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Template Directed Cyclo-glycosylation: Effect of the Anchoring Sites of the Spacer and Temperature in the Regio- and Stereo-selectivity of the Glycosylation

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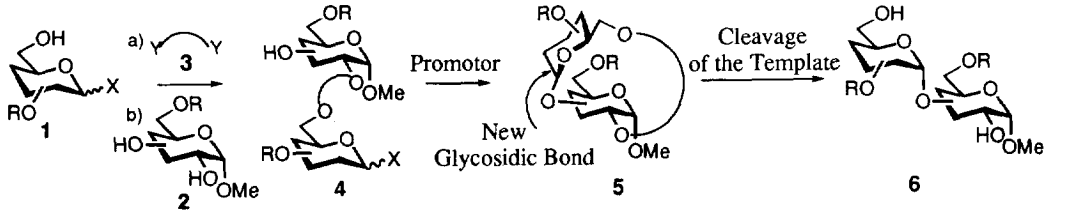
Abstract: The anchoring sites of the spacer and the reaction temperature have a remarkable effect on the regio- and stereo-selectivity of intramolecular macrocyclic glycosylation reactions of several template linked monosaccharides leading to macrocyclic disaccharides and thence to disaccharides.

As the interest in carbohydrate derivatives with biologically important properties is increasing,[1] the development of selective and efficient methods for the construction of glycosidic bonds is now becoming more and more important not only in carbohydrate chemistry but also in organic synthesis.[2] The practical and stereocontrolled synthesis of oligosaccharides is therefore an area of current interest, and particular attention has recently been paid to the development of regioselective non-enzymatic glycosylation methods that would obviate the need for circuitous protecting group strategies.

In this context we have recently reported on a novel strategy for glycosidic bond formation (Template Directed Cyclo-glycosylation, *TDCG*),[3,4] as shown in Scheme 1, which is based on an intramolecular *"cyclo-glycosylation"* reaction of an adduct, **4**, in which the glycosyl donor, **1**, and acceptor, **2**, have been covalently attached to a bifunctional spacer, **3**. The glycosidation step, then resulted in the formation of a macrocyclic species, **5**, in which the new glycosidic bond had been formed, and where cleavage of the template would led to the corresponding disaccharide **6**.

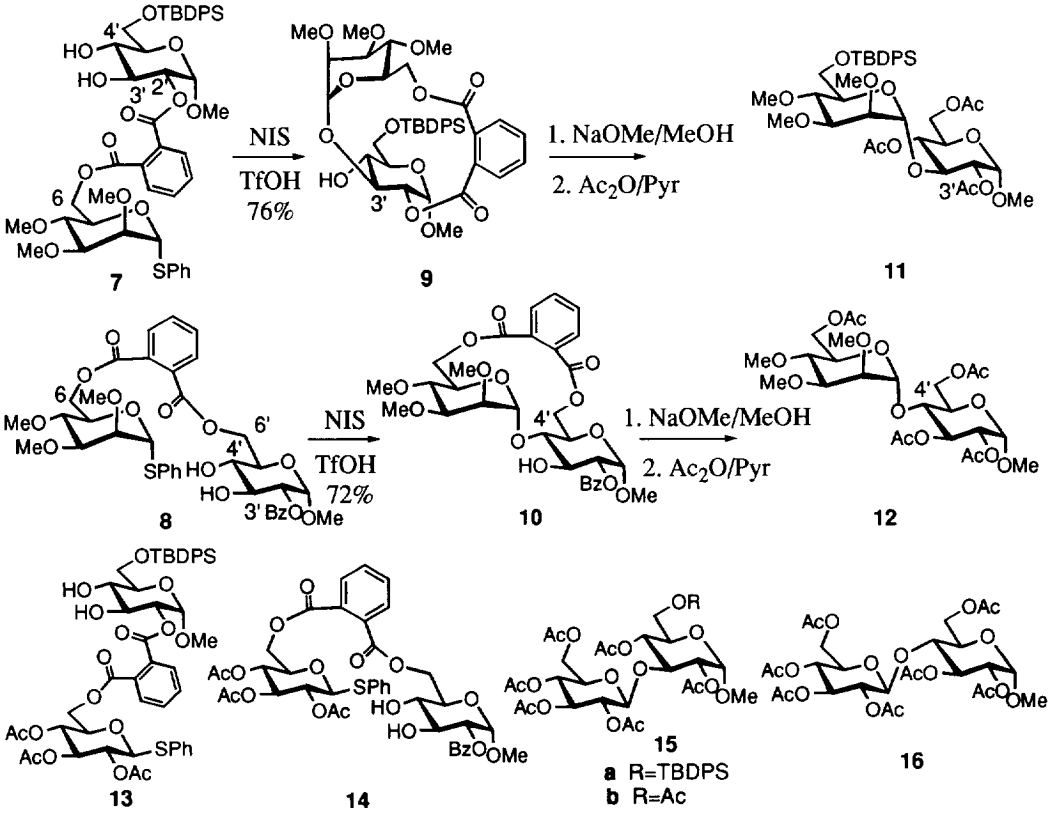
Scheme 1



We wish to disclose here, how the *TDCG* strategy is amenable to regio- and stereochemical control upon changes: *a)* in the topographic orientation of the anchoring hydroxyl groups for the template and *b)* on the reaction temperature.

Adduct **7**[5,6] was designed so that the anchoring sites of the template were 6-OH of the mannosyl donor and 2'-OH of the glucosyl acceptor, and so that 3'-OH and 4'-OH of the acceptor were free and therefore susceptible to regiochemical control on the glycosidic coupling. Similarly, mixed phthalic ester **8** was also designed with positions 3'-OH and 4'-OH of the acceptor free, but with a different anchoring site for the template in the glucosyl acceptor (6'-OH instead of 2'-OH, see Scheme 2). Both adducts underwent smooth glycosylation reaction at -78°C in methylene chloride in the presence of 4Å molecular sieves and with the N-iodosuccinimide/triflic acid, (NIS/TfOH), system as promotor.[7] Remarkably **7** reacted to give the 3'α– glycosidic macrolide **9**, while from the reaction of **8** only the regioisomeric 4'α– glycoside **10** was detected (^{1}H NMR, 300 MHz). For the purpose of structure assignment compounds **9** and **10** were correlated with disaccharides **11** and **12** respectively.

Scheme 2

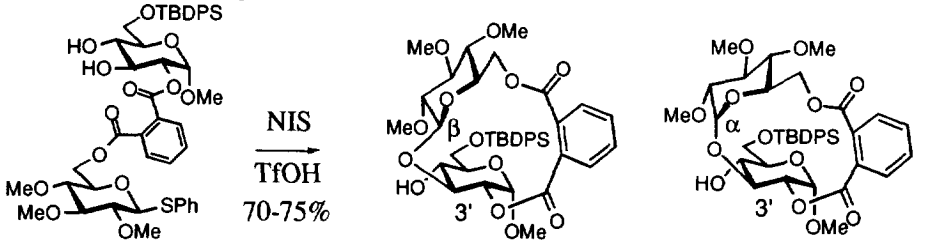


A similar pattern of behaviour was observed with adducts **13** and **14**. Mixed phthalic ester **13** afforded after glycosylation, removal of the template and final acetylation the 3'β– disaccharide **15a**, while a 4:6 mixture of 3'β– and 4'β– glycosides, **15b** and **16**,

was obtained upon glycosylation of **14** and similar post-glycosylation treatment of the initial product.

We next focused our attention on the effect of temperature on the stereoselectivity of the glycosylation reaction of adduct **17**. Reaction of **17** at room temperature with the NIS/TfOH system as catalyst afforded a roughly 1:1 mixture of 3'β– and 3'α– glycosidic macrolides **18** and **19** (Table, entry i). Lowering of the temperature had an effect on the stereoselectivity of the glycosidic coupling (see entries ii, iii and iv) that became more pronounced when the reaction was carried out at -78°C (entry v).

Table: Cyclo-glycosylation of phenyl thioglycoside **17**, with NIS/TfOH system as catalyst in anhydrous CH_2Cl_2 in the presence of 4Å molecular sieves.



17 **18** **19**

Entry	Temperature	Relative Ratio **18** : **19**[a]
i	r.t.	1 : 1
ii	0°C	1.2 : 1
iii	-20°C	1.3 : 1
iv	-50°C	1.7 : 1
v	-78°C	5.5 : 1

[a]The relative ratio was calculated from the integration of the H-2' protons in ^{1}H NMR (300 MHz) on the reaction crude, and is average of at least two runs.

In conclusion, we have shown how the *TDCG* strategy for glycosidic bond construction is amenable to regio- and stereo-chemical control. Thus, changes on the topographic orientation of the hydroxyl groups bearing the spacer have an effect on the transition state for the glycosylation and resulted in an interesting change of regiochemistry in the *TDCG* of **7** and **8**, where mannosyl donors were involved. The same tendency in regioselectivity, although less pronounced, was observed when adducts **13** and **14** (with glucosyl donors present) were subjected to *TDCG*. Although the effect of the temperature in the α/β selectivity of glycosylation reactions has not received much attention,[8] we anticipated that in the intramolecular variant the temperature could play an important role since interactions in the transition state would become more important at low temperature affecting the relative orientation on the approach of the oxonium ion and the hydroxyl group involved in the coupling. In agreement with this expectation, the ratio of glycosides **18** and **19** obtained from *TDCG* of **17** varied from a random 1:1 ratio at room temperature, to a 5.5:1 (β-selective) ratio when lowering the temperature to -78°C.

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5. All new compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic and analytical means.
6. The adducts reported in this paper were prepared in a regioselective manner from the corresponding monosaccharides by means of dibutylstannylidene acetal chemistry under microwave irradiation and details of these transformations will be reported elsewhere.
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