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STEREOCHEMICAL CORRELATIONS OF SECOIRIDOID AGLUCONES

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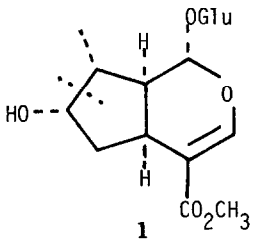
Summary: The secoiridoid, sweroside (**3a**), provides a convenient reference standard for the stereochemistry of secoiridoid aglucones that are important intermediates in the biosynthesis of plant iridoids and alkaloids. We describe how to obtain the aglucon of **3a** without C-5 epimerization or migration of the C-9,10 double bond, and physical and spectral parameters for its absolute stereochemistry through correlation with natural and synthetic compounds.

The biosynthesis of many cyclopentanomonoterpenoids (iridoids)[1] and the alkaloids that contain a structural subunit derived from the iridoids[2,3] requires the cleavage of a bond (---) in loganin (**1**) to form the secoiridoid, secologanin (**2a**)[4]. The aglucon of secologanin, **2b**, is involved formally in the biosynthetic pathways, but its instability towards rearrangement[5,6] has complicated studies of its chemistry and biochemistry. The aglucon (**3b**) of sweroside, **3a**, which is formed in vitro from **2a** by reduction and lactonization[7] as well as occurring naturally[8], does not structurally rearrange easily[9] but is known to undergo epimerization at C-5[10]. Therefore, **3b** could be a useful reference standard for the biosynthetically important secoiridoids if it can be obtained with its natural configuration at C-5, and if it can be distinguished from its configurational isomers by clear physical and chemical data.



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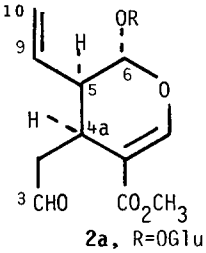
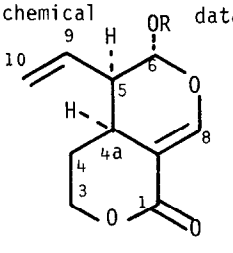
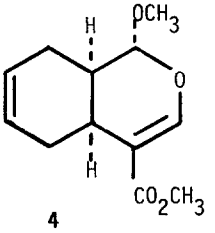


2a, R=OGlu
2b, R=H



3a, R=OGlu
3b, R=H



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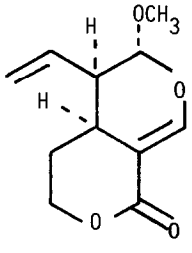
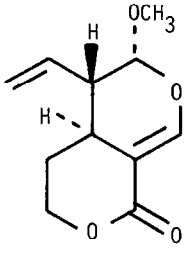
We took two approaches to providing the requisite data: synthesis of the four configurational isomers at C-5 and C-6 of the O-methyl acetals of **3b**, and isolation of the two C-5

epimers of **3b** as the anomeric mixture of their C-9,10 dihydro derivatives. The spectral data for these compounds permitted a clear distinction among the various configurational isomers. Furthermore, we were able to isolate the aglucon of 9,10-dihydro-**3a** by an experimental protocol that is useful for the isolation of C-3 acetal-protected secologanin aglucon.

The synthesis of the O-methyl acetals of **3b** cannot be done in a straightforward manner from sweroside, since treatment of **3a** with betaglucosidase in citrate buffer, pH 5, at room temperature (8 hr) usually gives only the C-5 epimer of **3b**[11]. Therefore, we developed a total synthesis of (-)-O-methyl sweroside aglucon from (+)-**4**[12], which was used to provide the two C-6 epimers, **5a** and **5b**, of 6-O-methyl sweroside aglucon for this study. The two C-6 epimers of 5-epi-5-O-methyl sweroside aglucon were prepared from 5-epi-**3b** by treatment of crude "sweroside aglucon" with 2,2-dimethoxypropane/methanol plus a catalytic amount of p-toluenesulfonic acid at reflux (8 hr). Two types of products resulted from this procedure: a 2:1 mixture of the desired 6-O-methyl acetals (43% yield), and a structural rearrangement product (31% yield). These could be distinguished easily by the much greater tlc mobility of the rearrangement product (**7**) versus the mixture of the C-6 O-methyl acetals (**6a** and **6b**), and by the absence of the signals for the C-6 OCH_3 and C-3 OCH_2 in the ^1H NMR of **7** versus **6a** and **6b** (Table 1). We encountered **7** with several of the standard methods for the formation of acetals at anomeric centers, but could not detect its corresponding hemiacetal in crude **3a** by nmr spectroscopy. Furuichi et al. also obtained **7**, rather than **6a**, as the final product in their total synthesis of (+)-**6a**[13], which we have brought to their attention. Two other secoiridoid aglucones are known to rearrange easily to internal acetals[6,14].



5a (6R)
5a (6S)



6a (6R)
6b (6S)

7

The two most useful spectral parameters for distinguishing the configuration at C-5 and C-6 of **5** and **6** are the vicinal coupling constants between the protons at C-4a and C-5 {**cis**=5.5 Hz;**trans**=11.2-11.4 Hz}, and the sign of the $[\alpha]_D$ or CD absorbance maxima for the C-6 isomers of **5** and 6 (Table 2).

TABLE 1. ^{1}H NMR SPECTRAL DATA FOR THE SWEROSIDE AGLUCON O-METHYL ACETALS[a].

(δ)[e]	5a	5b	6a	6b[b]	7
Position					
3	4.42(ddd)	4.44(ddd)	4.47(ddd)	4.47(ddd)	3.58-
	4.24-4.34(m)	4.22-4.32(m)	4.28(ddd)	4.23(ddd)	3.84(2H,m)
4	1.85-1.60(2H,m)	1.80-1.61(2H,m)	1.94(dddd);	2.05(dddd);	1.59(ddd);
			1.49(dddd)	1.51(dddd)	2.01(ddd)
4a	2.95(dddd,5.5Hz[c])	2.91(dddd,5.5Hz[c])	2.61(dddd,11.4Hz[c])	2.45(dddd,11.2Hz[c])	3.00(m)
5	2.60(ddd)	2.71(ddd)	2.09(ddd)	2.12(ddd)	2.62(br d)
6	4.90(d,1.6Hz[d])	5.05(d,1.8Hz[d])	4.93(d,2.4Hz[d])	4.81(d,8.7Hz[d])	5.28(br s)
8	7.65(d)	7.70(d)	7.61(d)	7.70(d)	7.80(s)
9	5.52(ddd)	5.58(ddd)	5.68(ddd)	5.59(ddd)	5.54(ddd)
10	5.25(dd);5.25(dd)	5.35(dd);5.26(dd)	5.26(dd);5.22(dd)	5.32(dd);5.23(dd)	5.08(ddd);
					5.14(ddd)
CO_2CH_3					3.70(s)

a 60 and 200 MHz for **7**; 200 MHz for **5** and **6**. b m.p. 149-150°C. c $J_{4a,5}$. d $J_{5,6}$. e all spectra were run in $CDCl_3$; chemical shifts are relative to TMS as the external standard.

TABLE 2. OPTICAL ROTATION AND CIRCULAR DICHROISM DATA FOR **5** AND **6**.

	5a	5b	6a	6b
$[\alpha]_D$[a] (deg)	-245(c=1.30)	+46(c=0.2)	-225(c=0.80)	+147(c=1.05)
[θ][b]	-20	+5.2	-12	+9.6
CD abs max[c] (nm)	-240	+240	-245	+242

a run at ambient temp in $CHCl_3$. b times 10^{+3}; run at ambient temp in EtOH. c no Cotton effects were seen.

The isolation of (-)-9,10-dihydro-**3b** was studied as a model for the isolation of **2b**. Treatment of (-)-9,10-dihydro-**3b** with betaglucosidase as before (48 hr) gave a 1:1 mixture of 9,10-dihydro-**3b** and (6RS)-5-epi-**3b** in 68% yield. These two C-5 epimers could be separated chromatographically (t-butylmethylether, silica gel), and distinguished by the ^{1}H NMR spectral data shown in Table 3. When the deglucosidation was done at 5°C (72 hr), the reaction mixture lyophilized, and the crude aglucon extracted with cold t-butylmethylether, then purified on deactivated silica gel at 5°C, pure 9,10-dihydro-**3b** was obtained in 38% yield as the only product without formation of its C-5 epimer. (Under such conditions, **3a** gave only its C-5 epimer.)

TABLE 3. NMR SPECTRAL DATA FOR 9,10-DIHYDRO SWEROSIDE AGLUCONES.

	Dihydro-**3b**		Dihydro-5-epi-**3b**	
(δ)[e]	^{1}H NMR[a]	^{13}C NMR[b]	^{1}H NMR[c]	^{13}C NMR[d]
Position				
3	4.34(q, ax); 4.50(ddd, eq)	68.5	4.30; 4.45	68.3
4a	3.08(dddd, $J_{4a,5}$=5.5 Hz)	28.0	2.53(dddd, $J_{4a,5}$=13 Hz)	29.8, 33.0
5	1.6-2.0(m, $J_{5,6}$=2.0 Hz)	38.8	2.03(dddd)	42.1, 42.7
6	5.54(d)	94.3	5.15(d), 5.53(d)	93.1, 98.2
8	7.63(d, $J_{8,4a}$=2.5 Hz)	153.8	7.59(d)	153.5, 155.2

a 200 MHz. b 50 MHz. c 80 MHz. d 25.2 MHz. e all spectra were run in $CDCl_3$ and chemical shifts are relative to TMS as the external standard.

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