Carbohydrate Research 345 (2010) 2146–2150

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

On the stereoselectivity of glycosidation of thiocyanates, thioimidates, and thioglycosides

Sophon Kaeothip, Steven J. Akins, Alexei V. Demchenko *

Department of Chemistry and Biochemistry, University of Missouri – St. Louis, One University Boulevard, St. Louis, MO 63121, USA

ARTICLE INFO

Article history:
Received 10 May 2010
Received in revised form 5 August 2010
Accepted 5 August 2010
Available online 10 August 2010

Keywords:
Glycosylation
Stereoselectivity
Protecting groups
Glycosyl donors

ABSTRACT

Comparative side-by-side glycosylation studies demonstrated that glycosyl thiocyanates, thioimidates, and thioglycosides provide comparative stereoselectivities in glycosylations. Very high α-stereoselectivity that was previously recorded for glycosyl thiocyanates can be achieved, but only if glycosyl acceptors are equipped with electron-withdrawing acyl substituents. Partially benzylated glycosyl acceptors provided relatively modest stereoselectivity, which was on a par with other common glycosyl donors. Accordingly, thioimidates and thioglycosides showed high stereoselectivity similarly to that of thiocyanates with different classes of acylated primary and secondary glycosyl acceptors.

The stereocontrolled introduction of glycosidic linkages[1,2] is arguably the most challenging aspect in the synthesis of oligosaccharides[3–9] and glycoconjugates.[10–12] While a 1,2-*trans* glycosidic linkage can be usually stereoselectively obtained by using the anchimeric assistance from the participatory neighboring substituent at C-2 (most commonly an ester[13] or recently introduced picolinyl),[14,15] the stereoselective formation of a 1,2-*cis* linkage still remains a notable challenge,[16] despite significant recent improvements.[17–19] In addition to the effect of protecting groups on the glycosyl donor, a myriad of other factors is known to have effect on the stereoselectivity of the chemical glycosylation;[20] and the effect of conformation,[21] solvent,[22–24] temperature,[25] metal coordination,[26] steric hindrance,[27,28] and remote participation[29–31] are only few to mention. It is commonly believed that a typical glycosylation follows the unimolecular mechanism with the rate-determining step being the glycosyl acceptor attack on the intermediate formed as a result of the leaving group departure.[32] Nevertheless, occasionally the effect of a leaving group itself may also have an influence on the anomeric stereoselectivity. However, it is often unclear whether this effect is a result of a bimolecular or close-ion pair rather than the unimolecular displacement mechanism, or other factors affecting this complex process.

As part of a program to develop new protocols for the stereocontrolled glycosylation, we have been investigating various classes of sulfur-based leaving groups ranging from conventional alkyl/aryl thioglycosides to relatively novel *S*-benzoxazolyl (SBox) or *S*-thiazolinyl (STaz) thioimidates. In particular, we were interested in a possible influence that different leaving groups may have on the outcome of glycosylations. While on a number of occasions we managed to achieve very good to excellent stereoselectivities, particularly with the SBox glycosides, these results have been occasionally outshadowed by other classes of glycosyl donors. For example, glycosyl thiocyanates that have been introduced two decades ago have proven to be very effective glycosyl donors for what then appeared to be 'stereospecific 1,2-*cis* glycosylations'.[33] Indeed, in a series of publications, Kochetkov et al., provided a convincing case of the power of this class of glycosyl donors.[33–37] Various hexose and pentose 1,2-*trans* thiocyanate glycosyl donors were found to provide 1,2-*cis* glycosides completely stereoselectively (or stereospecifically, as quoted in the original literature) with the only failure reported when the method was applied to the synthesis of β-mannosides.[38] Another attractive feature of this glycosylation approach is that the activation could be performed in the presence of a catalytic amount of promoter and at ambient temperature.

While tritylated acceptors were used in most of the reported transformations, a complementary procedure involving unprotected hydroxyl group was also developed.[35] The major drawback of this technique was modest yields obtained during both the synthesis of glycosyl thiocyanates and glycosidations thereof. This drawback was arguably related to the propensity of thiocyanates to isomerize into the corresponding isothiocyanates. The latter would remain inert under the glycosylation conditions leading to average to modest yields, which could be further diminished by the migration of acetyl substituents that have been used as protecting groups throughout the original reports. For example, when we reacted 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-β-D-glucopyranosyl thiocyanate **1**[37] with glycosyl acceptor **2**[39] in the presence of catalytic

* Corresponding author. Fax: +1 314 516 5342.
E-mail address: demchenkoa@umsl.edu (A.V. Demchenko).

0008-6215/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2010.08.003

amount (0.2 equiv) of triphenylmethyl perchlorate[40] ($TrClO_4$) in 1,2-dichloroethane (DCE) at ambient temperature, the corresponding 1,2-*cis*-linked disaccharide **5**[37] was obtained with complete stereoselectivity (conservative estimation α/β >25:1, although no evidence of the corresponding 1,2-*trans* anomer could be detected by ^{1}H NMR) yet only in a modest yield of 65% (Scheme 1). This result was in line with previously reported results for similar systems.[37]

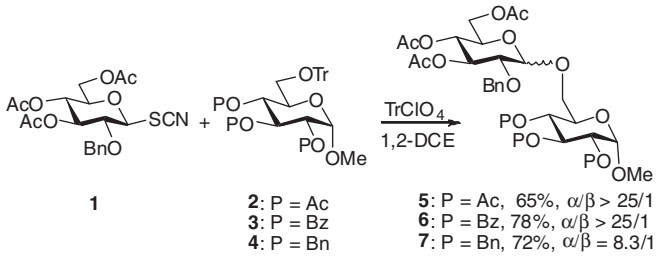
We assumed that the application of more stable benzoyl or benzyl protecting groups would enhance the overall stability of the glycosyl acceptor by reducing the acyl migration. Indeed, the disaccharide **6**,[41] derived from benzoylated glycosyl acceptor **3**,[42] was isolated in a significantly improved yield of 78% and with complete 1,2-*cis* stereoselectivity. However, when the structurally similar benzylated glycosyl acceptor **4**[43] was employed, the corresponding disaccharide **7**[44] was obtained in a yield of 72%, but as a mixture of diastereomers (α/β = 8.3:1). This notable decrease in the stereoselectivity of glycosyl thiocyanates, which were previously described as glycosyl donors capable of the concerted stereospecific displacement, was intriguing. To the best of our knowledge, this was the first example wherein thiocyanate **1** of the D-*gluco* series gave the anomeric mixture, although prior to this study the stereoselectivity of glycosyl thiocyanates was only investigated with partially acetylated acceptors.[37] Hence, this atypical observation led us to a decision to reinvestigate glycosidations of thiocyanates in a greater detail.

In principle, the effect of protecting groups on the reactivity of glycosyl acceptor has been noted.[16,45–47] It has been observed that strongly electron-withdrawing ester protecting groups decrease electron density at the hydroxyl group (or triphenylmethoxy as in the examples depicted in Scheme 1) thus lowering its nucleophilicity and hence reactivity in glycosylation. However, still very little is understood about the actual effect that the glycosyl acceptor protection may have on stereoselectivity of glycosylation.[48] Basic knowledge in this area implies that an enhanced stereocontrol could be achieved with the less nucleophilic acceptors (such as **2** or **3**). Occasionally, a mismatch between donor–acceptor pair may result in the unexpected stereoselectivity outcome and/or reduced yields.[49–53] Hence, at first, we attributed the result obtained for disaccharide **7** to the increased reactivity of the glycosyl acceptor **4**, which implies that the glycosidation of glycosyl thiocyanate donors follows unimolecular rather than the earlier proposed concerted push-pool mechanism.[33,37]

In order to extend this finding, we employed common benzoylated (**10**)[42] and benzylated (**11**)[54] 6-OH glycosyl acceptors that were subjected to systematic investigation with the thiocyanate donor **1** along with a variety of other thio-derivatives. As previously reported,[35] glycosyl thiocyanate **1** could be activated for reactions with non-tritylated acceptors in the presence of catalytic amount of TMSOTf. However, these rather sluggish reactions were commonly accompanied by the competing isomerization of glycosyl donor **1** into the corresponding isocyanate, which was reflected in low efficiency.[35] Although excellent stereoselectivity (α/β = 10.2:1) was observed with the benzoylated glycosyl acceptor **10**, the disaccharide **6** was obtained in only 45% yield (Table 1, entry 1). The reaction with the more reactive glycosyl acceptor **11** was more rapid (36 vs 48 h), which was also reflected in the improved yield of disaccharide (69%) yet displayed twofold reduced stereoselectivity (entry 2).

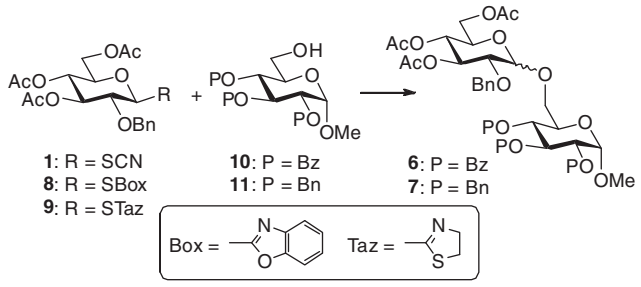
Since our key task was to compare glycosyl thiocyanates with other classes of thioglycosyl donors, such as thioimidates, we decided to search for the universal promoters of glycosylation that would activate both classes of glycosyl donors. If such promoters were available, one could standardize the reaction conditions across the spectrum of different classes of glycosyl donors to obtain comparable results by excluding the possibility of the promoter effect. Based on our previous reports, the most prominent results for glycosidation of *S*-benzoxazolyl (SBox, **8**)[41,55] and *S*-thiazolinyl (STaz, **9**)[44,56] glycosides have been obtained in the presence of AgOTf as the promoter. Hence, thiocyanate **1** was also investigated in the presence of stoichiometric amount of AgOTf. Relatively clean and fast activations (5–15 min) resulted in good yields for the coupling products **6** and **7** (78–84%, entries 3 and 4). This result could serve as a promising new beginning of comparative glycosylation studies with thiocyanates and thioimidates. However, somewhat lower overall stereoselectivity was observed in comparison with that seen in TMSOTf-promoted glycosidations (entries 1 and 2). Nevertheless, the trend remained the same, and the disaccharide **6** derived from the benzoylated glycosyl acceptor **10** was obtained in a notably higher α-stereoselectivity than its benzylated counterpart **7** from **11** (7.5:1 and 2.2:1, respectively). The latter result was particularly surprising considering the sturdy common knowledge of thiocyanates being among the most stereoselective glycosyl donors developed to date. Indeed, this example clearly illustrated that the effect of glycosyl acceptor and promoter of glycosylation cannot be underestimated and may have a prevailing effect on the reaction outcome.

When SBox or STaz glycosides (**8** and **9**, respectively) have been investigated, a very similar trend has been observed, although



Scheme 1. Reaction of thiocyanate **1** with differently protected 6-*O*-trityl glycosyl acceptors **2**–**4**.

Table 1
Glycosylations of various glycosyl donors **1**, **8**, and **9** with glycosyl acceptors **10** and **11**



Entry	Donor	Acceptor	Cond's	Time	Product, yield (%)	Ratio α/β[a]
1	**1**	**10**	A	48 h	**6**, 45	10.2/1
2	**1**	**11**	A	36 h	**7**, 69	5.0/1
3	**1**	**10**	B	5 min	**6**, 84	7.5/1
4	**1**	**11**	B	15 min	**7**, 78	2.2/1
5	**8**	**10**	B	1 h	**6**, 92	9.5/1
6	**8**	**11**	B	30 min	**7**, 84	3.8/1
7	**9**	**10**	B	2 h	**6**, 89	7.4/1
8	**9**	**11**	B	1.5 h	**7**, 81	2.7/1

Reagents and conditions: All glycosylations were performed in 1,2-dichloroethane under argon at rt: (A) TMSOTf (0.2 equiv); (B) AgOTf (1.0 equiv for **1**, 2.0 equiv for **8** and **9**), 3 Å molecular sieves.

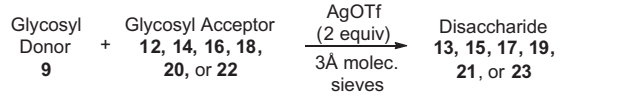
[a] Determined by comparison of integral intensities of the respective signals in ^{1}H NMR spectra.

these activations were slower than those of glycosyl thiocyanate **1**, and required at least 2.0 equiv of AgOTf. Again, disaccharide **6** derived from the benzoylated glycosyl acceptor **10** was obtained with a much higher (approximately threefold) α-stereoselectivity (entries 5 and 7) than its benzylated counterpart **7** from acceptor **11** (entries 6 and 8). It should be noted that the rate of the reaction did not clearly correlate with the stereoselectivity observed: for example, slower glycosidations of the STaz derivative **9** provided lower stereoselectivity than that of the SBox glycoside **8**.

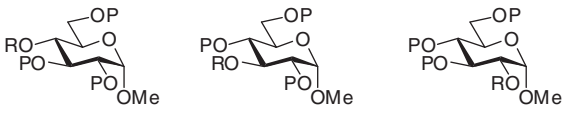
To gain a broader insight, a similar set of experiments has been performed using a variety of standard secondary glycosyl acceptors with the uniform benzoyl and benzyl protecting group pattern (**12**,[57] **14**,[58] **16**,[57] **18**,[59] **20**,[60] and **22**[61]). STaz glycosyl donor **9** was used in this comparative evaluation. As evident from the results presented in Table 2, the glycosylations of secondary glycosyl acceptors were in accordance with the observation made for primary glycosyl acceptors **10** and **11**. Thus, benzoylated glycosyl acceptors (**12**, **16** and **20**) gave consistently higher stereoselectivity (α/β ~12:1, entries 1, 3, and 5) for the formation of disaccharides (**13**, **17**, and **21**, respectively) than their benzylated counterparts (**14**, **18**, and **22**) provided for disaccharides **15**,[44] **19**, and **23**[44] (α/β ~6.5–9.3:1, entries 2, 4, and 6).

Since ethyl thioglycosides are inert in the presence of either TMSOTf or AgOTf, direct comparison of them with thiocyanates and thioimidates was not possible. Nevertheless, we supposed that this general study may benefit from the indirect comparison with a common ethyl thioglycosides, even though its activation required entirely different activation protocol. Indeed, a very similar trend was achieved when ethyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-1-thio-β-D-glucopyranoside[62] was glycosidated in the presence of NIS–TfOH (or other common promoters for thioglycoside activation).[63–66] For example, disaccharide **6** derived from the benzoylated glycosyl acceptor **10** was obtained in a significantly higher α-stereoselectivity than its benzylated counterpart **7** (6.8:1 vs 1.7:1, respectively). In addition, a very similar trend has been observed with per-benzylated STaz and SEt glycosyl donors (these results are not shown herein and will be reported elsewhere).

Table 2
The glycosylations of secondary glycosyl acceptors **12**, **14**, **16**, **18**, **20**, and **22** with the STaz donor **9**



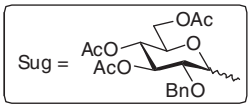
Entry	Acceptor	Time (h)	Product, yield (%)	Ratio α/β
1	**12**	16	**13**, 89	11.7/1
2	**14**	14	**15**, 90	6.8/1
3	**16**	12	**17**, 87	12.1/1
4	**18**	8	**19**, 85	6.51
5	**20**	12	**21**, 72	12.01
6	**22**	6	**23**, 87	9.31



12: P=Bz, R=H
13: P=Bz, R=Sug
14: P=Bn, R=H
15: P=Bn, R=Sug

16: P=Bz, R=H
17: P=Bz, R=Sug
18: P=Bn, R=H
19: P=Bn, R=Sug

20: P=Bz, R=H
21: P=Bz, R=Sug
23: P=Bn, R=H
23: P=Bn, R=Sug



In conclusion, we observed that protecting groups on glycosyl acceptor have a profound effect on stereoselectivity of glycosylation. The effect of protecting groups of glycosyl acceptor on the stereoselectivity of glycosylation seemed very directly correlated to their electron-withdrawal power. Thus, we demonstrated that much higher α-stereoselectivity can be obtained with glycosyl acceptors bearing more electron-withdrawing benzoyl substituents in comparison with that of their benzylated conterparts. This improvement was consistently achieved with all classes of glycosyl donors investigated (thiocyanates, thioimidates, and thioglycosides) and was practically independent on the leaving group used. Both primary and secondary glycosyl acceptors showed the same trend; and these results were in line with generally accepted principles of the effect of protecting groups on glycosyl acceptor. The actual effect remains unclear, but it is possible that a variety of factors may have to be considered: dipole moments of the entire molecule, dipole–dipole interactions, polarizability, donor–acceptor match-mismatch, the role of the promoter (and the activation mode), solvent, etc. Further investigation of the protecting and leaving group effects on stereoselectivity of glycosylation is currently underway in our laboratory.

1. Experimental

1.1. General

Column chromatography was performed on Silica Gel 60 (EM Science, 70–230 mesh), reactions were monitored by TLC on Kieselgel 60 F_{254} (EM Science). The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. 1, 2-Dichloroethane was distilled from CaH_2 directly prior to application in glycosylations. Molecular sieves (3 Å or 4 Å), used for reactions were crushed and activated in vacuo at 390 °C during 8 h in the first instance and then for 2–3 h at 390 °C directly prior to each application. AgOTf (Acros) was co-evaporated with toluene (3 × 10 mL) and dried in vacuo for 2–3 h directly prior to each application. ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 MHz, ^{13}C NMR spectra were recorded at 75 MHz (Bruker Avance). HRMS determinations were made with the use of JEOL MStation (JMS-700) Mass Spectrometer.

1.2. Typical glycosylation procedures

1.2.1. Method A. Typical AgOTf promoted glycosylation procedure

A mixture of the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3 Å, 200 mg) in $(ClCH_2)_2$ (2 mL) was stirred under argon for 1.5 h. Freshly conditioned AgOTf (0.11–0.22 mmol) was added and the reaction mixture was monitored by TLC. Upon completion (see Table), the reaction mixture was diluted with CH_2Cl_2 (20 mL), the solid was filtered off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with 20% aq $NaHCO_3$ (15 mL), water (3 × 10 mL), and the organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc–toluene gradient elution) to afford the corresponding disaccharide derivative.

1.2.2. Method B. TMSOTf-promoted glycosylation procedure

A mixture of the glycosyl donor (0.11 mmol) and glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in $(ClCH_2)_2$ (2 mL) was stirred for 1.5 h under argon. TMSOTf (0.022 mmol) was added and the reaction mixture was monitored by TLC. Upon completion, the reaction was quenched

with a drop of pyridine. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with 20% aq $NaHCO_3$ (15 mL) and water (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc–toluene gradient elution) to afford the corresponding disaccharide derivative.

1.2.3. Method C. NIS-TfOH promoted glycosidation of *S*-ethyl glycosides

A mixture of the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in $(ClCH_2)_2$ (2 mL) was stirred for 1.5 h under argon. NIS (0.22 mmol) and TfOH (0.022 mmol) were added and the reaction mixture was monitored by TLC. Upon completion, the reaction mixture was diluted with CH_2Cl_2 (20 mL), the solid was filtered off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with 20% aq $Na_2S_2O_3$ (15 mL) and water (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc–toluene gradient elution) to afford a disaccharide derivative.

1.2.4. Methyl 4-*O*-(3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α/β-D-glycopyranosyl)-2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside (13)

Compound **13** was obtained from **9** and **12** in 87% yield (α/β = 12.1:1). Analytical data for **13**: R_f = 0.46 (EtOAc–toluene, 3:7, v/v); ^{1}H NMR: δ, 1.97, 2.01, 2.02 (3s, 9H, 3 × $COCH_3$), 3.37 (dd, 1H, $J_{2',3'}$ = 5.8 Hz, H-2′), 3.45 (s, 3H, OCH_3), 4.09 (m, 1H, H-5′), 4.16–4.26 (m, 3H, H-4, 6a′, 6b′), 4.08 (m, 1H, $J_{5,6b}$ = 2.7 Hz, H-5), 4.66 (dd, 1H, H-6a), 4.78 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, H-6b), 4.85 (dd, 1H, $J_{4',5'}$ = 9.4 Hz, H-4′), 5.14 (d, 1H, $J_{1,2}$ = 2.1 Hz, H-1), 5.14–5.22 (m, 3H, H-1′, CH_2Ph), 5.36 (dd, 1H, $J_{3',4'}$ = 9.8 Hz, H-3′), 6.20 (dd, 1H, $J_{3,4}$ = 8.5 Hz, H-3), 7.03–8.10 (m, 20H, aromatic) ppm; ^{13}C NMR: δ, 20.8 (×3), 55.7, 62.1, 63.6, 68.5, 68.6, 68.7, 71.7, 72.2, 72.4, 73.1, 75.7, 76.4, 77.4, 97.0, 98.0, 127.8 (×2), 128.0, 128.5 (×2), 128.6 (×3), 128.8 (×3), 129.2, 129.9 (×4), 130.1, 130.2 (×2), 133.3, 133.6 (×2), 137.7, 165.4, 166.3 (×2), 169.9, 170.0, 170.7 ppm; HR-FAB MS: calcd for $C_{47}H_{55}O_{14}$ $[M+H]^+$: 843.3592; found: 843.3594.

1.2.5. Methyl 3-*O*-(3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α/β-D-glycopyranosyl)-2,4,6-tri-*O*-benzoyl-α-D-glucopyranoside (17)

Compound **17** was obtained from **9** and **16** in 89% yield (α/β = 11.7:1). Analytical data for **17**: R_f = 0.48 (EtOAc–toluene, 3:7, v/v); ^{1}H NMR: δ, 1.76, 1.78, 2.02 (3s, 9H, 3 × $COCH_3$), 3.27 (dd, 1H, $J_{2',3'}$ = 10.0 Hz, H-2′), 6.46 (s, 3H, OCH_3), 3.76–3.87 (m, 3H, H-6a′, 6b′, 1/2CH_2Ph), 4.06 (dd, 1H, $J_{5',6a'}$ = 10.4 Hz, $J_{5',6a'}$ = 5.3 Hz, H-5′), 4.17 (d, 1H, ^2J = 12.7 Hz, 1/2CH_2Ph), 4.33 (m, 1H, H-5), 4.45 (dd, 1H, $J_{6a',6b'}$ = 14.4 Hz, H-6a′), 4.56–4.62 (m, 2H; H-3, 6b′), 4.74 (dd, 1H, $J_{4',5'}$ = 9.8 Hz, H-4′), 5.06 (d, 1H, $J_{1',2'}$ = 3.7 Hz, H-1′), 5.10 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 5.22 (dd, 1H, $J_{3',4'}$ = 9.6 Hz, H-3′), 5.36 (dd, 1H, $J_{2,3}$ = 9.9 Hz, H-2), 5.68 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 6.91–8.06 (m, 20H, aromatic) ppm; ^{13}C NMR: δ, 20.7, 20.8, 20.9, 55.8, 61.8, 63.3, 67.8 (×2), 68.3, 71.4, 71.7, 72.5, 72.6, 76.3, 77.4, 97.3, 98.0, 127.9 (×2), 128.5 (×2), 128.6 (×2), 128.7 (×3), 129.9, 130.0 (×2), 130.2 (×2), 130.7 (×2), 133.3, 133.5, 133.6, 164.9, 165.8, 166.5, 169.7, 169.9, 170.8 ppm; HR-FAB MS: calcd for $C_{47}H_{48}O_{17}Na$ $[M+Na]^+$: 907.2789; found: 907.2790.

1.2.6. Methyl 3-*O*-(3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α/β-D-glycopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (19)

Compound **19** was obtained from **9** and **18** in 90% yield (α/β = 6.8/1). Analytical data for **19**: R_f = 0.50 (EtOAc/toluene, 3/7, v/v); ^{1}H NMR: δ, 1.91, 1.94, 2.06 (3s, 9H, 3 × $COCH_3$), 3.35 (s, 3H, OCH_3), 3.52–3.79 (m, 3H, H-2, 2′, 4), 3.76 (m, 1H, H-5), 3.89–3.93 (m, 2H, H-6a, 6b), 4.24 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 4.34–4.53 (m, 4H, H-6a′, 6b′, CH_2Ph), 4.59–4.68 (m, 4H, H-5′, CH_2Ph), 4.73 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.84 (d, 1H, J^2 = 12.0 Hz, 1/2CH_2Ph), 4.91 (dd, 1H, $J_{4',5'}$ = 10.3 Hz, H-4′), 5.49 (dd, 1H, $J_{3',4'}$ = 9.8 Hz, H-3′), 5.60 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1′), 6.90–7.35 (m, 20H, aromatic) ppm; ^{13}C NMR: δ, 20.9, 21.0, 21.1, 55.3, 62.0, 67.3, 68.6, 68.8, 70.0, 72.4, 72.8, 73.5, 73.7 (×2), 76.4, 77.4, 78.3, 78.9, 97.1, 97.7, 126.6 (×2), 127.4, 127.8 (×2), 127.9 (×2), 128.1 (×2), 128.5 (×4), 128.6 (×4), 128.8 (×3), 137.7, 137.9, 138.0, 138.6, 170.1, 170.3, 171.0 ppm; HR-FAB MS: calcd for $C_{47}H_{48}O_{17}Na$ $[M+Na]^+$: 907.2789; found: 907.2785.

1.2.7. Methyl 2-*O*-(3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α/β-D-glycopyranosyl)-3,4,6-tri-*O*-benzoyl-α-D-glucopyranoside (21)

Compound **21** was obtained from **9** and **20** in 72% yield (α/β = 12/1). Analytical data for **21**: R_f = 0.40 (EtOAc/toluene, 3/7, v/v); ^{1}H NMR: δ, 1.83 (s, 3H, $COCH_3$), 1.99 (s, 6H, 2 × $COCH_3$), 3.51 (s, 3H, OCH_3), 3.53–3.60 (m, 2H, H-2′, 5′), 3.87 (dd, 2H, $J_{6a',6b'}$ = 9.5 Hz, H-6a′, 6b′), 3.94 (dd, 1H, $J_{2,3}$ = 10.0 Hz, H-2), 4.39 (m, 1H, H-5), 4.46 (dd, 1H, $J_{6a,6b}$ = 12.1 Hz, H-6a), 4.57–4.60 (m, 2H, H-6b, 1/2CH_2Ph), 4.64 (d, 1H, J^2 = 12.1 Hz, 1/2CH_2Ph), 4.85 (dd, 1H, $J_{4',5'}$ = 9.6 Hz, H-4′), 4.88 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1′), 5.00 (d, 1H, $J_{1,2}$ = 3.1 Hz, H-1), 5.33 (dd, 1H, $J_{3',4'}$ = 9.6 Hz, H-3′), 5.54 (dd, 1H, $J_{4,5}$ = 9.9 Hz, H-4), 6.03 (dd, 1H, $J_{3,4}$ = 9.7 Hz, H-3), 7.28–8.06 (m, 20H, aromatic) ppm; ^{13}C NMR: δ, 20.7, 20.8, 21.0, 56.0, 61.3, 63.3, 67.8, 68.0, 68.1, 69.8, 71.6, 72.0, 73.4, 77.1, 97.5, 97.6, 128.1 (×3), 128.4, 128.6 (×6), 128.8 (×3), 129.1, 129.7, 129.9 (×4), 130.1 (×2), 133.3 (×2), 133.6, 137.9, 165.6, 165.7, 166.4, 169.9, 170.0, 170.7 ppm; HR-FAB MS: calcd for $C_{47}H_{48}O_{17}Na$ $[M+Na]^+$: 907.2789; found: 907.2788.

Acknowledgments

This work was supported by awards from the NSF (CHE-0547566) and the American Heart Association (0855743G). Dr. R. E. K. Winter and Mr. J. Kramer (UM—St. Louis) are thanked for HRMS determinations.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2010.08.003.

References

1. Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900–1934.
2. *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, 2008.
3. Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137–2160.
4. Boons, G. J. *Drug Discovery Today* **1996**, *1*, 331–342.
5. Osborn, H. M. I.; Khan, T. H. *Oligosaccharides their Synthesis and Biological Roles*; Oxford University Press, 2000.
6. Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523–1527.
7. Demchenko, A. V. *Lett. Org. Chem.* **2005**, *2*, 580–589.
8. Seeberger, P. H.; Werz, D. B. *Nature* **2007**, *446*, 1046–1051.
9. Smoot, J. T.; Demchenko, A. V. *Adv. Carbohydr. Chem. Biochem.* **2009**, *62*, 161–250.
10. Galonic, D. P.; Gin, D. Y. *Nature* **2007**, *446*, 1000–1007.
11. Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3215–3237.
12. Mallet, J. M.; Sinay, P.. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, New York, 2000; Vol. 1, pp 467–492.
13. Goodman, L. *Adv. Carbohydr. Chem. Biochem.* **1967**, *22*, 109–175.
14. Smoot, J. T.; Demchenko, A. V. *J. Org. Chem.* **2008**, *73*, 8838–8850.
15. Smoot, J. T.; Pornsuriyasak, P.; Demchenko, A. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 7123–7126.
16. Demchenko, A. V. *Curr. Org. Chem.* **2003**, *7*, 35–79.
17. Manabe, S.; Ishii, K.; Ito, Y. *J. Am. Chem. Soc.* **2006**, *128*, 10666–10667.
18. Kim, J. H.; Yang, H.; Park, J.; Boons, G. J. *J. Am. Chem. Soc.* **2005**, *127*, 12090–12097.
19. Kim, J. H.; Yang, H.; Boons, G. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 947–949.
20. Demchenko, A. V. *Handb. Chem. Glycosylation* **2008**, 1–27.
21. Whitfield, D. M. *Adv. Carbohydr. Chem. Biochem.* **2009**, *62*, 83–159.

22. Ishiwata, A.; Munemura, Y.; Ito, Y. *Tetrahedron* **2008**, *64*, 92–102.
23. Nair, L. G.; Fraser-Reid, B.; Szardenings, A. K. *Org. Lett.* **2001**, *3*, 317–319.
24. Demchenko, A.; Stauch, T.; Boons, G. J. *Synlett* **1997**, 818–820.
25. Birberg, W.; Lonn, H. *Tetrahedron Lett.* **1991**, *32*, 7453–7456.
26. Pornsuriyasak, P.; Vetter, C.; Kaeothip, S.; Kovermann, M.; Balbach, J.; Steinborn, D.; Demchenko, A. V. *Chem. Commun.* **2009**, 6379–6381.
27. Lucas, T. J.; Schuerch, C. *Carbohydr. Res.* **1975**, *39*, 39–45.
28. Houdier, S.; Vottero, P. J. A. *Carbohydr. Res.* **1992**, *232*, 349–352.
29. Ustyuzhanina, N.; Komarova, B.; Zlotina, N.; Krylov, V.; Gerbst, A. G.; Tsvetkov, Y.; Nifantiev, N. E. *Synlett* **2006**, 921–923.
30. Cheng, Y. P.; Chen, H. T.; Lin, C. C. *Tetrahedron Lett.* **2002**, *43*, 7721–7723.
31. Demchenko, A. V.; Rousson, E.; Boons, G. J. *Tetrahedron Lett.* **1999**, *40*, 6523–6526.
32. Mydock, L. K.; Demchenko, A. V. *Org. Biomol. Chem.*, in press.
33. Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N. *Tetrahedron Lett.* **1989**, *30*, 5459–5462.
34. Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V. *Bioorg. Khim.* **1990**, *16*, 701–710.
35. Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V. *Carbohydr. Res.* **1992**, *232*, C1–C5.
36. Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V. *Carbohydr. Res.* **1993**, *242*, C7–C10.
37. Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V. *Carbohydr. Res.* **1991**, *212*, 77–91.
38. Klimov, E. M.; Demchenko, A. V.; Malysheva, N. N.; Kochetkov, N. K. *Bioorg. Khim.* **1991**, *17*, 1660–1664.
39. Shi, L.; Zhang, G.; Pan, F. *Tetrahedron* **2008**, *64*, 2572–2575.
40. Dauben, H. J., Jr.; Honnen, L. R.; Harmon, K. M. *J. Org. Chem.* **1960**, *25*, 1442–1445.
41. Kamat, M. N.; Rath, N. P.; Demchenko, A. V. *J. Org. Chem.* **2007**, *72*, 6938–6946.
42. Zhang, F.; Zhang, W.; Zhang, Y.; Curran, D. P.; Liu, G. *J. Org. Chem.* **2009**, *74*, 2594–2597.
43. Iwashige, T.; Saeki, H. *Bull. Chem. Soc. Jpn.* **1967**, *15*, 1803–1806.
44. Pornsuriyasak, P.; Demchenko, A. V. *Chem. Eur. J.* **2006**, *12*, 6630–6646.
45. Sinay, P. *Pure Appl. Chem.* **1978**, *50*, 1437–1452.
46. Kitov, P. I.; Tsvetkov, Y. E.; Backinowsky, L. V.; Kochetkov, N. K. *Mendeleev Commun.* **1995**, 176–177.
47. Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819–6825. and references cited therein.
48. Beaver, M. G.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 1107–1118.
49. Paulsen, H.. In Bartmann, W., Trost, B. M., Eds.; Selectivity—a Goal for Synthetic Efficiency; Verlag Chemie: Weinheim, 1984; pp 169–190.
50. Jayaprakash, K. N.; Lu, J.; Fraser-Reid, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5894–5898.
51. Uriel, C.; Gomez, A. M.; Lopez, J. C.; Fraser-Reid, B. *Synlett* **2003**, 2203–2207.
52. Pozsgay, V.; Dubois, E. P.; Pannell, L. *J. Org. Chem.* **1997**, *62*, 2832–2846.
53. Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 180–183.
54. Kuester, J. M.; Dyong, I. *Justus Liebigs Ann. Chem.* **1975**, 2179–2189.
55. Kamat, M. N.; De Meo, C.; Demchenko, A. V. *J. Org. Chem.* **2007**, *72*, 6947–6955.
56. Demchenko, A. V.; Pornsuriyasak, P.; De Meo, C.; Malysheva, N. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3069–3072.
57. Zhang, Z.; Wong, C. H. *Tetrahedron* **2002**, *58*, 6513–6519.
58. Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, C10–C11.
59. Koto, S.; Takebe, Y.; Zen, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 291–293.
60. Agoston, K.; Kroeger, L.; Dekany, G.; Thiem, J. *J. Carbohydr. Chem.* **2007**, *26*, 513–526.
61. Sollogoub, M.; Das, S. K.; Mallet, J.-M.; Sinay, P. *C.R. Acad. Sci., Ser. II* **1999**, *2*, 441–448.
62. Ekelof, K.; Oscarson, S. *Carbohydr. Res.* **1995**, *278*, 289–300.
63. Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179–205.
64. Oscarson, S.. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, New York, 2000; Vol. 1, pp 93–116.
65. Codee, J. D. C.; Litjens, R. E. J. N.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769–782.
66. Zhong, W.; Boons, G.-J. *Handbook of Chemical Glycosylation*; Wiley-VCH: Weinheim, Germany, 2008. pp 261–303.