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Intramolecular Glycoside Bond Formation – A Rigid Spacer Concept for the Diastereoselective Linkage between Glycosyl Donor and Acceptor

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Abstract

α,α'-Dibromo-m-xylene gave compounds **5a,b** and **7** which contain a glycosyl donor and acceptor moiety. Activation of **5a,b** with NIS/TMSOTf as promoter system afforded β(1-4)-linkage leading to **6** as the only monomeric reaction product. Activation of **7** led also to β(1-4)-linkage affording **8** in very high yield.

Various approaches to intramolecular glycoside bond formation have been studied [1-9]; they are mainly based on attachment of the acceptor via a spacer to the 2-hydroxy group of the donor [1-5] or, alternatively, to the leaving group of the donor [6-9]. The functional substituent based approach generating five-membered cyclic transition states (spacer = SiR_2, CR_2) [1,3] resulted generally in good anomer selectivity; however, it is dependent on the configuration of the 2-hydroxy group and, depending on the spacer, this process may violate the ring closure rules, thus favoring competing reactions. With larger spacer systems at the 2-hydroxy group [4] or at any other position [5], due to missing steric constraints, often not only the anomer selectivity was found to be low but also the yields were modest.

The close proximity between glycosyl donor and acceptor in the active site of an enzyme is generated by specific binding between enzyme and substrates, this way leading to a structurally rigid array which enforces (regio- and) diastereoselective glycosylation formally under construction of large rings. In order to extend this concept to face-selective intramolecular glycoside bond formation a rigid spacer is required which, due to geometrical constraints, leads to diastereocontrol of this reaction. To this aim, the m-xylylene residue was chosen (Scheme 1). Attachment of the donor, for instance via the 6-hydroxy group, can be used. In the acceptor, any cyclic 1,3- or 1,2-*threo*- or -*erythro*-diol arrangement, structural entities practically common to all sugar residues, will allow for attachment to the spacer and provide the desired accepting hydroxy group. This design will keep the reacting centers in proper distance and should enforce the desired diastereoselection in the glycosylation process.

In order to investigate this concept, α,α'-dibromo-m-xylene was transformed with **1a** (α:β = 9:1) [10] in the presence of NaH as base and 15-crown-5 as supporting reagent into 6b-*O*-linked derivative **2a**. Similarly, from β-thioglycoside **1b** [10] 6b-*O*-linked derivative **2b** was obtained. Treatment of known 4,6-*O*-unprotected glucoside **3** [11] with dibutyltin oxide in toluene and then reaction with **2a,b** in the presence of TBAI afforded the desired 6a,6b-*O*-linked intermediates **5a,b**. Activation of the pentenyloxy leaving group in **5a** with NIS/TMSOTf [10] gave the desired (1-4)-disaccharide linkage, thus leading to 15-membered macrocyclic system **6** as the only monomeric product. The yield of **6** was concentration dependent and intermolecular oligomer formation was the competing reaction. **6** afforded known cellobioside **9** [12]. The same result could be obtained from **5b**. Thus, diastereofacial control in the glycosylation step is independent of the glycosyl donor configuration.

Obviously, the same product should be accessible by ligating 3-*O*-unprotected glucoside **4** [13] via the 3-hydroxy group onto **2**; thus, with **2b** under standard conditions the desired 3a,6b-*O*-linked intermediate **7** was obtained. Glycosylation gave again exclusively β(1-4)-linkage but now in 84% yield, thus exhibiting a high kinetic preference for the

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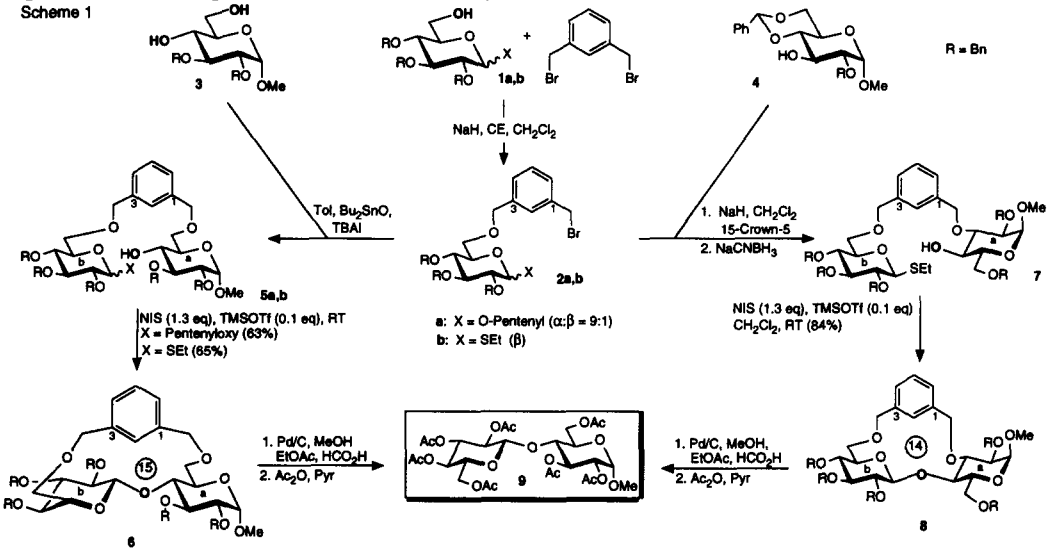
diastereoselective formation of a 14-membered macrocycle in which the four atoms of the acceptor moiety (ring a) have D-*threo*-arrangement. **8** led also to cellobioside **9.**

Scheme 1



Detailed NMR studies [14] of compounds **6** [15] and **8** [15] led to assignment of the carbon and hydrogen atoms. Molecular mechanics simulations (MM+, Hyperchem) showed that the conformation of the disaccharide moiety in **6** and **8** is only slightly different, though 3a,6b-*O*-linkage in a 14-membered ring is changed to 6a,6b-*O*-linkage in a 15-membered ring; this change is essentially accommodated by the 6b-methylene group which transforms from *gg*- (**6**) to *gt*-conformation (**8**). The energy minimized conformation of **8** is by 0.9 kcal/mol lower than that of **6**, thus, based on the assumption that the transition state geometries leading to **6** and **8** are similar to those of the products, the experimental findings are explained.

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[14] ^{1}H and ^{13}C assignments by DQF-COSY and HMQC spectra: Geyer A, Huchel U, Schmidt RR. Magn. Reson. Chem. submitted.
[15] ^{1}H NMR data (600 MHz, $CDCl_3$) **6**: δ = 3.06 (dd, 1 H, $J_{4,3} = J_{4,5}$ = 9.5 Hz, 4-Hb), 3.21 (dd, 1 H, $J_{5,6} = J_{5,4}$ = 9.5 Hz, 5-Hb), 3.36 (dd, 1 H, $J_{2,1}$ = 7.4 Hz, $J_{2,3}$ = 9.1 Hz, 2-Hb), 3.39 (dd, 1 H, $J_{3,2} = J_{3,4}$ = 9.1 Hz, 3-Hb), 3.47 (dd, 1 H, $J_{2,1}$ = 3.7 Hz, $J_{2,3}$ = 9.6 Hz, 2-Ha), 3.58-3.63 (m, 2 H, 5-Ha, 6-Ha), 4.22-5.02 (m, 17 H, $J_{1a,2a}$ = 3.7 Hz, 1-Ha, $J_{1b,2b}$ = 7.6 Hz, 1-Hb, 7 CH_2Ph). **8**: δ = 3.18 (m, 1 H, 5-Hb), 3.36-3.45 (m, 6 H, 6-Ha, 2-Hb, 3-Hb, OCH_3), 3.51-3.52 (m, 3 H, 2-Ha, 5-Ha, 6-Hb), 3.80-3.99 (m, 5 H, 6-Hb, 4-Ha, 3-Ha, 6-Ha, 4-Hb), 4.24-4.98 (m, 16 H, $J_{1b,2b}$ = 7.5 Hz, 1-Hb, $J_{1a,2a}$ = 3.7 Hz, 1-Ha, 7 CH_2Ph).