The Total Synthesis of Epibatidine

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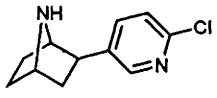
The synthesis of the potent analgesic alkaloid epibatidine **1**, employing as the key step a singlet oxygen reaction with 1-(2-chloro-5-pyridyl)cyclohexa-2,4-diene **2**, is described.

The structurally novel alkaloid epibatidine **1** was isolated from the Ecuadoran frog *Epipedobates tricolor*.[1] Its biological evaluation has shown potent analgesic efficacy by a non-opioid mode of action[1,2] and its total synthesis is consequently of wide interest. The presence of the 7-azabicyclo[2.2.1]heptane ring system with the 2-chloro-5-pyridyl group in an *exo*-orientation presents a challenge to the synthetic chemist. Several different approaches have been reported for the preparation of **1**.[3] In this communication we wish to disclose our synthetic studies leading to a total synthesis of epibatidine.



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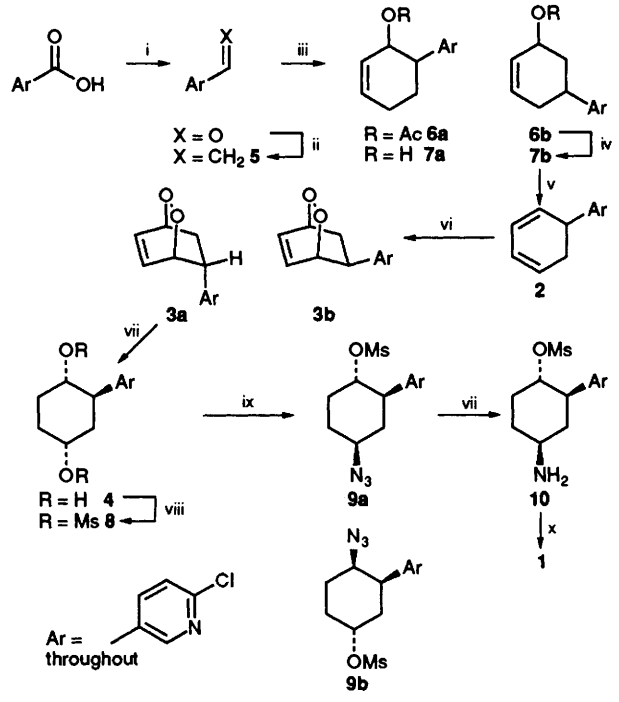
Our synthetic strategy employs the [4 + 2] addition reaction of 1-(2-chloro-5-pyridyl)cyclohexa-2,4-diene **2** with singlet oxygen, forming the bicyclic peroxide **3** as the key step (Scheme 1). It was hoped that the pyridyl substituent would confer a degree of 1,2-*anti*-diastereoselectivity upon this cycloaddition reaction, with complete 1,4-*syn*-stereocontrol resulting from the concerted nature of the reaction. Following oxygen–oxygen cleavage and olefin reduction, the resultant dihydroxy functionality **4** would be activated towards nucleophilic attack (*e.g.*, bis-sulfonate esters). A double-displacement with an ammonia equivalent, either stepwise or *in situ*, would generate epibatidine, wherein the relative configurations at C-1, -2 and -4 are all *syn*.



Scheme 1 *Reagents and conditions*: i, $LiAlH_4$, THF, 0 °C, followed by PCC, CH_2Cl_2, room temp, 41%; ii, Ph_3PCH_3Br, NaH, room temp, 85%; iii, 1-acetoxybuta-1,3-diene, 4-*tert*-butylcatechol, xylene, 140 °C, 50%; iv, K_2CO_3, aq. MeOH, room temp., 95% (combined yield of **7a**, and **7b**); v, 2,4-dinitrobenzenesulfenyl chloride, NEt_3, 1,2-dichloroethane, reflux, 86% from **7a**, 75% from **7b**; vi, oxygen, 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine, CCl_4, Hg lamp, room temp., 80%; vii, H_2, Rh/Al_2O_3, MeOH, room temp., 70%; viii, MsCl, NEt_3, dioxan, 0 °C, 93%; ix, NaN_3, DMF, 60 °C; x, $CHCl_3$, 0.01 mol dm^{-3}, 55 °C, 78%

Preparation of the required diene **2** was envisaged using the conversion of allylic alcohols to dienes, *via* [2,3]-sigmatropic rearrangement of the corresponding sulfenates followed by [2,3]-elimination of the resultant sulfoxides.[4] Diels–Alder reaction between 1-acetoxybuta-1,3-diene and an appropriate olefin would furnish, after acetate hydrolysis, the requisite allylic alcohol. Whilst it was expected that the Diels–Alder reaction would give a mixture of regio- and diastereo-isomers, each isomer would produce the same elimination product.

Reduction of commercially available 6-chloronicotinic acid followed by oxidation to the pyridyl aldehyde was achieved in an overall yield of 41%. Subsequent Wittig olefination afforded the required pyridyl dienophile **5**. Reaction of **5** with 1-acetoxybuta-1,3-diene (2.5 equiv.), in the presence of 4-*tert*-butylcatechol (10 mol%), in refluxing xylene resulted in the formation of a mixture of Diels–Alder products in 50% yield.† Examination of the ^1H NMR spectrum of the mixture revealed the presence of two regioisomers in a 9 : 1 ratio. The structure of the major regioisomer was assigned as **6a** by ^1H COSY experiments. The isomeric mixture was treated with potassium carbonate in aqueous methanol, to yield the allylic alcohols **7a** and **7b**. Treatment of each allylic alcohol, separated by column chromatography, with 2,4-dinitrobenzenesulfenyl chloride and triethylamine in refluxing 1,2-dichloroethane resulted in the rearrangement–elimination reaction, producing the same diene **2**.[4]

With diene **2** in hand the reaction with singlet oxygen was investigated.[5] Irradiation (400 W mercury vapour lamp) of a carbon tetrachloride solution of **2** in the presence of a photosensitizer (5,10,15,20-tetraphenyl-21*H*,23*H*-porphine) under an oxygen atmosphere produced two isomeric products, **3a** and **b**, in equal amounts, with a combined yield of 80%. While the lack of diastereoselectivity was disappointing, the rigidity of the bicyclic intermediates, **3a** and **3b**, which were separated by flash column chromatrography, enabled us to assign the stereochemistry unambiguously by ^1H NMR spectroscopy.‡ The required *trans* stereoisomer **3a** was treated with hydrogen over rhodium on alumina to execute oxygen–oxygen bond cleavage and reduction of the double bond in a single operation.[6] When palladium catalysts were used, the reductions were accompanied by hydrogenolysis of the pyridyl–chlorine bond. The diol **4** was converted to the bismesylate **8**, which was then treated with a single equivalent of sodium azide. The azidomesylate **9a** was isolated in 65% yield along with bis-azide (6%) and unchanged starting material (13%). None of the regioisomeric azidomesylate **9b** was observed. While **9b** could, in principle, be converted to **1**, the regioselectivity observed in this reaction was pleasing, since the reduction of azides in sterically hindered systems like **9b** was reported to be difficult.[3a] Azide **9a** was reduced, again using hydrogen over rhodium on alumina, and the resultant aminomesylate **10** heated at high dilution (0.01 mol dm^{-3}) in chloroform to yield epibatidine in 78% yield.[3a]

Pharmacological studies with synthetic epibatidine are currently being undertaken.

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Footnotes

† The starting dienophile **5** was recovered in 25% yield after 30 h. Extended reaction time resulted in polymerisation of the products.
‡ $\delta_H(CDCl_3$; 200 MHz) **3a** 1.61–1.72 (1H, m), 2.82 (1H, m), 3.70 (1H, m, CHPyr), 4.64 (1H, m), 4.85 (1H, m), 6.52–6.60 (1H, m), 6.86–6.94 (1H, m), 7.27 (1H, d, *J* 8.38 Hz), 7.42 (1H, dd, *J* 2.56, 8.68 Hz), 8.22 (1H, d, *J* 2.56 Hz); **3b** 1.98–2.20 (2H, m), 2.90 (1H, m, CHPyr), 4.42 (1H, m), 4.83 (1H, m), 6.73–6.90 (2H, m), 7.35 (1H, d, *J* 8.26 Hz), 7.42 (1H, dd, *J* 2.57, 8.26 Hz), 8.36 (1H, d, *J* 2.57 Hz).

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