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Studies on Monoterpene Glucosides and Related Natural Products. XLI.[1] Chemical Conversion of Geniposide into 10-Hydroxyloganin[2]

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Geniposide (**9**) was chemically converted into 10-hydroxyloganin (**3a**), which is presumed to be a precursor for secologanin (**2**). The stereoisomers **8a**, **18a** and **19a** were also prepared. The absolute configurations of these four compounds were determined on the basis of chemical reactions and NMR measurements.

Keywords——iridoid glucosides; geniposide; 10-hydroxyloganin; chemical conversion; NOE experiments

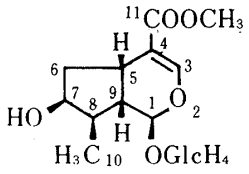
Around 1966, several research groups showed that the non-tryptophan moiety of indole alkaloids is of monoterpene origin.[4–7] Subsequently, Battersby *et al.* demonstrated that both loganin (**1**) and secologanin (**2**) play an important role in the biosynthesis of indole alkaloids, *i.e.*, secologanin (**2**) formed by the cyclopentane ring cleavage of loganin (**1**) undergoes condensation with tryptamine, leading to the formation of indole alkaloids.[8,9] At present, secologanin (**2**) is known to be a key intermediate not only for indole alkaloids but also for ipecacuanha alkaloids[10] and secoiridoid glucosides.[11] However, the mechanism of the formation of secologanin (**2**) from loganin (**1**) still remains obscure. For this process, Battersby proposed a mechanism involving the hydroxylation of loganin (**1**) to 10-hydroxyloganin (**3a**) followed by phosphorylation to the 10-phosphate and concerted cyclopentane ring cleavage of the last compound initiated by the elimination of the phosphoryloxy group.[12] Although no unequivocal evidence for this mechanism has so far been reported, it has been proved that the protons on C-7[9,11] and C-8[13] of loganin (**1**) are retained during the ring cleavage.

Meanwhile, Tietze succeeded in the total synthesis of 10-hydroxyloganin (**3a**)[14] and incidentally found that a base-catalyzed reaction of the tosylate (**4**) of 10-hydroxyloganin aglucone 1-O-methyl ether gave the oxetane-type compound (**6**), whereas the corresponding 7-epi derivative (**5**) furnished, through ring cleavage, secologanin aglucone 1-O-methyl ether (**7**).[15] However, the problem of whether or not 10-hydroxyloganin (**3a**) (or its 7-epimer (**8a**)) can actually be a biosynthetic precursor for secologanin (**2**) has not hitherto been discussed.

This paper deals with the chemical conversion of easily obtainable geniposide (**9**) into 10-hydroxyloganin (**3a**) which is indispensable for experiments to solve this important problem.

Hydroboration of an appropriate derivative of geniposide (**9**) would give a compound having the same plane structure as 10-hydroxyloganin (**3a**). Even if the configuration at C-7 and/or C-8 of the product differs from that of **3a**, this could be overcome in view of the easy epimerization of 8-epi-7-dehydrologanin tetraacetate (**10**) with an 8α-methyl group to 7-dehydrologanin tetraacetate (**11**) with an 8β-methyl group as well as the smooth Walden inversion of the C-7 hydroxy group of 7-epi-loganin tetraacetate (**12**).[16] For the protection of the hydroxy groups, benzylidene and benzyl groups would be suitable, because they survive hydroboration.

Geniposide (**9**) was treated with benzaldehyde and $ZnCl_2$ to yield 4′,6′-O-benzylidene-geniposide (**13**) (mp 223—225°), which was in turn benzylated with NaH and benzyl bromide in benzene–DMSO in the presence of tetra-*n*-butylammonium iodide to provide 4′,6′-O-benzylidene-2′,3′,10-tri-O-benzyl-geniposide (**14**) (mp 109—110°). This compound was then subjected to



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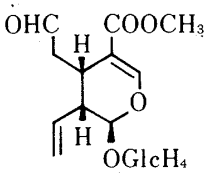

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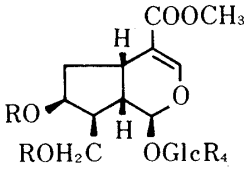
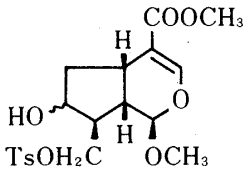
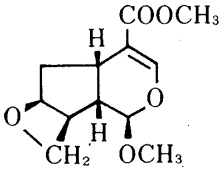


3a : R=H
3b : R=Ac



4 : ━ OH
5 : ┈ OH



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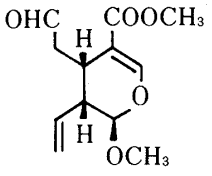

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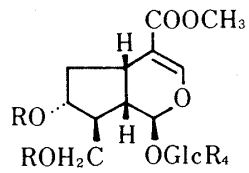
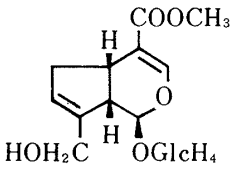


8a : R=H
8b : R=Ac



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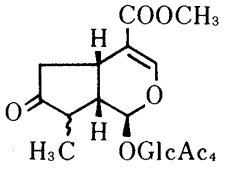
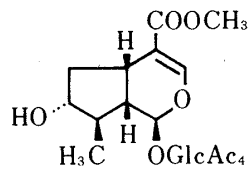


10 : ┈ CH_3
11 : ━ CH_3



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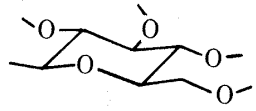
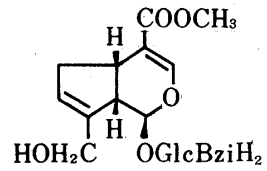


Fig. 1

hydroboration to yield the mono-ol (**15a**) in 53% yield. The proton nuclear magnetic resonance (^{1}H NMR) spectrum of **15a** lacked the signal of the vinyl group at δ 5.83 appearing in **14**, but showed a signal of a hydroxy group at δ 2.10—2.32, which disappeared on addition of D_2O. Furthermore, the spectrum of the acetate (**15b**) of **15a** showed a signal of an acetyl group at δ 1.99 and a double triplet assignable to a methine group bearing an acetoxy group at δ 5.07. These data clearly indicate that, as expected, the hydroxy group was introduced at the C-7 position. Since the hydroboration of compounds such as 1-methylcyclopentene is known to proceed through *cis* addition,[17] **15a** is assumed to be a (7*S*,8*R*)-compound formed by the attack of B_2H_6 from the less hindered convex face of the iridoid skeleton. The compound (**15a**) was then subjected to Jones oxidation to give the 7-dehydro derivative (**16**), which, without further purification, was reduced with $NaBH_4$ in dioxane, furnishing **15a** and another mono-ol (**17a**) (mp 110—111.5°) in a ratio of 7 to 13. The latter was thought to be the 7-epimer of **15a**, *i.e.*, the (7*R*, 8*R*)-compound. The inference regarding the stereochemistry of **15a** and **17a**



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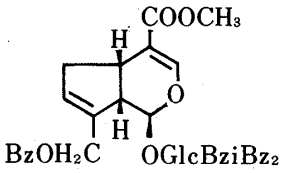

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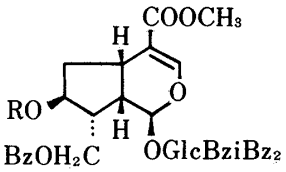
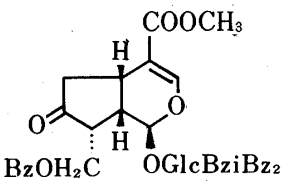


15a : R=H
15b : R=Ac
15c : R=Ts



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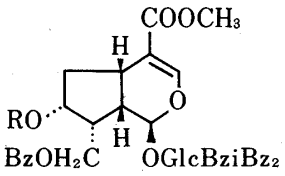
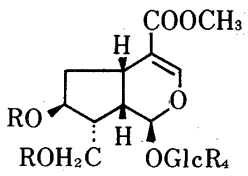
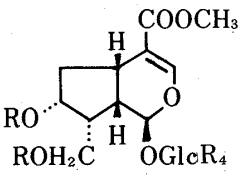


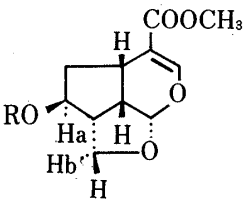
17a : R=H
17b : R=Ac
17c : R=Ts



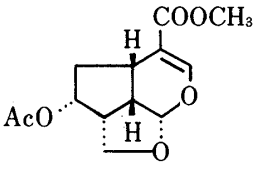
18a : R=H
18b : R=Ac



19a : R=H
19b : R=Ac



20a : R=H
20b : R=Ac
20c : R=Ts



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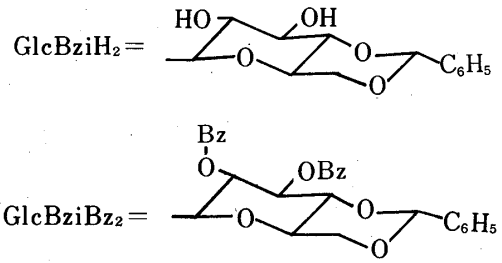
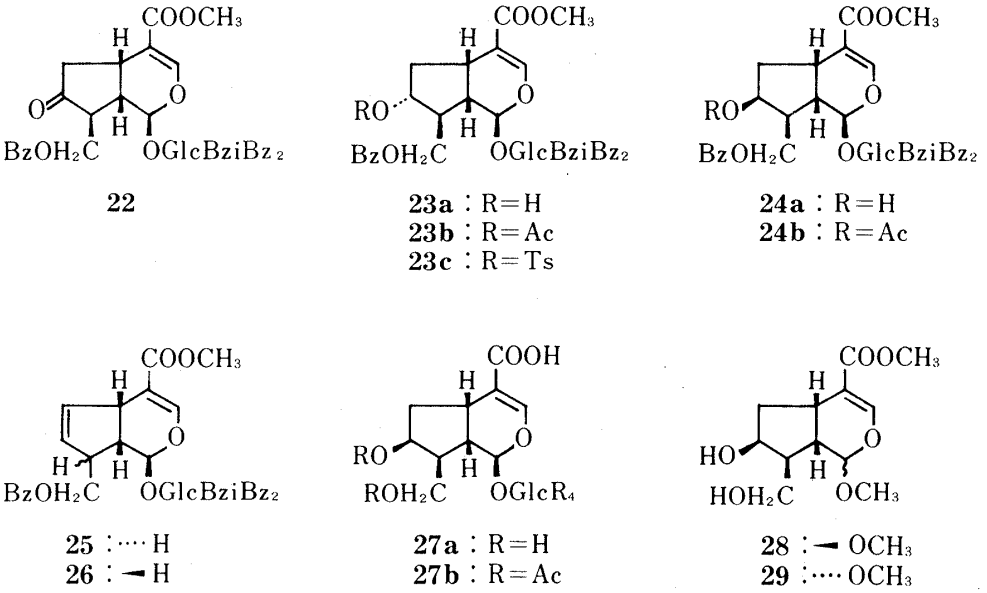


Bz=−$CH_2C_6H_5$

Fig. 2

was verified in the following way. Benzylidene and benzyl protecting groups of **15a** and **17a** were removed through hydrogenolysis over Pd–C to afford the free glucosides **18a** and **19a** (mp 199—201°), which on acetylation gave the hexaacetates **18b** (mp 139—140.5°) and **19b** (mp 95—98°), respectively. The compound (**18a**) was heated in 3.5% aq. HCl to yield the aglucone (**20a**), $C_{11}H_{14}O_5$ (mp 74—75°). The composition of **20a** as well as ^{1}H NMR data of its acetate (**20b**) (mp 65.5—66°) showing the presence of only one acetoxy group indicates that **20a** is an anhydro derivative. Therefore, it was deduced that the configuration at C-8 of **18a** and hence that of **15a** are *R*. Likewise, **19a** was converted into another anhydro derivative (**21**) (mp 81.5—82°), indicating the *R*-orientation at C-8 of **17a**. On the other hand, the ^{1}H NMR signal (in acetone-d_6) of the C-7 proton in **20b** appeared as a multiplet at δ 4.94, which collapsed to a double doublet (J=4.0 and 2.0 Hz) on irradiation of the C-8 proton at δ 2.97, whereas the corresponding signal of **21** appeared as a double triplet (J=11.0 and

6.5 Hz) at δ 5.10; these coupling constants suggest that the C-7 protons of **20b** and **21** assume the α-quasi-equatorial and β-quasi-axial configurations, respectively. This was supported by NOE experiments with the tosylate (**20c**) (mp 91—92.5°) of **20a**; *ca.* 5% NOE was observed between the C-7 Ha (δ 4.75, m) and the C-10 Hb (δ 3.51, dd, J=10.0 and 3.5 Hz). This finding is indicative of the configuration at C-7 of **20c** and hence that of **20a** being S. From these findings, it became evident that, of the stereoisomers of 10-hydroxyloganin (**3a**), **18a** and **19a**, the former is the (7*S*, 8*R*)-compound (designated as allo-10-hydroxyloganin), whereas the latter is the (7*R*, 8*R*)-compound (designated as 7-epi-allo-10-hydroxyloganin). Since the *R*-configuration is assigned to the C-8 position of the 7-dehydro derivative (**16**), the next step required for the conversion of **16** into **3a** should be epimerization at the C-8 position. This was achieved by PLC of **16** on silica gel with benzene-ether to afford the thermodynamically more favorable 4′,6′-O-benzylidene-2′,3′,10-tri-O-benzyl-7-dehydro-10-hydroxyloganin (**22**) (mp 122.5—124°). The latter gave on reduction with $NaBH_4$ a pair of C-7 epimers **23a** (mp 128.5—130.5°) and **24a** in a ratio of 13 to 1. As 7-dehydrologanin tetraacetate (**11**) is known to afford exclusively 7-epi-loganin tetraacetate (**12**) with 7R-chirality upon $NaBH_4$ reduction,[16] the major product (**23a**) and also its acetate (**23b**) are presumed to have 7*R*,8*S*-configuration, whereas the minor one (**24a**) has 7*S*,8*S*-orientation. Since the yield of **24a** in this reaction was so low, the conversion of **23a** into **24a** through Walden inversion was then attempted. Treatment of **23a** with TsCl in pyridine yielded the tosylate (**23c**) (mp 100—102°), which was in turn refluxed with tetraethylammonium acetate in dry acetone to give the acetate (**24b**) in 79% yield, along with a minor product (**25**) formed by the elimination of *p*-toluenesulfonic acid. The tosylates **15c** and **17c** also gave on Walden inversion, besides the major products **17b** and **15b**, minor elimination products **14** and **26**, respectively. The formation of the latter two products suggests *trans* stereochemistry for the elimination reaction. Since the elimination reaction of **23c** is also considered to proceed in the same fashion, exclusive formation of **25** from **23c** would amount to collateral evidence for the inference that the C-7 substituent and C-8 proton of **23c** are in *cis* configuration, *i.e.*, **23a** assumes the 7*R*,8*S*-configuration.



22

23a : R=H
23b : R=Ac
23c : R=Ts

24a : R=H
24b : R=Ac

25 : ···· H
26 : ━ H

27a : R=H
27b : R=Ac

28 : ━ OCH_3
29 : ···· OCH_3

Fig. 3

The compound (**23a**) was hydrogenated over Pd–C to remove the protecting groups, giving rise to 7-epi-10-hydroxyloganin (**8a**), which on acetylation afforded 7-epi-10-hydroxyloganin hexaacetate (**8b**) (mp 127—128°). The compound (**24b**) was subjected to Zemplén reaction to give **24a**, which was hydrogenated over Pd–C to afford the desired **3a**, $C_{17}H_{26}O_{11}\cdot 1/2$

H_2O; $[\alpha]_D^{27}$ −58.9° (lit. $[\alpha]_D^{20}$ −56°); λ_{max}^{MeOH} (log ε) 236 nm (4.05) (lit. λ_{max}^{MeOH} (log ε) 236 nm (4.02)). It gave on acetylation the hexaacetate (**3b**), $C_{29}H_{38}O_{17}\cdot H_2O$; $[\alpha]_D^{28}$ −54.0° (lit. $[\alpha]_D^{25}$ −58°); λ_{max}^{EtOH} (log ε) 232 nm (4.04) (lit. λ_{max}^{EtOH} (log ε) 232 nm (4.01)); $\nu_{max}^{CHCl_3}$ 1750, 1735, 1700 (sh), 1635 cm^{-1}; these data are in good accordance with those of the acetate reported by Tietze.[14] The compound (**3a**) was hydrolyzed to 10-hydroxyloganic acid (**27a**) followed by acetylation to afford 10-hydroxyloganic acid hexaacetate (**27b**), $C_{29}H_{38}O_{17}$. mp 138.5—139.5° (lit. mp 158°): $[\alpha]_D^{29}$ −52.1° (lit. $[\alpha]_D^{20}$ −56°); λ_{max}^{MeOH} (log ε) 229 nm (4.01) (lit. λ_{max}^{MeOH} (log ε) 234 nm (3.97)); ν_{max}^{KBr} 3155, 1760, 1740, 1715, 1640.

The stereotructure of **3a** was eventually established in the following way. The compound (**3a**) was hydrolyzed with β-glucosidase to give an aglucone, which was treated with Amberlite IR-120 (H^+-form) in dry MeOH giving rise to a pair of aglucone methyl ethers **28** and **29** in a ratio of 9 to 2. The ^1H NMR signal of the C-1 proton of **28** appeared at δ 4.49 as a doublet (J=6.0 Hz), whereas the corresponding signal of **29** appeared at δ 4.92 as a doublet (J=2.5 Hz). Comparison of these chemical shifts and coupling constants led us to the presumption that the C-1 proton of **28** is α, whereas that of **29** is β-oriented.[18] Furthermore, NOE experiments with **28** (in C_5D_5N) showed 6—9% NOE between the C-1 (δ 3.89, d, J=5.5 Hz) and C-8 (δ 1.26, m) protons as well as between the C-7 (δ 3.68, td, J=5.0 and 2.0 Hz) and C-8 protons, indicating the α-orientation of the protons on C-1, C-7 and C-8. Thus, it was demonstrated that **3a** is no other than the desired 10-hydroxyloganin, whereas **8a** is 7-epi-10-hydroxyloganin. Thus, we successfully prepared all the C-7 and C-8 stereoisomers of 10-hydroxyloganin.

In contrast to the overall yield of 0.04% for the total synthesis of 10-hydroxyloganin (**3a**) by Tietze,[14] the above method starting from an easily available natural product, geniposide (**9**), gave **3a** in 8.2% yield. Furthermore, our method is preferable to Tietze's for the preparation of labelled **3a** in terms of easy preparation of optically pure **3a** from geniposide (**9**) without resolution as well as the shortness of the synthetic process of **3a** from the 7-dehydro compound (**16**) following NaB^3H_4 reduction.

Experimental

General Procedures——Melting points were measured on a Yanagimoto micro-apparatus and are uncorrected. Optical rotations were taken with a Union PM 201 automatic digital polarimeter or a JASCO DIP-181 automatic digital polarimeter. Ultraviolet (UV) spectra were recorded on a Hitachi model 200-20 spectrophotometer, and infrared (IR) spectra on a Hitachi model 215 grating infrared spectrophotometer. NMR spectra were taken on a Varian A-60, a Varian HA-100 or a Hitachi R-22 spectrometer with TMS or DSS as the internal standard. Mass (MS) spectra were recorded on a JEOL JMS-01SG-2 spectrometer. Silica gel AR-100 (Mallinckrodt) was used for column chromatography and silica gel PF_{254} for medium pressure column chromatography. Furthermore, silica gel 60 GF_{254} was employed for thin-layer chromatography (TLC) and spots were visualized under UV light, or by treatment with I_2 vapor or anisaldehyde–H_2SO_4 reagent. Silica gel 60 GF_{254} or PF_{254} was used for preparative thin-layer chromatography (PLC), and the following solvent systems were employed: (I) benzene–Et_2O (8:2); (II) benzene–Et_2O (7:3); (III) $CHCl_3$–MeOH (9:1); (IV) $CHCl_3$–MeOH (7:3); (V) $CHCl_3$–MeOH (1:1); (VI) Et_2O. Bands were detected under UV light. The ratios of solvents are expressed by volume.

Conversion of Geniposide (9) into 4′,6′-O-Benzylidene-geniposide (13)——Geniposide (**9**) (32.74 g) and $ZnCl_2$ (34 g) were added to benzaldehyde (160 ml) and the reaction mixture was stirred overnight at room temperature. The resulting solution was diluted with H_2O (200 ml) and extracted with AcOEt (200 ml×3). The AcOEt layer was washed with satd. aq. NaCl and concentrated *in vacuo* to give an oily residue, which on crystallization from EtOH afforded crude crystalline 4′,6′-O-benzylidene-geniposide (**13**) (25.64 g). On the other hand, the mother liquor was concentrated *in vacuo* and the residue was chromatographed on silica gel (100 g); the column was eluted first with $CHCl_3$ (500 ml) to remove benzaldehyde, and then successively with 1% (200 ml), 2% (500 ml) and 3% MeOH–$CHCl_3$ (300 ml), collecting 100 ml fractions. On concentration, Fr. 8—10 also gave crude crystalline 4′,6′-O-benzylidene-geniposide (**13**) (5.99 g). The combined crystals (**13**) (total 31.63 g) were recrystallized from MeOH as colorless plates (26.26 g), mp 223—225°, $[\alpha]_D^{29}$ −17.3° (c=1.00, DMF). UV λ_{max}^{MeOH} nm (log ε): 236 (4.03). IR ν_{max}^{KBr} cm^{-1}: 3390, 1695, 1625, 1430, 760, 748, 695. NMR ($CDCl_3$) δ: 2.50—3.40 (2H, m, OH, disappeared on addition of D_2O), 3.71 (3H, s, $COOCH_3$), 4.22 (2H, br s, 10-H_2), 4.20—4.70 (1H, m, OH, disappeared on addition of D_2O), 4.84 (1H, d, J=7.0 Hz, 1′-H), 4.88 (1H, d, J=8.5 Hz, 1-H), 5.48 (1H, s, -CHPh), 5.78 (1H, m, 7-H), 7.17—7.63 (6H, m, 3-H and arom. H_5). *Anal.* Calcd for $C_{24}H_{28}O_{10}$: C, 60.50; H, 5.92. Found: C, 60.62; H, 5.89.

Conversion of 4′,6′-O-Benzylidene-geniposide (13) into 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-geniposide (14)——Compound (**13**) (10 g) and *n*-Bu_4NI (126 mg) were added to a stirred suspension of NaH (4.54 g) (50%, washed with dry petr. ether to remove mineral oil) in a mixture of benzene (180 ml) and DMSO (32 ml). The mixture was stirred for 15 min, then benzyl bromide (9 ml) was added and the whole was stirred at room temperature for 25 hr, diluted with H_2O and extracted with AcOEt (100 ml×3). The AcOEt extract was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (375 g); the column was eluted successively with benzene (3.4 l), 1% (1 l) and 2% Et_2O–benzene (3.2 l), collecting 200 ml fractions. On concentration, Fr. 28—38 afforded a crystalline substance (11.73 g), which was recrystallized from Et_2O–petr. ether to give **14** (9.85 g) as colorless needles, mp 109—110°, $[\alpha]_D^{27}$ −20.3° (c=0.99, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 237 (4.00). IR ν_{max}^{KBr} cm^{-1}: 1705, 1635, 1495, 1450, 745, 700. NMR ($CDCl_3$) δ: 3.64 (3H, s, $COOCH_3$), 4.18 (2H, br s, 10-H_2), 5.32 (1H, d, J=5.5 Hz, 1-H), 5.55 (1H, s, -C<u>H</u>Ph), 5.83 (1H, m, 7-H), 7.00—7.68 (21H, m, 3-H and arom. H_{20}). *Anal.* Calcd for $C_{45}H_{46}O_{10}$: C, 72.37; H, 6.21. Found: C, 72.31; H, 6.12.

Hydroboration of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-geniposide (14)——A solution of $NaBH_4$ (685 mg) in dry diglyme (4 ml) was added dropwise to a stirred solution of BF_3-etherate (2 ml) in dry diglyme (4 ml). Diborane gas generated was introduced into a stirred solution of **14** (9.52 g) in dry THF (80 ml) (cooled with ice-H_2O) by applying a slight pressure of N_2. After completion of the $NaBH_4$ addition (30 min), the B_2H_6 generator was heated for 30 min at 80° to ensure the complete transfer of the diborane. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 2 hr. After decomposition of the excess diborane by addition of H_2O (10 ml) the resulting organoborane was oxidized by adding 3 N NaOH followed by 30% H_2O_2 (each 2.5 ml) and the stirring was continued at room temperature for 30 min. The mixture was diluted with H_2O and extracted with benzene (80 ml×3). The benzene layer was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue (9.78 g) was chromatographed on silica gel (200 g); the column was eluted successively with benzene (0.3 l), 3% (1 l), 6% (1.5 l), 9% (1 l), 12% (0.6 l), 15% (1.2 l) and 20% Et_2O–benzene (1.4 l), collecting 100 ml fractions. The combined Fr. 44—45 were concentrated *in vacuo* to give a residue (1.52 g), which was rechromatographed on silica gel (50 g) in the same way as above to furnish 4′,6′-O-benzylidene-2′,3′,10-tri-O-benzyl-allo-10-hydroxyloganin (**15a**) (1.01 g) as a white powder. The combined Fr. 46—62 afforded pure **15a** (4.13 g). $[\alpha]_D^{27}$ −78.8° (c=1.05, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3410, 1705, 1635, 1495, 1450, 750, 740, 700. NMR ($CDCl_3$) δ: 2.05 (2H, t, J=7.0 Hz, 6-H_2), 2.10—2.32 (1H, m, OH, disappeared on addition of D_2O), 3.18 (1H, m, 5-H), 3.63 (3H, s, $COOCH_3$), 4.11 (1H, q, J=7.0 Hz, 7-H), 4.29 (1H, dd, J=10 and 4.5 Hz, 10-H),[19] 5.38 (1H, d, J=4.0 Hz, 1-H), 5.55 (1H, s, -C<u>H</u>Ph), 7.13—7.62 (21H, m, 3-H and arom. H_{20}). *Anal.* Calcd for $C_{45}H_{48}O_{11}$: C, 70.67; H, 6.33. Found: C, 70.43; H, 6.49.

Jones Oxidation of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-allo-10-hydroxyloganin (15a)——Jones reagent was added dropwise to a solution of **15a** (633 mg) in acetone (20 ml) with stirring under ice-cooling until the solution showed a persistent pale orange color. Stirring was continued for a further 30 min, then the excess reagent was reduced with MeOH, and the mixture was diluted with H_2O (100 ml) and extracted with $CHCl_3$ (100 ml×3). The $CHCl_3$ layer was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to give 4′,6′-O-benzylidene-2′,3′,10-tri-O-benzyl-7-dehydro-allo-10-hydroxyloganin (**16**) (622 mg) as a white powder. IR ν_{max}^{KBr} cm^{-1}: 1735, 1700, 1635, 1495, 1450, 750, 740, 700. NMR ($CDCl_3$) δ: 3.67 (3H, s, $COOCH_3$), 5.51 (1H, d, J=5.5 Hz, 1-H), 5.53 (1H, s, -C<u>H</u>Ph), 7.12—7.68 (21H, m, 3-H and arom. H_{20}).

$NaBH_4$ Reduction of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-7-dehydro-allo-10-hydroxyloganin (16)——A solution of $NaBH_4$ (82.5 mg) in H_2O (0.5 ml) was added to a stirred solution of **16** (705 mg) in dioxane (20 ml) and the reaction mixture was stirred at room temperature for 1 hr. After decomposition of the excess $NaBH_4$ by addition of acetone under ice-cooling, the mixture was diluted with H_2O (50 ml) and extracted with benzene (100 ml×3). The benzene layer was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue (678 mg) was chromatographed on silica gel (40 g); the column was eluted successively with 5% (100 ml), 8% (100 ml), 10% (500 ml), 12% (400 ml) and 15% Et_2O–benzene (300 ml), collecting 50 ml fractions. The combined Fr. 12—17 were concentrated *in vacuo* and the residue (346 mg) was recrystallized from EtOH to yield 4′,6′-O-benzylidene-2′,3′,10-tri-O-benzyl-7-epi-allo-10-hydroxyloganin (**17a**) (262 mg) as colorless needles, mp 110—111.5°, $[\alpha]_D^{26}$ −85.0° (c=0.99, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3500, 1685, 1635, 1495, 1450, 745, 695. NMR ($CDCl_3$) δ: 2.07 (1H, s, OH, disappeared on addition of D_2O), 3.68 (3H, s, $COOCH_3$), 5.57 (1H, s, -C<u>H</u>Ph), 5.59 (1H, d, J=7.0 Hz, 1-H), 7.15—7.65 (21H, m, 3-H and arom. H_{20}). *Anal.* Calcd for $C_{45}H_{48}O_{11}$: C, 70.67; H, 6.33. Found: C, 70.46; H, 6.60. The combined Fr. 19—27 gave a residue (164 mg), which was purified by PLC (solvent system I, 3 developments) to give **15a** (141 mg).

Catalytic Hydrogenation of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-allo-10-hydroxyloganin (15a)——A solution of **15a** (432 mg) in MeOH (30 ml) was hydrogenated over Pd-C (prepared from 5% $PdCl_2$–HCl solution (3.0 ml) and activated charcoal (DARCO G-60, 600 mg)). After completion of the H_2 uptake, the catalyst was filtered off and the filtrate was concentrated *in vacuo* to give a residue (228 mg), which was subjected to PLC (solvent system IV, *Rf* 0.24) to furnish allo-10-hydroxyloganin (**18a**) (167 mg) as a white powder, $[\alpha]_D^{29}$ −76.4° (c=0.89, MeOH). UV λ_{max}^{MeOH} nm (log ε): 237 (4.03). IR ν_{max}^{KBr} cm^{-1}: 3300, 1680, 1625. NMR (D_2O) δ: 3.75 (3H, s, $COOCH_3$), 5.58 (1H, d, J=4.5 Hz, 1-H), 7.49 (1H, s, 3-H). *Anal.* Calcd for $C_{17}H_{26}O_{11}\cdot 1/4H_2O$: C, 49.69; H, 6.50. Found: C, 49.59; H, 6.42.

Acetylation of Allo-10-hydroxyloganin (18a)——Compound (**18a**) (52.3 mg) was acetylated with Ac_2O and pyridine (each 0.5 ml) in the usual way and the product (94.2 mg) was recrystallized from EtOH to give allo-10-hydroxyloganin hexaacetate (**18b**) (50.2 mg) as colorless needles, mp 139—140.5°, $[\alpha]_D^{26}$ −65.7° (c=0.82, $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 233 (4.06). IR ν_{max}^{KBr} cm^{-1}: 1740, 1700, 1630. NMR ($CDCl_3$) δ: 1.94, 2.01, 2.03, 2.05, 2.10 (each s, 6×$OCOCH_3$), 3.72 (3H, s, $COOCH_3$), 5.36 (1H, d, J=3.5 Hz, 1-H), 7.37 (1H, br s, 3-H). *Anal.* Calcd for $C_{29}H_{38}O_{17}$: C, 52.89; H, 5.82. Found: C, 52.88; H, 5.71.

Catalytic Hydrogenation of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-7-epi-allo-10-hydroxyloganin (17a)——A solution of **17a** (301 mg) in MeOH (12 ml) was hydrogenated over Pd–C catalyst (prepared from 5% $PdCl_2$–HCl solution (1.5 ml) and activated charcoal (DARCO G-60, 500 mg)). After completion of the H_2 uptake, the catalyst was filtered off and the filtrate was concentrated *in vacuo* to give a residue (171 mg), which, on recrystallization from EtOH–AcOEt, afforded 7-epi-allo-10-hydroxyloganin (**19a**) (73.7 mg) as colorless needles, mp 199—201°, $[\alpha]_D^{27}$ −95.4° (c=1.00, MeOH). UV λ_{max}^{MeOH} nm (log ε): 238 (4.08). IR ν_{max}^{KBr} cm^{-1}: 3450—3200, 1670, 1625. NMR (D_2O) δ: 3.75 (3H, s, $COOCH_3$), 4.42 (1H, m, 7-H), 4.87 (1H, d, J=7.0 Hz, 1′-H), 5.64 (1H, d, J=7.5 Hz, 1-H), 7.54 (1H, s, 3-H). *Anal.* Calcd for $C_{17}H_{26}O_{11}$: C, 50.24; H, 6.45. Found: C, 50.16; H, 6.38.

Acetylation of 7-Epi-allo-10-hydroxyloganin (19a)——Compound (**19a**) (51.2 mg) was acetylated with Ac_2O and pyridine (each 0.5 ml) and the product (75.4 mg) was recrystallized from Et_2O–petr. ether to furnish 7-epi-allo-10-hydroxyloganin hexaacetate (**19b**) (31.4 mg) as colorless needles, mp 95—98°, $[\alpha]_D^{27}$ −84.7° (c=0.98, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 234 (4.08). IR ν_{max}^{KBr} cm^{-1}: 1740, 1695, 1635. NMR ($CDCl_3$) δ: 1.99, 2.01, 2.03, 2.09 (each s, 6×$OCOCH_3$), 3.72 (3H, s, $COOCH_3$), 5.62 (1H, d, J=5.0 Hz, 1-H), 7.43 (1H, br s, 3-H). *Anal.* Calcd for $C_{29}H_{38}O_{17}$: C, 52.89; H, 5.82. Found: C, 52.80; H, 5.80.

Acid Treatment of Allo-10-hydroxyloganin (18a)——A solution of **18a** (265 mg) in 3.5% aq. HCl (6 ml) was heated at 90° for 60 min. After cooling, the reaction mixture was diluted with H_2O (40 ml) and extracted with AcOEt (50 ml×3). The AcOEt layer was washed with H_2O, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (59.5 mg) was subjected to PLC (solvent system VI, 4 developments) to give an oily residue (48.1 mg), which was recrystallized from Et_2O–petr. ether to afford the anhydride (**20a**) (12.4 mg) as colorless plates, mp 74—75°, $[\alpha]_D^{25}$ +88.3° (c=0.45, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1695, 1640. NMR ($CDCl_3$) δ: 1.52 (1H, ddd, J=13.0, 9.5 and 4.0 Hz, 6-$H_{quasi-ax}$), 2.58 (1H, s, OH, disappeared on addition of D_2O), 3.59 (1H, dd, J=9.5 and 4.0 Hz, 10-H), 3.74 (3H, s, $COOCH_3$), 3.98 (1H, dd, J=9.5 and 8.0 Hz, 10-H), 4.16 (1H, m, 7-H), 5.42 (1H, d, J=4.0 Hz, 1-H), 7.55 (1H, s, 3-H). *Anal.* Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.34; H, 6.25.

Acetylation of the Anhydride (20a)——The anhydride (**20a**) (19.8 mg) was acetylated with Ac_2O and pyridine (each 0.5 ml) and the product (19.9 mg) was purified by PLC (solvent system II, *Rf* 0.28) to give the acetate (**20b**) (13.4 mg), which was recrystallized from Et_2O–petr. ether to furnish colorless needles (6.3 mg), mp 65.5—66°, $[\alpha]_D^{27}$ +50.1° (c=0.52, $CHCl_3$), UV λ_{max}^{EtOH} nm (log ε): 231 (4.03). IR ν_{max}^{KBr} cm^{-1}: 1730, 1690, 1640. NMR ($CDCl_3$) δ: 1.58 (1H, ddd, J=14.0, 10.5 and 4.0 Hz, 6-$H_{quasi-ax}$), 2.04 (3H, s, $OCOCH_3$), 2.40 (1H, ddt, J=14.0, 7.5 and 2.0 Hz, 6-$H_{quasi-eq}$), 2.76 (1H, td, J=9.5 and 5.0 Hz, 9-H), 2.75—3.15 (1H, m, 5-H), 3.14 (1H, m, 8-H), 3.67 (1H, dd, J=10.0 and 4.5 Hz, 10-H), 3.74 (3H, s, $COOCH_3$), 3.98 (1H, dd, J=10.0 and 8.5 Hz, 10-H), 5.01 (1H, m, 7-H), 5.40 (1H, d, J=5.0 Hz, 1-H), 7.54 (1H, d, J=1.0 Hz, 3-H). *Anal.* Calcd for $C_{13}H_{16}O_5$: C, 58.20; H, 6.01. Found: C, 58.18; H, 6.16.

Tosylation of the Anhydride (20a)——*p*-TsCl (410 mg) was added to a solution of **20a** (45.8 mg) in pyridine (2 ml). After standing overnight at room temperature, the reaction mixture was poured into ice-H_2O and extracted with $CHCl_3$ (30 ml×3). The $CHCl_3$ layer was washed successively with 1 N HCl, satd. aq. $NaHCO_3$, and H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue (74.5 mg) was purified by PLC (solvent system II, *Rf* 0.36) followed by recrystallization from Et_2O to give the tosylate (**20c**) (64.2 mg) as colorless plates, mp 91—92.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1645, 1360, 1175. NMR ($CDCl_3$) δ: 1.47 (1H, ddd, J=14.0, 10.0 and 4.0 Hz, 6-$H_{quasi-ax}$), 2.37 (1H, ddt, J=14.0, 7.5 and 2.0 Hz, 6-$H_{quasi-eq}$), 2.45 (3H, s, arom. CH_3), 3.51 (1H, dd, J=10.0 and 3.5 Hz, 10-H), 3.69 (3H, s, $COOCH_3$), 3.90 (1H, dd, J=10.0 and 8.5 Hz, 10-H), 4.75 (1H, m, 7-H), 5.37 (1H, d, J=5.0 Hz, 1-H), 7.50 (1H, s, 3-H), 7.23—7.97 (4H, $A'_2B'_2$ type arom. H_4). High resolution MS, Calcd for $C_{18}H_{20}O_5S$ (M^+): 380.0930. Found: 380.0931.

Conversion of 7-Epi-allo-10-hydroxylogain (19a) into the Corresponding Aglucone Acetate (21)——A solution of **19a** (274.4 mg) in 3.5% aq. HCl (6 ml) was heated at 90° for 80 min. After cooling, the mixture was diluted with H_2O (30 ml) and extracted with AcOEt (30 ml×5). The AcOEt layer was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The oily residue (71.7 mg) was acetylated with Ac_2O and pyridine (each 1.0 ml) and the product (63.1 mg) was subjected to PLC (solvent system II, 2 developments), yielding a colorless syrup (19.7 mg), which was recrystallized from Et_2O–petr. ether to give the aglucone acetate (**21**) (9.0 mg) as colorless needles, mp 81.5—82°, $[\alpha]_D^{26}$ +91.6° (c=0.23, $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε), 231 (4.01). IR ν_{max}^{KBr} cm^{-1}: 1725, 1695, 1640. NMR ($CDCl_3$) δ: 1.00—1.80 (1H, m, 6-H), 2.03 (3H, s, $OCOCH_3$), 2.33—3.33 (4H, m, 5-, 6-, 8- and 9-H_4), 3.72 (3H, s, $COOCH_3$), 3.73 (1H, dd, J=10.0 and 8.0 Hz, 10-H), 4.08 (1H, dd, J=10.0 and 4.5 Hz, 10-H), 5.10 (1H, dt, J=11.0 and 6.5 Hz, 7-H), 5.41 (1H, d, J=5.0 Hz, 1-H), 7.52 (1H, s, 3-H). *Anal.* Calcd for $C_{13}H_{16}O_5$: C, 58.20; H, 6.01. Found: C, 57.92; H, 5.86.

Epimerization of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-7-dehydro-allo-10-hydroxyloganin (16)——

Compound (**16**) (116 mg) was subjected to PLC (1 plate, solvent system I). A band around *Rf* 0.37 was scraped off and extracted with $CHCl_3$ (100 ml). Concentration of the $CHCl_3$ extract gave a residue (82.7 mg), which was recrystallized from Et_2O–petr. ether to afford 4′,6′-O-benzylidene-2′,3′,10-tri-O-benzyl-7-dehydro-10-hydroxyloganin (**22**) (73.6 mg) as colorless needles, mp 122.5—124°, $[\alpha]_D^{27}$ −134.3° (c=1.02, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1735, 1700, 1635, 1495, 1450, 750, 700. NMR ($CDCl_3$) δ: 3.58 (3H, s, $COOCH_3$), 5.58 (1H, s, –C<u>H</u>Ph), 5.68 (1H, d, J=2.5 Hz, 1-H), 7.13—7.72 (21H, m, 3-H and arom. H_{20}). *Anal.* Calcd for $C_{45}H_{46}O_{11}$: C, 70.85; H, 6.08. Found: C, 70.93; H, 5.87.

$NaBH_4$ Reduction of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-7-dehydro-10-hydroxyloganin (22)——A solution of $NaBH_4$ (87.1 mg) in H_2O (0.5 ml) was added to a stirred solution of **22** (794 mg) in dioxane (20 ml), and the reaction mixture was stirred for a further 1 hr at room temperature. The excess $NaBH_4$ was decomposed by addition of acetone under ice-cooling, and the mixture was diluted with H_2O (50 ml) and extracted with benzene (50 ml×4). The benzene layer was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue (754 mg) was reprecipitated from benzene–petr. ether, yielding 4′,6′-O-benzylidene-2′,3′,10-tri-O-benzyl-7-epi-10-hydroxyloganin (**23a**) (579 mg), which was purified by recrystallization from Et_2O–petr. ether to give colorless needles, mp 128.5—130.5°, $[\alpha]_D^{20}$ −70.5° (c=0.51, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3200, 1700, 1635, 1495, 1450, 755, 738, 700. NMR ($CDCl_3$) δ: 1.54 (1H, dt, J=13.0 and 7.0 Hz, 6-H), 1.89—2.20 (1H, m, OH, disappeared on addition of D_2O), 2.48 (1H, dt, J=13.0 and 6.5 Hz, 6-H), 2.91 (1H, m, 5-H), 3.61 (3H, s, $COOCH_3$), 4.05 (1H, m, 7-H), 4.30 (1H, dd, J=10.5 and 5.0 Hz, 10-H), 5.30 (1H, d, J=4.5 Hz, 1-H), 5.53 (1H, s, –C<u>H</u>Ph), 7.10—7.58 (21H, m, 3-H and arom. H_{20}). *Anal.* Calcd for $C_{45}H_{48}O_{11}$: C, 70.67; H, 6.33. Found: C, 70.64; H, 6.62. The mother liquor was concentrated *in vacuo* and the residue (176 mg) was chromatographed on silica gel (10 g); the column was eluted successively with 5% (50 ml), 8% (50 ml), 10% (100 ml) and 12% Et_2O–benzene (100 ml), collecting 25 ml fractions. The combined Fr. 8—9 were concentrated *in vacuo* to give 4′,6′-O-benzylidene-2′,3′,10-tri-O-benzyl-10-hydroxyloganin (**24a**) (47.8 mg) as a white powder, whereas the combined Fr. 10—11 afforded, after reprecipitation from benzene-petr. ether, **23a** (51.1 mg). **24a**, $[\alpha]_D^{18}$ −69.2° (c=1.02, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3430, 1695, 1625, 1490, 1445, 745, 735, 695. NMR ($CDCl_3$) δ: 2.37—2.67 (1H, m, OH, disappeared on addition of D_2O), 3.61 (3H, s, $COOCH_3$), 4.32 (1H, m, 7-H), 5.23 (1H, d, 1-H), 5.55 (1H, s, –C<u>H</u>Ph), 7.08—7.63 (21H, m, 3-H and arom. H_{20}). *Anal.* Calcd for $C_{45}H_{48}O_{11}$: C, 70.67; H, 6.33. Found: C, 70.78; H, 6.27.

Acetylation of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-allo-10-hydroxyloganin (15a)——Compound (**15a**) (53.9 mg) was acetylated with Ac_2O and pyridine (each 0.5 ml) and the product (53.4 mg) was purified by PLC (solvent system I, *Rf* 0.37) to give **15b** (48.4 mg) as a white powder. $[\alpha]_D^{29}$ −80.7° (c=0.81, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1730, 1700, 1635, 1495, 1450, 750, 740, 700. NMR ($CDCl_3$) δ: 1.99 (3H, s, $OCOCH_3$), 3.15 (1H, m, 5-H), 3.61 (3H, s, $COOCH_3$), 4.27 (1H, dd, J=10.0 and 4.5 Hz, 10-H), 4.89 (1H, d, J=8.0 Hz, 1′-H), 5.07 (1H, q, J=5.0 Hz, 7-H), 5.54 (1H, s, –C<u>H</u>Ph), 5.59 (1H, d, J=4.5 Hz, 1-H), 7.11—7.67 (21H, m, 3-H and arom. H_{20}). *Anal.* Calcd for $C_{47}H_{50}O_{12}$: C, 69.96; H, 6.25. Found: C, 69.92; H, 6.51.

Acetylation of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-7-epi-allo-10-hydroxyloganin (17a)——Compound (**17a**) (83.5 mg) was acetylated with Ac_2O and pyridine (each 0.8 ml) and the product (93.4 mg) was purified by PLC (solvent system I, *Rf* 0.30), giving **17b** (86.3 mg) as a white powder. $[\alpha]_D^{28}$ −86.5° (c=0.60, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1720, 1705, 1640, 1500, 1460, 755, 700. NMR ($CDCl_3$) δ: 1.87 (3H, s, $OCOCH_3$), 2.33 (1H, q, J=7.0 Hz, 9-H), 3.68 (3H, s, $COOCH_3$), 4.98 (1H, d, J=8.0 Hz, 1′-H), 5.47 (1H, d, J=8.0 Hz, 1-H), 5.56 (1H, s, –C<u>H</u>Ph), 7.17—7.56 (21H, m, 3-H and arom. H_{20}). *Anal.* Calcd for $C_{47}H_{50}O_{12}$: C, 69.96; H, 6.25. Found: C, 70.05; H, 6.48.

Acetylation of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-7-epi-10-hydroxyloganin (23a)——Compound (**23a**) (53.8 mg) was acetylated with Ac_2O and pyridine (each 0.5 ml) and the product (58.8 mg) was purified by PLC (solvent system I, *Rf* 0.36), giving the acetate (**23b**) (55.3 mg) as a white powder, $[\alpha]_D^{29}$ −98.5° (c=0.75, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1725, 1705, 1635, 1495, 1450, 750, 698. NMR ($CDCl_3$) δ: 1.93 (3H, s, $OCOCH_3$), 2.48 (1H, dd, J=15.0 and 7.0 Hz, 6-H), 3.03 (1H, m, 5-H), 3.62 (3H, s, $COOCH_3$), 4.28 (1H, dd, J=10.0 and 4.5 Hz, 10-H), 5.52 (1H, d, J=3.5 Hz, 1-H), 5.56 (1H, s, –C<u>H</u>Ph), 7.11—7.64 (21H, m, 3-H and arom. H_{20}). *Anal.* Calcd for $C_{47}H_{50}O_{12}$: C, 69.96; H, 6.25. Found: C, 69.86; H, 6.31.

Tosylation of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-allo-10-hydroxyloganin (15a)——A solution of **15a** (122 mg) and *p*-TsCl (108 mg) in pyridine (1 ml) was allowed to stand overnight at room temperature. The reaction mixture was worked up in the usual way. The crude product (141 mg) was subjected to PLC (solvent system I, *Rf* 0.48), giving the tosylate (**15c**) (119 mg) as a white powder. $[\alpha]_D^{27}$ −84.2° (c=0.99, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1700, 1635, 1495, 1450, 1360, 1175, 745, 735, 695. NMR ($CDCl_3$) δ: 2.40 (3H, s, arom. CH_3), 3.59 (3H, s, $COOCH_3$), 5.54 (1H, s, –C<u>H</u>Ph), 7.00—7.90 (25H, 3-H and arom. H_{24}). *Anal.* Calcd for $C_{52}H_{54}O_{13}S$: C, 67.96; H, 5.92; S, 3.49. Found: C, 67.81; H, 6.15; S, 3.38.

Walden Inversion of the Tosylate (15c)——Et_4NOAc (2.00 g) was added to a solution of the tosylate (**15c**) (860 mg) in dry acetone (50 ml) and the mixture was heated under reflux for 25 hr. Removal of the solvent by evaporation gave a residue, which was redissolved in $CHCl_3$ (150 ml). The $CHCl_3$ layer was washed successively with satd. aq. NaCl and H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to medium pressure column chromatography on silica gel (60 g); the column was eluted first with benzene (100 ml) and then successively with 5% (200 ml), 7% (200 ml) and 10% Et_2O–benzene (300 ml), collecting 10 g fractions. The combined Fr. 30—33 were concentrated *in vacuo* to give a residue (46.5 mg),

which was recrystallized from Et_2O–petr. ether to yield the olefin (**26**) (25.6 mg) as colorless needles, mp 118—119°. The combined Fr. 47—63 afforded a powdery substance (639 mg), which was identical with the above-mentioned **17b** (TLC, IR and NMR comparisons). **26**, $[\alpha]_D^{27}$ −145.5° (c=0.55, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1710, 1640, 1500, 1455, 755, 740, 700. NMR ($CDCl_3$) δ: 2.83 (1H, td, J=8.5 and 2.0 Hz, 9-H), 3.21 (1H, m, 5-H), 3.63 (3H, s, $COOCH_3$), 4.30 (1H, dd, J=10.0 and 4.5 Hz, 10-H), 5.56 (1H, s, -CHPh), 5.68 (1H, dt, J=6.0 and 2.0 Hz, 6-H or 7-H), 5.89 (1H, d, J=2.0 Hz, 1-H), 6.12 (1H, m, 7-H or 6-H), 7.05—7.58 (21H, m, 3-H and arom. H_{20}). *Anal.* Calcd for $C_{45}H_{46}O_{10}$: C, 72.37; H, 6.21. Found: C, 72.41; H, 6.32.

Tosylation of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-7-epi-allo-10-hydroxyloganin (17a)——A solution of **17a** (50.1 mg) and *p*-TsCl (38.2 mg) in pyridine (0.5 ml) was allowed to stand for 2 days. After further addition of *p*-TsCl (37.1 mg), the reaction mixture was allowed to stand for another 1 day. The conventional work-up of the mixture gave a crude product (60.8 mg), which was subjected to PLC (solvent system I). A band at around *Rf* 0.38 furnished **17c** (41.1 mg) as a white powder, $[\alpha]_D^{28}$ −70.1° (c=0.41, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1700, 1635, 1495, 1450, 1360, 1175, 750, 745, 700. NMR ($CDCl_3$) δ: 2.36 (3H, s, arom. CH_3), 3.66 (3H, s, $COOCH_3$), 5.47 (1H, d, J=7.5 Hz, 1-H), 5.59 (1H, s, -CHPh), 7.12—7.87 (25H, m, 3-H and arom. H_{24}). *Anal.* Calcd for $C_{52}H_{54}O_{13}S$: C, 67.96; H, 5.92; S, 3.49. Found: C, 67.67; H, 5.85; S, 3.49. From a band at around *Rf* 0.13, **17a** (10.9 mg) was recovered.

Walden Inversion of the Tosylate (17c)——A solution of **17c** (125 mg) and Et_4NOAc (360 mg) in dry acetone (15 ml) was refluxed for 20 hr. After removal of the solvent, the oily residue was diluted with $CHCl_3$ (50 ml), washed with satd. aq. NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to PLC (solvent system I). A band at around *Rf* 0.37 gave a powdery substance (21.9 mg), which was identical with an authentic sample of **15b** (TLC, IR and NMR comparisons). The band at around *Rf* 0.47 afforded a crystalline compound (73.9 mg), which was identical with an authentic specimen of **14** (TLC, IR and NMR comparisons).

Tosylation of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-7-epi-10-hydroxyloganin (23a)——Compound (**23a**) (235 mg) was tosylated with *p*-TsCl (158 mg) and pyridine (2 ml) in the usual way and the product (270 mg) was purified by PLC (solvent system I, *Rf* 0.45) followed by recrystallization from EtOH to give crystals of **23c** (237 mg), mp 100—102°, $[\alpha]_D^{23}$ −83.7° (c=1.03, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1700, 1630, 1490, 1450, 1360, 1175, 750, 700. NMR ($CDCl_3$) δ: 2.37 (3H, s, arom. CH_3), 3.59 (3H, s, $COOCH_3$), 5.36 (1H, d, J=4.0 Hz, 1-H), 5.55 (1H, s, -CHPh), 7.08—7.90 (25H, m, 3-H and arom. H_{24}). *Anal.* Calcd for $C_{52}H_{54}O_{13}S$: C, 67.96; H, 5.92; S, 3.49. Found: C, 67.90; H, 6.21; S, 3.63.

Walden Inversion of the Tosylate (23c)——A solution of **23c** (867 mg) and Et_4NOAc (1.90 g) in dry acetone (50 ml) was refluxed for 24 hr. The conventional work-up of the mixture afforded a crude residue, which was subjected to medium pressure column chromatography on silica gel (60 g); the column was eluted successively with benzene (100 ml), 5% (200 ml), 7% (300 ml) and 10% Et_2O–benzene (300 ml), collecting 10 g fractions. The combined Fr. 30—36 and 44—55 furnished **25** (77.9 mg) and **24b** (598 mg) as white powders, respectively. **24b**, $[\alpha]_D^{28}$ −74.9° (c=0.53, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1730, 1700, 1635, 1495, 1450, 750, 740, 700. NMR ($CDCl_3$) δ: 1.96 (3H, s, $OCOCH_3$), 3.60 (3H, s, $COOCH_3$), 4.27 (1H, dd, J=10.0 and 4.5 Hz, 10-H), 5.33 (1H, m, 7-H), 5.53 (1H, d, J=3.0 Hz, 1-H), 5.59 (1H, s, -CHPh), 7.08—7.75 (21H, m, 3-H and arom. H_{20}). *Anal.* Calcd for $C_{47}H_{50}O_{12}$: C, 69.96; H, 6.25. Found: C, 70.26; H, 6.46. **25**, $[\alpha]_D^{28}$ −41.1° (c=0.29, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1705, 1640, 1500, 1450, 750, 735, 698. NMR ($CDCl_3$) δ: 2.47 (1H, ddd, J=8.0, 7.0 and 4.0 Hz, 9-H), 3.04 (1H, m, 5-H), 3.63 (3H, s, $COOCH_3$), 4.26 (1H, dd, J=10.0 and 5.0 Hz, 10-H), 5.46 (1H, d, J=4.0 Hz, 1-H), 5.56 (1H, s, -CHPh), 5.60 (1H, dt, J=5.5 and 2.0 Hz, 6-H or 7-H), 6.06 (1H, dt, J=5.5 and 2.2 Hz, 7-H or 6-H), 7.06—7.57 (21H, m, 3-H and arom. H_{20}). *Anal.* Calcd for $C_{45}H_{46}O_{10}\cdot 1/2H_2O$: C, 71.51; H, 6.27. Found: C, 71.47; H, 6.42.

Catalytic Hydrogenation of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-7-epi-10-hydroxyloganin (23a)——A solution of **23a** (307 mg) in MeOH (12 ml) was hydrogenated over Pd–C (prepared from 5% $PdCl_2$–HCl solution (1.5 ml) and activated charcoal (DARCO G-60, 500 mg)). After completion of the H_2 uptake, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue (172 mg) was purified by PLC (solvent system IV, *Rf* 0.24) to give 7-epi-10-hydroxyloganin (**8a**) (132 mg) as a white powder. $[\alpha]_D^{17}$ −93.4° (c=0.92, MeOH). UV λ_{max}^{MeOH} nm (log ε): 236 (4.03). IR ν_{max}^{KBr} cm^{-1}: 3330, 1680, 1625. NMR (D_2O) δ: 3.75 (3H, s, $COOCH_3$), 5.42 (1H, d, J=6.0 Hz, 1-H), 7.53 (1H, d, J=1.0 Hz, 3-H). *Anal.* Calcd for $C_{17}H_{26}O_{11}\cdot 1/2H_2O$: C, 49.15; H, 6.55. Found: C, 49.11; H, 6.53.

Acetylation of 7-Epi-10-hydroxyloganin (8a)——7-Epi-10-hydroxyloganin (**8a**) (96.7 mg) was acetylated with Ac_2O and pyridine (each 1 ml) and the product (156 mg) was recrystallized from EtOH to give 7-epi-10-hydroxyloganin hexaacetate (**8b**) (107 mg) as colorless needles, mp 127—128°, $[\alpha]_D^{26}$ −94.9° (c=0.52, $CHCl_3$), UV λ_{max}^{EtOH} nm (log ε): 232 (4.04). IR ν_{max}^{KBr} cm^{-1}: 1755, 1735, 1705, 1635. NMR ($CDCl_3$) δ: 1.90, 1.94, 1.98, 2.01, 2.04, 2.07 (each s, 6×$OCOCH_3$), 3.71 (3H, s, $COOCH_3$), 7.32 (1H, d, J=2.0 Hz, 3-H). *Anal.* Calcd for $C_{29}H_{38}O_{17}$: C, 52.89; H, 5.82. Found: C, 52.87; H, 5.90.

Zemplén Reaction of the Acetate (24b)——Methanolic $NaOCH_3$ (0.1 N, 0.8 ml) was added to a solution of **24b** (236 mg) in dry MeOH (15 ml) and the mixture was refluxed for 30 min. After cooling, the mixture was diluted with H_2O (20 ml), neutralized with 1 N HCl and extracted with $CHCl_3$ (25 ml×3). The $CHCl_3$ layer was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue (217 mg) was purified by PLC (solvent system II, *Rf* 0.20) giving a white powder (203 mg). This compound was identical with an

authentic specimen of **24a** (TLC, IR and NMR comparisons).

Catalytic Hydrogenation of 4′,6′-O-Benzylidene-2′,3′,10-tri-O-benzyl-10-hydroxyloganin (24a)——A solution of **24a** (294 mg) in MeOH (12 ml) was hydrogenated over Pd–C (prepared from 5% $PdCl_2$–HCl solution (1.2 ml) and activated charcoal (DARCO G-60, 300 mg)). After completion of the H_2 uptake, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. Purification of the residue (167 mg) by PLC (solvent system IV, *Rf* 0.27) afforded 10-hydroxyloganin (**3a**) (138 mg) as a white powder, $[\alpha]_D^{27}$ −58.9° (c=0.58, MeOH). UV λ_{max}^{MeOH} nm (log ε): 236 (4.05). IR ν_{max}^{KBr} cm^{-1}: 3350, 1685, 1630. NMR (D_2O) δ: 3.76 (3H, s, $COOCH_3$), 4.38 (1H, m, 7-H), 4.81 (1H, d, J=8.0 Hz, 1′-H), 5.27 (1H, d, J=4.5 Hz, 1-H), 7.51 (1H, d, J=1.0 Hz, 3-H). *Anal.* Calcd for $C_{17}H_{26}O_{11}\cdot 1/2H_2O$: C, 49.15; H, 6.55. Found: C, 49.26; H, 6.45.

Acetylation of 10-Hydroxyloganin (3a)——10-Hydroxyloganin (**3a**) (56.6 mg) was acetylated with Ac_2O and pyridine (each 0.5 ml) in the usual way and the product (83.1 mg) was purified by PLC (solvent system VI, *Rf* 0.28) giving 10-hydroxyloganin hexaacetate (**3b**) (71.3 mg) as a white powder, $[\alpha]_D^{28}$ −54.0° (c=0.98, $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 232 (4.04). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1735, 1700 (sh), 1635. NMR ($CDCl_3$) δ: 1.93, 2.01, 2.03, 2.09 (each s, 6×$OCOCH_3$), 3.72 (3H, s, $COOCH_3$), 7.36 (1H, d, J=1.0 Hz, 3-H). *Anal.* Calcd for $C_{29}H_{38}O_{17}\cdot H_2O$: C, 51.48; H, 5.96. Found: C, 51.49; H, 5.74.

Alkaline Hydrolysis of 10-Hydroxyloganin (3a)——10-Hydroxyloganin (**3a**) (109.2 mg) was dissolved in 0.5 N aq. NaOH (2 ml) and the solution was stirred for 2.5 hr at room temperature. After neutralization of the solution with Amberlite IR-120 (H^+-form), the resin was filtered off and the filtrate was concentrated *in vacuo* to afford a residue (105.5 mg), which was purified by PLC (solvent system V, *Rf* 0.36) to give 10-hydroxyloganic acid (**27a**) (90.3 mg) as a white powder, $[\alpha]_D^{27}$ −62.7° (c=0.46, MeOH). UV λ_{max}^{MeOH} nm (log ε): 233 (4.03). IR ν_{max}^{KBr} cm^{-1}: 3330, 1670, 1625. NMR (D_2O) δ: 3.82 (2H, d, J=6.5 Hz, 10-H_2), 4.36 (1H, m, 7-H), 5.30 (1H, d, J=4.5 Hz, 1-H), 7.45 (1H, d, J=1.0 Hz, 3-H). *Anal.* Calcd for $C_{16}H_{24}O_{11}\cdot H_2O$: C, 46.83; H, 6.39. Found: C, 46.99; H, 6.30.

Acetylation of 10-Hydroxyloganic Acid (27a)——10-Hydroxyloganic acid (**27a**) (43.9 mg) was acetylated with Ac_2O and pyridine (each 1 ml) and the product (66.3 mg) was recrystallized from Et_2O to give 10-hydroxyloganic acid hexaacetate (**27b**) (31.0 mg) as colorless needles, mp 138.5—139.5°, $[\alpha]_D^{29}$ −52.1° (c=0.44, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 229 (4.01). IR ν_{max}^{KBr} cm^{-1}: 3155, 1760, 1740, 1715, 1640. NMR ($CDCl_3$) δ: 1.93, 1.98, 2.01, 2.02, 2.07 (each s, 6×$OCOCH_3$), 3.03 (1H, m, 5-H), 3.73 (1H, m, 5′-H), 4.90—5.67 (1H, m, COOH, disappeared on addition of D_2O), 7.42 (1H, s, 3-H). *Anal.* Calcd for $C_{28}H_{36}O_{17}$: C, 52.17; H, 5.63. Found: C, 51.90; H, 5.52.

Conversion of 10-Hydroxyloganin (3a) into the Corresponding Aglucone Methyl Ethers 28 and 29——β-Glucosidase (prepared from almonds) (27 mg) was added to a solution of **3a** (310 mg) in acetate buffer (pH 4.8) (45 ml). After standing at 39° for 15 hr, the reaction mixture was concentrated *in vacuo*. The residue was extracted with AcOEt (25 ml×4) and the combined AcOEt extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was purified by PLC (solvent system III, *Rf* 0.33) to give a colorless syrup (130 mg), which was dissolved in dry MeOH (7 ml) and stirred with Amberlite IR-120 (H^+-form) (980 mg) for 98 hr. The resin was filtered off and the filtrate was concentrated *in vacuo* to give an oily residue, which was subjected to PLC (solvent system VI, 4 developments). Of the two major bands, the more mobile one gave **29** (16.9 mg) as a colorless syrup, whereas the less mobile one afforded **28** (72.0 mg) as a colorless syrup. **28**, $[\alpha]_D^{29}$ −47.8° (c=0.60, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1690, 1625. NMR ($CDCl_3$) δ: 1.54 (1H, ddd, J= 14.0, 10.0 and 4.5 Hz, 6-H), 1.83—2.53 (3H, m, 6-H, 8-H and 9-H), 3.12 (1H, m, 5-H), 3.26 (2H, br s, OH, disappeared on addition of D_2O), 3.53 (3H, s, OCH_3), 3.71 (3H, s, $COOCH_3$), 4.49 (1H, d, J=6.0 Hz, 1-H), 7.46 (1H, d, J=1.0 Hz, 3-H). High resolution MS, Calcd for $C_{12}H_{18}O_6$ (M^+): 258.1103. Found: 258.1104. **29**, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1695, 1625. NMR ($CDCl_3$) δ: 1.77—2.65 (4H, m, 6-H_2, 8-H and 9-H), 3.03 (1H, m, 5-H), 3.09 (2H, br s, OH, disappeared on addition of D_2O), 3.45 (3H, s, OCH_3), 3.72 (3H, s, $COOCH_3$), 3.88 (2H, d, J=5.0 Hz, 10-H_2), 4.46 (1H, m, 7-H), 4.92 (1H, d, J=2.5 Hz, 1-H), 7.59 (1H, d, J=1.0 Hz, 3-H). High resolution MS, Calcd for $C_{12}H_{18}O_6$ (M^+): 258.1103. Found: 258.1100.

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References and Notes

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