Sweep Range
Fiducial
Proc. Options
Attenuation
Reference

Peak List and Parameters
Signal
Frequency
Frequency Offset
Power Level
Chemical Shift

533

58

Date: _____
 Title: _____
 Number of Scans: _____
 Accumulation: P1 _____
 Sample Size: _____
 Sample ID: _____
 Name of Scan: P1 _____
 Scan: _____
 First Offset: 31 _____
 Accumulation: P2 _____
 Name of Scan: P2 _____

Peak Name and Reference

Signal: _____
 Frequency: _____
 Frequency Offset: 31. _____
 Power Level: _____
 Damping Mode: _____

REMARKS

S34

Date: 2/2/84
 File: 2/2/84

61

CH
 Name of Subst. _____
 Abstraction # _____
 Sample # _____
 Sample Name _____
 Name of Lab _____
 Date _____
 Prep. Order # _____
 Abstraction # _____
 Name of Subst. _____
 Peak Prod. and Reference _____
 Signal _____ Address _____
 Frequency _____
 Frequency Offset 31 _____
 Power Level _____
 Displaying Mode _____
 At 11:55

235

63

S38

Hz 10 000
Hz 5 000
Hz 2 500

8 000
4 000
2 000

6 000
3 000
1 500

4 000
2 000
1 000

2 000
1 000
500

Hz 10 000

Hz 5 000

Hz 2 500

4 000

2 000

6 000

3 000

1 500

4 000

2 000

1 000

2 000

1 000

500

68

S40