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SYNTHESIS OF (+) AND (-) EPIBATIDINE

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ABSTRACT

A practical synthesis of epibatidine (**1**) was developed. The key step involved selective reduction of the 5,6-double bond of 7-(*tert*-butyloxycarbonyl)-2-(2-chloro-5-pyridyl)-3-(phenylsulfonyl)-7-azabicyclo[2.2.1]-heptane-2,5-diene (**4**) using nickel boride.

Epibatidine (**1**), a potent non-opioid analgesic, was isolated from skins of the Ecuadorian poison frog, *Epipedobates tricolor*, by Daly and co-workers.[1,2] It was reported to be an extremely potent nicotinic receptor agonist.[3,4] Nicotine has been found to be associated with several human disorders[5] such as Alzheimer's and Parkinson's diseases. Due to interest in the novel biological activity associated with **1** and its paucity in nature (1 mg isolated from 750 frogs), a practical synthesis that could be used to prepare larger quantities was required.

Several procedures[6-10] have been reported for the synthesis of **1** with two different approaches to the azabicyclic system. In the approaches reported by Broka,[6] Corey and co-workers,[7] and Fletcher and co-workers,[8] an appropriately 4-substituted cyclohexylamine which pos-

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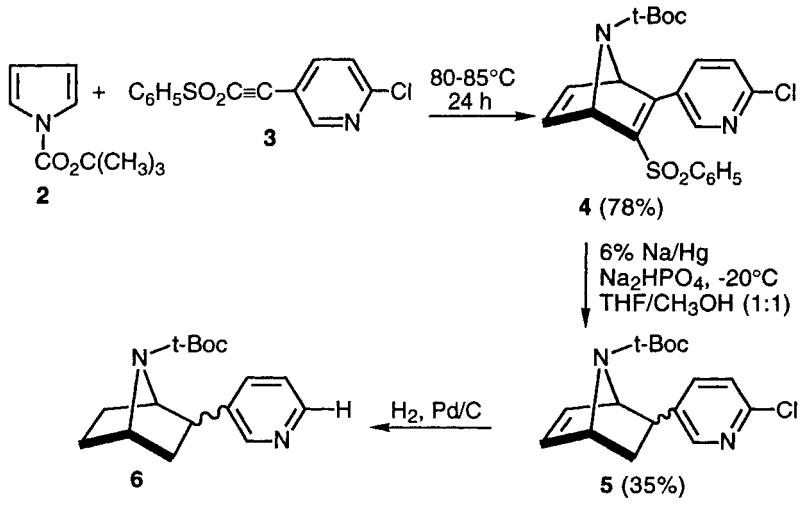
sessed a leaving group at the 4-position to generate the desired bicyclic ring system was used. In the other procedures reported by Huang and Shen[9] and Clayton and Regan,[10] a Diel's Alder approach with an N-protected pyrrole as the diene and a substituted acetylene as dienophile was used to generate the required azabicyclic system.

Since N-*tert*-butyloxycarbonyl-protecting groups can be removed under milder conditions than N-carbomethoxy groups, we expected that replacement of N-(carbomethoxy)pyrrole, used in the reported synthesis,[9] with N-(*tert*-butyloxycarbonyl)pyrrole would facilitate the synthesis of **1** (Scheme 1).

Scheme 1

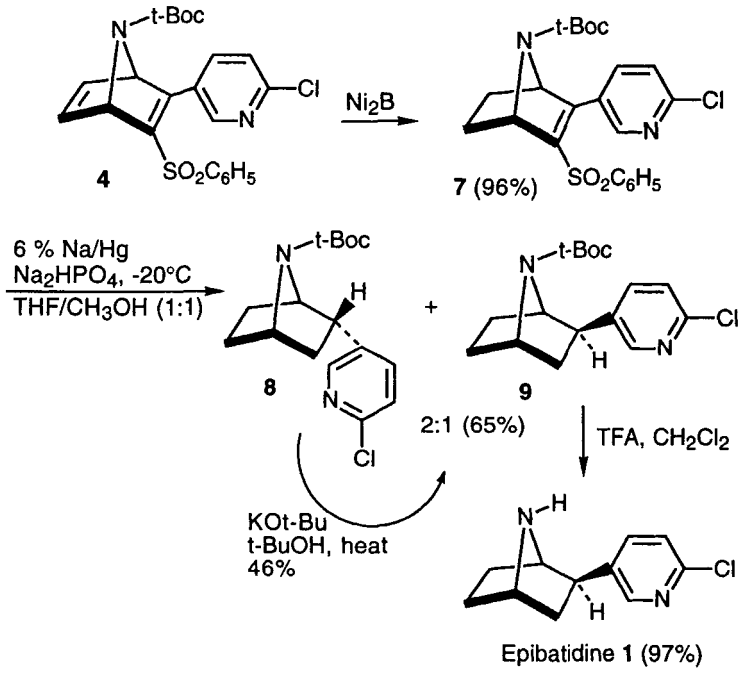


Heating the sulfone-activated dienophile **3**[9,11,12] with 5 equivalents of **2** at 80-85°C for 24 h gave 78% of **4**. Desulfonation and concomitant reduction of the conjugated double bond of the pure cycloadduct **4** was carried out using 6% sodium amalgam in methanol containing 4 equivalents of sodium dihydrogen phosphate.[13] This gave the *t*-Boc-dehydroepibatidine **5** in only 35% yield. The low yield may be due to the susceptibility of the cycloadduct **4** to undergo a retro Diels-Alder reaction.

More important, attempts to selectively reduce the double bond of **5** by hydrogenation at atmospheric pressure with 10% Pd/C as catalyst gave the norchloro N-Boc epibatidine **6**.

Both the problem of over-reduction and competing retro-Diels-Alder reaction occurring during the desulfonation of **4** were eliminated by using the route shown in Scheme 2. In this approach, the least substituted double bond of the cycloadduct **4** was selectively reduced using nickel boride to give 96% of **7**. Desulfonation and concomitant reduction of **7** proceeded cleanly to give 65% of a 2:1 mixture of the *endo* and *exo* isomers **8** and **9**. The *endo* isomer **8** was epimerised to the *exo* isomer **9** in 46% yield using the reported procedure of Fletcher and co-workers.[8] Deprotection of the N-Boc epibatidine **9** using trifluoroacetic acid at room

Scheme 2



temperature gave 97% of racemic epibatidine **1** as a white solid. Optical resolution[9] of (±)-**1** using di-*p*-toluoyl tartaric acid gave (+)- and (-)-**1** which were converted to their hydrochloride salts. The rotations of both the free base and the salts of (+)- and (-)-**1** were higher than those previously reported.[6-10]

In summary, we have developed a practical synthesis of epibatidine **1** which provides a 40% overall yield from **4**. Analogous procedures should be useful in preparing other analogs of **1**.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded at 250 MHz on a Bruker AM-250 spectrometer. Optical rotations were recorded at the sodium D line on a Rudolph Research Autopol III polarimeter (1 dm cell). Melting point was recorded on a Uni-melt Thomas Hoover capillary melting point apparatus in open capillary tubes and were uncorrected. Elemental analysis were performed by Atlantic Microlab, Inc., Norcross, Georgia.

7-(*tert*-Butyloxycarbonyl)-2-(2-chloro-5-pyridyl)-3-(phenylsulfonyl)-7-azabicyclo[2.2.1]heptane-2,5-diene (4). A mixture of 6.07 g (0.022 mol) of acetylene **3**[9,11,12] and 17.28 g (0.104 mol) of N-Boc pyrrole **2**[14] was stirred at 80-85°C for 24 h, the excess pyrrole was removed under high vacuo at 80-85°C to give a dark brownish residue which was purified by flash column chromatography (17.5% ethyl acetate in hexane). This gave on purification 6.84 g (78%) of pure cycloadduct **4** [Rf = 0.25 (3:1 hexane/ethyl acetate)]: ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9 H), 5.36 (br s, 2 H), 6.97 (br s, 2 H), 7.35 (d, 1 H), 7.49 (m, 2 H), 7.61 (m, 1 H), 7.74 (d, 2 H), 7.85 (m, 1 H), 8.40 (br s, 1 H).

7-(*tert*-Butyloxycarbonyl)-2-(2-chloro-5-pyridyl)-3-(phenylsulfonyl)-7-azabicyclo[2.2.1]heptane-2-ene (7). To a solution of 19.52 g (0.077 mol) nickel tetraacetate in 75 mL (5:1) ethanol/water was added

dropwise with stirring under nitrogen 2.97 g (0.077 mol) of sodium borohydride in 75 mL ethanol at room temperature. The black slurry obtained was stirred for additional 10 min. To the slurry was added 6.84 g (0.015 mol) of the cycloadduct **4** in 75 mL THF over a period of 30 min followed by dropwise addition of 13.1 mL (154 mmol) of concentrated HCl acid. The reaction mixture was stirred for 1 h or until judged complete as evidenced by TLC analysis [bright fluorescent spot above starting material (3:1 hexane/ethyl acetate)] of an aliquot of the reaction mixture. The reaction on completion was filtered through celite and the residue washed with 200 mL methylene chloride. The filtrate was rendered basic (pH 8-9) using saturated sodium bicarbonate solution. The organic layer was separated, dried (Na_2SO_4), filtered, and solvent removed in vacuo to give 6.63 g (96%) pure **7** as a yellow solid. The product can be further purified if needed by crystallization from ethyl acetate/hexane: ^1H NMR ($CDCl_3$) δ 1.19 (s, 9 H), 1.35 (t, J = 8.5 Hz, 1 H), 1.60 (t, J = 8.5 Hz, 1 H), 2.08 (m, 2 H), 4.86 (m, 2 H), 7.29 (d, J = 8.3 Hz, 1 H), 7.45 (m, 2 H), 7.55 (m, 1 H), 7.74 (m, 2 H), 7.82 (d of d, J = 8.3, 2.4 Hz, 1 H), 8.43 (d, J = 2.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.50, 26.01, 27.91, 64.21, 67.25, 81.30, 123.84, 125.41, 127.71, 129.41, 133.99, 139.57, 140.03, 149.30, 152.64, 154.97: mp 155-157°C. Anal. calcd for $C_{22}H_{23}ClN_2O_4S$: C, 59.12; H, 5.19; Cl, 7.93; N, 6.27; S, 7.17. Found: C, 59.27; H, 5.25; Cl, 8.00; N, 6.18; S, 7.16.

7-(*tert*-Butyloxycarbonyl)-2-(2-chloro-5-pyridyl)-7-azabicyclo-[2.2.1]heptane (8) and (9). To a solution of 2.01 g (4.5 mmol) of **7** in 20 mL MeOH and 20 mL anhydrous THF was added 3.19 g (0.023 mol) disodium hydrogen phosphate. The resulting slurry was cooled to -20°C and 8.67 g sodium amalgam (0.023 mol, freshly prepared and pulverized) was added. The resulting suspension was stirred under argon for 4.5 h at

-20°C or until the reaction was judged complete as evidenced by TLC analysis [disappearence of bright fluorescent spot for starting material (3:1 hexane/ethyl acetate)] of an aliquot of the reaction mixture. The reaction on completion was filtered through celite and the solvent removed in vacuo to give 2.83 g of crude product. Purification of the crude product by flash column chromatography (10% ethyl acetate in hexane) gave as a first fraction 1.2 g (43%) of pure racemic 2-endo isomer **8** [Rf = 0.1, 9:1 hexane/ethyl acetate]: ^{1}H NMR ($CDCl_3$) δ 1.4 (m, 2 H), 1.49 (s, 9 H), 1.59 (d of d, J = 5.6, 12.5 Hz, 2 H), 1.85 (m, 1 H), 2.31 (m, 1 H), 3.47 (m, 1 H), 4.32 (br S, 2 H), 7.29 (d, J = 8.3 Hz, 1 H), 7.47 (d of d, J = 8.3, 2.5 Hz, 1 H), 8.26 (d, J = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.86, 27.83, 29.67, 33.84, 43.08, 56.80, 59.86, 79.67, 123.43, 134.36, 138.14, 148.94, 149.10, 154.99. Further elution gave as a second fraction 0.6 g (22%) of pure 2-exo isomer **9** [Rf = 0.07, 9:1 hexane/ethyl acetate]: ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9 H), 1.60 (m, 2 H), 1.78 (m, 3 H), 2.01 (d of d, J = 9, 12.4 Hz, 1 H), 2.86 (d of d, J = 9, 5 Hz, 1 H), 4.16 (br s, 1 H), 4.34 (br s, 1 H), 7.24 (d, J = 8.3 Hz, 1 H), 7.64 (d of d, J = 8.3, 2.5 Hz, 1 H), 8.25 (d, J = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.88, 28.38, 29.29, 39.94, 44.45, 55.71, 61.54, 79.40, 123.661, 137.0, 139.79, 148.23, 148.78, 154.80.

Epimerization of 7-(*tert*-Butyloxycarbonyl)-2-(2-chloro-5-pyridyl)-7-azabicyclo[2.2.1]heptane (8). To 1.2 g (0.0039 mol) of **8** in 15 mL *tert*-butanol was added 4.6 mL (1 M solution in THF, 4.6 mmol) potassium *tert*-butoxide. The resulting solution was heated at reflux for 18 h, cooled and solvent removed in vacuo to give crude product. Purification of the crude by flash column chromatography (10% ethyl acetate in hexane) gave as a first fraction 0.48 g (44%) of starting isomer **8**. Further elution gave as a second fraction 0.33 g (46% based on unrecovered starting material) of pure isomer **9**.

Racemic 7-azabicyclo-2-(2-chloro-5-pyridyl)-[2.2.1]heptane (1). To a solution of 917 mg (2.97 mmol) of **9** in 30 mL methylene chloride was added dropwise with stirring under nitrogen 3.43 mL (44.5 mmol) of trifluoroacetic acid. The resulting solution was stirred for 3 h at room temperature and rendered basic (pH 8) using saturated K_2CO_3. The organic layer was separated and aqueous layer extracted twice with 10 mL methylene chloride. The organic layers were combined dried (Na_2SO_4), filtered, and the solvent removed in vacuo to give 0.73 g of crude product. The crude product was purified by flash chromatography [ethyl acetate, methylene chloride, (7 N NH_4OH in MeOH) (2:1:0.2)] to give 0.6 g (97%) of pure racemic epibatidine **1** as a white solid: ^1H NMR ($CDCl_3$) δ 1.58 (m, 5 H), 1.87 (d of d, J = 8.9, 12 Hz, 1 H), 2.75 (d of d, J = 8.9, 4.9 Hz, 1 H), 3.55 (s, 1 H), 3.78 (t, J = 3.84 Hz, 1 H), 7.24 (d, J = 8.3 Hz, 1 H), 7.77 (d of d, J = 8.3, 2.5 Hz, 1 H), 8.27 (d J = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 30.02, 31.21, 40.20, 44.30, 56.19, 62.57, 123.69, 137.55, 141.05, 148.58, 148.64.

Resolution of (±) Epibatidine. To a mixture of 560 mg (2.68 mmol) of racemic epibatidine and 1.09 g (0.0028 mol) of di-*p-toluyl*-d-tartaric acid was added 50 mL (4:1) isopropanol/water. The resulting mixture was heated on a steam bath until homogenous and let stand at room temperature for 12 h. The crystals obtained was filtered to give 0.894 g (54%) of di-*p*-toluoly tartrate salt of **1** as white crystalline solid {$[\alpha]_D$ = -102.5 (0.175, MeOH)}. The salt of **1** was recrystalized as described above using 30 mL of the same solvent system. This gave 0.439 g of pure di-*p*-toluoly tartrate salt of **1** as a white crystalline solid {$[\alpha]_D$ = -109.74 (0.195, MeOH)}; mp 200°C. The di-*p*-toluoly tartrate salt was dissolved in aqueous Na_2CO_3 (pH 8), and the free base generated was extracted with CH_2Cl_2. The methylene chloride layer was dried (Na_2SO_4) filtered, and

solvent removed in vacuo to give pure free base of **1** as a white solid {$[\alpha]_D$ = +7.06 (0.69, $CHCl_3$)}; mp 63°C. The free base was converted to hydrochloride salt and crystallized from CH_2Cl_2/ether to give pure (-)-epibatidine hydrochloride {$[\alpha]_D$ = -42.92 (0.29, MeOH)}; mp 217°C. Anal. calcd for $C_{11}H_{13}ClN_2$•HCl: C, 53.89; H, 5.76; N, 11.43. Found: C, 53.75; H, 5.75; N, 11.44.

The mother liquors from above were combined and evaporated to dryness, dissolved in water adjusted to pH 8 with saturated aqueous Na_2CO_3, and extracted with methylene chloride. The dried (Na_2SO_4) extracts were evaporated to give 370 mg (1.73 mmol) of yellowish white solid. To this was added 713 mg (1.85 mmol) of di-*p*-toluly-d-tartaric acid and 40 mL of (4:1) isopropanol/water and crystallized as described above for the (-) isomer to give 0.567 g (52%) of di-*p*-toluoly tartrate salt of **1** as a white crystalline solid {$[\alpha]_D$ = +113.2 (0.29, MeOH)}. The salt was recrystalized using 20 mL of the same solvent system as above to obtain 0.412 g of pure di-*p*-toluoly tartrate salt of **1** as a white crystalline solid {$[\alpha]_D$ = +115.8 (0.33, MeOH)}; mp 205°C. The salt was dissolved in aqueous Na_2CO_3 (pH 8), and the free base generated was extracted with CH_2Cl_2. The methylene chloride layer was dried (Na_2SO_4) filtered, and solvent removed in vacuo to give pure free base of **1** as a white solid {$[\alpha]_D$ = -6.43 (0.14, $CHCl_3$)}; mp 62°C. The free base was converted to the hydrochloride salt and crystallized from CH_2Cl_2/ether to give pure (+)-epibatidine hydrochloride {$[\alpha]_D$ = +42.62 (0.31, MeOH)}; mp 215°C. Anal. calcd for $C_{11}H_{13}ClN_2$•HCl: C, 53.89; H, 5.76; N, 11.43. Found: C, 53.64; H, 5.77; N, 11.27.

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References

(1) Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. J.; Karle, I. C. *J. Am. Chem. Soc.* **1980**, *102*, 830.

(2) Spande, T. F.; Garaffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475.

(3) Qian, C.; Li, T.; Shen, T. Y.; Libertine-Garaham, L.; Eckman, J.; Biftu, T.; Ip, S. *Eur. J. Pharmacol.* **1993**, *250*, R13-R14.

(4) Badio, B.; Daly, J. W. *Mol. Pharmacol.* **1994**, *45*, 563-569.

(5) Jarvick, M. E. *Br. J. Addict.* **1991**, *86*, 571.

(6) Broka, C. A. *Tetrahedron Lett.* **1993**, *34*, 3251.

(7) Corey, E. J.; Loh, T.-P.; AchyuthaRao, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600.

(8) Fletcher, S. R.; Baker, R.; Chambers, M. S.; Hobbs, S. C.; Mitchell, P. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1216-1218.

(9) Huang, D. F.; Shen, T. Y. *Tetrahedron Lett.* **1993**, *34*, 4477.

(10) Clayton, S. C.; Regan, A. C. *Tetrahedron Lett.* **1993**, *34*, 7493.

(11) Lee, W. J.; Oh, D. Y. *Syn. Lett.* **1990**, 290.

(12) Thomsen, M. W.; Handwerker, M. B.; Katz, S. A.; Belser, R. B. *J. Org. Chem.* **1988**, *53*, 906.

(13) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

(14) Grehn, L.; Ragnarsson, U. *Angew. Chem. Int. ed. engl.* **1984**, *23*, 296-297.

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