Synthesis of a Trisaccharide Related to the Cytotoxic Triterpenoid Saponins Isolated from the Bark of *Albizia procera*

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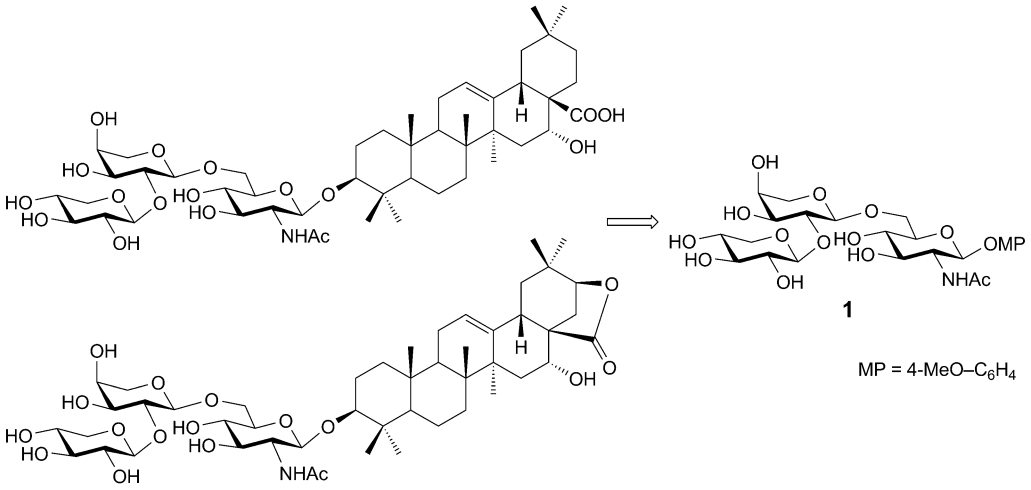
Chemical synthesis of a trisaccharide related to the cytotoxic triterpenoid saponins isolated from the bark of *Albizia procera* has been accomplished through a concise stepwise glycosylation strategy starting from commercially available D-xylose, 2-acetamido-2-deoxy-D-glucose and L-arabinose. The target trisaccharide was designed with a 4-methoxyphenyl (MP) aglycone to extend the scope of conversion to suitable glycoconjugates *via* selective removal of 4-methoxyphenyl (MP) group. An unexpected phenomenon, *i.e.*, the arabinosyl residue assumed the $^1C_4$ conformation instead of the typical $^4C_1$ form, was observed. Deprotection could restore the normal conformation.

Introduction. – Triterpenoid saponins, which are widely distributed in terrestrial plants and in some marine organisms, have been reported to present a broad spectrum of well-defined biological and physiological features such as anti-HIV, antitumor, and anti-inflammatory activities [1–11]. One of the common features of triterpenoid saponins is the presence of a 3-*O*-sugar residue [12–14]. It was reported that the naturally occurring triterpenoid saponins containing *N*-acetylglucosamine are rare; however, most of these exhibit important antiproliferative activities [15–17]. It is well-known that the glycosylation step usually occurs in the mature stage of triterpenoid saponins, yet the biosynthetic pathways for the formation of glycosides are nearly almost unknown. Therefore, chemical synthesis of triterpenoid saponins is needed to rationalize the biosynthetic pathway and to gain access to adequate amounts of triterpenoid saponins for promoting further pharmaceutical studies.

The bark of the plant *Albizia procera* is widely used as folk medicine in Egypt for the treatment of pregnancy and stomachache. Recently, *Melek et al.* reported the chemical structures of three new triterpenoid saponins containing *N*-acetylglucosamine, *i.e.*, proceraosides A, B, and D, isolated from the bark of *Albizia procera* which showed important *in vitro* cytotoxic activity against HEPG2 cell line. Here, we report the efficient synthesis of a trisaccharide related to the cytotoxic triterpenoid saponins isolated from the bark of *Albizia procera* as a 4-methoxyphenyl (MP) glycosides (*Scheme 1*) [18].

Results and Discussion. – For the synthesis of the target trisaccharide **1**, a stepwise glycosylation strategy was adopted involving the syntheses of suitably protected D-xylose, 2-acetamido-2-deoxy-D-glucose, and L-arabinose synthons. The choice of the 4-

Scheme 1. *Structures of the Triterpenoid Saponins and the Target Trisaccharide* **1**

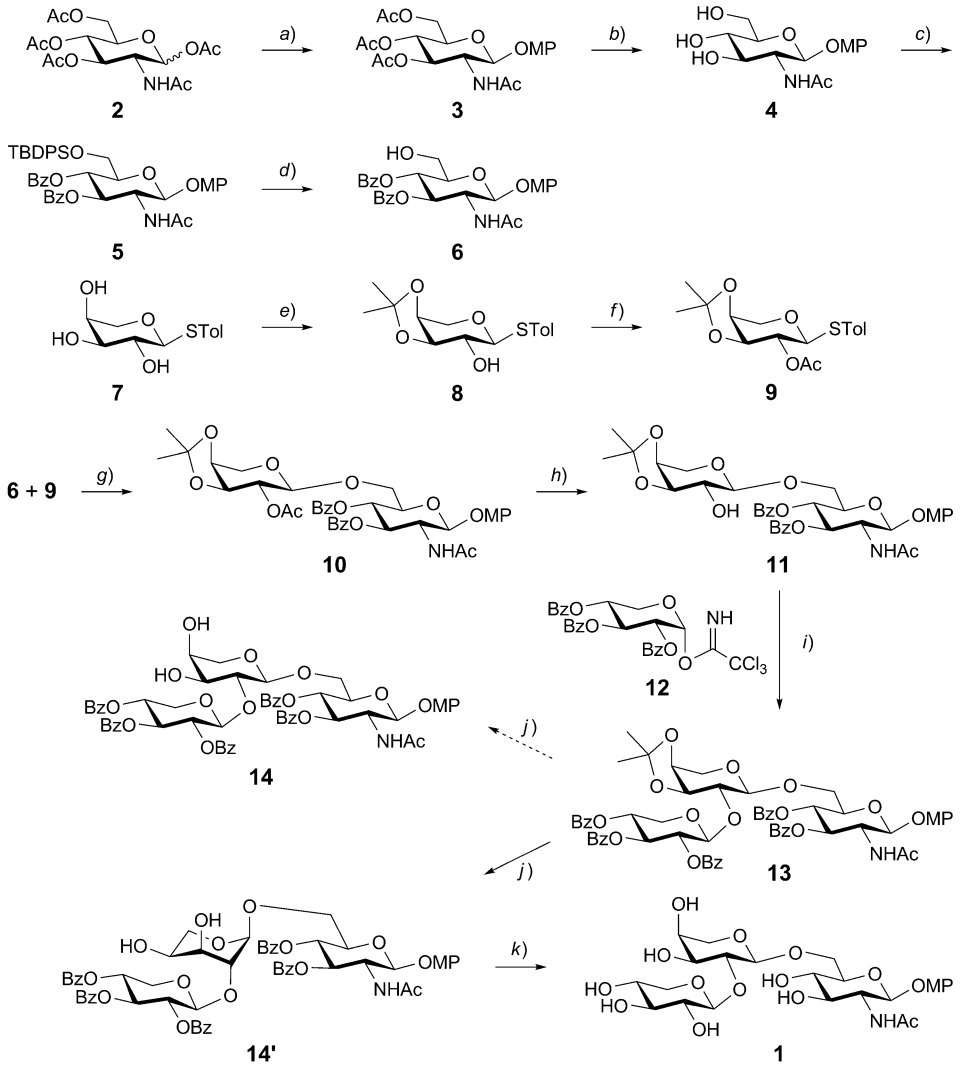


methoxyphenyl (MP) group at the reducing end was favored by the fact that it can be converted to suitable glycoconjugates through the ammonium ceric nitrate (CAN)-mediated oxidative cleavage [19].

As outlined in *Scheme 2*, 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-glucopyranose (**2**) was reacted with 4-methoxyphenol in the presence of $BF_3 \cdot Et_2O$ to afford the required 4-methoxyphenyl glycoside, *i.e.*, 4-methoxyphenyl 2-acetamido-3,4,6-tri-*O*-Ac-2-deoxy-β-D-glucopyranoside (**3**) in 86% yield [20]. Subsequently, the *O*-Ac groups were selectively removed using MeONa in MeOH, furnishing the corresponding 4-methoxyphenyl 2-acetamido-2-deoxy-β-D-glucopyranoside (**4**) in 90% yield [21]. Seletive protection of the primary OH group with a ^{t}BuPh$_2$Si (TBDPS) group employing ^{t}BuPh$_2$SiCl in pyridine, followed by benzoyl (Bz) protection of the other OH groups using BzCl afforded the completely protected compound **5**, 2-acetamido-3,4-di-*O*-benzoyl-6-*O*-[(*tert*-butyl)(diphenyl)silyl]-2-deoxy-β-D-glucopyranoside, in 83% yield over two steps [22]. Removal of the TBDPS group using Bu_4NF in THF gave the desired acceptor **6**, 2-acetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranoside, in 87% yield [23]. For the L-arabinose moiety, the known 1-thio-α-L-arabinopyranoside **7** was converted to its 3,4-isopropylidene derivative **8** in 96% yield using 2,2-dimethoxypropane in the presence of camphor-10-sulfonic acid (CSA) [24]. Finally, the L-arabinosyl donor **9** was obtained by protecting the 2-OH group of **8** as an acetate in 91% yield.

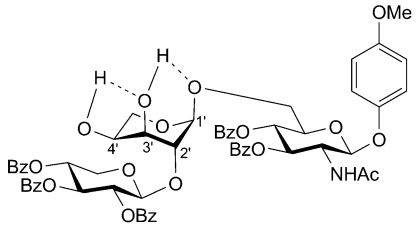
With the completion of the synthesis of acceptor **6** and donor **9**, we next turned our attention to a stepwise strategy for the efficient synthesis of the target trisaccharide **1**. Glycosylation between acceptor **6** and donor **9** was accomplished *via* thioglycoside activation with *N*-iodosuccinimide (NIS) in the presence of silver trifluoromethanesulfonate (TfOAg) to afford the disaccharide **10** in 86% yield. Subsequently, the Ac group at the O-atom of the disaccharide **10** was selectively removed using 1% AcCl in MeOH, furnishing the required disaccharide acceptor **11** in 90% yield [25]. Further

Scheme 2.



a) 4-Methoxyphenol, $BF_3 \cdot Et_2O$, CH_2Cl_2, $-30°$; 87%. *b*) MeONa, MeOH, r.t.; 97%. *c*) ^{t}BuPh$_2$SiCl (TBDPSCl), Py; PhCOCl (BzCl); 82% for two steps. *d*) Bu_4NF, THF, r.t.; 83%. *e*) 2,2-Dimethoxypropane, camphor-10-sulfonic acid (CSA), DMF; 96%. *f*) Ac_2O, 4-(Dimethylamino)pyridine (DMAP), Et_3N, CH_2Cl_2; 91%. *g*) *N*-Iodosuccinimide (NIS), TfOAg, CH_2Cl_2, 4-Å molecular sieves, 0°; 86%. *h*) 1% AcCl in MeOH, CH_2Cl_2, r.t.; 90%. *i*) **12**, Trimethylsilyl trifluoromethanesulfonate (TMSOTf), CH_2Cl_2, 4-Å molecular sieves, $-30°$; 87%. *j*) TsOH, CH_2Cl_2, MeOH; 89%. *k*) MeONa, CH_2Cl_2, MeOH; 80%.

glycosylation of the known donor, 2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl trichloroacetimidate (**12**) [26] with disaccharide acceptor **11** employing trimethylsilyl trifluoromethanesulfonate (TMSOTf) as promoter afforded the protected trisaccharide **13** in 87% yield. Deprotection of the isopropylidene ketal with TsOH in CH_2Cl_2 and MeOH gave the trisaccharide **14** in 89% yield [26][27]. However, it was found that the signal of H–C(1) of the arabinosyl residue of **14** was a broad *singlet*, which is also characterized by a large $^3J(3',OH)$ value of 9.1 Hz and a large $^3J(4',OH)$ value of 8.3 Hz in $CDCl_3$ (*Fig.*). These results indicated that the arabinosyl residue adopted the $^1C_4$ conformation instead of the typical $^4C_1$ form. We presumed that the $^1C_4$ conformation of compound **14** could be ascribed to cooperative O(4′)–H · O(3′)–H · O(1′) H-bonds [28][29]. This phenomenon was consistent with that reported in the literature [30]. Hence, the structure of **14** should be **14′**. Finally, removal of Bz groups using MeONa in MeOH furnished the target trisaccharide in 80% yield. Interestingly, the arabinopyranosyl moiety returned to the normal $^4C_1$ conformation, and this was supported by the H–C(1) signal of arabinopyranosyl moiety of **1** ($J(1',2') = 5.7$), and a large $^3J(3',OH)$ value of 9.1 Hz and a large $^3J(4',OH)$ value of 8.3 Hz in $CDCl_3$.



	HO–C(3')	HO–C(4')	
J	9.1	8.3	Hz
δ	3.65	3.91	ppm

Figure. *J(H,OH) and δ (OH) values of the intermediate* **14′** *in* $CDCl_3$. ---: Intramolecular H-bonds

Conclusions. – In summary, we have synthesized a trisaccharide related to the cytotoxic triterpenoid saponins isolated from the bark of *Albizia procera*. A concise stepwise glycosylation strategy was developed for the construction of the trisaccharide with a 4-methoxyphenyl aglycone which could extend the scope of conversions to suitable glycoconjugates *via* selective removal of 4-methoxyphenyl group. Interestingly, the arabinopyranosyl residue in **14′** adopted a $^1C_4$ conformation instead of the typical $^4C_1$ form, and deprotection of acyl groups led to the normal conformation.

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Experimental Part

General. Commercial reagents were used without further purification unless specified. Solvents were dried and redistilled prior to use in the usual way. TLC: Precoated silica gel *60* F_{254} plates (SiO_2; *E. Merck*). Flash column chromatography (CC): SiO_2 (200–300 mesh). Optical rotations: *PerkinElmer*

241MC 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.

*4-Methoxyphenyl 3,4,6-Tri-*O*-acetyl-2-(acetylamino)-2-deoxy-β-*D*-glucopyranoside* (**3**). Compound **2** (3.00 g, 7.70 mmol) and 4-methoxyphenol (783 mg, 6.42 mmol) were dissolved in dry CH_2Cl_2 (35 ml). $BF_3 \cdot Et_2O$ (1.20 ml, 9.63 mmol) was added at $-30°$. The mixture was allowed to warm to r.t. and stirred for 7 h. Then, the mixture was washed with sat. $NaHCO_3$ (3 × 20 ml) and NaCl (3 × 20 ml). The org. layer was dried (Na_2SO_4) and concentrated. The residue was purified by CC on SiO_2 (petroleum ether/AcOEt 3 :1) to afford **3** (2.91 g, 87%). White solid. $[\alpha]_D^{27} = -13.1$ ($c = 1.2$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 600 MHz): 7.96 (*d*, $J = 7.5$, NH); 6.93 (*d*, $J = 9.1$, 2 arom. H); 6.76 (*d*, $J = 9.1$, 2 arom. H); 5.95 (*d*, $J = 7.9$, H–C(1)); 5.39 (*t*, $J = 9.6$, H–C(3)); 5.16 (*t*, $J = 9.6$, H–C(4)); 4.29 (*dd*, $J = 12.1, 5.5$, H_a–C(6)); 4.15 (*ddd*, $J = 9.6, 7.9, 7.5$, H–C(2)); 4.07 (*dd*, $J = 12.1, 2.4$, H_b–C(6)); 3.84 – 3.81 (*m*, H–C(5)); 3.76 (*s*, MeO); 2.08, 2.06, 2.04, 1.96 (4*s*, 4 Me). HR-ESI-MS: 476.1546 ($[M + Na^+]$, $C_{21}H_{27}NNaO_{10}^+$; calc. 476.1527).

*4-Methoxyphenyl 2-(Acetylamino)-2-deoxy-β-*D*-glucopyranoside* (**4**). Compound **3** (2.50 g, 5.52 mmol) was dissovled in dry MeOH (50 ml), and a cat. amount of MeONa was added. After stirring for 30 min, the mixture was neutralized with resin (H^+); and the resin was filtered. The solvent was concentrated, and the residue was purified by CC (SiO_2; $CHCl_3$/MeOH 10 :1) to afford **4** (1.75 g, 97%). White solid. $[\alpha]_D^{27} = -9.8$ ($c = 1.1$, MeOH). ^{1}H-NMR (CD_3OD, 600 MHz): 6.91 (*d*, $J = 9.3$, 2 arom. H); 6.79 (*d*, $J = 9.3$, 2 arom. H); 5.16 (*d*, $J = 7.8$, H–C(1)); 4.87 (*t*, $J = 9.6$, H–C(3)); 4.35 (*t*, $J = 9.6$, H–C(4)); 3.97 (*dd*, $J = 12.3, 5.3$, H_a–C(6)); 3.68 (*dd*, $J = 9.6, 7.8$, H–C(2)); 3.65 (*s*, MeO); 3.41 (*dd*, $J =$ 12.4, 2.3, H_b–C(6)); 3.34 – 3.30 (*m*, H–C(5)); 1.82 (*s*, Me). HR-ESI-MS: 328.1369 ($[M + H^+]$, $C_{15}H_{22}NO_7^+$; calc. 328.1391).

*4-Methoxyphenyl 2-(Acetylamino)-3,4-di-*O*-benzoyl-6-*O*-[(*tert*-butyl)(diphenyl)silyl]-2-deoxy-β-*D*-glucopyranoside* (**5**). To a soln. of **4** (1.50 g, 4.59 mmol) in dry pyridine (20 ml) was added ^{t}BuPh$_2$SiCl (1.42 ml, 5.50 mmol), and the mixture was stirred at r.t. for 6 h. When TLC showed complete conversion of the starting material, BzCl (1.10 ml, 6.89 mmol) was added, and stirring was continued for 5 h. After complete conversion (TLC), the solvent was evaporated, and the residue was purified by CC (SiO_2; petroleum ether/AcOEt 6 :1) to afford **5** (2.91 g, 82%). White solid. $[\alpha]_D^{27} = -15.7$ ($c = 1.3$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 600 MHz): 8.15 – 7.16 (*m*, 24 arom. H); 5.98 (*d*, $J = 7.8$, H–C(1)); 5.89 (*d*, $J = 6.3$, NH); 5.55 (*t*, $J = 9.6$, H–C(3)); 4.87 (*t*, $J = 9.6$, H–C(4)); 4.33 (*dd*, $J = 12.0, 5.6$, H_a–C(6)); 3.95 (*ddd*, $J = 9.6, 7.8, 6.3$, H–C(2)); 3.78 (*s*, MeO); 3.56 (*dd*, $J = 12.0, 2.7$, H_b–C(6)); 3.39 – 3.27 (*m*, H–C(5)); 1.84 (*s*, NHCO*Me*); 1.03 (*s*, ^{t}Bu). ^{13}C-NMR ($CDCl_3$, 150 MHz): 171.2; 166.4; 166.2; 155.6; 151.0; 135.7; 135.6; 135.5; 133.1; 132.9; 132.7; 129.9; 129.8; 129.7; 128.3; 127.6; 127.5; 118.6; 114.4; 105.3 (C(1)); 79.6 (C(5)); 72.3 (C(3)); 69.9 (C(4)); 63.7 (C(6)); 55.8 (MeO); 55.3 (C(2)); 31.2 (Me_3C); 26.7 (Me_3C); 22.5 (*Me*CONH). HR-ESI-MS: 796.2936 ($[M + Na^+]$, $C_{45}H_{47}NNaO_9Si^+$; calc. 796.2911).

*4-Methoxyphenyl 2-(Acetylamino)-3,4-di-*O*-benzoyl-2-deoxy-β-*D*-glucopyranoside* (**6**). To a soln. of **5** (2.00 g, 2.59 mmol) in dry THF (10 ml) was added Bu_4NF (1.22g, 3.89 mmol), and the soln. was stirred at r.t. for 2 h. When TLC showed complete conversion of the starting material, the solvent was evaporated under reduced pressure. The residue was purified by CC (SiO_2; petroleum ether/AcOEt 4 :1) to afford **6** (1.15 g, 83%). White solid. $[\alpha]_D^{27} = -12.3$ ($c = 1.1$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 600 MHz): 8.10 – 7.41 (*m*, 14 arom. H); 5.87 (*d*, $J = 8.0$, H–C(1)); 5.78 (*d*, $J = 5.9$, NH); 5.65 (*t*, $J = 9.6$, H–C(3)); 4.83 (*t*, $J = 9.6$, H–C(4)); 4.41 (*dd*, $J = 12.1, 5.0$, H_a–C(6)); 3.89 (*ddd*, $J = 9.6, 8.0, 5.9$, H–C(2)); 3.67 (*s*, MeO); 3.57 – 3.64 (*m*, H–C(5), H_b–C(6)); 1.82 (*s*, NHCO*Me*). ^{13}C-NMR ($CDCl_3$, 150 MHz): 169.9; 166.3; 166.0; 153.7; 150.3; 135.7; 133.1; 132.7; 129.9; 129.7; 128.3; 127.9; 127.3; 118.4; 115.0; 105.0 (C(1)); 79.4 (C(5)); 72.6 (C(3)); 69.7 (C(4)); 63.2 (C(6)); 55.6 (MeO); 55.4 (C(2)); 22.5 (*Me*CONH). HR-ESI-MS: 558.1717 ($[M + Na^+]$, $C_{29}H_{29}NNaO_9^+$; calc. 558.1733).

*4-Methylphenyl 3,4-*O*-(1-Methylethylidene)-1-thio-α-*L*-arabinopyranoside* (**8**). To a soln. of **7** (2.00 g, 7.81 mmol) in DMF (10 ml) was added 2,2-dimethoxypropane (1.94 ml, 15.6 mmol) and camphor-10-sulfonic acid (CSA; 0.61 g, 2.56 mmol) at 50° under vacuum. After 5 h, the reaction soln. was diluted with AcOEt (80 ml) and then washed with sat. aq. $NaHCO_3$ and brine, and dried (Na_2SO_4). The solvent was removed, and the residue was purified by CC (SiO_2; petroleum ether/AcOEt 7 :1) to afford **8** (2.22 g, 96%). White solid. $[\alpha]_D^{27} = +23.1$ ($c = 1.6$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 600 MHz): 7.45 (*d*, $J = 8.3$, 2 arom. H); 7.11 (*d*, $J = 8.3$, 2 arom. H); 4.46 (*d*, $J = 7.8$, H–C(1)); 4.29 – 4.26 (*m*, H–C(4)); 4.23 (*dd*, $J = 8.1$, 4.0, H–C(3)); 4.08 (*dd*, $J = 12.7, 5.7$, H_a–C(5)); 3.76 (*dd*, $J = 13.2, 3.6$, H_b–C(5)); 3.63 – 3.60 (*m*, H–C(2));

2.33 (*s*, 3 H); 1.46 (*s*, 3 H); 1.33 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 150 MHz): 138.5; 133.2; 129.7; 128.1; 110.0 (Me_2C); 88.6 (C(1)); 77.9 (C(3)); 72.9 (C(4)); 71.3 (C(2)); 65.8 (C(5)); 27.8 (Me_2C); 26.1 (Me_2C); 21.0 (Me of TolS). HR-ESI-MS: 319.0994 ($[M+Na^+]$, $C_{15}H_{20}NaO_4S^+$; calc. 319.0975).

*4-Methylphenyl 2-*O*-Acetyl-3,4-*O*-(1-methylethylidene)-1-thio-α-*L*-arabinopyranoside* (**9**). To a soln. of **8** (1.50 g, 4.89 mmol) in CH_2Cl_2 (10 ml) were added Et_3N (1.06 ml, 7.52 mmol), Ac_2O (0.57 ml, 6.02 mmol), and 4-(dimethylamino)pyridine (DMAP; 13 mg, 0.10 mmol). The soln. was stirred at r.t. for 1.5 h, and then diluted with CH_2Cl_2 (100 ml) and washed with sat. $NaHCO_3$ and brine, and dried (Na_2SO_4). The solvent was removed, and the product was purified by CC (SiO_2; petroleum ether/AcOEt 8:1) to afford **9** (1.50 g, 91%). White solid. $[\alpha]_D^{27} = +26.9$ ($c = 1.8$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 600 MHz): 7.40 (*d*, *J* = 8.0, 2 arom. H); 7.12 (*d*, *J* = 8.0, 2 arom. H); 5.14 (*t*, *J* = 7.2, H–C(2)); 4.77 (*d*, *J* = 7.2, H–C(1)); 4.30 (*dd*, *J* = 7.2, 3.7, H–C(3)); 4.25–4.21 (*m*, H–C(4)); 4.17 (*dd*, *J* = 12.6, 5.3, H_a–C(5)); 3.77 (*dd*, *J* = 12.6, 3.6, H_b–C(5)); 2.34 (*s*, 3 H); 2.13 (*s*, 3 H); 1.57 (*s*, 3 H); 1.36 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 150 MHz): 170.3 (Me*C*O); 139.6; 133.2; 129.7; 128.3; 110.7 (Me_2C); 88.3 (C(1)); 77.9 (C(3)); 73.1 (C(4)); 71.6 (C(2)); 65.9 (C(5)); 28.1 (Me_2C); 26.3 (Me_2C); 21.3 (Me of TolS); 21.0 (*Me*CO). HR-ESI-MS: 361.1113 ($[M+Na^+]$, $C_{17}H_{22}NaO_5S^+$; calc. 361.1081).

*4-Methoxyphenyl 2-(Acetylamino)-6-*O*-[2-*O*-acetyl-3,4-*O*-(1-methylethylidene)-α-*L*-arabinopyranosyl]-3,4-di-*O*-benzoyl-2-deoxy-β-*D*-glucopyranoside* (**10**). A mixture of **6** (500 mg, 0.93 mmol), **9** (380 mg, 1.12 mmol), and 4-Å molecular sieves in dry CH_2Cl_2 (15 ml) was stirred at r.t. under Ar for 30 min and then cooled to 0°. *N*-Iodosuccinimide (NIS; 420 mg, 1.86 mmol) was added, followed by silver trifluoromethanesulfonate (TfOAg; 12 mg, 0.05 mmol), and the mixture was allowed to stir at 0° for 1 h, until TLC showed complete disappearance of **6**. The mixture was diluted with CH_2Cl_2 and filtered through *Celite*. The filtrate was successively washed with $Na_2S_2O_3$, $NaHCO_3$, and brine. The org. layer was collected, dried (Na_2SO_4), and evaporated. The residue was purified by CC (SiO_2; petroleum ether/AcOEt 4:1) to afford **10** (599 mg, 86%). White solid. $[\alpha]_D^{27} = +13.8$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 600 MHz): 8.01–7.49 (*m*, 14 arom. H); 5.89 (*d*, *J* = 7.9, H–C(1)); 5.71 (*t*, *J* = 9.7, H–C(3)); 5.55 (*d*, *J* = 5.9, NH); 5.16 (*dd*, *J* = 7.8, 6.8, H–C(2′)); 4.97 (*t*, *J* = 9.7, H–C(4)); 4.65 (*d*, *J* = 7.8, H–C(1′)); 4.41 (*dd*, *J* = 6.8, 5.8, H–C(3′)); 4.33–4.28 (*m*, H–C(4′), H_a–C(6)); 4.21 (*dd*, *J* = 12.1, 5.1, H_a–C(5′)); 4.06 (*ddd*, *J* = 9.7, 7.9, 5.9, H–C(2)); 3.77–3.69 (*m*, H_b–C(5′), H–C(5), H_b–C(6)); 3.63 (*s*, MeO); 2.15 (*s*, COMe); 1.83 (*s*, NHCO*Me*); 1.37, 1.56 (2*s*, 2 Me). ^{13}C-NMR ($CDCl_3$, 150 MHz): 171.4 (Me*C*O); 169.8 (Me*C*ONH); 166.7; 166.5; 153.6; 150.2; 136.3; 133.3; 132.7; 129.8; 129.7; 128.5; 127.9; 127.3; 119.3; 115.2; 110.9 (Me_2C); 109.5 (C(1′)); 105.0 (C(1)); 79.4 (C(5)); 78.3 (C(4′)); 77.6 (C(3)); 73.1 (C(2′)); 72.6 (C(4)); 71.5 (C(3′)); 69.7 (C(6)); 67.0 (C(5′)); 55.6 (MeO); 55.5 (C(2)); 28.3 (Me_2C); 26.5 (Me_2C); 21.3 (*Me*CONH); 21.0 (*Me*CO). HR-ESI-MS: 772.2596 ($[M+Na^+]$, $C_{39}H_{43}NNaO_{14}^+$; calc. 772.2574).

*4-Methoxyphenyl 2-(Acetylamino)-3,4-di-*O*-benzoyl-2-deoxy-6-*O*-[3,4-*O*-(1-methylethylidene)-α-*L*-arabinopyranosyl]-β-*D*-glucopyranoside* (**11**). To a soln. of **10** (500 mg, 0.67 mmol) in CH_2Cl_2 (8 ml) was added a soln. of 1% AcCl in MeOH (10 ml). The mixture was stirred overnight at r.t., and TLC (petroleum ether/AcOEt 4:1) indicated that the reaction was complete. The mixture was concentrated *in vacuo*. The residue was purified by CC (SiO_2; petroleum ether/AcOEt 3.5:1) to afford **11** (426 mg, 90%). White solid. $[\alpha]_D^{27} = +15.1$ ($c = 1.1$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 600 MHz): 8.02–7.51 (*m*, 14 arom. H); 5.91 (*d*, *J* = 7.7, H–C(1)); 5.69 (*t*, *J* = 9.3, H–C(3)); 5.61 (*d*, *J* = 6.3, NH); 5.00 (*t*, *J* = 9.3, H–C(4)); 4.53 (*d*, *J* = 7.9, H–C(1′)); 4.39 (*dd*, *J* = 8.6, 7.8, H–C(2′)); 4.37–4.27 (*m*, H–C(3′), H–C(4′), H_a–C(6)); 4.17 (*dd*, *J* = 11.9, 5.3, H_a–C(5′)); 4.03 (*ddd*, *J* = 9.3, 7.7, 6.3, H–C(2)); 3.77–3.71 (*m*, H–C(5), H_b–C(6)); 3.69 (*dd*, *J* = 11.9, 3.6, H_b–C(5′)); 3.65 (*s*, MeO); 1.81 (*s*, NHCO*Me*); 1.35, 1.57 (2*s*, 2 Me). ^{13}C-NMR ($CDCl_3$, 150 MHz): 169.9 (Me*C*ONH); 166.7; 166.3; 153.4; 150.2; 136.5; 133.3; 132.9; 129.7; 129.5; 128.6; 127.7; 126.9; 119.0; 115.2; 110.1 (Me_2C); 108.3 (C(1′)); 105.2 (C(1)); 79.8 (C(5)); 77.9 (C(4′)); 77.6 (C(3)); 73.3 (C(2′)); 72.9 (C(4)); 71.5 (C(3′)); 69.9 (C(6)); 67.0 (C(5′)); 55.6 (MeO); 55.4 (C(2)); 28.3 (Me_2C); 26.5 (Me_2C); 21.3 (*Me*CONH). HR-ESI-MS: 730.2497 ($[M+Na^+]$, $C_{37}H_{41}NNaO_{13}^+$; calc. 730.2473).

*4-Methoxyphenyl 2,3,4-Tri-*O*-benzoyl-β-*D*-xylopyranosyl-(1→2)-3,4-*O*-(1-methylethylidene)-α-*L*-arabinopyranosyl-(1→6)-2-(acetylamino)-3,4-di-*O*-benzoyl-2-deoxy-β-*D*-glucopyranoside* (**13**). A mixture of **11** (300 mg, 0.42 mmol), trichloroacetimidate **12** (308 mg, 0.51 mmol), and powdered 4-Å molecular sieves in dry CH_2Cl_2 (12 ml) were stirred for 30 min at r.t. and then cooled to −30°. TMSOTf (10 µl, 0.04 mmol) was added. After stirring at −30° for 1 h, the mixture was warmed up to r.t. for 30 min. The reaction was quenched by addition of Et_3N, and then the mixture was filtered. The filtrate

was concentrated and purified by CC (SiO_2; petroleum ether/AcOEt 3:1) to afford **13** (420 mg, 87%). White solid. $[\alpha]_D^{27} = +46.5$ ($c = 0.8$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 600 MHz): 8.20–7.19 (*m*, 29 arom. H); 5.97 (*d*, *J* = 7.8, H–C(1)); 5.86 (*t*, *J* = 9.6, H–C(3)); 5.63 (*dd*, *J* = 9.6, 7.0, H–C(2″)); 5.59–5.55 (*m*, H–C(4″), NH); 5.13 (*t*, *J* = 9.6, H–C(4)); 5.06 (*t*, *J* = 9.6, H–C(3″)); 4.99 (*d*, *J* = 7.0, H–C(1″)); 4.96 (*dd*, *J* = 9.1, 7.0, H–C(2′)); 4.65 (*d*, *J* = 7.3, H–C(1′)); 4.44–4.31 (*m*, H–C(3′), H–C(4′), H_a–C(5′), H_a–C(5″), H_a–C(6)); 4.09 (*ddd*, *J* = 9.6, 7.8, 6.5, H–C(2)); 3.77–3.71 (*m*, H–C(5), H_b–C(5″), H_b–C(6)); 3.73 (*dd*, *J* = 13.1, 2.9, H_b–C(5′)); 3.67 (*s*, MeO); 1.87 (*s*, NHCO*Me*); 1.37, 1.59 (2*s*, 2 Me). ^{13}C-NMR ($CDCl_3$, 150 MHz): 170.1 (Me*C*ONH); 166.7; 166.3; 165.9; 165.6; 165.3; 153.4; 150.2; 136.7; 136.5; 136.3; 133.3; 133.1; 132.9; 132.7; 132.6; 129.9; 129.7; 129.3; 128.6; 128.3; 127.9; 126.3; 118.9; 115.3; 110.5 (Me_2C); 108.5 (C(1′)); 107.9 (C(1″)); 105.2 (C(1)); 81.6 (C(2′)); 79.9 (C(5)); 78.6 (C(4′)); 77.9 (C(3′)); 77.7 (C(3)); 77.5 (C(2″)); 73.6 (C(4)); 72.9 (C(3″)); 71.5 (C(4″)); 69.7 (C(6)); 67.0 (C(5′)); 65.9 (C(5″)); 55.7 (MeO); 55.2 (C(2)); 28.3 (Me_2C); 26.7 (Me_2C); 21.1 (*Me*CONH). HR-ESI-MS: 1174.3691 ([$M + Na^+$], $C_{63}H_{61}NNaO_{20}^+$; calc. 1174.3679).

4-Methoxyphenyl 2,3,4-Tri-O-*benzoyl-β*-D-*xylopyranosyl-(1 → 2)-α*-L-*arabinopyranosyl-(1 → 6)-2-(acetylamino)-3,4-di*-O-*benzoyl-2-deoxy-β*-D-*glucopyranoside* (**14′**). A mixture of **13** (200 mg, 0.17 mmol) and TsOH (30 mg, 0.17 mmol) in CH_2Cl_2/MeOH 1:2 (12 ml) was stirred at r.t. When TLC (petroleum ether/AcOEt 3:1) showed that deprotection was complete, Et_3N (0.1 ml) was added, and the mixture was concentrated and purified by CC (SiO_2; petroleum ether/AcOEt 1.5:1) to afford **14′** (168 mg, 89%). White solid. $[\alpha]_D^{27} = +38.9$ ($c = 0.6$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 600 MHz): 8.10–7.10 (*m*, 29 arom. H); 5.96 (*d*, *J* = 7.8, H–C(1)); 5.87 (*t*, *J* = 9.6, H–C(3)); 5.65 (*dd*, *J* = 9.6, 7.0, H–C(2″)); 5.50–5.41 (*m*, H–C(4″), NH); 5.16 (*t*, *J* = 9.6, H–C(4)); 5.03 (*t*, *J* = 9.7, H–C(3″)); 4.95 (*t*, *J* = 3.7, H–C(2′)); 4.91 (*d*, *J* = 6.9, H–C(1″)); 4.61 (br. *s*, H–C(1′)); 4.46 (*dd*, *J* = 12.7, 3.7, H_a–C(5″)); 4.40–4.31 (*m*, H–C(3′), H–C(4′), H_a–C(6)); 4.07 (*ddd*, *J* = 9.6, 7.8, 6.3, H–C(2)); 3.91 (*d*, *J* = 8.3, HO–C(4′)); 3.90–3.80 (*m*, H–C(5), H_a–C(5′), H_b–C(5″), H_b–C(6)); 3.66 (*dd*, *J* = 13.3, 3.5, H_b–C(5′)); 3.65 (*d*, *J* = 9.1, HO–C(3′)); 3.64 (*s*, MeO); 1.85 (*s*, NHCO*Me*). ^{13}C-NMR ($CDCl_3$, 150 MHz): 170.3 (Me*C*ONH); 166.9; 166.3; 165.8; 165.6; 165.2; 153.4; 150.12; 136.7; 136.5; 136.3; 133.3; 132.9; 132.5; 132.6; 129.8; 129.7; 129.3; 128.6; 128.2; 127.7; 126.3; 119.0; 115.5; 108.3 (C(1′)); 107.7 (C(1″)); 104.9 (C(1)); 82.3 (C(2′)); 79.9 (C(5)); 78.3 (C(3′)); 77.6 (C(3)); 76.1 (C(2″)); 73.6 (C(4′)); 72.8 (C(3″)); 71.5 (C(4″)); 68.3 (C(4)); 67.0 (C(6)); 65.6 (C(5′)); 63.2 (C(5″)); 56.1 (MeO); 55.4 (C(2)); 21.1 (*Me*CONH). HR-ESI-MS: 1164.3387 ([$M + Na^+$], $C_{60}H_{57}NNaO_{20}^+$; calc. 1134.3365).

4-Methoxyphenyl β-D-*Xylopyranosyl-(1 → 2)-α*-L-*arabinopyranosyl-(1 → 6)-2-(acetylamino)-2-deoxy-β*-D-*glucopyranoside* (**1**). To a soln. of **14′** (100 mg, 0.09 mmol) in dry CH_2Cl_2/MeOH 1:2 (20 ml) was added a freshly prepared of MeONa in MeOH soln. (1.0M, 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 was subjected to CC (SiO_2; $CHCl_3$/MeOH 10:1) to give the target trisaccharide **1** (43 mg, 80%). White amorphous solids. $[\alpha]_D^{27} = +45.7$ ($c = 0.5$, $CHCl_3$). ^{1}H-NMR (CD_3OD, 600 MHz): 6.94 (*d*, *J* = 9.0, 2 arom. H); 6.83 (*d*, *J* = 9.0, 2 arom. H); 4.52 (*d*, *J* = 8.0, H–C(1)); 4.49 (*d*, *J* = 7.0, H–C(1″)); 4.39 (*d*, *J* = 5.7, H–C(1′)); 4.09 (*t*, *J* = 9.7, H–C(3)); 4.05 (*t*, *J* = 7.3, H–C(2″)); 3.96–3.91 (*m*, H–C(3″), H–C(4″)); 3.89 (*t*, *J* = 9.7, H–C(4)); 3.78–3.69 (*m*, H–C(2′), H–C(4′), H_a–C(5′), H_b–C(5′), H_a–C(5″)); 3.65 (*s*, MeO); 3.60–3.55 (*m*, H–C(2), H–C(3′), H_a–C(6)); 3.47–3.41 (*m*, CH_2(5), H_b–C(5″), H_b–C(6)); 1.91 (*s*, NHCO*Me*). ^{13}C-NMR (CD_3OD, 150 MHz): 171.1 (Me*C*ONH); 154.7; 150.5; 117.0; 115.1; 105.7 (C(1′)); 104.3 (C(1″)); 103.5 (C(1)); 83.6 (C(2′)); 81.3 (C(5)); 78.6 (C(3″)); 77.6 (C(3′)); 76.1 (C(2″)); 73.6 (C(3)); 72.8 (C(4)); 72.0 (C(4″)); 71.5 (C(4′)); 69.6 (C(6)); 68.7 (C(5″)); 67.5 (C(5′)); 56.3 (MeO); 55.7 (C(2)); 22.3 (*Me*CONH). HR-ESI-MS: 614.2079 ([$M + Na^+$], $C_{25}H_{37}NNaO_{15}^+$; calc. 614.2054).

REFERENCES

[1] G. R. Waller, K. Yamasachi, 'Saponins Used in Traditional and Modern Medicine', Plenum Press, New York, 1996.
[2] T. Tekeda, Y. Nakamura, S. Takashima, O. Yano, Y. Ogihara, *Chem. Pharm. Bull.* **1993**, *41*, 2132.
[3] C. Tani, Y. Ogihara, M. Mutuga, T. Nakamura, T. Tekeda, *Chem. Pharm. Bull.* **1996**, *44*, 816.

[4] Y. Seo, J. Hoch, K. M. Abdel, *J. Nat. Prod.* **2002**, *65*, 170.
[5] S. Krief, O. Thoison, T. Sevenet, R. W. Wrangham, C. Lavaud, *J. Nat. Prod.* **2005**, *68*, 897.
[6] M. Ukiya, T. Akihisa, K. Yasukawa, H. Tokuda, T. Suzuki, Y. Kimura, *J. Nat. Prod.* **2006**, *69*, 1692.
[7] D. L. Yu, Y. Sakurai, C. Chen, F. R. Chang, L. Huang, Y. Kashiwada, K. H. Lee, *J. Med. Chem.* **2006**, *49*, 5462.
[8] N. T. Dat, K. Bae, A. Wamiru, G. B. Mcmahon, S. Grice, M. Bona, J. A. Beutler, Y. H. Kim, *J. Nat. Prod.* **2007**, *70*, 839.
[9] T. Ohtsuki, T. Miyagawa, T. Koyano, T. Kowithayakorn, N. Kawahara, Y. Goda, M. Ishibashi, *J. Nat. Prod.* **2008**, *71*, 918.
[10] S. G. Ma, Y. C. Hu, S. S. Yu, Y. Zhang, X. G. Chen, J. Liu, Y. X. Liu, *J. Nat. Prod.* **2008**, *71*, 41.
[11] G. Cioffi, F. D. Piaz, A. Vassallo, F. Venturella, P. D. Caprariis, F. D. Simone, N. D. Tommasi, *J. Nat. Prod.* **2008**, *71*, 1000.
[12] T. Nakamura, C. Komori, Y. Lee, F. Hashimoto, S. Yahara, T. Nohara, A. Ejima, *Biol. Pharm. Bull.* **1996**, *19*, 564.
[13] H. J. Park, S. H. Kwon, J. H. Lee, K. H. Lee, K. Miyamoto, K. T. Lee, *Planta Med*. **2001**, *67*, 118.
[14] H. J. Jung, C. O. Lee, K. T. Lee, J. Choi, H. J. Parkm, *Biol. Pharm. Bull*. **2004**, *27*, 744.
[15] M. Abdel-Kader, J. Hoch, J. M. Berger, R. Evans, J. S. Miller, J. H. Wisse, S. W. Mamber, J. M. Dalton, D. G. I. Kingston, *J. Nat. Prod*. **2001**, *64*, 536.
[16] J. S. Sun, X. W. Han, B. Yu, *Carbohydr. Res.* **2003**, *338*, 827.
[17] M. C. Yan, Y. Liu, H. Chen, Y. Ke, Q. C. Xu, M. S. Cheng, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4200.
[18] F. R. Melek, T. Miyase, N. S. Ghaly, M. Nabil, *Phytochemistry* **2007**, *68*, 1261.
[19] B. Classon, P. J. Garegg, B. Samuelson, *Acta Chem. Scand., Ser. B* **1984**, *38*, 419.
[20] A. Fettke, D. Peikow, M. G. Peter, E. Kleinpeter, *Tetrahedron* **2009**, *65*, 4356.
[21] I. R. Greig, M. S. Macauley, I. H. Williams, D. J. Vocadlo, *J. Am. Chem. Soc*. **2009**, *131*, 13415.
[22] R. Schwoerer, R. R. Schmidt, *J. Am. Chem. Soc*. **2002**, *124*, 1632.
[23] B. Mukhopadhyay, R. A. Field, *Carbohydr. Res.* **2006**, *341*, 1697.
[24] D. Zheng, L. Zhou, Y. Y. Guan, X. Z. Chen, W. Q. Zhou, X. G. Chen, P. S. Lei, *Bioorg. Med. Chem. Lett*. **2010**, *20*, 5439.
[25] L. Q. Chen, S. D. Shi, Y. Q. Liu, Q. J. Gao, X. Yi, K. K. Liu, H. Liu, *Carbohydr. Res.* **2011**, *346*, 1250.
[26] T. T. Guo, Q. C. Liu, P. Wang, L. Zhang, W. Zhang, Y. X. Li, *Carbohydr. Res.* **2009**, *344*, 1167.
[27] Q. C. Liu, Z. Fan, D. Li, W. H. Li, T. T. Guo, *J. Carbohydr. Chem.* **2010**, *29*, 386.
[28] B. Bernet, A. Vasella, *Helv. Chim. Acta* **2000**, *83*, 995.
[29] B. Bernet, A. Vasella, *Helv. Chim. Acta* **2000**, *83*, 2055.
[30] Q. C. Liu, P. Wang, L. Zhang, T. T. Guo, G. K. Lü, Y. X. Li, *Carbohydr. Res.* **2009**, *344*, 1276.

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