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Explorations in Organic Chemistry Leading to the Total Synthesis of (±)-Gelsemine

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Supporting Information Available: Experimental procedures and characterization data for compounds **1**, **14-16**, **21-39**, **31**, **46-49**, **54-55**, **74-76**, **83**, and **102-109**. This material is available free of charge via the Internet at http://pubs.acs.org.

EXPERIMENTAL SECTION

General Procedures. All reaction glassware, transfer syringes and cannula were oven-dried or flame-dried under high vacuum. All moisture-sensitive reactions were performed under an inert atmosphere of nitrogen, or argon if the reactions were air sensitive as well. Flash chromatography was performed with E. Merck silica gel 60 (40–63 mm) and HPLC grade solvents. NMR spectra were obtained on a Varian XL400 (400 MHz), Varian XL300 (300 MHz), and Bruker 500 MHz, 400 MHz, 300 MHz instruments. Chemical shifts are reported in δ, coupling constants in Hz. Infrared spectra were recorded on a Perkin Elmer 1420 Ratio Recording Infrared Spectrophotometer, and IR are reported in cm^{-1}. Melting points are uncorrected.

Preparation of Diene 14. LiHMDS (110 mL, 1.0 M in THF) was added through an addition funnel to a solution of aldehyde **2** (16.1g, 89.4 mmol) and Wittig reagent **12** (63.4 g, 232 mmol) in 110 mL of THF at –10 °C over 1 h. The resulting mixture was stirred at this temperature for 30 min and taken up into ether, which was washed with saturated $NaHCO_3$ aqueous solution, brine, and dried ($MgSO_4$). Removal of the solvent followed by flash chromatography of the residue on silica gel (hexane/EtOAc 95:5) afforded diene **14** 19.5 g (71%) as pale yellow crystals: mp 104-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.85 (dd, J = 8.1, 1.3, 1H), 7.53 (dt, J = 7.9, 1.3, 1H), 7.35 (m, 2H), 6.32 (dd, J = 6.3, 3.2, 1H), 6.11 (dm, J = 9.6, 1H), 5.45 (dt, J = 9.5, 2.1, 1H), 5.26 (dd, J = 6.3, 3.2, 1H), 4.23 (m, 1H), 4.21 (t, J = 4.8, 1H), 2.90 (m, 1H), 2.45 (m, 1H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 149.3, 140.3, 136.2, 132.2, 131.5, 130.0, 129.1, 128.9, 126.9, 124.0, 77.4, 73.7, 47.2, 42.0, 35.5, 28.3; IR ($CHCl_3$) 3020, 2960, 1600, 1520, 1390, 1350, 1190, 1100, 930, 890, 845, 820, 650; HRMS calcd for $C_{18}H_{21}NO_3$: 299.1521, found 299.1528.

Hydroboration of Diene 14. In a flame-dried round-bottom flask equipped with a stir bar and an addition funnel, diene **14** (20.70 g, 69.15 mmol, 1.00 eq) was dissolved in 80 mL of Et_2O. The solution was cooled in an ice bath for 0.5 h and monochloroborane-methylsulfide (9.6 mL, 92.10 mmol, 1.33 eq) in 10 mL Et_2O was added dropwise. The reaction mixture was stirred at 0 °C until TLC (10% EtOAc in hexane) indicated absence of the starting diene 1.5 h later. It was worked up by the dropwise addition of 200 mL of ethanol, 60 mL of 4N NaOH, 50 mL of 30% H_2O_2. The mixture was refluxed for 15 minutes, and cooled to 25 °C. Solid NaCl was added to saturate the aqueous layer, and the mixture was extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$). The solvent was removed and the brown residue was subjected to a short silica gel column and recrystallized from 100% EtOAc to give 17.01 g (77%) of alcohol **15a** as pale yellow crystals: mp 122-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.85 (dd, J = 8.1, 1.3, 1H), 7.53 (dt, J = 7.9, 1.3, 1H), 7.35 (m, 2H), 5.94 (m, 1H), 5.67 (dm, J = 9.6, 1H), 4.33 (t, J = 4.8, 1H), 4.08 (br, 1H), 3.95 (m, 1H), 2.37 (m, 1H), 2.20 (dd, J = 13.0, 8.2, 1H), 2.05 (m, 1H), 1.53 (dt, J = 12.9, 5.1, 4.8, 1H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 149.8, 137.2, 132.0, 131.1, 129.3, 128.0, 127.0, 124.5, 73.8, 73.7, 72.7, 48.2, 41.5, 39.4, 34.0, 28; IR ($CHCl_3$) 3500, 2950, 2890, 1450, 1405, 1350, 1320, 1190, 1145, 1060, 990, 910, 845; HRMS calcd for $C_{18}H_{23}O_4$: 317.1627, found 317.1613.

The mother liquor was concentrated and the residue was purified by flash chromatography on silica gel (hexane/EtOAc, 3:1) to give 1.54 g (7%) of regioisomeric alcohol **15b** as pale yellow solid: mp 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.80 (dd, J = 8.0, 1.4, 1H), 7.52 (dt, J = 7.6, 1.4, 1H), 7.32 (m, 2H), 5.86 (m, 1H), 5.58 (dt, J = 9.8, 1.9, 1H), 4.68 (d, J = 2.7, 1H), 4.43 (t, J = 4.7, 1H), 4.06 (dd, J = 7.6, 1.5, 1H), 2.40 (m, 1H), 2.24 (t, J = 5.2, 1H), 2.09 (br, 1H), 1.98 (dd, J = 15.2, 7.6, 1H), 1.32 (m, 1H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 149.8, 137.2, 132.0, 131.1, 129.3, 128.0, 127.0, 124.5, 73.8, 73.7, 72.7, 48.2, 41.5, 39.4, 34.0, 28.2; IR ($CHCl_3$) 3500, 2920, 2880, 1560, 1460, 1325, 1300, 1060, 980, 850; HRMS calcd for $C_{18}H_{23}O_4$: 317.1627, found 317.1613.

Preparation of Ketone 16. In a flame-dried round bottom flask equipped with an addition funnel, a solution of oxalyl chloride (8.0 mL, 108 mmol, 2.0 eq) in 350 mL of CH_2Cl_2 was cooled to –78 °C. A solution of methyl sulfoxide (12.0 mL, 169 mmol, 3.15 eq) in 50 mL of CH_2Cl_2 was added dropwise from the addition funnel to the oxalyl chloride solution. The resulting mixture was stirred at –78 °C for 30 min. A solution of alcohol **15a** (17.01 g, 53.61 mmol, 1.00 eq) in 100 mL of CH_2Cl_2 was added dropwise to the reaction mixture. After addition of the substrate, it was stirred at –78 °C for 45 min. Et_3N (40.0 mL, 287 mmol, 5.35 eq) was added dropwise from the addition funnel and the resulting mixture was stirred for 30 min at –78 °C, followed by slowly warming to 0 °C. The pale yellow slurry was poured into H_2O, extracted with ether. The combined organic extracts were dried ($MgSO_4$), concentrated, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to afford 16.7 g of ketone **16** (98.7%) as pale yellow solid: mp 164-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.91 (dd, J = 8.1, 1.3, 1H), 7.50 (dt, J = 8.2, 1.2, 1H), 7.38 (t, J = 8.5, 1.3, 1H), 7.07 (dt, J = 8.0, 1.3, 1H), 6.15 (m, 1H), 5.63 (d, J = 9.7, 1H), 4.75 (m, 1H), 4.30 (t, J = 4.7, 1H), 2.89 (t, J = 5.1, 1H),

2.75 (m, 1H), 2.41 (m, 2H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) 214.2, 148.9, 136.2, 132.0, 131.5, 127.4, 124.3, 74.2, 71.9, 54.8, 48.8, 39.3, 37.4, 27.9; IR ($CHCl_3$) 2960, 1710, 1530, 1340, 1100, 740; HRMS calcd for $C_{12}H_{22}NO_4$: 316.1549, found 316.1537.

α-Methylenation of Ketone 16. In a flame-dried round bottom flask equipped with an addition funnel, LiHMDS (65 mL, 1.0 M in THF, 1.23 eq) from addition funnel was added to a solution of ketone **16** (16.7 g, 53.0 mmol) in 250 mL of THF at –78 °C. The resulting solution was stirred for 20 min at –78 °C. A solution of TESCl (12.0 mL, 71.5 mmol, 1.35 eq) in 20 mL of THF was added dropwise. The resulting solution was stirred for 15 min until TLC (hexane/EtOAc 3:1) indicated absence of the starting ketone and warmed to 0°C for 5 min. The reaction mixture was then poured into saturated $NaHCO_3$ aqueous solution, which was extracted with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated . The crude silyl enol ether was azeotroped twice with benzene and placed under high vacuum pull to give a brown powder, which was used in the next step without further purification. Eschenmoser's salt (12.0 g, 64.9 mmol, 1.22 eq) was measured and combined with the crude silyl enol ether in a glove box under Argon. CH_2Cl_2 (100 mL) was syringed into reaction flask. The reaction mixture was allowed to stir at 25 °C for overnight. The reaction mixture was poured into 100 mL 3N HCl (to cleave any residual silyl enol ether), and shaken several times. The aqueous solution was extracted by ether and the combined organic layers was washed with saturated Na_2CO_3 aqueous solution, brine, and dried ($MgSO_4$). Removal of the solvent afforded 550 mg of starting ketone **16**. The aqueous layer was basified with 300 mL 4N NaOH, pH paper registered a highly basic solution. The basic aqueous solution was extracted with CH_2Cl_2, the combined organic extracts were dried ($MgSO_4$), and concentrated to give 18.02 g of amine **21** (91%) as a foamy brown solid: ^{1}H NMR (400 MHz, $CDCl_3$) 7.90 (dd, J = 8.1, 1.2, 1H), 7.48 (dt, J = 8.1, 1.1, 1H), 7.36 (dt, J = 8.1, 1.3, 1H), 7.05 (dd, J = 7.9, 1.2, 1H), 6.21 (m, 1H), 5.62 (d, J = 9.7, 1H), 4.72 (m, 1H), 4.39 (t, J = 4.8, 1H), 2.92 (t, J = 5.0, 1H), 2.79 (m, 1H), 2.53 (m, 1H), 2.43 (t, 12.3, 1H) 2.30 (m, 1H) 2.24 (s, 6H) 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 216.7, 149.2, 136.4, 132.4, 132.3, 131.9, 127.6, 127.5, 124.7, 74.5, 70.7, 59.4, 58.9, 56.0, 45.6, 40.8, 39.7, 28.2; IR ($CHCl_3$) 3050, 2960, 2925, 2860, 2810, 2770, 1730, 1600, 1520, 1390, 1360, 1345, 1130, 1105; HRMS calcd for $C_{21}H_{29}N_2O_4$: 373.2127, found 373.2137.

Iodomethane (40.0 mL, 643 mmol, 12.1 eq) was syringed into a stirring solution of amine **21** (18.02 g, 48.28 mmol, 1.00 eq) in 240 mL of Et_2O and 80 mL of CH_2Cl_2 at 25 °C. Shortly after the addition of iodomethane, white precipitates began to fall out of solution. To insure complete quaternization of the amine, it was left to stir overnight at 25 °C. The white precipitates were filtered, redissolved in CH_2Cl_2, and basic Al_2O_3 was added. The resulting suspension was stirred for 15 min, and the solvent was removed. The solid residue was placed under high vacuum pull. The Al_2O_3 was loaded onto a column and eluted with CH_2Cl_2 until no more product was forthcoming to give 15.13 g of enone **22** (95%) as pale yellow solids: mp 155-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.95 (d, J = 8.2, 1.3, 1H), 7.52 (dt, J = 7.2, 1.2, 1H), 7.40 (dt, J = 8.2, 1.3, 1H), 7.06 (dd, J = 7.8, 1.2, 1H), 6.11 (m, 1H), 5.78 (s, 1H), 5.63 (d, J = 9.5, 1H), 5.19 (s, 1H), 4.75 (m, 1H), 4.30 (m, 1H), 3.30 (m, 1H), 3.05 (m, 1H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.5, 149.9, 149.0, 136.1, 132.4, 132.0, 129.7, 127.7, 127.4, 124.6, 112.0, 74.6, 70.4, 54.9, 45.1, 39.8, 28.1; IR ($CHCl_3$) 2980, 1720, 1520, 1390, 1360, 1345, 1250, 1170,

1100, 740; HRMS calcd for $C_{19}H_{22}NO_4$: 328.1549, found 328.1547.

Luche Reduction of Enone 22. Solid $CeCl_3 \cdot 7H_2O$ (22.81 g, 61.23 mmol, 1.33 eq) was added in one portion to a stirred solution of enone **22** (15.13 g, 46.11 mmol, 1.00 eq) in 400 mL of methanol (reagent grade) at –78 °C. After 10 min, $NaBH_4$ (2.25 g, 59.5 mmol, 1.29 eq) was added in one portion. The reaction mixture was stirred at –78 °C for 15 min and then warmed to 0 °C. The reaction was monitored by TLC (hexane/EtOAc 7:3). Saturated NH_4Cl aqueous solution was added to quench the reaction 50 min later. MeOH was removed by without heating of the water bath. The residue was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated to give 15.22 g of allylic alcohol **23** (99%) as pale yellow solid: mp 117-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.79 (dd, J = 8.2, 1.3, 1H), 7.61 (dd, J = 8.3, 1.3, 1H), 7.47 (dt, J = 8.3, 1.3, 1H), 7.33 (dt, J = 8.4, 1.3, 1H), 6.03 (m, 1H), 5.81 (m, 1H), 4.93 (br s, 3H), 4.57 (br s, 1H), 3.91 (m, 1H), 2.89 (t, J = 5.2, 1H), 2.70 (m, 1H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 154.8, 149.5, 139.0, 132.3, 131.7, 130.5, 128.3, 126.9, 126.5, 124.4, 105.4, 75.9, 74.1, 70.3, 46.7, 39.0, 28.2; IR ($CHCl_3$) 3460, 2970, 1523, 1356, 1184, 1086, 885, 733; HRMS calcd for $C_{19}H_{24}NO_4$: 330.1706, found 330.1713.

Hydroboration of 23. Allylic alcohol **23** (15.22 g, 46.10 mmol, 1.00 eq) was azeotroped with benzene twice. Solid 9-BBN dimer (25.05 g, 102.7 mmol, 2.23 eq) was measured and transferred to the reaction flask in a glove box under Argon. THF (250 mL) was syringed into the reaction flask. The reaction mixture was stirred overnight at 25 °C. TLC (hexane/EtOAc 7:3) indicated the consumption of starting material 14 h later. THF (100 mL) was added and the resulting solution was cooled to 0 °C. Ethanol (250 mL), 3N NaOH (100 mL), and 30% H_2O_2 (130 mL) were added slowly. The resulting mixture was refluxed for 1 h, and then cooled to 25 °C. The volatile organic solvent was removed and the residue was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), concentrated and the brown oily residue was purified by flash chromatography on silica gel (hexane/EtOAc 2:3) to afford 14.08 g of diol **24** (88%) as white solid: mp 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.78 (d, J = 8.1, 1H), 7.74 (d, J = 7.90, 1H), 7.50 (t, J = 7.9, 1H), 7.35 (t, J = 7.8, 1H), 6.02 (br d, J = 9.1, 1H), 5.85 (m, 1H), 5.04 (br s, 1H), 4.57 (m, 1H), 4.14 (t, J = 10.5, 1H), 3.90 (m, 1H), 3.76 (m, 1H), 2.72 (m, 1H), 2.51 (m, 1H), 2.31 (m, 1H), 2.06 (m, 1H), 1.30 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) 149.7, 139.1, 133.1, 131.2, 128.9, 128.5, 126.7, 123.8, 74.2, 73.9, 72.0, 60.6, 48.5, 48.0, 41.9, 39.7, 28.1; IR ($CHCl_3$) 3520 (s), 3400 (br), 2920, 2890, 2870, 1470, 1320, 1310, 1140. 1030. 980; HRMS calcd for $C_{19}H_{25}NO_5$: 347.1733, found 347.1727.

Formation of Oxetane 25. Et_3N (16.0 mL, 114.784 mmol, 2.85 eq) was added in one portion by syringe to a solution of diol **24** (14.00 g, 40.33 mmol, 1.00 eq) in 300 mL of CH_2Cl_2 and stirred for 10 min at –78 °C. Methanesulfonyl chloride (3.80 mL, 49.1 mmol, 1.22 eq) was added dropwise by syringe. The reaction mixture was stirred at –78°C until TLC (hexane/EtOAc 1:1) indicated consumption of starting diol 2.5 h later. The reaction mixture was poured into saturated $NaHCO_3$ aqueous solution, which was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated to a brown foam. The crude mesylate was azeotroped with benzene twice

and taken on to the next step without further purification. NaHMDS (1.0M in THF, 60 mL, 60.0 mmol, 1.49 eq) was added dropwise from an addition funnel to a solution of the crude mesylate in 300 mL of THF at –78 °C. The resulting mixture was kept in the freezer (–22 °C) overnight. The reaction mixture was poured into saturated $NaHCO_3$ aqueous solution, which was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated to a brown oil, which was purified by flash chromatography on silica gel (hexane/EtOAc 3:1) to afford 12.12 g of oxetane **25** (91%) as pale yellow solid: mp 108-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.78 (dd, J = 8.1, 1.2, 1H), 7.70 (dd, J = 8.1, 1.3, 1H), 7.42 (dt, J = 8.1, 1.2, 1H), 7.28 (dt, J = 8.1, 1.4, 1H), 6.20 (m, 1H), 6.03 (m, 1H), 5.23 (t, J = 6.7, 1H), 4.98 (m, 1H), 4.70 (t, J = 6.5, 1H), 4.42 (m, 1H), 3.63 (m, 1H), 3.04 (m, 1H), 2.48 (m, 2H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 150.4, 138.2, 133.6, 131.1, 130.6, 126.7, 126.1, 123.6, 88.9, 76.6, 74.1, 71.0, 46.1, 40.9, 40.0, 39.2, 28.1; IR ($CHCl_3$) 2980, 2930, 1520, 1355, 1190, 1150, 1100, 1010, 970, 740; HRMS calcd for $C_{19}H_{24}NO_4$: 330.1706, found 330.1715.

Hydrolysis of *tert*-Butyl Group 25. Trifluoroacetic acid (25 mL) was added in one portion to a solution of oxetane **25** (12.10 g, 36.65 mmol, 1.00 eq) in 50 mL of CH_2Cl_2 at 0 °C. The reaction was maintained at 0 °C and monitored by TLC (hexane/EtOAc 1:1). Large volume of toluene was added to reaction vessel and concentrated under high vacuum pull at 25 °C to give a brown oily residue, which was purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to yield 8.11 g of carbinol **26** (81%) as a yellow solid: mp 173-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.73 (m, 2H), 7.45 (dt, J = 7.7, 1.4, 1H), 7.30 (dt, J = 7.7, 1.2, 1H), 6.27 (m, 1H), 6.04 (m, 1H), 5.25 (t, J = 6.9, 1H), 4.94 (m, 1H), 4.70 (t, J = 6.4, 1H), 4.43 (m, 1H), 3.89 (m, 1H), 3.12 (m, 1H), 2.79 (m, 1H), 2.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 149.6, 137.3, 133.3, 131.4, 131.1, 127.0, 125.8, 123.9, 87.8, 74.3, 70.9, 45.6, 41.4, 40.2, 38.6; IR ($CHCl_3$) 3380 (br), 2940, 2860, 1520, 1350, 1150, 1010, 950, 740; HRMS calcd for $C_{15}H_{16}NO_4$: 274.1079, found 274.1078.

Preparation of Ketone 27. A solution of methyl sulfoxide (6.60 mL, 93.0 mmol, 3.14 eq) in 50 mL of CH_2Cl_2 was added dropwise from the addition funnel to a solution of oxalyl chloride (4.40 mL, 59.4 mmol, 2.01 eq) in 150 mL of CH_2Cl_2 at –78 °C and stirred for 30 min. A solution of alcohol **26** (8.11 g, 29.6 mmol, 1.00 eq) in 100 mL of CH_2Cl_2 was transferred to the addition funnel by cannulation and added dropwise to the reaction. The resulting mixture was stirred for 1 h at –78 °C. Et_3N (22.0 mL, 158 mmol, 5.33 eq) was syringed into addition funnel and diluted with 20 mL of CH_2Cl_2, and the solution was dripped into the reaction mixture. The reaction mixture was stirred at –78 °C for 20 min, then slowly warmed to 0 °C, and poured into H_2O, which was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), concentrated and the residue was purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to give 6.56 g of ketone **27** (81%) as a pale yellow solid: mp 160-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.85 (dd, J = 8.1, 1.4, 1H), 7.74 (dd, J = 8.0, 1.3, 1H), 7.53 (dt, J = 8.1, 1.3, 1H), 7.39 (dt, J = 8.3, 1.4, 1H), 6.20 (m, 2H), 5.49 (t, J = 7.0, 1H), 5.18 (br s, 1H), 4.91 (t, J = 6.5, 1H), 4.65 (m, 1H), 3.38 (m, 1H), 3.09 (m, 1H), 2.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 208.6, 148.8, 135.0, 133.1, 131.8, 130.9, 127.9, 127.6, 124.2, 82.2, 71.2, 53.3, 49.2, 46.0, 39.3; IR ($CHCl_3$) 2950, 2860, 1740,1520, 1340, 1120, 1020, 970,

735; HRMS calcd for $C_{15}H_{13}NO_4K$: 310.0482, found 310.0485.

Horner-Wadsworth-Emmons (HWE) Reaction of Ketone 27. A solution of triethylphosphonoacetate (7.70 mL, 38.8 mmol, 1.60 eq) in 50 mL of THF was added to a suspension of NaH (60% wt, 1.314 g, 32.85 mmol, 1.35 eq) in 100 mL of THF at 0 °C. The reaction mixture was stirred for 30 minutes at 0 °C and became clear. A solution of ketone **27** (6.57 g, 24.220 mmol, 1.00 eq) in 100 mL of THF was cannulated to the reaction, which was stirred at 0 °C until TLC (hexane/EtOAc 1:1) indicated completion of the reaction 1 hr later. The reaction mixture was poured into H_2O, which was extracted with Et_2O 3X. The combined organic extracts were dried ($MgSO_4$), concentrated and the residue was purified by flash chromatography on silica gel (hexane/EtOAc 7:3) to give 7.61 g of a 3:2 mixture of α,β-unsaturated esters **28a** and **28b** (92%).

Data for *Z*-isomer **28a**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.81 (d, *J* = 8.1, 1H), 7.76 (d, *J* = 7.9, 1H), 7.48 (t, *J* = 8.1, 1H), 7.34 (t, *J* = 8.1, 1H), 6.15 (m, 2H), 5.78 (s, 1H), 5.19 (t, *J* = 7.0, 1H), 4.88 (br s, 1H), 4.69 (t, *J* = 6.3, 1H), 4.42 (m, 2H), 4.16 (m, 2H), 3.30 (m, 1H), 3.18 (m, 1H), 1.29 (t, *J* = 6.9, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 165.9, 165.5, 149.4, 136.1, 133.2, 131.7, 130.1, 128.8, 127.5, 124.1, 108.9, 86.3, 69.3, 59.9, 51.9, 49.3, 43.8, 38.0, 14.2; IR ($CHCl_3$) 2950, 2900, 1700, 1660, 1520, 1340, 1195; HRMS calcd for $C_{19}H_{20}NO_5$: 342.1342, found 342.1333.

Data for *E*-isomer **28b**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.70 (dd, *J* = 8.0, 1.1, 1H), 7.63 (d, *J* = 8.0, 1H), 7.45 (dt, *J* = 8.1, 1.2, 1H), 7.32 (t, *J* = 7.8, 1H), 6.09 (m, 2H), 5.71 (s, 1H), 5.29 (t, *J* = 6.7, 1H), 5.00 (br s, 1H), 4.66 (t, *J* = 6.2, 1H), 4.29 (m, 4H), 3.08 (m, 2H), 1.30 (t, *J* = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 166.0, 163.8, 149.9, 135.4, 132.4, 131.1, 130.2, 128.4, 127.3, 123.7, 110.2, 87.4, 69.1, 60.2, 46.8, 45.9, 44.3, 42.4, 14.3; IR ($CHCl_3$) 2950, 2860, 1700, 1520, 1370, 1340, 1270, 1200, 1010; HRMS calcd for $C_{19}H_{19}NO_5K$: 380.0901, found 380.0906.

Reduction of 28a and 28b. DIBAl (1.0 M in CH_2Cl_2, 56.0 mL, 56.0 mmol, 2.51 eq) was added dropwise from an addition funnel to a solution of a 3:2 mixture of α,β-unsaturated ester **26a** and **26b** (7.61 g, 22.3 mmol, 1.00 eq) in 200 mL of CH_2Cl_2 at –78 °C. The reaction mixture was stirred at –78 °C until TLC (hexane/EtOAc 1:1) indicated absence of the starting esters. EtOAc was added to quench any residual DIBAl and the resulting solution was warmed to 0 °C. It was poured into ice-cold 1N HCl solution with stirring. The mixture was stirred in Erlenmeyer flask until two clear heterogeneous phases emerged, and these were then partitioned in a separatory funnel. The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), concentrated and the residue was purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to yield 5.88 g of a 3:2 mixture of allylic alcohols **29a** and **29b** (88%).

Data for *E*-isomeric alcohol **29b** (corresponding to ester **28b**): ^{1}H NMR (400 MHz, $CDCl_3$) 7.81 (dd, *J* = 8.1, 1.3, 1H), 7.78 (dd, *J* = 8.0, 1.3, 1H), 7.48 (dt, *J* = 8.2, 1.4, 1H), 7.33 (dt, *J* = 8.2, 1.4, 1H), 6.17 (m, 1H), 6.02 (m, 1H), 5.49 (t, *J* = 7.0, 1H), 5.20 (t, *J* = 7.0, 1H), 4.78 (m, 1H), 4.66 (t, *J* = 6.3, 1H), 4.29 (m, 3H), 3.55 (m, 1H), 3.11 (m, 1H), 2.97 (t, *J* = 6.7, 1H), 1.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 149.5, 147.7, 137.0, 133.2, 131.7, 129.9, 129.3, 127.3, 124.1, 117.1, 88.4, 69.5, 59.3, 47.5, 44.9, 43.4,

43.1; IR ($CHCl_3$) 3360 (br), 2950, 2860, 1520, 1340, 1005, 950, 735; HRMS calcd for $C_{17}H_{18}NO_4$: 300.1236, found 300.1227.

Data for *Z*-isomeric alcohol **29a** (corresponding to ester **28a**): ^{1}H NMR (400 MHz, $CDCl_3$) 7.78 (d, J = 7.9, 1H), 7.72 (d, J = 8.0, 1H), 7.47 (t, J = 7.8, 1H), 7.32 (t, J = 7.9, 1H), 6.10 (m, 2H), 5.50 (t, J = 6.9, 1H), 5.20 (t, J = 6.7, 1H), 4.84 (br s, 1H), 4.65 (t, J = 6.2, 1H), 4.36 (m, 1H), 4.13 (m, 2H), 3.34 (t, J = 7.0, 1H), 3.14 (m, 2H), 1.70 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 149.6, 148.2, 136.7, 133.0, 131.6, 130.1, 128.9, 127.2, 123.9, 116.6, 87.2, 69.3, 59.6, 50.8, 48.3, 44.5, 36.9; IR ($CHCl_3$) 3360 (br), 2950, 2860, 1515, 1340, 1005, 950, 735; HRMS calcd for $C_{17}H_{18}NO_4$: 300.1236, found 300.1241.

Johnson-Claisen Rearrangement of 29a and 29b. A mixture of allylic alcohols **29a** and **29b** (5.88g, 19.7 mmol, 1.00 eq) was azeotroped with benzene twice, and 150 mL of toluene (anhydrous) was syringed in under Argon. Triethyl orthoacetate (25.0 mL, 136 mmol, 6.94 eq) was added in one portion followed by the addition of propionic acid (100 μL, 1.34 mmol, 6.8 mol %). A reflux condenser was quickly attached and the reaction was set to reflux overnight. The reaction mixture was cooled to 25 °C and concentrated. The brown oily residue was purified by flash chromatography on silica gel (hexane/EtOAc 3:1) to afford 4.68 g of homoallylic ester **31** (64%) as an pale yellow oil and recovered starting allylic alcohols **29a** and **29b** (490 mg).

Data for ester **31**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.79 (dd, J = 8.1, 1.3, 1H), 7.75 (dd, J = 8.1, 1.3, 1H), 7.47 (dt, J = 8.1, 1.4, 1H), 7.34 (t, J = 7.9, 1.3, 1H), 6.24 (m, 2H), 6.05 (m, 1H), 5.31 (m, 3H), 4.67 (m, 2H), 4.34 (dd, J = 5.9, 5.5, 1H), 4.14 (m, 2H), 3.44 (dd, J = 6.7, 3.5, 1H), 3.02 (t, J = 6.8, 1H), 2.62 (m, 1H), 2.26 (AB d, J = 14.3, 1H), 2.08 (AB d, J = 14.3, 1H), 1.28 (t, J = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 170.6, 149.6, 138.3, 137.5, 133.5, 131.3, 128.7, 128.6, 127.0, 123.9, 116.7, 90.3, 69.0, 60.3, 56.6, 50.0, 43.5, 42.3, 42.1, 40.4, 14.2; IR ($CHCl_3$) 2950, 2860, 1720, 1515, 1340, 1160, 1010, 940, 730; HRMS calcd for $C_{21}H_{24}NO_5$: 370.1655, found 370.1652.

Hydrolysis of Ester 31. A mixture of ester **31** (4.68 g, 12.7 mmol, 1.00 eq), 50 mL of THF, 50 mL of 3N NaOH and 20 mL of was stirred at 25 °C for 2 h. Volatile organic solvents were removed under vacuum. The aqueous residue was partitioned with Et_2O, which washed with 1N NaOH. The combined aqueous basic layers were chilled in an ice bath and acidified with dropwise addition of 4N HCl until pH indicator registered an acidic solution at which point, white precipitates fell out of the aqueous medium. The precipitates were extracted into CH_2Cl_2, the combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 95:5) to afford 3.73 g of carboxylic acid **46** (86%) as pale yellow solid: mp 198-199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.76 (d, J = 8.1, 1H), 7.70 (d, J = 8.1, 1H), 7.44 (t, J = 7.8, 1H), 7.30 (t, J = 7.9, 1H), 6.22 (m, 2H), 6.03 (d, J = 9.8, 1H), 5.29 (m, 3H), 4.64 (m, 2H), 4.31 (m, 1H), 3.40 (dd, J = 5.7, 3.6, 1H), 3.02 (t, J = 6.9, 1H), 2.58 (br s, 1H), 2.27 (AB d, J = 14.7, 1H), 2.09 (AB d, J = 14.8, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 176.3, 149.5, 138.2, 137.4, 133.5, 131.4, 128.9, 128.5, 127.1, 124.0, 117.2, 90.2, 69.0, 56.3, 50.2, 43.4, 42.3, 41.8, 40.1; IR ($CHCl_3$) 3450, 2950, 2860, 1700, 1520, 1340; HRMS calcd $C_{19}H_{20}NO_5$: 342.1342, found 342.1349.

Curtius Rearrangement of Acid 46. Diphenyl phosphoryl azide (2.60 mL, 12.0 mmol, 1.00 eq) was added to a solution of carboxylic acid **46** (3.73 g, 10.9 mmol, 1.00 eq) and Et_3N (1.80 mL, 12.9 mmol, 1.18 eq) in 100 mL of benzene. The mixture was stirred at 25 °C for 30 min, and then refluxed for 1.5 h. It was then cooled to 25 °C and 20 mL of methanol (anhydrous) was added. The resulting solution was set to reflux for overnight, cooled to 25 °C and poured into 5% citric acid solution, which was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), concentrated and the oily residue was purified by flash chromatography on silica gel (hexane/EtOAc 7:3) to afford 3.624 g of methylcarbamate **47** (89%) as yellow solids: mp 142-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.77 (dd, J = 8.2, 1.3, 1H), 7.71 (dd, J = 8.0, 1.2, 1H), 7.45 (dt, J = 8.1, 1.8, 1H), 7.30 (t, J = 8.1, 1H), 6.09 (m, 3H), 5.35 (m, 2H), 5.25 (d, J = 17.8, 1H), 4.77 (br s, NH, 1H), 4.60 (m, 2H), 4.27 (m, 1H), 3.65 (s, 3H), 3.56 (dd, J = 6.8, 3.7, 1H), 3.14 (dd, J = 13.9, 9.2, 1H), 2.68 (m, 2H), 2.46 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 157.1, 149.4, 137.8, 137.5, 133.4, 131.4, 128.8, 128.1, 127.0, 123.9, 118.0, 90.1, 68.9, 59.1, 52.1, 48.2, 44.8, 43.4, 42.3, 38.1; IR (in $CHCl_3$) 3431, 3332, 2950, 2881, 1715, 1519, 1347, 1244, 1008, 974, 915, 733; HRMS calcd for $C_{20}H_{23}N_2O_5$: 371.1607, found 371.1597.

Formation of Pyrrolidine 48. Methyl carbamate **46** (1.40 g, 3.78 mmol, 1.00 eq) was azeotroped with benzene twice and placed under high vacuum for 2 h. Boron trifluoride etherate (0.50 mL, 3.78 mmol) was added to a solution of methyl carbamate **46** in 190 mL of CH_2Cl_2 at –78 °C. The resulting solution was warmed up to 0 °C and kept in the 12 °C refrigerator overnight. The reaction mixture was poured into saturated $NaHCO_3$ aqueous solution, which was extracted with CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$) and concentrated. The oily residue was purified by flash chromatography on silica gel (hexane/EtOAc 2:3) to afford 0.90 g of hydroxymethyl **48** (64%) as foamy solid: ^{1}H NMR (400 MHz, $CDCl_3$) (This contains rotamers) 7.93 (d, J = 8.1, 1H), 7.60 (t, J = 5.1, 1H), 7.46 (m, 2H), 6.13 (m, 2H), 5.79 (m, 1H), 5.34 (d, J = 11.7, 1H), 5.32 (d, J = 16.1, 1H), 4.66 (br s, 1H), 3.77 (m, 3H), 3.66 & 3.64 (s, major & minor rotamer, 3H), 3.60 & 3.49 (minor rotamer: d, J = 10.6, major rotamer: d, J = 10.5, 1H), 3.25 (d, J = 10.5, 1H), 2.66 (m, 1H), 2.49 (m, 1H), 2.29 (t, J = 7.7, 1H), 1.70 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (This contains rotamers) 154.34, 154.27, 149.7, 135.9, 135.8, 134.9, 133.0, 132.8, 130.6, 130.5, 129.6, 129.5, 127.9, 126.9, 125.6, 125.5, 117.9, 117.8, 61.7, 61.6, 61.4, 55.3, 55.0, 54.6, 54.3, 52.5, 52.3, 52.1, 49.9, 42.8, 39.04, 38.95; IR ($CHCl_3$) 3424 (br), 2952, 2877, 1684, 1523, 1457, 1391, 1349, 1132, 1033, 849, 731; HRMS calcd for $C_{20}H_{23}N_2O_5$: 371.1607, found 371.1596.

Preparation of Pivaloate 49. Et_3N (1.8 mL, 13 mmol, 3.2 eq) was added to a solution of hydroxymethyl **48** (1.500 g, 4.050 mmol, 1.00) in 20 mL of CH_2Cl_2 was cooled to 0 °C. The resulting solution was stirred for 10 min, and this was followed by the dropwise addition of 2,2,2-trimethylacetyl chloride (0.80 mL, 8.3 mmol, 2.05 eq). The reaction mixture was slowly warmed to 25 °C and stirred until TLC (hexane/EtOAc 1:1) indicated completion of the reaction 3.5 h later. The mixture was poured into saturated $NaHCO_3$ aqueous solution, which was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), concentrated, and the brown oily residue was purified by flash chromatography on silica gel (hexane/EtOAc 3:1) to yield 1.70 g of

pivaloate **49** (92%) as pale yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) (This contains rotamers) 7.90 (d, J = 7.2, 1H), 7.58 (t, J = 7.5, 1H), 7.44 (m, 2H), 6.13 (dd, J = 16.9, 10.7, 1H), 5.98 (m, 1H), 5.79 (m, 1H), 5.31 (d, J = 12.4, 1H), 5.30 (d, J = 16.1, 1H), 4.63 (br s, 1H), 4.16 (m, 2H), 3.62, 3.73 (s, minor rotamer, major rotamer hidden under δ 3.6, 1H), 3.59 (s, two rotamers, 3H), 3.50 (major rotamer: d, J = 10.7 & minor rotamer: d, J = 10.4, 1H), 3.22 (t, J = 10.3, 1H), 2.60 (t, J = 7.3, 1H), 2.40 (m, 2H), 1.18 & 1.14 (minor & major rotamer: s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (This contains rotamers) 178.3, 178.2, 154.1, 153.8, 149.7, 149.6, 135.7, 135.5, 134.8, 134.6, 133.2, 133.1, 130.4, 130.3, 129.6, 127.9, 127.4, 125.6, 125.4, 117.9, 117.8, 63.0, 62.9, 91.7, 61.3, 55.1, 54.6, 54.4, 54.2, 52.4, 52.2, 50.93, 50.87, 42.9, 42.8, 39.1, 38.9, 38.7, 27.1, 27.0; IR ($CHCl_3$) 3075, 2971, 2877, 1726, 1693, 1523, 1452, 1391, 1353, 1283, 1156, 1108, 920, 849, 731; HRMS calcd for $C_{25}H_{31}N_2O_6$: 455.2182, found 455.2188.

Reduction of Nitrobenzene 49 and *N*-Cbz Protection. HOAc (8.6 mL) was added to a suspension of nitrobenzene **49** (4.0 g, 8.8 mmol) and Zinc dust (40 g) in 135 mL of THF. The resulting mixture was stirred at 25 °C for 1 h and filtered on celite. The solid was washed with EtOAc and the combined filtrates were washed with saturated $NaHCO_3$ aqueous solution, brine, and dried ($MgSO_4$). Removal of the solvent afforded the crude aniline, which was dissolved in 90 mL of CH_2Cl_2. Saturated $NaHCO_3$ aqueous solution (90 mL) and CbzCl (2.25 mL, 2.25 eq.) were added and the resulting two-phase mixture was stirred at 25 °C for overnight. The organic phase was separated and the water layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel (hexane/ EtOAc 3:1) to give 4.7 g of the product (**55**, 96%): ^{1}H NMR (500 MHz, this contains rotamers) 7.5-7.1 (m, 5), 6.60 (s, 0.6 × 1, NH), 6.52 (s, 0.4 × 1, NH), 6.06 (dd, 1, J = 17.6, 11.0), 5.93-5.87 (m, 1), 5.77-5.74 (m, 1), 5.22-5.11 (m, 4), 4.27 (dd, 0.4 × 1, J = 10.1, 10.0), 4.20-4.11 (m, 1.6 × 1), 4.02-3.97 (m, 1), 3.71 (s, 0.4 × 1), 3.62 (s, 0.6 × 1), 3.58 (s, 0.4 × 3), 3.52 (s, 0.6 × 3), 3.47 (d, 0.6 × 1, J = 10.5), 3.44 (d, 0.4 × 1, J = 10.5), 3.20 (d, 0.6 × 1, J = 10.5), 3.18 (d, 0.4 × 1, J = 10.5), 2.52 (dd, 1, J = 8.0, 7.1), 2.41-2.27 (m, 2), 1.14 (s, 0.4 × 9), 1.12 (s, 0.6 × 9); ^{13}C NMR (100 MHz, this contains rotamers) 178.1, 154.4, 154.1, 153.8, 136.1, 136.0, 135.3, 135.1, 135.0, 134.9, 129.6, 129.3, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.6, 126.7, 126.3, 117.4, 117.2, 67.1, 63.1, 62.9, 61.8, 61.3, 60.3, 54.5, 54.1, 53.9, 52.7, 52.4, 52.2, 51.0, 50.8, 43.1, 42.9, 38.8, 38.6, 27.03, 26.99; IR ($CDCl_3$) 3296, 1726, 1704, 1693; HRMS calcd for $C_{33}H_{38}N_2O_6Na$ (MNa^+) 581.2628, found 581.2628.

Preparation of 54--Bromination and Hydroxylation. A solution of *N*-Cbz aniline **55** (1.625 g, 2.91 mmol) in 12 mL of dry CH_2Cl_2 and 17 mL of dry CCl_4 was added *N*-bromosuccinimide (518 mg, 2.91 mmol) and AIBN (48 mg, 0.29 mmol). The reaction mixture was subjected to sunlamp irradiation (300 watts light bulb) with the lamp distance adjusted as to be 55-60 °C as read on the thermometer near the reaction flask for 15 min. The resulting mixture was cooled to room temperature and taken up into ether, which was washed with saturated $NaHCO_3$ aqueous solution, brine and dried ($MgSO_4$). Removal of the solvent afforded the crude allyl bromide (**56**), which was not stable on silica gel. The NMR spectroscopic data were obtained from the crude sample of allyl bromide **56**.

A suspension of crude allyl bromide **56**, 15 mL of water and 15 mL of CF_3CH_2OH was treated with Ag_2O (338 mg, 1.46 mmol) in the dark for 15 min. The resulting mixture was filtered on a pad of celite and the precipitate was washed with EtOAc. The combined filtrates were washed with brine and dried ($NaSO_4$). Removal of the solvent following purification of the residue by flash chromatography on silica gel afforded 1.065 g (64.8%) of allyl alcohol **54**: ^{1}H NMR (400 MHz, $CDCl_3$) (This contains rotamers) 7.92 (m, 1H), 7.62 (m, 1H), 7.50 (m, 1H), 7.31 (m, 1H), 6.55 & 6.47 (minor rotamer: dd, J = 18.1, 11.0 & major rotamer: dd, J = 17.8, 11.3, 1H), 5.97 (br s, 1H), 5.44 & 5.42 (minor rotamer: d, J = 11.0 & major rotamer: d, J = 11.1, 1H), 5.29 & 5.27 (minor rotamer: d, J = 18.0 & major rotamer: d, J = 17.9, 1H), 4.39 (m, 2H), 4.09 (m, 2H), 3.67 & 3.66 (major & minor rotamer: s, 3H), 3.47 (m, 1H), 3.37 (d, J = 10.6, 1H), 2.68 (d, J = 8.0, 1H), 2.51 (m, 2H), 2.26 (d, J = 9.7, 1H), 1.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (This contains rotamers, missing carbamate carbonyl signal around δ 154) 178.2, 148.1, 136.3, 136.0, 133.1, 130.9, 130.1, 128.8, 124.5, 118.7, 67.2, 62.3, 61.4, 54.0, 52.9, 52.6, 52.4, 51.5, 49.4, 45.7, 38.8, 29.7, 27.2; IR ($CHCl_3$) 3440, 2970, 2930, 2880, 1700, 1530, 1470, 1400, 1350, 1290, 1160; HRMS calcd for $C_{25}H_{31}N_2O_7$: 471.2131, found 471.2117.

Eschenmoser-Claisen Rearrangement of 54. A solution of allylic alcohol **54** (750 mg, 1.31 mmol) and *N,N*-dimethylacetamide dimethyl acetal (4.2 mL, 20 eq.) in 39 mL of anhydrous *m*-xylene was heated at reflux for 3 h. The volatiles were removed under vacuum and the residue was dissolved in 10 mL of CH_2Cl_2, which was treated with silica gel and stirred at 25 °C for 3 h. The resulting mixture was filtered and the silica gel was rinsed with 1:1 hexane/EtOAc. The combined filtrate was evaporated and the residue was purified by flash chromatography on silica gel (3:1 hexane/EtOAc) to afford **75** (199 mg, 26%) followed by lactam **74** (354 mg, 45%).

Data for lactam **74**: ^{1}H NMR (400 MHz, $CDCl_3$, this contains rotamers) 7.36 (m, 4H), 7.21 (m, 3H), 6.95 (m, 1H), 6.11 (m, 2H), 5.59 (AB d, J = 9.6, 1H), 5.47 (AB d, J = 12.2, 1H), 5.34 (m, 2H), 5.21 (d, J = 17.5, 1H), 4.31 (m, 2H), 3.61 (m, 2H), 3.60 & 3.49 (minor & major rotamer: s, 3H), 3.11 (m, 1H), 3.25 (AB d, J = 15.6, 1H), 2.74 (t, J = 7.0, 1H), 2.48 (m, 3H), 1.19 & 1.15 (minor & major rotamer: s, 9H); IR ($CHCl_3$) 3390 (br), 3080, 3020, 2950, 2840, 2260, 1775, 1720, 1700, 1600, 1480, 1450, 1380, 1270, 1210, 1160, 1040, 1000, 920, 860, 775, 740.

Data for **75**: ^{1}H NMR (500 MHz, $CDCl_3$, this contains rotamers) 9.06 (s, 0.4 × 1, NH), 9.03 (s, 0.6 × 1, NH), 8.14-8.11 (m, 1), 7.37-7.20 (m, 6), 6.96-6.86 (m, 2), 6.27-6.21 (m, 1), 6.08 (d, 1, J = 9.7), 5.41-5.35 (m, 1), 5.19-5.08 (m, 2), 4.91 (d, 1, J = 10.9), 4.84 (d, 1, J = 17.6), 4.47 (s, 0.4 × 1), 4.42 (s, 0.6 × 1), 4.15-3.97 (m, 2), 3.59 (s, 0.4 × 3), 3.53 (s, 0.6 × 3), 3.28 (d, 0.6 × 1, J = 10.9), 3.23 (d, 0.4 × 1, J = 10.9), 3.04 (s, 3), 3.04-2.99 (m, 1), 2,72 (dd, 1, J = 7.1, 7.1), 2.55 (s, 1), 2.44-2.33 (m, 1), 1.15 (m, 9); ^{13}C NMR (100 MHz, $CDCl_3$, this contains rotamers) 178.2, 154.3, 153.9, 153.6, 153.4, 137.0, 136.8, 136.5, 135.6, 135.2, 134.9, 129.2, 129.1, 129.0, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 125.5, 122.2, 122.1, 120.3, 117.5, 117.3, 81.0, 80.9, 66.7, 63.1, 60.5, 60.1, 58.3, 58.0, 57.8, 57.7, 54.6, 52.4, 52.1, 50.2, 48.7, 48.5, 42.8, 42.7, 38.7, 27.1; IR ($CDCl_3$) 3326, 1730, 1705; HRMS calcd for $C_{34}H_{40}N_2O_7Na$ (MNa^+) 611.2731, found 611.2733. The stereochemistry of C7 quaternary center of **75** was determined by 2D

NOESY experiment. The cross peak between H9 (aromatic proton) and H19 (methine proton on the terminal vinyl group) was evident for a α-face phenyl group.

Conversion of 75 to allylic alcohol 54. A mixture of **75** (124.6 mg, 0.212 mmol), $TsOH•H_2O$ (40 mg, 1 eq.), 1.0 mL of CF_3CH_2OH and 1.0 mL of H_2O was heated at 70 °C for 2 h and cooled to room temperature. The reaction mixture was taken up into EtOAc, which was washed with saturated $NaHCO_3$ aqueous solution, brine, and dried (Na_2SO_4). Removal of the solvent followed by purification of the residue by flash chromatography on silica gel (hexane/EtOAc 2:1) afforded 99.0 mg (81%) of allylic alcohol **54**.

Hydrolysis of Lactam 74. A solution of lactam **74** (15 mg, 0.025 mmol, 1.00 eq) and NaOMe (40% wt in MeOH, 50 μL) in 2 mL of anhydrous methanol was stirred at 25 °C overnight. Saturated NH_4Cl solution was added and the organic volatile solvents were concentrated. The aqueous residue was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), concentrated, and the residue was purified by flash chromatography on silica gel (EtOAc) to give 7.0 mg of hydroxymethyl lactam **76** (74%) as a white powder: ^{1}H NMR (400 MHz, $CDCl_3$, this contains rotamers) 7.95 & 7.81 (minor & major rotamer: s, 1H), 7.20 (m, 2H), 7.04 (d, J = 7.3, 1H), 6.81 (d, J = 8.7, 1H), 6.20 (dd, J = 9.5, 7.1, 1H), 6.11 (dd, J = 17.6, 10.9, 1H), 5.66 (d, J = 9.6, 1H), 5.30 (d, J = 10.9, 1H), 5.21 (d, J = 17.6, 1H), 3.89 (m, 2H), 3.55 (m, 4H), 3.36 (minor rotamer: s, major rotamer is hidden under δ 3.55, 1H), 3.09 (d, J = 10.7, 1H), 3.00 (AB d, J = 16.4, 1H), 2.78 (m, 1H), 2.46 (br s, 1H), 2.38 (AB d, J = 16.2, 1H), 2.23 (t, J = 7.8, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, this contains rotamers) 170.4, 154.2, 136.7, 136.3, 131.3, 129.4, 128.6, 128.0, 125.6, 123.5, 118.1, 116.8, 62.4, 62.1, 61.4, 54.7, 54.4, 53.5, 52.3, 43.0, 41.5, 41.2; DEPT 135: 4 CH_2; IR ($CHCl_3$) 3450 (br), 2900, 2820, 1670, 1450, 1380, 1220, 1030, 750; HRMS calcd for $C_{22}H_{25}N_2O_4$: 381.1814, found 381.1814.

Reduction of 74. DIBAl (1.48 mL, 1.0M solution in THF, 2.5 eq.) was added to a solution of lactam (353.6 mg, 0.591 mmol) in 5 mL of THF at –78 °C. EtOAc was added to quench the extra DIBAl after the reaction was complete. The reaction mixture was warmed up to 0 °C and poured onto 1N HCl aqueous solution and stirred until it was clear. The aqueous layer was extracted by CH_2Cl_2 and the combined organic layers was dried (Na_2SO_4). The solvent was removed and the residue was purified on silica gel by flash chromatography (60% of EtOAc in hexane) to give 253 mg (86%) of aminal **102**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.56-7.48 (m, 1), 7.42-7.32 (m, 5), 7.21-7.11 (m, 2), 7.04-7.01 (m, 1), 6.35 (dd, 1, J = 17.7, 10.9), 6.18-6.12 (m, 1), 5.62-5.57 (m, 1), 5.45 (d, 1, J = 10.4), 5.42 (m, 1), 5.27 (m, 1), 5.21 (d, 1, J = 10.9), 5.14 (d, 1, J = 17.7), 5.10 (br s, 0.5 × 1, OH), 5.02 (br s, 0.5 × 1, OH), 3.92-3.76 (m, 2), 3.72 (s, 0.5 × 1), 3.63 (s, 0.5 × 3), 3.58 (s, 0.5 × 1), 3.54 (d, 0.5 × 1, J = 10.7), 3.52 (s, 0.5 × 3), 3.47 (d, 0.5 × 1, J = 10.7), 3.35 (s, 1), 3.09 (d, 1, J = 10.7), 2.81-2.75 (m, 1), 2.51 (dd, 1, J = 14.4, 4.7), 2.25-2.18 (m, 1), 1.97 (br s, 0.5 × 1, OH), 1.71 (br s, 0.5 × 1, OH), 1.59-1.50 (m, 1); ^{13}C NMR (100 MHz, $CDCl_3$, this contains two rotamers) 155.4, 155.2, 154.3, 137.2, 135.9, 135.6, 135.5, 135.4, 135.2, 130.3, 130.1, 128.66, 128.63, 128.4, 128.3, 128.0, 127.9, 127.0, 125.0, 124.9, 123.95, 123.90, 116.8, 116.7, 78.22, 78.16, 68.0, 67.9, 62.3, 62.4, 61.5, 55.3, 55.1, 54.9, 54.7, 54.6, 52.19, 52.15, 51.9, 51.7, 42.2, 41.04, 40.97, 39.5, 39.4; IR (neat) 3420, 1669;

HRMS m/z calcd for $C_{27}H_{34}N_2O_6Na$: 539.2158, found 539.2153.

Dehydration of Aminal 102. A suspension of excess $TsOH•H_2O$ and aminal (253 mg, 0.500 mmol) in 25 mL of CH_2Cl_2 was heated at reflux for 30 min and cooled down to 25 °C. The reaction mixture was washed with saturated $NaHCO_3$ aqueous solution and the aqueous layer were extracted by CH_2Cl_2. The combined organic layers was dried (Na_2SO_4) and the solvent was removed. The residue was purified on silica gel by flash chromatography (60% of EtOAc in hexane) to give 83.7 mg (72%) of enamide **103**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.99 (d, 0.6 × 1, J = 8.2), 7.91 (d, 0.4 × 1, J = 7.9), 7.39-7.26 (m, 2), 7.23-7.14 (m, 1), 7.13-7.04 (m, 2), 6.87 (d, 0.4 × 1, J = 6.9), 6.85 (d, 0.6 × 1, J = 7.6), 6.07 (dd, 1, J = 10.0, 9.0), 6.02 (dd, 1, J = 18.0, 10.7), 5.70 (d, 1, J = 10.0), 5.34-5.23 (m, 3), 5.15 (d, 1, J = 10.7), 5.08 (d, 0.6 × 1, J = 18.0), 5.06 (d, 0.4 × 1, J = 18.0), 3.91-3.74 (m, 2), 3.54 (s, 0.4 × 3), 3.48 (s, 0.6 × 3), 3.45-3.38 (m, 1), 3.34-3.32 (m, 1), 3.00 (d, 1, J = 11.0), 2.70-2.66 (m, 1), 2.16-2.11 (m, 1), 2.09 (s, 0.4 × 1), 2.06 (s, 0.6 × 1); ^{13}C NMR (125 MHz, $CDCl_3$, this contains rotamers) 154.4, 154.3, 152.1, 152.0, 137.13, 137.08, 136.8, 136.7, 135.69, 135.64, 132.1, 131.9, 130.06, 129.98, 129.93, 129.73, 129.2, 128.7, 128.5, 128.4, 128.2, 126.79, 126.75, 125.5, 125.4, 125.21, 125.13, 125.05, 124.97, 122.1, 120.5, 120.4, 117.0, 116.8, 68.29, 68.21, 61.9, 61.7, 61.6, 60.5, 60.0, 54.9, 54.8, 54.5, 54.32, 54.25, 54.17, 53.4, 52.4, 52.3, 43.5, 41.6; IR (neat) 3444, 1704 (s, br); HRMS calcd for $C_{30}H_{31}N_2O_5$ (MH+) 499.2233, found 499.2242.

Dihydroxylation of 103 and Oxidative Cleavage of the Diol. OsO_4 (3.6 mL, 0.14 mmol, 0.039 M in THF) was added to a solution of enamide **103** (69.0 mg, 0.139 mmol) in THF at –78 °C. The reaction solution was kept in the –25 °C freezer for overnight and treated with saturated $NaHSO_3$ aqueous solution for 4 hr at 25 °C. The resulting mixture was extracted with EtOAc and the combined organic layers were dried. The solvent was removed and the residue was purified by flash chromatography on silica gel (hexane/EtOAc 2:3) to give 22.7 mg (33%) of starting material and 32.2 mg (44%) of the diol.

$NaIO_4$ aqueous solution (0.60 mL, 0.2 M) was added to a solution of the diol in 1.8 mL of THF and 0.60 mL of H_2O. The resulting mixture was stirred at 25 °C for 6 hr and extracted with EtOAc. The combined organic layers was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 2:3) to give 32.0 mg (99.7%) of aldehyde **104**: ^{1}H NMR (500 MHz, $CDCl_3$) 9.10 (s, 0.5 × 1), 9.04 (s, 0.5 × 1), 8.92 (s, 0.5 × 1), 8.91 (s, 0.5 × 1), 7.56 (d, 1, J = 8.2), 7.48-7.22 (m, 7), 6.96 (d, 0.5 × 1, J = 7.6), 6.89 (d, 0.5 × 1, J = 7.9), 6.38 (ddd, 1, J = 9.5, 7.2, 3.8), 5.88 (dd, 1, J = 9.5, 1.3), 5.78 (dd, 0.5 × 1, J = 17.7, 12.0), 5.76 (dd, 0.5 × 1, J = 17.7, 12.0), 5.38 (d, 0.5 × 1, J = 12.0), 5.32 (d, 0.5 × 1, J = 12.0), 5.09-4.99 (m, 2), 4.91 (d, 0.5 × 1, J = 17.7), 4.89 (d, 0.5 × 1, J = 17.7), 3.66 (s, 0.5 × 1), 3.62 (s, 0.5 × 1), 3.58 (s, 0.5 × 3), 3.54 (s, 0.5 × 3), 3.51-3.40 (m, 3), 3.13 (d, 0.5 × 1, J = 10.7), 3.08 (d, 0.5 × 1, J = 10.7), 2.85 (d, 1, J = 9.1), 2.69-2.65 (m, 1), 2.14-2.05 (m, 1); ^{13}C NMR (125 MHz, $CDCl_3$) 192.7, 192.6, 164.4, 164.0, 154.7, 154.6, 153.6, 153.3, 136.3, 136.2, 135.0, 134.4, 134.2, 134.1, 132.6, 132.5, 130.60, 130.56, 130.2, 130.1, 129.9, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 120.9, 120.8, 116.7, 116.5, 69.3, 69.1, 61.9, 61.6, 60.92, 60.87, 58.7, 55.6, 55.0, 54.3, 54.1, 53.9, 53.8, 53.4, 52.5, 52.4, 51.7, 51.1, 42.2, 42.1; IR

(neat) 3436, 1746, 1698 (s, br); HRMS calcd for $C_{36}H_{44}N_2O_7$ (MH^+) 531.2131, found 531.2146.

Silylation of Aldehyde 104. TESOTf (0.025 mL, 0.11 mmol) was added to a solution of aldehyde (38.7 mg, 0.0729 mmol) and Et_3N (0.030 mL, 0.22 mmol) in 1.4 mL of CH_2Cl_2 at 0 °C. The reaction solution was stirred at 0 °C for 30 min and poured onto saturated $NaHCO_3$ aqueous solution and ice. The resulting mixture was extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 3:1) to give 24.7 mg (52%) of silyl ether **105**: ^{1}H NMR (500 MHz, $CDCl_3$) 9.06 (s, 0.5 × 1), 9.05 (s, 0.5 × 1), 8.912 (s, 0.5 × 1), 8.907 (s, 0.5 × 1), 7.57 (d, 1, J = 7.5), 7.45-7.23 (m, 7), 6.95 (d, 0.5 × 1, J = 7.5), 6.86 (d, 0.5 × 1, J = 7.5), 6.40-6.35 (m, 1), 5.80 (d, 1, J = 10.7), 5.76 (dd, 1, J = 17.7, 11.0), 5.38 (d, 0.5 × 1, J = 12.6), 5.32 (d, 0.5 × 1, J = 12.6), 5.05-5.02 (m, 1), 4.99 (d, 1, J = 11.0), 4.894 (d, 0.5 × 1, J = 17.7), 4.890 (d, 0.5 × 1, J = 17.7), 3.58-3.43 (m, 3), 3.56 (s, 0.5 × 3), 3.52 (s, 0.5 × 3), 3.40 (dd, 0.5 × 1, J = 9.8, 7.3), 3.33 (dd, 0.5 × 1, J = 9.8, 7.3), 3.11 (d, 0.5 × 1, J = 10.7), 3.06 (d, 0.5 × 1, J = 10.7), 2.82 (s, 1), 2.66-2.61 (m, 1), 2.17-2.13 (m, 0.5 × 1), 2.08-2.04 (m, 0.5 × 1), 0.90-0.83 (m, 9), 0.51-0.42 (m, 6); ^{13}C NMR (125 MHz, $CDCl_3$) 192.6, 192.5, 164.6, 164.1, 154.9, 154.2, 153.6, 153.2, 137.1, 136.9, 136.7, 136.5, 135.2, 134.7, 134.6, 134.43, 134.39, 132.6, 132.5, 130.62, 130.57, 129.7, 129.6, 128.8, 128.64, 128.60, 128.5, 128.2, 120.0, 119.7, 116.4, 116.1, 69.2, 69.0, 62.3, 61.5, 60.9, 60.6, 60.4, 58.6, 55.4, 54.9, 54.3, 54.2, 53.9, 52.2, 51.4, 50.8, 42.3, 6.8, 6.7, 4.4; IR (neat) 1747, 1714, 1704, 1690; HRMS calcd for $C_{36}H_{44}N_2O_7NaSi$ (MNa^+) 667.2816, found 667.2830.

Formation of Oxindole 106. A mixture of aldehyde **105** (37.6 mg, 0.0583 mmol) and K_2CO_3 (16 mg) and 0.6 mL of MeOH was stirred at 25 °C for 10 min and taken up into CH_2Cl_2, which was washed with saturated $NaHCO_3$ aqueous solution, brine, and dried (Na_2SO_4). The solvent was removed and the resulting aminal (34.4 mg, 95%) was azeotroped with toluene and pulled under high vaccum for 4 hr.

A mixture of TPAP (10 mg, 0.5 eq), NMO (12.9 mg, 2 eq.), the aminal and 1 mL of dry CH_2Cl_2 containing 4 Å molecular sieves was stirred at 25 °C for 12 h and passed a plug of silica gel. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (hexane/EtOAc 3:1) to give 27.8 mg (78%) of oxindole **106**: ^{1}H NMR (500 MHz, $CDCl_3$, this contains rotamors) 7.85 (d, 0.6 × 1, J = 8.5), 7.81 (d, 0.4 × 1, J = 8.0), 7.42 (d, 2, J = 7.6), 7.34-7.20 (m, 5), 7.13-7.03 (m, 1), 6.57-6.50 (m, 1), 6.13 (dd, 0.4 × 1, J = 8.2, 8.2), 6.08 (dd, 0.6 × 1, J = 8.2, 8.2), 5.53-5.47 (m, 1), 5.39 (d, 1, J = 12.6), 5.33 (d, 1, J = 12.6), 5.15 (d, 1, J = 11.0), 4.98 (d, 0.6 × 1, J = 17.5), 4.97 (d, 0.4 × 1, J = 17.5), 4.33 (s, 0.6 × 1), 4.26 (s, 0.4 × 1), 4.00-3.92 (m, 1.4), 3.79 (dd, 0.6 × 1, J = 11.9, 9.2), 3.61-3.49 (m, 1), 3.55 (s, 0.4 × 3), 3.53 (s, 0.6 × 3), 3.14 (d, 0.6 × 1, J = 11.2), 3.14 (d, 0.4 × 1, J = 11.2), 2.75 (dd, 0.4 × 1, J = 8.2, 7.2), 2.68 (dd, 0.6 × 1, J = 8.2, 7.2), 2.39-2.34 (m, 0.4 × 1), 2.33-2.28 (m, 0.6 × 1), 2.12 (s, 0.6 × 1), 2.09 (s, 0.4 × 1), 0.94-0.89 (m, 9), 0.59-0.53 (m, 6); ^{13}C NMR (125 MHz, $CDCl_3$, this contains rotamers) 174.71, 174.65, 155.09, 155.05, 154.1, 153.74, 153.70, 150.8, 150.7, 139.1, 138.3, 138.0, 134.9, 134.5, 134.1, 133.8, 129.20, 129.03, 128.98, 128.6, 128.5, 128.3, 125.5, 125.3, 125.1, 125.0, 124.8, 124.7, 115.3, 114.5, 114.3, 96.1, 68.7, 61.9, 61.7, 55.1, 54.8, 54.0,

53.8, 53.73, 53.68, 53.5, 52.3, 42.7, 42.5, 6.82, 6.78, 4.6, 4.5; IR (neat) 1775, 1732, 1704; HRMS calcd $C_{35}H_{42}N_2O_6NaSi$ (MNa^+) 637.2710, found 637.2688.

Desilylation of 106 with HF•Py. A solution of silyl ether **106** (15.4 mg, 0.025 mmol) in THF (1 mL) was added 0.05 mL of HF•Py and stirred at 0 °C for 30 min. The reaction was quenched with 0.5 mL of methoxytrimethylsilane and stirred at 25 °C for 30 min. The volatiles were removed and the residue was purified by flash chromatography on silica gel (hexane/EtOAc 1:2) to give 12.5 mg (100%) of free alcohol **107**: ^{1}H NMR (500 MHz, $CDCl_3$, this contains rotamers) 7.86 (d, 0.5 × 1, J = 8.3), 7.81 (d, 0.5 × 1, J = 8.0), 7.42 (d, 2, J = 8.6), 7.33-7.09 (m, 6), 6.53 (dd, 1, J = 17.7, 11.0), 6.15 (dd, 1, J = 8.9, 7.5), 5.47 (d, 1, J = 8.9), 5.39 (d, 1, J = 12.4), 5.34 (d, 1, J = 12.4), 5.16 (d, 1, J = 11.0), 4.99 (d, 0.5 × 1, J = 17.7), 4.97 (d, 0.5 × 1, J = 17.7), 4.31 (s, 0.5 × 1), 4.24 (s, 0.5 × 1), 4.03—3.98 (m, 1), 3.94 (dd, 1, J = 9.5, 9.2), 3.63-3.54 (m, 1), 3.57 (s, 3), 3.16-3.12 (m, 1), 2.79-2.74 (m, 1), 2.37-2.32 (m, 1), 2.17-2.14 (m, 1); ^{13}C NMR (125 MHz, $CDCl_3$, this contains rotamers) 174.7, 174.5, 154.2, 154.1, 150.7, 139.1, 138.9, 137.9, 137.7, 134.9, 133.6, 129.1, 128.9, 128.6, 128.5, 128.3, 125.7, 125.1, 125.0. 124.9, 115.4, 115.3, 114.7, 114.5, 68.7, 62.03, 61.95, 61.91, 61.7, 55.2, 54.7, 54.1, 54.0, 53.9, 53.8, 53.7, 53.5, 52.6, 52.4, 42.5; IR (neat) 3444, 1770, 1732, 1696.

Oxymercuration of 107. A 0.046 M solution of $Hg(OTf)_2$ *N,N*-dimethylaniline complex in CH_3NO_2 was prepared as reported in literature. A solution of oxindole **107** (12.5 mg, 0.025 mmol) and $Hg(OTf)_2$ *N,N*-dimethylaniline complex (1.5 mL) in 2.5 mL of CH_3NO_2 was stirred at 25 °C for 1 h and brine (3 mL) was added . The resulting mixture was stirred at 25 °C for 2 h and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to give 17.0 mg (92%) of product **108**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.86-7.80 (m, 1), 7.50 (d, 3, J = 7.4), 7.39 (dd, 2, J = 7.8, 7.5), 7.31-7.28 (m, 2), 7.19-7.16 (m, 1), 6.22 (dd, 1, J = 18.0, 11.0), 5.46 (d, 1, J = 11.0), 5.45 (d, 1, J = 12.6), 5.35 (d, 1, J = 12.6), 5.19 (d, 0.4 × 1, J = 18.0), 5.18 (d, 0.6 × 1, J = 18.0), 4.55 (s, 0.6 × 1), 4.42 (s, 0.4 × 1), 4.11 (d, 1, J = 11.0), 4.02-3.97 (m, 1), 3.97 (s, 1), 3.58 (s, 0.4 × 3), 3.55 (s, 0.6 × 3), 3.33 (d, 0.4 × 1, J = 11.0), 3.29 (d, 0.6 × 1, J = 11.0), 3.06-3.01 (m, 2), 2.75-2.72 (m, 1), 2.50-2.42 (m, 1), 1.92 (s, 1); ^{13}C NMR (100 MHz, $CDCl_3$) 176.9, 154.0, 150.2, 139.8, 139.7, 138.1, 138.0, 134.6, 129.0, 128.8, 128.6, 128.5, 128.3, 127.8, 125.0, 124.8, 118.2, 118.0, 114.5, 114.4, 72.6, 69.0, 64.0, 63.8, 59.8, 57.7, 57.4, 53.9, 52.6, 52.4, 51.8, 51.4, 51.1, 47.3, 47.2, 42.4, 38.0; IR ($CDCl_3$) 1782, 1738, 1698; HRMS calcd for $C_{29}H_{27}N_2O_6ClHgNa$: 759.1161, found 759.1162.

Reductive Demercuration of 108. A mixture of mercuric compound **108** (12.3 mg, 0.0167 mmol), 0.1 mL of CH_2Cl_2 and 0.1 mL of EtOH was added $NaBH_4$ solution (0.013 mL, 47.5 mg of $NaBH_4$ in 1 mL of 10% NaOH aqueous solution) and stirred at 25 °C for 30 min. The black mercury precipitate was filtered on a pad of celite and the filtrate was partitioned between brine and CH_2Cl_2. The organic layer was dried and concentrated to give a mixture of *N*-Cbz oxindole **109** and the debenzylated compound (**83**). The mixture of two compounds were dissolved in 0.5 mL of THF, which was added 0.05 mL of 10% NaOH aqueous solution and the resulting mixture was stirred at

25 °C for 1 h. The reaction mixture was taken into saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with EtOAc and the combined organic layers were dried and concentrated. The residue was purified by flash chromatography on silica gel to give 4.1 mg (67%) of product **83**: ^{1}H NMR 7.90 (br s, 0.4 × 1, NH), 7.88 (br s, 0.6 × 1, NH), 7.41 (d, 0.6 × 1, *J* = 8), 7.39 (d, 0.4 × 1, *J* = 8), 7.16 (dd, 0.6 × 1, *J* = 8, 8), 7.01 (dd, 0.4 × 1, *J* = 8, 8), 6.96 (dd, 0.6 × 1, *J* = 8, 8), 6.77 (d, 0.6 × 1, *J* = 8), 6.73 (d, 0.4 × 1, *J* = 8), 6.24 (dd, 0.4 × 1, *J* = 17.7, 11.0), 6.23 (dd, 0.6 × 1, *J* = 17.7, 11.0), 5.11 (d, 1, *J* = 11.0), 4.98 (d, 0.4 × 1, *J* = 17.7), 4.96 (d, 0.6 × 1, *J* = 17.7), 4.57 (s, 0.6 × 1), 4.44 (s, 0.4 × 1), 4.00-3.91 (m, 2), 3.76 (s, 1), 3.60 (s, 0.4 × 3), 3.57 (s, 0.6 × 3), 3.36 (d, 0.4 × 1, *J* = 11.1), 3.30 (d, 0.6 × 1, *J* = 11.1), 3.00 (d, 0.4 × 1, *J* = 11.1), 2.96 (d, 0.6 × 1, *J* = 11.1), 2.80 (br d, 1, *J* = 14.6), 2.44 (dd, 1, *J* = 7.5, 5.8), 2.30 (d, 0.6 × 1, *J* = 7.5), 2.24 (d, 0.4 × 1, *J* = 7.5), 1.99 (ddd, 1, *J* = 14.6, 5.8, 2.7), 1.86 (s, 1); ^{13}C NMR 178.4, 178.3, 154.2, 154.1, 140.2, 139.9, 137.1, 137.0, 131.1, 131.0, 129.6, 128.5, 128.3, 122.4, 122.2, 120.3, 115.3, 113.7, 113.5, 109.2, 109.1, 69.2, 64.8, 64.5, 60.8, 56.6, 56.4, 54.0, 53.4, 52.8, 52.5, 52.4, 52.3, 52.0, 44.7, 44.0, 35.51, 35.45, 23.0; IR (neat) 3253, 1716, 1700, 1684; HRMS calcd for $C_{21}H_{23}N_2O_4$ (MH^+) 367.1658, found 367.1649.

When demercuration was carried out in two-phase solvent CH_2Cl_2/H_2O (Fukuyama's procedure) with phase transfer catalyst $BnEt_3NCl$, the major product was *N*-Cbz oxindole **109**: ^{1}H NMR 7.81 (d, 0.4 × 1, *J* = 8.0), 7.77 (d, 0.6 × 1, *J* = 8.0), 7.52-7.48 (m, 1), 7.44-7.41 (m, 2), 7.35-7.23 (m, 4), 7.17-7.10 (m, 1), 6.08 (dd, 1, *J* = 17.7, 11.0), 5.39 (d, 1, *J* = 12.4), 5.34 (d, 1, *J* = 12.4), 5.15 (d, 1, *J* = 11.0), 5.01 (d, 0.4 × 1, *J* = 17.7), 4.99 (d, 0.6 × 1, *J* = 17.7), 4.52 (s, 0.6 × 1), 4.38 (s, 0.4 × 1), 3.99-3.91 (m, 2), 3.83 (br s, 1), 3.58 (s, 0.4 × 3), 3.55 (s, 0.6 × 3), 3.33 (d, 0.4 × 1, *J* = 10.9), 3.28 (d, 0.6 × 1, *J* = 10.9), 3.00 (d, 0.4 × 1, *J* = 10.9), 2.96 (d, 0.6 × 1, *J* = 10.9), 2.44 (dd, 1, *J* = 8.0, 5.7), 2.30 (d, 0.6 × 1, *J* = 8.0), 2.24 (d, 0.4 × 1, *J* = 8.0), 2.01 (ddd, 1, *J* = 14.5, 5.7, 2.6), 1.85 (s, 1); ^{13}C NMR (this contains two rotamers) 174.6, 174.5, 154.1, 154.0, 150.6, 138.4, 138.2, 136.2, 136.0, 135.0, 129.5, 129.3, 128.6, 128.5, 128.13, 128.06, 127.7, 124.6, 124.4, 114.9, 114.6, 114.5, 114.4, 69.6, 68.5, 64.6, 64.3, 60.7, 56.8, 56.6, 53.3, 52.9, 52.7, 52.5, 52.2, 44.1, 43.9, 35.5, 23.3; IR (neat) 1791, 1766, 1732, 1698; HRMS calcd for $C_{29}H_{29}N_2O_6$ (MH^+) 501.2026, found 501.2001.

Reduction of Methyl Carbamate 83 with $LiAlH_4$. $LiAlH_4$ (33 μL, 1M in THF, 4 eq.) was added dropwise to a solution of methylcarbamate **83** (3.0 mg, 0.0082 mmol) in THF (0.3 mL) at 0 °C. The resulting mixture was warmed up to 25 °C and stirred for 2h. The reaction was quenched by NH_4OH aqueous solution and filtered on the celite. The filtrate was taken in to EtOAc, which was washed with $NaHCO_3$ and brine, and dried. Removal of the solvent followed by purification of the residue by flash chromatograph on silica gel gave 2.1 mg (81%) of gelsemine (**1**): ^{1}H NMR 7.51 (br s, 1, NH), 7.36 (d, 1, *J* = 7.5), 7.13 (ddd, 1, *J* = 7.5, 7.5, 1.3), 6.94 (ddd, 1, *J* = 7.5, 7.5, 1.3), 6.72 (d, 1, *J* = 7.5), 6.18 (dd, 1, *J* = 17.7, 11.1), 5.03 (dd, 1, *J* = 11.1, 1.3), 4.88 (dd, 1, *J* = 17.7, 1.3), 4.04 (dd, 1, *J* = 11.1, 2.2), 3.84 (dd, 1, *J* = 11.1, 2.2), 3.76 (m, 1), 3.37 (s, 1), 2.76 (dd, 1, *J* = 14.2, 2.7), 2.70 (d, 1, *J* = 10.2), 2.35 (d, 1, *J* = 8.4), 2.25 (d, 1, *J* = 10.2), 2.24 (dd, 1, *J* = 8.4, 5.8), 2.18 (s, 3), 1.93 (ddd, 1, *J* = 14.2, 5.8, 2.7), 1.92 (s, 1); ^{13}C NMR 178.7, 140.0, 138.7, 132.0, 128.4, 128.0, 122.0, 112.3, 108.9, 72.2, 69.5, 66.3, 61.6, 54.08, 54.02, 50.8, 40.8, 38.3, 35.8, 22.9; IR ($CDCl_3$) 3202, 3080, 1712; HRMS calcd for $C_{20}H_{23}N_2O_2$ (MH^+) 323.1760, found 323.1766.