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Synthesis of sulfonic acid analogues of the non-reducing end trisaccharide of the antithrombin binding domain of heparin

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ABSTRACT

Three sulfonic acid trisaccharides related to the antithrombin-binding DEFGH domain of heparin were synthesised. Trisaccharides carrying the sulfonatomethyl moiety at position 2 or 6 were prepared in high yields by [DE+F] couplings using the same disaccharide uronate donor and the appropriate sulfonic acid acceptor, respectively. The trisaccharide with a 3-deoxy-3-sulfonatomethyl function could be obtained with high efficacy by a [D+EF] coupling where the carboxylic function of the EF uronate acceptor was created at a disaccharide level.

Heparin is a well-known member of the glycosaminoglycans and plays a crucial role in maintaining the haemostatic state of blood through interaction with antithrombin III (AT-III), a serine protease inhibitor that blocks thrombin and factor Xa in the coagulation cascade.[1] Heparin has been used clinically as an anticoagulant for more than seven decades.[2] Despite its usefulness, heparin-based therapy also leads to adverse effects including bleeding complications and heparin-induced thrombocytopenia (HIT).[3]

The isolation and structural elucidation of the antithrombin-binding pentasaccharide domain of heparin[2,4] led to the development of fondaparinux (**1**), the first synthetic antithrombotic drug, marketed in 2001 in Europe and in the USA under the name Arixtra.[5] Fondaparinux selectively inhibits factor Xa, minimises the risk factors in anticoagulant therapy and, compared to heparin and low molecular-weight heparin, it has a longer duration of action (Fig. 1).

Structure–activity relationship studies on a series of synthetic analogues of heparin pentasaccharide revealed that the type of negatively charged groups is crucial, the carboxylate groups may not be exchanged for sulfate esters, and an essential sulfate moiety cannot be exchanged for a phosphate without affecting the activity.[6] However, replacement of the sulfate group with an isosteric sulfonatomethyl moiety has not been investigated until now. We envisaged that isosteric sulfonate analogues of the AT-III binding pentasaccharide of heparin might provide further information on structure–activity relationships and might afford bioactive derivatives. It is interesting to note that the isosteric sulfonate and phosphonate analogues of mannose-6-phosphate proved to be highly active towards mannose-6-phosphate receptors.[7–9]

Therefore, we decided to prepare sulfonatomethyl-containing analogues of the heparin pentasaccharide by systematic replacement of the sulfate esters with a sodium sulfonatomethyl moiety. Idraparinux (**2**) was chosen as a reference compound, since it has increased anticoagulant activity and, having a non-glycosaminoglycan-type structure, it is much easier to synthesize compared to fondaparinux.[10,11] We have previously reported the synthesis of sulfonatomethyl analogues of the EF and GH fragments of compound **2**.[12]

Here, we present the synthesis of the trisaccharide sulfonic acid analogues of the DEF fragment of idraparinux (**2**).

By retrosynthetic analysis, application of the common DE disaccharide as donor (**6**) and the three sulfonic acid containing

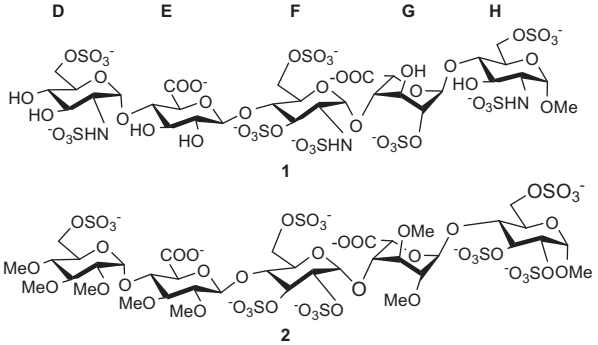

Figure 1. Structures of the synthetic antithrombotic drug fondaparinux (**1**) and the non-glycosaminoglycan anticoagulant idraparinux (**2**).

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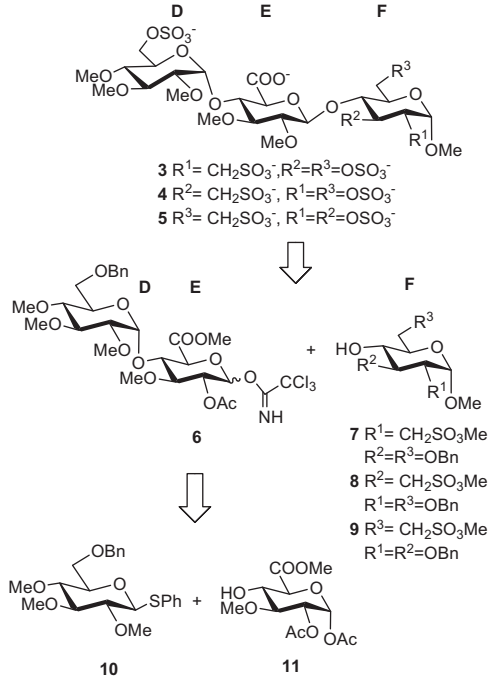
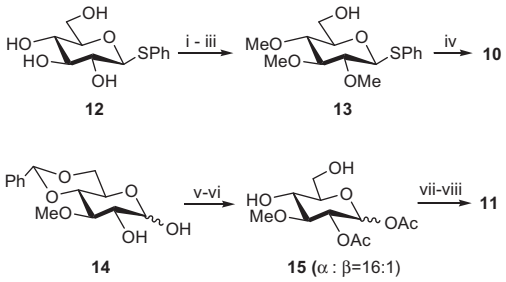
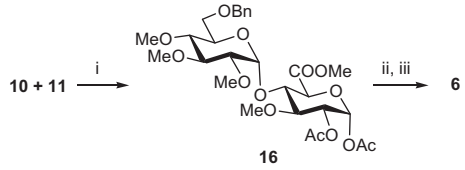


Figure 2. Retrosynthetic analysis of compounds **3**–**5**.



Scheme 1. Synthesis of the monosaccharide building blocks. Reagents and conditions: (i) TrCl, pyridine; (ii) MeI, NaH, DMF; (iii) 80% AcOH, 70 °C (80% over three steps); (iv) BnBr, NaH in DMF (96%); (v) Ac_2O, pyridine (93%); (vi) AcOH 80%, 70 °C (88%); (vii) TEMPO, $Ca(ClO)_2$, CH_2Cl_2, $NaHCO_3$, KBr, Bu_4NBr; (viii) CH_2N_2 (Et_2O), THF (59%).

monosaccharides as the acceptors **7**–**9** seemed to be the most efficient procedure for the preparation of the planned trisaccharides **3**–**5** (Fig. 2). The carboxylic acid function of unit E could be elaborated either at the disaccharide or the monosaccharide level.[13] The latter route was chosen since we assumed that the relatively inactive uronate acceptor **11** may increase the α-selectivity during formation of the interglycosidic bond of **6**.



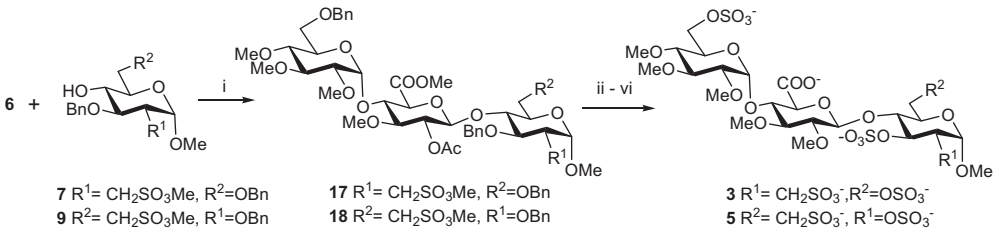
Scheme 2. Formation of the disaccharide uronate donor **6**. Reagents and conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, −45 °C, 1 h (72%, + 4% β-coupled disaccharide); (ii) THF, $BnNH_2$, rt, 5 h (92%); (iii) CH_2Cl_2, CCl_3CN, DBU, 0 °C, 30 min (85%).

The synthesis of the methylsulfonatomethyl-containing acceptors **7**–**9** was described recently,[12] the key step in their preparation being the stereoselective addition of a hydrogensulfite radical anion onto the exomethylene moiety of the appropriate glycoside derivatives.[14]

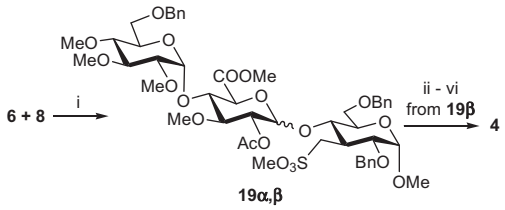
The non-reducing end building block **10** was prepared from phenyl 1-thio-β-D-glucopyranoside (**12**) via a series of routine transformations (Scheme 1). Tritylation and methylation followed by detritylation of the starting compound resulted in **13**,[15] benzylation of which gave the donor **10**. Synthesis of the uronate acceptor **11** started from the known 4,6-*O*-benzylidene-3-*O*-methyl-D-glucopyranose (**14**).[16] Acetylation and subsequent deacetalation of compound **14** afforded the 4,6-diol derivative **15**. In order to avoid protecting group manipulations to discriminate the primary and secondary hydroxy groups of **15**, TEMPO-based selective oxidation[17] was applied using calcium hypochlorite as co-oxidant.[18] Oxidation afforded the intermediate glucuronate, which after acidic work-up, was transformed into the methyl ester **11** by treatment with ethereal diazomethane. The product could be isolated in pure α-anomeric form by chromatographic purification.

Glycosylation of uronate acceptor **11** with phenylthioglucoside **10** in the presence of NIS and AgOTf at −45 °C gave the desired α-coupled disaccharide **16** in 72% yield, and the stereoisomeric disaccharide with a β-interglycosidic linkage was formed in a yield of only 4%. Selective deacetylation of the anomeric position with benzylamine and preparation of the corresponding imidate with trichloroacetonitrile and DBU afforded disaccharide donor **6** in 85% yield (Scheme 2).[19]

Glycosylation of the 2-deoxy-2-methylsulfonatomethyl acceptor **7** with disaccharide imidate **6** upon trimethylsilyl triflate activation afforded trisaccharide **17**, isolated exclusively in the β-coupled form due to the presence of the 2-*O*-acetyl participating group of the donor. The fully protected trisaccharide was deacetylated under Zemplén conditions to liberate the 2′-OH group. Treatment of the 2′-hydroxy derivative with methyl iodide and sodium hydride afforded the 2′-*O*-methyl ether in high yield. In addition, transformation of the sulfonic acid methyl ester into a sodium sulfonate moiety also occurred as a result of nucleophilic attack of the in situ formed sodium iodide. Next, the uronic ester was hydrolysed with sodium hydroxide to give the sodium uronate. Subsequent catalytic hydrogenation followed by *O*-sulfation afforded trisaccharide **3**, as the first isosteric sulfonatomethyl analogue of



Scheme 3. Construction of trisaccharide sulfonic acids **3** and **5**. Reagents and conditions: (i) TMSOTf, CH_2Cl_2, 4 Å MS, −30 °C to rt, 12 h (67% for **17**, 54% for **18**); (ii) MeOH, MeONa (80% from **17**, 88% from **18**); (iii) NaH, MeI, DMF (90% for **17**, 89% for **18**); (iv) 0.1 M NaOH, MeOH (92% for **17**, 92% for **18**); (v) H_2, Pd/C (10%); (vi) SO_3·py, DMF (71% for **3** over two steps, 75% for **5** over two steps).



Scheme 4. Construction of trisaccharide **4** using uronate donor **6**. Reagents and conditions: (i) CH_2Cl_2, 4 Å MS, TMSOTf, −30 °C to rt, 12 h (80% for the 1:1 mixture of the α- and the β-coupled product, 30% for **19β**); from **19β**: (ii) MeOH, MeONa (71%); (iii) NaH, MeI, DMF (82%); (iv) 0.1 M NaOH, MeOH (97%); (v) H_2, Pd/C (10%); (vi) SO_3·py, DMF (81% over two steps).

the DEF fragment of idraparinux. Synthesis of trisaccharide **5** was accomplished analogously, starting from acceptor **9** and donor **6** (Scheme 3).

Preparation of the third trisaccharide **4** was attempted in an analogous fashion. However, glycosylation of acceptor **8** possessing the sulfonatomethyl moiety at position 3 afforded the corresponding trisaccharide as a 1:1 mixture of the α- and β-coupled products; the targeted β-coupled trisaccharide could only be isolated in a yield of 30%. The unexpected formation of the α-linkage can occur as a result of steric hindrance between the carboxylic moiety of the donor and the sulfonate group of the acceptor, both situated on the β-side. Although the subsequent transformations leading to trisaccharide **4** took place smoothly and with high yields, the overall yield of the synthesis outlined in Scheme 4 was only 14%.

In order to improve the yield of the desired trisaccharide **4** another synthetic route involving a reverse sequence of glycosylations and oxidation to a carboxylate at a disaccharide level was elaborated. Compound **20**, prepared from **12** in two steps, was used as a donor to glycosylate acceptor **8** in the presence of the NIS-AgOTf promoter system, with the β-coupled disaccharide **21** being isolated exclusively. This reaction demonstrated that it was not the 3-sulfonatomethyl moiety per se, but the interaction between the carboxylate and sulfonate moieties which influenced unfavourably the glycosylation of **6** and **8**. Deacetalation of the fully protected **21** followed by TEMPO-catalysed selective oxidation using [bis(acetoxy)iodo]benzene (BAIB) as co-oxidant[20] and subsequent methyl esterification afforded uronate acceptor **22** (Scheme 5).

Glycosylation of acceptor **22** with thioglycoside donor **10** gave rise to the exclusive formation of the desired trisaccharide **23** in high yield. Removal of the *O*-acetyl groups of **23** resulted in the diol **24**. Methylation of the two liberated hydroxy groups and conversion of the uronic ester into sodium uronate followed by catalytic hydrogenolysis and subsequent *O*-sulfation afforded the target trisaccharide **4** possessing the sulfonatomethyl moiety at position 3. Methylation of diol **24** proved to be the crucial step of this reaction path since β-elimination at the uronic acid residue also occurred. It is interesting to note, that the former reaction path required the introduction of only one methyl ether and did not give rise to elimination. Nevertheless, despite the moderate yield of the methylation step, this reaction route resulted in a significant improvement in the yield of compound **4**, due to the high yielding glycosylations as well as the avoidance of the laborious synthesis of the glucuronic acceptor **11**. The overall yield of **4** via this route from **10** and **22** was 29% (Scheme 6).

In summary, three methanesulfonic acid trisaccharides as bioisosteric analogues of the DEF trisaccharide fragment of the fully *O*-sulfated, *O*-methylated non-glycosaminoglycan anticoagulant, idraparinux were synthesised.[21] A synthetic strategy based upon a [DE+F] coupling utilising a common disaccharide uronate donor proved to be very efficient to obtain the 2-sulfonatomethyl and 6-sulfonatomethyl derivatives. However, this method proved inefficient in the case of the 3-sulfonatomethyl-containing analogue **4** due to steric hindrance between the carboxylate group of the donor and the sulfonate moiety of the acceptor next to the glycosylation position. An improved synthesis of this trisaccharide was carried out by construction of an EF disaccharide applying a glucose donor and post-glycosidation oxidation. Biological investigation of the trisaccharides obtained as well as exploitation of the results for the synthesis of pentasaccharide sulfonic acid analogues are in progress.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.042.

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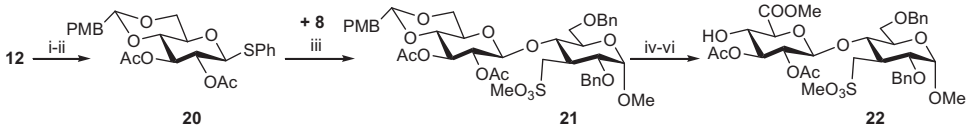
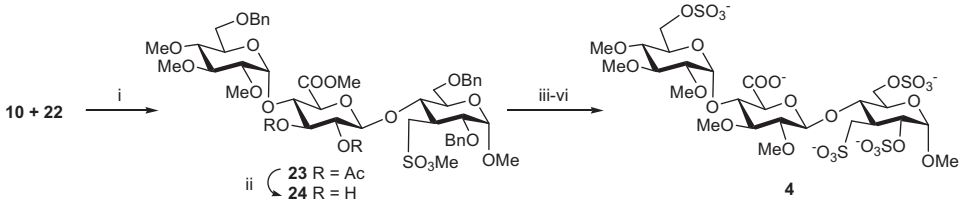


Scheme 5. Formation of the uronate donor **22** by post-glycosidation oxidation. Reagents and conditions: (i) 4-methoxybenzaldehyde dimethyl acetal, *p*-toluenesulfonic acid, CH_3CN, reflux (82%); (ii) Ac_2O, pyridine (94%); (iii) NIS, AgOTf, CH_2Cl_2, 4 Å MS, −20 °C to rt, 1 h (68%); (iv) 80% AcOH, rt, 1 h (81%); (v) BAIB, TEMPO, CH_2Cl_2, H_2O, 1 h; (vi) CH_2N_2·Et_2O, THF (79%).



Scheme 6. Improved synthesis of trisaccharide sulfonic acid **4**. Reagents and conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, −45 °C to −35 °C, 1 h (84%); (ii) MeOH, MeONa (87%); (iii) NaH, MeI, DMF (49%); (iv) 0.1 M NaOH, MeOH (97%); (v) H_2, Pd/C (10%); (vi) SO_3·py, DMF (81% over two steps).

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21. *Selected analytical data of key compounds*: Compound **3**: $[\alpha]_D$: +5.2 (*c* 0.17, H_2O); IR ν_{max} (KBr): 3455, 1635, 1219, 772, 673 cm^{-1}; ^1H NMR (D_2O, 500 MHz): δ 5.45 (d, 1H, $J_{1'',2''}$ = 3.6 Hz, H-1″), 5.17 (d, 1H, $J_{1,2}$ = 3.1 Hz, H-1), 4.65 (d, 1H, $J_{1',2'}$ = 7.7 Hz, H-1′), 4.41 (t, 1H, $J_{2,3}$ = 9.0 Hz, 1H, H-3), 4.38 (m, 2H, H-6a,b), 4.28 (d, 1H, $J_{6a'',6b''}$ = 10.8 Hz, H-6″a), 4.13 (d, 1H, H-6″b), 4.05 (m, 1H, H-5), 3.93 (t, 1H, *J* = 9.3 Hz, H-4), 3.90 (t, 1H, *J* = 9.6 Hz, H-4′), 3.87 (t, 1H, *J* = 9.3 Hz, H-5″), 3.72 (d, 1H, $J_{4',5'}$ = 9.8 Hz, H-5′), 3.63, 3.62, 3.60, 3.58, 3.56 (5 × s, 15H, 5 × OCH_3), 3.53 (m, 2H, H-3″, H-3′), 3.43 (m, 1H, $CH_2aSO_3^-$), 3.41 (s, 3H, OCH_3), 3.32 (m, 2H, H-4″, H-2″), 3.26 (t, 1H, *J* = 9.6 Hz, H-2′), 3.07, (dd, 1H, J_{gem} = 12.8 Hz, $J_{CH2b,2}$ = 3.2 Hz, $CH_2bSO_3^-$), 2.42 (m, 1H, H-2); ^{13}C NMR (D_2O, 125 MHz): δ 175.9 (CO), 102.1 (C-1′), 99.4 (C-1), 96.9 (C-1″), 86.6 (C-3″), 83.9 (C-2′), 82.8 (C-3′), 81.4 (C-2″), 79.0 (C-3), 78.0 (C-4″), 77.8 (C-5), 75.3 (C-4′), 74.8 (C-4), 70.5 (C-5′), 69.6 (C-5″), 67.2 (C-6), 66.9 (C-6″), 61.2, 60.8, 60.3, 59.9, 56.2, (6 × OCH_3), 48.8 ($CH_2SO_3^-$), 43.6 (C-2); Anal. Calcd for $C_{25}H_{39}Na_5O_{28}S_4$ (1030.77): C, 29.13; H, 3.81; S, 12.44. Found: C, 29.12; H, 3.82; S, 12.46.
Compound **4**: $[\alpha]_D$: +69.7 (*c* 0.07, H_2O); IR ν_{max} (KBr): 3448, 1632, 1219, 772, 670 cm^{-1}; ^1H NMR (D_2O, 360 MHz): δ 5.47 (d, 1H, $J_{1'',2''}$ = 3.6 Hz, H-1″), 5.08 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1), 4.59 (d, 1H, $J_{1',2'}$ = 7.8 Hz H-1′), 4.41–4.26 (m, 4H, H-2, H-6a,b, H-6″a), 4.14 (d, 1H, $J_{5'',6''}$ = 10.1 Hz, H-6″b), 4.05 (m, 1H, H-5), 3.91 (t, 1H, *J* = 9.3 Hz, H-4′), 3.85 (d, 1H, $J_{5'',6''}$ = 9.9 Hz, H-5″), 3.82 (t, 1H, *J* = 9.5 Hz, *J* = 10.3 Hz, H-4), 3.72 (d, 1H, *J* = 9.7 Hz, H-5′), 3.63–3.45 (m, 21H, $CH_2aSO_3^-$, H-3′, H-3″, 6 × OCH_3), 3.38–3.26 (m, 3H, H-2′, H-2″, H-4″), 3.19 (dd, 1H, $J_{CH2b,3}$ = 3.9 Hz, J_{gem} = 14.7 Hz, $CH_2bSO_3^-$), 2.52 (m, 1H, H-3); ^{13}C NMR (D_2O, 90 MHz): δ 175.2 (CO), 101.7 (C-1′), 96.6 (C-1), 96.2 (C-1″), 85.7 (C-3′), 83.0 (C-2′), 82.0 (C-3″), 80.5 (C-2″), 78.1 (C-4″), 76.9 (C-5′), 75.9 (C-2), 74.6 (C-4), 74.4 (C-4), 70.2 (C-5), 68.9 (C-5″), 66.4 (C-6), 66.2 (C-6″), 60.6, 60.4, 60.1, 59.5, 59.1, 55.3 (6 × OCH_3), 49.1 ($CH_2SO_3^-$), 37.4 (C-3); Anal. Calcd for $C_{25}H_{39}Na_5O_{28}S_4$, (1030.77): C, 29.13; H, 3.81; S, 12.44. Found: C, 29.11; H, 3.80; S, 12.43.
Compound **5**: $[\alpha]_D$: +40.2 (*c* 0.08, H_2O); IR ν_{max} (KBr): 3450, 1634, 1219, 772, 673 cm^{-1}; ^1H NMR (D_2O, 500 MHz): δ 5.46 (d, 1H, $J_{1'',2''}$ = 3.4 Hz, H-1″), 5.11 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.68 (d, 1H, $J_{1',2'}$ = 7.7 Hz, H-1′), 4.59, (t, 1H, *J* = 9.1 Hz, H-3), 4.38 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 4.27 (d, 1H, $J_{5'',6''}$ = 10.3 Hz, H-6″a), 4.12 (d, 1H, $J_{5'',6''}$ = 10.1 Hz, H-6″b), 3.96 (t, 1H, *J* = 7.9 Hz, H-5), 3.92 (m, 1H, H-4′), 3.87 (m, 1H, H-5″), 3.80 (t, 1H, *J* = 9.3 Hz, H-4), 3.74 (d, 1H, *J* = 9.7 Hz, H-5′), 3.63 (s, 9H, 3 × OCH_3), 3.58 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.62–3.50 (m, 2H, H-3′, H-3″), 3.45 (s, 3H, OCH_3), 3.38–3.27 (m, 3H, H-4″, H-2″, H-2′), 3.15 (m, 1H, H-7a), 3.03 (m, 1H, H-7b), 2.44 (m, 1H, H-6a), 1.99 (m, 1H, H-6b); ^{13}C NMR (D_2O, 125 MHz): δ 175.9 (CO), 102.5 (C-1′), 97.8 (C-1), 96.9 (C-1″), 86.5 (C-3′), 83.9 (C-2′), 82.8 (C-3″), 81.3 (C-2″), 78.9 (C-4″), 78.0 (C-4), 77.6 (C-5′), 77.1 (C-3), 76.2 (C-2), 75.1 (C-4′), 70.4 (C-5), 69.6 (C-5″), 66.9 (C-6″), 61.2, 60.8, 60.3, 59.9, 56.2, (6 × OCH_3), 48.1 (C-7), 27.1 (C-6); Anal. Calcd for $C_{25}H_{39}Na_5O_{28}S_4$ (1030.77): C, 29.13; H, 3.81; S, 12.44. Found: C, 29.16; H, 3.83; S, 12.42.