119. An Efficient Stereoselective Synthesis of (±)-Sweroside and (±)-Secologanin Aglucone *O*-Methyl Ethers

Preliminary communication

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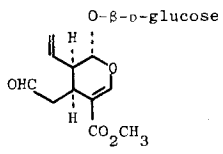
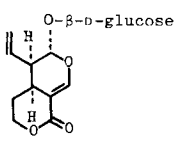
Summary

A seven-step stereoselective synthesis of (±)-sweroside aglucone *O*-methyl ether (**16a**) was achieved in 27% overall yield from 1,4-cyclohexadiene (**4**) and methyl diformylacetate (**5**). Secologanin aglucone *O*-methyl ether (**18a**) was then formed from **16a** in 90% overall yield by a straightforward process. The key step in the synthesis was a [2+2]-enone-photoannelation of **4** and **5** to form the key intermediate **6** which possessed the desired *cis*-fused ring configuration, and all the carbon atoms needed to complete the synthesis of **16a** and **18a**.

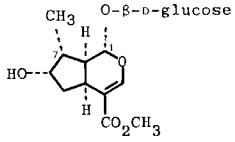
The title compounds are representatives of a large class of natural products known as the iridoids [1] [2]. They usually occur as glucosides[1]) of which secologanin (**1**), sweroside (**2**), and loganin (**3**) stand out as important intermediates in the plant biosynthesis of indole and isoquinoline alkaloids [4] [5].



1
Secologanin



2
Sweroside



3
Loganin

The pioneering synthetic endeavors of *Büchi et al.* have resulted in the synthesis of three iridoids: genipin [6], fulvoplumierin [7], and loganin [8]. In the first synthesis of loganin *Büchi* made use of a [2+2] photoaddition of methyl diformylacetate to a 3-cyclopentenol derivative. The photoaddition allowed the direct annelation of this symmetrical olefin to give the tetrahydrocoumalate moiety

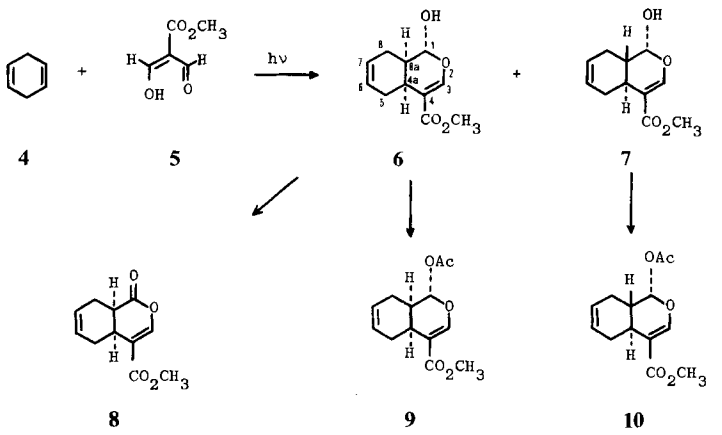
[1]) Notable recent exceptions are sarracenin [3a] and xylomollin [3b].

characteristic of many iridoids. The use of the achiral cyclopentenol gave only racemic photoproducts and the methyl group at C(7) had to be later added to the cyclopentane ring to complete the formation of the loganin skeleton. In our asymmetric total synthesis of loganin [9] we found that the chiral olefin (1*S*,2*R*)-2-methyl-3-cyclopenten-1-yl acetate underwent regioselectively the same [2+2]-photoaddition with high asymmetric induction to give directly the protected optically active loganin aglucone. This aglucone was readily converted into loganin pentaacetate upon glucosidation [8] [9].

We now report an extension of this work, an efficient [2+2]-photoannelation of methyl diformylacetate (**5**) to 1,4-cyclohexadiene (**4**) which adds selectively at only one of the two double bonds, and annelates in a *cis*-fashion to give the desired *cis*-ring-junction. The photoadduct **6** contains all the carbon atoms in functionalized form needed to complete the synthesis of the aglucones of either secologanin (**1**) or sweroside (**2**).

We irradiated a 10:1 mixture of 1,4-cyclohexadiene (**4**) and methyl diformylacetate (**5**) [8] [9] with a *Hanovia* 450 Watt lamp and a pyrex filter to obtain the desired photoproduct **6**[2]) in 62% yield along with 5% of the *trans*-ring-fused isomer **7** which was separated by column chromatography *(Scheme 1)*. This 12:1 mixture

Scheme 1



4 **5** **6** **7**

8 **9** **10**

slowly reverted to a 3:1 mixture on standing at 20° for six months. A sample of the initially formed photomixture was treated with acetic anhydride and pyridine to afford a 12:1 mixture of separable acylhemiacetals **9** and **10** in 95% yield. The 270-MHz-^{1}H-NMR. spectrum of **10** shows that H–C(4a) resonates at 4.18 ppm which is 1.3 ppm downfield from the signal of H–C(4a) of acylal **9**. This is consistent with a *cis*-1,3-diaxial orientation of H–C(4a) and AcO–C(1) in isomer **10** [J(1,8a) = 3.45 Hz, J(4a,8a) = 11.67 Hz] and an approximately *gauche* relationship of H–C(4a) and H–C(8a) in isomer **9** [J(4a,8a) = 4.26 Hz, J(1,8a) = 9.20 Hz].

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[2]) All new compounds exhibited appropriate UV., IR., NMR., and mass spectral characteristics and gave acceptable combustion analyses or high resolution mass spectral analyses.

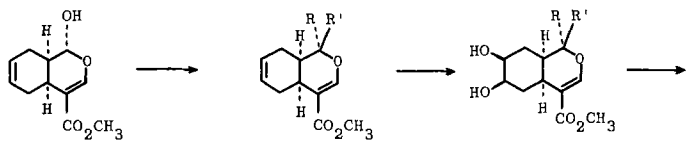
While the predominating theory [11] [12] did not allow a secure prediction of the stereochemical outcome of enone photoannelations, it was known that 5,6-ring-fused photoproducts possessed the *cis*-ring-junction [8] [9].

The relative configuration of **6** at the 4a,8a-bridgehead was firmly established by oxidation to the crystalline lactone **8** (m.p. 74–76°; 73% yield) with *Collins* reagent [10]. This lactone was distinctly different from the known *trans*-fused isomer [7] and was identical spectrally with the *cis*-fused lactone **8** used in an approach to genipin [6].

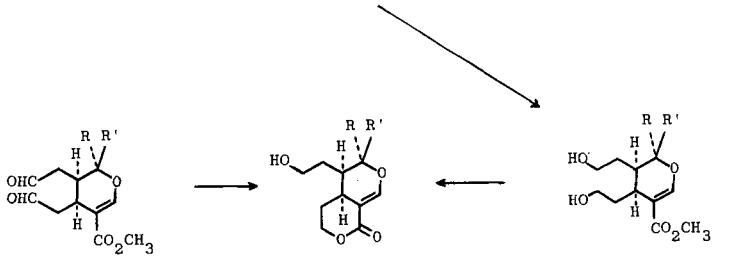
Thus, we were encouraged to also find that the photoaddition of **4** and **5** gave predominately the *cis*-6,6-ring-fused photoproduct **6**.

The acid-catalysed acetalization of **6** in methanol occurred *via* a C(1) carbonium ion to give quantitatively a 3:2 mixture of epimeric acetals **11a** and **11b** *(Scheme 2)*.

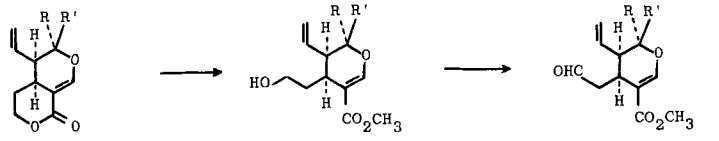
Scheme 2



6 **11a** R = CH_3O, R′ = H; **11b** R = H, R′ = CH_3O **12a** R = CH_3O, R′ = H; **12b** R = H, R′ = CH_3O



13a R = CH_3O, R′ = H; **13b** R = H, R′ = CH_3O **14a** R = CH_3O, R′ = H; **14b** R = H, R′ = CH_3O **15a** R = CH_3O, R′ = H; **15b** R = H, R′ = CH_3O



16a R = CH_3O, R′ = H; **16b** R = H, R′ = CH_3O **17a** R = CH_3O, R′ = H; **17b** R = H, R′ = CH_3O **18a** R = CH_3O, R′ = H; **18b** R = H, R′ = CH_3O

These acetals were *cis*-hydroxylated using the catalytic osmium tetroxide procedure of *VanRheenen et al.* [13] to give diol mixture **12** in 87% yield. Periodate cleavage at pH 5 yielded the unstable dialdehydes **13**. Exposure of **13** to excess sodium borohydride in isopropyl alcohol/water at 0° followed by chromatography directly gave hydroxy-lactone **14a** in 55% overall yield and **14b** in 33% yield from **12**.

The diols **15a** and **15b** (3:2 mixture) were prepared in 72% yield by ozonolysis of the mixture **11** at −78° in methanol and reduction of the ozonides with sodium borohydride in methanol at −78°, followed by column chromatography. Saponification of **15a** and **15b** gave the corresponding hydroxy-acids which were cyclized on heating in benzene to the pure hydroxy-lactones **14a** and **14b** in 50–65% yield.

Hydroxy-lactone **14a** was converted into the primary alkyl selenide with *o*-nitrophenyl selenocyanate and triphenylphosphine in pyridine [14]. Oxidation of the primary alkyl selenide with hydrogen peroxide [14] and elimination then gave in 85% yield (±)-sweroside aglucone *O*-methyl ether (**16a**) UV. (methanol): 243.5 nm (log ε 3.95). – IR. ($CHCl_3$): 1707 (C=O), 1621 cm^{-1} (C=C). – [90-MHz-NMR. ($CDCl_3$): 7.63 (*d*, J=2.4 Hz, 1 H, C=CHO); 5.77–5.09 (*m*, 3 H, $CH=CH_2$); 4.87 (*d*, J=1.9 Hz, 1 H, OCHO); 4.50–4.13 (*m*, 2 H, CH_2O); 3.49 (*s*, 3 H, CH_3O); 3.10–2.80 (*m*, 1 H); 2.68–2.50 (*m*, 1 H); 1.84–1.58 ppm (*m*, 2 H). – MS. (*m/e*): 210 (M^+)]. This sample of **16a** was identical with authentic material [15] [16].

In the same manner hydroxy lactone **14b** was dehydrated to form the C(1) epimer **16b** [90-MHz-NMR. ($CDCl_3$): 7.68 (*d*, J=2 Hz, 1 H, C=CHO); 5.80–5.10 (*m*, 3 H, $CH=CH_2$); 5.04 (*d*, J=1.9 Hz, 1 H, OCHO); 4.55–4.12 (*m*, 2 H, CH_2O); 3.57 (*s*, 3 H, CH_3O); 3.05–2.62 (*m*, 2 H); 1.86–1.62 ppm (*m*, 2 H). – UV. (methanol): 232 nm (log ε 4.05). – IR. ($CHCl_3$): 1705 (C=O), 1617 cm^{-1} (C=C). – MS. (*m/e*): 210 (M^+)]. The sweroside aglucone *O*-methyl ethers **16a** and **16b**[3]) were prepared in 27% and 16% overall yields, respectively, from methyl diformylacetate (**5**).

The individual sweroside aglucone *O*-methyl ethers were readily converted into the corresponding secologanin aglucone *O*-methyl ethers **18a** and **18b**[3]) as follows: Each lactone **16a** and **16b**[3]) was saponified with aqueous potassium hydroxide in isopropyl alcohol to the corresponding hydroxy-acid which was immediately treated with diazomethane to afford the hydroxy-ester **17a** and **17b**, respectively. Oxidation of hydroxy-ester **17a** with dicyclohexylcarbodiimide in dimethyl sulfoxide containing pyridine and trifluoroacetic acid [17] gave (±)-secologanin aglucone *O*-methyl ether (**18a**). – UV. (methanol): 235 nm (log ε 4.08). – IR. ($CHCl_3$): 1720 (CHO), 1704 (C=O), 1642 cm^{-1} (C=C). [90-MHz-NMR. ($CDCl_3$): 9.70 (*t*, J=1.7 Hz, 1 H, CH=O); 7.66 (*d*, J=2.7 Hz, 1 H, C=CHO); 5.60–4.90 (*m*, 3 H, $CH=CH_2$); 4.82 (*d*, J=4.2 Hz, 1 H, OCHO); 3.67 (*s*, 3 H, CO_2CH_3); 3.58 (*s*, 3 H, CH_3O); 3.60–3.20 (*m*, 1 H); 2.80–2.40 ppm (*m*, 3 H). – MS. (*m/e*): 240 (M^+)]. *Moffatt* oxidation [17] of hydroxy-ester **17b** afforded the C(1) epimer **18b**. – UV. (methanol): 235 nm (log ε 4.08). – IR. ($CHCl_3$): 1720 (CHO), 1703 (C=O), 1637 cm^{-1} (C=C). – [90-MHz-NMR. ($CDCl_3$): 9.66 (*d*×*d*, J=1.8 and 2.7 Hz, 1 H, CH=O); 7.52 (*d*, J=1.1 Hz, 1 H, C=CHO); 6.10–5.10 (*m*, 3 H, $CH=CH_2$); 4.83 (*d*, J=2.6 Hz, 1 H, OCHO); 3.71 (*s*, 3 H,

[3]) **16b** and **18b** are C(1)-epimers of the sweroside and secologanin aglucone *O*-methyl ethers, respectively.

CO_2CH_3); 3.44 (*s*, 3 H, CH_3O); 3.31–3.04 (*m*, 1 H); 2.84–2.34 ppm (*m*, 3 H). – MS. (*m/e*): 240 (M^+)]. **18a** and **18b** were prepared each in 88–90% overall yield from the sweroside aglucone *O*-methyl ethers **16a** and **16b**[3]), respectively. Interestingly, on attempted oxidation of hydroxy-ester **17a** with *N*-chlorosuccinimide and dimethyl sulfide in toluene [18], the sweroside aglucone *O*-methyl ether **16a** was reformed in 88% yield.

The present stereoselective synthesis of two key secoiridoid aglucone *O*-methyl ethers **16a** and **18a** has the advantage of good efficiency and high overall yields. We are currently studying the resolution and glucosidation of photoadduct **6** which would be a useful synthetic precursor for natural secoiridoids.

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REFERENCES

[1] *J.M. Bobitt & K.-P. Segebarth*, in 'Cyclopentanoid Terpene Derivatives', W.I. Taylor & A.R. Battersby, Ed., Marcel Dekker, New York, N.Y. 1969 pp. 1–145.
[2] *A.R. Battersby*, in 'The Alkaloids', Vol. 1, J.E. Saxton, Ed. (Specialist Periodical Reports), The Chemical Society, London 1971, pp. 31–47.
[3] a) *D.H. Miles, U. Kokpol, J. Bhattacharyya, J.L. Atwood, K.E. Stone, T.A. Bryson & C. Wilson*, J. Amer. chem. Soc. *98*, 1569 (1976); b) *I. Kubo, I. Miura & K. Nakanishi*, ibid *98*, 6704 (1976).
[4] *G.A. Cordell*, Lloydia *37*, 219 (1974).
[5] *H. Inouye, S. Ueda & Y. Takeda*, Heterocycles *4*, 527 (1976).
[6] *G. Büchi, B. Gubler, R.S. Schneider & J. Wild*, J. Amer. chem. Soc. *89*, 2776 (1967); *G. Büchi & R.S. Schneider*, unpublished results.
[7] *G. Büchi & J.A. Carlson*, J. Amer. chem. Soc. *90*, 5336 (1968); *J.A. Carlson*, Ph. D. Dissertation, Massachusetts Institute of Technology 1968.
[8] *G. Büchi, J.A. Carlson, J.E. Powell, Jr. & L.-F. Tietze*, J. Amer. chem. Soc. *92*, 2165 (1970); *95*, 540 (1973).
[9] *J.J. Partridge, N.K. Chadha & M.R. Uskoković*, J. Amer. chem. Soc. *95*, 532 (1973).
[10] *J.C. Collins, W.W. Hess & F.J. Frank*, Tetrahedron Letters *1968*, 3363.
[11] *P. de Mayo*, Accounts chem. Res. *4*, 41 (1971).
[12] *P. Margaretha*, Chimia *29*, 203 (1975).
[13] *V. VanRheenen, R.C. Kelly & D.Y. Cha*, Tetrahedron Letters *1976*, 1973.
[14] *P.A. Grieco, S. Gilman & M. Nishizawa*, J. org. Chemistry *41*, 1485 (1976).
[15] *L.-F. Tietze*, J. Amer. chem. Soc. *96*, 946 (1974).
[16] *G. Kinast & L.-F. Tietze*, Chem. Ber. *109*, 3626 (1976).
[17] *K.E. Pfitzner & J.G. Moffatt*, J. Amer. chem. Soc. *87*, 5670 (1965).
[18] *E.J. Corey & C.U. Kim*, J. Amer. chem. Soc. *94*, 7586 (1972).