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Iterative α-Glycosylation Strategy for 2-Deoxy- and 2,6-Dideoxysugars: Application to the One-Pot Synthesis of Deoxysugar-Containing Oligosaccharides

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This paper describes the development of an iterative and α-selective glycosylation method for 2-deoxyglycosyl and 2,6-dideoxythioglycoside donors based on the DMF modulation concept. We used NMR spectroscopy to probe the 2-deoxyglycosyl imidinium intermediate and elucidated the conditions to decrease the formation of glycal and thus to increase the reaction yields. Further elaboration of the glycosylation method opened the gate for an iterative one-pot synthesis of 2-deoxy- and 2,6-dideoxyglycoside-containing oligosaccharides.

Introduction

2-Deoxyglycosides and 2-deoxysugar-containing oligosaccharides are common in natural glycosylated products,[1] including landomycins,[2] olivomycins,[3] vancomycin,[4] and anthracyclines.[5] Removal or modification of the deoxysugar component of these compounds affects their bioactivities. A point in case is the deconjugation of anthracyclines and digitalis glycosides.[6] Such structure–activity relationships inspire organic chemists to optimize the medicinal properties of natural products and therapeutic agents through modification with simple deoxyglycoside or 2-deoxysugar-containing oligosaccharides.[7–9]

The simplest way to assemble an oligosaccharide is through one-pot glycosylation.[10] Previous one-pot glycosylation methods have been mainly developed for glycosyl substrates that bear a hydroxy or amino function at the C2 position, although these methods are generally impractical for 2-deoxysugars. The lack of a C2 substituent renders 2-deoxyglycosyl donors highly susceptible to elimination, and stereochemical control in glycosylation is difficult.[11] In the past, only a few one-pot glycosylation methods were investigated for the synthesis of 2-deoxysugar-containing oligosaccharides.[12] In most instances, 2-deoxysugar-containing oligosaccharides are often prepared through a stepwise glycosylation approach, which is time consuming and inefficient.[13]

We recently reported on the use of formamide as a modulator for glycosylation with C2-substituted glycosyl donors.[14] It is reasoned that 2-deoxyglycosyl donors are more reactive than their non-deoxy counterparts, as inferred from the highest reactivity value (RRV = 1000000) of 2-deoxythioglucoside relative to that of thioglucoside (RRV = 2000) and 2-azido-2-deoxythioglucoside (RRV = 200, Figure 1).[15] Whether or not the DMF-modulated glycosylation is useful for 2-deoxyglycosyl donors is questionable. Given the wide distribution of deoxysugars in natural glycosylated products and their utility in lead optimizations, it is desired to apply the DMF-modulated glycosylation to simplify the synthesis of 2-deoxysugar-containing oligosaccharides.

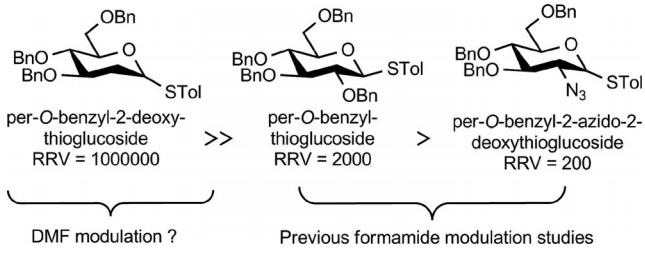

Figure 1. Comparison of the relative reactivity values (RRVs) of protected 2-deoxythioglucoside, thioglucoside, and 2-azido-2-deoxythioglucoside.

Results and Discussion

In formamide-modulated glycosylation, a glycosyl donor is activated and converted into α/β-glycosyl imidinium adducts in the presence of a formamide nucleophile. As the β-imidinium adduct is more reactive than the α-imidinium adduct, the former adduct would react predominately with the acceptor to give the glycosylation product with good α selectivity. As the key to the modulated glycosylation is the

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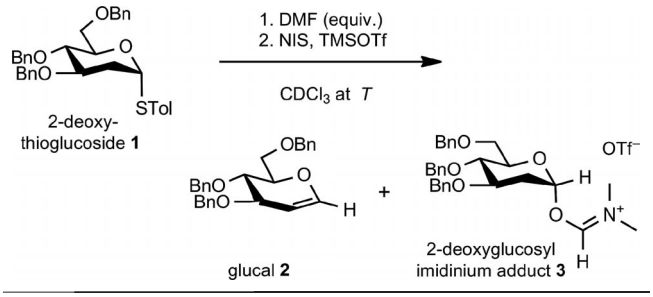
glycosyl imidinium adduct, we elucidated the conditions for the formation of the glycosyl imidinium adduct from a 2-deoxyglycosyl donor (Table 1).

Table 1. Result of the activation of thioglucoside **1** under different reaction conditions.

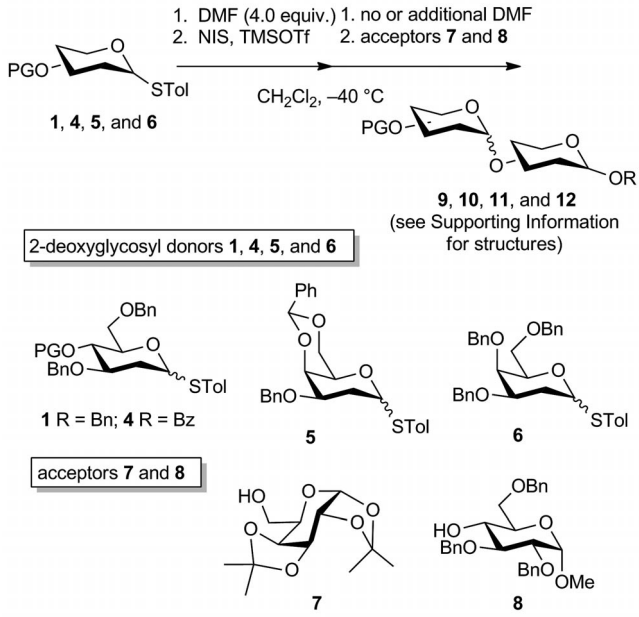


Entry	DMF [equiv.]	*T* [°C]	Ratio[a] [%]	
			2	**3**
1	4.0	0	100	n.d.
2	8.0	0	100	n.d.
3	4.0	–10	100	n.d.
4	4.0	–20	50	50
5	4.0	–40	≤5	95

[a] The **3**/**2** ratio was determined by comparing the integral of their anomeric signals in the ^{1}H NMR spectra; n.d.: not determined.

Thus, a mixture of 2-deoxythioglucoside **1** and DMF in $CDCl_3$ was treated with *N*-iodosuccinimide (NIS) and (trimethylsilyl)trifluoromethanesulfonate (TMSOTf).[16] The resulting mixture was then analyzed by NMR spectroscopy. At a reaction temperature of 0 °C, only elimination product glucal **2** was formed, irrespective of the amount of DMF added (4.0 or 8.0 equiv. with respect to **1**; Table 1, entries 1 and 2). Upon reducing the reaction temperature to below –10 °C, desired 2-deoxyglucosyl imidinium adduct **3** gradually emerged, and the formation of glucal **2** was reduced (Table 1, entries 3–5). Complete suppression of the formation of glucal came at –40 °C and below (Table 1, entry 5). The chemical identity and the α-anomeric configuration of imidinium adduct **3** were determined by the chemical shifts of the anomeric proton (H-1), H-2_{eq}, and H-2_{ax} at δ = 6.28, 2.58, and 1.97 ppm, respectively (Figure 2).[14,17] Additional evidence was obtained from the chemical shift of the anomeric carbon atom at δ = 107 ppm ($^1J_{C,H}$ = 180 Hz) and the correlation between the anomer ^{1}H and ^{13}C signals (refer to the NMR spectra in the Supporting Information). However, we were unable to detect the β-anomer of **3**, which may be attributed to its scarcity.

Based on the reaction conditions explored in the NMR spectroscopy study, we validated the DMF-modulated glycosylation with 2-deoxythioglucosyl donors **1** and **4** and 2-deoxythiogalactosyl donors **5** and **6** (Scheme 1, Table 2).



Scheme 1. Validation of the DMF-modulated glycosylation method with 2-deoxythioglycosyl donors **1**, **4**, **5**, and **6**; PG = protecting group, Bz = benzoyl.

Under the DMF modulation conditions, the glycosylation of primary galactosyl acceptor **7** with 2-deoxythiogalactosyl donor **5** at –40 °C afforded disaccharide **9** in a high 91% yield with an excellent 25:1 α/β ratio (Table 2, entry 1). Repeating the reaction with the conventional procedure decreased the reaction yield to 75% owing to the galactal formation (Table 2, entry 2). The glycosylation of **7** with 2-deoxythioglucosyl donor **4** in the presence of DMF

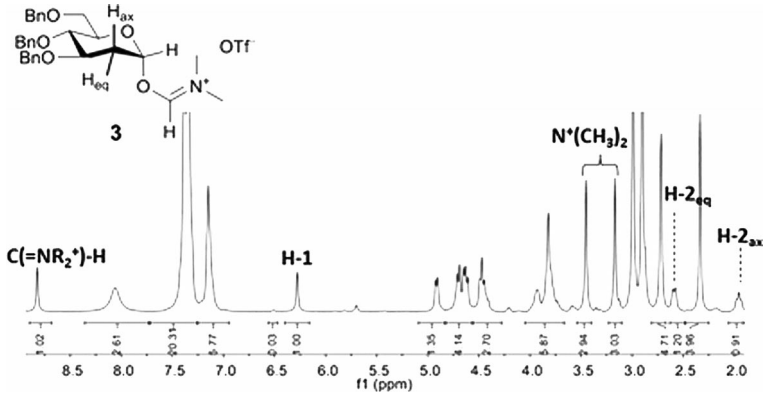


Figure 2. ^{1}H NMR of 2-deoxyglucosyl imidinium adduct **3** at –40 °C.

Table 2. Validation of the DMF-modulated glycosylation method with 2-deoxythioglycoside donors **1**, **4**, **5**, and **6**.

Entry	Donor, acceptor	DMF [equiv.]	Time [h]	Product, yield [%] (α/β[a])
1	**5**, **7**	4	3.0	**9**, 91 (25:1)
2	**5**, **7**	0[b]	3.0	**9**, 75 (19:1)
3	**4**, **7**	12[c]	12.0	**10**, 95 (7:1)
4	**4**, **7**	4	4.0	**10**, 93 (4:1)
5	**4**, **7**	0[b]	4.0	**10**, 80 (1:1)
6	**1**, **8**	4	10	**11**, 81 (32:1)
7	**1**, **8**	0[b]	10	**11**, 50 (3.5:1)
8	**6**, **8**	4	8.5	**12**, 82 (11:1)
9	**6**, **8**	0[b]	3.5	**12**, 72 (8:1)

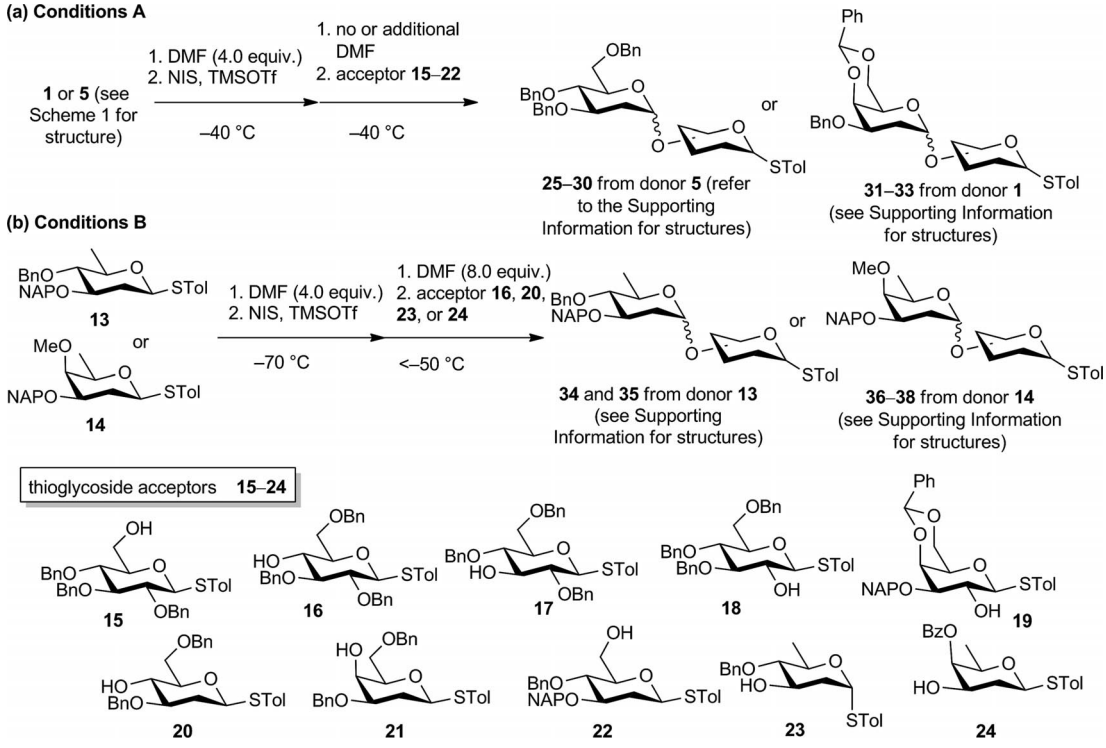
[a] The α/β ratios were determined by HPLC analysis; the HPLC chromatograms are given in the Supporting Information. [b] A conventional glycosylation procedure was applied in the absence of a DMF modulator. [c] An additional 8.0 equiv. of DMF was added to the mixture after the activation of the donor. Thus, the overall amount of DMF added was 12 equiv.

(4.0 equiv.) produced desired disaccharide **10** in a high 93% yield but with a moderate α/β ratio of 4:1 (Table 2, entry 4). The selectivity was improved by adding an additional amount of DMF (8.0 equiv.) after the donor activation (Table 2, entry 3). In comparison, no selectivity was observed in the absence of the DMF modulation (Table 2, entry 5). Other than galactosyl acceptor **7**, the DMF modulation procedure was effective for the glycosylation of glucosyl acceptor **8** with 2-deoxythioglucosyl donor **1** and 2-deoxythiogalactosyl donor **6** (Table 2, entries 6–9).

Encouraged by the results of the validation, we applied the DMF modulation to the glycosylation of thioglycosyl acceptors. The resulting glycosylation products would directly be used as glycosyl donors without modification, which would thus pave the way for iterative α-glycosylation. Accordingly, thioglycoside acceptors **15**–**19** and 2-deoxythioglycoside acceptors **20**–**24** were prepared for glycosylation with 2-deoxythioglycosyl donors **1** and **5** (Scheme 2). To broaden the scope of the investigation, 2,6-dideoxythioglycosyl donors, that is, thioolivoside **13** and thioolioside **14**, were included. Notably, these 2,6-dideoxyglycoside motifs occur frequently in natural products. Table 3 summarizes the results of this glycosylation study.

In the glycosylation with 2-deoxythioglycosyl donors **1** and **5**, a reaction temperature of –40 °C was applied for the activation of the donor and the coupling with the acceptor (conditions A, Scheme 2, a). In contrast, in the glycosylation with the 2,6-dideoxythioglycosyl donors, a lower reaction temperature of –70 °C was needed to avoid the glycal formation in the donor activation, and the temperature for coupling of the acceptor was kept below ≤–50 °C (conditions B, Scheme 2, b). For particular glycosylations, an additional amount of DMF (4.0 or 8.0 equiv.) was added to improve the α selectivity.

The glycosylation of thioglycosyl acceptors **15**–**22** with 2-deoxythioglycosyl donors **1** and **5** went smoothly, and disaccharide thioglycosides **25**–**33** were obtained in high 70–90% yield with α/β ratios spanning from 8:1 to >20:1 (Table 3, entries 1–9). No significant thio-transfer side reac-



Scheme 2. (a) Iterative α-glycosylation with 2-deoxythioglycosyl donors **1** and **5**. (b) Iterative α-glycosylation with 2,6-dideoxythioglycosyl donors **13** and **14**. (c) Thioglycoside acceptors **15**–**19** and 2-deoxythioglycosyl acceptors **20**–**24**; NAP = 2-naphthylmethyl.

Table 3. Glycosylation of thioglycosyl acceptors with 2-deoxythioglycosyl donors **1** and **5** and 2,6-dideoxy-thioglycosyl donors **13** and **14**.

Entry	Donor, acceptor	DMF [equiv.]	Time [h]	Product, yield [%] (α/β[a])
1	**1**, **15**[b]	12	7	**25**, 89 (8:1)
2	**1**, **16**[b]	4	18	**26**, 90 (15:1[d])
3	**1**, **17**[b]	4	24	**27**, 77 (11:1[d])
4	**1**, **18**[b]	4	27	**28**, 73 (9:1[d])
5	**1**, **19**[b]	12	20	**29**, 75 (>20:1[d])
6	**1**, **20**[b]	4	18	**30**, 70 (8:1[d])
7	**5**, **21**[b]	4	18	**31**, 74 (12:1[d])
8	**5**, **22**[b]	12	18	**32**, 81 (>20:1[d])
9	**5**, **15**[b]	12	20	**33**, 75 (11:1[d])
10	**13**, **16**[c]	12	30	**34**, 80 (12:1[d])
11	**13**, **20**[c]	12	24	**35**, 55 (α-only[e])
12	**14**, **16**[c]	12	20	**36**, 65 (16:1[d])
13	**14**, **23**[c]	8	18	**37**, 65 (α-only[e])
14	**14**, **24**[c]	12	36	**38**, 81 (>20:1[d])

[a] The α/β ratios of **26**–**34**, **36**, and **38** were determined by HPLC analysis (mighty gel 2.5–40 mm with hexane/CH_2Cl_2/EtOAc elution at 0.8 mL min^{-1}), and the ratio of **25** was based on ^{1}H NMR spectroscopy. [b] Conditions A were used. [c] Conditions B were used. [d] HPLC chromatograms are given in the Supporting Information. [e] The α-anomer was isolated, and the β-anomer was not detected.

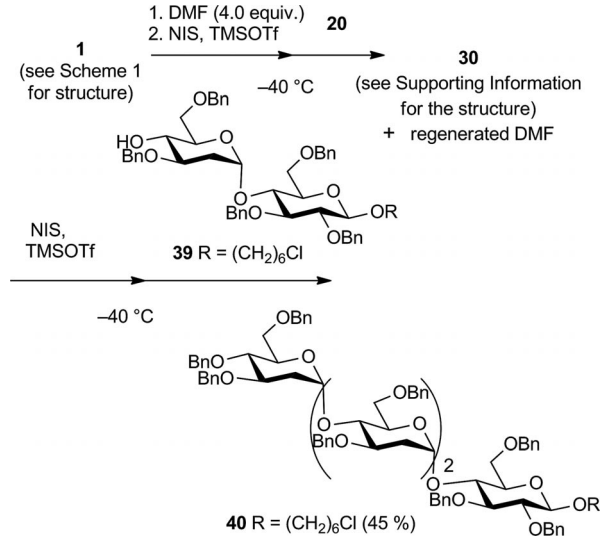
tion occurred under the glycosylation conditions.[18] The α selectivity was lower for primary glycosyl acceptor **15** than for secondary acceptor **16** (Table 3, entries 1 and 2). A similar trend was observed in glycosylations with 2-azido-2-deoxyglycosyl donors.[14b]

The glycosylation of thioglycosyl acceptors **16**, **20**, **23**, and **24** with 2,6-dideoxythioglycosyl donors **13** and **14** furnished expected disaccharide thioglycosides **34**–**38** in 55–81% yield with high to excellent α selectivity (Table 3, entries 10–14). Disaccharide **38** is commonly found in olivomycins[19] and chromomycins.[20]

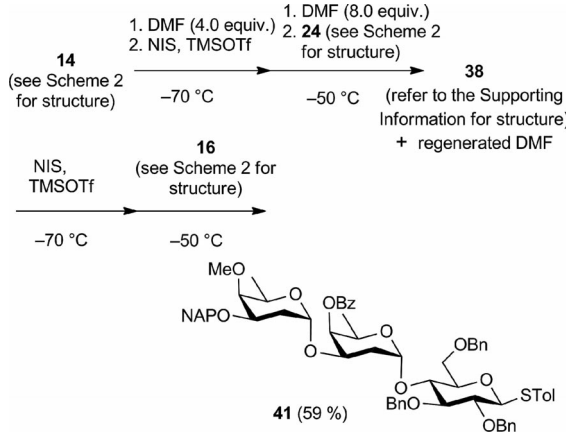
After examining the substrate scope of the glycosylation method, we proceeded to the one-pot synthesis of 2-deoxysugar-containing oligosaccharides. In this regard, protected tetrasaccharide glycoside **40** and trisaccharide thioglycoside **41** were selected as our models (Schemes 3 and 4).

The synthesis of **40** required 2-deoxythioglucosyl building block **1**, 2-deoxythioglucosyl building block **20**, and reducing end disaccharide building block **39** (Scheme 3). Thus, 2-deoxythioglucoside **1** was coupled with 2-deoxythioglucoside **20** using the DMF-modulated glycosylation method to furnish disaccharide intermediate **30**. The intermediate **30** and the regenerated DMF underwent a second modulated glycosylation to react with disaccharide **39** affording desired tetrasaccharide **40** in 45% yield.

The one-pot synthesis of trisaccharide target **41** was challenging, because both 2,6-dideoxythioglycoside building blocks **14** and **24** invoked are prone to undergo glycal formation. Our synthesis commenced with the coupling of thioolioside acceptor **24** with thioolioside donor **14** by using DMF-modulated glycosylation procedure B (Scheme 2, b). The reaction produced disaccharide thioglycoside **38** and regenerated the DMF (Scheme 4). After the first glycosylation was complete, the reaction temperature was brought to –70 °C; at which point disaccharide **38** was undertaken the second modulated glycosylation to couple with thioglucosyl acceptor **16**. As such, target **41** was obtained in 59% yield as a single isolable isomer.



Scheme 3. Iterative one-pot α-glycosylation for the synthesis of 2-deoxysugar-containing oligosaccharide **40**.



Scheme 4. Iterative one-pot α-glycosylation for the synthesis of 2-deoxysugar-containing oligosaccharide **41**.

Conclusions

We developed a simple α-selective glycosylation method for 2-deoxy- and 2,6-dideoxythioglycoside donors based on the DMF modulation concept. Further application of this method to oligosaccharide synthesis was demonstrated. As a number of natural products are glycosylated with deoxysugars, the DMF-modulated glycosylation method should prove useful for their preparation.

Supporting Information (see footnote on the first page of this article): Preparation or references for the preparation of glycosyl substrates **1**, **4**–**6**, **8**, **13**–**24**, and **39**; DMF-modulated glycosylation protocols for 2-deoxythioglycosyl donors; and NMR spectroscopic data.

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