Tetrahedron Letters No. 19, pp 1657 - 1658, 1978. 0040-4039/78/0501-1657. $02.00/0.

A FACILE SYNTHESIS OF D-EPIALLOMUSCARINE

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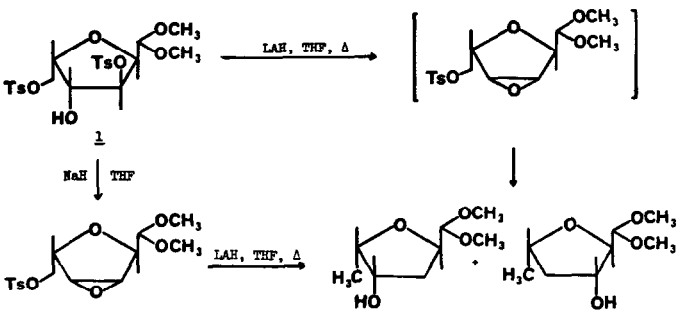
(Received in USA 28 December 1977; received in UK for publication 23 March 1978)

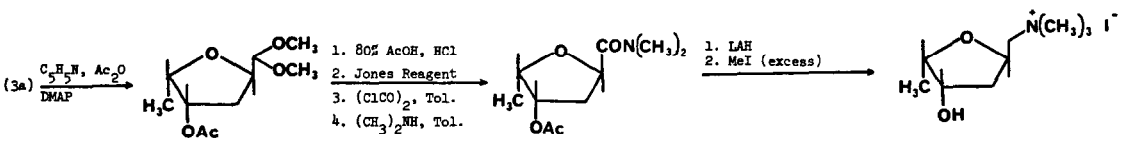
A great deal of interest has been generated over the years by muscarine and its isomers because of their marked physiological activity.[1a-c] Syntheses of muscarine derivatives, however, have generally involved extensive reaction schemes and concomitantly low product yields.[2a-c] We have long felt that access to the muscarine series could be readily achieved through common, naturally occurring sugars and now wish to report a facile and efficient synthesis of D-epiallomuscarine utilizing this approach.

Furanose 1, obtainable in 64% overall yield from D-glucose[3] was treated with an excess of lithium aluminum hydride in refluxing THF to afford a 3:2 mixture of diols 3a and 3b in quantitative yield [3a: ^{1}HNMR ($CDCl_3$, 220MHz) δ 1.22 (d, 3H, $C\underline{H}_3$), 1.25-1.30 (m, 1H, $C\underline{H}_2$), 2.00-2.10 (m, 1H, $C\underline{H}_2$), 3.40 (s, 6H, $OC\underline{H}_3$), 3.90-4.00 (dq, 1H, 5-C$\underline{H}$), 4.10-4.20 (m, 1H, C$\underline{H}$OH); 3b: ^{1}HNMR ($CDCl_3$, 220MHz) δ 1.31 (d, 3H, $C\underline{H}_3$), 1.55-1.70 (m, 1H, $C\underline{H}_2$), 2.25-2.40 (m, 1H, $C\underline{H}_2$), 2.65-2.86 (broad s, 1H, O$\underline{H}$), 3.43 (s, 3H, $OC\underline{H}_3$) 3.45 (s, 3H, $OC\underline{H}_3$), 4.06-4.25 (m, 2H, 2-$\underline{H}$ and 5-$\underline{H}$)]. After resolution of the diols by column chromatography (silica gel, ether: petroleum ether 2:1), 3a was converted to its acetate derivative 4, [4: ^{1}HMNR ($CDCl_3$, 220 MHz) δ 1.19 (d,3H, $C\underline{H}_3$), 1.20-1.30 and 2.20-2.25 (m, 1H each, $C\underline{H}_2$), 2.18 (s, 3H, OAc), 3.40 (s, 6H, acetal), 4.06-4.25 (m, 2H, 2-$\underline{H}$ and 5-$\underline{H}$), 4.24-4.25 (m, 1H, 5-$\underline{H}$), 4.22-4.30 (broad m, 1H, C$\underline{H}$OAc)] and then hydrolyzed with aqueous acid to the corresponding aldehyde.[4] As a result of its instability, the aldehyde was immediately oxidized *in situ* with Jones reagent. The resulting carboxylic acid was treated, in turn, with oxalyl chloride and dimethyl amine at 0°C to give dimethylamide 5 in 40% overall yield [^{1}HNMR, ($CDCl_3$, 220MHz) δ 1.21 (d, 3H, $C\underline{H}_3$), 1.25-1.35 and 2.00-2.20 (m, 1H each, $C\underline{H}_2$), 2.08 (s, 3H, OAc), 2.94 (s, 3H, $NC\underline{H}_3$), 3.08 (s, 3H, $NC\underline{H}_3$), 4.10-4.20 (m, 1H, 5-H), 4.78-4.88 (m, 1H, 2-$\underline{H}$), 4.25-4.30 (broad m, 1H, C$\underline{H}$OAc]. Reduction of 5 with lithium aluminum hydride in refluxing THF followed by quaternization of the product amine with excess methyl iodide afforded D-epiallomuscarine iodide 6 $[\alpha]_{25}^{D}$ = -2.5°, mp 194-195°C, in 70% yield. The infrared spectrum of 6 was identical in every respect with the published spectrum of racemic epiallomuscarine chloride.[1a]

The reduction of furanose 1 to diols 3a and 3b is believed to proceed through the intermediacy of epoxide 2. In support of this mechanism, it was found that treatment of 1 with 1.1 eq. of NaH in THF at ambient temperature gives epoxide 2[5] in 93% yield [2: ^{1}HNMR ($CDCl_3$, 220MHz) δ 2.46 (s, 3H, Ar-CH_3), 3.44 (s,3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.80 (q, 2H, CH_2), 4.05-4.11 (m, 3H, 5-H, 4-H, 3-H), 4.20-4.30 (m, 2H, 1-H, 2-H), 7.35 (d, 2H, =CH), 7.80 (d, 2H, =CH)]. Furthermore, reduction of 2 with lithium aluminum hydride affords the same 3:2 mixture of diols 3a and 3b previously obtained directly from 1. The predominance of diol 3a is probably attributable to a preferred orientation of the coordinated reducing agent. Additional studies on the reactions of 2 are currently in progress.



1 2 3a 3b



4 5 6

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