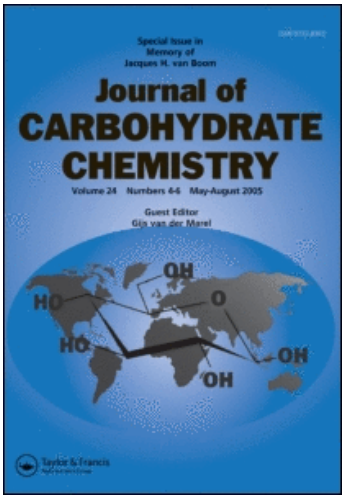

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Efficient Synthesis of Flaccidoside II, a Bioactive Component of Chinese Folk Medicine Di Wu

Qingchao Liu,[1] Lei Zhang,[1] Xiangpeng Li,[1] Tiantian Guo,[1] Peng Wang,[1] and Yingxia Li[2]

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A bidesmosidic triterpene saponin, flaccidoside II, which was isolated from Di Wu, a Chinese folk medicine from dry rhizome of *Anemone flaccida* Fr. Schmidt, was efficiently synthesized in a convergent approach. We employed two glycosyl trichloroacetimidate donors in a one-pot reaction as a key step.

[Supplementary materials are available for this article. Go to the publisher's online edition of the *Journal of Carbohydrate Chemistry* for the following free supplemental resource(s): ^{1}H NMR, ^{13}C NMR and HR mass spectra for all synthesized compounds, 2, 6, 9-11, and Flaccidoside II (**1**)

Keywords Bidesmosidic triterpene saponins; Flaccidoside II; Di Wu; Glycosyl trichloroacetimidates; One-pot reaction

INTRODUCTION

Saponins, glycosides of steroids and triterpenes, are widely distributed in plants and in some marine organisms.[1,2] It is noteworthy that more than half of the triterpene saponins are glycosides of oleanolic acid or its derivatives, with one sugar chain attached through an ether linkage at C-3 and another through an ester linkage at C-28,[3] which have been reported to present a broad spectrum of well-defined biological and pharmacological activities, including antitumor,[4–11] anti-inflammatory,[12] antifungal,[13–15] and anti-HIV.[16–18] Attracted by these interesting biological activities, several

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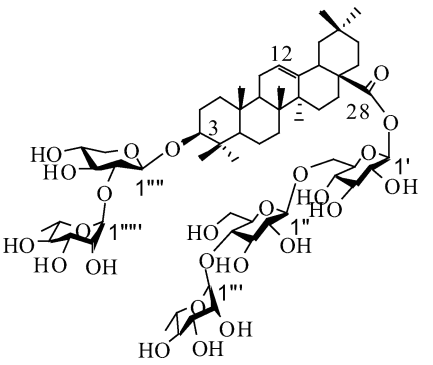


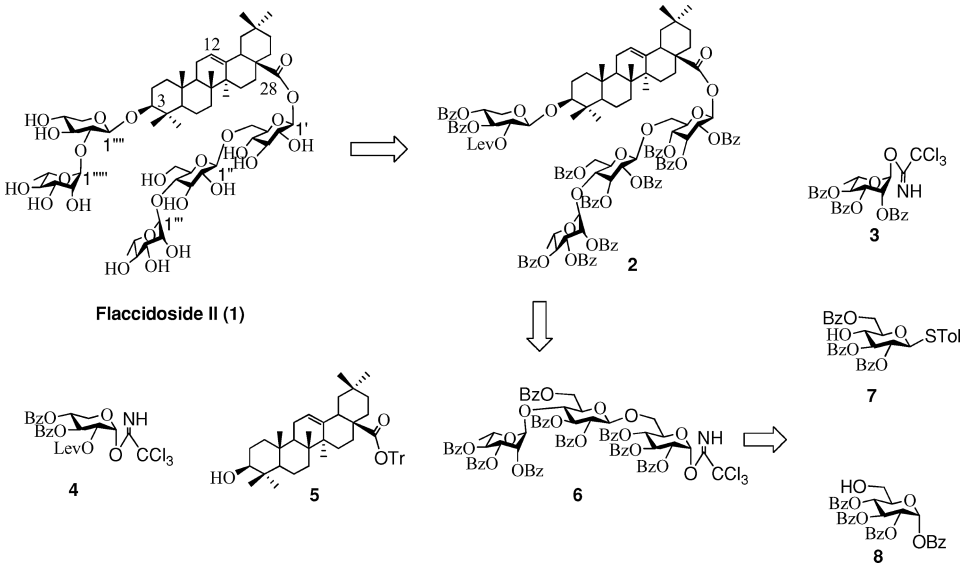
Figure 1: Structure of target compound flaccidoside II (**1**).

research groups reported on the synthesis of many oleanane-type triterpenoid saponins.[19–28] Notably, flaccidoside II, 3-*O*-(α-L-rhamnopyranosyl-(1→2)-β-D-xylopyranosyl) oleanolic acid α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl ester (Fig. 1), a bioactive component of Di Wu, which is a Chinese folk medicine from dry rhizome of *Anemone flaccida* Fr. Schmidt,[29–31] and 3,28-di-O-rhamnosylated oleanolic acid saponins mimicking components of Chinese folk medicine Di Wu have been synthesized by Du et al.[32,33] Based on the structural complexity and bioactivity study of flaccidoside II, we are interested in preparing this bidesmosidic triterpene saponin via a more convenient way. Herein, we report a full account on the synthesis of flaccidoside II.

RESULTS AND DISCUSSION

A few facile synthetic strategies for construction of the bidesmosidic oleanane-type saponins bearing the distinctive disaccharide, the α-L-rhamnopyranosyl-(1→2)-β-D-xylopyranosyl moiety, have been reported.[32] Fortunately, the development of glycosylation procedures by one-pot protocols has made the synthesis of oligosaccharides and glycoconjugates bearing complicated sugar moiety available or even easier.[34–46] Recently, by applying the "one-pot sequential glycosylation" procedure, we have successfully completed the synthesis of three bidesmosidic oleanolic acid saponins (Scabiosaponins E-G).[21] Encouraged by these accomplishments, we decided to adopt this strategy with two trichloroacetimidates as donors to complete the synthesis of the target molecule.[47] Such an approach would allow us to rapidly access a variety of structural analogs of flaccidoside II.

As shown in Scheme 1, saponin **1** can be retrosynthetically disconnected into two distinct fragments **2** and **3**.[48] The former could be assembled from three building blocks **4**,[21] **5**,[46] and **6** through two successive glycosylation

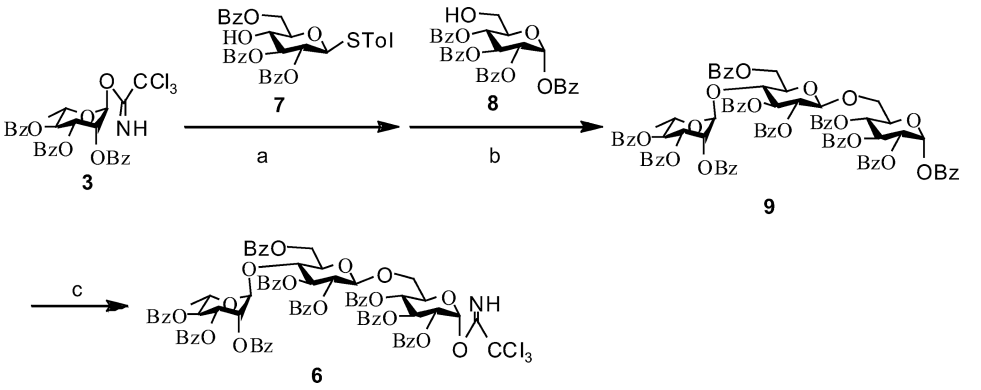


Scheme 1: Retrosynthesis of flaccidoside II (**1**).

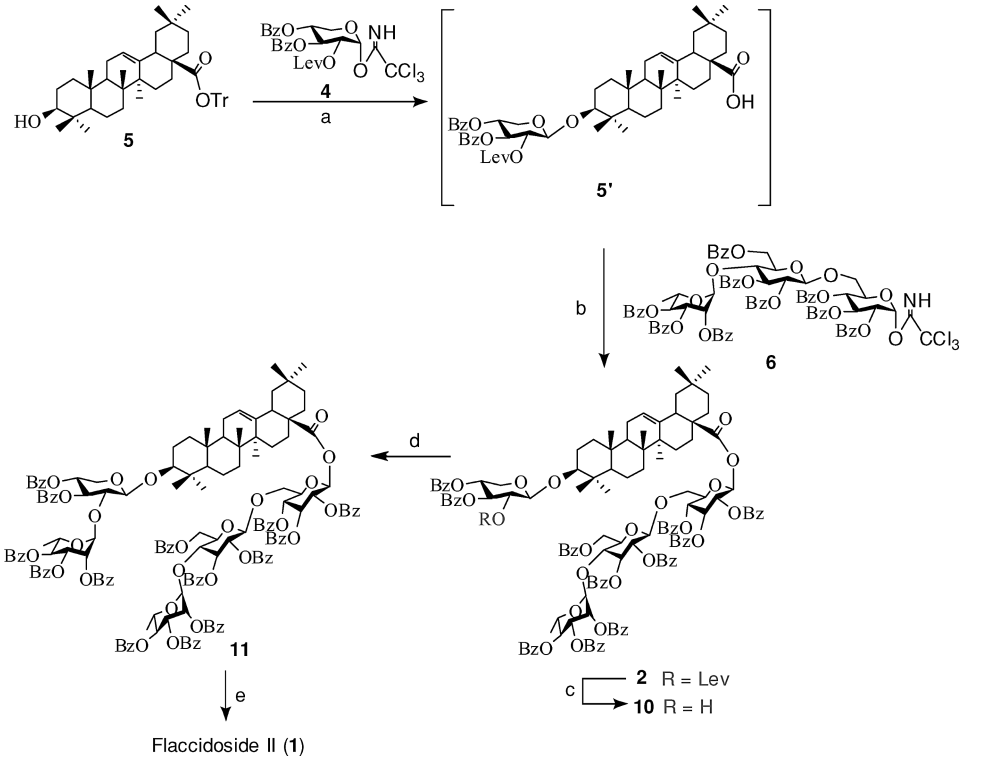
steps in the one-pot reaction. The trisaccharide moiety **6** may also be generated from the corresponding α-L-rhamnopyranosyl trichloroacetimidate **3**, 4-*O*-β-glucopyranoside **7**,[42] and 6-*O*-β-glucopyranoside **8**[49] via a one-pot glycosylation strategy.

With three building blocks **3**, **7**, and **8** in hand, we first constructed the trisaccharide moiety **6** by utilizing the thioglycoside and trichloroacetimidate as donors in a one-pot sequential glycosylation. As depicted in Scheme 2, coupling of *p*-tolyl 2,3,6-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside **7** and 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl trichloroacetimidate **2** was completed within 45 min with the use of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.2 equiv.) at –78°C, providing the desired disaccharide thioglycoside donor. Without purification, the reaction mixture was warmed to –10°C, and then the acceptor 1,2,3,4-tetra-*O*-benzoyl-α-D-glucopyranose(**8**) was added, followed by addition of *N*-iodosuccinimide (NIS, 2.0 equiv.) and TMSOTf (0.5 equiv.), affording the desired product **9** in a 75% yield for two steps. Selective debenzoylation on **9** with NH_2NH_2·HOAc in DMF, followed by C-1 Schmidt activation with trichloroacetonitrile (Cl_3CCN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry CH_2Cl_2, afforded the corresponding imidate **6** in a yield of 87% over two steps.

With an efficient synthetic access to the key trisaccharide moiety **6**, we then set about our final assembly of the target natural product flaccidoside II (**1**), which we thought could be prepared in an efficient way by one-pot sequential glycosylation employing two glycosyl trichloroacetimidates donors (Scheme 3). Herein, condensation of oleanolic ester **5** with 3,4-di-*O*-benzoyl-2-



Scheme 2: Synthesis of trisaccharide donor **6. Reagents and conditions:** (a) TMSOTf (0.2 equiv), CH_2Cl_2, 4 Å MS, –78°C; (b) NIS (2.0 equiv), TMSOTf (0.5 equiv), –10°C, 75% for two steps; (c) NH_2NH_2·HOAc, DMF; then Cl_3CCN, DBU, CH_2Cl_2, r.t., 87% for two steps.



Scheme 3: Synthesis of flaccidoside II (**1**). **Reagents and conditions:** (a) TMSOTf (0.3 equiv), CH_2Cl_2, 4 Å MS, –78°C → rt; (b) **6** (1.6 equiv), CH_2Cl_2, 4 Å MS, 0°C, 65% for two steps; (c) NH_2NH_2·HOAc, CH_2Cl_2-CH_3OH (1:1), 88%; (d) **3** (1.2 equiv), CH_2Cl_2, 4 Å MS, rt, 86%; (e) NaOMe, CH_2Cl_2-CH_3OH (1:2), 85%.

O-levulinoyl-β-D-xylopyranosyl trichloroacetimidate (**4**) under the promotion of TMSOTf (0.3 equiv) at –78°C for 30 min provided the desired product, which was then transformed into the key intermediate **5′** by warming to ambient temperature for 30 min. Following addition of a CH_2Cl_2 solution of the trisaccharide trichloroacetimidate donor **6** to the above mixture at 0°C, the desired glycoside **2** was obtained. Removing the Lev protecting group by treatment with NH_2NH_2·HOAc in CH_2Cl_2-CH_3OH finished the synthesis of **10** in 88% yield.[21] Glycosylation of saponin acceptor **10** with 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl trichloroacetimidate (**3**) catalyzed by TMSOTf gave the fully protected saponin derivative **11** in 86% yield. Finally, removal of the benzoyl groups with NaOMe in MeOH-CH_2Cl_2 afforded the target compound flaccidoside II (**1**) in 85% yield, whose analytical data are identical in all respects to those reported in the literature[31] (Table 1).

In conclusion, a highly efficient and practical method has been developed for the synthesis of flaccidoside II (**1**). The key to this approach is the use of one-pot sequential glycosylation, resulting in a significantly simplified synthetic procedure and isolation of intermediates. Further investigation on preparation and bioactive evaluation of its derivatives is currently under way in our research group.

EXPERIMENTAL

General methods

CH_2Cl_2 was distilled from CaH_2 under a N_2 atmosphere. DMF and CH_3OH were distilled from 4 MS under a N_2 atmosphere prior to use. TLC was performed on precoated Merck silica gel 60 F_{254} plates. Flash column chromatography was performed on silica gel (200–300 mesh, Qingdao, China). Optical rotations were determined with a JASCO P-1020 polarimeter. Melting points were determined with a Yanaco apparatus and are uncorrected. NMR spectra were recorded on a Jeol JNM-ECP 600-MHz spectrometer with Me_4Si as the internal standard, and chemical shifts recorded in δ value. Mass spectra were obtained on a Q-TOF GIOBAL mass spectrometer.

2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-1,2,3,4-tetra-*O*-benzoyl-α-D-glucopyranoside (9)

A mixture of thioglycoside **7** (66 mg, 0.11 mmol) and 4 MS (100 mg) in CH_2Cl_2 (5 mL) was stirred at rt under argon for 30 min, and then cooled to

Table 1: ^{1}H and ^{13}C NMR of glycoside moieties of natural product flaccidoside II (**1**) compared with synthesized compound **1**[a]

	1 (lit.)			1		
Position	^{1}H (ppm)	*J* (Hz)	^{13}C (ppm)	^{1}H (ppm)	*J* (Hz)	^{13}C (ppm)
1′	4.96 d	7.7	95.6	4.97 d	7.7	95.5
2′			73.9	3.92 t-like	8.7, 8.2	
3′			78.0	4.08–4.15 m		
4′			70.7	4.65–4.68 m		
5′			77.1	4.16–4.19 m		
6′-1			69.1	4.30–4.36 m		
6′-2				4.20–4.24 m		
1″	6.21 d	8.0	104.8	6.23 d	8.2	104.7
2″			75.3	4.08–4.15 m		
3″			76.4	4.40 t	9.2	83.9
4″			78.6	4.16–4.19 m		
5″			78.0	4.08–4.15 m		
6″-1			61.1	4.08–4.15 m		
6″-2				3.64 m		
1‴	5.83 br s		102.6	5.85 br s		102.6
2‴			72.5	4.65–4.68 m		
3‴			72.7	4.54 dd	9.1, 3.2	
4‴			73.9	4.30–4.36 m		
5‴			70.2	4.95 qd	9.1, 5.9	
6‴	1.69 d	6.0	18.5	1.69 d	6.0	
1⁗	4.79 d	6.9	106.1	4.81 d	7.3	106.0
2⁗			79.5	4.20–4.24 m		
3⁗			77.8	4.30–4.36 m		
4⁗			71.4	4.08–4.15 m		
5⁗-1			66.9	4.30–4.36 m		
5⁗-2				3.69 t	11.0	
1⁗′	6.51 br s		101.8	6.53 d	1.0	101.8
2⁗′			72.3	4.87 dd	3.2, 1.4	
3⁗′			72.5	4.69 dd	9.6, 3.2	
4⁗′			73.9	4.30–4.36 m		
5⁗′			69.7	4.76 qd	9.2, 6.0	
6⁗′	1.68 d	5.9	18.5	1.70 d	5.9	

[a]Spectra were measured in pyridine-d_5.

–78°C. At this temperature, a solution of TMSOTf (0.2 equiv.) in dry CH_2Cl_2 was injected, and after 10 min trichloroacetimidate **3** (142 mg, 0.23 mmol, 2.1 equiv.) in dry CH_2Cl_2 was added. The resulting mixture was stirred for additional 30 min and then warmed up to –10°C. To the above mixture was added a solution of acceptor **8** (66 mg, 0.11 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL), followed by NIS (50 mg, 0.11 mmol, 2.0 equiv.). After being stirred for 1 h, the reaction mixture was quenched with Et_3N and then filtered through a pad of Celite. The filtrate was concentrated. The residue was purified by silica gel column chromatography (4:1, petroleum ether–EtOAc) to give the trisaccharide moiety **9** (127 mg, 75% two steps) as a white solid. The amounts of the reactants

and the yield of product 9 were calculated based on acceptor **8**. R_f 0.41 (3:1, petroleum ether-EtOAc); $[\alpha]_D^{25}$ +37.3 (c 1.2, $CHCl_3$); IR (KBr) ν: 2947, 1729, 1607, 1465, 1259, 1089, 1068, 709 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.21–8.07 (m, 50 H, Ph-H), 6.69 (d, J = 3.7 Hz, 1 H, H-1), 6.18 (t, J = 9.9 Hz, 1 H, H-3), 5.86 (t, J = 10.0 Hz, 1 H, H-3′), 5.68 (dd, J = 9.9, 3.3 Hz, 1 H, H-3″), 5.55 (dd, J = 3.3, 1.5 Hz, 1 H, H-2″), 5.50–5.54 (m, 2 H, H-4, H-4″), 5.46 (dd, J = 9.9, 3.6 Hz, 1 H, H-2), 5.43 (dd, J = 10.0, 7.7 Hz, 1 H, H-2′), 5.20 (d, J = 1.5 Hz, 1 H, H-1″), 5.00 (dd, J = 12.5, 1.8 Hz, 1 H, H-6′-1), 4.93 (d, J = 7.7 Hz, 1 H, H-1′), 4.64 (dd, J = 12.5, 3.9 Hz, 1 H, H-6′-2), 4.45 (m, 1 H, H-5), 4.29 (t, J = 9.3 Hz, 1 H, H-4′), 4.05 (m, 1 H, H-6–1), 4.03 (m, 1 H, H-5′), 4.00 (dq, J = 9.9, 6.2 Hz, 1 H, H-5″), 3.79 (dd, J = 11.8, 5.6 Hz, 1 H, H-6–2), 0.76 (d, J = 6.2 Hz, 3 H, H-6″); ^{13}C NMR ($CDCl_3$): δ 171.1, 165.8, 165.6, 165.4, 165.0, 133.6, 133.4, 133.3, 133.2, 133.0, 132.9, 132.8, 130.0, 129.9, 129.8, 129.7, 129.4, 129.3, 129.1, 129.0, 128.8, 128.7, 128.6, 128.4, 128.3, 128.1, 100.8 (C-1), 98.8 (C-1″), 90.0 (C-1′), 73.8, 73.6, 72.3, 71.9, 71.4, 71.1, 70.5, 70.4, 69.5, 68.9, 67.8, 67.2, 62.5, 60.3, 17.0; HR-MALDI-MS: *m/z* calcd for $C_{88}H_{72}O_{25}Na$ [M+Na^+] 1551.4264; found: 1551.4255.

2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranosyl Trichloroacetimidate (6)

To a solution of **9** (120 mg, 0.08 mmol) in DMF was added NH_2NH_2·HOAc (9 mg, 0.1 mmol), and the mixture was stirred at rt overnight. After TLC (1:1, petroleum ether-EtOAc) indicated that the reaction was complete, the reaction mixture was concentrated under reduced pressure. The solid residue was purified by silica gel column chromatography (1:2, petroleum ether-EtOAc) to afford a white solid. To a mixture of the solid in CH_2Cl_2 (2 mL) were added trichloroacetonitrile (0.1 mL) and DBU (0.01 mL). The reaction mixture was stirred at rt for 2 h and then concentrated in vacuo. The solid residue was purified by silica gel column chromatography (1:3, petroleum ether-EtOAc) to afford **6** (109 mg, 87%) as a white solid. $[\alpha]_D^{25}$ +117 (c 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.40 (s, 1 H, N-H), 7.25–8.13 (m, 45 H, Ph-H), 6.68 (d, J = 3.4 Hz, 1 H, H-1), 6.18 (t, J = 9.9 Hz, 1 H, H-3), 5.86 (t, J = 9.2 Hz, 1 H, H-3′), 5.69 (dd, J = 10.1, 2.4 Hz, 1 H, H-3″), 5.56 (br s, 1 H, H-2″), 5.53 (t, J = 9.9 Hz, 1 H, H-4), 5.49 (t, J = 10.0 Hz, 1 H, H-4″), 5.40 (dd, J = 9.9, 3.4 Hz, 1 H, H-2), 5.36 (dd, J = 9.9, 7.7 Hz, 1 H, H-2′), 5.22 (s, 1 H, H-1″), 5.01 (dd, J = 12.1, 2.0 Hz, 1 H, H-6′-1), 4.96 (d, J = 7.7 Hz, 1 H, H-1′), 4.65 (dd, J = 12.4, 3.3 Hz, 1 H, H-6′-2), 4.43 (m, 1 H, H-5), 4.31 (t, J = 9.2 Hz, 1 H, H-4′), 4.10 (m, 1 H, H-6–1), 3.98–4.04 (m, 1 H, H-5′, H-5″), 3.82 (dd, J = 11.7, 5.8 Hz, 1 H, H-6–2), 0.77 (d, J = 5.7 Hz, 3 H, H-6″); ^{13}C NMR ($CDCl_3$): δ 165.9, 165.6, 165.4, 165.2, 160.3 (C = NH), 133.3, 133.2, 133.0, 132.9, 129.9, 129.8, 129.7, 129.4, 129.2,

129.0, 128.7, 128.4, 128.3, 128.2, 100.6 (C-1′), 98.7 (C-1″), 93.0 (C-1), 90.7, 73.9, 73.6, 72.3, 72.1, 71.4, 71.1, 70.7, 70.2, 69.5, 68.6, 67.8, 67.2, 62.5, 17.0; HR-MALDI-MS: *m/z* calcd for $C_{83}H_{68}NO_{24}Cl_3Na$ [M+Na$^+$] 1590.3094; found: 1590.3089.

3-*O*-(3,4-Di-*O*-benzoyl-2-*O*-levulinoyl-β-D-xylopyranosyl) Oleanolic Acid 2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl Ester (2)

A mixture of **5** (200 mg, 0.29 mmol), **4** (206 mg, 0.34 mmol, 1.2 equiv.), and 4 MS (400 mg) in dry CH_2Cl_2 (5 mL) was stirred at rt for 30 min and then cooled to –78°C. TMSOTf (15 μL, 0.09 mmol, 0.3 equiv.) was added slowly. After being stirred at –78°C for 30 min, the reaction mixture was warmed up to rt for 30 min, and then cooled to 0°C. A solution of **6** (674 mg, 0.43 mmol, 1.5 equiv.) in dry CH_2Cl_2 (5 mL) was injected slowly. The reaction mixture was stirred at 0°C for 30 min, and then warmed up to rt for another 30 min. The reaction was quenched by addition of Et_3N (0.3 mL) and then filtered. The filtrate was concentrated and purified by silica gel column chromatography (2:1, petroleum ether–EtOAc) to afford **2** (434 mg, 65% based on acceptor **5**) as a white solid, R_f = 0.27 (2:1, petroleum ether-EtOAc); $[\alpha]_D^{25}$ 20.7 (c 2.23, $CHCl_3$); IR (KBr) ν: 3069, 2945, 1735, 1596, 1451, 1265, 1062, 707 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.25–8.11 (m, 55 H, Ph-H), 5.86 (t, J = 9.7 Hz, 1 H, H-3′), 5.84 (d, J = 8.3 Hz, 1 H, H-1′), 5.82 (t, J = 9.6 Hz, 1 H, H-3″), 5.68 (dd, J = 10.2, 3.1 Hz, 1 H, H-3‴), 5.65 (t, J = 7.3 Hz, 1 H, H-3⁗), 5.60 (dd, J = 9.6, 8.3 Hz, 1 H, H-2′), 5.57 (br s, 1 H, H-2‴), 5.52 (t, J = 9.6 Hz, 1 H, H-4′), 5.47 (t, J = 9.6 Hz, 1 H, H-4‴), 5.43 (dd, J = 9.7, 7.7 Hz, 1 H, H-2″), 5.41 (br s, 1 H, H-12), 5.29 (m, 1 H, H-4⁗), 5.22 (m, 1 H, H-6′-1), 5.21 (s, 1 H, H-1‴), 4.99 (m, 2 H, H-1″, H-6″-1), 4.67 (d, J = 6.8 Hz, 1H, H-1⁗), 4.64 (dd, J = 12.4, 3.6 Hz, 1 H, H-6″-2), 4.35 (dd, J = 12.1, 4.5 Hz, 1H, H-5⁗-1), 4.25 (t, J = 9.3 Hz, 1H, H-4″), 4.11 (m, 1 H, H-5‴), 3.89–3.99 (m, 4 H, H-5′, H-5″, H-5⁗-2, H-6′-2), 3.51 (dd, J = 8.8, 7.0 Hz, 1 H, H-2⁗), 3.18 (dd, J = 11.9, 4.6 Hz, 1 H, H-3), 2.95 (dd, J = 13.7, 3.7 Hz, 1 H, H-18), 0.76 (d, J = 5.9 Hz, 3 H, H-6‴), 0.98, 0.96, 0.87, 0.85, 0.85, 0.71, 0.48 (s each, 3 H each, CH_3 × 7); ^{13}C NMR ($CDCl_3$): δ 205.1, 203.5 ($CH_3\underline{C}OCH_2CH_2\underline{C}O$), 175.5 (C-28), 171.2, 165.9, 165.6, 165.4, 165.3, 165.2, 165.1, 164.6, 143.0 (C-13), 133.3, 133.2, 133.0, 130.1, 130.0, 129.9, 129.8, 129.7, 129.5, 129.3, 128.9, 128.4, 128.3, 128.2, 122.6 (C-12), 103.3 (C-1⁗), 100.3 (C-1″), 98.9 (C-1‴), 91.9 (C-1′), 89.3 (C-3), 75.1, 74.0, 73.9, 73.6, 73.5, 73.4, 73.3, 73.2, 73.0, 72.6, 72.4, 71.4, 71.1, 70.5, 69.8, 69.5, 67.7, 55.3, 46.8, 41.6, 39.0, 38.9, 37.9, 33.0, 30.6, 29.6, 27.9, 25.4, 23.6, 17.0, 16.4, 15.3; HR-MALDI-MS: *m/z* calcd for $C_{135}H_{136}O_{34}Na$ [M+Na$^+$] 2323.8842; found: 2323.8805.

3-*O*-(3,4-Di-*O*-benzoyl-β-D-xylopyranosyl) Oleanolic Acid 2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3, 4-tri-*O*-benzoyl-β-D-glucopyranosyl Ester (10)

To a stirred solution of **2** (368 mg, 0.16 mmol) in CH_2Cl_2 (50 mL) and CH_3OH (50 mL) was added NH_2NH_2·HOAc (50 mg, 0.5 mmol). After 2 h, the solution was concentrated. The residue was purified by silica gel column chromatography (2:1, petroleum ether–EtOAc) to afford **10** (308 mg, 88%) as a white solid. $R_f = 0.20$ (2:1, petroleum ether-EtOAc); $[\alpha]_D^{25}$ 19.5 (c 2.01, $CHCl_3$); IR (KBr) ν: 3067, 2941, 1731, 1605, 1450, 1267, 1090, 706 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.24–8.11 (m, 55 H, Ph-H), 5.86 (t, $J = 9.6$ Hz, 1 H, H-3′), 5.82 (d, $J = 8.2$ Hz, 1 H, H-1′), 5.80 (t, $J = 9.6$ Hz, 1 H, H-3″), 5.65 (dd, $J = 10.2$, 3.2 Hz, 1 H, H-3‴), 5.48–5.59 (m, 3 H, H-2′, H-2‴, H-3⁗), 5.41 (t, $J = 9.6$ Hz, 1 H, H-4′), 5.36 (t, $J = 9.7$ Hz, 1 H, H-4‴), 5.36 (m, 2 H, H-12, H-2″), 5.30 (m, 1 H, H-4⁗), 5.19 (s, 1 H, H-1‴), 4.99 (m, 2 H, H-1″, H-6″-1), 4.64 (dd, $J = 12.4$, 3.5 Hz, 1 H, H-6″-2), 4.55 (d, $J = 6.9$ Hz, 1H, H-1⁗), 4.31 (dd, $J = 12.7$, 6.0 Hz, 1H, H-5⁗-1), 4.25 (t, $J = 9.6$ Hz, 1 H, H-4″), 4.09 (m, 1 H, H-5‴), 3.89–4.07 (m, 4 H, H-5′, H-5″, H-5⁗-2, H-6′-2), 3.80 (dd, $J = 8.8$, 7.1 Hz, 1 H, H-2⁗), 3.20 (dd, $J = 11.5$, 3.8 Hz, 1 H, H-3), 2.90 (dd, $J = 14.1$, 3.7 Hz, 1 H, H-18), 0.76 (d, $J = 6.0$ Hz, 3 H, H-6‴), 0.99, 0.99, 0.96, 0.88, 0.87, 0.81, 0.47 (s each, 3 H each, $CH_3 \times 7$); ^{13}C NMR ($CDCl_3$): δ 175.7 (C-28), 165.9, 165.6, 165.4, 165.2, 164.6, 143.0 (C-13), 133.3, 133.2, 133.0, 130.1, 130.0, 129.9, 129.8, 129.7, 129.6, 129.5, 129.3, 128.9, 128.4, 128.3, 128.2, 122.7 (C-12), 105.2 (C-1⁗), 100.4 (C-1″), 98.9 (C-1‴), 92.0 (C-1′), 89.8 (C-3), 75.2, 73.9, 73.6, 73.5, 73.4, 73.1, 73.0, 72.6, 72.5, 72.4, 71.5, 71.3, 71.1, 71.0, 69.8, 69.5, 67.8, 62.4, 60.3, 55.5, 41.6, 39.0, 36.7, 32.9, 30.6, 28.3, 25.4, 23.6, 22.7, 21.0, 17.0, 16.7, 16.6, 15.4, 14.2; HR-MALDI-MS: *m/z* calcd for $C_{130}H_{130}O_{32}Na$ [M+Na^+] 2225.8419; found: 2225.8438.

3-*O*-(2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzoyl-β-D-xylopyranosyl) Oleanolic Acid 2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3, 4-tri-*O*-benzoyl-β-D-glucopyranosyl Ester (11)

Compound **10** (220 mg, 0.1 mmol), trichloroacetimidate **3** (74 mg, 0.12 mmol), and powdered 4 molecular sieves (0.20 g) in dry CH_2Cl_2 (8 mL) were stirred for 40 min at rt, and then TMSOTf (0.005 mL, 0.01 mmol) was added dropwise. The mixture was stirred for 10 min followed by addition of Et_3N and filtration. The filtrate was concentrated and purified by silica gel column chromatography (3:2, petroleum ether-EtOAc) to afford **11** (228 mg, 86%) as a white solid, $R_f = 0.28$ (3:2, petroleum ether-EtOAc); mp 152–154°C; $[\alpha]_D^{25}$ 53.6

(c 1.12, $CHCl_3$); IR (KBr) ν: 3089, 2945, 1726, 1614, 1451, 1272, 1097, 1085, 1027, 709 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.26–8.10 (m, 73 H, Ph-H), 5.86 (t-like, J = 9.7, 9.6 Hz, 1 H, H-3′), 5.78–5.84 (m, 3 H, H-1′, H-3″, H-3‴), 5.71 (t-like, J = 7.3, 6.9 Hz, 1 H, H-3⁗), 5.66 (dd, J = 10.1, 3.2 Hz, 1 H, H-3⁗′), 5.61 (t-like, J = 10.1, 9.7 Hz, 1 H, H-4‴), 5.56–5.58 (m, 2 H, H-2′, H-2‴), 5.53 (m, 1H, H-2⁗′), 5.49 (t, J = 10.1 Hz, 1 H, H-4⁗′), 5.42 (t-like, J = 10.1, 9.6 Hz, 1H, H-4′), 5.35–5.38 (m, 3H, H-12, H-2″, H-1‴), 5.21–5.24 (m, 1 H, H-4⁗), 5.19 (s, 1 H, H-1⁗′), 5.00 (d, J = 8.2 Hz, 1 H, H-1″), 4.86 (d, J = 5.0 Hz, 1 H, H-1⁗), 4.63 (dd, J = 12.4, 3.7 Hz, 1 H, H-5′), 4.50–4.53 (m, 1 H, H-5‴), 4.39 (dd, J = 12.4, 4.6 Hz, 1 H, H-5⁗-1), 4.25 (t, J = 9.2 Hz, 1 H, H-4″), 4.08–4.13 (m, 2 H, H-2⁗, H-6′-2), 4.06–4.08 (m, 1 H, H-6″-1), 3.95–3.98 (m, 2 H, H-5⁗′, H-6″-2), 3.89–3.92 (m, 2 H, H-5″, H-6′-1), 3.65 (dd, J = 11.9, 6.9 Hz, 1 H, H-5⁗-2), 3.21 (dd, J = 11.9, 4.6 Hz, 1 H, H-3), 1.33 (d, J = 5.9 Hz, 3 H, H-6⁗′), 0.76 (d, J = 5.9 Hz, 3 H, H-6‴), 1.08, 0.96, 0.95, 0.87, 0.87, 0.82, 0.47 (s each, 3 H each, $CH_3\times7$); ^{13}C NMR ($CDCl_3$): δ 175.4, 165.7, 165.6, 165.5, 165.4, 165.2, 165.0, 143.0 (C-13), 133.4, 133.3, 133.2, 133.1, 133.0, 132.9, 129.9, 129.8, 129.7, 129.7, 129.6, 129.5, 129.2, 129.1, 128.5, 129.4, 128.3, 128.2, 128.2, 122.6 (C-12), 103.3 (C-1⁗), 100.3 (C-1″), 98.8 (C-1⁗′), 97.5 (C-1‴), 91.9 (C-1′), 89.3 (C-3), 75.1, 73.8, 73.5, 72.8, 72.3, 72.2, 71.8, 71.3, 71.0, 70.5, 70.3, 69.6, 69.4, 69.3, 67.6, 67.2, 66.6, 62.4, 61.2, 60.3, 55.6, 47.5, 46.7, 45.7, 41.5, 41.0, 39.1, 38.8, 38.7, 36.7, 33.7, 32.9, 31.8, 31.7, 30.9, 30.5, 29.6, 28.0, 27.9, 25.9, 25.3, 23.6, 23.3, 22.6, 18.1, 17.4, 16.9, 16.6, 16.4, 15.5, 14.2; HR-MALDI-MS: *m/z* calcd for $C_{157}H_{152}O_{39}Na$ [M+Na^+] 2683.9845; found: 2683.9803.

3-*O*-(α-L-Rhamnopyranosyl-(1→2)-β-D-xylopyranosyl) Oleanolic Acid α-L-Rhamnopyranosyl-(1→4)-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl Ester (1)

To a solution of **11** (200 mg, 0.08 mmol) in dry CH_2Cl_2–MeOH (1:2, 20 mL) was added a newly prepared NaOMe in MeOH solution (1.0 mol/L, 0.20 mL). The mixture was stirred at rt for 5 h and neutralized with Dowex H^+ resin to pH 7 and then filtered. The filtrate was concentrated and the resulting residue was purified by silica gel column chromatography (1:20:0.1, MeOH-$CHCl_3$-H_2O) to give **1** (76 mg, 85%) as white amorphous solids. R_f = 0.26 (1:20:0.1, MeOH-$CHCl_3$-H_2O); mp 191–193°C; $[\alpha]_D^{25}$ –29.6 (c 0.25, C_5H_5N); IR (KBr) ν: 3506, 2941, 1729, 1646, 1451, 1272, 1086, 1051 cm^{-1}; ^1H NMR (C_5D_5N): δ 6.53 (d, J = 1.0 Hz, 1 H, H-1⁗′), 6.23 (d, J = 8.2 Hz, 1 H, H-1″), 5.85 (br s, 1 H, H-1‴), 5.38 (t, J = 3.6 Hz, 1 H, H-12), 4.97 (d, J = 7.7 Hz, 1 H, H-1′), 4.95 (dq, J = 9.1, 5.9 Hz, 1 H, H-5‴), 4.87 (dd, J = 3.2, 1.4 Hz, 1 H, H-2⁗′), 4.81 (d, J = 7.3 Hz, 1 H, H-1⁗), 4.76 (dq, J = 9.2, 6.0 Hz, 1 H, H-5⁗′), 4.69 (dd, J = 9.6, 3.2 Hz, 1 H, H-3⁗′), 4.65–4.68 (m, 2 H, H-2‴, H-4′), 4.54 (dd, J = 9.1, 3.2 Hz, 1 H, H-3‴), 4.40 (t, J = 9.2 Hz, 1 H, H-3″), 4.20–4.24 (m, 2 H,

H-2‴′, H-6′-2), 4.16–4.19 (m, 2 H, H-4″, H-5′), 4.08–4.15 (m, 5 H, H-2″, H-3′, H-4‴′, H-5″, H-6″-1), 3.92 (t-like, $J = 8.7$, 8.2 Hz, 1 H, H-2′), 3.69 (t, $J = 11.0$ Hz, 1 H, H-5‴′-2), 3.64 (m, 1 H, H-6″-2), 3.28 (dd, $J = 11.9$, 4.1 Hz, 1 H, H-3), 3.14 (dd, $J = 13.8$, 4.1 Hz, 1 H, H-18), 1.70 (d, $J = 5.9$ Hz, 3 H, H-6⁗′), 1.69 (d, $J = 6.0$ Hz, 3 H, H-6‴), 1.23, 1.22, 1.18, 1.08, 0.87, 0.87, 0.86 (s each, 3 H each, $CH_3 \times 7$); ^{13}C NMR (C_5D_5N): δ 176.4 (C-28), 144.0 (C-13), 122.7 (C-12), 106.0 (C-1⁗′), 104.7 (C-1″), 102.6 (C-1‴), 101.8 (C-1⁗″), 95.5 (C-1′), 88.4 (C-3), 79.5, 78.6, 78.1, 77.9, 77.8, 77.0, 76.4, 75.2, 74.0, 73.9, 73.7, 72.6, 72.5, 72.3, 71.4, 70.7, 70.2, 69.6, 69.0, 66.8, 61.1, 56.0, 47.9, 46.9, 46.1, 42.0, 41.5, 39.8, 39.4, 38.9, 36.9, 33.9, 33.0, 32.4, 30.6, 29.9, 28.1, 27.9, 26.7, 25.9, 23.7, 23.6, 23.2, 18.6, 18.4, 17.4, 17.0, 15.6; ESIHR-MS: m/z calcd for $C_{59}H_{97}O_{25}$ [M+H$^+$]: 1205.6319; found: 1205.6345.

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