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IRIDOID AND PHENOLIC GLYCOSIDES FROM *HARPAGOPHYTUM PROCUMBENS*

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Key Word Index—*Harpagophytum procumbens*; Pedaliaceae; iridoid and phenolic glycosides; synthesis.

Abstract—A novel bioside, β-(3′,4′-dihydroxyphenyl)ethyl-*O*-α-L-rhamnopyranosyl(1 → 3)-β-D-glucopyranoside, was obtained from the secondary roots of *Harpagophytum procumbens*. It is accompanied by the known iridoid glucosides harpagoside, procumbide, and its 6′-*O*-*p*-coumaroyl ester, and phenolic glycosides, acteoside and isoacteoside, the latter pair being obtained from *H. procumbens* for the first time. The structures of these metabolites were differentiated by high resolution NMR studies, while that of the bioside is additionally supported by synthesis.

INTRODUCTION

The utilization of *Harpagophytum procumbens* DC. (devil's claw), indigenous to the Kalahari Desert and Namibian Steppes of Southern Africa, as an anti-arthritic and general detoxifying remedy in the folk medicine [1, 2] of the native Africans of Namibia, initiated numerous chemical [3–5] and pharmacological [6, 7] investigations of the constituents of its secondary roots. Our re-investigation was directed mainly at the phenolic contents.

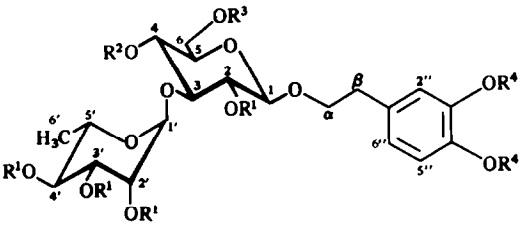
RESULTS AND DISCUSSION

The acetone extract of the dried secondary roots afforded the known iridoid glucosides, harpagoside [8–10], procumbide [11–14] and 6′-*O*-*p*-coumaroylprocumbide [15], and phenolic glycosides, acteoside **1** [16–20] (≡ verbascoside [19] ≡ kusaginin [21]) and isoacteoside **3** [18, 22]. The latter two metabolites were obtained from *H. procumbens* for the first time and were identified by means of ^{1}H NMR studies [*cf.* 18, 20, 22] at 500 MHz of their respective methyl ether acetates **2** and **4** (Table 1). Allocation of carbon signals was effected by ^{1}H–^{13}C heteronuclear correlations at 300 MHz (Table 2).

These compounds are accompanied by the novel bioside, β-3′,4′-(dihydroxyphenyl)ethyl-*O*-α-L-rhamnopyranosyl(1 → 3)-β-D-glucopyranoside **6** ($C_{20}H_{30}O_{12}$), which was identified as methyl ether acetate **7** by means of spectroscopic methods. 80 MHz ^{1}H NMR spectra of the bioside **6** revealed a strong resemblance to those of acteoside and isoacteoside lacking, however, the *trans*-caffeoyl moiety. ^{1}H NMR data (Table 1) at 300 MHz of the methyl ether acetate **7** confirmed an α-L-rhamnopyranosyl (δ4.79, J = 1.5 Hz, anomeric H; δ1.11, d, J = 6.3 Hz, 6′-Me) and β-D-glucopyranosyl unit (δ4.38, d, J = 8.0 Hz, anomeric H). Linkage of the rhamnosyl fragment to C-3 of the glucosyl moiety is defined by the chemical shift of H-3 (δ3.76, t, J = 9.5 Hz) to higher field than those at the remaining *O*-acylated glycosidic C-atoms (δ5.13–4.96). Non-equivalence of the α-methylene protons (δ3.61 and 4.08, both dt, J = 7.0, 9.5 Hz) of the phenethyl unit, results from their proximity to the C-1 chiral centre and the exoanomeric effect [*cf.* 18].

The close structural relationship between the bioside **6**, acteoside **1**, and isoacteoside **3** was demonstrated by mild alkaline hydrolysis of the methyl ether of isoacteoside **5** which afforded methyl-(3,4-di-*O*-methyl)caffeate and the methyl ether acetate **7** of the bioside following acetylation of the aqueous residue. Their co-existence in *H. procumbens* presumably reflects the biosynthetic formation of acteoside and isoacteoside from the bioside, while the established [23] physiological activity of the former pair may contribute to the claimed medicinal properties of the root extract.

Final proof for the position of linkage of the 3,4-dimethoxyphenethyl and α-L-rhamnopyranosyl entities to the central glucopyranosyl unit in bioside **6** was provided by synthesis (Scheme 1). Protection of the 1-, 2-, 4- and 6-hydroxyl groups of α-D-glucopyranose **8** afforded the di-*O*-isopropylidene derivative **9** [24] *via* ring contraction. Benzylation afforded the 3-*O*-benzyl analogue **10** [25, 26] which was transformed into an anomeric mixture (45% α: 55% β) of the tetra-*O*-acetylglucopyranoside **11** following successive cleavage with acidic methanol [27]



1 $R^1 = R^3 = R^4 = H$, $R^2 = t$-caffeoyl
2 $R^1 = R^3 = Ac$, $R^4 = Me$, $R^2 = t$-di-*O*-methylcaffeoyl
3 $R^1 = R^2 = R^4 = H$, $R^3 = t$-caffeoyl
4 $R^1 = R^2 = Ac$, $R^4 = Me$, $R^3 = t$-di-*O*-methylcaffeoyl
5 $R^1 = R^2 = H$, $R^4 = Me$, $R^3 = t$-di-*O*-methylcaffeoyl
6 $R^1 = R^2 = R^3 = R^4 = H$
7 $R^1 = R^2 = R^3 = Ac$, $R^4 = Me$

Table 1. ^{1}H NMR peaks (ppm) of phenolic glycoside methyl ether acetates 2,* 4* and 7† in $CDCl_3$. Splitting patterns and J values (Hz) are given in parentheses

	H	Acteoside 2	Isoacteoside 4	Bioside 7
Glucosyl	1	4.37 (*d*, 8.0)	4.39 (*d*, 8.0)	4.38 (*d*, 8.0)
	2	5.04 (*dd*, 8.0, 9.5)	5.05 (*dd*, 8.0, 9.5)	5.01 (*dd*, 8.0, 9.5)
	3	3.83–3.73 (*m*, overlapping OMe)	3.77 (*t*, 9.5)	3.76 (*t*, 9.5)
	4	5.18 (*t*, 9.5)	5.12 (*t*, 9.5)	5.06 (*t*, 9.5)
	5	3.60 (*dq*, 2.5, 10.0)	3.60 (*dq*, 2.5, 10.0)	3.54 (*dq*, 2.5, 10.0)
	6	4.15 (*dd*, 4.5, 12.5)	4.29 (*dd*, 2.5, 12.5)	4.21 (*dd*, 4.5, 12.5)
		4.11 (*dd*, 3.0, 12.5)	4.24 (*dd*, 4.5, 12.5)	4.09 (*dd*, 2.5, 12.5)
Rhamnosyl	1′	4.81 (*d*, 2.0)	4.79 (*d*, 2.0)	4.79 (*d*, 1.5)
	2′	5.02 (*dd*, 2.0, 3.3)	5.05 (*dd*, 2.0, 3.3)	5.08–5.03 (*m*)
	3′	5.08 (*dd*, 3.3, 10.0)	5.08 (*dd*, 3.3, 10.0)	5.08–5.03 (*m*)
	4′	4.90 (*t*, 10.0)	4.89 (*t*, 10.0)	4.97 (*t*, 9.5)
	5′	3.89–3.83 (*m*)	3.88–3.81 (*m*)	3.88–3.80 (*m*)
	6′-Me	1.02 (*d*, 6.3)	1.12 (*d*, 6.3)	1.11 (*d*, 6.3)
Phenethyl	2″	6.69 (*d*, 1.5)	6.70 (*d*, 1.5)	6.73 (*d*, 1.5)
	5″	6.74 (*d*, 8.0)	6.73 (*d*, 8.0)	6.79 (*d*, 8.0)
	6″	6.68 (*dd*, 1.5, 8.0)	6.69 (*dd*, 1.5, 8.0)	6.72 (*dd*, 1.5, 8.0)
	α	4.04 (*dt*, 7.0, 9.5)	4.06 (*dt*, 7.0, 9.5)	4.08 (*dt*, 7.0, 9.5)
		3.58 (*dt*, 7.0, 9.5)	3.62 (*dt*, 7.0, 9.5)	3.61 (*dt*, 7.0, 9.5)
	β	2.78 (*t*, 7.0)	2.81 (*t*, 7.0)	2.82 (*t*, 6.8)
t-Caffeoyl	2‴	6.97 (*d*, 1.5)	6.99 (*d*, 1.5)	
	5‴	6.81 (*d*, 8.0)	6.84 (*d*, 8.0)	
	6‴	7.04 (*dd*, 1.5, 8.0)	7.06 (*dd*, 1.5, 8.0)	
	α	6.22 (*d*, 16.0)	6.21 (*d*, 16.0)	
	β	7.60 (*d*, 16.0)	7.63 (*d*, 16.0)	
OMe		3.86, 3.85, 3.84, 3.80 (each *s*)	3.90, 3.89, 3.84, 3.80 (each *s*)	3.89, 3.85 (each *s*)
OAc		2.04, 2.03, 1.94, 1.88, 1.81 (each *s*)	2.10, 2.08, 1.998, 1.995, 1.93 (each *s*)	2.19, 2.05, 1.99, 1.98, 1.92 (× 2) (each *s*)

*500 MHz.
†300 MHz.

and acetylation. Due to the anomeric effect [28, 29], treatment of **11** with hydrogen bromide in acetic acid [30] afforded the 3-*O*-benzyl-1-bromo-α-D-glucopyranoside **12** which was immediately etherified with 3,4-dimethoxyphenethyl alcohol by a standard Koenigs–Knorr type reaction [31] to give the β-D-glucoside **13** (δ4.38, *d*, J = 8.0 Hz, H-1). Debenzylation of the latter followed by condensation with the 1-bromo-α-L-rhamnopyranoside‡ **15** and subsequent acetylation, afforded the bioside **7**, identical to the corresponding derivative of the natural product.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded at 80, 300 and 500 MHz in $CDCl_3$ and acetone-d_6 with TMS as reference. CD spectra were determined in MeOH. Media used for the separation of components were: Whatman No. 3 for PC, DC-Plastikfolin Kieselgel 60 F_{254} 0.25 mm for TLC and Kieselgel PF_{254} (1 mm, 20 × 20 cm) for prep. TLC. TLC bands were located under UV and/or H_2SO_4–HCHO (40:1) spray reagent. Prep. TLC bands were stripped with Me_2CO and those from PC with 70% aq. EtOH. Methylations were performed with excess CH_2N_2 over 48 hr at −15° and acetylations in Ac_2O–pyridine. Analyses were performed by Analytische Laboratorien, Fritz-Pregl-Strasse 24, 5270 Gummersbach 1 Elbach, West Germany.

Extractions and fractionation of iridoid and phenolic glycosides. The finely powdered root slices (1 kg) was de-waxed with *n*-hexane (1 × 3 l. 12 hr) and successively extracted with ether (1 × 3 l. 12 hr), EtOAc (1 × 3 l. 12 hr), Me_2CO (1 × 3 l. 12 hr) and MeOH (2 × 3 l. 24 hr) in a Soxhlet apparatus. The ether (27.23 g) and EtOAc (2.13 g) extracts did not contain phenolic substances ($AgNO_3$ and benzidine spray reagents on 2D paper chromatograms) and were not further investigated. A portion (11.3 g) of the acetone extract (18.4 g) was chromatographed on Sephadex LH-20 in EtOH to give fractions A (3.3 g, RR_t 55.4 hr), B (1.27 g, RR_t 70.9 hr), C (0.99 g, RR_t 87.2 hr) and D (4.06 g, RR_t 113.9 hr). Rechromatography [silica gel, $CHCl_3$–MeOH (3:1)] of fraction A afforded fractions Aa (2.46 g, RR_t 19.4 hr) and Ab (346 mg, RR_t 42.7 hr). The Aa fraction consisted of harpagoside and the Ab fraction of procumbide.

A portion (700 mg) of fraction B was separated by prep. TLC in $CHCl_3$–EtOH (2:1) to give two bands at R_f 0.50 (18 mg) and 0.33 (278 mg). The R_f 0.50 fraction afforded 6′-*O*-*p*-coumaroyl procumbide [15] as an amorphous solid.

The R_f 0.33 band afforded β-(3′,4′-dihydroxyphenyl) ethyl-*O*-α-L-rhamnopyranosyl(1 → 3)-β-D-glucopyranoside **6** as an amorphous solid; ^{1}H NMR (80 MHz, acetone-d_6): δ6.80 (1H, *d*, J

‡Prepared by successive acetylation (acetic anhydride–pyridine) and bromination (HBr–acetic acid) of α-L-rhamnopyranoside [30].

Table 2. ^{13}C NMR (75.432 MHz) peaks (ppm) of phenolic glycoside methyl ether acetates **2**, **4** and **7** in $CDCl_3$

	C	Acteoside **2**	Isoacteoside **4**	Bioside **7**
Glucosyl	1	100.78	100.92	100.86
	2	72.24	71.56	71.44
	3*	80.41	81.62	81.56
	4	69.22	69.69	69.48
	5	72.03	72.07	71.93
	6	62.33	62.14	62.05
Rhamnosyl	1′	98.88	99.54	99.48
	2′	70.08	69.83	69.79
	3′	68.47	68.75	68.73
	4′	70.69	70.54	70.49
	5′*	67.14	67.47	67.45
	6′	17.55	17.32	17.27
Phenethyl	α	70.69	70.80	70.76
	β	35.63	35.69	35.63
	1″	131.01	130.97	130.99
	2″	112.33	112.33	112.33
	3″†	148.55	148.59	148.57
	4″†	147.32	147.35	147.33
	5″	111.04	111.07	111.04
	6″	120.64	120.68	120.65
t-Caffeoyl	CO	165.32	166.71	
	α	114.22	114.92	
	β	146.21	145.39	
	1‴	126.77	127.14	
	2‴	109.54	109.49	
	3‴‡	151.35	151.12	
	4‴‡	149.08	149.07	
	5‴	110.92	110.87	
	6‴	122.76	122.88	
OMe		55.85 (×4)	55.89 (×4)	55.85 (×2)
$OCOCH_3$		20.90, 20.86, 20.65 (×3)	21.17, 20.99, 20.85, 20.69 (×2)	21.11, 20.96, 20.84 (×2), 20.65
$OCOCH_3$		170.61, 169.82 (×2) 169.32, 169.19	170.02, 169.89, 169.42, 169.31, 169.26	170.65, 170.00, 169.88, 169.39, 169.25 (×2)

*Distinguished by means of single frequency heteronuclear decoupling of the 6′-methyl protons leading to pronounced sharpening of the 5′-C.

†The shifts for the C-3″ and C-4″ resonances may be reversed.

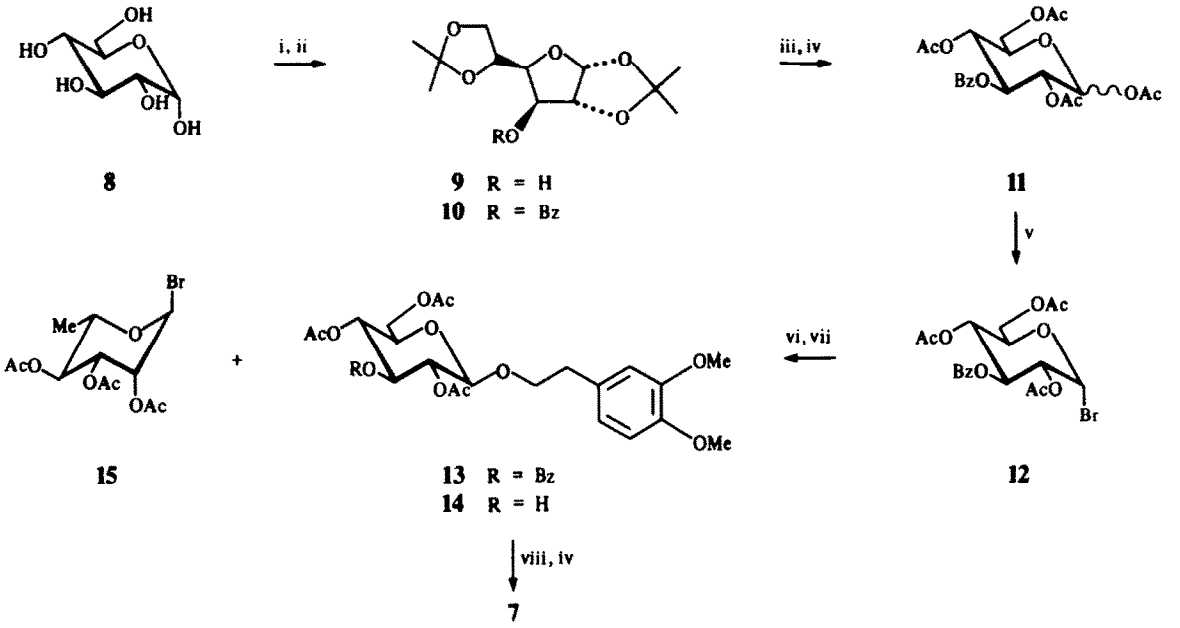
‡The shifts for the C-3‴ and C-4‴ resonances may be reversed.

= 1.8 Hz, H-2″), 6.75 (1H, *d*, *J* = 8.25 Hz, H-5″), 6.58 (1H, *dd*, *J* = 1.8, 8.25 Hz, H-6″), 5.20 (1H, *br s*, H-1′), 4.38 (1H, *d*, *J* = 7.5 Hz, H-1), 4.25–3.00 (12H, *m*, H-glycosidic + CH_2-α), 2.64 (2H, *t*, *J* = 7.25 Hz, H-β), and 1.23 (3H, *d*, *J* = 7.5 Hz, CH_3-6′). The bioside **6** (111 mg) was successively methylated and acetylated. Prep. TLC in hexane–Me_2CO–EtOAc (11:6:3) afforded the di-*O*-methyl hexa-*O*-acetyl derivative **7** (80 mg, R_f 0.36) of the bioside as a light yellow solid (found: C, 54.8; H, 6.0; $C_{34}H_{46}O_{18}$ requires: C, 55.0; H, 6.3%); ^{1}H and ^{13}C NMR (Tables 1 and 2, resp.); CD (*c* 0.0892): $[\theta]_{280}$ 0, $[\theta]_{260}$ 5400, $[\theta]_{240}$ 4400, and $[\theta]_{230}$ 0.

Fraction C consisted of a mixture of the compounds in fractions B and D and was not further investigated.

Separation of fraction D (4.06 g) by PC (2% aq. HOAc) gave two bands at R_f 0.63 (1.14 g) and 0.39 (2.19 g). The R_f 0.63 fraction gave β-(3′,4′-dihydroxyphenyl)ethyl-*O*-α-L-rhamnopyranosyl(1 → 3)-β-D-4-(*O*-caffeoyl)glucopyranoside **1** (acteoside) as a solid. ^{1}H NMR (80 MHz, acetone-d_6): δ 7.63 [1H, *d*, *J* = 16.0 Hz, H-β(vinylic)], 7.28–6.50 (6H, *m*, aromatic), 6.33 [1H, *d*, *J* = 16.0 Hz, H-α (vinylic)], 5.31 (1H, *s*, H-1′), 5.19–3.27 (13H, *m*, H-glycosidic + CH_2-α), 2.63 (2H, *t*, *J* = 6.25 Hz, CH_2-β), and 1.08 (3H, *d*, *J* = 6.25 Hz, CH_3-6′). Acteoside **1** (215 mg) was methylated and the mixture separated by prep. TLC in $CHCl_3$–EtOH (2:1) to give a band at R_f 0.25 (121 mg). A portion (90 mg) of this fraction was acetylated and subsequently separated by prep. TLC in hexane–Me_2CO–EtOAc (12:3:5) to give the tetra-*O*-methyl penta-*O*-acetyl derivative **2** (90 mg, R_f 0.21) as an amorphous solid (found: C, 57.9; H, 6.0; calc. for $C_{43}H_{54}O_{20}$: C, 58.0; H, 6.1%); ^{1}H and ^{13}C NMR (Tables 1 and 2); CD (*c* 0.1412): $[\theta]_{369}$ 0, $[\theta]_{318}$ −788 700, $[\theta]_{305}$ −649 900, $[\theta]_{290}$ −750 800, $[\theta]_{260}$ −107 300, and $[\theta]_{233}$ 0.

The R_f 0.39 fraction afforded β-(3′,4′-dihydroxyphenyl)ethyl-*O*-α-L-rhamnopyranosyl(1 → 3)-β-D-(6-*O*-caffeoyl)glucopyranoside **3** (isoacteoside) as an amorphous solid; ^{1}H NMR (80 MHz, acetone-d_6): 7.55 [1H, *d*, *J* = 16.0 Hz, H-β (vinylic)], 7.19–6.42 (6H, *m*, aromatic), 6.28 [1H, *d*, *J* = 16.0 Hz, H-α (vinylic)], 5.90–3.28 (13H, *m*, H-glycosidic + CH_2-α), 5.20 (1, *br s*, H-1′), 2.70 (2H, *t*, *J* = 6.25 Hz, CH_2-β), and 1.20 (3H, *d*, *J* = 6.25 Hz, CH_3-6′). Methylation of isoacteoside **3** (200 mg) followed by prep. TLC in C_6H_6–Me_2CO–MeOH (6:3:1) gave the tetra-*O*-methyl ether **5** (161 mg, R_f 0.32) which on acetylation (50 mg) and prep. TLC in C_6H_6–Me_2CO (4:1 × 2) afforded the



Reagents: (i) $(CH_3)_2CO-ZnCl_2-H_3PO_4$; (ii) BzCl–KOH; (iii) MeOH–1M H_2SO_4; (iv) Ac_2O–pyridine; (v) HBr–HOAc; (vi) β-(3,4-dimethoxyphenyl)ethanol–$Ag_2O-CaSO_4$–dry $CHCl_3$; (vii) H_2–Pd/C; (viii) $HgBr_2-Hg(CN)_2$–dry CH_3CN

Scheme 1.

tetra-*O*-methyl penta-*O*-acetyl derivative **4** (30 mg, R_f 0.35) as an amorphous solid (found: C, 57.8; H, 5.9; $C_{43}H_{54}O_{20}$ requires: C, 58.0; H, 6.1%); ^1H and ^{13}C NMR (Tables 1 and 2, resp.); CD (*c* 0.1412): $[\theta]_{358}$ 0, $[\theta]_{321}$ 17000, $[\theta]_{300}$ 10700, $[\theta]_{290}$ 13900, and $[\theta]_{250}$ 0.

Alkaline hydrolysis of isoacteoside **5**. The tetra-*O*-methyl ether of isoacteoside **5** (84.6 mg) was stirred in a 0.5% solution of NaOMe in MeOH (5 ml) at room temp. for 1 hr. The solvent was evaporated and the mixture resolved by prep. TLC in $C_6H_6-Me_2CO$ (7:3) to give two bands at R_f 0.75 (4.2 mg) and 0.25 (46.5 mg). The former fraction afforded methyl-(3,4-di-*O*-methyl)caffeate as a brown solid. Acetylation of the R_f 0.25 band gave the tetramethyl hexa-*O*-acetyl derivative **7** (59.2 mg) of the bioside **6**, identical to that of the natural product [^1H NMR (Table 1)].

Synthesis of the methyl ether acetate **7** *of the bioside* **6**. α-D-Glucose (40.5 g) was converted into the 1:2,5:6-di-*O*-isopropylidene derivative **9** (20.5 g, mp 110–111° [from $CHCl_3$–hexane (2:1)], lit. [24] mp 105–109°) according to the standard lit. [24] procedure. This derivative (5 g), benzyl chloride (24.4 g), and KOH (16.2 g) was heated at 130–150° for 2 hr. The mixture was cooled, diluted with H_2O (100 ml) and extracted with $CHCl_3$ (5 × 100 ml). The combined extract was washed with H_2O (5 × 200 ml), dried (Na_2SO_4) and evaporated to dryness. CC [silica gel; $C_6H_6-Me_2CO$ (9:1)] afforded the 3-*O*-benzyl analogue [25, 26] **10** (6.41 g) as a light yellow viscous syrup. ^1H NMR (80 MHz, $CDCl_3$): δ 7.32 (5H, *s*, aromatic), 5.90 (1H, *d*, *J* = 4.25 Hz, 1-H), 4.66 (2H, *s*, CH_2), 4.57 (1H, *d*, *J* = 4.25 Hz, H-2), 4.50–3.88 (4H, *m*, H-3,4,5,6), and 1.49, 1.42, 1.38, 1.29 (12H, 4 × *s*, 4 × Me). The 3-*O*-benzyl-di-*O*-isopropylidene-α-D-glucose **10** (10 g) was refluxed for 4 hr in MeOH (20 ml) containing 1 M H_2SO_4 (10 ml) [27]. The mixture was neutralized with 5% $NaHCO_3$ solution and evaporated to dryness. The residue was dissolved in dry MeOH, filtrated and the MeOH removed under red. press. Acetylation followed by prep. TLC in hexane–$C_6H_6-Me_2CO$ (13:4:3) afforded an anomeric mixture (45% α: 55% β) of the 3-*O*-benzyl-tetra-*O*-acetyl glucopyranoside **11** (6.57 g, R_f 0.20), ^1H NMR (80 MHz, $CDCl_3$): δ 6.30 [1H, *d*, *J* = 3.75 Hz, H-1 (α-anomer)], and 5.63 [1H, *d*, *J* = 8.25 Hz, H-1 (β-anomer)]. This mixture (2.01 g) was reacted for 30 min at 0° with a satd soln of HBr in HOAc (40 ml) [30]. After a further 2 hr at room temp., the mixture was poured into ice/H_2O (500 ml) and extracted with $CHCl_3$ (3 × 100 ml). The $CHCl_3$ was dried (Na_2SO_4, × 2) and removed under reduced pressure at 35°. CC [silica gel; hexane–Me_2CO–EtOAc (11:6:3)] afforded 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-1-bromo-α-D-glucopyranoside **12** as a yellow oil.

A solution of the 1-bromo-α-D-glucopyranoside **12** (993 mg) in dry alcohol-free $CHCl_3$ (20 ml) was added dropwise over a period of 1 hr in the dark to a stirred mixture of β-(3,4-dimethoxyphenyl)ethanol* (304 mg), freshly prepared silver oxide (700 mg) and dry $CaSO_4$ (2 g) in dry alcohol-free $CHCl_3$ (30 ml)† [31]. The mixture was filtered and the solvent removed under red. press. at 60°. Prep. TLC in hexane–Me_2CO–EtOAc (11:6:3) afforded 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-β-(3′,4′-dimethoxyphenyl)ethyl-β-D-glucopyranoside **13** as an amorphous solid (590 mg, R_f 0.43) (found: M^+, 560.4219; $C_{29}H_{36}O_{11}$ requires: M^+, 560.2258); ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.18 (5H, *m*, H-aromatic), 6.78 (1H, *d*, *J* = 8.5 Hz, H-5′), 6.73 (1H, *d*, *J* = 1.5 Hz, H-2′), 6.73 (1H, *dd*, *J* = 1.5, 8.5 Hz, H-6′), 5.12 (1H, *t*, *J* = 9.5 Hz, H-4), 5.05 (1H, *dd*, *J* = 8.0, 9.5 Hz, H-2), 4.57 (2H, *s*, Ar-CH_2), 4.38 (1H, *d*, *J* = 8.0 Hz, H-1), 4.22 (1H, *dd*, *J* = 4.5, 12.5 Hz, H-6), 4.11 (1H, *dd*, *J* = 2.5, 12.5 Hz, H-6), 4.09 (1H, *m*, H-α), 3.87, 3.85 (6H, each *s*, 2 × OMe), 3.63 (1H, *t*, *J* = 9.5 Hz, H-3), 3.59 (2H, *m*, H-5, α), 2.82 (2H, *t*, *J* = 6.5 Hz, CH_2-β), and 2.09, 1.98, 1.86 (9H, each *s*, 3 × OAc).

*Prepared by successive esterification (MeOH–conc. H_2SO_4), methylation ($Me_2SO_4-K_2CO_3-Me_2CO$) and $LiAlH_4$ reduction of 3,4-dihydroxyphenylacetic acid.

†Mixture pre-stirred in the dark for 1 hr.

The 3-*O*-benzyl-β-D-glucopyranoside **13** (207 mg) was hydrogenated (10% Pd-C, 100 mg) in EtOH (50 ml) under ambient conditions. The suspension was filtered and the solvent evaporated to give 2,4,6-tri-*O*-acetyl-β-(3',4'-dimethoxyphenyl)ethyl-β-D-glucopyranoside **14** (156 mg, R_f 0.25 as an amorphous solid (found: M^+, 470.2564; $C_{22}H_{30}O_{11}$ requires: M^+, 470.1788); ^{1}H NMR (300 MHz, $CDCl_3$): δ6.79 (1H, *d*, *J* = 8.5 Hz, H-5'), 6.74 (1H, *dd*, *J* = 1.5, 8.5 Hz, H-6'), 6.73 (1H, *d*, *J* = 1.5 Hz, H-2'), 4.93 (1H, *t*, *J* = 9.5 Hz, H-4), 4.86 (1H, *dd*, *J* = 8.0, 9.5 Hz, H-2), 4.43 (1H, *d*, *J* = 8.0 Hz, H-1), 4.30 (1H, *dd*, *J* = 4.5, 12.5 Hz, H-6), 4.15 (1H, *dd*, *J* = 2.5, 12.5 Hz, H-6), 4.10 (1H, *dt*, *J* = 6.5, 9.5 Hz, H-α), 3.89, 3.86 (6H, each *s*, 2 × OMe), 3.74–3.58 (3H, *m*, H-3,5,α), 2.84 (2H, *t*, *J* = 6.5 Hz, CH_2-β), 2.60 (1H, *d*, *J* = 6.5 Hz, 3-OH), and 2.13, 2.09, 2.00 (9H, each *s*, 3 × OAc).

Tetra-*O*-acetyl-α-L-rhamnopyranoside (2.5 g) was converted to 2,3,4-tri-*O*-acetyl-1-bromo-α-L-rhamnopyranoside **15** (*ca* 2.06 g) by means of HBr in HOAc [30]. A portion (150 mg) of this bromo derivative in dry acetonitrile (5 ml) was immediately added to a solution of 2,4,6-tri-*O*-acetyl-β-(3',4'-dimethoxyphenyl)ethyl-β-D-glucopyranoside **14** (33.7 mg), $HgBr_2$ (40 mg), and $Hg(CN)_2$ (30 mg) in dry acetonitrile (20 ml) and the mixture stirred at room temp. for 24 hr. After removal of the acetonitrile under red. pres. at 60°, $CHCl_3$ was added and the precipitated mercury salts filtered off. The organic phase was extracted with 1 M KBr soln (3 × 50 ml), washed with H_2O (2 × 100 ml), dried (Na_2SO_4), and evaporated to dryness. Due to partial de-acetylation, the mixture was acetylated and subsequently resolved by prep. TLC in hexane–Me_2CO–EtOAc (11:6:3) to afford the phenolic *O*-methyl ether hexa-*O*-acetyl derivative **7** (9.8 mg, R_f 0.40) of the bioside **6**, identical [^{1}H NMR (Table 1) and CD] to that obtained from the secondary roots of *H. procumbens*.

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