Synthesis of Anomeric Sulfur Analogues of CMP-Neu5Ac Containing Tethered Alkane or Arene

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Dedicated to the memory of Professor Ray Lemieux.

Abstract: A new approach to the synthesis of anomeric sulfur analogues of CMP-Neu5Ac containing alkane or arene linkage **1a**–**d** is described. The procedure involves the high β-stereoselectivity in sialylation of the peracetylated sialic acid methyl ester **4** with mercaptoalkyl (aryl) trichloroacetate **5a**–**d**, followed by selective deprotection of the trichloroacetyl group to the corresponding hydroxyalkyl and hydroxyaryl thioglycosides **2a**–**d**. Subsequent O-phosphitylation of **2a**–**d** with respective **3a** or **3c**, followed by oxidation and deprotection led to the isolation of the target compounds **1a**–**d** in good yields.

Key words: sialylation, hydroxyalkyl (aryl) thioglycosides, selective deprotection, sialyltransferase

Hypersialylation due to enhanced sialyltransferase activity is of vital importance in various biological events such as cell-cell adhesion, tumor cell metastasis and inflammation.[1] Sialic acids containing glycoconjugates are involved in different disease states, particularly in the control of tumor cell growth.[2] Sialyltransferase mediates the biosynthesis of sialylated glycoconjugates and its activity has been demonstrated as a potential marker of tumorogenesis.[3] Therefore, the design of potent and specific inhibitors of sialyltransferase has become a promising strategy for cancer treatment. Despite lacking the structure of the target enzyme or the enzyme-inhibitor complex, recent studies of sialyltransferase inhibitors[4] primarily focus on the design of carbohydrate mimetics including structural analogues of the donor or acceptor and the transition-state mimetics of the sialyl donor. In order to understand the substructural requirements for the catalytic and/or binding site of the sialyltransferase, it is highly desirable to design a specific probe. Our interest is in development of inhibitors that could explore interactions between inhibition activity and flexibility in the active site using a tethered moiety. Here, we would like to report the synthesis of anomeric sulfur analogues of CMP-Neu5Ac containing tethered alkane or arene **1a**–**d** (Figure 1).

The retrosynthetic analysis is depicted in Scheme 1. The sialylation/deprotection process (**4** + **5** → **2**) is the keystone of our strategy since it secures the correct stereochemistry at the anomeric carbon and at the same time provides a way to generate a variety of alcohol linkers. Next, the phosphitylation reaction[5] between the linker hydroxyl group and cytidinyl phosphitamide **3** forms the P-O bond. Finally, oxidation of the phosphorous and deprotection of CMP-Neu5Ac completes the formation of **1a**–**d**.

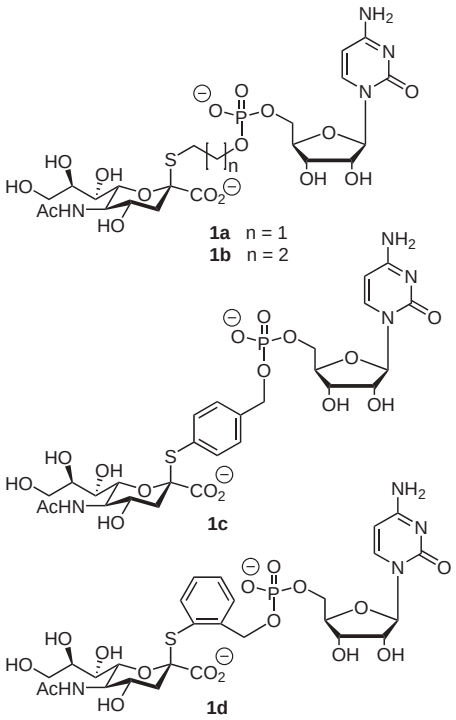

Figure 1 Structure of anomeric sulfur analogues of CMP-Neu5Ac containing tethered alkane or arene

Classically, synthesis of hydroxyalkyl and hydroxyaryl thioglycosides could utilize either thioglycosylation or anomeric S-alkylation strategies.[6] Although various protecting groups (acetyl, benzoyl, trimethylsilyl, *tert*-butyldiphenylsilyl) for the terminal hydroxyl of **5** were made, thioglycosylation reactions used to prepare **2a**–**d** either did not react, or formed disulfide, elimination products, or non-selective deprotection of the terminal alcohol.[7] In addition, S-alkylation pathway would necessitate multiple steps. Scheme 2 outlines an efficient approach for the synthesis of the requisite anomeric sulfur analogues of sialic acid **2a**–**d**. Treating the peracetylated sialic acid methyl ester **4**[8] with boron trifluoride in the presence of a corre-

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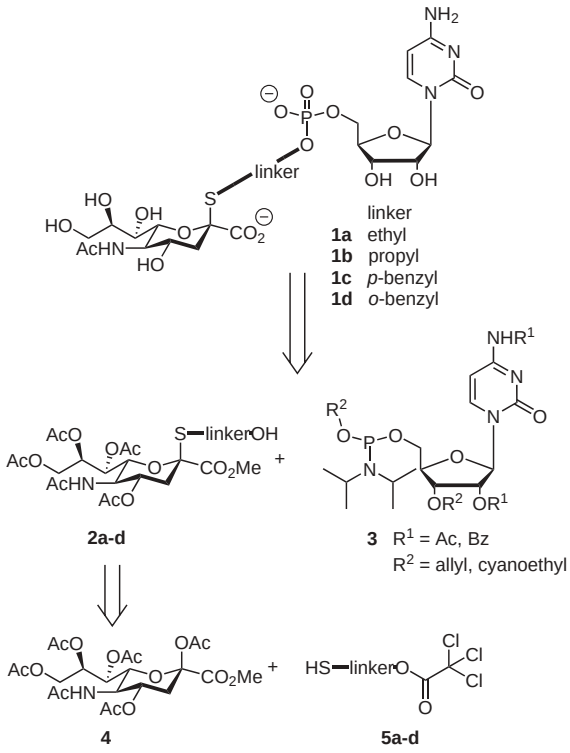
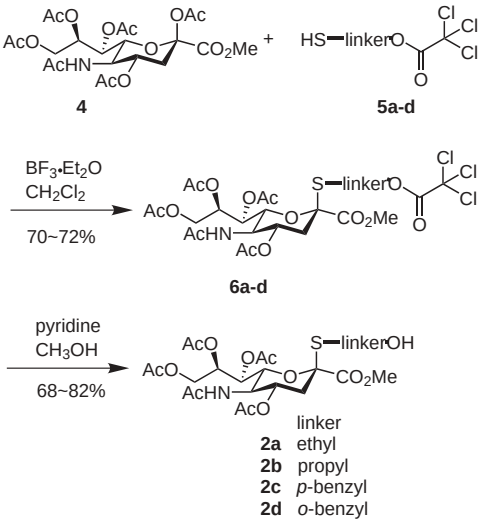


Scheme 1 Retrosynthetic analysis of target molecules **1a**–**d**



Scheme 2

sponding mercaptoalkyl (aryl) trichloroacetate **5a**–**d**[9] gave predominantly the β-anomers **6a**–**d** (β:α > 20:1)[10] in 70–72% yield without formation of alkyl or aryl disulfides and elimination products.

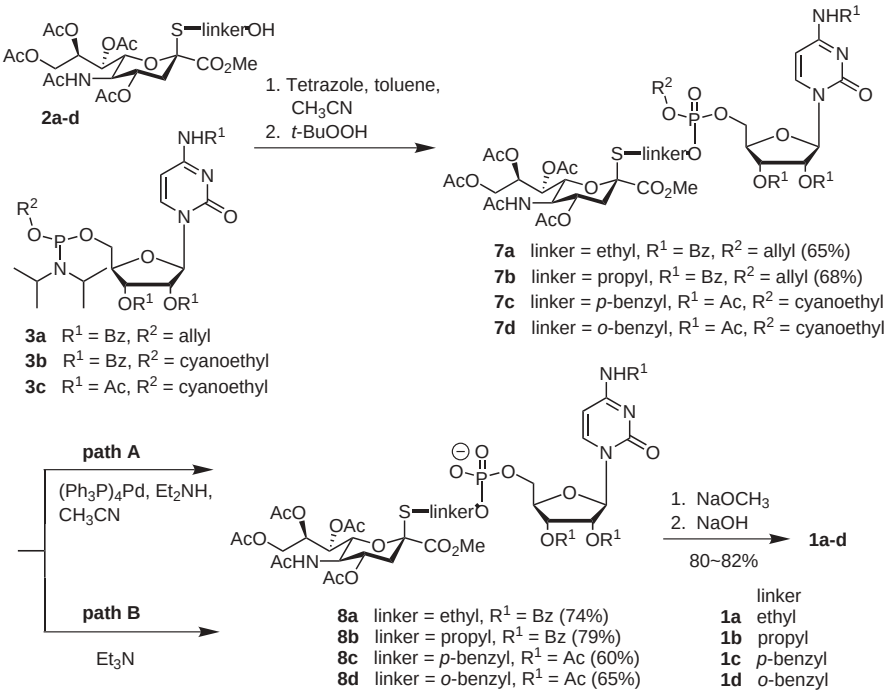
The trichloroacetyl group could be removed selectively by treatment with pyridine–methanol to afford the peracetylated hydroxyalkyl and hydroxyaryl thioglycosides **2a**–**d**. The NMR spectra of **2a**–**d**, displaying five sharp singlets at around δ = 2 ppm, confirm the formation of a single isomer without deacetylation.

O-Allylphosphate triesters **7a** and **7b** were generated from **2a**,**b** via a two-step procedure (Scheme 3). A benzoyl protected *O*-allyl tetraisopropylphosphordiamidite derivative, **3a**,[5a] was attached via phosphoramidite chemistry and subsequent oxidation with *tert*-butylhydroperoxide afforded the respective *O*-allylphosphate triesters **7a** and **7b** in 65–68% yield after purification. The allyl groups were removed under mild conditions by $Pd(PPh_3)_4$ with diethylamine as the nucleophile (Scheme 3, path A). Finally, deprotection of the acetyl, benzoyl and methylester groups by sequential treatment of compound **8a** and **8b** with sodium methoxide and sodium hydroxide afforded their corresponding target molecules **1a** and **1b**.

Mechanistically, the incorporation of CMP into the peracetylated hydroxyaryl thioglycosides **2c**,**d** with activated *O*-cyanoethyl tetraisopropylphosphordiamidite **3b** is also feasible. However, attempts to prepare the benzoyl protected *O*-cyanoethyl tetraisopropylphosphordiamidite **3b** gave low yields of desired product, possibly because the benzoyl protecting group afforded poor solubility of product and reactant in the reaction solvent (acetonitrile-*N*,*N*-dimethylformamide).

By changing the protecting group to the smaller acetyl group[5b,11] allowed reaction with **2c**,**d**[13] in the presence of tetrazole furnished the intermediate phosphite triesters in good yield. Subsequent oxidation under mild conditions (5.5 M *tert*-butylhydroperoxide in decane) gave the corresponding *O*-cyanoethylphosphate triesters **7c**,**d**, which were used in next step without further purification. Removal of the cyanoethyl group by treatment of **7c**,**d** with triethylamine afforded the acetyl protected phosphate diesters **8c** and **8d** as triethylammonium salt (Scheme 3, path B). Alkaline deprotection and subsequent saponification, as described for **1a**,**b**, produced the corresponding sodium salt **1c** and **1d** in 80–82% yield.

In conclusion, a new strategy for the β-stereoselective sialylation of the peracetylated sialic acid methyl ester **4** with mercaptoalkyl (aryl) trichloroacetate **5a**–**d** has been described. This one-step reaction avoids the problems of disulfide formation, elimination and additional steps. The hydroxyl moiety of the products **6a**–**d** can be selectively deprotected after sialylation providing the option for further regioselective modifications in the sialic acid group. On the basis of this approach, we have synthesized four sulfur analogues of CMP-Neu5Ac **1a**–**d** with various linkers between the sialic acid and CMP, shortening the number of synthetic steps to seven with overall yields of 17–25%. These new compounds can then be used to probe the structure of the active site of sialyltransferase. Application of this strategy to the synthesis of cyclic analogues[12] of CMP-Neu5Ac with linkers of variable length is currently underway.



Scheme 3

Acknowledgment

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(7) For example, treatment of **4** and 2-mercaptoethyl trimethylsilyl ether (or 2-mercaptoethyl *tert*-butyldiphenylsilyl ether) with boron trifluoride in dichloromethane gave the desired thioglycoside in low yield, along with the formation of large amounts of bis-(2-trimethylsilyloxyethyl) disulfide or bis-(2-*tert*-butyldiphenylsilyloxyethyl) disulfide. Condensation of the 2-chlorosialic acid with the 2-mercaptoethyl benzoate gave the thioglycoside in low yield. The products were contaminated with the sialic acid 2,3-elimination product, see: (a) Moreau, V.; Norrild, J. C.; Driguez, H. *Carbohydr. Res.* **1997**, *300*, 271. (b) Sabesan, S.; Neira, S.; Davidson, F.; Duus, J.; Bock, K. *J. Am. Chem. Soc.* **1994**, *116*, 1616.

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(9) The required compounds **5a**–**d** were prepared from corresponding mercaptoalkyl(aryl) alcohols, respectively, by treating them with trichloroacetyl chloride in dichloromethane at 0 °C for 4 h.
(10) The configuration of **6a**–**d** was determined by measuring the chemical shifts of H_{3eq} and H_4. The formation of β-anomer **6a** caused an upfield shift of H_{3eq} to δ = 2.52 ppm while the chemical shift of H_{3eq} of α-anomer **6a** remained δ = 2.72 ppm. In addition, H_4 is shifted in the other direction. Thus H_4 in the β-anomer **6a** occurs at δ = 5.41 ppm in contrast to the chemical shift of α-anomer at δ = 4.84 ppm. Several reports demonstrated that H_{3eq} of a β-linked alkyl thioglycoside of sialic acid diplayed a signal upfield relative to that of the corresponding α-anomer, see: (a) Ponpipom, M. M.; Bugianesi, R. L.; Shen, T. Y. *Can. J. Chem.* **1980**, *58*, 214. (b) Warner, T. G.; Lee, L. A. *Carbohydr. Res.* **1988**, *176*, 211.
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(12) CMP-Neu5Ac mimetics that contain a spiro-ring.
(13) Selected physical data. Compound **2a**: TLC (100% EtOAc): R_f = 0.40. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.89 (d, *J* = 9.3 Hz, 1 H), 5.44 (s, 1 H), 5.26 (td, *J* = 4.5, 11.0 Hz, 1 H), 5.21(m, 1 H), 4.96 (dd, *J* = 2.1, 12.2 Hz, 1 H), 4.42 (d, *J* = 10.4 Hz, 1 H), 4.05 (m, 2 H), 3.77 (s, 3 H), 3.75 (m, 1 H), 3.62 (m, 1 H), 2.84 (m, 1 H), 2.76 (m, 1 H), 2.58 (br s, 1 H), 2.50 (dd, *J* = 4.7, 13.8 Hz, 1 H), 2.12 (m, 1 H), 2.10 (s, 3 H), 2.05 (s, 3 H), 2.00 (s, 3 H), 1.98 (s, 3 H), 1.84 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.44, 170.89, 170.85, 170.36, 170.16, 168.47, 84.43, 72.73, 72.19, 69.33, 68.81, 62.52, 60.92, 52.90, 48.96, 36.97, 31.13, 22.99, 20.93, 20.85, 20.75, 20.65. HRMS-FAB: calcd for $C_{22}H_{34}NO_{13}S$ $(M + H)^+$: 552.1951. Found: 552.1961. Compound **2b**: TLC (100% EtOAc): R_f = 0.40. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 (d, *J* = 10.2 Hz, 1 H), 5.44 (t, *J* = 2.3 Hz, 1 H), 2.59 (m, 1 H), 5.23 (m, 1 H), 4.96 (dd, *J* = 2.5, 12.3 Hz, 1 H), 4.36 (dd, *J* = 2.3, 10.4 Hz, 1 H), 4.08 (m, 2 H), 3.80 (s, 3 H), 3.67 (m, 2 H), 2.72 (m,2 H), 2.51 (dd, *J* = 4.9, 13.8 Hz, 1 H), 2.46 (br s, 1 H), 2.17 (m, 1 H), 2.13 (s, 3 H), 2.06 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 1.86 (s, 3 H), 1.77 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.24, 170.98, 170.86, 170.36, 170.12, 168.35, 84.70, 72.67, 62.22, 69.31, 68.74, 62.52, 60.77, 52.84, 49.10, 37.04, 31.75, 24.83, 22.92, 20.91, 20.79, 20.72, 20.64. HRMS-FAB: calcd for $C_{23}H_{36}NO_{13}S$ $(M + H)^+$: 556.1907. Found: 556.1911. Anal. Calcd for $C_{23}H_{35}NO_{13}S$: C, 48.84; H, 6.24; N, 2.48; S, 5.67. Found: C, 48.59; H, 7.02; N, 2.37; S, 5.61. Compound **2c**: TLC (100% EtOAc): R_f = 0.40. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 5.79 (d, *J* = 10.2 Hz, 1 H), 5.42 (t, *J* = 2.5 Hz, 1 H), 5.39 (m, 1 H), 4.79 (td, *J* = 2.2, 8.5 Hz, 1 H), 4.66 (s, 2 H), 4.53 (dd, *J* = 2.5, 5.5 Hz, 1 H), 4.49 (dd, *J* = 2.4, 7.2 Hz, 1 H), 4.09 (m, 1 H), 4.01 (m, 1 H), 3.63 (s, 3 H), 2.63 (dd, *J* = 4.8, 13.9 Hz, 1 H), 2.52 (br s, 1 H), 2.10 (dd, *J* = 11.7, 13.9 Hz, 1 H), 2.08 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 1.98 (s, 3 H), 1.87 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.10, 170.92, 170.34, 170.10, 168.31, 143.06, 135.86, 127.60, 127.51, 88.28, 73.09, 72.80, 69.04, 68.81, 64.40, 62.56, 52.67, 49.27, 37.34, 23.05, 20.99, 20.82, 20.66. HRMS-FAB: calcd for $C_{27}H_{36}NO_{13}S$ $(M + H)^+$: 614.1907. Found: 614.1910. Compound **2d**: TLC (100% EtOAc): R_f = 0.50. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (m, 1 H), 7.36 (m, 2 H), 7.20 (m, 1 H), 5.93 (d, *J* = 10.2 Hz, 1 H), 5.41 (m, 2 H), 4.90 (d, *J* = 12.9 Hz, 1 H), 4.78 (d, *J* = 12.9 Hz, 1 H), 4.71 (td, *J* = 2.2, 8.3 Hz, 1 H), 4.67 (dd, *J* = 2.5, 10.5 Hz, 1 H), 4.58 (dd, *J* = 2.2, 12.3 Hz, 1 H), 4.09 (m, 2 H), 3.56 (s, 3 H), 2.73 (dd, *J* = 4.7, 13.8 Hz, 1 H), 2.63 (br s, 1 H), 2.15 (dd, *J* = 11.6, 13.8 Hz, 1 H), 2.11 (s, 3 H), 2.05 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.86 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.36, 171.00, 170.36, 170.25, 170.17, 168.49, 144.64, 136.84, 129.79, 129.25, 127.88, 89.29, 73.24, 73.13, 69.11, 68.76, 62.79, 62.54, 52.74, 48.92, 38.13, 22.93, 20.97, 20.80, 20.72, 20.62. HRMS-FAB: calcd for $C_{27}H_{36}NO_{13}S$ $(M + H)^+$: 614.1907. Found: 614.1913. Compound **1a**: ^{1}H NMR (400 MHz, D_2O): δ = 8.21 (d, *J* = 7.6 Hz, 1 H), 6.34 (d, *J* = 7.6 Hz, 1 H), 5.98 (d, *J* = 7.6 Hz, 1 H), 4.40–4.35 (m, 3 H), 4.28 (m, 1 H), 4.22 (d, *J* = 7.6 Hz, 1 H), 4.15 (m, 2 H), 4.04 (m, 2 H), 3.91–3.84 (m, 3 H), 3.70 (dd, *J* = 7.6 Hz, 1 H), 3.62 (d, *J* = 7.6 Hz, 1 H), 2.88 (m, 2 H), 2.54 (dd, *J* = 7.6 Hz, 1 H), 2.09 (s, 3 H), 2.06 (m, 1 H). ^{13}C NMR (100 MHz, D_2O): δ = 175.01, 173.43, 159.28, 148.55, 144.24, 95.34, 89.94, 85.17, 83.37 (d, *J* = 8.7 Hz), 74.40, 71.19, 69.99, 69.28, 68.12, 67.42, 64.87 (d, *J* = 4.0 Hz), 64.16 (d, *J* = 4.7 Hz), 63.50, 52.27, 39.59, 28.82 (d, *J* = 7.4 Hz), 22.25. ^{31}P NMR (D_2O, H_3PO_4 reference): δ = 0.12. HRMS-MALDI: calcd for $C_{22}H_{35}N_4O_{16}PSNa$ $(M + 2\ H + Na)^+$: 697.1403. Found: 697.1387. Compound **1b**: ^{1}H NMR (400 MHz, D_2O): δ = 8.00 (d, *J* = 7.6 Hz, 1 H), 6.17 (d, *J* = 7.6 Hz, 1 H), 6.03 (d, *J* = 4.0 Hz, 1 H), 4.37 (m, 2 H), 4.31 (m, 1 H), 4.22 (m, 1 H), 4.16 (d, *J* = 10.5 Hz, 1 H), 4.12 (m, 1 H), 4.03 (m, 1 H), 4.00–3.84 (m, 5 H), 3.70 (m, 1 H), 3.57 (d, *J* = 9.0 Hz, 1 H), 2.62 (m, 2 H), 2.50 (dd, *J* = 4.8, 13.6 Hz, 1 H), 2.10 (s, 3 H), 1.90 (m, 3 H). ^{13}C NMR (100 MHz, D_2O): δ = 176.46, 174.89, 165.72, 157.06, 141.69, 96.55, 89.49, 87.54, 82.86 (d, *J* = 8.7 Hz), 74.37, 71.08, 70.18, 69.42, 68.46, 67.96, 65.08 (d, *J* = 5.5 Hz), 64.25 (d, *J* = 4.8 Hz), 63.52, 52.45, 40.98, 29.47 (d, *J* = 7.2 Hz), 24.63, 22.26. ^{31}P NMR (D_2O, H_3PO_4 reference): δ = 0.36. HRMS-MALDI: calcd for $C_{23}H_{37}N_4O_{16}PSNa$ $(M + 2\ H + Na)^+$: 711.1559. Found: 711.1566. Compound **1c**: ^{1}H NMR (400 MHz, D_2O): δ = 8.02 (d, *J* = 7.9 Hz, 1 H), 7.56 (d, *J* = 8.1 Hz, 2 H), 7.43 (d, *J* = 8.1 Hz, 2 H), 6.10 (d, *J* = 7.9 Hz, 1 H), 5.88 (d, *J* = 3.7 Hz, 1 H), 4.96 (d, *J* = 8.1 Hz, 2 H), 4.50 (d, *J* = 10.4 Hz, 1 H), 4.30–4.17 (m, 5 H), 4.03 (m, 1 H), 3.95 (t, *J* = 10.2 Hz, 1 H), 3.84–3.77 (m, 2 H), 3.69–3.63 (m, 2 H), 2.72 (dd, *J* = 4.7, 13.7 Hz, 1 H), 2.12 (m, 1 H), 2.11 (s, 3 H). ^{13}C NMR (100 MHz, D_2O): δ = 174.97, 171.92, 158.97, 148.26, 144.00, 139.14 (d, *J* = 6.3 Hz), 135.39, 12911, 128.26, 95.04, 89.95, 89.91, 83.17 (d, *J* = 8.2 Hz), 74.24, 71.75, 70.20, 68.09, 68.53, 67.22 (d, *J* = 4.5 Hz), 66.95, 64.17 (d, *J* = 4.1 Hz), 63.18, 52.34, 39.95, 22.27. ^{31}P NMR (D_2O, H_3PO_4 reference): δ = 0.15. HRMS-MALDI: calcd for $C_{27}H_{37}N_4O_{16}PSNa$ $(M + 2\ H + Na)^+$: 759.1559. Found: 759.1567. Compound **1d**: ^{1}H NMR (400 MHz, D_2O): δ = 7.94 (d, *J* = 7.7 Hz, 1 H), 7.63 (m, 1 H), 7.50 (m, 1 H), 7.34 (m, 2 H), 6.00 (d, *J* = 7.7 Hz, 1 H), 5.92 (d, *J* = 3.7 Hz, 1 H), 5.19 (m, 1 H), 5.05 (m, 1 H), 4.28–4.19 (m, 6 H), 4.07 (m, 1 H), 3.94 (t, *J* = 10.2 Hz, 1 H), 3.77 (dd, *J* = 1.7, 11.4 Hz, 1 H), 3.66–3.60 (m, 2 H), 3.53 (d, *J* = 8.9 Hz, 1 H), 2.68 (dd, *J* = 4.6, 13.7 Hz, 1 H), 2.10 (s, 3 H), 1.97 (m, 1 H). ^{13}C NMR (100 MHz, D_2O): δ = 175.39, 174.91, 163.51, 154.25, 142.26, 138.00 (d, *J* = 6.9 Hz), 132.58, 132.06, 129.41, 128.89, 127.92, 95.98, 91.09, 89.80, 82.99 (d, *J* = 8.6 Hz), 74.47, 72.08, 70.31, 69.20, 68.64, 67.69, 66.50 (d, *J* = 4.7 Hz), 64.02 (d, *J* = 4.5 Hz), 63.27, 52.38, 41.67, 22.29. ^{31}P NMR (D_2O, H_3PO_4 reference): δ = 0.17. HRMS-MALDI: calcd for $C_{27}H_{37}N_4O_{16}PSNa$ $(M + 2\ H + Na)^+$: 759.1559. Found: 759.1545.