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Synthesis of long-chain monosaccharides via the coupling of three 'normal' sugar units via Wittig type methodology: unusual removal of the benzyl group under basic conditions

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ABSTRACT

The reaction of diacetonogalactose phosphonate **6** with 2,3:4,5-di-*O*-isopropylidene-D-arabinose (**7**) afforded C_{12}-higher sugar enone with an *E*-geometry across the double bond, which was converted into the fully protected C_{11}-aldehyde **16**. This compound was very unreactive and resistant toward the Wittig type and Tebbe reagents, but under PTC conditions, underwent a reaction with stabilized sugar phosphonate to afford C_{18}-enone **17**. Very surprisingly unusual removal of the benzyl blocks under these conditions was observed.

1. Introduction

The term 'higher carbon' is assigned to heptoses, octoses, and nonoses, which play an important role in the biology of living cells; many synthetic methods have been developed to prepare these important compounds.[1] Much less is known about sugars containing more than 10 carbon atoms in the chain,[2] which are very demanding synthetic targets and might possess interesting conformational and complexing properties. Their synthesis can be realized by iterative homologation of a parent monosaccharide by a small unit (e.g. C1–C3[3]).

A more economic method is represented by an elongation of a parent sugar with a longer sub-unit, either an achiral molecule[4] or, more conveniently, an already functionalized unit. One of the first examples of the latter approach was presented by Secrist in his synthesis of hikozamine, in which an unstabilized sugar phosphorane reacted with sugar aldehydes to afford unsaturated higher monosaccharides.[5] Soon after, other syntheses proposing convenient routes to such complicated molecules appeared in the literature.[6,7]

Herein we report a methodology, which allows for the convenient coupling of two sugar sub-units via their terminal positions. The first route involves conversion of the parent monosaccharide into an acetylene (according to the method reported by Corey[8]) which was then transformed into the *E*- or *Z*-higher sugar allylic alcohols (Fig. 1).[7,9] The second route was based on the coupling of two units via the reaction of stabilized sugar phosphoranes **2** or phosphonates **4** with sugar aldehydes, which provided higher sugar enones **5**. The highly stereoselective reduction of the carbonyl group with zinc borohydride to give **3**,[7,10,11] followed by the oxidation of the double bond afforded the higher sugars **1** (Fig. 2).[7,10,12]

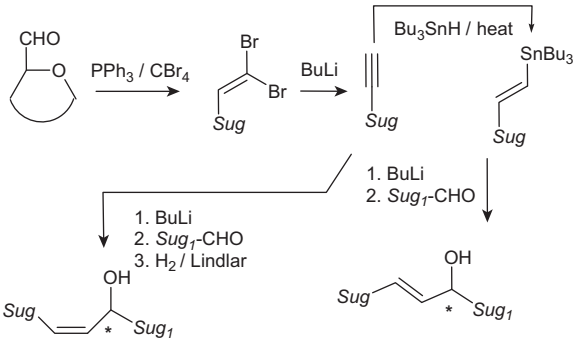

Figure 1. Synthesis of higher sugar allylic alcohols via acetylenic methodology.

Functionalization at both terminal positions of **1** (having 12–15 carbon atoms) should afford much higher analogues. Elongation at either end requires orthogonal protecting groups enabling the facile deprotection at both terminal positions.

The easily available 'diacetono-galactose' phoshonate **6**[13] and 2,3:4,5-di-*O*-isopropylidene-D-arabinose **7**[14] were chosen as the starting materials. The reaction of both units under mild PTC conditions provided higher sugar enone **8** in almost quantitative yield (Scheme 1). Reduction of the carbonyl group with zinc borohydride afforded, as expected,[11] single stereoisomer **9**. The D-*glycero*-configuration at the newly created stereogenic center was proven by

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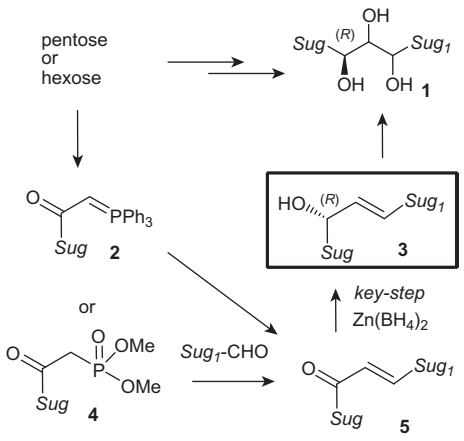
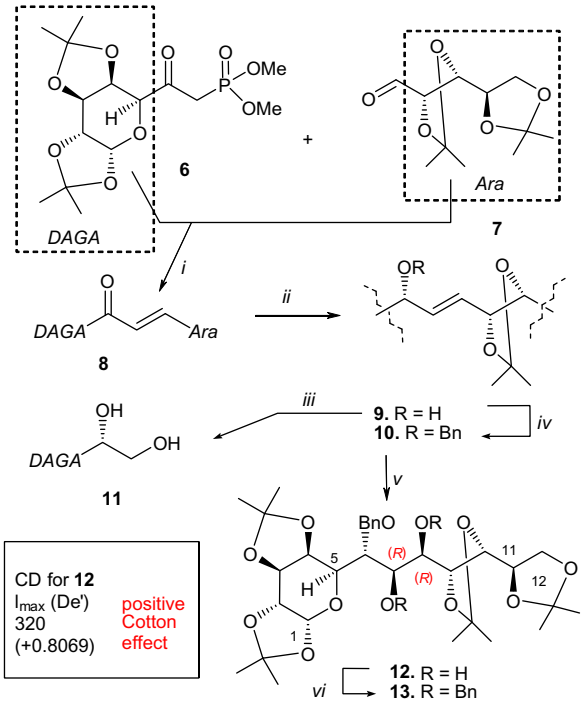


Figure 2. Synthesis of higher carbon sugars via phosphorane and phosphonate methodology.

its conversion into the known[15] 1,2:3,4-di-*O*-isopropyli-dene-D-*glycero*-α-D-*galacto*-heptose **11**.

Functionalization of the three carbon bridge connecting the sugar parts followed a route already reported[7,10] (Scheme 1). Osmylation of the double bond in **9** should lead to products whose configuration can be assigned on the basis of Kishi's rule.[16] This assignment, however, should always be verified by proof. It is known that the CD spectra of the molybdenum complexes of optically active *threo*-diols, allow us to connect the sign of the Cotton effect with their absolute configuration.[17] This methodology was used in our synthesis.

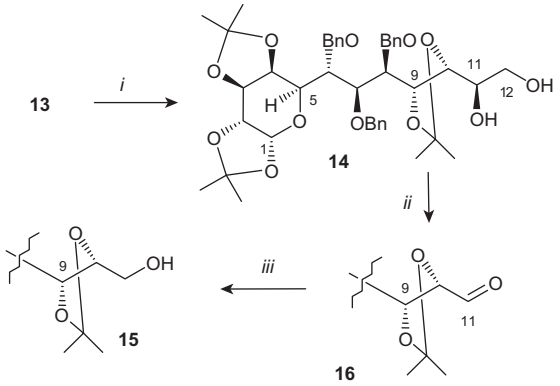


Scheme 1. Preparation of fully protected higher sugar. Reagents and conditions: (i) K_2CO_3, toluene, 18-crown-6, rt; (ii) $Zn(BH_4)_2$ ether; (iii) O_3, MeOH, then $NaBH_4$; (iv) BnBr, NaH, DMF; (v) (from **10**) OsO_4, NMO (cat.), 77%; (vi) BnCl, toluol, NaOH (50%), TEBACl.

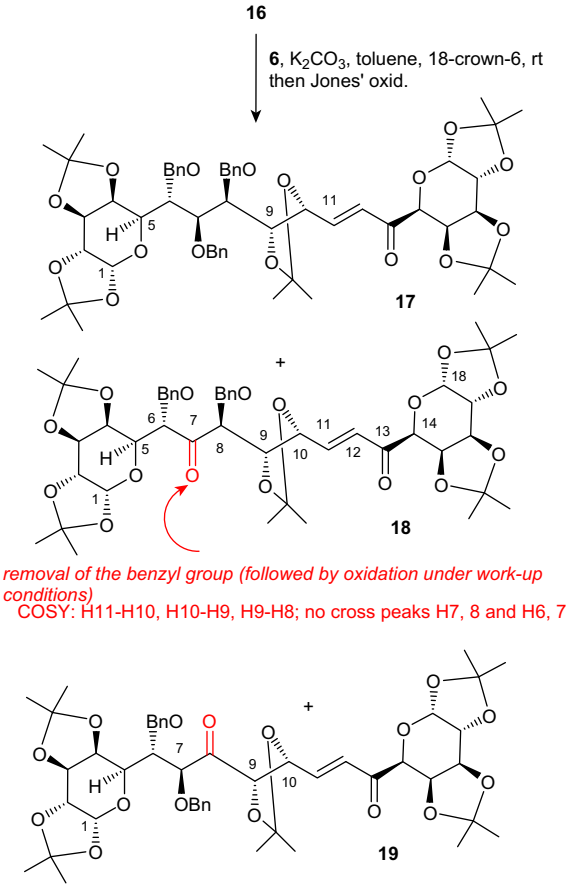
Protection of the free hydroxyl group in **9** provided ether **10**, which was treated with OsO_4 to afford the single stereoisomeric diol in good yield. The structure of **12** is proposed on the basis of Kishi's rule, and was verified by the CD spectrum of its complex with $Mo_2(OAc)_4$; the positive Cotton effect indicated unambiguously at the (7*R*,8*R*)-configuration for the newly created stereogenic centers.

When such a *cis*-dihydroxylation reaction was performed on the free allylic alcohol **9**, much lower stereoselectivity (2:1) was observed but with the same (*R*,*R*)-stereoisomer predominating (see Section 3).

The protection of both hydroxyl groups in **12** gave compound **13**, which was then subjected to selective hydrolysis. The terminal C11–C12-isopropylidene group was removed out preferentially to



Scheme 2. Selective deprotection of the terminal position in higher carbon sugar. Reagents and conditions: (i) H_2SO_4 (*c* 0.46), H_2O/THF 3:1; (ii) $NaIO_4$; (iii) $NaBH_4$.



Scheme 3. Synthesis of a 18-carbon sugar. Unexpected removal of the benzyl block under basic conditions.

afford diol **14** (Scheme 2), which was then converted into aldehyde **16** (characterized as alcohol **15**) by periodate cleavage.

The reaction of various nucleophiles with **16** should allow easy access to highly functionalized long-chain polyhydroxylated compounds. However, this aldehyde was very resistant toward simple Wittig reagents as well as Tebbe reagents. The low reactivity of other (similar) higher sugar aldehydes toward such species was also previously observed, although we found that they did react with stabilized phosphoranes under high pressure or with sugar phosphonates under PTC conditions.[7]

The reaction of aldehyde **16** with phosphonate **6** was successful and afforded the desired enone (in low yield), which was contaminated with two side-products, which were identified 'indirectly'. In order to remove the excess aldehyde from the post-reaction mixture we used an oxidative work-up; thus, the crude product was treated first with the Jones' reagent and then subjected to column chromatography (Scheme 3).

Three compounds were isolated: the desired enone **17** and two more products whose molecular mass was lower by 92 Daltons, to which structures **18** and **19** were assigned on the basis of the NMR data. The ^{13}C NMR spectrum of **18** indicated the absence of one benzyl group (only two signals of the quaternary C-atoms at δ: 138.06 and 138.01 ppm were seen) and the presence of two signals of the carbonyl group (δ: 210.38 and 195.86 ppm). This indicated the removal of one benzyl group leading to an alcohol which was oxidized to a ketone under the work-up conditions.

The precise assignment of the structure of this di-ketone was carried out on the basis of its COSY spectrum. The H8 signal in the spectrum of **18** showed a cross peak only to H9; alternatively the H6 correlated only to H5, which indicated that the initial hydroxyl located at the C7-position was oxidized to a ketone (Scheme 3). Similarly, structure **19** was also proven.

The hypothesis that compounds **18** and **19** are secondary products resulting from the decomposition of enone **17** should be excluded, since this enone was stable under the reaction conditions for at least 5 days, which means that removal of the benzyl group occurred directly from the aldehyde during the reaction. Moreover, aldehyde **16** by itself was also resistant under PTC in the absence of phosphonate **6**.

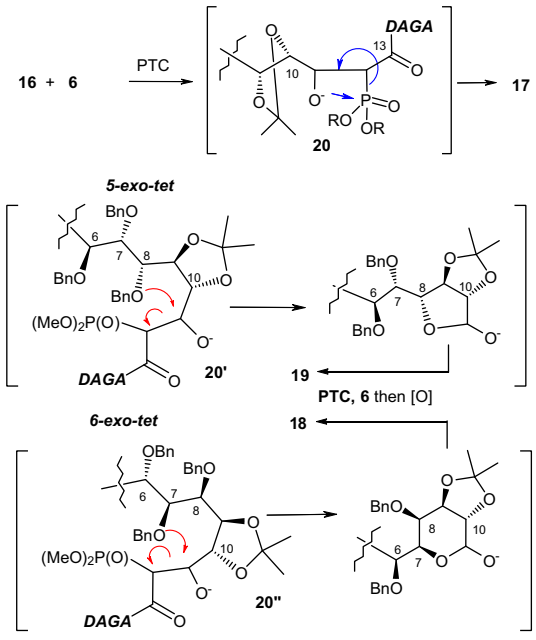


Figure 3. Proposed mechanism for the removal of the benzyl group under the PTC conditions.

The most plausible explanation of this phenomenon is shown in Figure 3. Normal decomposition of intermediate **20** led to the expected higher sugar enone **17**. However, since this expected rearrangement may not be quick enough, other processes are possible including the attack of the benzyloxy-oxygen functionality from the C-7 or C-8 positions with elimination of the anion of **6** and cyclization to a hemiacetal (6-*exo*-tet and 5-*exo*-tet, respectively). The resulting hemiacetals react with phosphonate **6** to afford the products lacking the benzyl group.

2. Conclusion

The most important result of this study was the observation of the deprotection of the benzyl ethers under basic conditions. To the best of our knowledge this is the first example of the removal of such a group in basic media. Also important is the selective hydrolysis of one out of four isopropylidene groups in a C-12 higher sugar, which opens up the possibility of the preparation of polyhydroxylated systems with long chains.

3. Experimental

3.1. General

The NMR spectra of all compounds/mixtures were measured in $CDCl_3$ solutions (unless otherwise stated) with the following spectrometers: Bruker DRX 500 (at 303 K) equipped with a TBI 500SB HC/BB-D-05 Z-G probehead, Varian-NMR-vnmrs 500 (at 298 K) equipped with a PFG Auto XDB (^1H–^{19}F/^{15}N–^{31}P 5 mm) direct probehead and Varian-NMR-vnmrs 600 (at 298 K) equipped with a PFG Auto XID (^1H/^{15}N–^{31}P 5 mm) indirect probehead. The concentration of all solutions containing pure compounds used for NMR measurements was about 20–30 mg in 0.6 cm^3 of solvent, whereas in the case of mixtures 40–60 mg of sample in 0.6 cm^3 of solvent. Standard experimental conditions and standard Bruker and Varian (Chempack 4.1) programs were used. To assign the structures, the following 1D and 2D experiments were employed: ^1H selective NOESY/TOCSY, 2D COSY/NOESY, 2D ^1H–^{13}C gradient selected HSQC and HMBC optimized for $^1J(C,H) = 146$ Hz and $^nJ(C,H) = 8$ Hz, respectively. The ^1H and ^{13}C NMR spectroscopic data are given relative to the TMS signal at 0.0 ppm. The ^1H and ^{13}C NMR signals of the phenyl in the benzyl groups occurring at the typical δ values are omitted for simplicity. Mass spectra were recorded with an ESI/MS Mariner (PerSeptive Biosystem) mass spectrometer. Optical rotations were measured with a Digital Jasco polarimeter DIP-360 ($\lambda = 589$ nm) for solutions in $CHCl_3$ (c 1) at room temperature. Column chromatography was performed on silica gel (Merck, 70–230 or 230–400 mesh); HPLC analyses were conducted with a Shimadzu Preparative Liquid Chromatograph LC-8A equipped with UV detector SPD-6A. Organic solutions were dried over anhydrous magnesium sulfate. THF was distilled from potassium prior to use.

3.2. Synthesis of the enone 8: 1,2,3,4,9,10,11,12-tetra-*O*-isopropylidene-7,8-dideoxy-7,8-didehydro-D-*arabino*–D-*galacto*-dodec-7(*E*)-ene-1,5-pyranos-6-ulose

To a solution of aldehyde **7** (0.58 g, 2 mmol) and phosphonate **6** (0.8 g, 2.1 mmol) in dry toluene (60 mL) anhydrous potassium carbonate (0.59 g) was added followed by a catalytic amount of 18-crown-6 (10 mg). After vigorous stirring at room temperature (until disappearance of the aldehyde; 48 h), water (100 mL) and AcOEt (100 mL) were added. The organic phase was separated and the aqueous one extracted with ethyl acetate (2 × 50 mL). The combined organic solutions were washed with water (2 × 50

mL), brine (50 mL), dried and concentrated, and the product was isolated by column chromatography (hexane–ethyl acetate, 9:1 to 4:1) as a colorless oil (980 mg, 2 mmol, 98%). $[\alpha]_D = -90.1$ (*c* 1, $CHCl_3$); ^1H NMR (500 MHz) δ: 7.02 (dd, $J_{7,8}$ = 15.8, $J_{8,9}$ = 4.4 Hz, H-8), 6.90 (dd, $J_{7,9}$ = 1.6 Hz, H-7), 5.67 (d, $J_{1,2}$ = 5.0 Hz, H-1), 4.65 (dd, $J_{3,4}$ = 7.8 Hz, $J_{2,3}$ = 2.3 Hz, H-3), 4.62 (dd, $J_{4,5}$ = 2.0 Hz, H-4), 4.58 (ddd, $J_{9,10}$ = 7.6 Hz, H-9), 4.37 (dd, H-2), 4.33 (d, H-5), 4.15–4.05 (m, 1H, H-11), 3.97–3.91 (m, 2H, H-12′, 12), 3.72 (dd, $J_{9,10} = J_{10,11}$ = 7.6 Hz, H-10), 1.57–1.30 (8 × s, C*Me*$_2$); ^{13}C NMR δ: 196.4 (C-6), 144.0 (C-8), 124.8 (C-7), 110.3, 109.8, 109.7, 108.9 (4 × C*Me*$_2$), 96.5 (C-1), 81.1, (C-10), 79.3 (C-9), 73.3 (C-5), 72.4 (C-4), 70.7 (C-3), 70.4 (C-2), 67.4 (C-11 + 12), 27.0, 26.7, 26.3, 26.0, 25.9, 25.2, 24.8, 24.3 (8 × C*Me*$_2$). Anal. Calcd for $C_{24}H_{36}O_{10} + ½H_2O$: C, 58.41; H, 7.56. Found: C, 58.51; H, 7.62.

3.3. Reduction of enone 8 to give 1,2,3,4,9,10,11,12-tetra-*O*-isopropylidene-7,8-dideoxy-7,8-didehydro-D-*gluco*–D-*galacto*-dodec-7(*E*)-eno-1,5-pyranose 9

To a cooled (to 0 °C) solution of enone **8** (11.68 g, 24 mmol) in dry ether (500 mL), zinc borohydride (30 mL of a 0.5 M solution in dry ether) was added. The mixture was stirred at 0 °C for 2.5 h, and then diluted with diethyl ether (250 mL). The excess zinc borohydride was decomposed with water (100 mL). Dilute (5%) sulfuric acid (50 mL) was then added. The organic phase was separated, washed with water (3 × 50 mL), brine (50 ml), dried, and concentrated. Product **9** was isolated by column chromatography (hexane–ethyl acetate, 9:1 to 5:1) as an oil (11.35 g, 23 mmol, 96.7%). $[\alpha]_D = -29.4$ (*c* 1, $CHCl_3$); ^1H NMR (500 MHz) δ: 6.01 (ddd, $J_{7,8}$ = 15.6, $J_{6,7}$ = 5.0, $J_{7,9}$ = 0,9 Hz, H-7), 6.93 (ddd, $J_{8,9}$ = 6.0, $J_{6,8}$ = 1.4 Hz, H-8), 5.56 (d, $J_{1,2}$ = 5.0 Hz, H-1), 4.61 (dd, $J_{3,4}$ = 8.0, $J_{2,3}$ = 2,4 Hz, H-3), 4.47 (dd, $J_{4,5}$ = 2.0 Hz, H-4), 4.42 (m, 1H, H-9), 4.38 (m, 1H, H-6), 4.31 (dd, 1H, H-2), 4.16–4.05 (m, 2H, H-11, 12′), 3.93 (dd, $J_{12,12'}$ = 8.5, $J_{11,12}$ = 5.4 Hz, H-12), 3.76 (dd, $J_{10,11}$ = 7.7 Hz, H-10), 3.7 (dd, $J_{5,6}$ = 6.7 Hz, H-5), 1.74 (1H, O*H*) 1.50–1.32 (8 × s, C*Me*$_2$); ^{13}C NMR δ: 132.6 (C-7), 129.6 (C-8), 109.6, 109.5, 109.4, 108.6 (4 × C*Me*$_2$), 96.5 (C-1), 81.1 (C-10), 79.5 (C-9), 76.5 (C-11), 71.4 (C-6), 71.3 (C-4), 70.8 (C-3), 70.5 (C-2), 69.2 (C-5), 66.82 (C-12), 26.98, 26.94, 26.6, 26.0, 25.9, 25.3, 24.9, 24.3 (8 × C*Me*$_2$). Anal. Calcd for $C_{24}H_{38}O_{10}$: C, 59.49; H, 7.87. Found: C, 59.32; H, 8.15.

3.4. Determination of the configuration at the newly created stereogenic center (C-6) in allylic alcohol 9

Allylic alcohol **9** (101 mg, 0.2 mmol) was dissolved in methylene chloride (20 mL) containing small amounts of methanol (1 mL). The mixture was cooled to −78 °C and ozone (ca. 3% in oxygen) was bubbled through the solution until blue color persisted (5 min.). Dimethyl sulfide (4 equiv) was added and the mixture was left at rt for 24 h. Then sodium borohydride was added, the mixture stirred at rt for another 24 h, and partitioned between water (20 mL) and ethyl acetate (10 mL). The organic phase was separated and the aqueous one extracted with ethyl acetate (3 × 10 mL). The combined organic solutions were washed with water (10 mL), brine (2 × 10 mL), dried, and concentrated. Chromatographic purification (hexane–EtOAc, 9:1 to 4:1) of the residue afforded the desired heptose (36 mg, 0.12 mmol, 59%), which was acetylated under the standard conditions (Py–Ac_2O–DMAP) to afford the known heptose **11**. ^1H NMR (200 MHz) δ: 5.58 (d, 1H, $J_{1,2}$ = 4.8 Hz, H-1), 5.26–5.19 (m, 1H, H-6), 4.71 (dd, 1H, $J_{3,4}$ = 9,6 Hz, $J_{2,3}$ = 2,6 Hz, H-3), 4.65 (dd, 1H, $J_{4,5}$ = 2,2 Hz, H-4), 4.41 (dd, 1H, H-2), 4.35 (dd, 1H, $J_{7,7'}$ = 4 Hz, $J_{6,7}$ = 2 Hz, H-7), 4.29 (dd, 1H, $J_{6,7'}$ = 10,6 Hz, H-7′), 4.1 (dd, 1H, $J_{5,6}$ = 9 Hz, H-5).

3.5. Benzylation of the allylic alcohol 9 to give 1,2,3,4,9,10,11,12-tetra-*O*-isopropylidene-6-*O*-benzyl-7,8-dideoxy-7,8-didehydro-D-*gluco*–D-*galacto*-dodec-7(*E*)-ene-1,5-pyranose 10

To a solution of alcohol **9** (11.35 g, 23 mmol) in DMF (500 mL) containing imidazole (100 mg), excess sodium hydride (2 g of a 60% solution in mineral oil) was added and the mixture was stirred at room temperature for 30 min. After cooling to 0 °C, benzyl bromide (5 mL, 42 mmol) was added and stirring was continued for two days. The mixture was diluted with ether (500 mL) and the excess hydride decomposed with methanol (100 mL). Water (250 mL) was then added. The organic phase was separated, and the aqueous one extracted with ether (3 × 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried, and concentrated. Product **10** was isolated by column chromatography (hexane–ethyl acetate, 9:1 to 4:1) as a brownish oil (8.56 g, 15 mmol, 63.5%). $[\alpha]_D = -23.8$ (*c* 1, $CHCl_3$); ^1H NMR δ: 5.9–5.81 (m, 2H, H-7, 8), 5.46 (d, $J_{1,2}$ = 4.9 Hz, H-1), 4.63 (d, *J* = 11.2 Hz,1H, PhC*H*$_2$O), 4.57 (dd, $J_{3,4}$ = 8 Hz, $J_{2,3}$ = 2.2 Hz, H-3), 4.51 (dd, $J_{4,5}$ = 1.7 Hz, H-4), 4.45 (d, *J* = 11.2 Hz, 1H, PhC*H*$_2$O), 4.41 (dd, $J_{5,6}$ = 7.7 Hz, $J_{6,7}$ = 5.0 Hz, H-6), 4.25 (dd, H-2), 4.18 (dd, $J_{11,12}$ = 6.1 Hz, H-11), 4.05 (m, 2H, H-9, 12′), 3.93 (dd, $J_{12,12'}$ = 8.5 Hz, H-12), 3.77 (dd, H-5), 3.69 (dd, $J_{10,11}$ = 9.2 Hz, H-10), 1.47–1.29 (8s, C*Me*$_2$); ^{13}C NMR δ: 131.9, 131.4 (C-8 + C-7), 109.5, 108.8, 108.4 (4 × C*Me*$_2$), 96.3 (C-1), 81.3 (C-5), 79.1 (C-6), 77.2 (C-9), 76.0 (C-11), 71.3, 70.9 (C-2), 70.7 (C-3), 70.4 (C-4), 69.52 (C-5), 68.1, 66.3 (C-12), 38.7, 30.6, 30.4, 28.9, and 26.99, 26.95, 26.5, 26.1, 26.0, 25.2, 25, 24.3 (8 × C*Me*$_2$). Anal. Calcd for $C_{31}H_{44}O_{10}$: C, 64.57; H, 7.69. Found: C, 64.47; H, 7.72.

3.6. The *cis*-dihydroxylation of the protected allylic alcohol 10 to give 1,2,3,4,9,10,11,12-tetra-*O*-isopropylidene-6-*O*-benzyl-7,8-dihydroxy-D-*manno*-D-*erytro*–D-*galacto*–dodec-1,5-pyranose 12

To a solution of **10** (152 mg, 0.26 mmol) in THF (5 mL), water (0.5 mL), *tert*-butanol, and 4-*N*-morpholine oxide (100 mg) were added followed by osmium tetraoxide (0.5 mL of a 2% solution in *tert*-BuOH) and the mixture was stirred in room temperature for ten days. Aqueous $NaHSO_3$ (1 mL) was added to decompose OsO_4. The mixture was stirred for 30 min, diluted with toluene (15 mL), filtered, and concentrated. The residue was dissolved in ethyl acetate (25 mL), washed with brine (2 × 10 mL), dried, and concentrated to give product **12**, which was isolated by column chromatography (hexane–ethyl acetate, 9:1 to 4:1) as an oil (70 mg). The unreacted starting material (80 mg) was recovered and oxidized again with OsO_4 to afford another crop of **12** (the overall yield: 125 mg, 0.22 mmol, 78%). Anal. Calcd for $C_{31}H_{46}O_{12}$: C, 60.97; H, 7.59. Found: C, 60.91; H, 7.71.

The configuration at the newly created stereogenic centers (C7, C8) was assigned by the CD spectroscopy of the complex of the diol with di-molybdenum tetracetate (Table 1). The positive Cotton effect indicated a (7*R*,8*R*)-configuration for diol **12**.

3.7. The *cis*-dihydroxylation of the free allylic alcohol 9

Allylic alcohol **9** (150 mg, 0.31 mmol) was oxidized according to the same procedure as for **10**. The product was isolated by column chromatography (hexane–ethyl acetate, 9:1 to 4:1) as a yellowish

Table 1
Assignment of the configuration of diol **12** by CD

λ_{max} ($\Delta\varepsilon'$)	λ_{max} ($\Delta\varepsilon'$)	Cotton effect	Configuration
271 (−0.4106)	320 (+0.8069)	+	(7*R*,8*R*)

oil (127 mg; 79%). The crude product was benzylated under standard conditions to afford a mixture of two diastereoisomeric products in a 2:1 ratio (as determined by the integration of the signal of H-1 at δ: 5.30 and 5.14 ppm). The main isomer was identical in all respects to compound **13** prepared below.

3.8. Benzylation of the diol 12 to give 1,2,3,4,9,10,11,12-tetra-*O*-isopropylidene-6,7,8-tri-*O*-benzyl-D-*manno*-D-*erythro*–D-*galacto*–dodec-1,5-pyranose 13

To a solution of **12** (2.6 g, 4.5 mmol) in toluene (180 mL), 50% aqueous NaOH (140 mL), benzyl chloride (4.8 mL, 42 mmol), and Bu_4NCl were added, and the mixture was stirred vigorously at room temperature for two days. Then it was partitioned between toluene (500 mL) and water (250 ml); the layers were separated, and the aqueous one extracted with ether (3 × 50 mL). The combined organic solutions were washed with water (2 × 50 mL), brine (50 mL), dried, concentrated, and the crude product **13** (8.5 g) was used for hydrolysis without further purification.

A small amount of the crude product was purified by column chromatography (hexane–EtOAc, 9:1 to 5:1) for analytical purposes. $[\alpha]_D = -26.3$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz) δ: 5.49 (d, 1H, $J_{1,2}$ = 4.8 Hz, H-1), 4.95 (d, J = 11.3 Hz, 1H, PhCH_2O), 4.82–4.66 (m, 4H, PhCH_2O), 4.62–4.58 (2H, H-3 + PhCH_2O), 4.51 (dd, J = 1.6 Hz, J = 8.14 Hz, H-4), 4.35–4.23 (m, 3H, H-2, 5, 8), 4.18 (dd, J = 6.5 Hz, J = 13.0 Hz, H-9), 4.14-3.93 (m, 6H, H-6, 7, 9, 10, 12, 12′), 1.46–1.26 (8s, CMe_2); ^{13}C NMR δ: 109.5, 109.2, 108.8, 108.7 (4 × CMe_2), 96.2 (C-1), 81.4 (C-7), 80.1 (C-9), 79.4 (C-10), 78.2, 77.7, 77.2 (C-6, 8, 11), 75.5, 74.9, 72.8 (3 × PhCH_2O), 71.1 (C-4), 70.9 (C-2), 70.7 (C-3), 66.5 (C-5), 66.3 (C-12), 27.3, 27.2, 26.6, 26.1, 25.8, 25.5, 25.2, 24.4 (8 × CMe_2). Anal. Calcd for $C_{45}H_{58}O_{12}$: C, 68.34; H, 7.39. Found: C, 68.45; H, 7.49.

3.9. Hydrolysis of 13 to give 1,2,3,4,9,10-tri-*O*-isopropylidene-6,7,8-tri-*O*-benzyl-11,12-dihydroxy-D-*manno*-D-*erytro*–D-*galacto*–dodec-1,5-pyranose 14

To a solution of crude **13** (8.5 g) in THF (600 mL) and water (200 mL), sulfuric acid (1.9 mL) was added and the mixture was stirred at room temperature for 12 days. Toluene (400 mL) was then added, after which the organic layer was separated and the aqueous one extracted with ether (3 × 50 mL). The combined organic layers were washed with concd aq $NaHCO_3$, water (3 × 50 mL), dried, concentrated, and the product was isolated by column chromatography (hexane–ethyl acetate, 9:1 to 4:1) as a yellow oil (1.61 g, 49%). The recovered substrate was subjected again to hydrolysis to give, after chromatography, another crop of product (overall yield of **14**: 2.31 g, 3.08 mmol, 70%). $[\alpha]_D = -55.9$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz) δ: 5.53 (d, $J_{1,2}$ = 4.8 Hz, H-1), 5.12 (d, J = 11.1 Hz, 1H, PhCH_2O), 4.86 (d, J = 11.3 Hz, 1H, PhCH_2O), 4.78 (d, J = 11.3 Hz, 1H, PhCH_2O), 4.71–4.52 (m, 5H, H-3, 4 and 3 × PhCH_2O), 4.35 (dd, $J_{4,5}$ = 1.1 Hz, $J_{5,6}$ = 9.4 Hz, H-5), 4.29 (dd, $J_{2,3}$ = 2.3 Hz, H-2), 4.23–4.18 (m, 2H, H-6, 8), 4.04 (d, $J_{6,7} = J_{7,8}$ = 7.8 Hz, H-7), 3.96–3.86 (m, 2H, H-9, 10), 3.71 (dd, $J_{12,12'}$ = 3.6 Hz, $J_{12,12'}$ = 11.4 Hz, H-12), 3.65–3.55 (m, 3H, H-11, 12′), 2.38–2.23 (m), 1.7 (–O*H*) 1.47–1.27 (6s, CMe_2); ^{13}C NMR δ: 109.8, 108.8, 108.6 (3 × CMe_2), 96.1 (C-1), 82.6 (C-7), 81.4 (C-9), 80.2 (C-10), 77.8 and 76.0 (C-6, 8), 75.5, 75.2, 72.8 (3 × PhCH_2O), 73.0 (C-11), 71.0 (C-4), 70.8 (C-2), 70.6 (C-3), 66.8 (C-5), 63.2 (C-12), 27.1, 26.5, 26.1, 25.8, 25.1, 24.3 (6 × CMe_2). Anal. Calcd for $C_{42}H_{54}O_{12}$: C, 67.18; H, 7.25. Found: C, 67.33; H, 7.57.

3.10. Synthesis of aldehyde 16

To a suspension of silica gel (400 mg) in methylene chloride (3.2 mL), sodium periodate (55.6 mg), and water (0.4 mL) were added, and the slurry was stirred vigorously at room temperature. After 15 min, a solution of diol **14** (157 mg, 0.21 mmol) in methylene chloride (0.4 mL) was added and the mixture was stirred at 30 °C for 4 days. Next, it was filtered and concentrated to afford aldehyde **16** as a colorless oil (68.5 mg, 0.09 mmol, 45%). This product was used for further transformations without purification.

3.11. Reduction of the aldehyde 16 to give 1,2,3,4,9,10-tri-*O*-isopropylidene-6,7,8-tri-*O*-benzyl-11-hydroxy-D-*xylo*-D-*erythro*–D-*galacto*–undec-1,5-pyranose 15

To a solution of crude **16** (65 mg, 0.09 mmol) in dry ether (10 mL), $NaBH_4$ (30 mg) was added, and the mixture was stirred at room temperature overnight; then it was partitioned between water (5 mL) and AcOEt (5 mL). The organic layer was separated, and the aqueous one extracted with ether (2 × 5 mL). The combined organic solutions were washed with water (2 × 5 mL), brine (5 mL), dried, and concentrated to afford product **15** as colorless oil (57.9 mg, 0.08 mmol, 89%). $[\alpha]_D = -35$ (*c* 1, $CHCl_3$); ^{1}H NMR (600 MHz) δ: 5.5 (d, $J_{1,2}$ = 4.8 Hz, H-1), 4.98 (d, J = 11.3 Hz, 1H, PhCH_2O), 4.81 (d, J = 11.1 Hz, 1H, PhCH_2O), 4.75 (d, J = 11.1 Hz, 1H, PhCH_2O), 4.7–4.57 (m, 4H, H-3 + 3 × PhCH_2O), 4.5 (dd, $J_{4,5}$ = 1.5 Hz, $J_{3,4}$ = 8.1 Hz, H-4), 4.28 (dd, $J_{5,6}$ = 9.8 Hz, H-5), 4.26 (dd, $J_{2,3}$ = 2.3 Hz, H-2), 4.18 (dd, $J_{6,7} = J_{7,8}$ = 7.1 Hz, H-7), 4.12 (dd, H-6), 4.04 (m, 1H, H-10), 3.97 (dd, $J_{8,9}$ = 7.2 Hz, H-8), 3.92 (dd, $J_{9,10}$ = 7.2 Hz, H-9), 3.72 (dd, $J_{10,11}$ = 1.8 Hz, $J_{11,11'}$ = 11.7 Hz, H-11), 3.61 (dd, $J_{10,11'}$ = 4.8 Hz, H-11′), 1.44–1.27 (6s, CMe_2); ^{13}C NMR δ: 109.1, 108.8, 108.7 (3 × CMe_2), 96.1 (C-1), 82.0 (C-8), 79.9 (C-10), 78.8 (C-7 + C-9), 77.7 (C-6), 75.3, 74.7, 72.9 (3 × PhCH_2O), 71.0 (C-4), 70.8 (C-7), 70.7 (C-3), 66.6 (C-2), 63.4 (C-11), 27.2, 26.8, 26.1, 25.8, 25.1, 24.4 (6 × CMe_2). *m*/*z* Calcd for $C_{41}H_{52}O_{11}Na$: 743.34018. Found: 743.33829.

3.12. Reaction of aldehyde 16 with phosphonate 6 to give 1,2,3,4,9,10,15,16,17,18-penta-*O*-isopropylidene-6,7,8-tri-*O*-benzyl-11,12-dideoxy-11,12-didehydro-D-*galacto*-D-*xylo*-D-*erythro*–D-*galacto*–octadeka-1,5;14,18-dipyranos-13-ulose 17

To a solution of aldehyde **16** (50 mg, 0.07 mmol) and phosphonate **6** (30.7 mg, 0.08 mmol) in dry toluene (2 mL) anhydrous potassium carbonate (20 mg) was added followed by catalytic amounts of 18-crown-6 (5 mg). The mixture was then stirred for two days at room temperature. Next, it was partitioned between water (5 mL) and AcOEt (5 mL). The organic phase was separated and the aqueous one extracted with ethyl acetate (2 × 5 mL). The combined organic solutions were washed with water (2 × 5 mL), brine (5 mL), dried, and concentrated.

The residue was dissolved in acetone (15 mL) to which Jones' reagent was added (0.3 mL) and the mixture was stirred for 3 h. The excess oxidant was decomposed with *iso*-propanol (1 mL). After the addition of toluene (20 mL), the solution was concentrated under vacuum (to remove acetone), washed with aqueous $NaHCO_3$ (3 × 5 mL), brine (5 mL), dried, and concentrated. The crude material was purified by column chromatography (hexane–ethyl acetate, 9:1 to 4:1) to afford enone **17** as a colorless oil (14.2 mg, 0.015 mmol, 21%). $[\alpha]_D = -47.2$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz) δ: 6.94 (dd, $J_{10,11}$ = 5.5 Hz, $J_{11,12}$ = 15.7 Hz, H-11), 6.9 (d, H-12), 5.65 (d, $J_{1,2}$ = 4.95 Hz, H-1), 5.1 (d, $J_{1',2'}$ = 4.95 Hz, H-1′), 4.87 (d, J = 11.3 Hz, 1H, PhCH_2O), 4.78 (d, J = 10.8 Hz, 1H, PhCH_2O), 4.76 (d, J = 10.5 Hz, 1H, PhCH_2O), 4.72–4.65 (m, 2H, H-10, PhCH_2O), 4.64–4.55 (m, 4H, H-3, H-16, H-15, PhCH_2O) 4.52 (d, J = 11.1 Hz, 1H, PhCH_2O), 4.48 (dd, 1H, $J_{4,5}$ = 1.6 Hz, $J_{3,4}$ = 8 Hz, H-4), 4.35 (dd, $J_{2,3}$ = 2.6 Hz, H-2), 4.31–4.28 (m, 3H, H-5, H-8, H-14), 4.26 (dd, $J_{2',3'}$ = 2.3 Hz, H-2′), 4.0 (dd, 1H, $J_{9,10}$ = 4.5 Hz, $J_{8,9}$ = 8 Hz, H-9), 3.96 (dd, 1H, $J_{5,6} = J_{6,7}$ = 9.3 Hz, H-6), 3.93 (dd, 1H, $J_{7,8}$ = 8.4 Hz, H-7), 1.48–1.28 (10s, CMe_2); ^{13}C NMR δ: 196.0 (C-13), 144.1 (C-11),

139.1 ($PhCH_2$ quat. C-atom), 139 ($2 \times PhCH_2$ quat. C-atom), 126.0 (C-12), 109.7, 109.5, 108.9, 108.8, 108.7 ($5 \times CMe_2$), 96.4 (C-1), 96.2 (C-1′), 81.9 (C-9), 81.5 (C-7), 78.6 (C-8), 77.6 (C-6), 77 (C-10), 75.6, 74.9 ($2 \times PhCH_2O$), 73.3 (C-14), 72.8 ($PhCH_2O$), 72.2 (C-15), 71.1 (C-4), 70.8 (C-17), 70.68, 70.65 (C-3, C-16), 70.4 (C-2), 66.3 (C-5), 26.95, 26.78, 26.07, 25.98, 25.79, 25.7, 25.1, 24.8, 24.4, 24.1 ($10 \times CMe_2$). *m*/*z* Calcd for $C_{54}H_{68}O_{16}Na$: 995.43996. Found: 995.44143.

When the reaction of **16** (100 mg, 0.14 mmol) and phosphonate **6** (61 mg, 0.16 mmol) was prolonged for 4 days, three products were obtained: the desired enone **17** (18.9 mg, 0.019 mmol, 14%), and two isomeric side products **18** and **19** in a 37% yield (45.3 mg, 0.051 mmol). Integration of the anomeric protons (at δ: 5.63 and 5.67) allowed us to assign a 1:1 ratio of **18** and **19**. HRMS for the mixture **18**/**19**; *m*/*z* Calcd for $C_{47}H_{60}O_{16}Na$: 903.37736. Found: 903.38171. This mixture was separated by preparative TLC (Silica Gel 60 F_{254}, 0.5 mm, hexane–ethyl acetate, 9:1) into pure isomers, which were characterized separately.

3.13. 1,2,3,4,9,10,15,16,17,18-Penta-*O*-isopropylidene-6,8-di-*O*-benzyl-11,12-dideoxy-11,12-didehydro–D-*galacto*-D-*xylo*-D-*glycero*–D-*galacto*–octadeca-1,5:14,18-dipyranose-7,13-diulose 18

$[\alpha]_D = -13.6$ (*c* 1, $CHCl_3$); ^1H NMR (500 MHz) δ: 7.0 (dd, $J_{10,11} = 4.3$ Hz, $J_{11,12} = 15.8$ Hz, H-11), 6.82 (dd, $J_{10,12} = 1.6$ Hz, H-12), 5.63 (d, $J_{1,2} = 4.7$ Hz, H-1), 5.49 (d, $J_{17,18} = 5$ Hz, H-18), 4.75 (d, $J_{5,6} = 9.4$ Hz, H-6), 4.72–4.68 (m, 1H, H-10), 4.65–4.6 (m, 3H, H-3, 16, $1 \times PhCH_2O$), 4.59 (d, 1H, H8), 4.58–4.55 (m, 2H, H-15, $1 \times PhCH_2O$), 4.47 (dd, $J_{4,5} = 1.3$ Hz, $J_{3,4} = 8.1$ Hz, H-4), 4.42–4.39 (m, 2H, $2 \times PhCH_2O$) 4.36 (dd, $J_{2,3} = 2.3$ Hz, H-2), 4.33 (d, $J_{14,15} = 2.2$ Hz, H-14), 4.3 (dd, $J_{16,17} = 2.4$ Hz, H-17), 4.09 (dd, H-5), 3.87 (dd, $J = 6.6$ Hz, $J = 8$ Hz, H-9), 1.49–1.28 (10s, CMe_2); ^{13}C NMR δ: 210.4 (C-7), 195.9 (C-13), 144.3 (C-11), 138.06 ($PhCH_2$ quat. C-atom), 138.01 ($PhCH_2$ quat. C-atom), 124.8 (C-12), 111.1, 109.8, 109.2, 109.1, 108.9 ($5 \times CMe_2$), 96.4 (C-1), 96.0 (C-18), 84.2, 80.2, 80.0, 79.2, 73.4 ($PhCH_2O$), 72.4 ($PhCH_2O$), 72.2, 72.0, 70.7, 70.7, 70.41, 70.38, 70.32, 69.8, 26.90, 26.88, 26.03, 26.02, 25.98, 25.8, 25.0, 24.8, 24.4, 24.3 ($10 \times CMe_2$).

3.14. 1,2,3,4,9,10,15,16,17,18-Penta-*O*-isopropylidene-6,7-di-*O*-benzyl-11,12-dideoxy-11,12-didehydro–D-*galacto*-D-*threo*-L-*threo*–D-*galacto*–octadeca-1,5;14,18-dipyranose-8,13-diulose 19

$[\alpha]_D = -17.8$ (*c* 1, $CHCl_3$); ^1H NMR (500 MHz) δ: 7.1 (dd, $J_{10,11} = 4.3$ Hz, $J_{11,12} = 15.8$, H-11), 6.84 (dd, $J_{10,12} = 1.6$ Hz, H-12), 5.67 (d, $J_{1,2} = 5.1$ Hz, H-1), 5.48 (d, $J_{17,18} = 5.1$ Hz, H-18), 4.88 (d, $J = 10.2$ Hz, 1H, $PhCH_2O$), 4.75 (m, $J_{9,10} = 9.5$ Hz, H-10), 4.72 (d, $J = 11.5$ Hz, 1H, $PhCH_2O$), 4.68–4.56 (m, 5H, H-3, H-16, H-7, $2 \times PhCH_2O$), 4.43 (dd, 1H, $J_{15,16} = 1.7$ Hz, $J_{14,15} = 8.2$ Hz, H-15), 4.38–4.35 (m, 2H, $J_{2,3} = 2.2$ Hz, H-14, H-2), 4.33–4.28 (m, $J_{16,17} = 2.4$ Hz, H-17), 4.14 (dd, 1H, $J_{4,5} = 2$ Hz, $J_{5,6} = 9.7$ Hz, H-5), 4.03–3.97 (m, 2H, $J_{6,7} = 7.1$ Hz, H-9, H-6) 3.89 (dd, 1H, $J_{3,4} = 10.2$ Hz, H-4), 1.49–1.26 (10s, CMe_2); ^{13}C NMR δ: 212.2 (C-8), 196.1 (C-13), 145.8 (C-11), 138.5 ($PhCH_2$ quat. C-atom), 138.0 ($PhCH_2$ quat. C-atom), 123.2 (C-12), 110.0, 109.8, 109.1, 108.8, 108.7 ($5 \times CMe_2$), 96.5 (C-1), 96.3 (C-18), 80.2, 80.0, 79.5, 79.0, 75.5, 73.7, 73.2, 72.3, 70.7, 70.6, 70.5, 70.4, 70.3, 66.7, 27.1, 27.0, 26.05, 25.97, 25.89, 25.85, 24.9, 24.8, 24.5, 24.3 ($10 \times CMe_2$).

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