SYNTHESIS OF D-ISOEPIALLOMUSCARINE

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D-ISOEPIALLOMUSCARINE is prepared in high yield from α-D-glucose by way of regio-, and stereo-selective epoxide ring opening using sodium phenyl selenide.

In a recent report,1 we have introduced the synthesis of D-epiallo-muscarine starting from inexpensive, optically active α-D-glucose. The potential biological activity of the muscarine series2a-c prompted us to prepare other analogues. We now would like to describe a similar sequence of reactions leading to isoepiallomuscarine which possesses the hydroxyl group at C-3 instead of C-4.

Furanose 1,3, obtainable in 64% overall yield from D-glucose was treated with 2.5 equivalents of sodium phenyl selenide in refluxing DMF to afford the corresponding diselenide 4 in quantitative yield, IR (neat) 3350, 1575 cm⁻¹; 1HNMR (CDCl₃, 220 MHz) δ 2.73 (bs, 1H, -OH), 3.02 (dd, 1H, C-4H), 3.33 (s, 3H, -OCH₃), 3.37 (s, 3H, -OCH₃), δ 3.35-3.60 (m, 2H, -CH₂), 3.88 (dd, 1H, C-2H), 4.09-4.20 (m, 2H, C-5H, C-3H), δ 4.26 (d, 1H, C-1H), 7.10-7.25 (m, 6H, ArH),
7.35-7.60 (m, 4H, ArH). Reductive removal of the phenylseleno group with W-4 Raney Nickel in THF at 25°C followed by acetylation afforded the acetate derivative 5 in 82% overall yield, IR (neat) 1725 cm⁻¹; ¹HNMR (CDCl₃, 220 MHz) δ 1.29 (d, 3H, -CH₃), 1.50-1.60 (m, 1H, C-4H), 2.05 (s, 3H, -OAc), 2.38-2.55 (m, 1H, C-4H), 3.40 (s, 6H, -OCH₃), 4.05 (dd, 1H, C-2H), 4.25 (d, 1H, C-1H), 4.25 (q, 1H, C-5H), 5.15-5.30 (m, 1H, C-3H). Conversion of compound 5 to the dimethylamide 6 was carried out in 35% overall yield by a previously described sequence, IR (neat) 1735, 1650 cm⁻¹; ¹HNMR (CDCl₃, 220 MHz) δ 1.35 (d, 3H, -CH₃), 1.59-1.70 (m, 1H, C-4H), 2.10 (s, 3H, -OAc), 2.55-2.70 (m, 1H, C-4H), 2.92 (s, 3H, N-CH₃), 3.15 (s, 3H, N-CH₃), 4.40 (q, 1H, C-5H), 4.81 (s, 1H, C-2H), 5.45-5.55 (m, 1H, C-3H).

Final transformation to D-isoepiallomuscarine was accomplished by reduction of 6 with lithium aluminum hydride followed by quaternization of the product amine with excess CH₃I. After recrystallization with 1:1 toluene-acetone, D-isoepiallomuscarine iodide was obtained in 72% yield as white needles, mp 182°C; [α]D²⁰ = -26.5°; IR (KBr) 3350 cm⁻¹; ¹HNMR (DMSO-d₆, 220 MHz) δ 1.23 (d, 3H, -CH₃), 1.35-1.55 (m, 1H, C-4H), 2.21-2.35 (m, 1H, C-4H), 3.15 (s, 9H, NMe₃), 3.39 (s, 1H, CH-NMe₃), 3.45-3.55 (m, 1H, CH-NMe₃), 3.85-3.95 (m, 1H, C-3H), 4.05-4.25 (m, 2H, C-2H, C-5H), 5.40 (d, 1H, -OH); Analysis Calculated for C₉H₂₀N₂O₂I, C, 35.89%; H, 6.69%; N, 4.65%. Found: C, 36.08%; H, 6.78%; N, 4.71%.

The formation of diselenide compound 4 is believed to proceed through the intermediacy of epoxide 3, formed by the rear-side attack of hydroxyl group at C-4, followed by ring opening resulting from the nucleophilic attack by NaSePh from the less sterically hindered side of C-4. The proposed mechanism was supported by the following observation: treatment of 1 with 1.1 equivalent of NaH in THF at ambient temperature gave epoxide 2 in 93% yield. Further reaction of 2 with NaSePh in refluxing DMF afforded the same product, diselenide 4, previously obtained directly from 1.

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1. Raney-Ni (W-4) MeOH (2% HC~) THF, R.T. 2. Jones Reagent Ac20, C5H5N (C~CO)~, Tol. N,N-dimethylamino- (Me)2NH, Tol. pyridine

1. LAH, THF, H3C OH 2. MeI (excess)

1. MeOH (2% HCl) 2. Jones Reagent 3. (ClCO)2, Tol. 4. (Me)2NH, Tol.
References and Notes:


5. The intermediacy of an epoxide under similar reaction conditions, has been reported in the reaction of 1 with NaOAc in refluxing DMF.


7. Compounds 4, 5, and 6 were isolated as oils.

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