Synthesis of O-1–O-6 Substituted Positional Isomers of d-Glucose–Thioether Ligands and Their Ruthenium Polypyridyl Conjugates

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Supporting Information

ABSTRACT: A library of positional isomers of d-glucose (O-1–O-6) as ligands and their 11 light-active ruthenium conjugates has been synthesized. A protecting group strategy without the necessity of using palladium on carbon for the modification for the 2-O and 4-O position allows for the incorporation of sulfur donor atoms as ligands for transition metal complexes.

INTRODUCTION

Carbohydrates are a class of biomolecules ubiquitously present in nature, comprising monosaccharides, oligosaccharides, and polysaccharides, of which monosaccharides cannot be hydrolyzed further into smaller units. These molecules are recognized as important building blocks in the cell wall of bacteria,1,2 in plants,3 in the exoskeleton of insects,4 in cell recognition processes,5 and in the backbone of RNA and DNA6 and are associated with many different physiological and disease-related processes.7,8 Among them, d-glucose is the most well-known monosaccharide as it serves as the primary source of chemical energy in eukaryotic cells for the production of ATP.9 Otto Warburg found that cancer cells have an increased glycolysis rate for the production of ATP compared to normal cells.10 As a consequence, glucose transporters (GLUTs) 1 and 3 are overexpressed in cancer cells.11 In recent years, there has been a growing interest in using this effect to selectively deliver molecules of interest to cancer cells. In the field of diagnostic imaging, the well-known radiotracer 2-deoxy-2-[18F]-fluorogucose (2-FDG) selectively accumulates in cancer cells since its metabolic breakdown is hampered by the replacement of a hydroxyl group on the 2-position of d-glucose by fluoride.12 This clinically approved agent allows PET imaging of tumors anywhere in the body. In the field of medicinal chemistry, gulosamidase has shown some success as a safer alternative for ifosfamide, an alkylating agent used in cancer treatment. The therapeutic efficiency of gulosamidase is thought to be higher due to its increased water solubility and preferred uptake in malignant cells versus normal cells.13 Recently, Palay et al. have demonstrated that a series of glucose conjugates of platinum-based medicines are taken up via GLUT1.14,15 This result is in contrast to the observation of Schubiger, who found that none of their radiodiagnostic glycoconjugates based on 99mTc were taken up via glucose transporters.16

For ruthenium(II) polypyridyl-based drugs, this effect has not been thoroughly investigated. Our group has been involved in a research program aimed at targeting ruthenium-based light-activated anticancer prodrugs to GLUT transporters by glucose conjugation.17,18 These photoactivated chemotherapeutic prodrugs are typically protected from binding to biomolecules in the dark by thioether ligands, which under visible light irradiation are photosubstituted by water, thereby activating the prodrug.19–21 En route to functionalizing such complexes with glucose, it came out that all available synthetic routes toward a series of positional isomers of glucose were incompatible with the presence of thioether ligands, which deactivate Pd/C catalysts used to deprotect benzyl protecting groups. For that reason, we developed and report here on a series of new synthetic routes toward all positional isomers of glucose that are compatible with the presence of sulfur-based ligands.22 As traces of palladium also often interfere with the biological activity of pharmaceuticals,23 these new routes do not make use of palladium catalysts. PEGylation of all positional isomers was also realized to vary the spacer between the thioether ligands and the glucose moiety. The coordination of the thioether–glucose ligands to known photoactive ruthenium(II) polypyridyl precursors afford 11 ruthenium–glucose conjugates (Figure 1) as a demonstration that such molecules can be obtained on a synthetical useful scale. Recent publications describe the more photophysical and/or biological properties of these type of complexes.17,18

RESULTS AND DISCUSSION

Five hydroxyl groups are available for modification in d-glucose, of which the 1-O position is modified via chemical glycosylation.24 Recently, Patra et al. have demonstrated that...
the spacer length exerts influence over the GLUT-mediated uptake of platinum complexes in cells; however, there is currently no established understanding of this effect in cationic ruthenium(II) polypyridyl compounds. Therefore, oligoethylene glycol spacers [OCH2CH2]n with varying lengths (n = 0−3) were introduced in glycoconjugates [5](PF6)2−[5](PF6)2 (Figure 1). The first complex in this series ([1](PF6)2) was synthesized starting from precursor 12 (Scheme 1). This building block and NaSMe were used in a SN2 reaction, ensuring the installment of the thioether group, according. This ligand was then reacted with [Ru(tpy)(bpy)Cl]Cl, affording the orange (λmax = 450 nm) glycoconjugate [1](PF6)2.

For complex [2](PF6)2, a three-step one-pot synthesis starting from peracetylated glucose 14 (Scheme 2) was adapted from Valerio et al., which afforded the trans-glucopyranoside as the only diastereoisomer. Treatment of this compound with sodium methoxide in methanol afforded fully deprotected 15 in a 55% overall yield. Subsequent reaction of this ligand with [Ru(tpy)(bpy)Cl]Cl then gave the orange complex [2](PF6)2.

A different approach was employed for the installment of the ethylene glycol-based linkers (n = 1−3) for complexes [3](PF6)2−[5](PF6)2 and [11]Cl2 (Figure 1). The disarmed Schmidt donor 20 (Scheme 3) was chosen due to its straightforward synthesis and robustness. The benzoyl protecting group in this building block was favored over the more common acetyl group, due to its lower reactivity. Furthermore, this donor was chosen to reduce the possible formation of orthoesters, a common side reaction when using acetyl-bearing donors. Commercially available 2-(methylthio)ethanol was used as an acceptor and condensed with donor 20, affording 21, which after de-O-benzoylation acquired deprotected 24. Compounds 25, 26, and 28 were acquired in a similar fashion using acceptors 18, 19, and 1,3-bis(methylthio)propan-2-ol, respectively. The synthesis of the corresponding ruthenium complexes was found to be straightforward, by reacting excess ligand with the ruthenium species [Ru(tpy)(bpy)Cl]Cl or [Ru(bpy)2Cl2]. Their purification, however, was found arduous due to the increased water solubility of these compounds.
Moderate to good yields (28% over neutral and negatively charged probes). To allow future bioprobes with a formal charge of +1 are taken up preferentially by Park and co-workers have demonstrated that glucose bioprobes with a formal charge of +1 are taken up preferentially over neutral and negatively charged probes. To allow future study of the effect on the overall charge for ruthenium(II) polyphenyl derivatives, a negative charge on the spectator terpyridine ligand was also synthesized. Compound 31 (Scheme 4) was prepared starting from thione, which was oxidized using in situ generated peracetic acid followed by hydrogenation using 10% palladium on carbon to reverse partial overoxidation to its N-oxide, affording ligand 30. A one-pot synthesis using (p-cymene)ruthenium(II) chloride dimethylformamide provided complex 31. Reaction of ligand 26 (Scheme 3) with this complex then gave the ruthenium complex 10 in moderate to good yields (28%–66%).

Demonstrations of the covalent modification of the 2-O position of D-glucose with an alkyl-based linker have been given by Dumas et al. and Patray and co-workers. Both groups chose a similar approach starting from methyl 3,5,6-tri-O-benzyl-α-D-glucal was protected using the β-methoxy benzyl (PMB) group, which was then condensed with dimethyldioxirane (DMDO) aminonidene method developed by the group of Danishefsky and attempted by Dumas et al. (Scheme 5). Using this method, D-glucal was protected using the β-methoxy benzyl (PMB) group, which was then condensed with dimethyldioxirane (DMDO) aminonidene method developed by the group of Danishefsky and attempted by Dumas et al. (Scheme 5). Using this method, D-
with tosylate 32 (Scheme 5) for the installment of the thioether moiety. This conversion proceeded smoothly, which is in contrast to the observation of Schubiger et al., who had to divert to the furanoside approach due to difficulties encountered during the installment of their iminodiacetic acid-based spacer.31 With compound 36 in hand, a recently described method37 using 37% hydrochloric acid in hexafluoroisopropanol (HFIP) was used to remove all four PMB groups simultaneously. After the reaction was quenched using Et3N, an intermediate species was observed (m/z = 463.4 found, 463.2 calcd) corresponding to the desired product H37 and a PMB group. This same intermediate was also observed in the presence of a mild reducing agent such as Et3SiH. However, when this intermediate was treated with MeNH2 in MeOH,38 the methyl thioether could be liberated, acquiring hemiacetal H37 in five steps (18% overall yield). After reaction of this compound with [Ru(tpy)(bpy)(H2O)](PF6)2 a glycoconjugate [Ru(tpy)(bpy)-H46]PF6 ([6]PF6) was acquired instead of [Ru(tpy)(bpy)-(H37)](PF6)2. This is most likely due to the relatively protic nature of the anomeric proton, resulting in deprotonation during purification on Sephadex and replacement of one of the PF6 counterions by the “charged” deprotonated glucose species as interpreted by elemental analysis. On mass, however, only the 2+ species is observed, indicating that reprotonation occurs in solution. This behavior was observed for all hemiacetal glucose derivatives.

The most straightforward thioether functionalization in these series of ligands was the modification of the 3-O position of d-glucose. Starting from diacetone glucose 38 (Scheme 6),39-41

**Scheme 6**

![Scheme 6](image)

**Reaction conditions:** (a) 32, NaH in DMF, 0 °C to rt, 16 h, 91%; (b) Amberlite IR-120 H+ in H2O, 60 °C, 24 h, 46%; (c) [Ru(tpy)(bpy)Cl]Cl in H2O, 80 °C, 16 h, 37%.

The thioether moiety was installed using 32 (Scheme 5), affording compound 39, which was subsequently hydrolyzed using Amberlite IR-120 H+, affording H40 in 42% overall yield. Glycoconjugation of H40 with [Ru(tpy)(bpy)Cl]Cl gave the orange (λmax = 450 nm) complex [Ru(tpy)(bpy)(40)]PF6 ([7]PF6).

The 4-O position of d-glucose was modified starting from acetobromo-α-d-glucose 40 (Scheme 7). Using a procedure first described by Kaji et al., this building block was converted in situ to its anomeric iodide, followed by a Koenigs–Knorr-type glycosylation with p-methoxy benzyl alcohol as an acceptor and Ag2CO3 as a base.42 De-O-acetylation furnished intermediate 41, followed by 4,6-O-benzylideneation and installment of PMB groups, affording fully protected 43 with this building block in hand, a reductive opening using NaCNBH3 and TFA liberated the 4-O position, which could then be alkylated via a Williamson etherification using 32 described in the previous sections, affording 45. Global deprotection was achieved by treatment with HFIP/HCl, which gave thiocarid ligand H46 in an 11% overall yield. The subsequent reaction of H46 with [Ru(tpy)-(bpy)(H2O)](PF6)2 afforded glycoconjugate [Ru(tpy)(bpy)(46)]PF6 ([8]PF6). The synthesis of H46 was also attempted via an alternative approach using α-methyl glucose following a similar protecting group strategy. However, this proved to be unsuccessful due to the inertness of the anomeric methyl acetel toward acid.

Finally, the 6-O position of d-glucose was easily modified starting from dimethyl glucose 48 (Scheme 8),43 which could be converted to 49 using a Williamson etherification with tosylate 32, followed by acid hydrolysis using dilute hydrochloric acid, affording methyl thioether H50 in 55% over two steps. Glycoconjugation with [Ru(tpy)(bpy)Cl]Cl afforded [Ru(tpy)-(bpy)(50)]PF6 ([9]PF6).

**Scheme 7**

![Scheme 7](image)

**Reaction conditions:** (a) (i) PMB–OH, I2, Ag2CO3 in Et2O, rt, 24 h, (ii) NaOMe in MeOH, rt, 4 h, 72% over two steps; (b) α,α,α-trimethoxytoluene, cat. p-TsOH–H2O in DMF, 60 °C, 16 h, 89%; (c) PMB–Cl, NaH in DMF, 0 °C to rt, 78%; (d) NaCNBH3, TFA in DMF, 0 °C to rt, 48 h, 95%; (e) 32, NaH in DMF, 0 °C to rt, 6 h, 78%; (f) cat. HCl in HFIP/DCM, 30 min, 29%; (g) [Ru(tpy)(bpy)-Cl]Cl in H2O, 80 °C, 64%.

**Scheme 8**

![Scheme 8](image)

**Reaction conditions:** (a) 32, NaH in DMF, 0 °C to rt, 3 h, 78%; (b) 2 M HCl in H2O, 60 °C, 1 h, 70%; (c) [Ru(tpy)(bpy)Cl]Cl in H2O, 80 °C, 16 h, 17%.

**CONCLUSION**

In this work, we have presented efficient and robust routes to all positional isomers of d-glucose bearing a thioether ligand bound to a light-cleavable ruthenium(II) polypyridyl complex. The
general protecting–deprotecting group strategy presented in this work is compatible with compounds bearing donor atoms such as sulfur, without the need of palladium catalysts until final coordination to the functional ruthenium compound. These routes might possibly be extended to application with other functionalized ligands, such as carboxylates, amines, or pyridines. The study of this library of ruthenium(II) glycoconjugates might shed light on the influence of the stereochemistry of glucose functionalization on GLUT-mediated uptake and the metabolism of the ruthenium–glucose conjugates by enzymes such as hexokinase II.

## EXPERIMENTAL SECTION

### General

Reagents were purchased from Sigma-Aldrich and used without further purification. 2,2′,6′-2″-Terpyridine (tpy) was ordered from ABCR GmbH & Co. Dry solvents were collected from a Pure SVE DMS solvent dispenser from Demaco. For all inorganic reactions, solvents were deoxygenated by bubbling dinitrogen through the solution for 30 min. All organic reactions were carried out under a dinitrogen atmosphere at rt. Flash chromatography was performed on silica gel (Screening devices B.V.) with a particle size of 40 μm. 

### Solvents and Reagents

Solve MD5 solvent dispenser from Demaco. For all inorganic reactions, Na2S2O3 (1 mol/L), NaHCO3 (2 mol/L), and charring at 10 min, the mixture was concentrated in vacuo, followed by purification of the residue over silica (10 to 50% Et2O in PE), yielding methyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside as a yellow foam (2.71 g, 7.24 mmol). This compound was then dissolved in dry MeOH (70 mL) followed by the addition of a catalytic amount of NaOMe, which after stirring overnight was quenched upon the addition of Amberlite IR-120 H+. Filtration was followed by concentration in vacuo, yielding the title compound as a colorless oil (1.48 g, 7.04 mmol, 57% over four steps): Rf = 0.63 (20% MeOH in DCM); IR (neat) 3336, 2923, 2881, 1415, 1017; 1H NMR (400 MHz, CD3OD) δ 4.35 (d, J = 9.6 Hz, 1H, H-1), 3.93 (d, J = 11.8 Hz, 1H, CHH H-6), 3.77–3.68 (m, 1H, CHH H-6), 3.48–3.35 (m, 3H, H-3, H-4, H-5), 3.31 (t, J = 9.1 Hz, 1H, H-2), 2.26 (s, 3H, SMe); 13C NMR (100 MHz, CD3OD) δ 87.1 (C-1, 81.8) (C-3, 79.3) (C-4), 73.5 (C-2), 71.3 (C-5), 62.7 (C-6), 12.0 (SMe); HRMS (ESI) m/z [M + Na]+ calc for C18H20O9SNa 323.0454, found 323.0444.

2-(Methylthio)ethoxyethanol (18). To a flame-dried round-bottom flask was added freshly prepared NaSMe (12.1 g, 15.5 mmol) under argon. Deoxygenated THF (50 mL) was added, followed by the addition of 2-((chloretioethoxy)ethanol (11.4 g, 14.3 mmol). This solution was heated at 60 °C for 6 h, after which it was allowed to cool to room temperature. The mixture was diluted with EtOAc (100 mL) and washed with aqueous NaHCO3 (2×) and water (1×). The layers were separated, and the organic layer was dried (Na2SO4) and concentrated in vacuo, affording a slightly yellowish oil (1.89 g, 13.9 mmol, 89%): IR (neat) 3427, 2907, 2866, 1611, 1512; 1H NMR (400 MHz, CDCl3) δ 3.68 (m, 2H, CH2), 3.62 (t, J = 6.7 Hz, 2H, CH2), 3.54 (d, J = 5.1 Hz, 2H, CH2), 2.94–2.81 (s, 1H, OH), 2.66 (t, J = 6.6 Hz, 2H, CH2), 2.10 (s, 3H, CH3); 13C NMR (100 MHz, CDCl3) δ 72.1 (CH2), 69.9 (CH2), 61.5 (CH3), 33.6 (SCH2), 15.8 (SCH3); HRMS (ESI) m/z [M + Na]+ calc for C11H20O2SNa 195.0454, found 195.0475.

2-(2-(Methylthio)ethoxy)ethoxyethanol (19). The procedure was followed as described for 18 using NaSMe (4.42 g, 60.4 mmol) and 2-(2-chloroethoxy)ethanol (10.0 g, 59.3 mmol). 19 was afforded as a colorless oil (9.25 g, 51.0 mmol, 85%): IR (neat) 3427, 2915, 2869, 1105, 1063; 1H NMR (400 MHz, CDCl3) δ 3.61–3.42 (m, 10H, 5 × CH2), 3.09 (s, 1H, OH), 2.60–2.50 (m, 2H, 1 × CH2), 2.03–1.94 (s, 3H, CH3); 13C NMR (100 MHz, CDCl3) δ 72.4 (CH2), 70.2 (CH2), 70.1 (CH2), 61.3 (CH3) 33.13 (SCH2), 15.7 (SCH3); HRMS (ESI) m/z [M + Na]+ calc for C13H24O3SNa 207.0312, found 207.0313.

2-(Methylthio)ethyl 2,3,4,6-tetra-O-benzoyl-β-D-glucopyranoside (21). 2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl trichloroacetimide (370 mg, 0.364 mmol) and 2-(methylthio)ethanol (100 μL, 1.15 mmol) were coevaporated three times with anhydrous toluene, after which they were dissolved in anhydrous DCM (36 mL). Freshly activated 4 Å molecular sieves were added, and the mixture was allowed to stir for 15 min, after which a catalytic amount of TMSOTf (0.20 μL, 111 mmol) was added. After stirring for 4 h at room temperature, the reaction was quenched upon the addition of Et3N (100 μL, 0.714 mmol) and concentrated in vacuo followed by purification of the residue over silica (10% to 50% EtOAc in PE), affording the title compound as a clear oil (270 mg, 0.410 mmol, 81%): Rf = 0.74 (30% EtOAc in DCM); IR (neat) 3064, 2922, 2853, 1720, 1258; 1H NMR (400 MHz, CDCl3) δ 8.80–8.02 (m, 2H, H arom), 8.00–7.96 (m, 2H, H arom), 7.94–7.90 (m, 2H, H arom), 7.80–7.78 (m, 2H, H arom), 7.60–7.57 (m, 2H, H arom), 5.93 (t, J = 9.7 Hz, 1H, H-3), 5.70 (s, J = 9.7 Hz, 1H, H-4), 5.56 (dd, J = 9.8, 7.8 Hz, 1H, H-2); 4.93 (dd, J = 7.8 Hz, 1H, H-1), 4.67 (dd, J = 12.2, 3.2 Hz, 1H, CHH H-6), 4.52 (dd, J = 12.1, 5.4 Hz, 1H, CHH H-6), 4.19 (dd, J = 8.6, 5.4, 3.2 Hz, 1H, H), 4.09 (dt, J = 10.2, 6.7 Hz, 1H, CHH OCH3), 3.78 (dt, J = 10.3, 7.3 Hz, 1H, CHH OCH3), 2.67 (t, J = 6.9 Hz, 2H, CH2SMe), 2.01 (s, 3H, CH3SMe); 13C NMR (100 MHz, CDCl3) δ 166.2 (C=O Bz), 165.9 (C=O Bz), 165.3 (C=O Bz), 136.2 (C=O Bz), 133.6 (C=O Bz), 133.4 (C=O Bz), 133.3 (C=O Bz).
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2-(2-(Methylthio)ethoxy)ethyl 2,3,4,6-tetra-O-benzoyl-β-D-glucopyranoside (25). The procedure described for 24 was followed, using protected glycoside 22 (560 mg, 0.780 mmol) and TFA/MeOH (10 mL, 1:1). Purification of the crude product silica (0 to 20% acetone in DCM) afforded the title compound as a colorless oil (294 mg, 0.474 mmol, 67%); mp 89.9° C; HRMS (ESI) m/z [M + Na]^+ calcd for C_{18}H_{26}O_{3}N _{5}SNa 391.1744, found 391.1735.

2-(2-(Methylthio)ethoxy)ethyl β-D-glucopyranoside (26). The protected glucoside 23 (973 mg, 1.28 mmol) was dissolved in MeOH (10 mL), after which a catalytic amount of NaOMe was added. The solution was allowed to stir for 16 h, after which Amberlite IR-120 H^+ was added, until reaching a neutral pH. The resin was filtered off, and the mixture was concentrated in vacuo. Purification of the residue over silica (0 to 10% MeOH in DCM) afforded the title compound as a colorless oil (400 mg, 1.17 mmol, 91%); R_f = 0.29 (10% MeOH in DCM); [α]_D^20 = 10.0° (MeOH); IR (neat) 3371, 2915, 2874, 1710, 1501; ^1H NMR (400 MHz, CDCl_3) δ 7.34 (t, J = 7.8 Hz, H-1), 7.09 (dd, J = 8.3, 1.4 Hz, H-2), 6.89 (m, H-3, H-4, H-5, H-6), 4.78 (dd, J = 9.6, 4.5 Hz, H-5), 4.66 (dd, J = 12.1, 3.1 Hz, HCH, H-6), 4.52 (dd, J = 9.9, 5.1 Hz, H-5, H-6), 4.03–3.95 (m, 1H, CHH—OHCH), 3.83 (m, 1H, CHH—CH), 3.69–3.56 (m, 2H, OCH_2), 3.55 (t, J = 6.9 Hz, 2H, OCH_2), 3.50–3.42 (m, 2H, OCH_2), 3.37 (t, J = 4.6 Hz, 2H, OCH_2), 2.64 (t, J = 6.9 Hz, 2H, CH_2SMe), 2.11 (s, 3H, SMe); ^13C NMR (101 MHz, CDCl_3) δ 161.1 (C=O Bz), 165.8 (C=O Bz), 165.2 (C=O Bz), 165.1 (C=O Bz), 133.3 (C=O Bz), 133.0 (C=O Bz), 132.8 (C=O Bz), 129.1 (CH_2SMe), 129.1 (CH_2SMe), 129.1 (CH_2SMe), 128.4 (CH_2SMe), 128.4 (CH_2SMe), 101.3 (C-1), 73.0 (C-3), 72.2 (C-2), 70.7 (OCH_3), 70.5 (OCH_3), 70.2 (OCH_3), 69.8 (C-4), 69.4 (OCH_3), 63.2 (OCH_2), 33.4 (CH_3SMe), 16.0 (CH_3SMe); HRMS (ESI) m/z [M + Na]^+ calcd for C_{18}H_{26}O_{3}NSNa 391.1744, found 391.1735.

2-(Methylthio)ethyl β-D-glucopyranoside (27). The protected glycoside 23 (240 mg, 0.410 mmol) was dissolved in MeOH (6 mL), after which a catalytic amount of NaOMe was added. The solution was allowed to stir for 16 h, after which Amberlite IR-120 H^+ was added, until neutral pH. The resin was filtered off, and the mixture was concentrated in vacuo. Purification of the residue over silica (0 to 10% MeOH in DCM) afforded the title compound as a colorless oil (80.0 mg, 0.315 mmol, 88%); R_f = 0.15 (5% MeOH in DCM); IR (neat) 3351, 2919, 2881, 1072, 1016; ^1H NMR (400 MHz, CDCl_3) δ 4.30 (t, J = 7.8 Hz, H-1), 4.03 (dt, J = 10.1, 7.1 Hz, HCH), 3.87 (dd, J = 11.9, 1.8 Hz, 1H, CHH H-1), 3.74 (dt, J = 10.1, 7.1 Hz, HCH, H-6), 3.69–3.64 (m, 1H, CHH H-6), 3.59–3.33 (m, 1H, H-4), 3.29–3.26 (m, 2H, H-3, H-5), 3.21–3.15 (m, 1H, H-2), 2.73 (t, J = 7.1 Hz, 2H, CH_2SMe), 2.13 (s, 3H, CH_3SMe); ^13C NMR (101 MHz, CDCl_3) δ 104.4 (C-1), 77.9 (C-3), 77.9 (C-4), 75.0 (C-2), 71.6 (C-5), 70.0 (OCH_3), 62.7 (C-6), 34.3 (CH_3SMe), 15.7 (CH_3SMe); HRMS (ESI) m/z [M + Na]^+ calcd for C_{14}H_{18}O_{4}NSNa 277.0714, found 277.0716.
redissolved in deoxygenated MeOH (5 mL) and heated to 60 °C. After the mixture was allowed to stir overnight at 40 °C under a nitrogen atmosphere, the reaction was filtered over Celite, concentrated, and purified via silica column chromatography (0 to 10% MeOH in DCM, affording the title compound as a brown material (193 mg, 0.306 mmol, 72%): 1H NMR (400 MHz, CDCl3) δ 7.92 (d, J = 7.7 Hz, 2H, T5, T5′), 7.49 (d, J = 7.7 Hz, 2H, T3, T3′), 7.40 (d, J = 8.8 Hz, 2H, CH2), 3.51 (m, 4H, 2 CH2 PMB), 4.76 (dd, J = 4.9, 1.9 Hz, 2H, CH2), 3.79 (s, 3H, CH3 PMB); HRMS (ESI) m/z [M + NH4]+ calcd for C15H17N3O5S, 314.0975, found 314.1022.

[Ru(S-tpyl)(bpy)(Cl)](31). Compound 30 (134 mg, 0.428 mmol) was dissolved in MeOH (10 mL), and to this solution was added 100 mg of freshly prepared NaH (0.405 mmol, 80%); the resulting purple mixture was heated at 70 °C for 12 h and concentrated in vacuo. The crude was then redissolved in H2O, followed by the addition of 10% Pd/C (32 mg) and purged with H2 (5 min). After stirring overnight at 40 °C under a nitrogen atmosphere, the reaction was filtered over Celite, concentrated, and purified via silica column chromatography (0 to 10% MeOH in DCM, affording the title compound as a brown solid (194 mg, 0.304 mmol, 75%): 1H NMR (400 MHz, CDCl3) δ 7.78 (d, J = 7.7 Hz, 2H, T5, T5′), 7.49 (d, J = 7.7 Hz, 2H, T3, T3′), 7.35 (d, J = 8.8 Hz, 2H, CH2), 3.50 (m, 4H, 2 CH2 PMB), 4.74 (dd, J = 4.9, 1.9 Hz, 2H, CH2), 3.79 (s, 3H, CH3 PMB); HRMS (ESI) m/z [M + NH4]+ calcd for C15H17N3O5S, 314.0975, found 314.1022.

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OCH₃), 3.85 (q, J = 5.2 Hz, 2H, CH₂OCH₂), 3.81 (s, 3H, CH₃PMB), 3.78 (s, 3H, CH₂PMB), 3.79 (s, 3H, CH₂PMB), 3.74—3.66 (m, 2H, H-6), 3.6—3.53 (m, 9H, H-3, 4 × OCH₃). 3.49 (t, J = 9.2 Hz, 1H, H-4), 3.40 (dd, J = 9.7, 5.1, 2.1 Hz, H-5), 3.29 (t, J = 8.3 Hz, 1H, H-2), 2.62 (t, J = 7.0 Hz, 2H, CHSmMe₂), 2.10 (s, 3H, CH₂SMe); 13C NMR (101 MHz, CDCl₃) δ 159.3 (C₆, arom), 159.3 (C₆, arom), 159.3 (C₄, arom), 131.1 (C₂, arom), 130.5 (C₂, arom), 130.4 (C₂, arom), 129.8 (C₈, arom), 129.7 (C₈, arom), 129.7 (C₆, arom), 113.8 (C₆, arom), 102.1 (C₁), 84.4 (C-4), 83.3 (C-2), 77.6 (C-5), 75.3 (CH₂, PMB), 74.9 (C₅, C-5), 74.7 (CH₂, PMB), 73.2 (CH₂, PMB), 72.1 (OCH₂), 70.9 (OCH₂), 70.9 (CH₂, PMB), 70.6 (OCH₂), 70.5 (OCH₂), 67.8 (OCH₂), 67.5 (C₆, C-6), 55.7 (CH₃ PMB); HRMS (ESI) m/z [M + Na]+ calcd for C₁₄H₂₀O₇Na 323.1107, found 323.1108.

(4-Methoxybenzyl)-β-D-glucopyranoside (H₄O). To a solution of 3 (309 mg, 1.03 mmol) in dry DMF (5 mL) were added 4-methoxybenzaldehyde dimethyl acetal (153 µL, 0.793 mmol) and t-PrOH·H₂O (10 mg, 0.05 mmol). The resulting mixture was heated at 60 °C for 16 h, after which it was concentrated in vacuo. Saturated aqueous NaHCO₃ (50 mL) was added and the mixture was further diluted with EtOAc (200 mL) and transferred to a separatory funnel. After the mixture was washed with aq NaHCO₃ (3x), water (3x) and brine (3x), the layers were separated, and the organic layer was dried (Na₂SO₄) and concentrated in vacuo. The resulting mixture was added until a neutral pH, filtered over Celite, diluted with EtOAc (200 mL), washed with brine, saturated aqueous NaHCO₃ (3x), dried (Na₂SO₄), and concentrated in vacuo.

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and brine (1x). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by silica column chromatography (0 to 20% EtOAc in PE) yielded the title compound 43 as a clear oil (447 mg, 0.680 mmol, 76%): $R_f$ = 0.74 (40% EtOAc in PE); IR (neat) 3480, 2986, 1612, 1516, 1244; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.43 (d, $J$ = 8.9 Hz, 2H, $H_{arom}$), 7.36–7.18 (m, 5H, $H_{arom}$), 7.00–6.78 (m, 6H, $H_{arom}$), 5.54 (s, 1H, CH benzylidine), 4.89 (d, $J$ = 11.4 Hz, 1H, CH$_2$ PMB), 4.82 (dd, $J$ = 10.8, 5.6 Hz, 2H, CH$_2$ PMB), 4.71 (dd, $J$ = 16.0, 10.7 Hz, 2H, CH$_2$ PMB), 4.65–4.57 (m, 2H, CH$_2$ PMB, H-1), 4.37 (dd, $J$ = 10.5, 5.0 Hz, 1H, CHH H-6), 3.82 (d, $J$ = 17.2 Hz, 2X CH$_2$ PMB), 3.82 (s, 2H, CH$_2$ PMB), 3.80 (s, 3H, CH$_2$ PMB), 3.69 (p, $J$ = 9.1 Hz, 2H, H-3, H-4), 3.49 (q, $J$ = 7.5 Hz, 1H, H-2), 3.40 (td, $J$ = 9.5, 5.0 Hz, 1H, H-5), 1.62 $^1$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.0 (C$_{arom}$), 159.5 (C$_{arom}$), 159.3 (C$_{arom}$), 153.8 (C$_{arom}$), 130.8 (C$_{arom}$), 130.6 (C$_{arom}$), 129.9 (C$_{arom}$), 129.8 (C$_{arom}$), 129.8 (C$_{arom}$), 129.3 (C$_{arom}$), 127.4 (C$_{arom}$), 113.9 (C$_{arom}$), 113.8 (C$_{arom}$), 113.7 (C$_{arom}$), 113.0 (C$_{arom}$), 103.0 (C-1), 101.2 (CH PMB, acetal), 81.9 (C-2), 81.5 (C-3), 80.7 (C-4), 75.1 (CH$_2$ PMB), 74.9 (CH$_2$ PMB), 71.4 (CH$_2$ PMB), 68.9 (C-6), 66.2 (C-5), 55.4 (3X CH$_2$ PMB), 55.3 (CH$_2$ PMB acetal); HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for C$_{38}$H$_{42}$O$_{10}$Na 681.2670, found 681.2671.

5-Methoxy-4-methyl-2,3,6-tri-O-(4-methoxybenzyl)-β-D-glucopyranoside (44). Fully protected glycosyl chloride 43 (400 mg, 0.610 mmol) was dissolved in DMF (12 mL), and to this solution was added freshly activated 4Å molecular sieves and fresh NaN$_3$BH$_3$ (385 mg, 6.13 mmol) and the organic layer was dried (Na$_2$SO$_4$) and concentrated in vacuo. The resulting residue was added dropwise to 20% EtOAc in PE which was added to the resulting residue over silica (0 to 15% MeOH in DCM) afforded the title compound 44 as a clear oil (13 mg, 0.038 mmol, 29%): $R_f$ = 0.57 (20% MeOH in DCM); IR (neat) 3370, 2918, 2873, 1104, 1077; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 5.09 (d, $J$ = 3.7 Hz, 1H, H-1r), 4.45 (d, $J$ = 7.7 Hz, 1H, H-1p), 4.02–3.58 (m, 28H), 3.47 (t, $J$ = 8.9 Hz, 1H, H-3p), 3.29–3.19 (m, 2H), 3.13 (dd, $J$ = 9.2, 7.9 Hz, 1H-2p), 2.68 (t, $J$ = 6.8 Hz, 4H, 2× CH$_2$OSME), 2.13 (s, 6H, 2× CH$_2$OSME); $^1$C NMR (100 MHz, CDCl$_3$) $\delta$ 98.2 (C-1p), 93.9 (C-5p), 80.5, 80.3, 78.3, 77.0, 76.3, 75.0, 73.9, 72.9, 72.0, 71.9, 71.5, 71.2, 62.5 (C-1p), 62.4 (C-1r), 34.3 (2× CH$_2$OSME), 15.9 (OCH$_3$OSM), and HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for C$_{34}$H$_{42}$NO$_{10}$SNa 834.3897, found 840.4028.

4-O-[(2-[(Methylthio)ethoxy]ethoxy]ethyl)-α-/β-D-glucopyranoside (46). Compound 44 (108 mg, 0.131 mmol) was dissolved in a mixture of DCM/HFIP (1:1, 2 mL), and to this solution were added 4 drops of 37% HCl. The mixture slowly turned red to deep purple in 30 min, after which it was quenched with Et$_3$N (0.5 mL) and concentrated in vacuo. The crude residue was redissolved in MeOH (5 mL); to this solution was added 40% HCl (120 H$_2$O was added), and the mixture was stirred for 5 min, filtered, and concentrated. Purification of the resulting residue over silica (0 to 15% MeOH in DCM) afforded the title compound 46 as a clear oil (13 mg, 0.038 mmol, 29%): $R_f$ = 0.57 (20% MeOH in DCM); IR (neat) 3370, 2918, 2873, 1104, 1077; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 5.09 (d, $J$ = 3.7 Hz, 1H, H-1r), 4.45 (d, $J$ = 7.7 Hz, 1H, H-1p), 4.02–3.58 (m, 28H), 3.47 (t, $J$ = 8.9 Hz, 1H, H-3p), 3.29–3.19 (m, 2H), 3.13 (dd, $J$ = 9.2, 7.9 Hz, 1H-2p), 2.68 (t, $J$ = 6.8 Hz, 4H, 2× CH$_2$OSME), 2.13 (s, 6H, 2× CH$_2$OSME); $^1$C NMR (100 MHz, CDCl$_3$) $\delta$ 98.2 (C-1p), 93.9 (C-5p), 80.5, 80.3, 78.3, 77.0, 76.3, 75.0, 73.9, 72.9, 72.0, 71.9, 71.5, 71.2, 62.5 (C-1p), 62.4 (C-1r), 34.3 (2× CH$_2$OSME), 15.9 (OCH$_3$OSM), and HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for C$_{34}$H$_{42}$NO$_{10}$SNa 834.3897, found 840.4028.
The title compound was synthesized analogous according to the procedure described for [1]PF6 using [Ru(ppy)(bpy)(H2O)]Cl (94.2 mg, 0.168 mmol) and 25 (71.0 mg, 0.238 mmol) in H2O (28 mL), allowing the title compound to be recrystallized from acetonitrile. The compound was characterized by 1H and 13C NMR spectroscopy and HRMS. The 1H NMR spectrum of the title compound in CD3OD showed the following signals: δ (ppm) 8.56 (s, 2H, T4, T4″), 8.26 (d, J = 8.1 Hz, 1H, H-7), 7.14 (d, J = 6.5 Hz, 2H, T5, T5″), 6.80 (dd, J = 7.9 Hz, 1H, H-8), 4.15 (s, 3H, OCH2SMe), 1.41 (s, 3H, OCH2SMe). The elemental analysis of the title compound was calculated for C36H41N5O7RuS4 and found for C36H41N5O7RuS4.

The title compound was synthesized analogous according to the procedure described for [1]PF6 using [Ru(ppy)(bpy)]Cl (102 mg, 0.182 mmol) and 26 (100 mg, 0.292 mmol) in H2O (30 mL), allowing the title compound to be isolated as a red solid (130 mg, 116.6 mmol, 65%). δ (ppm) 8.56 (s, 2H, T4, T4″), 8.26 (d, J = 8.1 Hz, 1H, H-7), 7.14 (d, J = 6.5 Hz, 2H, T5, T5″), 6.80 (dd, J = 7.9 Hz, 1H, H-8), 4.15 (s, 3H, OCH2SMe), 1.41 (s, 3H, OCH2SMe). The elemental analysis of the title compound was calculated for C36H41N5O7RuS4 and found for C36H41N5O7RuS4.
0.5H CHH OCH = C(α/β), 3.86 (ddd, J = 11.8, 2.3 Hz, 0.5H, CHH H-6α), 3.81–3.55 (m, 7.5H, CHH H-6α, CHH H-6β, H-3α, H-5α, H-5β, CHH OCH = C(α/β), 1.0 × 1 OCH = C(α/β) × 2 × OCH = C(α/β)), 3.51–3.47 (m, 2H, 2H), 3.45 (ddd, J = 6.4, 5.2, 1.6 Hz, 2H, OCH3), 3.30–3.20 (m, 1.5H, H-3β, H-4β, H-4α), 3.16 (ddd, J = 9.6, 3.5 Hz, 0.5H, H-2r), 2.91 (ddd, J = 8.9, 7.8 Hz, 0.5H, H-2β), 1.97–1.89 (m, 2H, CH2SMe), 1.43 (s, 1.5H, CH2SMe α), 1.42 (s, 1.5H, CH2SMe β); 13C NMR (126 MHz, CD3OD) δ 159.3 (Cq arom), 158.8 (Cq arom), 158.2 (Cq arom), 158.0 (Cq arom), 154.4 (Cq T-1 T′-1), 153.4 (Cq T-1), 150.8 (Cq T-1), 140.2 (Cq T-2 T′-2), 139.6 (Cq T-1 T′-1), 139.4 (Cq T-1 T′-1), 138.4 (Cq T-1), 129.9 (Cq T-1 T′-1), 129.3 (Cq T-2), 128.4 (Cq T-1), 126.3 (Cq T-2 T′-2), 126.0 (Cq T-2), 125.5 (Cq T-1 T′-1), 125.2 (Cq T-10), 98.2 (C-1β), 94.0 (C-1α), 87.6, 84.6, 74.7, 78.6, 71.3, 71.3, 71.2, 70.9, 68.4, 68.3, 62.8 (C-6α/β), 62.7 (C-6α/β), 35.7 (CH2SMe), 35.6 (CH2SMe), 15.4 (CH2SMe), 15.4 (CH2SMe); HRMS (ESI) m/z [M + H]+ calculated for C34H40N4O6S4 RuS6 416.6011, found 416.6028. Elemental analysis calcld (%) for [6]PF3H3O·C: 44.22; H: 4.89; N: 6.79. Found: 44.22; H: 4.78; N: 6.49.

[Ru(tpy)(bpy)(40)PF6(7)]PF6. The title compound was synthesized analogous to the procedure described for [1]PF6 using [Ru(tpy)(bpy)CI]Cl (59 mg, 0.105 mmol) and H40 (40 mg, 0.117 mmol) in H2O (18 mL), affecting the title compound as a red solid (42.4 mg, 39.3 mmol, 73%). 

[Ru(tpy)(bpy)(40)PF6(7)]PF6. The title compound was synthesized analogous to the procedure described for [1]PF6 using [Ru(tpy)(bpy)CI]Cl (59 mg, 0.105 mmol) and H40 (40 mg, 0.117 mmol) in H2O (18 mL), affecting the title compound as a red solid (42.4 mg, 39.3 mmol, 73%).
**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01342.

\(^1\)H and \(^{13}\)C spectra for 13, 15, 18, 19, 21–28, 30–32, 34–36, 38, H40, 41–45, H46, 49, H50, [\(\text{1} - (\text{PF}_6)_2\)−]−, [\(\text{5} - (\text{PF}_6)_2\)−], [\(\text{6} - \text{PF}_6\)−]and [\(\text{11} - \text{Cl}_3\).](PDF)

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**Notes**

The authors declare no competing financial interest.

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**NOTE ADDED AFTER ISSUE PUBLICATION**

Due to a production error, the corresponding author details for the first author were inadvertently omitted in the version that published on November 2, 2018. The authorship has been corrected and reposted on November 5, 2018.