Novel Glycosidation of α-D-Altropyranosides

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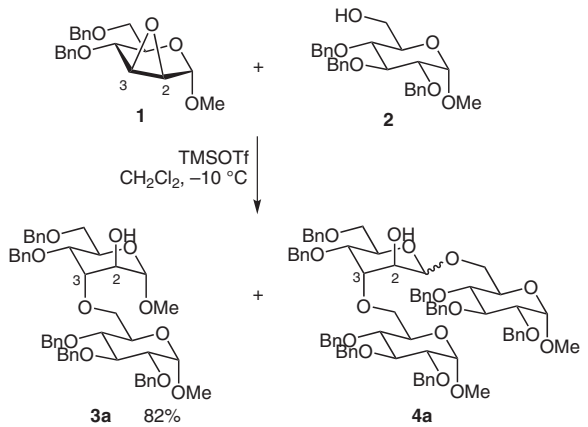
Abstract: A new glycosidation of α-D-altropyranosides, in which the 2-hydroxy group is not protected, was developed. The reaction proceeds via a 1,2-β-oxirane, which is formed in situ without extra steps for exchanging the 1-methoxy group to a more reactive leaving group. The glycoside bond of α-D-altropyranoside was shown to be weaker compared with those of α-D-glucopyranoside and α-D-mannopyranoside.

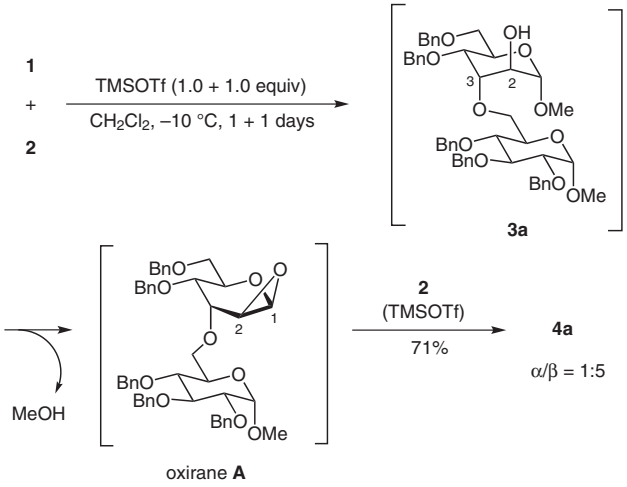
Key words: carbohydrates, glycosylations, epoxides, ring opening, D-altropyranoside

Since coyolosa, a natural ether-linked sugar, was isolated from *Acrocomia mexicana* as a unique 6,6′-ether-linked sugar,[1] we have investigated various syntheses of ether-linked pyranoses with the expectation of a new candidate in the search for drugs to combat diabetes.[2] Thus, we have achieved the synthesis of a novel 3,6′-ether-linked sugar (methyl α-D-altropyranoside) **3a** by nucleophilic ring opening of a 2,3-anhydro-α-D-mannopyranoside (oxirane) **1** (Scheme 1).[3] In the course of the study, a new type of three-pyranose-linked sugar **4a** with ether and glycosidic linkages was found to form as a minor product. Herein we describe the structure and mechanism of formation of this unique sugar **4a**, which led to a new glycosidation of α-D-altropyranosides. We further consider the interesting features of the glycosidic linkage in this rare sugar.



Scheme 1 Regioselective nucleophilic opening of 2,3-anhydro-α-D-mannopyranoside **1** with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**2**)

When the oxirane **1**[4] was treated with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**2**)[5] in the presence of excess trimethylsilyl triflate, we found that the product, the ether-linked sugar **3a**,[3] was gradually transformed into another product. A detailed analysis of the isolated minor product allowed us to determine the structure to be the three-pyranose-linked sugar **4a**. By extensive modification of the reaction conditions, we succeeded in improving the yield of **4a** (Scheme 2). In this case, the addition of trimethylsilyl triflate was divided into two parts. The initial addition of trimethylsilyl triflate (1 equiv) was followed by a second addition (1 equiv) to afford **4a** (α/β = 1:5) in 71% yield. This is the first example of a three-pyranose-linked sugar with ether and glycosidic linkages, which we have tentatively named a 'hybrid sugar'.



Scheme 2 One-pot formation of **4a** by etherification–glycosidation

Based on these results, we assumed that this reaction might be a one-pot etherification–glycosidation, as shown in Scheme 2. The initial addition of trimethylsilyl triflate promoted nucleophilic ring opening of oxirane **1** with **2** to provide the ether-linked sugar **3a**, which subsequently reacted with **2** after the second addition of trimethylsilyl triflate to give the hybrid sugar **4a** via oxirane **A**. Formation of **4a** from oxirane **A** and **2** is consistent with a previous report[6] showing that glycosidation of 1,2-anhydro sugars with similar acceptors gives glycosides.

It is noteworthy that methyl α-D-altropyranoside **3a**, in which the 2-OH group is not protected, was glycosidated easily. Such a 1,2-*trans*-D-altropyranoside appears to be a good substrate for intramolecular cyclization to form the oxirane **A**. Although the intermediate oxirane **A** was not

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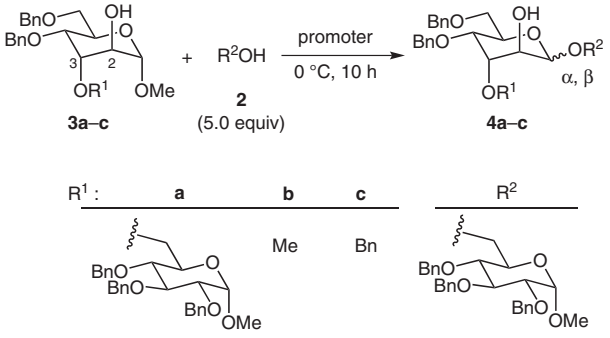
isolated, this sequence might be an alternative glycosidation of D-altropyranoside.[7]

To confirm this reaction mechanism, we first examined the latter glycosidation using **3a** as the glycosyl donor. As shown in Table 1, glycosidation of **3a** proceeded under acidic conditions to provide the three-pyranose-linked sugar **4a**. Although triflic acid (50%, α/β = 1:2.3) and tin(IV) chloride (55%, α/β = 1:4) appeared to be effective (entries 1 and 2), we found trimethylsilyl triflate to be the most promising promoter.

Table 1 Glycosidation of Methyl α-D-Altropyranosides **3a–c** with Methyl 2,3,4-Tri-*O*-benzyl-α-D-glucopyranoside (**2**)



Entry[a]	Substrate	Promoter[b]	Solvent	Product	Yield (%)	Ratio[c] α/β
1	**3a**	TfOH	CH_2Cl_2	**4a**	50	1:2.3
2	**3a**	$SnCl_4$	CH_2Cl_2	**4a**	55	1:4
3	**3a**	TMSOTf	CH_2Cl_2	**4a**	64	1:2.4
4	**3a**	TMSOTf[d]	CH_2Cl_2	**4a**	67	1:4.6
5	**3a**	TMSOTf[e]	CH_2Cl_2	**4a**	72	1:2.3
6	**3a**	TMSOTf	Et_2O	**4a**	59	1:0.7
7[f]	**3a**	TMSOTf	CH_2Cl_2	**4a**	63	1:4.7
8	**3b**	TMSOTf	CH_2Cl_2	**4b**	53	1:2.3
9	**3c**	TMSOTf	CH_2Cl_2	**4c**	77	1:2.9

[a] Reaction time was 10 h unless otherwise stated.
[b] 1.0 equivalent were used unless otherwise stated.
[c] Ratio of the isolated products.
[d] 2.0 equivalents were used.
[e] The molecular sieve MS4A was added.
[f] Reaction time of 44 h.

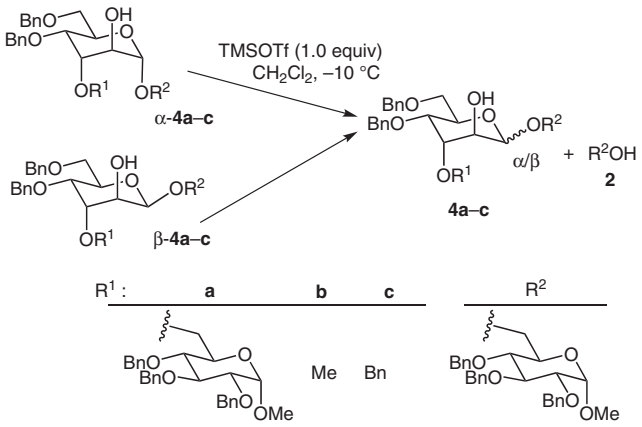
Reaction of **3a** with **2** (5 equiv) in the presence of trimethylsilyl triflate (1 equiv) in dichloromethane at 0 °C for ten hours afforded **4a** (64%, α/β = 1:2.4) (entry 3). While an excess amount of **2** (5 equiv) was necessary to obtain the product efficiently, an excess amount of trimethylsilyl triflate did not increase the yield. Instead, the ratio of anomers changed (α/β = 1:4.6) (entry 4). In contrast, the addition of molecular sieves (MS4A) increased the yield (72%) without changing the ratio of anomers (α/β = 1:2.3) (entry 5). A large solvent effect was observed; while selectivity for the β-anomer was usually achieved in dichloromethane, the ratio reversed in diethyl ether (α/β = 1:0.7) (entry 6). We next examined this glycosidation using methyl α-D-altropyranosides **3b** (OR^1 = OMe)[3] and **3c** (OR^1 = OBn)[3] as glycosyl donors (entries 8 and 9). Fortunately, the reaction proceeded smoothly to give **4b** and **4c**, respectively. It is useful that methyl 3,4,6-tri-*O*-benzyl-α-D-altropyranoside (**3c**) was converted into **4c** in good yield (77%, α/β = 1:2.9).

All these things make it clear that the 1,2-*trans*-altropyranoside **3**, in which the 2-OH group is not protected, actually reacted as a donor to give the sugar **4**.[8] It should be emphasized that the stable 1-methoxy group reacts as an excellent leaving group in this case, that is, there is no need for extra steps to exchange the methoxy group for a more reactive leaving group (e.g., Br, F).[9]

We also found that a longer reaction time changes the product distribution (entry 3 vs 7). It is possible that the α-anomer α-**4a** and β-anomer β-**4a** of **4a** exist in an equilibrium state. To reveal the equilibrium state, each isolated anomer was treated with trimethylsilyl triflate. The results are shown in Table 2. After five hours in dichloromethane, the pure α-**4a** anomer gave anomeric mixtures of **4a** (53%, α/β = 1:4) and cleaved alcohol **2** (39%) (entry 1). Similarly, β-**4a** provided anomeric mixtures of **4** (48%, α/β = 1:9) and **2** (34%) (entry 3). It is clear that the glycoside bond in **4** is so weak that it was cleaved by trimethylsilyl triflate in dichloromethane and that the previously cleaved alcohol **2** was glycosylated again in the presence of trimethylsilyl triflate. In this equilibrium, the β-anomer β-**4a** is preferred over the α-anomer α-**4a**. On the other hand, in diethyl ether pure α-**4a** and β-**4a** were recovered even after longer reaction times (entries 2 and 4). It is likely that diethyl ether, which has higher Lewis basicity, decreased the Lewis acidity of trimethylsilyl triflate so that glycoside bonds in α-**4a** and β-**4a** were retained at –10 °C. A similar equilibrium was observed for the anomers of **4b** and **4c** (entries 5–8). After treatment of the pure α-**4b** anomer with trimethylsilyl triflate in dichloromethane for ten hours, an anomeric mixture of **4b** was obtained (22%, α/β = 1:1.2) along with the alcohol **2** (63%) and a 1-OH D-altrose derivative (entry 5). Pure β-**4b** also gave anomeric mixtures of **4b** (25%, α/β = 1:1.3), **2** (58%), and a 1-OH D-altrose derivative (entry 6). In this case, since the amount of cleaved alcohol **2** increased, **4b** appeared to be a less stable glycoside. Examination of α-**4c** and β-**4c** resulted in similar recovery yields with an increase in the preference for β-**4c** (entries 7 and 8). We assume that the glycosidation of **4** was greatly affected by the bulky substitution at the 3-position of D-altropyranoside, which might be responsible for the tendency for 1,2-*cis*-glycosidation (i.e., β-**4** form), especially in **4a** (entries 1 and 3).

As a whole, it should be stressed that α-D-altropyranoside **3**, in which the 2-OH group is not protected, exists in an equilibrium in acidic conditions. In other words, the glycoside bond in unprotected D-altropyranoside **3** is essentially unstable.

Table 2 Stability of D-Altropyranoside **4**



Entry	Substrate	Conditions		Product		
		Solvent	Time (h)	Recovered yield (%) of **4**[a]	Ratio[b] α/β	Yield (%) of **2**
1	α-**4a**	CH_2Cl_2	5	53	1:4	39
2	α-**4a**	Et_2O	5	89	1:0	–
3	β-**4a**	CH_2Cl_2	5	48	1:9	34
4	β-**4a**	Et_2O	12	93	0:1	–
5	α-**4b**	CH_2Cl_2	10	22	1:1.2	63
6	β-**4b**	CH_2Cl_2	10	25	1:1.3	58
7	α-**4c**	CH_2Cl_2	10	15	1:2.6	37
8	β-**4c**	CH_2Cl_2	10	36	1:3.7	23

[a] Combined yield of α-**4** and β-**4**.
[b] Determined using HPLC.

We questioned whether the stereochemistry of the 1,2,3-positions of the α-D-altropyranoside **3** were the key factor in this glycosidation. To assess the importance of the configuration at the 1,2,3-positions of pyranoside, methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**5**) and methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**6**)[10] (Figure 1) were selected for comparison and subjected to trimethylsilyl triflate promoted glycosidation conditions.

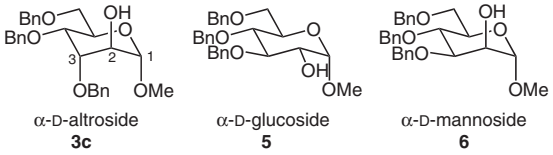
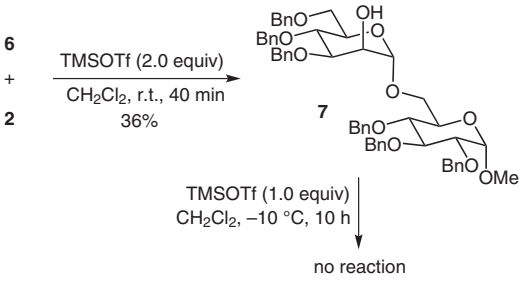


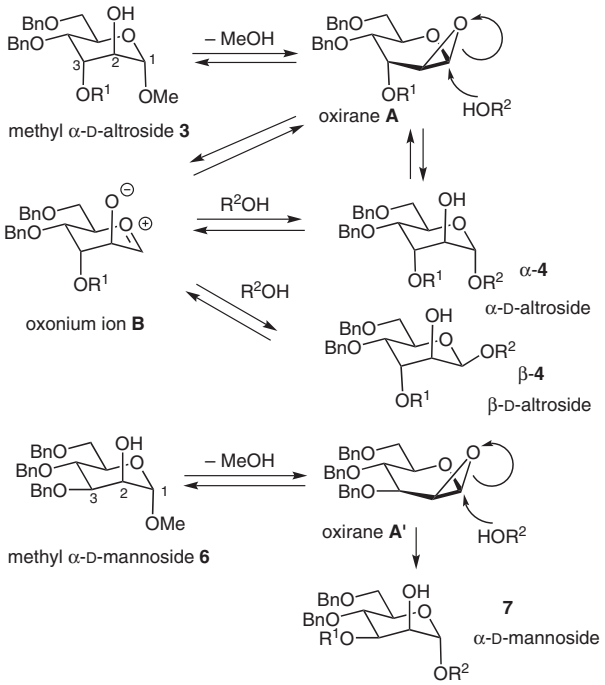
Figure 1 Three methyl α-D-pyranosides **3c**, **5**, and **6** with different stereochemistry at the 2,3-positions

While the reaction of the α-D-glucoside **5** did not proceed at all, the reaction of the α-D-mannoside **6** with **2** (4 equiv) in the presence of trimethylsilyl triflate afforded the sole product **7** (α-anomer)[11] in 36% yield (Scheme 3). The result agrees with our speculation that the reaction proceeds via the 1,2-β-oxirane formed in situ. In sharp contrast to the α-D-altroside **3c**, the mannoside **6** showed highly robust α-stereoselectivity. We further examined the stability of **7** under acidic conditions. After treatment with trimethylsilyl triflate at –10 °C for ten hours, the glycoside **7** was recovered completely. It is clear that the mannoside **7** is more stable than the altroside **4c** under acidic conditions and that no equilibrium is observed in this case.



Scheme 3 Trimethylsilyl triflate promoted glycosidation of methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside **6**

Judging from the above results, we can safely say that configuration of the 2-OH group in α-D-altroside and α-D-mannoside **3** and **6** is necessary for this glycosidation. One possible explanation for this glycosidation mechanism is shown in Scheme 4.



Scheme 4 Plausible reaction mechanisms of the glycosidation of **3** and **6**

The 1,2-*trans*-methyl α-D-altroside **3** and α-D-mannoside **6** appear to be good substrates for intramolecular cyclization to form the oxiranes **A** and **A′**, respectively. Although not isolated, the oxiranes **A** and **A′** would function as glycosyl donors. The reaction of oxirane **A** formed from **3** with an acceptor (R^2OH) should stereoselectively yield the α-altroside α-**4** through axial attack at the anomeric position in an S_N2-like manner. Similarly, the methyl α-D-mannoside **6** would stereoselectively provide the α-anomer **7** via the oxirane **A′**. In the case of the α-D-altroside **3**, however, the α-anomer α-**4** formed first is unstable so that the glycoside bond would be cleaved under acidic conditions to form the oxonium ion **B**. This is why a longer reaction time in the glycosidation step changes the product distribution and yields the β-anomer β-**4** in preference to the α-anomer α-**4**. Thus, it is possible that the oxirane **A**, oxonium ion **B**, and anomers of the α-D-altroside exist in equilibrium. It seems reasonable that the 1,3-diaxial strain in the α-anomer of α-D-altroside is so disadvantageous that the β-anomer is preferred in the reaction. Although there is scope for investigation of this reaction mechanism, we consider that the glycoside bond of α-D-altroside, in which the 2-OH group is not protected, is essentially weak. It is known that α-D-altrosides are not contained in natural polysaccharides. The reason may reside in the instability of the glycoside bond of α-D-altroside.

In conclusion, a new glycosidation of α-D-altropyranoside promoted by trimethylsilyl triflate was developed. The reaction might proceed via a 1,2-β-oxirane. Most advantageously, it is not necessary to exchange the stable methoxy group at the 1-position for a more reactive leaving group. We also found that the glycoside bond in D-altropyranoside is essentially weak.

All reactions sensitive to air or moisture were conducted under an argon atmosphere. Materials were obtained from commercial suppliers. All anhydrous solvents were purified according to standard methods. NMR spectra were recorded on a Jeol JNM-GSX600 spectrometer at 600 MHz for ^1H NMR and 150 MHz for ^{13}C NMR with TMS as an internal standard. EI-MS spectra were measured on a Jeol JMS-SX102A. FAB-MS were obtained with *m*-nitrobenzyl alcohol as a matrix. Analytical TLC was carried out using Merck silica gel 60 F_{254}. Column chromatography was performed using silica gel Wakogel C-300 (45–60 μm).

Hybrid Sugar 4a; One-Pot Procedure

TMSOTf (25 μL, 0.14 mmol) was added to a mixture of **1** (50 mg, 0.14 mmol) and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**2**, 652 mg, 1.40 mmol) in CH_2Cl_2 (1.4 mL) at –78 °C. The mixture was warmed to –10 °C and stirred for 1 d, and then TMSOTf (25 μL, 0.14 mmol) was added at –78 °C. The mixture was stirred at –10 °C for 1 d and then poured into a pH 7 phosphate buffer and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residual oil was subjected to column chromatography (silica gel, hexane–EtOAc, 5:2) to give α-**4a** (21 mg, 12%), β-**4a** (103 mg, 59%), and **3a** (22.2 mg, 19%).

Hybrid Sugar 4a by Glycosidation of 3a with 2; Typical Procedure

To a mixture of ether-linked sugar **3a** (53 mg, 0.06 mmol), **2** (149 mg, 0.32 mmol), and activated MS4A (20 mg) in CH_2Cl_2, TMSOTf (11 μL, 0.06 mmol) was added at –78 °C. The mixture was stirred at –78 °C for 10 h, the mixture was poured into a pH 7 phosphate buffer and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residual oil was subjected to column chromatography (silica gel, hexane–EtOAc, 5:2) to give α-**4a** (18 mg, 22%) and β-**4a** (40 mg, 50%).

Methyl (Methyl 2,3,4-Tri-*O*-benyl-α-D-glucopyranoside)-(6→3)-(4,6-di-*O*-benzyl-α-D-altropyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (α-4a)

R_f = 0.23 (hexane–EtOAc, 1:1); $[\alpha]_D^{22}$ +42.5 (*c* 0.5, $CHCl_3$).

^1H NMR (600 MHz, $CDCl_3$): δ = 7.26–7.15 (m, 40 H, Ar), 4.88 (d, *J* = 10.8 Hz, 1 H, $PhCH_2$), 4.87(d, *J* = 10.8 Hz, 1 H, $PhCH_2$), 4.79 (d, *J* = 11.4 Hz, 1 H, $PhCH_2$), 4.78 (d, *J* = 11.4 Hz, 1 H, $PhCH_2$), 4.73 (d, *J* = 10.8 Hz, 1 H, $PhCH_2$), 4.71 (d, *J* = 10.8 Hz, 1 H, $PhCH_2$), 4.67 (d, *J* = 12.0 Hz, 1 H, $PhCH_2$), 4.64 (d, *J* = 4.8 Hz, 1 H, H1), 4.62 (d, *J* = 11.4 Hz, 1 H, $PhCH_2$), 4.62 (d, *J* = 11.4 Hz, 1 H, $PhCH_2$), 4.56 (d, *J* = 12.0 Hz, 1 H, $PhCH_2$), 4.55 (d, *J* = 12.0 Hz, 1 H, $PhCH_2$), 4.52 (d, *J* = 3.6 Hz, 1 H, H1′), 4.51 (d, *J* = 12.0 Hz, 1 H, $PhCH_2$), 4.50 (d, *J* = 12.0 Hz, 1 H, $PhCH_2$), 4.50 (d, *J* = 3.6 Hz, 1 H, H1″), 4.39 (d, *J* = 12.0 Hz, 1 H, $PhCH_2$), 4.38 (d, *J* = 12.0 Hz, 1 H, $PhCH_2$), 4.29 (d, *J* = 12.0 Hz, 1 H, $PhCH_2$), 3.98 (dd, *J* = 4.2, 9.6 Hz, 1 H, H5), 3.92 (dd, *J* = 4.8, 8.4 Hz, 1 H, H2), 3.92 (m, 1 H, H6′), 3.89 (t, *J* = 9.6 Hz, 1 H, H3″), 3.89 (t, *J* = 9.6 Hz, 1 H, H3′), 3.80 (dd, *J* = 1.8, 10.8 Hz, 1 H, H6″), 3.77 (dd, *J* = 3.6, 4.2 Hz, 1 H, H4), 3.69–3.66 (m, 2 H, H5′, H5″), 3.60–3.58 (m, 2 H, H6′, H6′), 3.53 (dd, *J* = 3.6, 8.4 Hz, 1 H, H3), 3.51 (t, *J* = 9.6 Hz, 1 H, H4″), 3.43 (dd, *J* = 3.6, 9.6 Hz, 1 H, H2′), 3.41 (t, *J* = 9.6 Hz, 1 H, H4′), 3.39 (dd, *J* = 3.6, 9.6 Hz, 1 H, H2″), 3.36–3.32 (m, 2 H, H6, H6), 3.26 (s, 3 H, OCH_3), 3.24 (s, 3 H, OCH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = {138.8, 138.7, 138.6, 138.4, 138.3, 138.2, 138.1, 137.9, 128.4, 128.4, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.0, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 127.5, 127.4} (Ar), 102.0 (C1), 97.9 (C1″), 97.8 (C1′), 82.2 (C3″), 82.0 (C3′), 80.1 (C2″), 80.0 (C2′), 79.5 (C3), 78.0 (C4″), 77.7 (C4′), {75.7, 75.7, 74.9, 74.9, 74.8, 73.3, 73.3, 72.3} ($ArCH_2$), 73.0 (C4), 71.8 (C5), 70.6 (C2), 70.4 (C6″), 70.1 (C5″), 69.8 (C5′), 69.5 (C6), 66.5 (C6′), 55.1 (OCH_3), 55.1 (OCH_3).

HRMS (FAB, MeCN–NBA + NaI): *m*/*z* [M + Na] calcd for $C_{76}H_{84}O_{16}Na$: 1275.5657; found: 1275.5674.

Methyl (Methyl 2,3,4-Tri-*O*-benzyl-α-D-glucopyranoside)-(6→3)-(4,6-di-*O*-benzyl-β-D-altropyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (β-4a)

R_f = 0.41 (hexane–EtOAc, 1:1); $[\alpha]_D^{22}$ +27.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.17 (m, 40 H, Ar), 4.97 (d, *J* = 10.8 Hz, 1 H, $PhCH_2$), 4.93 (d, *J* = 10.8 Hz, 1 H, $PhCH_2$), 4.83 (d, *J* = 10.8 Hz, 1 H, $PhCH_2$), 4.83 (d, *J* = 10.8 Hz, 1 H, $PhCH_2$), 4.79 (d, *J* = 10.8 Hz, 1 H, $PhCH_2$), 4.78 (d, *J* = 1.8 Hz, 1 H, H1), 4.76 (d, *J* = 10.8 Hz, 1 H, $PhCH_2$), 4.76 (d, *J* = 12.6 Hz, 1 H, $PhCH_2$), 4.66 (d, *J* = 12.0 Hz, 1 H, $PhCH_2$), 4.64 (d, *J* = 12.6 Hz, 1 H, $PhCH_2$), 4.60 (d, *J* = 12.0 Hz, 1 H, $PhCH_2$), 4.54 (d, *J* = 10.8 Hz, 1 H, $PhCH_2$), 4.54 (d, *J* = 12.0 Hz, 1 H, $PhCH_2$), 4.54 (d, *J* = 12.0 Hz, 1 H, $PhCH_2$), 4.54 (d, *J* = 3.6 Hz, 1 H, H1′), 4.52 (d, *J* = 10.8 Hz, 1 H, $PhCH_2$), 4.51 (d, *J* = 3.6 Hz, 1 H, H1″), 4.49 (d, *J* = 12.0 Hz, 1 H, $PhCH_2$), 4.41 (d, *J* = 12.0 Hz, 1 H, $PhCH_2$), 4.10 (dd, *J* = 1.8, 10.8 Hz, 1 H, H6′), 3.99–3.97 (m, 2 H, H5, H6″), 3.97 (t, *J* = 9.0 Hz, 1 H, H3′), 3.93 (dd, *J* = 9.0, 9.6 Hz, 1 H, H3″), 3.88 (dd, *J* = 1.8, 4.8 Hz, 1 H, H2), 3.87 (dd, *J* = 4.8, 9.0 Hz, 1 H, H6), 3.82 (dd, *J* = 2.4, 9.0 Hz, 1 H, H6), 3.79 (ddd, *J* = 1.8, 6.0, 9.0 Hz, 1 H, H5′), 3.67–3.69 (m, 3 H, H3, H4, H5″), 3.61 (dd, *J* = 5.4, 10.8 Hz, 1 H, H6″), 3.59 (dd, *J* = 6.0, 10.8 Hz, 1 H, H6′), 3.49 (dd, *J* = 3.6, 9.0 Hz, 1 H, H2′), 3.45 (t, *J* = 9.0 Hz, 1 H, H4″), 3.40 (t, *J* = 9.0 Hz, 1 H, H4′), 3.38 (dd, *J* = 3.6, 9.6 Hz, 1 H, H2″), 3.32 (s, 3 H, OCH_3), 3.28 (s, 3 H, OCH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = {137.7, 137.7, 137.7, 137.6, 137.6, 137.6, 137.1, 137.1, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.3, 128.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9} (Ar), 98.5 (C1), 97.9 (C1″), 97.8 (C1′), 82.0 (C3′), 82.0 (C3″), 80.1 (C4″), 80.0 (C4′), 78.0 (C2″), 77.8 (C2′), 76.2 (C5), {75.8, 75.7, 75.0, 73.4, 73.3, 73.3} ($ArCH_2$), 73.3 (C6), {73.1, 73.0} ($ArCH_2$), 71.6 (C3), 70.8 (C4), 70.5 (C6″), 69.9 (C2), 69.8 (C5″), 69.5 (C5′), 68.2 (C6′), 55.1(OCH_3), 55.1(OCH_3).

HRMS (FAB, MeCN–NBA + NaI): *m*/*z* [M + Na] calcd for $C_{76}H_{84}O_{16}Na$: 1275.5657; found: 1275.5676.

Methyl (4,6-Di-*O*-benzyl-3-*O*-methyl-α-D-altropyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (α-4b)

R_f = 0.66 (hexane–EtOAc, 1:1); $[\alpha]_D^{20}$ +11.3 (*c* 0.4, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 25 H, Ar), 4.99 (d, *J* = 11.0 Hz, 1 H, $PhCH_2$), 4.88 (d, *J* = 11.0 Hz, 1 H, $PhCH_2$), 4.81 (d, *J* = 11.0 Hz, 1 H, $PhCH_2$), 4.78 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.76 (d, *J* = 1.4 Hz, 1 H, H1), 4.66 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.59 (d, *J* = 11.6 Hz, 1 H, $PhCH_2$), 4.57 (d, *J* = 12.3 Hz, 1 H, $PhCH_2$), 4.56 (d, *J* = 3.6 Hz, 1 H, H1′), 4.55 (d, *J* = 11.0 Hz, 1 H, $PhCH_2$), 4.53 (d, *J* = 12.3 Hz, 1 H, $PhCH_2$), 4.50 (d, *J* = 11.6 Hz, 1 H, $PhCH_2$), 4.11 (dd, *J* = 1.9, 10.7 Hz, 1 H, H6′), 3.99 (t, *J* = 9.6 Hz, 1 H, H3′), 3.93 (ddd, *J* = 2.8, 5.0, 9.1 Hz, 1 H, H5), 3.87 (dd, *J* = 1.4, 4.4 Hz, 1 H, H2), 3.86 (dd, *J* = 3.0, 9.1 Hz, 1 H, H4), 3.79 (ddd, *J* = 1.9, 5.5, 10.1 Hz, 1 H, H5′), 3.71 (dd, *J* = 2.8, 10.7 Hz, 1 H, H6), 3.68 (dd, *J* = 3.0, 4.4 Hz, 1 H, H3), 3.66 (dd, *J* = 5.0, 10.7 Hz, 1 H, H6), 3.63 (dd, *J* = 5.5, 10.7 Hz, 1 H, H6′), 3.51 (dd, *J* = 3.6, 9.6 Hz, 1 H, H2′), 3.43 (dd, *J* = 9.6, 10.1 Hz, 1 H, H4′), 3.42 (s, 3 H, OCH_3), 3.35 (s, 3 H, OCH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = {138.7, 138.4, 138.1, 138.1, 138.0, 128.5, 128.4, 128.4, 128.3, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5} (Ar), 98.6 (C1), 97.9 (C1′), 82.1 (C3′), 79.9 (C2′), 77.9 (C4′), 76.9 (C3), {75.8, 75.0, 73.4, 73.4} ($ArCH_2$), 72.9 (C5), 72.6 (C4), 71.9 ($ArCH_2$), 70.0 (C5′), 69.7 (C6), 68.8 (C2), 68.2 (C6′), 59.2 (OCH_3), 55.1 (OCH_3).

HRMS (FAB, MeCN–NBA + NaI): *m*/*z* [M + Na] calcd for $C_{49}H_{56}O_{11}Na$: 843.3721; found: 843.3727.

Methyl (4,6-Di-*O*-benzyl-3-*O*-methyl-β-D-altropyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (β-4b)

R_f = 0.39 (hexane–EtOAc, 1:1); $[\alpha]_D^{22}$ +45.2 (*c* 0.25, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 25 H, Ar), 4.96 (d, *J* = 10.7 Hz, 1 H, $PhCH_2$), 4.90 (d, *J* = 11.0 Hz, 1 H, $PhCH_2$), 4.82 (d, *J* = 10.7 Hz, 1 H, $PhCH_2$), 4.78 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.76 (d, *J* = 3.0 Hz, 1 H, H1), 4.71 (d, *J* = 11.0 Hz, 1 H, $PhCH_2$), 4.65 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.60 (d, *J* = 11.2 Hz, 1 H, $PhCH_2$), 4.59 (d, *J* = 3.6 Hz, 1 H, H1′), 4.51 (d, *J* = 11.2 Hz, 1 H, $PhCH_2$), 4.50 (d, *J* = 12.4 Hz, 1 H, $PhCH_2$), 4.42 (d, *J* = 12.4 Hz, 1 H, $PhCH_2$), 4.15 (ddd, *J* = 4.0, 4.0, 7.8 Hz, 1 H, H5), 4.02 (dd, *J* = 3.0, 5.8 Hz, 1 H, H2), 3.99 (dd, *J* = 3.9, 11.3 Hz, 1 H, H6′), 3.98 (t, *J* = 9.6 Hz, 1 H, H3′), 3.88 (dd, *J* = 3.3, 7.8 Hz, 1 H, H4), 3.74 (ddd, *J* = 1.9, 3.9, 9.6 Hz, 1 H, H5′), 3.63 (dd, *J* = 1.9, 11.3 Hz, 1 H, H6′), 3.58 (t, *J* = 9.6 Hz, 1 H, H4′), 3.57 (dd, *J* = 3.3, 5.8 Hz, 1 H, H3), 3.56 (dd, *J* = 4.0, 11.0 Hz, 1 H, H6), 3.52 (dd, *J* = 4.0, 11.0 Hz, 1 H, H6), 3.51 (dd, *J* = 3.6, 9.6 Hz, 1 H, H2′), 3.42 (s, 3 H, OCH_3), 3.35 (s, 3 H, OCH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = {138.8, 138.5, 138.2, 138.2, 138.2, 138.0, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 127.6, 127.5, 127.0} (Ar), 101.3 (C1), 98.0 (C1′), 82.2 (C3′), 80.0 (C2′), 78.3 (C3), 77.7 (C4′), {75.7, 74.8, 73.4, 73.4, 71.6} ($ArCH_2$), 71.6 (C4), 69.9 (C5′), 69.3 (C5), 69.3 (C6), 68.6 (C2), 66.4 (C6′), 58.0(OCH_3), 55.1(OCH_3).

HRMS (FAB, MeCN–NBA + NaI): *m*/*z* [M + Na] calcd for $C_{49}H_{56}O_{11}Na$: 843.3721; found: 843.3715.

Methyl (3,4,6-Tri-*O*-benzyl-α-D-altropyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (α-4c)

R_f = 0.56 (hexane–EtOAc, 1:1); $[\alpha]_D^{20}$ +20.7 (*c* 0.28, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.28–7.14 (m, 30 H, Ar), 4.91 (d, *J* = 11.0 Hz, 1 H, $PhCH_2$), 4.79 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.78 (s, 1 H, H1′), 4.72 (d, *J* = 11.0 Hz, 1 H, $PhCH_2$), 4.70 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.60 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.57 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.50 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.49 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.48 (d, *J* = 3.6 Hz, 1 H, H1), 4.45 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.44 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.44 (d, *J* = 11.6 Hz, 1 H, $PhCH_2$), 4.36 (d, *J* = 11.6 Hz, 1 H, $PhCH_2$), 4.04 (dd, *J* = 1.7, 10.7 Hz, 1 H, H6), 3.95 (ddd, *J* = 2.5, 4.7, 9.1 Hz, 1 H, H5′), 3.91 (t, *J* = 9.1 Hz, 1 H, H3), 3.89 (dd, *J* = 3.0, 4.1 Hz, 1 H, H3′), 3.80 (m, 2 H, H2′, H4′), 3.71 (ddd, *J* = 1.7, 5.5, 9.1 Hz, 1 H, H5), 3.64 (dd, *J* = 2.5, 10.7 Hz, 1 H, H6′), 3.60 (dd, *J* = 4.7, 10.7 Hz, 1 H, H6′), 3.57 (dd, *J* = 5.5, 10.7 Hz, 1 H, H6), 3.42 (dd, *J* = 3.6, 9.1 Hz, 1 H, H2), 3.34 (t, *J* = 9.1 Hz, 1 H, H4), 3.25 (s, 3 H, OCH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = {138.6, 138.3, 138.2, 138.0, 137.9, 128.4, 128.3, 128.3, 128.2, 128.2, 128.0, 127.9, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 127.5, 127.4} (Ar), 98.5 (C1), 97.8 (C1′), 82.0 (C3), 79.8 (C3′), 77.9 (C2′), 75.7 (C4′), 75.0 (C4), {74.3, 73.4} ($ArCH_2$), 73.3 (C5), 73.1 (C5′), {73.0, 73.0, 71.8, 70.0} ($ArCH_2$), 69.7 (C6), 69.5 (C6′), 68.1 (C2), 55.1 (OCH_3).

HRMS (FAB, MeCN–NBA + NaI): *m*/*z* [M + Na] calcd for $C_{55}H_{60}O_{11}Na$: 919.4034; found: 919.4033.

Methyl (3,4,6-Tri-*O*-benzyl-β-D-altropyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (β-4c)

R_f = 0.27 (hexane–EtOAc, 1:1); $[\alpha]_D^{22}$ +63.9 (*c* 0.925, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.16 (m, 30 H, Ar), 4.94 (d, *J* = 11.0 Hz, 1 H, $PhCH_2$), 4.78 (d, *J* = 2.5 Hz, 1 H, H1), 4.78 (d, *J* = 11.0 Hz, 1 H, $PhCH_2$), 4.77 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.71 (d, *J* = 11.3 Hz, 1 H, $PhCH_2$), 4.65 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.65 (d, *J* = 11.8 Hz, 1 H, $PhCH_2$), 4.60 (d, *J* = 11.3 Hz, 1 H, $PhCH_2$), 4.60 (d, *J* = 3.6 Hz, 1 H, H1′), 4.59 (d, *J* = 11.8 Hz, 1 H, $PhCH_2$), 4.54 (d, *J* = 11.7 Hz, 1 H, $PhCH_2$), 4.51 (d, *J* = 11.1 Hz, 1 H, $PhCH_2$), 4.43 (d, *J* = 11.7 Hz, 1 H, $PhCH_2$), 4.38 (d, *J* = 11.1 Hz,

1 H, $PhCH_2$), 4.16 (ddd, *J* = 2.8, 3.9, 7.7 Hz, 1 H, H5), 4.08 (dd, *J* = 2.5, 5.2 Hz, 1 H, H2), 4.00 (dd, *J* = 3.8, 11.5 Hz, 1 H, H6′), 3.95 (t, *J* = 9.6 Hz, 1 H, H3′), 3.88 (dd, *J* = 3.3, 7.7 Hz, 1 H, H4), 3.82 (dd, *J* = 3.3, 5.2 Hz, 1 H, H3), 3.73 (ddd, *J* = 1.9, 3.8, 9.6 Hz, 1 H, H5′), 3.60 (dd, *J* = 1.9, 11.5 Hz, 1 H, H6′), 3.55 (t, *J* = 9.6 Hz, 1 H, H4′), 3.54 (dd, *J* = 3.9, 10.7 Hz, 1 H, H6), 3.48 (dd, *J* = 3.6, 9.6 Hz, 1 H, H2′), 3.46 (dd, *J* = 2.8, 10.7 Hz, 1 H, H6), 3.31 (s, 3 H, OCH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = {138.7, 138.5, 138.2, 138.1, 137.9, 128.3, 128.3, 128.2, 128.2, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 127.5, 127.4, 127.4, 127.3} (Ar), 101.4 (C1′), 98.0 (C1), 82.1 (C3), 80.0 (C3′), 77.6 (C2′), 75.9 (C4′), 75.6 (C4), {74.7, 73.4} ($ArCH_2$), 73.4 (C5′), 73.3(C5), {72.4, 72.0, 71.5, 69.9} ($ArCH_2$), 69.2 (C6), 69.1 (C6′), 69.0 (C2), 55.1 (OCH_3).

HRMS (FAB, MeCN–NBA + NaI): *m*/*z* [M + Na] calcd for $C_{55}H_{60}O_{11}Na$: 919.4034; found: 919.4029.

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