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A NEW SYNTHETIC ROUTE TO (±)-PERHYDROHISTRIONICOTOXIN

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The first total synthesis of (±)-perhydrohistrionicotoxin (I), a useful neurotoxin,[1] was recently reported from these Laboratories.[2,3] We now describe a new, efficient and stereocontrolled route which leads to (±)-perhydrohistrionicotoxin via the intermediate II of our original synthesis.

Ethyl 2-cyclohexen-1-carboxylate (III)[4] was alkylated with ethyl 4-bromobutyrate following the procedure of Hermann et al.[5] to form the unsaturated diester IV which was converted to the spiro ketone V[6] (66% from III) by Dieckmann cyclization using 2.4 equiv of sodium hydride in dry THF (23 hr at 25°, 30 min at reflux) and hydrolysis-decarboxylation (THF-H_2O-H_2SO_4, 8:2:1 by vol at reflux for 4 hr). The ketone V upon treatment with hydroxylamine hydrochloride (1.2 equiv) and pyridine (5 equiv) in absolute ethanol at 25° for 18 hr furnished the oxime VI, mp 118-120°, (83%), further transformed into the oily O-benzyl derivative (VII, 98%) by reaction of the potassium salt with 1.2 equiv of benzyl bromide in dimethoxyethane (DME) for 2 hr at 25°. Reaction of VII with 1.5 equiv of N-bromosuccinimide in 2:1 DME-H_2O (150 ml/g of VII) at -20° for 1.25 hr proceeded with high positional specificity in the desired direction, i.e. attachment of oxygen to the starred carbon of the double bond. The major product (72% isolated yield) was the bromohydrin VIII, mp 106-107.5°. Two by-products, bromohydrin IX and bromoketone X (each formed to the extent of ca. 10%), were separated chromatographically and characterized. Bromoketone X could also be obtained by Jones oxidation of bromohydrin IX at 0°. Oxidation of bromohydrin VIII by Jones reagent (2 equiv, 1.5 hr at 0° and 0.5 hr at 25°) afforded the isomeric bromoketone XI (99% yield) as a chromatographically homogeneous, colorless oil. The location of bromine and carbonyl groups in the bromoketones X and XI was confirmed by the appearance in the pmr spectra of a sharp singlet due to the proton of Br-C-H at 4.71ppm and 4.32 ppm (downfield from internal tetramethylsilane), respectively. In each case the conformation of the six-membered ring is such as to place the bromine substituent in an equatorial arrangement as shown by the occurrence of carbonyl absorption in the infrared spectra of X and XI at 1739 cm^{-1} and 1730 cm^{-1}, respectively.[7]

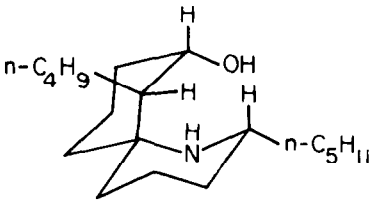
The direction of addition of HOBr to the double bond of VII was also indicated by the pmr spectra of the isomeric bromohydrins VIII and IX which exhibit sharp doublets due to the CHBr proton at 4.35 ppm (J=10 Hz) and 3.87 ppm (J=10 Hz), respectively (essentially unshifted in the corresponding acetate esters), and multiplets for the carbinol proton, centered at 3.66 and 4.43 ppm, respectively (each

shifted downfield by ca. 1.3 ppm by acetylation). The assignment of complete stereochemistry to the two bromohydrins, each of which must have a diequatorial arrangement of HO and Br groups in view of J=10 Hz observed for the CHBr proton, is also clear from the pmr spectra. The CHBr proton doublet is downfield (by 0.5 ppm) in VIII relative to IX whereas the carbinol (CH-O) proton multiplet is upfield (by ca. 0.8 ppm) in VIII relative to IX. These shifts are readily understood in terms of the stereoformulas shown for VIII and IX in which the C=N group should strongly deshield the CHBr proton in VIII and the CH-O- proton in IX.

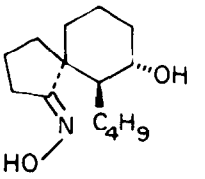
The predominant formation of bromohydrin VIII may be due to oxime-assisted bromonium ion formation and/or reaction as expressed in XII (attack of water at the starred carbon also being the diaxial mode of opening from this conformation). The diastereomeric bromonium ion (having Br on the opposite side of the ring relative to ion XII) may be expected to prefer conformation XIII. From this conformation diaxial opening would restrict attack of water to the starred carbon thereby eventuating in bromohydrin IX and the corresponding ketone X.

Although in principle a mixture of the bromoketones X and XI can be utilized in the present sequence, we used the pure bromoketone XI (from oxidation of the readily available crystalline bromohydrin VIII) for completion of the synthesis. The oxime of XI was prepared quantitatively by reaction with 1.5 equiv of hydroxylamine hydrochloride and 1.5 equiv of sodium acetate in acetic acid (6 ml/g of XI) at 25° for 2 hr. This bromooxime was then utilized according to a recently described strategy for attaching a nucleophilic carbon reagent alpha to carbonyl.[8] Exposure of the bromooxime to excess 1-lithio-1-butyne in THF at -78° led to formation of a blue color, due to the nitroso ene intermediate **XIV**. As the temperature of the reaction mixture was raised, the color began to fade (at ca. -20°) and then disappeared (at ca. -10°). Rapid isolation of product gave the acetylenic oxime XV which immediately and without purification was hydrogenated over Pd-C catalyst (10%) in ethyl acetate at 25° for 1.5 hr to give the tetrahydro derivative XVI (77% overall from XI). Cleavage of the free oxime function in XVI (6 equiv of aqueous titanium trichloride[9] in methanol containing 12 equiv of ammonium acetate) afforded stereospecifically ketone XVII (95%) which was debenzylated by hydrogenation in ethanol at 25° over Pd-C catalyst to form XVIII (98%). Reduction of the ketone XVIII using excess sodium in liquid ammonia-THF (5:1) at -78° for 0.5 hr with excess isopropyl alcohol as a proton source proceeded stereospecifically to form the hydroxy oxime II, mp 129-131°, (92% yield), identical chromatographically and spectroscopically with a sample synthesized as previously described.[2] The intermediate II is convertible to perhydrohistrionicotoxin (I) in a straightforward way.[2,3]

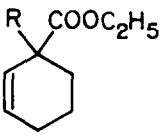
The synthetic route outlined here represents a practical method of synthesis of (±)-perhydrohistrionicotoxin. It also illustrates some interesting new chemistry including the functional-group induced, positionally specific addition of HOBr[10] to the oxime-olefin VII and a novel method for stereospecific and position-specific introduction of a nucleophilic n-butyl equivalent alpha to ketonic carbonyl (or alternatively of generating the electrophilic counterpart of a nucleophilic enolate for alkylation).[8,11,12]



I

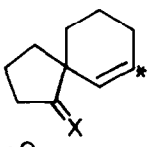


II



III, R = H

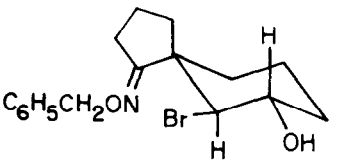
IV, R = $(CH_2)_3COOC_2H_5$



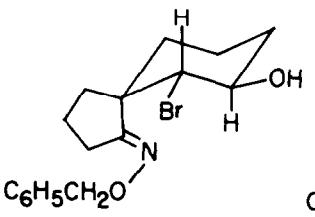
V, X = O

VI, X = NOH

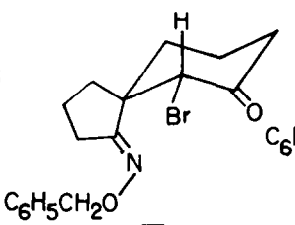
VII, X = $NOCH_2C_6H_5$



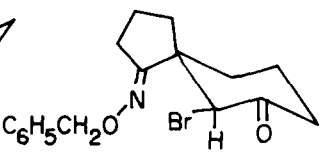
VIII



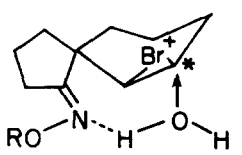
IX



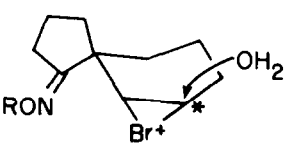
X



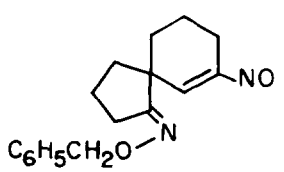
XI



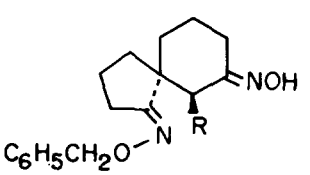
XII



XIII

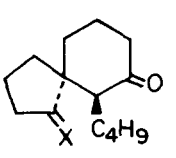


XIV



XV, R = $C_2H_5C{\equiv}C$

XVI, R = n-C_4H_9



XVII, $NOCH_2C_6H_5$

XVIII, X = NOH

References

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2. E. J. Corey, J. F. Arnett and G. N. Widiger, J. Amer. Chem. Soc., 97, 430 (1975).
3. For more recent syntheses see (a) M. Aratani, L. V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura, and S. Inoue, J. Org. Chem., 40, 2009 (1975); (b) T. Fukuyama, L. V. Dunkerton, M. Aratani, and Y. Kishi, J. Org. Chem., 40, 2011 (1975).
4. See (a) P. Markov and C. Ivanoff, Tetrahedron Letters, 1139 (1962); (b) S. J. Rhoads, J. K. Chattopadhyay and E. E. Waali, J. Org. Chem., 35, 3352 (1970); (c) F. Camps, J. Coll and J. Pascual, J. Org. Chem., 32, 2563 (1967). Reduction of benzoic acid by lithium in liquid ammonia gave the 1,4-dihydro derivative which was converted to cyclohexadien-1,3-carboxylic acid during isolation. Further reduction by lithium in liquid ammonia and esterification gave III.
5. J. L. Hermann, G. R. Kieczykowski and R. H. Schlessinger, Tetrahedron Letters, 2433 (1973). The ester III was converted to the lithio derivative using lithium diisopropylamide (1 equiv) and hexamethylphosphoricamide (1 equiv) in dry THF (tetrahydrofuran) at -78°; the subsequent alkylation was carried out at -20° for ca. 3 hr.
6. Satisfactory infrared, nuclear magnetic resonance and mass spectral data were obtained for all intermediates using purified, chromatographically homogeneous samples.
7. E. J. Corey, J. Amer. Chem. Soc., 75, 2301 (1953).
8. See E. J. Corey, L. S. Melvin, Jr. and M. F. Haslanger, Tetrahedron Letters, 3117 (1975).
9. G. H. Timms and E. Wildsmith, Tetrahedron Letters, 195 (1971).
10. For another interesting case of positionally specific HOBr addition to -CH=CH- see S. M. Roberts, Chem. Commun. 948 (1974).
11. In this regard it should be noted that the direct butylation of the oxime of XI by di-n-butylcopper-lithium or by n-butyllithium (cf. ref. 8) did not proceed in the desired sense, presumably for steric reasons.
12. This work was assisted financially by a grant from the U. S. National Science Foundation and a Fellowship to M. P. from the Swiss National Science Foundation.