# Studies on the Constituents of Solanaceous Plants. XIII.[1] A New Steroidal Glucuronide from Chinese *Solanum lyratum*

Shoji YAHARA,[a] Michiko OHTSUKA (née IKEDA),[a] Kimiko NAKANO[b] and Toshihiro NOHARA*,[a]

*Faculty of Pharmaceutical Sciences, Kumamoto University,[a] 5–1 Oe-honmachi, Kumamoto 862, Japan and Faculty of Pharmaceutical Sciences, Tokushima University,[b] 1–78 Shomachi, Tokushima 770, Japan.* *Received October 13, 1988*

**A new glucuronide, (22*R*)-3β,16β,22,26-tetrahydroxycholest-5-ene 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucuronopyranoside (1), was isolated from the aerial parts of Chinese *Solanum lyratum* THUNB. The structure of this new steroidal glucuronide was deduced by spectroscopic means and the identity of its aglycone was substantiated by comparison with an authentic sample derived from diosgenin acetate.**

**Keywords** Solanaceae; *Solanum lyratum*; (22*R*)-3β,16β,22,26-tetrahydroxycholest-5-ene; rhamnosyl glucuronoside; diosgenin E, F-ring cleavage; aluminum chloride–acetic anhydride reaction

The whole plant of *Solanum lyratum* THUNB. (Solanaceae) is called "baimaoteng" in China and has been used as a remedy for various cancers in the Shanghai region of China.[2] In addition, European *Solanum durcamara* L., of the same genus as *Solanum lyratum*, has been used for treatment of cancers and warts[3] from the time of Galen, and references regarding its use have appeared in the literature in many countries.[3] In 1965, Kupchan *et al.* isolated β-solamarine[3] as an anti-tumor substance from *Solanum dulcamala* L. In the preceding papers, we reported on the isolation and structure elucidation of a furostanol (SL-a), a spirostanol (SL-b) and two steroidal alkaloids (SL-c and SL-d) from the stem,[4] and a furostanol glucuronide from the fresh immature berry[5] of *Solanum lyratum* grown in Japan. Two new steroidal glucuronides[6] of a furostanol and a spirostanol derivative together with two known glycosides were obtained from the aerial parts of Chinese *Solanum lyratum*. Our continuing study of the above crude drug has led to the isolation of a further compound (**1**). This paper is concerned with the structural elucidation of **1**.

Compound **1** was obtained as a colorless amorphous powder, $[\alpha]_D$ +68.7°, showing strong carboxyl (1600 $cm^{-1}$) and hydroxyl (3400 $cm^{-1}$) absorptions in the infrared (IR) spectrum, and peaks due to $[M+K]^+$, $[M+Na]^+$ and $[M+H]^+$ at *m/z* 817, 801 and 779, respectively, in the positive fast atom bombardment mass spectrum (FAB-MS). Acid hydrolysis of **1** yielded an aglycone together with L-rhamnose and D-glucuronic acid. The carbon-13 nuclear magnetic resonance ($^{13}$C-NMR) spectrum of **1** revealed that the sugar moiety of **1** consisted of an α-L-rhamnopyranosyl-(1→2)-β-D-glucuronopyranoside (δ 102.1, 72.2, 71.8, 74.0, 69.6, 18.2, rha C-1—6, and 99.9, 78.8, 78.2, 73.4, 78.5, 175.3, glc UA C-1—6, respectively), whose chemical shifts were superimposable on those of 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucuronopyranosyl 3β-hydroxy-(25*R* and 26*S*)-spirost-5-ene[6] previously isolated from the same plant. The remaining twenty-seven carbon signals could be assigned to the aglycone moiety. Compound **1** showed a negative coloration with the Ehrlich reagent[7] and no absorption due to the spiroketal derivative in the IR spectrum, and thus it was considered to be a cholestane derivative. Moreover, the $^{13}$C-NMR spectrum of the aglycone part of **1** exhibited signals due to four oxygenated carbons at δ 76.8, 75.7, 73.3, and 67.5, suggesting that **1** is a tetrahydroxycholestane derivative. A comparative study of the $^{13}$C-NMR spectrum of the aglycone moiety of **1** with that of **3** β-cholestanol[8] disclosed the presence of hydroxyl groups at C-3, C-16, C-22 and C-26 in **1**, and the location of the sugar linkage at C-3–OH, by the glycosylation shifts.[9] The electron impact MS of (EI-MS) of **1** exhibited a peak at *m/z* 434 originated from the aglycone part. The signals in the $^1$H-NMR spectrum of the aglycone tetraacetate (**2**) could be assigned as follows: δ 3.86, 3.90 (each 1H, dd, *J*=6, 11 Hz, $H_2$-26), 4.60 (2H, m, H-3, H-22) and 4.83 (1H, t, *J*=6 Hz, H-16), 0.75 (3H, s, $H_3$-18), 0.91 (3H, d, *J*=6 Hz, $H_3$-27), 1.01 (3H, d, *J*=6 Hz, $H_3$-21) and 1.02 (1H, s, $H_3$-19), 5.36 (1H, d, *J*=4 Hz, H-5) and 2.00, 2.01, 2.04 and 2.06 (four acetyl signals). Accordingly, the structure of the aglycone of **1** was deduced to be 3,16,22,26-tetrahydroxycholest-5-ene.

In order to establish this structure involving the configurations at C-3, C-16, C-22 and C-25 on the aglycone, we

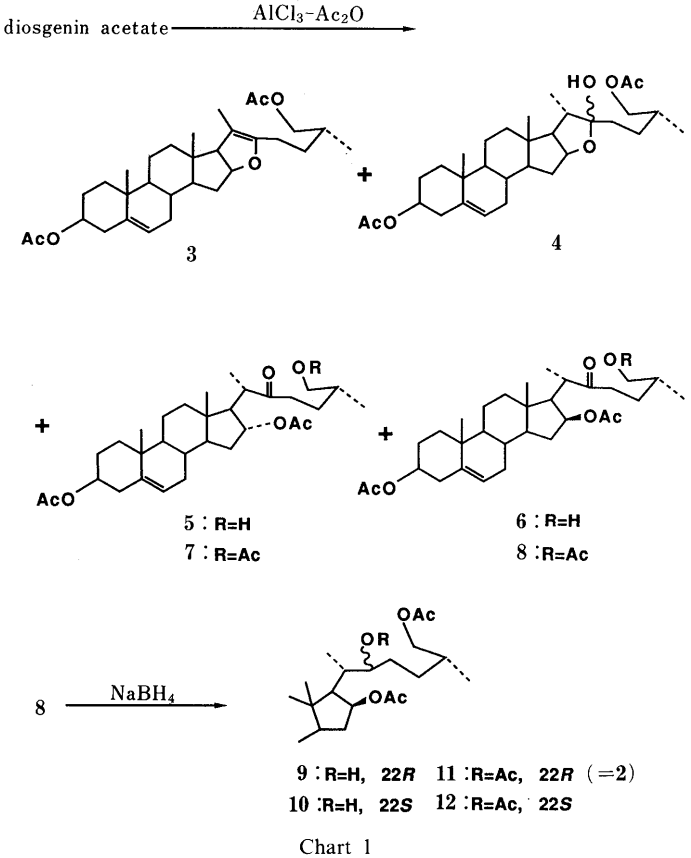



Chart 1

attempted to prepare the cholestane derivative corresponding to **2** from diosgenin. Treatment of diosgenin acetate with $AlCl_3$ in $Ac_2O$ according to Gould *et al.*[10] resulted in the formation of five products **4**—**8**, together with the known main product, pseudodiosgenin diacetate **3**. Compound **4** was positive with the Ehrlich reagent and showed peaks at *m/z* 498 and 438 due to $M^+ - H_2O$ and $M^+ -$ AcOH in the EI-MS. Signals at $\delta$ 3.92 (2H, m) and 4.58 (1H, m) in the $^1$H-NMR spectrum of **4** could be assigned to $H_2$-26 and H-3, which were adjacent to the two acetoxyl groups ($\delta$ 2.02 and 2.04). The structure of **4** was concluded to be 3$\beta$,22,26-trihydroxyfurost-5-ene 3,26-diacetate. Compounds **5** and **6** were negative with the Ehrlich reagent. They showed analogous patterns in their $^1$H- and $^{13}$C-NMR spectra; two tertiary methyl groups at C-10 and C-13, two secondary methyl groups at C-20 and C-25, two acetyl groups, one carbonyl group, two methine protons (H-3 and H-16) adjacent to the acetoxyl groups, and one methylene protons ($H_2$-26) next to the hydroxyl group were observed. The mechanism of production of **5** and **6** could be as shown in Chart 2. Accordingly, compounds

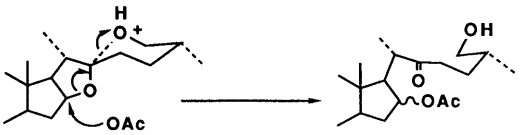
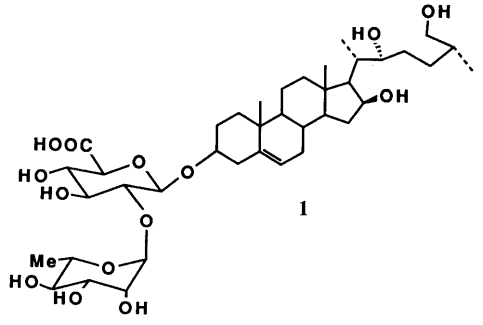



Chart 2

**5** and **6** were concluded to be 16-OAc epimers, the latter of which was converted into diosgenin by treatment with base followed by acid. Consequently, **5** and **6** could be represented as 3$\beta$,16$\alpha$,26-trihydroxycholest-5-ene 3,16-diacetate 22-one and 3$\beta$,16$\beta$,26-trihydroxycholest-5-ene 3,16-diacetate 22-one, respectively. Furthermore, compounds **7** and **8** were shown to be corresponding to the 26-*O*-acetyl derivatives of **5** and **6** by acetylation in the usual manner. Next, **8** was subjected to reduction with $NaBH_4$ followed by acetylation. The configuration at C-22 of the two epimeric products **7** and **8** was determined by the modified Horeau's method[11] to be *R* for **9** and *S* for **10**. Compound **11** of the **9**-acetyl derivatives was identical with **2**. Consequently, the structure of **1** could be represented as 3-*O*-$\alpha$-L-rhamno-pyranosyl-(1→2)-$\beta$-D-glucuronopyranosyl (22*R*)-3$\beta$,16$\beta$,22,26-tetrahydroxycholest-5-ene. This compound appears to be an important biogenetic precursor of spirostanol and furostanol glycosides.

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## Experimental

All melting points were taken on a Yanagimoto micro melting point apparatus (hot-stage type) and are uncorrected. The optical rotations were measured with a JASCO DIP-360 automatic digital polarimeter. The IR spectra were recorded with a Hitachi 215 spectrometer. The EI-MS were measured with a JEOL JMS-01SG and FAB-MS with a JEOL JMS-DX-300. The $^1$H- and $^{13}$C-NMR spectra were taken on JEOL JNM-GX-270 and JNM-GX-400 spectrometers using tetramethylsilane as an internal standard. Chromatographic columns were packed with Bondapak $C_{18}$ (Waters), silica gel (Merck 60, 70—230 mesh) and MCI gel CHP 20P (Mitsubishi Chemical Ind. Ltd., 70—150 $\mu$) and thin layer chromatography (TLC) plates were precoated with silica gel, Merck 60 $F_{254}$).

**Isolation of Compound 1** The fraction V (3.61 g) reported in the previous paper[6] was chromatographed over silica gel ($CHCl_3$ : MeOH : $H_2O$ = 6 : 4 : 1) to give fractions A—D. Fraction C was further subjected to Bondapac $C_{18}$ chromatography (MeOH : $H_2O$ = 2 : 3) to afford compound **1** (15 mg).

**Compound 1** Colorless amorphous powder, $[\alpha]_D^{18}$ −68.7° (*c* = 0.30, 50% MeOH). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3400, 1600. FAB-MS (*m/z*): 817 $[M+K]^+$, 801 $[M+Na]^+$, 779 $[M+H]^+$. EI-MS (*m/z*): 434 ($M^+$ of aglycone part), 416, 398, 318, 300, 285, 282, 271, 267, 253, 167, 253. $^{13}$C-NMR ($CDCl_3$) $\delta$: 37.3, 31.7, 76.8, 43.7, 140.7, 122.1, 31.6, 30.7, 50.1, 36.4, 20.9, 38.7, 40.1, 53.9, 31.8, 73.3, 62.8, 13.3, 19.4, 38.7, 18.4, 75.7, 29.9, 36.8, 36.1, 67.5, 13.7 (C-1—27), 99.9, 78.7, 78.2, 73.4, 78.5, 175.3 (glc UA C-1—6), 102.1, 72.2, 71.8, 74.0, 69.6, 18.2 (rha C-1—6).

**Acid Hydrolysis of 1** A solution of **1** (7 mg) in 1 N HCl MeOH (5 ml) was refluxed for 2 h and neutralized with 3% KOH–MeOH. The deposited salt was removed by passage through Sephadex LH-20 column with MeOH. The hydrolysate was examined by TLC ($CHCl_3$ : MeOH : $H_2O$ = 7 : 3 : 0.3 for the methyl glycosides of sugar) to detect the methyl glycosides of rhamnose (*Rf* 0.61) and glucuronic acid methyl ester (*Rf* 0.70). A solution of the hydrolysate in $Ac_2O$ (1 ml) and pyridine (2 ml) was left standing at room temperature overnight and evaporated to dryness under $N_2$ to yield the aglycone tetraacetate (**2**) (1.9 mg), $[\alpha]_D^{33}$ −58.0 (*c* = 0.10, $CHCl_3$). $^1$H-NMR ($CDCl_3$) $\delta$: 0.75 (3H, s, $H_3$-18), 0.91 (3H, d, *J* = 6 Hz, $H_3$-27), 1.01 (3H, d, *J* = 6 Hz, $H_3$-21), 1.02 (3H, s, $H_3$-19), 2.00, 2.01, 2.04, 2.06 (each 3H, s, 4 × Ac), 3.86, 3.90 (each 1H, dd, *J* = 6, 11 Hz, $H_2$-26), 4.60 (2H, m, H-3, -22), 4.83 (1H, t, *J* = 6 Hz, H-16), 5.36 (1H, d, *J* = 4 Hz, H-6).

**Reaction of Diosgenin Acetate with $AlCl_3$–$Ac_2O$ (Gould's Method)**[10] A mixture of diosgenin acetate (15.8 g), $AlCl_3$ (6.5 g) and $Ac_2O$ (300 ml) was refluxed for 6 h and then poured into ice water. The resulting precipitate was extracted with ether. The organic phase was washed with water, dried over $Na_2SO_4$ and evaporated to give a syrup (16.5 g), which was chromatographed over silica gel using *n*-hexane–acetone (10 : 1), *n*-hexane–AcOEt (10 : 1→4 : 1) and $CHCl_3$ to afford **3** (9.3 g), **4** (351 mg), **5** (48 mg), **6** (51 mg), **7** (145 mg) and **8** (243 mg). Compound **3**: Ehrlich reagent (+), white crystalline powder, mp 96—98 °C, $[\alpha]_D^{21}$ −29.1° (*c* = 1.14, pyridine). EI-MS *m/z*: 497 ($M^+$ − H), 437 ($M^+$ − AcOH − H). $^1$H-NMR ($CDCl_3$) $\delta$: 0.68 (3H, s, $H_3$-18), 0.94 (3H, d, *J* = 6 Hz, $H_3$-27), 1.03 (3H, s, $H_3$-19), 1.59 (3H, s, $H_3$-21), 2.02, 2.04 (each 3H, s, 2 × OAc), 3.91 (2H, d, *J* = 6 Hz, $H_2$-26), 4.40—4.84 (2H, m, H-3, H-16), 5.37 (1H, m, H-6). Compound **4**: Ehrlich reagent (+), $[\alpha]_D^{22}$ −59.4° (*c* = 0.69, pyridine). EI-MS *m/z*: 498 ($M^+ - H_2O$), 438 ($M^+$ − AcOH), 397 ($M^+ - 2 \times$ AcOH + H). $^1$H-NMR ($CDCl_3$) $\delta$: 0.80 (3H, s, $H_3$-18), 1.04 (3H, s, $H_3$-19), 2.02, 2.04 (each 3H, s, 2 × OAc), 3.92 (2H, m, $H_2$-26), 4.58 (2H, m, H-3, H-16), 5.34 (1H, m, H-6). Compound **5**: Ehrlich reagent (−), $[\alpha]_D^{21}$ −10.8° (*c* = 1.02, pyridine). EI-MS *m/z*: 498 ($M^+ - H_2O$), 456 ($M^+$ − AcOH), 438 ($M^+ - H_2O$ − AcOH), 282, 266, 253. $^1$H-NMR ($CDCl_3$) $\delta$: 0.88 (3H, s, $H_3$-18), 0.93 (3H, d, *J* = 6 Hz, $H_3$-27), 1.00 (3H, s, $H_3$-19), 1.00 (3H, d, *J* = 6 Hz, $H_3$-21), 2.03, 2.04 (each 3H, s, 2 × OAc), 3.46, 3.47 (each 1H, dd, *J* = 6, 11 Hz, $H_2$-26), 4.60 (1H, m, H-3), 5.18 (1H, ddd, *J* = 4,6,8 Hz, H-16), 5.35 (1H, d, *J* = 5 Hz, H-6). $^{13}$C-NMR ($CDCl_3$) $\delta$: 36.9, 27.7, 73.8, 38.1, 139.8, 122.1, 31.6, 31.5, 49.9, 36.6, 20.7, 39.3, 42.2, 56.4, 38.7, 75.2, 54.3, 16.2, 19.3, 42.9, 13.4, 214.3, 35.0, 26.5, 35.3, 67.5, 16.7 (C-1—27), 21.2, 21.3, 2 × 170.3 (2 × OAc). Acetylation of **5** in the usual manner gave a substance identical with **7**. Compound **6**, Ehrlish reagent (−), colorless needles, mp 166—169 °C, $[\alpha]_D^{21}$ +14.4° (*c* = 0.97, pyridine). EI-MS *m/z*: 498 ($M^+ - H_2O$), 456 ($M^+$ − AcOH), 438 ($M^+ - H_2O$ − AcOH), 282, 267, 253. $^1$H-NMR ($CDCl_3$) $\delta$: 0.87 (3H, s, $H_3$-18), 0.92 (3H, d, *J* = 7 Hz, $H_3$-27), 1.02 (3H, s, $H_3$-19), 1.14 (3H, d, *J* = 6 Hz, $H_3$-21), 1.97, 2.03 (each 3H, s, 2 × OAc), 3.43 (2H, d, *J* = 6 Hz, $H_2$-26), 4.61 (1H, m, H-3), 4.99 (1H, ddd, *J* = 4,6,8 Hz, H-16), 5.36 (1H, d, *J* = 5 Hz, H-6). $^{13}$C-NMR ($CDCl_3$) $\delta$: 36.9, 27.8, 73.8, 38.1, 139.7, 122.3, 31.7, 31.4, 49.9, 36.6, 20.8, 39.7, 42.0, 55.2, 38.5, 75.7, 54.0, 16.7, 19.3, 43.6, 13.3, 213.4, 34.9, 26.3, 35.3, 67.6, 16.8 (C-1—27), 21.1, 21.4, 169.7, 170.4 (2 × OAc). Compound **6** on alkaline saponification and subsequent acid treatment was converted to diosgenin. Acetylation of **6** gave a substance identical with **8**. Compound

**7**: $[\alpha]_D^{29}$ −14.7° ($c$=1.20, $CHCl_3$). $^1$H-NMR ($CDCl_3$) $\delta$: 0.82 (3H, s, $H_3$-18), 0.90 (3H, d, $J$=6 Hz, $H_3$-27), 0.95 (3H, d, $J$=6 Hz, $H_3$-21), 0.95 (3H, s, $H_3$-19), 1.97, 1.99, 2.00 (each 3H, s, 3×OAc), 3.58, 3.88 (each 1H, dd, $J$=6, 11 Hz, $H_2$-26), 4.54 (1H, m, H-3), 5.12 (1H, m, H-16), 5.30 (1H, br s, H-6). $^{13}$C-NMR ($CDCl_3$) $\delta$: 36.9, 27.7, 73.7, 38.1, 139.8, 122.1, 31.5, 31.4, 49.9, 36.4, 20.8, 39.2, 42.1, 56.4, 38.6, 75.1, 54.3, 16.4, 19.2, 42.8, 13.3, 213.3, 35.0, 26.8, 32.1, 68.7, 16.8 (C-1—27), 20.6, 21.1, 21.3, 2×170.1, 170.2 (3×OAc). Compound **8**: $[\alpha]_D^{29}$ +5.6° ($c$=0.75, $CHCl_3$). $^1$H-NMR ($CDCl_3$) $\delta$; 0.86 (3H, s, $H_3$-18), 0.91 (3H, d, $J$=6 Hz, $H_3$-27), 1.02 (3H, s, $H_3$-19), 1.15 (3H, d, $J$=7 Hz, $H_3$-21), 1.95, 2.02, 2.50 (each 3H, s, 3×OAc), 3.90 (2H, d, $J$=6 Hz, $H_2$-26), 4.60 (1H, m, H-3), 4.98 (1H, m, H-16), 5.36 (1H, br s, H-6). $^{13}$C-NMR ($CDCl_3$) $\delta$: 36.7, 27.6, 73.4, 37.9, 139.0, 121.6, 31.4, 31.1, 49.6, 36.4, 20.7, 39.4, 41.7, 54.8, 38.0, 75.3, 53.7, 16.5, 19.2, 43.3, 13.1, 211.4, 34.6, 26.6, 32.0, 68.5, 16.6 (C-1—27), 20.6, 20.9, 21.2, 168.7, 169.5, 170.2 (3×OAc).

**$NaBH_4$ Reduction of 8** Compound **8** (100 mg) was reduced with $NaBH_4$ (100 mg) in ether (50 ml) at room temperature for 4 h. The product (105 mg) was purified by silica gel column chromatography using *n*-hexane–AcOEt (3:1) as the eluent to give two epimeric products, **9** (12 mg) and **10** (30 mg). Compound **9**: $[\alpha]_D^{29}$ −69.2° ($c$=0.37, $CHCl_3$). $^1$H-NMR ($CDCl_3$) $\delta$: 0.74 (3H, s, $H_3$-18), 0.93 (3H, d, $J$=6 Hz, $H_3$-27), 0.97 (3H, d, $J$=7 Hz, $H_3$-21), 1.02 (3H, s, $H_3$-19), 3.46 (1H, t, $J$=6 Hz, H-22), 2.04, 2.03, 2.06 (each 3H, s, 3×OAc), 3.87, 3.92 (each 1H, dd, $J$=6, 11 Hz, $H_2$-26), 4.61 (1H, m, H-3), 4,93 (1H, t, $J$=7 Hz, H-16), 5.37 (1H, d, $J$=5 Hz, H-6). Compound **10**: $^1$H-NMR ($CDCl_3$) $\delta$: 0.91 (3H, s, $H_3$-18), 0.94 (3H, d, $J$=6 Hz, $H_3$-27), 0.97 (3H, d, $J$=7 Hz, $H_3$-21), 1.03 (3H, s, $H_3$-19), 2.03, 2.05, 2.07 (each 3H, s, 3×OAc), 3.45 (1H, t, $J$=6 Hz, H-22), 3.88, 3.99 (each 1H, dd, $J$=6, 11 Hz, $H_2$-22), 4.61 (1H, m, H-3), 5.06 (1H, ddd, $J$=4,7,8 Hz, H-16), 5.36 (1H, d, $J$=5 Hz, H-6).

**Determination of the Configuration (Modified Horeau's Method)[11] at C-22 of 9 and 10** Compounds **9** (2 mg) and **10** (2 mg) in pyridine (0.7 ml) were each treated with (+)-α-phenylbutyric anhydride (6 μl) and kept in a sealed tube at 40 °C for 1.5 h. Then, (+)-(*R*)-α-phenylethylamine (6 μl) was added. After 30 min, the mixture was diluted with dry ethyl acetate (50 μl) and a sample was analyzed by gas liquid chromatography (GLC) at 215 °C on a 4 mm×2 m column packed with 2% OV-17 ($N_2$ 1 kg/cm$^{-2}$). The relative proportion of the amides of (−)-*R*- and (+)-*S*-phenylbutyric acid was indicated by the peak height. The peak retention indices % were: **9**, 53:47 (22*R*); **10**, 56:44 (22*S*).

**The Acetates 11 and 12 of 9 and 10** Compounds **9** and **10** were each acetylated with $Ac_2O$ (0.5 ml) and pyridine (1 ml) in the usual manner and purified by silica gel column chromatography using *n*-hexane:AcOEt=5:1 as the solvent to give the corresponding acetates (**11** from **9**; **12** from **10**). Compound **11**: $[\alpha]_D^{29}$ −61.1° ($c$=0.53, $CHCl_3$). $^1$H-NMR ($CDCl_3$) $\delta$: 0.75 (3H, s, $H_3$-18), 0.92 (3H, d, $J$=7 Hz, $H_3$-27), 1.01 (3H, d, $J$=6 Hz, $H_3$-21), 1.02 (3H, s, $H_3$-19), 1.99, 2.03, 2.04, 2.06 (each 3H, s, 4×OAc), 3.85, 3.89 (each 1H, dd, $J$=6, 11 Hz, $H_2$-26), 4.61 (2H, m, H-3, -22), 4.83 (1H, t, $J$=7 Hz, H-16), 5.36 (1H, d, $J$=4 Hz, H-6). Compound **12**: $[\alpha]_D^{29}$ +5.5° ($c$=0.40, $CHCl_3$). $^1$H-NMR ($CDCl_3$) $\delta$: 0.89 (3H, s, $H_3$-18), 0.92 (3H, d, $J$=7 Hz, $H_3$-27), 0.98 (3H, d, $J$=7 Hz, $H_3$-21), 1.02 (3H, s, $H_3$-19), 2×2.03, 2.06, 2.11 (each 3H, s, 4×OAc), 3.88 (2H, d, $J$=6 Hz, $H_2$-26), 4.59 (1H, m, H-3), 4.70 (1H, m, H-22), 5.07 (1H, m, H-16), 5.36 (1H, d, $J$=4 Hz, H-6).

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