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SYNTHESES OF dl-METHYLOLEANDROSIDE AND dl-METHYLCYMAROSIDE

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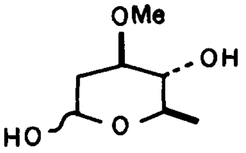
Oleandrose 1, a sugar component of cardiac glycosides1),2) and of antibiotic oleandomycin,3) has been synthesized by T. Reichstein et al.4) through a lengthy route from glucose. In this paper we should like to report simple syntheses of dl-methyloleandroside 6 and its C-3 epimer, dl-methylcymaroside 8.5)

The unsaturated alcohol 2, prepared from 2-ethoxy-6-methyl-3,4-dihydro-2H-pyran by the known procedure,6) was transformed by treatment with benzyl chloride - NaOH into the benzyl ether 3,7) b.p. 116 - 118° (1.5mm)(ν^{neat}_{max} 1605, 1500 cm^{-1}, τ^{CDCl_3} 8.7 (3H, d, J = 6Hz), 6.65 (3H, s), 5.5 (2H, s), 5.3 (1H, d, J = 1.5Hz), 4.2 (2H, m), 2.65 (5H, s)) in 93 % yield. Subsequent treatment of 3 in refluxing methanol with catalytic amount of p-TsOH gave two adducts, 4, b.p. 122 - 124° (2mm)(ν^{neat}_{max} 1500 cm^{-1}, τ^{CDCl_3} 8.73 (3H, d, J = 6Hz), 6.72 (3H, s), 6.6 (3H, s), 5.25 (1H, t, J = 2Hz), 5.4, 5.1 (2H, AB q, J = 12Hz), 2.7 (5H, s)) and 5, b.p. 162 - 163° (2mm)(ν^{neat}_{max} 1500 cm^{-1}, τ^{CDCl_3} 8.72 (3H, d, J = 6Hz), 6.57 (6H, s), 5.45 (2H, s), 5.31 (1H, t, J = 2Hz), 2.7 (5H, s)) in 65 and 21 % yield, respectively.8) Nmr spectra of 4 and 5 showed a triplet with J = 2Hz at τ 5.25 and 5.31 respectively, and showed that they are epimeric at C-3.

Hydrogenolysis of 4 with hydrogen over Pd-C afforded dl-methyloleandroside 6, (ν^{neat}_{max} 3420 cm^{-1}, τ^{CDCl_3} 8.7 (3H, d, J = 6Hz), 8.5 (1H, octet, J = 12 + 11 + 3.5Hz), 7.73 (1H, octet, J = 12 + 5 + 1.5Hz), 6.91 (1H, t, J = 9Hz), 6.7 (3H, s), 6.64 (3H, s), 5.27 (1H, q, J = 3.5 + 1.5Hz)) in 92 % yield. Coupling constants between ring protons obtained by first order analyses are in good agreement with those of methylchromoside C 7.9) Therefore, the configura-



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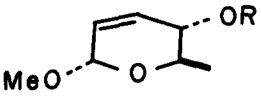
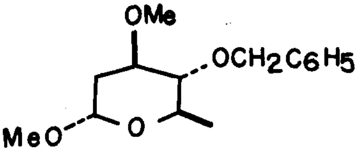


2 R = H

3 R = $CH_2C_6H_5$



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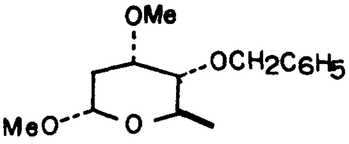

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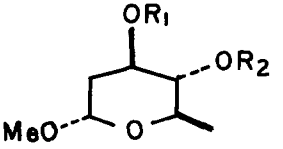
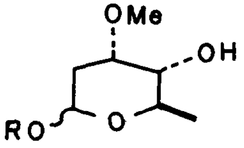


6 R_1 = Me R_2 = H

7 R_1 = H R_2 = H

10 R_1 = Me R_2 = Ac



8 R = Me

9 R = H

tion of **4** and **6** is expressed as shown in the figure. The stereochemistry of **6** is further confirmed by the nmr spectrum of the acetate **10**, b.p. 101 - 102.5° (2mm)(ν_{max}^{neat} 1750, 1230 cm^{-1}, τ^{CDCl_3} 8.84 (3H, d, J = 6Hz), 8.35 (1H, octet, J = 12 + 11 + 3.5Hz), 7.7 (1H, octet, J = 12 + 5 + 1.5Hz), 5.34 (1H, t, J = 9Hz), 5.25 (1H, q, J = 3.5 + 1.5Hz)).

Hydrogenolysis of **5** in methanol containing hydrogen chloride afforded an anomeric mixture (1 : 1) of dl-methylcymaroside **8**, (ν_{max}^{neat} 3440 cm^{-1}, τ^{CDCl_3} 8.8, 8.7 (each 3H, d, J = 6Hz), 6.55, 6.60, 6.63, 6.73 (each 3H, s), 5.47 (1H, q, J = 9 + 2.5Hz), 4.9 (1H, t, J = 3.6Hz)) in 91 % yield.

REFERENCES AND NOTES

1) R. Tschesche and G. Buschauer, *Ann.*, **603**, 59 (1957).

2) W. Neumann, *Ber.*, **70**, 1547 (1937).

3) H. Els, W. D. Celmer and K. Murai, *J. Am. Chem. Soc.*, **80**, 3777 (1958).

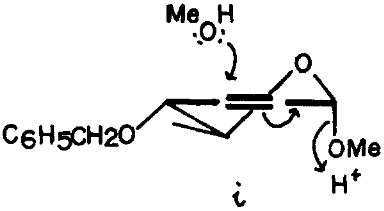
4) (a) E. Vischer and T. Reichstein, *Helv. Chim. Acta*, **27**, 1332 (1944).
   (b) F. Blindenbacher and T. Reichstein, *ibid.*, **31**, 2061 (1948).

5) The synthesis of optically active cymarose **9** from glucose has been reported;
   (a) C. A. Grob, and D. A. Prins, *ibid.*, **28**, 840 (1945).
   (b) D. A. Prins, *ibid.*, **29**, 378 (1946).

6) S. Yasuda and T. Matsumoto, *Tetrahedron Letters*, in press.

7) Satisfactory elemental analyses were obtained for all the compounds for which boiling points were given. All the compounds cited showed reasonable spectral data.

8) Similar addition of methanol to 2-methoxy-5,6-dihydro-2H-pyran has been known; F. Sweet and R. K. Brown, *Can. J. Chem.*, **46**, 1543 (1968). The reaction may proceed through the gross transition state **i** .



$\underset{\sim}{i}$

9) M. Miyamoto, Y. Kawamatsu, M. Shinohara, K. Nakanishi, Y. Nakadaira and N. S. Bhacca, Tetrahedron Letters, 2371 (1964).