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Stereoselective Synthesis of the Tetracyclic Core of Manzamine via the Vinylogous Amide Photocycloaddition Cascade§

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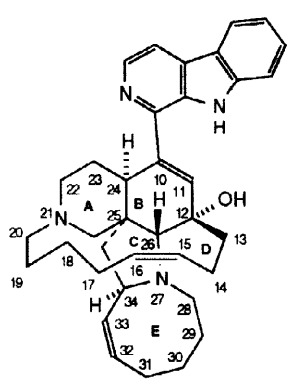
Abstract: The stereoselective preparation of the tetracyclic core of the manzamine alkaloids via the intramolecular vinylogous amide photocycloaddition/retro-Mannich fragmentation/Mannich closure cascade is described. The striking effect of unsaturation in the eight-membered ring on the stereoselectivity of the cycloaddition and a computational analysis of these results are presented.

Keywords: *Stereoselective, photochemistry, alkaloids, Mannich reaction*



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Introduction

In 1986, Higa, Jefford and co-workers reported the isolation of a structurally novel polycyclic alkaloid, manzamine A, **1**, from a sponge near the coast of Okinawa [1]. The unique structure of **1** consists of a β-carboline heterocycle as well as eight-and thirteen-membered rings on a pyrrolo[2,3-i]isoquinoline framework. The cytotoxic activity and novel structure of **1** (IC_{50}=0.07 mg/mL against P-388 mouse leukemia cells) have prompted efforts at its total synthesis in several laboratories [2]. Most of these efforts have been directed towards the assembly of the pyrrolo[2,3-i]isoquinoline core of manzamine via intramolecular Diels-Alder cycloaddition.

§Dedicated to our colleague and friend Professor Madeleine M. Joullié in celebration of forty years of distinguished teaching and research at the University of Pennsylvania.

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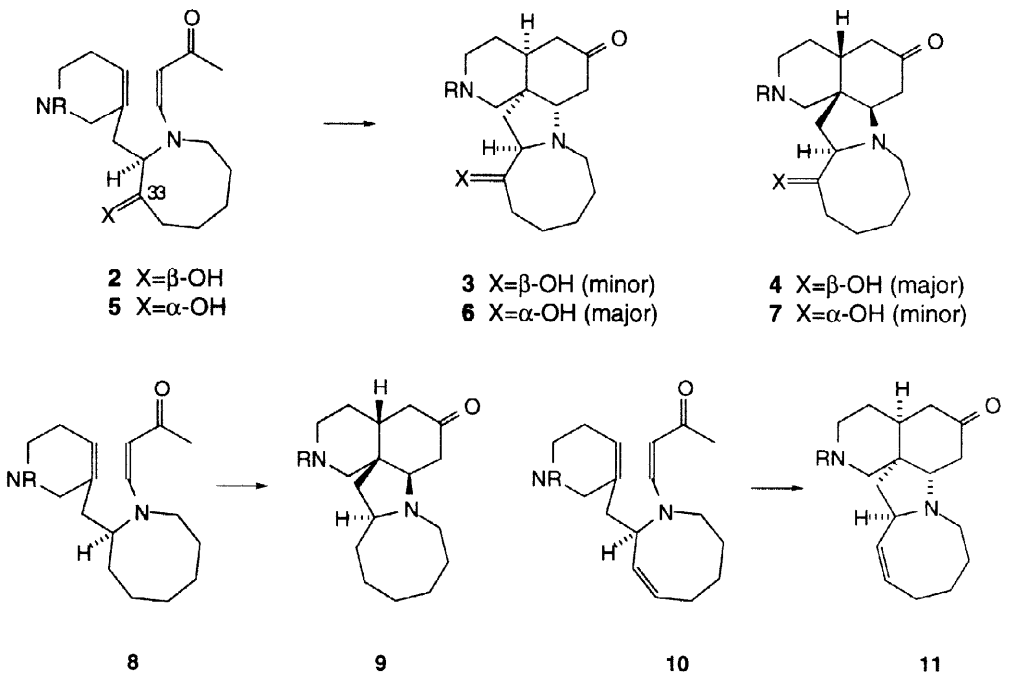
We have reported the application of the vinylogous amide photocycloaddition reaction/retro-Mannich fragmentation/Mannich closure sequence of **2** and **5** using an eight-membered ring template to effect a highly efficient synthesis of the manzamine tetracycle, **3/6** and **4/7**. In that work, we found that the diastereoselectivity of the cycloaddition depends critically on the stereochemistry of the C-33 substituent [3].

We have now examined the stereoselectivity of the photocycloaddition reaction as a function of the presence or absence of unsaturation in the eight-membered ring template, i.e., **8** or **10**, respectively. We report herein that the scalemic unsaturated photosubstrate **10** leads to the synthesis of the tetracyclic core of the manzamine alkaloids **11** with the efficient communication of stereochemical information from C-34 (azocine) to C-24 and C-25, leading to complete control of both relative and absolute stereochemistry in the assembly of the manzamine nucleus.

Scheme 2

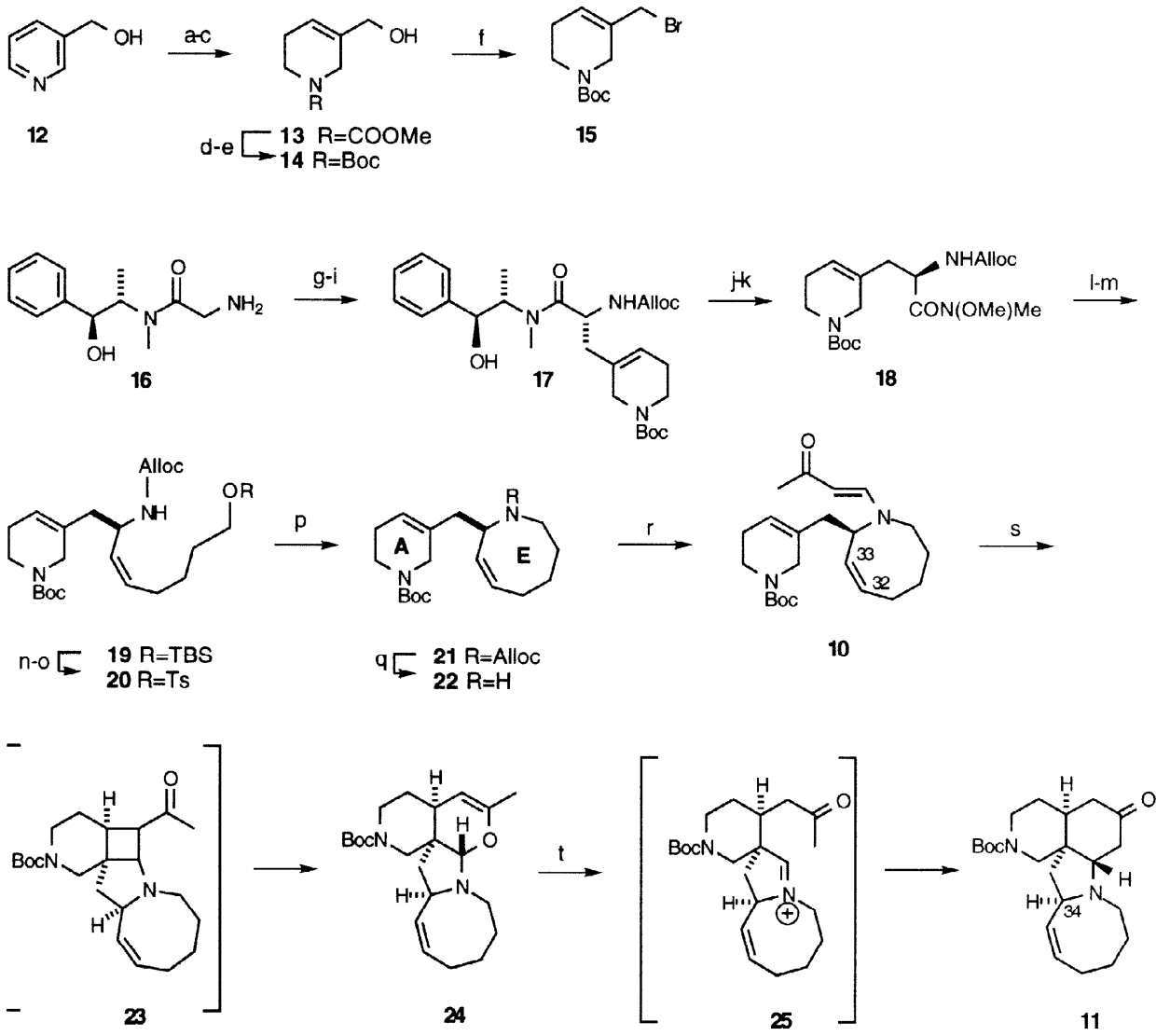


Results

The synthesis of **10**, containing the $\Delta^{32,33}$-E ring unsaturation, is outlined in Scheme 3. The control of absolute stereochemistry was established using the Myers pseudoephedrine alkylation [4] of **16** with **15**, which was prepared from pyridine-3-methanol **12** via N-alkylation, reduction, and conversion of the resulting allylic alcohol to the corresponding bromide. Hydrolysis of **17**, formation of the Weinreb amide, reduction to the corresponding aldehyde, followed by Wittig alkenylation gave the cis-alkene **19**. Conversion of the silyl ether to the tosylate then gave **20**, which on exposure to sodium hydride provided the eight-membered ring

product **21** in 82% yield [5]. Removal of the allyl carbamate of **21** gave the secondary amine, **22**, which on condensation with 3-butyn-2-one gave the unsaturated azocine vinylogous amide photosubstrate **10**. Irradiation of **10** led, via retro-Mannich fragmentation and cyclization of

Scheme 3



a. BnBr; b. $NaBH_4$; c. MeOCOCl, 50-60% (3 steps); d. KOH, aq. MeOH; e. Boc_2O, 89%; f. Ph_3P, Br_2, imidazole 93%; g. LDA, LiCl; h. **15**; i. AllocCl, 87%; j. 1. NaOH, 92%; k. EtOCOCl, NMM, HN(Me)OMe-HC l, 71%; l. LAH, 83%; m. KHMDS, $Ph_3P(CH_2)_5OTBSBr$, 75%; n.PPTS, MeOH, 98%; o. TsCl, 88%; p. NaH, 82%; q. $(PPh_3)_4Pd^0$, dimedone, 90%; r. 3-butyn-2-one, CH_2Cl_2, 87%; s. hv; t. HOAc-pyridine, CH_3CN, 58% (over 3 steps)

photoadduct **23**, to the formation of a single aminal **24**. Treatment of **24** with acetic acid buffered with pyridine gave, via ketoiminium **25**, the desired tetracyclic aminoketone **11** as a single diastereomer. The desired C-34α hydrogen stereochemistry in **11** was confirmed by X-ray crystallographic analysis of the derived 3,5-dinitrobenzamide (removal of Boc followed by

benzoylation). The sense of asymmetric induction from the unsaturated eight-membered photosubstrate **10** was therefore superior to that of either the cis or trans alcohol photosubstrates (Scheme 1).

Discussion

In an effort to determine the factors governing the observed stereoselectivities, the ground state conformations involved in the cycloadditions of **8** and **10** were analyzed by a systematic conformational search and subsequent energy minimizations of reactant conformations using the MM2* force field [6]. The calculations show an energy difference of 1.6 kcal/mol between the lowest energy conformers leading to **9** and **26**, favoring the formation of **9**, as is experimentally observed (Figure 1). In the most stable chair-boat conformation of the saturated ring **8**, the tetrahydropiperidinomethyl group is oriented orthogonal to the vinylogous amide plane, due to the $A^{1,3}$ effect of the vinylogous amide bonds [7]. Therefore, in this system, the vinylogous amide is located in the same plane as the nitrogen and attached carbons of the eight-membered ring and $A^{1,3}$ effects dictate the stereochemistry of the vinylogous amide as shown in **A**. The [2+2] cycloaddition then takes place on the top face of the vinylogous amide to give photoadduct **9** since the bicyclo[3.2.0]heptane moiety (B*/C) formed in the photocycloaddition reaction must necessarily be cis-fused. Therefore H_b, the vinylic hydrogen of the tetrahydropyridine ring, is anti relative to H_a, the C/E ring fusion methine, producing the incorrect relative stereochemistry in **9** for the synthesis of the manzamines.

Figure 1

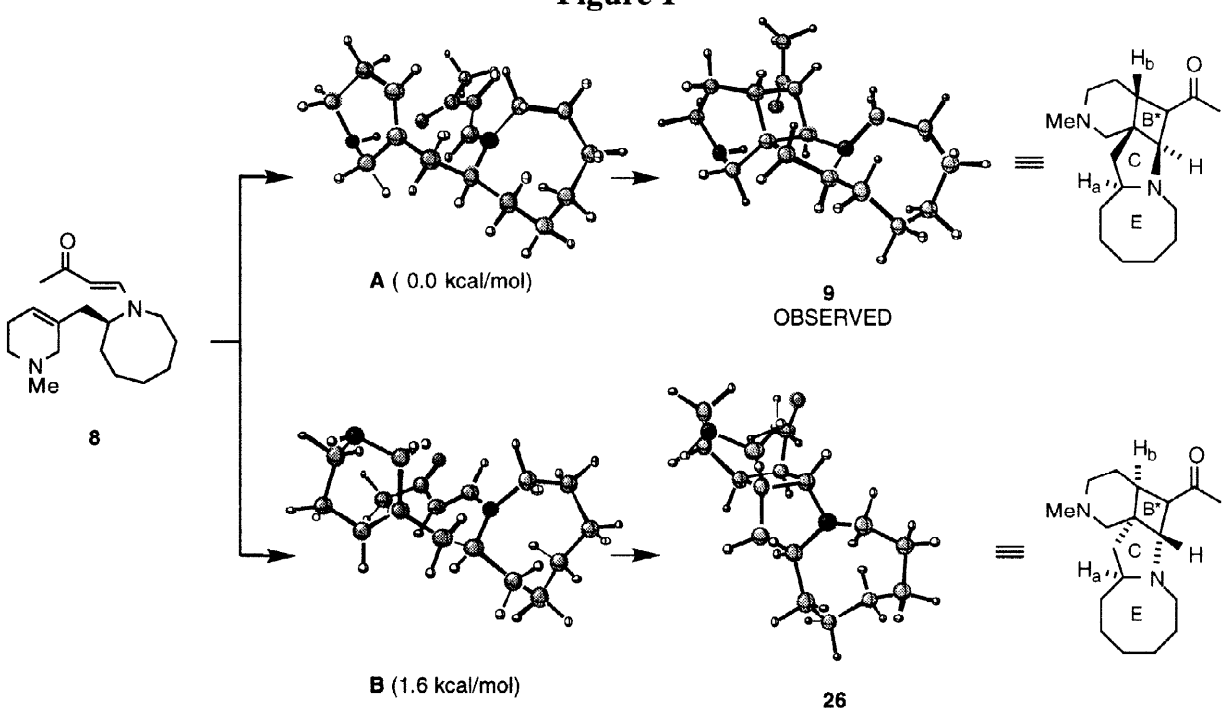
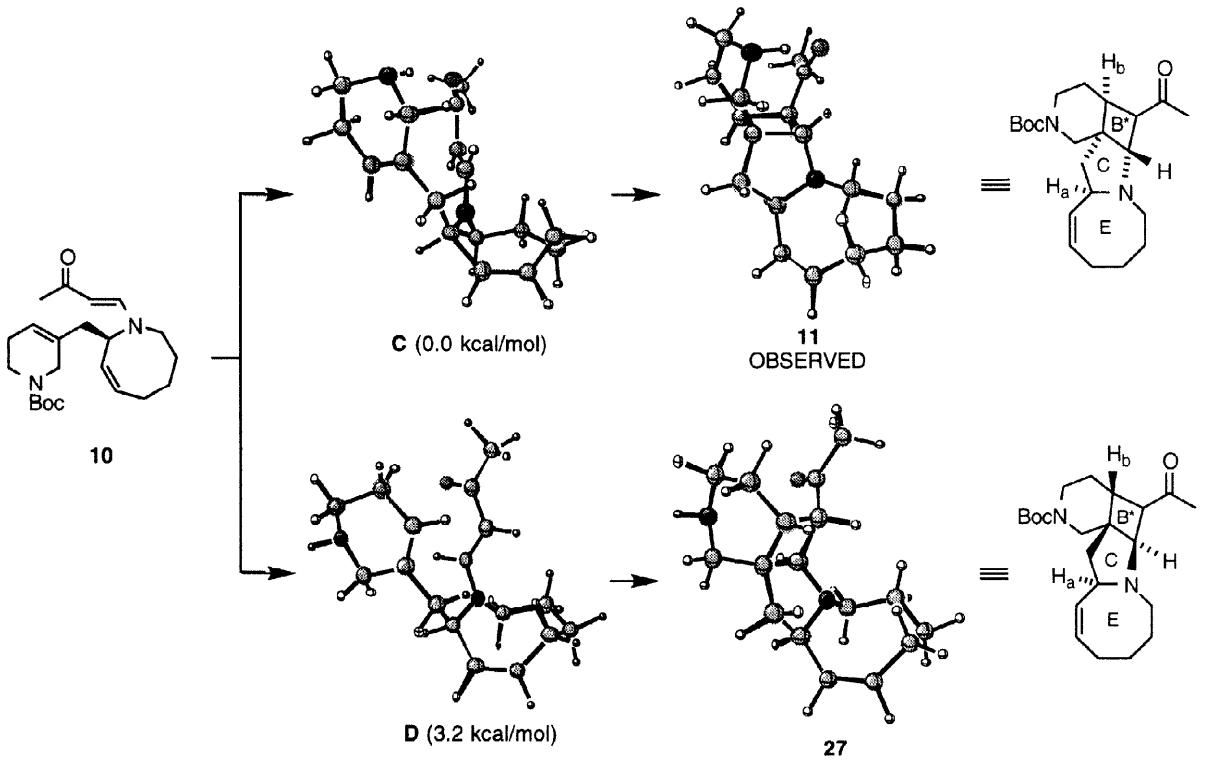


Figure 2



The striking difference in selectivity between the saturated azocine photosubstrate **8** and the unsaturated system **10** can be explained as a function of the different conformation of the eight-membered ring in **10**, as outlined in Figure 2. The calculations show an energy difference of 3.2 kcal/mol between the lowest energy transition structures leading to **11** and **27**, favoring the formation of the observed product, **11** (Figure 2). Introduction of unsaturation in the eight-membered ring **10** imparts a distortion away from the preferred chair-boat conformation of the eight-membered ring. The torsional strain along the C-33/C-34 bond effects a conformational change that places the enone moiety orthogonal to the ring plane, allowing alignment of the reacting alkenes in a manner conducive to the desired product stereochemistry, i.e., **11**.

Conclusions

The irradiation of the unsaturated eight-membered ring substrate **10** leads to a highly diastereoselective approach to the synthesis of the tetracyclic core of the manzamine alkaloids. The completion of the synthesis of manzamine A, **1**, using this approach is currently underway and our results will be reported in due course.

Experimental

N-Boc-tetrahydropyridine-3-methanol **14**:

A stirred solution of pyridine-3-methanol (300 g, 2.75 mol) in CH_2Cl_2 (1 L) was treated dropwise with benzyl bromide (345 mL, 2.90 mol) over a period of 4 hours. The mixture was allowed to stir overnight at room temperature and then evaporated to afford the crude salt as a viscous oil which was used without further purification in the next step. To a mechanically stirred solution of the forementioned salt in methanol (3 L, cooled in an ice-water bath) was added portionwise $NaBH_4$ (208 g, 5.50 mol) over 8 hours with constant cooling. On completion of the addition, the resulting mixture was allowed to warm to room temperature and stirred overnight. The methanol was removed under reduced pressure and the residue was treated with 1 N NaOH (2.5 L). The resulting mixture was extracted with diethyl ether (3 x 1 L) and the combined ethereal extracts were dried ($MgSO_4$) and evaporated to give 530 g of the crude N-benzyl-tetrahydropyridine as a thick oil which was used directly in the next step without further purification. To a solution of the aforementioned N-benzylamine in benzene (4 L) was added solid $NaHCO_3$ (116 g, 1.35 mol). Methyl chloroformate (256 mL, 3.3 mol) was added dropwise to the stirred mixture at room temperature over 2 hours. After the addition was completed, the mixture was heated to reflux for 16 hours. The solution was then allowed to cool to room temperature and the benzene was removed under reduced pressure. The resulting residue was dissolved in EtOAc (3 L) and was washed with water (500 mL), 0.5 M HCl (500 mL), brine (500 mL) and was then dried ($MgSO_4$) and the volatiles evaporated under reduced pressure. The bulk of the benzyl chloride was then removed by high vacuum distillation and the remaining crude methylcarbamate, which was isolated as a viscous syrup (235-280 g, 50-60%), was used without additional purification. A solution of the above crude methylcarbamate (235 g, 1.37 mol) in methanol (1.5 L) was treated with a solution of KOH (383 g, 6.8 mol) in water (1.5 L) and the resulting mixture was stirred mechanically at reflux for 18 hours. The reaction mixture was then cooled to 0°C with an ice-water bath and then treated with solid $NaHCO_3$ (571 g, 6.8 mol) and then di-*tert*-butyl-dicarbonate (298 g, 1.37 mol). The resulting mixture was stirred at 0°C for 1 hour and then room temperature for 4 hours. The methanol was then evaporated under reduced pressure and the remaining aqueous solution was extracted with EtOAc (3 x 800 mL). The combined organic extracts were washed with 0.5 M HCl (2 x 500 mL), water (500 mL), saturated $NaHCO_3$, then dried ($MgSO_4$) and the solvent evaporated to provide N-Boc-tetrahydropyridine **14** as a thick faint yellow oil (259 g, 89%). ^1H NMR (500 MHz, $CDCl_3$): 5.78 (bs, 1H); 4.01 (s, 2H); 3.87 (d, J = 1.5 Hz, 2H); 3.42 (t, J = 5.7 Hz, 2H); 2.10 (bs, 2H); 2.00 (bs, 1H); 1.43 (s, 9H). IR (thin film, cm^{-1}): 3430.0; 1697.3; 1422.5; 1161.0. HRMS calculated for $C_{11}H_{19}NO_3$ (M + NH_4): 231.1709; found: 231.1715.

Allylic bromide **15**:

To a stirred solution of Ph_3P (285 g, 1.09 mol) and imidazole (74 g, 1.09 mol) in CH_2Cl_2 (1.5 L) was added dropwise a solution of bromine (56 mL, 1.09 mol) in CH_2Cl_2 (800 mL) over

4 hours while the mixture was maintained at room temperature with a water bath. After the addition was completed, the mixture was allowed to stir for 1 hour at room temperature, and then treated with a solution of the allylic alcohol (193 g, 0.905 mol) in CH_2Cl_2 (500 mL), added dropwise over 2 hours. After stirring for 18 hours at room temperature, the solvent was evaporated under reduced pressure and the residue was treated with diethyl ether (500 mL). Slow addition of hexanes (1.5L) to the ethereal solution resulting in the precipitation of triphenylphosphine oxide and other salts, which were then filtered and washed with 1:1 ether:hexane (500 mL). The combined filtrates and washings were evaporated under reduced pressure to give the crude product which was filtered through a short column of silica gel (1:1 ether:hexanes) to remove any remaining impurities. Evaporation of the resulting solution afforded the bromide **15** as a colorless oil which slowly solidified after prolonged freezer storage to give a white waxy solid (232 g, 93%). ^1H NMR (500 MHz, $CDCl_3$): 5.96 (bs, 1H); 3.97 (s, 2H); 3.90 (s, 2H); 3.42 (t, J = 5.7 Hz, 2H); 2.11 (m, 2H); 1.44 (s, 9H). IR (thin film, cm^{-1}): 1695.1; 1418.4; 1164.7. HRMS calculated for $C_{11}H_{18}BrNO_2$ ($M + NH_4$): 293.0865; found: 293.0860.

Alkylated Pseudoephedrine Glycinamide **17**:

A 1-L round bottomed flask was flame-dried under argon and charged with 200 mL of dry THF and 63.0 mL (0.450 mol) of diisopropylamine. The solution was cooled to 0 °C and deoxygenated by alternately evacuating the vessel and flushing with argon three times. After deoxygenation, 169 mL of freshly titrated 2.59 M n-BuLi in hexanes (0.439 mol) was added via syringe over 30 minutes. The resulting solution was allowed to stir at 0 °C for 15 minutes. Separately, a 2-L, three-neck, round bottomed flask was equipped with an inlet adapter connected to a source of vacuum and argon, two rubber septa, and a Teflon coated magnetic stir bar. The flask was charged with 57.2 g (1.35 mol) of anhydrous lithium chloride, and with efficient stirring of the solid, was evacuated and flame-dried. After cooling to room temperature, the vessel was flushed with argon and charged with 50.0 g (0.225 mol) of solid (S,S)-(+)-pseudoephedrine glycinamide, and one of the septa was replaced with an adapter fitted with a thermometer for internal measurement of the reaction temperature. The solids were suspended in 500 mL of dry THF and the resulting milky-white slurry was cooled with an ice bath to an internal temperature of 0 °C. With efficient stirring the solution was deoxygenated by alternately evacuating the reaction vessel and flushing with argon three times. The LDA solution prepared above was then added to the (S,S)-(+)-pseudoephedrine glycinamide-lithium chloride slurry via wide-bore (12 gauge) cannula at such a rate that the internal temperature did not rise above 5 °C (approximately 90 minutes addition time). After completion of the addition, the resulting reaction mixture was stirred at 0 °C for 30 minutes. To the resulting pale yellow suspension was added a solution of the N-Boc-tetrahydropyridyl bromide **15** (56.49 g, 0.205 mol) in 100 mL of dry THF via cannula at such a rate that the internal temperature did not rise above 5 °C (approximately 60 minutes addition time). After the addition was complete the reaction was allowed to stir at 0 °C for 1 hour. The reaction was quenched with water (500

mL), and the bulk of the THF was removed under reduced pressure. The aqueous mixture was extracted with CH_2Cl_2 (1 x 1L, 2 x 500 mL), and the combined organics were dried over K_2CO_3, filtered through a plug of Celite and evaporated. Toluene (200 mL) was added and evaporated to remove residual diisopropylamine. The crude amine was dissolved in 500 mL of dioxane and a solution of Na_2CO_3 (43.3 g, 0.409 mol) in water (500 mL) was added. The mixture was cooled in an ice bath and 21.7 mL of allylchloroformate (0.205 mol) was added dropwise via syringe over a period of 30 minutes. After additional stirring for 30 minutes at 0 °C the reaction was allowed to warm to room temperature and stir for 1 hour. The bulk of the dioxane was evaporated and water (500 mL) was added. The mixture was extracted with CH_2Cl_2 (1 x 1L, 2 x 500 mL) and the combined extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated. Column chromatography (10-75% EtOAc-hexanes) afforded 88.8 g of the pure product as an off-white foam (87%, 2 steps). ^1H NMR (500 MHz, $CDCl_3$, * denotes minor rotamer peaks): 7.24-7.41 (m, 5H); 5.82-5.91 (m, 1H); *5.65 (bs, 1H); 5.59 (bs, 1H); 5.43 (d, J=8.0 Hz, 1H); *5.32 (m, 1H); 5.14-5.29 (m, 2H); *4.83 (m, 1H); 4.60-4.66 (m, 2H); 4.50 (m, 2H); *4.23 (m, 1H); 3.73-3.85 (m, 3H); 3.23-3.51 (m, 2H); 2.95 (s, 3H); *2.93 (s, 3H); 2.84 (m, 1H); *2.54 (m, 1H); 2.33-2.38 (m, 1H); 1.92-2.30 (m, 4H); 1.65 (s, 1H); 1.43 (s, 9H); 1.03 (d, J=6.2 Hz, 1H); *0.98 (d, J=7.3 Hz, 3H). ^{13}C NMR(125 MHz, CDCl3, * denotes minor rotamer peaks): 173.1; *172.5; 155.7; 154.8; *154.7; *141.7; 141.4; 132.6; 128.7; 128.3; 127.7; *127.6; 126.9; 126.5; 123.7; 117.5; *117.4; 79.5; *79.3; *75.7; 75.5; 75.3; 66.5; *66.3; 65.6; *65.5; *60.3; 58.1; 50.0; *49.1; 45.8; 40.4; 39.1; 38.2; 28.3; *27.3; 25.1; *20.9; *15.5; 14.2; *14.1. IR (thin film, cm^{-1}): 3420.0; 1695.8; 1420.0; 1162.9. HRMS calculated for $C_{27}H_{39}N_3O_6$ (M + H): 502.2917; found: 502.2919. [α] +62.5° (c=0.88, $CHCl_3$).

Weinreb Amide **18**:

A solution of the amide **17** (86.0 g, 0.171 mol) in methanol (600 mL) was treated with aqueous 2 M NaOH (428 mL, 0.855 mol) and the resulting solution was heated to reflux for 3 hours. After cooling the methanol was evaporated. Water (600 mL) was added and the mixture was washed with diethyl ether (3 x 500 mL). The aqueous portion was cooled in an ice bath and cautiously acidified to pH 2-3 with cold 6 M aqueous HCl over 1 hour. The mixture was then extracted with diethyl ether (2 x 1 L) and the combined extracts were washed with water (2 x 500 mL), dried ($MgSO_4$) filtered and evaporated to provide 56.5 g of the acid (93%) which was homogeneous by TLC and needed no further purification. ^1H NMR (500 MHz, *d*6-DMSO): 6.76 (d, J=8.3 Hz, 1H); 5.82-5.92 (m, 1H); 5.51 (s, 1H); 5.23 (dd. J=17.2, 1.2 Hz, 1H); 5.11 (dd, J=10.4, 1.1 Hz, 1H); 4.46 (dd, J=13.8, 5.0 Hz, 1H); 4.37 (dd, J=13.8, 5.0 Hz, 1H); 3.95 (bs, 1H); 3.53-3.77 (m, 3H); 3.34 (bs, 1H); 3.19 (m, 1H); 2.48 (m, 1H); 2.14 (t, J=11.1 Hz, 1H); 1.93 (bs, 2H); 1.38 (s, 9H). ^{13}C NMR(125 MHz, *d*6-DMSO): 176.7; 155.4; 153.9; 133.8; 132.6; 121.1; 116.6; 78.5; 64.1; 54.0; 45.6; 38.4; 28.0; 24.6. IR (thin film, cm^{-1}): 3410.6; 1695.7; 1246.9. HRMS calculated for $C_{17}H_{26}N_2O_6$ (M + NH_4): 377.1689; found: 377.1701. [α] +11.6° (c=0.99, MeOH). To a solution of the acid (17.0 g, 48 mmol) and N-

methyl-morpholine (11 mL, 0.1 mol) in CH_2Cl_2 (150 mL) at -30°C was added dropwise isobutyl chloroformate (6.2 mL, 48 mmol) at such a rate that the reaction temperature did not rise above -20°C. Stirring was then continued at -30°C for 3 hours. N,O-dimethyl hydroxylamine•HCl (3.9 g, 50 mmol) was then added portionwise over 1 hour. The reaction was then allowed to warm to room temperature and allowed to stir for 8 hours. The mixture was poured into water and extracted with diethyl ether (3 x 100 mL). The combined extracts were washed with 0.5 M HCl (100 mL), saturated $NaHCO_3$, brine and then dried ($MgSO_4$) and evaporated. Column chromatography (50% EtOAc-hexanes) afforded 13.5 g of the product as a thick colorless oil (71%). ^1H NMR (500 MHz, $CDCl_3$): 5.82-5.90 (m, 1H); 5.58 (bs, 1H); 5.32 (d, J=8.4 Hz, 1H); 5.24 (dd, J=17.2, 1.4 Hz, 1H); 5.15 (dd, J=10.4, 1.0 Hz, 1H); 4.78 (bs, 1H); 4.46-4.54 (m, 2H); 3.79 (bs, 2H); 3.75 (s, 3H); 3.43 (bs, 1H); 3.29 (bs, 1H); 3.16 (s, 3H); 2.37 (dd, J=13.8, 4.5 Hz, 1H); 2.18 (dd, J=13.6, 8.7 Hz, 1H); 2.05 (bs, 2H); 1.43 (s, 9H). ^{13}C NMR(125 MHz, CDCl3): 172.3; 155.8; 154.8; 132.7; 131.6; 123.7; 117.6; 79.5; 65.6; 61.6; 49.6; 45.4; 39.8; 38.4; 32.1; 28.4; 25.1. IR (thin film, cm^{-1}): 3311.7; 1718.8; 1696.2; 1669.8. HRMS calculated for $C_{19}H_{31}N_3O_6$ (M + NH_4): 415.2557; found: 415.2555. [α] +2.7° (c=1.65, $CHCl_3$).

Silyl ether **19**:

To an ice cold solution of the Weinreb amide (13.1 g, 32.96 mmol) in diethyl ether (330 mL) was added dropwise 1.0 M lithium aluminum hydride (Aldrich, 41.2 mL, 41.2 mmol). The resulting mixture was allowed to warm to room temperature and stir for 1 hour. The mixture was recooled in an ice bath and hydrolyzed by cautious dropwise addition of 0.5 M $KHSO_4$ (130 mL). Water (200 mL) was added and the aqueous portion was extracted with diethyl ether (2 x 100 mL). The combined ethereal extracts were washed with 0.5 M HCl (100 mL), saturated $NaHCO_3$, brine and then dried ($MgSO_4$) and evaporated to provide the analytically pure aldehyde as a pale yellow syrup (9.25 g, 83%), which was used immediately in the subsequent Wittig olefination. ^1H NMR (500 MHz, $CDCl_3$): 9.59 (s, 1H); 5.83-5.91 (m, 1H); 5.62 (bs, 1H); 5.32 (bs, 1H); 5.27 (d, J=17.2 Hz, 1H); 5.18 (dd, J=10.4, 1.2 Hz, 1H); 4.54 (d, J=5.5 Hz, 2H); 4.29 (m, 1H); 3.76 (bs, 2H); 3.31-3.44 (m, 2H); 2.51 (dd, J=14.5, 5.1 Hz, 1H); 2.30 (dd, J=14.2, 8.2 Hz, 1H); 2.08 (bs, 2H); 1.43 (s, 9H). ^{13}C NMR(125 MHz, CDCl3): 199.1; 155.9; 154.8; 132.4; 130.3; 124.4; 118.0; 79.8; 65.9; 58.4; 45.8; 39.8; 34.5; 28.4; 25.0. IR (thin film, cm^{-1}): 3336.7; 1693.9; 1681.7; 1650.9. HRMS calculated for $C_{17}H_{26}N_2O_5$ (M + NH_4): 356.2186 found: 356.2194. [α] +27.9° (c=1.345, MeOH). To a solution of (5-t-butyl-dimethylsilyloxypentyl)-triphenylphosphonium iodide (33.7 g, 57.09 mmol) in THF (190 mL) at 0° was added a 0.5 M solution of KHMDS in toluene (113 mL, 56.6 mmol) dropwise over 45 minutes. After stirring at 0° for 1.5 hours the mixture was cooled to -78°. A solution of the aforementioned aldehyde (9.20 g, 27.19 mmol) in THF (50 mL) was then added dropwise via cannula over 45 minutes. The reaction mixture was then allowed to slowly warm to room temperature over 2 hours. Saturated NH_4Cl (100 mL) was added and the bulk of THF was evaporated. Water (300 mL) was added to the residue which was then extracted with ether (3 x

200 mL). The combined extracts were washed with brine and then dried ($MgSO_4$) and evaporated. Column chromatography (15% EtOAc-hexanes) afforded 8.96 g of the (Z)-olefin as a thick colorless oil (63%). ^1H NMR (500 MHz, $CDCl_3$): 5.84-5.92 (m, 1H); 5.57 (bs, 1H); 5.47 (m, 1H); 5.26 (dd, J=17.2, 1.5 Hz, 1H); 5.16-5.20 (m, 2H); 4.46-4.58 (m, 4H); 3.79 (bs, 2H); 3.56 (t, J=6.4 Hz, 2H); 3.44 (m, 1H); 3.33 (m, 1H); 2.07-2.23 (m, 6H); 1.45-1.57 (m, 2H); 1.44 (s, 9H); 1.35-1.40 (m, 2H); 0.87 (s, 9H); 0.02 (s, 6H). ^{13}C NMR(125 MHz, CDCl3): 155.3; 154.8; 132.9; 132.7; 131.6; 129.7; 122.9; 117.5; 79.5; 65.4; 63.0; 47.3; 46.2; 41.4; 39.4; 32.5; 28.4; 27.5; 25.9; 25.8; 25.4; 18.3; -5.3. IR (thin film, cm^{-1}): 3328.9; 1697.8; 1246.7. HRMS calculated for $C_{28}H_{50}N_2O_5Si$ (M + NH_4): 540.3833 found: 540.3817. [α] -1.0° (c=1.01, $CHCl_3$).

Tosylate **20**:

A solution of the silyl ether **19** (8.62 g, 16.46 mmol) in methanol (100 mL) was treated wiht PPTS (827 mg, 3.29 mmol) and the resulting solution stirred for 3 hours at room temperature. The methanol was evaporated and the residue treated with diethyl ether (300 mL). The resulting solution was washed with water, brine, dried ($MgSO_4$) and evaporated. Column chromatography (50% EtOAc-hexanes) gave the intermediate alcohol as a colorless syrup (6.70 g, 99%). ^1H NMR (500 MHz, $CDCl_3$): 5.83-5.90 (m, 1H); 5.57 (bs, 1H); 5.46 (m, 1H); 5.24 (dd, J=17.2, 1.5 Hz, 1H); 5.15-5.20 (m, 3H); 4.66 (bs, 1H); 4.51 (bs, 3H); 3.77 (bs, 2H); 3.61 (dt, J=6.5, 1.1 Hz, 2H); 3.45 (m, 1H); 3.31 (m, 1H); 2.14-2.21 (m, 2H); 1.89-2.09 (m, 4H); 1.49-1.60 (m, 2H); 1.43 (s, 9H); 1.39-1.43 (m, 2H). IR (thin film, cm^{-1}): 3328.3; 1696.5. HRMS calculated for $C_{22}H_{36}N_2O_5$ (M + H): 409.2702, found: 409.2715. [α] +1.9° (c=0.87, $CHCl_3$). A 0°C solution of the alcohol (6.72 g, 16.47 mmol), triethylamine (4.6 mL, 32.94 mmol) and DMAP (201 mg, 1.65 mmol) in CH_2Cl_2 (50 mL) was treated with tosyl chloride (4.71 g, 24.7 mmol). The resulting solution was stirred at 0° for 30 minutes and then allowed to warm to room temperature overnight. Diethyl ether (400 mL) was added and the mixture was washed with 0.5 M HCl (100 mL), water, brine and then dried ($MgSO_4$) and evaporated. Column chromatography (25% EtOAc-hexanes) gave the product as a colorless syrup (8.14 g, 88%). ^1H NMR (500 MHz, $CDCl_3$): 7.75 (d, J=8.2 Hz, 2H); 7.31 (d, J=8.2 Hz, 2H); 5.82-5.90 (m, 1H); 5.56 (bs, 1H); 5.36 (m, 1H); 5.24 (dd, J=17.2, 1.6 Hz, 1H); 5.14-5.20 (m, 3H); 4.42-4.60 (m, 4H); 3.99 (t, J=6.4 Hz, 2H); 3.76 (s, 2H); 3.43 (m, 1H); 3.31 (m, 1H); 2.42 (s, 3H); 2.00-2.20 (m, 6H); 1.59-1.65 (m, 2H); 1.43 (s, 9H); 1.33-1.40 (m, 2H). ^{13}C NMR(125 MHz, CDCl3): 155.3; 154.8; 144.6; 133.3; 132.9; 131.7; 130.5; 129.8; 127.9; 123.1; 117.6; 79.5; 70.4; 65.4; 47.2; 46.1; 41.3; 40.0; 29.7; 28.5; 27.0; 25.3; 25.1; 21.6. IR (thin film, cm^{-1}): 3326.3; 1693.9; 1175.3. HRMS calculated for $C_{29}H_{42}N_2O_7$ (M + NH_4): 580.3057, found: 580.3064. [α] +1.0° (c=0.99, $CDCl_3$).

N-Alloc Azocine **21**:

The tosylate **20** (8.10 g, 14.39 mmol) in THF (100 mL) was added by syringe pump over 5 hours to a refluxing suspension of 60% NaH (864 mg, 21.6 mmol) in THF (600 mL). After

refluxing an additional hour the mixture was cooled and treated with saturated aqueous $NaHCO_3$ (50 mL), added slowly. The THF was evaporated and water (200 mL) was added. The mixture was extracted with diethyl ether (3 x 150 mL) and the combined extracts were washed with brine and then dried ($MgSO_4$) and evaporated. Column chromatography (20% EtOAc-hexanes) gave the product as a colorless syrup (4.44 g, 79%). ^1H NMR (500 MHz, $CDCl_3$): 5.86-5.94 (m, 1H); 5.66 (m, 1H); 5.49 (bs, 1H); 5.13-5.27 (m, 3H); 4.96,*4.83 (bs rotamers, 1H); 4.57 (m, 2H); 3.21-3.84 (m, 5H); 3.01 (m, 1H); 2.17-2.28 (m, 2H); 1.83-2.05 (m, 5H); 1.73 (m, 1H); 1.60 (m, 1H); 1.43 (s, 9H); 1.30 (m, 1H). ^{13}C NMR(125 MHz, CDCl3): 156.2; 155.6; 154.9; 133.2; 132.0; 128.4; 122.9; 117.4; 116.9; 79.4; 65.8; 53.2; 46.0; 43.1; 42.4; 40.1; 28.4; 27.1; 25.7; 25.6; 25.5; 25.2. IR (thin film, cm^{-1}): 1694.1; 1172.0. HRMS calculated for $C_{22}H_{34}N_2O_4$ (M + H): 391.2597, found: 391.2590. [α] +36.3° (c=1.69, $CDCl_3$).

Vinylogous Amide **10**:

To a stirred solution of **21** (1.63 g, 4.17 mmol) and dimedone (4.09 g, 29.2 mmol, 7 eq) in THF (40 mL) was added tetrakis(triphenylphosphine) palladium (100 mg, 0.08 mmol, 2 mol%) at room temperature. TLC analysis (30% EtOAc-hexanes) after 1 hour indicated complete consumption of starting material. The solvent was evaporated, diethyl ether was added (150 mL) and the resulting solution was washed with 0.5 M HCl (3 x 75 mL). The combined aqueous layers were washed with diethyl ether, brought to pH 10 with saturated sodium carbonate solution and extracted with diethyl ether (3 x 75 mL). The combined ethereal layers were dried (Na_2SO_4) and concentrated in vacuo to give the product (1.182 g, 93%). This crude product was used in the next reaction without purification. To a 0°C solution of the aforementioned secondary amine (590 mg, 1.9 mmol) in methylene chloride (5 mL) was added butynone (0.3 mL, 3.8 mmol, 2 eq) dropwise, and the resulting mixture warmed to room temperature with stirring over 12 hours. TLC analysis (50% EtOAc-hexanes) indicated complete consumption of starting material. Evaporation of volatiles gave a yellow oil, which was purified by column chromatography to give the product **10** as a slightly yellow oil (602 mg, 85%). ^1H NMR (500 MHz, $CDCl_3$): 7.24 (bs, 1H); 5.73 (d, 1H); 5.46 (bs, 1H); 5.19 (bs, 1H); 5.06 (d, 1H); 4.06~4.22 (m, 1H); 3.63~3.72 (m, 2H); 3.13~3.30 (m, 4H); 1.86~2.13 (m, 10H); 1.70 (bs, 1H); 1.17~1.51 (m, 11H). ^{13}C NMR (125 MHz, $CDCl_3$): 194.9; 154.6; 151.2; 134.1; 130.9; 127.5; 124.6; 79.5; 63.5; 45.3; 44.3; 40.5; 28.3; 25.6; 24.9; 23.5. IR (thin film, cm^{-1}): 1694.6; 1662.8; 1602.0; 158.9; 1167.3. [α] +38.5° (c=0.65, $CHCl_3$). HRMS calculated for $C_{22}H_{34}N_2O_3$ (M + H): 375.2647, found: 375.2658.

Manzamine Tetracycle **11**:

A solution of vinylogous amide (395 mg, 1.056 mmol) in acetonitrile (170 ml) in a photoreaction vessel (Pyrex) was degassed by bubbling Ar through the solution for 30 min. The resulting solution was then irradiated (450 watt Hanovia medium pressure mercury lamp) for 1h at room temperature under argon atmosphere. TLC analysis (70% EtOAc-hexanes) after 1h

indicated complete consumption of starting material. Evaporation of volatiles gave a yellow oil, which was dissolved in 100 mL of acetonitrile under argon. To this solution was added 1.66 ml of a solution of pyridinium acetate in acetonitrile (prepared by the addition of 2 mL pyridine and 1 mL acetic acid to 10 mL anhydrous acetonitrile), and the reaction mixture was heated to reflux for 3 h. The resulting mixture was cooled, evaporated, and the residual acetic acid and pyridine were removed azeotropically with toluene (50 ml). The resulting orange residue was purified by column chromatography (diethyl ether) to give **11** as a slightly yellow oil (189 mg, 58%). ^{1}H NMR (500 MHz, CD_2Cl_2): 5.73 (d, 1H); 5.49 (dd, 1H); 3.88 (s, 1H); 3.63 (d, 1H); 3.35~3.48 (m, 2H); 3.20 (d, 1H); 2.89 (t, 1H); 2.74 (dd, 1H); 2.35~2.51 (m, 4H); 2.12~2.28 (m, 4H); 1.55~1.83 (m, 6H); 1.43 (s, 9H); 1.30 (m, 1H). ^{13}C NMR (125 MHz, CD_2Cl_2, * denotes minor rotamer peaks.): 211.2; 155.0; 132.0; 130.2; 125.8*; 79.6; 65.5; 56.5; 51.0; 48.8; 44.6; 43.5*; 41.6; 41.2; 41.0; 38.1; 33.3*; 30.5; 30.1; 28.6; 28.5; 28.3; 27.7; 27.1; 26.5; 25.9*; 23.1*. IR (thin film, cm^{-1}): 1692.5; 1428.4; 1166.4. HRMS calculated for $C_{22}H_{34}N_2O_3$ (M + H): 375.2647, found: 375.2652. $[\alpha]$ +1.7^o (c=1.2, $CHCl_3$).

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