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Total Synthesis of (±)-Epibatidine.

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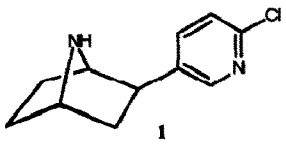
Abstract: (±)-1α-Nitro-2β-[3-(6-chloropyridyl)]-cyclohexanone, a key intermediate for a stereocontrolled synthesis of the alkaloid epibatidine, possessing a 7-azanorbornane structure to which is attached, in an *exo*-orientation, a 5-(2-chloropyridyl) substituent, has been prepared either by Diels-Alder reaction or tandem Michael reaction by way of 5-(2-nitrovinyl)-2-chloropyridine as common starting material and 2-trimethylsilyloxy-1,3-butadiene or methyl 3-oxo-4-pentenoate as counterparts respectively.

In 1992 Daly and coworkers reported the discovery and structural elucidation of epibatine **1**, a new alkaloid isolated from Ecuadorian poison frog, *Epipedobates tricolor*.[1] Subsequent studies has shown that the absolute configuration of this structurally unusual natural compound, featuring the 7-azabicyclo[2.2.1]heptane ring system with a 2-chloro-5-pyridyl substituent attached in the *exo*-orientation, is 1R,2R,4S.[2]



1

Preliminary biological essays, indicating that **1** is a very potent analgesic with a non-opiod mechanism of action, have established epibatidine as a singularly important target for total synthesis.

To date, different successful approaches[3-12] have been reported since Broka first described the preparation of **1** in racemic form, thus confirming the structure of the natural product.

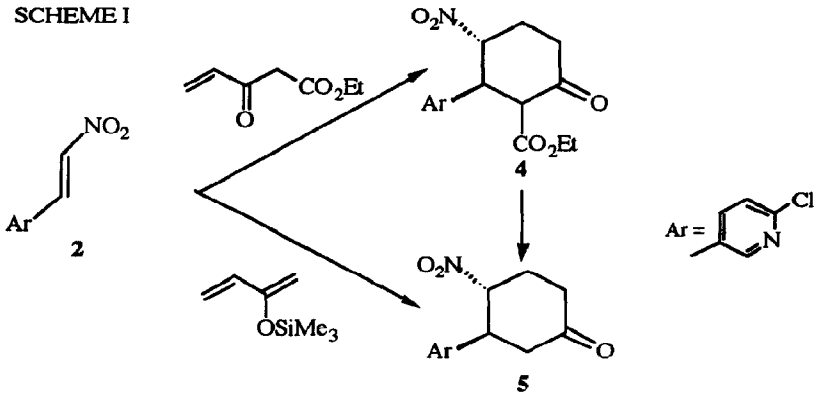
In connection with our program dealing with the tandem annulation chemistry of unsaturated nitroderivatives,[13] we wish to report in this paper a stereocontrolled route to **1** entailing the use of 5-(2-nitrovinyl)-2-chloropyridine **2** as the common starting material for two different approaches to the construction of the key cyclohexanone intermediate **5**.

Thus, the first approach is centered on a tandem Michael reaction occurring at room temperature simply by mixing equimolecular amount of **2**, easily prepared in 61% overall yield by methansulfonyl chloride-

triethylamine promoted dehydration of the Henry adduct of nitromethane and the known[7] 6-chloro-pyridine-3-carboxaldehyde in the presence of Al_2O_3,[14] and ethyl 3-oxo-4-pentenoate[15] in dioxane solution in the presence of benzyl-trimethylammonium methoxide. The completely enolized cyclic β-ketoester **4**, isolated in 46% yield[#], underwent deethoxycarbonylation on heating in wet DMSO containing LiCl to produce the crucial cyclohexanone **5** in 48% yield.

The latter could be obtained in a more straightforward way in 68% overall yield through thermal (120°C, 48h) Diels-Alder reaction between **2** and the easily available 2-trimethylsilyloxy-1,3-butadiene, followed by aqueous acid treatment of the crude cycloadduct.

SCHEME I



Transformation of **5** to epibatidine has been recently reported by Szántay and coworkers[8] by a five-step sequence including: a) $NaBH_4$ reduction of the carbonyl group to the corresponding β-secondary alcohol; b) mesylation; c) reduction of the nitro group to the corresponding α-amine; d) intramolecular nucleophilic substitution to generate the epimer of epibatine; e) tert-butoxide-promoted epimerization of the latter to produce epibatine.

In order to avoid the tedious epimerization step, we decided to look at a suitable device to secure the proper *anti*-stereochemistry of the functionalities involved in the nitrogen bridge formation.

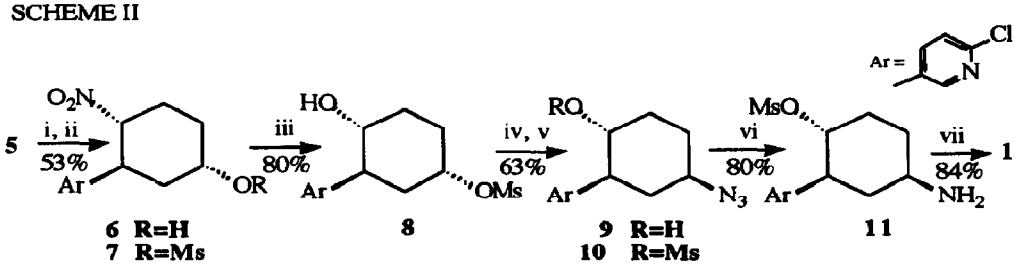
Thus, we envisaged a displacement of the easily separable mesylate **7** of the α–alcohol **6**, obtained as a 7:3 mixture with the corresponding β-epimer utilizing L-selectride instead of sodium borohydride, with an ammonia equivalent for the creation of a β-amino group, while the nitro group would act as a precursor of an α-hydroxylated function which would be subsequently activated for an intramolecular nucleophilic attack. Thus, submitting the nitromesylate **7** to oxidative Nef conditions usually used for the transformation of a secondary nitro group into a carbonyl and quenching the reaction mixture with $NaBH_4$, we were able to obtain the mesyloxyalcohol **8**.

The direct conversion of a nitro group into a hydroxyl group with complete retention of configuration of the involved center is noteworthy.

The reaction of the mesyloxycyclohenanol derivative **8** with sodium azide in DMF solution proceeded uneventfully to furnish the corresponding azidoalcohol **9**, which was subsequently esterified with methansulfonyl chloride to provide the azidomesylate **10**.

Reduction of the azide to the corresponding amine was easily accomplished by treatment with an excess of $SnCl_2$ in 1 : 1 MeOH: THF solution and the resulting aminomesylate **11** was heated in chloroform to produce epibatidine.

SCHEME II



Reagents: i, L-Selectride; ii, MsCl, Et_3N; iii, MeONa, O_3, -78°C, Me_2S, $NaBH_4$; iv, NaN_3, DMF; v, MsCl, Et_3N; vi, $SnCl_2$, MeOH : THF, 1:1, 25°C; vii, Δ.

In conclusion, the synthesis of (±)-epibatidine described here illustrates the applicability of tandem annulation chemistry of unsaturated nitroderivatives as a simple and easy method for the construction of substituted cyclohexanones and should provide access to structurally related analogs for pharmacological studies.

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All new compounds were fully characterised by spectroscopic data and microanalysis. The following representative compounds are reported :

7: mp=135-137°C (ether): ^{1}H NMR ($CDCl_3$); δ 8.29 (1H, d, J=2.5Hz), 7.5 (1H, dd, J=8.2, 2.6Hz), 7.2 (1H, d, J=8.2Hz), 5.1 (1H, m), 4.7 (1H, m), 3.7 (1H, m), 3.1 (3H, s) 2.4 (4H, m), 2.0-1.7 (2H, m).

8: oil; ^{1}H NMR ($CDCl_3$); δ 8.19 (1H, d, J=2.4Hz), 7.55 (1H, dd, J=8.2, 2.5Hz), 7.26 (1H, d, J=8.2Hz), 5.06 (1H, m), 3.8-3.6 (1H, m), 3.07 (3H, s), 3-2.8 (2H, m) 2.4-2.2 (2H, m), 2.1-1.7 (4H, m).

9: oil; ^{1}H NMR ($CDCl_3$); δ 8.2 (1H, d, J=2.4Hz), 7.55 (1H, dd, J=8.2, 2.4Hz), 7.28 (1H, d, J=8.2Hz), 3.8-3.6 (1H, m), 3.6-3.4 (1H, m) 2.7-2.5 (1H, m), 2.5-2.0 (4H, m), 1.8-1.5 (3H,m).

10: mp.=119-120°C (ether): ^{1}H NMR ($CDCl_3$); δ 8.29 (1H, d, J=2.6Hz), 7.6 (1H, dd, J=8.2, 2.6Hz), 7.36 (1H, d, J=8.2Hz), 4.61 (1H, dt, J=4.4, 10.7Hz), 3.51 (1H, m), 2.9 (1H, m) 2.52 (3H, s), 2.6-2.4 (1H, m), 2.3-2.1 (2H, m), 1.9-1.6 (3H, m).

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