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Unusual synthesis of carbohydrate *sec–sec* ether-linked pseudodisaccharides

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Abstract—In this paper, we describe the synthesis of *sec–sec* ether-linked pseudodisaccharides by the coupling of various secondary carbohydrate alcohols with di-*O*-isopropylidene allose 3-*O*-triflate. Reactions proceeded with inversion of configuration to give the 3-substituted di-*O*-isopropylidene glucose derivatives. The crystal structure of a *sec–sec* ether-linked pseudodisaccharide is reported.

Keywords: Ether-linked pseudodisaccharides; Glycomimetics; Sugar triflates

1. Introduction

The great significance of diverse carbohydrate structures in nature means that unusual modifications have a certain inherent interest as potentially biologically active molecules. One such class of structures is tail-to-tail ether-linked pseudodisaccharides, and recently several articles on the synthesis of such (6–6) tail-to-tail-linked structures (Chart 1a) have been published.[1–3] This followed the isolation of the hypoglycaemic, Coyolosa, which was reported to have such a structure,[4] although now, as a result of these studies, it appears that this reported structure is incorrect. Ether-linked pseudodisaccharides are not altogether unknown in nature though, and an exotoxin from *Bacillus thuringiensis* containing a primary–secondary Glc-(4–5)-Rib ether-linked pseudodisaccharide substructure was isolated[5] and subsequently synthesised[6] 30 years ago by Sorm and co-workers (Chart 1b). A few other reports of synthetic primary–primary and primary–*sec* ether-linked pseudodisaccharides also exist.[7–9]

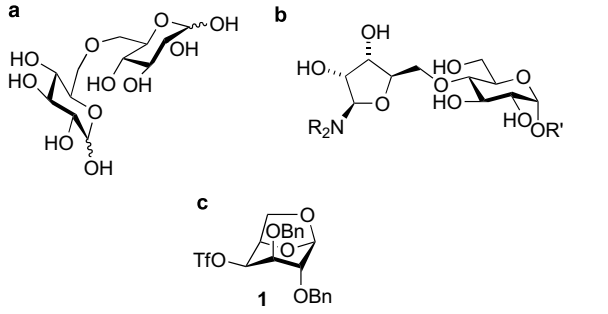

Chart 1. (a) A (6–6) ether-linked pseudodisaccharide synthesised by Haines; (b) ether-linked pseudodisaccharide portion of Thuringiensin, the *B. thuringiensis* exotoxin; (c) triflate **1** used for *sec–sec* ether synthesis by Paulsen.

sec–sec Ethers are much more challenging to synthesise than primary–*sec* or primary–primary ethers, as a Williamson-type synthesis necessarily requires an S_N2 reaction at a secondary carbon centre.[10] Substitution is often disfavoured with respect to the alternative E2 pathway that gives an alkene product. In a carbohydrate context, Paulsen and co-workers have reported the synthesis of various *sec–sec* ethers based on the coupling of saturated and unsaturated carbasugar C-1 alcohols with a secondary carbohydrate triflate **1**

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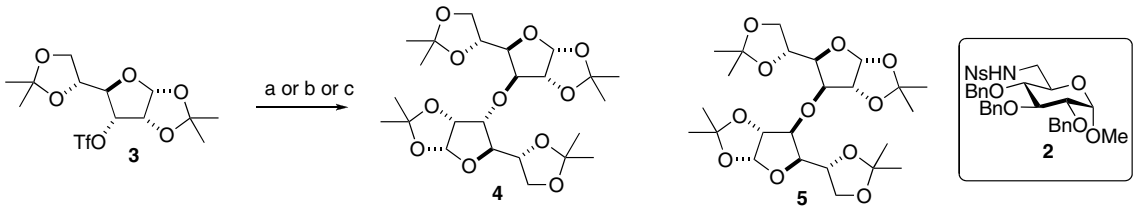


Scheme 1. Reagents and conditions: (a) **2**, NaH, DMF, rt; **4**, 48%; (b) NaH, DMF, rt; **4**, 52%; **5**, 8%; (c) NaOH, DMF, rt; **4**, 51%; **5**, 14%.

(Chart 1c).[11,12] Kovac and co-workers have seen ether-linked pseudodisaccharides as by-products in their tin acetal β-mannoside-forming alkylations; a *sec–sec* Glc-(2–4)-Glc ether was formed as the major product when the synthesis of glucosides was attempted using the same method.[13,14]

2. Results and discussion

As part of our research program on the synthesis of non-glycosidically linked carbohydrate analogues,[15] we were attempting the synthesis of a (3–6) amine-linked pseudodisaccharide. Treatment of the sulfonamide **2**[16] and triflate **3**[17] with sodium hydride in DMF resulted in the formation of a new product (Scheme 1). The sulfonamide **2** was recovered completely unreacted. The ^{1}H NMR spectra of the new compound showed signals consistent with two di-*O*-isopropylidene-protected sugar moieties, i.e., eight methyl singlets between 1.3 and 1.6 ppm; doublets for two anomeric protons at 5.79 and 5.87 ppm; the signal for H-2 at 4.70 ppm was a doublet ($J_{1,2}$ 3.5 Hz), with no coupling to H-3, consistent with a *gluco* configuration; the other H-2 signal at 4.64 ppm was a triplet (J 4.2 Hz) as expected for an *allo* configuration.[†] The mass spectrum showed a peak at *m/z* 525, consistent with $[M+Na]^+$ for M = 502. This data is consistent with a *gluco-allo* (3–3) ether-linked structure **4**, formed in 48% yield based on dimerisation of the triflate **3**.

We were also able to obtain crystals of **4** and to solve the X-ray structure, giving an unambiguous structural proof (Fig. 1).

We repeated the reaction in the absence of the sulfonamide. Triflate **3** was treated with sodium hydride in DMF. Once again, the unsymmetrical ether-linked disaccharide **4** was formed as the major product (52%), but now we isolated a minor amount of a second product. In its ^{1}H and ^{13}C NMR spectra, this compound only showed signals equivalent to a *gluco* configured

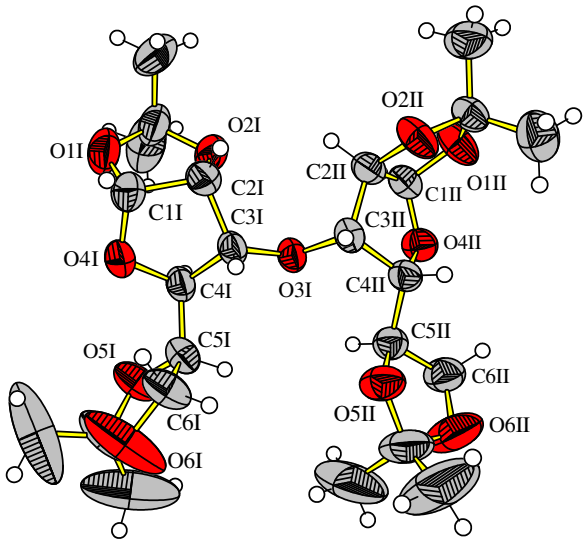


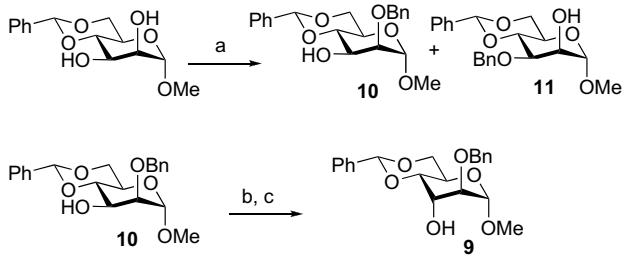
Figure 1. X-ray structure of **4** as thermal ellipsoids drawn at 50% probability and showing crystallographic atom numbering scheme. Selected dihedral angles (°): $C3^{II}$–$O3^{I}$–$C3^{I}$–$C4^{I}$, −166.2; $C3^{II}$–$O3^{I}$–$C3^{I}$–$C2^{I}$, +78.3; $C3^{I}$–$O3^{I}$–$C3^{II}$–$C2^{II}$, −99.7; $C3^{I}$–$O3^{I}$–$C3^{II}$–$C4^{II}$, +149.7. Bond angle (°): $C3^{I}$–$O3^{I}$–$C3^{II}$, +114.3. Bond lengths (Å): $O3^{I}$–$C3^{I}$, 1.412; $O3^{I}$–$C3^{II}$, 1.434.

diisopropylidene protected monosaccharide, with H-2 appearing as a doublet at 4.65 ppm ($J_{1,2}$ 3.6 Hz). However, its mass spectrum showed a peak at *m/z* 525, and thus it was assigned the C_2-symmetric dimeric structure **5** (i.e., with double inversion), formed in 8% yield.

The formation of these species may be explained by the partial hydrolysis of the triflate by trace hydroxide. Attack on the triflate sulfur would give the *allo* alcoholate (**7**−H$^+$), which could then attack a second triflate **3** by S_N2 reaction with inversion to give the unsymmetrical dimer **4**. Alternatively, S_N2 attack by hydroxide at C-3 of the carbohydrate with inversion would give the *gluco* alcohol **8**, which could then be deprotonated and attack a second triflate to give the C_2-symmetric dimer **5**. Even though we tried to carry out the reaction under anhydrous conditions, the formation of both of these products was always seen. Carrying out the reaction with sodium hydroxide rather than sodium hydride resulted in the formation of the same products (**4**, 51%; **5**, 14%).

In no case was any elimination product seen. Indeed, it has been shown previously that this triflate **3** is not prone to 1,2-elimination, even under strongly basic conditions.[18] Schmidt and co-workers have also carried

[†] The $^3J_{2,3}$ ^{1}H–^{1}H coupling constant is much smaller in *gluco* configured 1,2:5,6-di-*O*-isopropylidene derivatives than their C-3 epimers. For example, compare ^{1}H NMR data for *allo* **7** and *gluco* **8** alcohols. **7**: 4.60 (1H, dd, $J_{1,2}$ 3.9 Hz, $J_{2,3}$ 4.9 Hz, H-2), 5.80 (1H, d, H-1); **8**: 4.53 (1H, d, $J_{1,2}$ 3.7 Hz, H-2), 5.94 (1H, d, H-1).



Scheme 2. Reagents and conditions: (a) BnBr, Bu_4NHSO_4, DCM, NaOH, H_2O, 45 °C; **10**, 62%; **11** 20%; (b) PDC, 4 Å, DCM, 87%; (c) $NaBH_4$, THF, MeOH, −30 °C; **9**, 52%; **10**, 20%.

out S_N2 reactions on triflate **3** and other secondary carbohydrate triflates (**1** and 4-*epi*-**3**), but using the anion of carbohydrate hemiacetals to give glycoside products.[19] This prompted us to investigate the addition of external alcohols that could act as nucleophiles in potential S_N2 reactions.

Some secondary carbohydrate alcohols were synthesised by slightly modified procedures: **10**[20] and **11**[20] were formed from the monobenzylidene diol using Garegg's phase transfer conditions[21] in 62% and 20% yields, respectively. Compound **10** was then oxidised (87%) and the resulting ketone reduced[22] to give **9**[23] (52%) and **10** (20%), which were easily separable by column chromatography (Scheme 2).

Secondary carbohydrate alcohols **7**–**11** and carbasugar alcohol **12**[24] were treated with *allo* triflate **3** and NaH in DMF, and ether-linked pseudodisaccharides **4**,**5**,**13**–**16** were formed as the major product in all cases, although small amounts of the unsymmetrical **4** and symmetrical **5** dimers were often seen, especially when a large excess of triflate **3** was used (see Table 1). ^{1}H NMR coupling constants indicated that the furanose rings (labelled II in **4**,**13**–**16**) all had the *gluco* configuration. The fact that the only product detected derived from the alcohols **9**–**12** (i.e., in all cases where it was possible to distinguish) was the ether-linked pseudodisaccharide with inversion of configuration at C-3 of the triflate **3** is consistent with a straightforward S_N2 reaction mechanism.

In conclusion, we have discovered that *allo* triflate **3** behaves as a good electrophile for S_N2 reactions with secondary alkoxide nucleophiles, including furanoses, axial and equatorial pyranose hydroxyls and a carbasugar, under standard alkylation conditions, and have applied this to the synthesis of various *sec–sec* carbohydrate ether-linked pseudodisaccharides.

3. Experimental

3.1. General methods

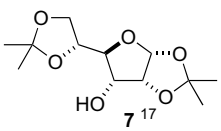
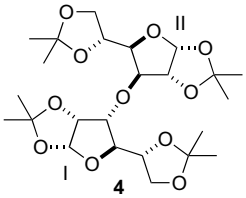
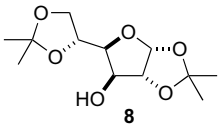
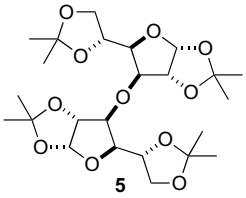
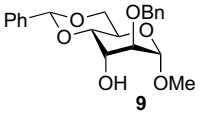
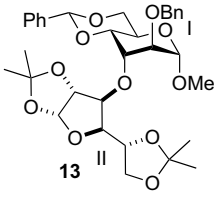
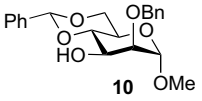
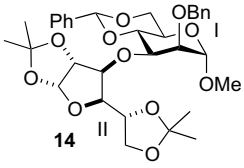
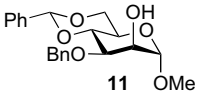
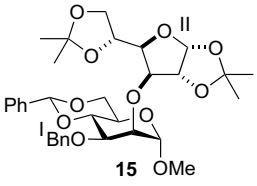
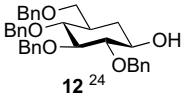
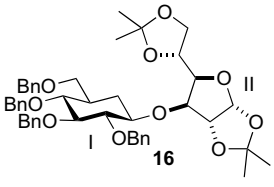
^{1}H NMR spectra were recorded on Bruker Avance II 400 (400 MHz), or 500 (500 MHz) spectrometers; multiplicities are quoted as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), apparent triplet (at) or apparent triplet of doublets (atd). Carbon nuclear magnetic resonance (^{13}C) spectra were recorded on Bruker Avance II 400 (100 MHz) or 500 (125 MHz) spectrometers and multiplicities assigned using DEPT. Spectra were assigned using COSY and HSQC experiments. All chemical shifts are quoted on the δ-scale in parts per million (ppm). Residual solvent signals were used as an internal reference. Low- and high-resolution (HRMS) electrospray (ESI) mass spectra were recorded using a Bruker Microtof instrument. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1 dm; concentrations are given in g/100 mL. Thin-layer chromatography (TLC) was carried out on Merck Kieselgel sheets, pre-coated with $60F_{254}$ Silica. Plates were visualised with UV light and developed using 10% sulfuric acid, or an ammonium molybdate (10% w/v) and cerium(IV) sulfate (2% w/v) solution in 10% sulfuric acid. Flash column chromatography was carried out on silica gel (35–70 μm, Grace). DMF was distilled or bought anhydrous from Aldrich; no difference between these qualities was seen. Reactions performed under an atmosphere of nitrogen were maintained by an inflated balloon.

3.2. Synthesis of alcohols

Synthesis of **10** and **11**: Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (5.11 g, 18.1 mmol) was dissolved in DCM (150 mL) and Bu_4NHSO_4 (1.23 g, 3.62 mmol) and benzyl bromide (3.78 mL, 31.8 mmol) were added. Sodium hydroxide (1.25 g) was dissolved in water (15 mL) and the solution added. The reaction mixture was heated to 45 °C. After 20 h, TLC (3:1 pentane–EtOAc) showed formation of major (R_f 0.8) and minor (R_f 0.4) products and little starting material (R_f 0.1) remaining. Dichloromethane (250 mL) was added, and the mixture washed with water (200 mL). The aqueous phase was re-extracted with DCM. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under diminished pressure. The residue was purified by flash column chromatography (6:1→3:1 pentane–EtOAc) to give **10** (4.21 g, 62%) and **9** (1.32 g, 20%). Starting diol (0.58 g, 11%) was also recovered.

Synthesis of **9**: Alcohol **10** (1.0 g, 2.69 mmol) was dissolved in DCM (25 mL) and 4 Å molecular sieves (6.5 g) and pyridinium dichromate (5.05 g, 13.4 mmol) were added. The reaction mixture was stirred at rt. Further PDC (1.0 g, 2.66 mmol) was added after 14 h, and again after a further 5 h. After a further 1 h, TLC (4:1 pentane–EtOAc) showed complete consumption of starting material (R_f 0.6) and formation of a major product (R_f 0.8). The reaction mixture was loaded directly onto a silica column and eluted with 25:1 DCM-ether to give the ketone (864 mg, 87%).

Table 1. Etherification reactions; all reactions carried out with NaH in DMF

Entry	Alcohol (1 equiv)	Equiv triflate **3**	Product	Yield[a] (%)
1	 **7**[17]	1.5	 **4**	89[b]
2	 **8**	1.5	 **5**	63[b]
3	 **9**	3.3	 **13**	78
4	 **10**	2.5	 **14**	95
5	 **11**	2.0	 **15**	64
6	 **12**[24]	2.0	 **16**	34

[a] Isolated yields based on alcohols.

[b] It is possible that small quantities of **4** and **5** derived solely from triflate **3** artificially inflate the yields in these cases. For entry 1, 0.28 equiv triflate **3** was recovered. For entry 2, 0.05 equiv triflate **3** was recovered, along with pseudodisaccharide **5** accounting for 0.33 equiv triflate **3**.

The ketone (860 mg, 2.32 mmol) was dissolved in THF (23 mL) and MeOH (3 mL) and cooled to −30 °C under N_2. Sodium borohydride (133 mg, 3.5 mmol) was added. Further $NaBH_4$ (10 mg, 0.26 mmol) was added, and after a further 45 min, TLC (3:1 pentane–EtOAc) showed complete conversion into major (R_f 0.3) and minor (R_f 0.5) products, and the absence of ketone (R_f 0.6). The reaction mixture was poured into a mixture of NH_4Cl (saturated aqueous) and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated under diminished pressure. The residue was purified by flash column chromatography (6:1 pentane–EtOAc) to give **10** (174 mg, 20%) and **9** (450 mg, 52%).

3.3. General procedure for the synthesis of pseudodisaccharides

Alcohol (0.05–0.78 mmol) **7**–**12** and allose triflate **3** (1.5–2.0 equiv) were dissolved in DMF (2.0 mL) at room temperature under nitrogen. NaH (2.0 equiv) was added

and the mixture stirred at room temperature. The reaction mixture turned brown within 10 min. Further triflate **3** was added if necessary. After TLC showed the formation of a major product (30 min–4 h 30 min), the reaction mixture was poured into brine (50 mL), extracted with ether (2 × 75 mL), dried ($MgSO_4$) and concentrated under diminished pressure. The crude product was purified by flash column chromatography.

3.4. 3-*O*-(1,2:5,6-Di-*O*-isopropylidene-3-deoxy-α-D-allofuranos-3-yl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (4)

R_f 0.3 (3:1 pentane–EtOAc); $[\alpha]_D^{24}$ +50.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32, 1.33, 1.35, 1.36, 1.41, 1.44, 1.49, 1.54 (24H, 8 × s, 4 × $C(CH_3)_2$), 3.89 (1H, dd, $J_{2,3}$ 4.7 Hz, $J_{3,4}$ 8.4 Hz, H-3^I), 3.92–4.11 (7H, m, H-4^I, H-6^I, H-6′^{I}, H-3^{II}, H-4^{II}, H-6^{II}, H-6′^{II}), 4.28 (1H, dat, *J* 4.0 Hz, *J* 6.8 Hz, H-5^I), 4.37 (1H, dat, *J* 5.9 Hz, *J* 7.5 Hz, H-5^{II}), 4.64 (1H, at, *J* 4.2 Hz, H-2^I), 4.70 (1H, d, $J_{1,2}$ 3.5 Hz, H-2^{II}), 5.79 (1H, d, $J_{1,2}$ 3.9 Hz, H-1^I), 5.87 (1H, d, H-1^{II}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.4, 25.4, 26.4, 26.4, 26.8, 27.0, 27.0, 27.0 (8 × q, 4 × C(*C*H$_3$)$_2$), 65.2, 67.6 (2 × t, C-6^I, C-6^{II}), 72.4 (d, C-5^{II}), 75.4 (d, C-5^I), 77.9 (d, C-2^I), 78.6, 80.3, 81.4, 82.5 (4 × d, C-4^{II}, C-3^{II}, C-4^I, C-3^I), 83.5 (d, C-2^{II}), 104.4 (d, C-1^I), 105.4 (C-1^{II}), 109.2, 109.7, 111.9, 113.1 (4 × s, 4 × *C*(CH$_3$)$_2$); ESIMS: *m*/*z* 525 (100%, $[M+Na]^+$); HRESIMS (*m*/*z*): calcd for $C_{24}H_{38}O_{11}Na$: 525.2306. Found 525.2339.

3.5. Bis(1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-glucofuranos-3-yl) ether (5)

R_f 0.6 (3:1 pentane–EtOAc); $[\alpha]_D^{24}$ −49.7 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29, 1.32, 1.40, 1.48 (24H, 4 × s, 8 × CH_3), 3.92 (2H, dd, $J_{5,6}$ 5.6 Hz, $J_{6,6'}$ 8.6 Hz, H-6), 4.04–4.09 (6H, m, H-3, H-4, H-6′), 4.15 (2H, atd, *J* 5.8 Hz, $J_{4,5}$ 7.8 Hz, H-5), 4.65 (2H, d, $J_{1,2}$ 3.6 Hz, H-2), 5.81 (2H, d, H-1). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.5, 26.3, 26.9, (3 × q, 4 × C(CH$_3$)$_2$), 67.8 (t, C-6), 72.4 (d, C-5), 81.1, 81.3 (2 × d, C-3, C-4), 82.3 (d, C-2), 105.7 (d, C-1), 109.1, 112.1 (2 × s, 2 × C(CH$_3$)$_2$); ESIMS: *m*/*z* 525 (100%, $[M+Na]^+$); HRESIMS (*m*/*z*): calcd for $C_{24}H_{38}O_{11}Na$: 525.2306. Found 525.2314.

3.6. 3-*O*-(Methyl 4,6-*O*-benzylidene-2-*O*-benzyl-3-deoxy-α-D-altropyranosid-3-yl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (13)

R_f 0.4 (3:1 pentane–EtOAc); $[\alpha]_D^{24}$ +28.8 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23, 1.29, 1.40, 1.45 (12H, 4 × s, 4 × CH_3), 3.37 (3H, s, OCH_3), 3.58 (1H, d, $J_{2,3}$ 2.6 Hz, H-2^I), 3.76 (1H, at, *J* 10.1 Hz, H-6^I), 3.96–4.08 (4H, m, H-3^I, H-4^I, H-6^{II}, H-6′^{II}), 4.15–4.24 (3H, m, H-3^{II}, H-4^{II}, H-5^I), 4.26 (1H, d, $J_{1,2}$ 3.6 Hz, H-2^{II}), 4.29 (1H, dd, $J_{5,6'}$ 5.2 Hz, H-6′^{I}), 4.50 (1H, aq, *J* 6.1 Hz, H-5^{II}), 4.57, 4.72 (1H, ABq, J_{AB} 12.0 Hz, $PhCH_2$), 4.68 (1H, s, H-1^I), 5.54 (1H, s, PhC*H*), 5.80 (1H, d, H-1^{II}), 7.26–7.41 (8H, m, Ar-H), 7.46–7.49 (2H, m, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.2, 26.5, 26.7, 27.0 (4 × q, 2 × C(*C*H$_3$)$_2$), 55.2 (q, OCH_3), 58.4 (d, C-5^I), 66.7 (t, C-6^{II}), 69.4 (t, C-6^I), 72.9 (t, Ph*C*H$_2$), 73.0 (d, C-5^{II}), 73.5, 76.3 (2 × d, C-3^I, C-4^I) 77.0 (d, C-2^I), 81.5, 82.5 (2 × d, C-3^{II}, C-4^{II}), 82.7 (d, C-2^{II}), 99.7 (d, C-1^I), 102.4 (d, Ph*C*H), 105.3 (d, C-1^{II}), 108.7, 111.7 (2 × s, *C*(CH$_3$)$_2$), 126.3, 128.1, 128.3, 128.4, 128.7, 129.1 (6 × d, Ar-CH) 137.3, 137.8 (2 × s Ar-C); ESIMS: *m*/*z* 637 (100%, $[M+Na]^+$); HRESIMS (*m*/*z*): calcd for $C_{33}H_{42}O_{11}Na$: 637.2619. Found 637.2626.

3.7. 3-*O*-(Methyl 4,6-*O*-benzylidene-2-*O*-benzyl-3-deoxy-α-D-mannopyranosid-3-yl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (14)

R_f 0.6 (3:1 pentane–EtOAc); $[\alpha]_D^{23}$ −4.9 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17, 1.21, 1.40, 1.47 (12H, 4 × s, 2 × C(CH$_3$)$_2$), 3.37 (3H, s, OCH_3), 3.77 (1H, dat, $J_{5,6'}$ 4.6 Hz, *J* 10.2 Hz, H-5^I), 3.85 (1H, dd, $J_{1,2}$ 1.7 Hz, $J_{2,3}$ 3.2 Hz, H-2^I), 3.86 (1H, at, *J* 10.2 Hz, H-6^I), 3.96 (1H, dd, $J_{5,6}$ 5.3 Hz, $J_{6,6'}$ 8.6 Hz, H-6^{II}), 3.98 (1H, dd, $J_{3,4}$ 3.2 Hz, $J_{4,5}$ 10.1 Hz, H-4^{II}), 4.02 (1H, dd, $J_{3,4}$ 8.8 Hz, H-3^I), 4.07 (1H, dd, $J_{5,6'}$ 6.0 Hz, H-6′^{II}), 4.10 (1H, dd, $J_{4,5}$ 10.1 Hz, H-4^I), 4.15 (1H, d, $J_{2,3}$ 3.0 Hz, H-3^{II}), 4.23–4.28 (2H, m, H-5^{II}, H-6′^{I}), 4.64 (1H, d, $J_{1,2}$ 1.6 Hz, H-1^I), 4.71, 4.83 (1H, ABq J_{AB} 12.0 Hz, $PhCH_2$), 4.82 (1H, d, $J_{1,2}$ 3.6 Hz, H-2^{II}), 5.62 (1H, s, PhC*H*), 5.75 (1H, d, H-1^{II}), 7.25–7.40 (8H, m, Ar-H), 7.49–7.53 (2H, m, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.4, 26.0, 26.9, 27.0 (4 × q, 2 × C(*C*H$_3$)$_2$), 55.0 (q, OCH_3), 64.4 (d, C-5^I), 68.0 (t, C-6^{II}), 68.9 (t, C-6^I), 72.4 (d, C-5^{II}), 73.8 (t, Ph*C*H$_2$), 77.3 (d, C-2^I) 77.8 (d, C-4^{II}), 78.2 (d, C-4^I), 81.6 (d, C-3^I), 83.5 (d, C-2^{II}), 83.6 (d, C-3^{II}), 100.7 (d, C-1^I), 101.6 (d, Ph*C*H), 105.4 (d, C-1^{II}), 109.3, 111.7 (2 × s, 2 × *C*(CH$_3$)$_2$), 126.0, 127.9, 128.1, 128.5, 129.0 (5 × d, Ar-CH), 137.6, 138.3 (2 × s, Ar-C); ESIMS: *m*/*z* 637 (100%, $[M+Na]^+$); HRESIMS (*m*/*z*): calcd for $C_{33}H_{42}O_{11}Na$: 637.2619. Found 637.2588.

3.8. 3-*O*-(Methyl 4,6-*O*-benzylidene-3-*O*-benzyl-2-deoxy-α-D-mannopyranosid-2-yl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (15)

R_f 0.5 (3:1 pentane–EtOAc); $[\alpha]_D^{24}$ −19.0 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17, 1.35, 1.42, 1.46 (12H, 4 × s, 2 × C(CH$_3$)$_2$), 3.35 (3H, s, OCH_3), 3.77 (1H, dat, $J_{5,6'}$ 4.1 Hz, *J* 9.6 Hz, H-5^I), 3.82 (1H, at, *J* 9.9 Hz, H-6^I), 3.86 (1H, dd, $J_{1,2}$ 1.5 Hz, $J_{2,3}$ 3.2 Hz, H-2^I), 3.91 (1H, dd, $J_{3,4}$ 9.8 Hz, H-3^I), 3.97 (1H, dd, $J_{5,6}$ 6.2 Hz,

$J_{6,6'}$ 8.4 Hz, H-6^{II}), 4.03 (1H, at, J 9.3 Hz, H-4^{I}), 4.04 (1H, d, $J_{3,4}$ 3.0 Hz, H-3^{II}), 4.09 (1H, dd, $J_{4,5}$ 7.8 Hz, H-4^{II}), 4.15 (1H, dd, $J_{5,6'}$ 6.1 Hz, H-6′^{II}), 4.23–4.31 (2H, m, H-6′^{I}, H-5^{II}), 4.70, 4.91 (1H, ABq, J_{AB} 11.7 Hz, PhCH$_2$), 4.78 (1H, d, $J_{1,2}$ 1.5 Hz, H-1^{I}), 4.81 (1H, d, $J_{1,2}$ 3.7 Hz, H-2^{II}), 5.62 (1H, s, PhC*H*), 5.83 (1H, d, H-1^{II}), 7.24–7.39 (8H, m, Ar-H), 7.48–7.50 (2H, m, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.6, 26.3, 26.9, 27.0 (4 × q, 2 × C(*C*H$_3$)$_2$), 55.0 (q, OCH$_3$), 63.9 (d, C-5^{I}), 67.8 (t, C-6^{II}), 69.0 (t, C-6^{I}), 72.9 (d, C-5^{II}), 73.7 (t, Ph*C*H$_2$), 75.7 (d, C-3^{I}), 79.6 (d, C-4^{I}), 80.2 (d, C-2^{I}), 81.4 (d, C-4^{II}), 83.5 (d, C-2^{II}), 85.4 (C-3^{II}), 100.6 (d, C-1^{I}), 101.6 (d, Ph*C*H), 105.6 (d, C-1^{II}), 109.1, 111.7 (2 × s, 2 × *C*(CH$_3$)$_2$), 126.2, 127.7, 127.7, 128.3, 128.5, 129.0 (6 × d, Ar-CH), 137.7, 138.6 (2 × s, Ar-C); ESIMS: m/z 637 (100%, [M+Na]$^+$); HRESIMS (m/z): calcd for $C_{33}H_{42}O_{11}Na$: 637.2619. Found 637.2641.

3.9. 3-*O*-(2,3,4,6-Tetra-*O*-benzyl-5a-carba-β-D-glucopyranosyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (16)

R_f 0.9 (3:1 pentane–EtOAc); $[\alpha]_D^{23}$ +9.3 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16, 1.33, 1.41, 1.44 (12H, 4 × s, 2 × C(CH$_3$)$_2$), 1.39 (1H, m, H-5a^{I}), 1.66 (1H, m, H-5^{I}), 2.15 (1H, dat, J 4.0 Hz, $J_{5a,5a'}$ 13.6 Hz, H-5a′), 3.37 (1H, at, J 9.0 Hz, H-2^{I} or H-3^{I}), 3.43–3.54 (4H, m, H-1^{I}, H-4^{I}, H-6^{I}, H-2^{I} or H-3^{I}), 3.57 (1H, dd, $J_{5,6'}$ 5.3 Hz, $J_{6,6'}$ 8.9 Hz, H-6′), 3.95–3.98 (2H, m, H-3^{II}, H-6^{II}), 4.08 (1H, dd, $J_{5,6'}$ 6.2 Hz, $J_{6,6'}$ 8.4 Hz, H-6′^{II}), 4.14 (1H, dd, $J_{3,4}$ 3.2 Hz, $J_{4,5}$ 7.0 Hz, H-4^{II}), 4.29 (1H, aq, J 6.4 Hz, H-5^{II}), 4.45 (2H, s, PhCH$_2$), 4.51 (1H, d, J 10.8 Hz, PhC*H*H′), 4.57 (1H, d, $J_{1,2}$ 3.8 Hz, H-2^{II}), 4.72 (1H, d, J 11.2 Hz, PhC*H*H′), 4.84–4.92 (4H, m, PhCH$_2$, 2 × PhCH*H*′), 5.60 (1H, d, H-1^{II}), 7.18–7.34 (20H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.6, 26.0, 26.8, 26.9 (4 × q, 2 × C(*C*H$_3$)$_2$), 30.0 (t, C-5a), 39.0 (d, C-5), 67.3 (t, C-6^{II}), 70.1 (t, C-6^{I}), 72.9 (d, C-5^{II}), 73.4, 75.4, 75.7, 75.9 (4 × t, 4 × PhCH$_2$), 79.9, 80.9, 81.0, 81.4, 82.9, 85.0, 86.6 (7 × d, C-1^{I}, C-2^{I}, C-3^{I}, C-4^{I}, C-2^{II}, C-3^{II}, C-4^{II}), 105.5 (d, C-5^{II}), 108.9, 111.6 (2 × s, 2 × C(CH$_3$)$_2$), 127.4, 127.7, 127.7, 127.8, 127.8, 127.9, 128.2, 128.5, 128.5, 128.6 (10 × d, Ar-CH), 138.5, 138.6, 138.8 (3 × s, 4 × Ar-C); ESIMS: m/z 803 (100%, [M + Na]$^+$), 819 (7%, [M+K]$^+$); HRESIMS (m/z): calcd for $C_{47}H_{56}O_{10}Na$: 803.3766. Found 803.3741.

3.10. Data collection and measurement

Single crystal X-ray diffraction patterns were recorded with an Oxford Diffraction Xcalibur-II kappa diffractometer equipped with an Enhance-III closed tube Mo-radiation source ($\lambda = 0.71073$ Å) X-ray source. The sample–detector distance was 50 mm and standard data collection routines delivered with the diffractometer was used for the data collection. Several ω scans were done at different ϕ to cover at least half of the Ewald sphere.

3.11. Structure solution and refinement

The structures were solved by direct methods using SHELXS 97 giving electron density maps where most of the non-hydrogen atoms could be resolved. The rest of the non-hydrogen atoms were located from different electron density maps and the structure model was refined with full matrix least square calculations on F^2 using the program SHELXL 97. All non-hydrogen atoms were refined with anisotropic displacement parameters and the hydrogens, which were placed at geometrically calculated positions and let to ride on the atoms they were bonded to, were given isotropic displacement parameters calculated as $\xi \cdot U_{eq.}$ for the non-hydrogen atoms with $\xi = 1.5$ for methyl hydrogens (–CH$_3$) and $\xi = 1.2$ for methylenic (–CH$_2$–) and methinic (CH) hydrogens.

The ring O4^{I}–C1^{I}–C2^{I}–C3^{I}–C4^{I} can be described by the Cremer–Pople parameters: $Q(2) = 0.395(3)$ Å and $\phi(2) = 301.2(4)°$ and the ring O4^{II}–C1^{II}–C2^{II}–C3^{II}–C4^{II} can be described by the parameters $Q(2) = 0.327(3)$ Å and $\phi(2) = 300.5(4)°$. Both sugar rings can be described with the T furanose pucker descriptor.

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Supplementary data

Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 662554. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.01.013.

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