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A New Approach for the Synthesis of (±)-*Trans*-10,11-Dihydroxy-5,6,6a,7,8,12b-Hexahydrobenzo[*a*]phenanthridine (Dihydrexidine)

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Abstract: *A novel method is reported for the synthesis of (±)-trans-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine (dihydrexidine, **6b**) employing as a key step the cyclization of the acid chloride of **3b**, via decarbonylation, to the hexahydrobenzo[a]phenanthridine **4b**.* Copyright © 1996 Elsevier Science Ltd

Dihydrexidine (**6b**) was been reported to be the first high potency, fully efficacious dopamine D_1 agonist.[1] It showed remarkable activity against MPTP-induced parkinsonism in monkeys[2] and is currently undergoing clinical trials as a potential treatment for Parkinson's disease. The original synthesis of **6b** by Brewster *et al.*[3] proceeded from a difficultly accessible beta-tetralone starting material through a low yielding photocyclization step, rendering the methodology relatively inefficient and uneconomical for production scale chemistry. In this communication, we wish to describe a novel method for the synthesis of **6b** involving facile and high yielding reactions that is amenable to large-scale reaction.

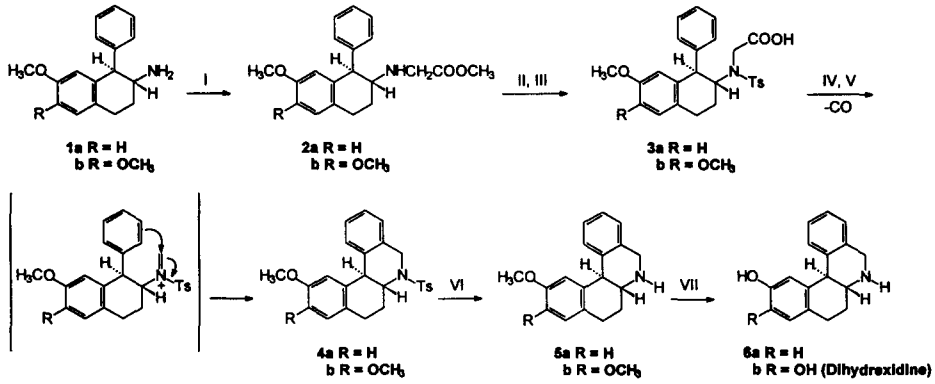
The synthesis begins with **1b**, which has been previously described and can be prepared on a large scale.[4,5] Alkylation of **1b** with one equivalent of methyl bromoacetate in DMF over potassium carbonate afforded an 85% yield of **2b**. N-Protection of **2b** using p-toluenesulfonyl-chloride, followed by selective hydrolysis of the methyl ester with 1N methanolic KOH, afforded the *N*-protected amino acid **3b** (80%).

Treatment of the acid chlorides of **3a** or **3b** with aluminium chloride in dichloromethane at temperatures from -78 °C to -5 °C led to the expected naphthobenzazepinones.[4] At room temperature, however, reaction of the acid chloride of **3b** surprisingly afforded a significant amount of **4b**. When the acid chloride was added to a suspension of aluminium chloride in dichloromethane at reflux, a gas was evolved and **4b** was the sole product, isolated in 85% yield. The structure of **4b** was unequivocally confirmed by comparison of its ^{1}H NMR and CIMS spectra with those of a sample of **4b** derived from authentic **5b**, and also by elemental analysis. Following standard procedures,[4] **4b** could be N-detosylated and O-demethylated to afford **6b**.

A mechanistic explanation analogous to the one proposed by Proctor and Thomson[6] for the aluminum chloride-catalyzed cyclization of the acid chloride of *N*-tosyl-2'-phenethylglycine

to form *N*-tosyl-tetrahydroisoquinoline can be envisaged for the present cyclization leading to **4b**. Elimination of carbon monoxide from the intermediate acylium ion is assisted by electron release from the nitrogen electron pair, followed by attack of the phenyl ring on the tosylated iminium species to yield the benzo[*a*]phenanthridines, with retention of the trans B/C ring configuration.

Scheme 1



I, $BrCH_2COOCH_3$, K_2CO_3; II, p-TsCl, Et_3N, CH_2Cl_2; III, 1N. methanolic KOH; H^+; IV, $(COCl)_2$, CH_2Cl_2; V, $AlCl_3$, CH_2Cl_2, reflux; VI, Red-Al, xylene, reflux; VII, BBr_3, CH_2Cl_2, -78 °C.

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