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Synthesis of Derivatives of C_{19} and C_{21} Dialdoses

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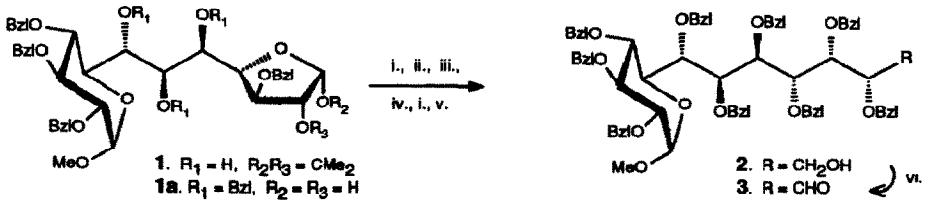
Abstract: *C_{12}-monosaccharide derivative 2 (obtained from C_{12}-dialdose 1 in 49% overall yield) was used as the starting material for the preparation of C_{19}- and C_{21}-monosaccharide derivatives. Coupling of aldehyde 3 (prepared from the parent alcohol 2) with the sugar derived phosphonates 8, 9, and 10 afforded the C_{21}- (11 and 12 respectively) and C_{19}- (13) monosaccharide derivatives. Aldehyde 3 reacted with phosphorane 7 and 14 under high pressure (13 kbarr) to afford C_{21}- and C_{19}-trans higher sugar enones 11 and 13. No reaction between aldehyde 3 and Wittig-type reagents (7 and 14) was observed under atmospheric pressure.*

The synthesis of higher carbon sugars having more than 10 carbon atoms in the chain has gained considerable attention in the past few years since some of them are components of antibiotics[1]. Also, they may be used as non-metabolized analogs of disaccharides in biological studies, and, moreover, the synthesis of such complicated molecules is a real challenge for stereocontrolled organic synthesis[2]. Many different methods for the preparation of the *"medium size"* (C_{10} - C_{15}) higher sugars have been developed[2a], but, there are only limited examples of the synthesis of higher analogs[2b,2c]. 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 developed a general method for the preparation of higher sugar dialdoses (C_{11} to C_{15}) by coupling two simple monosaccharide sub-units *via* a C_n- bridge (n = 0[3], 1[4], 2[5], and 3[6]). In this paper we would like to present ***the first synthesis of monosaccharide derivatives having 19 and 21 carbon atoms*** in the chain arising from the **coupling of two higher sugar sub-units** (C_{12} + C_7 and C_{12} + C_9). Since the Wittig methodology for construction of higher sugar enones worked best in our hands (for the C_{12} -dialdoses)[4] we used the same method for the synthesis of the target C_{19}- and C_{21}- molecules. First, the C_{12}-dialdose **1**[4c] was converted into fully protected dodecose **2** as is shown in Scheme 1.

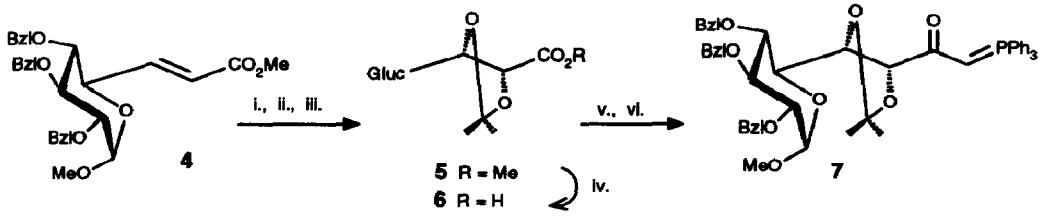


1. R_1 = H, R_2R_3 = CMe_2
1a. R_1 = Bzl, R_2 = R_3 = H

2. R = CH_2OH
3. R = CHO

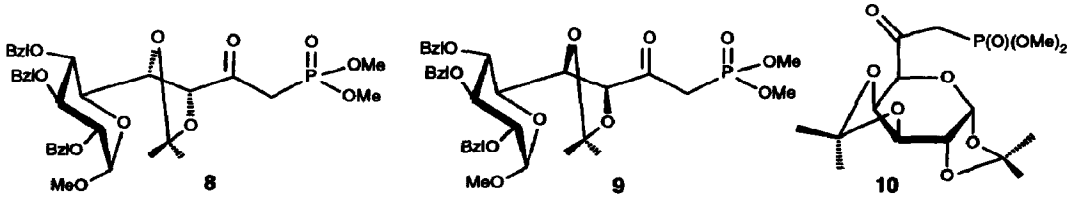
Scheme 1: i. $PhCH_2Br$, NaH, DMF, 2 h; ii. 50% CF_3COOH, THF, reflux, 2 h; iii. LAH, THF, reflux, 2 h; iv. TrCl, Et_3N, toluene, reflux, 5h; v. p-TsOH, MeOH\ether, reflux, 2 h, 49% from 1; vi. Swern oxidation.

Benzylation of 1 followed by hydrolysis afforded the partially protected C_{12}-dialdose (**1a**); surprisingly, this compound survived treatment with $NaBH_4$ and could be reduced to a triol only by $LiAlH_4$ in boiling THF. This product was converted into C_{12}-alcohol **2**[7] in 49% overall yield (from 1). Oxidation of **2** with PDC or under Swern conditions afforded aldehyde **3** in almost quantitative yield[7]. The sugar derived Wittig-type sub-unit **7** was prepared according to our previously published method[4] (see Scheme 2).

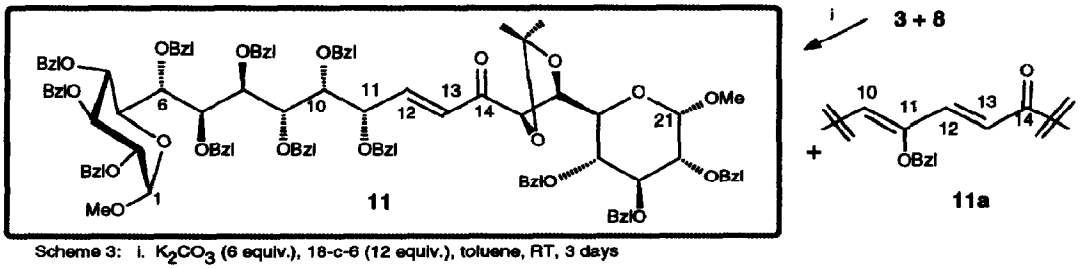


Scheme 2: i. ref. 8 ii. acetone, $CuSO_4$, p-TsOH, RT, 2 d.; iii. separation of diastereoisomers iv. NaOH\THF\H_2O; v. Im_2CO, benzene, 15 min; vi. $Ph_3P{=}CH_2$ (3 eqiuv.), C_6H_6, 2 h.

Sugar aldehydes (pentoses or hexoses) react readily with the sugar derived Wittig-type reagents (C_7) to afford trans higher sugar enones (Sug_1-CO-CH=CH-Sug_2)[4]. However, both aldehyde **3** and ylid **7**[9] were very unreactive; no reaction was observed even at 143° C (boiling xylene)! To check the reactivity of both compounds, aldehyde **3** was treated with very reactive ylid $Ph_3P{=}CH\text{-}CO_2Me$, and ylid **7** with acetaldehyde. No reaction was observed in both cases. We prepared, therefore, the phosphonate reagents: **8**, **9**, and **10**[10] since they should be much more nucleophilic than the corresponding ylids.



Under the conditions reported by Yonemitsu and co-workers (K_2CO_3, 18-crown-6, toluene)[11a] phosphonate **8** reacted with aldehyde **3** yielding the C_{21}-monosaccharide derivative **11** in 55% yield. The presence of a molecular ion at 1763 (M + Na^+) in the mass spectrum of the product proved the coupling of

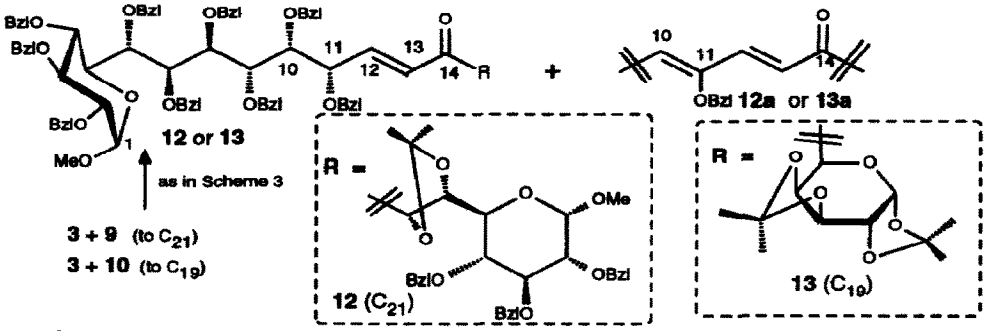


Scheme 3: i. K_2CO_3 (6 equiv.), 18-c-6 (12 equiv.), toluene, RT, 3 days

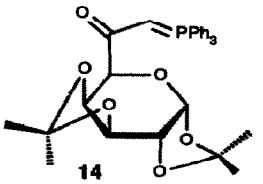
two sub-units (**3** and **8**) and the signals at δ: 6.98 and 6.80 with the coupling constant J = 15.9 Hz in the ^{1}H-NMR spectrum pointed to the *E*-configuration at the C_{12}-C_{13} alkenic bond[12]. The compound obtained by this method was contaminated with a side product assumed to be **11a** as shown by the signals at δ: 6.55 and 6.35 in the ^{1}H-NMR spectrum and the presence of a peak at 1655 [M + Na^+ - 108 (benzyl alcohol)] in the

mass spectrum[12].

Phosphonates **9** and **10** reacted under these conditions with aldehyde **3** to afford, likewise, the isomeric C_{21} and C_{19}- monosaccharides **12** and **13** in 58 and 60% yield respectively. Both of them were contaminated with the products assumed to be **12a** and **13a** respectively, arising from the elimination of benzyl alcohol under the reaction conditions[13].



To avoid this β-elimination the reaction should be performed without base present. Although aldehyde **3** did not react with sugar ylid **7** under normal conditions, the reaction under high pressure (13 kbarr) afforded C_{21} higher sugar enone **11** without any traces of the β-eliminated product. Reaction of **3** with ylid **14**[4a] under the same conditions (13 kbarr, 4 days) proceeded also without any β-elimination yielding only the C_{19} monosaccharide **13** in 53% yield but, as a mixture of *trans\cis* isomers in the ratio 92:8[14].



In conclusion, although aldehyde **3** was very unreactive towards the stabilized Wittig-type reagents (**7** and **14**) under normal conditions it reacted with both ylids under high pressure (13 kbarr, 80 °C) to afford C_{21} and C_{19} *trans* higher sugar enones **11** and **13**. The latter compounds were also prepared by reaction of **3** with the phosphonate reagents **8** and **10** but, under the reaction conditions (slightly basic) small amounts of the side products arising from the β-elimination of benzyl alcohol were observed (**11a** and **13a**). Phosphonate **9** (diastereoisomer of **8**) reacted similarly with **3** affording isomeric C_{21}-*trans* higher sugar enone **12** contaminated with small amount of the β-eliminated product **12a**.

The ***decreased reactivities*** of higher sugar fragments: C_{12}-aldehyde (**3**) and C_9-phosphorane (**7**) are noteworthy when compared to smaller molecules (*e.g.* C_6-sugar aldehydes or C_7-sugar-derived stabilized ylids[4]).

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7. Alcohol **2**: ms (LSIMS) calcd. for $C_{76}H_{80}O_{12}Na$ ($M+Na^+$): 1207.5547; found: 1207.5542. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.59 (d, $J_{1,2}$ = 3.6, H-1), 3.40 (dd, $J_{2,3}$ = 9.6, H-2), 3.29 (s, OMe), 2.06 (t, OH). Aldehyde **3**: mass spectrum (LSIMS) for $C_{76}H_{78}O_{12}Na$ ($M+Na^+$): 1205.

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9. Uronic acid **6** was reacted with 1,1-carbonyl-diimidazole (1.2 equiv.) in dry benzene at room temperature for 15 min. This mixture was added to $Ph_3P{=}CH_2$ (4 equiv.) in benzene, the whole was stirred at r.t. for 2 h, the product was isolated in usual way and crude **7** was purified by column chromatography. Yield 55%. Mass spectrum (LSIMS) 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 $(Ph_3P{=}CH\text{-}C{=}O)^+$. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.97 (dd, $J_{3,4}$ = 9.0, $J_{2,3}$ = 9.6, H-3), 3.55 (dd, $J_{1,2}$ = 3.6, H-2), 3.39 (1 H, H-4), 3.33 (s, OMe); the vinyl proton could not be seen because of overlap with aromatic signals.

10. Methyl uronate **5** was reacted with a three fold excess of $^{(-)}CH_2P(O)(OMe)_2$ [generated from trimethylphosphonoacetate in THF at -78 °C by action of $LiN(TMS)_2$] according to ref[11]. The product - phosphonate **8** - was isolated by column chromatography in 70% yield. Mass spectrum (LSIMS; *m*-nitrobenzyl alcohol was used as a matrix to which sodium acetate was added) calcd. for $C_{36}H_{45}O_{11}PNa$ ($M+Na^+$): 707.2597; found: 707.2593. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.62 (d, $J_{1,2}$ = 3.5, H-1), 4.55 (dd, $J_{5,6}$ = 1.7, $J_{6,7}$ = 6.2, H-6), 4.03 (dd, $J_{2,3}$ = 9.6, $J_{3,4}$ = 8.9, H-3), 3.93 (dd, $J_{4,5}$ = 10.2, H-5), 3.73 and 3.71 [2 d, $J_{H,P}$ = 11.3 Hz, $P(OMe)_2$], 3.39 (s, OMe), 3.13 (dd, $J_{9,9}$ = 14.2, $J_{9,P}$ = 22.5, one of H-9), 1.51 and 1.34 (2 s, CMe_2). Phosphonates **9** and **10** (structures of which were proved by ms and NMR spectra) were prepared likewise from appropriate methyl uronates in 50 - 70% yield .

11. *for preparation of phosphonates and their coupling with aldehydes see: a.* Ojikawa, Y.; Tanaka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3647; *b.* Horita, K.; Nagato, S.; Ojikawa. Y.; Yonemitsu, O. *Tetrahedron Lett.*, **1987**, *28*, 3253; *c.* Nicolau, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.*, **1988**, *110*, 4685; *d.* Yamanoi, T.; Akiyama, T.; Ishida, E.; Abe, H.; Anemiya, M.; Inazu, T. *Chem. Lett.*, **1989**, 335.

12. **11**. Mass spectrum (LSIMS): 1763 ($M+Na^+$), 1764 ($M+1+Na^+$), 1765 ($M+2+Na^+$). The ratio of M:(M+1):(M+2) was 8:10:6 and agreed well with calculated isotopic pattern for $C_{110}H_{116}O_{19}$ (79:100:65). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.98 (dd, $J_{11,12}$ = 5.2, $J_{12,13}$ = 15.9, H-12), 6.80 (dd, $J_{11,13}$ = 1.3 Hz, H-13), 3.38 and 3.28 (2 s, 2 OMe). **11a**: Ms (LSIMS): 1655 ($M+Na^+$-$PhCH_2OH$). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.55 (d, $J_{12,13}$ = 16.3, H-12), 6.35 (d, H-13). **12**. Ms: 1763 ($M+Na^+$). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.95 (dd, $J_{11,12}$ = 5.9, $J_{12,13}$ = 15.9, H-12), 6.70 (dd, $J_{11,13}$ = 1.2, H-13), 3.36 and 3.29 (2 s, 2 OMe). **12a**: Ms: 1655 ($M+Na^+$-$PhCH_2OH$). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.00 (d, $J_{12,13}$ = 16.3, H-12), 6.88 (d, H-13), 3.42 and 3.24 (2 s, 2 OMe).

13. Aldehyde **3** obtained from **2** by the Swern or PDC oxidation did not contain any β-eliminated product according to its (LSIMS) spectrum [no signal at 1099 ($M+Na^+$-$PhCH_2OH$) was detected].

14. Aldehyde **3** was reacted with ylid **14** under high pressure (13 kbarr, toluene at 80 °C, 4 days). The product was isolated by preparative t.l.c. in 53% yield. **13**: Ms (LSIMS): 1459 ($M+Na^+$). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.89 (dd, $J_{11,12}$ = 6.3, $J_{12,13}$ = 15.9, H-12), 6.71 (dd, $J_{11,13}$ = 1.1, H-13), 5.44 (d, $J_{18,19}$ = 5.0, H-19), 3.29 (s, OMe). Small amounts of the *cis* isomer (*ca* 8%) were detected δ: 6.60 (dd, $J_{11,13}$ = 0.8, $J_{12,13}$ = 11.7, H-13), 6.30 (dd, $J_{11,13}$ = 8.6, H-12).

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