Synthesis and Evaluation of Four Hederagenin Glycosides as α-Glucosidase Inhibitor

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The four hederagenin glycosides **1**–**4** were efficiently synthesized through one-pot sequential glycosylations with glycose 1-(trichloroacetimidate)s as donors, resulting in a significantly simplified synthetic procedure without isolation of glycosylation intermediates. The activity of the synthetic hederagenin glycosides **1**–**4** against α-glucosidase type IV was evaluated; hederagenin glycoside **4** containing an α-L-rhamnopyranosyl unit showed the best activity with an IC_{50} value of 47.9 μM.

Introduction. – α-Glucosidase is a membrane-bound enzyme at the epithelium of the small intestine, that cleaves glucose from disaccharides and oligosaccharides by hydrolysis. α-Glucosidase inhibitors are a class of compounds that inhibit the breakdown of oligo- and disaccharides from complex dietary carbohydrates, slow down the absorption of absorbable monosaccharides available, and reduce the postprandial insulin and glucose peak [1][2]. In fact, α-glucosidase inhibitors like acarbose, voglibose, and miglitol effectively compensate for defective early-phase insulin release by inhibiting postprandial absorption of monosaccharides, and have been approached for clinical use of the management of type-2 diabetes [3–5].

Hederagenin saponins are largely represented in nature and possess many biological activities such as hemolytic, antiviral, antimicrobial, fungicidal, molluscicidal, feeding deterrent, antimutagenic, or cytotoxic activity [6–19] (hederagenin = (3β,4α)-3,23-dihydroxyolean-12-en-28-oic acid). However, few researchers focus on the α-glucosidase activities of these hederagenin saponins. One of the reason is that the extraction of this kind of saponins from natural sources can be long and tedious and results in very small quantities of the desired saponin. Chemical synthesis and modification is known to be a powerful tool for the preparation of novel compounds with diverse structures for pharmacology studies and for the development of new chemical entities. In fact, the synthesis of hederagenin glycosides has attracted some attention [20–22]. Nevertheless, a more concise and efficient synthetic strategy towards hederagenin saponins require further investigations. Based on our experience in triterpenoid saponin synthesis [23–27], we developed a highly efficient synthesis of the four hederagenin glycosides **1**–**4** (*Fig.*), which were subsequently evaluated for α-glucosidase activity.

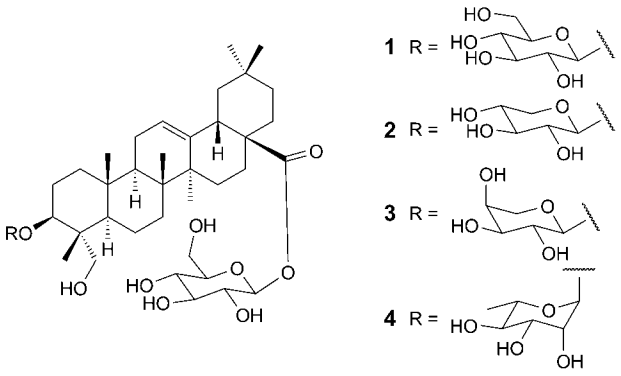


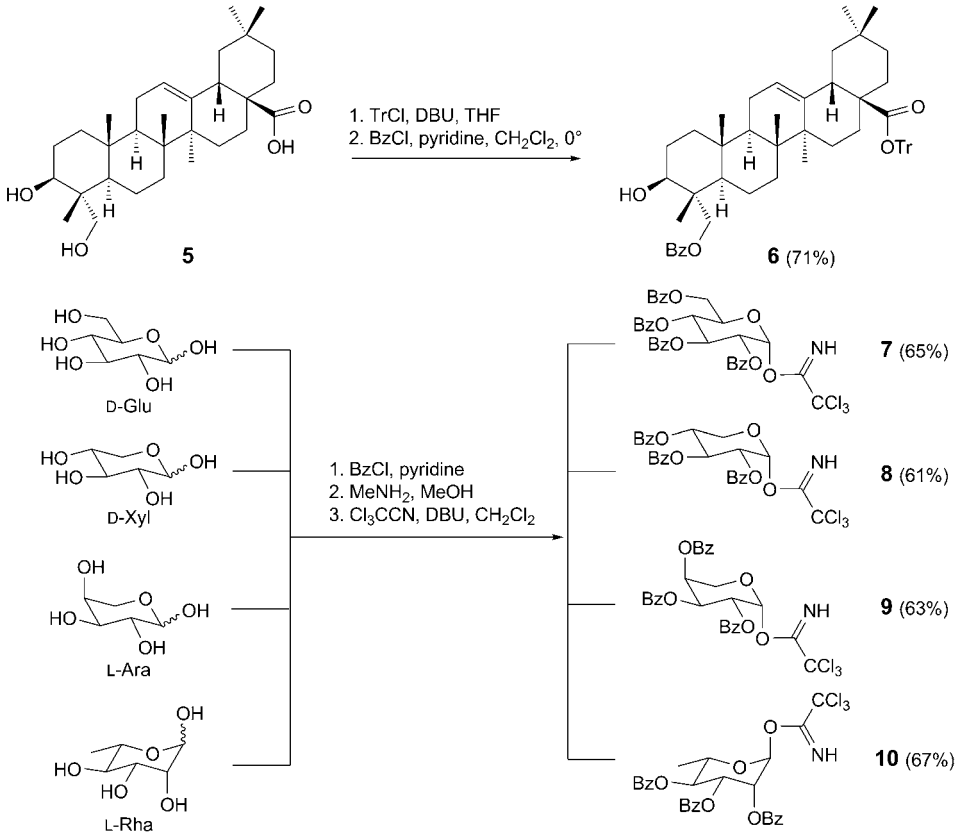
Figure. *Synhtesized hederagenin glycosides* **1**–**4**

Results and Discussion. – Construction of the glycosidic linkage with the aglycone is critical and difficult in the synthesis of saponins. Fortunately, the development of glycosylation procedures by one-pot protocols has made the synthesis of oligosaccharides and glycoconjugates bearing a complicated sugar moiety available or even easier [28–40]. Recently, by applying the 'one-pot sequential glycosylation' procedure, we have successfully completed the synthesis of several bidesmosidic oleanolic acid saponins [23–25][27]. Encouraged by these accomplishments, we decided to adopt this strategy with two glycose 1-(trichloroacetimidate)s as donors to achieve the synthesis of the hederagenin glycosides **1**–**4**. Such an approach would allow us to rapidly access a variety of structural analogs of hederagenin glycosides.

As shown in *Scheme 1*, hederagenin acceptor **6** was easily prepared in 71% yield from hederagenin (**5**), triphenylmethyl chloride (TrCl), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing tetrahedrofuran (THF), and then benzoyl chloride (BzCl) in pyridine at 0° [40]. Monosaccharide 1-(trichloroacetimidate) donors **7**–**10** were synthesized in a straightforward manner. Firstly, commercial monosaccharides (D-glucose, D-xylose, L-arabinose, and L-rhamnose (=6-deoxy-L-mannose) were perbenzoylated with BzCl in pyridine. Then regioselective removal of the benzoyl group at the anomeric position with $MeNH_2$ in MeOH, followed by treatment with trichloroacetonitrile (Cl_3CCN) and DBU in dry CH_2Cl_2, afforded the corresponding imidates **7**–**10** in yields of 60–70% over three steps [26].

With hederagenin acceptor **6** and glycosyl donors **7**–**10** in hand, we then set about assembling the target hederagenin glycosides **1**–**4** in a concise way a by one-pot sequential glycosylation with two glycose 1-(trichloroacetimidate) donors (*Scheme 2*). Thus, first the coupling of hederagenin acceptor **6** with monosaccharide donor **7**, **8**, **9**, or **10** in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate ($Me_3SiOSO_2CF_3$; 0.3 equiv) at −78° provided within 30 min the desired glycoside **11**, **12**, **13**, or **14**, which was then transformed into the key intermediate **11′**, **12′**, **13′**, or **14′** by warming to room temperature for 30 min. After addition of a CH_2Cl_2 solution of the glucose 1-(trichloroacetmidate) **7** to the above mixture at 0°, the desired product **15**, **16**, **17**, or **18** was obtained. Removal of all protecting benzoyl groups with MeONa in CH_2Cl_2/MeOH afforded the target hederagenin glycosides **1**–**4** in satisfactory yields.

Scheme 1



The activity of the synthetic hederagenin glycosides **1**–**4** against α-glucosidase type IV was evaluated, and the results are summarized in the *Table*. The data indicate that the synthetic hederagenin glycosides **1**–**4** were active. Among them, hederagenin glycoside **4** containing the α-L-rhamnopyranosyl unit showed the best activity with a IC_{50} value of 47.9 μM.

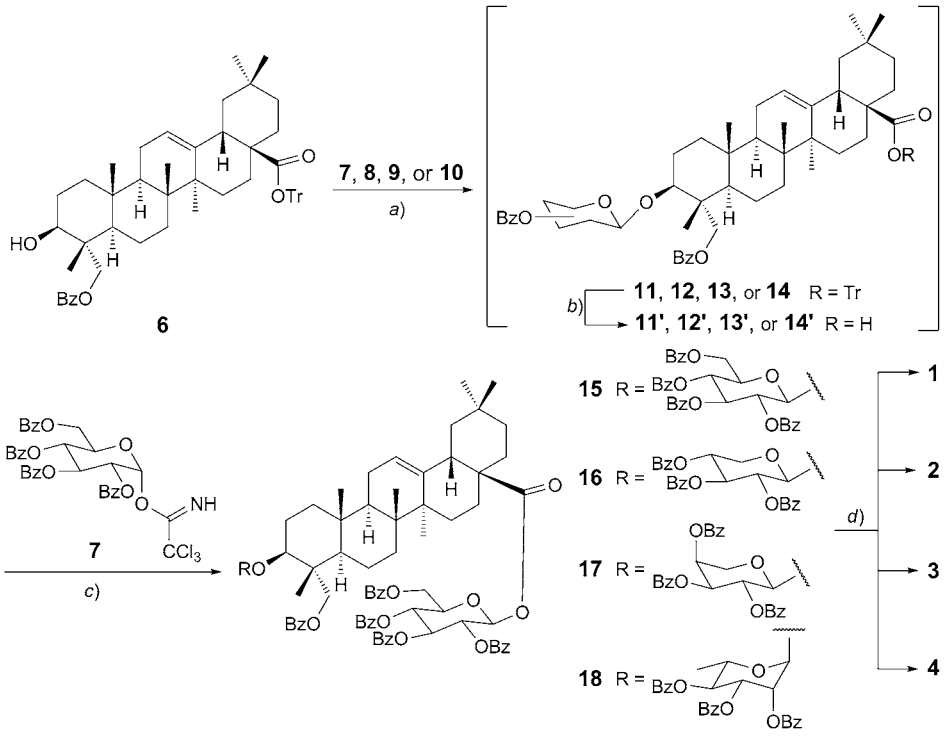
Table. *α-Glucosidase Inhibition by the Synthetic Hederagenin Glycosides* **1**–**4**

	1	**2**	**3**	**4**	Deoxynojirimycin[b])
IC_{50} [μM][a])	87.5 ± 3.5	98.3 ± 1.9	78.2 ± 6.3	47.9 ± 2.6	342.1 ± 8.9

[a]) The IC_{50} value was calculated from the dose-response curve of six concentrations of each test compound in triplicate. [b]) Standard

Conclusions. – In summary, a highly concise and practical strategy was developed for the synthesis of hederagenin glycosides **1**–**4**. The key to this approach is the use of a

Scheme 2



a) $Me_3SiOSO_2CF_3$ (0.3 equiv.), CH_2Cl_2, 4 Å molecular sieves, −78°, 30 min. *b*) R.t., 30 min. *c*) **7** (1.5 equiv.), $Me_3SiOSO_2CF_3$ (0.1 equiv.), CH_2Cl_2, 4 Å molecular sieves, 0°, 30 min; 68% for **15** (3 steps), 62% for **16** (3 steps), 60% for **17** (3 steps), 64% for **18** (3 steps). *d*) MeONa, CH_2Cl_2/MeOH 1:2; 87% for **1**, 83% for **2**, 89% for **3**, 87% for **4**.

one-pot sequential glycosylation, resulting in a significantly simplified synthetic procedure without isolation of the glycosylation intermediates. The hederagenin glycosides **1**–**4** were moderately active against α-glucosidase type IV. Further investigations on the preparation and bioactivity evaluation of hederagenin glycosides is currently under way in our research group.

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Experimental Part

General. Commercial reagents were used without further purification unless specified. Solvents were dried and redistilled in the usual way prior to use. TLC: precoated silica gel *60* F_{254} plates (SiO_2; *E. Merck*). Flash column chromatography (FC): silica gel (SiO_2; 200–300 mesh). Optical rotations: *Perkin–Elmer-241-MC* polarimeter. ^{1}H- and ^{13}C-NMR Spectra: *Jeol-JNM-ECP-600* spectrometer; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Q-TOF-Global* mass spectrometer; in *m*/*z*.

Triphenylmethyl (3β,4α)-23-(Benzoyloxy)-3-hydroxyolean-12-en-28-oate (**6**). A soln. of hederagenin (**5**; 500 mg, 1.06 mmol), TrCl (363 mg, 1.27 mmol), and DBU (0.26 ml, 1.70 mmol) in dry THF (15 ml) was refluxed for 10 h. The solvent was evaporated and the residue dissolved in pyridine (8 ml) and CH_2Cl_2 (12 ml), and then benzoyl chloride (0.17 ml, 1.48 mmol) was slowly added at 0°. After stirring for 1 h, the reaction was quenched by addition of MeOH, the mixture concentrated, the residue taken up with CH_2Cl_2, the CH_2Cl_2 phase washed with H_2O and brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC SiO_2, petroleum ether/AcOEt 12 : 1: **6** (616 mg, 71%). White solid. $[\alpha]_D^{27} = +16.7$ ($c = 0.85$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 600 MHz): 7.27 – 8.03 (*m*, 20 arom. H); 5.32 (*t*, *J* = 3.3, H–C(12)); 4.53 (*d*, *J* = 11.3, 1 H, CH_2(23)); 4.03 (*d*, *J* = 11.3, 1 H, CH_2(23)); 3.49 (*dd*, *J* = 13.7, 4.4, H–C(3)); 2.89 (*dd*, *J* = 13.5, 4.0, H–C(18)); 1.13, 0.99, 0.95, 0.90, 0.83, 0.74 (*s* each, 3 H each, 6 Me). ^{13}C-NMR ($CDCl_3$, 150 MHz): 179.1 (C(28)); 166.8; 143.7 (C(13)); 137.7; 137.5; 136.5; 132.4; 130.1; 129.6; 129.1; 128.4; 122.3 (C(12)); 72.5 (C(3)); 66.8 (C(23)); 48.3; 47.9; 46.9; 42.4; 41.5; 39.2; 38.4; 36.9; 33.1; 31.8; 27.8; 26.7; 25.8; 24.3; 23.3; 17.9; 17.1; 15.7; 12.1. HR-ESI-MS: 841.4831 ($[M + Na]^+$, $C_{56}H_{66}NaO_5^+$; calc. 841.4803).

Compounds **15** – **18**: *Typical Procedure.* A mixture of **6** (100 mg, 0.11 mmol), trichloroacetimidate **7**, **8**, **9**, or **10** (0.14 mmol, 1.2 equiv.), and powdered 4-Å molecular sieves in dry CH_2Cl_2 (5 ml) was stirred for 30 min at r.t. and then cooled to 0°. $Me_3SiOSO_2CF_3$ (15 µl, 0.09 mmol, 0.3 equiv.) was added slowly at −78°. After 30 min stirring at −78°, the mixture was warmed up to r.t. within 30 min, and then cooled again to 0°. A soln. of **7** (122 mg, 0.17 mmol, 1.5 equiv.) in dry CH_2Cl_2 (5 ml) was injected slowly. The mixture was stirred at 0° for 30 min, and then warmed up to r.t. within another 30 min. The reaction was quenched by addition of Et_3N and then the mixture filtered. The filtrate was concentrated and purified by a CC SiO_2, petroleum ether/AcOEt) to afford the products **15** – **18**.

2,3,4,6-Tetra-O-*benzoyl-β*-D-*glucopyranosyl (3β,4α)-23-(Benzoyloxy)-3-[(2,3,4,6-tetra*-O-*benzoyl-β*-D-*glucopyranosyl)oxy]okan-12-en-28-oate* (**15**): Yield 68%. $[\alpha]_D^{23} = +20.6$ ($c = 1.01$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 600 MHz): 7.31 – 8.05 (*m*, 45 arom. H); 5.97 (*t*, *J* = 9.7, 1 H, H–C(3″)); 5.93 (*d*, *J* = 8.3, H–C(1″)); 5.91 (*t*, *J* = 9.6, H–C(3′)); 5.57 – 5.71 (*m*, H–C(2′), H–C(2″), H–C(4′), H–C(4″)); 5.27 (*t*, *J* = 3.1, H–C(12)); 4.85 (*d*, *J* = 7.9, H–C(1′)); 4.61 (*dd*, *J* = 11.9, 3.2, 1 H, CH_2(6′)); 4.57 (*dd*, *J* = 11.9, 6.9, 1 H, CH_2(6′)); 4.51 (*dd*, *J* = 11.5, 2.8, 1 H, CH_2(6″)); 4.47 (*dd*, *J* = 11.5, 5.0, 1 H, CH_2(6″)); 4.35 (*d*, *J* = 11.3, 1 H, CH_2(23)); 4.27 – 4.31 (*m*, 2 H, H–C(5″), CH_2(23)); 4.15 (*m*, H–C(5′)); 3.69 (*dd*, *J* = 11.7, 3.7, H–C(3)); 3.19 (*dd*, *J* = 13.7, 4.0, H–C(18)); 1.07, 0.97, 0.95, 0.91, 0.77, 0.73 (*s* each, 3 H each, 6 Me). ^{13}C-NMR ($CDCl_3$, 150 MHz): 177.3 (C(28)); 165.9; 165.7; 165.4; 163.9; 163.4; 143.7 (C(13)); 138.3; 138.1; 137.8; 137.5; 136.5; 136.1; 133.5; 133.1; 132.9; 129.8; 129.6; 128.5; 128.1; 122.4 (C(12)); 105.4 (C(1′)); 96.7 (C(1″)); 89.3 (C(3)); 78.3; 77.5; 71.9; 70.5; 70.1; 67.1; 66.9; 66.2; 65.8; 62.6; 55.9; 47.9; 46.9; 41.7; 39.2; 36.7; 33.3; 31.9; 27.8; 26.7; 25.8; 24.6; 17.6; 17.1; 15.6. HR-MALDI-MS: 1755.6883 ($[M + Na]^+$, $C_{105}H_{104}NaO_{23}^+$; calc. 1755.6862).

2,3,4,6-Tetra-O-*benzoyl-β*-D-*glucopyranosyl (3β,4α)-23-(Benzoyloxy)-3-[(2,3,4-tri*-O-*benzoyl-β*-D-*xylopyranosyl)oxy]olean-12-en-28-oate* (**16**): Yield 62%. $[\alpha]_D^{23} = +23.1$ ($c = 0.96$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 600 MHz): 7.33 – 8.03 (*m*, 40 arom. H); 5.97 (*t*, *J* = 9.6, H–C(3″)); 5.93 (*d*, *J* = 8.7, H–C(1″)); 5.78 (*t*, *J* = 8.5, H–C(3′)); 5.71 – 5.74 (*m*, H–C(2″), H–C(4″)); 5.44 (*dd*, *J* = 8.2, 6.4, H–C(2′)); 5.30 (dt, *J* = 8.7, 4.6, H–C(4′)); 5.27 (*t*, *J* = 3.7, H–C(12)); 4.81 (*d*, *J* = 6.4, H–C(1′)); 4.53 (*dd*, *J* = 11.5, 2.8, 1 H, CH_2(6″)); 4.47 (*dd*, *J* = 11.0, 5.0, 1 H, CH_2(6″)); 4.43 (*dd*, *J* = 11.9, 4.6, 1 H, CH_2(5′); 4.37 (*d*, *J* = 11.5, 1 H, CH_2(23)); 4.29 (*d*, *J* = 11.5, 1 H, CH_2(23)); 4.26 (*m*, H–C(5″)); 3.67 (*dd*, *J* = 13.7, 3.7, H–C(3)); 3.61 (*dd*, *J* = 11.9, 7.8, 1 H, CH_2(5′)); 3.13 (*dd*, *J* = 14.3, 4.0, H–C(18)); 1.05, 0.97, 0.94, 0.89, 0.76, 0.73 (*s* each, 3 H each, 6 Me). ^{13}C-NMR ($CDCl_3$, 150 MHz): 177.5 (C(28)); 165.9; 165.6; 165.3; 163.9; 163.2; 143.6 (C(13)); 138.7; 138.0; 137.6; 136.4; 136.1; 133.5; 132.7; 129.8; 129.5; 128.3; 128.1; 122.5 (C(12); 104.3 (C(1′)); 96.7 (C(1″)); 89.5 (C(3)); 77.9; 77.1; 70.8; 70.5; 69.9; 67.1; 66.3; 65.7; 62.6; 56.0; 47.7; 46.5; 42.3; 39.1; 36.7; 33.5; 31.9; 27.8; 26.7; 25.9; 24.7; 17.6; 15.3. HR-MALDI-MS: 1621.6509 ($[M + Na]^+$, $C_{97}H_{98}NaO_{21}^+$; calc. 1621.6493).

2,3,4,6-Tetra-O-*benzoyl-β*-D-*glucopyranosyl (3β,4α)-23-Benzoyloxy)-3-[(2,3,4-tri*-O-*benzoyl-α*-L-*arabinopyranosyl)oxy]olean-12-en-28-oate* (**17**): Yield 60%. $[\alpha]_D^{23} = +30.6$ ($c = 1.03$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 600 MHz): 7.25 – 8.07 (*m*, 40 arom. H); 5.96 (*t*, *J* = 9.7, H–C(3″)); 5.93 (*d*, *J* = 8.3, H–C(1″)); 5.67 – 5.78 (*m*, H–C(2′), H–C(3′), H–C(2″), H–C(4″)); 5.58 (*dd*, *J* = 8.8, 3.4, H–C(4′)); 5.27 (*t*, *J* = 3.3, H–C(12)); 4.76 (*d*, *J* = 6.5, H–C(1′)); 4.43 – 4.56 (*m*, 3 H, CH_2(5′), CH_2(6″), CH_2(6″)); 4.36 (*d*, *J* = 11.7, 1 H, CH_2(23)); 4.27 (*m*, H–C(5″)); 4.23 (*d*, *J* = 11.5, 1 H, CH_2(23)); 3.85 (*dd*, *J* = 11.6, 6.3, 1 H, CH_2(5′)); 3.61 (*dd*, *J* = 14.3, 3.7, H–C(3)); 3.11 (*dd*, *J* = 13.9, 4.1, H–C(18)); 1.01, 0.95, 0.93, 0.89, 0.75, 0.73 (*s* each,

3 H each, 6 Me). ^{13}C-NMR ($CDCl_3$, 150 MHz): 177.3 (C(28)); 165.7; 165.6; 165.3; 163.5; 162.9; 143.5 (C(13)); 137.9; 137.6; 137.1; 136.4; 136.0; 133.7; 132.9; 129.8; 129.3; 128.1; 127.9; 122.5 (C(12)); 103.7 (C(1′)); 96.5 (C(1″)); 88.9 (C(3)); 78.1; 76.9; 70.3; 70.1; 69.3; 66.9; 66.3; 65.5; 61.9; 56.3; 47.9; 45.7; 43.7; 39.5; 36.7; 33.6; 31.9; 27.9; 25.6; 24.7; 17.3; 14.9. HR-MALDI-MS: 1621.6511 ($[M+Na]^+$, $C_{97}H_{98}NaO_{21}^+$; calc. 1621.6491).

2,3,4,6-Tetra-O-*benzoyl-β*-D-*glucopyranosyl (3β,4α)-2,3-(Benzoyloxy)-3-[(2,3,4-tri*-O-*benzoyl-6-deoxy-α*-L-*mannopyranosyl)oxy]olean-12-en-28*-oate (**18**): Yield 64%. $[\alpha]_D^{23} = +16.9$ ($c = 0.85$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 600 MHz): 7.24–8.11 (*m*, 40 arom. H); 5.95 (*t*, *J* = 9.7, 1 H, H–C(3″)); 5.91 (*d*, *J* = 8.5, H–C(1″)); 5.83 (*dd*, *J* = 10.2, 3.3, H–C(3′)); 5.65–5.72 (*m*, H–C(2′), H–C(4′), H–C(4″)); 5.56 (*dd*, *J* = 9.9, 8.0, H–C(2″)); 5.26 (*t*, *J* = 3.7, H–C(12)); 5.09 (*d*, *J* = 1.3, H–C(1′)); 4.47–4.53 (*m*, 2 H, CH_2(5′), CH_2(6″)); 4.41 (*dd*, *J* = 11.9, 5.1, 1 H, CH_2(6″)); 4.33 (*d*, *J* = 11.5, 1 H, CH_2(23)); 4.21 (*d*, *J* = 11.5, 1 H, CH_2(23)); 4.19 (*ddd*, *J* = 10.9, 5.4, 3.3, H–C(5″)); 3.93 (*m*, 1 H, CH_2(5′)); 3.63 (*dd*, *J* = 14.5, 4.0, H–C(3)); 3.15 (*dd*, *J* = 13.7, 3.9, H–C(18)); 1.35 (*d*, *J* = 6.2, Me(6′)); 1.03, 0.97, 0.95, 0.90, 0.75, 0.71 (*s* each, 3 H each, 6 Me). ^{13}C-NMR ($CDCl_3$, 150 MHz): 177.3 (C(28)); 166.1; 165.7; 165.4; 163.9; 163.1; 163.0; 143.3 (C(13)); 136.9; 136.7; 136.3; 136.0; 134.8; 133.7; 132.9; 129.6; 128.0; 127.5; 122.7 (C(12)); 98.1 (C(1′)); 96.7 (C(1″)); 88.7 (C(3)); 77.9; 76.7; 71.6; 69.7; 69.3; 66.5; 66.1; 63.2; 61.9; 56.7; 48.1; 45.7; 43.6; 39.5; 36.7; 33.7; 32.1; 27.9; 25.7; 23.8; 17.5; 15.1. HR-MALDI-MS: 1635.6671 ($[M+Na]^+$, $C_{98}H_{100}NaO_{21}^+$; calc. 1635.6650).

Hederagenin Glycosides **1**–**4**: *Typical Procedure.* To a soln. of one of the fully protected hederagenin glycosides **15**–**18** (50 mg) in dry CH_2Cl_2/MeOH 1:2 (10 ml) was added a freshly prepared MeONa/MeOH soln. (1.0 mol/l, 0.20 ml). The mixture was stirred at r.t. for 5 h and neutralized with *Dowex* H^+ resin to pH 7 and then filtered. The filtrate was concentrated and the resulting residue subjected to CC (SiO_2): hederagenin glycosides **1**–**4** as white amorphous solids.

β-D-*Glucopyranosyl (3β,4α)-3-β*-D-*Glucopyranosyloxy)olean-12-en-28-oate* (**1**): Yield 87%. $[\alpha]_D^{23} = +13.9$ ($c = 0.85$, MeOH). ^{1}H-NMR (C_5D_5N, 600 MHz): 6.34 (*d*, *J* = 8.1, H–C(1″)); 5.45 (*t*, *J* = 3.8, H–C(12)); 5.14 (*d*, *J* = 7.7, H–C(1′)); 4.55–4.58 (*m*, H–C(3′), H–C(3″)); 4.43 (*m*, H–C(2′), H–C(4′)); 4.25–4.29 (*m*, 4 H, H–C(2″), H–C(4″), CH_2(6′), CH_2(6″)); 4.23 (*d*, *J* = 11.5, 1 H, CH_2(23)); 4.01–4.07 (*m*, 4 H, H–C(5′), H–C(5″), CH_2(6′), CH_2(6″)); 3.73 (*d*, *J* = 11.5, 1 H, CH_2(23)); 3.63 (*dd*, *J* = 11.5, 4.5, H–C(3)); 3.21 (*dd*, *J* = 13.8, 3.7, H–C(18)); 1.22, 1.13, 0.99, 0.94, 0.89, 0.87 (*s* each, 3 H each, 6 Me). ^{13}C-NMR (C_5D_5N, 150 MHz): 176.4 (C(28)); 144.3 (C(13)); 123.1 (C(12)); 105.7 (C(1′)); 95.8 (C(1″)); 82.7 (C(3)); 79.3; 78.8; 78.6; 78.4; 76.0; 74.3; 71.8; 71.5; 65.3; 63.1; 62.6; 48.3; 48.1; 47.1; 46.5; 43.4; 42.3; 41.7; 40.0; 39.0; 37.2; 34.3; 33.4; 32.7; 30.9; 28.5; 26.3; 25.9; 24.1; 23.8; 18.5; 17.6; 16.3. HR-ESI-MS: 797.4701 ($[M+H]^+$, $C_{42}H_{69}O_{14}^+$; calc. 797.4681).

β-D-*Glucopyranosyl (3β,4α)-3-β*-D-*Xylopyranosyloxy)olean-12-en-28-oate* (**2**): Yield 83%. $[\alpha]_D^{23} = +14.3$ ($c = 0.71$, MeOH). ^{1}H-NMR (C_5D_5N, 600 MHz): 6.33 (*d*, *J* = 8.3, H–C(1″)); 5.41 (*t*, *J* = 3.3, H–C(12)); 4.86 (*d*, *J* = 7.1, H–C(1′)); 4.49–4.57 (*m*, H–C(3′), H–C(3″)); 4.38–4.43 (*m*, H–C(2′), H–C(2″), H–C(4″), H–C(4′)); 4.25–4.29 (*m*, 3 H, CH_2(5′), CH_2(5′), CH_2(6″)); 4.21 (*d*, *J* = 11.3, 1 H, CH_2(23)); 4.01–4.07 (*m*, 2 H, H–C(5″), CH_2(6″)); 3.69 (*d*, *J* = 11.3, 1 H, CH_2(23)); 3.57 (*dd*, *J* = 13.7, 4.0, H–C(3)); 3.19 (*dd*, *J* = 14.3, 3.7, H–C(18)); 1.20, 1.11, 0.99, 0.97, 0.91, 0.88 (*s* each, 3 H each, 6 Me). ^{13}C-NMR (C_5D_5N, 150 MHz): 176.5 (C(28)); 144.5 (C(13)); 123.3 (C(12)); 106.3 (C(1′)); 95.6 (C(1″)); 82.3 (C(3)); 79.2; 75.0; 74.5; 73.1; 71.7; 69.9; 66.7; 64.7; 62.3; 48.5; 47.6; 43.7; 42.3; 41.9; 40.1; 39.0; 37.5; 34.6; 33.5; 32.7; 31.1; 28.5; 26.3; 26.0; 24.3; 23.7; 23.3; 18.4; 17.3; 16.1. HR-ESI-MS: 767.4593 ($[M+H]^+$, $C_{41}H_{67}O_{13}^+$; calc. 767.4574).

β-D-*Glucopyranosyl (3β-4α)-(α*-L-*Arabinopyranosyloxy)olean-12-en-28-oate* (**3**): Yield 89%. $[\alpha]_D^{23} = +48.7$ ($c = 0.85$, MeOH). ^{1}H-NMR (C_5D_5N, 600 MHz): 6.31 (*d*, *J* = 7.6 Hz, H–C(1″)); 5.43 (*t*, *J* = 3.3, H–C(12)); 4.99 (*d*, *J* = 6.9, H–C(1′)); 4.59 (*d*, *J* = 3.6, H–C(4′)); 4.42–4.52 (*m*, H–C(2′), H–C(2″), H–C(3′), H–C(3″), H–C(4″)); 4.25–4.37 (*m*, 3 H, CH_2(5′), CH_2(5′), CH_2(6″)); 4.23 (*d*, *J* = 11.5, 1 H, CH_2(23)); 4.15–4.21 (*m*, 2 H, H–C(5″), CH_2(6″)); 3.75 (*d*, *J* = 11.3, 1 H, CH_2(23)); 3.59 (*dd*, *J* = 11.7, 4.0, H–C(3)); 3.23 (*dd*, *J* = 14.3, 3.7, H–C(18)); 1.20, 1.13, 0.98, 0.91, 0.90, 0.89 (*s* each, 3 H each, 6 Me). ^{13}C-NMR (C_5D_5N, 150 MHz): 176.7 (C(28)); 144.2 (C(13)); 123.1 (C(12)); 106.7 (C(1′)); 95.8 (C(1″)); 82.2 (C(3)); 79.3; 74.9; 74.3; 73.3; 71.4; 69.9; 66.7; 64.6; 62.4; 48.3; 47.6; 43.4; 42.2; 41.9; 40.2; 39.0; 37.2; 34.2; 33.4; 32.7; 30.9; 28.5; 26.3; 26.0; 24.1; 23.7; 23.5; 18.4; 17.6; 16.3. HR-ESI-MS: 767.4589 ($[M+H]^+$, $C_{41}H_{67}O_{13}^+$; calc. 767.4573).

β-D-Glucopyranosyl (3β,4α)-[(6-Deoxy-α-L-mannopyranosyl)oxy]olean-12-en-28-oate (**4**): Yield 87%. $[\alpha]_D^{23} = +15.7$ ($c = 0.63$, MeOH). ^{1}H-NMR ($CDCl_3$, 600 MHz): 6.32 (*t*, $J = 7.9$, H–C(1″)); 6.01 (br. *s*, H–C(1′)); 5.67 (*t*, $J = 9.3$, H–C(4″)); 5.53 (*dd*, $J = 9.7, 8.0$, H–C(2″)); 5.27 (*t*, $J = 3.7$, H–C(12)); 5.03 (br. *s*, H–C(2′)); 4.45–4.56 (*m*, H–C(3′), H–C(4′), H–C(5′), CH_2(6″)); 4.39 (*dd*, $J = 12.3$, 5.3, 1 H, CH_2(6″)); 4.37 (*d*, $J = 11.3$, 1 H, CH_2(23)); 4.17 (*d*, $J = 11.3$, 1 H, CH_2(23)); 4.10 (*m*, H–C(5″)); 3.67 (*dd*, $J = 13.8$, 4.1, H–C(3)); 3.19 (*dd*, $J = 14.1$, 3.7, H–C(18)); 1.67 (*d*, $J = 5.9$, Me(6′)); 1.19, 1.11, 0.99, 0.90, 0.88, 0.87 (*s* each, 3 H each, 6 Me). ^{13}C-NMR ($CDCl_3$, 150 MHz): 177.2 (C(28)); 165.9; 165.7; 165.3; 163.7; 163.1; 162.9; 143.5 (C(13)); 137.0; 136.7; 136.5; 136.1; 134.5; 133.7; 132.9; 129.3; 127.9; 127.6; 122.6 (C(12)); 103.1 (C(1′)); 96.6 (C(1″)); 88.3 (C(3)); 78.0; 76.7; 71.9; 69.5; 69.1; 66.5; 66.0; 63.2; 61.5; 57.0; 48.1; 45.9; 43.5; 39.4; 36.5; 33.9; 32.8; 28.1; 25.3; 23.7; 17.5; 15.3. HR-ESI-MS: 7781.4751 ($[M+H]^+$, $C_{42}H_{69}O_{13}^+$; calc. 781.4733).

α-Glucosidase Inhibition. The inhibitory activity of all samples against α-glucosidase type VI (*Sigma G6136*) was measured spectrophotometrically at pH 6.8 and at 37°, with 0.7 mM 4-nitrophenyl α-D-glucopyranoside (PNP-G) as a substrate and 0.017 units/ml of enzyme, in 50 mM sodium phosphate buffer containing 100 mM NaCl. As a positive control, 1-deoxynojirimycin (0.3 mM) was used, for which the same IC_{50} as given in [41] was determined. The increment in absorption at 400 nm due to the hydrolysis of PNP-G by α-glucosidase was monitored continuously with the spectrophotometer.

REFERENCES

[1] H. E. Lebovitz, *Endocrinol. Metab. Clin. North Am*. **1997**, *26*, 539.
[2] S. P. Clissold, C. Edward, *Drugs* **1988**, *35*, 214.
[3] H. S. Yee, N. T. Fong, *Pharmacotherapy* **1996**, *16*, 792.
[4] K. Yoshioka, K. Azukari, K. Ashida, Y. Kasamatsu, S. Yokoo, T. Yoshida, M. Kondo, *Horm. Metab. Res.* **1997**, *29*, 407.
[5] G. Pogano, S. Marena, L. Corgiat-Mansin, F. Cravero, C. Giorda, M. Bozza, C. M. Rossi, *Diabetes Metab.* **1995**, *21*, 162.
[6] K. Hostettmann, A. Marston, 'Saponins, Chemistry and Pharmacology of Natural Products', University Press, Cambridge, 1995.
[7] K. Hostettmann, *Helv. Chim. Acta* **1980**, *63*, 606.
[8] J. Quetin-Leclercq, R. Elias, G. Balansard, R. Bassler, L. Angenot, *Planta Med.* **1992**, *58*, 279.
[9] M. Chwalek, N. Lalun, H. Bobichon, K. Plé, L. Voutquenne-Nazabadioko, *Biochim. Biophys. Acta* **2006**, *1760*, 1418.
[10] T. Aoki, Y. Tanio, T. Suga, *Phytochemistry* **1976**, *15*, 781.
[11] T. Shinoda, T. Nagao, M. Nakayama, H. Serizawa, M. Koshioka, H. Okabe, A. Kawai, *J. Chem. Ecol.* **2002**, *28*, 587.
[12] V. Mshvildadze, R. Elias, R. Faure, L. Debrauwer, G. Dekanosidze, E. Kemertelidze, G. Balansard, *Chem. Pharm. Bull.* **2001**, *49*, 752.
[13] C. Barthomeuf, E. Debiton, V. Mshvildadze, E. Kemertelidze, G. Balansard, *Planta Med.* **2002**, *68*, 672.
[14] S. Rooney, M. F. Ryan, *Anticancer Res.* **2005**, *25*, 2199.
[15] S. S. M. Kumara, B. T. K. Huat, *Planta Med.* **2001**, *67*, 29.
[16] H.-J. Park, S.-H. Kwon, J.-H. Lee, K.-H. Lee, K.-I. Miyamoto, K.-T. Lee, *Planta Med.* **2001**, *67*, 118.
[17] S.-C. Bang, J.-H. Lee, G.-Y. Song, D.-H. Kim, M.-Y. Yoon, B.-Z. Ahn, *Chem. Pharm. Bull.* **2005**, *53*, 1451.
[18] K.-T. Lee, I.-C. Sohn, H.-J. Park, D.-W. Kim, G.-O. Jung, K.-Y. Park, *Planta Med.* **2000**, *66*, 329.
[19] P. Villani, T. Orsiere, I. Sari-Minodier, G. Bouvenot, A. Botta, *Ann. Biol. Clin.* **2001**, *59*, 285.
[20] K. Plé, M. Chwalek, L. Voutquenne-Nazabadioko, *Eur. J. Org. Chem.* **2004**, 1588.
[21] M. Chwalek, K. Plé, L. Voutquenne-Nazabadioko, *Chem. Pharm. Bull.* **2004**, *52*, 965.
[22] K. Plé, M. Chwalek, L. Voutquenne-Nazabadioko, *Tetrahedron* **2005**, *61*, 4347.
[23] T. Guo, Q. Liu, P. Wang, L. Zhang, W. Zhang, Y. Li, *Carbohydr. Res.* **2009**, *344*, 1167.
[24] Q. Liu, P. Wang, L. Zhang, T. Guo, G. Lv, Y. Li, *Carbohydr. Res.* **2009**, *344*, 1276.

[25] Q. Liu, L. Zhang, X. Li, T. Guo, P. Wang, Y. Li, *J. Carbohydr. Chem.* **2009**, *28*, 506.
[26] Q. Liu, Z. Fan, D. Li, W. Li, T. Guo, *J. Carbohydr. Chem.* **2010**, *29*, 386.
[27] T. Guo, Q. Liu, L. Zhang, P. Wang, Y. Li, *Synth. Commun.* **2011**, *41*, 357.
[28] S. Raghavan, D. Kahne, *J. Am. Chem. Soc.* **1993**, *115*, 1580.
[29] H. K. Chenault, A. Castro, *Tetrahedron Lett*. **1994**, *35*, 9145.
[30] S. V. Ley, H. W. M. Priepke, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2292.
[31] H. Yamada, T. Harada, T. Takahashi, *J. Am. Chem. Soc.* **1994**, *116*, 7919.
[32] H. Yamada, T. Harada, H. Miyazaki, T. Takahashi, *Tetrahedron Lett.* **1994**, *35*, 3979.
[33] S.-F. Lu, Q. Q. O'yang, Z.-W. Guo, B. Yu, Y.-Z. Hui, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2344.
[34] M. Yoshida, T. Kiyoi, T. Tsukida, H. Kondo, *J. Carbohydr. Chem.* **1998**, *17*, 673.
[35] H. Yamada, T. Kato, T. Takahashi, *Tetrahedron Lett.* **1999**, *40*, 4581.
[36] Z. Zhang, I. R. Ollmann, X.-S. Ye, R. Wischnat, T. Baasov, C.-H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 734.
[37] B. Yu, Z. Yang, H. Cao, *Curr. Org. Chem.* **2005**, *9*, 179.
[38] H. Yu, B. Yu, X. Wu, Y. Hui, X. Han, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1445.
[39] B. Yu, H. Yu, Y. Hui, X. Han, *Tetrahedron Lett.* **1999**, *40*, 8591.
[40] B. Yu, J. Xie, S. Deng, Y. Hui, *J. Am. Chem. Soc.* **1999**, *121*, 12196.
[41] N. Asano, E. Oseki, E. Kaneko, K. Matsui, *Carbohydr. Res.* **1994**, *258*, 255.

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