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Synthesis of alpha-Gal C-disaccharides

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ABSTRACT

The synthesis of C-disaccharides of α-D-galactopyranosyl-(1 → 3)-D-galactopyranose (α-Gal), potential tools for studying the biology of α-Gal glycans, is described. The synthetic strategy, centers on the reaction of two easily available precursors 1,2-O-isopropylidene-D-glyceraldehyde and an α-C-glactosyl-*E*-crotylboronate, which affords a mixture of two diastereomeric anti-crotylation products. The stereoselectivity of this reaction was controlled with (*R*)- and (S)-TRIP catalysts, and the appropriate diastereomer was transformed to C-linked disaccharides of α-Gal, in which the aglycone segment comprised O-, C- and S-glycoside entities that can enable glycoconjugate synthesis.

1. Introduction

The α-galactopyranosyl (α-Gal) motif commonly occurs in mammals and certain pathogens but generally not in humans and Old-World monkeys.[1] As α-Gal glycans are present on organs and tissue of pigs they are an obstacle to xenotransplantation to humans and monkeys as they elicit hyperacute immune rejection.[2,3] In contrast, the binding of anti-α-Gal antibodies to α-Gal containing glycans has been explored as an immunotherapeutic strategy, most notably against cancer and viral infection.[4–10] Relatedly, due to stimulation of α-Gal containing enterobacteria, humans contain varying levels of anti-α-Gal antibodies, which may have a protective role against pathogens with α-Gal glycans on their surface, with SARS and SARS CoV-2, being examples that have attracted recent attention.[11–15] Against this backdrop, there is interest in α-Gal mimetics for use as biomechanistic probes and therapeutic applications. Disaccharide and higher order saccharides (as opposed to simpler monosaccharides) have been targeted because of their higher affinity to α-Gal Abs and for interrogation of specific pathways, with analogues of **1** being popular (Fig. 1).[16–20] Herein we describe the synthesis of *C*-disaccharides of the α-Gal*p*-(1,3)-Gal*p* subunit of **1**.[21,22] The hydrolytic stability of such *C*-glycosides compared to their *O*-linked parents can mitigate stability issues that may hinder therapeutic applications of alpha-Gal, and together with their conformational properties, are relevant to their use as tools for studying alpha-Gal recognition.[23–27]

While several methods exist for the synthesis of *C*-glycosides with aryl or simple alkyl aglycone segments, these are generally not applicable to anomeric sp^3-sp^3 *C*-linked glycosides, in particular to the complex methylene linked disaccharide frameworks represented by **2**.[23,24,28–39] Towards this end, strategies involving the union of preformed "glycone" and "aglycone" subunits have been described, but the synthesis of precursors, and coupling procedures, yields and stereoselectivity can be problematic.[23,24,36,40–45] Approaches in which the glycone or aglycone residue is created in a *de novo* fashion may address these issues.[46–50] In this context, we have been developing a methodology that centers on the reaction of *C*-glycosyl crotylating agents and aldehydes, and elaboration of the products to stereochemically complex C-glycosides (Fig. 2).[51,52] Attributes of this strategy are the relatively easy access to the crotylation partners and the synthetic versatility of the crotylation products. Accordingly, we envisaged a synthesis of C-disaccharides like **2** starting from the crotylation reaction of the *C*-galactosyl-*E*-crotylboronate **5** and 1,2-*O*-isopropylidene-D-glyceraldehyde **6** to give the 3,4-*anti* crotylation product **4**, followed by transformation of **4** to analogues of **2**. This plan is of wider scope in that **4** can also be transformed to biologically relevant α-Gal-(1,3)-furanosides like **3**.[53]

2. Results and discussion

2.1. Synthesis of C-galactosyl crotylboronate 5

Our earlier synthesis of *E*-glycosylboronate like **5** followed the Ni $(cod)_2$ promoted reaction of an allylic acetate precursor with bis-(pinacolato)-diboron $(BPin)_2$, which required a glovebox procedure because of the sensitivity of the nickel pre-catalyst.[52,54] In the present work, we developed a modified procedure from an allylic chloride precursor and a palladium catalyst that did not require glovebox conditions (Scheme 1).[54,55] Thus, reaction of allylic chloride **7**, (prepared

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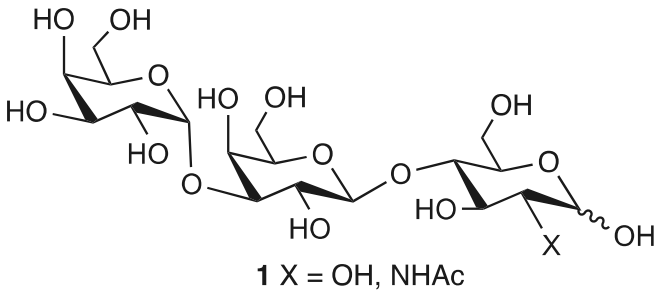


Fig. 1. α-Gal trisaccharide antigens.

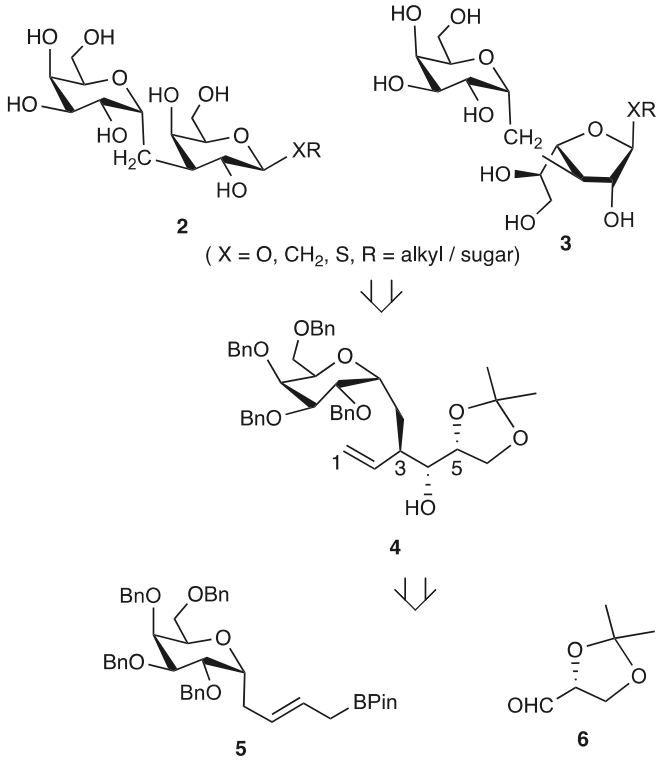
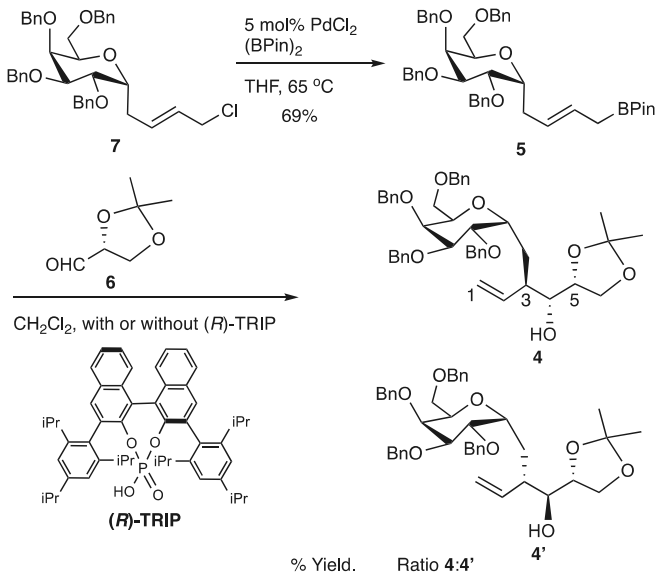


Fig. 2. The crotylation way to C-glycosides.

via a reported cross metathesis on *C*-allyl tetra-*O*-benzyl palactopyranoside and allyl chloride),[56] and $(BPin)_2$ in tetrahydrofuran, in the presence of catalytic $Pd(OAc)_2/PCy_3$ and K_3PO_4 provided the *E*-crotylboronate **5** in 71 % yield after chromatographic purification, and greater than 95 % *E:Z* selectivity as determined by ^1H NMR. It should be noted that **5** appeared to be stable under the conditions for flash column chromatography, some degree of decomposition was observed on thin layer chromatography plates. The stereochemistry of **5** was assigned by NMR comparisons with related *E*- and *Z*- C-glycosylcrotylboronates, and confirmed by stereochemical assignment in the subsequent crotylation products (*vide infra*).[52,54]

2.2. Crotylation reactions

The reaction of **5** and 2,3-*O*-isopropylidene D-glyceraldehyde **6**[57] in dichloromethane affoded a mixture of the two 3,4-*anti* crotylation products **4** and **4′** in 88 % yield in a respective ratio of 2:3 (Scheme 1). The stereochemistry of **4** and **4′** was assigned in subsequent disaccharide analogues and the structure of **4** was confirmed by X-Ray crystallography on the benzyl ether derivative **8** (Fig. 3, *vide infra*, Supplementary Material). When the reaction was performed with 15 mol % of (*R*)-TRIP, the stereoselectivity was reversed, albeit modestly, to give a 3:2 ratio in



Scheme 1. Synthesis of **5** and crotylation reactions.

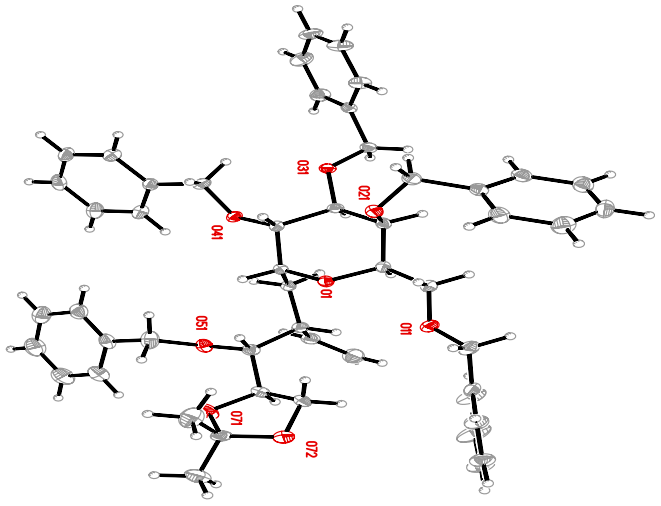
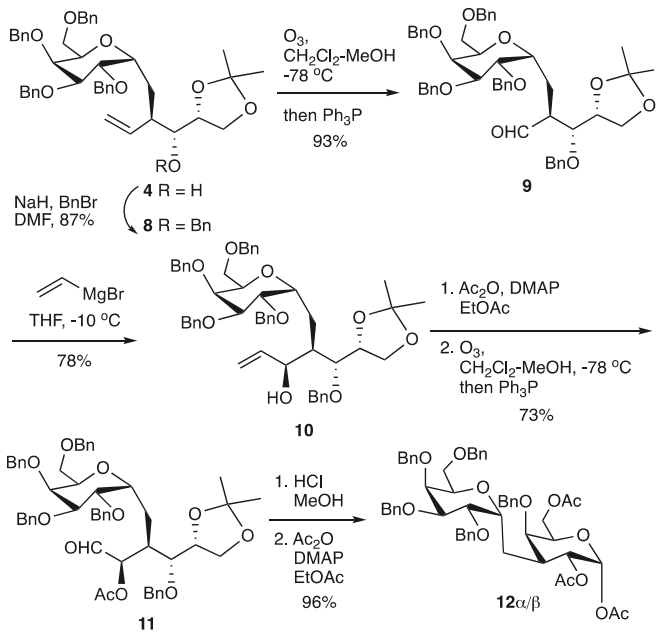


Fig. 3. X-ray crystal structure of benzyl ether **8** (CCDC number 2343201).

favor of the desired diastereomer **4**. The corresponding reaction with (*S*)-TRIP gave a 1:2 ratio of **4**:**4′**. The stereoselectvity trends for reactions with and without the TRIP catalysts were similar for the reactions of **6** and a mannose derived *E*-crotylboronate.[52]

2.3. Transformation of crotylation products to C-disaccharides

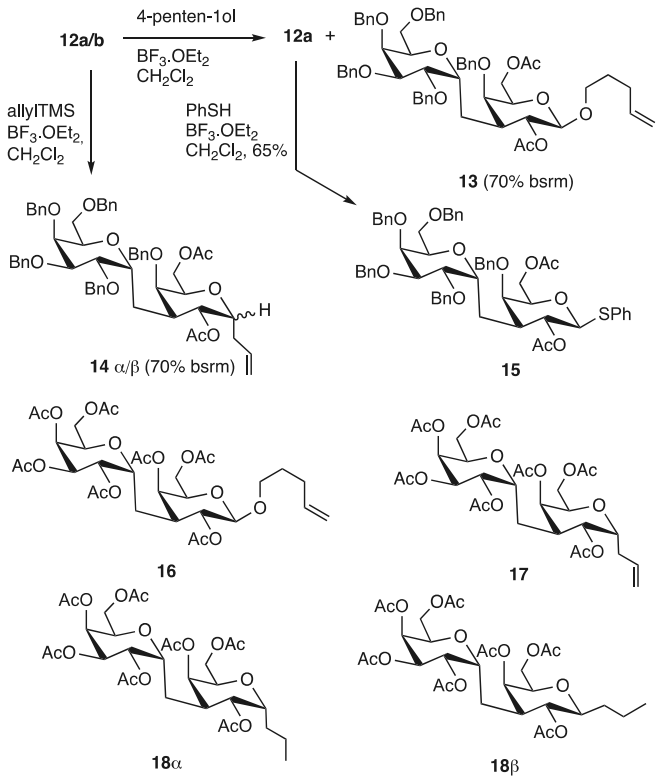
The crotylation product **4** was next transformed to a mixture of *C*-linked dipyranosyl acetates 12α/β (Scheme 2) Thus, benzylation on **4**, followed by ozonolysis of the product **8** and reaction of vinylmagnesium bromide with the derived aldehyde **9** provided a 7:1 mixture of allylic alcohol **10** in 78 % yield, and a minor product that was presumed to be a diastereomer of **10**. The stereochemistry of **10** was assigned in the eventual disaccharide derivatives (*vide infra*). Acetylation of **10** followed by ozonolysis of the product provided aldehyde **11**. Acid hydrolysis on **11** and acetylation of the crude product with acetic anhydride and DMAP in ethyl acetate, afforded acetate anomers **12**α/β in a 2/1 respective ratio, as an inseparable mixture. When the acetylation was



Scheme 2. Transformation of **4** to *C*-disaccharide **12**α/β.

performed with acetic anhydride in the presence of sodium acetate a 1/2 ratio of **12**α/β was observed.

The mixture **12**α/β was next transformed to C/O-, C/C- and C/S-anti-Gal disaccharide analogues, with versatile anomeric handles for glycoconjugate synthesis (Scheme 3).[5,8–10,16,18] Treatment of **12**α/β with 4-penten-1-ol in the presence of $BF_3.OEt_2$, provided the β-glycoside **13** in 70 % yield based on unreacted **12**α. When allyltrimethylsilane was used as the glycosyl acceptor in place of 4-penten-1-ol, a mixture of C-glycosides **14**α/β with a respective ratio of 3/2 was obtained in a similar



Scheme 3. Synthesis of C/O-, C/C- and C/S- disaccharides of anti-Gal.

yield based on unreacted **12**α. Under similar conditions, treatment of **12**α with thiophenol as the acceptor afforded the β-thioglycoside **15** with complete consumption of **12**α. The stereochemistry in the newly formed pyran ring in these disaccharide analogues was assigned by *J* coupling and NOE analysis on **13**, **14**α, **14**β and **15**, and their peracetate derivatives **16**, **17**, **18**α and **18**β, which were prepared via standard debenzylation and acetylation procedures (See Experimental and Supplementary Material for procedures and NMR data with peak assignments).

3. Conclusions

Bis *C*- and mixed *C/O*- and *C/S* disaccharides of anti-Gal were prepared. These syntheses centered on the ®-TRIP catalyzed reaction of a *C*-galactosyl crotylboronate, which was available in four steps from commercially available methyl α-D-galactopyranoside, and 2,3-*O*-isopropylidene D-glyceraldehyde, and transformation of the major crotylation product to the eventual targets via a straightforward *de novo* pyrano ring-forming strategy. Application of this methodology to higher order saccharide analogues and bioconjugates of anti-Gal are currently under investigation and will be reported in due course.

4. Materials and methods

4.1. General

Solvents were purified by standard procedures or used from commercial sources as appropriate. Petroleum ether refers to the fraction of petroleum ether boiling between 40 and 60 °C. Unless otherwise stated thin layer chromatography (TLC) was done on 0.25 mm thick precoated silica gel 60 (HF-254, Whatman) aluminium sheets and flash column chromatography (FCC) was performed using Kieselgel 60 (32–63 mesh, Scientific Adsorbents). Elution for FCC usually employed a stepwise solvent polarity gradient, correlated with TLC mobility. Chromatograms were observed under UV (short and long wavelength) light, and/or were visualized by heating plates that were dipped in a solution of ammonium (VI) molybdate tetrahydrate (12.5 g) and cerium (IV) sulfate tetrahydrate (5.0 g) in 10 % aqueous sulphuric acid (500 mL), or a solution of 20 % sulfuric acid in ethanol. NMR spectra were recorded using Varian Unity Plus 500 and Bruker Ultra Shield Plus 600 MHz instruments, in $CDCl_3$ or C_6D_6. Unless otherwise stated residual $CHCl_3$ and C_6H_6 were used as internal standards respectively (δ_H 7.27, 7.16, 4.80 and δ_C 77.2, 128.4 ppm). Chemical shifts are quoted in ppm relative to tetramethylsilane (δ_H 0.00) and coupling constants (J) are given in Hertz. First order approximations are employed throughout. High resolution mass spectrometry was performed on an Agilent 6520 Q-TOF instrument.

4.2. 4,4,5,5-tetramethyl-2-((E)-4-((2R,3S,4R,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)but-2-en-1-yl)-1,3,2-dioxaborolane (5)

A mixture of $Pd(OAc)_2$ (22 mg, 0.1 mmol) and PCy_3 (82 mg, 0.29 mmol) in dry THF (1 mL) was stirred under nitrogen for 20 min. A portion of this solution (0.7 mL) was added to a mixture of allylic chloride **7** (427 mg, 0.70 mmol) and bis(pinacolato)diboron (362 mg, 1.43 mmol) in dry THF (2.5 ml) under nitrogen. Powdered, anhydrous K_3PO_4 (200 mg, 0.94 mmol) was then added to the reaction mixture and the suspension stirred at rt for 1 h, at which the color of the reaction had changed from an original golden brown to black. The mixture was then diluted with a 1:1 mixture of ether:hexane (40 mL) and filtered through a short column of Celite. The filtrate was concentrated *in vacuo* and the residue purified by FCC to yield **5** (350 mg, 71 %): clear oil; R_f 0.38 (15 % EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$). δ 5.45 (m, 1H), 5.24 (m, 1H), 4.60 (apparent d, J = 12.1 Hz, 2H), 4.53–4.41 (m, 6H), 4.01 (m, 1H), 3.93 (m, 1H), 3.85 (m, 1H), 3.81 (m, 1H), 3.62–3.58 (m, 3H), 2.26 (m, 2H, J = 7.3 Hz), 1.56 (m, 2H), 1.15 (s, 12H). ^{13}C NMR (125 MHz,

$CDCl_3$) δ 138.7, 138.6, 138.5, 138.4, 128.3, 128.0, 127.8, 127.8, 127.7, 127.6, 126.6, 83.2, 76.3, 74.3, 73.2, 73.0 (2 signals), 72.9, 72.7, 71.0, 67.1, 31.3, 24.8, 16.4. HRMS (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{44}H_{53}BO_7Na$ 727.3784; Found 727.3782.

*4.3. (1R,2R)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(((2R,3S,4R,5S,6R)-3,4,5-tris-(benzyloxy)-6-((benzyloxy)methyl) tetrahydro-2H-pyran-2-yl)methyl)but-3-en-1-ol (**4**) and (1S,2S)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(((2R,3S,4R,5S,6R)-3,4,5-tris (benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl) but-3-en-1-ol (**4′**)*

A mixture of **5** (210 mg, 0.30 mmol) in CH_2Cl_2, (2 mL) and (*R*)-TRIP (40 mg, 0.05 mmol) was stirred at rt for 15 min. A solution of **6** (100 mg, 0.77 mmol) in CH_2Cl_2 (0.5 mL) was then added, and the reaction stirred for 16 h. The mixture was then diluted with 2 N NaOH and extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. This material was then dissolved in EtOAc and filtered through a short column of basic alumina to remove residual boronic acid side products and TRIP catalyst. The filtrate was evaporated under reduced pressure and the residue subjected to FCC (30 % EtOAc/hexane), to afford an unseparated mixture of **4** and **4′** (150 mg, 70 %), as a 2:1 respective ratio as determined by ^{1}H NMR. Careful FCC of this mixture provided separated **4** and **4′.** For **4**: clear oil; R_f = 0.40 (30 % EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.20 (m, 20H),5.91 (m,1H), 5.07 (dd, J = 1.9, 10.2 Hz, 1H), 4.97 (dd, J = 1.6, 17.3 Hz, 1H), 4.70–4.60 (m, 4H), 4.55 (m, 3H), 4.45 (apparent d, J = 12.0 Hz, 1H), 4.20 (m, 1H), 4.04 (apparent quartet, J = 7.2 Hz, 1H), 3.99 (m, 2H), 3.87 (dd, J = 6.4, 8.1 Hz, 1H), 3.82 (m, 2H), 3.73 (dd, J = 2.7, 7.3 Hz, 1H), 3.60 (m, 3H), 2.40 (bs, 1H, OH), 2.14 (m, 1H), 1.94 (m, 1H), 1.77 (m, 1H), 1.41 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.6, 138.4, 138.1, 128.6 (2 signals), 128.5, 128.3, 128.2, 128.0, 127.8, 127.7, 116.8, 109.5, 78.1, 77.4, 76.7, 74.5, 73.4, 73.3, 73.2, 73.1, 72.4, 68.6, 67.9, 66.1, 42.8, 29.2, 26.9, 25.8. HRMS (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{44}H_{52}O_8Na$ 731.3554; Found 731.3557. For **4′**: R_f 0.35 (30 % EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.15 (m, 20H), 5.67 (m, 1H), 5.05 (m, 2H), 4.73 (apparent d, J = 11.8 Hz, 1H), 4.62 (m, 3H), 4.50–4.35 (m, 4H), 4.02 (m, 1H), 3.85 (m, 3H), 3.74 (m, 3H), 3.55 (m, 3H), 3.27 (bd, J = 9.6 Hz, 1H), 2.96 (bs, 1H, OH), 2.32 (m, 1H), 1.80 (m, 1H), 1.52 (m, 1H), 1.30 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.6, 138.5, 137.7, 128.7, 128.6 (3 signals),128.5, 128.4, 128.3, 128.2, 128.1 (2 signals), 128.0, 127.9 (2 signals), 127.8, 117.5, 108.8, 78.1, 76.7, 74.9, 73.8, 73.6, 73.5, 73.4, 73.3, 72.9, 71.9, 69.8, 67.0, 45.0, 27.1, 26.8, 25.7. HRMS (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{44}H_{52}O_8Na$ 731.3554; Found 731.3557.

*4.4. (2R,3S,4R,5S,6R)-3,4,5-tris(benzyloxy)-2-((R)-2-((R)-(benzyloxy) ((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)but-3-en-1-yl)-6-((benzyloxy)methyl)tetrahydro-2H-pyran (**8**)*

A suspension of 60 % NaH in mineral oil (56 mg, 1.4 mmol) was added at 0 °C to a solution of **4** (280 mg, 0.40 mmol) and TBAI (30 mg, 0.08 mmol) in anhydrous DMF (2 mL), The mixture was stirred for 15 min at rt, then cooled to 0 °C. BnBr (0.0.12 mL, 1.01 mmol) was added, and the reaction was stirred at rt for 2 h, then quenched with methanol (0.1 mL), diluted with brine and extracted with EtOAc. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. FCC of the residue provided **8** (277 mg, 87 %) as a clear gum. R_f = 0.65 (25 % EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$) 7.30–7.10 (m, 25H), 5.84 (m, 1H), 4.92 (m, 2H), 4.84 (dd, J = 1.7, 17.3 Hz, 1H), 4.68 (app d, J = 11.7 Hz, 1H), 4.56 (m, 2H), 4.46 (m, 4H), 4.35 (m, 2H), 4.08 (m, 1H), 3.95 (m, 1H), 3.86 (m, 1H), 3.77 (m, 3H), 3.62 (m, 2H), 3.44 (dd, J = 4.8, 10.2 Hz, 1H), 3.40 (dd, J = 1.7, 8.3 Hz, 1H), 3.36 (t, J = 8.8 Hz, 1H), (m, 2H), 1.92 (m, 1H), 1.84 (m 1H), 1.60 (m, 1H), 1.32 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 138.8, 138.7, 138.6, 138.4, 138.3, 128.6, 128.5 (3 signals), 128.4, 128.2, 128.0, 127.9, 127.8 (2 signals), 127.7, 127.6, 127.5, 116.3, 109.4, 81.0, 80.0, 77.4, 76.5, 74.5, 74.0, 73.7, 73.5, 73.2, 73.1, 72.1, 69.0, 68.2, 66.1, 42.8, 29.3, 27.0, 26.1. HRMS (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{51}H_{58}O_8Na$ 821.4024; Found 821.4021.

*4.5. (2S,3R)-3-(benzyloxy)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(((2R,3S,4R,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl) tetrahydro-2H-pyran-2-yl)methyl)propanal (**9**)*

Ozone was bubbled through a solution of **8** (210 mg, 0.26 mmol) in a mixture of CH_2Cl_2 (5 mL) and methanol (1 mL) at −78 °C. Bubbling was continued until the color of the solution was pale blue, at which time TLC indicated complete disappearance of **8**. The mixture was then purged with nitrogen and Ph_3P (160 mg, 0.61 mol) was added. After stirring 3 h at rt, the solvent was evaporated under reduced pressure. FCC of the residue afforded **9** (195 mg, 93 %) as a clear oil. R_f = 0.20 (15 % EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (d, J = 2.7 Hz, 1H), 7.25 (m, 25H, ArH), 4.75–4.30 (m, 10*H*, PhCH), 4.23 (q, J = 7.4 Hz, 1H), 3.88 (m, 3H), 3.78 (m, 1H), 3.73 (m, 1H), 3.62 (dd, J = 2.7, 7.6 Hz, 1H), 3.57 (m, 3H), 3.44 (d, J = 4.5, 10.5 Hz, 1H), 2.30 (m, 1H), 2.17 (m, 1H), 1.73 (m, 1H), 1.34 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 138.6 (2 signals), 138.4 (2 signals), 138.3, 128.6 (2 signals), 128.5 (2 signals), 128.4, 128.2, 128.1 (2 signals), 128.0 (2 signals), 127.9, 127.8, 127.7 (2 signals), 109.9, 79.9, 78.7, 76.7, 74.4, 74.2, 73.7, 73.5, 73.4, 73.2, 72.1, 68.0, 66.3, 51.2, 26.8, 25.9. (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{50}H_{56}O_9Na$ 823.3817; Found 823.3817.

*4.6. (3S,4R,5R)-5-(benzyloxy)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(((2R,3S,4R,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl) tetrahydro-2H-pyran-2-yl)methyl)pent-1-en-3-ol (**10**)*

A 0.7 M vinyl magnesium bromide in THF (1.75 mL, 1.23 mmol) was added to a solution of **9** (190 mg, 0.24 mmol) in dry THF (2 mL) at 0 °C, under an atmosphere of nitrogen. The mixture was warmed to rt, stirred for an additional 30 min, then poured into saturated aqueous NH_4Cl and extracted with ether. The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. FCC of the residue afforded a mixture of **10** and an minor product, which was presumed to be a diastereomer of **10**, in a ratio of 7:1. For **10**: (155 mg, 78 %); clear gum; R_f = 0.50 (30 % EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 25H), 5.63 (m, 1H), 5.23 (d, J = 14.2 Hz, 1H), 5.04 (d, J = 10.6 Hz, 1H), 4.93 (app d, J = 11.2 Hz, 1H), 4.72 (app d, J = 11.6 Hz, 1H), 4.62 (s, 2H), 4.57 (app d, J = 11.7 Hz, 1H), 4.52 (bs, 1H), 4.42 (m, 5H), 4.30 (app d, J = 12.0 Hz, 1H), 3.95 (m, 1H), 3.86 (m, 1H), 3.81 (t, J = 2.1 Hz, 1H), 3.78 (t, J = 8.3 Hz, 1H), 3.67 (bs, 1H, OH), 3.61 (m, 2H), 3.47 (m, 2H), 3.33 (m, 1H), 1.75 (m, 2H), 1.45 (m, 1H), 1.35 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 138.6, 138.5, 138.4, 138.1, 128.5, 128.4 (3 signals), 128.3, 128.2, 128.0, 127.9, 127.8 (2 signals), 127.7 (2 signals), 127.6 (2 signals), 127.5, 114.9, 109.7, 82.1, 79.2, 78.5, 76.7, 75.0, 74.5, 73.5, 73.3, 73.8, 71.3, 71.0, 69.8, 68.4, 66.5, 40.1, 26.8, 25.9, 20.5. (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{52}H_{60}O_9Na$ 851.4130; Found 851.4132.

For minor product: (25 mg, 12 %); clear gum; R_f = 0.40 (30 % EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 25H), 5.81 (m, 1H), 5.17 (d, J = 14.2 Hz, 1H), 5.04 (d, J = 10.4 Hz, 1H), 4.84 (app d, J = 11.7 Hz, 1H), 4.70 (app d, J = 11.7 Hz, 1H), 4.55 (s, 2H), 4.40 (m, 6H), 4.31 (app d, J = 11.7 Hz, 1H), 4.13 (m, 1H), 3.90 (m, 1H), 3.80 (m, 4H), 3.52 (m, 4H), 3.40 (m, 1H), 2.92 (bs, OH), 1.60 (m, 3H), 1.34 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.3, 138.6, 138.4, 138.0, 128.5–127.5 (several signals, Ph), 115.7, 109.4, 81.9, 79.5, 76.8, 74.4, 73.5, 73.4, 66.5, 42.0, 29.7, 25.9, 25.7. (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{52}H_{60}O_9Na$ 851.4130; Found 851.4134.

4.7. (2R,3S,4R)-4-(benzyloxy)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxo-3-(((2R,3S,4R,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl)butan-2-yl acetate (11)

A mixture of **10** (150 mg, 0.18 mmol), DMAP (5 mg, 0.04 mmol) and acetic anhydride (0.10 mL, 1.05 mmol) in EtOAc (2 mL) was stirred for 30 min at rt. The reaction was then quenched with MeOH (0.10 mL), and the volatiles removed under reduced pressure. FCC of the residue gave the derived acetate (148 mg, 85 %) as a clear oil. $R_f = 0.55$ (30 % EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (m, 25H), 5.72 (m, 1H), 5.52 (m, 1H), 5.07 (m, 2H), 4.81 (app d, $J = 11.5$ Hz, 1H), 4.72 (app d, $J = 11.7$ Hz, 1H), 4.62 (s, 2H), 4.54 (app d, $J = 11.7$ Hz, 1H), 4.46 (app d, $J = 11.1$ Hz, 1H), 4.46 (m, 3H), 4.35 (app d, $J = 11.5$ Hz, 1H), 4.32 (app d, $J = 11.9$ Hz, 1H), 4.13 (m, 1H), 3.88 (m, 1H), 3.79 (t, $J = 6.2$ Hz, 1H), 3.6b (m, 1H), 3.63 (dd, $J = 2.8$, 8.4 Hz, 1H), 3.57 (m, 1H), 3.52 (t, $J = 8.3$ Hz, 1H), 3.45 (dd, $J = 2.1$, 7.5 Hz, 1H), 3.40 (dd, $J = 4.0$, 10.0 Hz, 1H), 1.77 (s, 3H), 1.75 (m, 3H), 1.31 (s, 3H), 1.38 (s, 3H). (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{54}H_{62}O_{10}Na$ 893.4235; Found 893.4242.

A portion of the material from the previous step (100 mg, 0.12 mmol) was subjected to the ozonolysis procedure described for the synthesis of **9**. FCC of the crude product provided **11** (86 mg, 86 %) as a clear oil. $R_f = 0.35$ (30 % EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.20 (m, 25H), 5.12 (d, $J = 3.2$ Hz, 1H), 4.77 (app d, $J = 11.6$ Hz, 1H), 4.72 (app d, $J = 11.6$ Hz, 1H), 4.65 (ABq, $J = 11.9$ Hz, $\Delta d = 05$ ppm, 2H), 4.57 (app d, $J = 11.8$ Hz, 1H), 4.45 (m, 4H), 4.36 (app d, $J = 11.9$ Hz, 1H), 3.97 (m, 1H), 3.92 (m, 3H), 3.82 (m, 1H), 3.68 (m, 3H), 3.60 (t, $J = 8.2$ Hz, 1H), 3.48 (m, 2H), 2.20 (m, 1H), 2.02 (s, 3H), 1.85 (m, 1H), 1.73 (m, 1H), 1.35 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 170.0, 138.7, 138.5, 138.4, 138.3 (2 signals), 128.6, 128.5 (2 signals), 128.3, 128.2, 128.1 (2 signals), 128.0, 127.9, 127.8, 127.7, 109.7, 79.9, 79.3, 79.1, 77.4, 76.8, 74.4 (2 signals), 73.7, 73.6, 73.4, 73.2, 72.1, 69.4, 68.2, 66.5, 39.4, 26.9, 26.1, 20.9. (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{53}H_{60}O_{11}Na$ 895.4028; Found 895.4038.

4.8. (2R,3R,4S,5R,6R)- and (2S,3R,4S,5R,6R)- 6-(acetoxymethyl)-5-(benzyloxy)-4-(((2R,3S,4R,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl)tetrahydro-2H-pyran-2,3-diyl diacetate (12α) and (12β)

A mixture of **11** (74 mg, 0.085 mmol) in THF (1.5 mL) and 2 N HCl (0.40 mL) was stirred at rt for 3 h. The mixture was then diluted with THF (10 mL) and evaporated under reduced pressure at rt. The residue was taken up in EtOAc (1 mL), NaOAc (20 mg) and Ac_2O (0.2 mL) were introduced, and the mixture stirred at rt for 72 h. MeOH (0.2 mL) was then added and stirring continued for 30 min. The volatiles were removed *in vacuo*, the residue triturated with EtOAc, and the filtrate evaporated under reduced pressure. FCC of the residue afforded **12**α/β (65 mg, 84 %) in a 1/2 respective ratio.

In an alternative procedure, a mixture of **11** (45 mg, 0.052 mmol) in THF (2 mL) and 2 N HCl (0.25 mL) was stirred at rt for 3 h. The pH of the solution was then adjusted to 4–5 by addition of solid $NaHCO_3$ and the volatiles removed *in vacuo*. The residue was taken up in EtOAc (2 mL), Ac_2O (0.2 mL) and DMAP (5 mg) introduced, and the mixture stirred at rt for 2 h. MeOH (0.2 mL) was then added, and the mixture processed as described in the previous procedure. FCC of the crude reaction product afforded **12**α/β (46 mg, 96 %) in a 2/1 respective ratio.

For **12**α/β (1/1): $R_f = 0.20$ (30 % EtOAc/hexane). ^{1}H NMR (500 MHz, C_6D_6) δ 7.25 (m, 25H), 6.82 (d, $J = 3.4$ Hz, 0.5H), 5.97 (d, $J = 7.2$ Hz, 0.5H), 5.64 (m, 1H), 4.60–4.20 (m, 16H), 4.03 (m, 2H), 3.82 (m, 2H), 3.78 (m, 1H), 3.65 (m, 1H), 2.88 (m, 0.5H), 2.47 (m, 0.5H), 2.28 (m, 0.5H), 2.22 (m, 0.5H), 1.96 (m, 0.5H), 1.82 (m, 0.5H), 1.74 (s, 1.5H), 1.71 (s, 1.5H), 1.64 (s, 3H), 1.59 (s, 1.5H), 1.57 (s, 1.5H). ^{13}C NMR (125 MHz, C_6D_6) δ 170.3, 170.2, 170.1, 170.0, 169.5, 169.3, 139.4 (2 signals), 139.1, 139.0, 138.8, 129.1–128.2 (several lines, buried under C_6D_6 triplet), 94.7, 90.4, 78.4, 78.3, 77.6, 77.3, 76.1 (2 signals), 75.9, 75.4 (2 signals), 73.9, 73.7, 73.6, 73.1, 71.3, 70.0, 68.4, 68.2, 64.5, 64.1, 41.8, 36.1, 36.1, 25.7, 25.5, 20.8 (2 signals), 20.7 (2 signals).

A separated sample of **12**α was obtained as unreacted material in the transformation of 12α/β to **13** and **14**α/β respectively (*vide infra*). For **12**α: $R_f = 0.20$ (30 % EtOAc/hexane). ^{1}H NMR (600 MHz, C_6D_6) δ 7.25 (m, 25H), 6.82 (d, $J = 3.4$ Hz, 1H, H1), 5.63 (dd, $J = 3.4$, 12.0 Hz, 1H, H2), 4.60–4.20 (m, 16H, 5x$PhCH_2$, H-5, CH_2-6, 1′, 5′, 6′), 4.05 (bs, 1H, H4), 3.99 (bt, $J = 3.0$ Hz, 1H, H4′), 3.84 (dd, $J = 3.5$, 6.7 Hz, 1H, H6′), 3.78 (m, 1H, H3′), 3.64 (m, 1H, H2′), 2.89 (m, 1H, 3H), 2.27 (m, 1H, Ha), 1.81 (m, 1H, Ha), 1.71 (s, 3H, Ac), 1.64 (s, 3H, Ac), 1.57 (s, 3H, Ac). ^{13}C NMR (125 MHz, C_6D_6) δ 170.3, 170.1, 169.3, 139.4 (2 signals), 139.1, 138.8, 129.0–128.0 (several lines, buried under C_6D_6 triplet), 90.4, 78.4, 77.2, 76.1 (2 signals), 75.4, 73.9, 73.7, 73.6, 73.5, 73.2, 73.1 (2 signals), 70.0, 68.4, 64.5, 36.1, 25.6, 20.7 (2 signals), 20.6. (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{54}H_{60}O_{13}Na$ 939.3926; Found 939.3926.

4.9. ((2R,3R,4S,5R,6R)-5-acetoxy-3-(benzyloxy)-6-(pent-4-en-1-yloxy)-4-(((2R,3S,4R,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl)tetrahydro-2H-pyran-2-yl)methyl acetate (13)

$BF_3.OEt_2$ (0.03 mL, 0.25 mmol) was added to a mixture of **12**α/β (19 mg, 0.021 mmol) and 4-penten-1-ol (0.02 mL, 0.20 mmol) in dry CH_2Cl_2 (1 mL) at rt, under nitrogen. The mixture maintained at this temperature for 3 h. Et_3N (0.02 mL) was then added, and the mixture diluted with saturated aqueous $NaHCO_3$ and extracted with ether. The organic extract was dried (Na_2SO_4) and evaporated under reduced pressure. FCC of the residue afforded recovered **12**α (9 mg) and **13** (7 mg, 70 % brsm) as a clear film. $R_f = 0.50$ (30 % EtOAc/hexane). ^{1}H NMR (500 MHz, C_6D_6) δ 7.50–7.00 (m, 25H, ArH), 5.77 (m, 1H, —CH═), 5.63 (dd, $J = 7.8$, 11.6 Hz, 1H, H2), 5.02 (m, 2H, ═CH_2), 4.65–4.35 (m, 15H, 5x$PhCH_2$, H-1, 1′, 5′, 6, 6′), 4.32 (m, 2H, H-3′, 6), 4.11 (t, $J = 3.1$ Hz, 1H, H4′), 3.96 (m, 3H, H-1″, 4, 6′), 3.87 (m, 1H, H3′), 3.72 (m, 2H, H-2′, 5), 3.48 (m, 1H, 1″), 2.52 (tt, $J = 2.8$, 11.3 Hz, 1H, H3), 2.33 (bt, $J = 13.0$ Hz, 1H, Ha), 2.11 (m, 3H, Ha, CH_2-3″), 1.92 (s, 3H, Ac), 1.76 (s, 3H, Ac), 1.64 (m, 2H, CH_2-2″). ^{13}C NMR (125 MHz, C_6D_6) δ 170.2, 170.0, 139.4 (3 signals), 139.1, 138.9, 129.0 (2 signals), 129.0–128.0 (several lines, buried under C_6D_6 triplet), 115.2, 103.3 (C1), 78.4, 77.1, 76.6, 75.8, 75.7, 75.4, 74.0, 73.7, 73.6, 73.4, 73.3, 72.1, 68.4, 68.3, 67.3, 64.4, 41.7, 30.8, 29.7, 26.1, 21.1, 20.8. (ESI) *m/z*: $[M+Na]^+$ Found 965.4451.

4.10. ((2R,3R,4S,5R,6R)- and (2R,3R,4S,5R,6S)- 5-acetoxy-6-allyl-3-(benzyloxy)-4-(((2R,3S,4R,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)methyl)tetrahydro-2H-pyran-2-yl)methyl acetate (14α) and (14β)

$BF_3.OEt_2$ (0.04 mL, 0.33 mmol) was added to a mixture of **12**α/β (32 mg, 0.035 mmol) and allyltrimethylsilane (0.05 mL, 0.32 mmol) in dry CH_2Cl_2 (2 mL) at rt, under nitrogen. The mixture was maintained at this temperature for 6 h. Et_3N (0.02 mL) was then added, and the mixture diluted with saturated aqueous $NaHCO_3$ and extracted with ether. The organic extract was dried (Na_2SO_4) and evaporated under reduced pressure. FCC of the residue using 30 % EtOAc/hexane afforded recovered **12**α (7 mg) and an unseparated mixture of **14**α/β (18 mg, 70 % brsm) in a respective ratio of 3/2. Further FCC on this mixture afforded **14**α and **14**β. For **14**α: clear film. $R_f = 0.25$ (2 % Et_2O/CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6) δ 7.40–7.00 (m, 25H, ArH), 5.85 (m, 1H, —CH═), 5.57 (dd, $J = 4.7$, 9.5 Hz, 1H, H2), 5.05 (m, 2H, ═CH_2), 4.70–4.20 (m, 16H, 5xPhCH2, H1, 1′, 5′, 6′, CH_2-6), 4.0 (m, 3H, H4, 4′, 6′), 3.90 (m, 2H, H2′, 3′), 3.82 (dd, $J = 5.0$, 9.8 Hz, 1H, H5), 2.56 (m, 2H, H1″, 3), 2.25 (m, 2H, H1″, a), 2.10 (m, 1H, Ha), 1.75 (s, 3H, Ac), 1.70 (s, 3H, Ac). ^{13}C NMR (125 MHz, C_6D_6) δ 170.4, 170.1, 139.6, 139.5, 139.4, 139.2, 138.9, 135.7, 129.0–128.0 (several lines), 117.0, 78.2, 78.0, 75.9, 75.6, 75.4, 74.0 (2 signals), 73.8, 73.5, 72.9, 72.6, 72.4, 72.1, 68.9, 63.9, 37.8, 32.1, 25.8, 20.9 (2 signals). (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{55}H_{62}O_{11}Na$ 921.4184; Found 921.4189.

For **14**β: $R_f = 0.35$ (2 % Et_2O/CH_2Cl_2). δ 7.32–6.90 (m, 25H, ArH),

5.95 (m, 1H, =CH—), 5.35 (t, J = 10.2 Hz, 1H, H2), 5.00 (m, 2H, =CH_2), 5.52–4.15 (m, 15H, 5xPhCH_2, H1′, 5′, 6′, CH_2-6), 3.99 (t, J = 3.6 Hz, 1H, H4′), 3.87 (m, 2H, H4, 6′), 3.69 (dd, J = 4.7, 6.1 Hz, 1H, H3′), 3.63 (bs, 1H, H2′), 3.54 t, =6.3 Hz, 1H, H5), 3.34 (m, 1H, H1), 2.35 (m, 3H, CH_2-1″, H3), 2.19 (t, J = 12.8 Hz, 1H, Ha), 1.93 (t, J = 12.0 Hz, 1H, Ha), 1.75 (s, 3H, Ac), 1.69 (3H, Ac). ^{13}C NMR (125 MHz, C_6D_6) δ 170.3, 170.2, 139.5, 139.4, 139.1, 139.0, 135.2, 129.0–128.0 (several lines), 117.0, 79.7, 78.9, 78.4, 77.2, 76.2, 75.9, 75.4, 73.9, 73.7, 73.6, 73.4, 73.3, 72.8, 68.3, 67.2, 64.8, 42.9, 37.6, 26.1, 21.1, 20.8. (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{55}H_{62}O_{11}Na$ 921.4184; Found 921.4190.

4.11. ((2R,3R,4S,5R,6S)-5-acetoxy-3-(benzyloxy)-6-(phenylthio)-4-(((2R,3S,4R,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl) tetrahydro-2H-pyran-2-yl)methyl)tetrahydro-2H-pyran-2-yl)methyl acetate (**15**)

$BF_3.OEt_2$ (0.015 mL, 0.12 mmol) was added to a mixture of **12**α (16 mg, 0.017 mmol) and thiophenol (0.03 mL, 0.29 mmol) in dry CH_2Cl_2 (1 mL) at −10 °C, under nitrogen. The mixture was allowed to warm to 0 °C and maintained at this temperature for 2 h. Et_3N (0.02 mL) was then added, and the mixture diluted with saturated aqueous $NaHCO_3$ and extracted with ether. The organic extract was dried (Na_2SO_4) and evaporated under reduced pressure. FCC of the residue afforded **15** (11 mg, 65 %) as a clear film. R_f = 0.50 (30 % EtOAc/hexane). ^{1}H NMR (600 MHz, C_6D_6) δ 7.66 (d, J = 8.4 Hz, 2H, ArH), 7.35–6.97 (m, 28H, ArH), 5.54 (t, J = 10.5 Hz, 1H, H2), 4.67 (d, J = 9.7 Hz, 1H, H1), 4.53 (m, 2H, 2xPhCH), 4.35 (m, 5H, 5xPhCH, H5′, 6′, 6), 4.23 (dt, J = 3.0, 8.8, 1H, H1′), 4.21 (app d, J = 11.5, 1H, PhCH), 4.14 (dd, J = 4.2, 11.2 Hz, 1H, H6), 4.01 (t, J = 3.2 Hz, 1H, H4′), 3.85 (m, 1H, H6′), 3.81 (bs, 1H, H4), 3.76 (dd, J = 2.7, 6.1 Hz, 1H, H3′), 3.62 (bs, H2′), 3.44 (dd, J = 4.4, 8.3, 1H, H5), 2.38 (tt, J = 2.6, 11.0, 1H, H3), 2.21 (bt, J = 11.5 Hz, 1H, Ha), 1.89 (bt, J = 11.5 Hz, 1H, Ha), 1.85 (s, 3H, Ac), 1.69 (s, 3H, Ac). ^{13}C NMR (125 MHz, C_6D_6) δ 170.1(2 signals), 139.4 (2 signals), 139.3, 139.1, 138.8, 135.1, 132.6, 129.0–128.0 (several lines, buried under C_6D_6 triplet), 88.1 (C1), 79.6, 78.4, 77.1, 75.6, 75.4, 75.3, 74.0, 73.7, 73.6, 73.4, 73.2, 70.6, 68.2, 67.1, 64.5, 43.3, 26.5, 21.2, 20.8. (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{58}H_{62}O_{11}SNa$ 989.3905; Found 989.3905.

4.12. (2R,3S,4R,5S,6R)-2-(acetoxymethyl)-6-(((2R,3R,4S,5R,6R)-3,5-diacetoxy-2-(acetoxymethyl)-6-(pent-4-en-1-yloxy)tetrahydro-2H-pyran-4-yl)methyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**16**)

Sodium (10 mg, 0.42 mmol) was added to a mixture of **13** (3.8 mg, 4.0 μmol) in liquid NH_3 (1 mL) and dry THF (2 mL) at −78 °C, under nitrogen. The mixture was stirred at this temperature until the blue color persisted for 1 min, then warmed to −33 °C and maintained this temperature for 1 min. Solid NH_4Cl (25 mg) and MeOH (05 mL) were then successively added, and the mixture warmed to rt, stirred at this temperature until excess NH_3 had evaporated and diluted with CH_2Cl_2 (2 mL). The resulting suspension was filtered through Celite, and the filtrate evaporated *in vacuo*. The residue was taken up in EtOAc (1 mL) and treated with Ac_2O (0.05 mL, 0.50 mmol) and DMAP (2 mg, 0.02 mmol) for 16 h at rt. MeOH (0.1 mL) was then added and the mixture evaporated *in vacuo*. FCC of the residue afforded **16** (1.5 mg, 54 %) as a clear film. R_f = 0.30 (50 % EtOAc/hexane). ^{1}H NMR (600 MHz, C_6D_6) δ 5.68 (m, 1H, —HC=), 5.66 (bs, 1H, H4′), 5.48 (m, 3H, H2′, 3′, 4), 5.32 (dd, 1H, J = 7.7, 11.8, 1H, H2), 4.96 (m, 2H, =CH_2), 4.88 (dd, J = 8.5, 11.8, 1H, H6′), 4.66 (bd, J = 11.4 Hz, 1H, H1′), 4.45 (d, J = 7.8 Hz, 1H, H1), 4.25 (m, 3H, H5′, CH_2-6),4.11 (dd, J = 4.1, 12.0 Hz, 1H, H6′), 3.85 (m, 2H, H5, H1″), 3.41 (m, 1H, H1″), 2.33 (bt, J = 11.5 Hz, H3), 2.05 (m, 2H, H3″), 1.93 (bt, J = 10.3 Hz, 1H, Ha), 1.86 (s, 3H, CH_3CO), 1.86 (s, 3H, CH_3CO), 1.76 (bs, 9H, 3xAc), 1.67 (s, 6H, 2xAc), 1.57 (m, partially buried, 2H, CH_2-H"), 1.56 (s, 3H, Ac), 1.44 (bt, J = 13.5 Hz, 1H, Ha). ^{1}H NMR (125 MHz, C_6D_6) δ 171.1, 170.6, 170.3, 170.0, 169.9, 169.7 (2 signals), 138.6, 115.4, 103.4 (C1), 74.3, 71.6, 71.3, 70.0, 69.0, 68.8, 67.6, 67.4 (2 signals), 62.6, 61.1, 40.0, 30.7, 29.6, 25.2, 20.8 (2 signals), 20.7, 20.6, 20.4 (2 signals), 20.1. (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{32}H_{46}O_{17}Na$ 725.2627; Found 725.2634.

4.13. (2R,3S,4R,5S,6R)-2-(acetoxymethyl)-6-(((2R,3R,4R,5R,6R)-3,5-diacetoxy-2-(acetoxymethyl)-6-allyltetrahydro-2H-pyran-4-yl)methyl) tetrahydro-2H-pyran-3,4,5-triyl triacetate (**17**)

Application of the two step Birch reaction-/acetylation protocol described for the synthesis of **16**, to α-C-allyl glycoside **14**α afforded **17** as an amorphous white solid, R_f = 0.30 (20 % hexane/Et_2O). ^{1}H NMR (500 MHz, C_6D_6) δ 5.77 (m, 1H, —HC=), 5.67 (t, J = 3.6 Hz, 1H, H4′), 5.58 (dd, J = 3.7, 7.1, 1H, H2′), 5.51 (m, 2H, H3′, 4), 5.33 (dd, J = 5.5, 11.4, 1H, H2), 5.08 (bd, J = 17.1, 1H, =CH), 5.04 (bd, J = 10.3 Hz, 1H, =CH), 4.79 (m, 1H, H6′), 4.70 (m, 1H, H1′), 4.46 (m, 1H, H1), 4.26 (dd, J = 6.8, 11.2, 1H, H6), 4.22 (m, 1H, H5′), 4.16 (dd, J = 6.8, 11.0, 1H, H6), 4.07 (dd, J = 4.0, 12.0, 1H, H6′), 3.99 (m, 1H, H5), 2.57 (m, 1H, H1″), 2.46 (bt, J = 11.4, 1H, H3), 2.21 (m, 1H, H1″), 1.94 (bt, J = 13.3 Hz, 1H, Ha), 1.76 (s, 3H, Ac), 1.74 (s, 3H, Ac), 1.72 (s, 3H, Ac), 1.67 (s, 3H, Ac), 1.66 (s, 3H, Ac), 1.63 (s, 3H, Ac), 1.61 (s, 3H, Ac), 1.35 (m, 1H, Ha). ^{1}H NMR (125 MHz, C_6D_6) δ 170.9, 170.4, 170.2, 169.9, 169.7, 169.5, 134.8, 117.3, 72.8, 70.9, 69.9, 69.6, 69.1, 68.9, 68.8, 68.1, 67.8, 62.8, 61.4, 35.1, 30.4, 24.5, 20.7, 20.6 (2 signals), 20.5, 20.4, 20.3, 20.2. (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{30}H_{42}O_{16}Na$ 681.2365; Found 683.2365.

4.14. (2R,3S,4R,5S,6R)-2-(acetoxymethyl)-6-(((2R,3R,4R,5R,6R)-3,5-diacetoxy-2-(acetoxymethyl)-6-propyltetrahydro-2H-pyran-4-yl)methyl) tetrahydro-2H-pyran-3,4,5-triyl triacetate (**18a**)

A mixture of **14**α (7.0 mg, 7.7 mmol), 10 % Pd/C with 50 % H_2O (10 mg), HCOOH (0.02 mL) in methanol (1 mL) was stirred under a balloon of hydrogen for 24 h at rt. The mixture was purged with nitrogen, filtered through Celite and the filtrate evaporated *in vacuo*. The residue was taken up in EtOAc (1 mL) and treated with Ac_2O (0.05 mL) and DMAP (2 mg, 16 mmol) for 16 h at rt. Methanol (0.05 mL) was then added and the solution evaporated under reduced pressure. FCC of the residue afforded **18**α (2.2 mg, 43 %) as a white amorphous solid. R_f = 0.30 (20 % hexane/Et_2O). ^{1}H NMR (500 MHz, C_6D_6) δ 5.67 (t, J = 3.5 Hz, 1H, H4′), 5.60 (dd, J = 4.1, 7.6 Hz, 1H, H2′), 5.49 (m, 2H, H3′, 4), 5.33 (dd, J = 5.6, 11.4 Hz, 1H, H2), 4.75 (m, 1H, H6′), 4.70 (m, 1H, H1′), 4.39 (m, 1H, H1), 4.21 (m, 3H, H5′, $CH_2$6), 4.08 (dd, J = 3.9, 11.6 Hz, 1H, H6′), 3.89 (t, J = 9.8 Hz, H5), 2.45 (bt, J = 11.4 Hz, H3), 1.95 (bt, J = 13.0 Hz, 1H, H1″), 1.78 (m, partially buried, 1H, Ha), 1.77 (s, 3H, Ac), 1.75 (s, 3H, Ac), 1.72 (s, 3H, Ac), 1.69 (s, 3H, Ac), 1.68 (s, 3H, Ac), 1.63 (s, 3H, Ac), 1.62 (s, 3H, Ac), 1.5 (m, 1H, H2″), 1.30 (m, 3H, H1″, 2″, a), 0.88 (t, J = 7.3 Hz, 3H, CH_3-3″). ^{1}H NMR (125 MHz, C_6D_6) δ 171.0, 170.5, 170.2, 1170.1, 189.8, 169.6, 73.2, 71.2, 71.0, 69.6, 69.0, 68.9, 68.3, 67.9, 63.1, 61.6, 35.2, 27.2, 24.5, 20.8, 20.7, 20.5, 20.4, 20.3, 19.2, 14.5. (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{30}H_{44}O_{16}Na$ 681.2522; Found 681.2525.

4.15. (2R,3S,4R,5S,6R)-2-(acetoxymethyl)-6-(((2R,3R,4R,5R,6S)-3,5-diacetoxy-2-(acetoxymethyl)-6-propyltetrahydro-2H-pyran-4-yl)methyl) tetrahydro-2H-pyran-3,4,5-triyl triacetate (**18b**)

C-allyl glycoside **14**β was subjected to the two step hydrogenolysis-acetylation protocol described for the synthesis of **18**α. FCC of the crude product afforded **18**β as a white amorphous solid. R_f = 0.35 (20 % hexane/Et_2O). ^{1}H NMR (500 MHz, C_6D_6) δ 5.67 (dd, J = 2.6, 4.5 Hz, 1H, H4′). 5.57 (bs, 1H, H4), 5.51 (bs, 2H, H2′, 3′), 5.16 (t, J = 10.2, 1H, H2), 4.88 (m, 1H, H6′), 4.68 (m, 1H, H1′), 4.25 (m, 3H, H5′, CH_2-6), 4.12 (dd, J = 3.8, 12.0 Hz. H6′), 3.78 (t, J = 6.8 Hz, 1H, H5), 3.37 (dt, J = 3.3, 8.2 Hz, 1H, H1), 2.29 (bt, J = 11.3 Hz, 1H, H3), 1.93 (ddd, J = 2.5, 6.4, 14.3 Hz, 1H, Ha), 1.76 (s, 3H CH_3CO), 1.75 (s, 3H CH_3CO), 1.74 (s, 3H CH_3CO), 1.72 (s, 3H CH_3CO), 1.67 (s, 3H CH_3CO), 1.65 (s, 3H CH_3CO), 1.62 (m, buried, 2H, CH_2-1″), 1.60 (s, 3H CH_3CO), 1.45 (m, 3H, Ha, CH_2-2″), 0.88 (t, J = 7.4 Hz, 3H, CH_3-3″). ^{1}H NMR (125 MHz, C_6D_6) δ 171.1,

170.6, 170.4, 170.3, 169.9, 169.7 (2 signals), 80.1, 76.7, 72.1, 71.6, 70.11, 69.1, 68.1, 67.6, 67.2, 62.9, 61.1, 41.1, 34.8, 25.6, 20.8, 20.7, 20.6, 20.4 (2 signals), 20.2, 19.1, 14.5. (ESI) *m/z*: $[M+Na]^+$ Calc for $C_{30}H_{44}O_{16}Na$ 681.2522; Found 681.2531.

Author contributions

The project was conceived and overseen by DRM. AA, ST, JP and DRM carried out the synthesis and analysis of new compounds. DRM wrote the paper with contributions from AA and ST.

CRediT authorship contribution statement

Alex Ann: Writing – original draft, Methodology. **Steven Truong:** Writing – original draft, Methodology, Data curation. **Jiwani Peters:** Methodology. **David R. Mootoo:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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