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Application of Stabilized Sugar-Derived Phosphoranes in the Synthesis of Higher Carbon Monosaccharides. First Synthesis of a C_{21}-Dialdose[1]

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Abstract: C_{21} Monosaccharide precursors **11** and **12** were synthesized by a coupling of a C_{12} aldehyde **1** with C_9 stabilized phosphoranes **2** and **3** respectively. The "smaller" C_{19} sugar **13** was prepared from a C_{12} aldehyde **1** and C_7 phosphorane **4**. All reactions with phosphoranes were performed under high pressure (13 kbar). No reaction was observed under normal pressure even at high temperature (*ca* 140°C). The synthesis of C_{19} and C_{21} monosaccharides was accomplished also under normal pressure when phosphoranes were replaced with more nucleophilic phosphonates; however, partially eliminated products (M - benzyl alcohol) were isolated together with higher sugar enones **11**, **12** and **13**. Sugar α-hydroxy-aldehydes (**14**) did not react with a C_9-phosphorane even under 13 kbar pressure, although reaction with a shorter analog - C_7 phosphorane **15** proceeded under normal pressure in boiling benzene. © 1998 Elsevier Science Ltd. All rights reserved.

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 due to the fact that they are components of antibiotics[2], they may-be used as non-metabolized analogs of disaccharides, and, what is also important, the synthesis of such complicated molecules presents a real challenge for organic chemists[3]. Such compounds, especially those being derivatives of higher alditols, might have unique conformational and biological properties, and, moreover, specific complexation with chiral organic cations might also be expected.

In the past few years we proposed a general method for the preparation of higher sugar dialdoses by coupling of terminal *C*-atoms of two sugar sub-units *via* the C_n bridge. This was accomplished by reaction of sugar-derived stabilized phosphoranes[4], sugar-vinyl[5], and propargyl[5c,6] anions and sugar allyltin derivatives[7] with aldehydes, what resulted in formation of C_{12} - C_{15} monosaccharides. The aldol condensation between two sugar aldehydes also yielded a higher monosacharide[8].

In this paper we would like to present an application of the Wittig methodology (which worked best in

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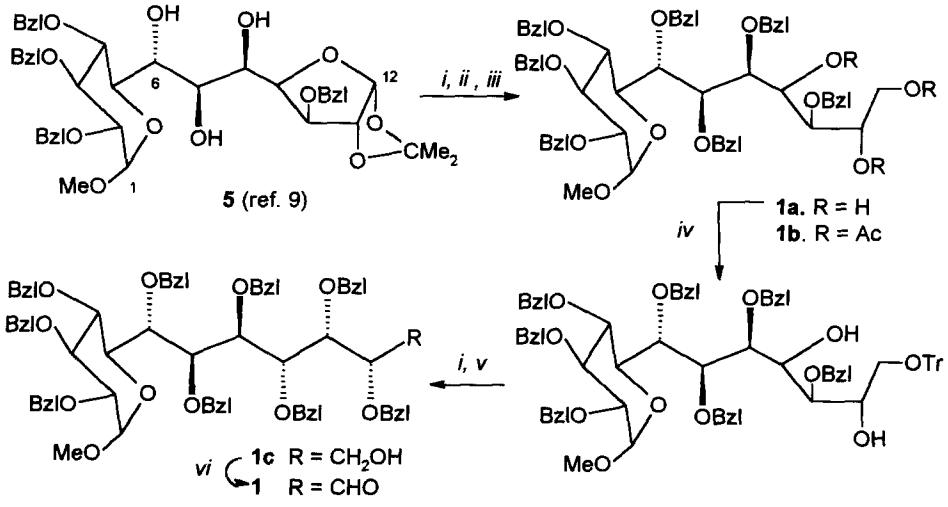
our hands) for the preparation of derivatives of C_{19} and C_{21}- monosaccharides. The scope and limitation of this approach will also be discussed.

RESULTS AND DISCUSSION

Synthesis of C_{19} - C_{21} higher carbon dialdoses was planned by a coupling of a C_{12} aldehyde **1** (Scheme 1) with various stabilized sugar-derived phosphoranes (**2**, **3**, and **4**; Scheme 2). Aldehyde **1** is readily available from higher-sugar triol **5**[9] by *a.* benzylation of three secondary hydroxyl groups, *b.* hydrolysis of 11,12-isopropylidene grouping, *c.* reduction of resulting hemiacetal with lithium aluminum hydride in boiling THF (surprisingly, under less drastic conditions no reduction was observed), *d.* tritylation of the primary hydroxyl group, *e.* protection of remaining secondary OH groups as benzyl ethers, *f.* de-tritylation, and finally *g.* oxidation of the CH_2OH (C12) with a Swern reagent[10] (Scheme 1).



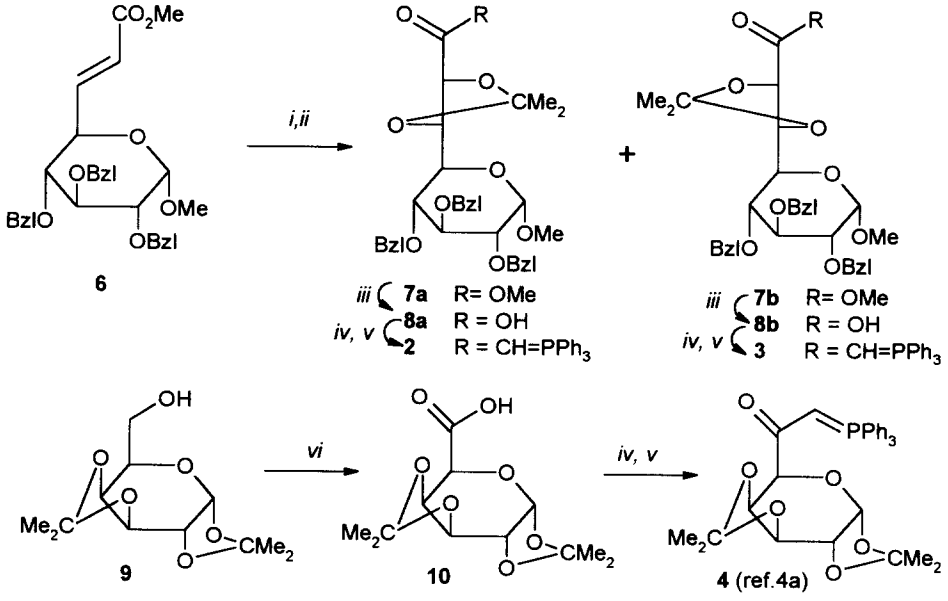
Scheme 1. *i.* BzlBr/NaH/DMF; *ii.* 50% aq. TFA/THF reflux 2 h; *iii.* $LiAlH_4$, THF, reflux, 2h; *iv.* TrCl/Et_3N/CH_2Cl_2; *v.* *p*-TsOH/MeOH; *vi.* Swern oxidation.

Phosphoranes **2-4** were prepared from appropriate uronic acids by reaction with N,N-carbonyl di-imidazole followed by treatment with $Ph_3P{=}CH_2$ according to a general method described for the preparation of C_{12} monosaccharides[4] (Scheme 2).

α,β-Unsaturated ester **6** was *cis*-hydroxylated to give a mixture of two well separable diastereoisomers[11] (in a 6:1 ratio) which were protected as acetonides **7a** and **7b**. Hydrolysis of these esters with sodium hydroxide in THF/water afforded free acids **8a** and **8b** which were treated with N,N'-carbonyl di-imidazole and next with methylenetriphenylphosphorane ($Ph_3P{=}CH_2$) to yield ylides **2** and **3** respectively. Ylide

4[4a] was prepared from diacetonogalactose (**9**) *via* oxidation to an acid **10** with the Jones reagent[12] and subsequent treatment with im_2CO followed by $Ph_3P{=}CH_2$.

Reaction of the above prepared ylides with C_{12}-aldehyde **1** under standard conditions was unsuccessful; both starting materials (ylide and aldehyde) **remained unchanged even at 140°C** (in boiling xylene), although the "shorter" analogs (C_7 ylide and C_6 aldehyde) usually reacted at room (or slightly elevated) temperature[4].



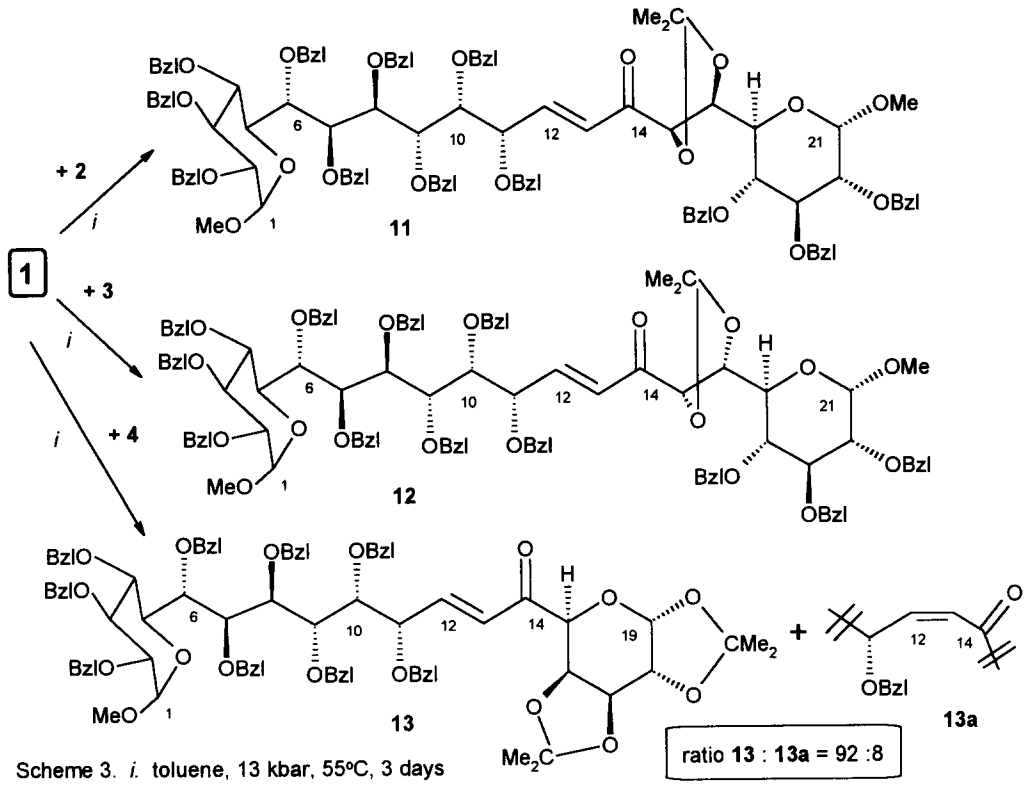
Scheme 2. *i.* ref. 11; *ii.* acetone, $Me_2C(OMe)_2$, H^+; *iii.* NaOH, water; *iv.* im_2CO, THF -78 °C; *v.* $Ph_3P{=}CH_2$, THF, -78 °C; *vi.* Jones oxidation

It should be pointed out that both components were ***extremely unreactive***; aldehyde **1** did not react even with $Ph_3P{=}CHCO_2Me$ and ylides **2** and **3** with simplest aldehydes (*e.g.* CH_3CHO or PhCHO) under atmospheric pressure.

There are two possible solutions to our problem: *a.* application of a high pressure technique and *b.* replacement of phosphoranes **2-4** with more nucleophilic phosphonates.

Reaction of C_{12} aldehydes with C_7 - C_9 ylides under high pressure.

The Wittig reaction has the negative volume of activation ($\Delta V^{\ddagger}$)[13] and, therefore, should be accelerated by the pressure. Indeed, reaction of phosphoranes **2-4** with aldehyde **1** under 13 kbar pressure at 55°C for three days resulted in a clean formation of appropriate α,β-unsaturated higher sugar precursors **11**, **12**, and **13**. Pure *trans* isomers of C_{21} higher sugar precursors (**11** and **12**) were formed in the reaction of **1** with C_9 ylides (**2** and **3**), while analogous reaction of **1** with a C_7 phosphorane gave a 92:8 mixture of *trans*:*cis* isomers (**13** and **13a** respectively, Scheme 3).



Scheme 3. *i.* toluene, 13 kbar, 55°C, 3 days

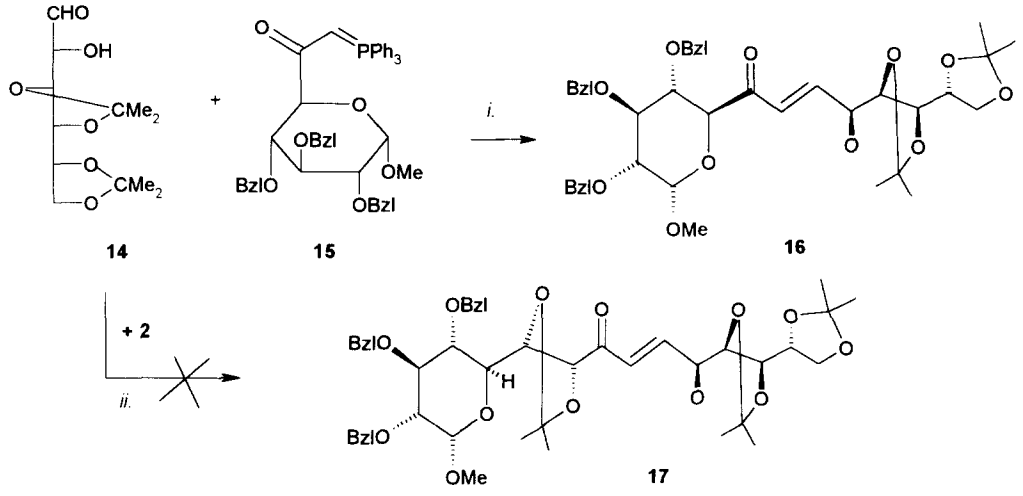
Structure of these higher sugar precursors were assigned on the basis of the ^{1}H NMR and mass spectra.

In the mass spectrum (sodium acetate was used as a source of Na^+ ion) of **11** three high-mass peaks that proved the structure of coupling product were seen at: 1763 ($M+Na^+$), 1764 ($M+1+Na^+$), and 1765 ($M+2+Na^+$) in the ratio 8:10:6; this agreed well with calculated isotopic pattern for $C_{110}H_{116}O_{19}$. In the ^{1}H NMR spectrum of **11** signals of the enone system (H-12, H-13) were observed at δ 6.98 and 6.80 ppm and the large coupling constant ($J_{12,13}$ = 15.9 Hz) pointed unambiguously at the *trans* junction. Similar data were found for isomeric C_{21} enone **12** (*see* Experimental). In the mass spectrum of C_{19} enone **13** presence of the peak at 1459 ($M+Na^+$) proved the coupling of both fragments, C_{12} (aldehyde **1**) and C_7 (ylide **4**). In the ^{1}H NMR spectrum of **13** two geometrical isomers were seen: *trans*-**13** (signals of H-12 and H-13, δ 6.89 and 6.71, J = 15.9 Hz) and *cis*-**11a** (δ 6.60 and 6.30 J = 11.7 Hz) in the ratio 92:8.

This high pressure Wittig methodology cannot be, however, extended to reaction with sugar-derived α-hydroxy aldehydes (*see* Scheme 4).

Readily available 3,4:5,6-di-*O*-isopropylidene-D-glucose[14] (**14**) reacted easily under normal pressure with a C_7 ylide **15** (although at elevated temperature) to afford higher sugar enone **16** but, the same aldehyde

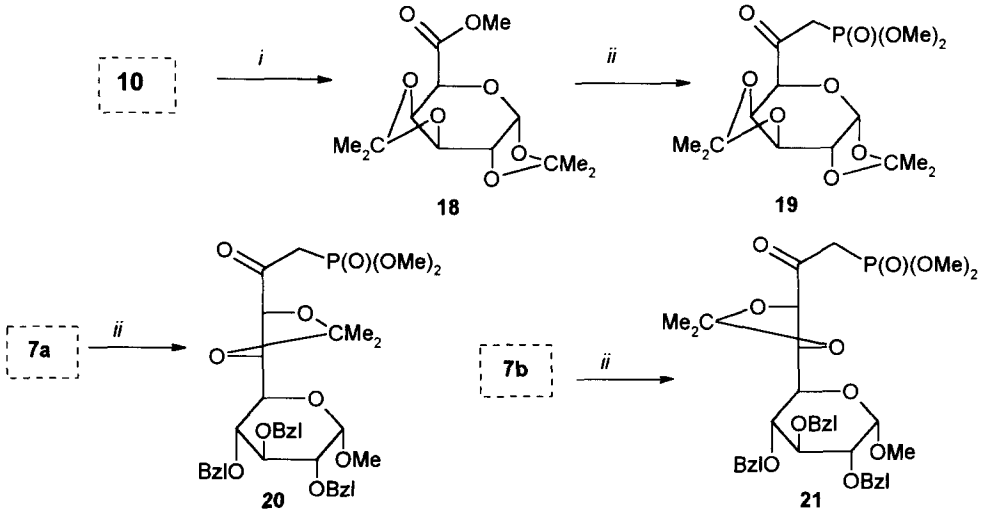
did not react with a C_9 ylide **2** even under high pressure (13 kbar, Scheme 4). No even traces of higher sugar enone **17** were found in the post-reaction mixture. We do not have the explanation of this phenomenon yet.



Scheme 4. *i.* benzene, reflux, 3 days; *ii.* toluene, 13 kbar, 55°C, 3 days

Preparation of C_7 - C_9 phosphonates and their reaction with sugar aldehydes

The alternative to the classical Wittig reaction is the application of more nucleophilic phosphonates (Wittig-Horner-Emmons modification[15]). For preparation of sugar phosphonates the method of Yonemitsu and co-workers[16] involving reaction of methyl esters with trimethyl-phosphonoacetate was applied (Scheme 5).

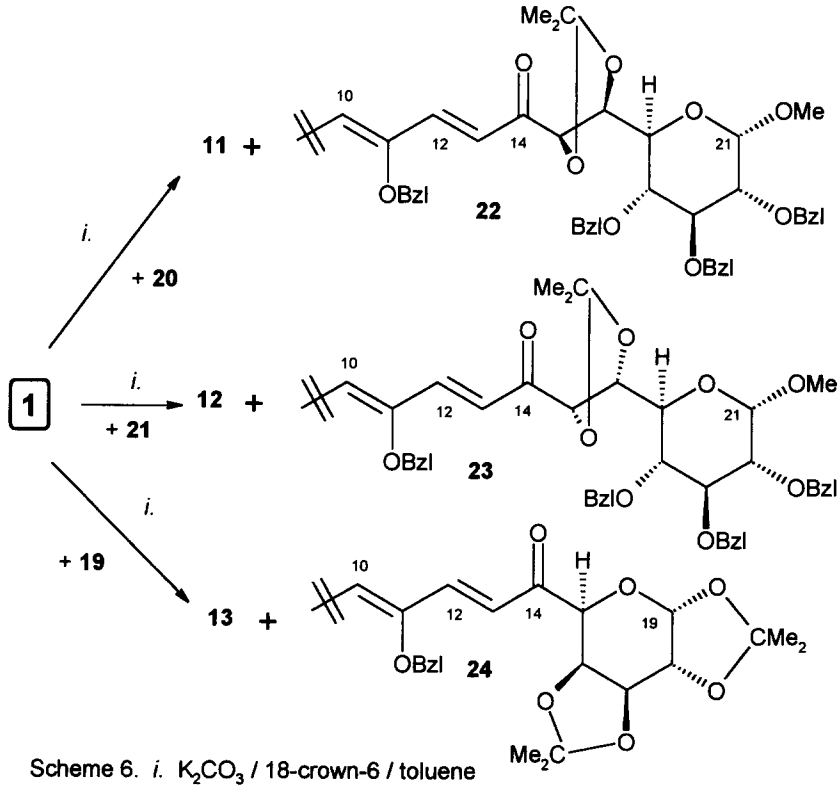


Scheme 5. *i.* CH_2N_2; *ii.* CH_3-P(O)$(OMe)_2$/BuLi/THF/-78°C

Thus, addition of methylene dimethylphosphonate anion (generated from trimethyl phosphonate and BuLi in THF at -78°C) to uronic esters **18**, **7a**, and **7b** afforded appropriate sugar phosphonates **19**, **20**, and **21** in *ca* 70% yield (see Experimental).

Treatment of a toluene solution of appropriate phosphonate (**20**, **21**, and **19**) and aldehyde **1** with potassium carbonate and 18-crown-6 afforded corresponding C_{21} and C_{19} derivatives **11**, **12**, and **13** but, in the ^{1}H NMR spectra of each crude higher sugar enone small amounts of elimination product (**22**, **23**, and **24** respectively) was detected (Scheme 6).

These eliminated products could not be isolated in pure form; their structures, however, could be deduced from the ^{1}H NMR spectra on the basis of additional signals in the vinylic region (*ca* 5-10% intensity, *see* Experimental).



Scheme 6. *i.* K_2CO_3 / 18-crown-6 / toluene

Scope and limitation of the Wittig methodology

"Medium-size" sugar phosphoranes (C_7) react with sugar aldehydes (C_6) under atmospheric pressure to afford higher sugar enones (up to C_{13}). Higher analogs (C_{19} and C_{21}) cannot be obtained under these conditions, because the C_9-phosphoranes and C_{12}-aldehydes are totally unreactive even at 140°C.

Such higher analogs can be obtained under high pressure conditions (with exception of α-hydroxy-aldehydes).

Replacement of phosphoranes with much more nucleophilic phosphonates provides desired C_{19} and C_{21} higher sugar precursors under atmospheric pressure but, small amounts of the β-eliminated compounds were observed as the side-products.

Experimental

General methods: NMR spectra were recorded with a Bruker AM 500 spectrometer for solutions in $CDCl_3$ (internal Me_4Si) unless otherwise stated. All resonances were assigned by COSY (^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. Column chromatography was performed on silica gel (Merck, 70-230 mesh). Organic solutions were dried over anhydrous magnesium sulfate. High-pressure reactions were performed in a piston-cylinder type apparatus according to ref. 17.

*Methyl 2,3,4,6,7,8,9,10,11-nona-*O*-benzyl-L-*threo*-L-*manno*-α-D-gluco-dodeca-1,5-pyranoside (**1c**).*

To a solution of 3-*O*-benzyl-1,2-*O*-isopropylidene-6-C-(methyl 2,3,4-tri-*O*-benzyl-D-*glycero*-α-D-*gluco*-hexopyranosid-6-yl)-L-*glycero*-α-D-*gluco*-hexo-1,4-furanose[9] (**5**; 3.86 g, 5 mmol) in dry DMF (50 mL) sodium hydride (50% dispersion in mineral oil, 1.0 g, 1.3 equiv.) was added and the mixture was stirred at room temperature for 30 min. Benzyl bromide (2.3 mL, 1.3 equiv.) was added and stirring was continued for another 2 h. Excess of hydride was decomposed by careful addition of water and the product was extracted with ether. Crude product was dissolved in 50% aqueous trifluoroacetic acid (50 mL) and THF (40 mL) and the mixture was boiled under reflux until tlc (hexane - ethyl acetate, 3:1) indicated disappearance of a starting material and formation of two (α,β-anomers at C12) more polar products (2 h). Toluene (100 mL) was added and trifluoroacetic acid was evaporated *in vacuum*. Organic phase was washed with water (30 mL), separated, dried and concentrated. This residue was dissolved in dry THF (50 mL) to which lithium aluminum hydride (1 g) was added and the mixture was boiled under reflux for 2h. Excess of hydride was decomposed with water and crude triol **1a** was isolated in usual manner. Small part of this material was characterized as triacetate [9,11,12-tri-*O*-acetyl-2,3,4,6,7,8-hexa-*O*-benzyl-L-*threo*-L-*manno*-α-D-*gluco*-1,5-pyranoside, (**1b**); HRMS *m/z* calcd for $C_{68}H_{74}O_{15}Na$ ($M+Na^+$) 1153.4925. Found 1153.4912; ^1H NMR (*inter alia*) δ: 5.46 (dd, *J* 3.0 and 7.3 Hz, H-9), 5.21 (m, H-11), 3.8 (dd, *J* 10.2 and 9.1 Hz, H-4), 3.99 (~t, H-3), 343 (dd, $J_{1,2}$ 3.6, $J_{2,3}$ 9.6 Hz, H-2), 3.26 (s, OMe), 1.89, 1.86, and 1.75 (3s, 3xOAc)].

Crude **1a** was dissolved in methylene chloride (50 mL) to which triethylamine (5 mL), DMAP (*ca* 50 mg) and trityl chloride (2.0 g) were added. The mixture was stirred at room temperature overnight, the crude product was benzylated (as for **5**) and the primary hydroxyl group (at C12) was de-protected with toluene-*p*-

sulfonic acid (0.5 g) in ether/methanol (20 mL, 1:1) at reflux for 3 h. Crude product - alcohol **1c** was isolated by column chromatography (hexane - ethyl acetate, 95:5 to 6:1) as an oil (3.26 g, 55% overall). MS *m/e* 1207 [$C_{76}H_{80}O_{12}Na$ ($M+Na^+$)]; ^1H NMR (*inter alia*) δ: 4.59 (d, $J_{1,2}$ 3.6 Hz, H-1), 3.97 (dd, $J_{2,3}$ 9.6, $J_{3,4}$ 9.1 Hz, H-3), 3.82 (dd, $J_{4,5}$ 10.0 Hz, H-4), 3.40 (dd, H-2), 3.29 (s, OMe), 2.06 (OH).

*Methyl 2,3,4,6,7,8,9,10,11-nona-*O*-benzyl-L-*threo*-L-*manno*-α-D-*gluco*-dodeca-1,5-pyranosid-12-ulose (1).* Aldehyde **1** was prepared by a Swern oxidation[10] of a parent alcohol; to a cooled to -78°C solution of oxalyl chloride (0.5 mL) in methylene chloride (30 mL) a solution of DMSO (3 mL) in CH_2Cl_2 (5 mL) was added carefully followed by a solution of **1c** (1.2 g, 1 mmol) in CH_2Cl_2 (5 mL). After stirring for 30 min at -78°C triethylamine (2 mL) was added, the mixture was slowly warmed to *ca* 0°C, and diluted with ether (50 mL). Water (20 mL) was added, the organic phase was separated, washed with 1N H_2SO_4, water, dried and concentrated. Crude aldehyde **1** [($C_{76}H_{78}O_{12}Na$) *m/z* 1205 (M+Na+) (the only signal >1000)] was used without further purification.

Preparation of methyl uronates

Methyl [methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-α-D-*gluco*-oct-6(E)-eno-1,5-pyranosid]uronate (**6**) was *cis*-hydroxylated with OsO_4/NMO according to Brimacombe[11] affording two diastereoisomeric diols in the ratio 6:1. Each diol (*ca 3* mmol) was separately dissolved in acetone (30 mL) to which dimethoxypropane (1.0 mL) was added followed by conc. H_2SO_4 (1 drop). After stirring overnight at room temperature toluene (50 mL) was added and acetone was evaporated *in vacuum*. Toluene solution was washed with water, dried and concentrated, and the product was purified by column chromatography (hexane - ethyl acetate, 6:1 to 3:1) to afford **7a** (from the main *cis*-hydroxylation product) or **7b**.

*Methyl (methyl 2,3,4-tri-O-benzyl-6,7-*O*-isopropylidene-L-*threo*-α-D-gluco-oct-1,5-pyranosid)-uronate* (**7a**; 1.58 g, 2.67 mmol, 89%); MS *m/z*; 615 [$C_{34}H_{40}O9Na$ ($M+Na^+$), 17%], 453 (18%), 91 (100%); ^1H NMR δ: 4.73 (H-7), 4.63 (d, $J_{1,2}$ 3.5 Hz, H-1), 4.58 (dd, $J_{5,6}$ 1.7, $J_{6,7}$ 6.6 Hz, H-6), 4.05 (dd, $J_{2,3}$ 9.6, $J_{3,4}$ 8.9 Hz, H-3), 3.98 (dd, $J_{4,5}$ 10.2 Hz, H-5), 3.64 (dd, H-4), 3.74 (s, CO_2Me), 3.54 (dd, H-2), 3.39 (OMe), 1.53 and 1.42 (2s, CMe_2).

*Methyl (methyl 2,3,4-tri-*O*-benzyl-6,7-*O*-isopropylidene-D-*threo*-α-D-*gluco*-oct-1,5-pyranosid)-uronate (7b)* was prepared from the minor product of *cis*-hydroxylation and was used without purification for the preparation of phosphonate **21**. HRMS *m/z* calcd for $C_{34}H_{40}O9Na$ ($M+Na^+$) 615.2570. Found 615.2528.

*Methyl 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranuronate (18).* 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranuronic acid (**10**) was obtained by a Jones oxidation of diacetonogalactose (**9**); this method is much more convenient than oxidation with potassium permanganate reported in literature[18]. Thus, alcohol **9** (6 g, 23 mmol) was dissolved in acetone (100 mL) and treated with the Jones reagent[12] (*ca* 30 mmol) until tlc (hexane - ethyl acetate, 1:1) indicated disappearance of the starting material (6 h). Toluene (200 mL) was

added and most of acetone was evaporated under reduced pressure. The organic phase was washed thoroughly with water, dried, and concentrated to give **10** (5.1 g, 18.6 mmol, 81%, m.p. 154°C lit.[18] 157°C), esterification of which with CH_2N_2 afforded methyl ester **18**.

Preparation of sugar-derived stabilized phosphoranes

Synthesis of the acids. To a solution of the ester (**7a** or **8a**, *ca* 1.0 g) in THF (10 mL) 3% aqueous sodium hydroxide (5 mL) was added and the mixture was stirred for 90 min at room temperature. Toluene (50 mL) was added and the mixture was acidified with 10% sulfuric acid. Organic phase was separated, washed with water thrice, dried and concentrated and the crude product (*ca* 0.9 g each) - methyl 2,3,4-tri-*O*-benzyl-6,7-*O*-isopropylidene-L-*threo*- and D-*threo*-α-D-*gluco*-oct-1,5-pyranosiduronic acid (**8a** and **8b** respectively) was used without further purification.

Reaction of the acid with im_2CO and $Ph_3P{=}CH_2$. To a solution of the uronic acid (1 mmol) in THF (10 mL) N,N'-carbonyl-diimidazole (1.2 equiv.) was added, the mixture was stirred at room temperature for 30 min, and this solution of a crude imidazolide was added with exclusion of a moisture to a solution of methylenetriphenylphosphorane (generated from 4 equiv. of Ph_3PCH_3I and 3.9 equiv. of 2.5M BuLi at -78°C for 2 h) in dry THF (50 mL). The mixture was stirred for 1 h at -78°C, warmed slowly to 10°C, and diluted with benzene (100 mL). Water was added, the organic phase was separated, washed with water, dried and concentrated, and the crude ylide was isolated by column chromatography (hexane - ethyl acetate, 4:1 to 1:4).

*(Methyl 2,3,4-tri-*O*-benzyl-6,7-*O*-isopropylidene-L-*threo*-α-D-gluco-oct-1,5-pyranosid-8-uronyl)-(triphenylphosphoranylidene)methane* (**2**; obtained from **8a** in 55% yield). HRMS calcd for $C_{52}H_{54}O_8P$ ($M+H^+$): 837.3556. Found: 837.3556. The main peak in ms (303) was assigned to fragment $(Ph_3P{=}CH{-}C{=}O)^+$. ^1H NMR δ: 3.97 (dd, $J_{3,4}$ 9.0, $J_{2,3}$ 9.6 Hz, H-3), 3.55 (dd, $J_{1,2}$ 3.6 Hz, H-2), 3.39 (H-4), 3.33 (OMe); the vinyl proton could not be seen because of overlap with aromatic signals.

*(Methyl 2,3,4-tri-*O*-benzyl-6,7-*O*-isopropylidene-D-*threo*-α-D-gluco-oct-1,5-pyranosid-8-uronyl)-(triphenylphosphoranylidene)methane* (**3**; obtained from **8b** in 50% yield). HRMS calcd for $C_{52}H_{54}O_8P$ ($M+H^+$): 837.3556. Found: 837.3547.

*(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranuronyl)-(triphenylphosphoranylidene)methane* (**4**) was obtained from diacetonogalacturonic acid **10** according to *ref. 4a.*

Reaction of sugar-derived phoshoranes with aldehydes under normal pressure

*Methyl 2,3,4-tri-*O*-benzyl-7,8-dideoxy-10,11:12,13-di-*O*-isopropylidene-6-ulos-D-*gluco-α-D-gluco-*tridecos-8(E)-1,5-pyranoside* (**16**). A solution of 3,4:5,6-di-*O*-isopropylidene-D-glucose[14] (**14**; 260 mg, 1 mmol) and ylide **15**[4b] (810 mg, 1.1 mmol) in dry benzene was boiled under reflux for 20 h. After this time tlc (hexane - ethyl acetate, 2:1) indicated disappearance of **14** and formation of a new product (visible under UV light) which was isolated by column chromatography (hexane - ethyl acetate, 4:1 to 2:1). Enone **16** (510 mg,

0.71 mmol, 71%); HRMS calcd for $C_{41}H_{50}O_{11}Na$ ($M+Na^+$): 741.3251. Found: 741.3260; ^1H NMR δ: 7.13 (dd, $J_{7,8}$ 15.7, $J_{8,9}$ 3.7 Hz, H-8), 6.69 (dd, $J_{7,9}$ 2.0 Hz, H-7), 4.61 (d, $J_{1,2}$ 3.5, H-1), 4.51 (m, H-9), 4.36 (d, $J_{4,5}$ 9.8, H-5), 4.14 (dd, $J_{13,13'}$ 8.8, $J_{12,13}$ 6.2 Hz, H-13), 3.94 (dd, $J_{12,13}$ 4.8 Hz, H-13'), 3.73 (t, J 8.3 Hz, H-10), 3.55 (dd, $J_{2,3}$ 9.7 Hz, H-2), 3.69 (dd, $J_{3,4}$ 9.3 Hz, H-4), 3.41 (s, CO_2Me), 1.39, 1.38, 1.35 and 1.33 (4s, 2xCMe_2); ^{13}C NMR δ: 146.8 (C-8), 127.0 (C-7), 98.8 (C-1), 79.4 (C-2), 79.2 (C-4), 73.1 (C-5), 67.8 (C-13), 55.8 (OMe), 26.9, 26.7, 26.4, and 25.0 (2x$C\underline{Me}_2$).

High pressure reaction of sugar phosphoranes with C_{12} aldehydes

A solution of aldehyde **1** (*ca* 30 mg) and appropriate ylide (1.5 equiv.) in toluene (2 mL) was placed in a piston-cylinder type apparatus[17] and kept at 13 kbar hydrostatic pressure at 55°C. After three days tlc (hexane - ethyl acetate, 4:1) indicated disappearance of the starting aldehyde and formation of a new, more polar product that was visible under UV light. Crude enone was purified by column chromatography (hexane - ethyl acetate, 6:1 to 4:1) to yield **11** (60% from **2**), **12** (55% from **3**), and **13** (53% from **4**).

Methyl 2,3,4,6,7,8,9,10,11-nona-O-*benzyl-12-deoxy-12*-C-*[methyl 2,3,4-tri*-O-*benzyl-9(E)-deoxy-6,7*-O-*isopropylidene-L*-threo-*α-D*-gluco-*nonapyranosid-8-ulos-9-ylidene]-L*-threo-*L*-manno-*α-D*-gluco-*dodeca-1,5-pyranoside (11)*; *m/z*: 1763 ($M+Na^+$), 1764 ($M+1+Na^+$), and 1765 ($M+2+Na^+$) in the ratio 8:10:6. ^1H NMR δ: 6.98 (dd, $J_{12,13}$ 15.9, $J_{11,12}$ 5.9 Hz, H-12), 6.70 (dd, $J_{11,13}$ 1.2 Hz, H-13), 3.36 and 3.27 (2s, 2 x OMe).

Methyl 2,3,4,6,7,8,9,10,11-nona-O-*benzyl-12-deoxy-12*-C-*[methyl 2,3,4-tri*-O-*benzyl-9(E)-deoxy-6,7*-O-*isopropylidene-D*-threo-*α-D*-gluco-*nonapyranosid-8-ulos-9-ylidene]-L*-threo-*L*-manno-*α-D*-gluco-*dodeca-1,5-pyranoside (12)*; *m/z*: 1763 ($M+Na^+$), ^1H NMR δ: 6.97 (dd, $J_{12,13}$ 15.9, $J_{11,12}$ 5.2 Hz, H-12), 6.80 (dd, $J_{11,13}$ 1.3 Hz, H-13), 3.38 and 3.28 (2s, 2 x OMe).

Methyl 2,3,4,6,7,8,9,10,11-nona-O-*benzyl-12-deoxy-12*-C-*[7(E-deoxy)-1,2:3,4-di-O-isopropylidene-α-D*-galacto-*heptopyranos-6-ulos-7-ylidene]-L*-threo-*L*-manno-*α-D*-gluco-*dodeca-1,5-pyranoside (13)* (unseparable mixture of *trans:cis* isomers in the ratio 92:8, 53%); *m/z*: 1459 ($M+Na^+$), ^1H NMR major (*trans*) isomer δ: 6.89 (dd, $J_{12,13}$ 15.9, $J_{11,12}$ 6.3 Hz, H-12), 6.71 (dd, $J_{11,13}$ 1.1 Hz, H-13), 5.64 (d, $J_{18,19}$ 5.0 Hz, H-19) 3.29 (s, OMe); minor isomer δ: 6.60 (dd, $J_{12,13}$ 15197 $J_{11,13}$ 0.8 Hz, H-13), 6.30 (dd, $J_{11,12}$ 8.6 Hz, H-12), 5.67 (d, $J_{18,19}$ 4.8 Hz, H-19).

Preparation of sugar phosphonates

A slightly modified literature procedure[16] was used. To a cooled to -78°C solution of trimethyl phosphonate (1.95 mmol, 0.21 mL) in dry THF (10 mL) under an argon atmosphere a 2.5M solution of butyllithium (0.75 mL, 1.9 mmol) was added by a syringe and the mixture was stirred for 15 min. Appropriate methyl uronate (0.65 mmol in 3 mL of THF) was added dropwise and the mixture was stirred until tlc (hexane - ethyl acetate, 1:1) showed disappearance of a starting material and formation of a new much more polar

product (*ca* 30 min). Aqueous ammonium chloride (5 mL) was added, the product was extracted with ethyl acetate and purified by column chromatography (hexane - ethyl acetate, 4:1 to 1:3).

*Dimethyl (methyl 2,3,4-tri-*O*-benzyl-6,7-*O*-isopropylidene-L-*threo*-α-D-*gluco*-nona-1,5-pyranosid-8-ulos-9-yl) phosphonate* (**20**; 70% yield): HRMS calcd for $C_{36}H_{45}O_{11}PNa$ ($M+Na^+$): 707.2597. Found: 707.2593. ^1H NMR δ: 4.71 (H-7), 4.62 (d, $J_{1,2}$ 3.5 Hz, H-1), 4.58 (dd, $J_{5,6}$ 1.7, $J_{6,7}$ 6.2 Hz, H-6), 4.03 (dd, $J_{2,3}$ 9.6, $J_{3,4}$ 8.9 Hz, H-3), 3.93 (dd, $J_{4,5}$ 10.2 Hz, H-5), 3.73 and 3.71 (2d, $J_{P,H}$ 11.3 Hz $P(OMe)_2$, 3.59 (dd, H-4), 3.52 (dd, H-2), 3.39 (OMe), 3.61 and 3.13 (AB pattern of CH_2, $J_{9,9'}$ 14.2, $J_{P,H}$ 22.4 Hz), 1.51 and 1.34 (CMe_2).

*Dimethyl (methyl 2,3,4-tri-*O*-benzyl-6,7-*O*-isopropylidene-D-*threo*-α-D-*gluco*-nona-1,5-pyranosid-8-ulos-9-yl) phosphonate* (**21**; 68% yield): HRMS calcd for $C_{36}H_{45}O_{11}PNa$ ($M+Na^+$): 707.2597. Found: 707.2599. ^1H NMR δ: 4.66 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 4.57 and 4.40 (AB pattern of H6-H7, $J_{5,6}$ 1.9, $J_{6,7}$ 8.1 Hz), 3.98 (dd, 1H, $J_{2,3}$ 9.5, $J_{3,4}$ 9.0 Hz, H-3), 3.93 (dd, 1H, $J_{4,5}$ 10.2 Hz, H-5), 3.75 and 3.70 (2d, $J_{P,H}$ 11.2 Hz $P(OMe)_2$), 3.70 (dd, $J_{4,5}$ 10.0 Hz, H-4), 3.54 (dd, 1H, H-2), 3.39 (OMe), 3.41 and 3.30 (AB pattern of CH_2, $J_{9,9'}$ 14.3, J_{PH} 22.8 Hz), 1.43 and 1.40 (2s, CMe_2).

*Dimethyl (1,2:3,4-Di-*O*-isopropylidene-α-D-galacto-heptopyranos-6-ulos-7-yl) phosphonate* (**19**; 75% yield): HRMS calcd for $C_{15}H_{25}O_9P$ (M^+): 381.1314; found: 381.1317. ^1H NMR δ: 5.64 (d, 1H, $J_{1,2}$ 4.9 Hz, H-1), 4.64 and 4.59 (AAB pattern of H3-H4, $J_{3,4}$ 7.8, $J_{4,5}$ 2.1 Hz), 4.36 (dd, 1H, $J_{2,3}$ 2.5 Hz, H-2), 4.32 (H-5), 3.82 and 3.79 ($P(OMe)_2$, $J_{P,H}$ 11.2 Hz), 3.65 and 3.08 ($J_{7,7'}$ 15.1, $J_{P,H}$ 20.5 and 21.8 Hz, H7,7'), 1.52, 1.42, 1.34, and 1.31 (4s, 2 CMe_2).

Reaction of sugar phosphonates with C_{12} aldehyde (1).

To a solution of aldehyde **1** (30 mg) and appropriate phosphonate (1.7 equiv. of **19**, **20**, and **21**) in toluene 4 (mL) containing 18-crown-6 (*ca* 30 mg) potassium carbonate (120 mg) was added and the mixture was stirred for 2 days at room temperature. After this time tlc (hexane - ethyl acetate, 4:1) indicated disappearance of most of aldehyde **1** and formation of a new more polar product that was visible under UV light. Water (3 mL) was added, the organic phase was separated, washed with water, dried and concentrated, and the crude product was purified by column chromatography (hexane - ethyl acetate, 6:1 to 4:1).

The ^1H NMR spectra of these products were identical with those from high pressure experiments except that *ca* 5-10% of additional signals in the vinylic region that could be connected with β-eliminated structures (**24, 22**, and **23** respectively) were seen. (signals of H12 and H13 for: **22** δ 6.55 and 6.35 *J* 16.3 Hz; **23** δ 7.00 and 6.80 *J* 16.3 Hz; **24** δ 6.70 and 6.45 *J* 16.0 Hz).

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