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Concise synthesis of two natural triterpenoid saponins, oleanolic acid derivatives isolated from the roots of *Pulsatilla chinensis*

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ABSTRACT

The first synthesis of two natural triterpenoid saponins, which were isolated from the roots of *Pulsatilla chinensis* and exhibited excellent in vitro cytotoxic activity against HL-60 cells, was concisely achieved in a convergent approach. We employed an odourless 2-methyl-5-*tert*-butylphenyl (Mbp) thioglycoside and trichloroacetimidate donors in one-pot reaction as a key step.

1. Introduction

Triterpenoid saponins, which are widely distributed in plants and in some marine organisms,[1–4] have been reported to present a broad spectrum of well-defined biological and pharmacological activities, including anti-tumour,[5–12] anti-inflammatory,[13] anti-fungal,[14–16] and anti-HIV.[17–19] Attracted by these interesting biological activities, several research groups have reported on the synthesis of many oleanane-type triterpenoid saponins.[20–28] Notably, the synthesis of β-hederin, hederacolchiside A_1 and its anologues with prominent anti-tumour activity were reported by Cheng and co-workers.[29,30] Recently, we were attracted by two naturally occurring oleanane-type triterpenoid saponins: 3-*O*-[β-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]oleanolic acid (**1**), and, 3-*O*-{β-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→4)]-α-L-arabinopyranosyl}oleanolic acid (**2**) (Fig. 1), which were isolated from the roots of *Pulsatilla chinensis* by Sashida and co-workers.[31] These triterpenoid saponins show prominent cytotoxic activity against HL-60 cells with an IC_{50} of 2.6 and 2.7 μg/mL, respectively.[31] Herein, we report the synthesis of the two natural saponins.

2. Results and discussion

The development of various glycosylation methods and sophisticated approaches using protecting group manipulations, especially the development of a 'one-pot sequential glycosylation' strategy, has greatly facilitated the synthesis of oligosaccharides and glycoconjugates bearing complicated sugar moieties.[32–41] By applying the 'one-pot sequential glycosylation' procedure, Yu and co-workers have successfully completed the synthesis of a group of natural dioscins and a bidesmosidic triterpene saponin.[42–44] However, thiols (such as thioethanol, thiophenol and thiocresol) utilized as precursors all have a repulsive smell, even far below toxic concentrations. Recently, Mallet and co-workers have successfully used the novel 2-methyl-5-*tert*-butylphenyl (Mbp) thioglycosides as odourless precursors for oligosaccharide synthesis.[45] In light of these considerations, we decided to adopt the 'one-pot sequential glycosylation' strategy with the combined use of Mbp thioglycosides and trichloroacetimidates as donors to complete the synthesis of the target molecules.

The glycosyl donors involved in the synthesis are shown in Scheme 1. Glycosyl trichloroacetimidates **3**[46,47] and **4**[48] were readily prepared in good yields from the corresponding 1-OH sugars. In our strategy, thioglycoside **8**, a latent glycosyl donor for the next glycosylation, was prepared from 1,2,3,4-tetra-*O*-acetyl-α,β-L-rhamnopyranoside (**5**),[49] in which the anomeric acetate group was replaced by the MbpS group in the presence of $BF_3{\cdot}OEt_2$, followed by deprotection of the hydroxyl groups to afford 2-methyl-5-*tert*-butylphenyl 1-thio-α-L-rhamnopyranoside (**7**) in an excellent yield. Then according to the simple one-pot strategy,[50] treatment of **7** with triethylorthoacetate and a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) formed the corresponding orthoesters, which were directly acetylated in situ to protect the remaining hydroxy group. Then the reaction mixture was diluted with dichloromethane and shaken with 1 M HCl to effect orthoes-

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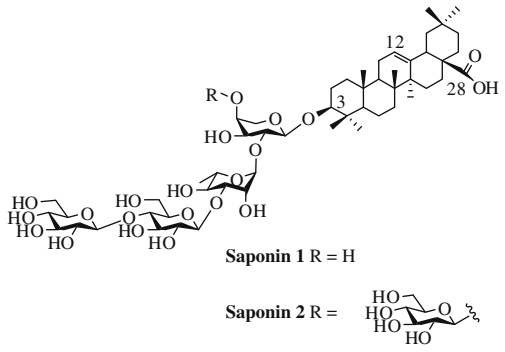
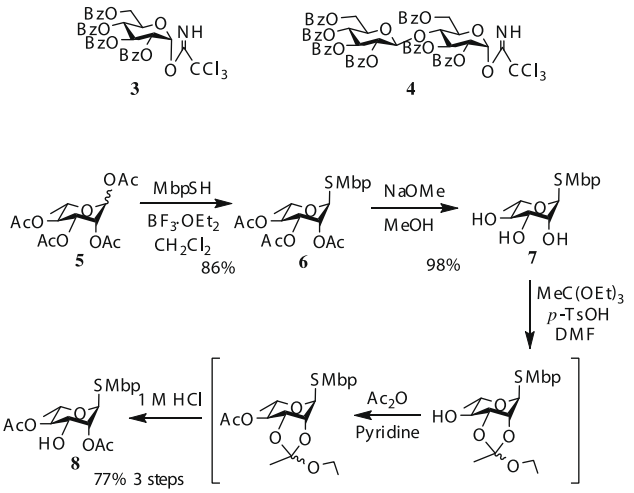


Figure 1. Structures of saponins **1** and **2**.



Scheme 1. Synthesis of Mbp thioglycoside **8** and the structure of glycosyl trichloroacetimidates **3** and **4**.

ter rearrangement, affording the desired 2-methyl-5-*tert*-butylphenyl 2,4-di-*O*-acetyl-1-thio-α-L-rhamnopyranoside (**8**) in satisfactory yield (77%, three steps).[51]

With an efficient synthetic access to the key intermediate **8**, we next turned our attention to a 'one-pot sequential glycosylation' strategy for the efficient synthesis of natural saponins **1** and **2** utilizing the Mbp thioglycosides and trichloroacetimidates as donors. As depicted in Scheme 2, coupling of Mbp thioglycoside **8** with imidate **4** was completed within 45 min with the use of catalytic amount of TMSOTf (0.2 equiv) at −78 °C, providing the desired trisaccharide Mbp thioglycoside donor. Without purification, the reaction mixture was warmed to −10 °C, then saponin acceptor **10**, which was readily derived from compound **9**, was added, followed by addition of *N*-iodosuccinimide (NIS) (2.0 equiv) and TMSOTf (0.5 equiv), affording the fully protected saponin **11** in a 76% yield for two steps. Removing the isopropylidene of **11** with the *p*-TsOH in CH_2Cl_2 and MeOH, intermediate **12** was achieved in 97% yield. Interestingly, the arabinopyranosyl residue in **12** adopted a $^1C_4$ conformation instead of the typical $^4C_1$ form. This conformational assignment was supported by a broad single peak of the H-1′ signal of arabinosyl moiety of **12**. This phenomenon was consistent with that reported in the literature.[30] Removal of the 28-*O*-benzyl group in **12** by hydrogenolysis in the presence of Pd/C, followed by removal of the benzoyl groups on the sugar residues with NaOMe in MeOH and CH_2Cl_2 afforded the expected natural saponin **1** in satisfactory yields. The arabinopyranosyl moiety returned to the normal $^4C_1$ conformation, and this was supported by the H-1′ signal of arabinopyranosyl moiety of **1** ($J_{1',2'}$ 5.9 Hz). The physical data for **1** are well in agreement with those reported in the literature (Table 1).[31]

Because of the abnormal ring conformation of the arabinose residue, the 4′-OH of **12** was in the equatorial position and should have a higher reactivity than the 3′-OH in the glycosylation, Cheng and co-workers have proved this point.[30] Herein, saponin **2** was further synthesized from the key intermediate **12**, which was coupled with 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate (**3**) in anhydrous CH_2Cl_2 in the presence of TMSOTf, regioselectively providing the corresponding product **13** in 89% yield. The chemical shift of the C-4′ changed from 71.8 ppm in **12** to 72.3 ppm in **13**, while the chemical shift of C-3′ in both **12** and **13** is 69.5 ppm. Finally removal of benzyl and benzoyl groups furnished saponin **2**, whose analytical data are identical in all respects to those reported in the literature (Table 1).[31]

In conclusion, an efficient and practical approach has been applied to the synthesis of triterpenoid saponins **1** and **2** with the use of Mbp thioglycoside and trichloroacetimidate donors, a process that should be of value in the synthesis of this kind of triterpenoid saponins for further pharmacological research.

3. Experimental

3.1. General methods

Commercial reagents were used without further purification unless specialized. Solvents were dried and redistilled prior to use in the usual way. Thin-layer chromatography (TLC) was performed on precoated E. Merck Silica Gel 60 F254 plates. Flash column chromatography was performed on silica gel (200–300 mesh, Qingdao, China). Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter. UV spectra were recorded on a Beckman DU 640 UV spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were taken on a JEOL JNM-ECP 600 spectrometer with tetramethylsilane as the internal standard, and chemical shifts are recorded in δ values. Mass spectra were recorded on a Q-TOF Global mass spectrometer.

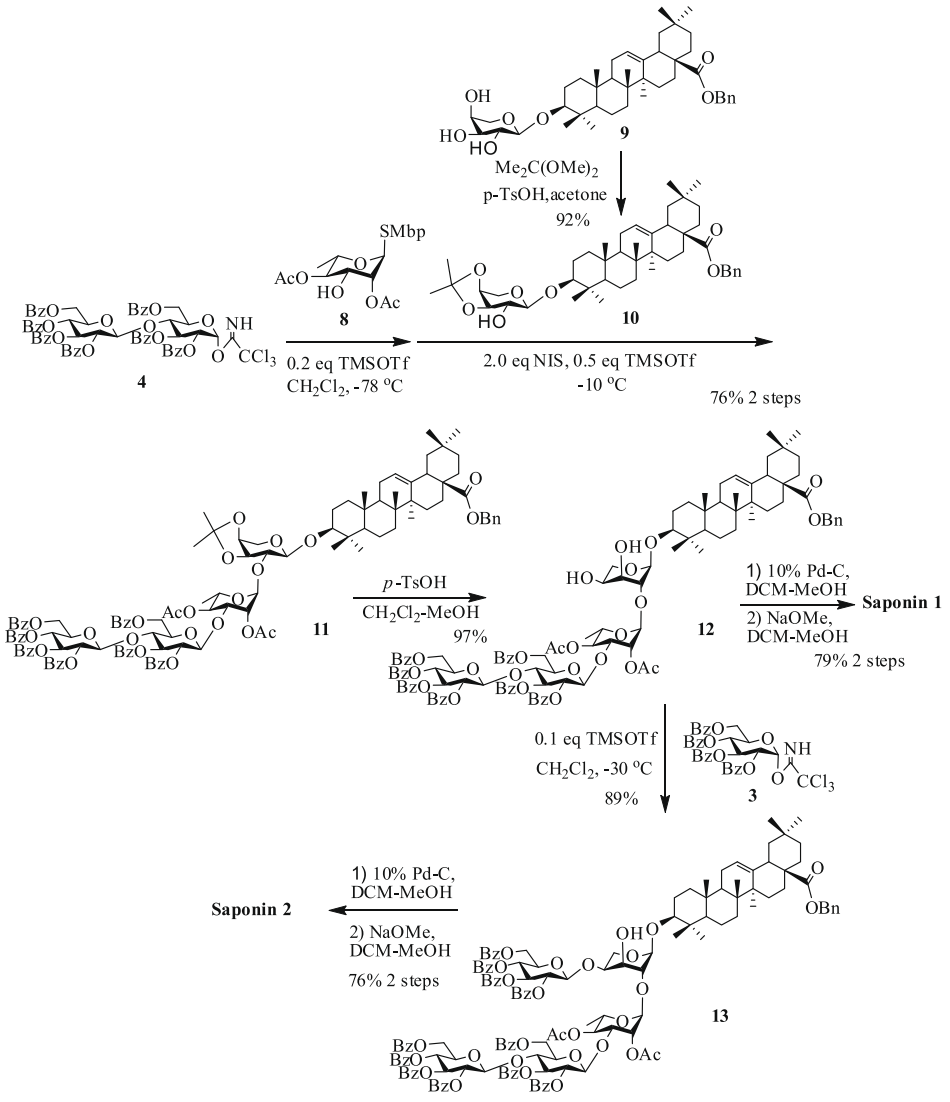
3.2. 2-Methyl-5-*tert*-butylphenyl 2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamnopyranoside (6)

A mixture of **5** (2.00 g, 6.02 mmol) and 2-methyl-5-*tert*-butylthiophenol (1.63 g, 9.03 mmol) was dissolved in CH_2Cl_2 (15 mL) and the solution was cooled to 0 °C. To the solution was slowly added $BF_3{\cdot}Et_2O$ (6.37 mL, 30.1 mmol) under an N_2 atmosphere. The reaction mixture was warmed to rt and stirred for 1 h until the starting material was consumed and the product **6** was formed. The reaction mixture was diluted with CH_2Cl_2 (60 mL) and sequentially washed with satd aq $NaHCO_3$ (15 mL × 3), and satd aq NaCl (15 × 2 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica-gel flash column chromatography (5:1–3:1 petroleum ether–EtOAc) to afford **6** as a white solid (2.34 g, 86%).

R_f 0.36 (4:1, petroleum ether–EtOAc); $[\alpha]_D^{23}$ −79 (*c* 1.55, $CHCl_3$); IR (KBr) ν_{max} 2973, 1747, 1365, 1217, 1050, 976, 894, 824, 746 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.53 (s, 1H, H_{arom}), 7.23 (d, 1H, *J* 6.6 Hz, H_{arom}), 7.15 (d, 1H, *J* 7.7 Hz, H_{arom}), 5.52 (s, 1H, H-1), 5.30–5.35 (m, 2H, H-2, H-4), 5.15 (t, 1H, *J* 9.9 Hz, H-3), 4.41 (dq, 1H, *J* 9.9, 5.5 Hz, H-5), 2.40 (s, 3H, CH_3 thio), 2.15, 2.08, 2.02 (s each, 3H each, CH_3CO × 3), 1.29 (s, 9H, *t*-Bu), 1.25 (d, 3H, *J* 5.5 Hz, H-6).

^{13}C NMR ($CDCl_3$): δ 170.3, 170.2, 170.1, 150.0, 137.0, 132.2, 130.3, 130.1, 125.4, 85.5 (C-1), 71.8, 71.4, 69.7, 68.0, 34.6, 31.5, 21.2, 21.0, 20.9, 20.5, 17.6.



Scheme 2. Synthesis of target compounds **1** and **2** by two sequential glycosylation steps.

HRESIMS: *m*/*z* calcd for [M+Na$^+$] $C_{23}H_{32}NaO_7S$: 475.1766; found: 475.1755.

3.3. 2-Methyl-5-*tert*-butylphenyl 1-thio-α-L-rhamnopyranoside (7)

A mixture of compound **6** (2.00 g, 4.42 mmol) and NaOMe (0.16 g, 4.42 mmol) in MeOH (15 mL) was stirred at rt for 20 min. The products **7** were detected on TLC (15:1 CH_2Cl_2–MeOH). After completion of the reaction, the reaction mixture was treated with Dowex H$^+$ resin and filtered. After concentration, the residue was purified by column chromatography on silica gel (20:1 CH_2Cl_2–MeOH) to give **7** (1.41 g, 98%) as a white solid; R_f 0.36 (15:1 CH_2Cl_2–MeOH); $[\alpha]_D^{23}$ −193 (*c* 1.50, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56 (d, 1H, *J* 2.0 Hz, H_{arom}), 7.24 (dd, 1H, *J* 7.6, 2.0 Hz, H_{arom}), 7.14 (d, 1H, *J* 7.6 Hz, H_{arom}), 5.41 (s, 1H, H-1), 4.27 (br s, 1H, H-2), 4.21 (t, 1H, *J* 9.6 Hz, H-4), 3.89 (br s, 1H, H-4), 3.64 (m, 1H, H-5), 2.40 (s, 3H, CH_3 thio), 1.30 (d, 3H, *J* 5.9 Hz, H-6), 1.28 (s, 9H, *t*-Bu).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.8, 136.4, 132.7, 129.9, 129.5, 127.2, 124.8, 87.5 (C-1), 73.7, 72.9, 72.4, 69.3, 34.5, 31.3, 31.2, 20.2, 19.5, 17.5.

HRESIMS: *m*/*z* calcd for [M+Na$^+$] $C_{17}H_{26}NaO_4S$: 349.1450; found: 349.1457.

3.4. 2-Methyl-5-*tert*-butylphenyl 2,4-di-*O*-acetyl-1-thio-α-L-rhamnopyranoside (8)

To a solution of compound **7** (1.35 g, 4.14 mmol) in dry DMF (15 mL), triethylorthoacetate (1.05 mL, 6.20 mmol) was added, followed by a catalytic amount of camphorsulfonic acid (CSA, 191 mg, 0.83 mmol). The mixture was stirred for 4 h. After complete conversion by thin-layer chromatography (TLC) (1:1 petroleum ether–EtOAc), Et_3N was added to neutralize the solution. Ac_2O (0.77 mL, 8.28 mmol), Et_3N (1.76 mL, 12.4 mmol), and DMAP (50 mg, 0.42 mmol) were added, and the mixture was allowed to stir for 1 h at room temperature. When TLC (2:1, petroleum ether–EtOAc) showed complete conversion, MeOH (0.5 mL) was carefully added to destroy excess Ac_2O, and the mixture was diluted with CH_2Cl_2 (80 mL). The organic layer was shaken with 1 M HCl (20 × 3 mL), followed by washing with satd aq $NaHCO_3$ (20 × 3 mL) and water (20 × 3 mL). Finally the organic layer was separated, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel column chromatography (6:1 petroleum ether–EtOAc) to give 8 (1.31 g, 77% three steps) as a white solid.

R_f 0.28 (3:1 petroleum ether–EtOAc); $[\alpha]_D^{23}$ −106 (*c* 1.65, $CHCl_3$); IR (KBr) ν_{max} 3498, 2957, 1747, 1377, 1225, 1101, 1050, 840, 778 cm^{-1}.

Table 1
^{1}H and ^{13}C NMR of glycoside moieties of natural products **1** and **2** compared with synthesized compounds **1** and **2**[a]

Position	1 (lit.)			1			2 (lit.)			2		
	^{1}H (ppm)	*J* (Hz)	^{13}C (ppm)	^{1}H (ppm)	*J* (Hz)	^{13}C (ppm)	^{1}H (ppm)	*J* (Hz)	^{13}C (ppm)	^{1}H (ppm)	*J* (Hz)	^{13}C (ppm)
1′	4.83 d	6.1	105.2	4.84 d	5.9	105.8	4.70 d	6.6	105.3	4.70 d	6.4	105.2
2′	4.52 dd	7.0, 6.1	75.7	4.50–4.58 m			4.43 dd	8.5, 6.6	76.1	4.44 dd	8.5, 6.4	
3′	4.22 m		74.4	4.22–4.33 m			4.16 dd	8.5, 3.5	74.3	4.15–4.19 m		
4′	4.23 m		69.2	4.22–4.33 m			4.23 m		69.9	4.20–4.36 m		
5′-1	4.29 dd	10.2, 3.9	65.6	4.22–4.33 m			4.40 dd	11.2, 2.8	65.2	4.40 dd	11.3, 2.9	
5′-2	3.79 brd	10.2		3.81 d	10.6		3.74 br d	11.2		3.75 br d	11.3	
1″	6.18 d	0.8	101.6	6.19 s		102.2	6.14 d	0.7	101.5	6.14 s		101.4
2″	4.93 dd	3.0, 0.8	71.7	4.97 br s			4.92 dd	2.9, 0.7	71.5	4.91 br s		
3″	4.75 dd	9.5, 3.0	83.5	4.77 dd	10.1, 3.7	83.9	4.74 dd	9.4, 2.9	83.2	4.74 dd	9.4, 3.0	82.9
4″	4.48 dd	9.5, 9.5	73.0	4.50-4.58 m			4.47 dd	9.4, 9.4	72.9	4.47 t	9.5	
5″	4.62 dq	9.5, 6.1	69.7	4.62 dq	9.2,5.5		4.63 dq	9.4, 6.1	69.7	4.63 dq	9.5, 6.0	
6″	1.55 d	6.1	18.4	1.56 d	5.9		1.56 d	6.1	18.5	1.56 d	6.0	
1‴	5.43 d	7.9	106.5	5.45 d	8.0	106.8	5.42 d	7.9	106.4	5.42 d	7.9	106.3
2‴	4.09 dd	9.1, 7.9	75.5	4.11 t-like	8.7, 8.3		4.08 dd	9.1, 7.9	75.4	4.08 dd	9.0, 7.8	
3‴	4.26 dd	9.1, 9.1	76.6	4.22-4.33 m			4.25 dd	9.1, 9.1	76.6	4.20–4.36 m		
4‴	4.36 dd	9.1, 9.1	81.1	4.36 t	9.2		4.31 dd	9.1, 9.1	81.2	4.20–4.36 m		
5‴	3.92 ddd	9.1, 3.6, 2.5	76.6	3.92 ddd	9.0,3.5,2.4		3.92 ddd	9.1,3.7,2.3	76.5	3.89–3.91 m		
6‴-1	4.55 dd	12.0, 3.6	61.8	4.50–4.58 m			4.53 dd	12.1, 3.7	61.8	4.49–4.53 m		
6‴-2	4.40 dd	12.0, 2.5		4.42 dd	12.4, 2.3		4.42 dd	12.1, 2.3		4.42 dd	12.0,2.3	
1⁗	5.19 d	7.9	105.0	5.20 d	7.8	105.5	5.15 d	7.9	104.9	5.15 d	7.9	104.9
2⁗	4.07 dd	9.0, 7.9	74.7	4.07 t-like	8.7, 8.3		4.05 dd	8.9, 7.9	74.7	4.06 dd	9.0, 7.9	
3⁗	4.20 dd	9.0, 9.0	78.2	4.22–4.33 m			4.18 dd	8.9, 8.9	78.2	4.15–4.19 m		
4⁗	4.16 dd	9.0, 9.0	71.5	4.17 t	9.2		4.15 dd	8.9, 8.9	71.4	4.15–4.19 m		
5⁗	3.99 ddd	9.0, 5.8, 2.4	78.4	4.00 ddd	9.1, 5.9, 25		3.98 ddd	8.9, 5.7, 2.5	78.4	3.98 m		
6⁗-1	4.51 dd	11.8, 2.4	62.4	4.50–4.58 m			4.51 dd	11.7, 2.5	62.4	4.49–4.53 m		
6⁗-2	4.27 dd	11.8, 5.8		4.22–4.33 m			4.26 dd	11.7, 5.7		4.20–4.36 m		
1⁗′							5.11 d	7.8	106.5	5.11 d	7.7	106.5
2⁗′							4.02 dd	8.9, 7.8	75.4	4.02 dd	8.7, 8.2	
3⁗′							4.19 dd	8.9, 8.9	78.4	4.15–4.19 m		
4⁗′							4.21 dd	8.9, 8.9	71.2	4.15–4.19 m		
5⁗′							3.89 ddd	8.9,5.1,2.5	78.7	4.20–4.36 m		
6⁗′-1							4.49 dd	11.9, 2.5	62.5	4.49–4.53 m		
6⁗′-2							4.35 dd	11.9, 5.1		4.20–4.36 m		

[a] Spectra were measured in pyridine-d_5.

^{1}H NMR ($CDCl_3$): δ 7.52 (d, 1H, *J* 2.2 Hz, H_{arom}), 7.24 (dd, 1H, *J* 7.7, 2.2 Hz, H_{arom}), 7.14 (d, 1H, *J* 7.7 Hz, H_{arom}), 5.39 (d, 1H, *J* 1.4 Hz, H-1), 5.35 (dd, 1H, *J* 2.4, 1.5 Hz, H-2), 4.93 (t, 1H, *J* 9.9 Hz, H-4), 4.36 (dq, 1H, *J* 9.9, 5.5 Hz, H-5), 4.06 (dd, 1H, *J* 9.9, 3.3 Hz, H-3), 2.40 (s, 3H, CH_3 thio), 2.17, 2.16 (s each, 3H each, $CH_3CO \times 3$), 1.29 (s, 9H, *t*-Bu), 1.24 (d, 3H, *J* 5.5 Hz, H-6).

^{13}C NMR ($CDCl_3$): δ 171.8, 170.7, 150.0, 137.0, 132.4, 130.3, 125.4, 85.6 (C-1), 75.1, 74.8, 69.5, 67.5, 34.6, 31.5, 31.4, 21.2, 20.5, 17.6;

HRESIMS: *m*/*z* calcd for [M+Na$^+$] $C_{21}H_{30}NaO_6S$: 433.1661; found: 433.1644.

3.5. Benzyl 3-*O*-[2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→3)-2,4-di-*O*-acetyl-α-L-rhamnopyranosyl-(1→2)-3,4-*O*-isopropylidene-α-L-arabinopyranosyl]oleanolate (11)

A solution of Mbp thioglycoside (**8**, 45 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) and 4 Å MS (80 mg) was stirred at room temperature under argon for 30 min, and then cooled to −78 °C. At this temperature, a solution of TMSOTf (0.2 equiv) in dry CH_2Cl_2 was injected, and after 10 min a trichloroacetimidate **4** (280 mg, 0.23 mmol, 2.1 equiv) in dry CH_2Cl_2 was added, respectively. The resulting mixture was stirred for additional 30 min and then warmed up to −10 °C. To the above-mentioned mixture was added a solution of saponin acceptor **10** (79 mg, 0.11 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL), followed by NIS (50 mg, 0.11 mmol, 2.0 equiv). After stirring for 1 h, the reaction was quenched with Et_3N, and then filtered through a pad of Celite. The filtrate was concentrated. The residue was purified by silica gel column chromatography (3:1 petroleum ether–EtOAc) to give the fully protected saponin **11** (167 mg, 76% two steps) as a white solid. The amounts of the reactants and the yields of the saponin products were calculated based on saponin acceptor **10**.

$[\alpha]_D^{23}$ +43.8 (*c* 2.50, $CHCl_3$); R_f 0.31 (2:1 petroleum ether–EtOAc); IR (KBr) ν_{max} 2938, 1735, 1451, 1264, 1089, 1066, 1023, 707 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.20–8.08 (m, 40H, Ph-H), 5.75 (t, 1H, *J* 9.2 Hz, H-3⁗′), 5.70 (t, 1H, *J* 9.6 Hz, H-3‴), 5.51 (t-like, 1H, *J* 9.2, 8.7 Hz, H-2‴), 5.40 (t-like, 1H, *J* 9.2, 8.3 Hz, H-2⁗′), 5.36 (t, 1H, *J* 9.6 Hz, H-4‴), 5.32 (t, 1H, *J* 3.7 Hz, H-12), 5.25 (br s, 1H, H-2″), 5.20 (s, 1H, H-1″), 5.13 (d, 1H, *J* 12.4 Hz, PhCHH), 5.09 (d, 1H, *J* 13.0 Hz, PhCHH), 4.99 (t-like, 1H, *J* 10.1, 9.7 Hz, H-6⁗′-1), 4.88 (d, 1H, *J* 7.8 Hz, H-1‴), 4.73 (d, 1H, *J* 7.3 Hz, H-1⁗′), 4.49 (m, 2H, H-6‴-1, H-6⁗′-2), 4.28 (t-like, 1H, *J* 9.7, 9.2 Hz, H-4⁗′), 4.15 (t, 1H, *J* 9.2 Hz, H-3″), 4.13 (d, 1H, *J* 7.3 Hz, H-1′), 4.07–4.10 (m, 1H, H-3′), 4.01 (dd, 1H, *J* 12.4, 2.7 Hz, H-5′-1), 3.95 (dd, 1H, *J* 11.5, 5.5 Hz, H-6‴-2), 3.91 (m, 1H, H-5″), 3.68–3.71 (m, 4H, H-4′, H-5′-2, H-5‴, H-5⁗′), 3.62–3.66 (m, 2H, H-2′, H-4″), 3.00 (dd, 1H, *J* 11.9, 4.6 Hz, H-3), 2.92 (dd, 1H, *J* 13.7, 3.7 Hz, H-18), 2.05, 1.96 (s each, 3H each, $CH_3CO \times 2$), 1.46, 1.42 (s each, 3H each, O-$(CH_3)_2$-O), 1.04 (d, 3H, *J* 6.0 Hz, H-6″), 1.18, 0.94, 0.93, 0.92, 0.86, 0.72, 0.63 (s each, 3H each, $CH_3 \times 7$).

^{13}C NMR ($CDCl_3$): δ 177.6 (C-28), 170.2, 169.6, 165.7, 165.6, 165.5, 164.8, 164.7, 143.8 (C-13), 136.5, 133.5, 133.4, 133.3, 129.8, 128.6, 128.5, 128.4, 128.1, 122.6 (C-12), 110.3 (O–$(CH_3)_2$C–O), 103.4 (C-1′), 101.5 (C-1⁗′), 101.2 (C-1‴), 94.6 (C-1″), 88.9 (C-3), 78.8, 76.3, 75.9, 74.7, 73.3, 73.1, 72.9, 72.4, 72.0, 71.9, 69.4, 66.3, 66.0, 62.8, 62.6, 62.1, 60.5, 55.9, 47.7, 46.8, 46.0, 41.8, 39.4, 39.2, 38.7, 36.8, 33.9, 33.2, 32.8, 32.5, 30.8, 29.8, 28.1, 27.8, 26.2, 26.0, 23.8, 23.5, 23.2, 21.2, 21.0, 20.1, 18.4, 17.4, 17.0, 16.4, 15.4, 14.3.

HRMALDI-MS: *m/z* calcd for $[M+Na]^+$ $C_{116}H_{128}O_{30}$: 2023.8383; found: 2023.8383.

3.6. Benzyl 3-*O*-[2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→3)-2,4-di-*O*-acetyl-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]oleanolate (12)

A mixture of compound **11** (150 mg, 0.075 mmol) and *p*-TsOH (13 mg, 0.075 mmol) in 1:2 CH_2Cl_2–MeOH (6 mL) was stirred at r.t. When TLC (3:2 petroleum ether–EtOAc) showed that deprotection had completed, Et_3N (0.1 mL) was added, and the mixture was concentrated and purified through a silica gel column chromatography (2:1 petroleum ether–EtOAc) to afford **12** (142 mg, 97%) as a white solid.

$[\alpha]_D^{22}$ +31.1 (*c* 3.20, $CHCl_3$); R_f 0.18 (2:1 petroleum ether–EtOAc); IR (KBr) ν_{max} 2933, 1726, 1448, 1255, 1083, 705 cm^{-1}.

^1H NMR ($CDCl_3$): δ 7.28–8.04 (m, 40H, Ph-H), 5.74 (t, 1H, *J* 9.3 Hz, H-3‴′), 5.70 (t, 1H, *J* 9.4 Hz, H-3‴), 5.50 (dd, 1H, *J* 9.4, 8.8 Hz, H-2‴), 5.33–5.39 (m, 2H, H-2‴′, H-4‴), 5.28 (t, 1H, *J* 3.8 Hz, H-12), 5.18 (br s, 1H, H-2″), 5.10 (d, 1H, *J* 12.6 Hz, PhCHH), 5.06 (d, 1H, *J* 12.7 Hz, PhCHH), 4.96 (t, 1H, *J* 9.9 Hz, H-4″), 4.91 (s, 1H, H-1″), 4.90 (d, 1H, *J* 8.8 Hz, H-1‴′), 4.80 (d, 1H, *J* 7.7 Hz, H-1‴), 4.62 (br s, 1H, H-1′), 4.58 (dd, 1H, *J* 12.1, 2.3 Hz, H-5′-1), 4.42 (dd, 1H, *J* 12.1, 1.8 Hz, H-5′-2), 4.26 (t, 1H, *J* 9.4 Hz, H-4‴′), 3.98–4.02 (m, 2H, H-3″, H-6‴-1), 3.84 (m, 1H, H-5‴), 3.69–3.80 (m, 7H, H-2′, H-3′, H-4′, H-5″, H-5‴′, H-6‴′-1, H-6‴′-2), 3.55 (dd, 1H, *J* 12.1, 4.4 Hz, H-6‴-2), 3.04 (dd, 1H, *J* 11.4, 3.7 Hz, H-3), 2.91 (dd, 1H, *J* 14.4, 4.1 Hz, H-18), 1.91, 1.90 (s each, 3H each, $CH_3CO \times 2$), 1.02 (d, 3H, *J* 6.1 Hz, H-6″), 1.11, 0.92, 0.89, 0.89, 0.86, 0.75, 0.59 (s each, 3H each, $CH_3 \times 7$).

^{13}C NMR ($CDCl_3$): δ 177.5 (C-28), 170.1, 169.5, 165.9, 165.8, 164.8, 144.0 (C-13), 136.5, 133.3, 129.8, 129.7, 129.5, 129.3, 128.6, 128.5, 128.4, 128.3, 128.1, 122.5 (C-12), 101.9 (C-1′), 101.2 (C-1‴), 101.0 (C-1‴′), 98.0 (C-1″), 90.4 (C-3), 75.8, 75.7, 72.9, 72.4, 72.0, 71.8 (C-4′), 71.5, 69.5 (C-3′), 66.9, 66.0, 62.7, 55.5, 47.7, 46.8, 46.0, 41.8, 41.5, 39.4, 39.1, 38.6, 36.8, 33.9, 33.2, 32.6, 32.4, 30.8, 29.8, 28.2, 28.0, 25.9, 25.8, 23.7, 23.4, 23.1, 20.9, 20.2, 18.3, 17.4, 16.9, 16.5, 15.4.

HRMALDI-MS: *m/z* calcd for $[M+Na]^+$ $C_{113}H_{124}O_{30}$: 1983.8065; found: 1983.8070.

3.7. Benzyl 3-*O*-{2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→3)-2,4-di-*O*-acetyl-α-L-rhamnopyranosyl-(1→2)-[2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)]-α-L-arabinopyranosyl}oleanolate (13)

A mixture of compound **12** (100 mg, 0.05 mmol), 4 Å molecular sieves (150 mg) and compound **3** (40 mg, 0.06 mmol) in dry CH_2Cl_2 (5 mL) was stirred at rt under argon for 30 min then cooled to −30 °C. TMSOTf (5 μL, 0.03 mmol) was added, and the reaction mixture was stirred for 30 min and then warmed to rt. The product **13** was detected on TLC (3:2 petroleum ether–EtOAc). After completion of the reaction, the reaction mixture was quenched with Et_3N (0.1 mL), diluted with CH_2Cl_2 (10 mL) and filtered. After concentration, the residue was purified by column chromatography on silica gel (2:1 petroleum ether–EtOAc) to give **13** (112 mg, 89%) as a white solid.

$[\alpha]_D^{22}$ +28.9 (*c* 1.35, $CHCl_3$); R_f 0.25 (2:1 petroleum ether–EtOAc); IR (KBr) ν_{max} 3400, 2930, 1731, 1451, 1264, 1093, 1023, 704 cm^{-1}.

^1H NMR ($CDCl_3$): δ 7.25–8.04 (m, 60H, Ph-H), 5.94 (t, 1H, *J* 9.9 Hz, H-3‴′), 5.74 (t, 1H, *J* 9.4 Hz, H-3‴), 5.68 (t, 1H, *J* 9.9 Hz, H-4‴′), 5.67 (t, 1H, *J* 9.4 Hz, H-3‴″), 5.52 (dd, 1H, *J* 9.9, 8.3 Hz, H-2‴′), 5.47 (dd, 1H, *J* 9.9, 7.7 Hz, H-2‴″), 5.35 (m, 2H, H-2‴, H-4‴″), 5.28 (t, 1H, *J* 3.6 Hz, H-12), 5.13 (dd, 1H, *J* 3.3, 1.7 Hz, H-2″), 5.10 (d, 1H, *J* 12.6 Hz, PhCHH), 5.08 (d, 1H, *J* 7.7 Hz, H-1‴′), 5.06 (d, 1H, *J* 12.7 Hz, PhCHH), 4.91 (t, 1H, *J* 9.9 Hz, H-4″), 4.89 (d, 1H, *J* 7.7 Hz, H-1‴″), 4.84 (d, 1H, *J* 1.1 Hz, H-1″), 4.75 (d, 1H, *J* 7.7 Hz, H-1‴), 4.68 (dd, 1H, *J* 12.1, 3.3 Hz, H-6‴′-1), 4.59 (d, 1H, *J* 10.4 Hz, H-5′-1), 4.44 (dd, 1H, *J* 12.1, 4.4 Hz, H-6‴′-2), 4.40 (d, 1H, *J* 3.9 Hz, H-1′), 4.37 (dd, 1H, *J* 12.7, 2.8 Hz, H-5′-2), 4.29 (t, 1H, *J* 9.3 Hz, H-4‴), 4.19 (m, 1H, H-5‴′), 4.03 (m, 1H, H-4′), 3.97–4.00 (m, 2H, H-3″, H-5‴), 3.90 (m, 1H, H-5‴″), 3.70–3.74 (m, 2H, H-6‴-1, H-6‴″-1), 3.67–3.69 (m, 3H, H-3′, H-5′, H-6‴-2), 3.62 (dd, 1H, *J* 5.5, 3.8 Hz, H-2′), 3.54 (dd, 1H, *J* 12.1, 3.8 Hz, H-6‴″-2), 2.96 (dd, 1H, *J* 11.5, 4.4 Hz, H-3), 2.90 (dd, 1H, *J* 15.4, 5.5 Hz, H-18), 2.04, 1.90 (s each, 3H each, $CH_3CO \times 2$), 0.96 (d, 3H, *J* 6.1 Hz, H-6″), 1.11, 0.92, 0.90, 0.84, 0.82, 0.67, 0.58 (s each, 3H each, $CH_3 \times 7$).

^{13}C NMR ($CDCl_3$): δ 177.7 (C-28), 170.1, 169.6 (CH_3CO), 166.0, 165.9, 165.8, 165.4, 165.0, 143.9 (C-13), 136.6, 133.7, 133.4, 130.0, 128.7, 128.6, 128.5, 128.4, 122.7 (C-12), 102.7 (C-1′), 101.6 (C-1‴′), 101.2 (C-1‴″), 101.1 (C-1‴), 97.2 (C-1″), 90.2 (C-3), 75.8, 75.4, 73.0, 72.5, 72.4, 72.3 (C-4′), 72.2, 72.1, 72.0, 71.0, 69.9, 69.5 (C-3′), 66.7, 66.1, 63.1, 62.7, 61.9, 55.8, 47.8, 46.9, 41.9, 41.6, 39.5, 39.2, 36.8, 33.3, 30.9, 29.9, 28.2, 26.1, 25.9, 23.9, 23.2, 21.0, 17.4, 17.0, 16.5, 15.5, 14.4.

3.8. 3-*O*-[β-D-Glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]oleanolic acid (1)

A mixture of **12** (60 mg, 0.03 mmol) and 10% Pd–C (30 mg) in 1:1 CH_2Cl_2–MeOH (8 mL) in the presence of AcOH (two drops) was stirred under 1 atm of H_2 for 4 h. The reaction mixture was then filtered, and the filtrate was concentrated to dryness to give a white solid. The solid was dissolved in 2:1 MeOH–CH_2Cl_2 (8 mL), and then NaOMe (40 mg) was added. After stirring at rt for 8 h, the solution was neutralized with ion-exchange resin (H^+), then filtered and concentrated. The residue was purified by column chromatography on silica gel (3:1 $CHCl_3$–MeOH) to give **1** (25 mg, 79% two steps) as a white solid.

Mp 235–237 °C; $[\alpha]_D^{25}$ −5.85 (*c* 0.60, 1:1 $CHCl_3$–MeOH); R_f 0.23 (2:1, $CHCl_3$–MeOH); IR (KBr) ν_{max} 3401, 2941, 1696, 1649, 1381, 1073 cm^{-1}.

^1H NMR (C_5D_5N): δ 6.19 (s, 1H, H-1″), 5.49 (t, 1H, *J* 3.6 Hz, H-12), 5.45 (d, 1H, *J* 8.0 Hz, H-1‴), 5.20 (d, 1H, *J* 7.8 Hz, H-1‴′), 4.97 (br s, 1H, H-2″), 4.84 (d, 1H, *J* 5.9 Hz, H-1′), 4.77 (dd, 1H, *J* 10.1, 3.7 Hz, H-3″), 4.62 (dq, 1H, *J* 9.2, 5.5 Hz, H-5″), 4.50–4.58 (m, 4H, H-2′, H-4″, H-6‴-1, H-6‴′-1), 4.42 (dd, 1H, *J* 12.4, 2.3 Hz, H-6‴-2), 4.36 (t, 1H, *J* 9.2 Hz, H-4‴), 4.22–4.33 (m, 6H, H-3′, H-4′, H-5′-1, H-3‴, H-3‴′, H-6‴′-2), 4.17 (t, 1H, *J* 9.2 Hz, H-4‴′), 4.11 (t-like, 1H, *J* 8.7, 8.3 Hz, H-2‴), 4.07 (t-like, 1H, *J* 8.7, 8.3 Hz, H-2‴′), 4.00 (ddd, 1H, *J* 9.1, 5.9, 2.5 Hz, H-5‴′), 3.92 (ddd, 1H, *J* 9.0, 3.5, 2.4 Hz, H-5‴), 3.81 (d, 1H, *J* 10.6 Hz, H-5′-2), 3.29–3.31 (m, 2H, H-3, H-18), 1.56 (d, 3H, *J* 5.9 Hz, H-6″), 1.33, 1.32, 1.14, 1..03, 0.98, 0.97, 0.85 (s each, 3H each, $CH_3 \times 7$).

^{13}C NMR (C_5D_5N): δ 180.4 (C-28), 145.4 (C-13), 123.2 (C-12), 106.8 (C-1‴), 105.8 (C-1′), 105.5 (C-1‴′), 102.2 (C-1″), 89.2 (C-3), 83.9 (C-3″), 81.6, 79.0, 78.8, 77.2, 76.2, 75.9, 75.3, 73.4, 72.2, 72.0, 70.3, 69.7, 66.1, 62.9, 62.3, 56.5, 48.6, 47.3, 42.7, 42.5, 40.3, 40.1, 39.4, 37.6, 34.8, 33.8, 33.7, 31.5, 28.9, 28.7, 27.2, 26.7, 24.3, 19.0, 18.0, 17.7, 16.1.

HRESIMS: *m/z* calcd for $C_{53}H_{85}O_{21}$ $[M-H^+]$: 1057.5583; found: 1057.5582.

3.9. 3-*O*-{β-D-Glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→4)]-α-L-arabinopyranosyl}oleanolic acid (2)

A mixture of **13** (50 mg, 0.02 mmol) and 10% Pd–C (25 mg) in CH_2Cl_2–MeOH (V:V/1:1, 8 mL) in the presence of AcOH (2 drops) was stirred under 1 atm of H_2 for 4 h. The reaction mixture was

then filtered and the filtrate was concentrated to dryness to give a white solid. The solid was dissolved in MeOH–CH_2Cl_2 (V:V/2:1, 8 mL), and then NaOMe (40 mg) was added. After stirring at rt for 8 h, the solution was neutralized with ion-exchange resin (H^+), then filtered and concentrated. The residue was purified by column chromatography on silica gel (1:1, $CHCl_3$–MeOH) to give **2** (19 mg, 76% two steps) as a white solid.

Mp 246–248 °C; $[\alpha]_D^{25}$ −7.52 (*c* 0.60, 1:1 $CHCl_3$–CH_3OH); R_f 0.21 (1:1 $CHCl_3$–MeOH); IR (KBr) ν_{max} 3412, 2930, 1692, 1505, 1077 cm^{-1}.

^1H NMR (C_5D_5N, 500 MHz): δ 6.14 (s, 1H, H-1″), 5.46 (t, 1H, *J* 3.0 Hz, H-12), 5.42 (d, 1H, *J* 7.9 Hz, H-1‴), 5.15 (d, 1H, *J* 7.9 Hz, H-1⁗), 5.11 (d, 1H, *J* 7.7 Hz, H-1⁗′), 4.91 (br s, 1H, H-2″), 4.74 (dd, 1H, *J* 9.4, 3.0 Hz, H-3″), 4.70 (d, 1H, *J* 6.4 Hz, H-1′), 4.63 (dq, 1H, *J* 9.5, 6.0 Hz, H-5″), 4.49–4.53 (m, 3H, H-6‴-1, H-6⁗-1, H-6⁗′-1), 4.47 (t, 1H, *J* 9.5 Hz, H-4″), 4.44 (dd, 1H, *J* 8.5, 6.4 Hz, H-2′), 4.42 (dd, 1H, *J* 12.0, 2.3 Hz, H-6‴-2), 4.40 (dd, 1H, *J* 11.3, 2.9 Hz, H-5′-1), 4.20–4.36 (m, 6H, H-3‴, H-4′, H-4‴, H-5⁗′, H-6⁗-2, H-6⁗′-2), 4.15–4.19 (m, 4H, H-3′, H-3⁗, H-4⁗, H-4⁗′), 4.08 (dd, 1H, *J* 9.0, 7.8 Hz, H-2⁗), 4.06 (dd, 1H, *J* 9.0, 7.9 Hz, H-2‴), 4.02 (dd, 1H, *J* 8.7, 8.2 Hz, H-2⁗), 3.98 (m, 1H, H-5⁗), 3.89–3.91 (m, 2H, H-5‴, H-5⁗′), 3.75 (br d, 1H, *J* 11.3 Hz, H-5′-2), 3.24 (dd, 1H, *J* 11.5, 4.2 Hz, H-3), 3.20 (dd, 1H, *J* 13.7, 3.7 Hz, H-18), 1.56 (d, 3H, *J* 6.0 Hz, H-6″), 1.29, 1.29, 1.12, 1.00, 0.97, 0.95, 0.82 (s each, 3H each, $CH_3 \times 7$).

^{13}C NMR (C_5D_5N, 125 MHz): δ 180.1 (C-28), 144.8 (C-13), 122.5 (C-12), 106.5 (C-1⁗′), 106.3 (C-1‴), 105.2 (C-1′), 104.9 (C-1⁗), 101.4 (C-1″), 88.7 (C-3), 82.9, 78.7, 78.1, 77.7, 76.1, 75.5, 75.2, 74.2, 72.7, 71.7, 71.6, 69.6, 64.7, 64.3, 62.6, 48.0, 46.6, 46.4, 42.1, 41.9, 39.7, 39.5, 37.0, 34.2, 33.2, 33.1, 32.0, 30.9, 30.7, 29.8, 29.5, 28.2, 28.1, 26.5, 26.1, 23.7, 22.8, 18.4, 18.3, 17.3, 17.0, 15.4, 14.1.

HRESIMS: *m*/*z* calcd for $C_{59}H_{95}O_{26}$ [M−H^+]: 1219.6112; found: 1219.6094.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.05.011.

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