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THE BITTER IRIDOIDS FROM *VIBURNUM URCEOLATUM*

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Key Word Index—*Viburnum urceolatum*; Caprifoliaceae; iridoids; urceloatosides A–D; bitter components.

Abstract—Four new bitter iridoid glucosides, including three bis-iridoids, were isolated from *Viburnum urceolatum* and their structures elucidated. They are composed of loganin or deoxyloganin as the aglucone esterified with either aromatic glucoside or with glucose in the 4-position.

INTRODUCTION

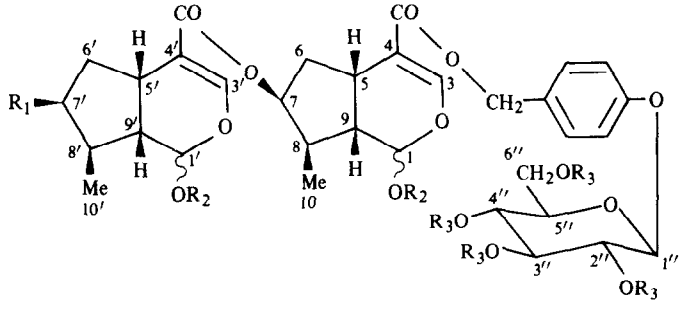
In the course of an investigation on the bitter principles of *Viburnum* species, we investigated a monoterpenoid glycoside, urceolide, isolated from *Viburnum urceolatum* [1]. As a result of our continued work on the same plant, the elucidation of the structures of three new bis-iridoids and an iridoid is reported now.

All of the new iridoids (named urceolatoside A–D) were recognized as the sources of bitterness from *V. urceolatum*.

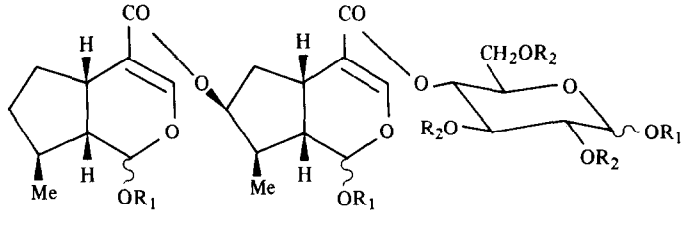
RESULTS AND DISCUSSION

The isolation and purification of the compounds are described in detail in the Experimental.

Compound **1**, urceolatoside A, $C_{33}H_{42}O_{14}$, amorphous; mp 136–140°, $[\alpha]_D$ −56°, showed a typical iridoid colour reaction by hydrochloric acid, and the IR spectrum showed strong absorption of a hydroxyl group (3400 cm^{-1}), benzene ring (1630, 1528), unsaturated ester (1720) and enol ether (1635). The ^1H NMR spectrum confirmed the existence of these functional groups [δ 1.08



	1	2	3	4	14	15	16	17	18	19
R_1	H	H	H	H	OH	OCOMe	OH	OCOMe	OMe	OH
R_2	H	COMe	Me	Me	H	COMe	Me	Me	Me	Me
R_3	H	COMe	H	COMe	H	COMe	H	COMe	Me	Me



	9	10	11	12	13
R_1	H	COMe	Me	Me	Me
R_2	H	COMe	H	COMe	Me

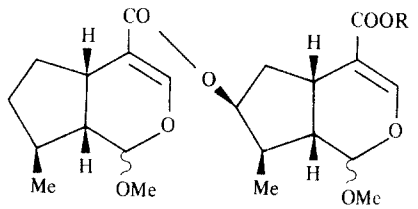
(6H, *d*, J = 7 Hz), 4.93 (2H, *m*), 5.02 (2H, *s*), 6.99, 7.30 (4H, A_2B_2, J = 10 Hz) and 7.38 (2H, *br s*)]. Acetylation of **1** gave a hexa-acetate (**2**), $C_{45}H_{54}O_{20}$, amorphous; $[\alpha]_D$ −55°, whose IR spectrum showed no hydroxyl absorption, and in the ^{1}H NMR spectrum, the signals from six acetoxyl groups were seen. Furthermore, doublets at δ5.93 and 6.00 showed the presence of two acetylated acetalic centers in **2**.

Upon methanolysis under mild conditions, **1** gave an anomeric mixture of dimethoxy compound **3** as seen from the ^{1}H NMR spectrum. Acetylation gave the corresponding mixture of tetra-acetates (**4**) which was separated into the diastereoisomeric mixtures of **4a** $[\alpha]_D$ +61° (major product) and **4b** $[\alpha]_D$ −8°. Compound **4a** was hydrolysed with 2N sodium hydroxide to afford two anomeric mixtures of carboxylic acids (**5** and **6**), and a phenolic glycoside (**7**). Compound **5**, $C_{11}H_{16}O_4$, was identical (IR, ^{1}H NMR) with authentic 1-*O*-methyl deoxyloganic acid aglycone (anomeric mixture) and **6** was further purified to give **6a** and **6b**, both having molecular formula of $C_{11}H_{16}O_5$, and their methyl esters ($[\alpha]_D$ −23.5° and +190°) were identical (IR, ^{1}H NMR, $[\alpha]_D$) with those reported for 1-*O*-methyl loganin aglycone and its anomer, respectively [2–4]. Compound **7** was hydrolysed with hydrochloric acid to give *p*-hydroxybenzyl alcohol and D-glucose. In the ^{1}H NMR spectrum, the signal due to the benzylic protons of **7** originally at δ4.80 (2H, *s*, pyridine-d_5) was shifted to 5.00 ($CDCl_3$)* by acetylation, and the chemical shift of the acetoxyl groups of the penta-acetate (**7a**) were at 2.07 and 2.08 (total 3H × 5). These data indicated that **7** had a benzylic hydroxyl group. The $W_{1/2}$ value of the anomeric proton of **7a** (at δ 5.68, J = 10 Hz) suggested that the glycosidic linkage must be β in **7**. Thus, the structure of **7** was determined to be *p*-(hydroxymethyl)phenyl-β-D-glucoside.

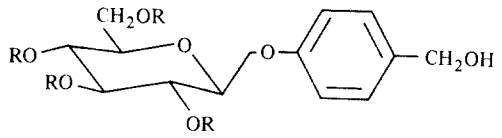
Treatment of **4a** with dilute sodium hydroxide in methanol gave an ester (**8**) as a mixture of diastereoisomers, $C_{23}H_{32}O_8$. The IR spectrum (1720, 1636, 960 and 930 cm^{-1}) and ^{1}H NMR spectrum [δ1.05 (3H, *d*, J = 6 Hz), 1.07 (3H, *d*, J = 6 Hz), 3.48, 3.60, 3.72 (total 9H, *s*) and 7.50 (2H, *s*)] suggested that **8** had a bis-iridoid structure. The chemical shift (δ5.02) of the signal of the benzylic protons of **1** showed the existence of acylated benzyl methylene in **1**. From the above data, the structure of **1** was determined to be as shown.

Compound **9**, urceolatoside B, was isolated as white crystals, mp 148–152°, $[\alpha]_D$ −15°, with a molecular formula $C_{26}H_{36}O_{13}\cdot 1/2\ H_2O$. Upon hydrolysis with acidic resin, **9** yielded D-glucose. The UV absorption at 246 nm (ε 11 000) was characteristic of the conjugated enol ether system which was confirmed by IR absorptions at 1720–1680 and 1620 cm^{-1}. The ^{1}H NMR spectrum exhi-

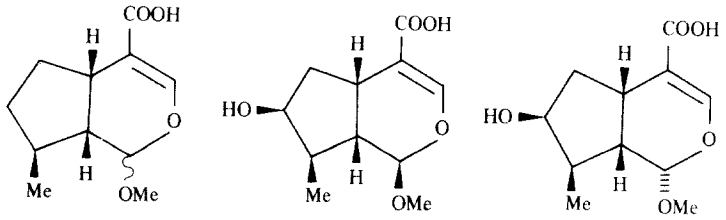
*The chemical shift of benzylic protons in the spectrum (in $CDCl_3$) of *p*-hydroxy benzylalcohol was δ4.54.



8 R = Me
8a R = H



7 R = H
20 R = Me



5 **6a** **6b**

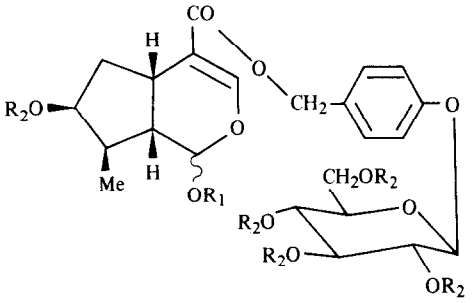
bited two singlets at δ7.54 (1H) and 7.58 (1H) due to the olefinic protons at C-3 and C-3′ of the iridoid, suggesting that **9** was likely to have a bis-iridoid structure. Acetylation of **9** afforded an amorphous hexa-acetate (**10**), $C_{38}H_{48}O_{19}$, whose ^{1}H NMR spectrum showed the signals due to six acetoxyl groups at δ2.00, 2.08 and 2.14. The three broad doublets which appeared at δ5.97 (1H, J = 3 Hz), 6.08 (1H, J = 2 Hz) and 6.30 (1H, J = 3 Hz) were assigned to acetylated hemiacetal protons. Methanolysis of **9** with methanol containing a catalytic amount of conc. hydrochloric acid yielded a diastereoisomeric mixture of methyl ethers (**11**), whose ^{1}H NMR spectrum showed signals at δ3.40–3.52 (total 9H, *s*). On acetylation with acetic anhydride–pyridine compound **11** afforded an amorphous triacetate (**12**) and its ^{1}H NMR spectrum indicated the presence of three acetoxyl groups at δ2.00–2.10 (3H × 3, *s*). Upon hydrolysis with 2 N sodium hydroxide, compound **12** afforded three acids which were identical with **5**, **6a** and **6b**, respectively. On mild alkaline hydrolysis, **12** gave the same kind of diastereoisomeric mixture as **8a**, $C_{22}H_{30}O_5$, and its methyl ester.

These facts confirmed that **9** had a bis-iridoid skeleton and C-1 of D-glucose in **9** was not acylated. In order to determine the position of the linkage between D-glucose and aglycone **8**, compound **11** was permethylated by the Purdie method, followed by alkaline hydrolysis. This procedure gave a mixture of methyl-2,3,6-tri-*O*-methyl-D-glucoside, **5**, **6a** and **6b**, showing that the ester linkage to the sugar was located at C-4 of D-glucose. The structure of **9** was, thus, shown to be as indicated.

Compound **14**, (urceolatoside C), was an amorphous powder, $C_{33}H_{42}O_{15}$, $[\alpha]_D$ −42.1°. The IR, UV and ^{1}H NMR spectra showed that **14** had an iridoid skeleton with an aromatic ring. [IR ν_{max} cm^{-1}: 3400, 1695, 1633 and 1518; UV λ_{max} nm (ε): 228 (11 000) and 238 (sh 10 600); ^{1}H NMR: δ1.07 (6H, *br d*, J = 6Hz), 5.07 (2H, *s*), 7.04, 7.41 (4H, A_2B_2, J = 9 Hz) and 7.44 (2H, *br s*)]. Acetylation of **14** afforded a hepta-acetate (**15**), amorphous, mp 88–89°, $C_{47}H_{56}O_{22}$, $[\alpha]_D$ −22.5° and its ^{1}H NMR spectrum confirmed the presence of seven aliphatic acetoxyl groups [2.04 (3H × 5, *s*) and 2.09 (3H × 2, *s*)]. Upon mild acidic methanolysis, **14** gave a mixture of diastereoisomers (**16**) and the ^{1}H NMR spectrum revealed the presence of two methoxyl groups at δ3.39 (*s*), 3.41 (*s*) and 3.44 (*s*) (total 6H). Without separation, the dimethyl ether, **16**, was hydrolysed with 2 N sodium hydroxide to give an epimeric mixture of acids **6** (2 mol) which was separated into two pure acids, **6a** and **6b**, and a phenolic glucoside (1 mol) which was identical with **7**. On acetylation, **16** gave a penta-acetate (**17**) whose IR spectrum showed no hydroxyl absorption and, in the ^{1}H NMR spectrum the signals due to the protons of five acetoxyl groups appeared at δ2.05 (3H × 5, *s*). These facts suggested that, like **1** and **9**, compound **14** has a bis-iridoid structure in which two loganic acid aglycones are linked to each other through an ester linkage.

The Purdie methylation of **16** afforded a hepta-methyl ether (**18**) and a hexa-methyl ether (**19**). The minor product **18** was shown to be the permethyl ether of **14** by its IR (no hydroxyl absorption) and ^{1}H NMR spectra [δ3.32, 3.39, 3.44, 3.49 (3H each, *s*) and 3.59 (3H × 3, *s*)]. Upon alkaline hydrolysis, compound **18** gave two anomeric mixtures of carboxylic acids which were identified as 1,7-di-*O*-methyl loganic acid aglycone and **6**, and a phenolic glycoside (**20**) which was hydrolysed with hydrochloric acid to give *p*-hydroxybenzyl alcohol and a methylated D-glucose identical with an authentic sample of 2,3,4,6-tetra-*O*-methyl-D-glucose. The IR spectrum of **19** showed the absorption of a hydroxyl group, and the ^{1}H NMR spectrum revealed the presence of six methoxyl groups [δ3.36, 3.43, 3.49, 3.51 (3H each, *s*) and 3.60 (3H × 2, *s*)]. Upon alkaline hydrolysis, compound **19** gave a single epimeric mixture of **6** (2 mol) and a phenolic methylated glycoside (1 mol) which was identical with **20**. On the basis of the above data, compound **14** has the structure shown.

Compound **21** (urceolatoside D), was obtained as a hygroscopic powder, mp 153–161°, $C_{23}H_{30}O_{11}$, $[\alpha]_D$ −42.5°, whose UV (236 nm, ε 6500), IR (3400, 1700, 1632 and 1518 cm^{-1}) and ^{1}H NMR spectra [δ1.10 (3H, *d*, J = 6 Hz), 1.40–2.50 (4H), 5.15 (2H, *s*), 7.19, 7.47 (4H, A_2B_2, J = 9 Hz) and 7.57 (1H, *s*)] indicated the presence of an aromatic ring and an iridoid skeleton besides a sugar moiety. Acetylation of **21** afforded a hexa-acetate (**22**) whose ^{1}H NMR spectrum showed the signals due to six acetoxyl groups [δ2.05 (3H × 5, *s*) and 2.09 (3H, *s*)] and an acetylated hemiacetal proton [6.05 (1H, *d*, J = 3 Hz)]. Upon treatment with hydrochloric acid, **21** gave D-glucose and a black polymeric product. On mild methanolysis, **21** afforded an epimeric mixture (2:1) of the monomethyl ether (**23**). This mixture was acetylated without separation, to give a penta-acetate (**24**). Upon hydrolysis with alkali, **24** gave an epimeric mixture of carboxylic acids which was identical with **6** and which was purified further to give **6a** and **6b**, and a phenolic glycoside which was identical with **7**. The chemical shift of the benzylic protons (δ5.15) indicated the presence of an acylated benzylmethylene in **21**. The structure of **21** was, therefore, revealed to be as shown.



	21	**22**	**23**	**24**
R_1	H	COMe	Me	Me
R_2	H	COMe	H	COMe

In the ^{1}H NMR spectra of **1**, **9**, **14** and **21**, the signals due to the hemiacetal protons of the iridoids and D-glucose were overlapped and the chemical shifts and coupling constants of the protons were not so clear as to permit the determination of the configurations of the anomeric carbons of the iridoid moieties. Also, the possibility that each of these compounds was a mixture of diastereoisomers, could not be excluded. However, all of these compounds may have the β-configuration at C-1 (s) of the loganic and deoxyloganic acid moieties, because each of them gave a single acetate and the iridoids, which have so far been reported as agluconic compounds, were indicated to be β-anomers [5].

The bis-iridoids, in which secoiridoids are included, have so far been isolated from *Cantleya* (Icacinaceae) [6], *Fraxinus* (Oleaceae) [7], *Dipsacus* (Dipsacaceae) [5] and *Erythraea* (Gentianaceae) [8] species and, recently, Uesato *et al.* [9] reported a dimeric iridoid in which the two iridoid moieties are linked through an acetal linkage. Compounds **1**, **9**, and **14** are the first examples of bisiridoids which consist of two intact iridoid aglucones joined through an ester linkage.

EXPERIMENTAL

Isolation. Fresh leaves of *V. urceolatum* (2 kg) were extracted with MeOH (2 × 10 l.). The combined MeOH solns were concd to dryness to afford a dark green residue (210 g). The residue was diluted with H_2O and extracted with Et_2O and then EtOAc. The EtOAc extract was evaporated to dryness (92 g), and the residue was extracted with $CHCl_3$–MeOH (93:7) to give a dark green syrup (37 g). The syrup was chromatographed on a column of Si gel, eluting with $CHCl_3$–MeOH with increasing MeOH content. From the fractions eluted with $CHCl_3$–MeOH (93:7), a monoterpenoid glycoside (130 mg) and **1** (500 mg) were afforded, successively.

The fractions eluted with $CHCl_3$–MeOH (9:1) gave **9** (640 mg), and those eluted with $CHCl_3$–MeOH (8:2) afforded **14** (420 mg) and **21** (400 mg) in succession.

Compound **1**. Amorphous powder from MeOH and Et_2O, mp 136–140°, $[\alpha]_D^{25}$ −56° (MeOH; *c* 0.36), UV λ_{max}^{MeOH} nm (ε): 204 sh (6600), 228 (18 000) and 240 (16 300); IR ν_{max}^{Nujol} cm^{-1}: 3400, 1720, 1635 and 1520; ^{1}H NMR (60 MHz; CD_3COCD_3): δ1.08 (6H, *d*, *J* = 7 Hz, H-10 and H-10′), 4.93 (3H, *m*, H-1, H-1′ and H-1″), 5.02 (2H, *s*, benzyl H), 6.99, 7.30 (4H, A_2B_2, *J* = 10 Hz, Ar-H) and 7.38 (2H, *br s*, H-3 and H-3′). In the ^{1}H NMR spectra of **1**, **9**, **14** and **21**, the signals due to the protons of sugar moieties were seen in the range δ3.40–5.20. (Found: C, 59.58; H, 6.01%. $C_{33}H_{42}O_{14}$ requires: C, 59.84; H, 6.39%.) Acetylation of **1** (80 mg) with Ac_2O–pyridine gave a hexa-acetate (**2**) (90 mg), amorphous, $[\alpha]_D^{25}$ −55° (MeOH; *c* 0.32), UV λ_{max}^{MeOH} nm (ε): 228 (27 700); IR ν_{max}^{Nujol} cm^{-1}: 1770, 1720, 1640 and 1520; ^{1}H NMR (100 MHz; $CDCl_3$): δ1.11 (6H, *br d*, H-10 and H-10′), 2.03, 2.05, 2.12 (6H each, *s*, COMe), 5.93, 6.00 (1H each, *d*, *J* = 3 Hz, H-1 and H-1′), 6.96, 7.34 (4H, A_2B_2, *J* = 9 Hz, Ar-H) and 7.37 (2H, *br s*, H-3 and H-3′). (Found: C, 58.73; H, 5.94%. $C_{45}H_{54}O_{20}$ requires: C, 59.08; H, 5.91%.)

Methanolysis of **1**. Compound **1** (200 mg) was dissolved in 10 ml dry MeOH containing one drop conc. HCl. The soln was stirred at room temp. under N_2 stream; after 12 hr the soln was diluted with H_2O and then extracted with Et_2O. The Et_2O extract was chromatographed over a column of Si gel ($CHCl_3$–MeOH, 97:3) to give an anomeric mixture of the dimethyl ether (**3**), amorphous powder (200 mg), $[\alpha]_D^{25}$ −25° (MeOH; *c* 0.40), UV λ_{max}^{MeOH} nm (ε): 218 (10 000); IR ν_{max}^{film} cm^{-1}: 3400, 1710, 1690, 1630 and 1515; ^{1}H NMR (100 MHz; CD_3COCD_3): δ1.12 (6H, *d*, *J* = 7 Hz, H-10 and H-10′), 3.57–3.60 (total 6H, *s*, OMe-1 and OMe-1′), 5.28 (2H, *s*, benzyl H), 7.35 and 7.65 (4H, A_2B_2, *J* = 10 Hz, Ar-H), and 7.38 (2H, *br s*, H-3 and H-3′). (Found: C, 60.66; H, 6.66%. $C_{35}H_{46}O_{14}$ requires: C, 60.87; H, 6.67%.) Compound **3** (140 mg) was acetylated with Ac_2O–pyridine (each 0.5 ml), worked-up as usual, and the crude product (**4**) was purified by Si gel chromatography ($CHCl_3$–MeOH, 95:5) to give tetra-acetates **4a** and **4b**. Compound **4a** (major product 64 mg), amorphous, $[\alpha]_D^{25}$ +61° (MeOH; *c* 0.18); IR ν_{max}^{film} cm^{-1}: 1770, 1710, 1690, 1630 and 1518; ^{1}H NMR (100 MHz; $CDCl_3$): δ1.04 (6H, *d*, *J* = 8 Hz, H-10 and H-10′), 2.20 (3H × 4, *s*, COMe), 3.38–3.53 (total 6H, *s*, OMe-1 and OMe-1′), 7.00 and 7.40 (4H, A_2B_2, *J* = 10 Hz, Ar-H) and 7.51 (2H, *br s*, H-3 and H-3′). Compound **4b**, amorphous, $[\alpha]_D^{25}$ −4° (MeOH; *c* 0.26); IR ν_{max}^{film} cm^{-1}: 1750, 1695, 1620 and 1500; ^{1}H NMR (100 MHz; $CDCl_3$): δ1.05 (6H, *m*, H-10 and H-10′), 2.05 (3H × 4, *s*, COMe), 3.42–3.48 (total 6H, *s*, OMe-1 and OMe-1′), 6.98 and 7.33 (4H, A_2B_2, *J* = 10 Hz, Ar-H) and 7.45 (2H, *br s*, H-3 and H-3′).

Alkaline hydrolysis of **4a**. Compound **4a** (200 mg) was refluxed with 2 N NaOH (20 ml) and MeOH (20 ml) for 30 min. The soln was acidified with HCl, extracted with Et_2O; the Et_2O extract was washed with H_2O, dried and evaporated to dryness. The residue was chromatographed on a column of Si gel to give oily **5** (55 mg) and **6** (48 mg). The H_2O layer was evaporated to dryness *in vacuo*, and the residue was dissolved in $CHCl_3$–MeOH (4:1) and subjected to CC on Si gel. The fractions eluted with $CHCl_3$–MeOH (4:1) gave a crystalline phenolic glucoside, **7** (35 mg). Compound **5**, IR ν_{max}^{film} cm^{-1}: 2650–2350, 1680 and 1630; ^{1}H NMR (100 MHz; $CDCl_3$): δ1.07 (3H, *d*, *J* = 7 Hz, H-10), 3.42–3.49 (total 3H, *s*, OMe-1), 4.52 and 4.86 (total 1H, *d* each, *J* = 7 and 4 Hz, H-1) and 7.47 (1H, *s*, H-3); MS *m/z* 212.1032 [M]$^+$; $C_{11}H_{16}O_4$ requires, 212.1047. Compound **5** was identical to an authentic sample of an epimeric mixture of 1-*O*-methyldeoxyloganic acid aglycone. Compound **6**, $[\alpha]_D^{25}$ +27.5° ($CHCl_3$; *c* 0.40), was purified further by Si gel chromatography ($CHCl_3$–MeOH, 97:3) to give epimers **6a** and **6b**. Compound **6a**, major epimer, IR ν_{max}^{film} cm^{-1}: 3400, 2650–2400, 1695, 1635 and 1190; ^{1}H NMR (100 MHz; $CDCl_3$): δ1.10 (3H, *d*, *J* = 7 Hz, H-10), 1.60–2.40 (4H, *m*, H-6, H-8 and H-9), 3.10 (1H, *m*, H-5), 3.48 (3H, *s*, OMe-1), 4.12 (1H, *m*, H-7), 4.60 (1H, *d*, *J* = 4 Hz, H-1), 5.20 (OH), 7.51 (1H, *br s*, H-3); MS *m/z* 228.1032 [M]$^+$; $C_{11}H_{16}O_5$ requires, 228.1010. Compound **6a** was methylated with CH_2N_2 in Et_2O to give a methyl ester (10 mg) $[\alpha]_D^{25}$ −23.8° ($CHCl_3$; *c* 0.20); IR ν_{max}^{film} cm^{-1}: 3450, 1705, 1633 and 1180; ^{1}H NMR (60 MHz; $CDCl_3$): δ1.10 (3H, *d*, *J* = 6.5 Hz, H-10), 1.40–2.50 (4H, *m*, H-6, H-8 and H-9), 3.10 (1H, *m*, H-5), 3.45 (3H, *s*, OMe-1), 3.66 (3H, *s*, COMe), 4.08 (1H, *m*, H-7), 4.59 (1H, *d*, *J* = 4 Hz, H-1) and 7.40 (1H, *d*, *J* = 1.5 Hz, H-3); EIMS (70 eV) *m/z* (rel. int.): 242 [M]$^+$ (6), 224 (5), 210 (7), 192 (11), 178 (8), 139 (9), 117 (14) and 85 (100).

These data were coincident with those of authentic (1*R*) 1-*O*-methyl loganin aglycone [2–4]. Compound **6b** (8 mg) IR spectrum differed from that of **6a** only in the range 1100–900 cm^{-1}, ^{1}H NMR (60 MHz; $CDCl_3$): δ1.10 (3H, *d*, *J* = 6.5 Hz, H-10), 3.43 (3H, *s*, OMe-1), 4.94 (1H, *d*, *J* = 3 Hz, H-1) and 7.56 (1H, *d*, *J* = 1 Hz, H-3); methyl ester of **6a** had an optical rotation of +190° ($CHCl_3$; *c* 0.10) and the spectra of the ester were coincident with those of (1*S*) 1-*O*-methyl loganin aglycone in the lit. [2, 3].

1-O-methyl deoxyloganic acid aglycone (**5**) *from deoxyloganin.* Deoxyloganin (226 mg) was dissolved in a buffer soln (NaOAc–HOAc, pH 4.9, 9 ml) and 40 mg β-glucosidase was added; the soln was allowed to stand for 2 days at 38°, then extracted with Et_2O. The Et_2O extract was evaporated to dryness. Deoxyloganin aglycone (98 mg), oil, was afforded after purification by Si gel chromatography, IR ν_{max}^{film} cm^{-1}: 3400, 1720, 1690 and 1630. The aglycone was dissolved in MeOH (2 ml) containing a drop of conc. HCl, stirred at room temp. overnight, then H_2O (20 ml) added. Extraction with Et_2O, and chromatography on a column of Si gel ($CHCl_3$–MeOH, 97:3) gave an ether, oil, (38 mg) IR ν_{max}^{film} cm^{-1}: 1750, 1720 and 1630; ^{1}H NMR (100 MHz; $CDCl_3$): δ1.07 (3H, *d*, *J* = 6 Hz, H-10), 3.48, 3.51 (total 3H, *s*, OMe-1), 3.70 (3H, *s*, COOMe), 4.54, 4.89 (total 1H, *d* each, *J* = 6 and 3 Hz, H-1) and 7.44 (1H, *s*, H-3). This was dissolved in 2 N NaOH (0.5 ml) and MeOH (1.5 ml), refluxed for 45 min and 10 ml H_2O added followed by extraction with Et_2O. The aq. layer was acidified with dil. HCl and extracted with Et_2O. The Et_2O extract was evaporated to dryness and the residue was chromatographed on a column of Si gel ($CHCl_3$–MeOH, 99:1) to

give **5** (8 mg) whose IR and ^{1}H NMR spectra were superimposable with those of the acid (**5**) derived from **3**.

Hydrolysis of **7**. Compound **7**, needles from MeOH–$CHCl_3$, mp 155–156°, IR ν_{max}^{Nujol} cm^{-1}: 3350, 1615 and 1510; ^{1}H NMR (100 MHz; pyridine-d_5): δ3.90–4.60 (6H, *m*, sugar protons), 4.80 (2H, *s*, benzyl H), 5.54 (1H, $W_{1/2}$ = 10 Hz, glucose H-1), 7.31 and 7.41 (4H, A_2B_2, J = 8 Hz, Ar-H). Acetylation of **7** in Ac_2O–pyridine gave a penta-acetate, IR ν_{max}^{film} cm^{-1}: 1740, 1610, 1590 and 1510; ^{1}H NMR (100 MHz; $CDCl_3$): δ2.08 (3H × 5, *s*, COMe), 5.00 (2H, *s*, benzyl H), 6.95 and 7.21 (4H, A_2B_2, J = 8 Hz, Ar-H). Compound **7** (30 mg) was dissolved in 5 ml 2 N HCl, refluxed for 1 hr, and the soln was extracted with Et_2O. The extract was evaporated to dryness and the residue was crystallized from MeOH to give needles (11 mg), mp 125–126° which were identical with authentic *p*-hydroxybenzyl alcohol. The aq. layer was neutralized with Amberlite IR-400, evaporated to dryness and the residue was identified as D-glucose by PC (*n*-BuOH–HOAc–H_2O, 4:1:2, R_f 0.34).

Mild alkaline hydrolysis of **4a**. Compound **4a** (140 mg) in 0.45 N NaOH (5 ml) and MeOH (9 ml) was stirred at 60° for 1 hr. The soln was extracted with Et_2O; the extract was washed with H_2O, dried and evaporated to dryness, to give **8** as an oil (27 mg). The aq. layer was acidified with dil. HCl and extracted with Et_2O; evaporation of the solvent gave an oily acid (**8a**) (26 mg). Compound **8**, IR ν_{max}^{film} cm^{-1}: 1720, 1636, 960 and 860; ^{1}H NMR (60 MHz; $CDCl_3$): δ1.05 (3H, *d*, J = 6 Hz, H-10 or H-10′), 1.07 (3H, *d*, J = 6 Hz, H-10 or H-10′), 3.48, 3.60 [total 6H, two *s*, intensity (4:3), OMe-1 and OMe-1′], 3.72 (3H, *s*, COOMe) and 7.50 (2H, *br s*, H-3 and H-3′). MS *m/z* 436.2118 $[M]^+$; $C_{23}H_{32}O_8$ requires, 436.2097. Compound **8a**, IR ν_{max}^{film} cm^{-1}: 1720, 1700, 1680, 1640 and 960; ^{1}H NMR (100 MHz; $CDCl_3$): δ1.06 (6H, *d*, H-10 and H-10′), 3.48 (6H, *s*, OMe-1 and OMe-1′), 7.38 and 7.50 (1H each, *s*, H-3 and H-3′). Upon methylation with CH_2N_2 in Et_2O, **8a** (10 mg) gave an ester (10 mg) whose IR and ^{1}H NMR spectra were superimposable with those of **8**.

Compound **9**. Prisms from Me_2CO–H_2O, mp 148–152°, $[\alpha]_D^{25}$ −15° (MeOH; *c* 0.30), UV λ_{max}^{MeOH} nm (ε): 246 (11 000); IR ν_{max}^{Nujol} cm^{-1}: 3400, 1720, 1700, 1680 and 1620; ^{1}H NMR (100 MHz; pyridine-d_5): δ0.84 (3H, *d*, J = 7 Hz, H-10 or H-10′), 0.94 (3H, *d*, J = 7 Hz, H-10 or H-10′), 7.54 and 7.58 (each 1H, *s*, H-3 and H-3′) besides signals for sugar protons. (Found: C, 55.00; H, 6.53%. $C_{26}H_{36}O_{13}\cdot 1/2\ H_2O$ requires: C, 55.21; H, 6.59%.) Compound **9** (100 mg) was acetylated with Ac_2O–pyridine (0.5 ml each) at room temp. The crude product was chromatographed on a column of Si gel. Elution with $CHCl_3$–MeOH (99:1) gave a hexa-acetate (**10**) (54 mg) as an amorphous powder mp 85–87°, $[\alpha]_D^{25}$ +71.4° (MeOH; *c* 0.06), IR ν_{max}^{Nujol} cm^{-1}: 1770, 1720, 1640 and 1220; ^{1}H NMR (100 MHz; $CDCl_3$): δ1.10 (6H, *br d*, H-10 and H-10′), 2.00, 2.08, 2.14 (total 18H, *s*, COMe), 5.97, 6.08, 6.30 (1H each, *br d*, J = 3, 2 and 3 Hz, H-1, H-1′, and sugar H-1), 7.31 and 7.37 (1H each, *s*, H-3 and H-3′). (Found: C, 56.37; H, 6.11%. $C_{38}H_{48}O_{19}$ requires: C, 56.43; H, 5.98%.)

Methanolysis of **9**. Compound **9** (100 mg) was dissolved in dry MeOH (3 ml) containing one drop of conc. HCl. The soln was stirred at 60° under a N_2 atmosphere for 1 hr. The soln was diluted with H_2O and extracted with Et_2O. The Et_2O extract was chromatographed on a column of Si gel to give an amorphous powder of **11** (75 mg), IR ν_{max}^{Nujol} cm^{-1}: 3400, 1700 and 1630; ^{1}H NMR (100 MHz; $CDCl_3$): δ1.07 (6H, *d*, J = 6 Hz, H-10 and H-10′), 3.40, 3.48, 3.52 [total 9H, three *s*, (5:3:2), C-1, C-1′ and sugar OMe-1), 7.49 (1H, *s*, H-3 or H-3′) and 7.54 (1H, *br s*, H-3 or H-3′). Compound **11** (62 mg) was acetylated with Ac_2O–pyridine (0.5 ml each) at room temp. to give a tri-acetate (**12**) (53 mg), IR ν_{max}^{Nujol} cm^{-1}: 1760, 1710, 1635 and 1230; ^{1}H NMR (100 MHz; $CDCl_3$): δ1.03 (3H, *d*, J = 7 Hz, H-10 or H-10′), 1.08 (3H, *d*, J = 8 Hz, H-10 or H-10′), 2.00, 2.05, 2.10 (total 9H, *s*, COMe), 3.40, 3.42, 3.46, 3.52 [total 9H, four *s*, (1:2:2:1), C-1, C-1′ and sugar OMe-1] and 7.46 (2H, *s*, H-3 and H-3′).

Alkaline hydrolysis of **12**. Compound **12** (51 mg) was refluxed with 2 N NaOH (2 ml) and MeOH (1.2 ml) for 30 min. The soln was acidified with dil. HCl and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried and concd to dryness. The residue was chromatographed on a column of Si gel to give three oily acids which were identical with **5** (6 mg), **6a** (3 mg) and **6b** (2.5 mg).

Mild alkaline hydrolysis of **12**. Compound **12** (150 mg) was dissolved in MeOH (9 ml) and 0.45 N NaOH (5 ml). The soln was stirred at 62° for 1 hr, extracted with Et_2O; the Et_2O extract was washed with H_2O, dried and evaporated to dryness. The IR and ^{1}H NMR spectra of the purified product (21 mg) were superimposable with those of **8**. From the acidified H_2O layer, 20 mg of the corresponding acid was recovered.

Purdie methylation followed by hydrolysis of **11**. Compound **11** (75 mg) in DMF (1 ml) was stirred with MeI (1 ml) and Ag_2O (200 mg) at 5° for 48 hr in the dark. The soln was diluted with $CHCl_3$ and filtered. The filtrate was evaporated and the residue was chromatographed on a column of Si gel to afford **13** as an oil (72 mg), IR ν_{max}^{film} cm^{-1}: no OH absorption, 1700 and 1625; ^{1}H NMR (60 MHz; $CDCl_3$): δ1.08 (6H, *br d*, H-10 and H-10′), 3.40 (3H × 6, *s*, OMe). Compound **13** (40 mg) in MeOH (1 ml) and 2 N NaOH (1 ml) was refluxed for 1 hr. The soln was acidified and extracted with $CHCl_3$, dried and evaporated to dryness. The residue was chromatographed on a Si gel column to give a mixture of acids and a methylated D-glucose (4 mg) which was identical with an authentic sample of methyl-2,3,6-tri-*O*-methyl D-glucoside by comparison on TLC ($CHCl_3$–MeOH, 97:3, R_f 0.32) and IR and ^{1}H NMR spectra.

Compound **14**. Amorphous powder, mp 134–138°, $[\alpha]_D^{25}$ −42.1° (MeOH; *c* 0.19), UV λ_{max}^{MeOH} nm (ε): 228 (11 000) and 238 sh (10 350); IR ν_{max}^{Nujol} cm^{-1}: 3400, 1695, 1633 and 1518; ^{1}H NMR (60 MHz; CD_3COCD_3): δ1.07 (6H, *br d*, J = 6 Hz, H-10 and H-10′), 5.07 (2H, *s*, benzyl H), 7.00, 7.36 (4H, A_2B_2, J = 9 Hz, Ar-H) and 7.44 (2H, *br s*, H-3 and H-3′). (Found: C, 58.48; H, 6.46%. $C_{33}H_{42}O_{15}$ requires: C, 58.40; H, 6.24%.) Acetylation of **14** (100 mg) in Ac_2O–pyridine (1 ml each) afforded a hepta-acetate (**15**) (95 mg), amorphous, mp 88–89°, $[\alpha]_D^{25}$ −22.5° (MeOH; *c* 0.20); IR ν_{max}^{Nujol} cm^{-1}: 1765, 1720, 1638 and 1515; ^{1}H NMR (60 MHz; $CDCl_3$): δ1.05 (6H, *br d*, J = 6 Hz, H-10 and H-10′), 2.04 (3H × 5, *s*, COMe), 2.09 (3H × 2, *s*, COMe), 6.07 (2H, *d*, J = 3 Hz, H-1 and H-1′), 7.00, 7.33 (4H, A_2B_2, J = 9.5 Hz, Ar-H) and 7.38 (2H, *br d*, J = 1.5 Hz, H-3 and H-3′). (Found: C, 57.65; H, 6.08%. $C_{47}H_{56}O_{22}$ requires: C, 58.02; H, 5.76%.)

Methanolysis of **14**. Compound **14** (85 mg) was dissolved in dry MeOH (6 ml), two drops of conc. HCl added and the mixture allowed to stand for 20 hr. The soln was diluted with H_2O and extracted with EtOAc, washed with H_2O, dried and evaporated to dryness *in vacuo*. The residue was chromatographed on a column of Si gel, to give a mixture of diastereoisomers of dimethyl ether (**16**), $[\alpha]_D^{25}$ −62.5° (MeOH; *c* 0.40), IR ν_{max}^{Nujol} cm^{-1}: 3450, 1718, 1635 and 1517; ^{1}H NMR (60 MHz; CD_3COCD_3): δ1.07 (6H, *br d*, J = 6 Hz, H-10 and H-10′), 3.39, 3.41, 3.44 (total 6H, *s*, OMe-1 and OMe-1′), 5.08 (2H, *s*, benzyl H), 7.14, 7.33 (4H, A_2B_2, J = 9.5 Hz, Ar-H) and 7.50 (2H, *d*, J = 1.5 Hz, H-3 and H-3′). (Found: C, 59.45; H, 6.55%. $C_{35}H_{46}O_{15}$ requires: C, 59.49; H, 6.52%.) Acetylation of **16** (38 mg) in Ac_2O–pyridine (0.5 ml each) gave a penta-acetate (**17**) (mixture, 40 mg), amorphous, IR ν_{max}^{Nujol} cm^{-1}: 1763, 1715, 1638 and 1517; ^{1}H NMR (60 MHz; $CDCl_3$): δ1.07 (6H, *d*, J = 6.5 Hz, H-10 and H-10′), 2.05 (3H × 5, *s*, COMe), 3.40, 3.46, 3.48 (total 6H, *s*, OMe-1 and OMe-1′), 4.63, 4.90 (total 2H, *d*, J = 4.5 and 3 Hz, H-1 and H-1′), 7.14, 7.33 (4H, A_2B_2, J = 9.5 Hz, Ar-H) and 7.48 (2H, *d*, J = 1.5 Hz, H-3 and H-3′).

Hydrolysis of **16**. Compound **16** (60 mg) in MeOH (2 ml) and 2 N NaOH (8 ml) was refluxed for 1 hr, diluted with H_2O and acidified with 10% HCl (congo red), extracted with EtOAc, washed with H_2O (twice), dried and evaporated to dryness. The residue (33 mg) was chromatographed on a column of Si gel, to give an acid (24 mg) which was identical with **6a** together with a small amount of an acid identical with **6b**. The H_2O layer was worked-up as described above to give a glucoside (15 mg) identical with **7**.

Purdie methylation of **16**. Compound **16** (100 mg) was dissolved in DMF (4 ml) and 1 g Ag_2O and 0.8 ml MeI added. The mixture was stirred for 2 days in the dark, a small amount of $CHCl_3$ added and the mixture filtered. The filtrate was worked-up as described for the methylation of **3**. On Si gel chromatography, fractions eluted with $CHCl_3$ gave a hepta-methyl ether (**18**) (25 mg), and fractions eluted with $CHCl_3$–MeOH (97:3) afforded a hexa-methyl ether (**19**) (60 mg). Compound **18**, amorphous, IR ν_{max}^{film} cm^{-1}: no OH absorption, 1720, 1635, and 1513; ^1H NMR (60 MHz; $CDCl_3$): δ1.03 (6H, *br d*, J = 5.5 Hz, H-10 and H-10′), 3.32, 3.39, 3.44, 3.49 (3H each, *s*, OMe), 3.59 (9H, *s*, OMe), 5.02 (2H, *s*, benzyl H), 7.01, 7.33 (4H, A_2B_2, J = 9 Hz, Ar-H), and 7.41 (2H, *d*, J = 1.5 Hz, H-3 and H-3′). Compound **19**, IR ν_{max}^{neat} cm^{-1}: 3450, 1710, 1622 and 1510; ^1H NMR (60 MHz; $CDCl_3$): δ1.02, 1.10 (3H each, *d*, J = 6 Hz, H-10 and H-10′), 3.36, 3.43, 3.46, 3.51 (3H each, *s*, OMe), 3.60 (6H, *s*, OMe), 5.05 (2H, *s*, benzyl H), 7.04, 7.32 (4H, A_2B_2, J = 9.5 Hz, Ar-H) and 7.39 (2H, *br d*, H-3 and H-3′).

Alkaline hydrolysis of **18**. Upon hydrolysis in 2 N NaOH (1 ml) and MeOH (1 ml), compound **18** (25 mg) gave a mixture of two acids (13 mg) and a phenolic glycoside (**20**) (9 mg). The mixture of the acids was separated further by chromatography on a column of Si gel to give **6** and an acid (**6′**) which was identified as 1,7-di-*O*-methyl loganic acid aglycone (anomeric mixture). Compound **6′**, IR ν_{max}^{film} cm^{-1}: 3200–2400, 1680, 1630 and 1190; ^1H NMR (60 MHz; $CDCl_3$): δ1.02 (3H, *br d*, J = 6 Hz, H-10), 3.21, 3.43 (total 6H, *s*, OMe), 4.5–5.1 (total 2H, *m*, H-1 and H-7), and 7.53 (1H, *br s*, H-3); EIMS (70 eV) *m/z* (rel. int.): 242 $[M]^+$ (3), 224 (1), 211 (3), 210 (5), 139 (16) and 85 (100). Compound **20**, amorphous, IR ν_{max}^{Nujol} cm^{-1}: 3460, 1613, 1510 and 1090; ^1H NMR (60 MHz; $CDCl_3$): δ3.19, 3.50, 3.62 (total 12H, *s*, OMe), 3.0–3.8 (6H, glucose protons), 4.59 (2H, *s*, benzyl H), 4.90 (1H, *m*, glucose H-1), 7.02 and 7.28 (4H, A_2B_2, J = 10 Hz, Ar-H). Compound **20** (8 mg) was refluxed in 2 N NaOH (1 ml) and MeOH (0.5 ml) for 1 hr. Work-up as usual gave *p*-hydroxybenzyl alcohol (mp 125–126°) and a methylated D-glucose which was identical with an authentic sample of 2,3,4,6-tetra-*O*-methyl-D-glucose by comparison of IR and ^1H NMR spectra and TLC (Si gel, $CHCl_3$–MeOH 90:10; R_f 0.70).

Alkaline hydrolysis of **19**. Compound **19** (50 mg) was dissolved in 2 N NaOH (1 ml) and MeOH (1 ml), refluxed for 1 hr and worked-up as above. The product was subjected to chromatography on Si gel ($CHCl_3$–MeOH, 97:3) to give a phenolic glucoside (16 mg) which was identical with **20**. The H_2O layer was acidified with 10% HCl and extracted with Et_2O. The Et_2O extract was evaporated to give an acid (32 mg) which was identical with **6**, and afforded **6a** and **6b** by further purification.

Compound (**21**). Hygroscopic powder, mp 153–161°, $[\alpha]_D^{25}$ −42.5° (MeOH; *c* 0.2), UV λ_{max}^{MeOH} nm (ε): 236 (6550); IR ν_{max}^{Nujol} cm^{-1}: 3400, 1700, 1632 and 1517; ^1H NMR (60 MHz; CD_3COCD_3): δ1.10 (3H, *d*, J = 6 Hz, H-10), 1.40–2.50 (4H), 5.15 (2H, *s*, benzyl H), 7.19, 7.47 (4H, A_2B_2, J = 9 Hz, Ar-H) and 7.57 (1H, *s*, H-3). (Found: C, 57.53; H, 6.57%. $C_{23}H_{30}O_{11}$ requires: C, 57.25; H, 6.26%.) Acetylation of **21** with Ac_2O–pyridine gave a hexa-acetate (**22**), amorphous, mp 67–72°, $[\alpha]_D^{25}$ −26.9° (MeOH; *c* 0.27), IR ν_{max}^{Nujol} cm^{-1}: 1765, 1720, 1640 and 1518; ^1H NMR (60 MHz; $CDCl_3$): δ1.05 (3H, *d*, J = 6 Hz, H-10), 2.05 (15H, *s*, COMe) 2.09 (3H, *s*, COMe), 3.10 (1H, *m*, H-5), 5.10 (2H, *s*, benzyl H), 6.05 (1H, *d*, J = 3 Hz, H-1), 6.99, 7.27 (4H, A_2B_2, J = 9 Hz, Ar-H) and 7.35 (1H, *d*, J = 1.5 Hz, H-3). (Found: C, 57.27; H, 5.92%. $C_{35}H_{42}O_{17}$ requires: C, 57.22; H, 5.72%.)

Methanolysis of **21**. Compound **21** (100 mg) in MeOH (10 ml) containing one drop of conc. HCl was allowed to stand for 20 hr. The soln was worked-up as described above to yield 80 mg methyl ether (**23**), $[\alpha]_D^{25}$ +45° (MeOH; *c* 0.30), IR ν_{max}^{Nujol} cm^{-1}: 3400, 1708, 1680, 1635, 1518 and 1080; ^1H NMR (60 MHz; CD_3COCD_3): δ1.09 (3H, *d*, J = 6 Hz, H-10), 3.41, 3.46 (total 3H, *s*, OMe-1), 4.78, 5.08 (total 1H, *d*, J = 4 and 2.5 Hz, H-1), 5.20 (2H, *s*, benzyl H), 7.13 and 7.51 (4H, A_2B_2, J = 9 Hz Ar-H). Compound **23** (80 mg) was acetylated in Ac_2O–pyridine (0.5 ml each) to give a penta-acetate mono-methyl ether (**24**) (75 mg), amorphous, IR ν_{max}^{Nujol} cm^{-1}: 1770, 1718, 1637 and 1516; ^1H NMR (60 MHz; $CDCl_3$): δ1.01 (3H, *d*, J = 6.5 Hz, H-10), 2.02 (15H, *s*, COMe), 3.36, 3.44 (total 3H, *s*, OMe-1), 4.57, 4.86 (total 1H, *d*, J = 4 and 3 Hz, H-1) 6.96, 7.29 (4H, A_2B_2, J = 10 Hz, Ar-H) and 7.41 (1H, *br s*, H-3). (Found: C, 58.15; H, 6.14. $C_{34}H_{42}O_{16}$ requires: C, 57.79; H, 5.95%.)

Alkaline hydrolysis of **24**. Compound **24** (60 mg) was hydrolysed in 2 N NaOH (2 ml) and MeOH (1.5 ml) and worked-up as described for the hydrolysis of **3** to yield a single acidic product (22 mg) which was identical with **6** and a glucoside (26 mg) which was identical with **7**.

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