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TOTAL SYNTHESIS OF (±)-trans-SWEROSIDE AGLUCONE O-METHYL ETHER

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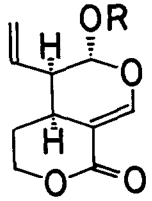
Sweroside (1) is a seco-iridoidal glycoside isolated from Swertia japonica Makino.[1] Recent publication of a total synthesis of sweroside aglucone O-methyl ether (2) by Tietze[2] prompted us to report a total synthesis of its epimer, trans-sweroside aglucone O-methyl ether.

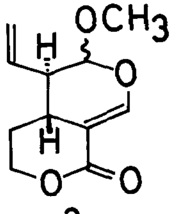
Acetoxydihydrodicyclopentadiene 4[3] was oxidized by the Lemieux's method to give a mixture of dicarboxylic acids, 5 and 6, from which a crystalline aid,[4] mp 193-196°, was isolated in 20% yield. Assignment of the structure 5 to this acid is not possible at this point; however, it will be verified in a later stage of the synthesis. Heating the acid 5 with acetic anhydride (2 h) followed by distillation gave an acid anhydride 7 (94%): mp 110-111°; ir ($CHCl_3$) 1800, 1740, 1720 cm^{-1}. The anhydride on standing with anhydrous methanol (room temperature, 48 h) was converted to a half ester 8 (82%): mp 131-135°; ir ($CHCl_3$) 3500-2500, 1720, 1700 cm^{-1}; nmr ($CDCl_3$) δ 2.00 (s,3), 3.60 ppm (s,3). The reduction of the ester group of 8 was achieved by treating a mixture of the half ester and ethanol with sodium in liquid ammonia to yield a lactone alcohol 9 (94%): ir (neat) 3400, 1710 cm^{-1}. Jones' oxidation of the alcohol 9 gave a keto lactone 10 (75%): ir (neat) 1730, 1710 cm^{-1}.[5]

Irradiation of a high-pressure mercury lamp (450 W) of 1% acetonitrile solution of the keto lactone 10 (24 h) formed an unsaturated aldehyde 11 (80%)[6]: ir (neat) 2700, 1720, 1620 cm^{-1}; nmr ($CDCl_3$) δ 5.76 (m, 2), 9.80 ppm (t, 1, J = 1 Hz), mass spectrum m/e 180 (M^+). Reduction of the aldehyde 11 with sodium



1 R = Glu

2 R = CH_3



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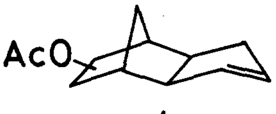

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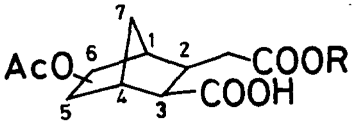
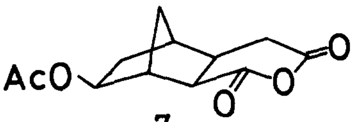


5 5-OAc, R = H

6 6-OAc, R = H

8 5-OAc, R = CH_3



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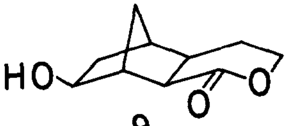

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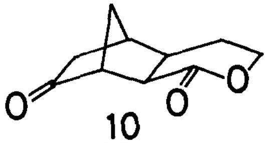

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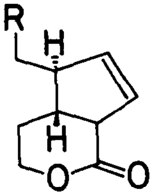
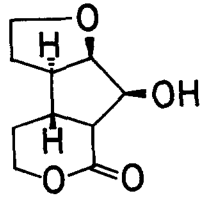


11 R = CHO

12 R = CH_2OH

13 R = CH_2OTs

14 R = CH_2OMs



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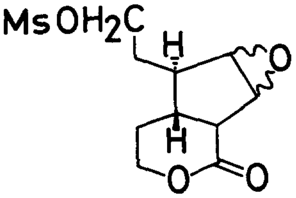

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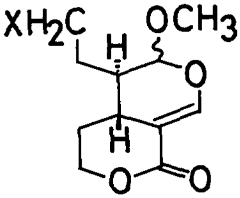
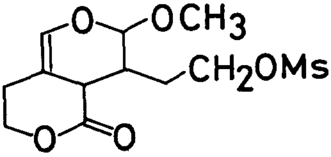
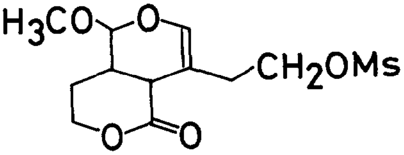


17 X = OMs

18 X = J



17a



17b

borohydride in aqueous methanol (5°, 15 min) gave an alcohol 12 (65%): ir ($CHCl_3$) 3440, 1715 cm^{-1}. The alcohol 12, on treatment with tosyl chloride and pyridine (5°, overnight), gave a tosylate 13 (70%): ir ($CHCl_3$) 1720, 1600, 1360, 1180 cm^{-1}. On the other hand, treatment of the alcohol 12 with mesyl chloride and pyridine (5°, overnight) yielded a mesylate 14 (84%): ir ($CHCl_3$) 1720, 1355, 1180 cm^{-1}.

Attempt was made to hydroxylate the double bond of the tosylate 13 with osmium tetraoxide. The reaction proceeded unexpectedly to form a cyclic ether 15 (75%): ir ($CHCl_3$) 3400, 1720 cm^{-1}. The second approach to the ring cleavage was epoxidation of the olefinic linkage. The mesylate 14 was oxidized with perbenzoic acid in chloroform (5°, 4 days) to produce an epoxide 16 (48%): mp 119.5-120.5°; ir ($CHCl_3$) 3040, 1725, 1360, 1173 cm^{-1}; nmr ($CDCl_3$) δ 3.00 (s, 3), 3.54 (d, 1, J = 3 Hz), 3.94 ppm (d, 1, J = 3 Hz). After several attempts to cleave the epoxy ring in vain because of the simultaneous solvolysis of the mesyl group, the epoxide 16 was treated with one mole of periodic acid in boiling acetone (30 min). The product was separated from unchanged epoxide (48%) by preparative tlc to give an alcohol, which was treated with methanol containing one drop of concentrated sulfuric acid. Preparative tlc of the product gave a methyl ether 17 (7.7%): uv (95% EtOH) 237.5 nm; ir ($CHCl_3$) 1700, 1630, 1175 cm^{-1}; nmr ($CDCl_3$) δ 2.98 (s, 3), 3.70 (s, 3), 5.24 (bs, 1), 7.82 ppm (s, 1). The signals for the anomeric and vinyl protons reveal that the product is composed of one anomer. In the earlier step of the synthesis, the crystalline acid prepared by the Lemieux oxidation of the starting acetate 4 was assumed to have the structure 5. If the acid had the structure 6, the product 17 with one vinyl proton would be assigned the structure 17a or 17b. The uv spectrum of 17, characteristic of the iridoidal glucoside, is not compatible with the structure 17a or 17b. This result excludes the possibility of the structure 6 for the crystalline acid.

Treatment of the mesylate 17 with sodium iodide in acetone (room temperature, 48 h) gave an iodide 18 (79%). The iodide 18 was refluxed in toluene with 1,9-diazabicyclo[5,4,0]undec-7-ene under nitrogen (1.5 h) to give *trans*-sweroside aglucone *O*-methyl ether (3) (84%): ir ($CHCl_3$) 1700, 1630, 1290, 1080 cm^{-1}; nmr ($CDCl_3$) δ 2.66 (m, 1), 3.00 (m, 1), 3.50-3.95 (m, 2), 3.70 (s, 3), 5.00-5.60 (m,4), 7.82 ppm (s, 1); mass spectrum *m/e* 210 (M^+).

The ir spectrum of the *trans* compound **3** is quite similar to that of the *cis* isomer **2**; an obvious difference in the nmr spectra consists in the vinyl proton signal, a singlet for compound **3** being contrasted to a doublet (δ 7.67 ppm, J = 2 Hz) for the *cis* isomer.

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REFERENCES AND FOOTNOTES

1. H. Inouye, S. Ueda, and Y. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **18**, 1856 (1970).
2. L.-F. Tietze, *J. Amer. Chem. Soc.*, **96**, 946 (1974).
3. The acetate was prepared from formyldihydrodicyclopentadiene [F. Bergmann and H. Japhe, *ibid.*, **69**, 1826 (1947)] by alkaline hydrolysis followed by acetylation with acetic anhydride and pyridine. Bp 100-115° (9 mm), lit bp 119-121° (10 mm). *Cf.* H. A. Bruson and T. W. Riener, *ibid.*, **67**, 1178 (1945). Dicyclopentadiene was generously suplied from the Hitachi Chemical Co. Ltd., to whom the authors are indebted.
4. Satisfactory elemental analyses were obtained for all the solid compounds.
5. The total synthesis of sweroside aglucone *O*-methyl ether from the endo lactone corresponding to **10** is in progress.
6. J. Meinwald and R. A. Chapman, *ibid.*, **90**, 3218 (1968).