Available online at www.sciencedirect.com
SCIENCE DIRECT®
Carbohydrate Research 338 (2003) 827–833
CARBOHYDRATE RESEARCH
www.elsevier.com/locate/carres

Synthesis of a typical *N*-acetylglucosamine-containing saponin, oleanolic acid 3-yl α-L-arabinopyranosyl-(1 → 2)-α-L-arabinopyranosyl-(1 → 6)-2-acetamido-2-deoxy-β-D-glucopyranoside

Jiansong Sun,[a] Xiuwen Han,[a,*] Biao Yu[b,*]

[a]*State Key Laboratory of Catalyst, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, PR China*
[b]*State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, PR China*

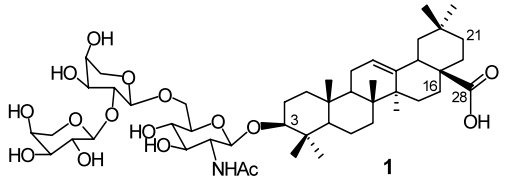
Received 30 December 2002; accepted 20 January 2003

Abstract

Oleanolic acid 3-yl α-L-arabinopyranosyl-(1 → 2)-α-L-arabinopyranosyl-(1 → 6)-2-acetamido-2-deoxy-β-D-glucopyranoside, a cytotoxic saponin isolated from *Acacia tenuifolia* and *Albizia subdimidiata* with a typical structure of the *N*-acetylglucosamine-containing plant saponins, was synthesized. The synthesis adopted a stepwise glycosylation fashion employing glycosyl trifluoroacetimidates **5** and **9** and thioglycoside **12** as donors.

1. Introduction

A great number of saponins from terrestrial plants, having enormous structural diversity, have been disclosed.[1] However, saponins containing *N*-acetylglucosamine are rare, with their numbers being less than 30 and structures highly conservative.[2–4] The aglycones of those saponins are oleanolic acid, echinocystic acid (with an additional 16α-OH), or acacic acid (with additional 16α,21β-OHs). Their 3-*O*-sugars exclusively begin with the β-D-*N*-acetylglucosamine residue, and extend mainly at its 6-OH. Saponin **1**, which was isolated from the Suriname rainforest plants *Acacia tenuifolia* and *Albizia subdimidiata*,[3] represents such a typical example. Its 3-*O*-sugar, α-L-Ara*p*-(1 → 2)-α-L-Ara*p*-(1 → 6)-β-D-GluNAc, also occurs in the calliandra saponins A-L from *Calliandra anomala*.[4] Saponin **1** shows significant activity against the A2780 and M109 lung cancer cell lines with an IC_{50} of 0.8 and 1.0 μg/mL, respectively.[3] Herein, we report the synthesis of this *N*-acetylglucosamine-containing plant saponin **1**.



1

2. Results and discussion

In contrast to the wide occurrence of triterpenoid saponins in nature, reports on their synthesis are only sporadic.[5,6] Previous experience has shown that construction of the glycosidic linkage with the aglycone is critical in the synthesis of saponins. The conditions for glycosylation of the aglycone are best developed at the monosaccharide level.[5–7] Besides, stepwise extension of the sugar chain could provide a versatile approach for synthesizing a glycoform family of saponins.[7] Herein, we adopt this strategy.

The glycosyl donors that are involved in the synthesis were prepared as shown in Scheme 1. Glycosyl trifluoroacetimidates **4**, **5**, **8**, and **9**[8b] were readily prepared in excellent yields (86–90%) from the corresponding 1-OH sugars (**2**,[9] **3**,[10] **6**,[11] and **7**,[8b] respectively) and *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride in the presence of K_2CO_3 in acetone. In contrast to the glucopyranose counterparts,[8] under the similar reaction

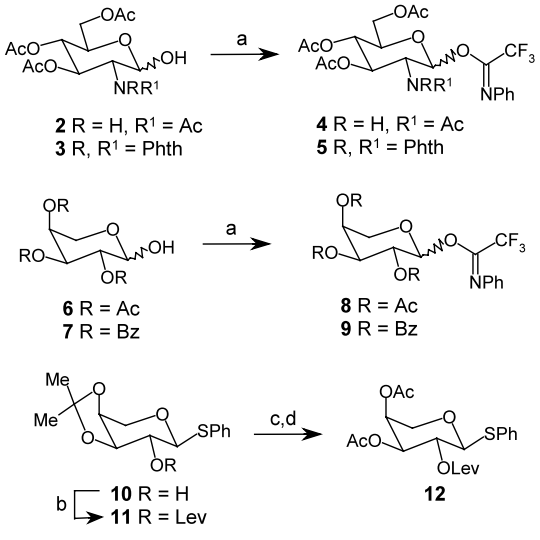
* Corresponding authors. Tel.: +86-21-64163300; fax: +86-21-64166128
E-mail address: byu@pub.sioc.ac.cn (B. Yu).

0008-6215/03/$ - see front matter
doi:10.1016/S0008-6215(03)00047-8

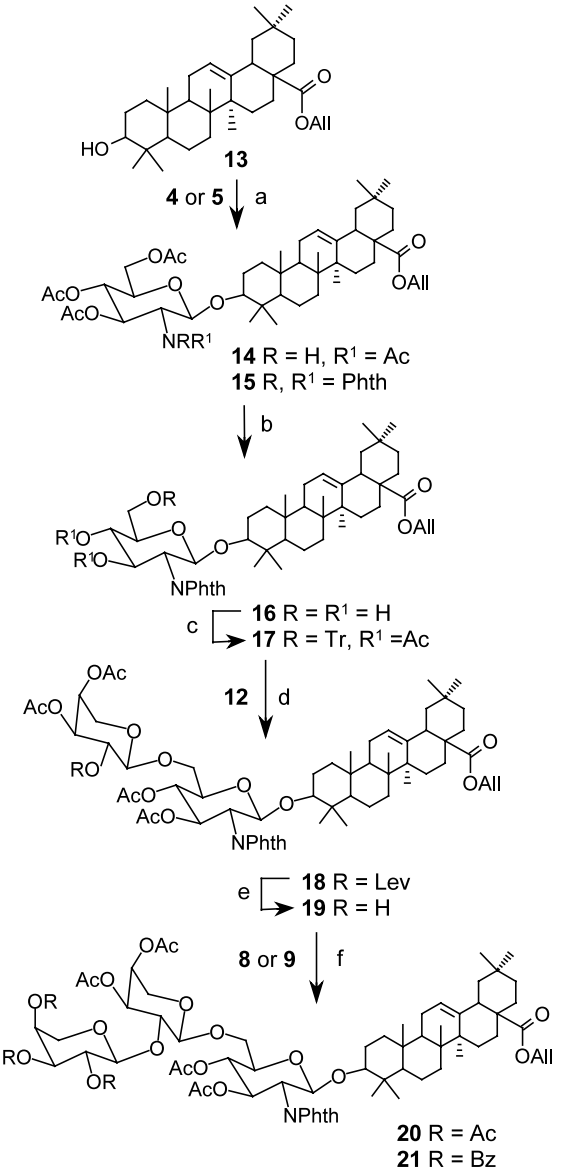
conditions, glucosamine 1-OH derivatives **2** and **3** predominantly led to the kinetically controlled β anomers[12] (**4**β:**4**α = 4.0:1, **5**β exclusively). This type of newly developed glycosyl donor has exhibited similar accessibility, stability, and reactivity as those of the corresponding trichloroacetimidates.[8] Phenyl 3,4-di-*O*-acetyl-2-*O*-levulinoyl-1-thio-α-L-arabinopyranoside (**12**) was easily prepared from phenyl 3,4-di-*O*-isopropylidene-1-thio-α-L-arabinopyranoside (**10**)[13] in three steps (87%). Compound **12** has a distinguishable 2-O-protection and was expected to be the synthon for the middle monosaccharide residue of saponin **1**.

Glycosylation of steroids and triterpenes is found to be unique; an ideal protocol employs the 2-*O*-benzoyl-glycosyl trichloroacetimidates as donors and a catalytic amount of TMSOTf as a promoter.[14] Not surprisingly, glycosylation of allyl oleanate **13**[14] with 2-acetamido-2-deoxy-D-glucopyranosyl trifluoroacetimidate (**4**) under the action of TMSOTf (0.05 equiv) led to the desired coupling product **14** in only 12% yield; the majority of the donor was transformed into the corresponding oxazoline derivative.[15] Instead, coupling of **13** with 2-deoxy-2-phthalimido-D-glucopyranosyl trifluoroacetimidate (**5**) under similar conditions afforded the desired glycoside **15** in quantitative yield. Removal of the acetate protection of **15** in 3% HCl–MeOH gave triol **16** (91%). The primary 6-OH on **16** was distinguished by a trityl group, then the remaining 3,4-OHs were protected with acetyl groups to provide **17** in 90% yield. Trityl ethers are known acceptors for glycosylation with thioglycosides.[6,16] Thus, coupling of trityl ether **17** with thioglycoside **12** under the promotion of NIS–TMSOTf led to the coupling product **18** in satisfactory yield (76%). Selective removal of the 2-*O*-levulinoyl group in the presence of hydrazine acetate in CH_2Cl_2–MeOH gave **19** (91%). Coupling of **19** with acetyl-protected arabinopyranosyl trifluoroacetimidate **8** under the promotion of TMSOTf (0.1 equiv) gave the expected trisaccharide **20** in only moderate yield (50%); a byproduct was isolated in considerable amount, which was shown by ^{1}H NMR spectroscopy to be the acetyl-transfer product, 28-*O*-allyl-oleatate-3-yl 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl-(1→6)-3,4-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside.

Therefore, benzoyl-protected arabinopyranosyl trifluoroacetimidate **9** was used under similar conditions



Scheme 1. Reagents and conditions: (a) $CF_3C(=NPh)Cl$, K_2CO_3, acetone, rt, 86% for **4**, 86% for **5**, 90% for **8**; (b) levulinic acid, DCC, DMAP, CH_2Cl_2, rt, 87%; (c) Dowex-50 (H^+), CH_3OH, rt; (d) Ac_2O, pyridine, rt, 100%.



Scheme 2. Reagents and conditions: (a) TMSOTf (0.05 equiv), CH_2Cl_2, 4 Å MS, 0 °C, 12% for **14**, 100% for **15**; (b) 3% HCl–CH_3OH, rt, 91%; (c) TrCl (10 equiv), pyridine, 50 °C; then Ac_2O, rt, 90%; (d) NIS (1.2 equiv)–TMSOTf (1.2 equiv), CH_2Cl_2, 4 Å MS, −20 °C, 76%; (e) NH_2NH_2·HOAc, CH_2Cl_2–CH_3OH, rt, 90%; (f) TMSOTf (0.1 equiv), CH_2Cl_2, 4 Å MS, rt, 50% for **20**, 76% for **21**.

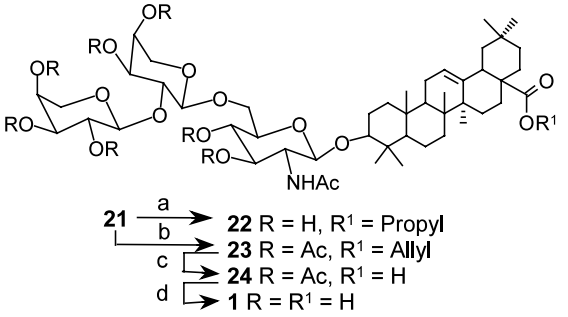
in the coupling with **19**; the coupling yield was improved, affording **21** in 76% yield (Schemes 2 and 3).

Deprotection of the phthalimide (Phth) in a heated solution of 95% ethanol (80 °C) in the presence of hydrazine hydrate, followed by acetylation (Ac_2O, pyridine), provided a major product whose ^1H NMR spectrum showed the absence of the signals from the 28-*O*-allyl group. Further O-deacetylation (MeONa, MeOH) produced **22** as a major product (24%, three steps). In comparison to the ^{13}C NMR data of the target saponin **1**,[3] the spectra of **22** showed additional signals (67.5, 23.3, 11.2 ppm, respectively) indicating an *O*-propyl group in the molecule. The upfield signal (179.9 ppm) for the 28-carbonyl carbon in **22** (cf. the 28-carboxylic acid carbon signal in **1** is at 184.7 ppm) is assignable to an ester function. A molecular weight of 989.7 $[M + Na^+]$ inferred from ESIMS further confirmed its structure to be the propyl ester **22**. Saturation of the double bond in the presence of hydrazine is not unprecedented.[17] However, the 12, 13 double bond on the triterpene skeleton was intact. The hindered 28-propyl ester was resistant to hydrolysis (0.35 M KOH, 60 °C, overnight).[18] Alternatively, the Phth group in **21** was removed in the presence of ethylenediamine in hot butanol (90 °C),[19] after acetylation (Ac_2O, pyridine), provided **23** in 80% yield. Cleavage of the allyl group under the action of $PdCl_2$ in methanol was sluggish,[20] affording **24** in only 46% yield, with the remaining **23** being recovered. Final removal of the *O*-acetyl groups in **23** (MeONa, MeOH) furnished the synthesis of saponin **1** (100%), whose physicochemical and spectral data are identical to those reported for the natural product.[3]

3. Experimental

3.1. General methods

Solvents were purified in the usual way. Thin layer chromatographys (TLCs) were performed on precoated plates of Silica Gel HF_{254} (0.5 mm, Yantai, China). Flash column chromatography was performed on Silica Gel H (10–40 μ, Yantai, China). Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter. NMR spectra were recorded on a Bruker AM 300 spectrometer with Me_4Si as the internal standard. *J* values were given in Hz. Mass spectra were obtained on a HP5989A or a VG Quatro mass spectrometer. Elemental analyses were performed on a Perkin–Elmer Model 2400 instrument.



Scheme 3. Reagents and conditions: (a) (i) $NH_2NH_2{\cdot}H_2O$, 95% EtOH, 80 °C; (ii) Ac_2O, pyridine, rt; (iii) MeONa, MeOH, rt, 24% (three steps); (b) $NH_2CH_2CH_2NH_2$, BuOH, 90 °C; then Ac_2O, pyridine, rt, 80%; (c) $PdCl_2$, MeOH, rt, 44%; (d) MeONa, MeOH, rt, 100%.

3.2. 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranosyl (*N*-phenyl)-trifluoroacetimidate (4)

To a solution of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranose (**2**)[9] (121 mg, 0.35 mmol) in acetone (3 mL) was added *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (85 mg, 0.41 mmol) and K_2CO_3 (75 mg, 0.54 mmol). After stirring at room temperature (rt) overnight, the mixture was filtered. The filtrates were evaporated to give a residue, which was applied to silica gel column chromatography (2:1 petroleum ether–EtOAc) to give **4** (155 mg, 86%, β:α = 4:1) as a white foam: R_f 0.85 (EtOAc). **4**β: $[\alpha]_D^{20}$ + 84.6° (*c* 1.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.33 (t, 1 H, *J* 7.8, NPh), 7.15 (t, 1 H, *J* 7.3, NPh), 6.82 (d, 2 H, *J* 7.7, NPh), 6.28 (br s, 1 H, NH), 5.72 (br s, 1 H, H-1), 5.26 (dt, 2 H, *J* 9.6, H-3, H-4), 4.51 (br t shape, 1 H, H-2), 4.26 (dd, 1 H, *J* 3.9, 12.4, H-6a), 4.11 (br d, 1 H, *J* 12.4, H-6b), 4.01 (br, 1 H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 170.5, 169.2, 168.2 (4 × OC(=O)Me), 146.3 (O–C=N), 128.5, 123.2, 120.1 (NPh), 89.1 (C-1), 70.7, 69.8, 67.3, 61.4, 53.1, 20.6, 20.5. EIMS (*m*/*z*): 518 (5%), 172 (26), 77 (34), 43 (100). Anal. Calcd for $C_{22}H_{25}F_3N_2O_9$: C, 50.97; H, 4.86; N, 5.46. Found: C, 50.73; H, 4.82; N, 5.04.

3.3. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-α-D-glucopyranosyl (*N*-phenyl)trifluoroacetimidate (5)

A similar procedure for the preparation of **4** was used for the preparation of **5**. Thus, 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranose (**3**)[10] (100 mg, 0.23 mmol) produced **5**β (118 mg, 86%, no α anomer was isolated) as a white foamy solid: R_f 0.31 (6:1 petroleum ether–EtOAc); $[\alpha]_D^{20}$ − 137.9° (*c* 1.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.91 (m, 2 H, Phth), 7.78 (m, 2 H, Phth), 7.27 (t, 2 H, *J* 7.6, NPh), 7.10 (t, 1 H, *J* 7.4, NPh), 6.74 (br, 1 H, NPh), 5.83 (br, 1 H, H-1), 5.25 (dt, 2 H, *J* 9.6, H-3, H-4), 4.57 (t, 1 H, *J* 9.6, H-2), 4.31 (dd, 1 H, *J* 3.9, 12.3, H-6a), 4.15 (br d, *J* 12.3, H-6b), 3.82 (br, 1 H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 170.0, 169.3, 167.3, 142.7, 134.5, 131.2, 128.6, 124.5, 123.7, 119.1, 92.7 (C-1), 72.7, 70.4, 68.2, 61.4, 53.6, 20.6, 20.5, 20.3. EIMS (*m*/*z*): 172 (6%), 139 (21), 97 (29), 43 (100). Anal. Calcd for

$C_{28}H_{25}F_3N_2O_{10}\cdot 0.5\ H_2O$: C, 54.60; H, 4.26; N, 4.55. Found: C, 54.60; H, 4.42; N, 4.41.

3.4. 2,3,4-Tri-*O*-acetyl-L-arabinopyranosyl 1-(*N*-phenyl)-trifluoroacetimidate (8)

A similar procedure for the preparation of **4** was used for the preparation of **8** (90%) from 2,3,4-tri-*O*-acetyl-L-arabinopyranose (**6**).[11] **8**: R_f 0.32 (4:1 petroleum ether–EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (t, 2 H, *J* 7.7), 7.13 (t, 1 H, *J* 7.7), 6.81 (d, 2 H, *J* 7.7), 6.57 (br, 1 H, H-1), 5.40 (d + s, 3 H, *J* 10.4, H-2, H-3, H-4), 4.12 (d, 1 H, *J* 12.9, H-5a), 3.92 (d, 1 H, *J* 13.2, H-5b), 2.17, 2.12, 2.05 (s each, 3 each, 3 × Ac); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 170.0, 143.1, 128.8, 124.6, 119.3, 93.3 (C-1), 68.3, 67.0, 66.9, 62.8, 20.8, 20.6, 20.5. ESIMS (*m*/*z*): 470.2 [M + Na^+]. Anal. Calcd for $C_{19}H_{20}F_3NO_8$: C, 51.01; H, 4.51; N, 3.13. Found: C, 51.02; H, 4.52; N, 3.01.

3.5. Phenyl 3,4-*O*-isopropylidene-2-*O*-levulinoyl-1-thio-α-L-arabinopyranoside (11)

To a solution of phenyl 3,4-*O*-isopropylidene-1-thio-α-arabinopyranoside (**10**)[13] (2.74 g, 9.7 mmol) and levulinic acid (5 mL, 48 mmol) in dry CH_2Cl_2 (10 mL) was added a dry CH_2Cl_2 (2 mL) solution containing DCC (5.01 g, 24 mmol) and DMAP (60 mg). After stirring at rt for 12 h, the mixture was filtered off the white solid. The filtrates were evaporated to give a reside, which was purified by silica gel column chromatography (4:1 petroleum ether–EtOAc) to give **11** (3.13 g, 87%) as a white amorphous solid: R_f 0.84 (80:1 CH_2Cl_2–CH_3OH); $[\alpha]_D^{20}$ + 9.0° (*c* 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51–7.27 (m, 5 H, SPh), 5.16 (dd, 1 H, *J* 5.7, 6.9, H-2), 4.87 (d, 1 H, *J* 7.2, H-1), 4.32–4.17 (m, 3 H, H-3, H-4, H-5a), 3.82 (m, 1 H, H-5b), 2.82–2.20 (m, 4 H), 2.96, 1.57, 1.37 (s each, 3 H each). Anal. Calcd for $C_{19}H_{24}O_6S$: C, 59.98; H, 6.36. Found: C, 60.04; H, 6.54.

3.6. Phenyl 3,4-di-*O*-acetyl-2-*O*-levulinoyl-1-thio-α-L-arabinopyranoside (12)

To a solution of **11** (100 mg, 0.26 mmol) in abs MeOH (15 mL) was added Dowex-50 (H^+). After stirring at rt for 3 h, the mixture was concentrated to give a residue, which was then dissolved in 1:1 Py–Ac_2O (2 mL). The resulting solution was stirred at rt overnight, and then concentrated. The residue was purified by silica gel column chromatography (3:1 petroleum ether–EtOAc) to give **12** (110 mg, 100%) as a white amorphous solid: R_f 0.15 (4:1 petroleum ether–EtOAc); $[\alpha]_D^{20}$ + 29.3° (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.27 (m, 5 H, SPh), 5.27 (m, 2 H, H-3, H-4), 5.13 (dd, 1 H, *J* 3.3, 8.8, H-2), 4.80 (d, 1 H, *J* 8.2, H-1), 4.17 (dd, 1 H, *J* 3.8, 12.6, H-5a), 3.70 (dd, 1 H, *J* 1.7, 12.6, H-5b), 2.81–2.61 (m, 4 H), 2.15, 2.10, 2.09 (s each, 3 H each). EIMS (*m*/*z*): 315 (14%), 139 (10), 99 (100), 97 (24), 43 (58). Anal. Calcd for $C_{20}H_{24}O_8S$: C, 56.59; H, 5.70. Found: C, 56.67; H, 5.74.

3.7. 28-*O*-Allyl-oleanate-3-yl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (14)

A mixture of the trifluoroacetimidate **4** (50 mg, 0.1 mmol), allyl oleanate **13** (60 mg, 0.12 mmol), and 4 Å MS (40 mg) in dry CH_2Cl_2 (3 mL) was stirred at rt for 30 min. Then a CH_2Cl_2 solution (1 mL) containing Me_3SiOTf (0.005 mmol) was added. After stirring for 30 min, Et_3N (0.5 mL) was added. The mixture was then filtered. The filtrates were concentrated to give a residue, which was subjected to silica gel column chromatography (1:1 petroleum ether–EtOAc) to give **14** (12 mg, 12%) as a white amorphous solid: R_f 0.48 (EtOAc); $[\alpha]_D^{20}$ + 30.3° (*c* 0.81, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90 (m, 1 H, allyl), 5.54 (d, 1 H, *J* 8.8), 5.35–5.19 (m, 4 H, allyl), 5.03 (t, 1 H, *J* 9.5), 4.70 (d, 1 H, *J* 8.2, H-1), 4.53 (m, 2 H), 4.25 (dd, 1 H, *J* 5.5, 12.2, H-6a), 4.12 (d, 1 H, *J* 10.2, H-6b), 3.88 (q, 1 H, *J* 9.2), 3.68 (m, 1 H), 3.10 (m, 1 H), 2.90 (m, 1 H), 2.08, 2.04, 2.03, 1.93 (s each, 3 H each, 4 × Ac), 1.61 (s, 6 H), 1.13 (s, 3 H), 0.92 (s, 6 H), 0.78 (s, 3 H), 0.72 (s, 3 H); ESIMS (*m*/*z*): 848.7 [M + Na^+]. Anal. Calcd for $C_{47}H_{71}NO_{11}\cdot H_2O$: C, 66.88; H, 8.71; N, 1.66. Found: C, 67.02; H, 8.54; N, 1.82.

3.8. 28-*O*-Allyl-oleanate-3-yl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (15)

A mixture of the trifluoroacetimidate **5** (310 mg, 0.5 mmol), allyl oleanate **13** (183 mg, 0.37 mmol), and 4 Å MS (60 mg) in dry CH_2Cl_2 (5 mL) was stirred at rt for 30 min. Then the mixture was cooled to 0 °C, and a CH_2Cl_2 solution (1 mL) containing Me_3SiOTf (0.05 equiv) was added. After stirring at this temperature for 30 min, Et_3N (0.1 mL) was added. The resulting mixture was filtered. The filtrates were concentrated to give a residue, which was purified by silica gel column chromatography (3:1 petroleum ether–EtOAc) to give **15** (336 mg, 100%) as a white amorphous solid: R_f 0.6 (2:1 petroleum ether–EtOAc); $[\alpha]_D^{20}$ + 60.6° (*c* 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86–7.72 (m, 4 H, Phth), 5.93–5.80 (m, 2 H), 5.40–5.10 (m, 5 H), 4.52 (m, 2 H), 4.38–4.30 (m, 2 H), 4.17 (dd, 1 H, *J* 2.2, 12.1, H-6′a), 3.88 (m, 1 H, H-5′), 3.07 (dd, 1 H, *J* 4.3, 11.6, H-3), 2.89 (m, 1 H), 2.10, 2.04, 1.84 (s each, 3 H each, 3 × Ac), 1.17, 0.93, 0.90, 0.85, 0.67, 0.59, 0.43 (s each, 3 H each, 7 × Me); ESIMS (*m*/*z*): 937.7 [M + Na^+]. Anal. Calcd for $C_{53}H_{71}NO_{12}\cdot H_2O$: C, 68.29; H, 7.89; N, 1.5. Found: C, 68.15; H, 7.59; N, 1.47.

3.9. 28-*O*-Allyl-oleanate-3-yl 2-deoxy-2-phthalimido-β-D-glucopyranoside (16)

A solution of **15** (48 mg, 0.016 mmol) in 3% HCl–CH_3OH (2 mL) was stirred at rt, and a precipitate appeared after 3 h. After continuous stirring overnight, Et_3N (0.5 mL) was added, and the mixture was concentrated in vacuum. The residue was subjected to silica gel column chromatography (8:8:1 petroleum ether–EtOAc–MeOH) to give **16** (41 mg, 100%) as a white amorphous solid: R_f 0.46 (8:8:1 petroleum ether–EtOAc–MeOH); $[\alpha]_D^{20}$ +63.8° (*c* 1.75, 1:1 $CHCl_3$–CH_3OH); ^{1}H NMR (300 MHz, C_5D_5N): δ 7.40 (m, 4 H, Phth), 5.80 (m 1 H), 5.54 (d, 1 H, *J* 8.5), 5.21–5.50 (m, 2 H), 4.65 (dd, 1 H, *J* 8.5, 10.7), 4.50 (m, 2 H), 4.39 (dd, 1 H, *J* 2.1, 11.9), 4.22 (dd, 1 H, *J* 5.0, 11.5), 4.09 (t, 1 H, *J* 9.5), 3.94 (m, 1 H), 3.00 (dd, 1 H, *J* 4.2, 11.3), 2.88 (m, 1 H), 1.00, 0.70, 0.69, 0.58, 0.52, 0.51, 0.46 (s each, 3 H each, 7 × Me); ESIMS (*m*/*z*): 810.7 [M + Na^+]. Anal. Calcd for $C_{47}H_{65}NO_9 \cdot 2\ H_2O$: C, 68.50; H, 8.44; N, 1.69. Found: C, 68.56; H, 8.11; N, 1.60.

3.10. 28-*O*-Allyl-oleatate-3-yl 3,4-di-*O*-acetyl-2-deoxy-2-phthalimido-6-*O*-trityl-β-D-glucopyranoside (17)

A mixture of **16** (50 mg, 0.06 mmol), TrCl (88 mg, 0.32 mmol), and DMAP (9 mg) in dry Py (2 mL) was stirred at 50 °C overnight. Then Ac_2O (2 mL) was added. The solution was stirred at rt for another 4 h, and was then concentrated in vacuum. The residue was purified by silica gel column chromatography (4:1 petroleum ether–EtOAc) to give **17** (64 mg, 90%) as a yellow solid: R_f 0.52 (4:1 petroleum ether–EtOAc); $[\alpha]_D^{20}$ + 77.1° (*c* 1.07, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80–7.72 (m, 4 H, Phth), 7.50–7.24 (m, 15 H, trityl), 5.89 (m, 1 H, allyl), 5.78 (dd, 1 H, *J* 9.2, 10.6), 5.41 (d, 1 H, *J* 8.5), 5.34–5.13 (m, 4 H), 4.52 (m, 2 H), 4.41 (dd, 1 H, *J* 8.5, 10.7), 3.77 (m, 1 H), 3.23–3.12 (m, 2 H), 2.90 (m, 1 H), 1.85, 1.72 (s each, 3 H each, 2 × Ac), 1.11, 0.93, 0.91, 0.89, 0.69, 0.64, 0.47 (s each, 3 H each, 7 × Me); ESIMS (*m*/*z*): 1137.6 [M + Na^+]. Anal. Calcd for $C_{70}H_{83}NO_{11}$: C, 74.24; H, 7.56; N, 1.24. Found: C, 74.23; H, 7.52; N, 1.17.

3.11. 28-*O*-Allyl-oleatate-3-yl 3,4-di-*O*-acetyl-2-*O*-levulinoyl-α-L-arabinopyranosyl-(1→6)-3,4-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (18)

A mixture of **17** (210 mg, 0.19 mmol), thioglycoside **12** (167 mg, 0.39 mmol), and 4 Å MS (80 mg) in dry CH_2Cl_2 (10 mL) was stirred at rt for 30 min, and then cooled to −20 °C. NIS (84 mg, 0.37 mmol) was added, followed by a dry CH_2Cl_2 solution (2 mL) of Me_3SiOTf (0.04 mL, 0.23 mmol). The resulting mixture was stirred for another 30 min before the addition of Et_3N (1 mL) and then filtration through a pad of Celite. The filtrates were concentrated to give a residue, which was subjected to silica gel column chromatography (3:2 petroleum ether–EtOAc) to afford **18** (170 mg, 6%) as a white amorphous solid: R_f 0.3 (2:1 toluene–EtOAc); $[\alpha]_D^{20}$ +53.7° (*c* 1.09, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84–7.71 (m, 4 H, Phth), 5.92–5.77 (m, 2 H), 5.39 (d, 1 H, *J* 8.2), 5.32–5.16 (m, 4 H), 5.04–4.96 (m, 2 H), 4.55 (d, 1 H, *J* 7.0), 4.50 (m, 1 H), 4.30 (dd, 1 H, *J* 8.5, 11.0), 4.05 (dd, 1 H, *J* 3.3, 12.9), 3.88 (m, 2 H), 3.73 (dd, 1 H, *J* 6.7, 11.6), 3.60 (dd, 1 H, *J* 1.6, 13.0), 3.08 (dd, 1 H, *J* 4.3, 12.5), 2.89–2.57 (m, 4 H, Lev), 2.20, 2.13, 2.08, 2.02, 1.85 (s each, 3 H each, 5 × MeCO), 1.06, 0.91, 0.88, 0.85, 0.66, 0.57, 0.41 (s each, 3 H each, 7 × Me); ESIMS (*m*/*z*): 1209.7 [M + Na^+]. Anal. Calcd for $C_{65}H_{87}NO_{19} \cdot 2\ H_2O$: C, 63.86; H, 7.5; N, 1.14. Found: C, 63.97; H, 7.40; N, 1.01.

3.12. 28-*O*-Allyl-oleanate-3-yl 3,4-di-*O*-acetyl-α-L-arabinopyranosyl-(1→6)-3,4-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (19)

To a solution of **18** (28 mg, 0.024 mmol) in dry CH_2Cl_2 (1 mL) was added a MeOH solution (1 mL) of hydrazine acetate (23 mg, 0.25 mmol). After stirring at rt for 3 h, the solution was concentrated. The residue was purified by silica gel column chromatography (3:2 petroleum ether–EtOAc) to give **19** (25 mg, 90%) as a white amorphous solid: R_f 0.3 (2:1 toluene–EtOAc); $[\alpha]_D^{20}$ +64.4° (*c* 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86–7.71 (m, 4 H, Phth), 5.83 (m + t, 2 H, *J* 9.7), 5.41 (d, 1 H, *J* 8.5), 5.32–5.16 (m, 5 H), 4.91 (dd, 1 H, *J* 3.6, 10.2), 4.50 (m, 2 H), 4.34 (dd, 1 H, *J* 4.5, 10.7), 4.27 (d, 1 H, *J* 7.7), 4.08 (t, 1 H, *J* 11.0), 3.99–3.86 (m, 3 H), 3.61 (m, 2 H), 3.04 (m, 1 H), 2.88 (m, 1 H), 2.14, 2.08, 2.04, 1.86 (s each, 3 H each, 4 × Ac), 1.08, 0.92, 0.89, 0.84, 0.66, 0.58, 0.41 (s each, 3 H each, 7 × Me); ESIMS (*m*/*z*): 1111.9 [M + Na^+]. Anal. Calcd for $C_{60}H_{81}NO_{17} \cdot 2\ H_2O$: C, 64.10; H, 7.62; N, 1.24. Found: C, 64.11; H, 7.47; N, 1.09.

3.13. 8-*O*-Allyl-oleanate-3-yl 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl-(1→2)-3,4-di-*O*-acetyl-α-L-arabinopyranosyl-(1→6)-3,4-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (20)

A mixture of **19** (74 mg, 0.07 mmol), trifluoroacetimidate **8** (49 mg, 0.11 mmol), and 4 Å MS (50 mg) in dry CH_2Cl_2 (3 mL) was stirred at rt for 30 min, then Me_3SiOTf (0.1 mL, 0.007 mmol) was added. After continuous stirring for another 30 min, Et_3N (0.5 mL) was added. The mixture was filtered through a pad of Celite. The filtrates were concentrated to give a residue, which was purified by silica gel column chromatography (2:1 toluene–EtOAc) to provide **20** (47.1 mg, 50%) as a white amorphous solid: R_f 0.24 (2:1 toluene–EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84–7.72 (m,

4 H, Phth), 5.92–5.79 (m, 2 H), 5.36 (d, 1 H, *J* 8.2), 5.32–5.00 (m, 9 H), 4.71 (d, 1 H, *J* 6.9), 4.64 (d, 1 H, *J* 4.5), 4.50 (m, 2 H), 4.27 (dd, 1 H, *J* 8.5, 10.7), 4.10–3.98 (m, 2 H), 3.89–3.62 (m, 5 H), 3.57 (dd, 1 H, *J* 3.2, 12.0), 3.10 (dd, 1 H, *J* 4.6, 12.0), 2.84 (m, 1 H), 1.08, 0.91, 0.89, 0.84, 0.66, 0.55, 0.43 (s each, 3 H each, 7 × Me); ESIMS (*m*/*z*): 1370.4 [M + Na^+].

3.14. 28-*O*-Allyl-oleanate-3-yl 2,3,4-tri-*O*-benzoyl-α-L-arabinopyranosyl-(1 → 2)-3,4-di-*O*-acetyl-α-L-arabinopyranosyl-(1 → 6)-3,4-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (21)

A similar procedure for the synthesis of **20** was employed for the synthesis of **21**. Compound **21** (319 mg, 76%) was obtained after silica gel column chromatography (1:1 petroleum ether–EtOAc) as a white amorphous solid: R_f 0.37 (3:2 petroleum ether–EtOAc); $[\alpha]_D^{20}$ + 103.3° (*c* 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06–7.31 (m, 19 H, Bz + Phth), 5.85 (m + t, 2 H, *J* 9.6), 5.72 (br s, 1 H), 5.67 (dd, 1 H, *J* 6.3, 8.6), 5.57 (dd, 1 H, *J* 3.4, 8.6), 5.39 (d, 1 H, *J* 8.2), 5.32–5.05 (m, 5 H), 4.92 (dd, 1 H, *J* 3.3, 9.0), 4.67 (d, 1 H, *J* 5.5), 4.44 (m, 2 H), 4.31 (dd, 1 H, *J* 8.3, 10.5), 4.04–3.88 (m, 6 H), 3.59 (dd, 1 H, *J* 2.2, 9.4), 3.14 (dd, 1 H, *J* 4.0, 11.5), 2.87 (m, 1 H), 2.04, 1.87 (s each, 3 H each, 2 × Ac), 1.89 (s, 6 H, 2 × Ac), 1.13, 0.94, 0.92, 0.81, 0.64, 0.54, 0.39 (s each, 3 H each, 7 × Me); ESIMS (*m*/*z*): 1554.3 [M + Na^+]. Anal. Calcd for $C_{86}H_{101}NO_{24}·H_2O$: C, 66.60; H, 6.70; N, 0.90. Found: C, 66.45; H, 6.85; N, 1.15.

3.15. 28-*O*-Propyl-oleanate-3-yl α-L-arabinopyranosyl-(1 → 2)-α-L-arabinopyranosyl-(1 → 6)-2-deoxy-2-acetamido-β-D-glucopyranoside (22)

A solution of **21** (102 mg, 0.075 mmol) and $NH_2NH_2·H_2O$ (2 mL) in EtOH (95%, 4 mL), after stirring at 80 °C for 6 h, was concentrated and coevaporated with toluene twice to give a residue. The residue was dissolved in 1:1 pyridine–Ac_2O (4 mL). The resulting solution, after stirring for 4 h, was concentrated. The residue was then dissolved in abs MeOH (4 mL) containing MeONa (70 mg). The solution was stirred at rt overnight, and then neutralized with Dowex-50 (H^+). Filtration and evaporation of the solvent gave a crude product, which was purified by silica gel column chromatography (3:1 $CHCl_3$–MeOH) to give **22** (18 mg, 24%) as a white amorphous solid: R_f 0.45 (30:5:4 EtOAc–CH_3OH–H_2O); ^{1}H NMR (300 MHz, CD_3OD): δ 5.26 (s, 1 H, H-12), 4.54 (d, 1 H, *J* 5.8), 4.51 (d, 1 H, *J* 6.8), 4.45 (d, 1 H, *J* 8.2), 4.08–4.43 (m, 17 H), 3.32 (m, 2 H), 3.19 (dd, 1 H, *J* 4.1, 11.2), 2.90 (m, 1 H), 1.96 (s, 3 H, NAc), 1.17, 0.97, 0.95, 0.94, 0.92, 0.77, 0.76 (s each, 3 H, 7 × Me); ^{13}C NMR (75 MHz, CD_3OD): δ 179.9, 173.7, 145.3, 124.2, 106.1, 105.2, 103.7, 90.8, 80.7, 76.8, 76.0, 74.5, 73.1, 72.3, 69.9, 69.7, 69.1, 67.5 67.3, 66.0, 58.1, 57.1, 47.4, 43.2, 43.1, 40.9, 40.2, 38.2, 35.1, 34.3, 34.1,33.8, 31.9, 29.0, 28.8, 27.3, 26.7, 24.8, 24.2, 23.4, 23.3, 19.6, 18.1, 17.4, 16.2, 11.2. ESIMS (*m*/*z*): 989.7 [M + Na^+].

3.16. 28-Allyl-*O*-oleanate-3-yl 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl-(1 → 2)-3,4-di-*O*-acetyl-α-L-arabinopyranosyl-(1 → 6)-3,4-di-*O*-acetyl-2-deoxy-2-acetamido-β-D-glucopyranoside (23)

A solution of **21** (75 mg, 0.055 mmol) in BuOH (2 mL) and $NH_2CH_2CH_2NH_2$ (2 mL) was stirred at 90 °C overnight, and then concentrated to give a residue. The residue was coevaporated with toluene and EtOH twice and then dissolved in 1:1 pyridine–Ac_2O (2 mL). The resulting mixture was stirred at rt for 4 h and then concentrated to give a residue, which was subjected to silica gel column chromatography (4:4:0.1 petroleum ether–EtOAc–EtOH) to provide **23** (48 mg, 80%) as a white amorphous solid: R_f 0.39 (40:1 CH_2Cl_2–CH_3OH); $[\alpha]_D^{20}$ + 17.9° (*c* 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (m, 1 H, allyl), 5.57 (d, 1 H, *J* 8.8), 5.30–5.13 (m, 6 H), 5.00 (m, 3 H), 4.68–4.50 (m, 4 H), 4.02–3.65 (m, 8 H), 3.52 (dd, 1 H, *J* 3.3, 11.8), 3.12 (dd, 1 H, *J* 4.5, 11.4), 2.88 (m, 1 H), 2.13 (m, 8 × Ac), 1.16, 0.92, 0.90, 0.98, 0.76, 0.74, 0.71 (s each, 3 H each, 7 × Me); ESIMS (*m*/*z*): 1281.5 [M + Na^+]. Anal. Calcd for $C_{65}H_{95}NO_{23}·H_2O$: C, 61.16; H, 7.66; N, 1.10. Found: C, 61.02; H, 7.86; N, 1.29.

3.17. Oleanolic acid-3-yl 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl-(1 → 2)-3,4-di-*O*-acetyl-α-L-arabinopyranosyl-(1 → 6)-3,4-di-*O*-acetyl-2-deoxy-2-acetamido-β-D-glucopyranoside (24)

A mixture of **23** (38 mg, 0.03 mmol) and $PdCl_2$ (2 mg, 0.01 mmol) in abs MeOH (4 mL) was stirred at rt for 48 h, and filtered through a pad of Celite. The filtrates were concentrated. The residue was subjected to silica gel column chromatography (2:2:0.1 petroleum ether–EtOAc–EtOH) to give **24** (16 mg, 44%) as a white amorphous solid: R_f 0.39 (2:2:0.1 petroleum ether–EtOAc–EtOH); $[\alpha]_D^{20}$ + 22.0° (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.56 (m, 1 H), 5.27–4.98 (m, 7 H), 4.67–4.57 (m, 3 H), 4.01 (m, 2 H), 3.85–3.47 (m, 6 H), 1.11, 1.10, 0.91, 0.89, 0.74, 0.73, 0.70 (s each, 3 H each, 7 × Me); ESIMS (*m*/*z*): 1241.7 [M + Na^+]. Anal. Calcd for $C_{62}H_{91}NO_{23}·3.5\ H_2O$: C, 58.11; H, 7.71; N, 1.09. Found: C, 57.92; H, 7.45; N, 1.10.

3.18. Preparation of oleanolic acid-3-yl α-L-arabinopyranosyl-(1 → 2)-α-L-arabinopyranosyl-(1 → 6)-2-acetamido-2-deoxy-β-D-glucopyranoside (1)

A solution of **24** (29 mg, 0.024 mmol) in abs MeOH (4 mL) containing MeONa (50 mg) was stirred at rt

overnight and then concentrated to give a residue, which was purified by silica gel column chromatography (3:1:0.1 $CHCl_3$–MeOH–AcOH) to afford **1** (20 mg, 90%) as a white amorphous solid: R_f 0.27 (3:1:0.2 $CHCl_3$–CH_3OH–AcOH); $[\alpha]_D^{20}$ +40.0° (*c* 0.51, MeOH) (Lit.[3] $[\alpha]_D^{26}$ +39° (*c* 1.00, MeOH)); ^1H NMR (300 MHz, CD_3OD): δ 5.26 (s, 1 H), 4.43 (d, 1 H, *J* 8.2), 4.55 (d, 1 H, *J* 5.8), 4.49 (d, 1 H, *J* 6.9), 1.17 (s, 3 H), 0.98 (s, 3 H), 0.95 (s, 6 H), 0.91 (s, 3 H), 0.82 (s, 3 H), 0.77 (s, 3 H); ^{13}H NMR (75 MHz, CD_3OD): δ 173.7, 145.6, 123.9, 106.1, 105.2, 103.7, 90.8, 80.7, 76.8, 76.0, 74.5, 73.8, 73.3, 72.4, 69.9, 69.7, 69.1, 67.4, 66.0, 58.0, 57.2, 47.7, 43.2 (2C), 40.9, 40.2, 40.0, 38.2, 35.3, 34.3, 34.2, 33.9, 31.9, 29.2, 28.8, 27.3, 26.8, 24.9, 24.3 (2C), 23.4, 19.6, 18.1, 17.4, 16.2. ESIMS (*m*/*z*): 946.7 [M + Na^+].

Acknowledgements

This work was supported by the National Natural Science Foundation of China (20172068, 29925203), the Ministry of Science and Technology of China (G1998051104), and the Shanghai/Hong Kong/Anson Research Foundation.

References

1. (a) Hostettmann, K.; Marston, A. *Saponins*; Cambridge University Press: New York, 1995;
(b) Waller, G. R.; Yamasaki, K. *Saponins Used in Traditional and Modern Medicine*; Plenum Press: New York, 1996;
(c) Waller, G. R.; Yamasaki, K. *Saponins Used in Food and Agriculture*; Plenum Press: New York, 1996.
2. (a) Ripperger, H.; Preiss, A.; Schmidt, J. *Phytochemistry* **1981**, *20*, 2434–2435;
(b) Okada, Y.; Shibata, S.; Ikekawa, T.; Javellana, A. M. J.; Kamo, O. *Phytochemistry* **1987**, *26*, 2789–2796;
(c) Okada, Y.; Shibata, S.; Javellana, A. M. J.; Kamo, O. *Chem. Pharm. Bull.* **1988**, *36*, 1264–1269;
(d) Cappani, G.; Orsini, F.; Sisti, M.; Verotta, L. *Phytochemistry* **1989**, *28*, 863–866;
(e) Maillard, M.; Adewunmi, O. O.; Hostettmann, K. *Helv. Chim. Acta* **1989**, *72*, 668–674;
(f) Orsini, F.; Pelizzoni, F.; Verotta, L. *Phytochemistry* **1991**, *30*, 4111–4115;
(g) Ikeda, T.; Fujiwara, S.; Araki, K.; Kinjo, J.; Nohara, T.; Miyoshi, T. *J. Nat. Prod.* **1997**, *60*, 102–107;
(h) Tezuka, Y.; Honda, K.; Banskota, A. H.; Thet, M. M.; Kadota, S. *J. Nat. Prod.* **2000**, *63*, 1658–1664.
3. (a) Abdel-Kader, M.; Hoch, J.; Berger, J. M.; Evans, R.; Miller, J. S.; Wisse, J. H.; Mamber, S. W.; Dalton, J. M.; Kingston, D. G. I. *J. Nat. Prod.* **2001**, *64*, 536–539;
(b) Seo, Y.; Hoch, J.; Abdel-Kader, M.; Malone, S.; Derveld, I.; Adams, H.; Werkhoven, M. C. M.; Wisse, J. H.; Mamber, S. W.; Dalton, J. M.; Kingston, D. G. I. *J. Nat. Prod.* **2002**, *65*, 170–174.
4. (a) Tekeda, T.; Nakamura, T.; Takashima, S.; Yano, O.; Ogihara, Y. *Chem. Pharm. Bull.* **1993**, *41*, 2132–2137;
(b) Tani, C.; Ogihara, Y.; Mutuga, M.; Nakamura, T.; Tekeda, T. *Chem. Pharm. Bull.* **1996**, *44*, 816–822.
5. (a) Saito, S.; Sasaki, Y.; Kuroda, K.; Hayashi, Y.; Sumita, S.; Nagamura, Y.; Nishida, K.; Isiguro, I. *Chem. Pharm. Bull.* **1993**, *41*, 539–543;
(b) Saito, S.; Ebashi, J.; Sumita, S.; Furumoto, T.; Nagamura, Y.; Nishida, K.; Isiguro, I. *Chem. Pharm. Bull.* **1993**, *41*, 1395–1401;
(c) Atopkina, L. N.; Uvarova, N. I.; Elyakov, G. B. *Carbohydr. Res.* **1997**, *303*, 449–451;
(d) Anufriev, V. Ph.; Malinovskaya, G. V.; Denisenko, V. A.; Uvarova, N. I.; Elyakov, G. B.; Kim, S. I.; Baek, N. I. *Carbohydr. Res.* **1997**, *304*, 179–182.
6. Yu, B.; Xie, J.; Deng, S.; Hui, Y. *J. Am. Chem. Soc.* **1999**, *121*, 12196–12197.
7. Yu, B.; Hui, Y. In *Glycochemistry*: *Principles*, *Synthesis and Applications*; Wang, P. G.; Bertozzi, C. R., Eds.; Marcel Dekker: New York, 2001; pp 167–174.
8. (a) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405–2407;
(b) Yu, B.; Tao, H. *J. Org. Chem.* **2002**, *67*, 9099–9102.
9. Probert, M. A.; Zhang, J.; Bundle, D. R. *Carbohydr. Res.* **1996**, *296*, 149–170.
10. Kretzschmar, G.; Stahl, W. *Tetrahedron* **1998**, *54*, 6341–6358.
11. Toshiyuki, M.; Hisashi, M.; Masahiro, Z.; Kazuhiro, H.; Masayuki, Y. *Chem. Pharm. Bull.* **1999**, *47*, 1717–1724.
12. Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235.
13. Nicolaou, K. C.; Trujillo, J. I.; Chibale, K. *Tetrahedron* **1997**, *53*, 8751–8778.
14. Deng, S.; Yu, B.; Xie, J.; Hui, Y. *J. Org. Chem.* **1999**, *64*, 7265–7266.
15. Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167–1195.
16. Boons, G.-J.; Bowers, S.; Coe, D. M. *Tetrahedron Lett.* **1997**, *38*, 3773–3776.
17. (a) Hanuš, P. J.; Voříšek, J. *Collect Czech. Chem. Commun.* **1929**, *1*, 223;
(b) Nitz, M.; Bundle, D. R. *J. Org. Chem.* **2001**, *66*, 8411–8423.
18. Ohtani, K.; Mizutani, K.; Kasai, R.; Tanaka, O. *Tetrahedron Lett.* **1984**, *25*, 4537–4540.
19. (a) Kanie, O.; Crawley, S. C.; Palac, M. M.; Hindsgaul, O. *Carbohydr. Res.* **1993**, *243*, 139–164;
(b) Konstantin, V.; Antonov, L. V.; Backinowsky, G.; Brade, L.; Holst, O.; Zamojski, A. *Carbohydr. Res.* **1998**, *314*, 85–93.
20. Bose, R.; Scheffold, R. *Angew. Chem.* **1976**, *88*, 578–579.