Studies on the Stereochemistry of Nucleophilic Additions to Tetrahydropyridinium Salts. A Stereospecific Total Synthesis of One of the Stereoisomers of Gephyrotoxin 223

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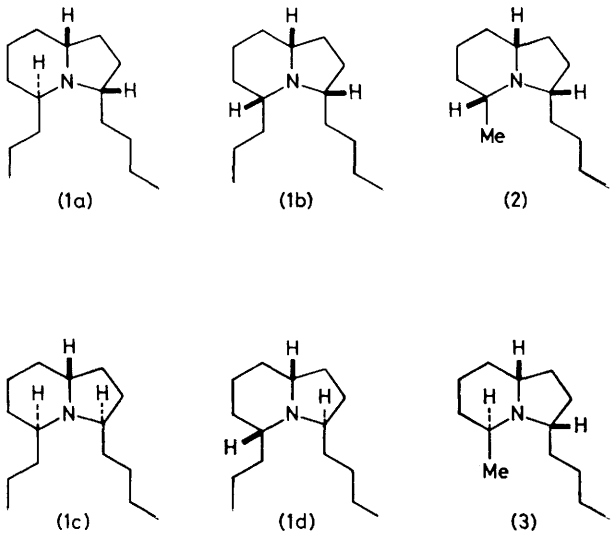
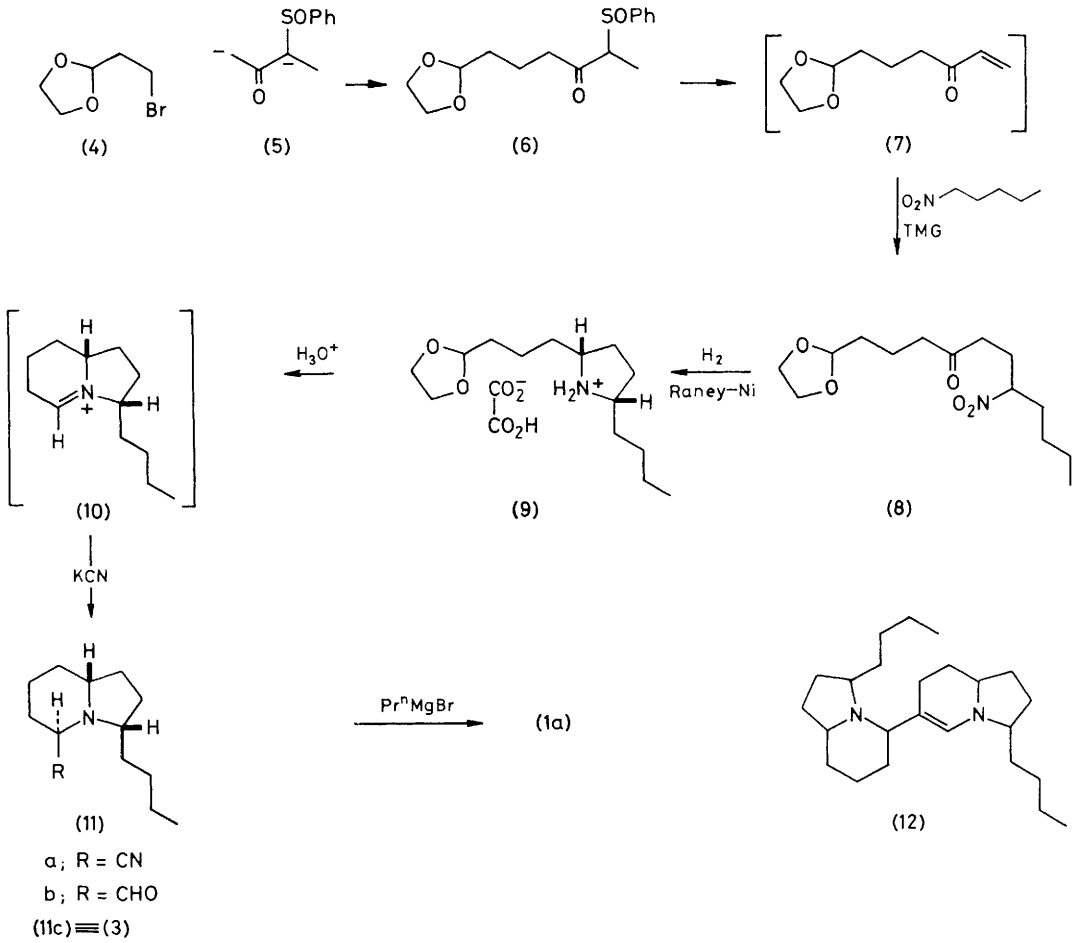
An efficient stereospecific total synthesis of one of the stereoisomers of gephyrotoxin 223 is described.

The skins of certain frogs (family *Dendrobates*) indigenous to South America are a rich source of a variety of neurotoxic alkaloids. Recently, a minute amount of an octahydroindolizine alkaloid was isolated and its gross structure determined by mass spectroscopy to be 3-butyl-5-propyloctahydroindolizidine.[1] Insufficient material was available to elucidate further its stereochemical features. Recently, one (**1d**) of the four possible diastereomers (**1a—d**) was synthesized and found not to be identical with the natural material.[2] If the stereoelectronic arguments advanced in the preceding paper[3] are valid one could, in principle, synthesize stereoselectively any one of the four possible diastereomers of gephyrotoxin 223.

Alkylation of the dianion of the ketosulphoxide (**5**)[4] with the bromoacetal (**4**)[5] provided (**6**) in 70% yield. Pyrolysis of (**6**) in refluxing CCl_4 afforded the sensitive enone (**7**) which, without isolation, was treated with 1-nitropentane and tetramethylguanidine[6] (TMG) to yield the nitroketone (**8**). Reduction of (**8**) over Raney-nickel provided a single stereoisomer which was isolated and purified as the corresponding oxalate salt (**9**) in 64% yield. Hydrolysis of (**9**) and cyclization afforded the tetrahydropyridinium salt (**10**). Attempts to convert (**10**) into the corresponding endocyclic enamine led only to dimerization [presumably to give (**12**)]. On the other hand treatment of the acidic mixture with cyanide led to the cyano-





amine (**11a**) in 96% yield. Once again only one stereoisomer was found. In order to confirm the stereochemical assignments, (**11a**) was reduced with Bu^i_2AlH to give the corresponding aldehyde (**11b**) and thereafter by Wolff-Kishner reduction to the known[3,7] monomorine I (**2**) epimer (**11c**) [≡ (**3**)]. The cyanoamine (**11a**) also serves as a latent form of the salt (**10**). Thus, when treated with excess of MeMgBr in ether at 0 °C, (**11a**) was converted directly into (**11c**) in 87% yield. No other stereoisomer was detected. Similarly, treatment of (**11a**) with Pr^nMgBr led stereospecifically to the 3-butyl-5-propyl-octahydroindolizine (**1a**). The high degree of stereoselectivity observed in these nucleophilic additions (hydride, cyanide, and Grignard reagents) is in agreement with the stereoelectronic arguments advanced previously[3] and provides a foundation for further studies aimed at the synthesis of the remaining two unknown gephyrotoxin 223 stereoisomers (**1b**) and (**1c**) as well as other alkaloids.

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