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# Synthesis of (25*R*)-ruscogenin-1-yl β-D-xylopyranosyl-(1 → 3)-[β-D-glucopyranosyl-(1 → 2)]-β-D-fucopyranoside

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**Abstract**

The synthesis of (25*R*)-ruscogenin-1-yl β-D-xylopyranosyl-(1 → 3)-[β-D-glucopyranosyl-(1 → 2)]-β-D-fucopyranoside, a saponin from the tuber of *Liriope muscari* (Decne.) Bailey, is described. 

*Keywords:* (25*R*)-Ruscogenin-1-yl β-D-xylopyranosyl-(1 → 3)-[β-D-glucopyranosyl-(1 → 2)]-β-D-fucopyranoside; Saponin; Synthesis

## 1. Introduction

Various *Ophiopogon* and *Liriope* species have been commonly used as a traditional Chinese herbal medicine under the name of Maidong, which possesses tonic effects [1]. Saponins are believed to be the active principles in Maidong plants. Thus far, more than 60 steroidal saponins have been isolated from these species, and most of these saponins are (25*R* or 25*S*)-ruscogenin-1-yl saponins [1]. Saponin **1**, namely (25*R*)-ruscogenin-1-yl β-D-xylopyranosyl-(1 → 3)-[β-D-glucopyranosyl-(1 → 2)]-β-D-fucopyranoside, with the typical structure, has been isolated from *Liriope muscari* (Decne.) Bailey [2]. This saponin was reported to have strong in vivo anti-inflammatory and immunopharmacological activities [3]. Herein, we report a total synthesis of this saponin [4].

## 2. Results and discussion

Saponin **1** was retrosynthetically disconnected into trisaccharide donor **2** and steroid acceptor **3** (Scheme 1). Trichloroacetimidate donor **2**, which lacks a functional group for neighboring-group participation, was envisioned to achieve the formation of the desired β D-glycosidic linkage via an SN2 reaction [5]. Steroid **3** would conceivably be derived from diosgenin by introduction of a 1β-OH. The 3-OH of **3** was believed to be more active than the 1β-OH and would, therefore, be protected as a TBS ether.

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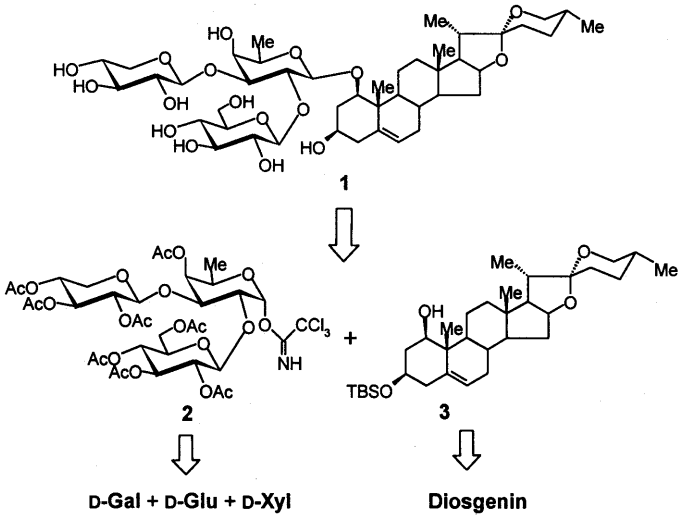
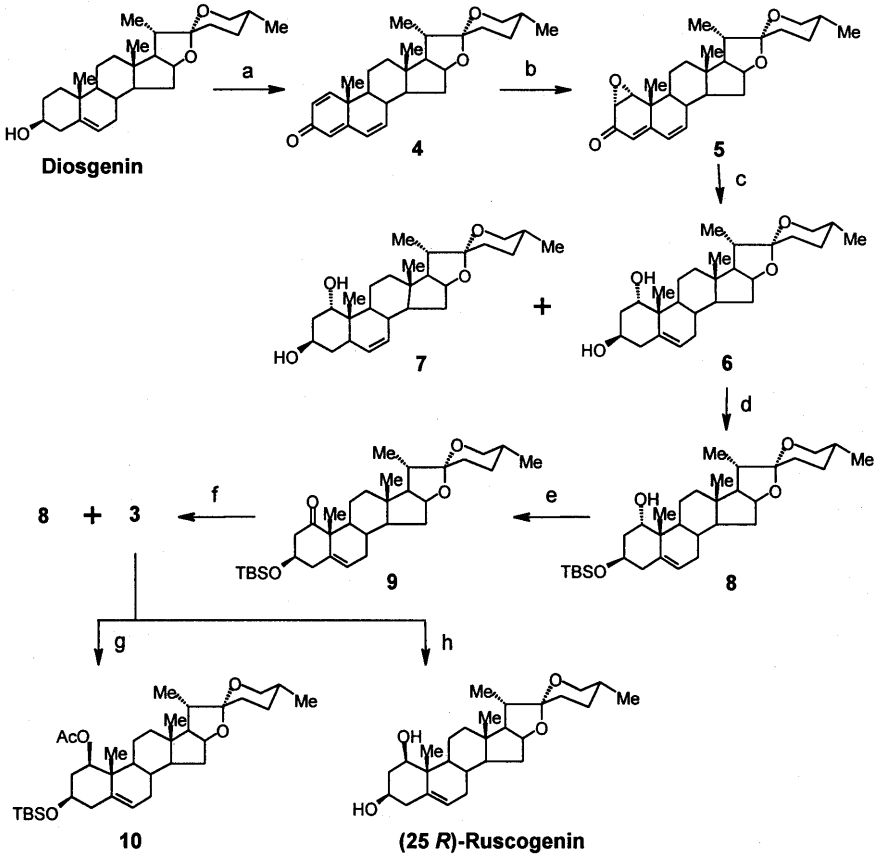
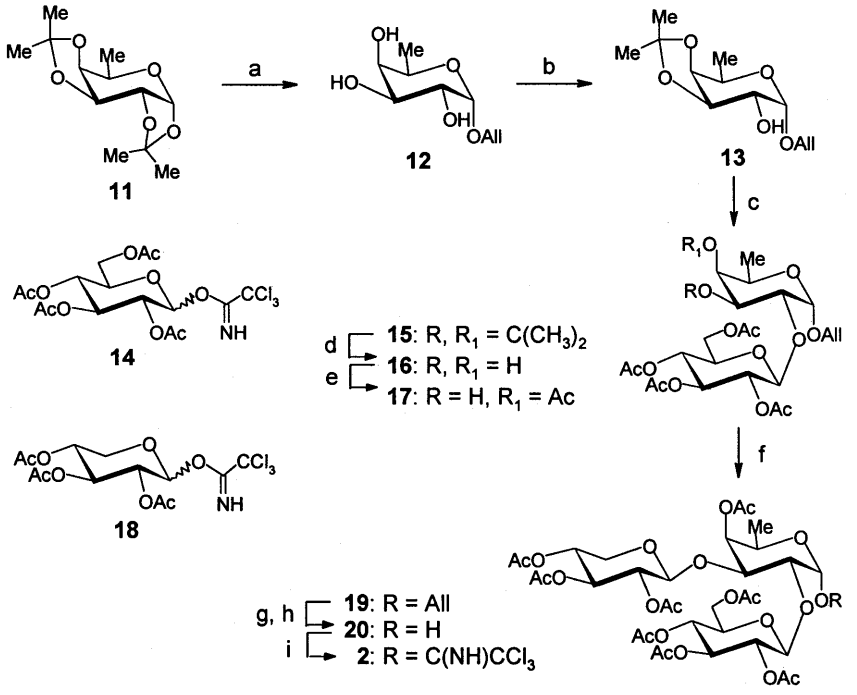



Scheme 1. Retrosynthesis of saponin **1**.

As shown in Scheme 2, the β-OH was readily introduced onto C-1 of the commercially available diosgenin using a similar strategy to that employed in the conversion of cholestane-type steroids into vitamin D and its analogues [6]. Oxidation of diosgenin with DDQ gave the trienone **4**, which was further oxidized with $H_2O_2$ in the presence of NaOMe to provide the epoxide **5**. The transformation of epoxide **5** into diol under $Li/NH_3$ reduction conditions was found to be capricious. Both $\Delta^5$-1α,3β-diol **6**, $\Delta^6$-1α,3β-diol **7** and several other unidentified products were produced in varying amounts. Under carefully controlled anhydrous conditions, **6** was obtained in ~50% yield, without any isomer **7** being detected. If a proton source was provided during the reduction by repeatedly charging with solid $NH_4Cl$ [7], **7** turned out to be the major product (42%). The $^1H$ NMR spectrum of **6** showed one broad doublet at 5.50 ppm (*J* 5.2 Hz) for H-6, while that of **7** showed two doublets at 5.39 ppm (*J* 10.0 Hz) and 5.28 ppm (*J* 10.0 Hz), respectively, for H-6 and H-7. Diol **6** was treated with *tert*-butylchlorodimethylsilane and imidazole in DMF to give **8**. Subsequently, attempts to invert the 1α-OH of **8** into the β configuration



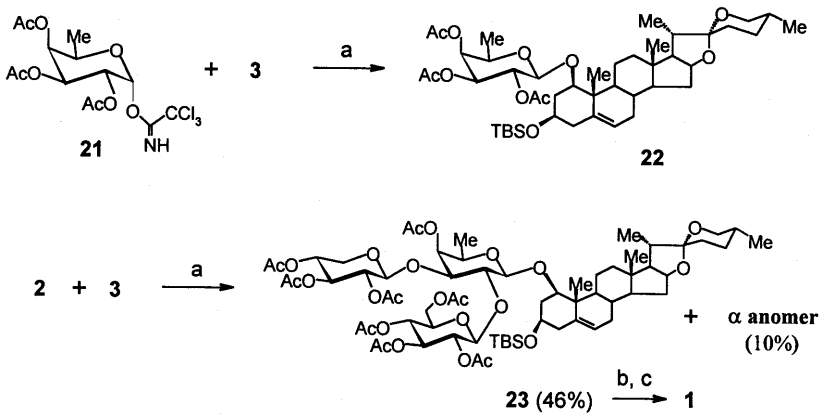

Scheme 2. Reagents and conditions: (a) DDQ, dioxane, reflux, 8 h, 69%; (b) $H_2O_2$, NaOMe, MeOH, rt, overnight, 68%; (c) $Li/NH_3$, THF, then $NH_4Cl$, ~50% (for **6**); (d) TBSCl, imidazole, DMF, rt, overnight, 100%; (e) PDC, $CH_2Cl_2$, rt, 92%; (f) $NaBH_4$, THF, 70% (for **3**); (g) $Ac_2O$, DMAP, pyridine, 94%; (h) 5 N HCl, acetone, rt, 1 h, 96%.




Scheme 3. Reagents and conditions: (a) 3% HCl, AllOH, 80 °C, 93%; (b) $(CH_3)_2C(OCH_3)_2$, TsOH (0.1 equiv), rt, 83%; (c) **14**, $BF_3{\cdot}Et_2O$ (0.7 equiv), $CH_2Cl_2$, 4 Å molecular sieves, −20 °C, 73%; (d) 50% HOAc, 60 °C, 93%; (e) $CH_3C(OCH_3)_3$, TsOH (0.1 equiv), rt, 20 min, then 20% HOAc, rt, overnight, 87%; (f) **18**, $BF_3{\cdot}Et_2O$ (0.7 equiv), $CH_2Cl_2$, 4 Å molecular sieves, −20 °C, 90%; (g) $ICF_2(CF_2)_4CF_2Cl$, $Na_2S_2O_4$, $NaHCO_3$, $CH_3CN–H_2O$, rt; (h) Zn, $NH_4Cl$, EtOH, reflux, 76% (2 steps); (i) $Cl_3CCN$, DBU, $CH_2Cl_2$, 81%.

by the Mitsunobu reaction [8] were unsuccessful. It could be explained that the reaction center at C-1 of **8** was seriously hindered by the methyl group at C-19 and the TBSO group at C-3. Therefore, an oxidation–reduction sequence was utilized to effectively epimerize the 1α-OH of **8**. Thus, **8** was oxidized by PDC to give ketone **9** (92%). Reduction of **9** with $NaBH_4$ mainly provided the expected 1β-OH product **3** (70%), with **8** being obtained in 25% yield. This stereoselectivity can be attributed to the bulkiness of TBS substitution on 3β-OH. Because in similar cases without 3-substitution, the 1α-epimer was the predominant product [9]. In order to confirm its structure, **3** was acetylated to give ester **10**. The $^1H$ NMR signal for H-1 was moved downfield from 3.50 ppm (in **3**) to 4.58 ppm (dd, *J* 11.9, 4.4 Hz), and an obvious NOE signal showed up between H-1 and H-3 of **10**. Furthermore, desilylation of **3** with 5 N HCl afforded (25*R*)-ruscogenin, whose physical data was identical to that of an authentic sample.

Trisaccharide trichloroacetimidate **2** was synthesized as shown in Scheme 3. 1,2:3,4-Di-*O*-isopropylidene-α-D-fucopyranoside (**11**), readily prepared from galactose in three steps [10], was treated with 3% HCl in allyl alcohol to give allyl α-D-fucopyranoside **12** in high yield (93%). Treatment of **12** with 2,2-dimethoxypropane and a catalytic amount of TsOH provided **13** with the 2-OH free. Glycosylation of **13** with 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl trichloroacetimidate (**14**) with promotion of $BF_3{\cdot}OEt_2$ led to the disaccharide **15** in good yield (73%). Removal of the *O*-isopropylidene group with 50% HOAc readily afforded diol **16**. Since it has been commonly found that the equatorial 3-OH is more active than the axial 4-OH for galactopyranose, arabinopyranose and fucopyranose derivatives [11], a regioselective glycosylation of **16**, giving a 1→3 linked product, was expected. However, glycosylation of **16** with 2,3,4-tri-*O*-acetyl-D-xylopyranosyl trichloroacetimidate (**18**) with promotion by $BF_3{\cdot}OEt_2$ gave a mixture of the 3-O-, 4-O-, and 3,4-di-O-xylosy-




Scheme 4. Reagents and conditions: (a) TMSOTf (0.2 equiv), $-5 \sim 0$ °C, $CH_2Cl_2$, 4 Å molecular sieves, 2 h, 69% (for **22**); (b) TMSOTf (2.0 equiv), $-78$ °C, $CH_2Cl_2$, 5 min; (c) MeONa–MeOH, rt, 3 h, 85%.

lated products in comparable amounts. Therefore, diol **16** was acetylated in a regioselective manner at 4-OH by treatment with triethylorthoacetate and a catalytic amount of TsOH, followed with 20% HOAc, providing **17** in 87% yield [12]. 2D $^1$H NMR analysis of **17** showed that the signal at 5.25 ppm (t, $J$ 3.4 Hz) corresponding to Fuc-H-4 moved downfield from 4.00 ppm in **16** to 5.25 ppm, demonstrating that only the 4-OH of **17** was masked with an acetyl group. Subsequently, **17** was easily xylosylated with **18** to give the desired trisaccharide **19** in high yield (90%). $^1$H NMR analysis of **19** showed that the signals for the anomeric protons were at 4.98 ppm (d, $J_{1,2}$ 3.2 Hz), 4.59 ppm (d, $J_{1',2'}$ 7.8 Hz), and 4.64 ppm (d, $J_{1'',2''}$ 6.3 Hz), respectively, indicating that the desired glycosidic linkages of 1α, 1′β, and 1″β were obtained.

Deallylation of trisaccharide **19** using $PdCl_2$ in HOAc [13], followed by treatment with $CCl_3CN$ and DBU, afforded the trisaccharide trichloroacetimidate **2** in 43% yield. The relatively low yield of the above transformation resulted from side reactions during deallylation under $PdCl_2$. For example, Wacker oxidation products were produced in considerable amounts, which were inseparable from the deallylation product **20** [14,15]. Therefore, we applied our recently developed method for deallylation [15]. Treatment of **19** with $C_6ClF_{12}I$ and $Na_2S_2O_4$–$NaHCO_3$ in $CH_3CN$–$H_2O$ provided the corresponding β-iodido-γ-perfluoroalkane derivative, which was then eliminated under Zn and $NH_4Cl$ in EtOH to afford **20** in 76% yield. Addition of **20** with $CCl_3CN$ afforded **2** in 81% yield. Trichloroacetimidate **2** was confirmed to be in the α configuration by $^1$H NMR analysis: $\delta$ 6.40 (d, 1 H, $J$ 3.5 Hz, H-1).

With donor **2** and acceptor **3** at hand, we sought to effect the final glycosylation to assemble the target saponin **1** (Scheme 4). However, coupling of **3** with trichloroacetimidate donors (either trisaccharide donor **2** or simple monosaccharide donor **21** [16]) under normal conditions for Schmidt's glycosylation [5] was found to be difficult, conceivably due to the steric hindrance of the 1β-OH of **3**. Finally, employing Schmidt's 'inverse procedure' [17] in which the acceptor **3** was first activated by a catalytic amount of TMSOTf before addition of the glycosyl donors (**21** or **2**), we obtained the desired glycosylation products **22** (69%) and **23** (46%, together with 10% of its α anomer), respectively. $^1$H NMR analysis of **23** showed the signals for three anomeric protons at 4.89 ppm (d, $J$ 7.8 Hz), 4.84 ppm (d, $J$ 7.7 Hz), and 4.31 ppm (d, $J$ 7.3 Hz), respectively, representing that the expected glycosidic 1′β, 1″β, 1‴β linkages were obtained. Desilylation of **23** with 2.0 equivalents of TMSOTf under low temperature ($-78$ °C) cleanly afforded the desired desilylated product (on TLC),[18] which was directly subjected to NaOMe–MeOH to furnish saponin **1** in 85% yield. The physical data for the synthetic sample was in good agreement with those reported [2].

## 3. Experimental

*General methods.*—See Ref. [19].

*(25R)-Spirostan-1,4,6-triene-3-one* (**4**).—A solution of diosgenin (4.49 g, 10.8 mmol) and dichlorodicyanobenzoquinone (DDQ) (7.38 g, 30.5 mmol) in dioxane (200 mL) was heated under reflux for 8 h, and then cooled, filtered and applied to a short column of silica gel ($CH_2Cl_2$) to gave a crude product, which was further purified by a silica gel column chromatography (3:1 petroleum ether–EtOAc) to afford **4** (3.04 g, 69%) as a white solid: mp 194–195 °C; $[\alpha]_D^{20}$ −109.5° (*c* 0.1, $CHCl_3$); IR (KBr); *v* 2972 (s), 1668 (s), 1049 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.04 (d, 1 H, *J* 10.0 Hz), 6.23 (d, 2 H, *J* 9.8 Hz), 6.02 (d, 1 H, *J* 13.3 Hz), 6.00 (s, 1 H), 4.42 (dd, 1 H, *J* 14.2, 7.5 Hz), 3.47 (m, 1 H), 3.35 (t, 1 H, *J* 10.9 Hz), 1.21 (s, 3 H), 0.97 (d, 3 H, *J* 6.9 Hz), 0.90 (s, 3 H), 0.80 (d, 3 H, *J* 6.2 Hz); EIMS (*m/z*): 409 $[M^+ + 1]$, 408 $[M^+]$; HREIMS (*m/z*): Calcd for $C_{27}H_{36}O_3$: 408.2664. Found: 408.2637.

*1α,2α-Epoxy-(25R)-spirostan-4,6-dien-3-one* (**5**).—$H_2O_2$ (30%, 1 mL) was added to a solution of trienone **4** (30 mg, 0.073 mmol) in MeOH (20 mL) containing 0.2% NaOMe. The mixture was stirred at 15 °C overnight and then diluted with ether (20 mL). The organic layer was dried and concentrated. The residue was purified by a silica gel column chromatography (3:1 petroleum ether–EtOAc) to give **5** (21.2 mg, 68%) as a white solid: mp 167–168 °C; $[\alpha]_D^{20}$ −17.1° (*c* 0.23, $CHCl_3$); IR (KBr): *v* 2981 (s), 1730 (s), 1670 (s), 1620, 1460, 1080 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 6. 08 (m, 2 H), 5.66 (d, 1 H, *J* 0.9 Hz), 4.44 (q, 1 H, *J* 10.0 Hz), 3.59 (d, 1 H, *J* 4.1 Hz), 3.48–3.45 (m, 2 H), 3.40 (t, 1 H, *J* 10.8 Hz), 1.20 (s, 3 H), 0.98 (d, 3 H, *J* 6.9 Hz), 0.90 (s, 3 H), 0.80 (d, 3 H, *J* 6.3 Hz); EIMS (*m/z*): 425 $[M^+ + 1]$, 424 $[M^+]$; HREIMS (*m/z*): Calcd for $C_{27}H_{36}O_4$ 424.2614. Found: 424.2649.

*(25R)-Spirostan-5-en-1α, 3β-diol* (**6**).—A three-necked flask was fitted with a dropping funnel, a cold-finger condenser filled with solid $CO_2$, and an inlet tube connected to an ammonia source, with gas drying by KOH. Argon was swept through the system for 10 min, and then ammonia (100 mL) was trapped in the flask. Lithium wire was cut into short pieces and added. After being stirred for 1 h, epoxide **5** (100 mg, 0.23 mmol) in THF (10 mL) was added dropwise during 30 min. The cooling bath was removed, and the mixture was allowed to warm to −40 °C for 20 min. The flask was dipped in a cooling bath and anhydrous $NH_4Cl$ was added during 2 h (note: take care! vigorous reaction). The mixture turned white and pasty. Most of the ammonia was removed in a stream of argon. The residue was diluted with ether, washed with brine and dried. Evaporation left a white solid that was applied to a silica gel column (1:1 petroleum ether–EtOAc) to afford **6** (54 mg, 53%) as a white solid: mp > 230 °C; $[\alpha]_D^{20}$ −160.7° (*c* 0.54, $CHCl_3$); IR (KBr); *v* 3441, 2954, 920, 900 $cm^{-1}$ (intensity 900 > 920). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.50 (brd, 1 H, *J* 5.7 Hz), 4.40 (q, 1 H, *J* 7.1 Hz), 3.51–3.31 (m, 4 H), 1.00 (s, 3 H), 0.92 (d, 3 H, *J* 6.8 Hz), 0.78 (m, 6 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 137.30, 125.39, 109.27, 80.73, 72.85, 66.83, 66.36, 62.05, 56.34, 41.83, 41.67, 41.36, 40.22, 39.48, 38.22, 31.86, 31.36, 30.27, 29.66, 28.78, 20.07, 19.46, 17.10, 16.23, 14.47; EIMS (*m/z*): 431 $[M^+ + 1]$, 430 $[M^+]$, 412 $(M^+ - H_2O)$.

*(25R)-Spirostan-6-en-1α,3β-diol* (**7**).—A solution of epoxide **5** (100 mg, 0.23 mmol) in dry liquid $NH_3$ (10 mL) and THF (10 mL) at −78 °C under argon was stirred for 1 h and warmed up to −30 °C. To the above solution, $NH_4Cl$ (110 mg) was added, followed by lithium pieces (12 mg). After the blue color faded, the addition of $NH_4Cl$ (80 mg) and lithium pieces (12 mg) was repeated six times. After the mixture was kept blue for 2 h, the reaction was charged with $NH_4Cl$ at −78 °C, then diluted with EtOAc (20 mL). The organic layer was washed with brine, dried over $Na_2SO_4$ and then concentrated. The residue was purified by a silica gel column chromatography (1:1 petroleum ether–EtOAc) to give **7** (42 mg, 42%) as a white solid: mp > 230 °C; $[\alpha]_D^{20}$ −167.8° (*c* 0.33, $CHCl_3$); IR (KBr): *v* 3441, 2954, 920, 900 $cm^{-1}$ (intensity 900 > 920). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.40 (brd, 1 H, *J* 12.0 Hz), 5.28 (brd, 1 H, *J* 12.0

Hz), 4.35 (m, 1 H), 3.98 (m, 1 H), 3.79 (t, 1 H), 3.41 (m, 1 H), 3.31 (t, 1 H, *J* 10.8 Hz), 0.90 (d, 3 H, *J* 6.8 Hz), 0.75 (s, 3 H), 0.74 (s, 3 H), 0.72 (d, 3 H, *J* 6.3 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 130.72, 128.03, 109.25, 80.81, 72.02, 67.21, 66.83, 62.07, 54.14, 46.60, 41.52, 39.80, 38.65, 38.42, 37.77, 36.96, 35.95, 31.58, 31.35, 30.24, 28.75, 20.45, 17.10, 16.48, 14.46, 12.47; EIMS (*m*/*z*): 431 [$M^+ + 1$], 430 [$M^+$], 412 [$M^+ - H_2O$]; HREIMS (*m*/*z*): Calcd for $C_{27}H_{42}O_4$: 430.3083. Found: 430.3095.

*3β-O-tert-Butyldimethylsilyl-(25R)-spirostan-5-en-1α-ol* (**8**).—A solution of **6** (342 mg, 0.80 mmol), *tert*-butylchlorodimethylsilane (145 mg, 0.96 mmol), and a catalytic amount of imidazole in DMF (8 mL) was stirred overnight. The mixture was poured into water and extracted with EtOAc. The combined extracts were washed with aq $NaHCO_3$, brine and water, respectively, and then dried over $Na_2SO_4$ and concentrated to dryness. The residue was purified by a silica gel column (6:1 petroleum ether–EtOAc) to afford **8** (218 mg, 100%) as a white solid: mp > 230 °C; $[\alpha]_D^{20}$ + 338.7° (*c* 0.11, $CHCl_3$); $^1$H NMR ($CDCl_3$): $\delta$ 5.50 (brd, 1 H, *J* 5.2 Hz), 4.35 (q, 1 H, *J* 7.1 Hz), 3.87 (m, 1 H), 3.75 (brs, 1 H), 3.41 (m, 1 H), 3.31 (t, 1 H, *J* 10.8 Hz), 0.98 (s, 3 H), 0.91 (d, 3 H, *J* 6.7 Hz), 0.82 (s, 9 H), 0.74 (d, 3 H), 0.70 (d, 3 H), 0.01(s, 6 H); EIMS (*m*/*z*): 526 [$M^+ - H_2O$], 487 ($M^+ - {}^t$Bu). Anal. Calcd for $C_{33}H_{56}O_4Si$: C 72.74; H 10.37. Found: C 72.62; H 10.67.

*3β-O-tert-Butyldimethylsilyl-(25R)-spirostan-5-en-1-one* (**9**).—To a solution of **8** (79 mg, 0.15 mmol) in $CH_2Cl_2$ (5 mL) was added pyridinium dichromate (PDC, 100 mg). The mixture was stirred at rt for 1 h and then filtered through a pad of Celite. The filtrates were concentrated. The residue was purified by silica gel column chromatography (20:1 petroleum ether–EtOAc) to give **9** (72 mg, 92%) as a white solid: mp 215–216 °C; $[\alpha]_D^{20}$ − 25.8° (*c* 0.06, $CHCl_3$); IR (KBr); *v* 2955, 2859, 1708 (s), 921, 901 cm$^{-1}$ (intensity 901 > 921). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.59 (brd, 1 H, *J* 5.3 Hz), 4.41 (m, 1 H), 3.74 (m, 1 H), 3.47 (m, 1 H), 3.37 (t, 1 H, *J* 10.6 Hz), 0.97 (d, 3 H, *J* 6.7 Hz), 0.94 (s, 12 H), 0.79 (d, 3 H), 0.78 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H); EIMS (*m*/*z*): 543 [$M^+ + 1$], 542 [$M^+$], 527 ($M^+ - Me$), 485 [$M^+ - {}^t$Bu, 100%]. Anal. Calcd for $C_{33}H_{54}O_4Si$: C, 73.01; H, 10.03. Found: C, 73.02; H 10.50.

*3β-O-tert-Butyldimethylsilyl-(25R)-ruscogenin* (**3**).—To a solution of **9** (110 mg, 0.20 mmol) in dry THF (20 mL) was added $NaBH_4$ (67 mg, 0.20 mmol). After being stirred at rt for 2 h, the reaction was quenched by addition of water (0.1 mL). The mixture was then concentrated in vacuo. The residue was purified by silica gel column chromatography (6:1 petroleum ether–EtOAc) to give **8** (27 mg, 25%) and **3** (77 mg, 70%) as white solids. **3**: mp > 230 °C; $[\alpha]_D^{20}$ − 76.3° (*c* 0.11, $CHCl_3$); IR (KBr); *v* 3481, 2953, 2860, 1045, 921, 900 cm$^{-1}$ (intensity 900 > 921); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.51 (brd, 1 H, *J* 5.6 Hz), 4.40 (q, 1 H, *J* 6.7 Hz), 3.55–3.39 (m, 4 H), 1.03 (s, 3 H), 0.91 (d, 3 H, *J* 6.7 Hz), 0.88 (s, 9 H), 0.79 (d, 3 H, *J* 6.0 Hz), 0.78 (s, 3 H), 0.09 (s, 6 H); EIMS (*m*/*z*): 544 [$M^+$], 543 [$M^+ - 1$], 526 [$M^+ - H_2O$], 487 [$M^+ - {}^t$Bu]. Anal. Calcd for $C_{33}H_{56}O_4Si$: C, 72.74; H, 10.37. Found: C, 72.34; H, 10.39.

*1β-O-Acetyl-3β-O-tert-butyldimethylsilyl-(25R)-ruscogenin* (**10**).—A solution of **3** (10 mg, 0.018 mmol) in $Ac_2O$ and pyridine (1:1, 2 mL) was stirred overnight and then concentrated with toluene to dryness. The residue was purified by a silica gel column chromatography (15:1 petroleum ether–EtOAc) to afford **10** (10 mg, 94%) as a white solid: mp. 210–211 °C; $[\alpha]_D^{20}$ − 120.7° (*c* 0.25, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.54 (brd, 1 H, *J* 5.2 Hz), 4.58 (dd, 1 H, *J* 11.9, 4.4 Hz), 4.38 (m, 1 H), 3.56–3.46 (m, 3 H), 3.36 (t, 1 H, *J* 10.7), 0.95 (d, 3 H, *J* 6.9 Hz), 0.87 (s, 12 H), 0.79 (d, 3 H, *J* 5.8 Hz), 0.77 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H); EIMS (*m*/*z*): 587 [$M^+ + 1$], 586 [$M^+$], 585 [$M^+ - 1$], 529 [$M^+ - {}^t$Bu].

*(25R)-Ruscogenin*.—To a solution of **3** (10 mg, 0.018 mmol) in acetone (5 mL) was added 5 N HCl (0.5 mL). After stirring at rt for 1 h, the solution was diluted with EtOAc (20 mL). The organic extract was washed with 5% $NaHCO_3$, dried over anhydrous $Na_2SO_4$ and evaporated to dryness. The residue was purified by silica gel column chromatography (1:1 petroleum ether–EtOAc) to give

(25*R*)-ruscogenin (7.6 mg, 96%) as a white solid: mp > 230 °C; $[\alpha]_D^{20}$ −91.4° (*c* 0.50, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.54 (brd, 1 H, *J* 5.6 Hz), 4.40 (m, 1 H), 3. 56 (m, 1 H), 3.48–3.41 (m, 2 H), 3.37 (t, 1 H, *J* 10.9 Hz), 1.05 (s, 3 H), 0.99 (d, 3 H, *J* 6.1 Hz), 0.97 (d, 3 H, *J* 6.6 Hz), 0.80 (s, 3 H). $^{13}C$ NMR: 138.2, 125.4, 109.3, 80.8, 77.9, 68.1, 66.9, 62.3, 56.5, 50.4, 42.9, 42.4, 42.0, 41.7, 40.1, 39.9, 32.4, 32.04, 32.0, 31.4, 30.3, 28.8, 23.8, 17.1, 16.3, 14.5, 13.0; EIMS (*m*/*z*): 430 [$M^+$], 412 [$M^+ - H_2O$]; HREIMS (*m*/*z*): Calcd for $C_{27}H_{42}O_4$: 430.3083. Found: 430.3047.

*Allyl* α-D-*fucopyranoside* (**12**).—1,2;3,4-Di-*O*-isopropylidene-α-D-fucopyranoside (**11**) (5.93 g, 24.3 mmol) was suspended and heated in a allyl alcohol solution (100 mL) containing 3% HCl at 80 °C for 2 h until the solution became clear. The resulting solution was then concentrated in vacuo to afford a colorless residue, which was purified by silica gel column chromatography (15:1 $CHCl_3$–MeOH) to give **12** (4.99 g, 93%) as a white solid: $[\alpha]_D^{20}$ +42.9° (*c* 0.8, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.93 (m, 1 H), 5.32 (m, 1 H), 4.88 (d, 1 H, *J* 3.7 Hz), 4.15 (m, 1 H), 4.08–3.98 (m, 2 H), 3.84–3.68 (m, 3 H); EIMS (*m*/*z*): 205 [$M^+ + 1$], 147 [$M^+ -$ OAll, 100%]. HREIMS (*m*/*z*): Calcd for $C_9H_{16}O_5 +$ 1-$H_2O$: 187.0892. Found: 187.0945.

*Allyl 3,4*-O-*isopropylidene*-α-D-*fucopyranoside* (**13**).—To a solution of **12** (3.0 g, 0.015 mol) and 2,2-dimethoxypropane (4.7 mL, 0.036 mol) in $CH_2Cl_2$ (10 mL) was added a catalytic amount of *p*-TsOH·$H_2O$. After stirring overnight, the mixture was neutralized with triethylamine and then concentrated. The residue was purified by silica gel column chromatography (4:1 petroleum–EtOAc) to give **13** (2.98 g, 83%) as a white solid: mp 47–48 °C; $[\alpha]_D^{20}$ +19.7° (*c* 0.5, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.91 (m, 1 H), 5.29–5.20 (m, 2 H), 4.86 (d, 1 H, *J* 3.9 Hz), 4.24 (dd, 1 H, *J* 12.4, 4.0 Hz), 4.21 (dd, 1 H, *J* 6.4, 6.0 Hz), 4.13 (ddd, 1 H, *J* 12.3, 6.9, 1.3 Hz), 4.05 (m, 1 H), 4.04 (m, 1 H), 3.79 (m, 1 H), 1.51 (s, 3 H), 1.34 (s, 3 H), 1.31 (d, 3 H); EIMS (*m*/*z*): 245 [$M^+ + 1$], 229 [$M^+ - CH_3$], 187 [$M^+ -$ OAll, 100%]; HREIMS (*m*/*z*): Calcd for $C_{12}H_{20}O_5$: 244.1311. Found: 244.1296.

*Allyl(2,3,4,6-tetra*-O-*acetyl*-β-D-*glucopyranosyl)*-(1→2)-*3,4*-O-*isopropylidene*-α-D-*fucopyranoside* (**15**).—To a suspension of **13** (0.96 g, 3.94 mmol), trichloroacetimidate **14** (2.13 g, 4.33 mmol), and 4 Å molecular sieves (1.0 g) in dry $CH_2Cl_2$ (10 mL) under argon at −40 °C, was added $BF_3{\cdot}Et_2O$ (0.25 mL, 1.87 mmol) dropwise. After stirring for 3 h, the mixture was treated with satd aq $NaHCO_3$ (1 mL) and then diluted with $CH_2Cl_2$ (100 mL). The organic layer was separated, dried with sodium sulfate and then concentrated in vacuo. The residue was purified by silica gel column chromatography (3:1 petroleum–EtOAc) to give **15** (1.65 g, 73%) as a white solid: mp 81–82 °C; $[\alpha]_D^{20}$ +47.0° (*c* 0.36, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.87 (m, 1 H), 5.29–5.02 (m, 5 H), 4.88 (d, 1 H, *J* 3.5 Hz), 4.86 (d, 1 H, *J* 7.9 Hz), 4.26–4.10 (m, 5 H), 4.02–3.98 (m, 2 H), 3.78 (m, 1 H), 3.67 (m, 1 H) 2.07, 2.03, 2.00, 1.95 (s each, 3 H each), 1.50, 1.33 (s each, 3 H each), 1.32 (d, 3 H, *J* 6.5 Hz); EIMS (*m*/*z*): 559 [$M^+ - CH_3$]. Anal. Calcd for $C_{26}H_{38}O_{14}$: C, 54.35; H, 6.62. Found: C, 53.97; H, 6.84.

*Allyl(2,3,4,6-tetra*-O-*acetyl*-β-D-*glucopyranosyl)*-(1→2)-α-D-*fucopyranoside* (**16**).—A solution of **15** (1.58 g, 0.75 mmol) in 50% AcOH (26 mL) was heated at 60 °C for 1.5 h and then concentrated in vacuo. The residue was purified by silica gel column chromatography (1:1 petroleum–EtOAc) to afford **16** (1.36 g, 93%) as a white solid: mp 131–132 °C; $[\alpha]_D^{20}$ +89.4° (*c* 0.1, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.92 (m, 1 H), 5.30 (dd, 1 H, *J* 17.3, 1.5 Hz), 5.21 (t, 1 H, *J* 9.4 Hz), 5.17 (t, 1 H, *J* 10.3 Hz), 5.06 (t, 1 H, *J* 9.7 Hz), 5.04 (dd, 1 H, *J* 9.4, 8.0 Hz), 4.98 (d, 1 H, *J* 3.1 Hz), 4.78 (m, 1 H), 4.20–3.97 (m, 6 H), 3.87 (t, 1 H, *J* 9.7 Hz), 3.84 (m, 1 H), 3.70 (m, 1 H), 2.08, 2.05, 2.03, 2.00 (s each, 3 H each), 1.28 (d, 3 H, *J* 6.5 Hz); ESIMS (*m*/*z*): 573 [$M + K^+$], 557 [$M + Na^+$], 553 [$M^+ + 1 + H_2O$]. Anal. Calcd for $C_{23}H_{34}O_{14}$: C, 51.66; H, 6.41. Found: C, 51.38; H 6.24.

*Allyl(2,3,4,6-tetra*-O-*acetyl*-β-D-*glucopyranosyl)*-(1→2)-*4*-O-*acetyl*-α-D-*fucopyranoside* (**17**).—To a solution of **16** (1.40 g, 2.62 mmol) in $CH_2Cl_2$ (20 mL) was added triethyl orthoacetate (2.2 mL) and *p*-TsOH·$H_2O$ (10

mg). After stirring at rt for 20 min, 20% HOAc (15 mL) was added, and the mixture was vigorously stirred overnight. $CH_2Cl_2$ (40 mL) was added to the mixture, and the solution was sequentially washed with water, aq $NaHCO_3$ and water. It was then dried and concentrated to a residue. The residue was purified by silica gel column chromatography (1:1 petroleum–EtOAc) to give (**17**) (1.32 g, 87%) as a white solid: mp 109–110 °C; $[\alpha]_D^{20}$ + 63.3° (*c* 0.39, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 5.92 (m, 1 H), 5.30–5.25 (m, 2 H), 5.21 (t, 1 H, *J* 9.5 Hz), 5.18 (t, 1 H, *J* 10.3 Hz), 5.07 (t, 1 H, *J* 9.7 Hz), 5.04 (dd, 1 H, *J* 9.6, 9.2 Hz), 5.01 (d, 1 H, *J* 3.4 Hz), 4.78 (d, 1 H, *J* 7.9 Hz), 4.20–4.15 (m, 4 H), 4.10 (m, 1 H), 4.05 (t, 1 H, *J* 12.8 Hz), 3.80 (m, 1 H, *J* 9.9 Hz), 3.72 (m, 1 H), 2.18, 2.08, 2.04, 2.03, 2.00 (s each, 3 H each), 1.13 (d, 3 H, *J* 6.7 Hz); ESIMS (*m*/*z*): 615 [M + $K^+$], 599 [M + $Na^+$], 594 ($M^+ + H_2O$). Anal. Calcd for $C_{25}H_{36}O_{15}$: C, 52.06; H, 6.30. Found: C, 52.08; H, 6.37.

*Allyl(2,3,4,6-tetra*-O-*acetyl*-β-D-*glucopyranosyl*)-(1→2)-[(*2,3,4-tri*-O-*acetyl*-β-D-*xylopyranosyl*)-(1→3)]-*4*-O-*acetyl*-α-D-*fucopyranoside* (**19**).—To a suspension of **17** (820 mg, 1.42 mmol), trichloroacetimidate **18** (659 mg, 1.56 mmol), and 4 Å molecular sieves (1.0 g) in dry $CH_2Cl_2$ (6 mL) under argon at −40 °C, was added $BF_3{\cdot}Et_2O$ (0.12 mL, 0.11 mmol) dropwise. After stirring for 3 h, the reaction mixture was treated with satd aq $NaHCO_3$ (4 mL) and then diluted with $CH_2Cl_2$ (20 mL). The organic layer was separated, dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (1:1 petroleum–EtOAc) to give **19** (0.74 g, 90%) and recovered **18** (250 mg) as white solids. **19**: mp 85–86 °C; $[\alpha]_D^{20}$ + 130.6° (*c* 0.13, $CHCl_3$); $^1$H NMR (600 Hz, $CDCl_3$): $\delta$ 5.91 (m, 1 H), 5.32–5.23 (m, 2 H), 5.19 (d, 1 H, *J* 10.4 Hz), 5.13 (t, 1 H, *J* 9.3 Hz), 5.06 (t, 1 H, *J* 10.0 Hz), 5.07 (t, 1 H, *J* 9.1 Hz), 5.02 (dd, 1 H, *J* 8.8, 8.5 Hz), 4.98 (d, 1 H, *J* 3.2 Hz), 4.94 (m, 1 H), 4.87 (dd, 1 H, *J* 8.7, 6.5 Hz), 4.64 (d, 1 H, *J* 6.3 Hz), 4.59 (d, 1 H, *J* 7.8 Hz), 4.22 (dd, 1 H, *J* 12.0 Hz), 4.15 (m, 2 H), 4.11 (m, 1 H), 4.10–4.04 (m, 2 H), 3.84 (m, 1 H), 3.70 (m, 1 H), 3.33 (m, 1 H, *J* 8.0 Hz), 2.16, 2.15, 2.14, 2.09, 2.03, 2.02, 2.01, 1.99 (s each, 3 H each), 1.09 (d, 3 H, *J* 6.4 Hz); ESIMS (*m*/*z*): 858 [M + 1 + $Na^+$], 853 [$M^+$ + 1 + $H_2O$]. Anal. Calcd for $C_{36}H_{50}O_{22}$: C, 51.78; H, 6.00. Found: C, 51.54; H 6.20.

*2,3,4,6-Tetra*-O-*acetyl*-β-D-*glucopyranosyl*-(1→2)-[(*2,3,4-tri*-O-*acetyl*-β-D-*xylopyranosyl*)-(1→3)]-*4*-O-*acetyl*-α-D-*fucopyranosyl trichloroacetimidate* (**2**). To a mixture of **19** (200 mg, 0.24 mmol) in $CH_3CN$–$H_2O$ (4:1, 15 mL), was added $C_6ClF_{12}I$ (135 mg, 0.29 mmol), followed by addition of a mixture of $Na_2SO_4$ (25 mg, 0.14 mmol) and $NaHCO_3$ (12 mg, 0.14 mmol). After stirring at rt for 1 h, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$ and then concentrated to give a residue. To a solution of the above residue in dry EtOH (5 mL) was added Zn (40 mg, 0.6 mmol) and $NH_4Cl$ (16 mg, 0.12 mmol). After refluxing for 10 min, the mixture was filtered. The filtrates were concentrated and then purified by silica gel column chromatography (1:1 petroleum ether–EtOAc) to give **20** (148 mg, 76%, a mixture of α, β anomers) as a white amorphous solid: $^1$H NMR analysis confirmed the removal of allyl group. To a solution of **20** (100 mg, 0.12 mmol) and trichloroacetonitrile (0.12 mL, 1.2 mmol) in $CH_2Cl_2$ (1 mL) was added DBU (0.014 mL, 0.09 mmol) dropwise at 0 °C. The mixture was stirred for 30 min and then directly purified by silica gel column chromatography (2:1 petroleum ether–EtOAc) to afford **2** (95 mg, 81%) as a white foam: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.50 (s, 1 H), 6.40 (d, 1 H, *J* 3.5 Hz), 5.31 (d, 1 H, *J* 3.6 Hz), 5.08 (m, 3 H), 4.90 (m, 3 H), 4.60 (d, 1 H, *J* 6.4 Hz), 4.47 (d, 1 H, *J* 9.4 Hz), 4.15 (m, 6 H), 3.72 (m, 1 H), 3.42 (m, 1 H), 2.20–1.90 (m, 24 H), 1.10 (d, 3 H, *J* 6.3 Hz). Trichloroacetimidate **2** was not stable and was directly used in the next glycosylation reaction.

*(25*R*) - 3*β - tert - *Butyldimethylsilyl - rusco-genin-1*β*-yl 2,3,4-tri*-O-*acetyl*-β-D-*fucopyranoside* (**22**).—A solution of **2** (38 mg, 0.070 mmol) in dry $CH_2Cl_2$ (3 mL) was stirred in the presence of 4 Å molecular sieves (5 mg) under argon at rt for 30 min. A solution of TMSOTf

in $CH_2Cl_2$ (0.1 N, 1.4 μL) was then added dropwise, followed by the addition of trichloroacetimidate **21** (34 mg, 0.079 mmol). After stirring for 2 h, the mixture was treated with satd aq $NaHCO_3$ (4 mL) and then diluted with $CH_2Cl_2$ (20 mL). The organic layer was separated, dried over sodium sulfate, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (2:1 petroleum ether–EtOAc) to give **22** (37 mg, 69%, based on **2**) as a white solid: mp 75–76 °C; $[\alpha]_D^{20}$ −26.6° (*c* 1.5, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 5.44 (brd, 1 H, *J* 5.5 Hz), 5.13 (m, 1 H), 5.02 (dd, 1 H, *J* 10.5, 7.4 Hz), 4.93 (m, 1 H), 4.35 (d, 1 H, *J* 7.4 Hz), 4.32 (m, 1 H), 3.66 (m, 1 H), 3.40–3.33 (m, 2 H), 3.29 (t, 1 H, *J* 10.8 Hz), 2.09, 1.97, 1.92 (s each, 3 H each), 1.11 (d, 3 H, *J* 6.3 Hz), 0.93 (s, 3 H), 0.88 (d, 3 H, *J* 6.9 Hz), 0.82 (s, 9 H), 0.74 (s, 3 H), 0.72 (d, 3 H, *J* 5.7 Hz); FABMS (*m*/*z*): 819 [$M^+ + 1$], 818 [$M^+$], 817 [$M^+ - 1$].

*(25*R*)-3-*O*-β-*tert*-Butyldimethylsilyl-ruscogenin-1β-yl 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl-(1→2)-[(2,3,4-tri-*O*-acetyl-β-*D*-xylopyranosyl)-(1→3)]-4-*O*-acetyl-β-*D*-fucopyranoside* (**23**).—A solution of **2** (24 mg, 0.04 mmol) in dry $CH_2Cl_2$ (3 mL) was stirred in the presence of 4 Å molecular sieves (50 mg) under argon at rt for 30 min. Then a solution of TMSOTf in $CH_2Cl_2$ (0.1 N, 8 μL) was added dropwise. After stirring for 20 min, trichloroacetimidate **3** (100 mg, 0.11 mmol) was added. The mixture was stirred for another 2 h and then treated with satd aq $NaHCO_3$ (4 mL) and diluted with $CH_2Cl_2$ (20 mL). The organic layer was separated, dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (1:1 petroleum ether–EtOAc) to give **23** (16 mg, 46%) and its α anomer (3 mg, 10%) as white amorphous solids. **23**: $[\alpha]_D^{20}$ −49.2° (*c* 0.09 in $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 5.55 (brd, 1 H, *J* 5.7 Hz), 5.18 (t, 1 H, *J* 9.3 Hz), 5.16 (m, 1 H), 5.12 (m, 1 H, *J* 9.7 Hz), 5.07 (m, 1 H, *J* 6.9 Hz), 4.91–4.86 (m, 2 H), 4.89 (d, 1 H, *J* 7.8 Hz), 4.85 (t, 1 H, *J* 9.1 Hz), 4.84 (d, 1 H, *J* 7.7 Hz), 4.39 (m, 1 H), 4.37 (m, 1 H, *J* 3.9 Hz), 4.31 (d, 1 H, *J* 7.3 Hz), 4.12 (dd, 1 H, *J* 12.4, 3.6 Hz), 4.09 (dd, 1 H, *J* 12.1, 4.0 Hz), 3.81 (dd, 1 H, *J* 9.7, 3.3 Hz), 3.75 (dd, 1 H, *J* 9.7, 7.3 Hz), 3.68 (m, 1 H), 3.57 (m, 1 H), 3.47–3.41 (m, 3 H), 3.37 (t, 1 H, *J* 10.5 Hz), 3.33 (dd, 1 H, *J* 12.1, 4.4 Hz); FABMS (*m*/*z*): 1321 [$M^+ + 1$], 1320 [$M^+$], 1265 [$M^+ + 1$-OAc]. HREIMS: Calcd for $C_{66}H_{100}O_{25}Si$: 1321.6350. Found: 1321.6401.

*(25*R*)-Ruscogenin-1β-yl β-*D*-glucopyranosyl-(1→2)-[β-*D*-xylopyranosyl-(1→3)]-β-*D*-fucopyranoside* (**1**).—Compound **23** (5 mg, 0.0038 mmol) was treated with TMSOTf (0.0095 mmol) in dry $CH_2Cl_2$ (3 mL) under argon for 10 min, followed by addition of neutral $Al_2O_3$ (3 mg), and then filtration. The filtrates were concentrated and dissolved in MeOH (2 mL) containing a catalytic amount of NaOMe. The mixture was stirred for 2 h and then concentrated to give a residue, which was purified by silica gel column chromatography (2:1 $CH_2Cl_2$–MeOH) to afford saponin **1** (2.8 mg, 85%) as a white amorphous solid: $[\alpha]_D^{20}$ −87.3° (*c* 0.11, pyridine, lit. −90.3°, *c* 0.63 [1]); $^1H$ NMR (pyridine-$d_5$): δ 5.85 (d, 1 H, *J* 7.0 Hz), 5.78 (brd, 1 H, *J* 5.9 Hz), 5.47 (d, 1 H, *J* 7.8 Hz), 5.20 (d, 1 H, *J* 6.9 Hz), 4.93 (dd, 1 H, *J* 10.5 Hz), 4.86 (dd, 1 H, *J* 3.0 Hz), 4.65–4.62 (m, 3 H), 4.58 (dd, 1 H), 4.54 (dd, 1 H, *J* 11.2, 5.3 Hz), 4.40–4.37 (m, 2 H), 4.31–4.27 (m, 4 H), 4.17 (t, 1 H, *J* 8.6 Hz), 4.15 (m, 1 H), 4.06 (dd, 1 H, *J* 11.8, 4.1 Hz), 3.90 (dd, 1 H, *J* 10.9 Hz), 3.88 (m, 1 H), 3.71 (m, 1 H), 3.65 (t, 1 H, *J* 10.6 Hz), 1.64 (d, 3 H, *J* 6.5 Hz), 1.47 (s, 3 H), 1.25 (d, 3 H, *J* 6.5 Hz), 1.12 (s, 3 H), 0.85 (d, 1 H, *J* 5.8 Hz); FABMS (*m*/*z*): 909 [$M + K^+$], 893 [$M + Na^+$], 871 [$M^+ + 1$], 869 [$M^+ - 1$]. HREIMS (*m*/*z*): Calcd for $C_{44}H_{70}O_{17}$: 871.4676. Found: 871.4691.

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