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Synthesis of Leonosides E and F derived from *Leonurus japonicas* Houtt

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ABSTRACT

Leonosides E and F, two natural phenylethanoid glycosides derived from *Leonurus japonicas* Houtt, which bear different trisaccharide moieties—one linear and one branched, were totally synthesized via a direct transglycosylation strategy. After trisaccharyl trichloroacetimidates **3** and **4** were prepared as glycosyl donors, they were coupled with the homovanillyl aglycon via silver triflate-promoted transglycosylation to successfully furnish the fully protected glycosides, which were globally deprotected to afford the target molecules in 6.77% and 10.08% overall yields for the longest linear synthetic sequence starting from **6** and **14**.

1. Introduction

Many natural products are glycosylated with diversified sugar chains which participate in a variety of biological functions.[1–3] For instance, digoxin, a trisaccharyl glycoside isolated from the plant *Digitalis lanata*, is now widely used in the treatment of various heart conditions.[4] OSW-1 is a cholestane glycoside isolated from the bulbs of *Ornithogalum saundersiae*, which has exhibited exceptionally potent cytotoxicities against various malignant tumor cells.[5,6] QS-21, a triterpene glycoside purified from the plant *Quillaja saponaria*, is currently under clinical investigation as a vaccine adjuvant.[7–9] Pharmaceutical Coramsine and Curaderm-BEC5 cream, whose primary ingredients are solasodine glycoalkaloids, have been applied to the treatment of various cancers in clinic.[10] Clearly, glycosylated natural products have valuable pharmacological properties, thus they are attractive candidates for new drug development and their synthetic and structure–activity relationship studies have drawn significant attention.[11–15]

The plants of the genus *Leonurus* have been widely used in China as a traditional medicine to deal with menstrual disorder, treat edema, and invigorate blood circulation.[16] Phytochemical investigations of these plants have uncovered a wide range of bioactive molecules, including phenylethanoid glycosides, labdane-type diterpenoids, flavonoids, and cyclic peptides that have been proved to exhibit anti-inflammatory, anti-platelet aggregation, and cytotoxic activities.[17–19] Recently, two phenylethanoid glycosides, Leonoside E (**1**), 2-(3-methoxyl-4-hydroxyphenyl)-ethyl α-L-arabinopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→3)-β-D-glucopyranoside, and Leonoside F (**2**), 2-(3-methoxyl-4-hydroxyphenyl)-ethyl α-L-rhamnopyranosyl-(1→3)-[β-D-glucopyranosyl-(1→6)]-β-D-glucopyranoside (Fig. 1), were isolated from the plant *Leonurus japonicas* Houtt and characterized by Zhang and co-workers.[20] In vitro studies revealed that these phenylethanoid glycosides exhibited potent hepatoprotective activity against D-galactosamine-induced toxicity in HL-7702 cells at the concentration of 10 μM. Being attracted by their peculiar oligosaccharide structures and potent bioactivity, we have performed the first total synthesis of Leonoside E and Leonoside F.

2. Results and discussion

We planned to adopt a direct transglycosylation strategy (Scheme 1) for the synthesis of the target phenylethanoid glycosides. The key intermediates were trisaccharyl trichloroacetimidates **3** and **4** that were used as glycosyl donors, and the common glycosyl acceptor was 3-methoxyl-4-benzoxylphenylethanol **5**.[21] Since all of the glycosidic linkages in **1** and **2** are *trans*, we utilized acyl groups, including both acetyl and benzoyl groups, for global hydroxyl group protection, to take advantage of the neighboring group participation for stereoselective *trans*-glycosylation.

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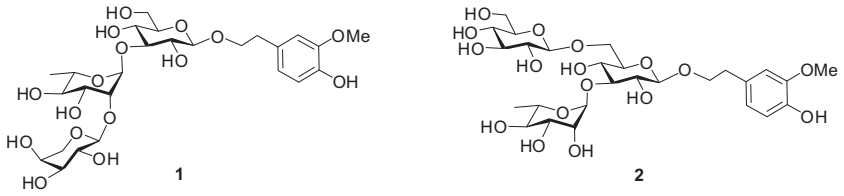
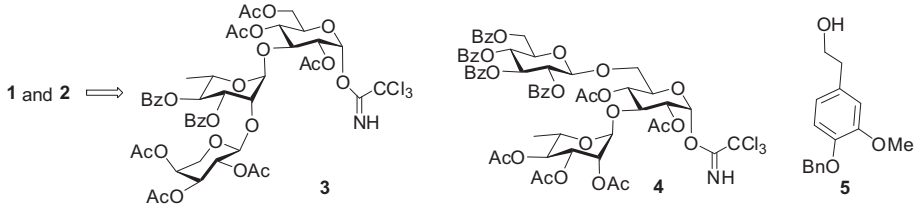
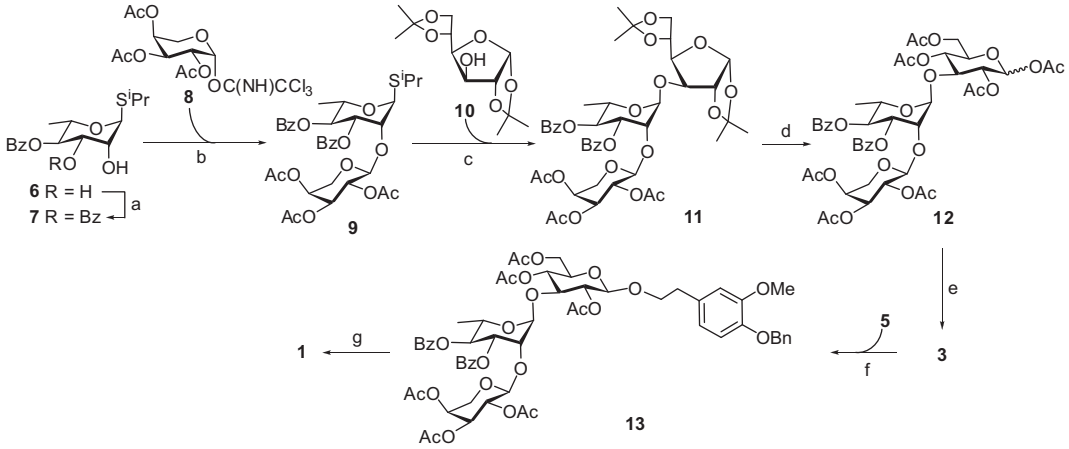


Figure 1. The chemical structures of Leonoside E (**1**) and Leonoside F (**2**).



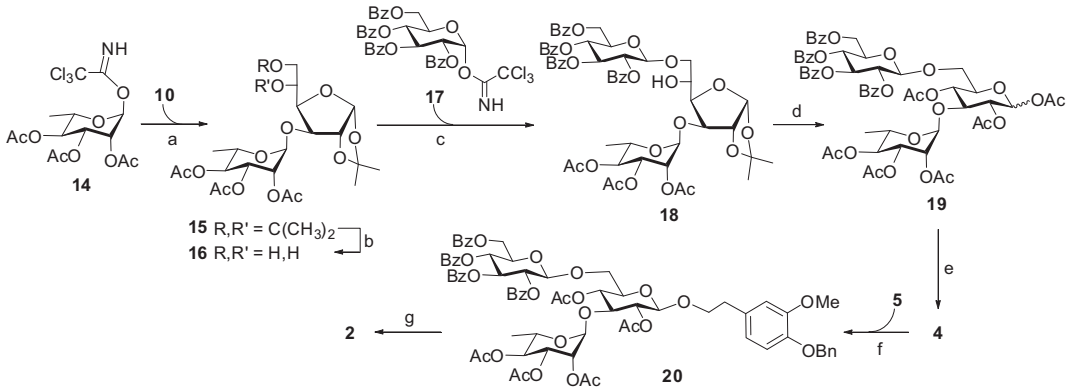
Scheme 1. Retrosynthetic plan for Leonoside E (**1**) and Leonoside F (**2**).



Scheme 2. Reagents and conditions: (a) BzCl, pyridine, −15 °C, 75%; (b) TMSOTf, CH_2Cl_2, 0 °C, 65%; (c) NIS, TMSOTf, CH_2Cl_2, −10 °C, 67%; (d) 90% TFA; then Ac_2O, pyridine, 71% (two steps); (e) hydrazine acetate, DMF, 0 °C; then Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 57% (two steps); (f) AgOTf, 4 Å molecular sieves, CH_2Cl_2, −40 °C, 64%; (g) H_2, $Pd(OH)_2$/C, MeOH; then 1 N NaOH, MeOH, 80% (two steps).

The synthesis of Leonoside E (**1**), as depicted in Scheme 2, commenced with regioselective benzoylation of isopropyl 4-*O*-benzoyl-1-thio-β-D-galactopyranside **6**[22] by benzoyl chloride in pyridine to obtain 3,4-di-*O*-benzoyl-1-thio-β-D-galactopyranside **7** in a good yield (75%). The downfield shift of the H-3 signal of **7** to δ 5.51 ppm in its ^{1}H NMR spectrum confirmed the correct regioselectivity. Glycosylation of **7** by trichloroacetimidate **8** in anhydrous CH_2Cl_2 at 0 °C under the promotion of trimethylsilyl triflate (TMSOTf) gave α-(1→2)-linked disaccharide **9** in a 65% yield. The α-linkage in **9** was assigned based on the coupling constant ($J_{1,2}$ = 7.2 Hz) of its arabinosyl H-1 signal at δ 4.52 ppm in the ^{1}H NMR spectrum. As the glucosyl residue in the trisaccharyl donor **3** has a glycosidic linkage at the 3-O-position, 1,2;5,6-di-*O*-isopyropylidene-α-D-glucofuranose (**10**), a commercially available inexpensive glucofuranose derivative with a free 3-OH group, was used as a glycosyl acceptor, which can be opened later to form the desired pyranose, for coupling with **9**. The reaction was promoted by N-iodosuccinimide (NIS) in the presence of a catalytic amount of TMSOTf to furnish the desired trisaccharide **11** in a good yield (67%), together with 10% of the corresponding β anomer. Trifluroacetic acid (TFA)-promoted cleavage of the isopropylidene groups in **11** was followed by acetylation with acetic anhydride in pyridine to generate trisaccahride **12** as an α,β-mixture (1:1 ratio) in a 71% overall yield for two steps. Compound **12** was converted into the trisaccharyl donor **3** in two steps (in a 57% overall yield), including (i) regioselective deacetylation of the anomeric position by hydrazine acetate[23] and (ii) trichloroacetimidation[24] of the free anomeric hydroxyl group by trichloroacetonitrile with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the promoter. This reaction afforded primarily the α-anomer. However, the transglycosylation between **3** and **5** in the presence of TMSOTf failed unexpectedly. It was found that aglycon **5** was unstable under the acidic condition involved. Thus, silver triflate (AgOTf) was used as a mild alternative promoter for this reaction,[25] which afforded the desired trisaccharide glycoside **13** in a 64% yield. The coupling constant ($J_{1,2}$ = 8.0 Hz) of the glucosyl H-1 of **13** at δ 4.40 ppm in its ^{1}H NMR spectrum indicated the β-linkage between the glucose residue and the aglycon. Finally, global deprotection was achieved in two steps including catalytic hydrogenolysis to remove the benzyl protection under a H_2 atmosphere in the presence of 10% $Pd(OH)_2$/C and full deacylation with 1 N aq sodium hydroxide in methanol, to afford the target Leonoside E (**1**) in an overall yield of 80%. The structure of **1** was fully characterized by ^{1}H NMR, ^{13}C NMR, and ESI-HRMS spectra.

Leonoside F (**2**) was prepared by a similar strategy, as shown in Scheme 3. First, the reaction between **10** and trichloroacetimidate



Scheme 3. Reagents and conditions: (a) TMSOTf, CH_2Cl_2, 0 °C, 83%; (b) 80% HOAc, 60 °C, 68%; (c) TMSOTf, CH_2Cl_2, 0 °C, 74%; (d) 90% TFA; then Ac_2O, pyridine, 70% (two steps); (e) hydrazine acetate, DMF, 0 °C; then Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 65% (two steps); (f) AgOTf, 4 Å molecular sieves, CH_2Cl_2, −40 °C, 68%; (g) H_2, $Pd(OH)_2$/C, MeOH; then 1 N NaOH, MeOH, 78% (two steps).

14 under the promotion of TMSOTf gave α-(1→3)-linked disaccharide **15** in an 83% yield. The 5,6-*O*-isopropylidene group in **15** was selectively cleaved with 80% HOAc at 60 °C to afford a diol **16** that was directly employed as a glycosyl acceptor. Glycosylation of **16** with 1.1 equiv of trichloroacetimidate donor **17** in anhydrous CH_2Cl_2 at 0 °C under the influence of TMSOTf was regioselective for the more reactive 6-OH group to produce β-(1→6)-linked trisaccharide **18** in a 74% yield. The coupling constant ($J_{1,2}$ = 7.9 Hz) of the glucosyl H-1 of **18** at δ 4.95 ppm in its ^{1}H NMR spectrum confirmed the β-configuration of the newly formed glycosidic linkage. Treatment of **18** with 90% TFA to remove the isopropylidene group followed by acetylation of the product with acetic anhydride in pyridine furnished **19** as an α,β-mixture (3:2 ratio) in a 70% overall yield for two steps. As described above, regioselective deacetylation of the anomeric position of **19** by hydrazine acetate and trichloroacetimidation with trichloroacetonitrile and DBU afforded the trisaccharyl donor **4** in a 65% overall yield for two steps. Next, **4** was coupled with **5** in the presence of silver triflate (0.5 equiv) to produce the fully protected form of Leonoside F (**20**) in a 68% yield. The β-linkage between the glycan and the aglycon was assigned based on the coupling constant ($J_{1,2}$ = 8.0 Hz) of the glucosyl H-1 of **20** at δ 4.14 ppm in its ^{1}H NMR spectrum. Subsequently, **20** was hydrogenolized in methanol under a H_2 atmosphere with 10% $Pd(OH)_2$/C as the catalyst, which was followed by saponification with 1 N aq NaOH in methanol, to give the target molecule **2** in an overall yield of 78% for two steps. The spectrographic data for the synthetic **2** were all fulfilled by its structure.

In summary, two natural phenylethanoid glycosides, Leonoside E (**1**) and Leonoside F (**2**), were synthesized by a highly convergent and efficient strategy. The syntheses were highlighted with the construction of the trisaccharyl trichloroacetimidate donors **3** and **4** first, followed by a tansglycosylation reaction under the influence of silver triflate to directly couple them with the aglycon **5**. The trisaccharide syntheses were significantly facilitated by using a commercially available glucofuranose derivative **10** as one of the building blocks, which was readily converted to glucopyranose later on through ring opening and closing. This intermediate also enabled easily protecting group manipulation and regioselective glycosylation in the presence of more than one free hydroxyl groups in the structure. Clearly, if revised glycans and aglycons were used for the tansglycosylation reaction, the present synthetic strategy could lead to a variety of Leonoside analogs or other phenylethanoid glycosides rapidly for structure–activity relationship studies and other biological applications.

3. Experimental section

3.1. General methods

Optical rotations were determined at 20 °C with a Rudolph Autopol I automatic polarimeter. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 400 spectrometer for solutions in $CDCl_3$ and CD_3OD. Chemical shifts are given in ppm downfield from internal Me_4Si. High-resolution mass spectra were performed by positive-mode electrospray ionization on a JEOL JMS-DX-303HF spectrometer. Thin-layer chromatography (TLC) was performed on the silica gel HF_{254} plate with detection by charring with 30% (v/v) H_2SO_4 in MeOH or by a UV detector. Column chromatography was conducted by elution of a silica gel column with ethyl acetate–petroleum ether (bp 60–90 °C) as the eluents. Solutions were concentrated at <60 °C under diminished pressure.

3.2. Isopropyl 3,4-di-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (7)

A solution of benzoyl chloride (0.8 mL, 6.88 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of isopropyl 4-*O*-benzoyl-1-thio-α-L-rhamnopyranoside **6**[22] (2.0 g, 6.13 mmol) in anhydrous CH_2Cl_2 (40 mL) containing 5 mL of pyridine at −30 °C within 10 min. The reaction mixture was stirred for 1 h with the temperature slowly warmed up to 0 °C, at the end of which time TLC (3:1 petroleum ether–ethyl acetate) indicated the completion of the benzoylation. The mixture was then diluted with CH_2Cl_2 (100 mL), and washed with 1 M aq HCl, water, and brine. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated. The resulting residue was purified by flash column chromatography (3:1 petroleum ether–ethyl acetate) to afford **7** (1.98 g, 75%) as a white foamy solid. $[\alpha]_D^{20}$ −72 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (d, 3H, *J* 6.2 Hz, H-6), 1.37 (d, 2 × 3H, *J* 6.7 Hz, –CH(CH_3)$_2$), 3.13 (m, 1H, –C*H*(CH_3)$_2$), 4.38 (dd, 1H, *J* 1.4, 3.0 Hz, H-2), 4.50 (m, 1H, H-5), 5.41 (d, 1H, *J* 1.4, H-1), 5.51 (dd, 1H, *J* 3.0, 9.8 Hz, H-3), 5.60 (t, 1H, *J* 9.8 Hz, H-4), 7.34–7.93 (m, 10H, *Ph*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.4, 23.6, 23.8, 35.9, 67.2, 71.4, 71.9, 73.1, 83.7, 165.6, 165.9; ESI-HRMS (positive mode): Calcd for ($C_{23}H_{26}O_6S$+NH_4^+): 448.1788; found *m*/*z*: 448.1800.

3.3. Isopropyl 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl-(1→2)-3,4-di-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (9)

To a solution of **7** (630 mg, 1.46 mmol) and 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl trichloroacetimidate **8** (677 mg, 1.61 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C was added TMSOTf (30 μL,

0.165 mmol) under N_2 protection. After the reaction mixture was stirred for 40 min, it was neutralized with triethylamine and concentrated, and the resulting residue was purified by flash column chromatography (3:1 petroleum ether–ethyl acetate) to yield **9** (655 mg, 65%) as a white foamy solid. $[\alpha]_D^{20}$ −3 (*c* 2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (d, 3H, *J* 6.2 Hz, H-6^{Rha}), 1.35, 1.37 (2 d, 2 × 3H, *J* 6.6 Hz, –CH(C*H*$_3$)$_2$), 2.06, 2.15, 2.16 (3 s, 3 × 3H, 3C*H*$_3$CO), 3.14 (m, 1H, –C*H*(CH$_3$)$_2$), 3.51 (dd, 1H, *J* 1.4, 13.0 Hz, H-5a^{Ara}), 4.40 (dd, 1H, *J* 3.0, 13.0 Hz, H-5b^{Ara}), 4.37 (dd, 1H, *J* 1.8, 2.7 Hz, H-2^{Rha}), 4.43 (m, 1H, H-5^{Rha}), 4.52 (d, 1H, *J* 7.1 Hz, H-1^{Ara}), 4.96 (dd, 1H, *J* 3.5, 9.6 Hz, H-3^{Ara}), 5.20 (br s, 1H, H-4^{Ara}), 5.35 (dd, 1H, *J* 7.1, 9.6 Hz, H-2^{Ara}), 5.43 (t, 1H, *J* 10.0 Hz, H-4^{Rha}), 5.49 (d, 1H, *J* 1.8 Hz, H-1^{Rha}), 5.52 (dd, 1H, *J* 2.7, 10.0 Hz, H-3^{Rha}), 7.35-8.00 (m, 10H, *Ph*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.5, 20.7 (2C), 20.9, 23.7, 23.9, 36.4, 63.4, 67.2, 67.7, 69.0, 70.0, 72.0, 72.3, 78.2, 83.4, 102.1, 165.5, 165.7, 169.7, 170.2, 170.4; ESI-HRMS (positive mode): Calcd for ($C_{34}H_{40}O_{13}S$+NH_4^+): 706.2528; found *m*/*z*: 706.2537.

3.4. 2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl-(1→2)-3,4-di-*O*-benzoyl-α-L-rhamnopyranosyl-(1→3)-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (11)

To a solution of **9** (613 mg, 0.89 mmol) and 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose **10** (232 mg, 0.89 mmol) in anhydrous CH_2Cl_2 (8 mL) was added NIS (300 mg, 1.34 mmol) and a catalytic amount of TMSOTf (18 μL, 0.1 mmol) at −10 °C under N_2 protection. The reaction mixture was stirred for 40 min, at end of which time TLC (2:1 petroleum ether–ethyl acetate) indicated the complete disappearance of **9**. The reaction mixture was neutralized with triethylamine and concentrated, and the residue was purified by flash column chromatography (2:1 petroleum ether–ethyl acetate) to yield **11** (520 mg, 67%) as a white foamy solid. $[\alpha]_D^{20}$ −4 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (d, 3H, *J* 6.0 Hz, H-6^{Rha}), 1.34, 1.41, 1.52 (3 s, 4 × 3H, C(C*H*$_3$)$_2$), 2.06, 2.16, 2.20 (3 s, 3 × 3H, 3C*H*$_3$CO), 3.52 (dd, 1H, *J* 1.2, 13.0 Hz, H-5a^{Ara}), 3.96-4.08 (m, 2H, H-6a^{Glu}, H-5b^{Ara}), 4.15 (dd, 1H, *J* 3.2, 9.0 Hz, H-4^{Glu}), 4.22–4.28 (m, 2H, H-5,6b^{Glu}), 4.43-4.51 (m, 3H, H-2,5^{Rha}, H-3^{Glu}), 4.52-4.56 (m, 2H, H-1^{Ara}, H-2^{Glu}), 4.97 (dd, 1H, *J* 3.5, 9.6 Hz, H-3^{Ara}), 5.11 (d, 1H, *J* 1.2 Hz, H-1^{Rha}), 5.20 (br s, 1H, H-4^{Ara}), 5.34 (dd, 1H, *J* 7.1, 9.6 Hz, H-2^{Ara}), 5.43 (t, 1H, *J* 10.0 Hz, H-4^{Rha}), 5.57 (dd, 1H, *J* 3.0, 10.0 Hz, H-3^{Rha}), 5.92 (d, 1H, *J* 3.6 Hz, H-1^{Glu}), 7.32–8.00 (m, 10H, *Ph*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 20.7, 20.8, 20.9, 25.4, 26.3, 26.8 (2C), 63.3, 67.0, 67.6, 68.3, 68.9, 70.0, 71.5, 71.8, 71.9, 75.9, 76.6, 81.1, 81.9, 96.4, 101.9, 105.3, 109.3, 112.0, 165.5, 165.7, 169.6, 170.2, 170.4; ESI-HRMS (positive ion): Calcd for ($C_{43}H_{52}O_{19}$+NH_4^+): 890.3441; found *m*/*z*: 890.3451.

3.5. 2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl-(1→2)-3,4-di-*O*-benzoyl-α-L-rhamnopyranosyl-(1→3)-1,2,4,6-tetra-*O*-acetyl-D-glucopyranose (12)

A solution of **11** (472 mg, 0.54 mmol) in 90% aq TFA (10 mL) was stirred at rt for 1 h. The reaction mixture was then co-evaporated with toluene (2 × 30 mL), and the resulting residue was dissolved into pyridine (5 mL) and acetic anhydride (3 mL). The reaction mixture was stirred overnight at rt, and then concentrated under diminished pressure. The resulting residue was purified by flash column chromatography (2:1 petroleum ether–ethyl acetate) to yield **12** (369 mg, α/β isomer ≈ 1:1, 71%) as a white foamy solid. $[\alpha]_D^{20}$ +36 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) for α isomer: δ 1.28 (d, 1H, *J* 6.2 Hz, H-6^{Rha}), 2.06, 2.09, 2.12, 2.13, 2.15, 2.18, 2.21 (7 s, 7 × 3H, 7C*H*$_3$CO), 3.48 (dd, 1H, *J* 1.2, 12.1 Hz, H-5a^{Ara}), 3.90 (dd, 1H, *J* 3.0, 12.1 Hz, H-5b^{Ara}), 3.98–4.12 (m, 3H, H-5^{Rha}, H-5,6a^{Glu}), 4.22–4.28 (m, 3H, H-2^{Rha}, H-3,6b^{Glu}), 4.50 (d, 1H, *J* 7.1 Hz, H-1^{Ara}), 4.93 (dd, 1H, *J* 3.5, 9.6 Hz, H-3^{Ara}), 5.13 (dd, 1H, *J* 3.6, 10.0 Hz, H-2^{Glu}), 5.19 (br s, 2H, H-1^{Rha}, H-4^{Ara}), 5.24 (t, 1H, *J* 10.0 Hz, H-4^{Glu}), 5.29 (dd, 1H, *J* 7.1, 9.6 Hz, H-2^{Ara}), 5.38 (t, 1H, *J* 10.2 Hz, H-4^{Rha}), 5.44 (dd, 1H, *J* 2.7, 10.2 Hz, H-3^{Rha}), 6.34 (d, 1H, *J* 3.6 Hz, H-1^{Glu}), 7.35–7.96 (m, 10H, *Ph*); ESI-HRMS (positive ion): Calcd for ($C_{45}H_{52}O_{23}$+NH_4^+): 978.3238; found *m*/*z*: 978.3247.

3.6. 2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl-(1→2)-3,4-di-*O*-benzoyl-α-L-rhamnopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-D-glucopyranosyl trichloroacetimidate (3)

To a solution of **12** (336 mg, 0.35 mmol) in DMF (5 mL) was added hydrazine acetate (64 mg, 0.70 mmol) at 0 °C. The reaction mixture was stirred for 2 h under this condition, when TLC (2:1 petroleum ether–ethyl acetate) indicated the completion of the reaction. The reaction mixture was diluted with EtOAc (40 mL), and washed successively with water (30 mL) and brine (30 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated, and the residue was then subjected to silica gel column chromatography (1:1 petroleum ether–EtOAc). The resultant product was dissolved in anhydrous CH_2Cl_2 (5 mL), and then to the solution was added trichloroacetonitrile (0.14 mL, 1.4 mmol) and DBU (20 μL) at 0 °C. The mixture was stirred for 1.5 h and concentrated, and the residue was purified by flash column chromatography (2:1 petroleum ether–ethyl acetate) to afford **3** (212 mg, 57% for two steps) as a white foamy solid. $[\alpha]_D^{20}$ +65 (*c* 2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (d, 3H, *J* 6.2 Hz, H-6^{Rha}), 2.05, 2.09, 2.10, 2.12, 2.17, 2.20 (6 s, 6 × 3H, 6C*H*$_3$CO), 3.49 (dd, 1H, *J* 1.0, 13.0 Hz, H-5a^{Ara}), 3.91 (dd, 1H, *J* 3.0, 13.0 Hz, H-5b^{Ara}), 4.03 (m, 1H, H-5^{Rha}), 4.09–4.18 (m, 2H, H-5,6a^{Glu}), 4.22–4.30 (m, 2H, H-2^{Rha}, h-6b^{Glu}), 4.33 (t, 1H, *J* 9.6 Hz, H-3^{Glu}), 4.49 (d, 1H, *J* 7.0 Hz, H-1^{Ara}), 4.93 (dd, 1H, *J* 3.5, 9.6 Hz, H-3^{Ara}), 5.16 (dd, 1H, *J* 3.6, 9.6 Hz, H-2^{Glu}), 5.18–5.21 (m, 1H, H-4^{Ara}), 5.23 (d, 1H, *J* 1.8 Hz, H-1^{Rha}), 5.28 (t, 1H, *J* 9.6 Hz, H-4^{Glu}), 5.30 (dd, 1H, *J* 7.0, 9.6 Hz, H-2^{Ara}), 5.39 (t, 1H, *J* 10.0 Hz, H-4^{Rha}), 5.46 (dd, 1H, *J* 2.8, 10.0 Hz, H-3^{Rha}), 6.57 (d, 1H, *J* 3.6 Hz, H-1^{Glu}), 7.32–8.01 (m, 10H, *Ph*), 8.70 (s, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.6, 20.2, 20.7 (2C), 20.8, 20.9, 21.0, 61.5, 63.3, 67.6 (2C), 68.2, 68.9, 69.9, 70.5, 71.3, 71.4, 72.2, 75.4, 75.5, 90.8, 93.2, 100.3, 101.9, 160.7, 165.5 (2C), 169.3, 169.7, 169.8, 170.1, 170.2, 170.7; Anal. Calcd for $C_{45}H_{50}Cl_3NO_{22}$: C, 50.83; H, 4.74; N, 1.32. Found: C, 50.85; H, 4.48; N, 1.40.

3.7. 3-Methoxyl-4-benzoxylphenylethyl 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl-(1→2)-3,4-di-*O*-benzoyl-α-L-rhamnopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-β-D-glucopyranoside (13)

To a solution of **3** (75 mg, 0.07 mmol) and 3-methoxyl-4-benzoxylphenylethanol **5** (18 mg, 0.07 mmol) in anhydrous CH_2Cl_2 (3 mL) was added 4Å molecular sieves (50 mg). The reaction mixture was stirred at rt for 30 min under a N_2 atmosphere, and then cooled to −40 °C. Silver triflate (10 mg, 0.04 mmol) was added in the dark. The reaction mixture was stirred for 2 h while it was slowly warmed up to 0 °C, neutralized with triethylamine, and concentrated. Purification of the resulting residue on a silica gel column using 3:2 petroleum ether–EtOAc as the eluents gave **13** (52 mg, 64%) as a white foamy solid. $[\alpha]_D^{20}$ +24 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (d, 3H, *J* 6.2 Hz, H-6^{Rha}), 1.93, 2.05, 2.10, 2.11, 2.13, 2.18 (6 s, 6 × 3H, 6C*H*$_3$CO), 2.82 (t, 2H, *J* 6.6 Hz, –OCH$_2$C*H*$_2$–), 3.48 (dd, 1H, *J* 1.2, 13.0 Hz, H-5a^{Ara}), 3.56–3.65 (m, 2H, H-5^{Glu}, –OC*H*$_2$CH$_2$–), 3.90 (s, 3H, –OC*H*$_3$), 3.89–3.95 (m, 2H, H-3^{Glu}, H-5b^{Ara}), 4.00 (m, 1H, H-5^{Rha}), 4.08–4.18 (m, 3H, H-6a^{Glu}, H-2^{Rha}, –OC*H*$_2$CH$_2$–), 4.25 (dd, 1H, *J* 4.8, 12.3 Hz, H-6b^{Glu}), 4.40 (d, 1H, *J* 8.0 Hz, H-1^{Glu}), 4.46 (d, 1H, *J* 7.2 Hz, H-1^{Ara}), 4.92 (dd, 1H, *J* 3.5, 9.6 Hz, H-3^{Ara}), 5.05 (d, 1H, *J* 1.7 Hz, H-1^{Rha}), 5.08 (dd, 1H, *J* 8.0, 9.6 Hz, H-2^{Glu}), 5.13 (s, 2H, -OC*H*$_2$Ph), 5.15 (t, 1H, *J* 9.6 Hz, H-4^{Glu}), 5.19 (m, 1H, H-4^{Ara}), 5.28 (dd, 1H, *J* 7.2, 9.6 Hz, H-

2^{Ara}), 5.35 (t, 1H, *J* 10.0 Hz, H-4^{Rha}), 5.41 (dd, 1H, *J* 2.8, 10.0 Hz, H-3^{Rha}), 6.66 (dd, 1H, *J* 1.8, 8.2 Hz, *Ph*), 6.76 (d, 1H, *J* 1.8 Hz, *Ph*), 6.80 (d, 1H, *J* 8.2 Hz, *Ph*), 7.26–7.97 (m, 10H, *Ph*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.5, 20.4, 20.7, 20.8, 20.9 (2C), 21.1, 35.6, 56.0, 62.1, 63.3, 67.5, 67.6, 68.9, 69.3, 70.0, 70.7, 71.1, 71.3 (2C), 72.1, 72.5, 75.6, 78.7, 100.2, 100.9, 101.9, 113.1, 114.1, 120.7, 146.6, 149.4, 165.4, 165.5, 169.2, 169.4, 169.7, 170.2 (2C), 170.8; ESI-HRMS (positive ion): Calcd for ($C_{59}H_{66}O_{24}$+NH_4^+): 1176.4282; found *m*/*z*: 1176.4284.

3.8. Leonoside E (1)

To a solution of **13** (38 mg, 0.033 mmol) in MeOH (5 mL) was added 10% $Pd(OH)_2$/C (10 mg), and the resulting suspension was stirred under H_2 atmosphere at rt overnight. The solid materials were filtrated off, and the solution was concentrated. The resulting product was then re-dissolved in MeOH (5 mL), to which was added 1 N aq NaOH dropwise until pH 10 was reached. The reaction mixture was stirred at rt for 3 h, and then neutralized with Amberlite IR 120 (H^+). The reaction solution was filtered off and concentrated. The resulting residue was purified by flash column chromatography (3:1 CH_2Cl_2–MeOH) to afford **1** (16 mg, 80%) as a white solid. $[\alpha]_D^{20}$ −19 (*c* 0.12, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 1.25 (d, 3H, *J* 6.2 Hz, H-6^{Rha}), 2.86 (br t, 2H, *J* 7.0 Hz, –OCH_2CH_2–), 3.27–3.34 (m, 2H), 3.35 (t, 1H, *J* 9.7 Hz), 3.41 (t, 1H, *J* 9.6 Hz), 3.48 (t, 1H, *J* 8.8 Hz), 3.53 (dd, 1H, *J* 3.5, 9.3 Hz), 3.56 (dd, 1H, *J* 1.2, 10.7 Hz), 3.65 (dd, 1H, *J* 7.2, 9.2 Hz), 3.69 (dd, 1H, *J* 5.4, 11.9 Hz), 3.72–3.80 (m, 3H), 3.86 (s, 3H, –OCH_3), 3.86–3.91 (m, 2H), 3.95–4.02 (m, 2H), 4.07 (m, 1H, –OCH_2CH_2–), 4.32 (d, 1H, *J* 7.9 Hz, H-1^{Glu}), 4.37 (d, 1H, *J* 7.2 Hz, H-1^{Ara}), 5.46 (d, 1H, *J* 1.3 Hz, H-1^{Rha}), 6.70 (m, 2H), 6.87 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 16.5, 35.4, 55.0, 61.3, 65.8, 68.4, 68.6, 68.8, 70.6, 70.8, 71.5, 73.0 (2C), 74.1, 76.5, 81.1, 83.5, 100.3, 102.8, 106.0, 112.4, 114.7, 121.0, 130.2, 144.5, 147.4; ESI-HRMS (positive ion): Calcd for ($C_{26}H_{40}O_{16}$+Na^+): 631.2209; found *m*/*z*: 631.2211.

3.9. 2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (15)

To a solution of 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate **14** (736 mg, 1.69 mmol) and **10** (400 mg, 1.54 mmol) in anhydrous CH_2Cl_2 (8 mL) at 0 °C was added TMSOTf (31 μL, 0.17 mmol) under N_2 protection. The reaction mixture was stirred for 1 h, then neutralized with Et_3N, and concentrated. The resulting residue was purified by flash column chromatography (2:1 petroleum ether–ethyl acetate) to yield **15** (679 mg, 83%) as a white foamy solid. $[\alpha]_D^{20}$ −58 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (d, 3H, *J* 6.2 Hz, H-6^{Rha}), 1.31, 1.35, 1.40, 1.50 (4 s, 4 × 3H, $C(CH_3)_2$), 2.03, 2.17 (3 s, 3 × 3H, $3CH_3CO$), 3.95 (dd, 1H, *J* 5.9, 8.5 Hz, H-$6a^{Glu}$), 4.10 (dd, 1H, *J* 3.3, 9.0 Hz, H-4^{Glu}), 4.19 (dd, 1H, *J* 6.1, 8.5 Hz, H-$6b^{Glu}$), 4.26–4.36 (m, 3H, H-$3,5^{Glu}$, H-5^{Rha}), 4.50 (d, 1H, *J* 3.7 Hz, H-2^{Glu}), 4.91 (d, 1H, *J* 1.2 Hz, H-1^{Rha}), 5.08 (t, 1H, *J* 9.8 Hz, H-4^{Rha}), 5.20 (dd, 1H, *J* 1.2, 3.4 Hz, H-2^{Rha}), 5.23 (dd, 1H, *J* 3.4, 9.8 Hz, H-3^{Rha}), 5.91 (d, 1H, *J* 3.7 Hz, H-1^{Glu}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.0, 20.6, 20.7, 20.8, 25.9, 26.4, 64.0, 66.9, 68.0, 69.0, 69.9, 70.6, 77.6, 79.0, 81.4, 95.0, 104.9, 111.6, 169.9 (2C), 170.1; ESI-HRMS (positive ion): Calcd for ($C_{24}H_{36}O_{13}$+NH_4^+): 550.2494; found *m*/*z*:550.2491.

3.10. 2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-1,2-*O*-isopropylidene-α-D-glucofuranose (16)

A solution of **15** (602 mg, 1.13 mmol) in 80% aq acetic acid (15 mL) was stirred at 60 °C for 2 h. The reaction mixture was co-evaporated with toluene (2 × 20 mL) to dryness. Purification of the resulting residue on a silica gel column using 1:1 petroleum ether–EtOAc as the eluents gave **16** (378 mg, 68%) as a white foamy solid. $[\alpha]_D^{20}$ −51 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (d, 3H, *J* 6.2 Hz, H-6^{Rha}), 1.31, 1.49 (2 s, 2 × 3H, $C(CH_3)_2$), 1.99, 2.04, 2.16 (3 s, 3 × 3H, $3CH_3CO$), 3.79 (dd, 1H, *J* 5.2, 11.2 Hz, H-$6a^{Glu}$), 3.92 (dd, 1H, *J* 3.2, 11.2 Hz, H-$6b^{Glu}$), 3.95–4.00 (m, 1H, H-5^{Glu}), 4.16–4.25 (m, 2H, H-4^{Glu}, H-5^{Rha}), 4.37 (d, 1H, *J* 3.0 Hz, H-3^{Glu}), 4.52 (d, 1H, *J* 3.7 Hz, H-2^{Glu}), 4.92 (d, 1H, *J* 1.4 Hz, H-1^{Rha}), 5.07 (t, 1H, *J* 9.8 Hz, H-4^{Rha}), 5.20 (dd, 1H, *J* 1.2, 3.4 Hz, H-2^{Rha}), 5.23 (dd, 1H, *J* 3.4, 9.8 Hz, H-3^{Rha}), 5.91 (d, 1H, *J* 3.7 Hz, H-1^{Glu}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 20.7, 20.8, 20.9, 26.1, 26.5, 64.2, 67.1, 68.1, 69.0, 70.0, 70.7, 78.0, 79.2, 81.6, 95.3, 104.9, 111.8, 170.0, 170.1, 170.3; ESI-HRMS (positive ion): Calcd for ($C_{21}H_{32}O_{13}$+NH_4^+): 510.2181; found *m*/*z*: 510.2180.

3.11. 2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-[2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)]-1,2-*O*-isopropylidene-α-D-glucofuranose (18)

To a solution of **16** (350 mg, 0.71 mmol) and 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate **17** (580 mg, 0.78 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was added TMSOTf (14 μL, 0.08 mmol) under N_2 protection. The reaction mixture was stirred for 1 h, neutralized by triethylamine, and then concentrated. The resulting residue was purified by flash column chromatography (1:1 petroleum ether–ethyl acetate) to yield **18** (563 mg, 74%) as a white foamy solid. $[\alpha]_D^{20}$ −10 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, 3H, *J* = 6.2 Hz, H-6^{Rha}), 1.26, 1.30 (2 s, 2 × 3H, $C(CH_3)_2$), 1.97, 2.01, 2.15 (3 s, 3 × 3H, $3CH_3CO$), 3.92 (dd, 1H, *J* 4.8, 10.6 Hz, H-$6a^{Glu}$), 3.92 (m, 1H, H-5^{Glu}), 4.07–4.15 (m, 2H, H-$6b^{Glu}$, H-5^{Glu}), 4.17–4.25 (m, 2H, H-4^{Glu}, H-5^{Rha}), 4.31 (d, 1H, *J* 3.5 Hz, H-3^{Glu}), 4.44 (dd, 1H, *J* 4.6, 12.2 Hz, H-$6a^{Glu}$), 4.45 (d, 1H, *J* 3.6 Hz, H-2^{Glu}), 4.74 (dd, 1H, *J* 3.0, 12.2 Hz, H-$6b^{Glu}$), 4.88 (s, 1H, H-1^{Rha}), 4.95 (d, 1H, *J* 7.9 Hz, H-1^{Glu}), 5.07 (t, 1H, *J* 9.8 Hz, H-4^{Rha}), 5.17–5.23 (m, 2H, H-$2,3^{Rha}$), 5.53 (dd, 1H, *J* 7.9, 9.7 Hz, H-2^{Glu}), 5.70 (t, 1H, *J* 9.7 Hz, H-4^{Glu}), 5.82 (d, 1H, *J* 3.6 Hz, H-1^{Glu}), 5.90 (t, 1H, *J* 9.7 Hz, H-3^{Glu}), 7.35-8.06 (m, 20H, *Ph*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 20.6, 20.7, 20.9, 26.2, 26.6, 62.7, 66.7, 67.0, 69.1, 69.4, 70.1, 70.6, 72.1, 72.3, 72.4, 72.9, 77.4, 78.9, 81.5, 95.2, 101.4, 105.0, 111.9, 165.1, 165.2, 165.7, 166.0, 169.8, 169.9, 170.1; ESI-HRMS (positive ion): Calcd for ($C_{55}H_{58}O_{22}$+NH_4^+): 1088.3758; found *m*/*z*: 1088.3762.

3.12. 2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-[2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)]-1,2,4-tri-*O*-acetyl-D-glucopyranose (19)

After a solution of **18** (493 mg, 0.46 mmol) in 90% aq TFA (10 mL) was stirred at rt for 1 h, the reaction mixture was co-evaporated with toluene (2 × 30 mL). The resulting residue was dissolved in pyridine (5 mL) and acetic anhydride (3 mL), and the mixture was stirred at rt overnight and then concentrated. The resulting residue was purified by flash column chromatography (2:1 petroleum ether–ethyl acetate) to yield **19** (373 mg, α/β isomer ≈ 3:2, 70%) as a white foamy solid. $[\alpha]_D^{20}$ +18 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, 1.2H, *J* 6.2 Hz, H-6^{Rha} of β isomer), 1.13 (d, 1.8H, *J* 6.2 Hz, H-6^{Rha} of α isomer), 1.89 (s, 1.8H), 1.95 (s, 3H), 1.99 (s, 1.2H), 2.04 (s, 2.4H), 2.05 (s, 1.8H), 2.06 (s, 3.6H), 2.11 (s, 1.2H), 2.13 (s, 3H), 3.60-3.73 (m, 1.8H), 3.75-3.91 (m, 1H), 3.85-3.96 (m, 2.2H), 4.09-4.18 (m, 1H), 4.45–4.51 (m, 1H, H-$6a^{Glu'}$), 4.60–4.66 (m, 1H, H-$6b^{Glu'}$), 4.71 (d, 0.4H, *J* 1.3 Hz, H-1^{Rha} of β isomer), 4.79 (d, 0.6H, *J* 1.8 Hz, H-1^{Rha} of α isomer), 4.81–5.07 (m, 5.4H, H-$1^{Glu'}$, H-$2,3,4^{Glu}$, H-$3,4^{Rha}$, H-2^{Rha} of β isomer), 5.11 (dd, 0.6H, *J* 1.8, 2.6 Hz, H-2^{Rha} of α isomer), 5.46–5.54 (m, 1.4H, H-1 of β isomer and H-$2^{Glu'}$), 5.64 (t, 0.4H, *J* 9.6 Hz, H-$4^{Glu'}$ of β isomer), 5.67 (t, 0.6H, *J* 9.6 Hz, H-$4^{Glu'}$ of α isomer), 5.88 (t, 0.4H, *J* 9.6 Hz, H-$3^{Glu'}$ of β isomer), 5.89 (t, 0.6H, *J* 9.6 Hz, H-$3^{Glu'}$ of α isomer), 6.14 (d, 0.6H, *J* 3.6 Hz, H-1^{Glu} of α isomer), 7.26–

8.02 (m, 20H, *Ph*); ESI-HRMS (positive ion): Calcd for ($C_{58}H_{60}O_{25}$+-NH_4^+): 1174.3762; found *m*/*z*: 1174.3765.

3.13. 2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-[2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)]-2,4-di-*O*-acetyl-D-glucopyranosyl trichloroacetimidate (4)

To a solution of **19** (350 mg, 0.30 mmol) in DMF (5 mL) at 0 °C was added hydrazine acetate (55 mg, 0.60 mmol). The reaction mixture was stirred at 0 °C for 2 h, when TLC (2:1 petroleum ether–ethyl acetate) indicated the completion of the reaction. The reaction mixture was diluted with EtOAc (50 mL), and washed successively with water (30 mL) and brine (30 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated, and the residue was subjected to silica gel column chromatography (1:1 petroleum ether–EtOAc). The product above was dissolved in anhydrous CH_2Cl_2 (5 mL), and to the solution was added trichloroacetonitrile (0.2 mL, 2.0 mmol) and DBU (20 μL) at 0 °C. The mixture was stirred for 2 h and concentrated. The resulting residue was purified by flash column chromatography (2:1 petroleum ether–ethyl acetate) to afford **4** (248 mg, 65% for two steps) as a white foamy solid. $[\alpha]_D^{20}$ +21 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (d, 3H, *J* 6.2 Hz, H-6^{Rha}), 1.96, 2.06, 2.13 (3 s, 5 × 3H, 5C*H*$_3$CO), 3.68 (dd, 1H, *J* 6.5, 11.6 Hz, H-6a^{Glu}), 3.79 (m, 1H, H-5^{Glu}), 3.92 (br d, 1H, *J* 11.6 Hz, H-6b^{Glu}), 3.98–4.08 (m, 2H, H-3,5$^{Glu'}$), 4.15 (m, 1H, H-5^{Rha}), 4.49 (dd, 1H, *J* 5.2, 12.1 Hz, H-6a$^{Glu'}$), 4.64 (dd, 1H, *J* 2.4, 12.1 Hz, H-6b$^{Glu'}$), 4.81-4.85 (br s, 2H, H-2^{Glu}, H-1^{Rha}), 4.90 (t, 1H, *J* 9.8 Hz, H-4^{Glu}), 4.95 (d, 1H, *J* 7.8 Hz, H-1$^{Glu'}$), 5.02 (t, 1H, *J* 10.0 Hz, H-4^{Rha}), 5.07 (dd, 1H, *J* 3.0, 10.0 Hz, H-3^{Rha}), 5.13 (br s, 1H, H-2^{Rha}), 5.49 (dd, 1H, *J* 7.8, 9.6 Hz, H-2$^{Glu'}$), 5.64 (t, 1H, *J* 9.6 Hz, H-4$^{Glu'}$), 5.86 (t, 1H, *J* 9.6 Hz, H-3$^{Glu'}$), 6.36 (d, 1H, *J* 3.1 Hz, H-1^{Glu}), 7.32-8.05 (m, 20H, *Ph*), 8.40 (s, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 20.3, 20.7, 20.8, 20.9, 21.0, 63.0, 65.6, 67.4, 68.2, 69.3, 69.6, 69.7, 70.5, 71.3, 71.7, 71.8, 72.3, 72.8, 77.8, 91.0, 92.7, 99.5, 100.7, 160.4, 165.1, 165.2, 165.8, 166.1, 169.6, 169.7, 170.0 (2C), 170.1; Anal. Calcd for $C_{58}H_{58}Cl_3NO_{24}$: C, 55.31; H, 4.64; N, 1.11. Found: C, 55.24; H, 4.81; N, 1.02.

3.14. 3-Methoxyl-4-benzoxylphenylethyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-[2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)]-2,4-di-*O*-acetyl-β-D-glucopyranoside (20)

To a solution of **4** (82 mg, 0.065 mmol) and **5** (16 mg, 0.062 mmol) in anhydrous CH_2Cl_2 (5 mL) was added 4Å molecular sieves (60 mg). The reaction mixture was stirred at rt for 30 min under a N_2 atmosphere, and then cooled to −40 °C. Silver triflate (11 mg, 0.04 mmol) was added in the dark. The reaction mixture was stirred for 2 h while it was slowly warmed up to 0 °C, then neutralized with triethylamine and concentrated. Purification of the resulting residue on a silica gel column using 3:2 petroleum ether–EtOAc as the eluents afforded **20** (57 mg, 68%) as a white foamy solid. $[\alpha]_D^{20}$ −1 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, 3H, *J* 6.2 Hz, H-6^{Rha}), 1.88, 1.94, 2.01, 2.02, 2.11 (5 s, 5 × 3H, 5C*H*$_3$CO), 2.52 (m, 2H, −OCH$_2$C*H*$_2$−), 3.24 (m, 1H, −OC*H*$_2$-CH$_2$−), 3.51 (m, 1H, H-5^{Glu}), 3.61 (t, 1H, *J* 9.6 Hz, H-3^{Glu}), 3.66 (br d, 1H, *J* 11.2 Hz, H-6a^{Glu}), 3.73 (m, 1H, –OC*H*$_2$CH$_2$–), 3.80 (m, 1H, H-5$^{Glu'}$), 3.86 (dd, 1H, *J* 2.0, 11.2 Hz, H-6b^{Glu}), 3.89 (s, 3H, -OC*H*$_3$), 4.13 (m, 1H, H-5^{Rha}), 4.14 (d, 1H, *J* 8.0 Hz, H-1^{Glu}), 4.47 (dd, 1H, *J* 5.4, 12.2 Hz, H-6a$^{Glu'}$), 4.64 (dd, 1H, *J* 3.0, 12.1 Hz, H-6b$^{Glu'}$), 4.70 (d, 1H, *J* 1.7 Hz, H-1^{Rha}), 4.77 (t, 1H, *J* 9.6 Hz, H-4^{Glu}), 4.88 (dd, 1H, *J* 8.0, 9.6 Hz, H-2^{Glu}), 4.91 (d, 1H, *J* 7.8 Hz, H-1$^{Glu'}$), 4.98 (t, 1H, *J* 9.8 Hz, H-4^{Rha}), 5.00-5.06 (m, 2H, H-2,3^{Rha}), 5.05 (s, 2H, –OC*H*$_2$Ph), 5.49 (dd, 1H, *J* 7.8, 9.6 Hz, H-2$^{Glu'}$), 5.66 (t, 1H, *J* 9.6 Hz, H-4$^{Glu'}$), 5.88 (t, 1H, *J* 9.6 Hz, H-3$^{Glu'}$), 6.58 (dd, 1H, *J* 1.8, 8.2 Hz, *Ph*), 6.68 (d, 1H, *J* 1.8 Hz, *Ph*), 6.79 (d, 1H, *J* 8.2 Hz, *Ph*), 7.24–8.06 (m, 25H, *Ph*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 20.5, 20.6, 20.8, 20.9, 21.0, 35.4, 56.0, 63.0, 65.3, 67.4, 68.8, 69.5, 69.8, 70.2, 70.3, 70.6, 71.1, 71.5, 71.9, 72.3, 72.8, 73.6, 81.2, 99.4, 100.5, 101.3, 113.2, 114.3, 120.7, 146.4, 149.5, 165.0, 165.2, 165.7, 166.1, 169.3, 169.5, 169.8, 170.0, 170.1; ESI-HRMS (positive ion): Calcd for ($C_{72}H_{74}O_{26}$+NH_4^+): 1372.4807; found *m*/*z*: 1372.4840.

3.15. Leonoside F (2)

To a solution of **20** (33 mg, 0.024 mmol) in MeOH (4 mL) was added 10% $Pd(OH)_2$/C (8 mg), and the resulting suspension was stirred under H_2 atmosphere at rt overnight. The solid materials were filtrated off, and the solution was concentrated. The resultant product was re-dissolved in MeOH (5 mL), to which was added 1 N aq NaOH dropwise until pH 10 was reached. The reaction mixture was stirred at rt for 3 h and neutralized with Amberlite IR 120 (H^+). The reaction solution was filtered and concentrated. The resulting residue was purified by flash column chromatography (3:1 CH_2Cl_2–MeOH) to afford **2** (12 mg, 78%) as a white solid. $[\alpha]_D^{20}$ −39 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 1.26 (d, 3H, *J* 6.2 Hz, H-6^{Rha}), 2.86 (br t, 2H, *J* 7.2 Hz, –OCH$_2$C*H*$_2$–), 3.23 (t, 1H, *J* 8.4 Hz), 3.26–3.38 (m, 4H), 3.41 (t, 1H, *J* 9.6 Hz), 3.45–3.52 (m, 3H), 3.68 (dd, 1H, *J* 5.4, 12.0 Hz), 3.72 (dd, 1H, *J* 3.4, 9.6 Hz, H-3^{Rha}), 3.77 (m, 1H), 3.82 (dd, 1H, *J* 4.6, 11.5 Hz, H-6), 3.86 (s, 3H, –OC*H*$_3$), 3.88 (dd, 1H, *J* 2.0, 12.0 Hz, H-6), 3.95 (dd, 1H, *J* 1.4, 3.3 Hz, H-2^{Rha}), 3.98–4.10 (m, 2H), 4.17 (dd, 1H, *J* 1.1, 10.9 Hz, H-6), 4.33 (d, 1H, *J* 7.9 Hz, H-1^{Glu}), 4.38 (d, 1H, *J* 7.7 Hz, H-1$^{Glu'}$), 5.18 (d, 1H, *J* 1.4 Hz, H-1^{Rha}), 6.67–6.73 (m, 2H), 6.87 (br s, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 16.5, 35.3, 55.1, 61.4, 68.4, 68.6 (2C), 70.2, 70.8, 70.9, 71.0, 72.6, 73.7, 74.3, 75.6, 76.6 (2C), 82.8, 101.3, 102.9, 103.5, 112.4, 114.7, 121.0, 130.2, 144.6, 147.5; ESI-HRMS (positive ion): Calcd for ($C_{27}H_{42}O_{17}$+Na^+): 661.2314; found *m*/*z*: 661.2313.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2013.07.012.

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