Peruvianosides A and B, Novel Triterpene Glycosides from the Bulbs of *Scilla peruviana*

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Two new rearranged lanosterol trisaccharides, peruvianosides A (**1**) and B (**2**), were isolated from fresh bulbs of *Scilla peruviana*. Their structures were established mainly by extensive 2D NMR analysis. Peruvianoside A (**1**) showed an inhibitory activity on cyclic adenosine monophosphate (AMP) phosphodiesterase.

Some plants of the subfamily Scilloideae in the Liliaceae are known to be poisonous,[1] and several cardenolide glycosides were isolated and identified.[2] In our previous chemical examinations concerning Scilloideae plants, the bulbs of *Camassia cusickii*,[3] *Ornithogalum thyrsoides*,[4] and *O. saundersiae*[5] were shown to contain cholestane saponins and other steroidal saponins, and to be devoid of cardenolide glycosides, despite their anticipated occurrence. As a part of a systematic study concerning the bioactive constituents of the bulbs of Scilloidese plants, we investigated the methanol extract of *Scilla peruviana*,[6] resulting in the isolation of two new rearranged lanosterol trisaccharides, called peruvianosides A (**1**) and B (**2**) (Chart 1). In this paper we report on a structural elucidation of the new lanosterol derivatives based on extensive 2D NMR spectral data, and their inhibitory activity on cyclic adenosine monophosphate (AMP) phosphodiesterase.

A methanolic extract of the bulbs of *S. peruviana* (4.0 kg) was partitioned between 1-butanol and H_2O. The 1-butanol-soluble phase was fractionated by silica-gel and octadecylsilanized (ODS) column chromatographies, followed by repeated HPLC to yield peruvianosides A (**1**) and B (**2**).

Peruvianoside A (**1**) was obtained as a white amorphous powder, $[\alpha]_D$ −23.2° (methanol). The molecular formula, $C_{49}H_{78}O_{20}$, was established by the negative-ion fast-atom-bombardment (FAB) mass spectrum (*m/z* 985 $[M-H]^-$) and elemental analysis. The IR spectrum was consistent with the presence of hydroxyl groups (3400 cm^{-1}) and an ester carbonyl group (1695 cm^{-1}); the latter was further supported by the ^{13}C NMR spectrum (δ=168.5). The ^1H NMR spectrum of **1** showed the presence of a $\underline{CH_3}$–C=CH group [δ=2.06 (d, J=1.2 Hz)], two $\underline{CH_3}$–CH groups [δ=1.80 (d, J=6.2 Hz) and 1.12 (d, J=6.9 Hz)], five $\underline{CH_3}$–C groups [δ=1.53, 1.40, 1.17, 1.16, and 1.01 (each s)], and a methoxyl group [δ=3.72 (s)]. The signal at δ=1.80 was typical for the methyl group of 6-deoxyhexose. In addition, signals for three anomeric protons at δ=6.40 (br s), 5.85 (d, J=7.5 Hz), and 4.97 (d, J=7.6 Hz) were indicated. The four ^{13}C signals at δ=144.1 (CH), 135.8 (C), 134.6 (C), and 130.1 (C) suggested the presence of a trisubstituted double bond and a tetrasubstituted double bond in the molecule. The ^{13}C signal at δ=97.8 was correlated to the ^1H signal at δ=5.47 (d, J=6.4 Hz) in the HMQC spectrum, which was shifted downfield to appear at δ=6.40 (d, J=7.2 Hz) on acetylation, suggesting the presence of a hemiacetal moiety. The ^{13}C signal at δ=83.1, which disappeared in the DEPT 135° spectrum, was assignable to a quaternary carbon with a hydroxyl group. Acid hydrolysis of **1** with 1 M (1 M=1 mol dm^{-3}) hydrochloric acid (dioxane–H_2O, 1:1) yielded D-glucose and L-rhamnose as the carbohydrate compounds, together with several unidentified artifactual sapogenols, which seemed to be derived from genuine aglycone under acidic conditions.

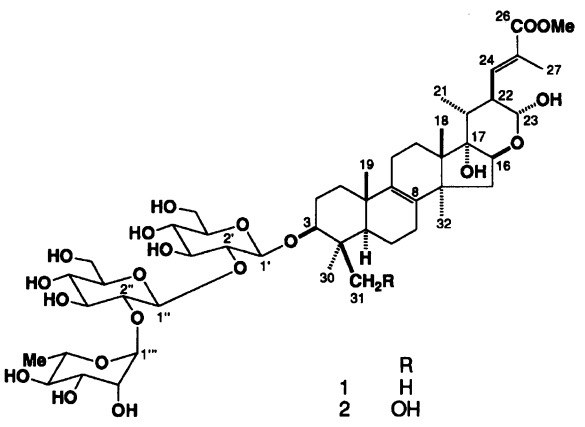

Chart 1.

A careful analysis of the ^1H–^1H COSY spectrum in conjunction with the HMQC data verified the spin networks of the aglycone moiety of **1**, giving rise to structural fragments, A—F, as shown in Fig. 1. The connectivities of segments A, B, and C, and five CH_3–C groups through quaternary carbons were established by interpretation of the HMBC spectrum, as shown in Fig. 2; the plain partial structure, thus constructed, was consistent with the C-1—C-14 portion (A—C rings) of lanost-8-en-3-ol. The configuration of the C-3 hydroxyl was confirmed to be β from the coupling constants of the H-3 methine signal (J=11.7 and 4.2 Hz) in the ^1H NMR spectrum of **1**. The A/B *trans* ring junction was supported by the NOEs observed in the phase-sensitive NOESY (PHNOESY) spectrum (Fig. 3).

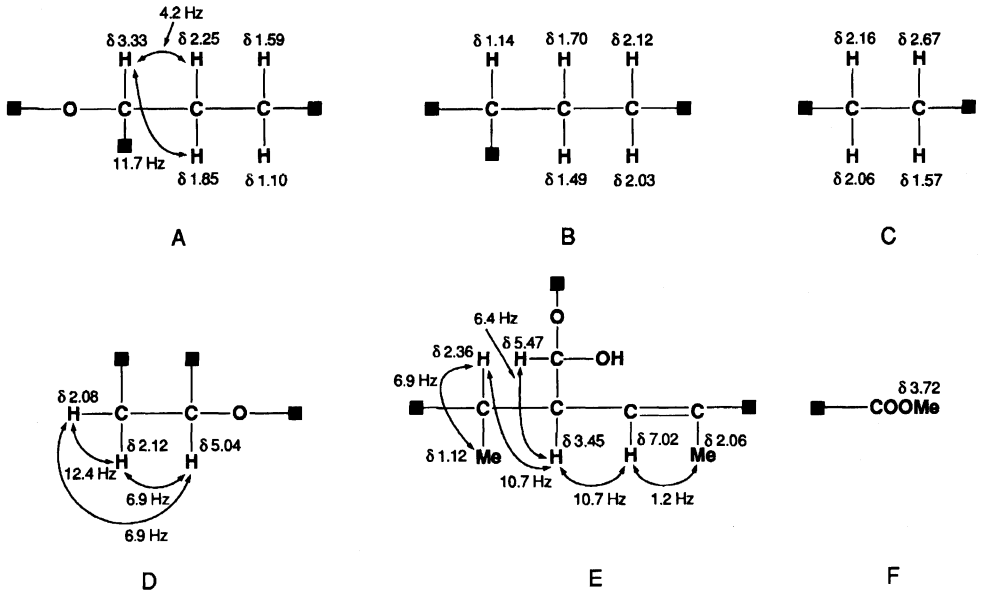

Fig. 1. Structural fragments of **1** shown by the ^{1}H–^{1}H COSY spectrum.

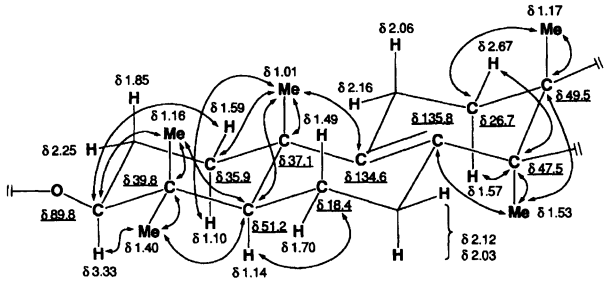

Fig. 2. ^{1}H and ^{13}C NMR chemical shifts, and ^{1}H–^{13}C long-range correlations of the A, B, and C rings of **1** in pyridine-d_5. The underlined figures indicate the ^{13}C NMR chemical shifts.

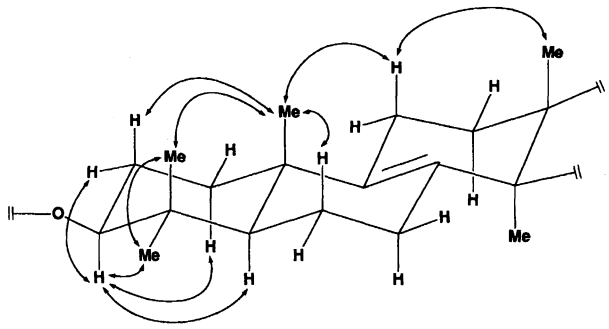

Fig. 3. NOEs at the A, B, and C rings of **1** in pyridine-d_5.

Furthermore, fragments D, E, and F, and the lanost-8-en-3β-ol portion were connected by the following HMBC data (Fig. 4). The ^{13}C signal due to the ester carbonyl group at δ=168.5 was correlated to the ^{1}H signal at δ=7.02 (H-24), 2.06 (H-27), and 3.72 (OMe), indicating a COOMe group linkage to the C-25 olefinic carbon. The quaternary carbon signal at δ=83.1 (C-17) showed correlation peaks with the ^{1}H signals at δ=5.04

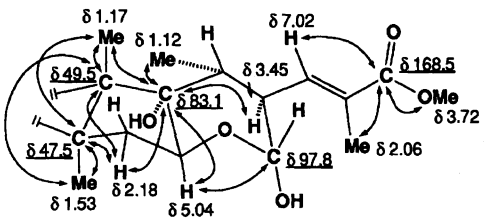

Fig. 4. ^{1}H–^{13}C long-range correlations of the D and E rings, and side chain of **1** in pyridine-d_5.

(H-16), 3.45 (H-22), 2.18 (H-15α), and 1.12 (H-21), which revealed that fragment D was linked to fragment E through the C-17 carbon. A cross peak between the ^{13}C signal at δ=97.8, assignable to the hemiacetal carbon and the ^{1}H signal at δ=5.04 (H-16), resulted in the formation of a six-membered hemiacetal ring between C-16 and C-23. The connections from C-17 to C-13 and from C-15 to C-14 were verified by multi-bonded couplings between H-18 (δ=1.17) and C-17 (δ=83.1), and between H-15α (δ=2.18) and C-14 (δ=47.5), respectively. An analysis of the PHNOESY spectrum made the stereochemistry assignable (Fig. 5). The H-18 methyl showed an NOE correlation with H-20 which, in turn, showed an NOE with H-23, indicating the 17*S**, 20*R**,

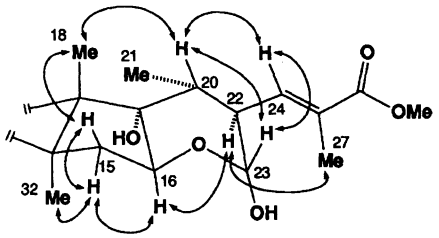

Fig. 5. NOEs of the D and E rings, and side chain of **1** in pyridine-d_5.

and 23R^* configurations. Other NOE networks between H-15α and H-16 and between H-16 and H-22 confirmed the 16S^* and 22R^* configurations. The H-24 olefinic proton showed NOEs with H-20 and H-23, and the H-27 methyl with H-22. Thus, the 24E situation was confirmed. The NOE between H-16 and H-22 further confirmed the preferred conformation of the six-membered hemiacetal ring to be a boat-form. The molecular model shows that such a conformation insures a minimum interaction between the migrated side chain and the H-18 methyl group. A significant downfield shift of the H-32 methyl protons compared with that of other lanost-8-ene derivatives[7] must be caused by an interaction with the C-17α hydroxyl group.

The structure of the sugar moiety and its linkage position to the aglycone were determined based on the following data. The proton spin system for each individual sugar was clarified by the ^{1}H–^{1}H COSY spectrum (Table 1), and assignments of the ^{13}C signals were carried out by tracing out the one-bond ^{1}H–^{13}C connectivities based on the use of the HMQC spectrum. A comparison of the ^{13}C assignments with those of reference methyl glycosides[8] indicated the presence of a terminal α-L-rhamnopyranosyl unit and two 2-substituted β-D-glucopyranosyl units. The β-configuration of the anomeric center of the glucose moieties was supported by the large J value of the anomeric proton in the ^{1}H NMR spectrum. Although the anomeric configuration of rhamnose can't be deduced from the J value of the anomeric proton, the ^{13}C shifts of the C-3 and C-5 positions showed remarkable difference between methyl α- and β-L-rhamnopyranosides.[8] In the HMBC spectrum, the anomeric proton signals at δ=6.40 (rhamnose), 5.85 (glucose), and 4.97 (glucose) showed correlations with the carbon signals at δ=78.7 (glucose C-2), 79.1 (glucose C-2), and 89.8 (aglycone C-3), respectively (Fig. 6).

Table 1. ^{1}H and ^{13}C NMR Chemical Shifts for the Trisaccharide Moiety of **1**[a]

	^{1}H (δ)		^{13}C (δ)
Glc 1′	4.97 d	(7.6)	105.2
2′	4.43 dd	(9.2, 7.6)	79.1
3′	4.55 dd	(9.2, 9.2)	79.4
4′	4.10 dd	(9.2, 9.2)	72.0
5′	3.92 ddd	(9.2, 5.0, 2.4)	77.9
6′a	4.54 dd	(10.8, 2.4)	61.5
6′b	4.38 dd	(10.8, 5.0)	
Glc 1″	5.85 d	(7.5)	102.1
2″	4.32 dd	(8.9, 7.5)	78.7
3″	4.25 dd	(8.9, 8.9)	79.4
4″	4.09 dd	(8.9, 8.9)	73.0
5″	3.86 ddd	(8.9, 5.7, 3.1)	77.5
6″a	4.50 dd	(10.8, 3.1)	62.9
6″b	4.31 dd	(10.8, 5.7)	
Rha 1‴	6.40 br s		102.2
2‴	4.76 br d	(3.2)	72.4
3‴	4.69 dd	(9.2, 3.2)	72.7
4‴	4.33 dd	(9.2, 9.2)	74.4
5‴	5.05 dq	(9.2, 6.2)	69.6
6‴	1.80 d	(6.2)	18.9

a) Spectra were measured in pyridine-d_5. J values in parentheses are expressed in Hz.

From the evidence presented above, the structure of **1** was elucidated.

Peruvianoside B (**2**), which has the molecular formula $C_{49}H_{78}O_{21}$, deduced from the negative-ion FABMS (m/z 1001 $[M-H]^-$) and elemental analysis, has one more oxygen atom than does **1**. In the ^{13}C NMR spectrum of **2**, the signal due to the C-31 methyl, which was observed at δ=16.7 in **1**, was displaced by the signal due to a hydroxymethyl carbon (δ=63.4). All other signals were almost superimposable between **1** and **2**. Thus, **2** was proved to be the hydroxy derivative of **1** at C-31.

Peruvianosides A (**1**) and B (**2**) have a new rearranged carbon skeleton based on lanosterol; the C-24—C-27 moiety of the side chain migrated to the C-22 position to form a six-membered hemiacetal ring between C-16 and C-23. In the triterpenoids so far reported, a dammarane derivative, pseudojujubogenin isolated from *Bacopa monniera*, is the only other example having a similar rearranged carbon skeleton to peruvianosides.[9] Although the plants of genus *Scilla* are expected to contain cardenolide glycosides, our chemical studies on *S. peruviana* showed that this plant contains abundant triterpenoid oligosaccharides instead of cardenolides.[10] Peruvianoside A (**1**) showed medium inhibitory activity on cyclic AMP phosphodiesterase (IC_{50} 23.5×10^{-5} M),[11] and may produce a positive inotropic effect through an increase in the intracellula cyclic AMP content.[12] Further biological tests which could be used to develope new positive inotropic drugs are in progress.

Experimental

Optical rotations were measured with a JASCO DIP-360 automatic polarimeter. IR spectra were recorded on a Hitachi 260-30 instrument, and MS on a VG AutoSpec E machine. 1D NMR spectra (ppm, J Hz) were taken with a Bruker AM-400, and 2D NMR spectra with a Bruker AM-500 spectrometer employing the standard Bruker software. HPLC was performed on a Tosoh HPLC system

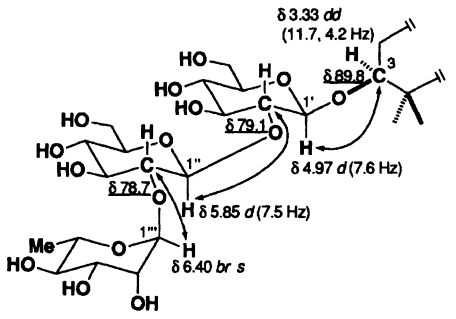

Fig. 6. ^{1}H–^{13}C long-range correlations of the saccharide moiety of **1** in pyridine-d_5.

(Tosoh Co. Ltd.: pump, CCPM; controller, CCP controller PX-8010; detector, RI-8010 or UV-8000) equipped with a Kaseisorb LC ODS-120-5 column (Tokyo-kasei-kogyo Co. Ltd.: 10 mm i.d. ×250 mm, ODS, 5 μm) for the preparative HPLC and a TSK gel SILICA-60 column (Tosoh Co. Ltd.: 4.6 mm i.d. ×250 mm, silica gel, 5 μm) for the sugar analysis.

Extraction and Isolation. Fresh bulbs of *S. peruviana* (4.0 kg) purchased from Heiwaen, Japan, were cut into pieces and extracted with hot MeOH. The MeOH extract was concentrated under reduced pressure. After removing of the solvent by evaporation, the MeOH extract was partitioned between *n*-BuOH and H_2O. Column chromatography of the *n*-BuOH extract on silica gel with $CHCl_3$–MeOH, with increasing proportion of MeOH (4:1, 2:1, and 1:1), and finally with MeOH, gave four fractions. Fraction 3 was chromatographed on silica gel with EtOAc–MeOH (4:1) and ODS with MeOH–H_2O (13:7) to give a mixture of **1** and **2**, which was further subjected to repeated preparative HPLC with MeOH–H_2O (7:3) and MeOH–H_2O–2-methoxyethanol (12:6:1) to yield **1** (492 mg) and **2** (159 mg).

Peruvianoside A (1). A white amorphous powder, $[\alpha]_D^{30}$ −23.2° (*c* 0.50, MeOH). Found: C, 58.12; H, 7.95%. Calcd for $C_{49}H_{78}O_{20}\cdot H_2O$: 58.55; H, 8.02%. Negative-ion FABMS *m/z* 985 $[M-H]^-$, 839 $[M-Rha]^-$, and 677 $[M-Rha-Glc]^-$; IR (KBr) 3400 (OH), 2930 (CH), 1695 (C=O), 1635 (C=C), 1440, 1365, 1285, 1235, 1065, 1025, 925, 805, and 745 cm^{-1}; ^1H NMR (pyridine-d_5) δ=7.02 (1H, dd, *J*=10.7 and 1.2 Hz, H-24), 5.47 (1H, d, *J*=6.4 Hz, H-23), 5.04 (1H, dd, *J*=6.9 and 6.9 Hz, H-16), 3.72 (3H, s, OMe), 3.45 (1H, ddd, *J*=10.7 10.7 and 6.4 Hz, H-22), 3.33 (1H, dd, *J*=11.7 and 4.2 Hz, H-3), 2.36 (1H, dq, *J*=10.7 and 6.9 Hz, H-20), 2.18 (1H, dd, *J*=12.4 and 6.9 Hz, H-15α), 2.08 (1H, dd, *J*=12.4 and 6.9 Hz, H-15β), 2.06 (3H, d, *J*=1.2 Hz, H-27), 1.53 (3H, s, H-32), 1.40 (3H, s, H-30), 1.17 (3H, s, H-18), 1.16 (3H, s, H-31), 1.12 (3H, d, *J*=6.9 Hz, H-21), and 1.01 (3H, s, H-19). Signals for the saccharide moiety were shown in Table 1; ^{13}C NMR (pyridine-d_5) δ=35.9, 27.1, 89.8, 39.8, 51.2, 18.4, 26.6, 135.8, 134.6, 37.1, 21.2, 26.7, 49.5, 47.5, 40.9, 80.7, 83.1, 20.2, 19.2, 36.7, 11.9, 44.5, 97.8, 144.1, 130.1, 168.5, 13.4, 28.3, 16.7, and 27.9 (C-1—C-32), and 51.6 (OMe). Signals for the saccharide moiety were shown in Table 1.

Acetylation of 1. Compound **1** (48 mg) was acetylated with Ac_2O in pyridine. Usual work-up and chromatography on silica gel with hexane–Me_2CO (3:2) to give the corresponding decaacetate (**1a**) (57.1 mg). IR (KBr) 3440 (OH), 2950 (CH), 1745 (C=O), 1430, 1365, 1220, 1035, and 935 cm^{-1}; ^1H NMR (pyridine-d_5) δ=6.91 (1H, dd, *J*=10.7 and 1.0 Hz, H-24), 6.40 (1H, d, *J*=7.2 Hz, H-23), 5.82 (1H, dd, *J*=9.7 and 9.7 Hz, H-3″), 5.80 (1H, dd, *J*=10.0 and 3.7 Hz, H-3‴), 5.71 (1H, dd, *J*=9.5 and 9.5 Hz, H-3′), 5.67 (1H, dd, *J*=10.0 and 10.0 Hz, H-4‴), 5.66 (1H, dd, *J*=3.7 and 1.4 Hz, H-2‴), 5.47 (1H, br s, OH), 5.43 (1H, dd, *J*=9.7 and 9.7 Hz, H-4″), 5.37 (1H, d, *J*=1.4 Hz, H-1‴), 5.36 (1H, dd, *J*=9.5 and 9.5 Hz, H-4′), 5.22 (1H, d, *J*=7.7 Hz, H-1″), 4.88 (1H, d, *J*=7.7 Hz, H-1′), 4.77 (1H, dd, *J*=7.4 and 7.4 Hz, H-16), 4.70 (1H, dq, *J*=10.0 and 6.2 Hz, H-5‴), 4.69 (1H, dd, *J*=12.1 and 4.6 Hz, H-6″a), 4.61 (1H, dd, *J*=12.1 and 4.9 Hz, H-6′a), 4.42 (1H, dd, *J*=12.1 and 2.6 Hz, H-6′b), 4.41 (1H, dd, *J*=12.1 and 2.6 Hz, H-6″b), 4.36 (1H, dd, *J*=9.5 and 7.7 Hz, H-2′), 4.21 (1H, ddd, *J*=9.7, 4.6 and 2.6 Hz, H-5″), 4.10 (1H, dd, *J*=9.7 and 7.7 Hz, H-2″), 4.07 (1H, ddd, *J*=9.5, 4.9 and 2.6 Hz, H-5′), 3.70 (3H, s, OMe), 3.45 (1H, ddd, *J*=10.7, 10.7 and 7.2 Hz, H-22), 3.25 (1H, dd, *J*=11.7 and 4.3 Hz, H-3), 2.32 (1H, dq, *J*=10.7 and 6.5 Hz, H-20), 2.19×2, 2.16, 2.15, 2.08, 2.05, 2.04, 2.03×2, and 1.99 (each 3H, s, Ac), 1.93 (3H, d, *J*=1.0 Hz, H-27), 1.64 (3H, d, *J*=6.2 Hz, H-6‴), 1.51 (3H, s, H-32), 1.30 (3H, s, H-30), 1.13 (3H, s, H-18), 1.09 (3H, s, H-31), 1.08 (3H, d, *J*=6.5 Hz, H-21), and 1.06 (3H, s, H-19).

Acid Hydrolysis of 1. A solution of **1** (20 mg) in 1 M HCl (dioxane–H_2O, 1:1) (5 ml) was heated at 100 °C for 1 h. After cooling, the reaction mixture was neutralized by passage through an Amberlite IRA-93ZU (OH^- form) (Organo Co. Ltd.), and subjected to silica-gel column chromatography with a gradient mixture of $CHCl_3$–MeOH (19:1, 9:1, 4:1, 2:1, and 1:1) to yield uncharacterized compounds and a mixture of glucose and rhamnose. The sugar mixture (2 mg) was treated with (−)-α-methylbenzylamine (10 mg) and $Na[BH_3CN]$ (12 mg) at 40 °C for 4 h, followed by acetylation with Ac_2O in pyridine containing a catalytic amount of 4-(dimethylamino) pyridine (5 mg). The reaction solution was concentrated under reduced pressure, and applied to preparative TLC with hexane–Me_2CO (4:1) to yield the 1-[(*S*)-*N*-acetyl-α-methylbenzylamino]-1-deoxyalditol acetate derivatives of the monosaccharides, which were analyzed by HPLC under the following conditions: solvent, hexane–EtOH (19:1); flow rate, 0.8 ml min^{-1}; detection, UV 230 nm. The derivatives of D-glucose and L-rhamnose were detected.[13]

Peruvianoside B (2). A white amorphous powder, $[\alpha]_D^{30}$ −24.0° (*c* 0.50, MeOH). Found: C, 56.95; H, 7.70%. Calcd for $C_{49}H_{78}O_{21}\cdot 2H_2O$: 56.64; H, 7.95%. Negative-ion FABMS *m/z* 1001 $[M-H]^-$, 855 $[M-Rha]^-$, and 693 $[M-Rha-Glc]^-$; IR (KBr) 3400 (OH), 2940 (CH), 1695 (C=O), 1635 (C=C), 1440, 1375, 1295, 1240, 1125, 1065, 1020, 930, 805, and 750 cm^{-1}; ^1H NMR (pyridine-d_5) δ=7.00 (1H, br d, *J*=10.0 Hz, H-24), 6.38 (1H, br s, H-1‴), 5.83 (1H, d, *J*=7.1 Hz, H-1″), 5.45 (1H, d, *J*=6.2 Hz, H-23), 4.93 (1H, d, *J*=7.8 Hz, H-1′), 3.72 (3H, s, OMe), 2.05 (3H, br s, H-27), 1.79 (3H, d, *J*=6.1 Hz, H-6‴), 1.51 (3H, s, H-32), 1.49 (3H, s, H-30), 1.11 (3H, s, H-18), 1.10 (3H, d, *J*=6.2 Hz, H-21), and 0.85 (3H, s, H-19); ^{13}C NMR (pyridine-d_5) δ=35.6, 27.1, 91.6, 43.8, 52.0, 18.5, 26.6, 135.6, 134.1, 36.6, 21.2, 26.7, 49.4, 47.5, 40.9, 80.7, 83.1, 20.2, 19.5, 36.6, 11.9, 44.5, 97.7, 144.1, 130.1, 168.5, 13.4, 22.7, 63.4, and 27.9 (C-1—C-32), 51.6 (OMe), 105.2, 79.1, 78.1, 69.8, 78.0, and 61.3 (C-1′—C-6′), 102.0, 78.8, 79.2, 71.8, 78.0, and 62.6 (C-1″—C-6″), and 102.1, 72.3, 72.7, 74.3, 69.5, and 18.9 (C-1‴—C-6‴).

Assay of Cyclic AMP Phosphodiesterase Activity. The phosphodiesterase activity was assayed through a modification of the method of Thompson and Brooker, as described in a previous paper.[11a]

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