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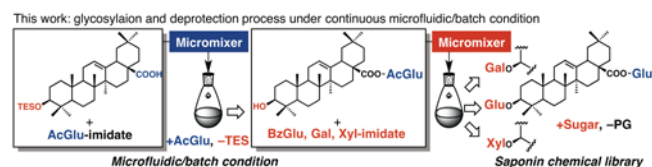
# Synthesis of bisdesmosidic oleanolic acid saponins via a glycosylation-deprotection sequence under continuous microfluidic/batch conditions

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## GRAPHICAL ABSTRACT



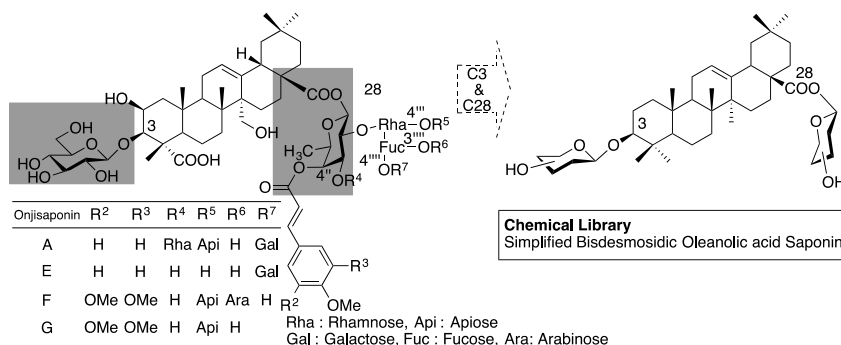
## ABSTRACT

We report the first synthesis of a series of bisdesmosidic oleanolic acid saponins using microflow reactor Comet X-01 via a continuous flow glycosylation-batch deprotection sequence. The main results of this study can be summarized as follows: (1) The microfluidic glycosylation of oleanolic acid at C-28 was achieved in quantitative yield and was applied to the synthesis of six C-28-monoglycosidic saponins. (2) The microfluidic glycosylation of oleanolic acid at C-3 was achieved in good yield without orthoester byproduct formation, and was applied to the synthesis of three bisdesmosidic saponins. (3) The continuous synthesis of saponins via a microfluidic glycosylation-batch deprotection sequence was achieved in four steps involving two purifications. Thus, the continuous microfluidic glycosylation-deprotection process is expected to be suitable for the preparation of a library of bisdesmosidic oleanolic acid saponins for in vivo pharmacological studies.

## INTRODUCTION

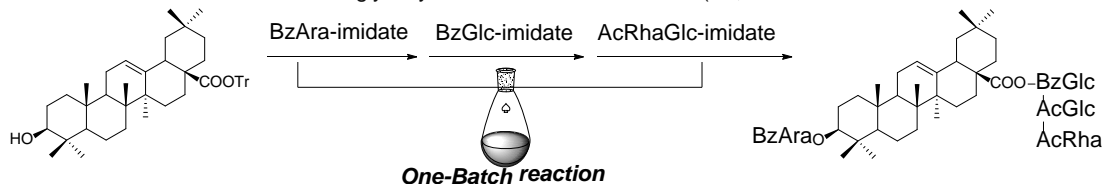
Naturally occurring saponins, found in plants and echinoderms, have several biological activities including cytotoxic, antitumor, anti-inflammatory, and interfacial properties<sup>1</sup>. Thus, they have been widely used as detergents, emulsifiers, and medicinal drugs. During our studies on the biological effects of saponins, several onjisaponins isolated from the rhizomes of *Polygala tenuifolia* Willd were found to be active as nasal vaccine adjuvants<sup>2</sup>. However, the development of a pure saponin-based drug has been hampered by the low yields and high costs associated with their isolation from natural sources. Moreover, the total synthesis of saponins<sup>3</sup> based on the regio- and stereoselective formation of a glycosidic linkage using a variety of sugars in the presence of many hydroxyl groups on the aglycon and sugar moieties is a challenging task. Recently, we synthesized a series of simplified oleanolic acid saponins glycosylated at the C-28 carboxyl, which revealed that the introduction of a 4-*O*-cinnamoyl glucosyl ester moiety enhanced the vaccine adjuvant activity<sup>4</sup>; nevertheless, the adjuvant activity was much lower than that of onjisaponins.

In order to improve the mucosal adjuvant activity and gain a deeper understanding of the structure-activity relationship, a library of glycoforms differing in carbohydrate composition, linkages, and position is required. In particular, we focused on the synthesis of the simplified saponin oleanolic acid 3,28-bisdesmoside<sup>5</sup> because some bisdesmosidic saponins with a complex carbohydrate structure, such as QS-21<sup>6</sup>, have shown adjuvant activity<sup>7</sup> (**Figure 1**). A sequential one-pot method has been reported for the efficient synthesis of bisdesmosidic saponins<sup>5</sup>; however, in the one-pot approach only one saponin compound is obtained. On the other hand, in a stepwise approach, isolation of a monosaccharide glycosyl acceptor as an intermediate after the first glycosylation followed by glycosylation with different glycosyl donors would result in the generation of a saponin library (**Figure 2**). Unfortunately, this stepwise method disturbs a continuity of reaction sequence. Moreover, glycosylation reactions usually require extensive protecting group manipulations, and the additional protection/deprotection steps by conventional procedures leads to lengthy and impractical synthetic schemes (e.g., synthesis of QS-21)<sup>6</sup>. Thus, the construction of a saponin library is a laborious and time-consuming task.

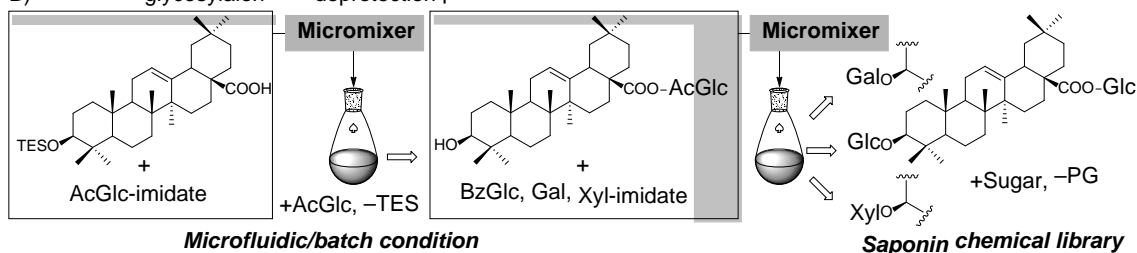


**Figure 1. Structure of onjisaponins and simplified synthetic bisdesmosidic oleanolic acid saponins.**

A) Previous work: multiple successive glycosylation in one-batch reaction (Yu, 1999)



B) This work: glycosylation and deprotection process under continuous microfluidic/batch condition



**Figure 2. Synthesis of bisdesmosidic oleanolic acid saponins to construct saponin chemical library**

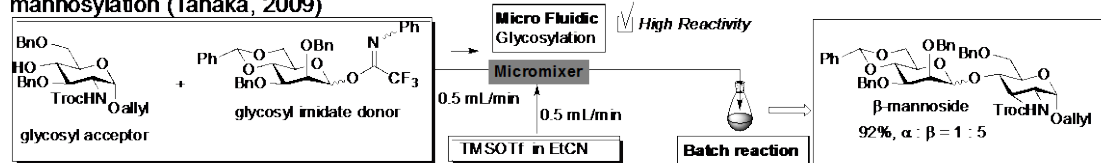
In order to solve this problem, we turned our attention to continuous flow synthesis<sup>8</sup> including flow microreactor synthesis<sup>9</sup>. Microfluidic synthesis has various advantages compared to conventional batch synthesis strategies: (1) strict control of temperature, stirring, and reaction time, (2) easy scale-up, (3) safe and reproducible operations, and (4) possibility of reactions involving short-lived reactive intermediates<sup>10</sup>.

Microflow reactors<sup>11</sup>, (e.g., Silicon microfluidic reactor, PFA reactor<sup>12</sup>, Comet X-01<sup>13</sup>) have been widely used in carbohydrate synthesis for glycosylation reactions (**Figure 3-A**). However, microfluidic glycosylations have not been extensively studied for saponin synthesis because of solubility and reactivity limitations of medium-sized triterpenoid acceptors.

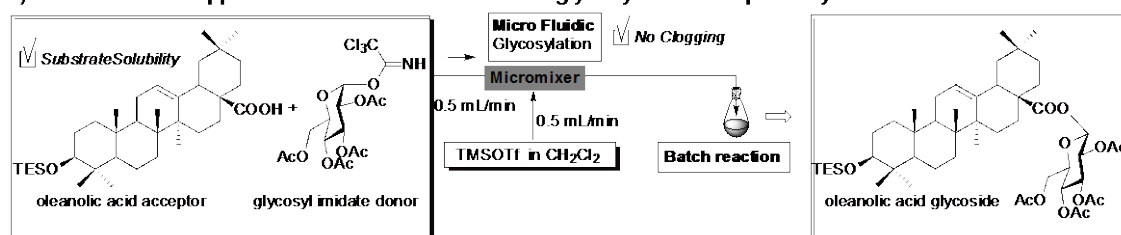
In this study, it was expected that microfluidic glycosylation conditions would benefit from the advantages of microflow reactors. Thus, the glycosylation step of the synthesis of a simplified saponin was carried out for the first time in a microflow reactor (**Figure 3-B**). In addition, continuous glycosylation and deprotection processes for the synthesis of saponins, such as bisdesmosides, can be efficiently performed in microfluidic reactors, that would allow shorter synthetic routes without the need of purification steps and make the saponin chemical library (**Figure 2-B**).

In this paper, we describe the glycosylation of oleanolic acid at C-28 and C-3 in a microfluidic system and a continuous flow glycosylation-batch deprotection process for the synthesis of bisdesmosidic oleanolic acid saponins with different sugar moieties.

A) The example of previous work: Synthesis of a Man  $\beta$  (1-4) GlcNTroc fragment under microfluidic  $\beta$ -mannosylation (Tanaka, 2009)



B) This work: The application of microflow reactor for glycosylation in saponin synthesis



**Figure 3. Applications of microflow reactor for glycosylation.**

## RESULTS AND DISCUSSION

### Glycosylation at C-28

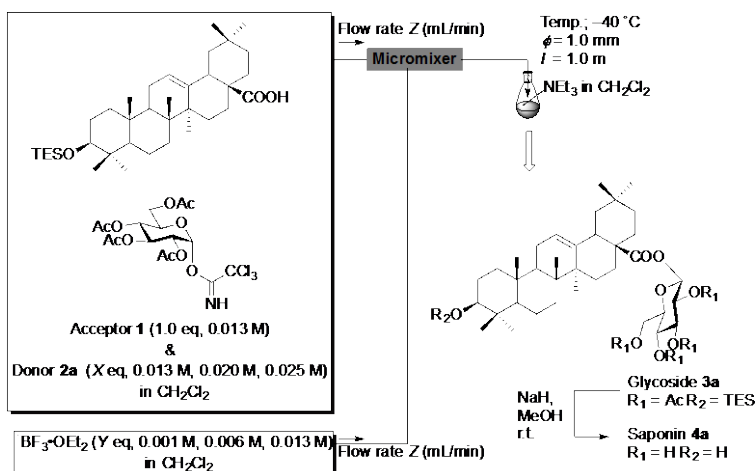
We initially investigated the glycosylation of oleanolic acid at C-28 in a microfluidic system. The Schmidt conditions<sup>14</sup> were considered for the microfluidic glycosylation, whereas C-28 glycosylation has been reported such as Koenigs-Knorr<sup>15</sup> glycosylation and a phase-transfer catalyst conditions<sup>16</sup> which are not suitable for microfluidic systems due to clogging of the silver salts.

Substrate solubility in the reaction medium is an important requirement for successful microfluidic reactions; thus, a key feature of this study is the solubility of oleanolic acid derivatives in  $\text{CH}_2\text{Cl}_2$ , solvent used for Schmidt glycosylation. We decided to synthesize oleanolic acid acceptor **1**<sup>4</sup> with a triethylsilyl (TES) protecting group at C-3 following

Gin's method, which showed improved solubility in  $\text{CH}_2\text{Cl}_2$  as well as different reactivity at C-3 and C-28 allowing for orthogonal deprotection. Accordingly, acceptor **1** was prepared from commercially available oleanolic acid via 3,28-double protection followed by treatment with silica gel to remove the 28-*O*-TES group. On the other hand, selective protection of the C-3-OH with an acetyl (Ac) group was attempted by a stepwise protection-deprotection sequence, resulting in only 32% yield of the desired C-3 Ac-protected acceptor<sup>16</sup>.

Next, we attempted the microfluidic  $\beta$ -selective glycosylation of oleanolic acid at C-28<sup>17</sup>, after preparation of acceptor **1** and imidate donor **2a**<sup>18</sup>, and the reaction conditions were optimized by changing the following parameters: (1) the amount of glycosyl imidate donor **2a**; (2) the amount of  $\text{BF}_3 \cdot \text{OEt}_2$ , used as an activator (catalytic or stoichiometric); and (3) the flow rate in the microreactor. A solution of acceptor **1** and donor **2a** in  $\text{CH}_2\text{Cl}_2$  and a solution of  $\text{BF}_3 \cdot \text{OEt}_2$  in  $\text{CH}_2\text{Cl}_2$  were prepared and mixed using a Comet X-01 micromixer at  $-40^\circ\text{C}$  (see supporting information, SI-table 1). As shown in **Table 1**, in our initial attempts, the microfluidic glycosylation was carried out at different flow rates (0.4-0.7 mL/min) and ratios of donor **2a** to  $\text{BF}_3 \cdot \text{OEt}_2$ . The use of 1.0 eq of donor **2a** slightly promoted the glycosylation except at the flow rate of 0.6 mL/min (entries 5-12), whereas the use of 2.0 eq of **2a** significantly improved the reaction efficiency to provide glycoside **3a**<sup>4</sup> (entries 13-20). In an effort to examine the possibility of decreasing the required amount of **2a**, additional conditions were tested; however, the glycosylation did not proceed effectively when 1.5 eq of **2a** were used (entries 21-23). Moreover, a catalytic amount (0.1 eq) of  $\text{BF}_3 \cdot \text{OEt}_2$  did not promote the reaction even at the efficient flow rate of 0.6 mL/min (entry 24). Interestingly, with 2.0 eq of **2a**, a lower yield was obtained at a flow rate of 0.8 mL/min as compared with those at 0.4-0.6 mL/min (entry 25), whereas the glycosylation at the low flow rate of 0.1 mL/min proceeded in excellent yield (entry 26). These results indicate that, in the presence of an excess amount of **2a**, a sufficient residence time was required for complete glycosylation. In contrast to the batch reaction in the presence of  $\text{MS4}\text{\AA}$ <sup>19</sup>, under microfluidic conditions the glycosylation proceeded to completion even when the amount of  $\text{BF}_3 \cdot \text{OEt}_2$  was decreased (entry 27). These results suggest that the efficient mixing of reactants in the microflow reactor resulted in the efficient activation of **2a** by  $\text{BF}_3 \cdot \text{OEt}_2$  followed by rapid coupling with **1**.

**Table 1. Synthesis of glycoside 3a under microfluidic system at various reaction condition and saponin 4a by deprotection.**



Entry	Donor <b>2a</b> X [eq]	BF <sub>3</sub> •OEt <sub>2</sub> Y [eq]	Flow rate Z [mL/min]	Yield <sup>c</sup> [%]
1			0.4	no reaction
2	1.0	0.1	0.5	no reaction
3			0.6	no reaction
4			0.7	no reaction
5			0.4	4.9
6	1.0	0.5	0.5	17
7			0.6	48
8			0.7	3.6
9			0.4	2.6
10	1.0	1.0	0.5	4.5
11			0.6	51
12			0.7	4.5
13			0.4	quant.
14	2.0	0.5	0.5	quant.
15			0.6	quant.
16			0.7	quant.
17			0.4	76
18	2.0	1.0	0.5	quant.
19			0.6	quant.
20			0.7	quant.
21 <sup>a</sup>		0.1	0.6	0.9
22 <sup>a</sup>	1.5	0.5	0.6	59
23 <sup>a</sup>		1.0	0.6	66
24 <sup>a</sup>		0.1	0.6	11
25 <sup>a</sup>	2.0	0.5	0.8	75
26 <sup>a</sup>		0.5	0.1	quant.
27 <sup>b</sup>	2.0	1.0	-	86

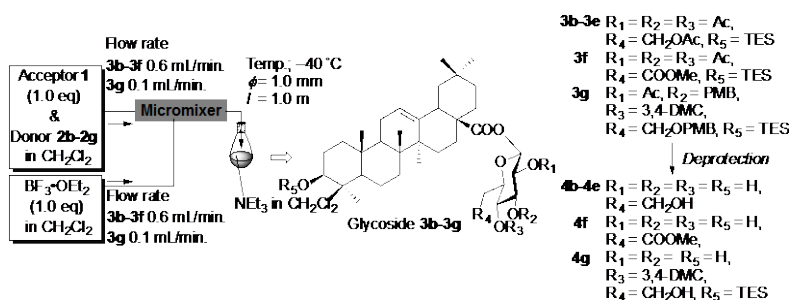
a Additional experiments were performed except enties 1-20. b The reaction was performed using a flask apparatus. c Isolated yield.

The scope and limitation of the microfluidic glycosylation at C-28 was examined with various sugar moieties (**Table 2**). Acetylated galactosyl-, xylosyl-, mannosyl-, rhamnosyl-, glucuronyl-, and cinnamoyl-type (**2b–2g**, respectively) imidate donors were prepared according to previous reports<sup>20</sup>, and the results of their microfluidic glycosylation reactions are summarized in **Table 2**. Protected glycosides **3c** and **3f** were obtained in moderate yields because of the low reactivity of the corresponding donors due to the electron-withdrawing 5'-methylene or carboxyl moiety, which decreased the nucleophilicity of the 1'-anomeric hydroxyl group (entries 2 and 3). On the other hand, **3b**, **3d**, **3e**, and **3g** were obtained in high yields (entries 1, 4, 5 and 6). In particular, the glycosylation of **1** (1.0 eq) with 3,4-dimethoxycinnamoyl (3,4-DMC) donor **2g** (1.0 eq) in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  (10.0 eq) at a flow rate of 0.1 mL/min proceeded smoothly to produce protected cinnamoyl glucoside **3g**<sup>4</sup> in quantitative yield (entry 6), in contrast to the corresponding batch reaction<sup>4</sup> (61% yield).

With protected C-28-glycosides in hand, Ac and TES deprotection of **3a**, **3b**, **3c**, **3d**, and **3e** was performed by treatment with NaH (60% dispersion in mineral oil) and MeOH at room temperature followed by acidification to pH 4 with Dowex resin to afford saponins **4a**<sup>4</sup>, **4b**<sup>16a</sup>, **4c**<sup>16a</sup>, **4d**, and **4e**<sup>16a</sup>, respectively, in excellent yields (entries 1, 2, 3, and 4). On the other hand, glucuronyl saponin **4f**<sup>21</sup> was obtained in low yield because of the unhydrolyzed methyl ester at the 6' position. Other deprotection conditions, such as alkaline hydrolysis with KOH<sup>22</sup> and dealkylation with dodecyl methyl sulfide<sup>23</sup>, were resulted in the undesired simultaneous cleavage of the 6'-methyl and 28-glycosyl ester moieties in **3f** (entry 5). As for compound **3g**, the deprotection was conducted according to our previous report<sup>4</sup> (entry 6).

The structures of the C-28-glycosidic saponins were determined by <sup>1</sup>H NMR, <sup>13</sup>C NMR, <sup>1</sup>H-<sup>1</sup>H COSY, HMQC, and HMBC analyses, which confirmed the glycosidic linkage at C-28, except for mannosyl glycoside **4d** and rhamnosyl glycoside **4e**<sup>24</sup>. The anomeric configuration in **4d** and **4e** was determined by GATE-1 decoupling experiments<sup>25</sup> to give  $\alpha$  conformation (see SI-IV-2,  $J_{\text{C-H}} = 173.4$  Hz for **4d**,  $J_{\text{C-H}} = 173.0$  Hz for **4e**).

**Table 2. The application of glycosylation at C-28 under microfluidic system and synthesis of various C-28-monoglycoside saponin.**

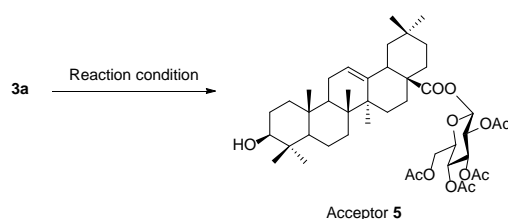


Entry	Donor		Deprotection condition	Glycoside		Saponin	
	eq.	Structure		Product	Yield <sup>a</sup> (%)	Product	Yield <sup>a</sup> (%)
1	2.5		NaH (0.1 eq.), MeOH (0.05 M), r.t., 1 h	<b>3b</b> (β only)	quant.	<b>4b</b> (β only)	quant.
2	2.0		NaH (0.1 eq.), MeOH (0.1 M), r.t., 1 h	<b>3c</b> (β only)	66	<b>4c</b> (β only)	99
3	2.0		NaH (0.1 eq.), MeOH (0.05 M), r.t., 40 min	<b>3d</b> (α only)	93	<b>4d</b> (α only)	quant.
4	2.0		NaH (0.1 eq.), MeOH (0.1 M), r.t., 30 min	<b>3e</b> (α only)	94	<b>4e</b> (α only)	quant.
5	2.0		NaH (0.1 eq.), MeOH (0.05 M), r.t., 3.5 h	<b>3f</b> (β only)	74	<b>4f</b> (β only)	27
6	1.0		1) NaH (6.4 eq.), MeOH (0.02 M), CH <sub>2</sub> Cl <sub>2</sub> (0.08 M), r.t., 1.5 h 2) DDQ (2.0 eq.), H <sub>2</sub> O (0.2 M), CH <sub>2</sub> Cl <sub>2</sub> (0.01 M), r.t., 17 h	<b>3g</b> (β only)	quant.	<b>4g</b> (β only)	23

<sup>a</sup> Isolated yield.

Encouraged by the results of the oleanolic acid glycosylation at C-28 in a flow microreactor, acceptor **5** was prepared from glycoside **3a** by deprotection of the TES ether at C-3 in order to attempt the microfluidic glycosylation at C-3 (**Table 3**). Acidic (AcOH-THF-H<sub>2</sub>O 5:11:3<sup>26</sup>) and mildly acidic (TBAF/THF-AcOH<sup>27</sup>) conditions gave selectively deprotected product **5** in moderate yield along with non-selectively deprotected **4a** (entries 1 and 2). Selective removal of the TES group at C-3 was not achieved under the above conditions because of the steric hindrance of the dimethyl groups at C-23 and C-24. On the other hand, treatment with excess ZnBr<sub>2</sub> in aqueous CH<sub>2</sub>Cl<sub>2</sub><sup>28</sup> afforded acceptor **5** in excellent yield (entry 3). Thus, we were able to achieve the microfluidic C-28 glycosylation of oleanolic acid in quantitative yield without byproduct formation as well as efficient conditions for the subsequent selective C-3 TES deprotection, which was applied to a continuous glycosylation-deprotection reaction.

**Table 3. Synthesis of acceptor 5**



Entry	Reaction condition	Yield <sup>a</sup> (%)
1	AcOH-THF-H <sub>2</sub> O (5:11:3) (0.1M), 16 h	65
2	TBAF, THF (5.0 eq.) AcOH (5.0 eq.), 24 h	68
3	ZnBr <sub>2</sub> (5.0 eq.) H <sub>2</sub> O (5.0 eq.) CH <sub>2</sub> Cl <sub>2</sub> (0.25 M), 16 h	97

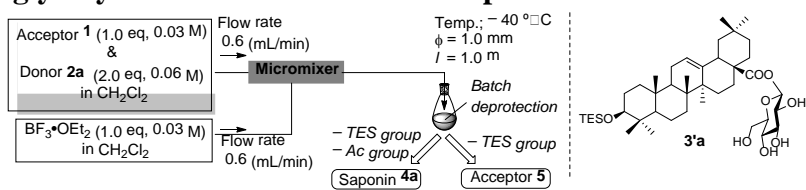
<sup>a</sup> Isolated yield.

### Continuous reaction of microfluidic C-28 glycosylation-deprotection

The advantages of the microfluidic glycosylation reactions of oleanolic acid at C-28 are beneficial for the development of a continuous glycosylation-deprotection process by avoiding the purification of the protected glycoside intermediate. Thus, we attempted the continuous C-28 glycosylation-C-3 selective TES deprotection process of oleanolic acid (**Table 4**). In view of the changes in physical properties required for saponin synthesis, the continuous reaction system was designed based on safety and solubility criteria. In the continuous system, the microfluidic glycosylation at C-28 was performed under the previously optimized conditions, whereas the subsequent protecting group removal required the addition of a suitable deprotecting reagent instead of the quenching reagent triethylamine. Using small amounts of NaH (60% dispersion in mineral oil, 1.5 or 3.0 eq) in MeOH at room temperature, the deprotection reaction did not proceed in the continuous system (entries 1 and 2), indicating that NaH was quenched by  $\text{BF}_3 \cdot \text{OEt}_2$ . On the other hand, in the batch deprotection reaction, when excess NaH (10.0 eq) was used, only byproduct **3'a** was obtained by neutralization with Dowex resin after methanolysis (entry 3). Acidification to pH 4 with Dowex resin after methanolysis resulted in TES deprotection to afford saponin **4a** in excellent yield over two steps (entry 4).

For the synthesis of glycosyl acceptor **5** in the continuous system, regioselective TES deprotection was investigated. Treatment with TBAF/THF-AcOH afforded **5** in only 24% yield over two steps because of the use of different solvents in the two reactions (entry 5). When 5.0 eq of  $\text{ZnBr}_2$  and  $\text{H}_2\text{O}$  were used at  $-40\text{ }^\circ\text{C}$  to room temperature, acceptor **5** was obtained in 55% yield over two steps (entry 6). In contrast to the batch synthesis of acceptor **5**, the deprotection conditions in the continuous system were dependent on the concentration of acceptor **5** in  $\text{CH}_2\text{Cl}_2$ , solvent used for the microfluidic C-28 glycosylation. Hence, we increased the amount of  $\text{ZnBr}_2$  and  $\text{H}_2\text{O}$  (10.0 eq), which provided acceptor **5** in 78% yield over two steps (entry 7). These results indicate that it is important to carefully select the type and concentration of the deprotecting reagent so that the deprotection step is not affected by the glycosylation conditions used in the microfluidic system.

**Table 4. Continuous synthesis for preparation of saponin 4a and acceptor 5 under microfluidic glycosylation at C-28 and batch deprotection.**



Entry	Deprotection condition with batch apparatus	Result	
		Product	yield <sup>a</sup> (2 steps, %)
1	NaH (1.5 eq.), MeOH, r.t., 1 h	<b>3a</b>	quant.
2	NaH (3.0 eq.), MeOH, r.t., 1 h	<b>3a</b>	quant.
3	NaH (4.5~10 eq.), MeOH, r.t., 40 min, neutralized to pH 7	<b>11</b>	40~89
4	NaH (10 eq.), MeOH, r.t., 40 min, neutralized to pH 4	<b>4a</b>	95
5	TBAF, THF (5.0 eq.), AcOH (2.5 eq.), r.t., 2 days	<b>5</b>	24
6	ZnBr <sub>2</sub> (5.0 eq.) H <sub>2</sub> O (5.0 eq.), CH <sub>2</sub> Cl <sub>2</sub> (6 mL), r.t., 30 min	<b>5</b>	55
7	ZnBr <sub>2</sub> (10 eq.) H <sub>2</sub> O (10 eq.), CH <sub>2</sub> Cl <sub>2</sub> (6 mL), r.t., 30 min	<b>5</b>	78

<sup>a</sup> Isolated yield.

### Glycosylation at C-3

The glycosylation of oleanolic acid at C-3 was performed under microfluidic system (**Table 5**), besides trying a batch system for comparison with the microfluidic method (see supporting information, SI-table 2). The glycosylation using acetylated **2a** did not give the protected diglycoside **7a**; instead, the acyloxonium ion intermediate derived from the acetyl imidate donor produced orthoester **8a**<sup>29</sup>, which then rearranged to acetylated oleanolic acid **9**. The structure of orthoester **8a** was determined by a chemical shift on the <sup>1</sup>H NMR at anomeric proton compared to  $\beta$  glycosidic bond. The batch glycosylation using benzoylated glucosyl imidate donor **6a**<sup>30</sup> minimize the orthoester formation (see supporting information in detail).

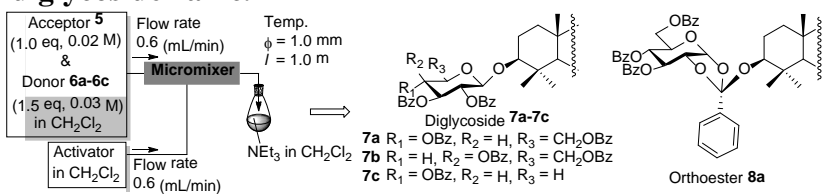
As shown in **Table 5**, the C-3 glycosylation in a microfluidic system using the same amount of **6a** (1.5 eq) used for the batch experiment. Glycosyl acceptor **5** and donor **6a** were dissolved in CH<sub>2</sub>Cl<sub>2</sub> and mixed with various amounts of activator in CH<sub>2</sub>Cl<sub>2</sub> at various temperatures using a Comet X-01 microreactor at a 0.6 mL/min flow rate. After flowing through the reactor tube (1.0 m, i.d.: 1.0 mm), the mixture was quenched by addition of a triethylamine solution in CH<sub>2</sub>Cl<sub>2</sub> in a batch apparatus.

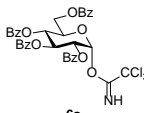
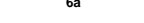
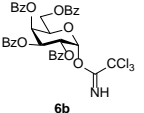
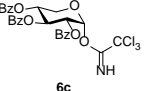
Micro-mixing of **5**, benzoyl donor **6a**, and 1.0 eq of BF<sub>3</sub>•OEt<sub>2</sub>, did not afford **7a** at all (entry 1), and analytical TLC showed incomplete reaction of acceptor **5**. To improve the reaction, we tested TMSOTf as an activator. Micro-mixing of **5**, **6a**, and a catalytic amount of TMSOTf at different temperatures provided diglycoside **7a** in only about 20% yield (entries 2-5), and orthoester **8b** was observed as a byproduct in about 60% yield. Mild reaction conditions utilizing catalytic TMSOTf in lower temperature, caused the preferential formation of **8b**<sup>29</sup>. On the other hand, a stoichiometric amount of TMSOTf promoted the C-3 glycosylation at room temperature, and diglycoside **7a** was obtained in 83% yield without formation of orthoester **8b** (entry 7), whereas at 0 °C the yield of **7a** was decreased (entry 6). These results indicate that rapid activation by an appropriate amount of TMSOTf at a suitable temperature was critical for C-3 glycosylation. Notably, microfluidic C-3 glycosylation required a lower amount of donor **6a** and resulted in an increased yield of **7a** as compared to the batch reaction.

In order to examine the versatility of this approach, the microfluidic C-3 glycosylation was applied to different carbohydrates. Benzoylated galactosyl- and xylosyl-type (**6b** and **6c**, respectively) imidate donors were prepared from the corresponding commercially available monosaccharides by literature procedures<sup>30</sup>. Under the optimized conditions, the microfluidic glycosylation at C-3 afforded protected diglycosides **7b** and **7c** in 71% and 81% yield, respectively (entries 8 and 9), which are about 10% higher than the yields of the corresponding batch reactions.

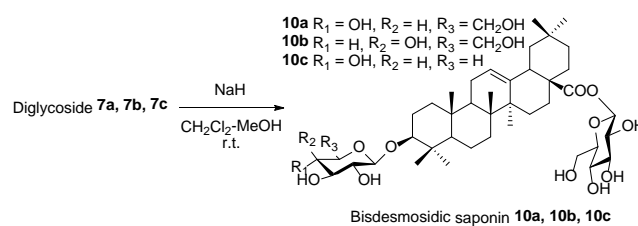
Next, deprotection of all acyl groups in **7a**, **7b**, and **7c** by treatment with NaH (60% dispersion in mineral oil) and MeOH at room temperature afforded known bisdesmosidic saponins **10a**<sup>31</sup>, **10b**<sup>16a, 32</sup>, and **10c**<sup>16b</sup> in 93%, 74%, and 87% yield, respectively (**Table 6**).

On the basis of these results, we envisioned the continuous synthesis of saponins by a consecutive glycosylation-deprotection process. Moreover, suitable conditions were found for the glycosylation at C-3 without orthoester byproduct formation. In addition, it should be noted that the efficiency of these transformations, with trace amounts of unreacted substrates and byproducts, allows for the easy isolation of the desired bisdesmosidic saponins by column chromatography.

**Table 5. The study of glycosylation at C-3 under microfluidic system toward synthesis of diglycoside 7a-7c.<sup>a</sup>**


Entry	Donor (1.5 eq.)	Activator (eq.)	Temp (°C)	7a-7c (%)	8a (%)
1		BF <sub>3</sub> •OEt <sub>2</sub> (1.0)	r.t.	0	0
2		TMSOTf (0.1)	-40	20 <sup>b</sup>	65 <sup>b</sup>
3		TMSOTf (0.1)	-20	22 <sup>b</sup>	54 <sup>b</sup>
4		TMSOTf (0.1)	0	24 <sup>b</sup>	66 <sup>b</sup>
5		TMSOTf (0.1)	r.t.	27 <sup>b</sup>	34 <sup>b</sup>
6		TMSOTf (1.0)	0	47 <sup>c</sup>	0
7		TMSOTf (1.0)	r.t.	83 <sup>c</sup>	0
8		TMSOTf (1.0)	r.t.	71 <sup>c</sup>	- <sup>d</sup>
9		TMSOTf (1.0)	r.t.	81 <sup>c</sup>	- <sup>d</sup>

<sup>a</sup> Results under the batch conditions; See SI-Table 2 in supporting information. <sup>b</sup> The yield was based on the 7a / 8a ratio by measurement of <sup>1</sup>H-NMR. <sup>c</sup> Isolated yield. <sup>d</sup> Corresponding orthoester was not observed.

**Table 6. Synthesis of bisdesmosidic saponin 10a, 10b, 10c.**

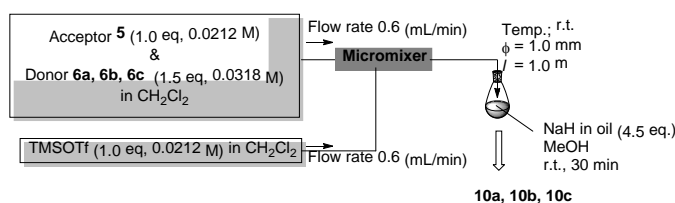
Entry	Diglycoside	Bisdesmosidic saponin	Yield <sup>a</sup>
1	<b>7a</b>	<b>10a</b>	93
2	<b>7b</b>	<b>10b</b>	74
3	<b>7c</b>	<b>10c</b>	87

<sup>a</sup> Isolated yield.

### Continuous reaction of microfluidic C-3 glycosylation-deprotection

We attempted the continuous C-3 glycosylation-acyl deprotection sequence (**Table 7**). Gratifyingly, bisdesmosidic saponins **10a**, **10b**, and **10c** were obtained in about 40% yield over two steps by treatment with 4.5 eq of NaH (60% dispersion in mineral oil) in MeOH at room temperature. Thus, bisdesmosidic saponins could be readily prepared from acceptor **1** in about 30% total yield over four steps involving two purification operations.

**Table 7. Continuous synthesis of bisdesmosidic saponins under microfluidic glycosylation at C-3 and batch deprotection of acyl groups.**



Saponin			
Entry	Donor (1.5 eq.)	Product	Yield <sup>a</sup> (2 steps, %)
1	<b>6a</b>	<b>10a</b>	47
2	<b>6b</b>	<b>10b</b>	43
3	<b>6c</b>	<b>10c</b>	47

<sup>a</sup> Isolated yield.

### The assignments of bisdesmosidic acid saponins

In this work, we determined for the first time the detailed structure of synthetic bisdesmosidic saponins **10a**, **10b**, and **10c**, and the spectral data of their sugar moieties are shown<sup>33</sup> in **Table 8**. Because of overlapping of the sugar proton signals, the chemical structures of the synthesized saponins could not be identified by <sup>1</sup>H-NMR spectroscopy even by comparison with previous reports<sup>16a</sup>, and it was therefore necessary to resort to TOCSY experiments<sup>34</sup>. The <sup>1</sup>H-NMR chemical shifts, multiplicities, and coupling constants of the sugar signals were assigned by <sup>1</sup>H-<sup>1</sup>H COSY and 1D TOCSY spectra; HSQC and HSQC-TOCSY experiments were used to assign the chemical shifts and multiplicities in the <sup>13</sup>C-NMR spectra and the corresponding sugar proton signals (see SI-IV-3). The β-anomeric configuration of the 28-*O*-sugar and 3-*O*-sugar was demonstrated by the large *J* values (7.5-8.5 Hz). The HMBC correlations between the anomeric proton (1'-H or 1''-H) and C-28 or C-3 confirmed the presence of glycosidic linkages. Interestingly, the <sup>1</sup>H-NMR spectra of diglycosidic saponins showed differences in the multiplicities of the 2'-H and 3'-H signals of the 28-*O*-sugar moiety, suggesting that the nature of the 3-*O*-sugar moiety affected the conformation of the saponin.

**Table 8. <sup>1</sup>H- and <sup>13</sup>C-NMR spectral assignments for sugar moieties of bisdesmosidic saponin 10a, 10b, 10c.**

	28- <i>O</i> - β-Glc			3- <i>O</i> - β-Glc		
		δH	δC		δH	δC
<b>10a</b>	1'	6.30 (d, 8.0)	95.9	1"	4.91 (d, 8.0)	107.0
	2'	4.18 (t, 8.5)	74.2	2"	4.01 (t, 8.0)	75.9
	3'	4.26 (dd, 9.0, 8.5)	78.9	3"	4.22 (dd, 8.5, 8.0)	78.8
	4'	4.34 (dd, 9.5, 9.0)	71.2	4"	4.20 (dd, 9.0, 8.5)	71.9
	5'	4.00 (ddd, 9.5, 4.0, 2.0)	79.5	5"	3.98 (ddd, 9.0, 5.0, 2.0)	78.4
	6'	4.43 (dd, 12.0, 2.0)	62.2	6"	4.56 (dd, 12.0, 2.0)	63.1
<b>10b</b>		4.38 (dd, 12.0, 5.0)			4.37 (dd, 12.0, 5.0)	
	28- <i>O</i> - β-Glc			3- <i>O</i> - β-Gal		
		δH	δC		δH	δC
	1'	6.33 (d, 8.0)	95.9	1"	4.87 (d, 8.0)	107.0
	2'	4.22 (dd, 8.5, 8.0)	74.2	2"	4.46 (dd, 9.0, 8.0)	75.9
	3'	4.30 (dd, 9.0, 8.5)	78.9	3"	4.19 (dd, 9.0, 3.0)	73.2
<b>10c</b>	4'	4.37 (dd, 9.5, 9.0)	71.1	4"	4.60 (dd, 3.0, 1.0)	71.9
	5'	4.04 (ddd, 9.5, 4.0, 3.0)	79.5	5"	4.13 (td, 6.0, 1.0)	70.3
	6'	4.48 (dd, 12.0, 3.0)	62.2	6"	4.50 (dd, 12.0, 6.0)	62.5
		4.41 (dd, 12.0, 4.0)			4.45 (dd, 12.0, 6.0)	
	28- <i>O</i> -β-Glc			3- <i>O</i> - β-Xyl		
		δH	δC		δH	δC
<b>10c</b>	1'	6.33 (d, 8.5)	95.9	1"	4.84 (d, 7.5)	107.8
	2'	4.21 (dd, 8.5, 8.0)	74.2	2"	4.03 (dd, 8.5, 7.5)	75.6
	3'	4.30 (t, 9.0)	78.9	3"	4.18 (t, 8.5)	78.7
	4'	4.38 (dd, 9.5, 9.0)	71.1	4"	4.24 (ddd, 10.0, 8.5, 5.0)	71.2
	5'	4.04 (ddd, 9.5, 4.0, 2.0)	79.5	5"	4.39 (dd, 11.0, 5.0)	67.3
	6'	4.47 (dd, 12.0, 2.0)	62.2		3.79 (dd, 11.0, 5.0)	
		4.41 (dd, 12.0, 4.0)				

## CONCLUSION

In conclusion, we achieved the first C-28 and C-3 glycosylation of oleanolic acid in a microfluidic system in quantitative and good yields, respectively. Six C-28-monoglycosidic and three bisdesmosidic saponins were synthesized, and their detailed structures were determined. The advantages of the microfluidic glycosylation were exploited for the development of a continuous glycosylation-deprotection sequence for saponin synthesis. This simple continuous method is based on the addition of a deprotecting reagent, instead of a quenching reagent, after the glycosylation step. Three bisdesmosidic saponins could be easily prepared from oleanolic acid via continuous microfluidic glycosylation-batch deprotection in 28-31% total yield. By reducing the number of purification steps, this synthetic approach using a microflow reactor could readily provide a wide variety of bisdesmosidic saponins and find application in the development of a saponin library for biological assays.

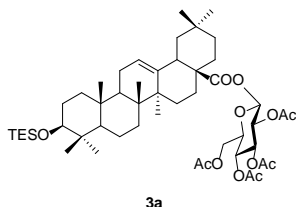
## EXPERIMENTAL SECTION

### General Information.

All reactions were carried out under argon atmosphere in dried glassware, unless otherwise noted. All reagents were purchased from Tokyo Kasei Kogyo, Kanto Chemical, Wako Pure Chemical Industries, Fluka or Aldrich companies and used without further purification, unless otherwise noted. Dry DMF, THF, and CH<sub>2</sub>Cl<sub>2</sub> were purchased from Kanto Chemical Co. Pre-coated silica gel plates with a fluorescent indicator (Merck 60 F254) were used for analytical and preparative thin layer chromatography. Flash column chromatography was carried out with Kanto Chemical silica gel (Kanto Chemical, silica gel 60N, spherical neutral, 0.040-0.050 mm, Cat. No. 37 563-84). Powdered and pre-dried molecular sieves 4Å were used in glycosylation. Detection was carried out by staining with phosphomolybdic acid resulted in blue spots and application of UV (254 nm). <sup>1</sup>H NMR spectra were recorded on Agilent Technologies 400-MR (400 MHz), 400-MR DD2 (400 Hz), NMR DD2 400NB (400 MHz) spectrometers. <sup>13</sup>C NMR spectra were recorded on Agilent Technologies 400-MR (400 MHz), 400-MR DD2 (400 Hz), NMR DD2 400NB (400 MHz) spectrometers. The chemical shifts are expressed in ppm downfield from the internal solvent peaks for CDCl<sub>3</sub> (7.26 ppm, <sup>1</sup>H-NMR), CD<sub>3</sub>OD (3.31 ppm, <sup>1</sup>H-NMR), pyridine-*d*<sub>5</sub> (8.73 ppm, <sup>1</sup>H NMR), CDCl<sub>3</sub> (77.0 ppm, <sup>13</sup>C NMR), CD<sub>3</sub>OD (49.0 ppm, <sup>13</sup>C-NMR) or pyridine-*d*<sub>5</sub> (150.0 ppm, <sup>13</sup>C-NMR) and J values are given in Hertz. The coupling patterns are denoted s (singlet), d (doublet), dd (double doublet), ddd (double double doublet), t (triplet), dt (double triplet), q (quartet), m (multiplet), or br (broad). All infrared spectra were measured on a JASCO FT/IR-460 spectrometer and absorbance bands are reported in wavenumber (cm<sup>-1</sup>). High- and low-resolution mass spectra were measured on a JEOL JMS-T100 LP, JMS-700 MStation and JEOL JMS-AX505 HA spectrometer. Optical rotations were measured by using JASCO DIP-370 and P-2200 polarimeter.

**Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, 2, 3, 4, 6-Tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl ester (3a)**

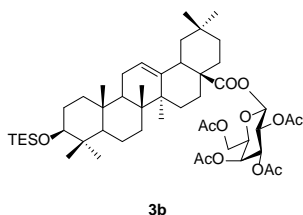
**MicroFlow.** A solution of  $\text{BF}_3 \cdot \text{OEt}_2$  (6.0  $\mu\text{L}$ , 0.0478 mmol, 0.006 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (7.5 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **2a** (94.2 mg, 0.1912 mmol, 0.025 M) and acceptor **1** (54.6 mg, 0.0956 mmol, 0.013 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (7.5 mL) was injected to the micromixer by the same syringe pump



at the flow rate of 0.6 mL/min and mixed at  $-40^\circ\text{C}$ . After the reaction mixture was allowed to flow at  $-40^\circ\text{C}$  for an additional 100 sec through a Teflon reactor tube ( $\phi = 1.0$  mm,  $l = 1.0$  m), the mixture was quenched by addition of triethylamine (3.0  $\mu\text{L}$ ) diluted in  $\text{CH}_2\text{Cl}_2$ . The mixture was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 20 g, hexane : AcOEt = 6 : 1) afforded **3a** (90.5 mg, 0.100 mmol, quant.) as a white foamy solid.  $R_f = 0.43$  (hexane : AcOEt = 2 : 1);  $[\alpha]_D^{26} +25.1$  ( $c$  1.00,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  : 5.58 (d,  $J = 8.0$  Hz, 1H, 1'-H), 5.31 (dd,  $J = 4.8$  Hz, 3.2 Hz, 1H, 12-H), 5.25 (dd,  $J = 10.0$  Hz, 9.1 Hz, 1H, 4'-H), 5.18 (dd,  $J = 9.1$  Hz, 8.0 Hz, 1H, 2'-H), 5.13 (t,  $J = 9.1$  Hz, 1H, 3'-H), 4.27 (dd,  $J = 12.5$  Hz, 4.3 Hz, 1H, 6'-H), 4.04 (dd,  $J = 12.5$  Hz, 2.2 Hz, 1H, 6'-H), 3.79 (ddd,  $J = 10.0$  Hz, 4.3 Hz, 2.2 Hz, 1H, 5'-H), 3.19 (m, 1H, 3-H), 2.78 (m, 1H, 18-H), 2.06 (s, 3H,  $-\text{OCOCH}_3$ ), 2.02 (s, 3H,  $-\text{OCOCH}_3$ ), 2.01 (s, 6H,  $-\text{OCOCH}_3 \times 2$ ), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H, 21-H), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.93 (m, 9H,  $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ ), 0.89 (m, 1H, 1-H), 0.88 (s, 6H, 23-H, 30-H), 0.87 (s, 6H, 25-H, 29-H), 0.72 (s, 3H, 24-H), 0.69 (s, 3H, 26-H), 0.65 (m, 1H, 5-H), 0.56 (m, 6H,  $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ );  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  : 175.6 (C-28), 170.6 ( $-\text{OCOCH}_3$ ), 170.2 ( $-\text{OCOCH}_3$ ), 169.4 ( $-\text{OCOCH}_3$ ), 169.0 ( $-\text{OCOCH}_3$ ), 142.8 (C-13), 122.9 (C-12), 91.5 (C-1'), 79.4 (C-3), 72.8 (C-4'), 72.3 (C-5'), 69.8 (C-2'), 68.0 (C-3'), 61.5 (C-6'), 47.5 (C-5), 46.7 (C-9), 45.7 (C-17), 41.6 (C-19), 41.0 (C-14), 39.2 (C-18), 38.4 (C-8), 38.4 (C-4), 36.8 (C-1), 33.7 (C-10), 32.9 (C-21), 32.8 (C-29), 32.8 (C-7), 31.7 (C-22), 30.6 (C-20), 28.4 (C-23), 27.6 (C-15), 27.6 (C-2), 25.6 (C-27), 23.4 (C-30), 23.4 (C-16), 22.8 (C-11), 20.7 ( $-\text{OCOCH}_3$ ), 20.7 ( $-\text{OCOCH}_3$ ), 20.6 ( $-\text{OCOCH}_3$ ), 20.6 ( $-\text{OCOCH}_3$ ), 18.5 (C-6), 16.9 (C-26), 16.0 (C-24), 15.3 (C-25), 7.0 ( $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ ), 5.2 ( $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ ); IR (NaCl)  $\text{cm}^{-1}$   $\nu$  : 2950 ( $=\text{C-H}$ ), 1692 ( $-\text{C=O}$ ), 1075 ( $-\text{C-O-}$ ); HRMS (ESI-TOF)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd for  $\text{C}_{50}\text{H}_{80}\text{O}_{12}\text{SiNa}$  923.5317; Found 923.5326.

**Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, 2, 3, 4, 6-tetra-*O*-acetyl- $\beta$ -D-**

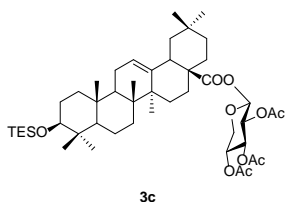
**galactopyranosyl ester (3b) *MicroFlow*.** A solution of  $\text{BF}_3 \cdot \text{OEt}_2$  (55  $\mu\text{L}$ , 0.4379 mmol,



0.03 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (14.6 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **2b** (539 mg, 1.095 mmol, 0.075 M) and acceptor **1** (250 mg, 0.4379 mmol, 0.03 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (16.4 mL) was injected to the micromixer

by the same syringe pump at the flow rate of 0.6 mL/min and mixed at  $-40^\circ\text{C}$ . After the reaction mixture was allowed to flow at  $-40^\circ\text{C}$  for an additional 100 sec through a Teflon reactor tube ( $\phi = 1.0$  mm,  $l = 1.0$  m), the mixture was quenched by addition of triethylamine (0.24 mL) diluted in  $\text{CH}_2\text{Cl}_2$ . The mixture was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 80 g, hexane :  $\text{AcOEt} = 5 : 1$ ) afforded **3b** (413 mg, 0.458 mmol, quant.) as a white solid.  $R_f = 0.40$  (hexane :  $\text{AcOEt} = 2 : 1$ );  $[\alpha]_D^{22} +44.1$  ( $c$  1.00,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  : 5.55 (d,  $J = 8.5$  Hz, 1H, 1'-H), 5.40 (dd,  $J = 3.5$  Hz, 1.0 Hz, 1H, 4'-H), 5.35 (dd,  $J = 10.4$  Hz, 8.4 Hz, 1H, 2'-H), 5.32 (dd,  $J = 3.3$  Hz, 3.3 Hz, 1H, 12-H), 5.07 (dd,  $J = 10.4$  Hz, 3.5 Hz, 1H, 3'-H), 4.10 (m, 2H, 6'-H), 4.00 (ddd,  $J = 7.2$  Hz, 5.9 Hz, 1.2 Hz, 1H, 5'-H), 3.20 (dd,  $J = 11.1$  Hz, 4.3 Hz, 1H, 3-H), 2.80 (dd,  $J = 13.9$  Hz, 4.0 Hz, 1H, 18-H), 2.16 (s, 3H,  $-\text{OCOCH}_3$ ), 2.03 (s, 3H,  $-\text{OCOCH}_3$ ), 2.02 (s, 3H,  $-\text{OCOCH}_3$ ), 1.99 (s, 3H,  $-\text{OCOCH}_3$ ), 1.95 (m, 1H, 11-H), 1.86 (m, 2H, 16-H), 1.65 (m, 2H, 22-H), 1.61 (m, 1H, 19-H), 1.58 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.49 (m, 1H, 6-H), 1.49 (m, 2H, 9-H), 1.45 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.33 (m, 1H, 6-H), 1.30 (m, 1H, 21-H), 1.22 (m, 1H, 21-H), 1.18 (m, 1H, 7-H), 1.15 (m, 1H, 19-H), 1.12 (s, 3H, 27-H), 1.02 (m, 1H, 15-H), 0.95 (t,  $J = 7.6$  Hz, 9H,  $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ ), 0.91 (m, 1H, 1-H), 0.90 (s, 12H, 23-H, 25-H, 29-H, 30-H), 0.74 (s, 3H, 24-H), 0.73 (s, 3H, 26-H), 0.68 (m, 1H, 5-H), 0.58 (m, 6H,  $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ );  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  : 175.6 (C-28), 170.3 ( $-\text{OCOCH}_3$ ), 170.2 ( $-\text{OCOCH}_3$ ), 169.9 ( $-\text{OCOCH}_3$ ), 169.1 ( $-\text{OCOCH}_3$ ), 142.9 (C-13), 122.8 (C-12), 92.0 (C-1'), 79.4 (C-3), 71.4 (C-5'), 70.9 (C-3'), 67.5 (C-2'), 66.8 (C-4'), 60.8 (C-6'), 55.3 (C-5), 47.6 (C-9), 46.8 (C-17), 45.8 (C-19), 41.7 (C-14), 41.0 (C-18), 39.5 (C-1), 39.3 (C-8), 39.3 (C-4), 36.9 (C-10), 33.8 (C-21), 33.0 (C-7), 33.0 (C-29), 31.6 (C-22), 30.6 (C-20), 28.4 (C-23), 27.8 (C-15), 27.7 (C-2), 25.6 (C-27), 23.5 (C-11), 23.4 (C-16), 22.8 (C-30), 20.7 ( $-\text{OCOCH}_3$ ), 20.6 ( $-\text{OCOCH}_3$ ), 20.6 ( $-\text{OCOCH}_3$ ), 20.5 ( $-\text{OCOCH}_3$ ), 18.5 (C-6), 17.0 (C-26), 16.0 (C-24), 15.4 (C-25), 7.0 ( $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ ), 5.3 ( $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ ); IR (KBr)  $\text{cm}^{-1}$   $\nu$  : 2957 (=C-H), 1752 (C=O), 1067 (C-O-); HRMS (ESI-TOF)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd for  $\text{C}_{50}\text{H}_{80}\text{O}_{12}\text{SiNa}$ : 923.5317; Found 923.5307.

**Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, 2, 3, 4-tri-*O*-acetyl- $\beta$ -D-xylopyranosyl ester (**3c**)** *MicroFlow*

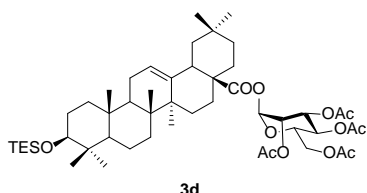


A solution of  $\text{BF}_3 \cdot \text{OEt}_2$  (72.0  $\mu\text{L}$ , 0.5705 mmol, 0.0316 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (18 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **2c** (480 mg, 1.1411 mmol, 0.0634 M) and acceptor **1** (326 mg, 0.5705 mmol, 0.0317 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (18 mL) was injected to the micromixer by the same

syringe pump at the flow rate of 0.6 mL/min and mixed at  $-40^\circ\text{C}$ . After the reaction mixture was allowed to flow at  $-40^\circ\text{C}$  for an additional 100 sec through a Teflon reactor tube ( $\phi = 1.0$  mm,  $l = 1.0$  m), the mixture was quenched by addition of triethylamine (79.4  $\mu\text{L}$ ) diluted in  $\text{CH}_2\text{Cl}_2$ . The mixture was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 25 g, hexane : AcOEt = 6 : 1) afforded **3c** (312 mg, 0.0941 mmol, 66%) as a white foamy solid.

$R_f = 0.43$  (hexane : AcOEt = 2 : 1);  $[\alpha]_{\text{D}}^{22} +28.2$  ( $c$  1.00,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  : 5.63 (d,  $J = 6.8$  Hz, 1H, 1'-H), 5.31 (t,  $J = 3.5$  Hz, 1H, 12-H), 5.20 (t,  $J = 8.1$  Hz, 3'-H), 5.05 (dd,  $J = 8.1$  Hz, 6.8 Hz, 1H, 2'-H), 5.13 (m,  $J = 9.1$  Hz, 1H, 4'-H), 4.12 (m, 1H, 5'-H), 3.49 (dd,  $J = 13.6$  Hz, 8.4 Hz, 1H, 5'-H), 3.20 (m, 1H, 3-H), 2.84 (m, 1H, 18-H), 2.06 (s, 3H,  $-\text{OCOCH}_3$ ), 2.05 (s, 3H,  $-\text{OCOCH}_3$ ), 2.04 (s, 3H,  $-\text{OCOCH}_3$ ), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H, 21-H), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.93 (m, 9H,  $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ ), 0.89 (m, 1H, 1-H), 0.88 (s, 6H, 23-H, 30-H), 0.87 (s, 6H, 25-H, 29-H), 0.72 (s, 3H, 24-H), 0.69 (s, 3H, 26-H), 0.65 (m, 1H, 5-H), 0.56 (m, 6H,  $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ );  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  : 175.6 (C-28), 169.8 ( $-\text{OCOCH}_3 \times 2$ ), 169.0 ( $-\text{OCOCH}_3$ ), 143.0 (C-13), 123.0 (C-12), 91.7 (C-1'), 79.5 (C-3), 71.0 (C-3'), 69.3 (C-2'), 68.3 (C-4'), 62.5 (C-5'), 55.2 (C-5), 47.6 (C-9), 46.8 (C-17), 45.7 (C-19), 41.7 (C-14), 39.2 (C-18), 38.7 (C-8), 38.4 (C-4), 37.0 (C-1), 33.7 (C-10), 32.9 (C-21), 32.9 (C-29), 32.8 (C-7), 31.9 (C-22), 30.6 (C-20), 28.0 (C-23), 27.7 (C-15), 27.1 (C-2), 25.6 (C-27), 23.5 (C-30), 23.4 (C-16), 22.8 (C-11), 20.7 ( $-\text{OCOCH}_3$ ), 20.7 ( $-\text{OCOCH}_3$ ), 20.6 ( $-\text{OCOCH}_3$ ), 18.3 (C-6), 16.9 (C-26), 15.5 (C-24), 15.3 (C-25); IR (KBr)  $\text{cm}^{-1}$   $\nu$  : 2933 (=C-H), 1760 (C=O); HRMS (ESI-TOF)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd for  $\text{C}_{47}\text{H}_{76}\text{O}_{10}\text{SiNa}$  851.5074; Found 851.5078.

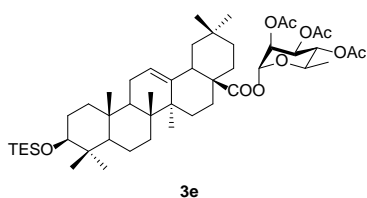
**Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, 2, 3, 4, 6-tetra-*O*-acetyl- $\alpha$ -D-mannopyranosyl ester (**3d**).** A solution of  $\text{BF}_3 \cdot \text{OEt}_2$  (62  $\mu\text{L}$ , 0.5070 mmol, 0.0035 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (16.4 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **2d** (500 mg, 1.0148 mmol, 0.0619 M) and acceptor **1** (289.5 mg, 0.5070 mmol, 0.0309 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (16.4 mL)



was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at  $-40^\circ\text{C}$ . After the reaction mixture was allowed to flow at  $-40^\circ\text{C}$  for an additional 3 min through a Teflon reactor tube ( $\phi = 1.0$  mm,  $l = 1.0$  m), the mixture was quenched by addition of triethylamine (0.26 mL) diluted in  $\text{CH}_2\text{Cl}_2$ . The mixture was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 40 g, hexane : AcOEt = 9 : 1) afforded **3d** (414.7 mg, 0.4601 mmol, 93 %) as a white solid.  $R_f = 0.40$  (hexane : AcOEt = 2 : 1);  $[\alpha]_D^{22} +51.6$  ( $c$  1.00,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  : 6.06 (d, 2.0 Hz, 1H, 1'-H), 5.36 (t,  $J = 3.5$  Hz, 1H, 12-H), 5.32 (t,  $J = 10.0$  Hz, 1H, 4'-H), 5.26 (dd,  $J = 10.0$  Hz, 3.2 Hz, 1H, 3'-H), 5.17 (dd,  $J = 3.2$  Hz, 2.0 Hz, 1H, 2'-H), 4.29 (dd,  $J = 12.3$  Hz, 5.0 Hz, 1H, 6'-H), 4.07 (dd,  $J = 12.3$  Hz, 2.3 Hz, 1H, 6'-H), 3.99 (ddd,  $J = 10.0$  Hz, 5.0 Hz, 2.3 Hz, 1H, 5'-H), 3.18 (dd,  $J = 11.0$  Hz, 4.5 Hz, 1H, 3-H), 2.83 (dd,  $J = 13.8$  Hz, 4.0 Hz, 1H, 18-H), 2.14 (s, 3H,  $-\text{OCOCH}_3$ ), 2.06 (s, 3H,  $-\text{OCOCH}_3$ ), 2.05 (s, 3H,  $-\text{OCOCH}_3$ ), 1.98 (s, 3H,  $-\text{OCOCH}_3$ ), 1.93 (m, 2H, 11-H), 1.86 (m, 2H, 16-H), 1.62 (m, 1H, 19-H), 1.60 (m, 2H, 22-H), 1.57 (m, 1H, 15-H), 1.53 (m, 1H, 1-H), 1.51 (m, 1H, 9-H), 1.50 (m, 1H, 6-H), 1.47 (m, 2H, 2-H), 1.42 (m, 2H, 7-H), 1.31 (m, 1H, 21-H), 1.31 (m, 1H, 6-H), 1.20 (m, 1H, 21-H), 1.16 (m, 1H, 19-H), 1.12 (s, 3H, 27-H), 1.08 (m, 1H, 15-H), 0.97 (t,  $J = 7.9$  Hz, 9H,  $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ ), 0.92 (s, 6H, 29-H, 30-H), 0.90 (s, 3H, 23-H), 0.90 (m, 1H, 1-H), 0.89 (s, 3H, 25-H), 0.73 (s, 3H, 24-H), 0.71 (s, 3H, 26-H), 0.68 (m, 1H, 5-H), 0.58 (m, 6H,  $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ );  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  : 174.7 (C-28), 170.6 ( $-\text{OCOCH}_3$ ), 169.8 ( $-\text{OCOCH}_3$ ), 169.6 ( $-\text{OCOCH}_3$ ), 169.6 ( $-\text{OCOCH}_3$ ), 142.7 (C-13), 123.4 (C-12), 90.2 (C-1'), 79.5 (C-3), 71.0 (C-5'), 68.9 (C-3'), 68.3 (C-2'), 65.5 (C-4'), 62.2 (C-6'), 55.3 (C-5), 47.6 (C-9), 47.2 (C-17), 45.7 (C-19), 41.6 (C-14), 41.2 (C-18), 39.3 (C-8), 38.4 (C-1, C-4), 36.9 (C-10), 33.7 (C-21), 33.0 (C-7), 32.7 (C-29), 32.2 (C-22), 30.6 (C-20), 28.4 (C-23), 27.7 (C-15), 27.5 (C-2), 25.8 (C-27), 23.5 (C-30), 23.3 (C-16), 23.3 (C-11), 20.7 ( $-\text{OCOCH}_3$ ), 20.7 ( $-\text{OCOCH}_3$ ), 20.7 ( $-\text{OCOCH}_3$ ), 20.6 ( $-\text{OCOCH}_3$ ), 18.5 (C-6), 16.9 (C-26), 16.0 (C-24), 15.3 (C-25), 7.0 ( $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ ), 5.3 ( $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ ); IR (KBr)  $\text{cm}^{-1}$   $\nu$  : 2952 ( $=\text{C-H}$ ), 1755 ( $-\text{C=O}$ ),

1697 (-C=C-), 1057 (-C-O-); HRMS (ESI-TOF)  $m/z$ :  $[M+Na]^+$  Calcd for  $C_{50}H_{80}O_{12}SiNa$  923.5317; Found 923.5303.

**Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, 2, 3, 4-tri-*O*-acetyl- $\alpha$ -L-rhamnopyranosyl ester (**3e**)** *MicroFlow*. A solution of  $BF_3 \cdot OEt_2$  (12.5  $\mu$ L, 0.1002 mmol, 0.0334 M) dissolved in  $CH_2Cl_2$  (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **2e** (87.1 mg, 0.2004 mmol, 0.0668 M) and acceptor **1** (57.2 mg, 0.1002 mmol, 0.0334 M) dissolved in  $CH_2Cl_2$  (3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at  $-40^\circ C$ . After the reaction mixture was allowed to flow at  $-40^\circ C$  for an additional 100 sec through a Teflon reactor tube ( $\phi = 1.0$  mm,  $l = 1.0$  m), the mixture was quenched by addition of triethylamine (13.9  $\mu$ L) diluted in  $CH_2Cl_2$ . The mixture was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 30 g, hexane : AcOEt = 10 : 1  $\rightarrow$  8 : 1  $\rightarrow$  7 : 1  $\rightarrow$  5 : 1) afforded **3e** (79.3 mg, 0.0941 mmol, 94%) as a white solid.  $R_f = 0.56$  (hexane : AcOEt = 2 : 1);  $[\alpha]_D^{22} +16.0$  ( $c$  1.00,  $CHCl_3$ );  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$  : 6.02 (d,  $J = 2.0$  Hz, 1H, 1'-H), 5.32 (t,  $J = 3.2$  Hz, 1H, 12-H), 5.27 (dd,  $J = 10.0$  Hz, 3.3 Hz, 1H, 3'-H), 5.20 (dd,  $J = 3.3$  Hz, 2.0 Hz, 1H, 2'-H), 5.13 (t,  $J = 10.0$  Hz, 1H, 4'-H), 3.94 (m, 1H, 5'-H), 3.20 (m, 1H, 3-H), 2.90 (m, 1H, 18-H), 2.16 (s, 3H, -OCOCH<sub>3</sub>), 2.08 (s, 3H, -OCOCH<sub>3</sub>), 2.00 (s, 3H, -OCOCH<sub>3</sub>), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H, 21-H), 1.20 (d,  $J = 6.2$  Hz, 3H, 6'-CH<sub>3</sub>), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.93 (m, 9H, -Si(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>), 0.89 (m, 1H, 1-H), 0.88 (s, 6H, 23-H, 30-H), 0.87 (s, 6H, 25-H, 29-H), 0.72 (s, 3H, 24-H), 0.69 (s, 3H, 26-H), 0.65 (m, 1H, 5-H), 0.56 (m, 6H, -Si(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$  : 174.7 (C-28), 169.9 (-OCOCH<sub>3</sub>), 169.8 (-OCOCH<sub>3</sub>), 169.8 (-OCOCH<sub>3</sub>), 143.6 (C-13), 122.9 (C-12), 90.1 (C-1'), 78.9 (C-3), 70.3 (C-4'), 69.0 (C-3'), 68.9 (C-5'), 68.7 (C-2'), 55.2 (C-5), 47.5 (C-9), 47.3 (C-17), 45.6 (C-19), 41.8 (C-14), 41.7 (C-18), 39.4 (C-8), 38.7 (C-4), 38.4 (C-1), 37.0 (C-10), 33.7 (C-21), 33.0 (C-29), 32.7 (C-7), 32.5 (C-22), 30.7 (C-20), 28.1 (C-23), 27.5 (C-15), 27.1 (C-2), 25.8 (C-27), 23.5 (C-30), 23.4 (C-16), 22.9 (C-11), 20.8 (-OCOCH<sub>3</sub>), 20.8 (-OCOCH<sub>3</sub>), 20.6 (-OCOCH<sub>3</sub>), 18.3 (C-6), 17.5 (6'-CH<sub>3</sub>), 17.0 (C-26), 15.6 (C-24), 15.3 (C-25), 7.0 (-Si(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>), 5.3 (-Si(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>); IR (KBr)  $cm^{-1}$   $\nu$  : 2924 (=C-H), 1761 (-C=O); HRMS (ESI-TOF)  $m/z$ :  $[M+Na]^+$  Calcd for  $C_{48}H_{78}O_{10}SiNa$  865.5231;

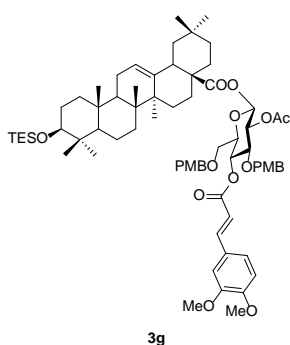


Found 865.5237.

**Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, methyl 2, 3, 4-tri-*O*-acetyl- $\beta$ -D-glucopyranuronosyl ester (**3f**) *MicroFlow*.** A solution of  $\text{BF}_3 \cdot \text{OEt}_2$  (39  $\mu\text{L}$ , 0.3097 mmol, 0.03 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (10.3 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **2f** (296.5 mg, 0.6194 mmol, 0.0601 M) and acceptor **1** (176.8 mg, 0.3097 mmol, 0.03 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (10.3 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at  $-40^\circ\text{C}$ . After the reaction mixture was allowed to flow at  $-40^\circ\text{C}$  for an additional 3 min through a Teflon reactor tube ( $\phi = 1.0$  mm,  $l = 1.0$  m), the mixture was quenched by addition of triethylamine (0.17 mL) diluted in  $\text{CH}_2\text{Cl}_2$ . The mixture was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 40 g, hexane : AcOEt = 6 : 1) afforded **3f** (203.9 mg, 0.2298 mmol, 74%) as a white solid.  $R_f = 0.40$  (hexane : AcOEt = 2 : 1);  $[\alpha]_D^{24} +30.9$  ( $c$  0.98,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  : 5.63 (d,  $J = 8.1$  Hz, 1H, 1'-H), 5.31 (dt,  $J = 3.7$  Hz, 1H, 12-H), 5.30 (t,  $J = 9.5$  Hz, 1H, 3'-H), 5.23 (t,  $J = 9.5$  Hz, 1H, 4'-H), 5.20 (dd,  $J = 9.5$  Hz, 8.1 Hz, 1H, 2'-H), 4.12 (d,  $J = 9.5$  Hz, 1H, 5'-H), 3.72 (s, 3H,  $-\text{COOCH}_3$ ), 3.20 (dd,  $J = 11.1$  Hz, 4.4 Hz, 1H, 3-H), 2.81 (dd,  $J = 14.0$  Hz, 4.0 Hz, 1H, 18-H), 2.03 (s, 3H,  $-\text{OCOCH}_3$ ), 2.02 (s, 3H,  $-\text{OCOCH}_3$ ), 2.02 (s, 3H,  $-\text{OCOCH}_3$ ), 1.96 (m, 2H, 11-H), 1.87 (m, 1H, 16-H), 1.64 (m, 2H, 22-H), 1.62 (m, 1H, 19-H), 1.60 (m, 1H, 15-H), 1.58 (m, 1H, 2-H), 1.56 (m, 1H, 1-H), 1.54 (m, 1H, 16-H), 1.52 (m, 1H, 6-H), 1.50 (m, 1H, 9-H), 1.49 (m, 1H, 2-H), 1.40 (m, 1H, 7-H), 1.35 (m, 1H, 6-H), 1.31 (m, 1H, 21-H), 1.21 (m, 1H, 21-H), 1.18 (m, 1H, 19-H), 1.12 (s, 3H, 27-H), 1.03 (m, 1H, 15-H), 0.95 (t,  $J = 8.0$  Hz, 9H,  $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ ), 0.90 (s, 3H, 23-H), 0.90 (s, 3H, 25-H), 0.89 (m, 1H, 1-H), 0.89 (s, 3H, 29-H), 0.89 (s, 3H, 30-H), 0.74 (s, 3H, 24-H), 0.71 (s, 3H, 26-H), 0.68 (m, 1H, 5-H), 0.58 (m, 6H,  $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ );  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  : 175.5 (C-28), 169.9 ( $-\text{OCOCH}_3$ ), 169.4 ( $-\text{OCOCH}_3$ ), 168.9 ( $-\text{OCOCH}_3$ ), 166.7 (C-6'), 142.7 (C-13), 123.0 (C-12), 91.2 (C-1'), 79.5 (C-3), 72.9 (C-5'), 72.0 (C-3'), 69.7 (C-2'), 69.3 (C-4'), 55.3 (C-5), 52.9 ( $-\text{COOCH}_3$ ), 47.6 (C-9), 46.8 (C-17), 45.7 (C-19), 41.7 (C-14), 41.0 (C-18), 39.3 (C-4), 39.3 (C-10), 38.5 (C-1), 36.9 (C-8), 33.7 (C-21), 33.7 (C-29), 33.0 (C-7), 31.6 (C-22), 30.6 (C-20), 28.4 (C-23), 27.7 (C-2), 27.7 (C-15), 25.7 (C-27), 23.4 (C-30), 23.4 (C-16), 22.8 (C-11), 20.6 ( $-\text{OCOCH}_3$ ), 20.6 ( $-\text{OCOCH}_3$ ), 20.4 ( $-\text{OCOCH}_3$ ), 18.5 (C-6), 16.9 (C-26), 16.4 (C-24), 15.4 (C-25), 7.0 ( $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ ), 5.3 ( $-\text{Si}(\text{CH}_2\text{CH}_3)_3$ ) IR (KBr)  $\text{cm}^{-1}$   $\nu$  : 2952 ( $=\text{C-H}$ ), 1759 ( $-\text{C=O}$ ), 1698 ( $-\text{C=C-}$ ), 1068

(-C-O-); HRMS (ESI-TOF)  $m/z$ :  $[M+Na]^+$  Calcd for  $C_{49}H_{78}O_{12}SiNa$  909.5160; Found 909.5147.

**Olean-12-en-28-olic acid, 3-*O*-triethylsilyl-, 2'-*O*-acetyl-, 3',6'-*O*-(4-methoxybenzyl)-, 4-*O*-[(*E*)-3, 4-dimethoxycinnamoyl]- $\beta$ -D-glucopyranosyl ester (**3g**) MicroFlow.** A solution of  $BF_3 \cdot OEt_2$  (12.0  $\mu$ L, 0.0976

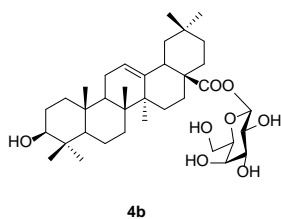


mmol, 0.0976 M) dissolved in  $CH_2Cl_2$  (1.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.1 mL/min. Also, a solution of donor **2g** (7.8 mg, 9.76  $\mu$ mol) and acceptor **1** (5.6 mg, 9.76  $\mu$ mol) dissolved in  $CH_2Cl_2$  (7.5 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.1 mL/min and mixed at  $-40^\circ C$ . After the reaction mixture was allowed to flow at  $-40^\circ C$  for an additional 18 min through a Teflon reactor tube ( $\phi = 1.0$  mm,  $l$

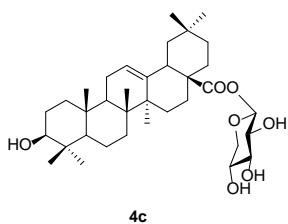
$= 1.0$  m), the mixture was quenched by addition of triethylamine (3.0  $\mu$ L) diluted in  $CH_2Cl_2$ . The mixture was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 7.5 g, hexane : AcOEt = 5 : 1) afforded **3g** (12.3 mg, 9.76  $\mu$ mol, quant.) as a colorless oil.  $R_f = 0.29$  (hexane : AcOEt = 2 : 1);  $[\alpha]_D^{27} +21.1$  ( $c$  1.00,  $CHCl_3$ );  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$  : 7.57 (d,  $J = 16.0$  Hz, 1H,  $PhCH=CH$ ), 7.21 - 6.73 (m, 11H, Ph-H), 6.14 (d,  $J = 16.0$  Hz, 1H,  $PhCH=CH$ ), 5.56 (d,  $J = 7.8$  Hz, 1H, 1'-H), 5.33 (m, 1H, 12-H), 5.27 (t,  $J = 9.2$  Hz, 1H, 4'-H), 5.22 (dd,  $J = 9.4$  Hz, 7.8 Hz, 1H, 2'-H), 4.54 (m, 2H,  $-CH_2Ph$ ), 4.40 (m, 2H,  $-CH_2Ph$ ), 3.93 (s, 6H,  $-OCH_3 \times 2$ ), 3.79 (t,  $J = 9.4$  Hz, 1H, 3'-H), 3.71 (ddd,  $J = 9.4$  Hz, 4.7 Hz, 3.7 Hz, 1H, 5'-H), 3.68 (s, 3H,  $-OCH_3$ ), 3.67 (s, 3H,  $-OCH_3$ ), 3.57 (dd,  $J = 11.0$  Hz, 3.7 Hz, 1H, 6'-H), 3.51 (dd,  $J = 11.0$  Hz, 4.7 Hz, 1H, 6'-H), 3.21 (m, 1H, 3-H), 2.84 (m, 1H, 18-H), 2.00 (s, 3H,  $-OCOCH_3$ ), 1.99 (m, 1H, 11-H), 1.87 (m, 2H, 16-H), 1.63 (m, 2H, 22-H), 1.62 (m, 1H, 19-H), 1.59 (m, 1H, 15-H), 1.58 (m, 1H, 11-H), 1.56 (m, 1H, 1-H), 1.52 (m, 1H, 6-H), 1.51 (m, 1H, 9-H), 1.47 (m, 2H, 2-H), 1.34 (m, 1H, 6-H), 1.33 (m, 2H, 21-H), 1.18 (m, 2H, 7-H), 1.15 (m, 1H, 19-H), 1.13 (s, 3H, 27-H), 1.04 (m, 1H, 15-H), 0.98 (m, 9H,  $-Si(CH_2CH_3)_3$ ), 0.91 (s, 3H, 23-H), 0.90 (m, 4H, 1-H, 30-H), 0.89 (s, 3H, 29-H), 0.88 (s, 3H, 25-H), 0.75 (s, 6H, 24-H, 26-H), 0.69 (m, 1H, 5-H), 0.59 (m, 6 H,  $-Si(CH_2CH_3)_3$ );  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$  : 175.9 (C-28), 168.8 ( $-OCOCH_3$ ), 165.6 (4'- $OCO$ -), 159.2, 159.0, 151.3, 149.2, 145.6 ( $PhCH=CH$ ), 143.0 (C-13), 129.9, 129.9, 129.7, 129.6, 129.4, 129.3, 127.1, 122.9, 122.8 (C-12), 114.8 ( $PhCH=CH$ ), 113.7, 113.6, 113.6, 110.9, 109.5, 91.9 (C-1'), 79.5 (C-3'), 79.4 (C-3), 74.4 (C-5'), 73.2 ( $-CH_2Ph$ ), 73.1 ( $-CH_2Ph$ ), 71.3 (C-2'), 70.3 (C-4'), 68.7 (C-6'), 56.0 ( $-OCH_3$ ), 55.8 ( $-OCH_3$ ), 55.3 (C-5), 55.1 ( $-OCH_3$ ), 55.0 ( $-OCH_3$ ), 47.6 (C-9), 46.8 (C-17), 45.8 (C-19),

41.7 (C-14), 40.9 (C-18), 39.3 (C-8), 39.3 (C-4), 38.5 (C-1), 36.9 (C-10), 33.8 (C-21), 33.0 (C-29), 32.9 (C-7), 31.7 (C-22), 30.6 (C-20), 28.4 (C-23), 27.8 (C-15), 27.7 (C-2), 25.6 (C-27), 23.5 (C-30), 23.4 (C-16), 22.7 (C-11), 20.9 (-OCOCH<sub>3</sub>), 18.5 (C-6), 17.0 (C-26), 16.0 (C-24), 15.4 (C-25), 7.0 (-Si(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>), 5.2 (-Si(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>); IR (NaCl) cm<sup>-1</sup> ν : 2951 (=C-H), 1753 (-C=O), 1631 (-C=C-), 1514 (-C=C-), 1066 (-C-O-); HRMS (ESI-TOF) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>71</sub>H<sub>100</sub>O<sub>14</sub>SiNa 1227.6780; Found 1227.6772.

**Olean-12-en-28-oic acid, 3-hydroxy-, β-D-galactopyranosyloxy ester (4b).** To a solution of **3b** (200 mg, 0.2219 mmol) in MeOH (4.4 mL) at ambient temperature was added NaH (0.88 mg, 0.0222 mmol, 60% disp.). The reaction mixture was stirred at ambient temperature for 1 h, neutralized with Dowex H<sup>+</sup> resin to pH 4 and filtered. The filtrate was concentrated under reduced pressure to give the pure saponin **4b** (144.4 mg, 0.2333 mmol, quant.) as a white solid without further purification. *R*<sub>f</sub> = 0.43 (CHCl<sub>3</sub>: MeOH = 5 : 1); [α]<sub>D</sub><sup>22</sup> +74.2 (*c* 0.25, MeOH); <sup>1</sup>H-NMR (400 MHz, pyridine-*d*<sub>5</sub>) δ : 6.29 (d, *J* = 8.2 Hz, 1H, 1'-H), 5.46 (dd, *J* = 3.4 Hz, 3.4 Hz, 1H, 12-H), 4.68 (m, 1H, 3'-H), 4.65 (m, 1H, 2'-H), 4.51 (ddd, *J* = 10.9 Hz, 6.5 Hz, 6.5 Hz, 1H, 6'-H), 4.41 (ddd, *J* = 10.8 Hz, 5.4 Hz, 5.4 Hz, 1H, 6'-H), 4.25 (m, 1H, 4'-H), 4.21 (m, 1H, 5'-H), 3.45 (m, 1H, 3-H), 3.22 (dd, *J* = 4.2 Hz, 4.2 Hz, 1H, 18-H), 2.35 (m, 1H, 2-H), 2.06 (m, 2H, 11-H), 1.94 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.78 (m, 1H, 22-H), 1.77 (m, 1H, 19-H), 1.68 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (m, 1H, 6-H), 1.48 (m, 1H, 7-H), 1.40 (m, 1H, 6-H), 1.38 (m, 1H, 7-H), 1.35 (m, 1H, 21-H), 1.30 (m, 1H, 19-H), 1.24 (s, 6H, 23-H, 27-H), 1.16 (s, 3H, 26-H), 1.13 (m, 2H, 15-H), 1.09 (m, 1H, 21-H), 1.04 (s, 3H, 24-H), 0.99 (m, 1H, 1-H), 0.94 (s, 3H, 25-H), 0.91 (s, 3H, 29-H), 0.88 (s, 3H, 30-H), 0.85 (m, 1H, 5-H); <sup>13</sup>C-NMR (100 MHz, pyridine-*d*<sub>5</sub>) δ : 176.6 (C-28), 144.3 (C-13), 123.0 (C-12), 96.4 (C-1'), 78.2 (C-3), 77.9 (C-5'), 75.9 (C-4'), 71.6 (C-3'), 70.2 (C-2'), 62.0 (C-6'), 56.0 (C-5), 48.3 (C-9), 47.1 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.1 (C-21), 33.3 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.9 (C-23), 28.4 (C-15), 28.3 (C-2), 26.2 (C-27), 24.0 (C-30), 23.8 (C-16), 23.5 (C-11), 19.0 (C-6), 17.7 (C-26), 16.7 (C-24), 15.8 (C-25).; IR (KBr) cm<sup>-1</sup> ν : 3435 (-O-H), 2949 (=C-H), 1736 (-C=O), 1719 (-C=C-), 1070 (-C-O-); HRMS (ESI-TOF) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>36</sub>H<sub>58</sub>O<sub>8</sub>Na 641.4029; Found 641.4016.

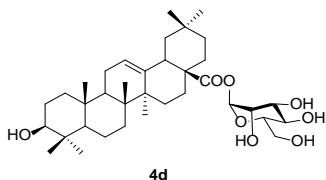


**Olean-12-en-28-oic acid, 3-hydroxy-,  $\beta$ -D-xylopyranosyloxy ester (4c).** To a solution of **3c** (200 mg, 0.241 mmol) in MeOH (2.4 mL) at ambient temperature was added NaH (0.96 mg, 0.024 mmol, 60% disp.). The reaction mixture was stirred at ambient temperature for 1 h, neutralized with Dowex H<sup>+</sup> resin to pH 4 and filtered, rinsed with MeOH (20 mL). The filtrate was



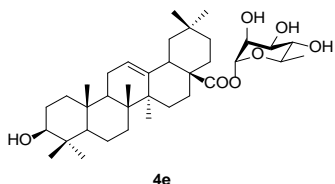
concentrated under reduced pressure to give the pure **4c** (141 mg, 0.239 mmol, 99%) as a white solid without further purification.  $R_f$  = 0.59 (CHCl<sub>3</sub> : MeOH = 5 : 1);  $[\alpha]_D^{22}$  +41.7 (*c* 0.31, MeOH); <sup>1</sup>H-NMR (400 MHz, pyridine-*d*<sub>5</sub>)  $\delta$  : 6.25 (d,  $J$  = 7.0 Hz, 1H, 1'-H), 5.48 (t,  $J$  = 3.3 Hz, 1H, 12-H), 4.40 (dd,  $J$  = 11.0 Hz, 4.0 Hz, 1H, 5'-H), 4.23-4.19 (m, 3H, 2'-H, 3'-H, 4'-H), 3.85 (dd,  $J$  = 11.0 Hz, 10.0 Hz, 1H, 5'-H), 3.45 (dd, 10.7 Hz, 5.7 Hz, 1H, 3-H), 3.27 (dd,  $J$  = 14.2 Hz, 3.8 Hz, 1H, 18-H), 2.32 (m, 1H, 15-H), 2.10 (m, 2H, 16-H), 2.05 (m, 1H, 22-H), 1.97 (m, 2H, 11-H), 1.85 (m, 2H, 15-H, 22-H), 1.80 (m, 1H, 19-H), 1.68 (m, 1H, 9-H), 1.54 (m, 2H, 1-H, 6-H), 1.51 (m, 2H, 7-H), 1.37 (m, 2H, 6-H, 21-H), 1.30 (m, 1H, 19-H), 1.25 (s, 3H, 27-H), 1.24 (s, 3H, 23-H), 1.18 (m, 1H, 2-H), 1.15 (m, 1H, 21-H), 1.12 (s, 3H, 26-H), 1.05 (s, 3H, 24-H), 1.00 (m, 1H, 1-H), 0.95 (s, 3H, 30-H), 0.94 (s, 6H, 25-H, 29-H), 0.86 (m, 1H, 5-H); <sup>13</sup>C-NMR (100 MHz, pyridine-*d*<sub>5</sub>)  $\delta$  : 176.7 (C-28), 144.3 (C-13), 123.1 (C-12), 96.4 (C-1'), 78.4 (C-2'), 78.2 (C-3), 73.8 (C-3'), 71.0 (C-4'), 67.9 (C-5'), 56.0 (C-5), 48.3 (C-9), 47.3 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.0 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.2 (C-21), 33.4 (C-7), 33.3 (C-29), 32.9 (C-22), 31.0 (C-20), 29.0 (C-23), 28.4 (C-15), 28.3 (C-2), 26.2 (C-27), 24.0 (C-11), 23.8 (C-30), 23.5 (C-16), 19.0 (C-6), 17.7 (C-26), 16.7 (C-24), 15.8 (C-25); IR (KBr) cm<sup>-1</sup>  $\nu$  : 3407 (-O-H), 2940 (=C-H), 1744 (-C=O), 1032 (-C-O-); HRMS (ESI-TOF)  $m/z$ : [M+Na]<sup>+</sup> Calcd for C<sub>35</sub>H<sub>56</sub>O<sub>7</sub>Na 611.3924; Found 611.3908.

**Olean-12-en-28-oic acid, 3-hydroxy-,  $\alpha$ -D-mannopyranosyloxy ester (4d).** To a solution of **3d** (200 mg, 0.2219 mmol) stirring in dry MeOH (4.4 mL) was added sodium hydride (0.88 mg, 0.0222 mmol). The mixture was stirred at ambient temperature for 40 min, neutralized with Dowex H<sup>+</sup> resin to pH 4 and filtered. The filtrate was concentrated under reduced pressure to give the pure saponin **4d** (150.5 mg, 0.2432 mmol, quant.) as a white solid.  $R_f$  = 0.53 (CHCl<sub>3</sub>: MeOH= 5 : 1);  $[\alpha]_D^{22}$  +67.9 (*c* 0.24, MeOH); <sup>1</sup>H-NMR (400 MHz, pyridine-*d*<sub>5</sub>)  $\delta$  : 6.89 (d,  $J$  = 1.6 Hz, 1H, 1'-H), 5.40 (t,  $J$  = 3.5 Hz, 1H, 12-H), 4.86 (dt, 9.5 Hz, 5.0 Hz, 1H, 4'-H), 4.68 (ddd,  $J$  = 10.0 Hz, 9.5 Hz, 6.5 Hz, 1H, 3'-H), 4.65 (ddd,  $J$  = 11.5 Hz, 6.0 Hz, 2.0 Hz, 1H,



6'-H), 4.63 (ddd,  $J = 10.0$  Hz, 4.5 Hz, 1.6 Hz, 2'-H), 4.56 (ddd,  $J = 11.5$  Hz, 6.5 Hz, 5.0 Hz, 1H, 6'-H), 4.51 (ddd,  $J = 9.5$  Hz, 5.0 Hz, 2.0 Hz, 1H, 5'-H), 3.44 (ddd,  $J = 10.9$  Hz, 5.4 Hz, 5.4 Hz, 1H, 3-H), 3.17 (dd,  $J = 13.8$  Hz, 4.0 Hz, 1H, 18-H), 2.05 (m, 1H, 11-H), 2.02 (m, 2H, 2-H), 1.88 (m, 1H, 22-H), 1.85 (m, 2H, 16-H), 1.83 (m, 1H, 15-H), 1.78 (m, 1H, 11-H), 1.75 (m, 1H, 19-H), 1.64 (m, 1H, 9-H), 1.58 (m, 1H, 22-H), 1.53 (m, 1H, 1-H), 1.53 (m, 1H, 6-H), 1.47 (m, 1H, 7-H), 1.39 (m, 1H, 21-H), 1.34 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.24 (s, 3H, 23-H), 1.23 (m, 1H, 19-H), 1.21 (s, 3H, 27-H), 1.14 (m, 1H, 21-H), 1.11 (m, 1H, 15-H), 1.04 (s, 3H, 24-H), 1.00 (m, 1H, 1-H), 0.95 (s, 3H, 30-H), 0.93 (s, 3H, 26-H), 0.91 (s, 3H, 29-H), 0.86 (s, 3H, 25-H), 0.83 (m, 1H, 5-H);  $^{13}\text{C}$ -NMR (100 MHz, pyridine- $d_5$ )  $\delta$  : 176.1 (C-28), 144.2 (C-13), 123.2 (C-12), 95.5 (C-1'), 78.5 (C-5'), 78.2 (C-3), 73.2 (C-3'), 71.4 (C-2'), 68.5 (C-4'), 62.8 (C-6'), 55.9 (C-5), 48.2 (C-9), 47.5 (C-17), 46.2 (C-19), 42.2 (C-14), 42.0 (C-18), 39.9 (C-8), 39.5 (C-4), 39.1 (C-1), 37.4 (C-10), 34.1 (C-21), 33.3 (C-7), 33.3 (C-29), 32.9 (C-22), 31.0 (C-20), 28.9 (C-23), 28.2 (C-15), 28.1 (C-2), 26.1 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 18.9 (C-6), 17.6 (C-26), 16.7 (C-24), 15.8 (C-25); IR (KBr)  $\text{cm}^{-1}$   $\nu$ : 3382 (-O-H), 2933 (=C-H), 1697 (-C=O); HRMS (ESI-TOF)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd for  $\text{C}_{36}\text{H}_{58}\text{O}_8\text{Na}$  641.4029; Found 641.4014. GATEI (400 MHz, pyridine- $d_5$ )  $\delta$  : 95.5 (C-1'),  $^1J_{\text{C,H}} = 173.4$  Hz.

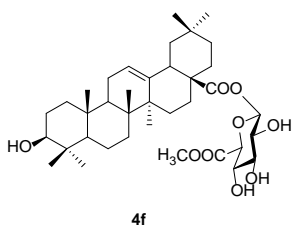
**Olean-12-en-28-oic acid, 3-hydroxy-,  $\alpha$ -L-rhamnopyranosyloxy ester (4e).** To a solution of **3e** (200 mg, 0.237 mmol) in MeOH (2.3 mL) at ambient temperature was added NaH (0.948 mg, 0.024 mmol, 60% disp.). The reaction mixture was stirred at ambient temperature for 30 min, neutralized with Dowex



$\text{H}^+$  resin to pH 4 and filtered, rinsed with MeOH (20 mL). The filtrate was concentrated under reduced pressure to give the pure **4e** (150 mg, 0.248 mmol, quant.) as a white solid without further purification.  $R_f = 0.57$  ( $\text{CHCl}_3$  : MeOH = 5 : 1);  $[\alpha]_D^{22} +25.7$  ( $c$  1.00, MeOH);  $^1\text{H}$ -NMR (400 MHz, pyridine- $d_5$ )  $\delta$  : 6.83 (d,  $J = 1.5$  Hz, 1H, 1'-H), 5.46 (t,  $J = 3.3$  Hz, 1H, 12-H), 4.61 (dd,  $J = 3.3$  Hz, 1.5 Hz, 1H, 2'-H), 4.54 (dd,  $J = 8.8$  Hz, 3.3 Hz, 1H, 3'-H), 4.39 (t,  $J = 8.8$  Hz, 1H, 4'-H), 4.39 (m, 1H, 5'-H), 3.45 (dd, 10.7 Hz, 5.7 Hz, 1H, 3-H), 3.17 (dd,  $J = 14.2$  Hz, 3.8 Hz, 1H, 18-H), 2.05 (m, 1H, 16-H), 2.01 (m, 1H, 2-H), 1.95 (m, 2H, 11-H), 1.86 (m, 2H, 2-H, 22-H), 1.75 (m, 2H, 16-H, 19-H), 1.72 (d,  $J = 5.5$  Hz, 3H, 6'- $\text{CH}_3$ ), 1.64 (m, 1H, 9-H), 1.61 (m, 1H, 22-H), 1.57 (m, 2H, 1-H, 6-H), 1.46 (m, 1H, 7-H), 1.41 (m, 1H, 21-H), 1.36 (m, 1H, 6-H), 1.30 (m, 2H, 7-H, 19-H), 1.25 (s, 3H, 23-H), 1.22 (s, 3H, 27-H), 1.17 (m, 1H, 21-H), 1.12 (m, 2H, 15-H), 1.06 (s, 3H, 26-H), 1.00 (m, 1H, 1-H), 0.92 (s, 3H, 24-H), 0.92 (s, 3H, 25-H), 0.92 (s, 3H, 29-H), 0.89 (s, 3H, 30-H), 0.87 (m, 1H, 5-H);  $^{13}\text{C}$ -NMR (100 MHz, pyridine- $d_5$ )  $\delta$  :

176.0 (C-28), 143.6 (C-13), 123.5 (C-12), 95.5 (C-1'), 78.2 (C-3), 73.6 (C-4'), 73.0 (C-3'), 72.7 (C-5'), 71.6 (C-2'), 55.9 (C-5), 48.1 (C-9), 47.5 (C-17), 46.1 (C-19), 42.2 (C-14), 42.1 (C-18), 39.9 (C-8), 39.5 (C-1), 39.0 (C-4), 37.5 (C-10), 34.1 (C-21), 33.4 (C-7), 33.2 (C-22), 33.1 (C-29), 31.0 (C-20), 29.0 (C-23), 28.2 (C-15), 28.1 (C-2), 26.1 (C-27), 24.0 (C-11), 23.7 (C-30), 23.4 (C-16), 18.9 (6'-CH<sub>3</sub>), 18.9 (C-6), 17.2 (C-26), 16.7 (C-24), 15.7 (C-25); IR (KBr) cm<sup>-1</sup> v : 3431 (-O-H), 2927 (=C-H), 1743 (-C=O), 1061 (-C-O-); HRMS (ESI-TOF) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>36</sub>H<sub>58</sub>O<sub>7</sub>Na: 625.4080; Found 625.4070. GATEI (400 MHz, pyridine-*d*<sub>5</sub>) δ : 95.5 (C-1'), <sup>1</sup>J<sub>C,H</sub> = 173.0 Hz.

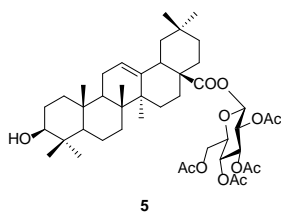
**Olean-12-en-28-oic acid, 3-hydroxy-, methyl-β-D-glucopyranuronosyl ester (4f).**



To a solution of **3f** (143.3 mg, 0.1615 mmol) stirring in dry MeOH (3.23 mL) was added sodium hydride (0.53 mg, 0.0162 mmol). The mixture was stirred at ambient temperature for 3.5 h, neutralized with Dowex H<sup>+</sup> resin to pH 4 and filtered. The filtrate was concentrated under reduced pressure to give the

crude product. Purification by flash column chromatography (silica gel 20 g, CHCl<sub>3</sub> : MeOH = 20 : 1) afforded **4f** (28.2 mg, 0.0436 mmol, 27%) as a white solid. *R*<sub>f</sub> = 0.53 (CHCl<sub>3</sub>: MeOH= 5 : 1); [α]<sub>D</sub><sup>23</sup> +61.1 (*c* 0.19, MeOH); <sup>1</sup>H-NMR (400 MHz, pyridine-*d*<sub>5</sub>) δ : 6.37 (d, *J* = 7.9 Hz, 1H, 1'-H), 5.45 (t, *J* = 3.5 Hz, 1H, 12-H), 4.70 (d, *J* = 9.6 Hz, 1H, 5'-H), 4.52 (dt, *J* = 9.6 Hz, 5.5 Hz, 1H, 4'-H), 4.34 (m, 1H, 3'-H), 4.28 (m, 1H, 2'-H), 3.64 (s, 3H, -COOCH<sub>3</sub>), 3.45 (ddd, *J* = 10.0 Hz, 5.0 Hz, 5.0 Hz, 1H, 3-H), 3.21 (dd, *J* = 13.8 Hz, 4.2 Hz, 1H, 18-H), 2.32 (m, 1H, 2-H), 2.08 (m, 1H, 11-H), 1.95 (m, 1H, 11-H), 1.95 (m, 2H, 16-H), 1.89 (m, 1H, 22-H), 1.85 (m, 1H, 2-H), 1.84 (m, 1H, 15-H), 1.76 (m, 1H, 19-H), 1.76 (m, 1H, 22-H), 1.67 (dd, *J* = 10.5 Hz, 7.2 Hz, 1H, 9-H), 1.57 (m, 1H, 1-H), 1.54 (m, 1H, 6-H), 1.51 (m, 1H, 7-H), 1.39 (m, 1H, 6-H), 1.37 (m, 1H, 7-H), 1.34 (m, 1H, 21-H), 1.26 (m, 1H, 19-H), 1.24 (s, 3H, 23-H), 1.24 (s, 3H, 27-H), 1.17 (m, 1H, 15-H), 1.12 (s, 3H, 26-H), 1.08 (m, 1H, 21-H), 1.05 (s, 3H, 24-H), 1.00 (m, 1H, 1-H), 0.97 (s, 3H, 25-H), 0.89 (s, 3H, 29-H), 0.88 (s, 3H, 30-H), 0.85 (m, 1H, 5-H); <sup>13</sup>C-NMR (100 MHz, pyridine-*d*<sub>5</sub>) δ : 176.6 (C-28), 170.3 (C-6'), 144.1 (C-13), 123.2 (C-12), 95.7 (C-1'), 78.2 (C-3), 78.2 (C-3'), 77.9 (C-5'), 73.8 (C-2'), 73.2 (C-4'), 55.9 (C-5), 52.2 (-COOCH<sub>3</sub>), 48.3 (C-9), 47.2 (C-17), 46.3 (C-19), 42.2 (C-14), 41.9 (C-18), 40.1 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.1 (C-21), 33.3 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.9 (C-23), 28.3 (C-2), 28.3 (C-15), 26.2 (C-27), 24.0 (C-30), 23.7 (C-16), 23.5 (C-11), 19.0 (C-6), 17.6 (C-26), 16.7 (C-24), 15.8 (C-25); IR (KBr) cm<sup>-1</sup> v : 3455 (-O-H), 2942 (=C-H), 1752 (-C=O), 1719 (-C=C-), 1090 (-C-O-); HRMS (ESI-TOF) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>37</sub>H<sub>58</sub>O<sub>9</sub>Na 669.3979; Found 669.3963.

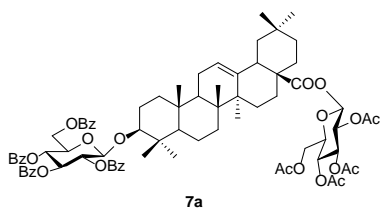
**Olean-12-en-28-oic acid, 3-hydroxy-, 2, 3, 4, 6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl ester (**5**).** To a stirred solution of **3a** (100 mg, 0.110 mmol) at ambient temperature in



dry  $\text{CH}_2\text{Cl}_2$  (0.25 M) was added  $\text{ZnBr}_2$  (125 mg, 0.550 mmol) followed by  $\text{H}_2\text{O}$  (9.9  $\mu\text{L}$ , 0.550 mmol). The reaction mixture was stirred at ambient temperature for 10 min before it was quenched sat. aq.  $\text{NaHCO}_3$  (1 mL). The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (10 mL). The organic layer was washed with sat.

aq.  $\text{NaHCO}_3$  (5 mL),  $\text{H}_2\text{O}$  (5 x 60 mL), and, brine (5 mL). The organic layer was dried with sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel 10 g, hexane :  $\text{AcOEt}$  = 3 : 1  $\rightarrow$  2 : 1  $\rightarrow$  1 : 1) afforded **5** (84 mg, 0.107 mmol, 97%) as a white foamy solid.  $R_f$  = 0.40 (hexane :  $\text{AcOEt}$  = 1 : 1);  $[\alpha]_D^{22} +35.4$  ( $c$  1.00,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.58 (d,  $J$  = 8.0 Hz, 1H, 1'-H), 5.31 (t,  $J$  = 3.5 Hz, 1H, 12-H), 5.25 (t,  $J$  = 9.3 Hz, 1H, 3'-H), 5.18 (dd,  $J$  = 9.3 Hz, 8.0 Hz, 1H, 2'-H), 5.13 (dd,  $J$  = 10.0 Hz, 9.3 Hz, 1H, 4'-H), 4.27 (dd,  $J$  = 12.5 Hz, 4.4 Hz, 1H, 6'-H), 4.05 (dd,  $J$  = 12.5 Hz, 2.4 Hz, 1H, 6'-H), 3.79 (ddd,  $J$  = 10.0 Hz, 4.4 Hz, 2.4 Hz, 1H, 5'-H), 3.19 (m, 1H, 3-H), 2.78 (m, 1H, 18-H), 2.06 (s, 3H, - $\text{OCOCH}_3$ ), 2.02 (s, 3H, - $\text{OCOCH}_3$ ), 2.01 (s, 6H, - $\text{OCOCH}_3$  x2), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H, 21-H), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.89 (m, 1H, 1-H), 0.88 (s, 6H, 23-H, 30-H), 0.87 (s, 6H, 25-H, 29-H), 0.72 (s, 3H, 24-H), 0.69 (s, 3H, 26-H), 0.65 (m, 1H, 5-H);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 175.6 (C-28), 170.5 (- $\text{OCOCH}_3$ ), 170.0 (- $\text{OCOCH}_3$ ), 169.4 (- $\text{OCOCH}_3$ ), 168.9 (- $\text{OCOCH}_3$ ), 142.8 (C-13), 122.8 (C-12), 91.5 (C-1'), 78.8 (C-3), 72.8 (C-3'), 72.4 (C-5'), 69.9 (C-2'), 68.0 (C-4'), 61.5 (C-6'), 55.1 (C-5), 47.5 (C-9), 46.8 (C-17), 45.7 (C-19), 41.6 (C-14), 39.3 (C-18), 38.7 (C-8), 38.4 (C-4), 36.8 (C-1), 33.7 (C-10), 32.9 (C-21), 32.8 (C-29), 32.8 (C-7), 31.7 (C-22), 30.5 (C-20), 28.0 (C-23), 27.7 (C-15), 27.1 (C-2), 25.6 (C-27), 23.4 (C-30), 23.3 (C-16), 22.8 (C-11), 20.6 (- $\text{OCOCH}_3$ ), 20.5 (- $\text{OCOCH}_3$ ), 20.5 (- $\text{OCOCH}_3$ ), 20.5 (- $\text{OCOCH}_3$ ), 18.2 (C-6), 16.9 (C-26), 15.5 (C-24), 15.3 (C-25); IR (KBr)  $\text{cm}^{-1}$   $\nu$ : 3445 (-O-H), 2933 (=C-H), 1760 (-C=O), 1036 (-C-O-); HRMS (ESI-TOF)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd for  $\text{C}_{44}\text{H}_{66}\text{O}_{12}\text{Na}$  809.4452; Found 809.4444. The purity of **5** synthesized by continuous reaction was compared to with the corresponding compound in stepwise synthesis by a proton NMR spectrum (see supporting information in detail).

**Olean-12-en-28-oic acid, 3-[(2, 3, 4, 6, -tetra-*O*-benzoyl- $\beta$ -D-glucopyranosyl) oxy]-, 2, 3, 4, 6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl ester (**7a**) *MicroFlow*.** A solution of

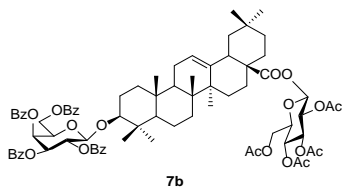


TMSOTf (12.0  $\mu$ L, 0.0640 mmol, 0.0213 M) dissolved in dry  $\text{CH}_2\text{Cl}_2$  (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **6a** (71.0 mg, 0.0941 mmol, 0.0314 M) and acceptor **5** (50.0 mg, 0.0640

mmol, 0.0213 M) dissolved in dry  $\text{CH}_2\text{Cl}_2$  (3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at ambient temperature. After the reaction mixture was allowed to flow at ambient temperature for an additional 100 sec through a Teflon reactor tube ( $\phi = 1.0$  mm,  $l = 1.0$  m), the mixture was quenched by addition of triethylamine (9.0  $\mu$ L, 0.0640 mmol) diluted in  $\text{CH}_2\text{Cl}_2$ . The mixture was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 20 g, toluene : AcOEt = 10 : 1  $\rightarrow$  6 : 1  $\rightarrow$  4 : 1) afforded **7a** (72.5 mg, 0.0531 mmol, 83%) as a white solid.  $R_f = 0.41$  (toluene : AcOEt = 4 : 1);  $[\alpha]_D^{22} + 31.9$  ( $c$  0.30,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  : 8.03-7.28 (m, 25H, Ar-H), 5.90 (t,  $J = 9.5$  Hz, 1H, 3''-H), 5.58 (t,  $J = 9.5$  Hz, 1H, 4''-H), 5.56 (dd,  $J = 9.5$  Hz, 8.0 Hz, 1H, 2''-H), 5.55 (d,  $J = 8.0$  Hz, 1H, 1'-H), 5.32 (t,  $J = 3.3$  Hz, 1H, 12-H), 5.24 (t,  $J = 9.3$  Hz, 1H, 3'-H), 5.17 (dd,  $J = 9.3$  Hz, 8.0 Hz, 1H, 2'-H), 5.12 (dd,  $J = 10.0$  Hz, 9.3 Hz, 1H, 4'-H), 4.85 (d,  $J = 8.0$  Hz, 1H, 1''-H), 4.59 (dd,  $J = 12.0$  Hz, 3.6 Hz, 1H, 6''-H), 4.54 (dd,  $J = 12.0$  Hz, 6.6 Hz, 1H, 6''-H), 4.27 (dd,  $J = 12.5$  Hz, 4.4 Hz, 1H, 6'-H), 4.17-4.09 (m, 1H, 5''-H), 4.04 (dd,  $J = 12.5$  Hz, 2.4 Hz, 1H, 6'-H), 3.78 (ddd,  $J = 10.0$  Hz, 4.4 Hz, 2.4 Hz, 1H, 5'-H), 3.09 (m, 1H, 3-H), 2.82 (m, 1H, 18-H), 2.06 (s, 3H,  $-\text{OCOCH}_3$ ), 2.02 (s, 3H,  $-\text{OCOCH}_3$ ), 2.00 (s, 3H,  $-\text{OCOCH}_3$ ), 1.99 (s, 3H,  $-\text{OCOCH}_3$ ), 1.97 (m, 1H, 16-H), 1.84 (m, 2H, 2-H, 11-H), 1.82 (m, 1H, 2-H), 1.80 (m, 1H, 19-H), 1.78 (m, 2H, 22-H), 1.70 (m, 1H, 16-H), 1.42 (m, 2H, 1-H, 15-H), 1.39 (m, 1H, 9-H), 1.38 (m, 1H, 6-H), 1.33 (m, 2H, 7-H, 21-H), 1.26 (m, 1H, 6-H), 1.21 (m, 1H, 21-H), 1.16 (m, 1H, 19-H), 1.12 (m, 1H, 7-H), 1.08 (s, 3H, 27-H), 1.00 (m, 1H, 15-H), 0.91 (s, 6H, 29-H, 30-H), 0.83 (s, 3H, 25-H), 0.74 (m, 1H, 1-H), 0.68 (s, 6H, 23-H, 24-H), 0.63 (s, 3H, 26-H), 0.59 (m, 1H, 5-H);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  : 175.5 (C-28), 170.5 ( $-\text{OCOCH}_3$ ), 170.0 ( $-\text{OCOCH}_3$ ), 169.4 ( $-\text{OCOCH}_3$ ), 168.9 ( $-\text{OCOCH}_3$ ), 166.0 ( $-\text{OCOPh}$ ), 165.8 ( $-\text{OCOPh}$ ), 165.3 ( $-\text{OCOPh}$ ), 160.0 ( $-\text{OCOPh}$ ), 142.8 (C-13), 133.4, 133.2, 133.0, 133.0, 129.8, 129.7, 129.7, 129.7, 129.6, 129.4, 129.0, 128.8, 128.8, 128.4, 128.3, 128.3, 128.2, 128.2, 122.8 (C-12), 103.2 (C-1''), 91.5 (C-1'), 90.7 (C-3), 72.9 (C-3''), 72.8 (C-3'), 72.4 (C-5'), 72.1 (C-4''), 72.0 (C-5''), 70.3 (C-2''), 69.9 (C-2'), 68.0 (C-4'), 63.4 (C-6''), 61.5 (C-6'), 55.4 (C-5), 47.5

(C-9), 46.8 (C-17), 45.8 (C-19), 41.6 (C-14), 40.9 (C-18), 39.2 (C-8), 38.7 (C-1), 38.2 (C-4), 36.6 (C-10), 33.7 (C-21), 33.0 (C-29), 32.8 (C-7), 31.7 (C-22), 30.6 (C-20), 27.7 (C-23), 27.6 (C-15), 25.8 (C-2), 25.6 (C-27), 23.4 (C-30), 23.3 (C-16), 22.8 (C-11), 20.7 (-OCOCH<sub>3</sub>), 20.5 (-OCOCH<sub>3</sub>), 20.5 (-OCOCH<sub>3</sub>), 20.5 (-OCOCH<sub>3</sub>), 18.0 (C-6), 16.9 (C-26), 16.2 (C-24), 15.2 (C-25); IR (KBr) cm<sup>-1</sup> ν : 2950 (=C-H), 1737 (-C=O), 1069 (-C-O-); HRMS (ESI-TOF) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>78</sub>H<sub>92</sub>O<sub>21</sub>Na 1387.6029; Found 1387.6001.

**Olean-12-en-28-oic acid, 3-[(2, 3, 4, 6, -tetra-*O*-benzoyl-β-D-galactopyranosyl oxy)-, 2, 3, 4, 6-tetra-*O*-acetyl-β-D-glucopyranosyl ester (7b)**

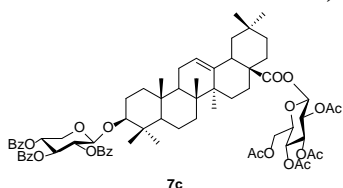


**MicroFlow.** A solution of TMSOTf (35.0 μL, 0.1922 mmol, 0.0214 M) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (9.0 mL) was injected to the micromixer by using the syringe pump at the flow rate

of 0.6 mL/min. Also, a solution of donor **6b** (213 mg, 0.2883 mmol, 0.0320 M) and acceptor **5** (150 mg, 0.1922 mmol, 0.0214 M) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (9.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at ambient temperature. After the reaction mixture was allowed to flow at ambient temperature for an additional 100 sec through a Teflon reactor tube ( $\phi$  = 1.0 mm, *l* = 1.0 m), the mixture was quenched by addition of triethylamine (27 μL, 0.1922 mmol) diluted in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL). The mixture was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 20 g, toluene : AcOEt = 20 : 1 → 18 : 1 → 17 : 1) afforded **7b** (185 mg, 0.1355 mmol, 71%) as a white solid. *R*<sub>f</sub> = 0.54 (toluene : AcOEt = 4 : 1); [ $\alpha$ ]<sub>D</sub><sup>23</sup> +74.2 (*c* 0.35, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  : 8.12-7.34 (m, 25H, Ar-H), 5.95 (dd, *J* = 3.4 Hz, 1.0 Hz 1H, 4''-H), 5.83 (dd, *J* = 10.0 Hz, 8.0 Hz, 1H, 2''-H), 5.60 (dd, *J* = 10.0 Hz, 3.4 Hz, 1H, 3''-H), 5.57 (d, *J* = 8.0 Hz, 1H, 1'-H), 5.33 (t, *J* = 3.3 Hz, 1H, 12-H), 5.24 (t, *J* = 9.2 Hz, 1H, 3'-H), 5.17 (dd, *J* = 9.2 Hz, 8.0 Hz, 1H, 2'-H), 5.12 (dd, *J* = 10.0 Hz, 9.2 Hz, 1H, 4'-H), 4.82 (d, *J* = 8.0 Hz, 1H, 1''-H), 4.66 (dd, *J* = 11.6 Hz, 7.4 Hz, 1H, 6''-H), 4.43 (dd, *J* = 11.6 Hz, 6.0 Hz, 1H, 6''-H), 4.30 (ddd, *J* = 7.4 Hz, 6.0 Hz, 1.0 Hz, 1H, 5''-H), 4.27 (dd, *J* = 12.5 Hz, 4.4 Hz, 1H, 6'-H), 4.04 (dd, *J* = 12.5 Hz, 2.4 Hz, 1H, 6'-H), 3.78 (ddd, *J* = 10.0 Hz, 4.4 Hz, 2.4 Hz, 1H, 5'-H), 3.13 (m, 1H, 3-H), 2.82 (m, 1H, 18-H), 2.06 (s, 3H, -OCOCH<sub>3</sub>), 2.02 (s, 3H, -OCOCH<sub>3</sub>), 2.01 (s, 3H, -OCOCH<sub>3</sub>), 1.99 (s, 3H, -OCOCH<sub>3</sub>), 1.97 (m, 1H, 16-H), 1.86 (m, 1H, 2-H), 1.80 (m, 2H, 11-H), 1.76 (m, 1H, 2-H), 1.63 (m, 1H, 19-H), 1.62 (m, 2H, 22-H), 1.53 (m, 1H, 16-H), 1.42 (m, 1H, 1-H), 1.38 (m, 2H, 9-H, 15-H), 1.34 (m, 2H, 6-H, 7-H), 1.26 (m, 1H, 6-H), 1.18 (m, 2H, 21-H), 1.14 (m, 1H, 19-H), 1.12 (m, 1H, 7-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H,

15-H), 0.92 (s, 6H, 29-H, 30-H), 0.85 (s, 3H, 25-H), 0.76 (m, 1H, 1-H), 0.70 (s, 3H, 23-H), 0.69 (s, 3H, 26-H), 0.66 (s, 3H, 24-H), 0.62 (m, 1H, 5-H);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 175.6 (C-28), 170.6 (-O $\text{C}\text{OCH}_3$ ), 170.1 (-O $\text{C}\text{OCH}_3$ ), 169.4 (-O $\text{C}\text{OCH}_3$ ), 168.9 (-O $\text{C}\text{OCH}_3$ ), 166.0 (-O $\text{C}\text{OPh}$ ), 165.7 (-O $\text{C}\text{OPh}$ ), 165.6 (-O $\text{C}\text{OPh}$ ), 165.2 (-O $\text{C}\text{OPh}$ ), 142.8 (C-13), 133.5, 133.2, 133.2, 133.0, 133.0, 129.7, 129.7, 129.5, 129.5, 129.0, 129.0, 128.9, 128.7, 128.5, 128.5, 128.4, 128.2, 122.8 (C-12), 103.8 (C-1''), 91.5 (C-1'), 90.9 (C-3), 72.8 (C-3'), 72.4 (C-5'), 71.8 (C-3''), 71.2 (C-5''), 71.0 (C-2''), 69.9 (C-2'), 68.2 (C-4''), 68.0 (C-4'), 62.1 (C-6''), 61.5 (C-6'), 55.4 (C-5), 47.5 (C-9), 46.8 (C-17), 45.8 (C-19), 41.6 (C-14), 39.3 (C-18), 38.7 (C-8), 38.3 (C-4), 36.6 (C-1), 33.7 (C-10), 33.0 (C-21), 32.8 (C-29), 31.7 (C-7), 30.6 (C-22), 29.7 (C-20), 27.7 (C-23), 27.7 (C-15), 25.9 (C-2), 25.6 (C-27), 23.4 (C-30), 23.3 (C-16), 22.8 (C-11), 20.7 (-O $\text{C}\text{OCH}_3$ ), 20.6 (-O $\text{C}\text{OCH}_3$ ), 20.6 (-O $\text{C}\text{OCH}_3$ ), 20.6 (-O $\text{C}\text{OCH}_3$ ), 18.0 (C-6), 16.9 (C-26), 16.2 (C-24), 15.2 (C-25); IR (KBr)  $\text{cm}^{-1}$   $\nu$ : 2952 (=C-H), 1735 (-C=O), 1069 (-C-O-); HRMS (ESI-TOF)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd for  $\text{C}_{78}\text{H}_{92}\text{O}_{21}\text{Na}$  1387.6029; Found 1387.6019.

**Olean-12-en-28-oic acid, 3-[(2, 3, 4, -tri-*O*-benzoyl- $\beta$ -D-xylopyranosyl) oxy]-, 2, 3, 4, 6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl ester (**7c**)**

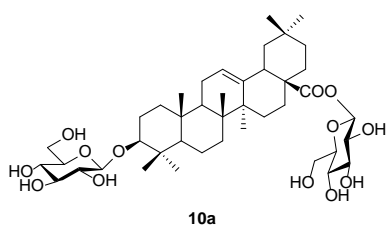


**MicroFlow.** A solution of TMSOTf (35.0  $\mu\text{L}$ , 0.1922 mmol, 0.0214 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (9.0 mL) was injected to the micromixer by using the syringe pump at the flow rate

of 0.6 mL/min. Also, a solution of donor **6c** (175 mg, 0.2883 mmol, 0.0320 M) and acceptor **5** (150 mg, 0.1922 mmol, 0.0214 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (9.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at ambient temperature. After the reaction mixture was allowed to flow at ambient temperature for an additional 100 sec through a Teflon reactor tube ( $\phi = 1.0$  mm,  $l = 1.0$  m), the mixture was quenched by addition of triethylamine (27  $\mu\text{L}$ , 0.1922 mmol) diluted in  $\text{CH}_2\text{Cl}_2$  (1.0 mL). The mixture was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 20 g, toluene : AcOEt = 20 : 1  $\rightarrow$  18 : 1  $\rightarrow$  17 : 1) afforded **7c** (193 mg, 0.1567 mmol, 81%) as a white solid.  $R_f = 0.54$  (toluene : AcOEt = 4 : 1);  $[\alpha]_D^{23} +17.5$  ( $c$  0.30,  $\text{CHCl}_3$ );  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.10-7.31 (m, 25H, Ar-H), 5.78 (t,  $J = 8.0$  Hz, 1H, 3''-H), 5.57 (d,  $J = 8.0$  Hz, 1H, 1'-H), 5.44 (dd,  $J = 8.0$  Hz, 6.1 Hz, 1H, 2'-H), 5.33 (t,  $J = 3.3$  Hz, 1H, 12-H), 5.24 (t,  $J = 9.3$  Hz, 1H, 3'-H), 5.17 (dd,  $J = 9.3$  Hz, 8.0 Hz, 1H, 2'-H), 5.12 (dd,  $J = 10.0$  Hz, 9.2 Hz, 1H, 4'-H), 4.84 (d,  $J = 6.1$  Hz, 1H, 1''-H), 4.43 (dd,  $J = 12.0$  Hz, 4.6 Hz, 1H, 5''-H), 4.27 (dd,  $J = 12.5$  Hz, 4.4 Hz, 1H, 6'-H), 4.04

(dd,  $J = 12.5$  Hz, 2.4 Hz, 1H, 6'-H), 3.78 (ddd,  $J = 10.0$  Hz, 4.4 Hz, 2.4 Hz, 1H, 5'-H), 3.63 (dd,  $J = 12.0$  Hz, 8.0 Hz, 1H, 5''-H), 3.13 (dd,  $J = 11.5$  Hz, 4.8 Hz, 1H, 3-H), 2.81 (m, 1H, 18-H), 2.06 (s, 3H, -OCOCH<sub>3</sub>), 2.02 (s, 3H, -OCOCH<sub>3</sub>), 2.01 (s, 3H, -OCOCH<sub>3</sub>), 2.00 (s, 3H, -OCOCH<sub>3</sub>), 1.94 (m, 1H, 16-H), 1.86 (m, 2H, 11-H), 1.79 (m, 2H, 2-H), 1.64 (m, 2H, 1-H, 19-H), 1.61 (m, 2H, 22-H), 1.51 (m, 1H, 16-H), 1.48 (m, 1H, 9-H), 1.42 (m, 1H, 15-H), 1.39 (m, 2H, 6-H, 7-H), 1.26 (m, 2H, 6-H, 21-H), 1.22 (m, 1H, 21-H), 1.18 (m, 1H, 19-H), 1.14 (m, 1H, 7-H), 1.10 (s, 3H, 27-H), 1.03 (m, 1H, 15-H), 0.98 (m, 1H, 1-H), 0.90 (s, 6H, 29-H, 30-H), 0.89 (s, 3H, 25-H), 0.77 (s, 3H, 23-H), 0.70 (s, 3H, 26-H), 0.69 (m, 1H, 5-H), 0.65 (s, 3H, 24-H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 175.6 (C-28), 170.6 (-OCOCH<sub>3</sub>), 170.0 (-OCOCH<sub>3</sub>), 169.4 (-OCOCH<sub>3</sub>), 168.9 (-OCOCH<sub>3</sub>), 165.5 (-OCOPh), 165.5 (-OCOPh), 165.0 (-OCOPh), 142.8 (C-13), 135.8, 133.5, 133.3, 133.2, 133.0, 130.1, 129.8, 129.8, 129.4, 129.2, 129.1, 128.9, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 122.9 (C-12), 102.7 (C-1''), 91.5 (C-1'), 89.9 (C-3), 72.8 (C-3'), 72.4 (C-5'), 71.0 (C-2''), 69.9 (C-2'), 69.5 (C-4''), 68.0 (C-4'), 61.6 (C-5''), 61.5 (C-6'), 55.4 (C-5), 47.5 (C-9), 46.8 (C-17), 45.7 (C-19), 41.6 (C-14), 41.0 (C-18), 39.3 (C-8), 38.9 (C-4), 38.4 (C-1), 36.7 (C-10), 33.7 (C-21), 33.0 (C-29), 32.8 (C-7), 31.7 (C-22), 30.6 (C-20), 27.7 (C-23), 27.7 (C-15), 25.8 (C-2), 25.6 (C-27), 23.4 (C-30), 23.4 (C-16), 22.8 (C-11), 20.7 (-OCOCH<sub>3</sub>), 20.6 (-OCOCH<sub>3</sub>), 20.6 (-OCOCH<sub>3</sub>), 20.5 (-OCOCH<sub>3</sub>), 18.1 (C-6), 16.9 (C-26), 16.2 (C-24), 15.3 (C-25); IR (KBr) cm<sup>-1</sup>  $\nu$ : 2946 (=C-H), 1759 (-C=O), 1070 (-C-O-); HRMS (ESI-TOF)  $m/z$ : [M+Na]<sup>+</sup> Calcd for C<sub>70</sub>H<sub>86</sub>O<sub>19</sub>Na 1253.5661; Found 1253.5649.

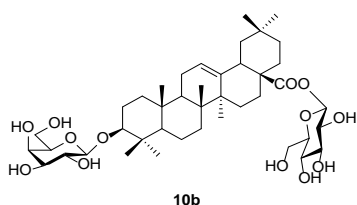
### Olean-12-en-28-oic acid, 3-( $\beta$ -D-glucopyranosyloxy)-, $\beta$ -D-glucopyranosyl ester



**(10a).** To a solution of **7a** (100 mg, 0.0732 mmol) in dry MeOH (1.4 mL) and CH<sub>2</sub>Cl<sub>2</sub> (1.4 mL) was added NaH (3.0 mg, 0.0732 mmol 60% disp.). The mixture was stirred at ambient temperature for 1 h, neutralized with Dowex H<sup>+</sup> resin to pH 7 and filtered. The filtrate was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 20 g, CHCl<sub>3</sub> : MeOH = 5 : 1  $\rightarrow$  4 : 1  $\rightarrow$  3 : 1) afforded **10a** (53 mg, 0.0679 mmol, 93%) as a white solid.  $R_f$  = 0.08 (CHCl<sub>3</sub> : MeOH = 5 : 1);  $[\alpha]_D^{24}$  +18.4 ( $c$  1.00, CH<sub>3</sub>OH); <sup>1</sup>H-NMR (400 MHz, pyridine-*d*<sub>5</sub>)  $\delta$ : 6.30 (d,  $J = 8.0$  Hz, 1H, 1'-H), 5.40 (t,  $J = 3.3$  Hz, 1H, 12-H), 4.91 (d,  $J = 8.0$  Hz, 1H, 1''-H), 4.56 (dd,  $J = 12.0$  Hz, 2.0 Hz, 1H, 6''-H), 4.43 (dd,  $J = 12.0$  Hz, 2.0 Hz, 1H, 6'-H), 4.38 (dd,  $J = 12.0$  Hz, 5.0 Hz, 1H, 6'-H), 4.37 (dd,  $J = 12.0$  Hz, 5.0 Hz, 1H, 6''-H), 4.34 (dd,  $J = 9.5$  Hz, 9.0 Hz, 1H, 4'-H), 4.26 (dd,  $J = 9.0$  Hz, 8.5 Hz, 1H, 3'-H), 4.22 (dd,  $J = 8.5$  Hz,

8.0 Hz, 1H, 3''-H), 4.20 (dd,  $J = 9.0$  Hz, 8.5 Hz, 1H, 4''-H), 4.18 (t,  $J = 8.5$  Hz, 1H, 2'-H), 4.01 (t,  $J = 8.0$  Hz, 1H, 2''-H), 4.00 (ddd,  $J = 9.5$  Hz, 4.0 Hz, 2.0 Hz, 1H, 5'-H), 3.98 (ddd,  $J = 9.0$  Hz, 5.0 Hz, 2.0 Hz, 1H, 5''-H), 3.39 (dd,  $J = 14.0$  Hz, 4.2 Hz, 1H, 3-H), 3.21 (dd,  $J = 14.0$  Hz, 3.9 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.32 (s, 3H, 23-H), 1.28 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.11 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 3H, 24-H), 0.96 (m, 1H, 1-H), 0.92 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H);  $^{13}\text{C}$ -NMR (100 MHz, pyridine- $d_5$ )  $\delta$ : 176.6 (C-28), 144.3 (C-13), 123.2 (C-12), 107.0 (C-1''), 95.9 (C-1'), 89.0 (C-3), 79.5 (C-5'), 78.9 (C-3'), 78.8 (C-3''), 78.4 (C-5''), 75.9 (C-2''), 74.2 (C-2'), 71.9 (C-4''), 71.2 (C-4'), 63.1 (C-6''), 62.2 (C-6'), 56.0 (C-5), 48.2 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.1 (C-21), 33.3 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.4 (C-23), 28.4 (C-15), 26.7 (C-2), 26.3 (C-27), 23.9 (C-30), 23.8 (C-16), 23.5 (C-11), 18.7 (C-6), 17.6 (C-26), 17.1 (C-24), 15.7 (C-25) IR (KBr)  $\text{cm}^{-1}$   $\nu$ : 3441 (-O-H), 2939 (=C-H), 1735 (-C=O), 1069 (-C-O-); HRMS (ESI-TOF)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd for  $\text{C}_{42}\text{H}_{68}\text{O}_{13}\text{Na}$  803.4558; Found 803.4558. TOCSY (400 MHz, pyridine- $d_5$ ) mixing time  $\tau_m = 150$  ms.

**Olean-12-en-28-oic acid, 3-( $\beta$ -D-galactopyranosyloxy)-,  $\beta$ -D-glucopyranosyl ester**

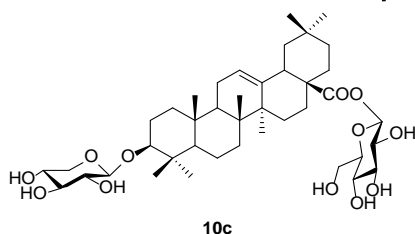


**(10b).** To a solution of **7b** (137 mg, 0.1003 mmol) in dry MeOH (1.0 mL) and  $\text{CH}_2\text{Cl}_2$  (1.0 mL) was added NaH (4.0 mg, 0.1003 mmol 60% disp.). The mixture was stirred at ambient temperature for 1 h, neutralized with Dowex  $\text{H}^+$  resin to pH 7 and filtered. The filtrate was

concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 20 g,  $\text{CHCl}_3$  : MeOH = 5 : 1  $\rightarrow$  4 : 1  $\rightarrow$  3 : 1) afforded **10b** (58 mg, 0.0743 mmol, 74%) as a white solid.  $R_f = 0.36$  ( $\text{CHCl}_3$  : MeOH = 3 : 1);  $[\alpha]_{\text{D}}^{24} +24.2$  ( $c$  1.00,  $\text{CH}_3\text{OH}$ );  $^1\text{H}$ -NMR (400 MHz, pyridine- $d_5$ )  $\delta$ : 6.33 (d,  $J = 8.0$  Hz, 1H, 1'-H), 5.43 (t,  $J = 3.3$  Hz, 1H, 12-H), 4.87 (d,  $J = 8.0$  Hz, 1H, 1''-H), 4.60 (dd,  $J = 3.0$  Hz, 1.0 Hz, 1H, 4''-H), 4.50 (dd,  $J = 12.0$  Hz, 6.0 Hz, 1H, 6''-H), 4.48 (dd,  $J = 12.0$  Hz, 3.0 Hz, 1H, 6'-H), 4.46 (dd,  $J = 9.0$  Hz, 8.0 Hz, 1H, 2''-H), 4.45 (dd,  $J = 12.0$  Hz, 6.0 Hz, 1H, 6''-H), 4.41 (dd,  $J = 12.0$  Hz, 4.0 Hz, 1H, 6'-H), 4.37 (dd,  $J = 9.5$  Hz, 9.0 Hz, 1H, 4'-H), 4.30 (dd,  $J = 9.0$  Hz, 8.5 Hz, 1H, 3'-H), 4.22 (dd,  $J = 8.5$  Hz, 8.0 Hz, 1H, 2'-H), 4.19 (dd,  $J = 9.0$  Hz, 3.0 Hz, 1H, 3''-H), 4.13 (td,  $J = 6.0$  Hz, 1.0 Hz, 1H,

5''-H), 4.04 (ddd,  $J = 9.5$  Hz, 4.0 Hz, 3.0 Hz, 1H, 5'-H), 3.37 (dd,  $J = 12.0$  Hz, 4.5 Hz, 1H, 3-H), 3.19 (dd,  $J = 14.0$  Hz, 3.9 Hz, 1H, 18-H), 2.35 (m, 1H, 15-H), 2.26 (m, 1H, 2-H), 2.08 (m, 2H, 11-H), 1.95 (m, 2H, 16-H), 1.81 (m, 1H, 2-H), 1.76 (m, 2H, 22-H), 1.72 (m, 1H, 19-H), 1.61 (m, 1H, 9-H), 1.40 (m, 2H, 1-H, 6-H), 1.43 (m, 1H, 7-H), 1.34 (m, 2H, 21-H), 1.31 (m, 1H, 6-H), 1.29 (s, 3H, 23-H), 1.26 (s, 3H, 27-H), 1.23 (m, 1H, 19-H), 1.17 (m, 1H, 15-H), 1.09 (s, 3H, 26-H), 1.04 (m, 1H, 7-H), 0.96 (s, 3H, 24-H), 0.93 (m, 1H, 1-H), 0.90 (s, 3H, 29-H), 0.88 (s, 3H, 30-H), 0.82 (s, 3H, 25-H), 0.77 (m, 1H, 5-H);  $^{13}\text{C}$ -NMR (100 MHz, pyridine- $d_5$ )  $\delta$ : 176.6 (C-28), 144.3 (C-13), 123.2 (C-12), 107.0 (C-1''), 95.9 (C-1'), 88.9 (C-3), 79.5 (C-5'), 78.9 (C-3'), 76.9 (C-5''), 75.5 (C-3''), 74.2 (C-2'), 73.2 (C-2''), 71.1 (C-4'), 70.3 (C-4''), 62.5 (C-6''), 62.2 (C-6'), 56.0 (C-5), 48.2 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.2 (C-21), 33.3 (C-29), 33.3 (C-7), 32.7 (C-22), 31.0 (C-20), 28.4 (C-23), 28.4 (C-15), 26.8 (C-2), 26.3 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 18.7 (C-6), 17.6 (C-26), 17.2 (C-24), 15.7 (C-25); IR (KBr)  $\text{cm}^{-1}$   $\nu$ : 3398 (-O-H), 2948 (=C-H), 1735 (-C=O), 1074 (-C-O-); HRMS (ESI-TOF)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd for  $\text{C}_{42}\text{H}_{68}\text{O}_{13}\text{Na}$ : 803.4558; Found 803.4551. TOCSY (400 MHz, pyridine- $d_5$ ) mixing time  $\tau_m = 150$  ms.

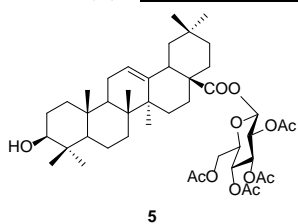
**Olean-12-en-28-oic acid, 3-( $\beta$ -D-xylopyranosyloxy)-,  $\beta$ -D-glucopyranosyl ester (**10c**).**



To a solution of **7c** (159 mg, 0.1291 mmol) in dry MeOH (2.4 mL) and  $\text{CH}_2\text{Cl}_2$  (1.2 mL) was added NaH (5.16 mg, 0.1291 mmol, 60% disp.). The mixture was stirred at ambient temperature for 50 min, neutralized with Dowex  $\text{H}^+$  resin to pH 7 and filtered. The filtrate was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 20 g,  $\text{CHCl}_3$  : MeOH = 10 : 1) afforded **10c** (77.9 mg, 0.1037 mmol, 87%) as a white solid.  $R_f = 0.48$  ( $\text{CHCl}_3$  : MeOH = 3 : 1);  $[\alpha]_D^{24} +20.6$  ( $c$  1.00,  $\text{CH}_3\text{OH}$ );  $^1\text{H}$ -NMR (400 MHz, pyridine- $d_5$ )  $\delta$ : 6.33 (d,  $J = 8.5$  Hz, 1H, 1'-H), 5.44 (t,  $J = 3.3$  Hz, 1H, 12-H), 4.84 (d,  $J = 7.5$  Hz, 1H, 1''-H), 4.47 (dd,  $J = 12.0$  Hz, 2.0 Hz, 1H, 6'-H), 4.41 (dd,  $J = 12.0$  Hz, 4.0 Hz, 1H, 6''-H), 4.39 (dd,  $J = 11.0$  Hz, 5.0 Hz, 1H, 5''-H), 4.38 (dd,  $J = 9.5$  Hz, 9.0 Hz, 1H, 4'-H), 4.30 (t,  $J = 9.0$  Hz, 1H, 3'-H), 4.24 (ddd,  $J = 10.0$  Hz, 8.5 Hz, 5.0 Hz, 1H, 4''-H), 4.21 (dd,  $J = 9.0$  Hz, 8.5 Hz, 1H, 2'-H), 4.18 (t,  $J = 8.5$  Hz, 1H, 3''-H), 4.04 (ddd,  $J = 9.5$  Hz, 4.0 Hz, 2.0 Hz, 1H, 5'-H), 4.03 (dd,  $J = 8.5$  Hz, 7.5 Hz, 1H, 2''-H), 3.79 (dd,  $J = 11.0$  Hz, 5.0 Hz, 1H, 5''-H), 3.36 (dd,  $J = 12.0$  Hz, 4.5 Hz, 1H, 3-H), 3.21 (dd,  $J = 14.0$  Hz, 3.9 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.20 (m, 1H, 2-H), 2.13 (m, 2H, 11-H), 2.00 (m, 2H, 16-H),

1.94 (m, 1H, 2-H), 1.92 (m, 2H, 22-H), 1.77 (m, 1H, 19-H), 1.66 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.47 (m, 2H, 6-H, 7-H), 1.37 (m, 2H, 21-H), 1.31 (s, 3H, 23-H), 1.29 (m, 1H, 6-H), 1.27 (s, 3H, 27-H), 1.25 (m, 1H, 19-H), 1.19 (m, 1H, 15-H), 1.12 (s, 3H, 26-H), 1.08 (m, 1H, 7-H), 1.00 (s, 3H, 24-H), 0.98 (m, 1H, 1-H), 0.93 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.88 (s, 3H, 25-H), 0.83 (m, 1H, 5-H);  $^{13}\text{C}$ -NMR (100 MHz, pyridine- $d_5$ )  $\delta$  : 176.7 (C-28), 144.3 (C-13), 123.1 (C-12), 107.8 (C-1''), 95.9 (C-1'), 88.8 (C-3), 79.5 (C-5'), 78.9 (C-3'), 78.7 (C-3''), 75.6 (C-2''), 74.2 (C-2'), 71.2 (C-4''), 71.1 (C-4'), 67.3 (C-5''), 62.2 (C-6'), 56.0 (C-5), 48.2 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.7 (C-4), 39.0 (C-1), 37.2 (C-10), 34.2 (C-21), 33.3 (C-29), 33.3 (C-7), 32.7 (C-22), 31.0 (C-20), 28.4 (C-23), 28.4 (C-15), 26.9 (C-2), 26.3 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 18.7 (C-6), 17.6 (C-26), 17.1 (C-24), 15.8 (C-25); IR (KBr)  $\text{cm}^{-1}$   $\nu$  : 3390 (-O-H), 2959 (=C-H), 1730 (-C=O), 1075 (-C-O-); HRMS (ESI-TOF)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd for  $\text{C}_{41}\text{H}_{66}\text{O}_{12}\text{Na}$  773.4452; Found 773.4455. TOCSY (400 MHz, pyridine- $d_5$ ) mixing time  $\tau_m$  = 150 ms.

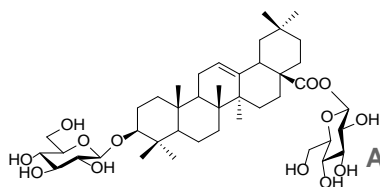
**Olean-12-en-28-oic acid, 3-hydroxy-, 2, 3, 4, 6-tetra-O-acetyl- $\beta$ -D-glucopyranosyl ester (5)** Continuous Flow glycosylation and Batch deprotection.



5

$\text{BF}_3 \cdot \text{OEt}_2$  (12.0  $\mu\text{L}$ , 0.0956 mmol, 0.0320 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **2a** (94.2 mg, 0.1912 mmol, 0.0637 M) and acceptor **6** (54.6 mg, 0.0956 mmol, 0.0320 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed in a thermostatic bath at  $-40^\circ\text{C}$ . After the reaction mixture was allowed to flow at  $-40^\circ\text{C}$  through a Teflon reactor tube ( $\phi = 1.0$  mm,  $l = 1.0$  m), the crude mixture of **3a** was introduced into a flask, which was cooled to  $-40^\circ\text{C}$  and connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at ambient temperature in flask added  $\text{ZnBr}_2$  (216 mg, 0.956 mmol) and  $\text{H}_2\text{O}$  (17.2  $\mu\text{L}$ , 0.956 mmol) in advance. After the reaction was completed, the reaction mixture was quenched with  $\text{NEt}_3$ , filtered by celite, rinsed with  $\text{CH}_2\text{Cl}_2$  (20 mL). The filtrate was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 20 g, hexane :  $\text{AcOEt} = 3 : 1 \rightarrow 2 : 1 \rightarrow 3 : 2$ ) afforded **5** (58.4 mg, 0.0748 mmol, 78%) as a white foamy solid by two steps.

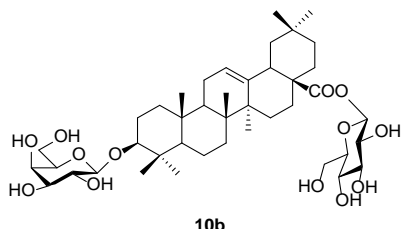
**Olean-12-en-28-oic acid, 3-( $\beta$ -D-glucopyranosyloxy)-,  $\beta$ -D-glucopyranosyl ester (10a)** Continuous Flow glycosylation and Batch deprotection.



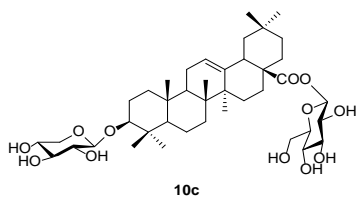
10a

(11.5  $\mu\text{L}$ , 0.0635 mmol, 0.0212 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **6a** (71.0 mg, 0.0954 mmol, 0.0318 M) and acceptor **5** (50.0 mg, 0.0635 mmol, 0.0212 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed in a thermostatic bath at ambient temperature. After the reaction mixture was allowed to flow at ambient temperature through a Teflon reactor tube ( $\phi = 1.0$  mm,  $l = 1.0$  m), the crude mixture of **7a** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at ambient temperature in flask added NaH (11.5 mg, 0.2858 mmol, 60% disp.) and MeOH (12 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex  $\text{H}^+$  resin to pH 7 and filtered, rinsed with MeOH (20 mL). The filtrate was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 20 g,  $\text{CHCl}_3$  : MeOH = 10 : 1  $\rightarrow$  8 : 1  $\rightarrow$  6 : 1) afforded **10a** (23.3 mg, 0.0298 mmol, 47%) as a white solid by two steps.

**Olean-12-en-28-oic acid, 3-( $\beta$ -D-galactopyranosyloxy)-,  $\beta$ -D-glucopyranosyl ester (**10b**)** *Continuous Flow glycosylation and Batch deprotection.* A solution of TMSOTf



(11.5  $\mu\text{L}$ , 0.0635 mmol, 0.0212 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **6b** (71.0 mg, 0.0954 mmol, 0.0318 M) and acceptor **5** (50.0 mg, 0.0635 mmol, 0.0212 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed in a thermostatic bath at ambient temperature. After the reaction mixture was allowed to flow at ambient temperature through a Teflon reactor tube ( $\phi = 1.0$  mm,  $l = 1.0$  m), the crude mixture of **7b** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at ambient temperature in flask added NaH (11.5 mg, 0.2858 mmol, 60% disp.) and MeOH (12 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex  $\text{H}^+$  resin to pH 7 and filtered, rinsed with MeOH (20 mL). The filtrate was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 20 g,  $\text{CHCl}_3$  : MeOH = 10 : 1  $\rightarrow$  8 : 1  $\rightarrow$  6 : 1) afforded **10b** (21.5 mg, 0.0275 mmol, 43%) as a white solid by two steps.

**Olean-12-en-28-oic acid, 3-( $\beta$ -D-xylopyranosyloxy)-,  $\beta$ -D-glucopyranosyl ester (**10c**)****Continuous Flow glycosylation and Batch deprotection.**

$\mu\text{L}$ , 0.0635 mmol, 0.0212 M) dissolved in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **6c** (71.0 mg, 0.0954 mmol, 0.0318 M) and acceptor **5** (50.0 mg, 0.0635 mmol, 0.0212 M) dissolved in  $\text{CH}_2\text{Cl}_2$

(3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed in a thermostatic bath at ambient temperature. After the reaction mixture was allowed to flow at ambient temperature through a Teflon reactor tube ( $\phi = 1.0$  mm,  $l = 1.0$  m), the crude mixture of **7c** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at ambient temperature in flask added NaH (11.5 mg, 0.2858 mmol, 60% disp.) and MeOH (12 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex  $\text{H}^+$  resin to pH 7 and filtered, rinsed with MeOH (20 mL). The filtrate was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (silica gel 20 g,  $\text{CHCl}_3 : \text{MeOH} = 10 : 1 \rightarrow 9 : 1$ ) afforded **10c** (22.5 mg, 0.0300 mmol, 47%) as a white solid by two steps.

The purity of **10a**, **10b**, **10c** was compared to with corresponding compound in stepwise synthesis by a proton NMR spectrum (see supporting information in detail).

**ASSOCIATED CONTENT**

\* Supporting Information<sup>[1]</sup> The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.XXXXX.

<sup>1</sup>H and <sup>13</sup>C NMR spectra for synthetic compound (PDF)

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**Note**

The authors declare no competing financial interest.

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