An Approach to the Synthesis of the Manzamine Alkaloids via the Vinylogous Amide PHotocycloAddition/Retro-Mannich Fragmentation/Mannich Closure Cascade (pharM)

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Abstract. The application of the vinylogous amide [2+2] **ph**otocyclo**a**ddition/**r**etro-Mannich fragmentation/**M**annich closure cascade (**pharM**) to the synthesis of the pentacyclic ring system of the anti-leukemic marine alkaloid manzamine A is presented. Two approaches to the synthesis of the requisite pentacycle are described: (a) the transannular photocycloaddition of an 18-membered vinylogous amide; and (b) photocycloaddition of an acyclic vinylogous amide, followed by macrolactamization of the derived **pharM** closure product to generate the pentacyclic ring system.

INTRODUCTION

The intramolecular [2+2] enone-alkene photocycloaddition represents one of the most useful methods for carbon–carbon bond formation.[1] Compared to the more frequently employed intramolecular Diels–Alder cycloaddition, the [2+2] photocycloaddition reaction is less sensitive to steric effects, and therefore provides a valuable method for the establishment of sterically hindered carbon centers. Introduction of nitrogen at the β carbon of the enone chromophore further expands the scope of this methodology by making possible the synthesis of nitrogen-containing ring systems.[2]

During the course of our studies on the application of the intramolecular dioxenone photocycloaddition reaction to the synthesis of perhydrohistrionicotoxin, we observed that fragmentation of photoadduct **2** (Scheme 1) led to the formation of a mixture of the desired azaspiroundecane ring system, **5**, and aminal **3**, the product of retro-Mannich fragmentation of the cyclobutane photoadduct, i.e., **6**.[3] This observation provided the impetus for future investigations in our laboratory on the utility of the resulting iminium moiety for subsequent carbon–carbon-bond-forming reactions.[4]

We reasoned that a suitably substituted ketoiminium intermediate, derived from the photocycloaddition/retro-Mannich fragmentation of a vinylogous amide, could undergo a final carbon–carbon-bond-forming reaction, via Mannich closure, as outlined in Scheme 2. In the event, irradiation of **7** led to the isolation of the neutral photoaddition/fragmentation product **9** (R = H) in excellent yield. Activation of the imine by methylation with trimethyloxonium tetrafluoroborate gave the ketoiminium **9** (R = Me), which on exposure to dimethylaminopyridine gave **10** in excellent overall yield.

The viability of this reaction cascade for the synthesis of perhydroindoles had therefore been established and this methodology was subsequently applied to a synthesis of mesembrine **12** from vinylogous amide photosubstrate **11** and to a formal total synthesis of vindorosine from photosubstrate **13**, which was in turn derived from L-tryptophan. The establishment of all of the stereochemical relationships shown in **14** by a single stereocenter in photosubstrate **13** is a particularly noteworthy feature of this approach. We report herein the application of this same strategy to the synthesis of the pentacyclic ring system of manzamine A.

The isolation of manzamine A, **15** (Scheme 5), was first reported in 1986 by Higa[5] and soon after in 1987 by Nakamura et al.[6] Higa isolated approximately 100 mg of the hydrochloride salt from 735 g wet wt of the sponge

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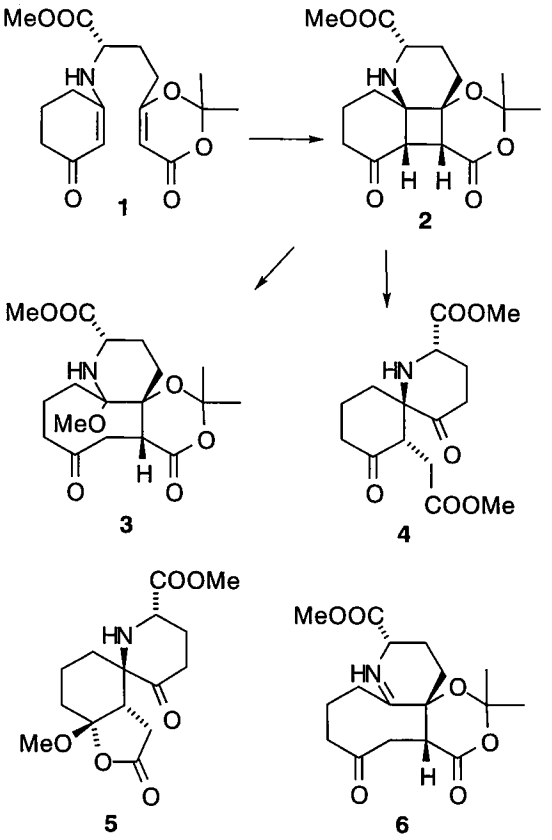
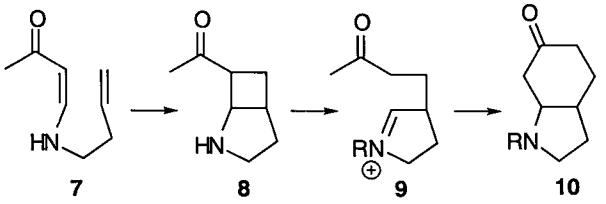
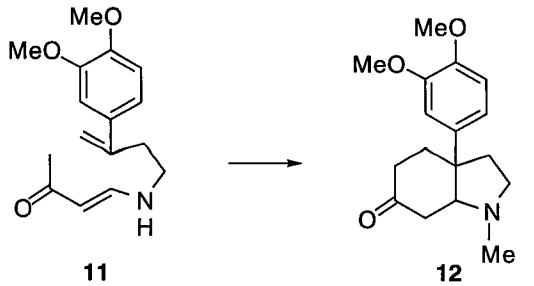


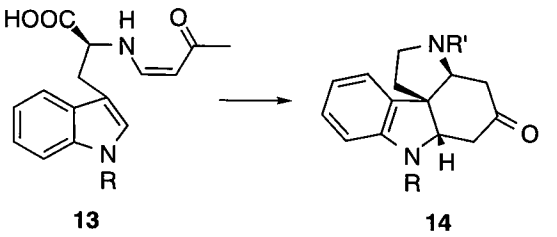
Scheme 1



Scheme 2



Scheme 3



Scheme 4

Haliclona found off the coast of Manzamo, Okinawa. This novel alkaloid was found to be active against P388 mouse leukemia cells (IC_{50} = 0.12 μM). Its structure as well as its relative and absolute stereochemistry was determined unambiguously by X-ray crystallography. The presence of the β-carboline moiety is noteworthy, as it is not commonly found in marine isolates and it is also a powerful DNA intercalator, roughly equivalent to the naphthoate moiety of neocarzinostatin.[7]

The complex structure and bioactivity of manzamine A have attracted the attention of synthetic groups worldwide. While the total synthesis has not yet been reported, several research groups have reported syntheses of the tetracyclic core of the manzamine ring system (ABDE). The synthetic efforts reported are impressive, especially with respect to the elegant development and use of the Diels–Alder cycloaddition for the assembly of the tricyclic core of the manzamine ring system.[8] The optimal synthesis of manzamine would be a convergent route which leads to the direct assembly of the ABCDE pentacyclic ring system. Such an approach is described in the following section.

EXPERIMENTAL PROCEDURES

Moisture-sensitive reactions were carried out in flame-dried glassware under an argon or nitrogen atmosphere. Ethyl ether and tetrahydrofuran were distilled from sodium/benzophenone. Benzene, toluene, methylene chloride, and acetonitrile were distilled from calcium hydride. Methanol was distilled from magnesium metal. Commercial reagents were used as received.

Thin layer chromatography was carried out using 0.25 mm E. Merck silica gel plates. The plates were visualized with UV-light or by staining with phosphomolybdic acid or ceric sulfate solution. Column chromatography was performed using 230–400 mesh (particle size 0.04–0.063 mm) silica gel supplied by E. Merck. The proportion of silica gel and the solvent flow rates are those suggested by Still (Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923).

Photolyses were carried out at low concentration. The solution was purged of oxygen by a stream of dry nitrogen maintained for at least 30 min prior to irradiation. Bubbling was maintained for the duration of the reaction. All irradiations were carried out using a 450-W Hanovia medium-pressure mercury lamp in an immersion well. Acetonitrile used in

photolyses was irradiated under a nitrogen atmosphere through a quartz filter for 4 h prior to distillation from calcium hydride. Benzene used in photolyses was irradiated through a quartz filter for 4 h, then extracted several times with concentrated sulfuric acid, washed with water, saturated aqueous sodium bicarbonate, and finally dried by filtration through silica gel, before distillation over calcium hydride.

Infrared spectra were recorded on either a Perkin-Elmer 261B infrared spectrophotometer or a Perkin-Elmer 1600 series Fourier-transform infrared spectrophotometer. Unless otherwise noted, infrared spectra were recorded neat on a sodium chloride plate. UV spectra were recorded on an IBM 9420 UV-visible spectrophotometer using acetonitrile as solvent in 1-cm quartz cells. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. NMR spectra were obtained on a Bruker AM-500 spectrometer. NMR spectra were typically recorded in $CDCl_3$ as solvent and referenced relative to tetramethylsilane (δ 0.00) or chloroform (δ 7.24) for proton and $CDCl_3$ (δ 77.0) for carbon. High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center on either a VG micromass 70/70H high-resolution double-focusing electron impact/chemical ionization spectrometer or a VG ZAB-E spectrometer. Single-crystal X-ray diffraction structure determinations were performed by Dr. Pat Caroll at the University of Pennsylvania.

Oxime 37

Sodium hydride (60% dispersion in mineral oil, 630 mg, 16 mmol) was placed in a 250-mL round-bottom flask under nitrogen and washed 3 times with 50 mL pentane to remove the mineral oil. After pentane evaporation, THF (70 mL) was added and the mixture was cooled to 0 °C. A solution of 2-carboxymethylcycloheptanone (2.24 g, 13 mmol) in THF (30 mL) was added, and the reaction stirred at room temperature until gas evolution ceased and almost all the solid had dissolved. A solution of freshly prepared 3-chloromethylpyridine (1.53 g, 12 mmol) in THF (30 mL) was added, and the solution was heated at reflux for 10 h under nitrogen, at which time TLC (2:1 petrol/ethyl acetate) showed no ketoester and only a trace of halopyridine. The reaction mixture was poured into 250 mL pH 7 phosphate buffer, and the aqueous extracted with methylene chloride. The extracts were dried over magnesium sulfate and evaporated to yield 3.22 g (94%) crude product. This crude oil was stirred in 20 mL 10% KOH until all the methyl ester had saponified (about 5 h). The mixture was then acidified with conc HCl, and heated to 90 °C until gas evolution ceased (about 2 h). After cooling to room temperature, the reaction mixture was made basic (20% KOH), extracted with methylene chloride, dried, and evaporated to yield 2.22 g (84%) of alkylated ketone, which was clean by NMR. Further purification by flash chromatography (EtOAc) on a small amount of material was performed for purposes of spectral data, but the crude oil was generally used in subsequent steps.

^{1}H NMR: 8.45 (d, 1H, J = 1.6 Hz); 8.3 (d, 1H, J = 1.7 Hz); 7.43 (dt, 1H, J = 1.9, 7.9 Hz); 7.19 (dd, 1H J = 4.9, 7.8 Hz); 3.08 (dd, 1H, J = 6.4, 13.8 Hz); 2.8–2.9 (m, 1H); 2.59 (dd, 1H, J = 7.7, 13.8 Hz); 2.4–2.5 (m, 2H); 1.2–2.0 (m, 8H).

^{13}C NMR: 214.6; 150.4; 147.6; 136.6; 135.4; 123.2; 53.1; 43.3; 34.9; 30.6; 29.0; 28.7; 23.9.

IR (cm^{-1}): 3300; 2950; 1700; 1420.

To a solution of ketone (2.22 g, 10.9 mmol) in methanol (50 mL) was added hydroxylamine hydrochloride (1.49 g, 21.4 mmol), and sodium bicarbonate (1.49 g, 56 mmol). The mixture was heated at reflux for 5 h, at which time no starting material remained by TLC (1:1:10 acetonitrile/2-propanol/chloroform), and two new product spots had appeared. The mixture was poured into 150 mL water and extracted with methylene chloride. The organic layer was dried over magnesium sulfate and evaporated. Flash chromatography yielded 1.4g (60% yield, 50% for the two steps) of the two stereoisomeric oximes as a white powder. A small quantity of the individual oximes could be obtained for spectral data, but the bulk of the material was carried through the rearrangement step as a mixture of the two oximes, **37**.

trans oxime:

^{1}H NMR: 9.08 (s, 1H); 8.4 (m, 2H); 7.41 (dt, 1H, J = 1.8, 7.8 Hz); 7.18 (m, 1H); 2.90 (dd, 1H, J = 6.3, 13.3 Hz); 2.82 (m, 1H); 2.6–2.7 (m, 2H); 2.1 (m, 1H); 1.7–1.9 (m, 4H); 1.5 (m, 1H); 1.15–1.3 (m, 3H).

^{13}C NMR: 163.9; 150.4; 147.3; 136.7; 135.6; 123.2; 45.3; 37.5; 32.4; 30.4; 26.6; 25.7; 25.2.

IR (cm^{-1}): 3400 (br); 2800; 1580 (sm); 1430; 945.

Mass spectrum *m/z* (rel. int.): 219 (M+1, 100), 201 (25), 181 (5), 124 (12), 108 (6).

HRMS calculated for $C_{13}H_{19}N_2O$ (M+1):219.1497; found: 219.1512.

cis oxime:

^{1}H NMR: 10.1 (s, 1H); 8.4 (m, 2H); 7.58 (m, 1H); 7.2 (m, 1H); 3.43 (m, 1H); 3.01 (dd, 1H, J = 3.8, 13.5 Hz); 2.6 (dd, 1H, J = 9.0, 13.5 Hz); 2.4 (m, 1H); 1.7–2.1 (m, 5H); 1.2–1.4 (m, 4H); 1.0 (m, 1H).

^{13}C NMR: 165.5; 150.3; 147.3; 136.9; 135.6; 123.2; 40.0; 35.8; 31.8; 30.6; 30.3; 29.3; 27.0.

IR (cm^{-1}): 3400 (br); 2800; 1580 (sm); 1430; 945.

Mass spectrum *m/z* (rel. int.): 219 (M+1, 100), 124 (18), 106 (80).

HRMS calculated for $C_{13}H_{19}N_2O$ (M+1):219.1497; found: 219.1518.

Lactam 38

To a 100-mL flask containing conc sulfuric acid (40 mL) was added a mixture of oximes **37** (3.98 g, 18.3 mmol) in portions. When all the solid had dissolved, the solution was heated to 110–120 °C for 20 min, then cooled to room temperature and poured onto ice. The reaction mixture was made basic at 0 °C with 50% NaOH, then extracted with methylene chloride. The organic layer was dried over magnesium sulfate and evaporated. The crude product (4.0 g) showed a mixture of 2 lactams: the desired lactam **38** and the isomeric lactam, in a ratio of 6:4, respectively. Lactam was purified by HPLC (mobile phase 1:1:5 acetonitrile/2-propanol/chloroform) to give 2.15 g lactam **38** (54%).

^{1}H NMR: 8.45 (m, 2H); 7.48 (d, 1H, J = 8.2 Hz); 7.2 (m, 1H); 5.56 (br d, 1H, J = 10.2 Hz); 3.75 (m, 1H); 2.75 (m, 2H);

2.38 (m, 1H); 2.26 (m, 1H).

^{13}C NMR: 177.6 (C=O); 150.1 (CH); 147.8 (CH); 136.4 (CH); 133.9; 123.2 (CH); 53.5 (CH); 38.9; 38.0; 33.5; 28.1; 26.0; 24.2.

IR (cm^{-1}): 3300–3400 (br); 2950; 1650.

Mass spectrum *m/z* (rel. int.): 219 (M+1, 100), 201 (12), 162 (6), 147 (6), 121 (46).

HRMS calculated for $C_{13}H_{19}N_2O$ (M+1):219.1497; found: 219.1490.

Amine 39

To a solution of lactam **38** (200 mg, 0.9 mmol) in methylene chloride (20 mL) was added trimethyloxonium tetrafluoroborate (277 mg, 1.9 mmol). The resulting mixture was stirred for 12 h at room temperature under nitrogen. The solvent was evaporated and the solid residue was utilized in the next step without purification (371 mg, 96%).

^{1}H NMR (CD_3OD): 8.8 (s, 1H); 8.7 (d, 1H); 8.45 (d, 1H); 7.98 (t, 1H); 4.4 (m, 1H); 4.38 (s, 3H); 4.15 (s, 3H), 2.94 (m, 1H); 2.65 (m, 1H).

A solution of the salt (331 mg, 0.78 mmol) in dry methanol (20 mL) was cooled in an ice bath, and sodium borohydride (139 mg, 3.68 mmol) was added in portions. On complete addition, the resulting solution was stirred at room temperature under nitrogen for 10 h. The methanol was removed under reduced pressure, and the residue was dissolved in 15 mL water. The aqueous layer was extracted with methylene chloride, and the organic extracts were dried over magnesium sulfate and evaporated to yield 149 mg (86%) crude diamine.

^{1}H NMR: 5.5 (s, 1H); 3.0 (m, 1H); 2.80 (m, 2H); 2.7 (m, 1H); 2.6 (m, 1H); 2.45 (m, 2H); 2.35 (s, 3H); 2.18 (br s, 2H); 1.98 (d, 2H, J = 7.3 Hz); 1.3–1.8 (m, 10H).

^{13}C NMR: 133.8; 121.3 (CH); 57.2; 55.2 (CH); 51.7; 47.5; 45.8 (CH_3); 43.7; 34.2; 29.6; 27.8; 26.0; 25.0; 24.0.

Mass spectrum *m/z* (rel. int.): 223 (M+1, 38), 111 (100).

HRMS calculated for $C_{14}H_{26}N_2$ (M+1): 223.2174; found: 223.2160.

Photosubstrate 41

To a solution of the amine **39** (84 mg, 0.38 mmol) in absolute ethanol (3 mL) was added sodioformylacetone (51 mg, 0.47 mmol) and conc HBr (43 μL, 0.38 mmol). The solution was heated at reflux until no more starting material remained by GC (30 min). The solvent was removed under reduced pressure, and the solid residue was dissolved in 10 mL water and extracted with four 10-mL portions of methylene chloride. The organic extracts were dried over magnesium sulfate and evaporated to give 87 mg of a crude oil, which was purified by flash chromatography (10% methanol/methylene chloride) to give 54 mg of **41** as a light yellow oil (49%).

^{1}H NMR: 7.4 (br s, 1H); 5.4 (br s, 1H); 5.1 (d, 1H); 3.25 (m, 2H); 3.2 (dd, 2H); 2.8 (br s, 2H); 2.38 (s, 3H); 2.13 (s, 3H).

^{13}C NMR: 195.7, 156 (broad signal), 132.1, 124.1, 66.5, 57.9, 57.8, 54.1, 52.1, 51.9, 46.3, 46.2, 44.2, 42.0, 30.5, 27.0, 26.5, 26.4, 26.1, 25.2, 25.0, 24.9.

IR:2935.4 cm^{-1}, 1648.5, 1591.1.

Mass spectrum *m/z* (rel. int.): 290 (M$^+$, 21), 180 (70), 131 (22), 110 (100).

HRMS calculated for $C_{18}H_{30}N_2O$: 290.2358, found: 290.2353.

Irradiation of Photosubstrate 41

A solution of photosubstrate **41** (94 mg) in benzene (200 mL) was placed in a photoreactor with a Pyrex filter and degassed with a stream of dry nitrogen for 30 min, then irradiated under a continuous stream of nitrogen for 90 min, at which time no more starting material remained by TLC (85:14:1 chloroform/methanol/aq. ammonium hydroxide). The solvent was removed under reduced pressure to yield 94 mg of **42**.

^{1}H NMR: 5.08 (s, 1H); 4.5 (m, 1H); 3.2 (m, 1H); 2.2 (s, 3H); 2–3.1 (m, 7H); 1.6 (s, 3H); 1.2–1.6 (m, 13H).

^{13}C NMR: 151.5; 97.8; 97.6; 66.7; 59.4; 55.9; 52.1; 46.7; 42.8; 35.3; 31.9; 31.5; 29.0; 28.6; 24.0; 22.9; 19.4.

Photosubstrate 50

Sodioformylacetone (475 mg, 4.4 mmol) was added to a solution of the amine hydrochloride (1.12g, 3.5 mmol) in absolute ethanol (50 mL). Two drops of conc HBr were added, and the reaction mixture was heated at reflux under nitrogen for 4 h. The solvent was evaporated under reduced pressure and the solid residue was partitioned between 50 mL ether and 50 mL satd sodium bicarbonate. The organic layer was separated and the aqueous extracted with three 50-mL portions of ether. The combined ether extracts were washed with 25 mL brine, dried over magnesium sulfate, and evaporated to yield 1.02 g crude oil. This oil was purified by flash chromatography (5% methanol/ethyl acetate) to yield 663 mg vinylogous amide **50** and 140 mg starting amine. This amine was resubjected to the above reaction conditions to yield an additional 150 mg vinylogous amide **50** for a total of 813 mg product (66%).

^{1}H NMR (320 K): 7.56 (br s, 1H); 5.56 (br s, 1H); 5.26 (d, 1H, J = 13.1 Hz); 3.65–4.0 (m, 3H); 3.70 (s, 3H); 3.44 (br t, 2H, J = 5.1 Hz); 3.26 (br s. 2H); 2.70 (br s, 1H); 2.63 (td, 1H, J = 11.2, 4.0 Hz); 2.35 (br s, 1H); 2.27 (dd, 1H, J = 10.1, 15.4 Hz); 2.12 (s, 3H); 2.05–2.1 (m, 2H); 1.3–1.9 (m, 6H).

^{13}C NMR (320 K): 211.7; 195.7; 155.8; 152.7 (broad); 130.9 (broad); 123.5 (broad); 98.1 (broad); 52.5; 46.2 (broad); 45.7; 40.2 (broad); 39.7; 31.7 (broad); 28.5 (broad); 27 (broad); 25.9; 25.0.

IR (neat, cm^{-1}): 3500 (broad); 2900; 1705; 1665; 1605; 1560; 1450; 1370; 1250; 1200; 1115; 960.

Mass spectrum *m/z* (rel. int.): 349 (M+1, 100), 320 (10), 263 (10), 166 (50), 117 (20).

HRMS calculated for $C_{19}H_{29}N_2O_4$ (M+1): 349.2127, found: 349.2180.

Fused Pyrrole 51

Compound **50** (21 mg, 0.06 mmol) in acetonitrile (150 mL) was placed in a photoreactor with a Pyrex filter and degassed by bubbling through a stream of dry nitrogen for 30 min. The solution was then irradiated under a stream of nitrogen for 1 h, at which point no more starting material remained by TLC (5% methanol/ethyl acetate). The solvent was evaporated and the crude photoadduct was purified by flash chromatography (gradient of 1:1petrol/ethyl acetate to (2% methanol/ethyl acetate) to yield 5 mg pyrrole **51** (25%).

^{1}H NMR: 7.1 (s, 1H); 5.37 (br s, 1H); 3.92 (m, 2H); 3.84 (br

s, 2H); 3.69 (s, 3H); 3.45 (br s, 4H); 2.60 (m, 2H); 2.31 (s, 3H); 1.98 (m, 2H); 1.2–1.7 (m, 6H).

^{13}C NMR: 193.2; 135.7; 135.1; 127.4; 121.8; 118.6; 117.5; 52.3; 51.0; 46.2; 40.5; 30.9; 29.9; 29.6; 27.8; 27.6; 24.9; 24.7.

IR (cm^{-1}, neat): 2900; 1700; 1650; 1520; 1445; 1405; 1385; 1240.

Vinylogous Amide cis-Alcohol 55

The vinylogous amide **50** (470 mg, 1.35 mmol) was dissolved in THF (25 mL) under nitrogen and cooled to –78 °C. To this solution was added L-Selectride (1.0 M in THF, 1.65 mL, 1.65 mmol). The reaction was stirred for 30 min at –78 °C, then quenched by addition of 25 mL saturated aqueous ammonium chloride. The mixture was then warmed to room temperature and extracted with four 30-mL portions of ether. The combined ether extracts were washed with 25 mL brine, dried over magnesium sulfate, and evaporated to yield a yellow oil, which was purified by flash chromatography (5% methanol/ethyl acetate) to give 320 mg alcohol **55** plus 44 mg recovered starting material (68%yield, 75% based on recovered starting material).

^{1}H NMR: 7.82 (br s, 1H); 5.60 (br s, 1H); 5.13 (d, 1H); 3.7–3.9 (m, 4H); 3.57 (s, 3H); 3.55 (m, 1H); 3.45 (br s, 2H); 2.95 (m, 1H); 2.62 (m, 1H); 2.59 (dd, 1H, J = 4.4, 14.4 Hz); 2.10 (s, 3H); 2.08–2.1 (br s, 2H); 1.5–1.8 (m, 7H); 1.38 (m, 1H).

^{13}C NMR (320 K): 195.5; 155.9; 151.5; 131.7; 123.1; 72.4; 62.8; 52.4; 50.3; 45.8; 40.3; 36.3; 33.4; 27.3; 24.9; 21.9.

IR (cm^{-1}, neat): 3450 (broad), 2900, 2800, 1705, 1595, 1550, 1450, 1250.

Mass spectrum *m/z* (rel. int.): 351 (M+1, 100), 196 (38), 154 (13).

HRMS calculated for $C_{19}H_{31}N_2O_4$ (M+1):351.2284, found: 351.2265.

Ketoalcohols 58 and 59

Compound **55** (539 mg, 1.5 mmol) in acetonitrile (200 mL) was placed in a photoreactor with a Pyrex filter and degassed by bubbling through a stream of dry nitrogen for 30 min at 0 °C. The solution was then irradiated under a stream of nitrogen at 0 °C for 12 h, at which point no more starting material remained by TLC (5% methanol/ethyl acetate). The solvent was then evaporated and the crude oil was dissolved in 20 mL acetonitrile and treated with triethylamine hydrochloride (223 mg, 1.6 mmol), and the resulting solution was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure and the crude solid was placed on a vacuum pump for 2 h to remove any free triethylamine, then redissolved in 20 mL of acetonitrile and treated with dimethylaminopyridine (220 mg, 1.8 mmol). The resulting solution was heated at reflux for 8 h, then stirred at room temperature for an additional 10 h. The solvent was evaporated and the crude solid was partitioned between 50 mL ether and 50 mL 5% aqueous potassium carbonate solution. The ether was separated and the aqueous was extracted with three 50-mL portions of ether. The combined ether extracts were washed with 25 mL brine, dried over magnesium sulfate, and evaporated to yield a crude oil, which was purified by flash chromatography (3% ethanol/ether) to yield 156 mg compound **58** and 67 mg compound **59** (41% yield, 2.3/1 ratio of products).

Compound **58** (major isomer):

^{1}H NMR (pyridine-d_5, 320 K): 4.16 (m, 1H); 3.69 (s, 3H); 3.5–3.75 (m, 3H); 3.19(d, 1H, J = 13.5 Hz); 3.12 (m, 1H); 2.65 (m, 1H); 2.58 (s, 1H); 2.4–2.5 (m, 2H); 2.29 (dd, 1H, J = 4.6, 16.8 Hz); 2.05–2.2 (m, 3H); 1.9–2.0 (m, 2H); 1.7 (m, 1H); 1.35–1.6 (m, 8H); 1.26 (m, 1H).

^{13}C NMR (pyridine-d_5, 320 K): 210.3; 156.3; 71.3 (CH); 70.3 (CH); 67.7 (CH); 53.3; 52.5 (CH_3); 49.2; 44.3; 42.2; 40.8; 40.4; 37.7; 37.1 (CH); 33.8; 29.4; 27.4; 26.5; 26.3.

Mass spectrum *m/z* (rel. int.): 351 (M+1, 100), 333 (12), 291 (20), 278 (20), 265 (50), 148 (15).

HRMS calculated for $C_{19}H_{31}N_2O_4$ (M+1): 351.2284, found: 351.2314.

Compound **59** (minor isomer):

^{1}H NMR (pyridine-d_5, 320 K): 4.3 (m, 1H); 4.1 (m, 1H); 3.68 (s, 3H); 3.55–3.7 (m, 3H); 3.42 (m, 1H); 3.1–3.3 (m, 2H); 2.4–2.6 (m, 6H); 2.2 (m, 1H); 2.08 (m, 1H); 1.2–2.0 (m, 10H).

^{13}C NMR (pyridine-d_5, 320 K): 210.5; 156.1; 71.8 (CH); 66.2 (CH); 64.0 (CH); 52.3 (CH_3); 51.9; 47.2; 42.9; 42.4; 42.3; 37.8 (CH); 37.5; 36.4; 34.0; 29.24; 29.19; 27.6; 25.2.

IR (cm^{-1}, neat): 3450; 2900, 1705, 1450, 1250.

Mass spectrum, *m/z* (rel. int.): 351 (M+H, 100); 265 (12); 220 (12); 205 (22).

HRMS calculated for $C_{19}H_{31}N_2O_4$ (M+H): 351.2284, found: 351.2272.

Diketone 60

A solution of oxalyl chloride (50 µL) in methylene chloride (1.5 mL) was cooled to –60 °C in a dry ice/chloroform bath. The solution was treated with DMSO (100 µL) in methylene chloride (1 mL), followed by a solution of alcohol **58** (106 mg, 0.3 mmol) in methylene chloride (2 mL). The reaction mixture was stirred for 15 min at –60 °C, then treated with triethylamine (500 µL). After an additional 20 min at –60 °C, the reaction was warmed to room temperature and poured into 10 mL of water. The aqueous was extracted with four 10-mL portions of ether, and the combined ether extracts were washed with 10 mL brine, dried over magnesium sulfate, and evaporated. Purification by flash chromatography (1:1 petrol/ethyl acetate) yielded 66 mg dione **60** (63%).

^{1}H NMR (320 K): 3.75 (m, 1H); 3.71 (s, 3H); 3.54 (d, 1H, J = 13.5 Hz); 3.1–3.2 (m, 3H); 3.04 (ddd, 1H, J = 3.3, 3.3, 10 Hz); 2.78 (m, 1H); 2.62 (m, 1H); 2.42 (m, 1H); 2.45 (dd, 1H, J = 9.0, 17.5 Hz); 2.3–2.38 (m, 2H); 2.21 (m, 1H); 2.10 (dd, 1H, J = 7.6, 13.2 Hz); 2.02 (m, 1H); 1.94 (m, 1H); 1.75–1.85 (m, 4H); 1.60 (dd, 1H, J = 10.0, 13.0 Hz); 1.35–1.55 (m, 3H); 1.0–1.1 (m, 1H).

^{13}C NMR (320 K): 217.9; 209.8; 156.1; 71.7 (CH); 68.8 (CH); 55.2; 52.8 (CH_3); 48.7; 43.6; 43.3; 40.2; 40.0; 39.1; 36.9 (CH); 36.7; 30.2; 27.2; 27.1; 26.3.

IR (cm^{-1}, neat): 3600, 2900, 1705, 1450, 1250.

Mass spectrum, *m/z* (rel. int.): 349 (M+1, 70); 320 (100); 277 (300); 218 (18); 162 (10).

HRMS calculated for $C_{19}H_{29}N_2O_4$ (M+1): 349.2127, found: 349.2135.

Diketone 61

A solution of oxalyl chloride (50 µL) in methylene chloride (1.5 mL) was cooled to –60° in a dry ice/chloroform bath. The

solution was treated with DMSO (100 μL) in methylene chloride (1 mL), followed by a solution of alcohol **59** (39 mg, 0.3 mmol) in methylene chloride (2 mL). The reaction mixture was stirred for 15 min at –60°, then treated with triethylamine (500 μL). After an additional 20 min at –60°, the cooling bath was removed and the reaction was poured into 10 mL of water. The aqueous was extracted with four 10-mL portions of ether, and the combined organics were washed with 10 mL brine, dried over magnesium sulfate, and evaporated. Purification by flash chromatography (1:1 petrol/ethyl acetate) yielded 19 mg dione **61** (49%).

^{1}H NMR (320 K): 4.04 (d, 1H, J = 13.2 Hz); 3.71 (s, 3H); 3.64 (m, 1H); 3.37 (dd, 1H, J = 5.8, 10.2 Hz) 3.15–3.3 (m, 5H); 2.5–2.7 (m, 2H); 2.50 (m, 1H); 2.38 (dd, 1H, J = 10.2, 13.6 Hz); 2.26 (dd, 1H, J = 10.1, 14.1 Hz); 2.0–2.25 (m, 4H); 1.7–1.9 (m, 3H); 1.5–1.7 (m, 3H); 1.38 (m, 1H); 1.05 (m, 1H).

^{13}C NMR (320 K): 217.6; 209.7; 155.9; 68.8; 65.7; 52.6; 51.6; 50.5; 44.5; 42.1; 41.7; 38.3; 37.6; 37.5; 36.9; 30.2; 28.8; 27.2; 25.8.

IR (neat, cm^{-1}): 3600 (broad); 2900; 1705; 1450; 1420; 1250.

Mass spectrum, *m/z* (rel. int.): 349 (M+H, 45); 320 (100); 278 (30); 218 (12); 189 (20); 131 (25).

HRMS calculated for $C_{19}H_{29}N_2O_4$ (M+H): 349.2127, found: 349.2113.

*Reduction of trans-Alcohol **62** plus cis-Alcohol **63***

A solution of ketone **49** (1.27 g, 3.42 mmol) in absolute ethanol (40 mL) was treated with sodium borohydride powder (800 mg, 21 mmol). The resulting cloudy solution was stirred at room temperature for 6 h, at which time no starting material remained by TLC (2:1 petrol/ethyl acetate). The ethanol was removed under reduced pressure and the solid residue was taken up in 40 mL 5% aqueous potassium carbonate and 40 mL ether. The organic was separated and the aqueous was extracted with three 40-mL portions of ether. The combined ether extracts were washed with 20 mL brine, dried over magnesium sulfate, and evaporated to yield a mixture of the epimeric alcohols. These were separated and purified by flash chromatography (2 columns: 1:1 ether/petrol, 2:1 petrol/ethyl acetate) to yield 242 mg of the trans alcohol (more polar) and 929 mg of the cis alcohol (less polar), overall yield 92%, 3.8/1 ratio of cis to trans alcohols.

trans alcohol **63**:

^{1}H NMR (320 K): 7.1–7.3 (m, 5H); 5.68 (br s, 1H); 3.9 (m, 2H); 3.75 (dd, 2H, J = 13.3 Hz); 3.70 (s, 3H); 3.6–3.7 (m, 2H); 3.4–3.6 (m, 2H); 2.65–2.8 (m, 2H); 2.4–2.5 (m, 2H); 2.24 (dd, 1H, J = 7, 14 Hz); 2.13 (br s, 2H); 1.2–2.0 m, 7H).

^{13}C NMR (320 K): 156.0 (C=O); 140.3; 135.4 (broad); 129.1 (CH); 128.1 (CH); 126.9 (CH); 121.5 (broad, CH); 77.6 (CH); 63.8 (broad, CH); 59.4 (broad); 52.4 (CH_3); 49.1; 46.1; 40.4 (broad); 35.8; 34.4; 27.3; 26.8; 26.0; 25.0 (broad).

IR (neat, cm^{-1}): 3400; 2900; 1705; 1450; 1245.

Mass spectrum, *m/z* (rel. int.): 372 (M^+, 42); 218 (100); 174 (8).

HRMS calculated for $C_{22}H_{32}N_2O_3$: 372.2413, found: 372.2422.

cis alcohol **62**:

^{1}H NMR (320 K): 7.34 (d, 2H, J = 7 Hz); 7.28 (t, 2H, J = 7 Hz); 7.22 (t, 1H, J = 7 Hz); 5.67 (br s, 1H); 4.03 (d, 1H, J = 13.9 Hz); 3.9 (m, 2H); 3.71 (s, 3H); 3.65–3.75 (m, 2H); 3.50 (m, 2H); 3.05 (m, 1H); 2.67 (m, 1H); 2.58 (dt, 1H, J = 4.4, 8.5 Hz); 2.35–2.5 (m, 2H); 2.14 (br s, 2H); 1.2–2.0 M, 8H).

^{13}C NMR (320 K):156.1; 141.2; 134.0 (broad); 128.6; 128.1; 126.6; 121.7 (broad); 73.8; 57.3; 56.0; 52.4; 51.2; 46.2; 40.5; 34.9; 32.7; 27.9; 27.7; 25.0; 23.6.

IR (neat, cm^{-1}): 3450; 2850; 1700; 1450; 1240.

Mass spectrum *m/z* (rel. int.): 373 (M+H, 15); 218 (100); 174 (10); 126 (12).

HRMS calculated for $C_{22}H_{33}N_2O_3$ (M+H): 373.2491, found: 373.2516.

*Vinylogous Amide **64***

Trans-alcohol **63** (232 mg, 0.6 mmol) was dissolved in methanol (15 mL). To this solution was added conc HCl (330 μL) and palladium black (21 mg, 0.2 mmol). The reaction mixture was then placed under a hydrogen balloon until no starting material remained by TLC (ethyl acetate, about 30 min). The palladium was filtered off, and the solvent was removed under reduced pressure. The residue was dissolved in 10 mL of 5% aqueous potassium carbonate, and extracted with five 20-mL portions of ether, dried, and evaporated to yield 155 mg of crude amine. This was dissolved in absolute ethanol (15 mL) and treated with sodioformyl acetone (104 mg, 0.96 mmol) and conc HBr (100 μL). The solution was heated to reflux for 12 h, at which time no starting material remained by TLC (5% methanol/ethyl acetate). The solvent was removed under reduced pressure, and the residue was dissolved in 10 mL of 5% aqueous potassium carbonate and extracted with six 10-mL portions of ether. The combined organic extracts were washed with 10 mL brine, dried over magnesium sulfate, and evaporated. The crude residue was purified by flash chromatography (5% MeOH/EtOAc) to yield 118 mg vinylogous amide **64** (54% for 2 steps).

^{1}H NMR (320 K): 7.39 (d, 1H, J = 12.6 Hz); 5.51 (br s, 1H); 5.09 (d, 1H, J = 12.9 Hz); 3.9 (m, 1H);3.7–3.8 (m, 4H); 3.69 (s, 3H); 3.43 (m, 2H); 3.23 (m, 2H); 2.73 (m, 1H); 2.19 (m, 1H); 2.07 (s, 3H); 2.0–2.1 (m, 2H); 1.45–1.9 (m, 7H).

^{13}C NMR (320 K): 195.2; 155.8; 151.5 (broad); 131.7 (broad); 123.8; 96.6 (broad); 72.4; 68.8 (broad); 52.4; 46.8 (broad); 45.8; 40.2 (broad); 36.6; 35.9 (broad); 27.4 (broad); 25.9 (broad); 24.9 (broad); 24.4; 23.0 (broad).

IR (neat, cm^{-1}): 3350; 2900; 2800; 1705; 1595; 1550; 1450; 1250.

Mass Spectrum *m/z* (rel. int.): 350 (M^+, 100); 262 (8); 195 (32); 154 (10).

HRMS calculated for $C_{19}H_{30}N_2O_4$: 350.2206; found: 350.2217.

*Tetracyclic Ketoalcohols **65** and **66***

Compound **64** (115 mg, 0.33 mmol) in acetonitrile (220 mL) was placed in a photoreactor with a Pyrex filter and degassed by bubbling through a stream of dry nitrogen for 30 min at 0 °C. The solution was then irradiated under a stream of nitrogen at 0 °C for 3 h, at which point no more starting material remained by TLC (5% methanol/ethyl acetate). The

solvent was then evaporated and the crude oil was dissolved in 15 mL acetonitrile and treated with triethylamine hydrochloride (50 mg, 0.36 mmol), and the resulting solution was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure and the crude solid was placed on a vacuum pump for 2 h to remove any free triethylamine, then redissolved in 15 mL of acetonitrile and treated with DMAP (40 mg, 0.33 mmol). The resulting solution was refluxed for 8 h, then stirred at room temperature for an additional 10 h. The solvent was evaporated and the crude solid was partitioned between 20 mL ether and 20 mL 2.5% aqueous potassium carbonate solution. The ether was separated and the aqueous was extracted with three 20-mL portions of ether. The combined ether extracts were washed with 15 mL brine, dried over magnesium sulfate, and evaporated to yield a crude oil which was purified by flash chromatography (ethyl acetate) to yield 31 mg clean compound **66** and 21 mg compound **65**, along with 8 mg of a mixture (52% yield of **66** and **65**, isolated ratio 3:2). Irradiation of compound **64** (22 mg) in diethyl ether (250 mL) at –78 °C under identical conditions resulted in a single aminal photoproduct by ^{1}H NMR, which on treatment with triethylamine hydrochloride followed by DMAP yielded 8 mg of compound **66** (36%), with no detectable **65** formed.

Compound **66**:

^{1}H NMR (320 K, pyridine-d_5): 4.4 (d, 1H, J = 13 Hz); 3.8 (m, 1H); 3.69 (s, 3H); 3.27 (m, 1H); 2.9–3.0 (m, 2H); 2.85 (m, 1H); 2.72 (m, 1H); 2.5–2.65 (m, 4H); 2.45 (m, 1H); 2.2 (m, 1H); 2.1 (m, 1H); 1.2–2.0 (m, 12H).

^{13}C NMR (320 K, pyridine-d_5): 209.8; 156.0; 76.2 (CH); 67.2 (CH); 65.1 (broad); 52.3; 51.9 (broad); 47.6 (broad); 44.3; 43.3 (broad); 42.9; 39.1; 38.0; 35.9; 29.7; 28.5; 24.8.

IR (neat, cm^{-1}): 3450; 2900; 1705; 1460; 1250.

Mass spectrum, *m/z* (rel. int.): 351 (M+H, 100); 291 (30); 265 (42); 148 (12).

HRMS calculated for $C_{19}H_{31}N_2O_4$ (M+H): 351.2284, found: 351.2259.

Compound **65:**

^{1}H NMR: 3.7–3.8 (m, 3H); 3.67 (s, 3H); 3.5–3.6 (m, 2H); 3.4 (m, 1H); 3.1 (m, 2H); 3.18 (m, 1H); 2.2–2.9 (m, 7H); 1.2–2.0 (m, 10H).

Iodide 78

2-Trimethylsilyl ethylchloroformate (10g, 55 mmol) in toluene (15 mL) was added dropwise over 10 min to *N*-carbomethoxy-3-chloromethyl-Δ^3-tetrahydropyridine (11 g, 50 mmol) in toluene (90 mL). After refluxing 1.5 h the solution was cooled to room temperature and the solvent removed in vacuo to give 17.9 g brown oil. The crude oil was purified by flash chromatography using 20% ethyl ether/petroleum ether as the eluent to give 7.1 g of the corresponding N-TEOC compound as a light yellow oil in 50% yield (R_f: 30% ethyl ether/petroleum ether, PMA = 0.38).

^{1}H NMR (500 MHz, $CDCl_3$): 5.91 (s, 1H); 4.17 (t, 2H, J = 8.3 Hz); 3.99 (s, 4H); 3.48 (s, 2H); 2.15 (s, 2H); 0.99 (t, 2H, J = 8.6 Hz); 0.01 (s, 9H).

^{13}C NMR (125.7 MHz, $CDCl_3$): 155.9; 126.09; 125.42; 63.60; 60.33; 46.88; 43.93; 24.82; 17.79; –1.48.

IR (neat, cm^{-1}): 2953; 1698; 1433; 1360; 1338; 1285; 1237; 1200.

Sodium iodide (6.1 g, 41 mmol) and the above N-TEOC allylic chloride (5.67 g, 20.5 mmol) in acetone (120 mL) were heated to reflux overnight. The solution was filtered and the solvent removed in vacuo. The residue was partitioned between water and methylene chloride and the aqueous layer extracted with methylene chloride. The combined organic phases were dried over magnesium sulfate and the solvent removed in vacuo. The residue was purified by flash chromatography using 30% ethyl ether/petroleum ether as the eluent to give 6.85g of **78** as a yellow oil in 91% yield. (R_f: 30% ethyl ether/petroleum ether, PMA or UV = 0.38).

^{1}H NMR (500 MHz, $CDCl_3$): 6.05 (s, 1H); 4.19 (t, 2H, J = 8.4 Hz); 4.08 (s, 2H); 3.86 (s, 2H); 3.48 (s, 2H); 2.04 (s, 2H); 1.01 (t, 2H, J = 8.1 Hz); 0.03 (s, 9H).

^{1}H NMR (125.7 MHz, 320 K, $CDCl_3$): 6.02 (s, 1H); 4.18 (t, 2H, J = 8.3 Hz); 4.06 (s, 2H); 3.84 (s, 2H); 3.45 (t, 2H, J = 5.8 Hz); 2.02 (s, 2H); 0.99 (t, 2H, J = 8.3 Hz); 0.01 (s, 9H).

^{13}C NMR (125.7 MHz, $CDCl_3$): 155.68; 133.38; 124.64; 63.54; 45.01; 39.81; 25.28; 17.87; 7.18; –1.47.

IR (neat, cm^{-1}): 2951; 1700; 1431; 1360; 1283; 1239.

Azocines 76 and 77

A suspension of lithium aluminum hydride (5 g, 130 mmol) in a solution of 2-azacyclooctanone (6.19 g, 43.8 mmol) in tetrahydrofuran (150 mL) was heated to reflux for 15 h. After cooling to room temperature, water (2.4 mL), 50% sodium hydroxide (2.4 mL), followed by water (7.2 mL) were added. The suspension was filtered and the precipitate washed with methylene chloride. The combined organic phases were dried over magnesium sulfate and evaporated to give 3.86 g (68%) of amino alcohol.

The crude amino alcohol (4.66 g, 36.1 mmol), di-*t*-butyl dicarbonate (8.5 mL, 37 mmol) and triethylamine (8 mL, 57 mmol) in methanol (70 mL) were stirred at ambient temperature overnight. The solvent was removed in vacuo and the residue purified by flash chromatography using ethyl acetate as the eluent to give 6.4 g (77% yield) of product as a light yellow oil (R_f: diethyl ether, PMA = 0.46).

^{1}H NMR (500 MHz, $CDCl_3$, rotamers): 4.49 (d, 1H, J = 6.7 Hz); 3.88–3.62 (m, 3H); 3.53–3.12 (m, 2H); 2.92–2.84 (m, 1H); 2.40–2.36 (m, 0.3H); 1.86–1.29 (m, 7H); 1.45 (s, 9H).

^{13}C NMR (125.7 MHz, $CDCl_3$, rotamers): 157.89; 80.24; 80.12; 71.13; 70.39; 53.21; 52.98; 49.66; 49.02; 33.58; 32.96; 28.42; 28.39; 26.97; 26.82; 25.95; 22.57; 22.20.

IR (neat, cm^{-1}): 3425; 2930; 1693; 1667; 1479; 1415; 1366; 1286; 1245.

Mass spectrum *m/z* (rel. int.): 230 (M+1, 68); 191 (42); 174 (100); 130 (24).

HRMS calculated for $C_{12}H_{23}NO_3$ (M+H): 230.1756 found: 230.1765.

Dimethyl sulfoxide (5 mL, 71 mmol) in methylene chloride (14 mL) was added over 5 min to oxalyl chloride (2.7 mL, 31 mmol) in methylene chloride (70 mL) at –78° C. After stirring 20 min, the crude amino alcohol (6.4 g, 27.9 mmol) in methylene chloride (30 mL) was added over 7 min. After stirring 15 min, triethylamine (20 mL, 143 mmol) was added over 5 min. The dry ice bath was removed and the solution

warmed to room temperature. The solution was poured into water (200 mL) and extracted with methylene chloride (3 × 30 mL). The combined organic phases were dried over magnesium sulfate and the solvent was removed in vacuo to give 7.8 g light yellow oil. Purification by flash chromatography using 30% ethyl ether/petroleum ether gave 5.9 g of **76** as a light yellow oil in 93% yield (R_f: 40% ethyl ether/petroleum ether, PMA = 0.46).

^{1}H NMR (500 MHz, 320 K, $CDCl_3$, rotamers): 3.84 (bs, 2H); 3.77 (bs, 2H); 3.45–3.35 (m, 4H); 2.32–2.46 (m, 4H); 1.60–1.70 (m, 2H); 1.45–1.62 (m, 4H); 1.38–1.45 (m, 9H).

^{13}C NMR (125.7 MHz, 320 K, $CDCl_3$, rotamers): 215.75; 215.59; 155.81; 155.03; 80.51; 80.38; 57.32; 57.01; 49.07; 48.39; 38.83; 38.78; 28.78; 28.35; 27.01; 26.76; 25.80.

IR (neat, cm^{-1}): 2930; 1694; 1427; 1396; 1366; 1285; 1241.

Mass spectrum *m/z* (rel. int.): 245 (M+NH_4, 72); 228 (40); 189 (100); 172 (28); 128 (28).

HRMS calculated for $C_{12}H_{21}NO_3$ (M+NH_4): 245.1865 found: 245.1878.

The crude amino alcohol (4.0 g, 31 mmol), benzyl bromide (5.8 g, 34 mmol), and potassium carbonate (4.7 g, 34 mmol) in acetonitrile (25 mL) were heated to reflux overnight. After cooling to room temperature, the solution was poured into water (100 mL) and extracted with methylene chloride. The solvent was removed in vacuo and the residue purified by flash chromatography using 60% ethyl ether/petroleum ether to give 4.9 g of product as a light yellow oil in 72% yield (R_f: 40% ethyl ether/petroleum ether, PMA = 0.30).

^{1}H NMR (500 MHz, $CDCl_3$): 7.35–7.20 (m, 5H); 3.65 (dd, 2H, *J* = 13.3 Hz, 24.5 Hz); 3.62–3.55 (m, 1H); 2.77–2.59 (m, 3H); 2.51–2.45 (m, 1H); 1.89–1.67 (m, 4H); 1.65–1.45 (m, 5H).

^{13}C NMR (125.7 MHz, $CDCl_3$): 128.87; 128.33; 127.02; 70.30; 64.63; 58.45; 56.34; 33.76; 26.80; 25.95; 21.61.

IR (neat, cm^{-1}): 3358; 2920; 1494; 1452; 1352.

Mass spectrum *m/z* (rel. int.): 220 (M+1, 100); 202 (12); 174 (9); 160 (15); 134 (20).

HRMS calculated for $C_{14}H_{21}NO$ (M+H): 220.1701 found: 220.1685.

Dimethyl sulfoxide (3.8 mL, 54 mmol) in methylene chloride (11 mL) was added over 5 min to oxalyl chloride (2.2 mL, 25 mmol) in methylene chloride (57 mL) at –78 °C. After stirring 10 min, the amino alcohol (4.9 g, 22 mmol) in methylene chloride (5 mL) was added over 5 min. After stirring 15 min, triethylamine (16 mL, 115 mmol) was added over 5 min. The dry ice bath was removed and the solution warmed to room temperature. The solution was poured into water (100 mL) and extracted with methylene chloride. The combined organic phases were dried over magnesium sulfate and the solvent removed in vacuo to give 4.5 g light yellow oil. Purification by flash chromatography using 20% ethyl ether/petroleum ether as the eluent gave 4.3 g (88% yield) of **77** as a light yellow oil.

A solution of azacyclooctanone **77** (3.48 g, 16.0 mmol) in tetrahydrofuran (33 mL) was added over 14 min to lithium bis(trimethylsilyl amide) (1.0M in tetrahydrofuran, 18 mL, 18 mmol) in tetrahydrofuran (64 mL) at –78 °C. The solution was warmed to 0 °C and stirred for 1 h. The solution was cooled to –78 °C and hexamethylphosphoramide (11 mL, 63 mmol) was added. The allylic iodide **78** (6.06 g, 16.5 mmol) in tetrahydrofuran (33 mL) was added over 11 min. The reaction flask was stirred for 3 days at –15 °C. The solution was poured into water (200 mL) and extracted with diethyl ether (4 × 100 mL). The combined ether extracts were washed with brine and dried over magnesium sulfate. The solvent was removed in vacuo and the residue purified by flash chromatography using 25% ethyl ether/petroleum ether as the eluent to give 4.25 g of **79** (58% yield) and 1.44 g of **79** contaminated with the ketone starting material **77** (R_f of **79**: 60% ethyl ether/petoleum ether = 0.66).

^{1}H NMR (500 MHz, 320 K, $CDCl_3$): 7.35 (d, 2H, *J* = 7.3 Hz); 7.29 (t, 2H, *J* = 7.5 Hz); 7.21 (t, 1H, *J* = 7.3 Hz); 5.53 (s, 1H); 4.16 (t, 2H, *J* = 8.3 Hz); 3.95–3.85 (m, 1H); 3.76 (dd, 3H, *J* = 34.8 Hz, 13.3 Hz); 3.50–3.35 (m, 2H); 3.23–3.09 (m, 2H); 2.78–2.70 (m, 1H); 2.50–2.37 (m, 2H); 2.28–2.20 (m, 1H); 2.10–1.99 (m, 3H); 1.97–1.87 (m, 1H); 1.78–1.67 (m, 1H); 1.65–1.38 (m, 3H); 0.97 (t, 2H, *J* = 8.3 Hz); 1.0–0.88 (m, 1H); 0.00 (s, 9H).

^{13}C NMR (125.7 MHz, 320 K, $CDCl_3$): 217.04; 155.49; 139.10; 134.06; 128.93; 128.21; 127.11; 120.93; 69.02; 63.03; 60.96; 51.68; 46.02; 40.00; 39.04; 30.51; 26.79; 26.48; 25.86; 24.79; 17.71; –1.67.

IR (neat, cm^{-1}): 2940; 2260; 1700; 1440; 1360; 1340; 1285; 1245.

Mass spectrum *m/z* (rel. int.): 457 (M+1, 45); 429 (14); 216 (22); 188 (100); 131 (34).

HRMS calculated for $C_{26}H_{40}N_2O_3Si$ (M+1): 457.2886 found: 457.2851.

Vinylogous Amide ***81***

Palladium black (13 mg) was added to the benzyl amine **79** (428 mg, 0.937 mmol) and conc HCl (0.15 mL, 1.7 mmol) in methanol (15 mL) under a nitrogen atmosphere. The flask was then purged with hydrogen and stirred for 30 min. The flask was purged with nitrogen and the contents filtered through Celite. The solvent was evaporated and the residue treated with 5% potassium carbonate (50 mL) and extracted with methylene chloride The combined extracts were dried over magnesium sulfate and removed in vacuo to give 0.366 g yellow oil. Purification by flash chromatography using 60% ether/petroleum ether as the eluent gave 200 mg (58% yield) of amine as a yellow oil and 147 mg starting material **79** in 89% yield based on recovered starting material R_f: ethyl ether, PMA = 0.59).

^{1}H NMR (500 MHz, 320 K, $CDCl_3$): 5.53 (s, 1H); 4.09 (t, 2H, *J* = 8.3 Hz); 3.82–3.63 (m, 2H); 3.49–3.40 (m, 1H); 3.35–3.26 (m, 1H); 3.02–2.95 (m, 1H); 2.94–2.87 (m, 1H); 2.80–2.70 (m, 1H); 2.63–2.57 (m, 1H); 2.18–1.89 (m, 5H); 1.85–1.77 (m, 1H); 1.67–1.38 (m, 5H); 1.0–0.95 (m, 1H); 0.90 (t, 2H, *J* = 8.3 Hz); –0.06 (s, 9H).

^{13}C NMR (125.7 MHz, 320 K, $CDCl_3$): 220.80; 155.50; 131.20; 123.70; 66.06; 63.25; 49.59; 45.21; 40.03; 37.76; 36.58; 30.28; 29.44 27.10; 25.42; 24.85; 17.74; –1.65.

IR (neat, cm^{-1}): 3520; 3360; 2940; 1700; 1440; 1330; 1240.

Mass spectrum *m/z* (rel. int.): 367 (M+1, 100); 339 (21);

323 (39); 249 (18); 240 (19); 196 (33); 168 (38); 131 (32).

HRMS calculated for $C_{19}H_{34}N_2O_3Si$ (M+1): 367.2417 found: 367.2431.

The undecyneone (0.65 g, 2.9 mmol) in diethyl ether (5 mL) was added dropwise over 20 min to sodium bis(trimethylsilylamide) (3.2 mL) in ethyl ether (30 mL) at –78 °C. After stirring at –78 °C for 30 min, ethyl formate (0.6 mL, 7.4 mmol) was added. The dry ice bath was removed and the solution stirred for 2 h. The solvent was removed in vacuo and to the residue was added ethanol (20 mL), the amine (0.887 g, 2.42 mmol) and concentrated (48%) HBr (0.36 mL, 3.2 mmol). After refluxing for 1 h and 45 min the solution was cooled to room temperature and stirred overnight. The excess ethanol was removed in vacuo and to the residue was added saturated sodium bicarbonate (30 mL). The aqueous was extracted with chloroform (3 × 20 mL) and the combined organics were dried over magnesium sulfate. The solvent was removed in vacuo and the residue purified by flash chromatography using ethyl ether as the eluent to give 1.10 g (76% yield) of **81** as a yellow oil (R_f: diethyl ether, PMA = 0.24).

^{1}H NMR (500 MHz, 320 K, $CDCl_3$): 7.57 (d, 1H, J = 12.1 Hz); 5.51 (s, 1H); 5.22 (d, 1H, J = 13.0 Hz); 4.14 (t, 2H, J = 8.4 Hz); 4.07 (q, 2H, J = 14.3, 7.1 Hz); 4.02–3.85 (br s, 1H); 3.82–3.68 (m, 2H); 3.47–3.39 (m, 1H); 3.36–3.29 (m, 1H); 3.28–3.15 (m, 2H); 2.72–2.53 (m, 2H); 2.42 (dt, 2H, J = 7.4, 2.6 Hz); 2.35 (t, 2H, J = 7.5 Hz); 2.33–2.26 (m, 1H); 2.25–2.19 (m, 1H); 2.18–2.10 (m, 4H); 2.09–1.95 (m, 2H); 1.85–1.71 (m, 2H); 1.70–1.55 (m, 2H); 1.54–1.42 (m, 1H); 1.41–1.28 (m, 1H); 1.20 (t, 2H, J = 7.1); 0.96 (t, 2H, J = 8.4 Hz); 0.00 (s, 9H).

^{13}C NMR (125.7 MHz, 320 K, $CDCl_3$): 211.73; 197.53; 173.06; 155.56; 152.30; 131.02; 126.02; 97.20; 80.53; 79.34; 73.0 (br); 63.43; 60.13; 45.80; 40.69; 40.04; 39.68; 33.20; 31.5 (br); 27.2 (br); 25.84; 25.00; 24.75; 24.75; 24.36; 18.46; 18.25; 17.85; 14.15; –1.54.

IR (neat, cm^{-1}): 2955; 1705; 1565; 1435; 1375; 1245.

Mass spectrum *m/z* (rel. int.): 601 (M+1, 100); 573 (34); 543 (8).

HRMS calculated for $C_{33}H_{52}N_2O_6Si$ (M+1): 601.3673: found: 601.3682.

Macrocyclic Vinylogous Amide 82

Lithium hydroxide (187 mg, 4.46 mmol) in water (10 mL) was added to the ethyl ester **81** (0.52 g, 0.866 mmol) in methanol (30 mL). After stirring for 5 h the solution was diluted with water (20 mL), cooled to 0 °C, and acidified with conc HCl. The aqueous was saturated with sodium chloride and extracted with ethyl acetate (3× 15 mL). The combined organics were washed with brine and dried over magnesium sulfate. The solvent was removed in vacuo and the residue filtered through silica using 0–30% methanol/ethyl acetate as the eluent to give 376.1 mg (76% yield) of acid as a foam (R_f: ethyl acetate, PMA = 0.16).

Dicyclohexylcarbodiimide (70 mg, 0.34 mmol) in dichloromethane (1 mL) was added dropwise to the acid (162 mg, 0.283 mmol) and pentafluorophenol (80 mg, 0.43 mmol) in dichloromethane (2 mL) at 0 °C. After stirring for 2 h the solvent was removed in vacuo and the residue purified by flash chromatography using 50% ethyl acetate/petroleum ether as the eluent to give 173 mg (83% yield) of TEOC-carbamate as a foam (R_f: ethyl acetate, PMA = 0.47).

^{1}H NMR (500 MHz, $CDCl_3$): 7.73–7.48 (bm, 1H); 5.05 (s, 1H); 5.24 (d, 1H, J = 13.0 Hz); 4.15 (t, 2H, J = 8.2 Hz); 3.90–3.68 (m, 2H); 3.53–2.95 (m, 3H); 2.78 (t, 2H, J = 7.5 Hz); 2.66–2.52 (m, 2H); 2.49–2.40 (m, 2H); 2.38–2.13 (m, 6H); 2.12–1.95 (m, 2H); 1.94–1.20 (m, 12H); 0.98 (t, 2H, J = 8.2 Hz); 0.02 (s, 9H).

^{13}C NMR (125.7 MHz, $CDCl_3$): 212 (b); 197.71; 169.14; 155.62; 153 (b); 139 (b); 131 (b); 96 (b); 81.25; 78.55; 73 (b); 63.57; 46.5 (b); 45.71; 40.92; 39.62; 33.92; 32.11; 25.59; 24.91; 24.70; 24.02; 18.50; 17.83; 17.83; –1.49.

IR (neat, cm^{-1}): 2960; 1805; 1715; 1680; 1610; 1575; 1445; 1530; 1385; 1260.

Mass spectrum *m/z* (rel. int.): 739 (M+1, 100); 711 (30); 470 (58).

HRMS calculated for $C_{37}H_{47}F_5N_2O_6Si$ (M+1): 739.3201 found: 739.3211.

Tetrabutyl ammonium fluoride (1.0 M in tetrahydrofuran, 4.6 mL) was added dropwise to the TEOC-carbamate (1.1 g, 1.83 mmol) in acetonitrile (18 mL). The solution was then heated to 60 °C for 2 h. Saturated sodium bicarbonate (15 mL) was added and the excess solvent removed in vacuo. The residue was partitioned between water (35 mL) and chloroform (20 mL). The phases were separated and the aqueous extracted with chloroform (3 × 20 mL). The combined organics were washed with brine and dried over magnesium sulfate. The solvent was removed in vacuo to give 1.34 g of secondary amine as a dark yellow oil. R_f (methanol, PMA) = 0.15.

^{1}H NMR (500 MHz, 320 K, $CDCl_3$): 7.52 (d, 1H, J = 12.6 Hz); 5.41 (s, 1H); 5.15 (d, 1H, J = 13.0 Hz); 4.00 (q, 2H, J = 14.2, 7.1 Hz); 3.93–3.75 (br s, 1H); 3.20–3.07 (m, 2H); 3.06–2.98 (m, 1H); 2.77–2.65 (m, 2H); 2.57–2.46 (m, 2H); 2.36 (t, 2H, J = 7.4 Hz); 2.29 (t, 2H, J = 7.4 Hz); 2.26–2.15 (m, 1H); 2.14–2.02 (m, 6H); 1.97–1.80 (m, 2H); 1.78–1.65 (m, 6H); 1.63–1.49 (m, 2H); 1.47–1.20 (m, 2H); 1.13 (t, 3H, J = 7.1 Hz).

^{13}C NMR (500 MHz, 320 K, $CDCl_3$): 211.87; 197.35; 172.87; 152.48; 133.07; 123.52; 96.74; 80.38; 79.17; 73 (br); 59.95; 47.58; 42.44; 40.51; 39.48; 33.02; 32.46; 27.14 (br); 25.67; 24.67; 24.20; 23.97; 19.57; 18.30; 18.08; 14.00.

IR (neat, cm^{-1}): 3320; 2940; 1725; 1665; 1565; 1435; 1375.

Mass spectrum *m/z* (rel. int.): 457 (M+H, 100); 428 (5); 362 (19); 332 (20); 223 (32).

HRMS calculated for $C_{27}H_{40}N_2O_4$ (M+H): 457.3066 found: 457.3041.

To the secondary amine was added methanol (11 mL), triethylamine (1.1 mL, 7.89 mmol), 4-dimethyl amminopyridine (70 mg, 0.57 mmol), and di-*t*-butyl dicarbonate (0.75 mL, 3.26 mmol). After stirring overnight, the excess solvent was removed in vacuo and the residue purified by flash chromatography using ethyl ether as the eluent to give 0.952 g (93% yield) of BOC-carbamate as a yellow oil. R_f (ethyl acetate, PMA) = 0.58.

^{1}H NMR (500 MHz, 320 K, $CDCl_3$): 7.67 (d, 1H, J = 12.25 Hz); 5.53 (s, 1H); 5.27 (d, 1H, J = 12.25 Hz); 4.10 (q, 2H, J = 7.2 Hz); 4.03–3.90 (bm, 1H); 3.80–3.69 (m, 2H); 3.48–3.18 (m, 3H); 2.77–2.55 (m, 2H); 2.46 (dt, 2H, J = 7.5 Hz, 2.0 Hz); 2.38 (t, 2H, J = 7.5 Hz); 2.36–2.29 (bm, 1H); 2.27–2.13 (m,

6H); 2.11–1.96 (m, 2H); 1.90–1.32 (m, 20H); 1.23 (t, 3H, J = 7.2 Hz); 1.30–1.18 (m, 2H).

^{13}C NMR (125.7 MHz, 320 K, $CDCl_3$): 212 (b); 197.58; 173.17; 154.71; 153 (b); 131 (b); 123 (b); 97 (b); 80.58; 79.68; 79.47; 60.23; 45.82; 40.70; 39.73; 33.30; 32 (b); 29.67; 28.49; 25.91; 25.19; 24.89; 24.45; 18.55; 18.34; 14.23.

IR (neat, cm^{-1}): 2931; 1730; 1695; 1665; 1607; 1563; 1422; 1366; 1246.

Mass spectrum *m/z* (rel. int.): 557 (M+1, 33); 503 (13); 457 (16); 362 (15); 332 (100); 305 (20).

HRMS calculated for $C_{12}H_{26}O_2Si$ (M+1): 557.3590 found: 557.3585.

Lithium hydroxide monohydrate (282 mg, 6.72 mmol) in water (15 mL) was added to the ester (698.5 mg, 1.255 mmol) in methanol (45 mL). After stirring for 2 days the excess methanol was removed in vacuo and the aqueous was cooled to 0 °C and acidified with conc HCl. The aqueous was extracted with ethyl acetate (2 × 25 mL) and the combined organics washed with brine and dried over magnesium sulfate. The solvent was removed in vacuo and the residue (0.59 g yellow oil) was filtered through silica using ethyl acetate as the eluent to give 487 mg product (76% yield) as a yellow oil. R_f (ethyl acetate, PMA) = 0.31.

^{1}H NMR (500 MHz, 320 K, $CDCl_3$): 7.69 (d, 1H, J = 12.5 Hz); 5.54 (s, 1H); 5.28 (d, 1H, J = 12.5 Hz); 4.15–3.93 (m, 1H); 3.88–3.59 (m, 2H); 3.50–3.12 (m, 4H); 2.75–2.41 (m, 4H); 2.45 (t, 2H, J = 7.0 Hz); 2.39–2.12 (m, 6H); 2.10–1.97 (m, 2H); 1.93–1.31 (m, 20H).

^{13}C NMR (125.7 MHz, 320 K, $CDCl_3$): 211.84; 198.77; 175.76; 155.02; 153 (b); 131 (b); 124 (b); 92 (b); 80.87; 80.06; 79.52; 72 (b); 64.5 (b); 45.76; 41 (b); 39.72; 32.96; 32 (b); 28.49; 25.90; 25.40; 25.04; 23.91; 18.59; 18.37.

Mass spectrum *m/z* (rel. int.): 529 (M+1, 24); 429 (22); 304 (100); 249 (35); 140 (50).

HRMS calculated for $C_{30}H_{44}O_6N_2$ (M+1): 529.3277 found: 529.3291.

Dicyclohexylcarbodiimide (81 mg, 0.39 mmol) in dichloromethane (1 mL) was added dropwise to the acid (157 mg, 0.297 mmol) and pentafluorophenol (69 mg, 0.37 mmol) in dichloromethane (2 mL) at 0 °C. After stirring for 2 h the solvent was removed in vacuo and the residue purified by flash chromatography using 40% ethyl acetate/petroleum ether as the eluent to give 190.1 mg (92% yield) of ester as a foam. R_f (80% ethyl acetate/petroleum ether, PMA) = 0.60.

^{1}H NMR (500 MHz, $CDCl_3$): 7.70–7.45 (m, 1H); 5.49 (s, 1H); 5.21 (d, 1H, J = 13.0 Hz); 4.11–3.77 (bm, 1H); 3.74–3.61 (m, 2H); 3.50–3.00 (m, 3H); 2.75 (t, 2H, J = 7.5 Hz); 2.63–2.50 (m, 1H); 2.43 (t, 2H, J = 6.9 Hz); 2.35–2.11 (m, 6H); 2.09–1.20 (m, 22H).

^{13}C NMR (125.7 MHz, $CDCl_3$, rotamers): 212 (b); 197.54; 169.05; 154.62; 152.07; 141.99; 140.34; 138.78; 136.76; 131.17; 123.90; 97.31; 81.19; 79.57; 78.46; 73.13; 63.52; 54 (b); 48.85; 46.28; 45.92; 45.32; 40.56; 39.50; 33.90; 32.01; 30.79; 28.34; 26.91; 25.78; 25.05; 24.87; 24.61; 23.94; 18.41; 17.94.

IR (neat, cm^{-1}): 2910; 1775; 1685; 1650; 1555; 1510; 1405; 1355; 1235.

Mass spectrum *m/z* (rel. int.): 717 (M+23, 100); 695 (29); 595 (17); 500 (5); 470 (58).

HRMS calculated for $C_{36}H_{43}O_6N_2F_5$ (M+Na): 717.2939 found: 717.2931.

A solution of trifluoroacetic acid (21 mL) and anisole (6 mL) were added dropwise over 5 min to the vinylogous amide (363 mg, 0.522 mmol) in dichloromethane (46 mL). After stirring overnight the solvent was removed in vacuo. The crude trifluoroacetate salt was dissolved in acetonitrile (42 mL) and added over 25 h to Hünig's base (21 mL) in refluxing acetonitrile (70 mL). The mixture was refluxed for an additional 18 h after the addition of substrate. The solvent was removed in vacuo and the residue (0.783 g black/brown oil) was purified by flash chromatography using ethyl acetate as the eluent to give 182.3 mg of **82** as a white foam (85% yield for 2 steps).

cis-Alcohol 83

L-Selectride (1.0 M tetrahydrofuran, 0.5 mL) was added dropwise to the macrocycle **82** (91.0 mg, 0.222 mmol) in tetrahydrofuran (7.3 mL) at –78 °C. After 1 h saturated ammonium chloride (5 mL) was added and the dry ice bath removed. At room temperature enough water was added to dissolve the precipitate. The solution was extracted with methylene chloride (3 × 20 mL). The combined organics were washed with brine and dried over magnesium sulfate. The solvent was removed in vacuo and the residue purified by flash chromatography using 5% isopropyl alcohol/ethyl acetate as the eluent to give 70.9 mg (78% yield) of **83** as a clear film. R_f (90% ethyl acetate/isopropyl alcohol, PMA) = 0.30.

^{1}H NMR (500 MHz, 360 K, toluene-d_8): 7.88–7.55 (bm, 1H); 5.42 (s, 1H); 5.14 (d, 1H, J = 12.9 Hz); 3.85–3.21 (m, 6H); 3.19–3.03 (m, 1H); 2.82–2.60 (m, 2H); 2.55–1.69 (m, 14H); 1.65–0.75 (m, 10H).

^{13}C NMR (500 MHz, $CDCl_3$, rotamers): 197.45; 171.40; 149.51; 132.65; 183.57; 98.22; 81.30; 80.85; 80.15; 73.91; 72.35; 64.89; 51 (b); 48.15; 42.08; 37.85; 36.92; 36.02; 34.1; 33.19; 32.53; 29.73; 27.32; 25.49; 24.94; 24.75; 23.66; 22.86; 22.04; 18.32; 17.48; 17.12.

IR (neat, cm^{-1}): 3410; 2955; 1650; 1610; 1560; 1440; 1245.

Mass spectrum *m/z* (rel. int.): 413 (M+1, 38); 217 (30); 131 (100).

HRMS calculated for $C_{25}H_{36}N_2O_3$ (M+1): 413.2790 found: 413.2804.

Macrocyclic Alkene 85

Hydrogen was purged for 46 min through ethyl acetate (15 mL) and pyridine (15 mL) containing the alkyne **83** (199 mg, 0.482 mmol) and 5% palladium on barium sulfate (40.5 mg). The solution was then stirred under a hydrogen atmosphere for 45 min. The flask was purged with argon and the contents were filtered through Celite to give 215 mg of **85** as a foam. R_f (10% ethanol/ethyl acetate, PMA) = 0.23.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers): 7.98 (d, 0.7H, J = 12.2 Hz); 7.70–7.41 (bm, 0.3H); 5.74 (s, 0.6H); 5.61 (s, 0.4H); 5.41–5.20 (m, 2H); 5.18–5.02 (m, 1H); 4.49–4.35 (m, 0.5H); 4.05–3.05 (m, 9H); 2.90–2.58 (m, 2H); 2.52–1.12 (m, 20H); 0.95–0.75 (m, 2H).

^{13}C NMR (125.7 MHz, $CDCl_3$, rotamers): 198.46; 172.36; 171.45; 154.23; 149.80; 133.10; 130.67; 130.31; 129.84;

129.47; 126.0; 124.34; 123.43; 96.55; 73.87; 71.92; 70.46; 65.45; 61.81; 52.14; 48.81; 43.57; 42.44; 38.70; 37.86; 36.61; 33.90; 33.49; 32.99; 29.66; 27.40; 26.93; 26.67; 26.13; 25.84; 25.28; 24.86; 24.77; 22.01; 21.34.

IR (neat, cm^{-1}): 3380; 2935; 1615; 1550; 1440; 1240.

Mass spectrum *m/z* (rel. int.): 415 (M+1, 100); 357 (14); 314 (19); 233 (19); 196 (48).

HRMS calculated for $C_{25}H_{38}N_2O_3$ (M+1): 415.2960 found: 415.2943.

Photolysis of 85

Argon was purged for 30 min through acetonitrile (100 mL) containing the vinylogous amide **85** (11.8 mg, 0.0285 mmol). The solution was irradiated through a Pyrex filter for 1 h. The solvent was removed in vacuo to give 18.8 mg brown film. Proton NMR of the residue suggested the presence of an iminium moiety. To the residue was added acetonitrile (10 mL) and 4-dimethylaminopyridine (12 mg, 0.098 mmol). After refluxing for 7.5 h the solvent was removed in vacuo and the residue purified by flash chromatography using 80% ethyl acetate/hexane as the eluent to give 4.0 mg of **89** (34% yield). R_f (90% ethyl acetate/isopropyl alcohol, PMA) = 0.55.

^{1}H NMR (500 MHz, $CDCl_3$): 5.61 (s, 1H); 4.62 (d, 1H, J = 9.25 Hz); 4.15–4.05 (m, 1H); 3.97–3.80 (m, 2H); 3.70–3.49 (m, 2H); 3.00–2.86 (m, 2H); 2.49–1.80 (m, 10H); 1.79–1.02 (m, 16H); 0.91–0.68 (m, 3H).

^{13}C NMR (125.7 MHz, $CDCl_3$): 212.3; 172.8; 132.9; 122.0; 96.1; 79.7; 69.36; 56.35; 50.87; 47.29; 45.07; 41.44; 39.10; 39.06; 38.51; 36.19; 33.63; 29.69; 28.07; 27.00; 25.90; 25.48; 25.25; 24.72; 22.72.

IR (neat, cm^{-1}): 2930; 1710; 1640; 1450; 1225.

Mass spectrum *m/z* (rel. int.): 414 (M^+, 100); 386 (8); 357 (8); 317 (13); 233 (35); 121 (100).

HRMS calculated for $C_{25}H_{38}N_2O_3$ (M^+): 414.2882 found: 414.2885.

Saturated Macrocyclic Vinylogous Amide 86

The alkene **85** (9.3 mg, 0.022 mmol) and RhCl $(PPh_3)_3$ (18 mg) in benzene (10 mL) were stirred under a hydrogen atmosphere for 48 h. The contents were adsorbed on silica and purified by flash chromatography using 95% ethyl acetate/isopropyl alcohol as the eluent to give 7.1 mg of **86** and 3.7 mg of a mixture of starting material and product (>76% yield). R_f (80% ethyl acetate/ethyl alcohol, PMA) = 0.32.

^{1}H NMR (500 MHz, 360 K, toluene-d_8): 8.05–7.70 (bm, 1H); 5.52 (s, 1H); 5.12 (d, 1H, J = 12.8 Hz); 4.44–3.86 (bm, 1H); 3.76–3.69 (m, 1H); 3.65–3.10 (m, 3H); 2.97–2.62 (m, 2H); 2.41–2.21 (m, 3H); 2.20–2.10 (m, 2H); 2.00–1.91 (m, 1H); 1.90–1.81 (m, 1H); 1.80–1.12 (m, 23H).

^{13}C NMR (125.7 MHz, toluene-d_8): 198.30; 197.35; 171.53; 170.77; 152.98; 151.09; 135.05; 133.35; 123.80; 122.68; 94.97; 73.18; 71.82; 66.66; 52.1; 49.32; 43.74; 43.06; 42.58; 41.82; 38.24; 37.2; 36 (b); 34.39; 34.02; 32.98; 32.27; 28.64; 28.56; 28.29; 28.18; 27.91; 27.63; 27.59; 27.47; 26.86; 26.75; 25.92; 25.41; 25.37; 25.18; 25.00; 22.68.

IR (neat, cm^{-1}): 3375; 1660; 1570; 1460; 1310.

Mass spectrum *m/z* (rel. int.): 417 (M+1, 100); 154 (54); 136 (68); 107 (42).

HRMS calculated for $C_{25}H_{40}N_2O_3$ (M+1): 417.3117 found: 417.3105.

Acyclic cis-Alcohol 91

L-Selectride (1.0 M in tetrahydrofuran, 2.8 mL) was added dropwise to the ketone **90** (952 mg, 1.71 mmol) in tetrahydrofuran (20 mL) at –78 °C. After 43 min saturated aqueous ammonium chloride (3 mL) was added and the mixture was warmed to room temperature. Saturated sodium bicarbonate (20 mL) was added and the mixture was extracted with chloroform (3 × 10 mL). The ether extract was washed with brine and dried over magnesium sulfate. The solvent was removed in vacuo and the residue (1.7 g yellow oil) purified by flash chromatography using ethyl acetate as the eluent to give 359 mg of **91** and 234 mg of slightly impure **91** (>60% yield). R_f (ethyl acetate, PMA) = 0.26.

^{1}H NMR (500 MHz, $CDCl_3$): 7.79 (d, 1H, J = 13.0 Hz); 5.54 (s, 1H); 5.05 (d, 1H, J = 13. Hz); 4.06 (q, 2H, J = 7.2 Hz); 3.80–3.61 (m, 3H); 3.51–3.42 (m, 1H); 3.40–3.29 (m, 3H); 2.94–2.88 (m, 1H); 2.60–2.52 (m, 1H); 2.43–2.31 (m, 3H); 2.35 (t, 2H, J = 7.6 Hz); 2.20–2.10 (m, 4H); 2.05–1.96 (m, 2H); 1.80–1.52 (m, 12H); 1.40 (s, 9H); 1.39–1.29 (m, 1H); 1.19 (t, 3H, J = 7.2 Hz).

^{13}C NMR (125.7 MHz, $CDCl_3$): 197.58; 173.37; 154.73; 150.98; 131.86; ; 123.19; 96 (b); 80.70; 79.50; 79.14; 72.54; 62.47; 60.23; 50.51; 46.1 (b); 45.3 (b); 40.70; 39.44; 36.52; 33.38; 33.14; 28.38; 27.40; 25.17; 24.95; 24.26; 21.86; 18.51; 18.21; 14.12.

IR (neat, cm^{-1}): 3374; 2930; 1732; 1695; 1552; 1421; 1365; 1286; 1244.

Mass spectrum *m/z* (rel. int.): 559 (M+1, 94); 459 (11); 351 (28); 325 (29); 225 (100).

HRMS calculated for $C_{32}H_{50}N_2O_6$ (M+1): 559.3747 found: 559.3741.

Preparation of Tetracyclic Ketones 92 and 93

Argon was purged for 30 min through an acetonitrile (70 mL) solution containing the cis-alcohol **91** (97 mg, 0.174 mmol). The solution was then irradiated through a pyrex filter while maintaining an argon purge. The temperature of the solution was maintained at 17 °C during the photoylsis. After 3 h the solvent was removed in vacuo and to the residue was added acetonitrile (4 mL) and triethylamine hydrochloride (27 mg, 0.196 mmol). After stirring for for 2 days the solvent was removed in vacuo and to the residue was added acetonitrile (5 mL) and 4-dimethylaminopyridine (28 mg, 0.223 mmol). The solution was then refluxed 8 h and then stirred overnight at room temperature. The solvent was removed in vacuo and to the residue was added 10% potassium carbonate (20 mL). The aqueous was extracted with ethyl ether (3 × 15 mL) and the combined organics were washed with brine and dried over magnesium sulfate. The solvent was removed in vacuo and the residue purified by flash chromatography using 60% petroleum ether/ethyl ether to ethyl ether as the eluent, to give 22.5 mg of **92** and 13.8 mg of **93**. R_f (ethyl ether, PMA) = 0.65 and 0.41, respectively.

Data for **92**

^{1}H NMR (500 MHz, $CDCl_3$): 4.09 (q, 2H, J = 7.1 Hz); 3.53 (d, 1H, J = 13.8 Hz); 3.50–3.45 (m, 1H); 3.32–3.26 (m, 1H); 3.06–2.81 (m, 3H); 2.72–2.64 (m, 3H); 2.52–2.42 (m, 2H);

2.36 (t, 2H, J = 7.4 Hz); 2.31–2.17 (m, 3H); 2.12–2.00 (m, 3H); 1.89–1.65 (m, 10H); 1.62–1.31 (m, 6H); 1.42 (s, 9H); 1.22 (t, 3H, J = 7.1 Hz); 1.21–1.12 (m, 1H).

^{13}C NMR (500 MHz, $CDCl_3$): 211.02; 173.29; 154.68; 81.34; 79.98; 79.82; 75.74; 69.17; 67.00 (b); 62.42; 60.20; 53.42; 50.8 (b); 49.7 (b); 45.02; 42.48; 39.5 (b); 36.97; 33.95; 33.32; 28.96; 28.42; 27.74; 25.56; 24.21; 19.41; 18.25; 17.37; 14.20.

IR (neat, cm^{-1}): 2926; 1734; 1696; 1430; 1365; 1247; 1156.

Mass spectrum *m/z* (rel. int.): 559 (M+1, 33); 459 (5); 260 (41); 126 (100).

HRMS calculated for $C_{32}H_{50}N_2O_6$ (M+1): 559.3746 found: 559.3756.

Data for **93**

^{1}H NMR (500 MHz, $CDCl_3$): 4.10 (q, 2H, J = 7.1 Hz); 3.60 (d, 1H, J = 13.2 Hz); 3.56–3.50 (m, 1H); 3.18–3.04 (m, 2H); 3.01–2.76 (m, 3H); 2.71–2.60 (m, 1H); 2.37 (t, 2H, J = 7.5 Hz); 2.29–1.91 (m, 10H); 1.82–1.60 (m, 10H); 1.57–1.33 (m, 5H); 1.45 (s, 9H); 1.23 (t, 3H, J = 7.1 Hz); 1.29–1.19 (m, 1H).

^{13}C NMR (125.7 MHz, $CDCl_3$): 211.85; 173.17; 154.79; 80.35; 80.21; 79.87; 74.88; 69.73; 65.68; 60.26; 52.32; 51.27; 43.45; 42.39; 41.56; 38.93; 36.27; 33.76; 33.20; 30.36; 29.67; 28.47; 27.64; 27.41; 25.12; 24.30; 21.1 (b); 18.23; 17.15; 14.22.

IR (neat, cm^{-1}): 2926; 1733; 1694; 1430; 1365; 1247; 1156.

Mass spectrum *m/z* (rel. int.): 559 (M+1, 19); 358 (14); 240 (33); 126 (100).

HRMS calculated for $C_{32}H_{50}N_2O_6$ (M+1): 559.3746 found: 559.3764.

Preparation of 94 and 95

(The diastereomers **92** and **93** were separated and converted to **95** and **94**, respectively. However the yields were higher if **92** and **93** were converted to **94** and **95** as a diastereomeric mixture and then separated at the pentafluoro ester stage): Dimethyl sulfoxide (110 mg, 1.41 mmol) in dichloromethane (1.4 mL) was added dropwise to oxalyl chloride (80 mg, 0.63 mmol) in dichloromethane (1.5 mL) at –60 °C. After 5 min a mixture of **92** and **93** (0.32 g, 0.573 mmol) in dichloromethane (2 mL) was added dropwise. After 10 min triethylamine (0.4 mL, 7.2 mmol) was added and the cold bath removed. After warming to room temperature, aqueous pH7 buffer (5 mL) was added and the mixture extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over magnesium sulfate and removed in vacuo to give 0.292 g oil (crude yield 92%).

Data for **93a**

R_f (90% ethyl ether/petroleum ether, PMA) = 0.45.

^{1}H NMR (500 MHz, $CDCl_3$, 320 K): 4.11 (q, 2H, J = 7.1 Hz); 3.60–3.51 (m, 1H); 3.39–3.28 (m, 2H); 3.18–3.02 (m, 3H); 3.44–2.74 (m, 3H); 2.51 (dd, 2H, J = 18.3, 7.2 Hz); 2.37 (t, 2H, J = 7.4 Hz); 2.30–2.11 (m, 6H); 2.09–1.95 (m, 4H); 1.86–1.61 (m, 7H); 1.58–1.40 (m, 3H); 1.46 (s, 9H); 1.23 (t, 3H, 7.1 Hz); 1.08–0.97 (m, 1H).

^{13}C NMR (125.7 MHz, $CDCl_3$): 219.39; 211.88; 173.11; 154.88; 80.15; 80.02; 71.58; 60.29; 57.67; 51.48; 50.58 (b); 44.89; 40.77; 38.16; 36.74; 36.12; 33.20; 30.57; 29.25; 29.18; 28.43; 27.48; 26.08; 25.83; 24.27; 18.27; 17.26; 14.22.

IR (neat, cm^{-1}): 2931; 1732; 1698; 1428; 1366; 1280; 1248.

Mass spectrum *m/z* (rel. int.): 557 (M+1, 100); 391 (10); 140 (15).

HRMS calculated for $C_{32}H_{48}N_2O_6$ (M+H): 557.3590 found: 557.3576.

Lithium hydroxide (150 mg, 3.57 mmol) in water (6 mL) was added to the ethyl ester **92a** and **93a** (0.29 g, 0.52 mmol) in methanol (18 mL). After stirring for 48 h the excess solvent was removed in vacuo and to the residue was added pH 7 buffer (15 mL). The mixture was extracted with ethyl acetate (3 × 10 ml) and the combined organics dried over magnesium sulfate. The solvent was removed in vacuo to afford 0.274 g acid (quantitative crude yield). R_f (ethyl acetate, PMA) = 0.26 (streak). Dicyclohexyl carbodiimide (27 mg, 0.13 mmol) in dichloromethane (0.8 mL) was added dropwise to the crude acid (46 mg, 0.087 mmol) and pentafluorophenol (24 mg, 0.13 mmol) in dichloromethane (1 mL). After stirring 2 h the solvent was removed in vacuo and the residue purified by flash chromatography using 70% ethyl ether/hexane as the eluent to give 43 mg of **94/95** as a foam (71% yield).

Data for **95**

R_f (ethyl ether/petroleum ether, PMA) = 0.41.

^{1}H NMR (500 MHz, $CDCl_3$): 4.03 (d, 1H, J = 7.4 Hz); 3.68–3.55 (bm, 1H); 3.51–3.35 (m, 2H); 3.30–3.20 (m, 1H); 3.16–3.06 (m, 1H); 3.04–2.86 (m, 2H); 2.77 (t, 2H, J = 7.4 Hz); 2.61–2.50 (m, 1H); 2.35–2.04 (m, 3H); 2.02–1.86 (m, 4H); 1.84–1.63 (m, 4H); 1.62–1.38 (m, 3H); 1.46 (s, 9H); 1.38–0.96 (m, 9H).

IR (neat, cm^{-1}): 2926; 1788; 1694; 1624; 1520; 1428; 1246.

Mass spectrum *m/z* (rel. int.): 717 (M+Na, 66); 695 (100); 666 (28); 639 (59); 490 (24); 391 (58).

HRMS calculated for $C_{36}H_{43}F_5N_2O_6$ (M+Na): 717.2939 found: 717.2956.

Data for **92a**

R_f (90% ethyl ether/petroleum ether, PMA) = 0.58.

^{1}H NMR (500 MHz, $CDCl_3$, 320 K): 4.09 (q, 2H, J = 7.1 Hz); 3.78–3.41 (bm, 2H); 3.32–3.22 (m, 2H); 3.18–2.88 (bm, 1H); 2.86–2.76 (m, 2H); 2.70–2.57 (m, 1H); 2.42–2.12 (m, 9H); 2.36 (t, 2H, J = 7.5 Hz); 2.05–1.49 (m, 3H); 1.84–1.66 (m, 6H); 1.62–1.39 (m, 4H); 1.47 (s, 9H); 1.36–1.29 (m, 1H); 1.22 (t, 3H, J = 7.2 Hz); 1.11–1.01 (m, 1H).

^{13}C NMR (125.7 MHz, $CDCl_3$): 219.17; 211.54; 173.07; 154.58; 80.57; 80.25 (b); 79.70; 71.99 (b); 60.31; 58.86; 52.5 (b); 47.92; 45.83; 40.36; 39.58; 38.24; 36.94; 35.83; 33.24; 30.58; 28.37; 27.88; 27.19 (b); 26.02 (b); 25.29 (b); 24.29; 18.29; 17.19; 14.21.

IR (neat, cm^{-1}): 2928; 1732; 1699; 1428; 1366; 1279; 1248.

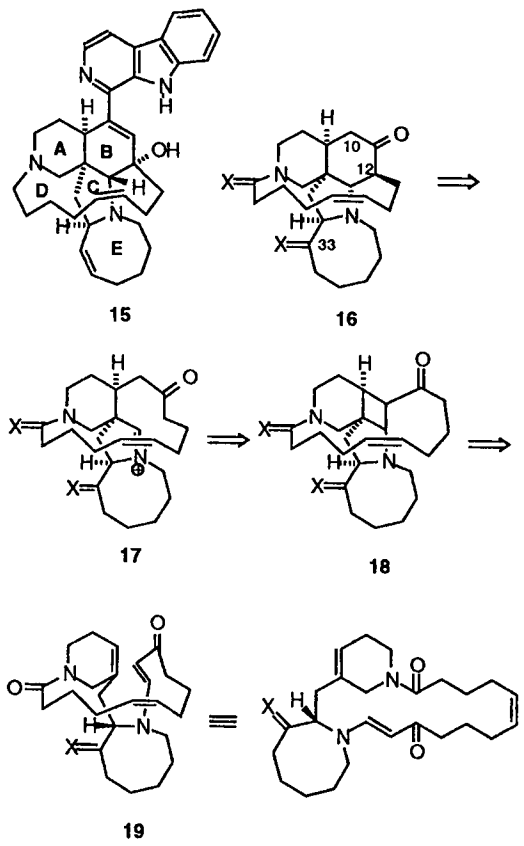
Mass spectrum *m/z* (rel. int.): 557 (M+1, 74); 391 (9); 276 (100); 124 (22).

HRMS calculated for $C_{32}H_{48}N_2O_6$ (M+H): 557.3590 found: 557.3584.

Data for **94**

R_f (ethyl ether/petroleum ether, PMA)= 0.49.

^{1}H NMR (500 MHz, $CDCl_3$): 4.12–4.06 (bm, 0.4H); 3.89–3.69 (m, 0.6H); 3.57–3.36 (m, 1H); 3.32–3.19 (m, 2H); 3.11–2.88 (m, 1H); 2.85–2.52 (m, 3H); 2.75 (t, 2H, J = 7.4 Hz); 2.48–2.11 (m, 9H); 2.07–1.88 (m, 5H); 1.86–1.62 (m, 6H); 1.61–1.17 (m, 12H); 1.10–0.98 (m, 1H).



Scheme 5

^{13}C NMR (125.7 MHz, $CDCl_3$, rotamers): 219.13; 211.46; 169.00; 154.72; 142.17; 140.17; 138.89; 136.88; 81.31; 80.49; 78.83; 72.65; 58.86; 53.1 (b); 47.93; 45.81; 40.36; 39.70; 38.22; 36.97; 35.89; 33.91; 32.14; 30.57; 28.36; 27.89; 26.03; 25.3 (b); 24.02; 18.05; 17.20.

IR (neat, cm^{-1}): 2929; 1791; 1700; 1521; 1429; 1366; 1279; 1249.

Mass spectrum *m/z* (rel. int.): 717 (M+Na, 73); 695 (100); 666 (25); 639 (69); 375 (77).

HRMS calculated for $C_{36}H_{43}F_5N_2O_6$ (M+Na): 717.2939 found: 717.2958.

Synthesis of Pentacyclic Manzamine ***96***

Trifluoroacetic acid (1.93 mL) was added dropwise to the tetracycle **94** (34 mg, 0.0489 mmol) and anisole (0.4 mL) in dichloromethane (4.1 mL). After stirring for 6 h the solvent was removed in vacuo. The residue was diluted with acetonitrile (15 mL) and the solution added by syringe pump over 9 h to Hünig's base (2.5 mL) in refluxing acetonitrile (37 mL). After a total of 21 h at reflux the solution was cooled to room temperature and the excess solvent was removed in vacuo. To the residue was added 10% potassium carbonate (10 mL) and the mixture extracted with chloroform (3 × 5 mL). The combined organic phases were washed with brine and dried over magnesium sulfate. The solvent was removed in vacuo to give 33.4 mg of residue. Purification by flash chromatography using 90% ethyl acetate/hexane to 5% methanol/ethyl acetate gave 10.3 mg of pentacycle **96** (51% yield). mp slow decompositon at 180 °C. R_f (ethyl acetate, PMA) = 0.29. (Cyclization of **95** gave a 47% yield of **96**).

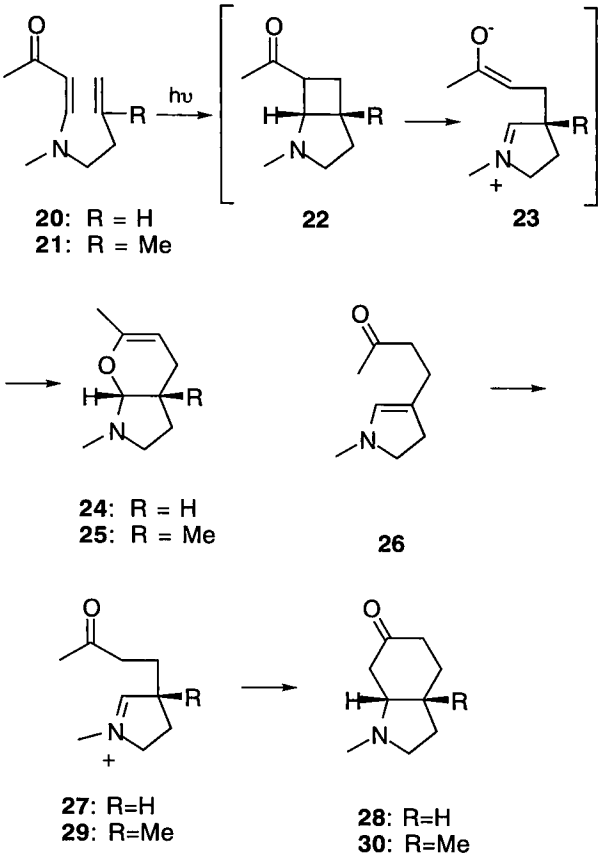
^{1}H NMR (500 MHz, $CDCl_3$, rotational isomers): 4.54 (dd, 1H, J = 13.3, 1.8 Hz); 4.15 (d, 1H, J = 7.6 Hz); 3.93–3.85 (m, 1H); 3.46 (dd, 1H, J = 11.9, 6.7 Hz); 3.21–3.08 (m, 1H); 3.06 (dd, 1H, J = 12.7, 3.7 Hz); 3.00 (dd, 1H, J = 13.8, 3.0 Hz); 2.83–2.59 (m, 4H); 2.55–2.04 (m, 9H, 2.02–1.72 (m, 6H); 1.64–1.41 (m, 5H); 1.31–116 (m, 2H); 1.10–0.95 (m, 1H).

^{13}C NMR (125.7 MHz, $CDCl_3$): 221.25; 209.53; 169.84; 83.26; 80.07; 71.57; 66.32; 58.25; 57.89; 48.84; 46.60; 45.72; 42.13; 38.34; 37.94; 36.11; 30.81; 30.00; 29.81; 28.46; 26.50; 23.23; 20.50; 16.09; 14.19.

IR (neat, cm^{-1}): 2924; 1699; 1641; 1452.

Mass spectrum *m/z* (rel. int.): 411 (M+1, 100); 382 (31); 272 (11); 162 (8).

HRMS calculated for $C_{25}H_{34}N_2O_3$ (M+1): 411.2647 found: 411.2658.



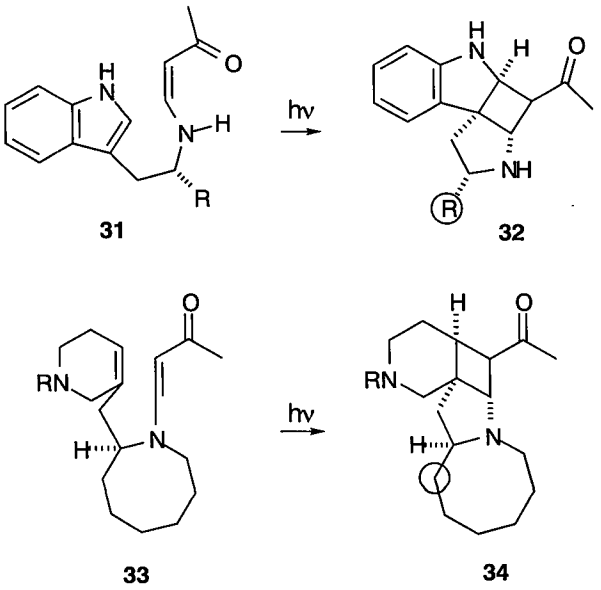
Scheme 6

RESULTS AND DISCUSSION

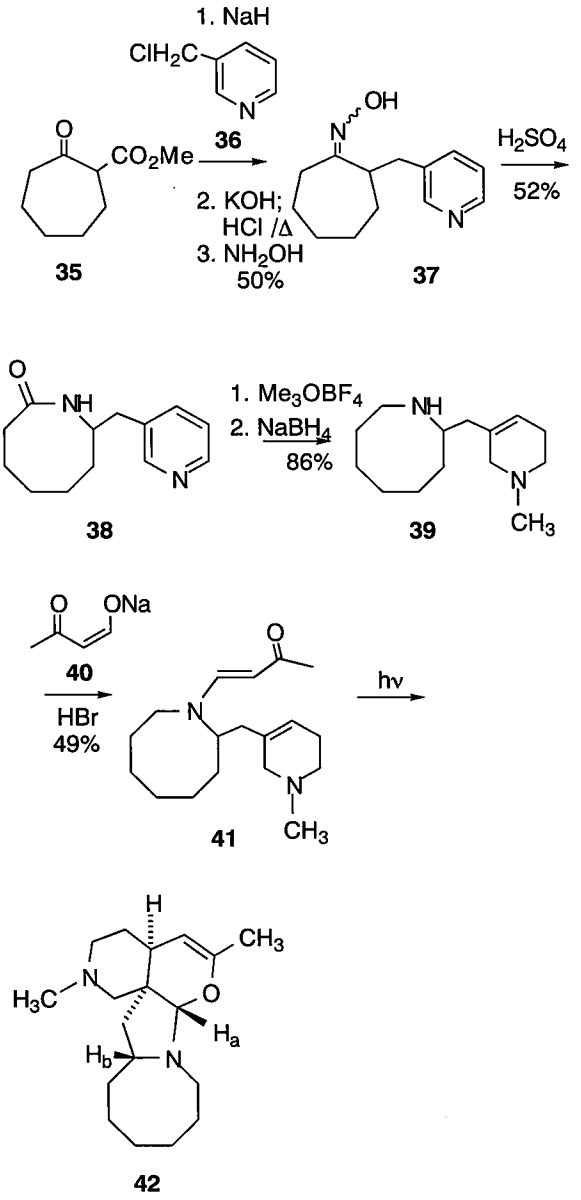
Our retrosynthetic analysis is outlined in Scheme **5**. We reasoned that C-11 ketone **16**, which embodies the perhydroindolone retron that results from the pharM sequence, would serve as a suitable precursor for incorporation of the C-10 β-carboline and the C-12 tertiary hydroxyl. Also, the alkene of eight-membered ring unsaturation could be derived from a suitable substituent (X) at C-33. The pentacycle **16** could be derived from Mannich closure of the ketoiminium **17**, which could in turn be derived from the retro-Mannich fragmentation of the cyclobutane **18**. The cyclobutane **18** would be derived from the transannular [2+2] photocycloaddition of macrocyclic vinylogous amide **19**. This retrosynthesis represents a highly efficient construction in which an ADE* substrate is converted essentially in one pot to the ABCDE pentacycle of manzamine.

Before testing the proposed retrosynthetic analysis, it was necessary to establish that the intramolecular vinylogous amide photoaddition/fragmentation methodology could be extended to the photocycloaddition of tertiary vinylogous amides, i.e., lacking the N–H bond present in the previously described secondary vinylogous amide photosubstrates (Scheme 2). These tertiary vinylogous amides would necessarily not (1) enjoy the hydrogen-bonding stabilization of the excited state chromophore or (2) produce zwitterionic fragmentation products which could lead to neutral ketoimines via proton transfer.

In the event, irradiation of the tertiary vinylogous amide **20** produced a mixture of aminal **24** and keto-



Scheme 7



Scheme 8

enamine **26** (Scheme 6). Treatment of the mixture with wet acetonitrile gives exclusively ketoenamine **26**, which can be converted to the ketoiminium **27** by treatment with glacial acetic acid. Photolysis of **21**, where the formation of an enamine moiety is precluded, led exclusively to the aminal **25**. Treatment of **25** with triethylammonium hydrochloride gave the ketoiminium **29**. Alternatively, photolysis of **21** in the presence of triethylamine hydrochloride directly gave the ketoiminium **29**. The ketoiminiums **27** and **29** have previously been cyclized to the Mannich products **28** and **30**, respectively, thereby unequivocally establishing

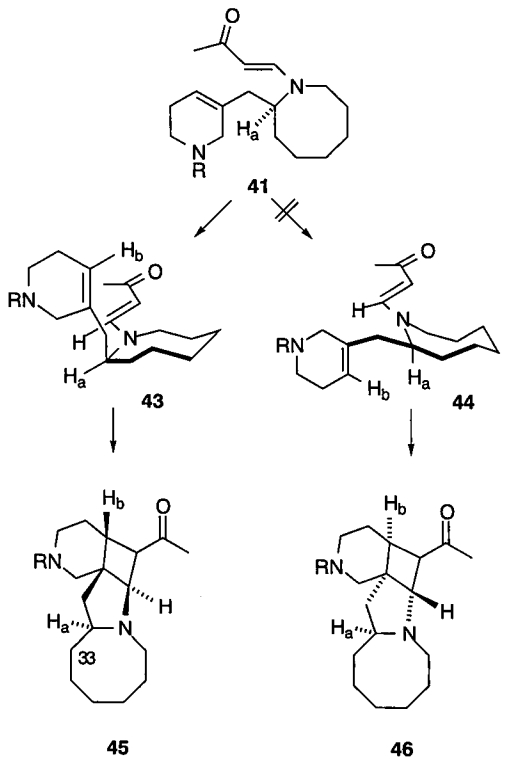
the viability of the tertiary vinylogous amides in the reaction sequence.[9]

Synthesis of the Tetracyclic Core of the Manzamine Alkaloids

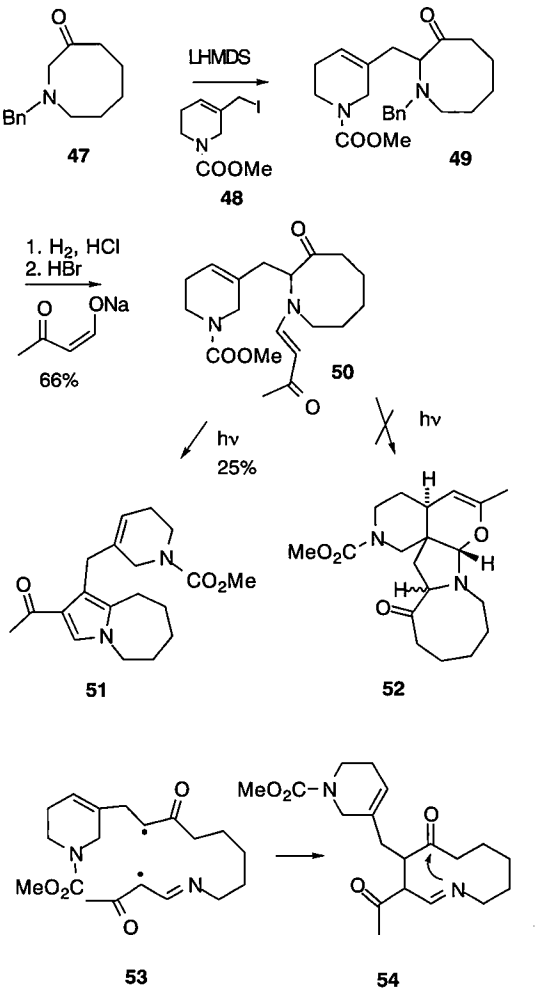
While the model studies with simple acyclic tertiary vinylogous amides suggested that the desired photocycloaddition was feasible, the level and sense of asymmetric induction in the photocycloaddition of tertiary vinylogous amides was not known. Previous results from our laboratory had established that high levels of asymmetric induction are possible with acyclic secondary amides (**31** to **32**, Scheme 7). It is important to note, however, that the sense of asymmetric induction observed in the irradiation of **31** is opposite to that which is required for the synthesis of manzamine, **33**→**34**. That is, the substituent R (circled) is on the concave face of the 4–5 ring system in **32**. For the proposed manzamine construction, the analogous substituent (circled) must be on the convex face of the 4–5 ring system in **34**. One of the primary goals of this preliminary study was therefore to determine if the sense of induction would be the same for secondary (H-bonding) and tertiary (non-H-bonding) vinylogous amide photosubstrates.

We first examined the viability of the proposed pharM sequence for the synthesis of manzamine with photosubstrate **41**, the synthesis of which is outlined in Scheme 8. Alkylation of cycloheptanone-2-methylcarboxylate with 3-pyridyl methyl chloride **36**, followed by ester hydrolysis, decarboxylation, and treatment with hydroxylamine gave **37**. Exposure of oxime **37**, as a 55:45 mixture of geometric isomers, to acidic Beckmann rearrangement conditions afforded lactam **38** as the major product. The alternative Beckmann rearrangement product (not shown), resulting from the migration of the unsubstituted methylene group, was obtained in 43% yield. The lactam **38** was treated with two equivalents of trimethyloxonium tetrafluoroborate followed by reduction with sodium borohydride to afford the substituted azocine **39**. Condensation of **39** with sodium formyl acetone **40** gave the desired photosubstrate **41**.

Photolysis of a benzene solution of **41** produced the

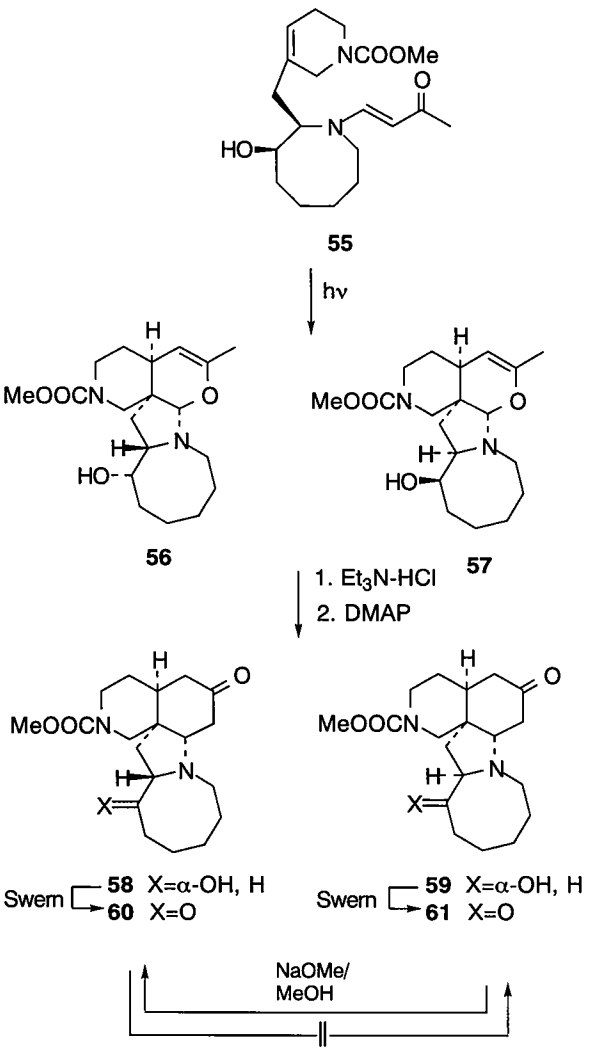


Scheme 9



Scheme 10

aminal **42** as a single diastereomer (Scheme 8). The relative relationship of H_a and H_b was established by an nOe experiment. Irradiation of H_a produced a 15% nOe enhancement of H_b. While this result establishes that a manzamine tetracycle can be prepared via the pharM cascade, the trans relative stereochemistry of H_a and H_b, which is required for the stereoselective synthesis of the manzamine nucleus, remains to be established. This stereochemical outcome, albeit disappointing in the context of the proposed manzamine synthesis, was consistent with the results obtained in our vindorosine construction, i.e., Scheme 7,[10] and can be explained with the conformations shown in Scheme 9. Assuming an sp2-hybridized nitrogen conjugated to the enone chromophore, allylic strain should fix the vinylogous amide stereochemistry as shown with the enone oriented away from the tetrahydropiperidinomethyl group. X-ray and experimental data have established that 2-alkyl substituents on N-acyl piperidines and related systems prefer a pseudoaxial orientation as shown in **43**. As the photocycloaddition of a 1,6-heptadiene necessarily leads to the formation of a cis-fused bicyclo [3.2.0] heptane moiety, the cycloaddition of **43** must occur from the top face of the vinylogous amide to give **45**, in which the undesired trans relationship of H_a and H_b is necessarily established. Alternatively, approach of the pseudoequatorially oriented piperidinomethyl group to the bottom face of the vinylogous amide, the less favored pathway shown in **44** that would lead to the formation of **46**, is not observed. Since epimerization of H_a leads to the effective interconversion of **45** and **46** via the corresponding enantiomers, introduction of a carbonyl group at C-33 could permit the establishment of the correct relative stereochemistry in the manzamine tetracycle, as the eight-membered ring in **44** should be more stable on the convex face of the BC ring system, i.e., **46**.

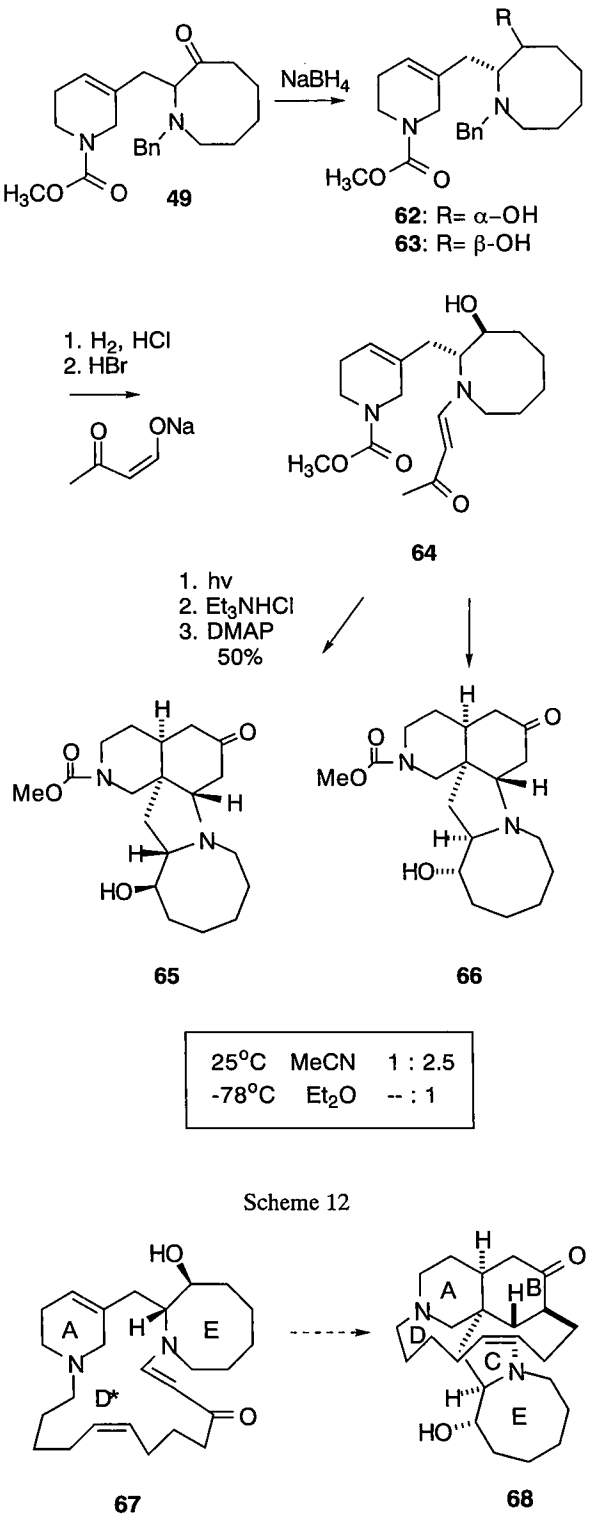


Scheme 11

The synthesis of the C-33 keto photosubstrate **50** is outlined in Scheme 10. Regioselective alkylation of the conjugate base of azacyclooctanone **47**,[11] with allylic iodide **48** gave **49**. Debenzylation of the amine followed by condensation with sodium formyl acetone afforded the C-33 keto photosubsubstrate **50**. Irradiation of **50** led to the rapid formation of a new product, the spectroscopic properties of which were not consistent with those of the desired aminal **52**,[12] but rather with the ring-contracted pyrrole **51**. The formation of **51** could be rationalized by homolytic cleavage of the carbon–nitrogen bond as shown in **53**, followed by cyclization of the resulting diradical to ten-membered ring ketoimine **54**, which undergoes transannular condensation to form the observed pyrrole product.

To preclude the alpha cleavage of the azocinone ring that begins the cascade of reactions leading to the formation of the pyrrole product **51** (Scheme 10), we turned to the C-33 carbinol photosubstrate **55**, which was readily available as the cis isomer via reduction of **50** with L-Selectride. Photolysis of the cis-alcohol **55** afforded a 2:1 mixture of aminals **56** and **57**, which were not isolated but treated directly with triethylamine hydrochloride (to convert the aminal to ketoiminium) followed by 4-dimethylaminopyridine (to effect Mannich closure) to afford tetracycles **58** and **59**. The relative stereochemical relationships in the major adduct could be established unambiguously by a series of nOe experiments.

Unequivocal proof for the ring fusion stereochemistry was based on the X-ray structure obtained for diketone **60**, obtained via oxidation of tetracycle **58**.



Scheme 12

Scheme 13

The minor isomer **59** was also oxidized to afford the isomeric diketone **61**. Treatment of **61** with sodium methoxide led to the formation of diketone **60**. Separate treatment of **60** with sodium methoxide gave no reaction, establishing that the undesired C-34β hydrogen stereochemistry was thermodynamically favored in this system! Efforts to effect epimerization of the errant C-34 stereocenter in the major product **60**, either by equilibration or by a sequence of C-34 selenation and reduction, were unsuccessful. Similarly, conversion of the C-33 hydroxyl substituent to the corresponding acetate, or to the benzyl or silyl ethers, did not significantly increase the amount of the minor diastereomer (with the correct relative stereochemistry for the synthesis of manzamine) formed in the pharM cascade.

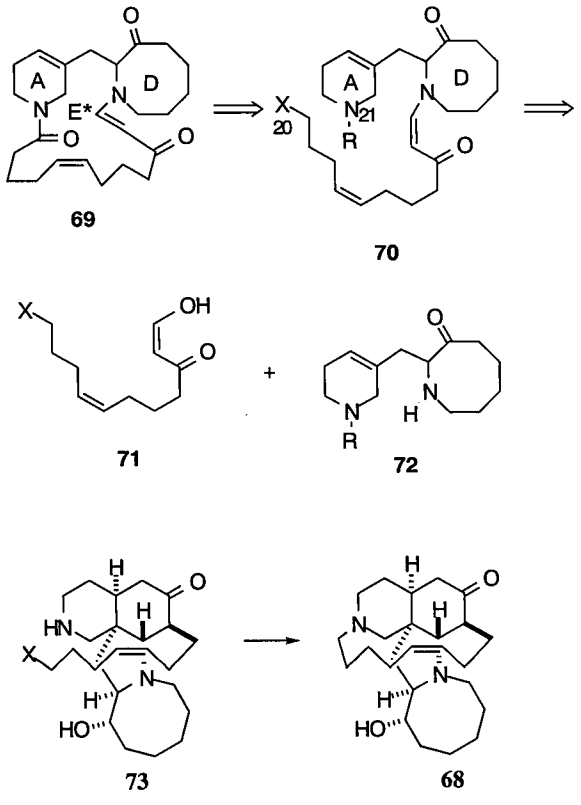
We next examined the effect of the C-33 hydroxyl stereochemistry on the stereochemical outcome of the photocycloaddition. While the C-33 trans-hydroxyl photosubstrate **64** could not be prepared from the cis-alcohol **55** via Mitsunobu inversion, it was obtained as the minor product of reduction of azocinone **50** (Scheme 10) with sodium borohydride. Photolysis of **64** followed by treatment with triethylamine hydrochloride and 4-dimethylaminopyridine afforded two tetracyclic products **65** and **66** in a 1 to 2.5 ratio (Scheme 12). The relative stereochemistry of **65** and **66** was established by oxidation of the major isomer **66** to the diketone **61**, which had previously been obtained on oxidation of **59** (Scheme 11). Epimerization of the C-33 hydroxyl group from cis to trans had therefore led, for the first time, to the selective formation of the tetracyclic core of the manzamine alkaloids with the correct relative stereochemistry. Photolysis of **64** at –78 °C gave exclusively **66** in 37% overall yield (three steps). The basis for this pronounced effect of the C-33 oxygen stereochemistry on the stereochemical outcome of the photocycloaddition is not clear, and further studies are currently underway in our laboratory to establish the basis for the observed stereoselectivities. With the successful conversion of the AE photosubstrate **64** to the tetracyclic core of manzamine **66**, we turned our attention to the ADE* macrocyclic photosubstrate **67** (Scheme 13), the pharM reaction of which could lead to the direct formation of the ABCDE pentacycle of manzamine A, i.e., **68**.

Synthesis and Study of Macrocyclic Vinylogous Amide Photosubstrates

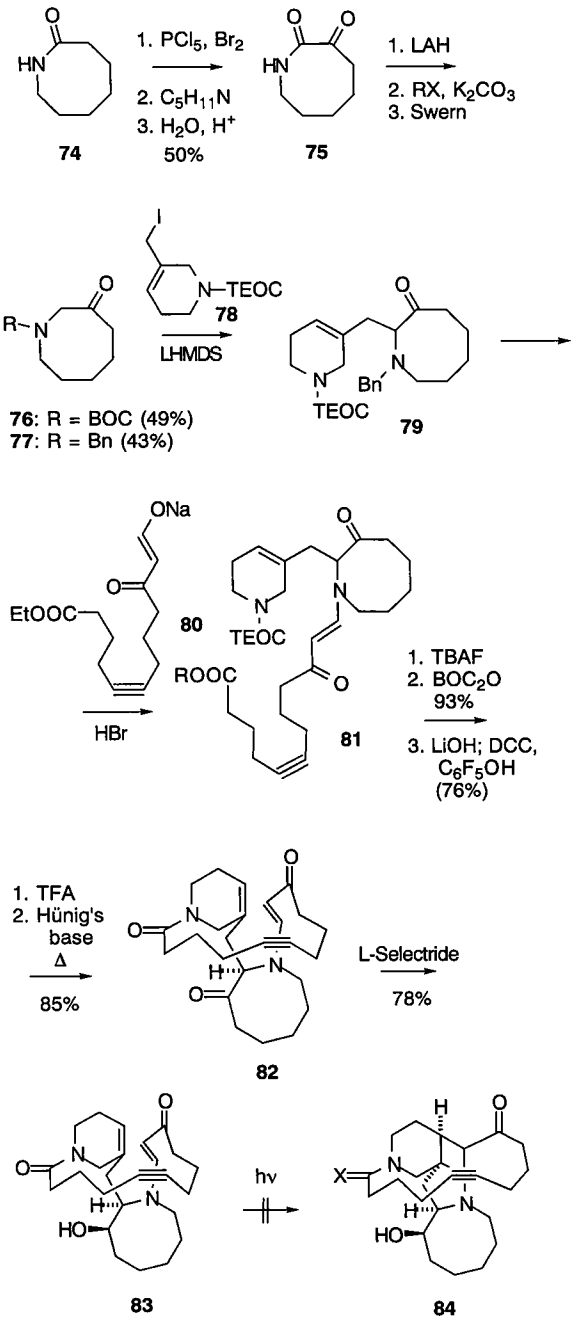
The macrocyclic photosubstrate **69** could be prepared via connection of C-20 and N-21 by either macrocyclic acylation (X = COOR) or alkylation (X = CH_2X)

of **70**, which could in turn be prepared by condensation of secondary amine **72** with functionalized β-ketoaldehyde **71** (Scheme 14). Application of the pharM sequence to **70** should lead to the formation of **73**, which could undergo subsequent macrolactamization to give the desired pentacycle **68**. Therefore, vinylogous amide **70** could be a viable intermediate for the synthesis of the pentacyclic ring system of the manzamines via transannular photocycloaddition of **69**, or via macrocyclization of pharM product **73**, if the transannular photocycloaddition cannot be achieved.

To avoid the low yields characteristic of the formation of azocine **76/77** via Dieckmann cyclization, we opted to prepare **76** from a readily available eight-membered ring precursor. Oxidation of commercially available caprolactam to α-keto lactam **74** by a three-step dibromination, bromo-elimination, and hydrolysis sequence had been reported by Brouillette.[13] Reduction of the α-keto lactam **75** with lithium aluminum hydride afforded the corresponding α-amino alcohol. Reaction of the azocine nitrogen with either di-*t*-butyl dicarbonate or benzyl bromide followed by Swern oxidation gave azocines **76** and **77**, respectively. This overall transformation represents an efficient method for the carbonyl transposition of an amide to an α-amino ketone. Although this sequence is longer than the Dieckmann cyclization route, it can be performed more conveniently on larger scale and has been used for the preparation of tens of grams of the N-benzyl α-aminoketone **77**. While alkylation of the N-BOC azocinone **76** led to a mixture of O-alkylated and C, O-dialkylated products, alkylation of the N-benzyl azocinone **77** with the A ring iodide **78** [the methyl



Scheme 14

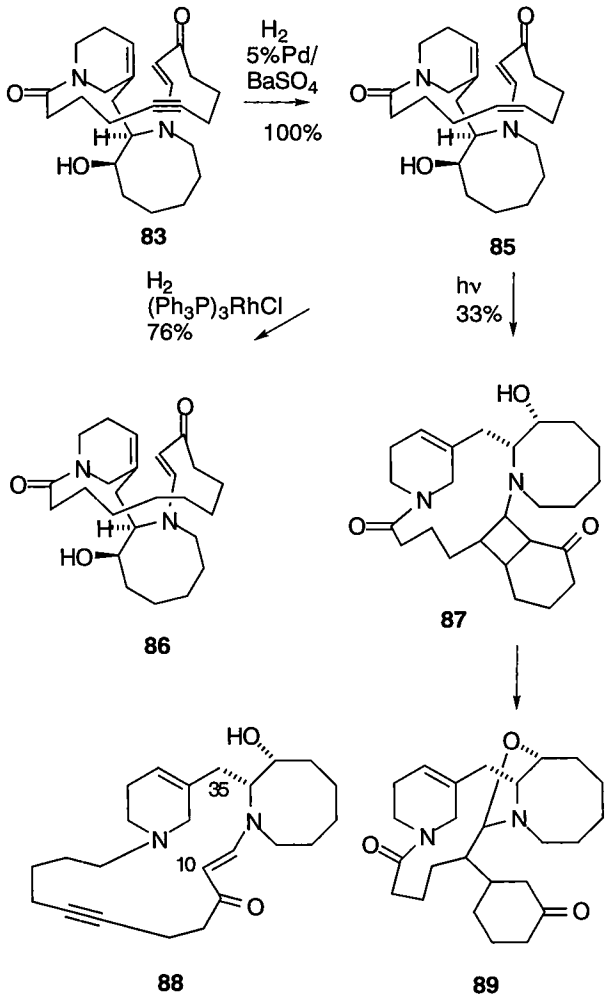


Scheme 15

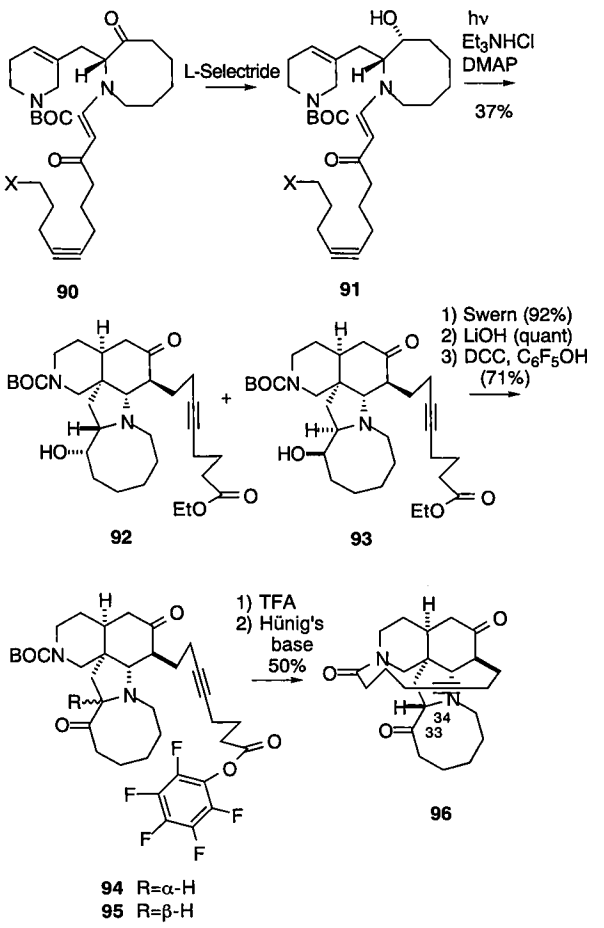
carbamate of **48** (Scheme 10) was replaced by the more labile TEOC moiety] under the same conditions afforded the desired AE coupled product **79** in good yield (Scheme 15).

The incorporation of the requisite D ring carbon atoms onto the vinylogous amide chromophore could be achieved by condensation of the secondary amine derived from **79** with formylketone **80**. Although a cis-alkene is required in the thirteen-membered ring for the synthesis of manzamine, we opted to proceed with an alkyne for two reasons: (1) the alkyne reduces the degrees of conformational freedom of the pro-D chain and should be beneficial for macrocyclizations; [14] and (2) the alkyne has a unique position in the ^{13}C NMR spectra and offers a valuable reference point for the interpretation of spectral data. We elected to employ a C-21 ester moiety since the yields of macrolactamizations are typically higher than those of macroalkylations.[15] Condensation of **80**, which was prepared from the corresponding methyl ketone[16] (NaHMDS, HCOOEt) with **79** under the previously described conditions led to the formation of the substituted vinylogous amide **81**. After considerable experimentation, the macrocyclization could be achieved in excellent yield based on the work of Still, making gram quantities of macrocyclic photosubstrate available. The TEOC group was first replaced with a BOC protecting group. Hydrolysis of the C-21 ester and coupling of the resulting acid with pentafluorophenol furnished the corresponding N-BOC pentafluorophenyl ester. TFA-induced BOC deprotection gave the crude TFA salt, which was dissolved in acetonitrile and added slowly to Hünig's base in refluxing acetonitrile, leading to the formation of the macrocyclic vinylogous amide **82** in excellent yield.[17]

To preclude the formation of pyrrole products as described in Scheme 10, the azocinone was treated with



Scheme 16



Scheme 17

L-Selectride to give the cis-alcohol **83**. Irradiation of **83** under conditions identical to those previously described for the non-macrocyclic vinylogous amides led to none of the desired photoaddition product **84**. Analysis of the proton NMR of the crude photolysate revealed the presence of a complex mixture containing multiple olefinic moieties. Varying reaction conditions (temperature range from –78 to 80 °C) and solvent, as well as attempting to trap the putative ketoiminium intermediate with sodium cyanoborohydride, led to none of the desired products. In each case, NMR spectral analysis revealed that the vinylogous amide was destroyed but that the tetrahydropyridine ring alkene was intact.

In an effort to explore alternative macrocyclic conformations that could be more conducive to the desired photocycloaddition, we examined both the partial and complete hydrogenation of the alkyne to give macrocyclic vinylogous amides **85** and **86** (Scheme 16). Lindlar reduction of **83** gave the cis-alkene **85**. Reaction of **85** with Wilkinson's catalyst delivered the fully saturated macrocyclic vinylogous amide **86**. The NMR spectrum of the crude photolysate obtained on irradiation of **86** was similar to that of macrocyclic alkene **83**. In contrast, the irradiation of **85** led to the formation of a new ketoiminium product. However, NMR analysis revealed that the major product obtained on chromatographic purification of the reaction mixture contained the A-ring alkene intact. The spectral evidence was most consistent with aminal **89** which would be derived from photoadduct **87**, i.e., the product resulting from transannular photocycloaddition with the macrocyclic alkene instead of the A-ring olefin.

The formation of **89** establishes that the transannular photocycloaddition of an eighteen-membered ring is possible and that modification of the macrocyclic conformation has a pronounced impact on the reaction outcome. The difficulty in obtaining the desired transannular [2+2]cycloaddition product is underscored by the solid-state structure of **88**, which establishes that the pro-E ring is fully extended, as indicated in **88**, making the distance between the chromophore and the A-ring alkene ca. 7 A. The conformation of the macrocyclic photosubstrates **83** and **86** appears to be better suited to 1,5 hydrogen atom abstraction by C-10 of the chromophore onto C-35 allylic hydrogen than to the desired [2+2]photocycloaddition.

Synthesis of the Pentacyclic Ring System of Manzamine via Non-Macrocyclic Vinylogous Amide Photosubstrates

The failure of the macrocyclic vinylogous amide photosubstrates to undergo the desired transannular photocycloaddition led us to examine the alternative strategy outlined in Scheme 17, i.e., the application of the pharM sequence to an AE vinylogous amide to give the tetracyclic ABCE ring system following by macrolactamization to generate the pentacyclic ring system. The synthesis and reactivity of non-macrocyclic vinylogous amide **91** is outlined in Scheme 17.

Irradiation of **91**, obtained by reduction of **90** with L-Selectride, followed by treatment with triethylamine hydrochloride and heating with DMAP, afforded the tetracycles **92** and **93** in a 2:1 ratio, respectively. Oxidation to the C-33 ketone, followed by pentafluoroester formation and macrolactamization gave **96**, containing the pentacyclic core of the manzamine alkaloids. The epimerization of the critical C-34 stereocenter on cyclization of **94** to **96** precludes oxidation of the C-33 hydroxyl prior to macrocyclization.[18]

CONCLUSIONS

The successful application of the intramolecular vinylogous amide photocycloaddition/retro-Mannich fragmentation/Mannich closure (pharM) cascade to the synthesis of the ABCDE pentacyclic ring system of manzamine A described herein attests to the utility of this methodology for the synthesis of stereochemically dense, complex structures. The role of the C-33 hydroxyl stereochemistry on the stereochemical outcome of the photocycloaddition reaction has been examined in some detail. Either sense of asymmetric induction is possible in the photocycloaddition as a function of the stereochemistry of the C-33 substituent. The completion of the total synthesis of manzamine A requires some functional group transformations and the incorporation of the β-carboline moiety. Further studies are currently underway in our laboratory and our results will be reported in due course.

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