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Intramolecular Glycosylation under Neutral Conditions for Synthesis of 1,4-Linked Disaccharides

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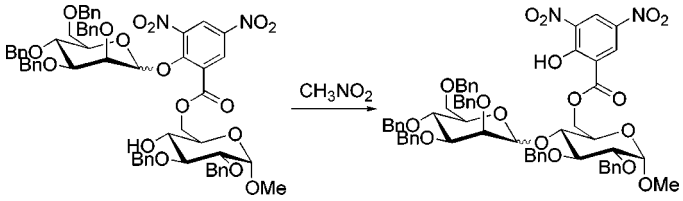
ABSTRACT



A new method for intramolecular glycosylation, in which the donor and acceptor were linked via a 3,5-dinitrosalicylic acid derivative, was developed. Simply dissolving the tethered glycoside in CH_3NO_2 and warming to 40–60 °C led to formation of 1,4-linked disaccharides under neutral, hence, exceptionally mild, conditions.

The increased interest in glycobiology[1] has led to considerable efforts in the development of new techniques for general and efficient glycosylations[2] in the synthesis of biologically active oligosaccharides. One way of directing the regio- and stereochemical outcome of the glycosylation is to tether the donor and acceptor moieties prior to an intramolecular glycosylation.[2c,3] Efficient and stereoselective formation of 1,6-linked disaccharides by intramolecular glycosylation has often been reported, whereas reported techniques for glycosylation of the more hindered and less reactive 4-OH are rare and afford moderate yields and stereoselectivity.[4] By far most glycosylation techniques, whether intermolecular or intramolecular, rely on Lewis acid activation of the glycosyl donor prior to glycosylation.

Very recently,[5] we have developed a method for *inter*molecular glycosylation under neutral conditions. In this glycosylation technique, the anomeric leaving group is methyl 3,5-*di*nitro*sal*icylate (DISAL) or its *para* regioisomer. While these aryl glycosides are stable upon storage at 5 °C and stable for days in CH_2Cl_2 and other nonpolar solvents, they become efficient glycosyl donors in polar, aprotic solvents such as *N*-methylpyrrolidinone (NMP). Simple alcohols, e.g., methanol, were glycosylated stereospecifically, whereas more sterically hindered alcohols, e.g., monosaccharides, were glycosylated with α-selectivity. We envisioned

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that a modified DISAL glycosyl donor, in which the alcohol esterified by the benzoic moiety is not methanol but the 6-OH of a partially protected carbohydrate (Figure 1, **A**), would

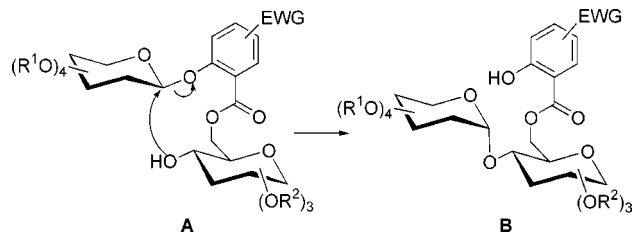
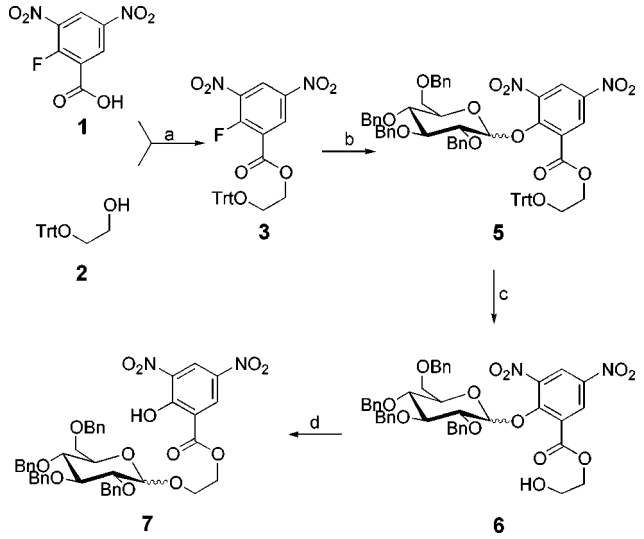


Figure 1. Design for a new intramolecular glycosylation method. EWG = electron withdrawing group (e.g., NO_2); R^1, R^2 = protecting groups.

allow intramolecular glycosyl transfer to 4-OH by a 1,9-glycosyl shift (Figure 1, **B**).

Initially, studies on this new intramolecular glycosylation strategy were carried out with ethylene glycol as a simple model for a carbohydrate diol (Scheme 1). The linker

Scheme 1. Initial Studies of Intramolecular Glycosylation[a]

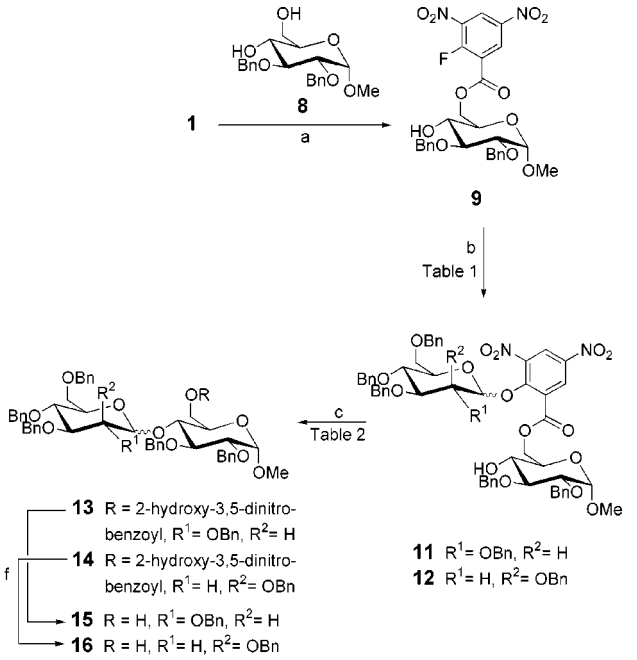


[a] Reagents: (a) i. $(COCl)_2$ (1.0 equiv), DMF (0.1 equiv) in CH_2Cl_2; ii. 2,6-lutidine (2.5 equiv); iii. **2** (1.1 equiv), overall 78%; (b) **3** (1.2 equiv), DMAP (0.3 equiv), **4** (1.0 equiv), Li_2CO_3 (2.0 equiv) in CH_2Cl_2, 90%; (c) HCOOH, Et_2O−toluene, 46%; (d) NMP−CH_3CN, 40 °C, 39%.

precursor, 2-fluoro-3,5-dinitrobenzoic acid **1**,[5] was attached to the acceptor, trityl 2-hydroxyethyl ether **2**,[6] via an ester bond, giving the corresponding benzoic ester **3** in 78% yield. Reaction of **3** and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **4** by nucleophilic aromatic substitution gave the aryl glycoside **5**. Using a "double base" system[5] with an excess of Li_2CO_3 to drain HF from the reaction and a substoichiometric amount of DMAP to transfer protons to the insoluble base, 90% of **5** with an α/β ratio of 6:1 was obtained. Next, the protecting group of the acceptor moiety was removed by treatment with formic acid in Et_2O−toluene to give the tethered glycoside **6** in 46% yield. This moderate yield was probably due to partial hydrolysis of the aryl glycosidic bond during aqueous workup and purification by column chromatography. Dissolving the α-anomer of **6** in NMP−CH_3CN and warming to 40 °C caused a rearrangement to give the desired acylated 2-hydroxyethyl glucopyranoside **7** in 39% yield with an α/β ratio of 2.7:1.

Subsequently, the strategy was implemented for disaccharide synthesis (Scheme 2). The partially protected glycosyl

Scheme 2. Synthesis of 1,4-Linked Disaccharides by Intramolecular Glycosylation[a]



[a] Reagents: (a) i. $(COCl)_2$ (1.0 equiv), DMF (0.1 equiv) in CH_2Cl_2; ii. 2,6-lutidine (2.5 equiv); iii. **8** (1.0 equiv), overall 63%; (b) **9** (1.2 equiv), 1,4-dimethylpiperazine (0.6 equiv) or DMAP (0.3 equiv), Li_2CO_3 (2.0 equiv), **4** or **10** (1.0 equiv) in CH_2Cl_2, see Table 1 for yields; (c) CH_3NO_2, 40 °C, 37% **13**, 58% **14**; (f) NaOMe, MeOH, rt, 95% **15**, 93% **16**.

acceptor methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **8** was esterified with 2-fluoro-3,5-dinitrobenzoic acid **1** to give the *O*-6 benzoic ester **9** in 63% yield. The high regioselectivity of the *O*-acylation obliterated the need for transient protection of *O*-4. The "donors" 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **4** or 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose **10** were attached to the linker moiety by nucleophilic aromatic substitution to form the aryl glycosides **11** and **12**, respectively. In the "double base" system both DMAP and 1,4-dimethylpiperazine (DMP) were used as organic bases in substoichiometric amounts (Table 1). With DMP promotion the β-gly-

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Table 1. Aryl Glycoside Formation by Nucleophilic Aromatic Substitution on **9**

donor moiety	base	yield (α/β)[a]	isolated yield (α/β)
4	DMAP[b]	75% **11** (2.4:1)	
4	DMP[c]	80% **11** (<1:25)	67% **11** (1:9.5)
10	DMAP[b]	75% **12** (4:1)	53% **12** (1:0)
10	DMP[c]	60% **12** (<1:8)	

[a] Yields and anomeric distributions are determined by peak areas in analytical HPLC. [b] 0.3 equiv of DMAP, 5 h at room temperature. [c] 0.6 equiv of DMP (1,4-dimethylpiperazine), 17 h at room temperature.

cosides were formed predominantly in all cases, whereas the faster DMAP-promoted reaction led to formation of the α-glycosides.

Previous experiments on DISAL glycosides had shown that once the aryl glycoside is formed, it does not undergo racemization under the reaction conditions.[5] Similarly, we found that the α/β ratio of the tethered glycosides was constant throughout the DMAP-promoted reaction. We speculate that DMP-promoted arylation predominantly gives the β-glycoside by selective reaction of the more nucleophilic β-alkoxide, while the faster DMAP-promoted arylation presumably proceeds by reaction of the initially predominantly α-configured alkoxide. Yields of aryl glycosides **11** and **12** were in the range of 60−80% with both DMP and DMAP promotion.

The tethered glycosides **11** and **12** were subjected to conditions similar to those used in the model studies (Table 2), and it was rewarding to observe that they did indeed undergo intramolecular transglycosylation to form the corresponding 1,4-linked disaccharides **13** and **14**, respectively. Under neutral conditions in CH_3NO_2 at 60 °C, the intramolecular glycosylation reaction favored formation of β-glucosides and α-mannosides. Yields of the glycosyl transfer according to HPLC were 37% for the glucose derivative **13** (Table 2, entry 1) and 58% for the mannose derivative **14** (Table 2, entry 2), respectively. The latter was isolated in 49% yield with an anomeric distribution of α/β 3.7:1, the starting material **12** having the anomeric distribution of α/β 1.3:1.

Addition of base to the reaction mixtures in the intramolecular glycosylation was detrimental (Table 2, entry 3), whereas substitution of CH_3NO_2 for NMP, CH_3CN, or THF led to degradation of the aryl glycosides. The tethered aryl glycosides were also subjected to Lewis acid conditions (Table 2, entries 4−7). Yields of these reactions were lower than those for the neutral glycosylations, and the α-selectivity in the formation of mannoside **14** also decreased significantly.

The stereoselectivity of the glycosyl transfer reaction changed for some donor/acceptor combinations in going from basic through neutral to acidic conditions (Table 2). However, the differences are too small to draw firm conclusions to the differences in reaction pathways. We observed that upon dissolution in CH_3NO_2 and other polar solvents, the tethered glycosides slowly underwent in situ anomerization (5−15% α from pure β) during glycosylation under neutral or basic conditions. Finally, removal of the DISAL linker was performed by Zemplén deacylation, liberating the 6-OH of disaccharides **15** and **16** in 95% and 93% yields, respectively.

In crossover experiments, secondary alcohols, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose or cyclohexanol, were added as competing nucleophiles in equimolar amounts to the glycosyl transfer reaction of **11** in CH_3NO_2. The secondary alcohol 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, comparable in nucleophilicity to the 4-OH of the tethered acceptor **11**, did *not* give the corresponding *inter*molecular glycosylation product, as the only disaccharide observed was formed by *intra*molecular glycosyl transfer. However, the more reactive cyclohexanol gave the *inter*molecularly formed glycoside as the major product.[7] This indicated that the glycosylation, although not concerted, did take place within the solvent cage unless a nucleophile significantly better than the tethered acceptor was added to the solvent.

To reveal if any hydrolysis of the tethered glycoside occurred during HPLC analysis, a control experiment was performed in which a large excess of MeOH was added to the glycosyl transfer reaction of **12** after 41 h and prior to preparation of HPLC samples. No methyl glycoside was formed under these circumstances, indicating that all of the tethered glycoside **12** had undergone the expected 1,9-glycosyl shift, elimination, or hydrolysis *prior* to dilution in MeOH.

Table 2. Screening of Conditions for Intramolecular Glycosylation

entry	tethered glycoside (α/β)	promoter[a]	solvent	temp, °C	reaction time	hydrolysis[b,c]	yield (α/β)[b]	isolated yield (α/β)
1	**11** (0:1)		CH_3NO_2	60	15 h	48%	**37% 13** (1:1.7)	**24% 13** (1:1.3)
2	**12** (1.3:1)		CH_3NO_2	40	41 h	15%	**58% 14** (3.7:1)	**49% 14** (3.7:1)
3	**11** (0:1)	base[d]	CH_3NO_2	60	40 h	>50%	<20% **13** (1:1.7)	
4	**11** (0:1)	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78 to 0	24 h	50%	27% **13** (2.1:1)	
5	**11** (0:1)	$FeCl_3$	CH_2Cl_2	20	10 min	75%	5% **13** (1:1.2)	
6	**11** (0:1)	TMSOTf	CH_2Cl_2	20	10 min	65%	10% **13** (1:1)	
7	**12** (1.3:1)	$BF_3{\cdot}OEt_2$	CH_2Cl_2	20	90 min	58%	20% **14** (1:1)	

[a] Bases: 3−5 equiv. Lewis acids: 2 equiv. [b] Yields, anomeric distributions, and hydrolysis are determined by peak areas in analytical HPLC. [c] Hydrolysis of aryl glycosides **11** and **12** forming free 1-OH glycopyranoses and esters of 3,5-dinitrosalicylic acid. [d] 2,6-Di-*tert*-butyl-4-(dimethylamino)pyridine, 2,6-lutidine, Et_3N, or DIPEA.

In conclusion, we have developed a new method for intramolecular glycosylation of the 4-OH of D-glucose under neutral, and, hence, extremely mild, conditions. Monosaccharide donors and acceptors were 1,6-linked by a 3,5-dinitrosalicylic acid moiety (DISAL) to form tethered glycosides, which underwent intramolecular transglycosylation to give the expected 1,4-linked disaccharides via 1,9-glycosyl shifts. Yields were somewhat reduced by competing hydrolysis. Further modifications in the implementation of this new concept for intramolecular glycosylation might allow improvements in yields and stereochemical control.

(7) The ratio between the inter- and intramolecular glycosylation products was 5.2:1 (cyclohexyl glycoside vs **13**).

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Supporting Information Available: General experimental procedures for synthesis of esters **3** and **9**, aryl glycosides **5**−**6** and **11**−**12**, and glycosides **7** and **13**−**16**. Complete analytical data for compounds **3**, **5**−**7**, **9**, and **11**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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