A Novel Strategy for Regio- and Stereo-control in Glycosylation Reactions: Template-directed Cyclo-glycosylation of Monosaccharides

Serafín Valverde,* Ana M. Gómez, Amparo Hernández, Bernardo Herradón and J. Cristóbal López

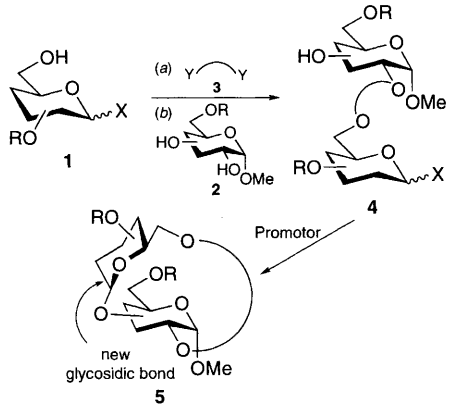
Instituto de Química Orgánica General (CSIC) Juan de la Cierva 3, 28006 Madrid, Spain

Intramolecular glycosylation of several glucose derived glycosyl donor and acceptors that are linked, at O-6 and O-2 respectively, to a bifunctional spacer results in the regio- and stereo-controlled formation of 13-membered macrocyclic glycosides which can be easily converted to disaccharides.

The emergence of information on the important role that carbohydrate structures have in biological processes[1] has triggered a renewed interest in the development of new oligosaccharide syntheses.[2,3] In spite of the new developments the synthesis of oligosaccharides is still far from being a routine exercise, and among the important problems that remain to be solved are the stereochemical outcome (α:β ratio) of the carbohydrate coupling reactions, and the question of regioselectivity (when more than one hydroxy group is involved).[4] In general, diastereoselectivity in the glycosidic coupling is normally attained by neighboring group participation[5] or heterogeneous catalysis,[6] and regioselectivity is achieved when the glycosyl acceptor has only one free hydroxy group, thus requiring complicated protecting group strategies. More recently several groups have reported on some novel methods for stereocontrolled glycosylation in which the glycosyl acceptor is 'intramolecularly delivered' onto the glycosyl donor and the stereochemistry of the newly formed glycosidic bond is then assured by geometrical restrictions in the 5-membered transition state intermediates.[7–11]

We now disclose a novel strategy[12] for the stereocontrolled construction of glycosidic bonds which also provides some discrimination between the hydroxy groups in the acceptor (regiocontrol). The approach, outlined in Scheme 1, involves the sequential covalent attachment of the glycosyl donor **1**, and acceptor **2**, to a suitable bifunctional template, **3**, to generate an adduct **4**, that is subjected to a glycosidic macrocyclisation step, cyclo-glycosylation,[13] to yield the macrocyclic disaccharide **5**. In implementing such an approach we hypothesised that the regio- and stereo- selectivity in the formation of the glycosidic bond will be the result of geometrical restrictions in the transition state affecting: (*a*) the size of the macrocycle (regioselectivity), and (*b*) the relative orientation in the approach of the oxonium ion and the hydroxy group (stereoselectivity or α:β selectivity).

Here we report the results of initial experiments in which the template has been anchored at O-6 and O-2 of the glycosyl donor and acceptor respectively, and where the nature of the template, **3** (phthalic and succinic anhydride, **8** and **13**, were chosen for this study, *vide infra*), and the protecting groups in the glycosyl donor have been changed.



1 **2** **4** **5**

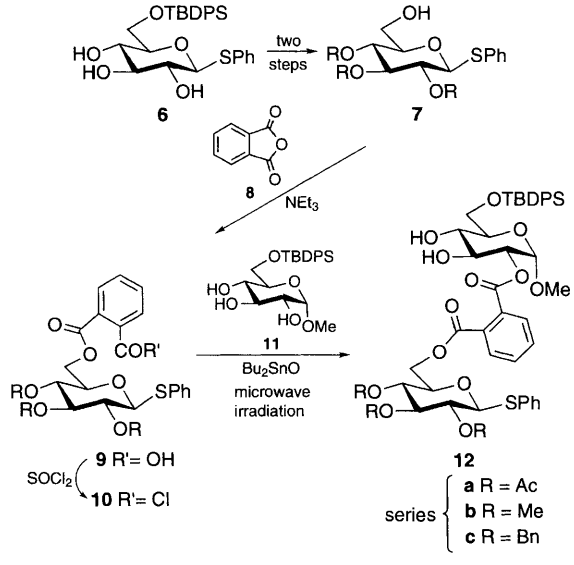
Scheme 1

Glycosyl donors **7**, readily prepared from phenyl thioglycoside **6** (Scheme 2), were reacted with phthalic anhydride **8** to afford aromatic esters **9**† that upon activation with thionyl chloride were regioselectively coupled, by use of dibutylstannylidene acetals under microwave irradiation,[14] at the O-2 position with methyl glycoside **11** to produce the mixed phthalic esters **12**.† Compound **14**, in which a more conformationally mobile template has been incorporated, was analogously prepared from **7a**, by using succinic anhydride as the bifunctional tether (Scheme 3).

The size of the templates was chosen so as the ring size of the resulting macrocycle (13- or 14-membered depending on whether glycosylation takes place at O-3 or O-4) would lie well in the region of favoured ring closure.[15]

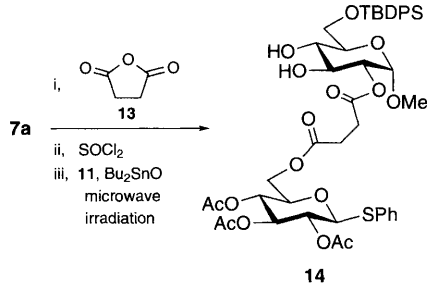
Macrocyclic glycosylation on phenylthioglycosides **12** and **14**, was carried out by use of the *N*-iodosuccinimide–triflic acid (NIS–TfOH) system.‡[16] The reactions were normally finished within 10 min and the chemical yields for the macrocyclic glycosides were good (65–80%).

Reaction of acetylated thioglycosides **12a** and **14** (Table 1) led exclusively to cycloadducts **15a** and **16** respectively (entries i and iv), where glycosylation has taken place regioselectively at position 3, and the stereochemistry at the newly formed



6 **7** **12**

Scheme 2



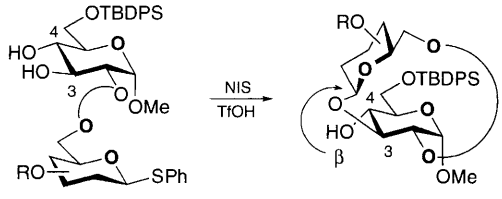
14

Scheme 3

glycosidic bonds was found to be β (*vide infra*).§ Analogous reaction of ether-substituted adducts **12b** and **c** (entries ii and iii) was also completely regioselective, thus leading to 3β-glycosides **15b** and **c** as major isomers, although in these cases minor amounts of the corresponding 3α-glycosides were also isolated. Thus no effect on the reaction course was observed by changing the template (entries i and iv), and modification of the protecting groups on the glycosyl donor, from participating acetates (**12a**, **14**) to non-participating ethers (**12b**, **c**), led to virtually the same stereochemical results. This last observation seems to be in agreement with our initial hypothesis that cycloglycosylation could imply a substantial control of the regio- and stereo-chemical pathways of the reaction, although more experimentation will be needed to ascertain the nature of these restrictions.

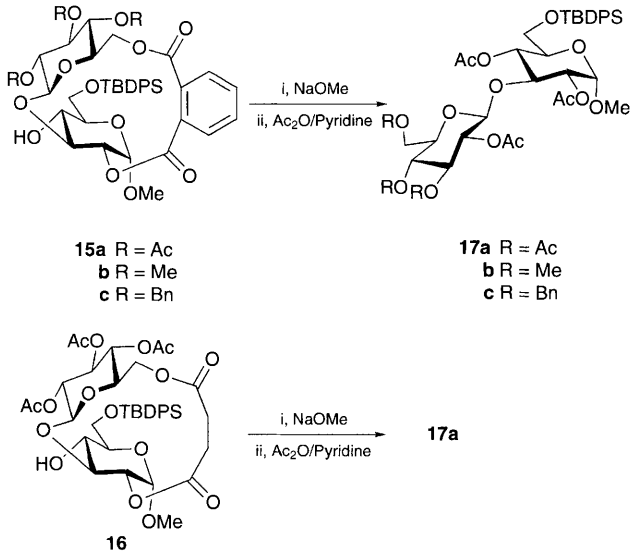
Stereochemical assignment of the newly formed glycosides **15a–c**, **16**, was carried out in the corresponding acyclic disaccharides **17a–c** (Scheme 4), readily obtained from the corresponding macrolides by removal of the template followed by peracetylation, on the basis of their coupling constants (^{1}H NMR, 500 MHz) and the chemical shifts of the anomeric carbons (^{13}C NMR).¶

Table 1 Cycloglycosylation of phenyl thioglycosides **12a–c** and **14** with NIS-TfOH system as catalyst in anhydrous CH_2Cl_2 in the presence of 4 Å molecular sieves.



Entry	Substrate	*T*/°C	Yield (%)	Product[a]
i	**12a**	room temp.	80[b]	**15a**
ii	**12b**	0	78[c]	**15b**
iii	**12c**	0	70[c]	**15c**
iv	**14**	room temp.	65[b]	**16**

[a] Variable amounts (5–10%) of hydrolysis products were also detected. [b] No other isomer was detected by ^{1}H NMR (500 MHz). [c] The corresponding 3-α isomers (*ca.* 15%) were also isolated.



Scheme 4

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Footnotes

† All new compounds gave satisfactory spectral and analytical data.

‡ *Representative procedure for cyclo-glycosylation*: The adduct, that had been azeotropically dried with toluene and kept under vacuum, was dissolved in dry CH_2Cl_2 (*ca.* 0.02 mmol ml^{-1}) under argon, and pulverised activated molecular sieves (4 Å) were added. After 10 min, NIS (1.6 equiv.) was added to the resulting solution at 0 °C followed by 2 drops of a saturated solution of TfOH in dry CH_2Cl_2. The progress of the reaction was monitored by TLC and quenched by addition of 10% sodium thiosulfate solution. The organic layer was washed with saturated sodium bicarbonate and brine and dried. Flash chromatography afforded the corresponding products.

§ Similar selectivity was obtained when an α-thiophenyl or a phenyl sulfoxide group were used as activators for the anomeric centre in the glycosyl donors. The latter was activated for glycosylation with trifluoromethanesulfonic anhydride, according to Kahne *et al.* in ref. 3.

¶ Selected ^{1}H and ^{13}C NMR data ($CDCl_3$, 500 MHz; numbering of protons is that of carbohydrate numbering) for dissaccharides **17a** and **17c**; For **17a** δ_H 4.83 (m, 1 H, H-4), 4.63 (d, 1 H, J = 8.1 Hz, H-1′) and 4.09 (t, 1 H, J = 8.0 Hz, H 3); δ_C 96.4 (C-1) and 100.7 (C-1′). For **17c** δ_H 4.92 (m, 1 H, H-4), 4.49 (d, 1 H, J = 8.8 Hz, H-1′) and 4.12 (t, 1 H, J = 9.6 Hz, H-3); δ_C 96.5 (C-1) and 103.7 (C-1′).

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