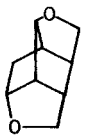

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Registry No. 3, 3853-88-1; 3 anhydride, 2746-19-2; 5, 1200-88-0; 5 diacid chloride, 4582-21-2; 6, 51606-65-6; 8, 73971-18-3; 9, 73971-19-4; 10, 5826-27-7; 11, 73971-20-7; thallium(III) trifluoroacetate, 23586-53-0; 5-norbornene-*trans*-2,3-dicarbinol, 699-96-7.

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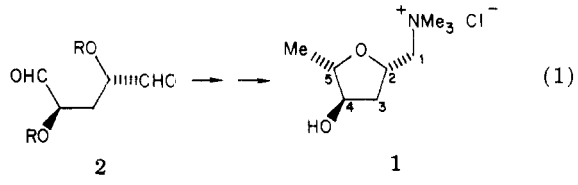
Chelation-Controlled Synthesis of (±)-Muscarine

Summary: The chelation-controlled addition of Grignard reagents to chiral α-alkoxy aldehydes to give threo diol derivatives is synthetically useful in highly oxygenated systems and is used here as the key step in a novel synthesis of (±)-muscarine from cyclopentadiene.

Sir: We recently reported that various organometallic reagents could be reacted with chiral α- and β-alkoxy aldehydes to give addition products with moderately high relative asymmetric induction.[1] In order to delineate the scope of this type of reaction and to illustrate its use, we have undertaken chelation-controlled syntheses of several naturally occurring materials of biological interest. One of these compounds is muscarine (1), the major cholinomimetic constituent of the poisonous mushroom *Amanita muscaria* or fly agaric.[2]

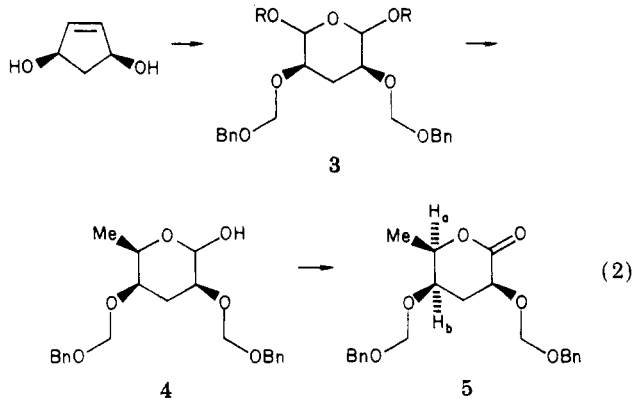
The central transformation in this synthesis is the stereoselective addition of a methyl nucleophile to the meso dialdehyde 2 (eq 1). On the basis of our previous work,



2 1 (1)

it was anticipated that the addition of a Grignard reagent would proceed via Cram's cyclic transition state[3] and yield the corresponding threo alcohol.[1] Internal etherification with inversion at C-5 would then produce a tetrahydrofuran having the connectivity and stereochemistry of 1.

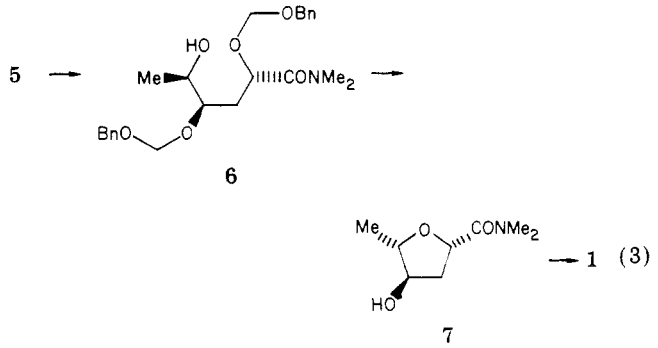
Our preparation of the required dialdehyde 2 (R = CH_2OBn) began with the singlet oxygenation product of cyclopentadiene[4] which was protected ($PhCH_2OCH_2Cl$, *i*-Pr_2NEt; 25 °C) and ozonized [(a) O_3, CH_2Cl_2, −78 °C; (b) Zn, HOAc, 0–25 °C]. The product of these operations turned out not to be 2 itself but the corresponding cyclic hydrate 3 (R = H) (eq 2). Interestingly, this compound



3 4 5 (2)

was not changed by treatment with methylmagnesium bromide under a variety of conditions. Since the lack of reactivity presumably derives from rapid conversion to the dialkoxide, the hydrate was converted to the corresponding diacetate (3, R = Ac) so that methyl Grignard addition might provide in situ generation[5] of 2 and subsequent chelation-controlled addition to one of the α-alkoxy aldehydes. Although the outcome of the desired Grignard reaction was strongly dependent on precise reaction conditions,[6] we were able to produce 4 reproducibly with (5–6):1 threo–erythro stereoselectivity by the addition of 3 (R = Ac) to excess methylmagnesium bromide in 2-methyltetrahydrofuran at −35 °C. The desired threo product (4) was readily separated[7] from the minor erythro isomer and a trace of the double-addition product by flash chromatography.[8] The overall isolated yield of pure 4 was 40% from the starting cyclopentenediol.[9]

Although the threo assignment was ultimately proven by conversion of 4 to muscarine, stereochemical support was provided at this stage by ^1H NMR examination of the derived lactone 5 ($CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2; 90% yield) and its C-5 epimer. These compounds displayed the expected values for $J_{a,b}$ of 3 and 9 Hz, respectively. Final conversion to muscarine proceeded unexceptionally. Thus, treatment of the lactone 5 (eq 3) with dimethylamine (C_6H_6, 25 °C,



6 7 (3)

(1) W. C. Still and J. A. Schneider, *Tetrahedron Lett.*, 1035 (1980).
(2) (a) C. H. Eugster, *Adv. Org. Chem.*, **2**, 427 (1960); (b) S. Wilkinson, *Q. Rev., Chem. Soc.*, **15**, 153 (1961); (c) J. Whiting, Y.-K. Au-Young, and B. Belleau, *Can. J. Chem.*, **50**, 3322 (1972); (d) P.-C. Wang, Z. Lysenko, and M. M. Joullie, *Tetrahedron Lett.*, 1657 (1978); (e) T. Matsumoto, A. Ichihara, and N. Ito, *Tetrahedron*, **25**, 5889 (1969); (f) A. M. Mubarak and D. M. Brown, *Tetrahedron Lett.*, 2453 (1980).
(3) D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959).
(4) C. Kaneko, A. Sugimoto, and S. Tanaka, *Synthesis*, 876 (1974).
(5) The kinetic requirement here is that elimination of acetate from the monoalkoxide to yield 2 be faster than the addition of methyl Grignard to the second acetate and furthermore that the addition of methyl Grignard to 4 be slow.
(6) The choice of solvent was particularly important (Et_2O gave large proportions of double-addition product even at partial conversion while THF gave good yields of the monoaddition product but poor asymmetric induction).
(7) Thin-layer chromatogram (silica gel, 40% ethyl acetate in petroleum ether): 4, R_f 0.20; 5-epi-4, R_f 0.35; double addition product, R_f 0.10.
(8) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
(9) All yields refer to pure, chromatographed, and fully characterized materials.

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3 h) produced an amide (**6**; 97%) which was mesylated (MsCl, Et_3N, CH_2Cl_2; 93%) and deprotected (H_2, 10% Pd/C, CF_3CH_2OH; 81%) to give the racemic modification of the known tetrahydrofuran amide **7** directly [mp 68–70 °C (lit.[2c] mp 57 °C for optically active **7**)]. Lithium aluminum hydride reduction (Et_2O, reflux, 1 h) gave (±)-normuscarine which was converted to the methiodide (CH_3I), and the counterion was exchanged (AgCl, H_2O)[2a] to yield (±)-muscarine chloride [mp 146–148 °C (lit.[2a] mp 147–148 °C)]. The structures of (±)-normuscarine and (±)-muscarine chloride were confirmed by direct comparison with authentic materials.[10]

(10) Racemic muscarine chloride was obtained from Sigma Chemical Co. Normuscarine was prepared by pyrolysis of muscarine chloride [C. H. Eugster, *Helv. Chim. Acta*, **39**, 1002 (1956)].

We should finally add that 5-epimuscarine (epiallomuscarine) was prepared in a directly analogous fashion from the minor (erythro) product of the Grignard reaction described above. Interestingly, the required erythro adduct can be made the major product if methyllithium is used in place of methylmagnesium bromide in the conversion of **3** (R = Ac) to **4**.[11]

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