Use of Furanoid Glycals in Oligosaccharide Synthesis

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Abstract: Furanoid glycals **3**, **4** and **9**, containing a 3-*O*-silyl protecting group, are readily epoxidized with DMD to give the respective shelf-stable α-1,2-anhydrofuranoses **7**, **8** and **10**. The latter oxiranes react smoothly and stereoselectively under the agency of $ZnCl_2$ with a variety of primary and allylic secondary glycosyl acceptors (*e.g.* **1**, **11-13**) resulting in the exclusive formation of β-linked disaccharides (*e.g.* **14-18**) in yields comparable to those obtained starting from 1,2-anhydropyranoses. Furthermore, the dimeric glucofuranoside **18** was transformed into the corresponding 2'-deoxyfuranoside **20**, the β-mannofuranoside **21** and the (1→2)-branched furanoside **22**.

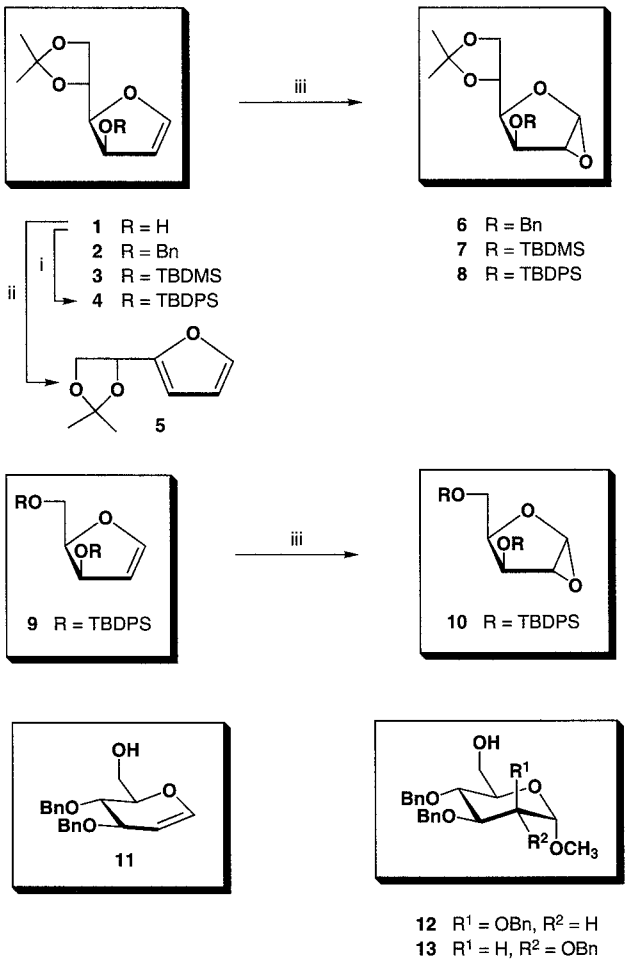
During the past decades, glycals have been the subject of considerable interest in carbohydrate chemistry[1] and natural product synthesis.[2] The use of glycals in oligosaccharide synthesis gained a new impetus by the advent of the stereoselective two-step glycosylation approach of Danishefsky *et al.*[3] Thus, conversion of a pyranoid glycal with 3,3-dimethyldioxirane (DMD) is followed by $ZnCl_2$-mediated condensation of the resulting 1,2-anhydropyranose with a glycosyl acceptor. The merit and usefulness of this methodology was nicely illustrated in the synthesis of various complex oligosaccharides in solution[4] and on a solid support.[5]

In contrast, no examples of oligosaccharide synthesis *via* oxidative coupling of furanoid glycals have been reported. The latter is mainly due to the intrinsic lability of the 1,2-epoxide function in 1,2-anhydrofuranose derivatives.

We here report an approach towards the synthesis of furanoside-containing oligosaccharides using 3-*O*-silyl-protected 1,2-anhydrofuranoses **7**, **8** and **10** as stable furanosyl donors.

Initially, the stability of the 3-*O*-benzyl-protected α-1,2-anhydrofuranose derivative **6** (see Scheme 1) was explored. To this end, known glucal **1**[6] was benzylated and the resulting fully protected glucal **2**[7] was epoxidized[8] with DMD[9] to give the 1,2-anhydroglucofuranose **6**. NMR-analysis revealed that epoxide **6** slowly degraded upon storage.

Moreover, $ZnCl_2$-mediated condensation of freshly prepared oxirane **6** with glucal acceptor **11**[10] provided only negligible amounts of the expected disaccharide (**14**, R = Bn in Scheme 2).[11] It was reasoned that the presence of an electron-withdrawing benzoyl substituent at the 3-OH function of glucal **1** would increase the stability of the corresponding 1,2-anhydrofuranose (**6**, R = Bz). Treatment, however, of **1** with benzoyl chloride in pyridine resulted in the isolation of furan **5**.[12] On the other hand, silylation of **1** with *tert*-butyldimethylsilyl chloride (TBDMSCl) followed by epoxidation of glucal **3**[13] led to the α-1,2-oxirane **7**, which could be stored at room temperature without any appreciable trace of decomposition. Moreover, glycosylation of the pyranoid glucal acceptor **11** with 1,2-epoxide **7** in the presence of $ZnCl_2$ provided exclusively the β-linked dimer **14** (see Scheme 2) in 40% yield (60% based on consumed acceptor). It was also established that the more acid-stable *tert*-butyldiphenylsilyl (TBDPS)-group had a beneficial effect on the yield of the glycosylation. Thus, treatment of the 3-*O*-TBDPS-protected glucal **4** with DMD gave the stable α-1,2-oxirane **8**. $ZnCl_2$-promoted condensation[14] of epoxide **8** with acceptor **11** yielded the β-linked disaccharide glucal **15**[15] in 62% yield (81% based on consumed acceptor). Similarly, reaction of **8** with secondary furanoside glucal acceptor **1** afforded exclusively the β-linked dimer glucal **16** in an



Scheme 1: (i) TBDPSCl, imidazole, DMF, 12 h, 95%; (ii) BzCl, pyr, 1 h, 88%; (iii) DMD, CH_2Cl_2/acetone, 0 °C, 5 min, 94-96%.

acceptable yield (25%, 71% based on recovered acceptor). Apart from this, 3,5-di-*O*-TBDPS-protected furanoid xylal **9**, prepared by the method of Castillón *et al.*,[16] was epoxidized with DMD to give the α-1,2-anhydro derivative **10**. Coupling of oxirane **10** with mannopyranosyl acceptor **12**[17] furnished the β-linked disaccharide **17** (54% yield, 78% referring to consumed acceptor).

At this stage, it is of interest to note that the generation of a free 2'-OH group is an additional feature of the oxidative coupling approach. The latter aspect is exploited in the conversion of the dimeric glucofuranoside **18**, readily accessible by coupling of **8** with **13**, into the 2'-deoxyfuranoside **20**, the β-mannofuranoside derivative **21** and the (1→2)-linked trimer **22** by the following sequence of events. Condensation of the primary hydroxyl in glucosyl acceptor **13**[18] with 1,2-anhydroglucofuranose **8** gave the β-linked disaccharide **18** in 53% yield (74% based on reacted acceptor). Deoxygenation of **18** was readily effected according to Barton[19] to afford the 2'-deoxy-glucofuranoside **20** in 74% yield over the two steps. Moreover, disaccharide **18** was transformed[20] into its $C_{2'}$-epimer **21** in an overall yield of 48% by Albright-Goldman oxidation[21] and subsequent $NaBH_4$-reduction of the intermediate 2'-ulose derivative. The identity of β-D-mannofuranoside

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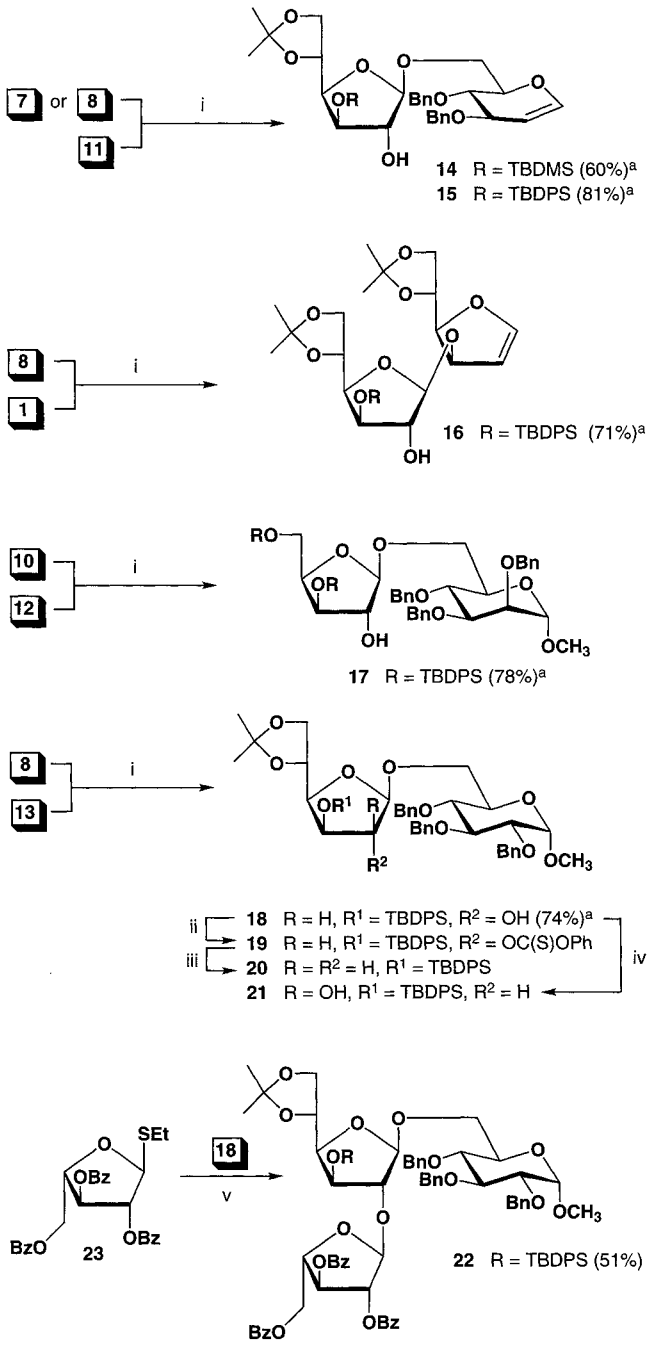

Scheme 2: (i) $ZnCl_2$, THF, 0 °C, 5-15 min; (ii) PhOC(S)Cl, DMAP, CH_3CN, 10 h, 94%; (iii) $Et_3NH_3PO_2$, AIBN, dioxane, reflux, 1 h, 79%; (iv) a. DMSO/Ac_2O (2:1, v/v), 12 h; b. $NaBH_4$, CH_2Cl_2/MeOH (1:1, v/v), 0 °C, 1 h, 48%; (v) NIS, *cat.* TfOH, $ClCH_2CH_2Cl$/THF (3:1, v/v), 1 h, 51%. [a] yields based on consumed acceptor.

dimer **21** was unambiguously ascertained by mass spectrometry as well as ^1H NMR and ^{13}C NMR spectroscopy. Finally, the free 2'-hydroxyl in **18** was glycosylated with the thioethyl L-arabinofuranosyl donor **23**[22] in the presence of the promoter *N*-iodosuccinimide (NIS) and catalytic triflic acid (TfOH)[23] to give the α-(1→2)-linked trisaccharide **22** in 51% yield.

In conclusion, the results presented in this paper demonstrate that the oxidative coupling of furanoid glycals presents a useful approach towards the stereoselective construction of furanoside-containing oligosaccharides. A major drawback of the latter methodology, *i.e.* the intrinsic lability of the intermediate 1,2-anhydrofuranose derivatives, can be overcome by protection of the 3-hydroxyl function with a silyl group. The resulting shelf-stable glycosyl donors can be coupled under the agency of $ZnCl_2$ with both primary and allylic secondary glycosyl acceptors to form exclusively β-linked furanosides in yields comparable to those of 1,2-anhydropyranose coupling reactions. Moreover, the free 2'-OH group, formed in each coupling step, can be further processed to construct 2'-deoxy furanoside derivatives, β-mannofuranosides and (1→2)-linked furanosides.

Acknowledgement

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(14) *General procedure for the oxidative coupling of furanoid glycals:* Under a continuous stream of dry nitrogen, a solution of freshly prepared DMD[9] (15 mL, 0.08 M) was added dropwise to a stirred and cooled (0 °C) solution of the appropriate furanoid glycal (1.0 mmol) in dichloromethane (5 mL). The reaction mixture was concentrated *in vacuo* at room temperature to give the respective 1,2-anhydrofuranose as a white solid in nearly quantitative yield (94-96%). To a cooled (0 °C) and stirred solution of the latter 1,2-anhydrofuranose (1.0 mmol) and the appropriate glycosyl acceptor (1.0 mmol) in THF (3 mL) was added dropwise under a continuous stream of dry nitrogen a solution of $ZnCl_2$ in THF (1.0 M, 1.5 mL). After TLC-analysis (25% EtOAc/light petroleum) indicated complete consumption of the furanosyl donor (5-15 min), the reaction mixture was diluted with EtOAc (50 mL),

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washed with sat. aq. NaCl (2 x 25 mL) and aq. $NaHCO_3$ (1 M, 15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (0-35% EtOAc/light petroleum) and Sephadex LH-20 gel filtration (eluent: CH_2Cl_2/MeOH, 2:1, v/v) afforded the corresponding disaccharide as a white foam.

(15) (a) Representative spectral data of 1,5-anhydro-3,4-di-*O*-benzyl-2-deoxy-6-*O*-(3-*O*-*tert*-butyldiphenylsilyl-5,6-*O*-isopropylidene-β-D-glucofuranosyl)-D-*arabino*-hex-1-enitol (**15**): ^1H NMR ($CDCl_3$): δ 7.85-7.15 (m, 20H, H_{arom}), 6.38 (dd, 1H, H_1, $J_{1,2}$ = 6.1 Hz, $J_{1,3}$ = 1.1 Hz), 4.89 (dd, 1H, H_2, $J_{2,3}$ = 2.6 Hz), 4.71 (AB, 2H, CH_2 Bn), 4.66 (d, 1H, $H_{1'}$, $J_{1',2'}$ = 1.8 Hz), 4.58 (AB, 2H, CH_2 Bn), 4.23 (ddd, 1H, H_3, $J_{3,4}$ = 7.6 Hz), 4.22 (d, 1H, $H_{3'}$, $J_{3',4'}$ = 1.2 Hz), 4.20-4.06 (m, 4H, $H_{6A}/H_{6B}/H_{4'}/H_{5'}$), 4.03 (m, 1H, H_5), 4.01 (dd, 1H, $H_{6'A}$, $J_{5',6'A}$ = 1.9 Hz, $J_{6'A,6'B}$ = 10.6 Hz), 3.83 (dd, 1H, H_4, $J_{4,5}$ = 8.8 Hz), 3.79 (m, 1H, $H_{2'}$), 3.65 (dd, 1H, $H_{6'B}$, $J_{5'6'B}$ = 5.2 Hz), 1.63 (bs, 1H, 2'-OH), 1.43, 1.37 (2 x s, 2 x 3H, CH_3 isoprop), 0.88 (s, 9H, CH_3 *t*-Bu). ^{13}C {^1H} NMR ($CDCl_3$): δ 144.6 (C_1), 138.3, 138.2 (C_q Bn), 136.1-127.4 (C_{arom}), 134.1, 132.8 (C_q TBDPS), 108.8 (C_q isoprop), 108.7 ($C_{1'}$), 99.8 (C_2), 83.9, 81.0, 78.0, 76.5, 76.0, 74.4, 73.6 ($C_3/C_4/C_5/C_{2'}/C_{3'}/C_{4'}/C_{5'}$), 73.7, 70.4 ($CH_2$ Bn), 67.5, 66.5 ($C_6/C_{6'}$), 26.9 (CH_3 *t*-Bu), 26.7, 25.4 (CH_3 isoprop), 19.3 (C_q *t*-Bu). MS (m/z): 767 $(M+H)^+$, 784 $(M+NH_4)^+$; (b) Dimer glucal **15** was condensed with mannoside acceptor **12** *via* an additional oxidative coupling step (*cf.* benzoylation of the free 2'-OH group, DMD-mediated epoxidation and $ZnCl_2$-catalyzed condensation with **12**) providing the respective β-(1→6)-linked trisaccharide in 56% overall yield.

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