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FORMAL SYNTHESIS OF EPIBATIDINE

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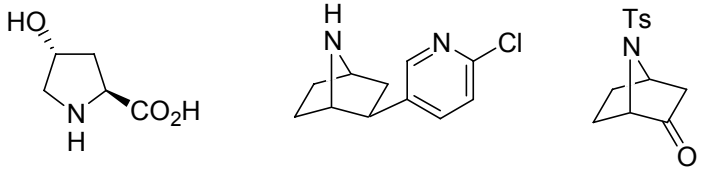
Abstract—A straightforward formal synthesis of epibatidine has been established starting from *trans*-(2*S*,4*R*)-4-hydroxyproline.

1. INTRODUCTION

In view of structural framework of *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**), it possesses three functional groups that can be easily modified, including 1-amino, 2-carboxylate and 4-hydroxy groups.[1] The skeleton represents out the significant feature for producing a series of different carbon framework[2] using an efficient modification. Here we report a straightforward formal synthesis of epibatidine (**2**) has been established starting from *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**) as shown in Figure 1.

Figure 1.



trans-4-hydroxyproline (**1**) (+)-epibatidine (**2**) (+)-**3**

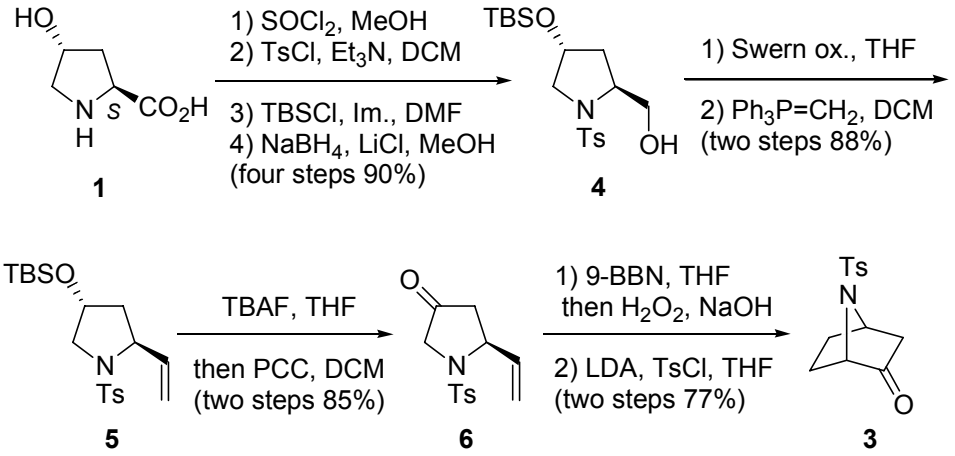
Epibatidine was first isolated from the skin extract of the Ecuadorian poison frog *Epipedobates tricolor* by Daly and co-workers in 1992.[3a] Subsequently, it was reported containing extremely higher potency as an analgesic approximately 200 times more potent then morphine.[3c-3d] Because of its scarcity and interesting biological activities, more than sixty synthetic reports have published.[3e-3mm] Compound (**3**) was already chosen as a key intermediate for synthesizing epibatidine in the literature.[3p,3x-3y]

2. RESULTS AND DISCUSSION

In Scheme 1, *N*-Ts-proline methyl ester was readily obtained from *trans*-4-hydroxyproline (**1**) in two steps, i.e. methylation with thionyl chloride and methanol in -78 ^{o}C and *N*-tosylate protection with *p*-toluenesulfonyl chloride and triethylamine in an ice bath. Next, *N*-Ts-proline methyl ester was silylated

with *t*-butyldimethylsilyl chloride and imidazole to give *O*-TBS-proline ester. Reduction of *O*-TBS-proline ester with sodium borohydride in the presence of lithium chloride furnished alcohol (**4**). Thus, synthesis of alcohol (**4**) was achieved in four steps from *trans*-4-hydroxyproline (**1**) in 90% overall yield with only once purification.

Scheme 1. Formal synthesis of epibatidine (**2**).



With alcohol (**4**) in hand, alcohol (**4**) was transformed into olefin (**5**) by Swern oxidation and Wittig olefination protocol. Ketone (**6**) was obtained by desilyation of compound (**5**) with tetrabutylammonium fluoride followed by oxidation of the resulting alcohol with pyridinium chlorochromate and Celite under the one-pot condition. Chain extension to the olefin (**6**) was achieved by hydroboration with 9-borabicyclo[3.3.1]nonane to provide the alcohol.[4a-4b] Finally, exposure of the corresponding alcohol to *p*-toluenesulfonyl chloride and lithium diisopropylamide caused simultaneous tosylation and cyclization,[5] providing the bicyclic ketone (**3**). The ^{1}H-NMR spectral data was in accordance with the reported in the literature.[3p,3y] During the intramolecular ring closure process, the fused azabicyco[3.2.0]heptane framework was not observed under this basic condition.

3. CONCLUSION

In summary, we have developed a straightforward approach for synthesizing the 7-azabicyclo[2.2.1]heptane ring system (**3**) and applied this route to the formal synthesis of epibatidine (**2**) in nine steps provided 51% overall yield.

4. EXPERIMENTAL

General. Dichloromethane (DCM) and tetrahydrofuran (THF) were distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of

dry nitrogen with magnetic stirring. Extract was dried with anhydrous magnesium sulfate before concentration *in vacuo*. Crude products were purified using preparative TLC or column chromatography on silica gel. All reported temperatures were uncorrected.

(2*S*,4*R*)-1-(4-Methylphenylsulfonyl)-2-hydroxylmethyl-4-(*t*-butyldimethylsilyloxy)pyrrolidine (4). Thionyl chloride (2.5 g, 21.0 mmol) was added to a stirred solution of *trans*-4-hydroxyproline (**1**) (1.31 g, 10.0 mmol) in methanol (20 mL) at –78 °C for 10 min. The mixture was stirred in an ice bath for 30 min then at rt for 30 min, followed by reflux for 3 h. Concentration *in vacuo* followed by azotropic removal of water using benzene (50 mL) gave methyl 4-hydroxyproline hydrochloride (1.81 g, 100%). Triethylamine (3.1 g, 30.6 mmol) and *p*-toluenesulfonyl chloride (1.91 g, 10.0 mmol) were added to a solution of the resulting product (1.81 g) in dichloromethane (40 mL) in an ice bath. After stirring at the same temperature for 10 h, the mixture was concentrated *in vacuo*. Ethyl acetate (40 mL) was added to the residue, and the solution was washed with 0.1 N aqueous hydrogen chloride solution (10 mL), saturated sodium bicarbonate solution and brine, dried, filtered, then concentrated *in vacuo* to yield *N*-toluenesulfonyl methyl 4-hydroxyprolinate (2.93 g, 98%). Without further purification, *t*-butyldimethylsilyl chloride (1.51 g, 10.0 mmol) and imidazole (1.0 g, 14.7 mmol) were added to a solution of the resulting product (2.93 g, 9.8 mmol) in dimethylforamide (15 mL) at rt. After stirring at the same temperature for 2 h, the mixture was concentrated *in vacuo*. Ethyl acetate (40 mL) was added to the residue, and the solution was washed with 0.1 N aqueous hydrogen chloride solution (10 mL), saturated sodium bicarbonate solution and brine, dried, filtered, then concentrated *in vacuo* to give the methyl *N*-toluenesulfonyl-4-[*O*-*t*-butyldimethylsilyloxy]prolinate (3.93 g, 97%). Without further purification, lithium chloride (1.22 g, 28.8 mmol) and sodium borohydride (1.09 g, 28.8 mmol) were added to a solution of the crude product (3.93 g) in methanol (30 mL) at rt. After stirring at the same temperature for 12 h, the mixture was concentrated *in vacuo*. Ethyl acetate (60 mL) was added to the residue, and the solution was washed with 0.1 N aqueous hydrogen chloride solution (10 mL), saturated sodium bicarbonate solution and brine, dried, filtered, then concentrated *in vacuo*. Recrystallization from hexane and ethyl acetate (*ca.* 2:1) yielded the products (**4**). The residue was purified by column chromatography (hexane/ethyl acetate=2/1) to yield compound (**4**) (3.47 g, 95%). mp = 87-89 °C (hexane/ethyl acetate); $[\alpha]^{22}_{D}$ –18.12° (*c* 0.13, $CHCl_3$); IR ($CHCl_3$) 3500, 2930, 2800, 1600 cm^{-1}; EI-MS: $C_{18}H_{31}NO_4SSi$ m/z (%) = 91 (100), 142 (17), 155 (23), 328 (22), 385 (M^+, 1); HRMS (EI, M^+) calcd for $C_{18}H_{31}NO_4SSi$ 385.1743, found 385.1745; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.26 (br s, 1H), 3.89 (d, *J* = 10.8 Hz, 1H), 3.69-3.61 (m, 3H), 3.22 (d, *J* = 10.8 Hz, 1H), 3.04 (br s, 1H), 2.42 (s, 3H), 1.95-1.86 (m, 1H), 1.77-1.74 (m, 1H), 0.70 (s, 9H), -0.08 (s, 3H), -0.10 (s, 3H); Anal. Calcd for $C_{18}H_{31}NO_4SSi$ C, 56.07; H, 8.10; N, 3.63. Found C, 56.01; H, 8.19; N, 3.78. The total yield of four steps was 90%.

(2*S*,4*R*)-1-(4-Methylphenylsulfonyl)-2-vinyl-4-(*t*-butyldimethylsilyloxy)pyrrolidine (5).

A stirred solution of oxalyl chloride (400 mg, 3.15 mmol) in dichloromethane (20 mL) was mixed with dimethyl sulfoxide (400 mg, 5.1 mmol) at –78 °C. The solution was warmed to –40 °C for 15 min and recooled to –78 °C, and then a solution of alcohol (**4**) (1.0 g, 2.6 mmol) in dichloromethane (10 mL) was added dropwise for 90 min followed by excess triethylamine (4 mL, 28.5 mmol) for 30 min. The reaction mixture was warmed to rt and poured into saturated aqueous ammonium chloride solution (2 mL), and concentrated. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with brine and water, dried, filtered and concentrated to produce crude aldehyde (950 mg, 2.48 mmol). To a stirred solution of methyltriphenylphosphonium iodide (10.0 g, 4.0 mmol) in dry tetrahydrofuran (40 mL) was added *n*-butyllithium (2.0 mL, 1.6 M, 3.2 mmol) at –78 °C. The orange red colored mixture was stirred at –78 °C for 1 h. The aldehyde product (950 mg, 2.48 mmol) was added to the reaction mixture at –78 °C *via* a syringe and the mixture was further stirred at –78 °C for 8 h. The reaction was quenched with aqueous saturated ammonium chloride (10 mL) and the mixture was extracted with ether (3 x 50 mL) and the combined organic layers were washed with brine (2 x 20 mL), dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 15/1) afforded compound (**5**) (871 mg, two steps 88% from compound (**4**)) as a colorless solid. mp = 81-83 °C (hexane/ethyl acetate); $[\alpha]^{21}_{D}$ –54.25° (*c* 0.1, $CHCl_3$); EI-MS: $C_{19}H_{31}NO_3SSi$ m/z (%) = 91 (100), 149 (15), 155 (15), 270 (18), 324 (12), 381 (M^+, 1); HRMS (EI, M^+) calcd for $C_{19}H_{31}NO_3SSi$ 381.1794, found 381.1796; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.91 (ddd, *J* = 7.5, 10.5, 17.0 Hz, 1H), 5.21 (d, *J* = 17.0 Hz, 1H), 5.13 (d, *J* = 10.5 Hz, 1H), 4.26-4.23 (m, 1H), 4.02 (dd, *J* = 7.5, 14.5 Hz, 1H), 3.65 (dd, *J* = 5.0, 11.0 Hz, 1H), 3.18 (dd, *J* = 1.5, 11.0 Hz, 1H), 2.41 (s, 3H), 1.85-1.75 (m, 2H), 0.72 (s, 9H), -0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.19, 139.12, 134.30, 129.48 (2x), 127.73 (2x), 115.26, 69.48, 61.17, 57.58, 42.57, 25.55 (3x), 21.45, 17.81, -4.99, -5.08; Anal. Calcd for $C_{19}H_{31}NO_3SSi$ C, 59.80; H, 8.19; N, 3.67. Found C, 60.03; H, 8.33; N, 3.45.

(2*S*)-1-(4-Methylphenylsulfonyl)-2-vinylpyrrolidin-4-one (6).

A solution of tetra-*n*-butylammonium fluoride (1.2 mL, 1.0 M, 1.2 mmol) in tetrahydrofuran (3 mL) was added to a solution of compound (**5**) (381 mg, 1.0 mmol) in tetrahydrofuran (3 mL) at rt for 1 h. A mixture of dichloromethane (20 mL), pyridinium chlorochromate (1.08 g, 5.0 mmol) and Celite (1.0 g) was added to the stirring reaction. After being stirred at rt for 10 h, the mixture was filtered through a short silica gel column. The filtrate was dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 5/1) yielded compound (**6**) (225 mg, two steps 85% from compound (**5**)) as a colorless solid. mp = 110-112 °C (hexane/ethyl acetate); $[\alpha]^{22}_{D}$ +56.50° (*c* 0.14, $CHCl_3$); EI-MS: $C_{13}H_{15}NO_3S$ m/z (%) = 91 (100), 155 (4), 265 (M^+, 1); HRMS (EI, M^+) calcd for $C_{13}H_{15}NO_3S$ 265.0773, found 265.0774; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.81

(ddd, *J* = 6.0, 10.0, 17.5 Hz, 1H), 5.28 (d, *J* = 17.5 Hz, 1H), 5.21 (d, *J* = 10.0 Hz, 1H), 4.60-4.56 (m, 1H), 3.73 (d, *J* = 18.5 Hz, 1H), 3.66 (d, *J* = 18.5 Hz, 1H), 2.49 (dd, *J* = 9.0, 18.5 Hz, 1H), 2.45 (s, 3H), 2.34 (dd, *J* = 4.0, 18.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.29, 144.30, 135.88, 134.31, 129.96 (2x), 127.60 (2x), 117.12, 59.34, 53.27, 43.38, 21.45; Anal. Calcd for $C_{13}H_{15}NO_3S$ C, 58.85; H, 5.70; N, 5.28. Found C, 59.11; H, 5.98; N, 5.38.

(1*S*,4*R*)-7-(4-Methylphenylsulfonyl)-7-azabicyclo[2.2.1]heptan-2-one (3).

To a stirred solution of olefin (**6**) (133 mg, 0.5 mmol) in tetrahydrofuran (20 mL) was added 9-borabicyclo[3.3.1]nonane (0.5 M in THF, 2 mL, 2.0 mmol) *via* syringe under nitrogen system. The mixture was heated at reflux for 2 h. Oxidation was carried out by dropwise addition of a solution of 4.5 mL of 35% hydrogen peroxide/0.5 N sodium hydroxide/water (vol: 4:4:1). The mixture was held an additional 1 h at reflux temperature and the mixture was extracted with ether (3 x 50 mL) and the combined organic layers were washed with brine (2 x 20 mL), dried, filtered and evaporated to yield the crude product alcohol (127 mg, 0.45 mmol). Without further purification, a solution of lithium diisopropylamide (1.0 M in THF, 1.2 mL, 1.2 mmol) in tetrahydrofuran (5 mL) was added to a solution of the crude resulting alcohol (127 mg, 0.45 mmol) in tetrahydrofuran (10 mL) at -78 °C. *p*-Toluenesulfonyl chloride (115 mg, 0.6 mmol) dissolved in tetrahydrofuran (5 mL) was added dropwise at -78 °C . The mixture was stirred at 0 °C for 30 min and then stirred at 25 °C for 10 h. The reaction was quenched with aqueous saturated ammonium chloride (1 mL) and the mixture was extracted with ether (3 x 50 mL) and the combined organic layers were washed with brine (2 x 20 mL), dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 3/1) afforded compound (**3**) (102 mg, two steps 77% from compound (**6**)) as a colorless solid. mp = 134-136 °C (hexane/ethyl acetate); $[\alpha]^{22}_D$ +52.55° (*c* 0.05, $CHCl_3$); IR ($CHCl_3$) 1760, 1150 cm^{-1}; EI-MS: $C_{13}H_{15}NO_3S$ m/z (%) = 91 (100), 105 (36), 145 (19), 155 (13), 237 (11), 265 (M^+, 1); HRMS (EI, M^+) calcd for $C_{13}H_{15}NO_3S$ 265.0773, found 265.0773; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 4.59 (t, *J* = 5.0 Hz, 1H), 4.10 (d, *J* = 5.0 Hz, 1H), 2.44 (s, 3H), 2.40 (dd, *J* = 6.0, 18.0 Hz, 1H), 2.18-2.06 (m, 2H), 1.93 (d, *J* = 18.0 Hz, 1H), 1.67-1.57 (m, 2H); Anal. Calcd for $C_{13}H_{15}NO_3S$ C, 58.85; H, 5.70; N, 5.28. Found C, 59.93; H, 5.88; N, 5.49. The ^{1}H-NMR spectral data were in accordance with the reported in the literature 3p and 3y.

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