FULL PAPER

First Examples of α-(1→4)-Glycosylation Reactions on Ionic Liquid Supports

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We have developed the first α-(1→4)-glycosylation reactions on ionic liquid supports. The purification steps involve simple liquid/liquid extractions. The positive influence of the soluble support on the stereoselectivity was proved, and the recyclable character of the ionic liquid was demonstrated.

Introduction

The concept of chemistry on supports has made possible the development of new environmentally friendly methodologies. To rise to this challenge, chemical reactions on insoluble polystyrene solid supports,[1] on fluorinated phases,[2] on soluble polyethyleneglycol resins,[3] or, more recently, on ionic liquids (ILs) have been extensively studied. Under these conditions, the purification steps involve simple solid/liquid filtrations or liquid/liquid extractions, thus avoiding expensive and time-consuming chromatographic purification procedures. Moreover, as the reagents can be used in excess, higher yields can often be reached.

Among these supports, task-specific ionic liquids (TSIL) form a promising new class of soluble supports for organic synthesis.[4] They combine a higher loading capacity compared to those of solid supports and the advantages of soluble supports, i.e., the ability to run reactions under homogeneous conditions[5] and to use conventional methodologies for the analysis of reaction mixtures. Moreover, their solubilities can usually be tuned by the selection of an appropriate cation/anion pair. Ionic liquid supports have been successfully used in the synthesis of small molecules[6] as well as peptides,[7] oligoribonucleotides,[8] and oligosaccharides.

In the latter context, three examples of (1→6)-glycosylations by using an ionic liquid support are described in the literature.[9–11] All of the approaches use an ester linkage that is stable under the glycosylation conditions and is easily cleavable under mild conditions. The ILs were grafted onto either the C-6 position of the glycoside donor or onto the C-4 position of the glycoside acceptor. The stereoselectivities were controlled by the activation methods used. In 2006, Chan developed a β-(1→6)-glycosylation on [mim][BF$_4$] support using sulfoxide activation, and achieved moderate yields.[9] After an oxidation/coupling sequence, a trisaccharide was obtained. In the same year, Wang synthesized disaccharides by α- and β-(1→6)-glycosylation on [mim][PF$_6$] support with a trichloroacetamide (TCA) donor at –40 °C, with excellent yields and 90–95% purities.[10] Pathak reported an α-(1→6)-glycosylation between mannosyl fluoride anchored on [mim][PF$_6$] and p-thiotolyl glycoside as acceptor with good yields.[11] By using this latter methodology, α-(1→6)-tetra- and -octamannopyranose were obtained without the need of column purification.

In this paper, we report the first successive α-(1→4)-glycosylation reactions on an ionic liquid support. Several consecutive coupling steps were realized by using only simple liquid/liquid extraction to purify the intermediates. The recovered ionic liquid support was efficiently recycled. Moreover, we proved that the ionic support had a positive influence on the stereoselectivity of the coupling reaction.

In the course of our work on the synthesis of modified cyclodextrins through an opening/homologation/closing sequence, we were interested in the use of ionic soluble supports for glycosylation reactions. In our initial synthetic strategy, we ascertained the feasibility of two successive α-selective glycosylations at the anomeric and at the C-4 positions of a glucose derivative supported on ionic liquid. The overall synthetic process is depicted in Figure 1. Sugar **S1**, conveniently protected and activated, is grafted onto an ionic liquid support by a covalent linkage on the primary alcohol function. The α-(1→4)-glycosylation reaction on the support would then be carried out in the presence of an excess of unsupported sugar **S2**. The supported disaccharide, which should be easily isolated and purified by simple washing, would then be submitted to a second glycosylation reaction with the appropriate sugar **S3**. The supported trisaccharide should then be cleaved and isolated in pure form without requiring chromatography. Finally, the ionic support may be recycled.

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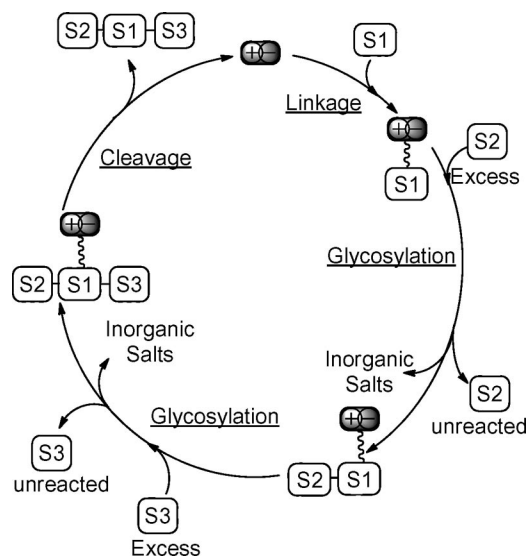
Figure 1. Overall synthetic process.

Results and Discussion

Stable and easily accessible anomeric thioglycosides are among the most effective and commonly used glycosyl donors in the chemical synthesis of oligosaccharides. To achieve a double α-(1→4)-glycosylation, we synthesized the original supported acceptor/donor monosaccharide **1** activated at the C-1 position and having a free hydroxy group at the C-4 position (Scheme 1). To predominantly achieve α-glycosylation, we used a nonparticipating benzyl protecting group at the C-2 position. A flexible spacer composed of a long chain of five carbon atoms separates the imidazolinium cation from the ester linkage.
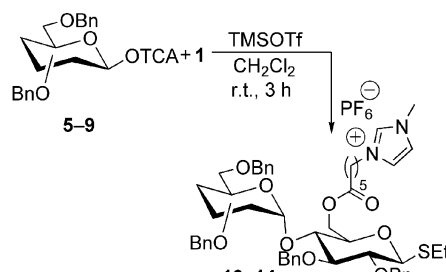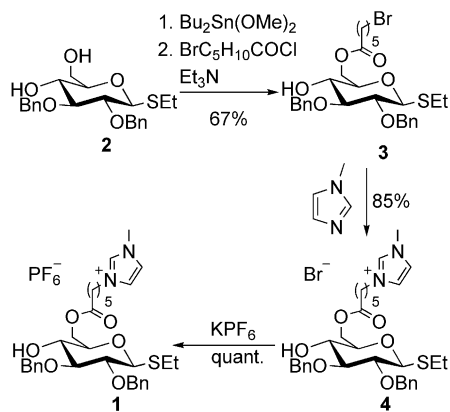

Scheme 1. Synthesis of monosaccharide **1**.

Ethyl 2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside (**2**) was synthesized from acetylglucose in five steps according to published methods, with a global yield of 63%.[12] To selectively introduce the spacer at the C-6 position, a stannylene acetal was formed by treatment with dibutyltin dimethoxide.[13] The esterification reaction was carried out with 5-bromopentanoyl chloride in the presence of triethylamine at room temperature during 3 h to give ester **3** with 67% yield. Addition of methylimidazole in acetonitrile at

100 °C afforded the ionic compound **4** with 85% yield in 5 h. Finally, ion metathesis with potassium hexafluorophosphate gave the desired hydrophobic ionic liquid **1** quantitatively. Thus, supported sugar **1** was obtained in 36% overall yield from commercial acetylglucose in nine steps (Scheme 1).

To obtain the more stable α-glycosylation product, thermodynamic conditions (room temperature, more than 1.5 h reaction time) were chosen. However, the use of a participating solvent was avoided so that the possible influence of the ionic support on the stereoselectivity could be established. The α-(1→4)-glycosylation reaction was therefore carried out in dichloromethane by using 1.5 equiv. of TCA donors and trimethylsilyl triflate (TMSOTf) as a strong Lewis acid during 3 h (Table 1 and Figure 2). The protected β-trichloroacetimidates **5β–9β** (derived from glucose, galactose, mannose, maltose, and cellobiose, respectively) were successfully used as substrates. The excess of donor sugar was quantitatively recovered (in its unactivated form) by extracting the crude product with diethyl ether. The inorganic salts were removed by washing a solution of the crude product in dichloromethane with water. The corresponding supported α-(1→4)-disaccharides **10–14** were obtained after purification by simple liquid/liquid extractions, with yields ranging from 76 to 89% (Table 1). Complete α-selectivity was usually observed, except for the protected mannose **7** (Table 1, Entry 3) and cellobiose **9** (Table 1, Entry 5), which showed a 96:4 α/β selectivity. The α/β ratio was determined by ^{1}H NMR spectroscopic analysis on the basis of integrated ratios of the anomeric hydrogen atom. Except for compounds **12** and **14**, only one anomeric ^{1}H NMR signal (t, J = 3.0–3.6 Hz) corresponding to the α-isomer was observed at the newly formed glycosidic bond.

Table 1. Glycosylation on ionic liquid supports.

Entry	Donor	Product	α/β	Yield [%]
1	**5β**	**10**	>99:1	89
2	**6β**	**11**	>99:1	84
3	**7β**	**12**	96:4	81
4	**8β**	**13**	>99:1	76
5	**9β**	**14**	96:4	78
6	**5α**	**10**	85:15	77
7[a]	**5β**	**10**	>99:1	87

[a] Recycling of the ionic liquid support.

To investigate the influence of the ionic support, the glycosylation reaction was carried out with activated glucose derivative **3** in the absence of the imidazolium group
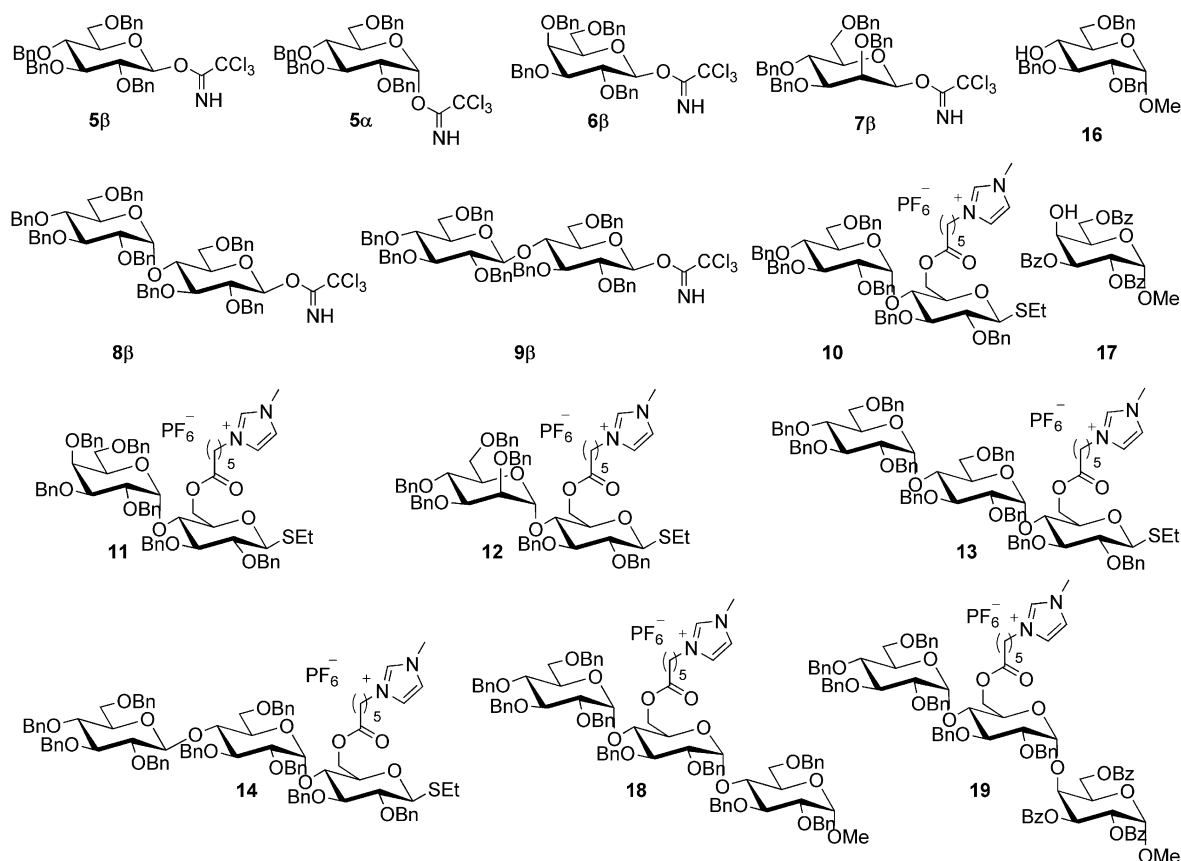
Figure 2. Structures of the reagents and products.

(Scheme 2). The functionalized glucose **3** was treated with TCA glucoside **5β** under the same conditions as those applied for the reaction of **1**. The disaccharide **15** was obtained with similar yield (90%) but with lower stereoselectivity (α/β = 9:1) after tedious purification by column chromatography. Surprisingly, the use of α-trichloroacetimidate **5α** derived from glucose as donor and **1** as acceptor, predominantly afforded the α-glycoside, albeit with a lower α/β ratio (85:15; see Table 1, Entry 6).
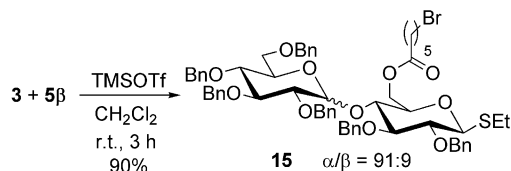

Scheme 2. Control coupling without the imidazolium group.

Selectivity studies on glycosylation reactions with ionic liquids used as solvent were reported by Poletti[14] and Toshima,[15] with a nonparticipating group at the C-2 position. However, whereas triflate-based ionic liquids induced β-selectivity (presumably by coordination of the triflate counterion on the α-face of the glycosyl donor), no influence of the hydrophobic, noncoordinating anion PF_6^- during the glycosylation of 2-propanol with trichloroacetimidates in 1-butyl-3-methylimidazolium hexafluorophosphate [bmim]-[PF_6] was observed.[14] The stereochemistry of the product was dependent on the anomeric configuration of the donor, with an inversion of the configuration with low selectivity usually being reported.

From supported disaccharides **10**, we developed a second α-(1→4)-glycosylation reaction with two new acceptors, **16** and **17**. Supported thioglycoside donor **10** was activated by N-bromosuccinimide (NBS) in the presence of TMSOTf (Scheme 3). From protected glucose **16** and galactose **17**, two α-(1→4)-trisaccharides **18** and **19** were obtained after successive washing with diethyl ether and extraction with dichloromethane and water. Good yields (78 and 85%) and complete α-stereoselectivity after 3 h of stirring at 0 °C were observed. As for the first coupling reaction, only the α-isomers were detected by ^{1}H NMR spectroscopy.
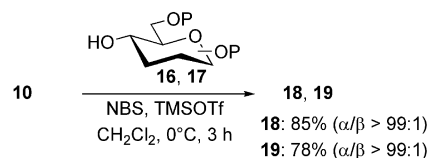
Scheme 3. Second glycosylation of disaccharide **10**.

Cleavage of the ester linkage and the recyclability of the ionic liquid were then studied. The ester linker was quantitatively cleaved in the presence of lithium hydroxide in a water/acetonitrile mixture in 5 h at room temperature (Scheme 4). After evaporation of the acetonitrile, the or-

ganic compounds were extracted with dichloromethane and washed with water. The dried organic phase was then washed with diethyl ether to separate disaccharide **20** from the insoluble supported acid **21**.
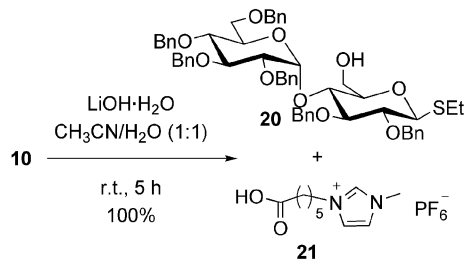
Scheme 4. Product isolation.

To recycle the IL, the carboxylic acid **21** was treated with thionyl chloride in *N,N*-dimethylformamide (DMF) at room temperature for 4 h to afford the corresponding acyl chloride in 78% yield (Scheme 5). Addition of the protected glucose unit **22**, activated as its stannylene acetal, led to the desired supported saccharide **1** in 63% yield after 3 h of stirring at room temperature in the presence of a base. In addition to the possible recyclability of the support, this reaction shows that the ionic support can be grafted onto the glycoside as a whole, rather than constructed stepwise as mentioned previously (see Scheme 1).
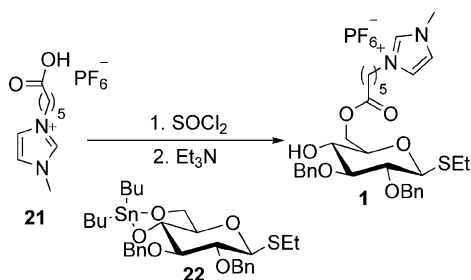
Scheme 5. Recycling of the IL.

The glycosylation reaction between the recycled IL **1** and **5β** (Table 1, Entry 7) led to the supported disaccharide **10** without loss of reactivity or selectivity. A similar yield (87%) was observed after simple extraction with diethyl ether and washing with water. Complete α-(1→4)-stereoselectivity was preserved, thus demonstrating the recyclability of the ionic liquid.

Conclusions

We have synthesized new acceptor/donor units supported on ionic liquid. The first examples of successive selective α-(1→4)-glycosylation reactions of various mono- and disaccharides with two methods of activation in good yields have been developed. All of the purification steps were carried out by simple washing or liquid/liquid extractions, thus avoiding the need for inconvenient column chromatography. The glycosylation reaction with trichloroacetimidate donors is α-selective, regardless of the configuration (α/β) of the

donor. Very high diastereoisomeric excesses were obtained with β-trichloroacetimidates. Finally, the recyclability of the IL was demonstrated, and the stereoselectivity was preserved with the recycled ionic support. This methodology will be applied for the synthesis of more complex oligosaccharides. Studies on the influence of the counterion and of the length of the spacer between the saccharide and the IL are in progress.

Experimental Section

General: Unless otherwise stated, ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in deuterated solvents with a Bruker AC 300 spectrometer, operating at 300, 75, and 282 MHz, respectively. IR spectra were recorded with a Perkin–Elmer 16 PC FTIR instrument, and data are expressed in cm^{–1}. Electrospray mass spectra were recorded with an Esquire-LC ion-trap mass spectrometer (ITMS) (Bruker Daltonics, Wissembourg, France). High-resolution mass spectra (HRMS) were performed with an LCTOF Premier XE (Micromass, Manchester, UK) instrument equipped with an ESI source. The spectra were acquired in W mode in positive mode. Elemental compositions were obtained with a mass accuracy better than 5 ppm. All reactions were monitored by analytical thin-layer chromatography using pre-coated silica gel plates. Visualization was accomplished under UV light (254 nm). Flash chromatography was performed by using silica gel (230–400 mesh). Unless otherwise noted, chemicals were used as received without further purification. Dichloromethane and acetonitrile were distilled from calcium hydride under nitrogen. Toluene was distilled from sodium under nitrogen. Cyclohexane and ethyl acetate were distilled prior to use. Trichloroacetimidates **5β**–**9β** were prepared by using the reported procedure[16] with Cs_2CO_3 as base. Trichloroacetimidate **5α** was purchased from Aldrich.

2,3-Di-*O*-benzyl-6-*O*-(6-bromohexanoyl)-1-ethylthio-β-D-glucopyranose (3): 2,3-Di-*O*-benzyl-1-ethylthio-β-D-glucopyranose (**2**; 2.67 g, 6.61 mmol) was dissolved in toluene (20 mL) in a distillation apparatus. $Bu_2Sn(OMe)_2$ (1.67 mL, 7.27 mmol, 1.1 equiv.) was added, and the mixture was stirred under argon at 80 °C for 2 h. The reaction mixture was then concentrated to half of the original volume by distillation. 6-Bromohexanoyl chloride (1.32 mL, 8.59 mmol, 1.3 equiv.) and Et_3N (0.036 mL, 0.33 mmol, 5%) were added at 0 °C to the concentrated mixture. The reaction mixture was stirred at room temp. for 3 h, then poured into water. After evaporation of the organic solvents, the crude product was dissolved in dichloromethane and washed with water. The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/EtOAc, 6:4) to yield **3** (2.58 g, 4.43 mmol, 67%) as a yellow oil. $[a]_D^{20} = 10.2$ (c = 1.00, $CHCl_3$). MS (ESI): m/z = 605 [M + Na][+]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.31 (m, 10 H, Ar), 4.94 (dd, J = 1.5, 3.0 Hz, 2 H, CH_2-Ph), 4.75 (dd, J = 4.5, 5.7 Hz, 2 H, CH_2-Ph), 4.48 (d, J = 9.6 Hz, 1 H, 1-H), 3.51–3.37 (m, 6 H, 2-H, 3-H, 4-H, 5-H, 6-H, 6′-H), 2.78–2.73 (m, 2 H, CH_2), 2.37 (t, J = 7.2 Hz, 2 H, S-CH_2-CH_3), 1.90–1.85 (m, 2 H, CH_2), 1.68–1.62 (m, 4 H, 2 CH_2), 1.50–1.41 (m, 2 H, CH_2), 1.33 (t, J = 4.2 Hz, 3 H, S-CH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9 (C=O), 140.2, 138.4, 137.8, 128.7–128.1 (Ar), 85.7 (C-1), 85.4 (C-3), 81.4 (C-5), 75.6 (CH_2-Ph), 75.5 (CH_2-Ph), 70.1 (C-4), 63.5 (C-2), 62.9 (C-6), 33.9 (S-CH_2-CH_3), 33.6 (CH_2), 32.4 (CH_2), 27.7 (CH_2), 25.3 (CH_2), 24.1 (CH_2), 15.2 (S-CH_2-CH_3) ppm. $C_{28}H_{37}BrO_6S$ (581.56): calcd. C 57.83, H 6.41, S 5.51; found C 57.90, H 6.52, S 5.48.

[6-(2,3-Di-*O*-benzyl-1-ethylthio-β-D-glucopyranos-6-yl)-6-oxohexyl]-1-methyl-1*H*-imidazol-3-ium Bromide 4: Compound **3** (2.1 g, 3.61 mmol) and 1-methylimidazole (0.431 mL, 5.42 mmol, 1.5 equiv.) in acetonitrile (20 mL) were stirred under argon at reflux temperature for 5 h. The mixture was concentrated under reduced pressure, and the crude product was washed with Et$_2$O (3 × 30 mL). The diethyl ether phase was removed by decanting to yield **4** (2.03 g, 3.07 mmol, 85%) as a viscous yellow oil. $[a]_D^{20}$ = 9.2 (*c* = 1.00, CHCl$_3$). MS (ESI): *m/z* = 583 [M]$^+$. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.46 (s, 1 H, N$_2$C-H), 7.39–7.22 (m, 12 H, Ar, Im), 4.93 (d, *J* = 9.9 Hz, 2 H, CH$_2$-Ph), 4.77 (d, *J* = 11 Hz, 1 H, CH-Ph), 4.73 (d, *J* = 11 Hz, 1 H, CH-Ph), 4.47 (d, *J* = 9.6 Hz, 1 H, 1-H), 4.28 (m, 2 H, 6-H, 6′-H), 4.11 (m, 2 H, 5-H, 4-H), 3.85 (s, 3 H, CH$_3$), 3.51–3.37 (m, 4 H, 2-H, 3-H), 2.78–2.71 (m, 2 H, CH$_2$), 2.34 (t, *J* = 7.2 Hz, 2 H, S-CH$_2$-CH$_3$), 1.87–1.79 (m, 2 H, CH$_2$), 1.71–1.65 (m, 4 H, 2 CH$_2$), 1.38–1.28 (m, 3 H, S-CH$_2$-CH$_3$) ppm. ^{13}C NMR (75 MHz, CD$_3$CN): δ = 174.2 (C=O), 140.7 (N$_2$C), 139.7 (Ar), 137.5 (Ar), 129.4 (Ar), 129.3 (Ar), 129.3 (Ar), 129.2 (Ar), 129.1 (Ar), 129.0 (Ar), 128.8 (Ar), 128.7 (Ar), 128.5 (Ar), 128.4 (Ar), 124.7 (Im), 123.3 (Im), 85.9 (C-1), 85.4 (C-3), 81.4 (C-5), 77.4 (CH$_3$), 75.6 (CH$_2$-Ph), 75.5 (CH$_2$-Ph), 70.4 (C-4), 64.3 (C-2), 50.1 (C-6), 37.0 (CH$_2$), 34.5 (CH$_2$), 30.4 (CH$_2$), 26.1 (S-CH$_2$-CH$_3$), 25.4 (CH$_2$), 23.9 (CH$_2$), 15.3 (S-CH$_2$-CH$_3$) ppm.

[6-(2,3-Di-*O*-benzyl-1-ethylthio-β-D-glucopyranos-6-yl)-6-oxohexyl]-1-methyl-1*H*-imidazol-3-ium Hexafluorophosphate (1): Potassium hexafluorophosphate (0.625 g, 3.40 mmol, 1.1 equiv.) was stirred with **4** (2 g, 3.09 mmol) in a mixture of acetonitrile and water (1:1, 20 mL) at room temp. for 2 h. The solvents were removed under reduced pressure, and the crude product was dissolved in dichloromethane, then washed with water and brine. The organic layer was dried (MgSO$_4$), filtered, and the solvent was evaporated to obtain **1** (2.25 g, 3.09 mmol, 100%) as a viscous yellow oil. $[a]_D^{20}$ = 11.3 (*c* = 1.00, CHCl$_3$). MS (ESI): *m/z* = 583 [M]$^+$. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.48 (s, 1 H, N$_2$C-H), 7.39–7.16 (m, 32 H, Ar, Im), 5.27 (t, *J* = 3.6 Hz, 1 H, 1′-H), 4.99 (d, *J* = 10.8 Hz, 2 H, CH$_2$-Ph), 4.91 (d, *J* = 9.9 Hz, 1 H, CH$_2$-Ph), 4.86 (d, *J* = 11 Hz, 1 H, CH$_2$-Ph), 4.81 (d, *J* = 10.6 Hz, 2 H, CH$_2$-Ph), 4.80 (d, *J* = 11.4 Hz, 1 H, CH$_2$-Ph), 4.76 (d, *J* = 9.6 Hz, 1 H, 1-H), 4.75 (s, 1 H, CH$_2$-Ph), 4.71 (s, 1 H, CH$_2$-Ph), 4.61 (s, 1 H, CH$_2$-Ph), 4.31 (m, 2 H, 2 6-H), 4.13 (m, 2 H, 4-H, 5-H), 4.11–4.03 (m, 1 H, 4′-H), 4.01 (t, *J* = 9.7 Hz, 1 H, 2′-H), 3.87 (s, 3 H, CH$_3$), 3.78–3.61 (m, 5 H), 3.53–3.36 (m, 4 H), 2.98 (d, *J* = 2.4 Hz, 1 H), 2.81–2.69 (m, 2 H), 2.36 (t, *J* = 7.2 Hz, 2 H), 1.88–1.79 (m, 2 H), 1.72–1.63 (m, 4 H), 1.35–1.31 (m, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 174.3 (C=O), 140.5–137.6 (Ar), 129.5–128.6 (Ar), 124.7 (Im), 123.4 (Im), 92.3 (C-1′), 87.1 (C-1), 85.6 (C-3), 82.8 (C-5), 81.0 (C-3′), 78.9, 78.8, 76.8, 76.1, 75.8, 74.5, 74.2 (C-4′), 71.6 (C-4), 71.2 (C-5′), 69.6 (C-2), 50.3 (C-6), 37.1, 34.6, 30.5, 26.2, 25.5, 25.0, 15.9 ppm. ^{19}F NMR (282.5 MHz, CDCl$_3$): δ = –72.1 (d, $^1J_{P,F}$ = 710 Hz) ppm. HRMS (ESI): calcd. for C$_{32}$H$_{43}$N$_2$O$_6$S [M]$^+$ 583.2842; found 583.2858.

General Procedure A. Glycosylation with TCA Donors: Under argon, at 0 °C, TCA donor **5–9** (1.5 equiv.) in dichloromethane was added to a solution of **1** in dichloromethane, in the presence of molecular sieves (4 Å). TMSOTf (0.75 equiv.) was added, and the solution was stirred at room temp. for 1.5 h. The reaction mixture was concentrated under reduced pressure and washed three times with Et$_2$O. The solvent was removed by decanting, and the obtained oil was dissolved in dichloromethane and washed with water and brine. The organic phase was dried (MgSO$_4$), filtered, and the solvent was evaporated under reduced pressure to obtain the desired disaccharide as a viscous yellow oil.

{6-[4-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-2,3-di-*O*-benzyl-1-ethylthio-β-D-glucopyranos-6-yl]-6-oxohexyl}-1-methyl-1*H*-

imidazol-3-ium Hexafluorophosphate (10): Compound **5** (20 mg, 29.3 μmol) and **1** (14 mg, 19.5 μmol) in dried dichloromethane (2 mL) were treated with TMSOTf (1.4 μL, 14.7 μmol) according to Procedure A. Compound **10** (22 mg, 17.4 μmol, 89%) was obtained as a yellow oil. $[a]_D^{20}$ = 13.4 (*c* = 1.00, CHCl$_3$). MS (ESI): *m/z* = 1105 [M]$^+$. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.50 (s, 1 H, N$_2$C-H), 7.40–7.12 (m, 32 H, Ar, Im), 5.23 (t, *J* = 3.6 Hz, 1 H, 1′-H), 4.97 (d, *J* = 10.8 Hz, 2 H, CH$_2$-Ph), 4.85 (d, *J* = 9.9 Hz, 2 H, CH$_2$-Ph), 4.82 (d, *J* = 11 Hz, 2 H, CH$_2$-Ph), 4.80 (d, *J* = 10.8 Hz, 2 H, CH$_2$-Ph), 4.79 (d, *J* = 12 Hz, 2 H, CH$_2$-Ph), 4.78 (d, *J* = 11 Hz, 2 H, CH$_2$-Ph), 4.71 (d, *J* = 9.6 Hz, 1 H, 1-H), 4.33 (m, 2 H, 2×6-H), 4.15 (m, 2 H, 4-H, 5-H), 4.05–4.01 (m, 1 H, 2′-H), 3.96 (t, *J* = 9.3 Hz, 1 H, 4′-H), 3.89 (s, 3 H, CH$_3$), 3.73–3.41 (m, 7 H, 2-H, 3-H, 3′-H, 4′-H, 5′-H, 2×6′-H), 2.79–2.71 (m, 2 H, CH$_2$), 2.38 (t, *J* = 7.2 Hz, 2 H, S-CH$_2$-CH$_3$), 1.88–1.79 (m, 2 H, CH$_2$), 1.69–1.63 (m, 6 H, 3 CH$_2$), 1.38–1.32 (m, 3 H, S-CH$_2$-CH$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 173.1 (C=O), 139.3 (N$_2$C), 138.8–136.3 (Ar), 128.5–127.4 (Ar), 123.5 (Ar), 122.2 (Im), 91.1 (C-1′), 85.9 (C-1), 84.4 (C-3), 81.6 (C-5), 81.1 (C-3′), 79.8 (CH$_2$-Ph), 77.7 (CH$_2$-Ph), 77.6 (CH$_3$), 75.6 (CH$_2$-Ph), 74.9 (CH$_2$-Ph), 74.6 (CH$_2$-Ph), 73.3 (CH$_2$-Ph), 73.0 (C-4′), 70.4 (C-4), 70.0 (C-5′), 68.4 (C-2′), 63.4 (C-2), 49.1 (C-6), 35.9, 33.4, 29.7, 25.0, 24.9, 24.3, 23.8, 14.7 ppm. ^{19}F NMR (282.5 MHz, CDCl$_3$): δ = –73.8 (d, $^1J_{P,F}$ = 710 Hz) ppm.

General Procedure B. Glycosylation with Thioethyl Activation: Acceptor **16** or **17** (1.5 equiv.) in dichloromethane was added to a solution of **10** in dichloromethane in the presence of molecular sieves (4 Å) under argon at 0 °C. NBS (1.2 equiv.) and TMSOTf (0.75 equiv.) were added, and the mixture was stirred at room temp. for 3 h. The reaction mixture was concentrated under reduced pressure and washed three times with Et$_2$O. The solvents were removed by decantation, and the obtained oil was dissolved in dichloromethane and washed with water and brine. The organic phase was dried (MgSO$_4$), filtered, and the solvent was evaporated under reduced pressure to obtain the desired trisaccharide as a viscous yellow oil.

{6-[2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-1-methoxy-α-D-glucopyranos-6^{II}-yl]-6-oxohexyl}-1-methyl-1*H*-imidazol-3-ium Hexafluorophosphate (18): Compound **10** (20 mg, 15.8 μmol) and **16** (5 mg, 10.1 μmol) in dried dichloromethane (2 mL) were treated with TMSOTf (1.1 μL, 11.9 μmol) and NBS (3 mg, 19.0 μmol) according to Procedure B. Compound **18** (22 mg, 13.4 μmol, 85%) was obtained as a viscous yellow oil. $[a]_D^{20}$ = 45.7 (*c* = 1.00, CHCl$_3$). MS (ESI): *m/z* = 1508 [M]$^+$. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.47 (s, 1 H, N$_2$C-H), 7.38–7.10 (m, 47 H, Ar, Im), 5.45 (d, *J* = 3.8 Hz, 1 H, 1″-H), 5.21 (t, *J* = 3.6 Hz, 1 H, 1′-H), 4.94 (d, *J* = 10.8 Hz, 2 H, CH$_2$-Ph), 4.91 (d, *J* = 9.9 Hz, 1 H), 4.83–4.81 (m, 3 H), 4.79 (d, *J* = 10.8 Hz, 1 H), 4.77 (d, *J* = 12 Hz, 2 H, CH$_2$-Ph), 4.75–4.71 (m, 4 H, 1-H, CH$_2$-Ph), 4.41–4.36 (m, 2 H, 2×6-H), 4.31 (s, 2 H), 4.17–4.03 (m, 2 H, 4′-H, 5-H), 4.04–3.90 (m, 3 H, 4″-H, 2″-H), 3.90 (t, *J* = 9.1 Hz, 1 H, 2′-H), 3.86 (s, 3 H, CH$_3$), 3.68–3.43 (m, 13 H), 3.3 (s, 3 H), 2.93 (d, *J* = 6.8 Hz, 1 H, CH$_2$), 2.71–2.65 (m, 2 H, CH$_2$), 2.35 (m, 2 H, CH$_2$), 1.86–1.71 (m, 2 H, CH$_2$), 1.66–1.63 (m, 4 H, 2 CH$_2$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 173.5 (C=O), 139.7–136.8 (Ar), 128.9–127.8 (Ar), 123.9 (Im), 122.6 (Im), 91.8 (C-1″), 91.5 (C-1′), 86.3 (C-1), 84.7 (C-3), 82.0, 81.5 (C-5), 80.2 (C-3′), 80.0, 78.1 (CH$_2$-Ph), 78.0 (CH$_2$-Ph), 77.5 (CH$_3$), 76.0 (CH$_2$-Ph), 75.7 (CH$_2$-Ph), 75.3 (CH$_2$-Ph), 75.0 (CH$_2$-Ph), 73.9 (CH$_2$-Ph), 73.4 (C-4′), 70.9, 70.8 (C-4), 70.7 (C-5′), 70.4 (C-2′), 63.8 (C-2), 62.9, 55.5, 49.5 (C-6), 36.3, 33.8, 25.4, 24.7, 24.2 ppm. ^{19}F NMR (282.5 MHz, CDCl$_3$): δ = –73.3 (d, $^1J_{P,F}$ = 710 Hz) ppm.

$C_{92}H_{103}F_6N_2O_{17}P$ (1653.77): calcd. C 66.82, H 6.28; found C 66.81, H 6.33.

Hydrolysis of Ester 10: Compound **10** (30 mg, 23.7 µmol) was dissolved in an acetonitrile/water mixture (1:1, 4 mL) containing lithium hydroxide (3 mg, 94.8 µmol, 4 equiv.), and the solution was stirred at room temp. for 5 h. The solvents were evaporated under reduced pressure, and the crude product was dissolved in dichloromethane, and washed with water and brine. The organic phase was dried (MgSO₄), filtered and the solvent was evaporated under reduced pressure. The obtained oil was extracted three times with Et₂O, and the solvent was removed by decanting. The resulting disaccharide **20** (22 mg, 23.7 µmol, 100%) was obtained after evaporation of the Et₂O as a colorless oil. The carboxylic acid supported on ionic liquid **21** was recovered as the phase insoluble in diethyl ether (8 mg, 23.7 µmol, 100%).

Compound 20: R_f = 0.42 (cyclohexane/EtOAc, 7:3). $[a]_D^{20}$ = 9.2 (c = 1.00, CHCl₃). MS (ESI): m/z = 950 [M + Na]⁺. ¹H NMR (300 MHz, CDCl₃): δ = 7.85 (m, 2 H), 7.58 (m, 1 H), 7.49–7.34 (m, 2 H), 7.34–7.14 (m, 25 H), 5.24 (t, J = 3.6 Hz, 1 H), 4.94 (d, J = 10.8 Hz, 1 H), 4.93 (d, J = 9.9 Hz, 1 H), 4.89 (d, J = 11 Hz, 1 H), 4.84 (d, J = 10.8 Hz, 1 H), 4.82 (d, J = 12 Hz, 1 H), 4.77 (d, J = 11 Hz, 1 H), 4.72 (d, J = 11 Hz, 1 H), 4.64 (d, J = 12 Hz, 1 H), 4.55 (s, 1 H), 4.50 (s, 1 H), 4.47 (d, J = 9.6 Hz, 1 H), 4.46 (d, J = 3 Hz, 1 H), 4.11 (t, J = 7.2 Hz, 2 H), 4.05–4.02 (m, 1 H), 3.96 (t, J = 9.3 Hz, 1 H), 3.81–3.29 (m, 19 H), 2.93 (d, J = 6.5 Hz, 1 H), 2.73–2.70 (m, 2 H), 1.38–1.28 (m, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 138.8, 138.4, 138.2, 138.1, 138.0, 137.7, 136.3, 128.5–128.3 (Ar), 128.1–127.7 (Ar), 127.5, 127.3, 126.9, 126.5, 123.5, 122.1, 102.8, 98.0, 86.0, 85.0, 84.5, 82.8, 81.9, 81.5, 81.2, 79.4, 79.3, 78.1, 77.4, 75.6–75.2, 74.4, 73.7, 73.5, 72.3, 71.6, 68.3, 63.9, 62.8, 49.8, 36.4, 29.8, 14.9 ppm. $C_{56}H_{62}O_{10}S$ (927.15): calcd. C 72.54, H 6.74, S 3.46; found C 72.48, H 6.81, S 3.41.

Compound 21: MS (ESI): m/z = 342 [M]⁺. ¹H NMR (300 MHz, CDCl₃): δ = 11.9 (br. s, 1 H), 8.5 (s, 1 H), 6.88 (m, 1 H), 6.84 (m, 1 H), 3.79 (t, J = 7.2 Hz, 2 H), 3.57 (s, 3 H), 2.61 (t, J = 7.2 Hz, 2 H), 1.52–1.42 (m, 2 H), 1.04–0.91 (m, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 179.4, 137.0, 123.0, 122.9, 47.9, 37.0, 29.7, 27.0, 24.4 ppm. ¹⁹F NMR (282.5 MHz, CDCl₃): δ = –74.5 (d, $^1J_{P,F}$ = 710 Hz) ppm. $C_{10}H_{17}F_6N_2O_2P$ (342.22): calcd. C 35.10, H 5.01; found C 35.21, H 5.13.

Recycling of Carboxylic Acid Supported on Ionic Liquid 21: Compound **21** (8 mg, 23.7 µmol) was dissolved in distilled dichloromethane (2 mL). Thionyl chloride (12.9 µL, 177.8 µmol, 7.5 equiv.) and dried DMF (1 µL) were then added at 0 °C, and the reaction mixture was stirred at 0 °C for 3 h, then added dropwise at 0 °C to a solution ethyl 2,3-di-O-benzyl-4,6-O-dibutyl-stannylidene-1-thio-β-D-glucopyranoside (**22**; 16.6 mg, 26.1 µmol, 1.1 equiv.) in distilled dichloromethane (2 mL). Et₃N (0.18 µL, 1.3 µmol, 5.5%) was added at 0 °C and the reaction mixture was stirred at room temp. for 3 h. After evaporation of the solvents, the crude product was washed with Et₂O (3 × 30 mL), and the solvents were removed by decanting to yield **1** (15.4 mg, 21.1 µmol, 89%) as a viscous yellow oil.

Supporting Information (see footnote on the first page of this article): Synthesis and analytical data of products **11**–**15** and **19**.

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