Synthesis of Ether-Linked Sugar by Nucleophilic Opening of Carbohydrate Oxiranes

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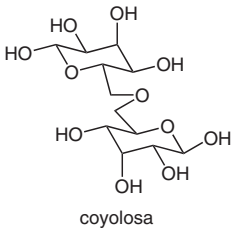
Abstract: A new synthesis of ether-linked sugar utilizing the nucleophilic ring-opening reaction of carbohydrate α- or β-oxirane was developed. The reaction of 2,3-anhydro-α-D-mannopyranosides resulted in the expected high regioselectivity. In contrast, 2,3-anhydro-α-D-allopyranosides showed an unusual regioselectivity shift. The differentiating properties of carbohydrate α- or β-oxirane were investigated by comparing various conditions of the reaction.

Key words: carbohydrates, epoxides, ethers, ring opening, regioselectivity

It was a promising discovery when coyolosa (Figure 1) was isolated from *Acrocomia mexicana* as a unique 6,6′-ether-linked sugar.[1] Since coyolosa has significant effects on fasting blood glucose levels, new light has been shed on the ether linkage of sugars[2] with the expectation of a new candidate in the search for drugs to combat diabetes.



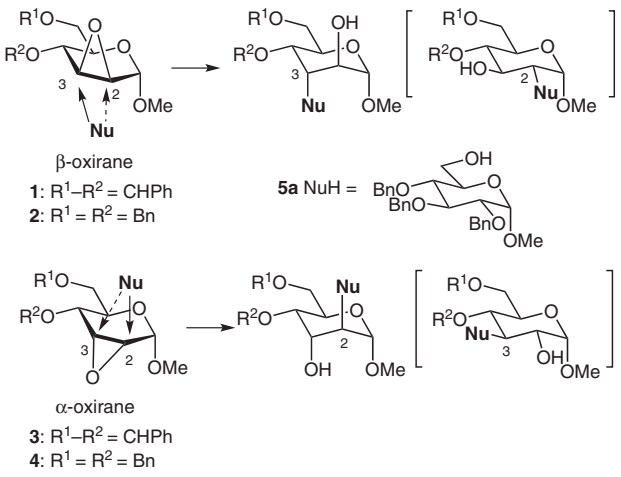
coyolosa

Figure 1

We have therefore investigated a novel synthesis of 6,6′-ether-linked pyranoses through an acetalization–reduction procedure.[3] While this approach was successfully applied to the synthesis of various new ether-linked sugars,[4] we continued to examine an alternative method by which an ether linkage could be introduced at other positions of pyranoses. Herein, we describe a new synthesis of ether-linked sugar by regiospecific nucleophilic opening of carbohydrate oxiranes.

Carbohydrate oxiranes are useful in synthetic studies.[5] Numerous studies have been carried out on 1,2-anhydro sugars as glycosyl donors in glycosylation.[6] 1,6/2,3-Anhydro sugars were demonstrated to be appropriate intermediates in the preparation of various carbohydrate derivatives.[7] We became interested in the oxirane ring opening of 2,3-anhydropyranosides and examined the regioselective nucleophilic attack by the hydroxy group of another pyranoside, by which ether-linked pyranosides could be provided efficiently.

The ring-opening reaction of carbohydrate oxirane with strong anionic nucleophiles (e.g., N_3^-) has been investigated with great interest.[8] However, the use of weakly nucleophilic reagents has not been fully established. We therefore studied the nucleophilic opening of carbohydrate α- and β-oxiranes with alcohols or alkoxides under various conditions (Scheme 1).



Scheme 1 Regioselective nucleophilic opening of the oxirane on a six-membered ring

In general, the nucleophilic opening of an oxirane on a six-membered ring results in high regioselectivity; only an axial attack occurs (Fürst–Plattner rule[9]). Thus, nucleophiles are presumed to attack the C-3 carbon of 2,3-β-oxirane, and the transition state requires the linearity of the entering nucleophile with a C–O bond to be broken to provide the 2,3-*trans*-diaxial conformation.[10] Similarly, nucleophiles should attack the C-2 carbon of 2,3-α-oxirane to provide the 2,3-*trans*-diaxial conformation (Scheme 1). We therefore examined the regioselectivity of the reaction under various conditions. Particularly informative are comparisons of basic conditions using metal alkoxide as a nucleophile and acidic conditions using alcohol as a nucleophile in the presence of a Lewis acid as promoter.

First, we investigated the regioselectivity of the ring opening of the β-oxirane derivatives methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**),[11] and methyl

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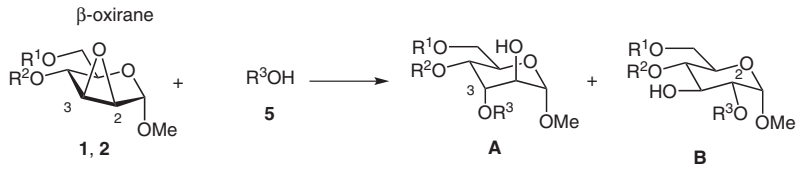
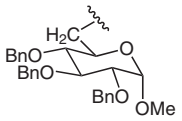
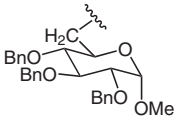
Table 1 Nucleophilic Ring Opening of β-Oxiranes **1** and **2** with Alcohols **5**[a]



Entry	β-Oxirane	5	R^1	R^2	R^3	Base (equiv)	Solvent	Time (h)	Product	Yield[b] (%)	Ratio[c] (**A**/**B**)
1	**1**	**5a**	CHPh			NaH (4)	DMF–THF (1:1)	2	**6**	84	1:0
2	**1**	**5a**	CHPh			MeLi (10)	DMF–THF (1:1)	6	**6**	45	1:0
3	**2**	**5a**	Bn	Bn		NaH (4)	DMF–THF (1:1)	12	**7**	34	1:0
4	**2**	**5a**	Bn	Bn		MeLi (10)	DMF–THF (1:1)	12	**7**	68	1:0
5	**2**	**5a**	Bn	Bn		MeLi (10)	toluene	6	**7**	53	10:1
6	**2**	**5b**[d]	Bn	Bn	Me	NaH (8)	–	16	**8**	76	1:0
7	**2**	**5c**[d]	Bn	Bn	Bn	NaH (8)	–	2	**9**	55	4.5:1

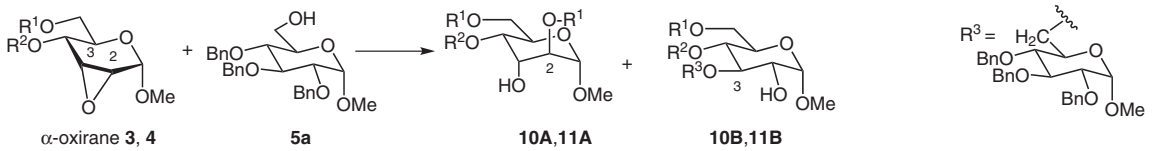
[a] Reagents and conditions: **1** or **2** (1 equiv), **5** (10 equiv), base, solvent, reflux.
[b] The combined yield of the products.
[c] The ratio of the isolated products.
[d] Used as solvent.

2,3-anhydro-4,6-di-*O*-benzyl-α-D-mannopyranoside (**2**)[12] by the nucleophilic reaction of the alkoxides derived from the corresponding hydroxy derivatives methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**5a**),[13] methanol (**5b**), and benzyl alcohol (**5c**) (Table 1).

As shown in Table 1, the ring-opening reaction of β-oxiranes **1** and **2** required an excess amount of metal alkoxide (10 equiv)[14] and harsh conditions (refluxing DMF–THF, 1:1). The conformationally locked substrate **1** reacted with the sodium alkoxide of **5a** to give the 3,6′-ether-linked sugar **6A**[15] in 84% yield, with no formation of **6B** observed (Table 1, entry 1); as expected, the reaction was highly regioselective. This is the first example of the synthesis of the 3,6′-ether-linked sugar (the 3-position of D-altroside and the 6-position of D-glucoside are linked by ether bonding). Using lithium alkoxide lowered the yield of **6A**, but complete regiospecificity was also observed (Table 1, entry 2). We then examined **2**, which does not have a rigidly locked conformation. The reaction with the sodium alkoxide of **5a** gave only the 2,3-*trans*-diaxial compound **7A**[15]in 34% yield (Table 1, entry 3). In this case, the lithium alkoxide of **5a** proved to be a better nucleophile, affording **7A** in 68% yield (Table 1, entry 4). Interestingly, a slight amount of **7B** was obtained (**7A**/**7B** = 10:1) when toluene was used instead of *N*,*N*-dimethylformamide–tetrahydrofuran as the solvent (Table 1, entry 5). Sodium methoxide and sodium benzyloxide were also examined as nucleophiles (Table 1, entries 6 and 7). While sodium methoxide attacked C-3 regioselectively to give α-D-altropyranoside **8A**[15] in 76% yield (entry 6), the bulkier sodium benzyloxide, less potent as a nucleophile, gave mixture of products **9A** and **9B** (**9A**[16]/**9B**[17] = 4.5:1) in 55% yield (entry 7). As a whole, the stereochemical outcome in the reaction of β-oxiranes **1** and **2** is the result of the expected stereoelectronic preference for axial attack by the metal alkoxide. It is difficult to achieve the unusual C-2 attack in this oxirane.

We next investigated the regioselectivity of the ring-opening reaction of α-oxiranes **3**[18] and **4** using the metal alkoxides of **5a** (Table 2). Even the conformationally locked substrate **3** gave mixtures of the 2,3-*trans*-diaxial **10A**[15] and the 2,3-*trans*-diequatorial **10B**[15] in 64% yield (**10A**/**10B** = 8.1:1) (Table 2, entry 1). A marked selectivity shift was observed in the case of the more flexible oxirane **4** (**11A**[15]/**11B**[15] = 1.5:1) (Table 2, entry 3). A large solvent effect, which is a common feature of the reaction with lithium alkoxide, was also observed. While the best result with regard to the selectivity for C-2 attack was obtained with tetrahydrofuran (**11A**/**11B** = 4.3:1) (Table 2, entry 4), less polar solvents (benzene and toluene) increased the ratio of C-3 attack (entries 9 and 10). It is likely that the lithium ion, which has a strong ability to form a chelate structure with the oxygen atoms of the pyranoside substrate, and the solvent cooperatively functioned to provide

Table 2 Nucleophilic Ring Opening of α-Oxiranes **3** and **4** with Alkoxides[a]



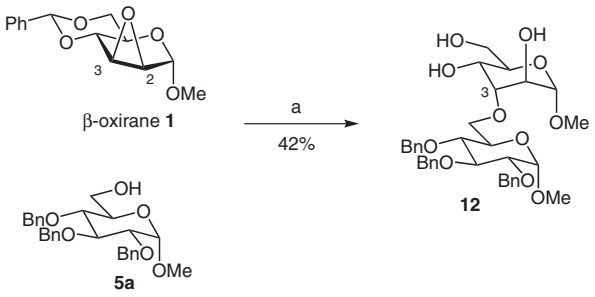
Entry	α-Oxirane	R^1	R^2	Equiv of **5a**	Base (equiv)	Solvent	Time (h)	Product	Yield[b] (%)	Ratio[c] (**A**/**B**)
1	**3**	CHPh		4	NaH (4)	DMF–THF (1:1)	1.5	**10**	64	8.1:1[d]
2	**3**	CHPh		20	NaH (4)	DMF–THF (1:1)	2.5	**10**	88	7.8:1[d]
3	**4**	Bn	Bn	10	NaH (4)	DMF–THF (1:1)	2	**11**	84	1.5:1
4	**4**	Bn	Bn	10	MeLi (10)	THF	13.5	**11**	71	4.3:1
5	**4**	Bn	Bn	10	MeLi (10)	DMF–THF (1:1)	5.5	**11**	77	4:1
6	**4**	Bn	Bn	10	MeLi (10)	DMSO[e]	4	**11**	95	2.9:1
7	**4**	Bn	Bn	10	MeLi (10)	MeCN	13	**11**	84	2.8:1
8	**4**	Bn	Bn	10	MeLi (10)	dioxane	11	**11**	89	2.5:1
9	**4**	Bn	Bn	10	MeLi (10)	benzene	33	**11**	59	1.1:1
10	**4**	Bn	Bn	10	MeLi (10)	toluene	12	**11**	83	1.1:1
11	**4**	Bn	Bn	10	*t*-BuOK (4)	DMF–THF (1:1)	18	**11**	61	1.1:1
12	**4**	Bn	Bn	10	*t*-BuOK (4)	toluene	2	**11**	85	1:1

[a] Reagents and conditions: **3** or **4** (1 equiv), **5a**, base, solvent, reflux.
[b] The combined yield of the products.
[c] The ratio was determined by NMR.
[d] The ratio of the isolated products.
[e] At 125 °C.

the various conformations to **4**, leading to such a change in the regioselectivity. In sharp contrast to lithium alkoxide, potassium alkoxide gave very low regioselectivity (Table 2, entries 11 and 12). We have so far not succeeded in obtaining excellent C-2 selectivity with metal alkoxides. However, it should be noted that C-3 attack, which is generally recognized as stereoelectronically unfavorable, was frequently observed in this case. α-Oxiranes **3** and **4** are probably more flexible than β-oxiranes **1** and **2**, and this would lead to the difference in the degree of regioselectivity.

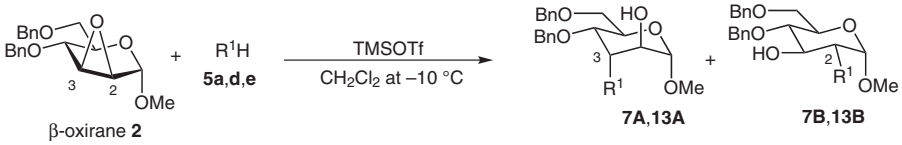
Next, we investigated acidic conditions. For this, a strong Lewis acid is needed to activate the oxirane. A survey of a number of Lewis acids was carried out, and trimethylsilyl triflate was found to be the most promising promotor. First, the conformationally locked substrate **1** was treated with **5a** in the presence of trimethylsilyl triflate (1 equiv) (Scheme 2). It was found, however, that 4,6-benzylidene protection was unstable under such strongly acidic conditions, and a major byproduct was detected, which was determined to be the partially deprotected ether-linked version of product **12**. To avoid a cumbersome separation process, we adopted the ring-opening reaction followed by acidic deprotection of the benzylidene group (AcOH, THF) to obtain triol **12** as the product (Scheme 2). Although the addition of a small amount of tetramethylurea (TMU)[19] to this system increased the yields, further improvement was not likely.[20]

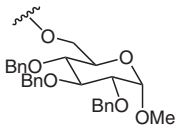
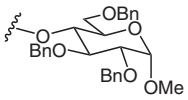
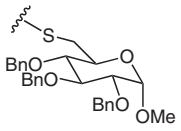
We therefore turned to oxirane **2**, of which the conformation is not rigidly locked. The reaction proceeded highly regioselectively to provide the 2,3-*trans*-diaxial **7A** (Table 3, entry 1). When a large excess of nucleophile **5a** (10 equiv) was used in the presence of trimethylsilyl triflate (1 equiv), **7A** was obtained as the sole product in 82% yield (Table 3, entry 1). It is interesting that invariable regioselectivity was again observed in this case. Un-



Scheme 2 Nucleophilic ring opening of **1** with **5a** promoted by trimethylsilyl triflate. *Reagents and conditions*: (a) 1. TMSOTf, TMU, CH_2Cl_2; 2. AcOH, THF.

Table 3 Nucleophilic Ring Opening of β-Oxirane **2** with Alcohol Promoted by Trimethylsilyl Triflate[a]



Entry	5	R^1	Equiv of 5	Time (h)	Product	Yield[b] (%)	Ratio[c] (A/B)
1	**5a**		10	24	**7**	82	1:0
2	**5d**		4	27	–	0	
3	**5e**		10	5	**13**	66	1:0

[a] Reagents and conditions: **2** (1 equiv), **5**, TMSOTf (1 equiv), CH_2Cl_2, –10 °C.
[b] The combined yield of the products.
[c] The ratio of the isolated products.

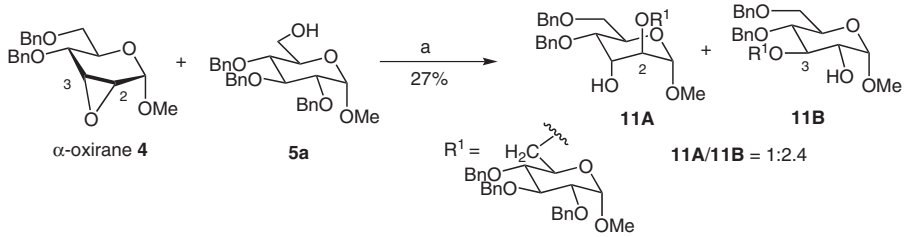
fortunately, no reaction occurred with the secondary hydroxyl group of carbohydrate **5d**[21] (Table 3, entry 2). It is likely that the poor nucleophilicity and the bulkiness of the secondary alcohol prevent the reaction from occurring. Yet the strongly nucleophilic thiol **5e**[22] reacted with β-oxirane **2** to give the corresponding **13A** stereoselectively in 66% yield (Table 3, entry 3). It should be stressed that the ring-opening reaction of β-oxirane **2** occurred stereospecifically at the C-3 position in all cases.

Finally, ring opening of α-oxiranes **3** and **4** was examined under acidic conditions. This gave messy reactions, although the addition of the boron trifluoride–diethyl ether complex[23] to the system partially improved the results. It is strange that the 4,6-benzylidene-protected **3** provided stereoelectronically unfavored **10A** (structure shown in Table 2) solely, but in very low yield (7%). The reaction of the more flexible **4** gave mixtures of 2,3-*trans*-diaxial **11A** and 2,3-*trans*-diequatorial **11B** (**11A/11B** = 1:2.4) (Scheme 3). Although limited, the data suggest a tendency of α-oxirane to give the 2,3-*trans*-diequatorial product under acidic conditions.

Our results showed that the orientation of the oxirane on the pyranose ring affects the reactivity and regioselectivity toward nucleophilic ring-opening reactions. 2,3-Anhydro-α-D-mannopyranosides (β-oxiranes) afforded the 3,6′-ether-linked sugar selectively in good yields. In contrast, the reaction of 2,3-anhydro-α-D-allopyranosides (α-oxiranes) resulted in an unusual selectivity shift. Although we have only limited information on the properties of α- and β-oxiranes, a closer examination of these compounds might contribute to further progress in the ring-opening reactions of carbohydrate oxiranes in the future.

In conclusion, a new synthesis of ether-linked sugar utilizing nucleophilic ring opening was developed. We also found that the differentiating property of 2,3-α-D-oxirane affects the results of the nucleophilic ring-opening reaction.

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 AL-400 spectrometer at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Chemical shifts are given relative to TMS as an internal standard.



Scheme 3 Nucleophilic ring opening of **4** with **5a** promoted by trimethylsilyl triflate. *Reagents and conditions*: (a) TMSOTf, $BF_3{\cdot}OEt_2$, CH_2Cl_2.

EI and ESI mass spectra were measured on JEOL JMS-SX102A and JEOL LCMS-ITTOF spectrometers, respectively. FAB mass spectra were obtained with *m*-nitrobenzyl alcohol (NBA) as a matrix. Melting points were determined on a Yanaco micro melting point apparatus. Analytical TLC was carried out on Merck silica gel 60 F_{254}. Column chromatography was performed on silica gel (Wakogel C-300, 45–60 μm).

Oxiranes 2 and 4

$Pd(OH)_2$/C (30 mg) was added to **1** or **3** (290.5 mg, 1.10 mmol) in EtOH (110 mL). The reaction mixture was stirred at r.t. for 12 h under an atmosphere of H_2. After filtration, the filtrate was evaporated to give the crude diol, which was directly dissolved in DMF–THF (5:1, 12 mL). The mixture was treated with 60% NaH in oil (114 mg), and BnCl (0.4 mL, 3.4 mmol) at 0 °C and gradually warmed to r.t. After the mixture had stirred for 6.5 h, ice water (100 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The crude product was purified by chromatography (silica gel, EtOAc–hexane, 1:4); this gave **2** (from **1**) or **4** (from **3**).

Methyl 2,3-Anhydro-4,6-di-*O*-benzyl-α-D-mannopyranoside (2)

Yield: 337 mg (86%); R_f = 0.50 (EtOAc–hexane, 1:2); $[\alpha]_D^{23}$ +169.4 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 10 H), 4.91 (s, 1 H, H1), 4.71 (d, *J* = 11.6 Hz, 1 H), 4.59 (d, *J* = 12.0 Hz, 1 H), 4.48 (d, *J* = 12.0 Hz, 1 H), 4.47 (d, *J* = 11.6 Hz, 1 H), 3.72 (ddd, *J* = 9.2, 4.8, 1.6 Hz, 1 H, H5), 3.64 (d, *J* = 9.2 Hz, 1 H, H4), 3.62 (dd, *J* = 9.2, 1.6 Hz, 1 H, H6), 3.56 (dd, *J* = 9.2, 4.8 Hz, 1 H, H6), 3.45 (s, 3 H), 3.35 (d, *J* = 3.6 Hz, 1 H, H3), 3.08 (d, *J* = 3.6 Hz, 1 H, H2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 137.3, 128.3, 128.3, 128.2, 128.2, 128.0, 127.9, 127.9, 127.8, 127.6, 127.4, 95.9, 73.1, 72.0, 68.9, 68.9, 67.1, 55.4, 53.3, 49.6.

MS (EI, 70 eV): *m*/*z* = 356 [M^+].

HRMS (EI): *m*/*z* calcd for $C_{21}H_{24}O_5$: 356.1623; found: 356.1622.

Methyl 2,3-Anhydro-4,6-di-*O*-benzyl-α-D-allopyranoside (4)

Yield: 330 mg (83%); R_f = 0.50 (EtOAc–hexane, 1:1); $[\alpha]_D^{20}$ +129.8 (*c* 1.00, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.08–7.43 (m, 10 H), 4.76 (s, 1 H), 4.67 (d, *J* = 11.8 Hz, 1 H), 4.63 (d, *J* = 12.4 Hz, 1 H), 4.60 (d, *J* = 11.8 Hz, 1 H), 4.50 (d, *J* = 12.4 Hz, 1 H), 3.99 (dd, *J* = 9.6, 1.7 Hz, 1 H, H4), 3.93 (ddd, *J* = 9.6, 3.9, 2.2 Hz, 1 H), 3.72 (dd, *J* = 10.7, 3.9 Hz, 1 H), 3.65 (dd, *J* = 10.7, 2.2 Hz, 1 H), 3.48 (dd, *J* = 4.2, 3.0 Hz, 1 H), 3.46 (s, 3 H), 3.42 (dd, *J* = 4.2, 1.7 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.0, 138.0, 128.3, 128.3, 128.3, 127.8, 127.6, 94.8, 73.4, 71.8, 71.6, 68.5, 66.7, 55.7, 54.6, 51.6.

MS (EI, 70 eV): *m*/*z* = 356 [M^+].

HRMS (EI): *m*/*z* calcd for $C_{21}H_{24}O_5$: 356.1623; found: 356.1619.

3,6′-Ether-Linked Sugar 6A

A 60% suspension of NaH in oil (30.2 mg, 0.76 mmol) was added to a soln of **5a** (878 mg, 1.89 mmol) in DMF–THF (1:1, 1.9 mL) at 0 °C, and the mixture was stirred at r.t. After 30 min, **1** (50 mg, 0.19 mmol) was added to the mixture, which was subsequently stirred at reflux for 2 h. H_2O (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (300 mL). The crude product was purified by chromatography (silica gel, EtOAc–hexane, 3:7); this gave **6A**.

Yield: 122 mg (84%); mp 158 °C; R_f = 0.29 (EtOAc–hexane, 1:1); $[\alpha]_D^{20}$ +56.9 (*c* 1.00, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.50–7.21 (m, 20 H), 5.55 (s, 1 H), 4.94 (d, *J* = 10.7 Hz, 1 H), 4.85 (d, *J* = 11.0 Hz, 1 H), 4.85 (d, *J* = 10.7 Hz, 1 H), 4.71 (d, *J* = 12.1 Hz, 1 H), 4.69 (d, *J* = 11.0 Hz, 1 H), 4.58 (m, 2 H), 4.57 (d, *J* = 12.1 Hz, 1 H), 4.32 (m, 1 H), 4.28 (dd, *J* = 9.9, 5.2 Hz, 1 H), 3.98 (m, 1 H), 3.94 (t, *J* = 9.4 Hz, 1 H), 3.93 (m, 1 H), 3.90 (dd, *J* = 11.8, 1.9 Hz, 1 H), 3.90 (m, 1 H), 3.84 (dd, *J* = 11.8, 5.2 Hz, 1 H), 3.74 (m, 2 H), 3.63 (t, *J* = 9.4 Hz, 1 H), 3.42 (dd, *J* = 9.4, 3.6 Hz, 1 H), 3.33 (s, 3 H), 3.32 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 138.5, 138.2, 137.6, 128.9, 128.3, 128.2, 127.9, 127.8, 127.7, 127.5, 127.4, 126.3, 102.5, 101.9, 97.8, 82.1, 80.2, 77.9, 76.5, 75.7, 74.8, 74.8, 73.4, 70.9, 69.9, 69.5, 69.3, 58.5, 55.5, 54.9.

MS (FAB) (MeCN–NBA + NaI): *m*/*z* = 752 [M + Na].

HRMS (FAB) (MeCN–NBA + NaI): *m*/*z* calcd for $C_{42}H_{50}O_{11}Na$: 751.3095; found: 751.3096.

Compounds 7A and 7B

A 1.6 M soln of MeLi in Et_2O (0.95 mL, 1.52 mmol) was added to a soln of **2** (54.2 mg, 0.152 mmol) and **5a** (707 mg, 1.52 mmol) in toluene (1.5 mL) at 0 °C, and the mixture was refluxed for 6 h. H_2O (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The crude product was purified by chromatography (silica gel, EtOAc–hexane, 3:2); this gave **7A** (46%) and **7B** (5%).

Compound 7A

Yield: 60 mg (46%); R_f = 0.32 (EtOAc–hexane, 1:1); $[\alpha]_D^{23}$ +47.3 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.15 (m, 25 H), 4.90 (d, *J* = 10.8 Hz, 1 H), 4.79 (d, *J* = 11.2 Hz, 1 H), 4.75 (d, *J* = 10.8 Hz, 1 H), 4.67 (d, *J* = 12.4 Hz, 1 H), 4.62 (d, *J* = 12.0 Hz, 1 H), 4.59 (d, *J* = 11.2 Hz, 1 H), 4.53 (d, *J* = 11.6 Hz, 1 H), 4.52 (d, *J* = 3.6 Hz, 1 H), 4.50 (d, *J* = 11.6 Hz, 1 H), 4.49 (d, *J* = 3.6 Hz, 1 H), 4.44 (d, *J* = 12.4 Hz, 1 H), 4.43 (d, *J* = 12.0 Hz, 1 H), 4.07 (dd, *J* = 3.8, 2.0 Hz, 1 H), 3.91 (t, *J* = 9.6 Hz, 1 H), 3.91 (dd, *J* = 7.2, 4.0 Hz, 1 H), 3.80 (dd, *J* = 3.8, 3.6 Hz, 1 H), 3.77 (d, *J* = 9.6 Hz, 1 H), 3.73–3.68 (m, 1 H), 3.68 (d, *J* = 9.6 Hz, 1 H), 3.61 (dd, *J* = 7.2, 3.6 Hz, 1 H), 3.55 (dd, *J* = 4.8, 2.0 Hz, 1 H), 3.55 (dd, *J* = 4.8, 2.0 Hz, 1 H), 3.48 (t, *J* = 9.6 Hz, 1 H), 3.39 (dd, *J* = 9.6, 3.6 Hz, 1 H), 3.29 (s, 3 H), 3.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 138.3, 138.3, 138.0, 137.9, 128.3, 128.3, 128.3, 128.3, 128.3, 128.1, 127.9, 127.9, 127.8, 127.8, 127.6, 127.6, 127.6, 127.5, 127.4, 102.6, 98.0, 81.9, 79.9, 79.1, 77.8, 75.7, 74.9, 73.3, 73.3, 71.6, 70.0, 69.6, 72.4, 70.7, 70.6, 69.9, 55.6, 55.2.

MS (FAB) (MeCN–NBA + NaI): *m*/*z* = 843 [M + Na].

HRMS (FAB) (MeCN–NBA + NaI): *m*/*z* calcd for $C_{49}H_{56}O_{11}Na$: 843.3720; found: 843.3726.

Compound 7B

Yield: 5.8 mg (5%); mp 158 °C; R_f = 0.57 (EtOAc–hexane, 1:1); $[\alpha]_D^{22}$ +47.9 (*c* 0.30, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.30–7.15 (m, 25 H), 4.89 (d, *J* = 10.7 Hz, 1 H), 4.81 (d, *J* = 11.1 Hz, 1 H), 4.80 (d, *J* = 11.0 Hz, 1 H), 4.74 (d, *J* = 10.7 Hz, 1 H), 4.73 (d, *J* = 3.6 Hz, 1 H), 4.72 (d, *J* = 12.2 Hz, 1 H), 4.60 (d, *J* = 11.0 Hz, 1 H), 4.60 (d, *J* = 12.2 Hz, 1 H), 4.56 (d, *J* = 3.6 Hz, 1 H), 4.55 (d, *J* = 12.1 Hz, 1 H), 4.46 (d, *J* = 11.1 Hz, 1 H), 4.42 (d, *J* = 12.1 Hz, 1 H), 3.97 (t, *J* = 9.1 Hz, 1 H), 3.93 (dd, *J* = 11.0, 3.6 Hz, 1 H), 3.90 (t, *J* = 9.6 Hz, 1 H), 3.66–3.62 (m, 4 H), 3.60–3.56 (m, 2 H), 3.49 (t, *J* = 9.1 Hz, 1 H), 3.46 (dd, *J* = 9.6, 3.6 Hz, 1 H), 3.31 (dd, *J* = 9.1, 3.6 Hz, 1 H), 3.31 (s, 3 H), 3.22 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.8, 138.5, 138.5, 138.1, 138.0, 128.5, 128.4, 128.3, 128.3, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 98.2, 97.7, 81.9, 81.2, 80.0, 77.5, 77.4, 75.7, 74.9, 74.4, 73.8, 73.5, 72.4, 70.4, 69.7, 69.6, 68.6, 55.4, 55.0.

MS (FAB) (MeCN–NBA + NaI): *m*/*z* = 843 [M + Na].

HRMS (FAB) (MeCN–NBA + NaI): *m*/*z* calcd for $C_{49}H_{56}O_{11}Na$: 843.3721; found: 843.3732.

Methyl 4,6-Di-*O*-benzyl-3-*O*-methyl-α-D-altropyranoside (8A)

A 60% suspension of NaH in oil (84.0 mg, 2.10 mmol) was added to a soln of **2** (93.6 mg, 0.263 mmol) in MeOH (1.05 mL) at 0 °C and the mixture was refluxed for 16 h. H_2O (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The crude product was purified by chromatography (silica gel, EtOAc–hexane, 1:1); this gave **8A**.

Yield: 77.2 mg (76%); R_f = 0.18 (EtOAc–hexane, 1:1); $[\alpha]_D^{18}$ +77.3 (*c* 0.27, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 10 H), 4.63 (d, *J* = 11.8 Hz, 1 H), 4.61(d, *J* = 3.0 Hz, 1 H), 4.59 (d, *J* = 11.0 Hz, 1 H), 4.54 (d, *J* = 12.1 Hz, 1 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 4.17 (ddd, *J* = 7.4, 4.4, 3.3 Hz, 1 H), 3.95 (dd, *J* = 5.6, 3.0 Hz, 1 H), 3.90 (dd, *J* = 7.4, 3.6 Hz, 1 H), 3.70 (dd, *J* = 10.7, 4.4 Hz, 1 H), 3.66 (dd, *J* = 10.7, 3.3 Hz, 1 H), 3.56 (dd, *J* = 5.6, 3.6 Hz, 1 H), 3.45 (s, 3 H), 3.42 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.1, 138.0, 128.4, 128.3, 127.9, 127.7, 127.6, 102.2, 78.7, 73.5, 71.8, 71.7, 69.5, 69.3, 58.8, 55.8.

MS (EI, 70 eV): *m*/*z* = 388 [M^+].

HRMS (EI): *m*/*z* calcd for $C_{22}H_{28}O_6$: 388.1886; found: 388.1886.

Methyl 3,4,6-Tri-*O*-benzyl-α-D-altropyranoside (9A) and Methyl 2,4,6-Tri-*O*-benzyl-α-D-glucopyranoside (9B)

A 60% suspension of NaH in oil (82.2 mg, 2.05 mmol) was added to a soln of **2** (91.5 mg, 0.257 mmol) in BnOH (1.28 mL) at 0 °C and the mixture was refluxed for 2 h. H_2O (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The crude product was purified by chromatography (silica gel, EtOAc–hexane, 3:7); this gave **9A** [yield: 53.3 mg (45%)] and **9B** [yield: 12.4 mg (10%)].

Compounds 10A and 10B

A 60% suspension of NaH in oil (30.2 mg, 0.76 mmol) was added to a soln of **5a** (1.76 g, 3.78 mmol) in DMF–THF (1:1, 3.8 mL) at 0 °C and the mixture was stirred at r.t. After 30 min, **3** (50 mg, 0.19 mmol) was added to the mixture, which was then stirred at reflux for 2.5 h. H_2O (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The crude product was purified by chromatography (silica gel, EtOAc–hexane, 3:7); this gave **10A** (78%) and **10B** (10%).

Compound 10A

Yield: 106.8 mg (78%); R_f = 0.4 (EtOAc–hexane, 1:1); $[\alpha]_D^{18}$ +47.2 (*c* 1.00, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.39–7.19 (m, 20 H), 5.43 (s, 1 H), 4.92 (d, *J* = 10.7 Hz, 1 H), 4.88 (d, *J* = 11.0 Hz, 1 H), 4.74 (d, *J* = 10.7 Hz, 1 H), 4.73 (d, *J* = 12.1 Hz, 1 H), 4.63 (d, *J* = 1.1 Hz, 1 H), 4.61 (d, *J* = 12.1 Hz, 1 H), 4.54 (d, *J* = 11.0 Hz, 1 H), 4.53 (dd, *J* = 3.6 Hz, 1 H), 4.23 (dd, *J* = 10.0, 5.2 Hz, 1 H), 4.07 (ddd, *J* = 10.0, 10.0, 5.2 Hz, 1 H), 4.07 (m, 1 H), 3.94 (t, *J* = 9.3), 3.78 (dd, *J* = 10.0, 3.0 Hz, 1 H), 3.73 (dd, *J* = 11.0, 4.5 Hz, 1 H), 3.69 (t, *J* = 10.0 Hz, 1 H), 3.67 (ddd, *J* = 9.3, 4.5, 1.7 Hz, 1 H), 3.63 (dd, *J* = 11.0, 1.7 Hz, 1 H), 3.60 (dd, *J* = 3.3, 1.1 Hz, 1 H), 3.45 (t, *J* = 9.3 Hz, 1 H), 3.45 (dd, *J* = 9.3, 3.6 Hz, 1 H), 3.33 (s, 3 H), 3.31 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 129.3, 128.7, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 126.4, 102.4, 100.3, 98.2, 82.3, 80.1, 78.7, 77.8, 76.8, 76.1, 75.2, 73.6, 70.5, 70.0, 69.4, 67.2, 58.4, 55.8, 55.5.

MS (FAB) (MeCN–NBA + NaI): *m*/*z* = 752 [M + Na].

HRMS (FAB) (MeCN–NBA + NaI): *m*/*z* calcd for $C_{42}H_{48}O_{11}Na$: 751.3095; found: 751.3038.

Compound 10B

Yield: 13.5 mg (10%); R_f = 0.47 (EtOAc–hexane, 1:1); $[\alpha]_D^{18}$ +41.0 (*c* 0.50, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.35–7.07 (m, 20 H), 5.43 (s, 1 H), 4.87 (d, *J* = 11.0 Hz, 1 H), 4.74 (d, *J* = 11.0 Hz, 1 H), 4.73 (d, *J* = 2.5 Hz, 1 H), 4.70 (d, *J* = 12.0 Hz, 1 H), 4.66 (d, *J* = 10.7 Hz, 1 H), 4.58 (d, *J* = 12.0 Hz, 1 H), 4.58 (d, *J* = 3.9 Hz, 1 H), 4.54 (d, *J* = 10.7 Hz, 1 H), 4.21 (dd, *J* = 10.2, 4.7 Hz, 1 H), 4.15 (dd, *J* = 11.7, 2.2 Hz, 1 H), 3.87 (t, *J* = 9.6 Hz, 1 H), 3.84 (dd, *J* = 11.7, 2.2 Hz, 1 H), 3.74 (ddd, *J* = 10.2, 10.2, 5.0 Hz, 1 H), 3.67–3.64 (m, 4 H), 3.59 (ddd, *J* = 9.9, 2.2, 2.2 Hz, 1 H), 3.46 (m, 1 H), 3.45 (dd, *J* = 9.6, 3.9 Hz, 1 H), 3.38 (s, 3 H), 3.27 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 128.9, 128.4, 128.3, 128.3, 128.2, 128.0, 127.9, 127.9, 127.9, 127.5, 127.5, 126.0, 101.4, 99.8, 98.2, 81.9, 81.2, 80.9, 80.0, 77.2, 75.7, 75.1, 73.4, 73.2, 71.3, 70.6, 69.0, 62.7, 55.4, 55.3.

MS (FAB) (MeCN–NBA + NaI): *m*/*z* = 752 [M + Na].

HRMS (FAB) (MeCN–NBA + NaI): *m*/*z* calcd for $C_{42}H_{48}O_{11}Na$: 751.3095; found: 751.3070.

Compounds 11A and 11B

A 1.6 M soln of MeLi in Et_2O (0.88 mL, 1.4 mmol) was added to a soln of **5a** (650 mg, 1.4 mmol) in DMSO (1.40 mL) at 0 °C and the mixture was stirred at r.t. After 0.5 h, **4** (50 mg, 0.14 mmol) was added and the mixture was refluxed for 4 h. H_2O (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The crude product was purified by chromatography (silica gel, EtOAc–hexane, 1:3); this gave the mixture of **11A** and **11B**.

Yield: 108.8 mg (95%); **11A/11B** = 2.9:1.

Compound 11A

R_f = 0.45 (EtOAc–hexane, 1:1); $[\alpha]_D^{20}$ +71.9 (*c* 1.00, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.35–7.18 (m, 25 H), 4.97 (d, *J* = 11.0 Hz, 1 H), 4.87 (d, *J* = 11.3 Hz, 1 H), 4.80 (d, *J* = 11.0 Hz, 1 H), 4.78 (d, *J* = 12.0 Hz, 1 H), 4.73 (d, *J* = 1.4 Hz, 1 H), 4.65 (d, *J* = 12.0 Hz, 1 H), 4.63 (d, *J* = 12.0 Hz, 1 H), 4.57 (d, *J* = 11.3 Hz, 1 H), 4.54 (d, *J* = 3.6 Hz, 1 H), 4.53 (d, *J* = 12.0 Hz, 1 H), 4.52 (d, *J* = 11.4 Hz, 1 H), 4.37 (d, *J* = 11.4 Hz, 1 H), 4.10 (m, 1 H), 4.00 (ddd, *J* = 9.9, 3.6, 3.6 Hz, 1 H), 3.97 (t, *J* = 9.9 Hz, 1 H), 3.76 (dd, *J* = 9.6, 3.6 Hz, 1 H), 3.73 (m, 5 H), 3.61 (dd, *J* = 3.9, 1.4 Hz, 1 H), 3.49 (dd, *J* = 9.9, 3.6 Hz, 1 H), 3.47 (t, *J* = 9.9 Hz, 1 H), 3.38 (s, 3 H), 3.31 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 128.5, 128.4, 128.4, 128.3, 128.3, 128.1, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 99.7, 97.7, 82.0, 79.9, 78.1, 77.7, 75.7, 74.9, 73.4, 73.3, 71.3, 72.2, 70.3, 69.6, 69.5, 66.5, 66.0, 55.3, 55.1.

MS (FAB) (MeCN–NBA + NaI): *m*/*z* = 844 [M + Na].

HRMS (FAB) (MeCN–NBA + NaI): *m*/*z* calcd for $C_{49}H_{56}O_{11}Na$: 843.3720; found: 843.3719.

Compound 11B

R_f = 0.45 (EtOAc–hexane, 1:1); $[\alpha]_D^{20}$ +81.3 (*c* 1.00, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.35–7.06 (m, 25 H), 4.89 (d, *J* = 10.7 Hz, 1 H), 4.80 (d, *J* = 10.7 Hz, 1 H), 4.74 (d, *J* = 2.0 Hz, 1 H), 4.73 (d, *J* = 10.7 Hz, 1 H), 4.70 (d, *J* = 11.8 Hz, 1 H), 4.65 (d, *J* = 10.7 Hz, 1 H), 4.61 (d, *J* = 3.3 Hz, 1 H), 4.58 (d, *J* = 11.8 Hz, 1 H), 4.57 (d, *J* = 10.7 Hz, 1 H), 4.56 (d, *J* = 12.1 Hz, 1 H), 4.43 (d, *J* = 12.1 Hz, 1 H), 4.36 (d, *J* = 10.7 Hz, 1 H), 4.25 (dd, *J* = 12.1, 1.9 Hz, 1 H), 3.90 (dd, *J* = 9.4, 8.5 Hz, 1 H), 3.81 (dd, *J* = 12.1, 2.2 Hz, 1 H), 3.68 (t, *J* = 8.5 Hz, 1 H), 3.66 (m, 3 H), 3.59 (m, 3 H), 3.48 (dd, *J* = 9.4, 3.3 Hz, 1 H), 3.48 (m, 1 H), 3.34 (s, 3 H), 3.27(s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.7, 138.1, 138.0, 138.0, 137.9, 128.4, 128.4, 128.3, 128.3, 127.9, 127.9, 127.7, 127.6, 127.5, 99.2,

98.2, 86.0, 81.8, 80.2, 77.3, 77.2, 75.7, 75.1, 74.7, 73.5, 73.5, 72.8, 71.5, 71.0, 70.3, 68.5, 55.5, 55.1.

MS (FAB) (MeCN–NBA + NaI): *m/z* = 844 [M + Na].

HRMS (FAB) (MeCN–NBA + NaI): *m/z* calcd for $C_{49}H_{56}O_{11}Na$: 843.3720; found: 843.3716.

Triol 12

TMSOTf (34 μL, 0.19 mmol) and TMU (11 μL, 0.10 mmol) were added to a soln of **5a** (350 mg, 0.76 mmol) and **1** (50 mg, 0.19 mmol) in CH_2Cl_2 (2.72 mL) at –78 °C. The reaction mixture was gradually warmed to –10 °C and stirred for 4.5 h. Sat. aq $NaHCO_3$ (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The crude product was dissolved in AcOH–THF (1:1, 5 mL) and stirred for 12 h. The reaction mixture was poured into sat. aq $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). Purification by chromatography (silica gel, MeOH–CH_2Cl_2, 4:96) gave triol **12**.

Yield: 51 mg (42%); R_f = 0.23 (CH_2Cl_2–MeOH, 15:1); $[\alpha]_D^{29}$ +66.0 (*c* 0.50, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.32–7.21 (m, 15 H), 4.96 (d, *J* = 10.8 Hz, 1 H), 4.87 (d, *J* = 10.8 Hz, 1 H), 4.83 (d, *J* = 10.8 Hz, 1 H), 4.79 (d, *J* = 12.6 Hz, 1 H), 4.73 (d, *J* = 10.8 Hz, 1 H), 4.67 (d, *J* = 12.6 Hz, 1 H), 4.62 (d, *J* = 3.6 Hz, 1 H), 4.60 (d, *J* = 1.8 Hz, 1 H), 4.15 (dd, *J* = 10.2, 2.4 Hz, 1 H), 3.97 (t, *J* = 3.6 Hz, 1 H), 3.92 (dd, *J* = 1.8, 3.6 Hz, 1 H), 3.88 (dd, *J* = 3.6, 14.4 Hz, 1 H), 3.87–3.83 (m, 2 H), 3.79 (dd, *J* = 4.8, 11.4 Hz, 1 H), 3.72 (ddd, *J* = 9.6, 4.2, 2.4 Hz, 1 H), 3.64 (t, *J* = 9.6 Hz, 1 H), 3.61 (t, *J* = 3.6 Hz, 1 H), 3.58 (dd, *J* = 10.2, 2.4 Hz, 1 H), 3.51 (dd, *J* = 9.6, 3.6 Hz, 1 H), 3.36 (s, 3 H), 3.32 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.6, 138.0, 128.5 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 101.7, 98.2, 81.8, 80.2, 79.7, 77.4, 75.9, 74.9, 73.5, 70.1, 69.8, 69.7, 68.7, 64.2, 62.7, 55.4, 55.3.

MS (FAB) (MeCN–NBA + NaI): *m/z* = 664 [M + Na].

HRMS (FAB) (MeCN–NBA + NaI): *m/z* calcd for $C_{35}H_{44}O_{11}Na$: 663.2781; found: 663.2773.

Compound 13A

TMSOTf (27.9 μL, 0.155 mmol) was added to a soln of **5e** (743 mg, 1.55 mmol) and **2** (55.1 mg, 0.16 mmol) in CH_2Cl_2(1.55 mL) at –10 °C, and the mixture was stirred for 5 h. Ice water (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The crude product was purified by chromatography (silica gel, EtOAc–hexane, 1:3); this gave **13A**.

Yield: 85.6 mg (66%); R_f = 0.10 (EtOAc–hexane, 1:1); $[\alpha]_D^{23}$ +31.0 (*c* 0.60, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 25 H), 4.96 (d, *J* = 10.9 Hz, 1 H), 4.86 (d, *J* = 10.7 Hz, 1 H), 4.79 (d, *J* = 10.9 Hz, 1 H), 4.75 (d, *J* = 12.1 Hz, 1 H), 4.63 (d, *J* = 12.1 Hz, 1 H), 4.61 (d, *J* = 3.6 Hz, 1 H), 4.59 (d, *J* = 11.5 Hz, 1 H), 4.54 (d, *J* = 11.5 Hz, 1 H), 4.54 (d, *J* = 10.7 Hz, 1 H), 4.54 (d, *J* = 4.7 Hz, 1 H), 4.48 (d, *J* = 11.5 Hz, 1 H), 4.48 (d, *J* = 11.5 Hz, 1 H), 4.05 (m, 1 H), 3.94 (d, *J* = 9.6 Hz, 1 H), 3.93 (dd, *J* = 6.1, 4.4 Hz, 1 H), 3.88 (m, 1 H), 3.77 (ddd, *J* = 9.6, 8.0, 2.5 Hz, 1 H), 3.55 (m, 2 H), 3.48 (dd, *J* = 9.6, 3.6 Hz, 1 H), 3.40 (s, 3 H), 3.40 (s, 3 H), 3.33 (t, *J* = 9.6 Hz, 1 H), 3.13 (dd, *J* = 14.0, 2.5 Hz, 1 H), 3.11 (dd, *J* = 8.0, 4.4 Hz, 1 H), 2.69 (dd, *J* = 14.0, 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 138.0, 137.9, 137.8, 137.7, 128.4, 128.3, 128.3, 128.2, 127.9, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 102.7, 97.8, 81.9, 80.4, 79.8, 76.1, 75.7, 75.2, 73.4, 73.3, 73.0, 71.7, 71.3, 71.0, 70.0, 55.7, 55.3, 51.5, 34.6.

MS (FAB) (MeCN–NBA + NaI): *m/z* = 860 [M + Na].

HRMS (FAB) (MeCN–NBA + NaI): *m/z* calcd for $C_{49}H_{56}O_{10}SNa$: 859.3492; found: 859.3485.

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