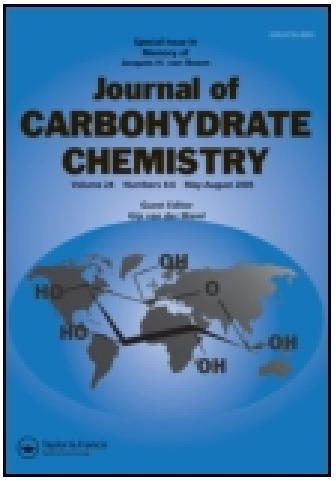

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[R_4N] [AOT]: A Surfactant Ionic Liquid as a Mild Glycosylation Promoter

M. Carmen Galan [a], Anh Tuan Tran [a], Julien Boisson [a], David Benito [a], Craig Butts [a], Julian Eastoe [a] & Paul Brown [a]
[a] School of Chemistry, University of Bristol, Bristol, BS8 1TS, UK
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M. Carmen Galan, Anh Tuan Tran, Julien Boisson, David Benito, Craig Butts, Julian Eastoe, and Paul Brown

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

[RN_4][AOT] is a versatile surfactant ionic liquid that can be used in combination with N-Iodosuccinimide to promote the room temperature glycosylation of thiophenyl glycoside donors. The conditions are mild, with no requirement for molecular sieves, and are compatible with a wide range of donors and protecting groups. Under these conditions, a different range of disaccharides have been obtained in good to excellent yields and good stereoselectivities. Furthermore, the anomeric outcome of the glycosylation reaction using glycosyl donors with no participating group at C-2 could be tuned by switching the solvent from DCM to MeCN.

Keywords Oligosaccharides; Glycosylation; Ionic liquids; Surfactant ionic liquids

INTRODUCTION

Many synthetic efforts have been devoted over the years toward finding reagents that could efficiently promote glycosidic bond formation.[1–3] However, despite the many efforts, there is still a need for the development of reliable reagents that can be generally applied to oligosaccharide synthesis and that are applicable to both laboratory and industrial-scale preparation.

Herein, we describe the first synthetic application of ionic liquids based on surfactant sulphonate anions ([R_4N][AOT] **1a–1d**, figure in Table 1). This new class of ionic liquids can be used in combination with *N*-Iodosuccinimide (NIS) as a selective and mild promoter in glycosylation reactions with thiophenyl glycoside donors.

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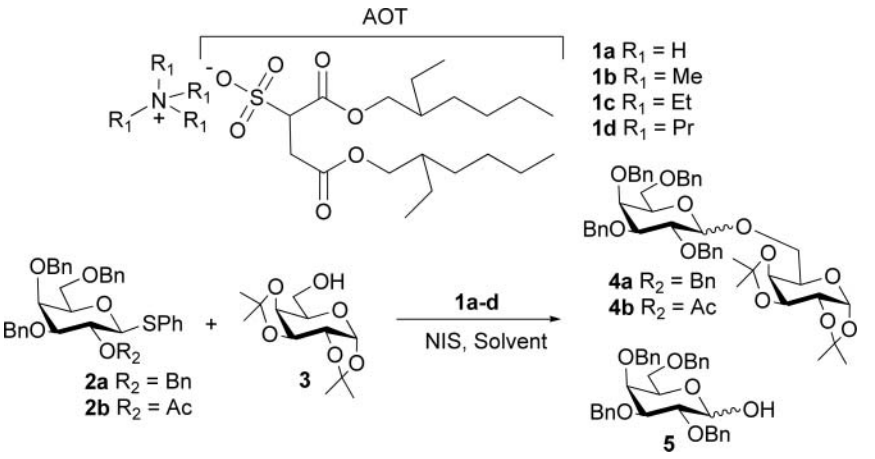
Address correspondence to M. Carmen Galan, School of Chemistry, University of Bristol, Bristol BS8 1TS UK. E-mail: M.C.Galan@bristol.ac.uk

Table 1: Summary of glycosylation reactions with thioglycoside donor **2** and model acceptor **3** in the presence of different ILs **1a–d** at rt to yield disaccharide **4**



Entry[a]	Donor	Promoter[b]	Temp. (°C)	Solvent	Yield (%)	α/β ratio[c]
1	**2a**	**1a**	rt	DCM	45	2:1
2	**2a**	**1b**	rt	DCM	90	1.2:1
3	**2a**	**1c**	rt	DCM	88	1.3:1
4	**2a**	**1d**	rt	DCM	92	1.1:1
5	**2a**	NaAOT	rt	DCM	50[c] + s.m.	1:1
6	**2a**	**1b** (50% w/w)	rt	DCM	82	1:1
7	**2a**	**1b**	−78	DCM	s.m.[d]	—
8	**2a**	**1b**	−40 to 0	DCM	94	1:1
9	**2a**	**1b** (50% w/w)	−40 to 0	DCM	84	1.3:1
10	**2a**	**1b**	rt	MeCN	80	1:3
11	**2a**	**TMSOTf/NIS**	−40	MeCN	75	1:3
12	**2b**	**1b**	0	DCM	88	Only β

[a]Unless indicated otherwise, all reactions at rt.
[b]Unless indicated, IL is used in 10% w/w.
[c]Determined by NMR spectroscopy (^{1}H and HMQC data).
[d]Reaction quenched after 18 h.
s.m., recovered starting material (glycosyl donor); rt, room temperature.

In the last few years, ionic liquids (ILs) have emerged as a new class of environmentally attractive solvents that can be used for a broad number of synthetic applications.[4–7] The high polarity of ILs can provide strong accelerating effects to reactions involving cationic intermediates. ILs possess many unique physicochemical properties, such as excellent solubilizing properties for most organic and inorganic compounds, and having high thermal stability and wide liquid temperature ranges. ILs are considered green solvents due to the very low vapor pressures and their potential for recyclability. ILs are also chemically diverse owing to the huge number of possible cation/anion combinations

that can be synthesized and have been used to facilitate a wide range of chemical transformations, including acetylation, ortho-esterification, benzylidenation, and glycosylation reactions of carbohydrates.[8–16] As part of our program to develop new methods and strategies for oligosaccharide synthesis, we became interested in the application of ionic liquids in this area of research. We have recently reported the use of [bmim][OTf] (1-butyl-3-methylimidazolium triflate) as a mild, recyclable, and versatile IL solvent/promoter of room temperature (rt) glycosylation reactions using trichloroacetimidate and thiophenyl glycoside donors.[12] We also showed that [bmim][OTf] could selectively activate "armed" glycosyl donors in the presence of "disarmed" ones and we demonstrated its applicability in regio- and chemoselective glycosylation reactions and in reactivity-based one-pot coupling reactions.[15]

Studies from our group aimed at understanding the scope and limitations of imidazolium-based ILs on the rt activation of glycosyl donors[13] showed that the choice of counterion in the IL is key to promote these types of reactions, while modifications on the imidazolium cation did not have a significant effect on the IL reactivity toward the glycosylation reaction or on the stereoselectivity of the products.

Although the use of imidazolium-based ILs offers many attractive features,[7] there are also some known drawbacks associated with imidazolium salts, such as relative expense, unknown toxicity, environmentally hazardous starting materials, issues with purification of the IL materials, and incompatibility with reactions involving active metals or strong bases due to the acidity of the C-2 proton of the imidazolium ion.[7,17,18] A new class of ionic liquid surfactants has recently been reported as an alternative to imidazolium-based systems.[19,20] A key feature of this new class of ionic salts is the use of quaternary ammonium as cations and bis(2-ethyl-1-hexyl) sulfosuccinate (AOT) as the anion component. Moreover, this new class of ILs is easily prepared from cheap, environmentally benign, and commercially available starting materials by a simple ion-exchange process.

RESULTS AND DISCUSSION

Based on our previous observations with respect to the imidazolium trifluoromethylsulfonate [mim] (OTf) ILs, combined with our search for a more versatile promoter with a wider range of activation toward glycosylation reactions than [bmim][OTf], we have explored the application of AOT-based ILs in rt glycosylation reactions. We focused on thioglycosides as a suitable leaving group due to their wide applicability and effectiveness on this type of transformation.[21] To that end, a series of tetra-alkyl ammonium-based ILs, with differing alkyl groups and AOT as the counterion (X^-), compounds [R_4N][AOT] **1a–d**, were prepared following slightly modified reported procedures.[20]

Initial experiments to test the ability of ILs **1a–d** to efficiently promote glycosidic bond formation were performed with armed thioglycoside donor **2a** and commercial 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **3** as model acceptor in the presence of NIS (Table 1). Thus, activation of **2a** at rt in dichloromethane proceeded smoothly with ILs **1b–d** and as a result disaccharide **4a** was obtained in excellent yields of 88% to 92% as approximately 1:1 α/β-mixtures within 2 h (Table 1, entries 2–4). When $[NH_4]$[AOT] **1a** was used as promoter (Table 1, entry 1), the reaction procedeed faster than with ILs **1b–d,** but only 45% of the desired product was obtained along with hydrolyzed donor **5**.[22] As a control, sodium AOT was used as a promoter under the same reaction conditions described above (Table 1, entry 5); however, the reaction proceeded very slowly and stalled after 24 h, with only 50% of desired product **4a** isolated.

It has been shown that when using [emim][OTf] (1-ethyl-3-methylimidazolium trifluoromethanesulfonate) as a solvent in glycosylation reaction with TMSOTf at low temperatures, the anion can take part in the glycosylation and biases the attack of the glycosyl acceptor reaction by the formation of a transient α-glycosyl triflate, which preferentially leads to β-glycoside products.[23] We hypothesized that due to the bulk of the AOT anion, if such participation took place during the reaction at low temperatures, it should lead to α-glycosides as the anion would prefer the less hindered β-face. To that purpose, thioglycosyl donor **2a** was subjected to the glycosylation reaction conditions described above at -78°C using IL **1b** as the promoter (Table 1, entry 7); however, no reaction was observed as **1b** froze at such low temperature. Performing the glycosylation reaction at slightly higher temperatures (-40°C to 0°C) did not change the stereo-outcome of the product 1:1 α/β, 94% yield) (Table 1, entry 9). It is important to note that increasing the amount of IL to 50% (w/w) did not have an effect on the stereoselectivity of the glycosylation and the overall yield of the reaction was slightly lower (82% to 84%) due to partial hydrolysis of the donor. This was observed at both low (-40°C to 0°C) or room temperatures presumably due to low levels of water in the IL, which become more relevant at increased amounts of IL in the reaction (Table 1, entries 6 and 9).

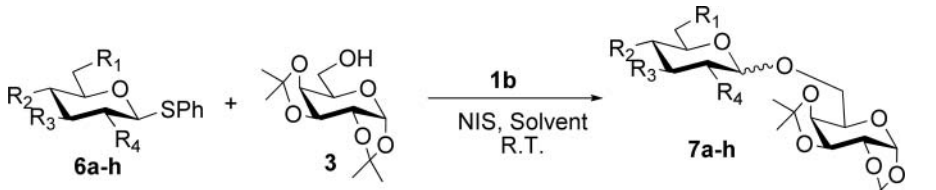
The nature of the solvent is known to represent a key factor in the stereoselectivity of glycosylation reactions.[24–26] For instance, reactions in acetonitrile of glucopyranosides tend to yield 1,2-*trans*-glucoside (β linkage) as the major product via an axial nitrilium ion intermediate that directs the attack of the incoming nuclophile to the β-face.[27] The solvent effect dominates the stereoselectivity as long as there is no participating effect of neighboring groups (i.e., participation of a C-2 neighboring group in the glycosyl donor, predominantly leading to a 1,2-*trans*-glycosidic linkage irrespective of the solvent).[28] To investigate if a participating solvent could be used to affect the stereo-outcome of the product in the presence of IL **1d** during the reaction, donor **2a** was

subjected to the same reaction conditions previously described but using acetonitrile as the solvent. Disaccharide product **4a**[29] was obtained in 80% yield as a 1:3 (α/β ratio), showing an increase in β selectivity (Table 1, entry 10). Reaction of **2a** with acceptor **3** under traditional activation using NIS /TMSOTf at -40°C also afforded a similar yield and α/β ratio (75%, 1:3 a/b, Table 1, entry 11). Reaction of **2b**, which bears an ester neighboring participating group at C-2 with acceptor **3** at 0°C using **1d** as promoter in DCM, afforded product **4b**[30] in good yields (88%) as exclusively the β-anomer (Table 1, entry 12). These results suggest that the AOT counterion of **1d** does not directly participate in the reaction mechanism but that $[RN_4][AOT]$ works by activation of NIS to slowly form I^+, which in turn can activate thioglycosyl donor **2a**. Furthermore, no interference of the IL with solvent or neighboring participating effects during the glycosylation reaction were observed, demonstrating that traditional approaches to control the stereoselectivity of the products are compatible with this new class of IL activators.

Previous thioglycoside activation by [bmim][OTf]/NIS combinations was not efficient at temperatures below 0°C.[12] On the basis that AOT-based ILs are more reactive toward promoting glycosylation at low temperatures, we rationalized that perhaps this new class of surfactant ILs could be used in glycosylations with a wider range of glycosyl donors in terms of reactivity toward glycosylation. To explore the reactivity boundaries of differently protected thioglycosides, a series of glucose-based thioglycoside donors (**6a**,[31] **6b**,[32] **6c**,[33] **6d**,[34] and **6e**[35]) possessing different reactivity profiles[36–43] were prepared in good yields following reported procedures and their couplings with **3** as a model acceptor in the presence of **1b** and NIS were monitored (Table 2).

Thus, activation of **6a** and **6b** proceeded smoothly under the reaction conditions described above at rt and within 2 h and as a result products **7a**[44] and **7b**[45] were isolated in 72% (1.4:1 α/β) and 78% (3:1 α/β), respectively (Table 2, entries 1 and 3). Changing the reaction solvent from dichlomethane to a participating solvent such acetonitrile increased the amount of β-anomer in the final product, as expected, and afforded a slightly better overall yield. In this instance, **7a** was isolated in 80% (1:3 α/β), and **7b** in 98% (1:4 α/β) (Table 2, entries 2 and 4). "Super-armed"[46] donor **6c**, which bears a neighboring participating group at C-2, yielded the corresponding disaccharide product **7c**[47] in 95% yield within 15 min at 0°C as the β-anomer (Table 2, entry 5). The same reaction conditions were applied to the reaction of less active thioglycosides **6d** and **6e**. It is expected that acyl substituents have a disarming effect on thioglycosides,[48] and thus it was not surprising the stability observed for peracetylated **6d** under the mild reaction conditions (Table 2, entry 6). When 0.03 equiv. of TMSOTf was added to the reaction, the desired product **7d**[44] was obtained in 76% yield as the β-anomer (Table 2, entry 7). It has also been shown that although more active than peracetylated glycosides, 4,6-*O*-benzylidene-protected pyranosyl systems, such as **6e**, are also less active glycosyl donors than their

Table 2: Summary of glycosylation reactions with thioglycoside donor **6a–h** and model acceptor **3** in the presence of ILs **1b**/NIS at rt to yield disaccharide **7a–h**



6a, 7a R_1=R_2=R_3=R_4=OBn
6b, 7b R_1=OAc, R_2=R_3=R_4=OBn
6c, 7c R_1=R_2=R_3=OBn, R_4=OAc
6d, 7d R_1=R_2=R_3=R_4=OAc
6e, 7e R_1=R_2=OCHPh, R_3=OAc, R_4=NHTroc

Entry[a]	Donor	Solvent	Yield (%)	Product	α/β ratio[b]
1	**6a**	DCM	72	**7a**	1.4:1
2	**6a**	MeCN	80	**7a**	1:3
3	**6b**	DCM	78[c]	**7b**	3:1
4	**6b**	MeCN	98[d]	**7b**	1:4
5	**6c**	DCM	95[e,f]	**7c**	Only β
6	**6d**	DCM	s.m.[g]	**7d**	—
7	**6d**	DCM	76[h]	**7d**	Only β
8	**6e**	DCM	75	**7e**	Only β

[a]Unless indicated otherwise, all reactions at rt.
[b]Determined by NMR spectroscopy (^{1}H and HMQC data).
[c]Reaction time = 5 h.
[d]Reaction time = 30 min.
[e]Reaction time = 15 min.
[f]Reaction temperature = 0°C.
[g]Reaction quenched after 18 h.
[h]0.03 equiv TMSOTf used.
s.m., recovered starting material (glycosyl donor).

4,6-di-*O*-benzyl congeners, because the formation of oxycarbenium cations is disfavored, due to the greater strain the conformational deformation imposes on the transfused bicyclic nucleus.[37,48] To further probe the scope of activation of **1b** at rt, 4,6-*O*-benzylidene, N-Trichloethylchloroformate (N-Troc)-protected **6e** was subjected to the reaction conditions and disaccharide **7e** was isolated in 75% yield (β-anomer only) (Table 2, entry 8).

In general, conversion yields for reactions where **1b** was used as the glycosyl activator at rt were comparable and in some cases exceeded those achieved in reactions where TMSOTf was used at −40°C as the activator.[12,13]

CONCLUSIONS

In conclusion, we have shown the first synthetic application of a new class of surfactant ILs **1b–1d** in the mild activation of thioglycosides when used

in combination with NIS. The glycosylation conditions are mild and compatible with a range of hydroxyl-protecting groups, such as acetates, benzyl ethers, and acetals, and are also amenable to NH_2-masking strategies, that is, trichloroethylcarbamate (Troc). Mechanistically, we suggest **1b** works by slow activation of NIS to release I^+ in situ, which in turn activates the thioglycosides. We have also shown that **1b** is a more reactive activator than [mim][OTf] while still discerning the less active (peracetylated) donors. Work is under way to utilize this new class of ILs in one-pot glycosylation reactions where chemoselective activation of the glycoside donors is important.

EXPERIMENTAL

General Methods

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, were 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 the 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 hours 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- to 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]), and the crude material was applied to the column as a solution in CH_2Cl_2 or by preadsorption 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 mm Hg (diaphragm pump) or 0.1 mm Hg (oil pump), as appropriate, and a high vacuum line at rt. ^{1}H NMR and ^{13}C NMR spectra were measured in the solvent stated with 400 or 500 MHz Varian *INOVA* 400 and 500 instruments, respectively. Chemical shifts quoted in parts per million from $SiMe_4$ and coupling constants (J) are 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 an HP-MALDI instrument using gentisic acid matrix.

Synthesis of ILs 1a–1d

Synthesis of the compounds has been described elsewhere.[19] Na-AOT was purchased from Sigma-Aldrich and purified by Soxhlet extraction using dry acetone and subjected to repeated centrifugation. Five grams of Na-AOT was then dissolved in a 30-mL water:ethanol mix (1:1 v/v) and slowly passed through an ion-exchange resin (Amberlite IR-120, Sigma-Aldrich). The H-AOT solutions were neutralized by tetra-alkylammonium hydroxide solutions (1 equiv.) (Sigma-Aldrich, used as bought). The solvent was then removed and dried in vacuo for 24 h. The synthesized surfactants were characterized by elemental analysis and NMR, all being consistent with experimental chemical structures. The solvent was removed under reduced pressure and dried in vacuo for 24 h. ILs were redissolved in toluene and concentrated under vacuum to coevaporate any traces of residual water and left drying for 18 h under high vacuum at rt before being used in glycosylation reactions.

General Protocols for Glycosylation Reactions

Typical IL-promoted glycosylation procedures

IL (**1a**–**1d**) (10% to 50% w/w) was added to a stirred suspension of thioglycoside donor (1.5 equiv.), glycosyl acceptor (1 equiv.), and NIS (2 equiv.) in dry dichloromethane (2–3 mL). The mixture was left stirring for 2 h at rt unless stated otherwise in the table. 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 all the product was in the ether phase. 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 oligosaccharide products.

Typical IL(1d) + TMSOTf-promoted glycosylation procedure

Trimethylsilyl trifluoromethanesulfonate (0.03 equiv.) and **1d** (10% w/w) were added to a stirred suspension of thioglycoside donor **6d** (50 mg, 1.5 equiv.), glycosyl acceptor (1 equiv.), and NIS (2 equiv.) in dry dichloromethane (2–3 mL). The mixture was left stirring at rt for 3 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

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 all the product was in the ether phase. Interestingly, 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 oligosaccharide **7d**.

*1,2:3,4-Di-O-isopropylidene-6-O-(4,6-O-benzylidene-2-deoxy-2-(2,2,2-trichloroethoxycarbonyl-amino)-β-*D*-glucopyranosyl)-β-*D*-galactopyranoside 7e*

^{1}H NMR (CD_3OCD_3, 400 MHz): δ = 7.51–7.49 (m, 2H, Ph), 7.37–7.36 (m, 3H, Ph), 5.63 (s, 1H, C$\underline{H}$Ph), 5.45 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1), 4.80 (d, 1H, J = 12.0 Hz, C$\underline{H}_2$ *Troc*), 4.77 (d, 1H, 1H, $J_{NH,2}$ = 10.5 Hz, N$\underline{H}$), 4.73 (d, 1H, J = 12.0 Hz, C$\underline{H}_2$ *Troc*), 4.72 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1′), 4.60 (dd, 1H, $J_{3,4}$ = 2.5 Hz, $J_{3,2}$ = 8.0 Hz, H-3), 4.32 (dd, 1H, $J_{2,3}$ = 2.5 Hz, $J_{2,1}$ = 5.0 Hz, H-2) 4.30–4.27 (m, 2H, H-4′, H6a′), 4.97–3.93 (m, 3H), 3.75 (t, 1H, $J_{6b,5} = J_{6b,6a}$ = 10.5 Hz, H-6b′), 3.62–3.54 (m, 3H), 3.45 (td, 1H, H-5′), 1.50 (s, 3H, C$\underline{H}_3$), 1.37 (s, 3H, C$\underline{H}_3$), 1.31 (s, 6H, 2xC$\underline{H}_3$). ^{13}C NMR (CD_3OCD_3, 100 MHz): δ = 156.1 (CO, *Troc*), 139.7, (C_q, Ph), 130.7, 129.3, 178.7 (C$\underline{H}$, Ph), 101.0, 109.6 ($CH_3\underline{C}CH_3$), 101.2 (C-1′), 102.7 (C$\underline{H}$Ph), 97.6 (C-1), 84.2 ($\underline{C}Cl_3$, *Troc*), 83.3 (C-5), 75.5 (C$\underline{H}_2$ *Troc*), 72.4, 72.0, 71.9, 70.0, 69.7, 68.3, 67.8, 60.0, 58.8 27.1, 26.9, 25.8, 25.2. ESI-HRMS for $C_{28}H_{36}Cl_3NNaO_{12}$), calcd.: 706.1201; found: 706.1198.

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