Phosphonate *versus* phosphorane method in the synthesis of higher carbon sugars. Preparation of D-*erythro*-L-*manno*-D-*gluco*-dodecitol

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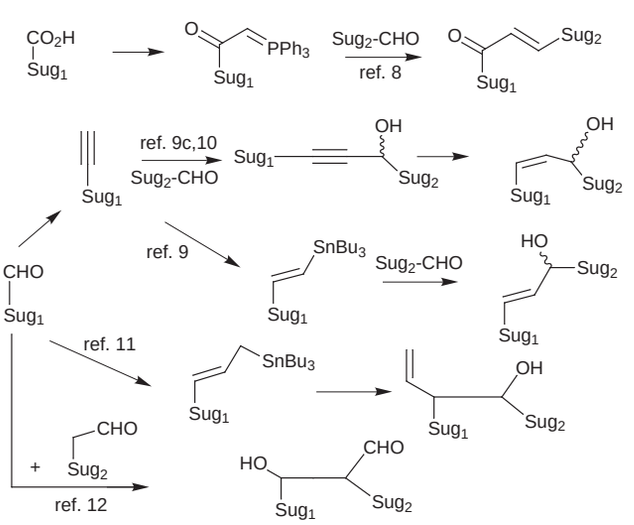
Higher sugar (C_{12} and C_{13}) dialdose precursors **5**, **10** and **15** were obtained by a coupling of C_7-phosphorane **1** or C_7-phosphonates **2** and **13** with C_5- or C_6-sugar aldehydes. These compounds were converted into higher dialdoses by (i) stereoselective reduction of a carbonyl group with zinc borohydride followed by (ii) osmylation of the resulting allylic alcohols. One of these derivatives – compound **8a** – was converted into D-*erythro*-L-*manno*-D-*gluco*-dodecitol **23** on a 0.5 g scale.

Introduction

The synthesis of higher carbon sugars having more than 10 carbon atoms in the chain has gained considerable attention in the past two decades, since they are components of some antibiotics[1] and might be used as non-metabolised analogues of disaccharides. Preparation of such compounds can be accomplished now almost routinely,[2] although for a long time it presented a real challenge for organic chemists. The synthesis of higher alditols, however, is not easy, and little is known about the properties of such compounds, although they might have unique conformational and biological properties, and their specific complexation with chiral organic cations might be expected. As was pointed out in 1993 by Köll '*the conformational behaviour of the 20 diastereoisomers of octitols in solution as well as in crystalline state is almost unknown*';[3] even less is known about decitols.[4] This results from the low accessibility of such compounds. The higher alditols are usually available by Brimacombe's C_2-iteration methodology,[5] although several more efficient syntheses have been reported: D-*erythro*-L-*ido*-L-*gulo*-dodecitol was obtained in low yield as a side product during electrochemical reduction of D-glucose,[6] and the *cis*-hydroxylation of sugar-derived diolefins leading to decitols and dodecitols was described recently.[7]

In the past few years we have proposed a general method for the preparation of higher sugar dialdoses (Scheme 1) by a coupling of terminal C-atoms of two sugar sub-units *via* the C_n bridge. This was accomplished by reaction of sugar-derived stabilised phosphoranes,[8] sugar-vinyl[9] and propargyl[10] anions and sugar allyltin derivatives[11] with aldehydes, which resulted in formation of C_{12}–C_{15} monosaccharides. The aldol condensation between two sugar aldehydes also yielded a higher monosaccharide.[12] Recently a C_{21}-monosaccharide[13] was prepared by a high-pressure Wittig methodology.

The main disadvantage of Wittig methodology is the low yield of conversion of uronic acids into stabilised phosphoranes.[8] We have found that replacing the phosphorane with the more nucleophilic phosphonate (which can be prepared in much higher yield) may improve the overall yield of higher carbon sugars.



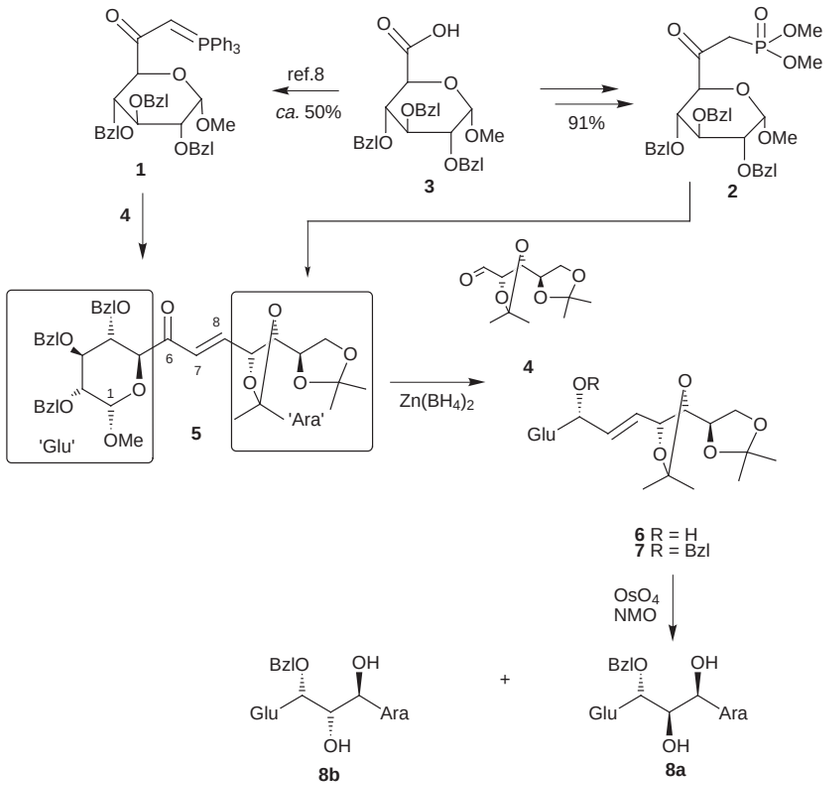
Scheme 1

Results and discussion

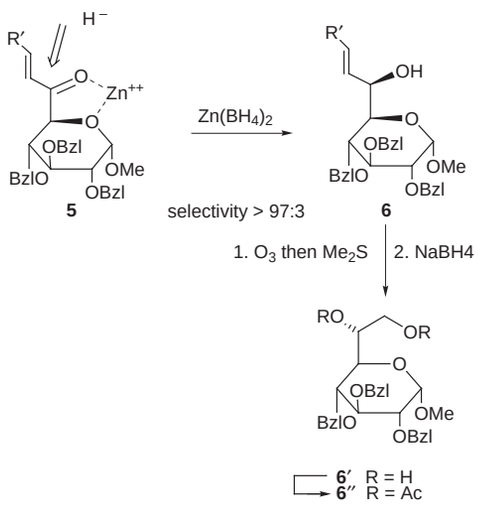
We faced serious problems in conversion of higher sugar dialdoses (prepared by methods presented in Scheme 1) into higher alditols. Here we present a useful methodology for the high-yield, selective preparation of convenient higher sugar precursors in which both sugar 'sub-units' are blocked with easily removable protecting groups.

As a starting material phosphorane **1**[8] – easily obtained from methyl 2,3,4-tri-*O*-benzyl-α-D-glucosiduronic acid **3** – was employed. Treatment of phosphorane **1** with 2,3:4,5-di-*O*-isopropylidene-D-arabinose[14] **4** resulted in clean formation of higher sugar enone **5**. Although the yield of this process amounted to 70%, the overall yield of enone **5** from acid **3** was low because the conversion of uronic acid **3** into phosphorane **1** could be achieved in only 50%. Therefore, the alternative starting material – phosphonate **2** – was used. Compound **2** was prepared according to the method of Yonemitsu and coworkers[15] from the methyl ester of uronic acid **3** in 91% yield. Treatment of a toluene solution of reactants **2** and **4** with K_2CO_3 and 18-crown-6 gave a 90% yield of the *E*-enone **5**. This compound was selectively reduced with zinc borohydride to yield the allyl alcohol **6** (see Scheme 2).

The high selectivity of the reduction was explained by a cyclic model presented in Scheme 3; complexation of zinc cation to both ketone- and ring-oxygen atoms fixes the conformation and makes the attack of hydride anion available only from the less hindered side of the molecule, *i.e.* from 'behind the ring'.[8b] The D-*glycero*-configuration of allylic alcohol **6** was confirmed by chemical degradation to the known[16] methyl D-*glycero*-α-D-*gluco*-heptopyranoside (**6′**; see Experimental section).



Scheme 2



Scheme 3

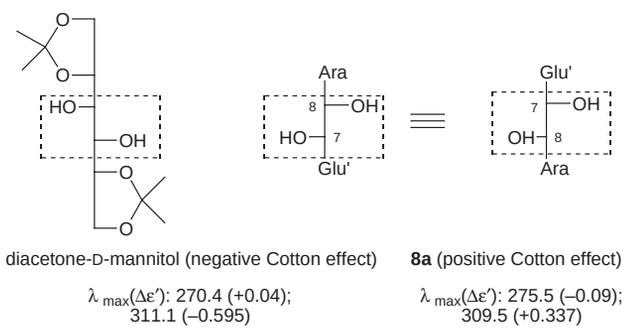


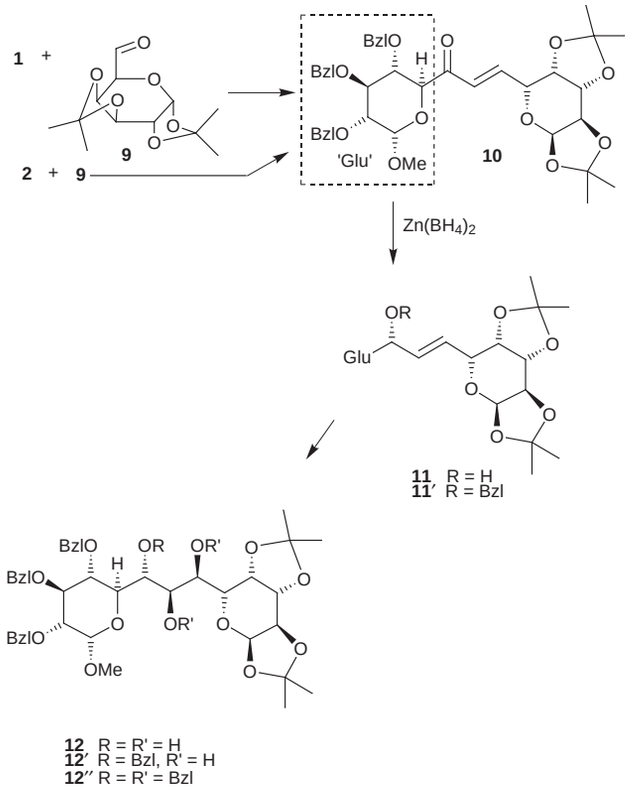
Fig. 1 CD spectra of $Mo_2(OAc)_4$ complexes with diacetone-D-mannitol and compound **8a**.

Protection of the free hydroxy group in compound **6** as the benzyl ether **7** and subsequent osmylation of the double bond gave – with very high selectivity – diol **8a** (ratio **8a**:**8b** = 96:4). Configuration of the main isomer **8a** was assigned on the basis of Kishi's rule[17] according to which the attack of osmylating agent occurs from the side opposite to (any) alkoxy groups. In compound **7** both alkoxy groups flanking the double bond point in the same direction (Scheme 2) and the attack of OsO_4 should lead with high selectivity to diol **8a**. This assumption was verified by the circular dichroism (CD) spectra of chiral diol **8a** with dimolybdenum tetraacetate $[Mo_2(OAc)_4]$.[18] In Fig. 1 the CD spectra of diacetone-D-mannitol and diol **8a** with $[Mo_2(OAc)_4]$ are presented. The Cotton effects in these two complexes were *opposite*, which showed that the configuration of the diol groupings should also be opposite. This result supported our assumption based on Kishi's model.

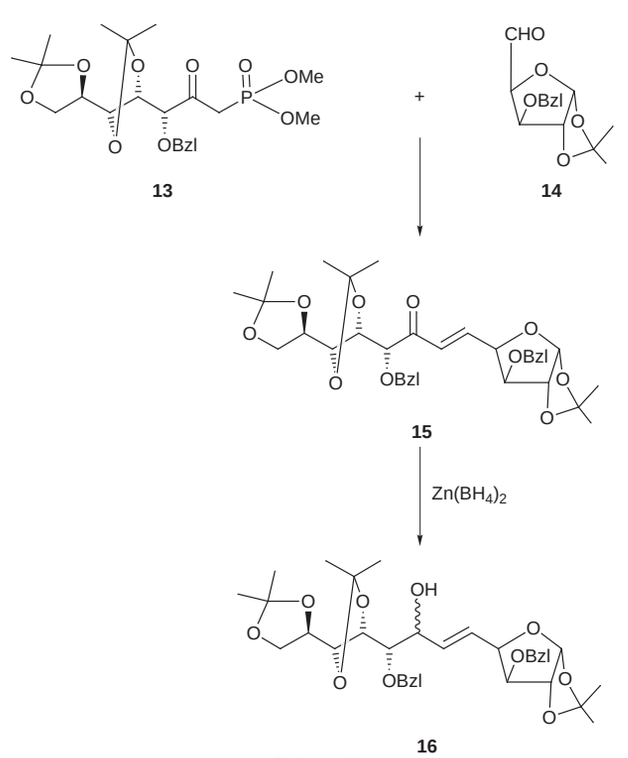
Similarly, a C_{13}-enone **10** was prepared from 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose **9** and ylide **1** (80%) or aldehyde **9** and phosphonate **2** (85%). Reduction of enone **10** with $Zn(BH_4)_2$ afforded a single isomer **11**, the configuration of which was assigned also by chemical degradation to compound **6′** (see Experimental section). Osmylation of alkene **11** was highly stereoselective and led to a single stereoisomeric triol **12** (Scheme 4). The configuration of product **12** could be, therefore, safely assigned on the basis of Kishi's rule, but it was also verified by independent methods. Thus, protection of the hydroxy function in the alcohol **11** as benzyl ether **11′** and subsequent osmylation afforded diol **12′**, the configuration of which was assigned on the basis of its CD spectrum with $[Mo_2(OAc)_4]$ (see Experimental section). Benzylation of diol **12′** afforded compound **12″**, which was identical with the product of per-benzylation of triol **12**.

Reaction of phosphonate **13**[19] with 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranos-1,4-ulose **14** proceeded with high yield to afford *E*-enone **15**. Reduction of compound **15** with $Zn(BH_4)_2$ was – contrary to previous examples – non-selective; alcohol **16** was produced as a 3:2 mixture of stereoisomers (Scheme 5, see Experimental section).

The explanation of the lack of selectivity is presented in structure **I**. Although the complexation of zinc cation to carbonyl- and α-oxygen atoms fixes the conformation, the



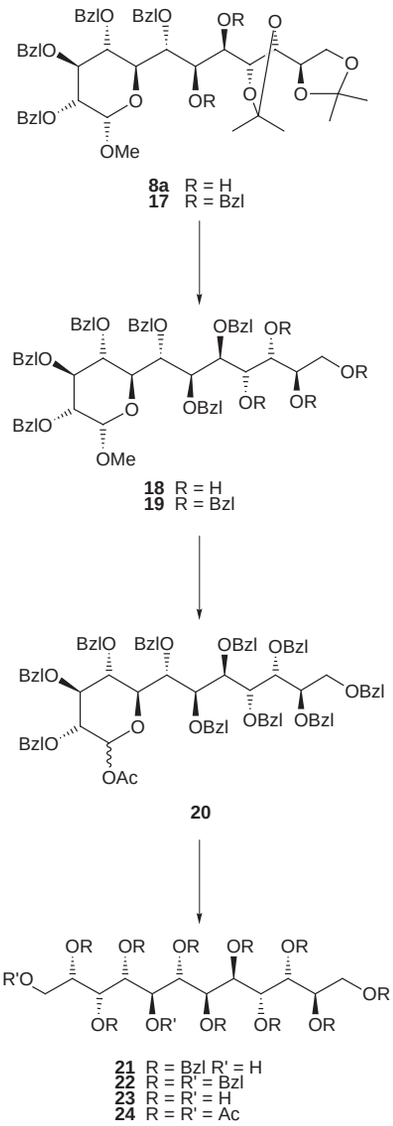
Scheme 4



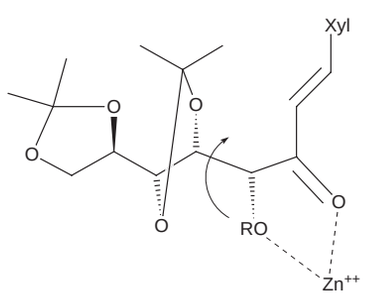
Scheme 5

differentiation between the *re* and *si* sides of the molecule is not significant, because of the free rotation around the adjacent C–C bond.

The methodology of transformation of higher carbon dialdoses into higher alditols is illustrated by the conversion of methyl 2,3,4,6-tetra-*O*-benzyl-9,10:11,12-di-*O*-isopropylidene-D-*erythro*-L-*manno*-α-D-*gluco*-dodeco-1,5-pyranoside **8a** into D-*erythro*-L-*manno*-D-*gluco*- (= L-*threo*-L-*allo*-D-*manno*-)dodecitol **23** (see Scheme 6). Diol **8a** was benzylated to hexakisbenzyl ether **17** in which the isopropylidene groups were hydrolysed with sulfuric acid in methanol to afford tetraol **18**. Benzylation



Scheme 6



I

of this compound gave deca-*O*-benzyl ether **19** from which the methoxy group was removed by acetolysis to provide dodecose **20** as a mixture of α,β-anomers. Reduction of this product with lithium aluminium hydride afforded diol **21** which was contaminated with a more polar product assumed to be a partially debenzylated dodecitol (this could happen during acetolysis). This crude mixture was, therefore, benzylated to give fully protected derivative **22**. Catalytic removal of the benzyl protecting groups (H_2/Pd) led to free D-*erythro*-L-*manno*-D-*gluco*- (= L-*threo*-L-*allo*-D-*manno*-)dodecitol **23** [0.5 g, 25% overall yield (7 steps from compound **8a**)].

Conclusions

We have demonstrated that the precursors of higher alditols – higher sugar enones **5**, **10**, or **16** – can be obtained by a coupling

of sugar-derived phosphoranes, or sugar phosphonates, with sugar aldehydes. The latter method is more practical, since sugar phosphonates can be prepared in much higher yields than can sugar phosphoranes. Transformation of higher sugar enones into alditols can be conveniently performed on a quite large scale, and no special techniques are required for the isolation of the final products.

Experimental

NMR spectra were recorded with a Bruker AM 500 and a Varian Gemini 200 spectrometer for solutions in $CDCl_3$ (internal Me_4Si), unless otherwise stated; *J*-values are given in Hz. Most of the resonances were assigned by 2D (^1H–^1H and ^1H–^{13}C) correlations. Mass spectra [LSIMS (*m*-nitrobenzyl alcohol was used as a matrix to which sodium acetate was added)] were recorded with a AMD-604 (AMD Intectra GmbH, Germany) mass spectrometer. The optical rotation (compound **23**) was measured on a JASCO P-1020 digital polarimeter, and the $[\alpha]_D$-value is in units of 10^{-1} deg cm^2 g^{-1}. Column chromatography was performed on silica gel (Merck, 70–230 mesh). Organic solutions were dried over anhydrous magnesium sulfate. Methyl 2,3,4-tri-*O*-benzyl-7-deoxy-7-triphenylphosphoranylidene-α-D-*gluco*-heptopyranoid-6-ulose **1** was prepared in 50% yield from uronic acid **3** according to the methodology of ref. 8.

General procedure for reaction of sugar phosphoranes with sugar aldehydes (method A)

Phosphorane **1** (3 mmol) and an appropriate aldehyde (**4** or **9**, 3 mmol) were stirred in dry benzene (30 cm^3) at rt until TLC (hexane–ethyl acetate, 2:1) indicated disappearance of both starting materials and formation of a new, less polar product that was visible under UV light. The crude higher sugar enone was purified by column chromatography (hexane–ethyl acetate, 5:1 to 3:1).

General procedure for reaction of sugar phosphonates with sugar aldehydes (method B)

An appropriate sugar phosphonate (**2** or **13**, 3 mmol), sugar aldehyde (**4**, **9** or **14**, 3 mmol) and 18-crown-6 (3 mmol) in toluene (30 cm^3) were stirred overnight at rt with potassium carbonate (10 mmol). After this time TLC (hexane–ethyl acetate, 2:1) indicated disappearance of both starting materials (16 h) and formation of a new, less polar product that was visible under UV light. The mixture was partitioned between toluene and brine, the organic phase was separated, washed with water, dried and concentrated, and the product was isolated as in method **A**.

General method for reduction of higher sugar enones with zinc borohydride (method C)

To a cooled (0 °C) solution of an appropriate enone (2 mmol) in dry diethyl ether (15 cm^3) was added $Zn(BH_4)_2$ (~ 5 cm^3 of a 0.5 M solution in diethyl ether) and the mixture was stirred for 30 min at 0 °C. Excess of borohydride was decomposed with water, the organic phase was separated, washed successively with dil. sulfuric acid and water, dried and concentrated, and the crude product was purified by column chromatography (hexane–ethyl acetate, 4:1 to 2:1).

General procedure for benzylation reaction (method D)

A solution of an appropriate alcohol (~2 g) in DMF (30 cm^3) was stirred with sodium hydride (50% dispersion in mineral oil; 1.2 equiv. per hydroxy group) for 30 min; benzyl bromide (1.1 equiv. per one hydroxy group) was added and the mixture was stirred at rt for 2–3 h (TLC monitoring in hexane–ethyl acetate, 2:1). Excess of hydride was carefully decomposed with water, the mixture was partitioned between diethyl ether and water, and the organic phase was separated, washed with water, dried and concentrated. Crude product was purified by column chromatography (hexane–ethyl acetate, 6:1 to 2:1).

General method for *cis*-hydroxylation (method E)

To a solution of an olefin (2 mmol) in a mixture of THF (15 cm^3), *tert*-butyl alcohol (1 cm^3) and water (0.5 cm^3) was added NMO (2.5 mmol) followed by osmium tetraoxide (0.8 cm^3 of a ~2% solution in toluene). The mixture was stirred for 48–72 h (TLC monitoring in hexane–ethyl acetate, 2:1), then was diluted with methanol (20 cm^3), and 40% aq. sodium hydrogen sulfite was added. The mixture was stirred for 30 min, filtered through Celite, concentrated, and partitioned between water and diethyl ether. The organic phase was separated, dried and concentrated, and the crude product(s) was (were) purified by column chromatography (hexane–ethyl acetate, 4:1 to 3:2).

Methyl 2,3,4-tri-*O*-benzyl-7,8-dideoxy-9,10:11,12-di-*O*-isopropylidene-D-*arabino*-α-D-*gluco*-dodec-7(*E*)-eno-1,5-pyranosid-6-ulose 5. This was prepared from phosphorane **1** and 2,3:4,5-di-*O*-isopropylidene-D-arabinose[14] **4** in 75% yield (method **A**) or from phosphonate **2** and aldose **4** in 90% yield (method **B**) [HRMS: Calc. for $C_{40}H_{48}O_{10}Na$ (M + Na$^+$): *m*/*z*, 711.3145. Found: *m*/*z*, 711.3190] (Found: C, 69.5; H, 7.0. Calc. for $C_{40}H_{48}O_{10}$: C, 69.75; H, 7.02%); δ_H 3.40 (3 H, s, OCH_3), 3.56 (1 H, dd, $J_{1,2}$ 3.5, $J_{2,3}$ 9.0, H-2), 3.59 (1 H, t, $J_{9,10} = J_{10,11} = 8.2$, H-10), 3.68 (1 H, dd, $J_{3,4}$ 9.4, $J_{4,5}$ 9.8, H-4), 3.90 (H-12), 4.04 (1 H, dd, H-4), 4.10 (2 H, m, H-11 and H′-12), 4.35 (1 H, d, H-5), 4.48 (1 H, m, H-9), 6.66 (1 H, dd, $J_{7,8}$ 15.8, $J_{7,9}$ 1.6, H-7) and 7.03 (1 H, dd, $J_{8,9}$ 4.4, H-8); δ_C 25.1, 26.6, 26.7, 26.9 (2 × C*Me*$_2$), 56.8 (OCH_3), 67.5 (C-12), 72.9 (C-5), 77.0 (C-11), 79.2 (C-9), 79.3 (C-2), 81.2 (C-10), 81.7 (C-3), 98.7 (C-1), 126.7 (C-7), 144.8 (C-8) and 195.2 (C-6).

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-*C*-[methyl (*E*)-2,3,4-tri-*O*-benzyl-7-deoxy-α-D-*gluco*-heptopyranosid-6-ulos-7-ylidene]-α-D-*galacto*-pyranose 10. This was prepared from compound **1** and 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose[20] **9** in 80% yield (method **A**) or from reactants **2** and **9** in 85% yield (method **B**) [HRMS: Found: *m*/*z*, 739.3128. Calc. for $C_{41}H_{48}NaO_{11}$ (M + Na$^+$): *m*/*z*, 739.3095]; δ_H 1.28, 1.32, 1.34 and 1.49 (12 H, 4 s, 2 × C*Me*$_2$), 3.41 (3 H, s, OCH_3), 3.55 (1 H, dd, $J_{1,2}$ 3.5, $J_{2,3}$ 9.7, H-2), 3.68 (1 H, dd, $J_{3,4}$ 9.2, $J_{4,5}$ 9.7, H-4), 4.03 (dd, H-3), 4.26 (1 H, dd, $J_{9,10}$ 2.1, $J_{10,11}$ 7.8, H-10), 4.34 (1 H, dd, $J_{12,13}$ 5.0, $J_{11,12}$ 2.4, H-12), 4.37 (1 H, d, H-5), 4.45 (1 H, m, H-9), 4.60 (1 H, H-11), 4.61 (1 H, d, H-1), 5.58 (1 H, d, H-13), 6.67 (1 H, dd, $J_{7,8}$ 15.7, $J_{7,9}$ 2.0, H-7) and 6.96 (1 H, dd, $J_{8,9}$ 4.1, 8); δ_C 24.3, 24.8, 25.8 and 26.1 (2 × C*Me*$_2$), 55.8 (OCH_3), 67.6 (C-9), 70.5 (C-12), 70.8 (C-11), 72.6 (C-10), 73.0 (C-5), 79.1 (C-4), 79.4 (C-2), 81.8 (C-3), 96.4 (C-13), 98.7 (C-1), 108.6 and 109.6 (2 × *C*Me$_2$), 127.5 (C-7), 143.1 (C-8) and 195.0 (C-6).

3,8-Di-*O*-Benzyl-5,6-dideoxy-1,2:9,10:11,12-tri-*O*-isopropylidene-D-*altro*-D-*gluco*-dodec-5(*E*)-eno-1,4-furanos-7-ulose 15. This was prepared from phosphonate **13** and 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose **14** in 75% yield (method **B**) [HRMS: Found: *m*/*z*, 647.2872. Calc. for $C_{35}H_{44}NaO_{10}$ (M + Na$^+$): *m*/*z*, 647.2832]; δ_H(200 MHz) *inter alia* 1.28, 1.30 (2×), 1.33, 1.40 and 1.50 (3 × C*Me*$_2$), 6.01 (1 H, d, $J_{1,2}$ 3.7, H-1), 6.87 (1 H, dd, $J_{5,6}$ 15.8, $J_{4,6}$ 1.3, H-6) and 7.05 (1 H, dd, $J_{5,4}$ 4.7, H-5); δ_C(50 MHz) 25.7, 26.7, 27.1, 27.2, 27.4 and 27.8 (3 × C*Me*$_2$), 68.3 (C-12), 77.4, 77.7, 80.4, 83.4, 83.7, 105.5 (C-1), 110.2, 110.9 and 112.4 (3 × *C*Me$_2$), 127.2 (C-6), 141.3 (C-5) and 196.8 (C-7).

Dimethyl (methyl 2,3,4-tri-*O*-benzyl-α-D-*gluco*-heptopyranosid-6-ulos-7-yl)phosphonate 2. To a cooled (to −78 °C) solution of dimethyl methylphosphonate (7.44 g, 6.4 cm^3, 60 mmol) in dry THF (100 cm^3) was added a solution of butyllithium (2.5 M in hexane; 24 cm^3, 60 mmol) and the mixture

was stirred for 15 min under argon. A solution of methyl (methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosid)uronate **3** (9.84 g, 20 mmol; prepared by esterification of methyl 2,3,4-tri-*O*-benzyl-α-D-glucosiduronic acid **3** with diazomethane) was added, the mixture was stirred for another 15 min, and was then partitioned between ethyl acetate and brine. The organic phase was separated, washed with water, dried and concentrated, and the crude product was purified by column chromatography (hexane–ethyl acetate, 1:1 to 1:3) to afford title phosphonate **2** as an oil (9.41 g, 91%) [HRMS: Found: *m*/*z*, 607.2074. Calc. for $C_{31}H_{37}NaO_9P$ (M + Na^+): *m*/*z*, 607.2073]; δ_H(200 MHz) 3.47 (3 H, s, OCH_3), 3.55 (1 H, dd, $J_{2,3}$ 9.7, H-2), 3.67 (dd, $J_{4,5}$ 9.9, $J_{3,4}$ 9.0, H-4), 3.74 [d, $J_{P,H}$ 11.3, P(OCH_3)], 3.77 [d, $J_{P,H}$ 11.4, P(OCH_3)], 4.07 (1 H, dd, H-3), 4.40 (d, H-5) and 4.64 (d, H-1); δ_C 49.1 (d, $J_{C-7,P}$ 128.8, C-7), 52.9 [d, $J_{C,P}$ 6.8, P(OCH_3)], 53.1 [d, $J_{C,P}$ 7.1, P(OCH_3)], 55.5 (OCH_3), 73.8 (C-5), 78.8 (C-4), 79.3 (C-2), 81.8 (C-3), 98.6 (C-1) and 198.5 (d, $J_{C-6,P}$ 6.6, C-6).

Methyl 2,3,4-tri-*O*-benzyl-7,8-dideoxy-9,10:11,12-di-*O*-isopropylidene-D-*gluco*-α-D-*gluco*-dodec-7(*E*)-eno-1,5-pyranoside 6. This was obtained as an oil in 95% yield by reduction of enone **5** (method **C**) [HRMS: Found: *m*/*z*, 713.3360. Calc. for $C_{40}H_{50}NaO_{10}$ (M + Na^+): *m*/*z*, 713.3301]; δ_H 3.38 (3 H, s, OCH_3), 3.41 (1 H, dd, $J_{3,4}$ 9.0, $J_{4,5}$ 9.9, H-4), 3.47 (1 H, dd, $J_{1,2}$ 3.6, $J_{2,3}$ 9.6, H-2), 3.77 (1 H, dd, $J_{5,6}$ 3.7, H-5), 4.02 (1 H, dd, H-3), 4.31 (1 H, t, $J_{8,9} = J_{9,10} = 6.6$, H-9), 4.38 (1 H, $J_{6,7}$ 7.2, H-6), 4.59 (1 H, d, H-1), 5.75 (1 H, ddd, $J_{7,8}$ 15.6, *J* 0.9, H-7) and 5.94 (1 H, ddd, *J* 1.0, H-8); δ_C 25.2, 25.3, 26.6 and 26.9 (2 × C*Me*$_2$), 56.8 (OCH_3), 62.7 (C-12), 72.0 (C-6), 72.4 (C-5), 78.9 (C-4), 79.9 (C-9), 80.1 (C-2), 81.2 (C-10), 82.2 (C-3), 97.8 (C-1), 109.4 and 109.7 (2 × *C*Me$_2$), 130.7 (C-8) and 131.0 (C-7).

Determination of the configuration of allylic alcohol 6. A solution of alcohol **6** (230 mg, 0.33 mmol) in methylene dichloride (25 cm^3) was ozonolyzed at −78 °C until the blue colour persisted (*ca*. 15 min; also monitoring in hexane–ethyl acetate, 1:2). Dimethyl sulfide (0.5 cm^3) was added to decompose the ozonide, and then the mixture was stirred for 15 min at rt and concentrated *in vacuo*. The residue was dissolved in methanol (20 cm^3) and reduced with sodium borohydride (30 mg) for 30 min to afford diol **6′** and 2,3:4,5-di-*O*-isopropylidene-D-arabinitol. Compound **6′** (105 mg, 0.21 mmol, 64%) was isolated by column chromatography (hexane–ethyl acetate, 2:1 to 1:2) and compared on TLC with methyl 2,3,4-tri-*O*-benzyl-D- and -L-*glycero*-α-D-*gluco*-heptopyranoside (these diols have slightly different polarities on TLC in toluene–methanol, 9:1, 2 developments).[16] Compound **6′** was *different* from the L-*glycero*-D-*gluco*-isomer and had the same polarity as the D-*glycero*-D-*gluco*-derivative. The ^1H NMR spectrum of its diacetate was identical with that reported for synthetic methyl 6,7-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-*glycero*-α-D-*gluco*-heptopyranoside **6″**. The most diagnostic resonance was that of H-6: for the D-*glycero*-derivative **6″** δ = 5.48 (ddd, *J* 2.0, 3.3 and 8.4) and for its L-*glycero*-diastereoisomer δ = 5.60 (ddd, *J* 1.4, 6.1 and 7.3).[16] The signal of H-6 in the product obtained by degradation of compound **6** resonated at δ 5.47 (ddd, *J* 2.0, 3.3 and 8.2).

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-*C*-[methyl 2,3,4-tri-*O*-benzyl-7-deoxy-D-*glycero*-α-D-*gluco*-heptopyranosid-7(*E*)-ylidene]-α-D-galactopyranose 11. This was obtained as an oil in 90% yield by reduction of enone **10** (method **C**). [HRMS: Found: *m*/*z*, 741.3239. Calc. for $C_{41}H_{50}NaO_{11}$ (M + Na^+): *m*/*z*, 741.3251]; δ_H 1.25, 1.33, 1.34 and 1.50 (2 × C*Me*$_2$), 3.38 (3 H, s, OCH_3), 3.39 (1 H, dd, $J_{3,4}$ 9.2, $J_{4,5}$ 10.2, H-4), 3.57 (1 H, dd, $J_{1,2}$ 3.6, $J_{2,3}$ 9.6, H-2), 3.80 (1 H, dd, $J_{5,6}$ 3.4, H-5), 4.02 (1 H, dd, H-3), 4.12 (1 H, dd, $J_{9,10}$ 1.9, $J_{10,11}$ 7.9, H-10), 4.26 (1 H, m, H-9), 4.28 (1 H, dd, $J_{12,13}$ 5.0, $J_{11,12}$ 2.4, H-12), 4.42 (1 H, m, H-6), 4.61 (1 H, d, H-1), 5.52 (1 H, d, H-13) and 5.85 (2 H, m, H-7, -8); δ_C 24.3 (2×), 24.8 and 25.9 (2 × C*Me*$_2$), 68.4 (C-9), 70.3 (C-12), 72.0 (C-6), 73.3 (C-5), 73.8 (C-10), 79.0 (C-4), 80.2 (C-2), 82.4 (C-3), 96.4 (C-13), 97.9 (C-1) and 130 (C-7, -8). Configuration of this product was determined by chemical degradation to compound **6′** (analogously as for **6**). Thus, from 108 mg (0.15 mmol) of the allylic alcohol **11**, 64 mg of diol **6′** (0.13 mmol, 86%) were obtained.

(7*R*/*S*)-3,8-Di-*O*-benzyl-5,6-dideoxy-1,2:9,10:11,12-tri-*O*-isopropylidene-D-*arabino*-α-D-*gluco*-dodec-5(*E*)-eno-1,4-furanose 16. This was obtained as an oil in 85% yield by reduction of enone **15** (method **C**) [HRMS: Found: *m*/*z*, 649.2970. Calc. for $C_{35}H_{46}NaO_{10}$ (M + Na^+): *m*/*z*, 649.2989]. In the ^1H NMR spectrum of a crude mixture all signals were duplicated, confirming a mixture of stereoisomers (7*R*/*S*) had been obtained. Acetylation of this mixture (Ac_2O–Py–DMAP) afforded a crude mixture of acetates in which all signals were also duplicated. Integration of a *CH*$_3$CO resonance (δ_H 2.04 and 1.83 for both isomers) indicated a ~3:2 proportion of isomers.

Methyl 2,3,4,6-tetra-*O*-benzyl-7,8-dideoxy-9,10:11,12-di-*O*-isopropylidene-D-*gluco*-α-D-*gluco*-dodec-7(*E*)-eno-1,5-pyranoside 7. This was obtained as an oil in 95% yield from the alcohol **6** according to method **D** [HRMS: Found: *m*/*z*, 803.3816. Calc. for $C_{47}H_{56}NaO_{10}$ (M + Na^+): *m*/*z*, 803.3772].

Methyl 2,3,4,6-tetra-*O*-benzyl-9,10:11,12-di-*O*-isopropylidene-D-*erythro*-L-*manno*-α-D-*gluco*- and -D-*erythro*-L-*ido*-α-D-*gluco*-dodeca-1,5-pyranoside 8a and 8b. Osmylation of ene **7** (3.9 g, 5 mmol) according to method **E** gave title compounds **8a** (2.85 g, 3.5 mmol, 70%) and **8b** (115 mg, 0.14 mmol, 2.8%).

*Compound **8a**.*—[HRMS: Found: *m*/*z*, 837.3821. Calc. for $C_{47}H_{58}NaO_{12}$ (M + Na^+): *m*/*z*, 837.3826]; δ_H 1.26, 1.31, 1.33 and 1.39 (2 × C*Me*$_2$), 3.39 (3 H, s, OCH_3), 3.52 (1 H, dd, $J_{1,2}$ 3.5, $J_{2,3}$ 9.6, H-2), 3.72 (1 H, dd, $J_{3,4}$ 9.2, H-4), 3.87 (1 H, H-7), 3.95 (2 H, m, H-5 and -12), 4.03 (1 H, dd, H-3), 4.10 (2 H, H-8 and H′-12), 4.15 (1 H, H-6) and 4.64 (1 H, d, H-1); δ_C 25.1, 26.3, 26.8 and 26.9 (2 × C*Me*$_2$), 55.0 (OCH_3), 67.7 (C-12), 69.6, 70.6 (C-6), 70.8, 76.5, 78.8 (C-5), 80.1 (C-2), 80.2, 80.7 (C-4), 82.8 (C-3), 97.8 (C-1) and 109.4 and 110.1 (2 × *C*Me$_2$). The CD spectrum of compound **8a** with [$Mo_2(OAc)_4$] showed a positive Cotton effect (see Fig. 1), thus confirming that the configuration of the diol grouping is opposite to that in diacetone-D-mannitol and the same as that assigned on the basis of Kishi's rule.

*Compound **8b**.*—[MS: 837 (M + Na^+)]; selected data δ_H 1.33 (2 × C*Me*$_2$), 1.34, 1.35, 1.41, 3.52 (1 H, dd, $J_{1,2}$ 3.5, $J_{2,3}$ 9.7, H-2), 3.83 (1 H, dd, $J_{3,4}$ 8.7, $J_{4,5}$ 9.7, H-4), 4.06 (1 H, d, H-3) and 4.60 (1 H, d, H-1); δ_C 25.1 (2 × C*Me*$_2$), 26.4, 27.0, 27.1, 55.4 (OCH_3), 67.6 (C-12), 79.9 (C-2), 81.0 (C-4) and 97.9 (C-1).

(7*R*)-1,2:3,4-Di-*O*-isopropylidene-7-*C*-(methyl 2,3,4-tri-*O*-benzyl-α-D-*gluco*-hexopyranosid-6-yl)-L-*threo*-α-D-*galacto*-heptopyranose 12. Osmylation of ene **11** (1.5 g, 2.02 mmol) according to method **E** gave triol **12** (1.07 g, 1.42 mmol, 70.3%) as a single stereoisomer [HRMS: Found: *m*/*z*, 775.3349. Calc. for $C_{41}H_{52}NaO_{13}$ (M + Na^+): *m*/*z*, 775.3306]; δ_H 1.30, 1.36, 1.41 and 1.48 (2 × C*Me*$_2$), 3.39 (s, 3 H, OCH_3), 3.51 (1 H, dd, $J_{1,2}$ 3.6, $J_{2,3}$ 9.6, H-2), 3.73 (1 H, t, $J_{3,4} = J_{4,5} = 9.4$, H-4), 3.85 (1 H, dd, $J_{5,6}$ 5.4, $J_{4,5}$ 9.7, H-5), 3.92 (1 H, dd, $J_{6,7}$ 9.1, $J_{7,8}$ 1.4, H-7), 4.02 (1 H, dd, H-3), 4.06 (1 H, dd, H-6), 4.28 (1 H, dd, $J_{11,12}$ 2.4, $J_{12,13}$ 4.9, H-12), 4.45 (1 H, dd, $J_{10,11}$ 8.1, H-10), 4.61 (1 H, d, H-1) and 4.61 (1 H, dd, H-11); δ_C 24.3, 25.1, 25.9 and 26.0 (2 × C*Me*$_2$), 55.8 (OCH_3), 66.5 (C-7), 69.0, 69.3 (C-6), 69.4 (C-5), 70.6 (C-11), 70.8 (C-10), 70.9 (C-12), 75.6, 79.8 (C-4), 80.1 (C-2), 82.2 (C-3), 96.3 (C-13), 98.0 (C-1) and 108.8 and 109.1 (2 × *C*Me$_2$).

Assignment of the configuration of triol 12. Alcohol **11** was benzylated according to method **D** and the resulting ether **11′**

was osmylated (according to method **E**) to give a single stereoisomer **12′** (in 90% yield). The CD spectrum of the complex of diol **12′** with $[Mo_2(OAc)_4]$ showed a positive Cotton effect [$\lambda_{max}(\Delta\varepsilon)$]: 278 (−0.033) and 328.5 (0.205). Benzylation of this diol (method **D**) afforded hexa-*O*-benzyl derivative **12″**, *m*/*z* 1045 ($M + Na^+$). Selected data δ_H 1.06, 1.14, 1.24 and 1.40 ($2 \times CMe_2$), 3.14 (OCH_3) and 5.41 (1 H, d, $J_{1,2}$ 5.0, H-1); δ_C 24.5 (double intensity), 25.5 and 26.0 ($2 \times CMe_2$), 54.9 (OCH_3), 65.6, 69.7, 70.2, 70.8 and 70.9 ($5 \times CH$), 72.0, 72.8, 73.1, 73.8, 74.9 and 75.3 ($6 \times CH_2$), 76.6, 76.8, 78.4 (double intensity), 79.8, 82.6, 96.6 and 97.9 ($8 \times CH$) and 108.0 and 108.5 ($2 \times CMe_2$).

NMR spectra of this compound were identical with the spectra of the product prepared by per-benzylation of triol **12**.

D-*erythro*-L-*manno*-D-*gluco*- (= L-*threo*-L-*allo*-D-*manno*)-dodecitol 23. Benzylation of diol **8a** (7.7 g, 9.46 mmol) according to method **D** gave methyl 2,3,4,6,7,8-hexa-*O*-benzyl-9,10:11,12-di-*O*-isopropylidene-D-*erythro*-L-*manno*-α-D-*gluco*-dodeco-1,5-pyranoside **17**, which was hydrolysed (in refluxing methanol containing 5% of 50% aq. sulfuric acid) to give methyl 2,3,4,6,7,8-hexa-*O*-benzyl-D-*erythro*-L-*manno*-α-D-*gluco*-dodeco-1,5-pyranoside **18** (6.8 g, 79% overall yield from diol **8a**), *m*/*z* 927 ($M + Na^+$).

Benzylation of this tetraol (method **D**) led to methyl 2,3,4,6,7,8,9,10,11,12-deca-*O*-benzyl-D-*erythro*-L-*manno*-α-D-*gluco*-dodeco-1,5-pyranoside (**19**, 8 g, 84%), *m*/*z* 1297 ($M + Na^+$); δ_C(50 MHz; DEPT 135°) 54.9 (OCH_3), 69.4 (C-12), 69.7 (CH), 71.6, 71.9, 72.0, 72.4, 73.2 (triple intensity), 73.9, 74.4 and 75.2 ($10 \times OCH_2Ph$), 77.1, 77.5, 78.0 (double intensity), 78.5, 78.7, 79.3, 79.9 and 82.7 ($9 \times CH$) and 97.7 (C-1).

This product (7.5 g, 5.88 mmol) was dissolved in ethyl acetate (45 cm^3) containing acetic anhydride (90 cm^3) to which conc. sulfuric acid (30 drops) was added and the mixture was stirred at rt for 20 min. More ethyl acetate (300 cm^3) was added, the mixture was washed successively with water (2×200 cm^3), aq. sodium hydroxide (to pH ~8) and water, and dried. Evaporation of the mixture afforded acetate **20** as a mixture of α/β anomers [δ_H(200 MHz) 5.61 [d, $J_{1,2}$ 8.1, H-1(β)] and 6.27 [d, $J_{1,2}$ 3.6, H-1(α)] (α : β = 7 : 1).

Compound **20** was dissolved in THF (50 cm^3) and reduced with an excess of $LiAlH_4$ (1.3 g, 35.3 mmol) for 2 h at rt to yield 2,3,4,6,7,8,9,10,11,12-deca-*O*-benzyl-D-*erythro*-L-*manno*-D-*gluco*-dodecitol **21** as an oil, which was contaminated (TLC hexane–ethyl acetate 1 : 1) with a more polar product assumed to be partially debenzylated derivative (one or more benzyl groups were probably removed under the condition of acetolysis). This crude mixture was benzylated according to method **D** to afford fully protected derivative **22** (5.8 g, 69% overall yield from glycoside **19**), *m*/*z* 1466 ($M + 1 + Na^+$) and 1465 ($M + Na^+$); δ_C(50 MHz; DEPT 135°) 70.0, 71.5, 71.7, 71.9, 72.0, 72.4, 72.9, 73.0, 73.1, 73.4, 74.0, 74.4 and 74.6 (double intensity) ($14 \times CH_2$) and 77.2, 78.25, 78.31, 78.8, 79.0, 79.2, 79.4, 80.2, 80.4 and 80.7 ($10 \times CH$).

This compound (4.0 g, 2.77 mmol) was dissolved in a mixture of diethyl ether (30 cm^3) and ethyl alcohol (120 cm^3) and hydrogenated with vigorous stirring over 10% Pd/C (~0.5 g) for 72 h. After that time TLC indicated the disappearance of the starting material and formation of a new product that was not mobile even in ethyl acetate containing 5% methanol and 2% water. The mixture was filtered through Celite and the filter was washed with methanol (~0.5 cm^3); concentration of the combined filtrate and washings gave mostly an oily residue that contained only traces of desired product. The Celite layer was then subsequently washed with boiling water, which was concentrated to give crude dodecaol **23**. Recrystallisation of the residue from aq. acetone afforded the title product as fine crystals (0.54 g, 54%), mp 213–223 °C; $[\alpha]_D$ + 3 (*c* 2.0, DMSO); δ_C[50 MHz; D_2O; DEPT 135° (dioxane: δ_C 66.5 was used as internal standard)] 62.4 and 63.3 ($2 \times CH_2$) and 68.1, 68.6, 69.2 (double intensity), 70.1, 70.9, 71.0, 71.7, 72.1 and 72.9 ($10 \times CH$).

Acetylation of a part of this material (50 mg, 0.138 mmol) with Ac_2O–Py–DMAP overnight afforded per-acetate **24** (98.8 mg, 83%), δ_C(50 MHz; $CDCl_3$) 61.5 and 61.8 ($2 \times CH_2OAc$), 66.6, 66.7, 67.2, 67.7, 68.1 (double intensity), 68.7, 68.8, 69.3 and 69.6 ($10 \times CHOAc$), 169.20 (double intensity) and 169.36, 169.56, 169.65, 169.73 (triple intensity), 169.82, 169.90, 170.07 and 170.37 ($12 \times COCH_3$) [Found: C, 50.4; H, 6.4. $C_{36}H_{50}O_{24}$ (866.77) requires C, 49.89; H, 5.81%]; *m*/*z* 867 (45%, $M + H^+$), 807 (100, $M + H^+ - AcOH$); after addition of NaOAc, *m*/*z* 889 (100%, $M + Na^+$) [Found: *m*/*z*, 889.26093. Calc. for $C_{36}H_{50}NaO_{24}$ ($M + Na^+$): *m*/*z*, 889.25897].

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