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SYNTHETIC ENTRY INTO CYCLOPENTYL ANALOGS OF MUSCARINE

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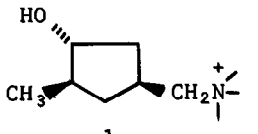
As a result of recent work, it is apparent that desether muscarine (1), the cyclopentyl analog of muscarine (2), parallels the activity and specificity of muscarine at the cholinergic receptor.[2] This communication reports a stereoselective entry into the substituted cyclopentane system.



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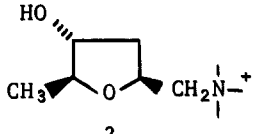


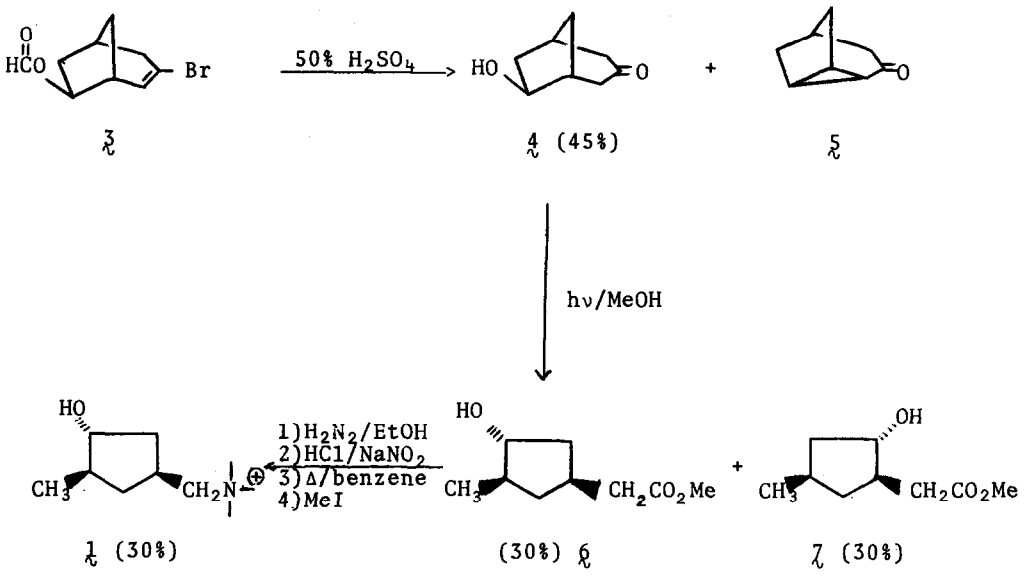
2

Earlier we reported a photochemical route[2b] depicted in Scheme 1 which gave the desired desether muscarine 1 in an overall yield of 4% from bromoformate 3.[3] Need for sufficient quantities of 1 for resolution and oxidation[2b] studies prompted development of a second route.

An attractive entry into cyclopentyl derivatives such as 1 is the stereospecific opening of a symmetrical intermediate giving 1,2-trans substitution. For this purpose, the epoxy amide 10 was selected for three reasons: (1) the opening of epoxides with reagents like lithium dimethyl cuprate are generally regarded to be stereospecific[4] and yield trans-1-hydroxy-2-methyl derivatives, (2) the trans-epoxy amide should be obtainable by a stereoselective epoxidation of the N,N-dimethyl-3-cyclopentenyl carboxamide 9 by modification of the procedure of Henbest,[5] and (3) conversion of the dimethyl amide to the quater-

nary amine should be straightforward.

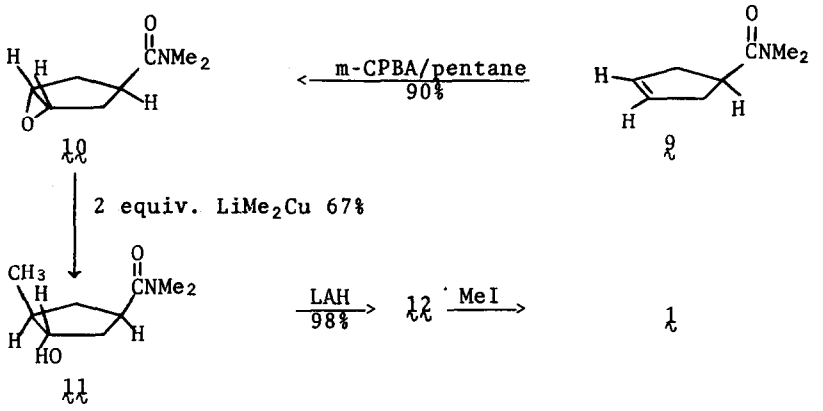
Scheme 1. Photochemical Route



(overall from 3, 4%)

The route chosen is shown in Scheme 2 and gave the desired desether muscarine 1 in an overall yield of 60% from amide 9 as follows. A pentane solution of N,N-dimethyl-3-cyclopentenylcarboxamide[7] (9), obtained in 83% yield from the known 3-cyclopentenylcarboxylic acid[6] (8) via the acid chloride, was treated with m-chloroperbenzoic acid[5] to give the trans-epoxy amide 10 (90%) as an oil. After purification by silica gel chromatography the epoxy amide 10 exhibited characteristic infrared and nmr absorption spectra: ir (film) 6.11 (amide carbonyl), 8.00 and 11.90 μ (epoxide) and nmr ($CDCl_3$) δ 3.53 (s, 2H epoxymethines), 3.01 (s, 3H, NCH_3), 2.92 (s, 3H, NCH_3), 3.1-2.6 (m, 1H, carboxymethine) and 2.32-1.82 (m, 4H, cyclopentylmethylenes).

Scheme 2. Epoxide Route



The trans-epoxy amide 10 was treated with lithium dimethyl cuprate[4] to give the amido alcohol 11 (67%) via a stereospecific opening of the epoxide. The infrared spectrum of the product oil showed absorptions at (film) 2.94 br (OH) and 6.17 μ (amide carbonyl) and the nmr ($CDCl_3$) at δ 3.8-3.4 (m, 1H, hydroxymethine), 3.67 (br s, 1H, OH), 3.1 (s, 3H, NCH_3), 2.92 (s, 3H, NCH_3), 2.5-1.5 (m, 5H, ring protons) and 1.0 (d, 3H, ring CH_3, J = 7 Hz). Reduction of the hydroxyamide with a four fold excess of lithium aluminum hydride gave, after workup, a 98% crude yield of the hydroxy amine 12 which was purified and further characterized as the methyl iodide salt 1. Spectral characteristics of 12 were in accord with the assigned structure: ir (film) 2.95 μ (OH) and no carbonyl and nmr ($CDCl_3$) δ 3.8-3.4 (m, 1H, hydroxymethine), 2.7 (br s, 1H, OH), 2.18 (br s, 8H, NCH_3, NCH_2), 2.3-1.5 (m, 6H, cyclopentyl H), and 1.02 (d, 3H, J = 7 Hz, ring CH_3). The salt obtained upon treatment of 12 with methyl iodide at room temperature in ether had identical physical and spectral properties when compared with 1 obtained by the photochemical route.

Acknowledgments

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References

1. a. NDEA Title IV Fellow 1970-1973.
   b. Undergraduate Research Participant, Summer 1972.
2. (a) Reported in part at the American Chemical Society Meeting, Dallas, Texas, 1973, MEDI D 31. (b) Also see K. G. R. Sundelin, R. A. Wiley, R. S. Givens, and D. R. Rademacher, J. Med. Chem., 15, 235 (1973) and (c) R. S. Givens and D. R. Rademacher, ibid, 17, 457 (1974) for biological activity of 1 and its oxidation product.
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