SYNTHESIS OF 6-AZA-BICYCLO[3,2,1]OCTAN-3-ONES VIA VINYLOGOUS IMIDE PHOTOCHEMISTRY: AN APPROACH TO THE SYNTHESIS OF THE HETISINE ALKALOIDS

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SUPPLEMENTARY MATERIAL

(Experimental procedures and spectral characterization for **5**, **6**, **8**, **16**, **17**, **19** and **20**)

Boc-protected vinylogous amide **5**:

Allyamine (1.5 mmol, 85 mg) was dissolved in absolute MeOH (5 ml) and stirred at 0 oC under Ar atmosphere. 3-Butyn-2-one (1.5 mmol, 102 mg) was added dropwise and the ice-bath was removed to allow the reaction to warm to room temperature. After 2 hours the volatiles were removed in vacuo to give the crude vinylogous amide as an orange oil (185 mg, 99%). The crude vinylogous amide was analytically pure and subject to the next reaction. 1H NMR (500 MHz, CDCl3): 9.75 (bs, 1H); 6.56-6.61 (dd, 1H); 5.78-5.86 (m, 1H); 5.19 (d, 1H); 5.14 (d, 1H); 5.00 (d, 1H); 3.74-3.77 (m, 2H); 2.03 (s, 3H). 13C NMR (125 MHz, CDCl3): 197.5; 153.2; 165.3; 117.6; 94.9; 51.1; 29.2. IR (thin film, cm-1): 3261.9; 1651.3. HRMS calculated for C12H19NO3 (M+Na): 148.0738, found: 148.0737.

The crude vinylogous amide (1.5 mmol) was dissolved in anhydrous dichloromethane (5 ml) and stirred at 0 oC under Ar atmosphere. Di-t-butyl dicarbonate (1.5 mmol, 330 mg) was added in one portion followed by an addition of catalytic amount of

dimethylaminopyridine(10 mg) and the ice bath was removed. It was stirred for 10 hours at room temperature, when the solvent was removed in vacuo and the resulted syrup was purified by column chromatography (petroleum ether/ethyl ether = 2/1) to yield **5** as a colorless oil (335 mg, 99.4 % for two steps). 1H NMR (500 MHz, CDCl3): 8.10-8.13 (d, 1H); 5.68-5.73 (m, 1H); 5.48-5.51 (d, 1H); 5.14-5.16 (d, 1H); 5.07-5.11 (d, 1H); 4.12-4.13 (t, 2H); 2.20 (s, 3H); 1.50 (s, 9H). 13C NMR (125 MHz, CDCl3): 198.6; 153.0; 143.2; 131.8; 117.8; 109.5; 84.0; 47.0; 28.3; 28.1. IR (thin film, cm-1): 1725.4; 1688.2; 1623.8; 1529.0. HRMS calculated for C12H19NO3 (M+Na): 248.1263, found: 248.1251.

Bicyclic crossed photoadduct **6**:

A solution of Boc-protected vinylogous amide **5** (176 mg, 0.78 mmol) in acetonitrile (70 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 lamp) for 1 h at room temperature under argon atmosphere. TLC analysis (petroleum ether/ethyl ether = 1:1) indicated complete consumption of starting material. Evaporation of volatiles gave a colorless oil, which was purified by column chromatography (petroleum ether/ethyl ether = 1:1) to yield **6** as a colorless oil(150 mg, 85%). 1H NMR (500 MHz, CDCl3): 4.62-6.78 (bd, 1H); 3.37-3.44 (bt, 1H); 3.16 (bs, 1H); 3.06 (bs, 1H); 2.69 (s, 1H); 1.97 (s, 3H); 1.70-1.73 (m, 1H); 1.43-1.49 (s, 9H); 1.25-1.27 (d, 1H). 13C NMR (125 MHz, CDCl3, * denotes minor rotamer peaks): 206.9; 156.0; 80.2; 80.0*; 62.8*; 62.5; 57.9; 47.2; 46.2; 40.6; 37.3; 28.7; 28.6*. IR (thin film, cm-1): 1697.6 (broad). HRMS calculated for C12H19NO3 (M+Na): 248.1263, found: 248.1251.

N-Boc-6-azabicyclo[3,2,1]octan-3-one **8**:

A solution of Boc-protected photoadduct **6** (0.2 mmol, 45 mg) in absolute ethanol (10 ml) was heated at reflux for 1h under Ar atmosphere, when TLC analysis indicated complete conversion to enecarbamate **7** and catalytic amount of pyridinium p-toluenesulfonate (2 mg) was added. The reaction mixture was refluxed for 3 days and cooled to room temperature. The volatiles were evaporated and the residue was purified by column chromatography (petroleum ether/ether = 2/3) to afford **8** as a colorless oil (39 mg, 87%). 1H NMR (500 MHz, CDCl3, * denotes minor rotamer peaks): 4.33* (bs), 4.15 (bs, 1H); 3.36-3.42(m, 2H); 3.30-3.32 (d, 1H); 3.22-3.24* (d); 2.83-2.87* (d); 2.72-2.76 (d, 1H); 2.69 (s, 2H); 2.49 (s, 4H); 2.29-2.32 (d, 2H); 2.08-2.15 (m, 3H); 1.87-1.91 (dd, 2H); 1.43* (s); 1.41 (s, 9H). 13C NMR (125 MHz, CDCl3, * denotes minor rotamer peaks): 209.3*; 209.0; 135.7; 79.8;79.6*; 53.26; 52.9*; 52.3*; 52.0; 48.2*; 48.0; 47.7; 47.2*; 36.0*; 35.4; 34.2*; 33.2; 30.3; 29.9; 28.5. IR (thin film, cm-1): 1716.1; 1633.9; 1417.7. HRMS calculated for C12H19NO3 (M+Na): 248.1263, found: 248.1251.

Boc-protected vinylogous amide **16**:

The known primary amide **15** (2 mmol, 240 mg) was dissolved in anhydrous toluene (10 ml) and stirred at 0 oC under Ar atmosphere. 5 ml of 1.5 M solution of DIBAL-H in toluene was added dropwise over 20 min period. Then it was warmed to room temperature and stirred overnight. The reaction was cooled to 0 oC again and quenched by a slow addition of EtOAc (10 ml) and the resulted aluminum salt was removed by a filtration through a pad of Celite. The volume of the filtrate was reduced in vacuo to *ca.* 2 ml and it was diluted with 5 ml of anhydrous dichloromethane. The solution was cooled to 0 oC and stirred under Ar atmosphere followed by dropwise addition of 3-butyn-2-one (2 mmol 136

mg). It was allowed to warm to room temperature and after 1 h TLC analysis indicated complete conversion of the primary amine to the vinylogous amide. Then di-t-butyl dicarbonate (2 mmol, 440 mg) and Dimethylaminopyridine (10 mg) were added and the reaction was stirred overnight. The solvents were removed in vacuo and the residue was purified by column chromatography (petroleum ether/ ethyl ether = 3/2) to give **16** as a colorless oil (418 mg, 75% for three steps). 1H NMR (500 MHz, CDCl3): 8.13-8.16(d, 1H); 5.48-5.51(d, 1H); 5.40-5.41 (t, 1H); 4.01 (s, 2H); 2.21 (s, 3H); 1.97-1.98(t, 2H); 1.83 (bs, 2H); 1.58-1.63 (m, 4H); 1.51 (s, 9H). 13C NMR (125 MHz, CDCl3): 197.6; 152.5; 142.9; 131.0; 125.5; 83.2; 50.1; 30.3; 29.6; 28.0; 26.3; 24.8; 22.4. IR (thin film, cm-1): 1725.6; 1688.3; 1623.0; 1591.6. HRMS calculated for C16H25NO3 (M+Na):302.1732, found: 302.1733.

Tricyclic crossed photoadduct **17**:

A solution of vinylogous amide **16** (240 mg, 0.86 mmol) in acetonitrile (140ml) in a photoreaction vessel (pyrex) was degassed by a bubbling Ar through the solution for 30 min. Then the solution was irradiated (450 watt Hanovia mercury lamp) for 2 h at room temperature under Ar atmosphere. TLC analysis indicated complete consumption of starting material. Evaporation of volatiles and purification of the residue by column chromatography (petroleum ether/ethyl ether = 5/4) afforded **17** as a colorless oil (206 mg, 86%). 1H NMR (500 MHz, CDCl3, * denotes minor rotamer peaks): 4.49(s, 1H); 4.34*(s); 3.21-3.33 (d, 1H); 3.26*(d); 3.07 (s, 2H); 2.92* (s); 2.87-2.89 (d, 1H); 2.00-2.05 (m, 8H); 1.81-1.83 (m, 2H); 1.64-1.71 (m, 4H); 1.51-1.54 (m, 2H); 1.32-1.45 (m, 13H); 1.01 (bs, 2H). 13C NMR (125 MHz, CDCl3, * denotes minor rotamer peaks): 208.9; 155.7; 155.2*; 80.0; 63.3*; 62.7; 54.8*; 54.5; 52.8; 51.7; 48.0; 28.7; 24.9; 23.6; 22.7;

22.1. IR (thin film, cm-1): 1695.1. HRMS calculated for C16H25NO3 (M+Na):302.1732, found: 302.1741.

Tricyclic Mannich cyclization product **19**:

A solution of Boc-protected photoadduct **17** (0.18 mmol, 50 mg) in absolute ethanol (10ml) was heated at reflux for 1h under Ar atmosphere, when TLC analysis indicated compete conversion to enecarbamate **18** and catalytic amount of pyridinium p-toluenesulfonate (2mg) was added. The reaction mixture was refluxed for 3 days and cooled to room temperature. The volatiles were evaporated and the residue was purified by column chromatography (petroleum ether/ether = 2/3) to afford **19** as a colorless oil (42 mg, 84%). 1H NMR (500 MHz, CDCl3, * denotes minor rotamer peaks): 3.97-3.98(t, 1H); 3.83-3.84*(t, 1H); 3.52-3.54 (dd, 1H); 3.44-3.47* (dd, 1H); 3.00-3.03 (d, 1H); 2.95-2.97* (d, 1H); 2.83-2.88 (dt, 1H); 2.71-2.75* (dt, 1H); 2.32-2.43 (m, 5H); 2.20-2.26 (m, 2H); 1.72-1.83 (m, 7H); 1.61-1.68 (m, 6H); 1.40-1.46 (m, 24H); 1.13-1.27 (m, 9H). 13C NMR (125 MHz, CDCl3): 210.5; 155.4; 80.3; 60.3; 59.7; 57.6; 57.4; 51.7; 51.3; 48.4; 48.0; 47.8; 47.4; 41.6; 31.7; 28.7; 26.0; 24.8; 21.4. IR (thin film, cm-1): 1716.1; 1693.9; 1395.3. HRMS calculated for C16H25NO3 (M+Na):302.1732, found: 302.1749.

Hydrazone **20**:

Tricyle **19** (28 mg, 0.1 mmol) was dissolved in 2 ml of dichloromethane and stirred at 0 oC. 0.5 ml of trifluoroacetic acid was added dropwise and the ice-bath was removed. The reaction was stirred at ambient temperature for 2 h and the volitiles were removed in vacuo. The resulted brown oil was dissloved in CH2Cl2 (20 ml) and neutralized with Sat. NaHCO3 solution. The organic layer was separated and dried with anhydrous Na2SO4.

The solvent was removed in vacuo and the crude ketoamine was dissolved in 2 ml of anhydrous CH2Cl2 and stirred at 0 oC under Ar atmosphere. Triethylamine (20 mg, 0.2 mmol) was added via a syringe followed by an addition of 4-bromobenzoyl chloride in one portion. The reaction mixture was stirred at 0 oC and monitored by TLC (petroleum ether/ethyl ether = 1/2). After 3 h, the reaction was diluted with ethyl ether (10 ml) and washed with sat. NaHCO3. The organic layer was dried with anhydrous MgSO4 and the solvents were removed in vacuo. The resulted brown syrup was purified by column chromatography (petroleum ether/ethyl ether = 1/2) to afford the corresponding 4-bromobenzamide as a colorless oil (27 mg, 73 % for two steps). 1H NMR (500 MHz, CDCl3, * denotes minor rotamer peaks): 7.50-7.53 (d, 2H); 7.23-7.29 (d, 2H); 4.48-4.49 (t, 1H); 3.82-3.85* (dd); 3.78* (s); 3.52-3.54 (dd, 1H); 3.21-3.24* (d); 3.05-3.09 (dt, 1H); 2.98-3.00 (d, 1H); 2.45-2.51 (m, 2H); 2.28-2.40 (m, 4H); 1.54-2.00 (m, 10H); 1.12-1.46 (m, 12H). 13C NMR (125 MHz, CDCl3, * denotes minor rotamer peaks): 208.2; 207.5*; 170.0*; 169.4; 131.9*; 131.7; 128.4; 128.0; 62.5; 59.9; 56.9; 54.1; 51.1; 48.8; 48.3; 46.9*; 46.7*; 43.1; 41.1; 31.5; 31.2; 25.9*; 24.4; 24.3*; 21.1; 20.1*. IR (thin film, cm-1): 2919.3; 2850.4; 1714.4; 1693.7; 1395.8. HRMS calculated for C18H20BrNO2 (M+Na):384.0575, found: 384.0559. The 4-bromobenzamide (25 mg, 0.07 mmol) was dissolved in 0.3 ml of THF/ethyl ether(anhydrous, 1/1) mixture and stirred at room temperature. 14 mg (0.75 mmol) of *p*-toluenesulfonhydrazide was added in one portion and the reaction mixture was stirred overnight under Ar atmosphere. The reaction turned cloudy with white precipitates and the solvents were removed in vacuo and the resulted white powder was recrystallized in CH2Cl2 to provide the hydrazone **20** as crystalline solids (34 mg, 91%, m.p. 172 oC) which was subject to a X-ray crystallography experiment. 1H NMR (500 MHz, CDCl3, * denotes minor rotamer peaks): 8.08 (s, 1H); 7.78-7.81 (d, 2H); 7.51-7.53* (d); 7.41-7.45 (m, 2H); 7.30-7.32* (d); 7.25-7.27 (d, 2H); 7.17-7.19* (d); 7.06-7.08 (d, 2H); 4.37 (s, 1H); 3.70-3.72* (d); 3.63* (s); 3.28-3.35 (m, 2H); 3.05-3.08* (d); 2.85-2.87 (d, 1H); 2.65-2.68* (d); 2.51-2.54* (d); 2.42-2.43 (d, 4H); 2.35-2.40 (d, 1H); 2.19-2.22 (d, 1H); 1.96-1.99 (d, 1H);

1.89-1.92* (d); 1.65-1.74 (m, 4H); 1.52-1.62 (m, 5H); 1.47-1.49 (d, 1H); 1.22-1.30 (m, 7H); 0.98-1.13*(m). IR (thin film, cm-1): 2917.4; 2848.7; 1614.2; 1417.6. HRMS calculated for C25H28BrN3O3S (M+Na):552.0932, found: 552.0957.