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Scope and limitations of imidazolium-based ionic liquids as room temperature glycosylation promoters

M. Carmen Galan *, Kevin Jouvin, Dimitri Alvarez-Dorta

School of Chemistry, University of Bristol, Bristol BS8 1TS, UK

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ABSTRACT

The scope and limitations of imidazolium-based ionic liquids as room temperature glycosylation promoters have been studied. Herein, we report the effects of modifying the structure of the imidazolium cation and how important the choice of counter ion becomes on model glycosylation reactions of thioglycosides at room temperature in the presence of *N*-iodosuccinimide (NIS).

1. Introduction

Carbohydrates continue to be a central focus of research in chemistry, biology and material science.[1–3] Although many chemical approaches have been developed, the synthesis of complex oligosaccharides is still troublesome.[4,5] Thus, there is great interest in the development of novel and general strategies that will lead to the efficient synthesis of complex carbohydrates. Factors including the choice of leaving group at the anomeric position of the donor, the selection of protecting groups in both the donor and acceptor moieties, the solvent system, and the choice of promoter need to be considered when carrying out the synthesis of glycosides.[6] Glycosidic bond formation is a crucial step in oligosaccharide synthesis but despite many efforts, there is still a need to identify a general, mild, and convenient glycosylation promoter.

Room temperature ionic liquids (RTILs) have recently emerged as a new class of solvents for a wide range of organic reactions.[7–9] The high polarity of RTILs can provide strong accelerating effects to reactions involving cationic intermediates[7] and in particular they have been shown to exhibit excellent solubilizing properties, facilitating a wide range of chemical transformations, including acetylation, ortho-esterification, benzylidenation, and glycosylation reactions of carbohydrates.[10–15]

As part of our program to develop new methods and strategies for oligosaccharide synthesis, we became interested in the application of ionic liquids for glycosylation reactions. We have recently reported the use of [bmim][OTf] **1a** as a mild and versatile ionic liquid (IL) promoter for the room temperature glycosylation of both thiophenyl and trichloroacetimidate glycoside donors; the conditions are mild, and compatible with a range of hydroxyl-protecting groups, such as acetates, benzyl ethers, acetals, and also amenable to NH_2 masking strategies, that is, phthalimide (Phth) and trichloroethylcarbamate (Troc). We have also shown that **1a** can selectively promote activated (armed) trichloroacetimidate glycosyl donors and thiophenyl glycosides in combination with NIS, while less active (disarmed) donors required the addition of catalytic triflic acid. Initial mechanistic studies suggest that **1a** can facilitate glycosylation reactions by the slow release of catalytic amounts of triflic acid and that **1a** also protects the newly formed glycosidic linkage from hydrolysis.[15]

It is well established that ILs can be fine-tuned by changing the anion or cation to produce derivatives with different physical and chemical properties.[9,16] With that in mind, we decided to explore the scope of modified ILs by generating a series of imidazolium-based ILs **1a–n**, with differing R_1 and R_2 groups and different counter ions (X^-) (Fig. 1) and testing their effectiveness in glycosylation reactions to gain a better understanding of the IL-promoted glycosylation and to find an optimum IL to carry out the reaction. We focused on thioglycosides as a suitable glycosyl donor due to its wide applicability and effectiveness on these types of reactions.[17]

Herein, we report the effects of modified ionic liquids on model glycosylation reactions of thioglycosides at room temperature.

2. Results and discussion

Previously, we demonstrated that triflate-based **1a** was successfully used to catalyze the glycosylation reaction of thioglycosides,[15] moreover the participation of triflated ionic liquids in the reaction mechanism involving trichloroacetimidates has also been

* Corresponding author. Tel.: +44 1179287654; fax: +44 1179298611.
E-mail address: M.C.Galan@bristol.ac.uk (M.C. Galan).

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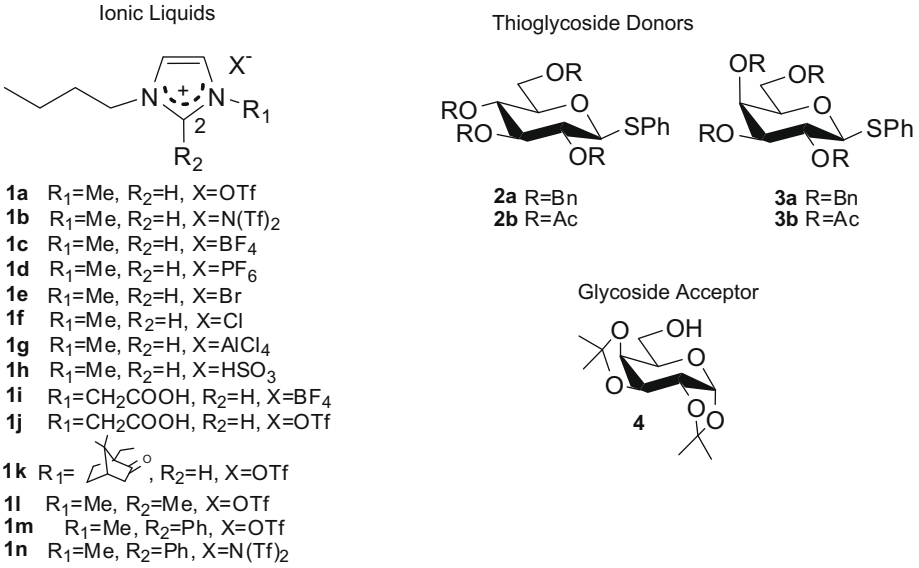


Figure 1. Ionic liquids, thioglycoside donors, and model acceptor used in this study.

reported.[18] In order to study the effect of the counter ion, a series of commercial ILs were screened for their ability to promote glycosylation reactions. These ILs contained 1-butyl-3-methylimidazolium as the cation with a variety of counter ions. In brief, anions such as bis(trifluoromethylsulfonyl)imide ($N(TfO)_2^-$) **1b** and PF_6^- **1d**, which are widely used in catalytic applications and grant hydrophobic properties to the IL.[19–21] Hydrophilic ILs with counter ions such as, BF_4^- **1c**, Br^- **1e** and Cl^- **1f** and acidic IL **1g** containing chloroaluminate ($Cl{\cdot}AlCl_3^-$) as the anion, which have been successfully used as a dual Lewis acid catalyst/solvent in the sulfamoylation of arenes.[22,23] Finally, hydrogen sulfate (HSO_4^-) containing **1h**, a Bronsted acidic IL.[24] For the purpose of the study, a series of glucose- and galactose-based thioglycoside donors were prepared following reported procedures. Thus phenyl 2,3,4,6,-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **2a**,[25] phenyl 2,3,4,6,-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **2b**,[26] phenyl 2,3,4,6,-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside **3a**[27] and phenyl 2,3,4,6,-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside **3b**[25] were obtained in good yields and reacted with commercial 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **4** as model acceptor in the presence of the different ILs **1a–n** (Fig. 1) to yield the corresponding disaccharides (Fig. 2).

Initial screen of glycosylation was performed with armed thioglycoside donor **2a**, (Table 1). Reactions with **1b** as the promoter, which contains a bistriflimide-based counter ion, (Table 1, entry 3), gave the corresponding disaccharide **6a**[28] (Fig. 2) in yields comparable to those of the reaction carried out in the presence of **1a** at room temperature[15] or TMSOTf at low temperatures (Table 1, entries 1 and 2). An increase in the α-linked disaccharide was noted for **1b** when compared to the reaction carried out with TMSOTf, which was also observed in reactions promoted by **1a**. On the other hand, reactions carried out with more hydrophilic ILs **1c–i** (Table 1, entries 4–10) resulted in no reaction or degradation of the starting materials. These results clearly highlight the importance of the choice of counter ion in the IL and further emphasizes the role of triflate- and triflimide-based anions for catalyzing these types of glycosylation reactions.

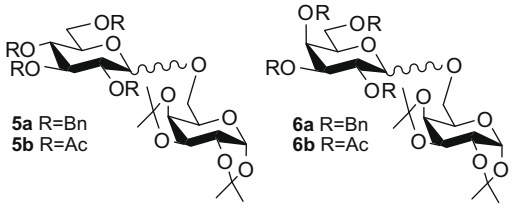
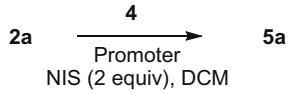


Figure 2. Structures of glycoside products **6–7**.

Table 1
Summary of glycosylation reactions with thioglycoside donor **2a** and model acceptor **4** in the presence of different IL promoters at room temperature to yield disaccharide **5a**



Entry	Promoter	Yield (%)	Ratio α/β	Reaction time (h)
1	TMSOTf [a]	75	0.02/1	3
2	**1a**	77	0.40/0.60	3
3	**1b**	86	0.52/0.48	6
4	**1c**	s.m.	—	24
5	**1d**	<5 + s.m.	N.D.	24
6	**1e**	s.m.	—	24
7	**1f**	s.m.	—	24
8	**1g**	<10 + s.m.	N.D.	24
9	**1h**	s.m.	—	24
10	**1i**	s.m.	—	24
11	**1j**	65	0.52/0.48	3
12	**1k**	71	0.55/0.45	3
13	**1l**	77	0.54/0.46	2
14	**1m**	97	0.58/0.43	1
15	**1n**	80	0.53/0.47	6

N.D. not determined.
s.m. starting material.
[a] The reaction was performed in DCM with TMSOTf (0.2 equiv) at −40 °C.

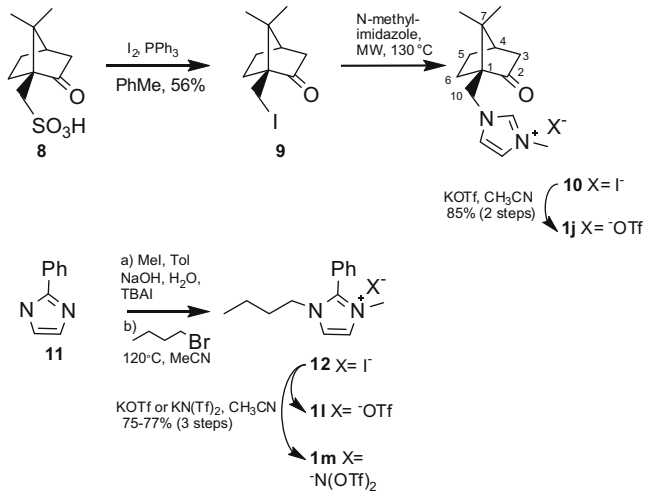
Having demonstrated the significance of the counter ion, we next studied the effect that substituents on the imidazolium moiety will induce in the glycosylation reaction. To that end, tethered imidazolium carboxylic acid **1i**[29] was prepared and BF_4^- was chosen as an inert counter ion, so that any glycosylation product observed could only be attributed to the modification at R_1. Nonetheless, no reaction was observed and the starting material was recovered. When **1j**,[29] which contains a OTf^- as counter ion was used, the reactivity of the IL toward promoting glycosylation was restored, confirming the importance of the counter ion (Table 1, entries 10 and 11).

Chiral ILs (CILs) have become very popular in the recent years as a source for novel chiral solvents that can influence the outcome of asymmetric reactions.[30] In particular, camphor derivatives have proved to be excellent chiral auxiliaries due to their special steric demands and more recently, they have been used to some success, in controlling the diastereoselectivity in Diels–Alder reactions, as either the anion or cation of the IL.[31,32] Camphor-derived imidazolium triflate **1k**, was prepared by a modified literature procedure.[31] In brief, treatment of (1*S*)-(+)-camphorsulfonic acid **8** with iodine in the presence of triphenylphosphine yielded the 10-iodo camphor intermediate **9**, which was further reacted with *N*-methylimidazole applying microwave conditions to afford the imidazolium salt **10**. Anion metathesis with KOTf afforded **1k** in a 48% overall yield. (Scheme 1). When **1k** was used as a promoter in the glycosylation reaction of **2a** with **4** (Table 1, entry 12), the reaction proceeded in good yields at room temperature, however no change in the diastereoselectivity was observed when comparing the α/β ratio of the reaction with those obtained for active ILs **1a** and **1b** (Table 1, entries 2, 3 and 12).

In our previous studies, 1-butyl-2,3-dimethyl imidazolium triflate **1l** was synthesized and used to investigate the role of the H-2 of the imidazolium moiety in **1a** in the activation of the glycosyl donor.[15] (Table 1, entry 13) Interestingly, the reaction with **1l** yielded the corresponding glycosyl products in good yields and the reaction time was shortened, suggesting that substitution at R_2 of the imidazolium ring had an effect on the rate of the reaction. To further exploit that observation, ILs **1m** and **1n**, which bear a phenyl substituent at R_2 and a $^-$OTf or $^-N(Tf)_2$, respectively, as counter ions, were prepared from 2-phenylimidazole **11** following a literature procedure[33] and tested in the glycosylation reaction of glycosyl donor **2a** with acceptor **4**. Reactions proceeded in excellent yields, at room temperature and in a third of the time. In addition, no change in the stereoselectivity was noted when comparing it with the α/β ratios obtained for reactions with **1a** or **1b** (Table 1, entries 2, 3, 14 and 15).

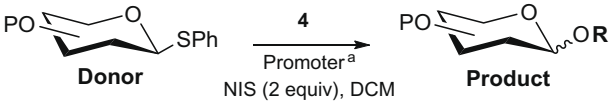
Encouraged by these results, we decided to extend our studies to other common thiophenyl glycosides. Activated perbenzylated galactopyranoside **3a** and disarmed peracetylated thioglycosides **2b** and **3b** were tested with IL promoters **1a**, **1l,** and **1m**, which showed the best reactivities in the initial screening, with model glycosyl acceptor **4** (Table 2).

In general, conversion yields for activated glycoside **3a** were good with all of the tested ILs at room temperature in comparison to the reaction carried out at −40 °C with TMSOTf (Table 2, entries 1–4). Furthermore, an increase in the α/β ratio was also observed for reactions promoted at room temperature by ILs in this screen, as it was shown in the glucoside series (Table 1). It is important to note that reactions with **1m** (R_2 = Ph) as co-solvent/promoter with 'armed' donor **3a** and **3b**, proceeded faster, reactions were complete within 1 h, while reactions with **1l** (R_2 = Me) were complete after 2 h and **1a** (R_2 = H) 3 h, as determined by TLC. These results suggest that by introducing hydrophobic groups at the R_2 position of the imidazolium cation, we can increase the reactivity of the IL toward promoting this type of glycosylation reactions.



Scheme 1. Preparation of ionic liquids **1k–m**.

Table 2
Summary of glycosylation reactions of thioglycoside donors **3a**, **2b,** and **3b** with model acceptor **4**



Entry	Donor	Promoter	Yield (%)	Product	Ratio α/β	Reaction time (h)
1	**3a**	TMSOTf[b]	75	**6a**	0.02/1	3
2	**3a**	**1a**	97	**6a**	0.78/1	3
3	**3a**	**1l**	90	**6a**	0.75/1	2
4	**3a**	**1m**	72	**6a**	0.67/1	1
5	**2b**	TMSOTf [b]	70	**5b**	Only β	3
6	**2b**	**1a**, TMSOTf	80	**5b**	Only β	3
7	**2b**	**1l**	s.m.	—	—	24
8	**2b**	**1m**	10 + s.m.	**5b**	Only β	24
9	**3b**	TMSOTf [b]	83	**6b**	Only β	3
10	**3b**	**1a**, TMSOTf	95	**6b**	Only β	3
11	**3b**	**1l**	s.m.	—	—	24
12	**3b**	**1m**	20 + s.m.	**6b**	Only β	24

s.m. starting material.
[a] Unless indicated otherwise, reactions were carried out at room temperature.
[b] The reaction was performed in DCM with TMSOTf (0.2 equiv) at −40 °C.

Previously, we reported that peracetylated thioglycoside donors, which are electronically deactivated species (disarmed)[34] could not be efficiently activated by **1a**, but that the addition of catalytic triflic acid (0.2 mol %) was sufficient to carry out the reactions while still at room temperature and in good yields.[15] With that in mind, reactions of peracetylated thioglycoside donors **2b** and **3b** with model acceptor **4** were carried out with the more reactive **1m** and **1l**. However only starting material was recovered for reactions with **1m** (Table 2, entries 7 and 11) and only small amounts of product (10% **5b** and 20% **6b**) were detected for reactions carried out with **1l** after 16 h (Table 2, entries 8 and 12). In terms of the reactivity of the IL, the results are encouraging and efforts are underway to find a more reactive IL that could activate 'disarmed' glycosides by finding the optimum substitution at R_2 of the imidazolium cation.

3. Summary

In summary, we have shown that imidazolium-based ILs bearing triflate or triflimide counter ions serve as room temperature selective glycosylation promoters for activated (armed) thiophenyl glycosyl donors, thus we have further demonstrated the importance of the choice of counter ion when choosing an IL to promote these types of glycosidic bond-forming reactions. Furthermore, substitutions at R_1 of the imidazolium cation do not have an effect on the reactivity or diastereoselectivity of thioglycoside glycosylations, while modifications at R_2 have an effect in the rate of glycosidic bond-forming reactions. The stereoselectivity of the glycosylation reactions is significantly affected by the IL, with an increase in the amount of α glycoside products. The ability to recycle the IL promoter is also very attractive in terms of green

chemistry, and in general the ability of ILs to promote glycosylation reactions at room temperature is amenable to cost effective automated oligosaccharide synthetic protocols where no strict control of low temperatures will be required.

4. Experimental

4.1. General

Chemicals were purchased from Aldrich and Fluka and used without further purification. Molecular sieves were activated at 350 °C for 3 h and cooled under vacuum. Dry solvents, where necessary, where obtained by distillation using standard procedures or by passage through a column of anhydrous alumina using equipment from Anhydrous Engineering (University of Bristol) based on Grubbs' design. Reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen; glassware, syringes, and needles were either flame dried immediately prior to use or placed in an oven (150 °C) for at least 2 h and allowed to cool either in a desiccator or under an atmosphere of dry nitrogen; liquid reagents, solutions or solvents were added via syringe or cannula through rubber septa; solid reagents were added via Schlenk type adapters. Typical reactions were carried out in 40–50 mg scale. Reactions were monitored by TLC on Kieselgel 60 F254 (Merck). Detection was by examination under UV light (254 nm) and by charring with 10% sulfuric acid in methanol. Flash chromatography was performed using silica gel [Merck, 230–400 mesh (40–63 μm)], the crude material was applied to the column as a solution in CH_2Cl_2 or by pre-adsorption onto silica, as appropriate. Extracts were concentrated under reduced pressure using both a Büchi rotary evaporator (bath temperatures up to 40 °C) at a pressure of either 15 mmHg (diaphragm pump) or 0.1 mmHg (oil pump), as appropriate, and a high vacuum line at room temperature. ^{1}H NMR and ^{13}C NMR spectra were measured in the solvent stated at 400 or 600 MHz on JOEL JNM-GX400, JOEL Eclipse 400 or Varian *INOVA* 600 instruments, respectively. Chemical shifts quoted in parts per million from $SiMe_4$ and coupling constants (*J*) given in hertz. Multiplicities are abbreviated as: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or combinations thereof. Negative ion matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectra were recorded using a HP-MALDI instrument using gentisic acid matrix. Water content measure by Karl Fisher titration in a Metrohm 756 KF Coulometer equipped with a diaphragm free cell and 703 Titration Stand. The KF reagent is Hydranal-Coulomat AG from Riedel-deHaen.

4.2. General protocols for glycosylation reactions

4.2.1. Typical IL (1a–f) promoted glycosylation procedures

4.2.1.1. (A) For activated thiophenyl donors 2a and 3a with glycosyl acceptors 4. IL (**1a**–**n**) (300 μL) was added to a stirred suspension of thioglycoside donor (1.5 equiv), glycosyl acceptor (1 equiv), and NIS (2 equiv) in dry dichloromethane (3–10 mL). The mixture was left stirring at rt or 1–16 h. TLC (hexane/ethyl acetate, 1:1, v/v) indicated completion of the reaction. The mixture was neutralized with triethylamine (2 equiv) and concentrated under reduced pressure. The sirup mixture was then washed with diethyl ether (4 × 30 mL) to extract the product from the ionic liquid, which was monitored by TLC to ensure the product was in the ether phase. Interestingly, NIS shows preferential solubility in the ionic liquid phase for **1a–b** and **1l–n**, thus it did not extract into the ether portion. The washes were then collected and after evaporation of the solvent, the residue was further purified by flash silica gel chromatography (gradient hexane/ethyl acetate, 3:1 to 1:1, v/v) to yield the corresponding oligosaccharides **5a** and **6a**.

4.2.1.2. (B) For deactivated thiophenyl donors 2b and 3b with glycosyl acceptors 4. Trimethylsilyl trifluoromethanesulfonate (0.2 equiv) was added to a stirred suspension of 1-butyl-3-methyl imidazolium triflate **1a**, thioglycoside donor (1.5 equiv), glycosyl acceptor (1 equiv), and NIS (2 equiv) in dry dichloromethane (3–10 mL). The mixture was left stirring at rt for 6 h. TLC (hexane/ethyl acetate, 1:1, v/v) indicated completion of the reaction. The mixture was neutralized with triethylamine (2 equiv) and concentrated under reduced pressure. The syrup mixture was then washed with diethyl ether (4 × 30 mL) to extract the product from the ionic liquid, which was monitored by TLC to ensure the product was in the ether phase. Interestingly, NIS showed preferential solubility in the [bmim][OTf] phase and it did not extract into the ether portion. The washes were then collected and after evaporation of the solvent, the residue was further purified by flash silica gel chromatography (gradient hexane/ethyl acetate, 3:1 to 1:1, v/v) to yield the corresponding oligosaccharides **5b** and **6b**.

4.2.2. Typical TMSOTf-promoted glycosylation procedures

4.2.2.1. (C) For thiophenyl donors 2b and 3b with glycosyl acceptors 4. Trimethylsilyl trifluoromethanesulfonate (0.4 equiv) was added to a stirred suspension of thiophenyl donor (1.5 equiv), glycosyl acceptor (1 equiv), NIS (2 equiv) and freshly activated powdered molecular sieves 4 Å (50–200 mg) in dry dichloromethane (3–10 mL). The mixture was left stirring at −40 °C for 3 h and then let stir at room temperature for another hour. TLC (hexane/ethyl acetate, 1:1, v/v) indicated completion of the reaction. The mixture was neutralized with triethylamine (2 equiv) and then filtered over Celite. The filtrate washings were combined and concentrated under reduced pressure. The residue was then diluted in dichloromethane (30 mL), washed successively with a saturated aqueous solution of $NaHCO_3$ (10 mL), water (2 × 10 L), and brine (10 mL), followed by drying over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash silica gel chromatography (gradient hexane/ethyl acetate, 3:1 to 1:1, v/v) to yield the corresponding oligosaccharides **5b** and **6b**.

4.2.3. 1-Methyl-3-[(1*S*,4*R*)-(2-oxo-7,7-dimethylbicyclo[2.2.1]hept-1-yl)methyl]imidazolium trifluoromethanesulfonate (1k)

10-Iodocamphor **5** (100 mg, 0.39 mmol) and *N*-methylimidazole (40 mg, 0.50 mmol) were added in a microwave vial in EtOAc (80 μL) and sealed under N_2. Irradiation at 130 °C for 5 h at 50 W. The immiscible layer of ionic liquid was then separated from the EtOAc and the crude ionic mixture was dissolved in dry acetonitrile (0.5 mL) and KOTf added (75 mg, 0.4 mmol). The mixture was stirred under N_2 for 24 h. Inorganic salts were filtered over a short pad of Celite. The filtrate was evaporated to dryness and washed with hexane and EtOAc. The solid was then dried under high vacuum to yield **1k** (109 mg, 0.33 mmol). δ_H (400 MHz, $CDCl_3$) 9.52 (s, 1H, NC*H*N), 7.61 (s, 1H, NC*H*CHN), 7.45 (s, 1H, NCHC*H*N), 4.22 (d, 1H, *J*14.2 Hz, H-10), 3.93 (3H, s, CH_3N), 2.31 (1H, ddd, *J* 18.7, 4.6, 1.8 Hz, H-3a), 2.25-2.12 (m, 3H, H-4, H-6a, H-5a), 1.85 (d, 1H, *J* 18.7 Hz, H-3b), 1.33-1.18 (m, 2H, H-6b, H-5b), 1.13 (s, 3H, H-8), 0.84 (s, 3H, H-9). δ_C (100.26 MHz, $CDCl_3$) 216.3 (C, C-2), 137.3 (CH, NCHN), 123.6 (CH, NCHCHN), 123.2 (CH, NCHCHN), 60.9 (C, C-1), 47.2 (CH_2, C-10), 46.4 (CH_3, C-7), 43.6 (CH_3), 41.4 (CH_2, C-3), 36.5 (CH, C-4), 25.3 (CH_2, C-5), 25.3 (CH_2, C-6), 19.6 (CH_3, C-8 or C-9), 19.4 (CH_3, C-8 or C-9). δ_F (283 MHz, $CDCl_3$) −77.07 (s, 3F, OSO_2CF_3)) HRMS-FAB: *m*/*z* calcd for $C_{14}H_{21}N_2O$: 233.1654; found: 233.1657.

4.2.4. Characterization data for disaccharides synthesized

4.2.4.1. 1,2:3,4-Di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl-α-D-galactopyranose (5a). Prepared following procedure A. Spectroscopic data in agreement with literature data.[28]

4.2.4.2. 1,2:3,4-Di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranose (5b). Prepared following procedures B and C. Spectroscopic data in agreement with literature data.[28]

4.2.4.3. 1,2:3,4-Di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-α-D-galactopyranose (6a). Prepared following procedure A. Spectroscopic data in agreement with literature data.[35]

4.2.4.4. 1,2:3,4-Di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-galactopyranose (6b). Prepared following procedures B and C. Spectroscopic data in agreement with literature data.[36]

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