A Concise Enantioselective Synthesis of (+)-Muscarine from (*R*)-*O*-Benzylglycidol [(*R*)-Benzyloxymethyloxirane]

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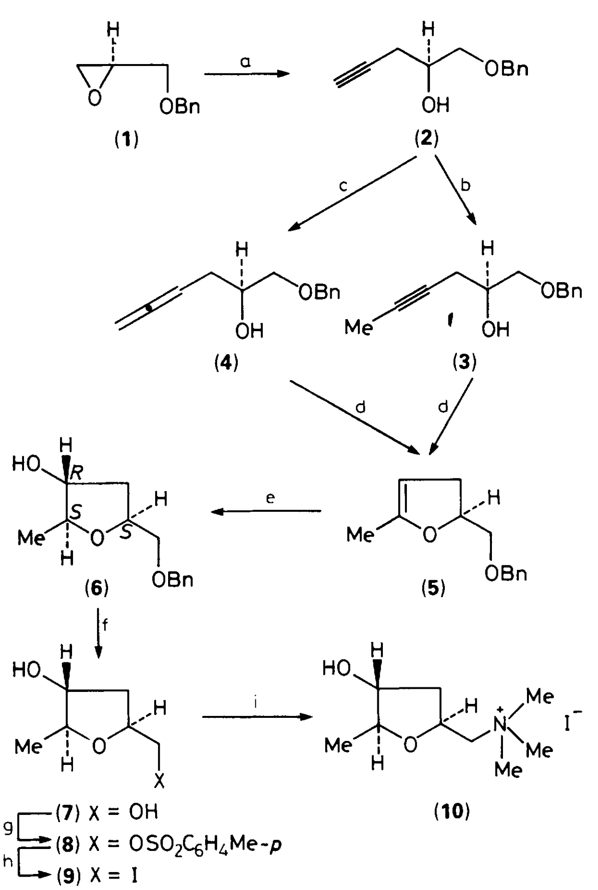
A concise enantioselective synthesis of (+)-muscarine has been established *via* the novel formation of a 3,4-dihydrofuran starting from (*R*)-*O*-benzylglycidol.

Although there are some precedents,[1] the synthesis of 2,3-dihydrofurans from non-cyclic precursors is rather difficult. We report here the simple formation of a chiral 2,5-disubstituted-2,3-dihydrofuran from both acetylenic and allenic precursors which led to a highly efficient synthesis of (+)-muscarine, a cholinomimetic alkaloid isolated from several species of poisonous mushrooms.[2,3]

Alkylation of the acetylene alcohol (**2**) obtained[4] in an excellent yield from (*R*)-*O*-benzylglycidol[5] (**1**), with methyl iodide in the presence of n-butyl-lithium afforded the internal



Bn = CH_2Ph

Scheme 1. *Reagents and conditions*: a, lithium acetylide–ethylenediamine complex, Me_2SO; b, Bu^nLi, hexamethylphosphoric triamide, MeI, tetrahydrofuran (THF), −78 °C to room temp.; c, CuBr (2 equiv.), $(CH_2O)_n$ (2 equiv.), di-isopropylamine, dioxane, reflux; d, $KOBu^t$ (2 equiv.), Me_2SO, 60 °C; e, dicyclohexylborane, THF, 25 °C, then H_2O_2, NaOH, EtOH; f, H_2, $Pd(OH)_2$–C, MeOH, g, *p*-$MeC_6H_4SO_2Cl$, pyridine, CH_2Cl_2; h, NaI, butan-2-one; i, excess of Me_3N/EtOH.

acetylene† (**3**), $[\alpha]_D^{24}$ + 12.2° (*c* 2.04, $CHCl_3$) in 88% yield. On the other hand, treatment of (**1**) with paraformaldehyde and di-isopropylamine in the presence of copper(II) bromide[6] furnished the allenic alcohol (**4**), $[\alpha]_D^{20}$ + 4.6° (*c* 1.03, $CHCl_3$) in 70% yield. Upon exposure to potassium t-butoxide (2 equiv.) in dimethylsulphoxide (DMSO) at 60 °C, both the acetylene (**3**) and the allene[7] (**4**) furnished the same 2,3-dihydrofuran (**5**) within 10 min. The product was very unstable in the presence of acids;‡ however, it could be handled without serious deterioration under basic and neutral conditions. Hydroboration[8] of (**5**) using dicyclohexylborane followed by oxidation with alkaline hydrogen peroxide brought about stereoselective introduction of the 4-hydroxy group on the opposite face of the 2-substituent to furnish the trisubstituted tetrahydrofuran (**6**), $[\alpha]_D^{23}$ −13.0° (*c* 1.0, $CHCl_3$) with the (2*S*,3*R*,5*S*) configuration in overall yields of 65 and 76% from (**3**) and (**4**), respectively.§ Catalytic debenzylation of (**6**) gave the known diol[3c] (**7**), $[\alpha]_D^{22}$ −6.2° (*c* 0.5, $CHCl_3$), lit.[3c] $[\alpha]_D^{25}$ −6.0° (*c* 0.5, $CHCl_3$), in 88% yield, which could be converted into L-(+)-muscarine iodide (**10**), m.p. 150—151 °C, $[\alpha]_D^{27}$ + 7.55° (*c* 0.98, H_2O), lit.[3b] m.p. 147—148 °C, $[\alpha]_D^{21}$ +6.2° (*c* 2.1, H_2O), *via* the tosylate (**8**) and the iodide (**9**) in 38% overall yield.

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† Satisfactory analytical and spectral data were obtained for all new compounds.

‡ Compound (**5**) decomposed with dilute aqueous acids as well as on a silica-gel plate.

§ A minor amount of an epimer (<5%) was also obtained as a readily separable by-product (SiO_2 column).