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# Combinatorial Synthesis of Oligosaccharide Library of 2,6-Dideoxysugars

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**Abstract**: Two combinatorial libraries composed of linear trisaccharides of 2,6-dideoxy-L-sugars have been constructed: All possible regioisomeric trisaccharides with 2-iodo and with 2-deoxy moieties were synthesized by an iodonium ion-catalyzed "stereoselective-yet-nonregioselective" glycosylation reaction. 

Combinatorial synthesis is a widely recognized methodology for identifying compounds with specific biological activity that have potential as clinical drugs. Many reports have appeared concerning combinatorial synthesis of peptides, nucleic acids, and small organic molecules;[1] however, only a few approaches[2-4] have been described for constructing a library of oligosaccharides, even though these molecules constitute an important class of biomolecules with a variety of biological activities.[5]

Through "random glycosylation" reactions of an unprotected glycosyl acceptor and a protected glycosyl donor, the Hindsgaul group has succeeded in obtaining all the possible regio- and stereoisomers.[2] The Boons group has also used *O*-benzyl protected building blocks to prepare a trisaccharide library.[3] This approach allowed them to control regioselectivity and generate a mixture of stereoisomers of the glycosidic linkages. A third approach taken by the Kahne group was the "selective glycosylation" of a large number of suitably protected glycosyl donors and acceptors. They were able to control both regio- and stereoselectivity and thereby generate a single oligosaccharide structure on beads.[4] However, these approaches may require enormous work to prepare each synthetic building block.

In this report we describe another approach which involves "divergent" synthesis of an oligosaccharide library by a combination of "stereoselective-yet-nonregioselective" glycosylation, in order to control the stereoselectivity of the glycosidic linkages and generate a large number of linkage-position isomers and the "defined" chemical transformation for further modification of the produced linear oligosaccharides composed of 2,6-dideoxy-L-sugar. Because dideoxy-L-sugar are often found in the components of antitumor agents as a DNA sequence specific binder,[6] a new class of DNA-binding oligosaccharide structure may be discovered through such oligosaccharide library.

In our strategy (Scheme 1) a glycal (**1**),[7,8] a basic building block, was non-regioselectively coupled in the presence of I(*sym*-collidine)$_2$ClO$_4$[9] with a glycosyl acceptor (**3**) containing two free hydroxyl groups to produce, with a strict axial anomeric configuration, two regioisomers (**4a** and **5a**) in equal amounts. The coupling products were sequentially *O*-acetylated (to avoid branching) and *O*-desilylated (**4b** and **5b**) to become

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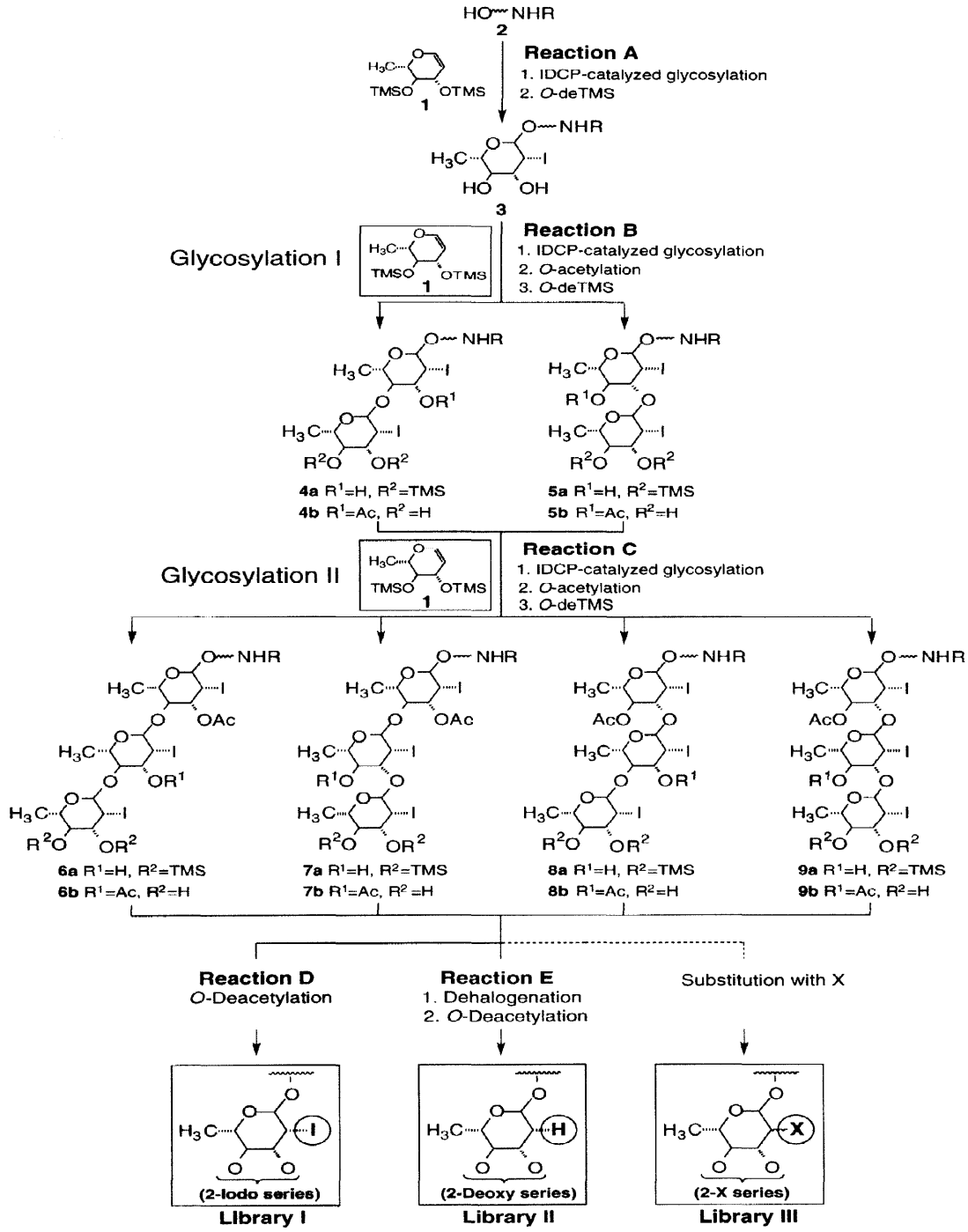


**Scheme 1. Construction scheme of oligosaccharide libraries.** Reagents and conditions: Reaction A: 1) I(*sym*-collidine)$_2$ClO$_4$, $CH_2Cl_2$, MS4A, 0°C; 2) $Bu_4NF$, AcOH, THF, 0°C (78% overall yield); Reaction B: 1) I(*sym*-collidine)$_2$ClO$_4$, $CH_2Cl_2$, MS4A, –78°C (94% yield as a mixture of **4a** and **5a**); 2) $Ac_2O$, pyridine, 3) HF-pyridine, THF (67% yield as a mixture of **4b** and **5b**); Reaction C: 1) I(*sym*-collidine)$_2$ClO$_4$, $CH_2Cl_2$, MS4A, 0 °C (73% yield as a mixture of **6a**, **7a**, **8a**, and **9a**); 2) $Ac_2O$, pyridine, 3) HF-pyridine, THF (73% yield as a mixture of **6b**, **7b**, **8b**, and **9b**); Reaction D: $NH_4OH$, MeOH (91% yield); Reaction E: 1) $Bu_3SnH$, VAZO®, toluene (62% yield), 2) $NH_4OH$, MeOH (66% yield).

an acceptor for the next glycosylation reaction. This procedure was repeated until desired oligosaccharide length was achieved. Through these sequential glycosylation reactions, a versatile 2-iodo group was introduced into every monosaccharide residue. At the end of the scheme, the mixture of regioisomeric oligosaccharides was *O*-deprotected to yield the **Library I** with 2-iodo groups. For further modification, the 2-iodo groups were reduced to give the 2-deoxy derivatives that constitute **Library II**; substitution of the 2-iodo group with X could be used to form a third **Library III** possessing an X group at the *C*-2 position.

Peracetylated 6-deoxy-L-glucal was deacetylated ($K_2CO_3$-MeOH) and trimethylsilylated (TMSCl, $Et_3N$, DMAP) to give 6-deoxy-3,4-di-*O*-TMS-L-glucal **1**[10] in 69% yield. Coupling of **1** and a tether, 6-trifluoroacetamidohexanol **2**, with iodonium di(*sym*-collidine)perchlorate (IDCP) as an activator in $CH_2Cl_2$ gave an α-glycoside **3** in 78% yield after desilylation ($Bu_4NF$, AcOH). The first "non-selective" glycosylation was examined with the donor glucal **1** and the acceptor **3** with the 3- and 4-OH groups free: equimolar amounts of **1** and **3** were mixed in the presence of 1.5 equiv of IDCP at either 0 °C or –78 °C in $CH_2Cl_2$. In both cases, a mixture α(1→4)- and α(1→3)-linked disaccharides[11] (**4a** and **5a**, respectively) was obtained in an approximate ratio of 6:4[12] in 80–90% yield.†

Prior to the combinatorial glycosylation we examined, as a separate experiment, the second non-selective glycosylation on the individual disaccharide **4b**[10] and **5b**.[10] Reaction of **1** with the α(1→4)-linked disaccharide **4b** at 0 °C in $CH_2Cl_2$ gave a mixture of two trisaccharides **6a** (α(1→4)-α(1→4)-linked) and **7a** (α(1→4)-α(1→3)-linked) in a ratio of 6:4 in 74% yield.† Glycosylation of **1** and the α(1→3)-linked disaccharide **5b** under the same conditions gave a mixture of two trisaccharides **8a** (α(1→3)-α(1→4)-linked) and **9a** (α(1→3)-α(1→3)-linked) in a ratio of 4:6 in 62% yield.†

For the combinatorial glycosylation, the mixture of the disaccharide products of the first coupling reaction (Glycosylation I) was acetylated in order to avoid the formation of branched oligosaccharides. It was subsequently *O*-desilylated (HF–pyridine) to give a mixture acceptors **4b** and **5b** (the ratio was 54:46). Glycosylation II (IDCP-catalyzed reaction) of **1** with the mixture of **4b** and **5b** in $CH_2Cl_2$ at 0 °C gave a mixture of four regioisomers in 73% yield:† α(1→4)-α(1→4)-, α(1→4)-α(1→3)-, α(1→3)-α(1→4)-, and α(1→3)-α(1→3)-trisaccharides (**6a**, **7a**, **8a**, and **9a**, respectively) in a reasonably good "non-selectivity" of 36:21:20:23.[12] The acetyl group and *N*-trifluoroacetyl group of the trisaccharides were removed with $NH_4OH$ in MeOH, and the free amino group was capped with an acetyl group ($Ac_2O$ in MeOH). The products were purified by gel filtration (Sephadex LH-20 with $CHCl_3$-MeOH) to give **Library I**. Dehalogenation of the 2-iodo group of the mixture of **6b–9b** was further carried out with $Bu_3SnH$ and VAZO® (1,1'-azobis(cyclohexanecarbonitrile)), in hot toluene to give the corresponding 2-deoxy oligosaccharides (**Library II**) in 62% yield.†

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†Products were purified by flash column chromatography as a mixture of all the regioisomers, and yields were calculated based on their weight.

In summary, we have developed a concise approach to a combinatorial synthesis of an oligosaccharide library by a "stereoselective-yet-nonregioselective" glycosylation reaction that generates an oligosaccharide library composed of linkage-position isomers. We used this approach to construct two libraries: **Library I** contained regioisomeric trisaccharides composed of 2-iodo-L-mannose, and **Library II** contained the corresponding 2-deoxy trisaccharides.

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10. All new compounds were separately synthesized, purified and characterized by NMR and high-resolution mass spectroscopic analysis as the authentic compounds.
11. The linkages of the regioisomeric products were determined by $^1$H NMR spectra of their acetate derivatives (**4b** and **5b**). In the $^1$H NMR spectrum of **4b** which is an α(1→4)-linked disaccharide, the H-3 proton (the 3-OH group was unsubstituted with sugar but acetylated) appeared downfield at δ4.48 ppm as a doublet of doublets ($J$= 4.3 and 8.3 Hz). On the other hand, in the $^1$H NMR spectrum of α(1→3)-linked disaccharide **5b**, the H-4 proton appeared downfield at δ5.06 ppm as a triplet ($J$=9.6 Hz).
12. All ratios of the products were determined by integrals of the anomeric protons in the non-reducing end sugar residues in the $^1$H NMR spectra.