SYNTHESIS OF D-ISOEPIALLOMUSCARINE

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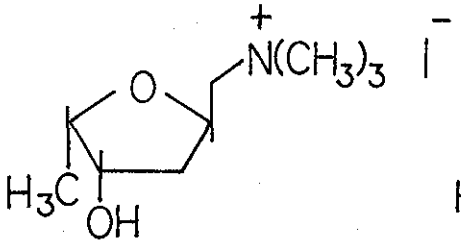
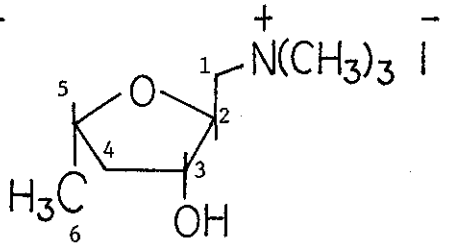
D-Isoepiallomuscarine is prepared in high yield from α-D-glucose by way of regio-, and stereo-selective epoxide ring opening using sodium phenyl selenide.

In a recent report,[1] we have introduced the synthesis of D-epiallomuscarine starting from inexpensive, optically active α-D-glucose. The potential biological activity of the muscarine series[2a-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.



Epiallomuscarine

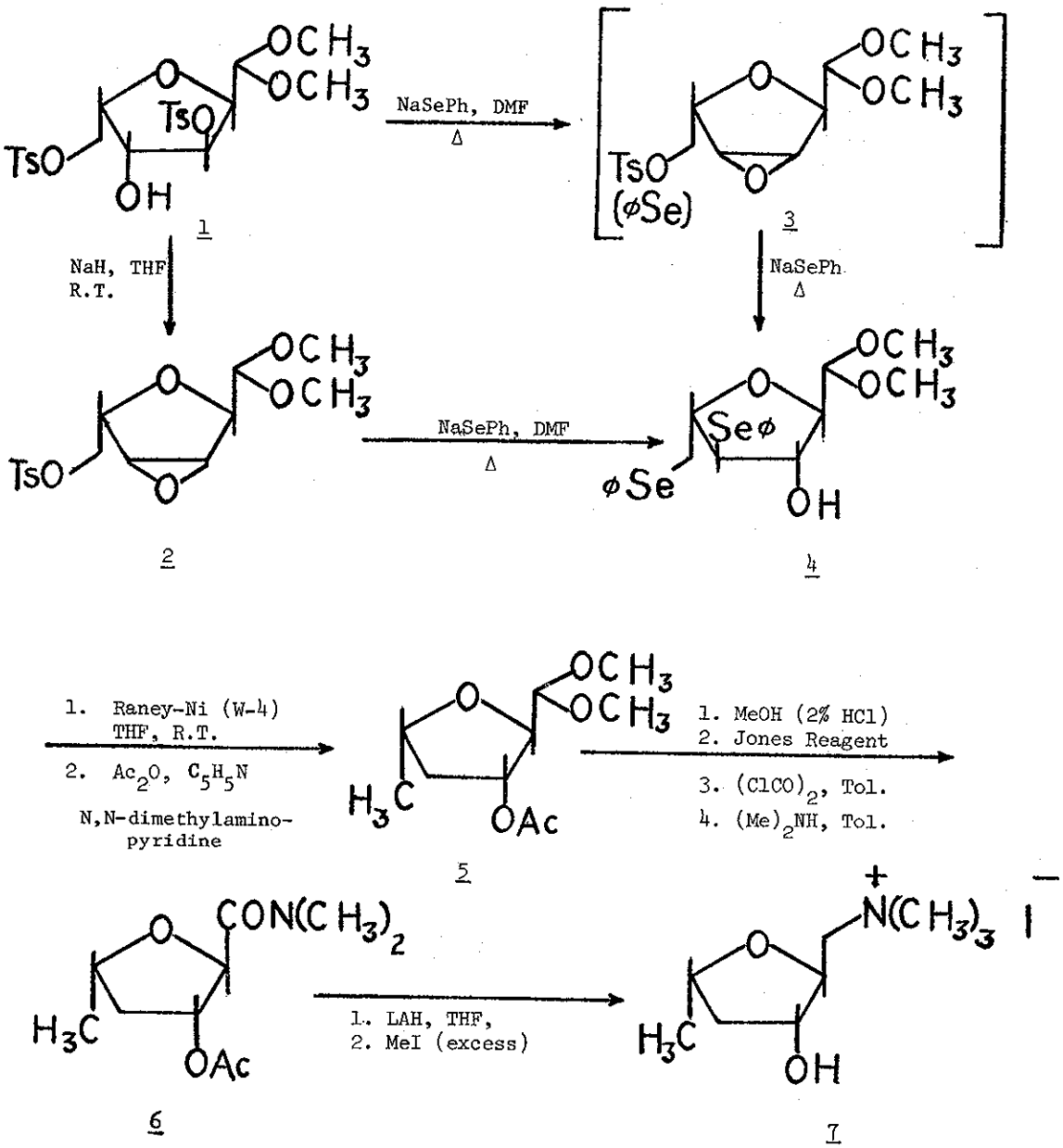


Isoepiallomuscarine

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, 1575cm^{-1}; ^{1}HNMR ($CDCl_3$, 220 MHz) δ 2.73 (bs, 1H, -OH), 3.02 (dd, 1H, C-4H), 3.33 (s, 3H, $-OCH_3$), 3.37 (s, 3H, $-OCH_3$), δ 3.35-3.60 (m, 2H, $-CH_2$), 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[4] in THF at 25°C followed by acetylation afforded the acetate derivative 5 in 82% overall yield, IR (neat) 1725 cm^{-1}; ^{1}HNMR ($CDCl_3$, 220 MHz) δ 1.29 (d, 3H, $-CH_3$), 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, $-OCH_3$), 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,[1] IR (neat) 1735, 1650 cm^{-1}; ^{1}HNMR ($CDCl_3$, 220 MHz) δ 1.35 (d, 3H, $-CH_3$), 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, $N-CH_3$), 3.15 (s, 3H, $N-CH_3$), 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 CH_3I. After recrystallization with 1:1 *toluene-acetone*, D-isoepiallomuscarine iodide was obtained in 72% yield as white needles, mp. 182°C; $[\alpha]_D^{EtOH}$=-26.5°; IR (KBr) 3350 cm^{-1}; ^{1}HNMR (DMSO-d_6, 220 MHz) δ 1.23 (d, 3H, $-CH_3$), 1.35-1.55 (m, 1H, C-4H), 2.21-2.35 (m, 1H, C-4H), 3.15 (s, 9H, $-NMe_3$), 3.39 (s, 1H, $CH-NMe_3$), 3.45-3.55 (m, 1H, $CH-NMe_3$), 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 $C_9H_{20}NO_2I$, 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 rearside 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.[5,6] 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[1] in 93% yield. Further reaction of 2 with NaSePh in refluxing DMF afforded the same product, diselenide 4,[7] previously obtained directly from 1.


NaSePh, DMF
Δ
NaH, THF
R.T.
NaSePh
Δ
NaSePh, DMF
Δ
1. Raney-Ni (W-4)
THF, R.T.
2. Ac2O, C5H5N
N,N-dimethylamino-pyridine
1. MeOH (2% HCl)
2. Jones Reagent
3. (ClCO)2, Tol.
4. (Me)2NH, Tol.
1. LAH, THF,
2. MeI (excess)

References and Notes:

1. P. C. Wang, Z. Lysenko, and M. M. Joullié, Tetrahedron Letters, 000, (1978).
2. a) C. H. Eugster, Advances in Organic Chemistry, Methods and Results., p. 427-456, Interscience Publishers, Inc., New York (1960), and references cited therein.
   b) P. Wasser, Experientia, VII7, 300 (1961).
   c) J. Whiting, Y. K. AuYoung and B. Belleau, Can. J. Chem., 50, 3322 (1972).
3. T. Ogawa, M. Matsui, H. Ohrui, H. Kuzuhara and S. Emoto, Agr. Biol. Chem., Vol. 36, No. 8, p. 1449-1451 (1972).
4. Prepared according to L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis" Vol. 1, J. Wiley and Sons, Inc., New York, New York, 1967, p. 729.
5. The intermediacy of an epoxide under similar reaction conditions, has been reported in the reaction of 1 with NaOAc in refluxing DMF. T. Ogawa, M. Matsui, H. Ohrui, H. Kuzuhara and S. Emoto, Agr. Biol. Chem., Vol. 36, No. 9, p. 1655-1657 (1972).
6. N. R. Williams, Advan. Carbohyd. Chem., 25, 155 (1970).
7. Compounds 4, 5, and 6 were isolated as oils.

Received, 18th March, 1978