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Synthesis of chacotriose analogues

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Abstract—We report here the synthesis of three chacotriose analogues, namely β-L-fucopyranosyl-(1→2)-[β-L-fucopyranosyl-(1→4)]-D-glucopyranose, β-L-fucopyranosyl-(1→2)-[β-L-fucopyranosyl-(1→4)]-D-galactopyranose, and α-L-rhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→4)]-α-D-galactopyranose.

Keywords: Oligosaccharides; Chacotriose analogues; Trichloroacetimidate method

1. Introduction

The large family of saponins has received considerable attention because of their varied pharmaceutical properties.[1] Since ancient times, plant extract containing saponins have been used in traditional (indigeneous) medicine. Among the large number of glycoconjugates, we have been interested in the steroidal glycoalkaloids[2] isolated from *Solanum* plants. Most *Solanum* species contain a major steroidal glycoalkaloid with the aglycone bound to chacotriose, α-L-rhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→4)]-D-glucopyranose. Chacotriose, in particular, is present in solamargine and chaconine. In these two cases, it is associated at the anomeric position by the steroidal alkaloids solasodine or solanidine. There are also oligosaccharidic counterparts to chacotriose, in particular solatriose, α-L-rhamnopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→3)]-D-galactopyranose. These steroids present many properties.[3] However glycosides-containing chacotriose are consistently more active than their solatriose-containing counterparts.[4]

The role of the glycon part is often limited to improve the biological effect of the active form, without any specificity for any particular organ. Kuo and coworkers,[5] for example, reported that the chacotriosyl moiety of solamargine plays a crucial role in triggering cell death by apoptosis. However, some monosaccharides, such as L-fucose or D-galactose, have specific receptors on a given organ and play a important role in the body.[6] L-fucose and D-galactose are important recognition component of cell-surface glycans. A number of L-fucose or D-galactose-containing glycoconjugates have been reported to be involved in a variety of biological functions, such as growth regulation, receptor function, cell–cell interaction, and antigenicity.[7] They play a role in the inflammation process[8] as a component of sialyl Lewis^X.[9]

The biological effects of the steroids and their low availability from natural sources, make them an important synthetic target. Thus much research was thus directed toward the chemical synthesis of chacotriose and analogues.[10–14] We have recently published a paper on the peracetylated chacotriose.[14] We report here strategies to obtain some chacotriose analogues. Specifically We have replaced the central D-glucose unit by a D-galactose unit, or the L-rhamnose units by L-fucose.

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2. Results and discussion

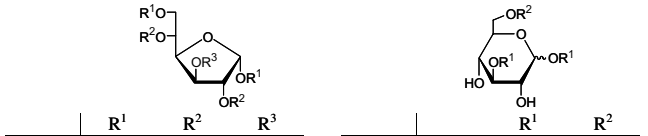
Chacotriose, is the glucidic moiety of the saponins solamargine and chaconine. It has a central D-glucose unit joined at O-2 and O-4 by two L-rhamnose units. The glycosteroids and difficulty to obtain in quantity. For the present quest we describe the synthesis of three chacotriose analogues: β-L-fucopyranosyl-(1 → 2)-[β-L-fucopyranosyl-(1 → 4)]-D-galactopyranose, β-L-fucopyranosyl-(1 → 2)-[β-L-fucopyranosyl-(1 → 4)]-D-galactopyranose, and α-L-rhamnopyranosyl-(1 → 2)-[α-L-rhamnopyranosyl-(1 → 4)]-α-D-galactopyranose.

The strategy adopted was to protect the glucose unit partially leaving only the 2-OH and 4-OH groups available for glycosidic bond formation with two L-rhamnopyranose or L-fucopyranose units. For this purpose, three steps were required, using selective pivaloylation.

Compound **4** was readily prepared in large amount (20-g scale) starting from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**).[15] Compound **2** was prepared by condensing **1** with benzyl bromide[16] in 83% yield. Removing the isopropylidene protection by 3:2 HOAc–H_2O followed by selective protection of the anomeric hydroxyl with benzyl alcohol in the presence of acetyl chloride[17] afforded compound **3** (71% yield, α/β, 3:1) (Scheme 1).

The anomeric mixture **3α/3β** was separated by crystallization with ether–EtOAc. Position 6 of **3α** was then selectively protected with pivaloyl chloride[18] in pyridine to give benzyl 3-*O*-benzyl-6-*O*-pivaloyl-α-D-glucopyranoside (**4**) in 82% yield.

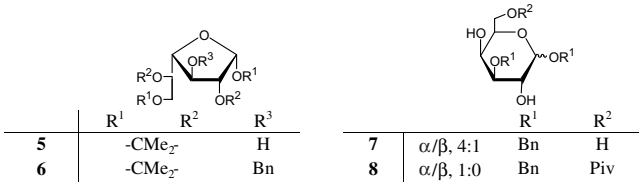
By the same method, we also prepared the galactosylated acceptor **8**, starting from 1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (**5**).[19] Removing the isopropylidene protection of **6** with 3:2 HOAc–H_2O followed by selective protection of the anomeric hydroxyl with benzyl alcohol in the presence of acetyl chloride[17] afforded compound **7** (65% yield, α/β, 4:1). The anomeric mixture **7α/7β** (α/β, 4:1) was separated by conventional work up: acetylation following by deacetylation. Position 6 of **7α** was selectively protected with pivaloyl chloride[18] in pyridine to give benzyl 3-*O*-benzyl-6-*O*-pivaloyl-α-D-galactopyranoside (**8**) in 76% yield (Scheme 2).



	R^1	R^2	R^3
1	-CMe_2-		H
2	-CMe_2-		Bn

		R^1	R^2
3	α/β, 3:1	Bn	H
4	α/β, 1:0	Bn	Piv

Scheme 1.



	R^1	R^2	R^3
5	-CMe_2-		H
6	-CMe_2-		Bn

		R^1	R^2
7	α/β, 4:1	Bn	H
8	α/β, 1:0	Bn	Piv

Scheme 2.

The 2-OH and 4-OH groups of the D-glucose or D-galactose acceptors **4** or **8** were glycosylated with the trichloroacetimidate donors **9**[20] or **10**[21] by using boron trifluoride etherate ($BF_3{\cdot}Et_2O$)[22] as promoter to give the fully protected chacotrioside analogues **11a**, **12a**, and **13a** (Table 1) (Scheme 3).

However, if the glycosyl donor is L-fucose (entry 1) the yield of trisaccharide becomes lower. To overcome this disadvantage, we used the '*inverse procedure*' (IP) described by Schmidt and Kinzy[22] in which the hydroxyl groups of the acceptor (**4**) are activated with $BF_3{\cdot}Et_2O$ before addition of the donor. Under these conditions (entry 2) the yield was increased to a significant degree (61% yield). This improved yield was also observed in entries 3 and 4. The yield is thus increased by 31%. However when the donor is L-rhamnose, the glycosylation yield was best by even the '*normal procedure*'.

Trisaccharides **11a**, **12a**, and **13a** were then peracetylated by a similar sequence. The protected trisaccharides were treated with hydrogen in the presence of Pd/C (10%) to give **11b**–**13b** and, then with NaOH to remove the pivaloyl and acetyl groups, and were subsequently acetylated to obtain the desired peracetylated chacotrioside analogues **11c**, **12c**, and **13c**.

3. Experimental

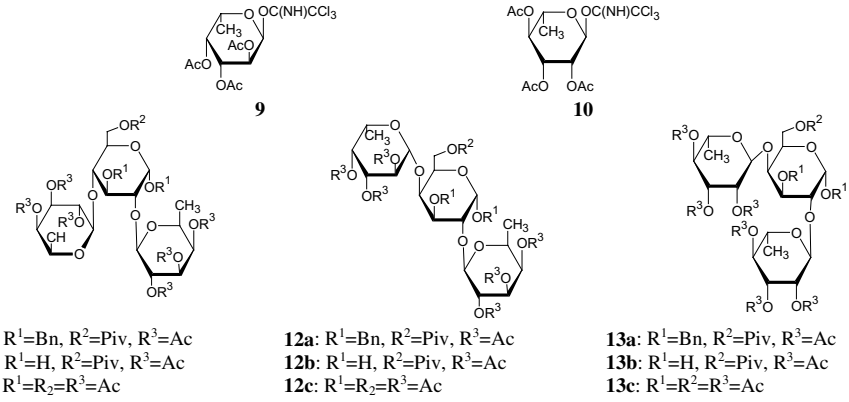
3.1. General methods

Melting points were determined on an electrothermal automatic apparatus, and are uncorrected. Optical rotations for solutions in $CHCl_3$ were measured at 25 °C

Table 1. Glycosylation of compound **4** and **8**

Entries	Conditions	Acceptor	Donor	Product	Yield (%)
1	NP (**4**/**9** = 1:3)	**4**	**9**	**11a**	30
2	IP (**4**/**9** = 1:3)	**4**	**9**	**11a**	61
3	NP (**8**/**9** = 1:3)	**8**	**9**	**12a**	35
4	IP (**8**/**9** = 1:3)	**8**	**9**	**12a**	66
5	NP (**8**/**10** = 1:3)	**8**	**10**	**13a**	68
6	IP (**8**/**10** = 1:3)	**8**	**10**	**13a**	74

NP, normal procedure; IP inverse procedure.



Scheme 3.

with a Jasco digital polarimeter model DIP-370 using a sodium lamp. NMR spectra were recorded with a Bruker WB-300 instrument for solutions in $CDCl_3$ (internal Me_4Si). All compounds were characterized by ^1H, ^{13}C, DEPT, ^1H–^1H COSY, and ^1H–^{13}C experiments. Reactions were monitored by high-performance liquid chromatography (HPLC) (Waters 721) using a reverse-phase column RP-18 (E. Merck). Analytical thin-layer chromatography (TLC) was performed on E. Merck aluminum-backed silica gel (Silica Gel F254). Column chromatography was performed on silica gel (60 mesh, Matrex) by gradient elution with hexane–acetone or hexane–EtOAc (in each case the ratio of silica gel to product mixture to be purified was 30:1).

3.2. Benzyl 3-*O*-benzyl-D-glucopyranoside (3)

A suspension of diacetal derivative **2**[16] (60 g, 171 mmol) in 60% aq HOAc was stirred for 12 h, at 90 °C. The solvent (aq HOAc) was removed by coevaporation with toluene (500 mL). The residue was dissolved in benzyl alcohol (200 mL) and acetyl chloride (27 mL) was added at 0 °C. After 24 h at rt, the mixture was neutralized with solid $NaHCO_3$, filtered, and concentrated under reduced pressure. Chromatography of the residue on a silica gel column (7:3 hexane–acetone) gave **3** in 71% yield (α/β, 3:1); anomer **3α**, oil, $[\alpha]_D$ +75.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38–7.28 (Ph), 5.01, 4.74 (2d, 2H, *CH*$_2$–Ph), 4.97 (d, 1H, $J_{1,2}$ 3.2 Hz, H-1), 4.76, 4.55 (2d, 2H, *CH*$_2$–Ph), 3.78 (d, 1H, $J_{5,6}$ 3.8 Hz, H-6a), 3.67 (m, 2H, H-2, H-5), 3.61 (m, 2H, H-3, H-4); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 137.3–128.3 (Ph), 98.4 (C-1), 83.3 (C-3), 75.4 (*CH*$_2$–Ph), 73.2 (C-2), 71.8 (C-4), 70.5 (C-5), 70.3 (*CH*$_2$–Ph), 62.6 (C-6); anomer **3β**, white crystals, mp 102–107 °C; $[\alpha]_D$ −45.3 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.27 (Ph), 5.03 (dd, 1H, $J_{2,3}$ 9.5 Hz, H-2), 4.86, 4.62 (2d, 2H, $J_{Ha,Hb}$ 12.4 Hz, *CH*$_2$–Ph), 4.72, 4.69 (2d, 2H, $J_{Ha,Hb}$ 11.3 Hz, *CH*$_2$–Ph), 4.48 (d, 1H, $J_{1,2}$ 8.0 Hz, H-1), 3.90 (dd, 1H, $J_{6a,6b}$ 11.9 Hz, H-6a), 3.80 (dd, 1H, H-6b), 3.72 (dd, 1H, $J_{3,4}$ 9.3 Hz, H-3), 3.55 (dd, 1H, $J_{4,5}$ 9.2 Hz, H-4), 3.35 (m, 1H, $J_{5,6a}$ 4.7 Hz, $J_{5,6b}$ 3.4 Hz, H-5); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 138.0–128.0 (Ph), 100.4 (C-1), 82.9 (C-3), 75.7 (C-5), 74.9 (*CH*$_2$–Ph), 73.3 (C-2), 71.2 (*CH*$_2$–Ph), 70.8 (C-4), 62.3 (C-6). Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.71; H 6.78.

3.3. Benzyl 3-*O*-benzyl-6-*O*-pivaloyl-α-D-glucopyranoside (4)

To a solution of **3α** (20 g, 55 mmol) in pyridine (200 mL), pivaloyl chloride (10.2 mL, 82 mmol) was slowly added at 0 °C. After being stirred for 2 h, the mixture was diluted with EtOAc, and washed with 20% aq HCl, satd aq $NaHCO_3$, and then brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue on a silica gel column (9:1 hexane–EtOAc) gave **4** as an oil in 71% yield; $[\alpha]_D$ −47.1 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.28 (Ph), 4.94 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.91, 4.73 (2d, 2H, *CH*$_2$–Ph), 4.82, 4.65 (2d, 2H, *CH*$_2$–Ph), 4.43 (dd, 1H, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.38 (dd, 1H, H-6b), 3.71 (dd, 1H, $J_{2,3}$ 9.0 Hz, H-2), 3.55 (m, 1H, $J_{3,4}$ 8.7 Hz, H-3), 3.48 (m, 2H, $J_{5,6a}$ 4.5 Hz, $J_{5,6b}$ 2.5 Hz, H-5, H-4), 1.24 (s, 9H, C*Me*$_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 169.9 (*C*O), 138.5–128.1 (Ph), 97.5 (C-1), 82.6 (C-3), 75.0 (*CH*$_2$–Ph), 73.2 (C-2), 70.6 (C-4), 70.5 (*CH*$_2$–Ph), 70.2 (C-5), 63.4 (C-6), 39.4 (*C*Me$_3$), 27.6 (C*Me*$_3$). Anal. Calcd for $C_{24}H_{32}O_7$: C, 67.57; H, 7.21. Found: C, 67.63; H 7.25.

3.4. Benzyl 3-*O*-benzyl-α-D-galactopyranoside (7)

A procedure similar to that for the preparation of **3** was employed. A suspension of diacetal derivative **6**[19] (30 g, 95 mmol) in 60% aq HOAc was stirred at 90 °C for 12 h. The solvent was removed by coevaporation with toluene (250 mL). The residue was dissolved in benzyl alcohol (100 mL) and acetyl chloride (13.5 mL) was added at 0 °C. After 24 h at rt, the mixture was neutralized with solid $NaHCO_3$, filtered, and concentrated under reduced

pressure. Chromatography of the residue on a silica gel column (6:4 hexane–acetone) gave **7** as an oil in 65% yield (α/β, 4:1). A sole anomer (α) was obtained by acetylation; anomer **7α** white crystals, mp 75–78 °C; $[\alpha]_D$ −29.0 (*c* 1.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 139.1–128.6 (Ph), 99.0 (C-1), 77.2 (C-3), 75.4 (C-4), 72.8, 70.6 (*CH*$_2$–Ph), 68.4 (C-2), 63.7 (C-5), 62.5 (C-6). Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.68; H 6.74.

3.5. Benzyl 3-*O*-benzyl-6-*O*-pivaloyl-α-D-galactopyranoside (8)

To a solution of **7α** (20 g, 55 mmol) in pyridine (250 mL) was slowly added pivaloyl chloride (10.2 mL, 82 mmol) at 0 °C. After being stirred for 2 h, the mixture was diluted with EtOAc, and washed with 20% aq HCl, satd aq $NaHCO_3$, and then brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue on a silica gel column (9:1 hexane–EtOAc) gave **8** as an oil in 76% yield; $[\alpha]_D$ −69.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.53–7.28 (Ph), 5.20 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 4.78–4.49 (m, 4H, *CH*$_2$–Ph), 4.25 (dd, 1H, $J_{2,3}$ 10.0 Hz, H-2), 4.22 (dd, 1H, $J_{4,5}$ 3.8 Hz, H-4), 4.20, 3.98 (m, 2H, $J_{6a,6b}$ 9.6 Hz, m, H-6), 3.85 (dd, 1H, $J_{3,4}$ 3.4 Hz, H-3), 3.65 (m, 1H, $J_{5,6a}$ 1.8 Hz, $J_{5,6b}$ 4.5 Hz, H-5), 1.24 (s, 9H, C*Me*$_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 169.9 (*C*O), 139.1–128.6 (Ph), 98.9 (C-1), 77.1 (C-3), 74.6 (C-4), 71.9, 70.6 (*CH*$_2$–Ph), 68.4 (C-2), 63.5 (C-5), 63.1 (C-6), 37.2 (*C*Me$_3$), 27.6 (C*Me*$_3$). Anal. Calcd for $C_{24}H_{32}O_7$: C, 67.57; H, 7.21. Found: C, 67.61; H 7.24.

3.6. Benzyl 2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl-(1 → 2)-[2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl-(1 → 4)]-3-*O*-benzyl-6-*O*-pivaloyl-α-D-glucopyranoside (11a)

Procedure 1: To a suspension of **4** (250 mg, 0.56 mmol), **9**[16] (740 mg, 1.7 mmol) and 4 Å MS (500 mg) in dry CH_2Cl_2 (5 mL) at −60 °C under N_2 was added a solution of $BF_3{\cdot}Et_2O$ (3.2×10^{-2} mL, 0.28 mmol) in CH_2Cl_2. After being stirred for 2 h at rt, the reaction was quenched with Et_3N, filtered, and concentrated. Chromatography of the residue on a silica gel column (3:1 hexane–EtOAc) gave **11a** as a white solid in 30% yield; *Procedure 2*: To a stirred suspension of **4** (250 mg, 0.56 mmol) and 4 Å MS (500 mg) in dry CH_2Cl_2 (5 mL) at −60 °C under N_2, was added a solution of $BF_3{\cdot}Et_2O$ (32 μL in CH_2Cl_2, 0.28 mmol) followed by a solution of **9** (740 mg, 1.7 mmol) in CH_2Cl_2 (2 mL). The reaction was allowed to warm to rt, and stirred for 2 h, and then quenched by addition of NEt_3. The mixture was diluted with CH_2Cl_2 (20 mL), filtered, and concentrated under reduced pressure. Chromatography of the residue on a silica gel column (3:1 hexane–EtOAc) gave **11a** as a white solid in 61% yield; mp 55–57 °C; $[\alpha]_D$ +2.6 (*c* 0.5, $CHCl_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ **glucose** 169.8 (*C*O), 137.9–128.26 (Ph), 99.1 (C-1), 83.6 (C-3), 78.6 (C-2), 75.2 (C-4), 75.8, 70.3 (*CH*$_2$–Ph), 73.1 (C-5), 63.7 (C-6), 39.1 (*C*Me$_3$), 27.7 (C*Me*$_3$), **fucose (1 → 4)** 171.2–170.0 (CH$_3$*C*O), 100.5 (C-1), 71.7 (C-3), 70.6 (C-4), 69.9–69.6 (C-2, C-5), 21.0–21.2 (*CH*$_3$CO), 16.2 (C-6), **fucose (1 → 2)** 101.6 (C-1), 71.5 (C-3), 71.0 (C-4), 69.9–69.6 (C-2, C-5), 16.3 (C-6). Anal. Calcd for $C_{49}H_{64}O_{21}$: C, 59.51; H, 6.52. Found: C, 59.48; H, 6.50.

3.7. 2,3,4-Tri-*O*-acetyl-β-L-fucopyranosyl-(1 → 2)-[2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl-(1 → 4)]-1,3,6-tri-*O*-acetyl-D-glucopyranose (11c)

A mixture of prehydrogenated 10% Pd–C catalyst (50 mg) and **11a** (250 mg, 0.25 mmol) dissolved in 1:1 MeOH–dioxane (10 mL) was shaked in a hydrogen atmosphere (1 atm) during 12 h at 50 °C. The catalyst was filtered off and concentrated under reduced pressure to give an oil. A solution of the crude and NaOH (150 mg, 3.1 mmol) dissolved in 1:1:1 H_2O–MeOH–THF (15 mL) was stirred at 40 °C for 2 h, then neutralized with Dowex-50 (H^+ form), filtered, and concentrated. The mixture (**11b**) was dissolved in pyridine (10 mL) and added Ac_2O (1 mL). After 24 h at 5 °C, the solution was concentrated, diluted with EtOAc, and washed with 20% aq HCl, satd aq $NaHCO_3$, and then brine. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Chromatography of the residue on a silica gel column (9:1 hexane–EtOAc) gave **11c** as a white solid in 46% yield; mp 85–86 °C; $[\alpha]_D$ +26.1 (*c* 0.4, $CHCl_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ **glucose** 171.5–169.0 (CH$_3$*C*O), 89.9 (C-1), 77.4 (C-4), 76.9 (C-2), 72.3 (C-3), 70.3 (C-5), 61.9 (C-6), 21.3–21.0 (*CH*$_3$CO), **fucose (1 → 4)** 99.9 (C-1), 71.5 (C-3), 71.3 (C-4), 69.9 (C-2), 69.3 (C-5), 16.5 (C-6), **fucose (1 → 2)** 100.3 (C-1), 71.3 (C-3), 71.0 (C-4), 69.9 (C-2), 69.4 (C-5), 16.4 (C-6). Anal. Calcd for $C_{36}H_{50}O_{23}$: C, 50.82; H, 5.92. Found: C, 50.77; H, 5.89.

3.8. Benzyl-2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl-(1 → 2)-[2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl-(1 → 4)]-3-*O*-benzyl-6-*O*-pivaloyl-α-D-galactopyranoside (12a)

A procedure similar to that for the preparation of **11a** was employed. Treatment of **8** (250 mg, 0.56 mmol) and **9**[16] (740 mg, 1.7 mmol) with $BF_3{\cdot}Et_2O$ (3.2×10^{-2} mL, 0.28 mmol) gave **12a** as a white solid in 35% (procedure 1) or 66% yield if we use the '*inverse procedure*' (procedure 2); mp 88–89 °C; $[\alpha]_D$ −25.4 (*c* 0.2, $CHCl_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ **galactose** 171.1–170.3 (*C*O), 138.7–128.1 (Ph), 96.6 (C-1), 77.3 (C-3), 75.7 (C-4), 73.2, 68.3 (*CH*$_2$–Ph), 68.2, 68.0 (C-2, C-5), 63.9 (C-6), 39.2 (*C*Me$_3$), 27.6 (C*Me*$_3$), **fucose (1 → 4)** 99.3 (C-1), 71.1 (C-4), 70.6 (C-3), 69.5 (C-2), 69.1 (C-5), 21.3

(CH_3CO), 16.6 (C-6), **fucose** (**1** → **2**) 99.9 (C-1), 71.4 (C-4), 70.1 (C-3), 69.7 (C-2), 69.1 (C-5), 16.6 (C-6). Anal. Calcd for $C_{49}H_{64}O_{21}$: C, 59.51; H, 6.52. Found: C, 59.45; H, 6.48.

3.9. 2,3,4-Tri-*O*-acetyl-β-L-fucopyranosyl-(1 → 2)-[2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl-(1 → 4)]-1,3,6-tri-*O*-acetyl-D-galactopyranose (12c)

A mixture of prehydrogenated 10% Pd–C catalyst (50 mg) and **12a** (250 mg, 0.25 mmol) dissolved in 1:1 MeOH–dioxane (10 mL) was shaked in a hydrogen atmosphere (1 atm) during 12 h at 50 °C. The catalyst was filtered off and the solution concentrated under reduced pressure to give an oil. A solution of the crude and NaOH (150 mg, 3.1 mmol) dissolved in 1:1:1 H_2O–MeOH–THF (15 mL) was stirred at 40 °C for 2 h, then neutralized with Dowex-50 (H^+ form), filtered, and concentrated. The mixture (**12b**) was dissolved in pyridine (10 mL) and added Ac_2O (1 mL). After 24 h at 5 °C, the solution was concentrated, diluted with EtOAc, and washed with a 20% aq HCl, satd aq $NaHCO_3$, and then brine. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Chromatography of the residue on a silica gel column (9:1 hexane–EtOAc) gave **12c** as a white solid in 45% yield; mp 91–95 °C; $[\alpha]_D$ −21.0 (*c* 0.1, $CHCl_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ **galactose** 171.5–169.0 (CH_3CO), 89.4 (C-1), 73.4 (C-4), 71.5 (C-2), 71.0 (C-3), 70.5 (C-5), 61.9 (C-6), 21.2–20.8 (CH_3CO), **fucose** (**1** → **4**) 100.1 (C-1), 71.5 (C-3), 70.3 (C-4), 69.5 (C-2, C-5), 16.3 (C-6), **fucose** (1 → 2) 100.5 (C-1), 71.7 (C-3), 70.1 (C-2, C-4), 69.7 (C-5), 16.3 (C-6). Anal. Calcd for $C_{36}H_{50}O_{23}$: C, 50.82; H, 5.92. Found: C, 50.75; H, 5.87.

3.10. Benzyl-2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1 → 2)-[2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1 → 4)]-3-*O*-benzyl-6-*O*-pivaloyl-α-D-galactopyranoside (13a)

A procedure similar to the method used for the preparation of **11a** was employed. Treatment of **8** (250 mg, 0.56 mmol) and **10**[17] (740 mg, 1.7 mmol) with $BF_3{\cdot}Et_2O$ (3.2×10^{-2} mL, 0.28 mmol) gave **13a** as a white solid in 68% (procedure 1) or 74% yield if we use the '*inverse procedure*' (procedure 2); mp 78–81 °C; $[\alpha]_D$ −16.4 (*c* 0.2, $CHCl_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ **galactose** 171.2–170.3 (*C*O), 138.5–128.5 (Ph), 96.6 (C-1), 77.4 (C-3), 75.6 (C-4), 73.4, 68.5 (CH_2–Ph), 68.8 (C-2), 68.0 (C-5), 63.9 (C-6), 39.5 (CMe_3), 27.7 (CMe_3), **rhamnose** (**1** → **4**) 99.5 (C-1), 70.6 (C-4), 70.2 (C-2), 68.4 (C-3), 67.8 (C-5), 21.1–20.4 (CH_3CO), 17.2 (C-6), **rhamnose** (**1** → **2**) 99.9 (C-1), 70.9 (C-4), 70.1 (C-3), 69.5 (C-2), 67.7 (C-5), 17.6 (C-6). Anal. Calcd for $C_{49}H_{64}O_{21}$: C, 59.51; H, 6.52. Found: C, 59.48; H, 6.46.

3.11. 2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl-(1 → 2)-[2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1 → 4)]-1,3,6-tri-*O*-acetyl-α-D-galactopyranose (13c)

A mixture of prehydrogenated 10% Pd–C catalyst (50 mg) and **13a** (250 mg, 0.25 mmol) dissolved in 1:1 MeOH–dioxane (10 mL) was shaked in a hydrogen atmosphere (1 atm) during 12 h at 50 °C. The catalyst was filtered off and concentrated under reduced pressure to give an oil. A solution of the crude and NaOH (150 mg, 3.1 mmol) dissolved in 1:1:1 H_2O–MeOH–THF (15 mL) was stirred at 40 °C for 2 h, then neutralized with Dowex-50 (H^+ form), filtered, and concentrated. The mixture (**13b**) was dissolved in pyridine (10 mL) and added Ac_2O (1 mL). After 24 h at 5 °C, the solution was concentrated, diluted with EtOAc, and washed with 20% aq HCl, satd aq $NaHCO_3$, and then brine. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Chromatography of the residue on a silica gel column (9:1 hexane–EtOAc) gave **13c** as a white solid in 49% yield; mp 87–88 °C; $[\alpha]_D$ −35.2 (*c* 0.1, $CHCl_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ **galactose** 171.5–169.0 (CH_3CO), 89.7 (C-1), 73.4 (C-4), 71.9 (C-2), 70.8 (C-3), 70.5 (C-5), 62.0 (C-6), 21.2–20.6 (CH_3CO), **rhamnose** (**1** → **4**) 99.4 (C-1), 70.6 (C-4, C-2), 68.7 (C-3), 68.1 (C-5), 17.5 (C-6), **rhamnose** (**1** → **2**) 99.0 (C-1), 70.6 (C-4), 70.3 (C-2), 68.7 (C-3), 67.9 (C-5), 17.5 (C-6). Anal. Calcd for $C_{36}H_{50}O_{23}$: C, 50.82; H, 5.92. Found: C, 50.78; H, 5.89.

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