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Carbohydrate Sulfonic Acids

Synthesis of *C*-2- and *C*-3-Sulfonatomethyl *O*- and *S*-Glycosides by Horner–Wadsworth–Emmons Olefination

Dániel Eszenyi,[a] Attila Mándi,[b] Mihály Herczeg,[a] Attila Bényei,[a] István Komáromi,[c] and Anikó Borbás*[a]

Abstract: The applicability of the Horner–Wadsworth–Emmons olefination to the introduction of the sulfonatomethyl moiety at the 2- and 3-positions of orthogonally protected *O*- and *S*-glycosides has been studied. The conformational preferences and relative energies of the exo- and endocyclic alkenesulfonic acids obtained were analysed by high-temperature molecular dynamics and DFT calculations. Thioglycosides bearing a sulfonatomethyl moiety at the secondary position have been prepared for the first time. Finally, the attempted synthesis of 2-sulfonatomethyl glucoside by nucleophilic substitution reaction is also described.

Introduction

Sulfated carbohydrates play essential roles in many diverse biological processes including blood clotting, inflammation, the inhibition and promotion of tumour growth as well as host–pathogen interactions.[1] The isosteric sulfonic acid analogues of carbohydrate sulfates are enzymatically stable compounds that can be used as tools to better understand these biological functions or to develop leads for new anti-coagulant, anti-tumour and anti-microbial agents. Accordingly, various approaches have been developed for producing sulfonic acid analogues of the sulfated Lewis X trisaccharide,[2] glucose 6-sulfate,[3] sulfated glycolipids[4,5] and heparin.[6] Moreover, carbohydrate sulfonates are of interest as bioisosters of phosphates and carboxylates such as nucleotides,[7–9] mannose-6-phosphate[10,11] and sialic acid derivatives.[12–15]

Some years ago we initiated a research project to prepare isosteric sulfonic acid analogues of the anti-thrombin binding pentasaccharide domain of heparin to access new anti-coagulants.[6,16–22] Recently, we demonstrated that the blood clotting inhibitory activity of the parent highly sulfated pentasaccharide could be improved by the replacement of the primary sulfate esters with a sodium sulfonatomethyl group.[19] Continuing on from this, we targeted the synthesis of further pentasaccharide analogues bearing the sulfonic acid moiety at secondary positions by using thioglycoside building blocks bearing a sulfonatomethyl moiety at the 2- or 3-position. Unfortunately, the majority of the methods published for the synthesis of carbohydrate sulfonic acids are incompatible with thioglycosides, which are susceptible to oxidation, and a modified new synthetic approach is necessary to circumvent this problem.

Horner–Wadsworth–Emmons (HWE) olefination is a powerful and reliable reaction providing access to a variety of alkenic compounds bearing various functional groups including sulfides.[23,24] Previous investigations have demonstrated that different sulfonate-stabilized phosphonates are efficient olefinating agents allowing the preparation of α,β-unsaturated sulfonates from both aldehydes and ketones.[25,26] Surprisingly, this method has scarcely been applied to the synthesis of carbohydrate sulfonic acids, with only three examples reported in the literature.[4,7,19] Therefore, we decided to study the HWE-based route to glycosyl donor and acceptor building blocks bearing the sulfonatomethyl group at secondary positions.

As it has been reported that a 2-*C*-methyl-D-*gluco* derivative could be obtained in good yield from the corresponding 2-*O*-triflyl-α-D-mannopyranoside upon treatment with MeLi,[27] we considered nucleophilic substitution of mannose-2-*O*-triflate derivatives with lithiated methanesulfonate ester to be a feasible approach to 2-sulfonatomethyl-containing glucosides.

Results and Discussion

The synthesis started from compounds **1**–**3**, all of which are easily available from the corresponding α-D-*manno*- and β-D-glucopyranosides in two steps, namely acetalation and regioselective etherification (Figure 1). We planned to prepare the corresponding 2-sulfonatomethyl glucoside from the mannoside derivative **1*((<=Author: 1 inserted, correct?))*** both by nucleophilic displacement and HWE olefination, whereas glucosides **2** and **3** could give access to 2- and 3-sulfonatomethyl derivatives through the HWE reaction. Owing to the orthogonal protection pattern of **1**–**3**, the planned sulfonatomethyl derivatives could

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be useful building blocks in the synthesis of oligosaccharide sulfonic acids.

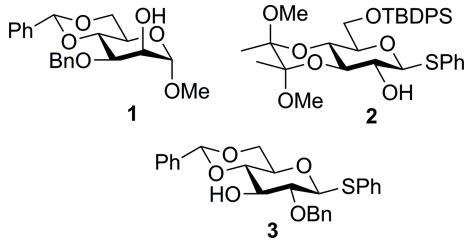
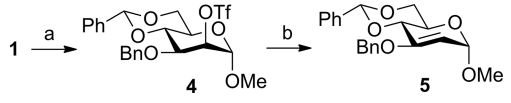


Figure 1. Starting compounds **1**–**3**.

First we applied the nucleophilic approach to transform **1**[28] into a *C*-2-sulfonatomethyl glucoside. Compound **1** was treated with triflic anhydride in the presence of pyridine to afford **4**,[27] which was treated with lithiated ethyl methanesulfonate in THF. It is known that S_N2 reactions of 2-sulfonylated α-D-mannopyranosides occur with difficulty.[29] Indeed, a very sluggish reaction was observed and consumption of **4** was incomplete even after 5 d. As a result, instead of the expected nucleophilic substitution reaction only β-elimination took place to provide the unsaturated **5**[30] in 21 % yield (Scheme 1).



Scheme 1. Attempted nucleophilic substitution route to 2-*C*-sulfonatomethyl glucoside. Reagents and conditions: a) Tf_2O, abs. CH_2Cl_2, abs. pyridine, –10 °C; b) *n*BuLi, CH_3SO_3Et, THF, –78 °C to r.t., 5 d, 21 % over two steps.

Next, compound **1** was oxidized by the Swern method and the resulting 2-ulose **6** was subjected to HWE olefination with the lithiated ethylsulfonylphosphonate reagent in THF. The reaction after 4 h furnished a mixture of **7a** and **7b**. However, the conversion of ketone **6*((<=Author: Change correct?))*** was incomplete and separation of the products and remaining starting compound was difficult. Surprisingly, after an overnight reaction, enopyranoside **8** was also formed, decreasing the yield of the expected derivatives **7a** and **7b** (Table 1, entry 2). The isomerization of exocyclic alkenes into the endocyclic isomers upon Wittig reaction or Horner–Wadsworth–Emmons olefination of cyclic ketones has been reported previously in the literature.[31] We were pleased to find that almost complete conversion of **6** without the formation of **8** was observed after 6 h and that the global yield of **7a**,**b** reached 78 %. Our attempts to further increase the yields of the desired sulfonatomethylene derivatives by changing THF to different ether-type solvents were unsuccessful (Table 1, entries 4–6, Scheme 2).

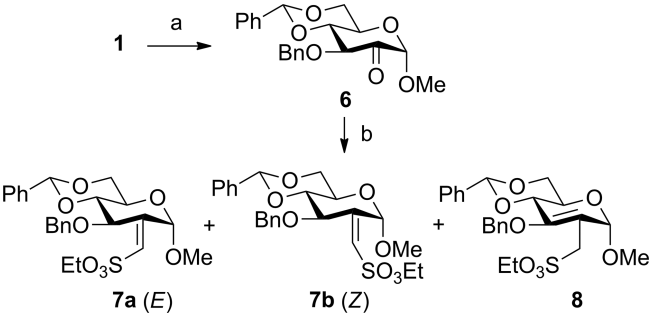
ROESY experiments were performed for configurational assignment of the two geometric sulfonate isomers. A strong effect between 3-H and the methylene proton in the ROESY spectrum demonstrates the *Z* configuration of **7b** (Figure 2).

The significant differences observed in the ^{1}H NMR spectroscopic data of **7a** and **7b** suggest that they adopt different conformations. The 1-H signal at δ = 6.38 ppm and the large vicinal 3-H/4-H coupling $J_{3,4}$ = 9.8 Hz demonstrate that **7b** has a chair-like conformation. Based on both the upfield shift of 1-H to 5.35 ppm and the smaller 3-H/4-H coupling constant ($J_{3,4}$ = 6.3 Hz), the *E* isomer **7a** prefers a boat-like conformation, probably due to allylic strain between the sulfonate and 2-*O*-benzyl moieties.

Table 1. HWE olefination of **6** in different solvents.

Entry	Solvent	*T* [°C]	Reaction time [h]	Yield[a] [%] **7a**	**7b**	**8**
1	THF	–78 to –15	4 h	15	52	–
2	THF	–78 to r.t.	16 h	7	46	25
3	THF	–78 to +10	6 h	17	61	–
4	Et_2O	–78 to r.t.	6 h	6	10	2
5	Bu_2O	–78 to r.t.	6 h	3	11	4
6	*t*BuOMe	–78 to r.t.	6 h	16	23	6

[a] Isolated yields after silica gel column chromatography.



Scheme 2. Oxidation and subsequent HWE olefination of **1**. Reagents and conditions: a) DMSO, $(COCl)_2$, DIPEA, –78 °C, 82 %; b) $(EtO)_2POCH_2SO_3Et$, *n*BuLi; see Table 1 for the details.

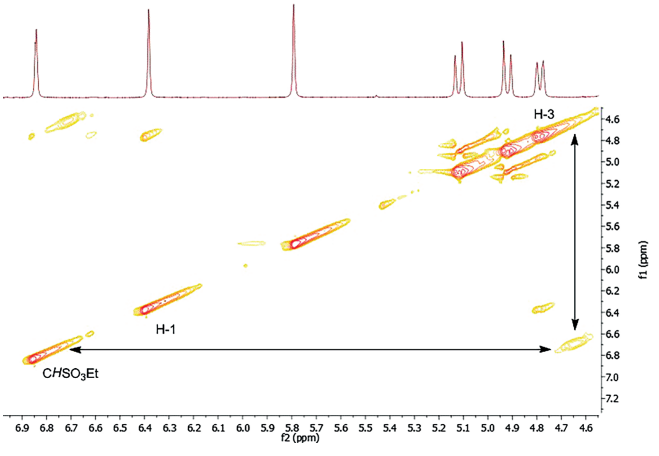


Figure 2. Diagnostic part of the ROESY spectrum of **7b**.

To gain an insight into the conformational preferences and relative energies of compounds **7a**, **7b** and **8**, high-temperature molecular dynamics and DFT calculations were performed.[32] B3LYP/6-31G(d) re-optimization of the clustered high-temperature dynamics structures by neglecting the rotation of the Ph, SO_3Et and OMe groups resulted in global minima, in agreement with the experimental findings. Compound **7b** adopts a $^4C_1$-like sugar ring with $\omega_{O5-C1-C2-C3}$ = 47.3° and $\omega_{C3-C4-C5-O5}$ = –61.4° (φ: 286.570°, θ: 10.193°, *Q*: 0.546), whereas **7a** has $\omega_{O5-C1-C2-C3}$ = –44.1° and $\omega_{C3-C4-C5-O5}$ = –58.9° value (φ: 304.753°, θ: 84.808°, *Q*: 0.751) corresponding to a $B_{2,5}$ conformation.[33]

These data are also in agreement with the results of single-crystal X-ray diffraction studies performed on the 3-deoxy-3-*C*-sulfonatomethylene derivative **19a** (see below). In the case of **8**, the $\omega_{O5-C1-C2-C3}$ and $\omega_{C3-C4-C5-O5}$ values are 7.6 and –57.1°, respectively (φ: 311.702°, θ: 51.588°, Q: 0.518), that is, halfway between the E_5 and $^{O}H_5$ conformation in the lowest-energy conformer (Figure 3).[34]

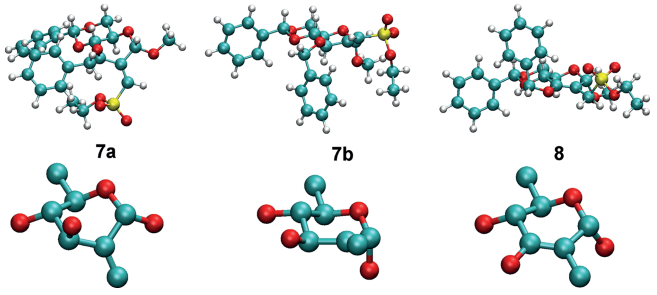
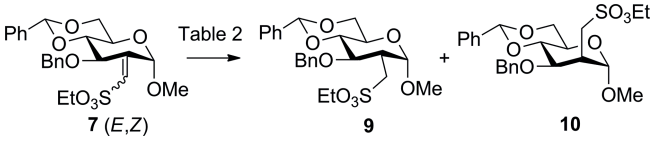


Figure 3. Computed DFT-optimized global minima of **7a**, **7b** and **8** (top) along with their sugar ring conformations and first non-hydrogen atoms (bottom; hydrogen atoms are not displayed).

Compound **7a** has a substantially higher energy than **7b**. At the B3LYP/6-31G(d) gas-phase level of theory the energy difference between the global minima is 21.8 kJ/mol. Although the solvent may compensate somewhat the difference or rotation of the neglected groups may have an impact on the relative energies, the results show a clear preference for the *Z* isomer over the *E* isomer. Interestingly, the global energy minimum of **8** has an even lower energy than that of **7b**. The energy difference is 31.9 kJ/mol at the applied level of theory, that is, according to in vacuo calculations the yields of the three emerging products are expected to be **8** >> **7b** >> **7a**.

Continuing the planned synthetic route towards the targeted sulfonatomethyl derivative, saturation of the double bond was studied. Catalytic hydrogenation of either the *E* or *Z* isomer, respectively, showed high stereoselectivity in favour of the *gluco*-configured product **9** (Scheme 3). Double-bond reduction of **7b** with sodium borohydride also took place with good stereoselectivity to afford a mixture of the *gluco* and *manno* derivatives in an 87:13 ratio. On the preparative scale, sodium borohydride turned out to be more efficient, providing compound **9** in 66 % yield from the *E*,*Z* mixture with the *manno*-configured derivative **10** also isolated in 10 % yield (Table 2).



Scheme 3. Saturation of compound **7** by catalytic hydrogenation or sodium borohydride reduction.

Reduction of the 2,3-unsaturated compound **8** by catalytic hydrogenation failed, probably due to steric hindrance of the endocyclic double bond.

The configuration at C-3 of **9** and **10** was determined by the vicinal coupling constants. The α-D-*gluco* configuration of the main product **9** was deduced from the $J_{1,2}$ = 3.5 Hz and $J_{2,3}$ = 8.8 Hz coupling constants, and the X-ray data corroborate this

Table 2. Reaction leading to the saturation of compound **7**.

Entry	Starting compound	Reagents	Conditions	Ratio[a]/yield[b] [%] of products	
				9	**10**
1	**7b** (*Z* isomer)	H_2, Pd^0/C	CH_2Cl_2, r.t., 2 h	95	5
2	**7a** (*E* isomer)	H_2, Pd^0/C	CH_2Cl_2, r.t., 2 h	89	11
3	**7b** (*Z* isomer)	$NaBH_4$	MeOH, r.t., 3 h	87	13
4	**7** (*E*,*Z* mixture)	H_2, Pd^0/C	CH_2Cl_2, r.t., 2 h	49	4
5	**7** (*E*,*Z* mixture)	$NaBH_4$	MeOH, r.t., 2 h	66	10

[a] Entries 1–3, determined by ^{1}H NMR analysis of the product mixture. [b] Entries 4 and 5, isolated yield of products after silica gel column chromatography.

assignment (Figure 4). The singlet 1-H signal and the small 2-H/3-H coupling ($J_{2,3}$ = 5.7 Hz) in the ^{1}H NMR spectrum demonstrate the α-D-*manno* configuration of **10**. Although compound **9** can be used in the synthesis of heparinoid derivatives (e.g., sulfonic acid containing anti-coagulants), the *manno* derivative **10** might also be a valuable building block for bioactive mannose-containing oligosaccharide mimics. Among others, the potent anti-angiogenic, anti-tumour and anti-metastatic agent PI-88 bearing a highly sulfated 3,6-branched oligomannoside structure is a potential synthetic target.[35,36]

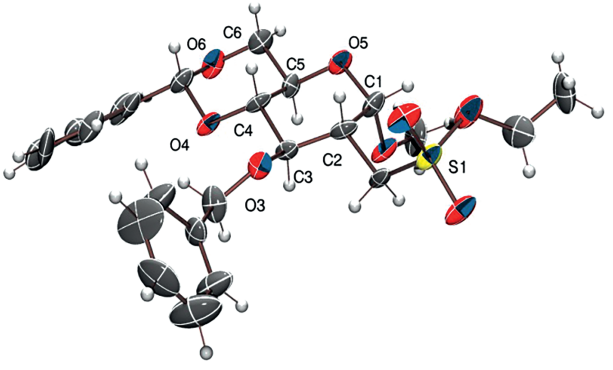
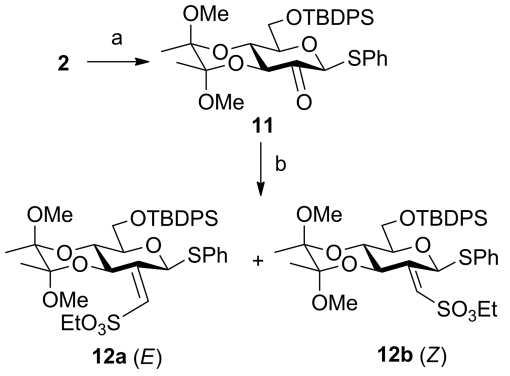


Figure 4. ORTEP view of **9** with partial numbering scheme. Ellipsoids are drawn at the 50 % probability level. Selected bond lengthd [Å] and torsion angles [°]: C1–C2 1.562(16), C2–C3 1.478(16), C3–O3 1.425(12), C3–C4 1.517(14), C4–C5 1.514(15), C1–O5 1.429(12); O5–C1–C2–C3 48.0, C3–C4–C5–O5 –56.0.

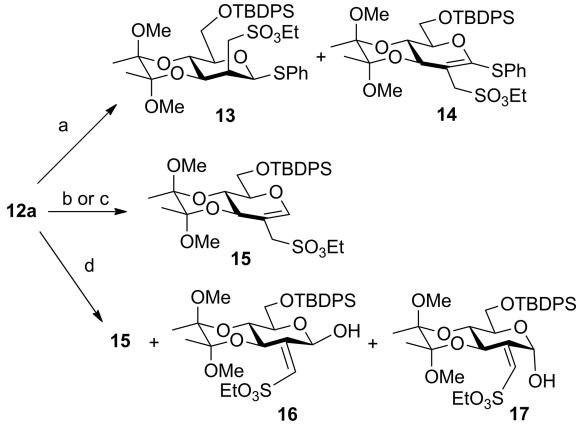
Hence, we focused our attention on the HWE olefination of thioglycosides. First, the oxidation of compound **2**[37] with Dess–Martin periodinane afforded ketone **11**, which was treated with the sulfonyl-stabilized phosphonate anion. Applying the optimized conditions, the Horner–Wadsworth–Emmons reaction resulted in a 7:1 mixture of the *E*- and *Z*-configured *exo*-methylene ■■ ((<=Author: change correct?)) ■■ derivatives **12a**,**b** in 73 % global yield (Scheme 4). The *E* configuration of the major isomer **12a** was ascertained by contact between 1-H and the methylene proton in the ROESY spectrum.

Reduction of the major product with sodium borohydride afforded a mixture of the saturated product **13** and the endocyclic **14** in a ratio of 1:1 (Scheme 5). The configuration at C-2 of compound **13** was deduced from the singlet 1-H and 2-H signals in its ^{1}H NMR spectrum. The unexpected formation of **14** can be explained by the isomerization of the exocyclic alkene into the more stable endocyclic isomer, which takes place com-



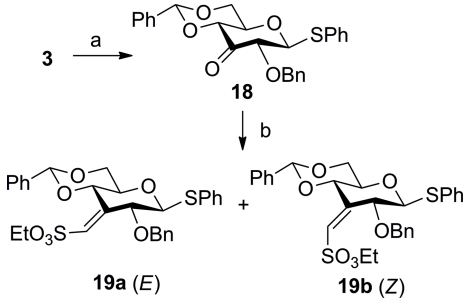
Scheme 4. HWE olefination of **11**. Reagents and conditions: a) Dess–Martin periodinane, CH_2Cl_2, r.t.; b) $(EtO)_2POCH_2SO_3Et$, *n*BuLi, abs. THF, –78 to 0 °C, 6 h, 73 % global yield over two steps (*E*/*Z* ≈ 7:1).

petitively with the reduction. As sodium borohydride can only reduce an activated double bond, compound **14** remained intact during the reduction reaction as it has a non-activated double bond. Catalytic hydrogenation has previously been applied successfully to the saturation of a 6-*C*-sulfonatomethylene heptosyl thioglycoside derivative.[19] However, catalytic hydrogenation of **12a** led to the isomerization of the double bond and desulfurization instead of the desired saturation reaction to provide the 2-substituted glycal **15**. Using Pd/C under 10 bar H_2, compound **12a** was sluggishly transformed into **15**, whereas in the presence of Raney-Ni, this transformation took place readily. (Although thee desulfurization of *S*-alkyl and -aryl compounds with Raney nickel is a well-known reaction, it generally requires a very large excess of Ra-Ni and elevated temperatures.)[38] Catalytic transfer hydrogenation with Pd/C and triethylsilane[39] was also carried out resulting in a 3:1:1 ■■ ((<= Author: 2:1:1 ? see caption to Scheme 5)) ■■ mixture of the unsaturated derivatives **15**, **16** and **17**. It is worth mentioning that the hemiacetal derivatives **16** and **17** were formed from an unstable product of higher chromatographic mobility during the work-up procedure.



Scheme 5. Reductive transformations of compound **12a**. Reagents and conditions: a) $NaBH_4$, MeOH, r.t., 3 h, 38 % of **13**, 37 % of **14**; b) Ra-Ni, H_2, overnight, 78 %; c) Pd^0/C, 10 bar H_2, 60 h 35 % (45 % of **12a** was recovered); d) Pd^0/C, 10 equiv. Et_3SiH, 1 h, 24 % of **15**, 10 % of **16**, 12 % of **17**.

Finally, compound **3**[40] was oxidized by the Swern method and the 3-ulose **18** obtained was treated with the lithiated ethylsulfonylphosphonate reagent under the optimized conditions to produce the 3-*C*-sulfonatomethylene derivatives **19a** and **19b** in 68 % global yield (Scheme 6). The *E* and *Z* isomers were formed in an approximately 2:1 ratio, and the configuration of the crystalline major product **19a** was determined from the X-ray structure (Figure 5).



Scheme 6. Synthesis and HWE olefination of ulose **18**. Reagents and conditions: a) DMSO, $(COCl)_2$, DIPEA, –78 °C, 87 %; b) $(EtO)_2POCH_2SO_3Et$, *n*BuLi, abs. THF, –78 to 0 °C, 6 h, 44 % of **19a**, 24 % of **19b**.

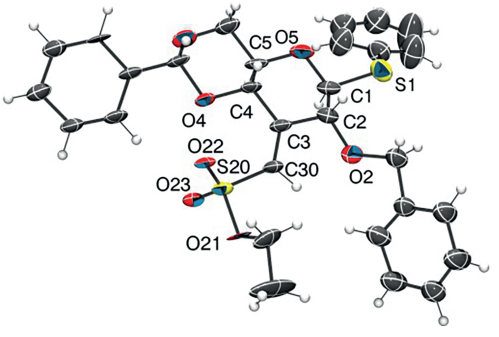
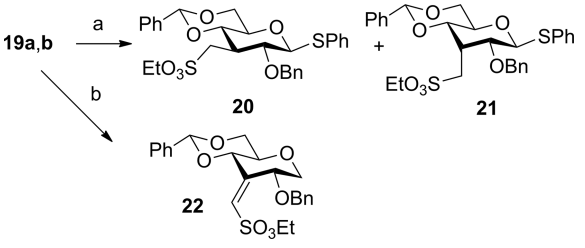


Figure 5. ORTEP view of **19a** with partial numbering scheme. Ellipsoids are drawn at the 50 % probability level. Only one of two positions of the disordered benzyl group is shown. Selected bond lengths [Å] and torsion angles [°]: C1–S1 1.760(17), C2–C3 1.54(2), C3–C30 1.32(2), C30–S20 1.769(16), C5–O5 1.456(19), C1–O5 1.42(2); O5–C1–C2–C3 51.3, C3–C4–C5–O5 –58.8.

Sodium borohydride reduction of **19a**,**b** took place with high efficacy to provide the saturated products **20** and **21** in 69 % overall yield (Scheme 7). The ratio was 4:1 in favour of the *allo* isomer, according to the integration of the benzylidene proton (δ = 5.55 ppm for the *allo* isomer and δ = 5.61 ppm for the *gluco* isomer). The catalytic hydrogenation of **19a**,**b** in the presence of Pd/C led to negligible conversion after 3 days, whereas the Raney-Ni-mediated reduction led to desulfurization without affecting the carbon–carbon double bond to provide **22** in 32 % yield.



Scheme 7. Reduction of compound **19**. Reagents and conditions: a) $NaBH_4$, MeOH, r.t., 3 h, 69 % of a mixture of **20** and **21**; b) Ra-Ni, H_2, 32 %.

Conclusions

Horner–Wadsworth–Emmons (HWE) olefination proved to be an efficient method for the introduction of the sulfonatomethylene moiety at secondary positions of the *O*- and *S*-glycosides. For saturation of the double bond, sodium borohydride reduction was applied successfully in all cases. Catalytic hydrogenation was also a useful method for the transformation of the *O*-glycoside **7** into the saturated product. However, in the case of thioglycosides, catalytic hydrogenation led to desulfurization or allylic isomerization of the double bond instead of saturation, independently of the nature of the catalyst.

We have found that the anomeric configuration has a great influence on the stereochemical outcome of both the olefination and the reduction reactions. Upon the HWE reaction, the formation of the *Z* isomer was preferred from α-glycoside **6**, whereas the *E* configuration was preferred in the case of β-glycoside **11**. Saturation of the double bond showed high *gluco* selectivity for α-glycoside **7** and exclusive *manno* selectivity for β-glycoside **12**. These results suggest that 2-*C*-sulfonatomethyl glucopyranosides may be available from the corresponding 2-ulosyl α-thioglycosides.

The undesired formation of the endoglycal derivatives upon prolonged olefination (**8**) and saturation (**14** or **15**) can be explained by the higher thermodynamic stability of the endocyclic derivatives over the exocyclic congeners. The results of high-temperature molecular dynamics and DFT calculations corroborated these results.

Utilisation of the *gluco*-configured sulfonatomethyl derivatives for the synthesis of heparinoid pentasaccharide sulfonic acids as potential anti-coagulants is under way in our laboratory. The orthogonally protected *manno*-configured sulfonic acid derivative may also be a useful building block in the synthesis of sulfonic acid analogues of sulfated oligomannosides such as the anti-tumour and anti-metastatic agent PI-88.

Experimental Section

General Methods: Optical rotations were measured at room temperature with a Perkin–Elmer 241 automatic polarimeter. TLC analysis was performed on Kieselgel 60 F_{254} (Merck) silica gel plates with visualization by immersion in a sulfuric acid solution (5 % in EtOH) followed by heating. Column chromatography was performed on silica gel 60 (Merck 0.063–0.200 mm) and flash column chromatography was performed on silica gel 60 (Merck 0.04–0.063 mm). Organic solutions were dried with $MgSO_4$ and concentrated under vacuum. ^1H (360 and 400 MHz) and ^{13}C NMR (90.54 and 100.28 MHz) spectra were recorded with Bruker DRX-360 and DRX-400 spectrometers. 2D COSY, ^1H-^{13}C HSQC and 2D ROESY experiments were performed to assist NMR assignments. Chemical shifts are referenced to $SiMe_4$ (δ = 0.00 ppm for ^1H nuclei) and to the residual solvent signal ($CDCl_3$: δ = 77.00 ppm for ^{13}C nuclei). MS (MALDI-TOF) analysis was carried out in positive reflectron mode with a BIFLEX III mass spectrometer (Bruker, Germany) with delayed-ion extraction. The matrix solution was a saturated solution of 2,4,6-trihydroxyacetophenone (THAP) in MeCN. Elemental analysis (C, H, S) was performed with an Elementar Vario MicroCube instrument. X-ray diffraction data for compounds **9** and **19a** were collected with a Bruker Nonius MACH3 diffractometer at 293 K with Mo-K_α radiation (λ = 0.71073 Å) or with an Oxford Diffraction SuperNova diffractometer at 293 K with Cu-K_α radiation (λ = 1.54184 Å), respectively. All non-hydrogen atoms were refined anisotropically.

CCDC 1483395 (for **9**) and 1483396 (for **19a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Computational Section: The molecular dynamics simulations (500 ns, 1200 K constant temperature, 1 fs time step) and the preliminary geometry optimizations using the suitably developed GAFF empirical force field on the equidistantly saved 500000 trajectory snapshot geometries were carried out by means of the Amber molecular dynamics simulation package.[32,41] Distance-based clustering of both the GAFF and the DFT-optimized structures was performed for the heavy atoms of the sugar ring, the dioxane ring, the double bond and the first connecting heavy atoms by applying a 0.5 Å cut-off with an in-house code (written by A. Mándi). B3LYP/6-31G(d) density functional calculations were carried out by using the Gaussian 09 package.[42] Ball-and-stick representations of the conformers were generated by using the VMD software.[43]

Puckering values were generated based on the model proposed by Cremer and Pople using the Cremer–Pople Parameter Calculator.[33]

Methyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-trifluoromethylsulfonyl-α-D-mannopyranoside (4):[27] A solution of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**;[28] 370 mg, 1.00 mmol) in dry CH_2Cl_2 (1.5 mL) and dry pyridine (0.2 mL) was cooled to –10 °C and trifluoromethanesulfonic anhydride (0.16 mL) in dry CH_2Cl_2 (0.5 mL) was added dropwise. After stirring for 1 h the reaction mixture was diluted with CH_2Cl_2, extracted with water, 1 N HCl solution and a saturated aqueous $NaHCO_3$ solution, dried and concentrated. The crude product (241 mg) was used in the next step without purification. R_f = 0.78 (1:1 *n*-hexane/ethyl acetate). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.55–7.19 (m, 10 H, arom.), 5.58 (s, 1 H, C*H* benzylidene), 5.07 (s, 1 H, 1-H), 4.86–4.70 (m, 3 H, CH_2Ph, 2-H), 4.29–4.18 (m, 1 H, 3-H), 4.06–3.96 (m, 2 H), 3.86–3.74 (m, 2 H), 3.34 (s, 3 H, OCH_3) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 137.3, 137.1 (2 C, 2 C_q arom.), 128.9–126.0 (10 C, arom.), 120.2 (CF_3), 101.6 (*C*H benzylidene), 98.7 (C-1), 83.2, 78.0, 72.2, 63.6 (C-2, C-3, C-4, C-5), 73.0 (*C*H_2Ph), 68.3 (C-6), 55.2 (O*C*H_3) ppm.

Methyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hex-2-enopyranoside (5):[30] Ethyl methanesulfonate (0.43 mL, 0.955 mmol) was dissolved in abs. THF (2 mL) and the stirred mixture was cooled to –78 °C under argon before 2.5 M *n*-butyllithium (0.166 mL, 0.955 mmol) was added dropwise. After 30 min at this temperature a solution of **4** (241 mg, 0.477 mmol) in THF (4 mL) was added and the mixture was warmed to room temperature. After stirring for 5 d the reaction mixture was diluted with ethyl acetate, extracted with saturated aqueous ammonium chloride and water, dried and concentrated. The crude product was purified by column chromatography to yield **5** (35 mg, 21 % over two steps) as a colourless syrup. lit:[30] $[\alpha]_D^{24}$ = –59 (*c* = 0.6, $CHCl_3$); R_f = 0.40 (65:35 C_6H_{14}/ethyl acetate). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.57–7.20 (m, 10 H, arom.), 5.56 (s, 1 H, C*H* benzylidene), 5.00 (d, $J_{1,2}$ = 2.61 Hz, 1 H, 1-H), 4.90 (d, J_{gem} = 12.07 Hz, 1 H, CH_{2a} benzyl), 4.77 (d, J_{gem} = 12.10 Hz, 1 H, CH_{2b} benzyl), 4.74–4.70 (m, 1 H, 2-H), 4.33–4.21 (m, 2 H, 4-H, 6-H_a), 4.10 (dt, $J_{5,6a}$ = 9.65, $J_{5,6b}$ = 9.65 Hz, $J_{4,5}$ = 4.57 Hz, 1 H, 5-H), 3.82 (t, J_{gem} = 10.23, $J_{5,6}$ = 10.23 Hz, 1 H, 6-H_b), 3.40 (s, 3 H, OCH_3) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 154.4 (C-3), 137.2, 136.0 (2 C, 2 C_q arom.), 128.9–126.3 (10 C, arom.), 102.1 (*C*H benzylidene), 97.2, 95.8, 74.9, 69.4, 69.0, 63.6 (C-1, C-2, C-4, C-5. C-6, CH_2 benzyl), 55.4 (O*C*H_3) ppm.

Methyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-deoxy-2-*C*-(*E*)-(ethylsulfonatomethylene)-α-D-*arabino*-hexopyranoside (7a), Methyl

3-*O*-Benzyl-4,6-*O*-benzylidene-2-deoxy-2-*C*-(*Z*)-(ethylsulfonatomethylene)-α-D-*arabino*-hexopyranoside (7b) and Methyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-deoxy-2-*C*-(ethylsulfonatomethyl)-α-D-*erythro*-hex-2-enopiranoside (8): Ethyl diethylphosphorylmethanesulfonate[19,25] was dissolved in the current solvent (see Table 1) and the stirred mixture was cooled to –78 °C under argon before 2.5 M *n*-butyllithium was added dropwise. After 30 min at this temperature a solution of **6** in the current solvent and THF (1.5 mL) was added and the mixture was warmed to room temperature. After 6 h the mixture was diluted with CH_2Cl_2, extracted with saturated aqueous ammonium chloride and water, dried and concentrated. The crude product was purified by column chromatography (65:15:20 C_6H_{14}/ethyl acetate/toluene) to give **7a**, **7b** and **8**.

7b: Colourless syrup, $[\alpha]_D$ = –20.54 (*c* = 0.50, $CHCl_3$); R_f = 0.65 (6:4 C_6H_{14}/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.45 (m, 10 H, arom.), 6.84 (d, *J* = 1.7 Hz, 1 H, C*H*SO_3Et), 6.38 (s, 1 H, 1-H), 5.79 (s, 1 H, C*H* benzylidene), 5.12 (d, J_{gem} = 11.6 Hz, 1 H, CH_{2a} benzyl), 4.92 (d, J_{gem} = 11.6 Hz, 1 H, CH_{2b} benzyl), 4.79 (d, $J_{3,4}$ = 9.8 Hz, 1 H, 3-H), 4.51 (dd, $J_{3,4}$ = 10.3, $J_{4,5}$ = 4.8 Hz, 1 H, 4-H), 4.38 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, $SO_3CH_2CH_3$), 4.23 (dt, $J_{5,6}$ = 9.9, $J_{4,5}$ = 4.8 Hz, 1 H, 5-H), 3.98 (t, J_{gem} = 10.4, $J_{5,6}$ = 10.4 Hz, 1 H, 6-H_a), 3.92 (t, J_{gem} = 9.7, $J_{5,6}$ = 6.7 Hz, 1 H, 6-H_b), 3.66 (s, 3 H, OCH_3), 1.58 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, $SO_3CH_2CH_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.0 (C-2), 137.5, 137.2 (C_q), 129.2, 128.6, 128.3, 128.1, 128.0, 126.1 (10 C, arom.), 121.4 (*C*HSO_3Et), 101.5 (*C*H benzylidene), 95.2 (C-1), 84.1 (C-4), 76.0 (C-3), 74.6 (CH_2 benzyl), 68.8 (C-6), 67.3 ($SO_3CH_2CH_3$), 63.1 (C-5), 55.6 (OCH_3), 14.9 ($SO_3CH_2CH_3$) ppm. $C_{24}H_{28}O_8S$ (476.54): calcd. C 60.49, H 5.92, S 6.73; found C 60.24, H 6.09, S 6.82.

7a: Colourless syrup; R_f = 0.52 (6:4 C_6H_{14}/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.41 (m, 10 H, arom.), 6.88 (d, *J* = 1.1 Hz, 1 H, C*H*SO_3Et), 5.74 (s, 1 H, C*H* benzylidene), 5.35 (s, 1 H, 1-H), 5.30 (d, $J_{3,4}$ = 6.3 Hz, 1 H, 3-H), 5.08 (d, J_{gem} = 11.0 Hz, 1 H, CH_{2a} benzyl), 4.98 (d, J_{gem} = 10.95 Hz, 1 H, CH_{2b} benzyl), 4.54 (d, $J_{5,6}$ = 5.37 Hz, 1 H, 6-H_a), 4.45–4.38 (m, 2 H, $SO_3CH_2CH_3$), 4.16–4.10 (m, 1 H, 4-H), 4.02–3.89 (m, 2 H, 5-H, 6-H_b), 3.63 (s, 3 H, OCH_3), 1.52 (t, $^3J_{H,H}$ = 7.13 Hz, 3 H, $SO_3CH_2CH_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.8 (C-2), 137.5, 136.8 (2 C, 2 C_q arom.), 128.8, 128.1, 128.0, 127.4, 125.9 (11 C arom., *C*HSO_3Et), 101.2 (*C*H benzylidene), 99.2 (C-1), 83.0 (C-4), 74.5 (C-3), 73.5 (CH_2 benzyl), 68.9 (C-6), 66.7 ($SO_3CH_2CH_3$), 63.7 (C-5), 55.2 (OCH_3), 14.7 ($SO_3CH_2CH_3$) ppm. $C_{24}H_{28}O_8S$ (476.54): calcd. C 60.49, H 5.92, S 6.73; found C 60.66, H 5.81, S 6.92.

8: $[\alpha]_D$ = –16.75 (*c* = 1.34, $CHCl_3$); R_f = 0.63 (6:4 C_6H_{14}/ethyl acetate). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.51–7.26 (m, 10 H, arom.), 5.58 (s, 1 H, C*H* benzylidene), 5.29 (s, 1 H, 1-H), 5.17 (d, J_{gem} = 10.68 Hz, 1 H, CH_{2a} benzyl), 4.95 (d, J_{gem} = 10.68 Hz, 1 H, CH_{2b} benzyl), 4.46–4.37 (m, 2 H, CH_2SO_3Et), 4.31 (dd, J_{gem} = 10.26, $J_{5,6a}$ = 4.56 Hz, 1 H, 6-H_a), 4.19 (q, $^3J_{H,H}$ = 7.01 Hz, 1 H, $SO_3CH_{2a}CH_3$), 4.18 (q, $^3J_{H,H}$ = 7.00 Hz, 1 H, $SO_3CH_{2b}CH_3$), 4.06 (td, *J* = 10.02, *J* = 9.84 Hz, $J_{5,6a}$ = 4.54 Hz, 1 H, 5-H), 3.85 (t, J_{gem} = 10.34, $J_{5,6b}$ = 10.34 Hz, 1 H, 6-H_b), 3.60 (d, $J_{4,5}$ = 14.14 Hz, 1 H, 4-H), 3.45 (s, 3 H, OCH_3), 1.32 (t, $^3J_{H,H}$ = 7.09 Hz, 3 H, $SO_3CH_2CH_3$) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 154.2 (C-2), 136.8, 136.4 (2 C, 2 C_q arom.), 129.1, 128.4, 128.2, 126.1 (10 C, arom.), 106.9 (C-3), 101.8 (*C*H benzylidene), 97.4 (C-1), 74.2 (C-4), 72.7 (CH_2 benzyl), 69.1 (C-6), 66.7 ($SO_3CH_2CH_3$), 63.7 (C-5), 56.2 (OCH_3), 46.9 (CH_2SO_3Et), 15.0 ($SO_3CH_2CH_3$) ppm. $C_{24}H_{28}O_8S$ (476.54): calcd. C 60.49, H 5.92, S 6.73; found C 59.99, H 5.81, S 6.69.

Methyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-deoxy-2-*C*-(ethylsulfonatomethyl)-α-D-glucopyranoside (9) and Methyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-deoxy-2-*C*-(ethylsulfonatomethyl)-α-D-mannopyranoside (10)

Method A: Sodium borohydride was added to a solution of **7a** and **7b** (100 mg) in methanol (10 mL) and CH_2Cl_2 (5 mL). After stirring for 3 h the mixture was concentrated. Methanol was added and the mixture was concentrated again. This step was repeated two more times. The residue was dissolved in CH_2Cl_2 and extracted with saturated aqueous ammonium chloride and water, dried and concentrated. The crude product was purified by column chromatography to yield **9** (66 mg, 66 %) and **10** (10 mg, 10 %) as a white crystalline solid.

Method B: Palladium on activated charcoal (30 mg, 10 m/m%) and Et_3N (30 µL) were added to a solution of **7a** and **7b** (300 mg) in methanol (10 mL) and CH_2Cl_2 (5 mL). When the reaction was completed, the mixture was diluted with CH_2Cl_2, filtered through Celite and concentrated. The crude product was purified by column chromatography to give **9** (144 mg, 49 %) and **10** (12 mg, 4 %).

9: White crystals, m.p. 113–120 °C. $[\alpha]_D$ = +79.46 (*c* = 0.41, $CHCl_3$); R_f = 0.48 (65:20:15 C_6H_{14}/ethyl acetate/toluene). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.52–7.24 (m, 10 H, arom.), 5.61 (s, 1 H, C*H* benzylidene), 5.06 (d, $J_{1,2}$ = 3.47 Hz, 1 H, 1-H), 4.97 (d, J_{gem} = 11.43 Hz, 1 H, CH_{2a} benzyl), 4.57 (d, J_{gem} = 11.44 Hz, 1 H, CH_{2b} benzyl), 4.28 (dd, J_{gem} = 9.51, $J_{5,6a}$ = 4.00 Hz, 1 H, 6-H_a), 4.21–4.11 (m, 2 H, $SO_3CH_2CH_3$), 3.88–3.71 (m, 3 H, 6-H_b, 5-H, 4-H), 3.64 (dd, *J* = 10.45, *J* = 8.79 Hz, 1 H, 3-H), 3.42 (dd, J_{gem} = 14.54, $J_{2,CH2a}$ = 1.93 Hz, 1 H, C$H_{2a}SO_3$Et), 3.37 (s, 3 H, OCH_3), 3.23 (dd, J_{gem} = 14.52, $J_{2,CH2b}$ = 10.82 Hz, 1 H, C$H_{2b}SO_3$Et), 2.48–2.37 (m, 1 H, 2-H), 1.31 (t, $^3J_{H,H}$ = 7.10 Hz, 3 H, $SO_3CH_2CH_3$) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 137.8, 137.3 (2 C, 2 C_q arom.), 128.9–125.9 (10 C, arom.), 101.3 (*C*H benzylidene), 98.5 (C-1), 83.9 (C-4), 74.6 (CH_2 benzyl), 74.5 (C-3), 68.9 (C-6), 66.5 ($SO_3CH_2CH_3$), 62.3 (C-5), 55.2 (OCH_3), 47.1 (CH_2,SO_3Et), 42.0 (C-2), 14.8 ($SO_3CH_2CH_3$) ppm. $C_{24}H_{30}O_8S$ (478.56): calcd. C 60.23, H 6.32, S 6.70; found C 61.01, H 6.56, S 6.61.

10: White syrup, $[\alpha]_D$ = +3.6 (*c* = 0.14, $CHCl_3$); R_f = 0.42 (65:20:15 C_6H_{14}/ethyl acetate/toluene). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.53–7.22 (m, 10 H, arom.), 5.57 (s, 1 H, C*H* benzylidene), 5.01 (s, 1 H, 1-H), 4.75 (d, J_{gem} = 11.80 Hz, 1 H, CH_{2a} benzyl), 4.69 (d, J_{gem} = 11.80 Hz, 1 H, CH_{2b} benzyl), 4.29–4.20 (m, 3 H, 6-H_a, $SO_3CH_2CH_3$), 4.16 (dd, $J_{3,4}$ = 10.1, $J_{2,3}$ = 5.7 Hz, 1 H, 3-H), 3.88–3.69 (m, 3 H, 5-H, 6-H_b, $CH_{2a}SO_3$Et), 3.53 (t, $J_{3,4}$ = 9.50, $J_{4,5}$ = 9.50 Hz, 1 H, 4-H), 3.37 (s, 4 H, OCH_3, C$H_{2a}SO_3$Et), 3.16 (dd, J_{gem} = 14.57, $J_{2,CH2b}$ = 10.58 Hz, 1 H, C$H_{2b}SO_3$Et), 2.93 (dd, $J_{2,CH2b}$ = 10.56, $J_{2,3}$ = 5.61 Hz, 1 H, 2-H), 1.35 (t, $^3J_{H,H}$ = 7.11 Hz, 3 H, $SO_3CH_2CH_3$) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 137.8, 137.3 (2 C, 2 C_q arom.), 129.0–126.0 (10 C, arom.), 101.6 (*C*H benzylidene), 100.4 (C-1), 79.7 (C-4), 73.0 (C-3), 72.6 (CH_2 benzyl), 68.9 (C-6), 66.7 ($SO_3CH_2CH_3$), 62.9 (C-5), 55.2 (OCH_3), 45.8 (CH_2SO_3Et), 40.0 (C-2), 14.9 ($SO_3CH_2CH_3$) ppm. $C_{24}H_{30}O_8S$ (478.56): calcd. C 60.23, H 6.32, S 6.70; found C 59.73, H 6.21, S 6.54.

Phenyl 6-*O*-*tert*-Butyldiphenylsilyl-3,4-*O*-(2′,3′-dimethoxybutane-2′3′-diyl)-1-thio-β-D-*arabino*-hexopyranoside-2-ulose (11): Dess–Martin periodinane (687 mg, 1.62 mmol) was added to a solution of **2**[37] (675 mg, 1.08 mmol) in dry CH_2Cl_2. After stirring for 1 h at room temperature, the mixture was diluted with diethyl ether and NaOH (432 mg, 10.8 mmol) in H_2O (8.3 mL) was added and the mixture stirred vigorously for 10 min. The organic layer was separated and washed with water three times, dried and concentrated. The crude product was used in the next step without purification. R_f = 0.40 (7:3 C_6H_{14}/ethyl acetate). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.79–7.14 (m, 15 H, arom.), 5.40 (s, 1 H, 1-H), 4.62 (d, $J_{3,4}$ = 10.5 Hz, 1 H, 3-H), 4.19 (t, $J_{3,4}$ = 10.0, $J_{4,5}$ = 10.0 Hz, 1 H, 4-H), 4.03–3.91 (m, 3 H, 5-H, 6-H_a, 6-H_b), 3.25 (s, 3 H, OCH_3 butanedione), 3.17 (s, 3 H, OCH_3 butanedione), 1.39 (s, 3 H, CH_3 butanedione), 1.28 (s, 3 H, CH_3 butanedione), 1.06 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 194.0 (C-2), 135.8–127.5 (18 C, arom.), 100.7, 99.6 (2 C, 2 C_q butanedione), 89.2 (C-1), 78.9, 75.2, 68.3 (3 C, C-3, C-4, C-5), 62.1 (C-6), 48.5, 48.2 (2 C, 2 OCH_3 butanedione), 26.8 (3 C, 3 CH_3, *t*Bu), 19.3

(C_q, *t*Bu), 17.6, 17.5 (2 C, 2 CH_3 butanedione) ppm. $C_{34}H_{42}O_7SSi$ (622.24): calcd. C 65.57, H 6.80, S 5.15; found C 63.11, H 6.51, S 4.98.

Phenyl 6-*O*-*tert*-Butyldiphenylsilyl-2-deoxy-2-*C*-(*E*)-(ethylsulfonatomethylene)-3,4-*O*-(2′,3′-dimethoxybutane-2′3′-diyl)-1-thio-β-D-*arabino*-hexopyranoside (12a) and Phenyl 6-*O*-*tert*-Butyldiphenylsilyl-2-deoxy-2-*C*-(*Z*)-(ethylsulfonatomethylene)-3,4-*O*-(2′,3′-dimethoxybutane-2′3′-diyl)-1-thio-β-D-*arabino*-hexopyranoside (12b): Ethyl diethylphosphorylmethanesulfonate (141 mg, 0.540 mmol) was dissolved in abs. THF and the stirred mixture was cooled to –78 °C under argon before 2.5 M *n*-butyllithium (234 μL, 0.585 mmol) was added dropwise. After 30 min at this temperature **11** (281 mg, 0.452 mmol) dissolved in abs. THF was added dropwise and the mixture was warmed to 0 °C ■■ ((<= Author: temp. added, correct?)) ■■ . When complete conversion of the starting material was observed (by TLC), a saturated ammonium chloride solution was added. The mixture was diluted with dichloromethane and the organic layer was washed with water three times, dried, filtered and concentrated. The crude product was purified by silica gel chromatography to give **12a** (202 mg, 61 %) and **12b** (26 mg, 9 %) ■■ ((<=Author: total yield of 73% given in caption to Scheme 4)) ■■ .

12a: Yellow syrup, $[\alpha]_D$ = +24.21 (*c* = 0.04, $CHCl_3$); R_f = 0.67 (7:3 C_6H_{14}/ethyl acetate). ^{1}H NMR (400 MHz, acetone): δ = 7.80–7.28 (m, 15 H, arom.), 6.83 (dd, $J_{3,CH}$ = 2.4, $J_{1,CH}$ = 1.3 Hz, 1 H, C*H*SO_3Et), 5.82 (d, $J_{1,CH}$ = 1.0 Hz, 1 H, 1-H), 4.81 (dd, $J_{3,4}$ = 9.7, $J_{3,CH}$ = 2.4 Hz, 1 H, 3-H), 4.19 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, $SO_3CH_2CH_3$), 4.02–3.96 (m, 3 H, 4-H, 6-H_a, 6-H_b), 3.92 (dt, *J* = 9.9, 3.1 Hz, 1 H, 5-H), 3.31 (s, 3 H, OCH_3 butanedione), 3.21 (s, 3 H, OCH_3 butanedione), 1.37 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, $SO_3CH_2CH_3$), 1.33 (s, 3 H, CH_3 butanedione), 1.25 (s, 3 H, CH_3 butanedione), 1.07 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (101 MHz, acetone): δ = 149.0 (C-2), 136.8, 136.5, 135.8, 134.5, 134.0, 131.7, 130.8, 130.3, 128.8, 128.7, 128.5 (18 C, arom.), 125.8 (CHSO_3Et), 101.4, 100.5 (2 C, 2 C_q butanedione), 86.3 (C-1), 79.7 (C-5), 71.8 (C-3), 68.1 (C-4), 67.4 ($SO_3CH_2CH_3$), 63.5 (C-6), 49.0, 48.6 (2 C, 2 OCH_3 butanedione), 27.5 (3 C, 3 CH_3, *t*Bu), 20.0 (C_q, *t*Bu), 18.1, 17.6 (2 C, 2 CH_3 butanedione), 15.3 ($SO_3CH_2CH_3$) ppm. $C_{37}H_{48}O_9S_2Si$ (728.25): calcd. C 60.96, H 6.64, S 8.80; found C 62.11, H 6.82, S 8.85.

12b: Yellowish syrup, $[\alpha]_D$ = –51.22 (*c* = 0.04, $CHCl_3$); R_f = 0.65 (7:3, C_6H_{14}/ethyl acetate). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.72–7.21 (m, 15 H, arom.), 6.87 (d, $J_{1,CH}$ = 1.9 Hz, 1 H, C*H*SO_3Et), 6.43 (dd, $J_{1,3}$ = 2.6, $J_{1,CH}$ = 2.1 Hz, 1 H, 1-H), 4.52 (dd, $J_{3,4}$ = 10.5, $J_{1,3}$ = 2.6 Hz, 1 H, 3-H), 4.37–4.28 (m, 2 H), 4.21–4.08 (m, 2 H), 4.03–3.92 (m, 2 H, 4-H, 5-H, 6-H_a, 6-H_b, $SO_3CH_2CH_3$), 3.29 (s, 3 H, OCH_3 butanedione), 3.10 (s, 3 H, OCH_3 butanedione), 1.39 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, $SO_3CH_2CH_3$), 1.37 (s, 3 H, CH_3 butanedione), 1.27 (s, 3 H, CH_3 butanedione), 1.03 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 151.4 (C-2), 135.8, 135.7, 134.5, 133.6, 130.9, 129.7, 129.7, 129.4, 129.2, 127.8, 127.7 (18 C, arom.), 118.2 (CHSO_3Et), 100.3, 99.0 (2 C, 2 C_q butanedione), 81.5 (C-1), 79.2, 66.9, 65.4 (C-3, C-4, C-5), 67.5 ($SO_3CH_2CH_3$), 66.2 (C-6), 48.5, 48.3 (2 C, 2 OCH_3 butanedione), 26.9 (3 C, 3 CH_3, *t*Bu), 19.4 (C_q, *t*Bu), 17.8, 17.7 (2 C, 2 CH_3 butanedione), 15.2 ($SO_3CH_2CH_3$) ppm. $C_{37}H_{48}O_9S_2Si$ (728.25): calcd. C 60.96, H 6.64, S 8.80; found C 63.28, H 6.79, S 8.92.

Phenyl 6-*O*-*tert*-Butyldiphenylsilyl-2-deoxy-2-*C*-(ethylsulfonatomethyl)-3,4-*O*-(2′,3′-dimethoxybutane-2′3′-diyl)-1-thio-β-D-mannopyranoside (13) and Phenyl 6-*O*-*tert*-Butyldiphenylsilyl-2-deoxy-2-*C*-(ethylsulfonatomethyl)-3,4-*O*-(2′,3′-dimethoxybutane-2′3′-diyl)-1-thio-D-*arabino*-hex-1-enopyranoside (14): Sodium borohydride (15.5 mg, 0.410 mmol) was added to a solution of **12a** (113 mg, 0.164 mmol) in methanol (10 mL) and CH_2Cl_2 (5 mL). After stirring for 3 h the mixture was concentrated. Methanol was added and the mixture was concentrated again. This step was repeated two more times. The residue was dissolved in CH_2Cl_2 and extracted with saturated aqueous ammonium chloride and water, dried and concentrated. The crude product was purified by column chromatography (85:15 C_6H_{14}/ethyl acetate) to give the products **13** (46 mg, 38 %) and **14** (44 mg, 37 %).

13: White crystals, m.p. 152–159 °C. $[\alpha]_D$ = –9.11 (*c* = 0.21, $CHCl_3$); R_f = 0.63 (7:3 C_6H_{14}/ethyl acetate). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.77–7.12 (m, 15 H, arom.), 4.97 (s, 1 H, 1-H), 4.36 (dd, *J* = 6.9, 2.7 Hz, 1 H), 4.02–3.32 (m, 1 H, skeleton protons, CH_2SO_3Et), 3.27 (s, 3 H, OCH_3 butanedione), 3.20 (s, 3 H, OCH_3 butanedione), 2.94 (s, 1 H, 2-H), 1.43 (t, $^3J_{H,H}$ = 6.9 Hz, 3 H, $SO_3CH_2CH_3$), 1.29 (s, 3 H, CH_3 butanedione), 1.26 (s, 3 H, CH_3 butanedione), 1.06 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 136.0, 135.6, 131.0, 129.8, 129.0, 127.8, 127.3, 134.5 (15 C, arom.), 133.7, 133.0 (3 C, 3 C_q arom.), 100.5, 100.0 (2 C, 2 C_q butanedione), 85.9 (C-1), 79.3, 70.6, 63.1 (3 C, C-3, C-4, C-5), 67.2 ($SO_3CH_2CH_3$), 61.9 (C-6), 48.2 (2 C, 2 OCH_3 butanedione), 45.4 (CH_2SO_3Et), 40.3 (C-2), 27.0 (3 C, 3 CH_3, *t*Bu), 19.4 (C_q, *t*Bu), 17.8, 17.7 (2 C, 2 CH_3 butanedione), 15.1 ($SO_3CH_2CH_3$) ppm. $C_{37}H_{50}O_9S_2Si$ (730.27): calcd. C 60.79, H 6.89, S 8.77; found C 59.78, H 6.41, S 8.57;

14: Yellow syrup, $[\alpha]_D$ = +74.80 (*c* = 0.28, $CHCl_3$); R_f = 0.76 (7:3 C_6H_{14}/ethyl acetate). ^{1}H NMR (400 MHz, acetone): δ = 7.65–7.17 (m, 15 H, arom.), 4.75 (d, $J_{3,4}$ = 9.2 Hz, 1 H, 3-H), 4.42 (dd, J_{gem} = 14.2, *J* = 0.6 Hz, 1 H, C$H_{2a}SO_3$Et), 4.34 (dq, $^3J_{H,H}$ = 7.1, *J* = 1.5 Hz, 2 H, $SO_3CH_2CH_3$), 4.31–4.25 (m, 1 H, 5-H), 4.26 (d, J_{gem} = 14.2 Hz, 1 H, CH_{2b},SO_3Et), 4.09 (dd, $J_{4,5}$ = 10.5, $J_{3,4}$ = 9.2 Hz, 1 H, 4-H), 3.99 (dd, J_{gem} = 11.8, $J_{5,6a}$ = 3.2 Hz, 1 H, 6-H_a), 3.91 (dd, J_{gem} = 11.7, $J_{5,6b}$ = 2.1 Hz, 1 H, 6-H_b), 3.34 (s, 3 H, OCH_3 butanedione), 3.23 (s, 3 H, OCH_3 butanedione), 1.35 (s, 3 H, CH_3 butanedione), 1.33–1.26 (m, 3 H, $SO_3CH_2CH_3$), 1.30 (s, 3 H, CH_3 butanedione), 0.97 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (101 MHz, acetone): δ = 136.5, 136.2, 130.6, 130.5, 130.0, 128.6, 128.6, 127.9 (15 C, arom.), 134.1, 133.7, 133.4 (3 C, 3 C_q arom.), 107.5, 101.5, 101.1, 79.8 (C-5), 68.1 ($SO_3CH_2CH_3$), 67.1 (C-3), 65.4 (C-4), 62.1 (C-6), 49.2 (CH_2SO_3Et), 48.8, 48.6 (2 C, 2 OCH_3 butanedione), 27.4 (3 C, 3 CH_3, *t*Bu), 19.8 (C_q, *t*Bu), 18.3, 18.2 (2 C, 2 CH_3 butanedione), 15.5 ($SO_3CH_2CH_3$) ppm. $C_{37}H_{48}O_9S_2Si$ (728.25): calcd. C 60.96, H 6.64, S 8.80; found C 62.91, H 6.65, S 8.86.

1,5-Anhydro-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-*C*-(ethylsulfonatomethyl)-3,4-*O*-(2′,3′-dimethoxybutane-2′3′-diyl)-D-*arabino*-hex-1-enitol (15)

Method A: Pd^0/C (10 wt.-%, 16 mg) was added to a solution of **12a** (157 mg, 0.215 mmol) in CH_2Cl_2 (2 mL) and stirred under H_2 (10 bar). After 3 d the mixture was diluted with CH_2Cl_2, filtered through Celite and concentrated. The crude product was purified by column chromatography (85:15 C_6H_{14}/ethyl acetate) to give **15** (47 mg, 35 %).

Method B: Raney-Ni slurry (220 mg) was added to a solution of **12a** (321 mg, 0.440 mmol) in methanol (10 mL) and CH_2Cl_2 (2 mL) and stirred under H_2 overnight. When the reaction was completed, the mixture was filtered through Celite and concentrated. The crude product was purified by column chromatography (85:15 C_6H_{14}/ethyl acetate) to give **15** (212 mg, 78 %).

15: Colourless syrup. $[\alpha]_D$ = +37.10 (*c* = 0.06, $CHCl_3$); R_f = 0.24 (85:15 C_6H_{14}/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.33 (m, 10 H, arom.), 6.44 (d, $J_{1,3}$ = 1.8 Hz, 1 H, 1-H), 4.72–4.68 (m, 1 H, 3-H), 4.31 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, $SO_3CH_2CH_3$), 4.17–4.11 (m, 4 H, 4-H, 5-H, C$H_{2a}SO_3$Et), 4.02 (d, J_{gem} = 11.8 Hz, 1 H, 6-H_a), 3.94 (d, J_{gem} = 11.4 Hz, 1 H, 6-H_b), 3.56 (d, J_{gem} = 14.5 Hz, 1 H, C$H_{2b}SO_3$Et), 3.35 (s, 3 H, OCH_3 butanedione), 3.26 (s, 3 H, OCH_3 butanedione), 1.40 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, $SO_3CH_2CH_3$), 1.37 (s, 3 H, CH_3 butanedione), 1.34 (s, 3 H, CH_3 butanedione), 1.04 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.0 (C-1), 136.0, 135.6, 133.8, 133.1, 129.8, 129.8, 127.8,

127.7 (12 C, arom.), 100.6, 100.5, 100.0 (3 C, C-2, 2 C_q butanedione,), 77.8, 65.1, 64.9 (3 C, C-3, C-4, C-5), 66.8 ($SO_3CH_2CH_3$), 61.4 (C-6), 48.6, 48.5 (2 C, 2 OCH_3 butanedione), 47.9 (CH_2SO_3Et), 27.0 (3 C, 3 CH_3, *t*Bu), 19.5 (C_q, *t*Bu), 18.0, 17.9 (2 C, 2 CH_3 butanedione), 15.4 ($SO_3CH_2CH_3$) ppm. $C_{31}H_{44}O_9SSi$ (620.25): calcd. C 59.97, H 7.14, S 5.16; found C 56.73, H 6.97, S 5.08.

6-*O*-*tert*-Butyldiphenylsilyl-2-deoxy-2-(*E*)-(ethylsulfonatomethylene)-3,4-*O*-(2′,3′-dimethoxybutane-2′3′-diyl)-β-D-*arabino*-hexopyranose (16), 6-*O*-*tert*-Butyldiphenylsilyl-2-deoxy-2-(*E*)-(ethylsulfonatomethylene)-3,4-*O*-(2′,3′-dimethoxybutane-2′3′-diyl)-α-D-*arabino*-hexopyranose (17) and Compound 15: Et_3SiH (408 μL, 2.551 mmol) and Pd^0/C (10 wt.-%, 19 mg) was added to a solution of **12a** (186 mg, 0.255 mmol) in CH_2Cl_2 (10 mL) and stirred under H_2. After 1 h, when the starting material had completely disappeared, the mixture was filtered through a pad of Celite and concentrated. The crude product was purified by column chromatography (95:5 → 7:3 C_6H_{14}/ethyl acetate) to give **15** (38 mg, 24 %), **16** (17 mg, 10 %) and **17** (19 mg, 12 %).

16: Colourless syrup, $[\alpha]_D$ = +84.82 (*c* = 0.13, $CHCl_3$); R_f = 0.14 (8:2 C_6H_{14}/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.67 (m, 4 H, arom.), 7.48–7.36 (m, 6 H, arom.), 6.37 (d, $J_{3,CH}$ = 2.5 Hz, 1 H, $CHSO_3Et$), 5.33 (s, 1 H, 1-H), 4.95 (dd, $J_{3,4}$ = 9.9, $J_{3,CH}$ = 2.5 Hz, 1 H, 3-H), 4.31–4.26 (m, 2 H, $SO_3CH_2CH_3$), 4.17 (ddd, $J_{4,5}$ = 10.1, $J_{5,6a}$ = 3.9, $J_{5,6b}$ = 2.2 Hz, 1 H, 5-H), 3.99–3.85 (m, 3 H, 6-H_a, 6-H_b, 4-H), 3.37 (s, 3 H, OCH_3 butanedione), 3.19 (s, 3 H, OCH_3 butanedione), 1.43 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, $SO_3CH_2CH_3$), 1.38 (s, 3 H, CH_3 butanedione), 1.30 (s, 3 H, CH_3 butanedione), 1.06 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.6 (C-2), 136.1, 136.0, 135.8, 135.7, 129.8, 127.9, 127.7, 127.7 (12 C, arom.), 124.0 ($CHSO_3Et$), 95.7 (C-1), 71.6 (C-5), 68.2 (C-3), 68.0 (C-4), 66.5 ($SO_3CH_2CH_3$), 62.5 (C-6), 48.9, 48.3 (2 C, 2 OCH_3 butanedione), 27.0 (3 C, 3 CH_3, *t*Bu), 19.5 (C_q, *t*Bu), 17.7, 17.2 (2 C, 2 CH_3 butanedione), 15.0 ($SO_3CH_2CH_3$) ppm. MS (MALDI-TOF): *m*/*z* = 659.4 $[M + Na]^+$. $C_{31}H_{44}O_{10}SSi$ (636.24): calcd. C 58.47, H 6.96, S 5.03; found C 59.46, H 7.02, S 4.98.

17: Colourless syrup, $[\alpha]_D$ = +70.23 (*c* = 0.19, $CHCl_3$); R_f = 0.25 (8:2 C_6H_{14}/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.65 (m, 4 H, arom.), 7.44–7.33 (m, 6 H, arom.), 6.61 (s, 1 H, 1-H), 6.43 (d, $J_{3,CH}$ = 2.3 Hz, 1 H, $CHSO_3Et$), 4.82 (dd, $J_{3,4}$ = 10.0, $J_{3,CH}$ = 2.3 Hz, 1 H, 3-H), 4.26–4.17 (m, 2 H, $SO_3CH_2CH_3$), 4.14–4.09 (m, 1 H, 5-H), 3.98 (dd, J_{gem} = 11.5, $J_{5,6a}$ = 3.5 Hz, 1 H, 6-H_a), 3.89 (t, $J_{3,4}$ = 10.0, $J_{4,5}$ = 10.0 Hz, 1 H, 4-H), 3.85 (dd, J_{gem} = 11.5, $J_{5,6b}$ = 1.9 Hz, 1 H, 6-H_b), 3.26 (s, 3 H, OCH_3 butanedione), 3.23 (s, 3 H, OCH_3 butanedione), 1.39–1.35 (m, 6 H, $SO_3CH_2CH_3$, CH_3 butanedione), 1.32 (s, 3 H, CH_3 butanedione), 1.02 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.2 (C-2), 136.1, 135.7, 133.2, 129.8, 129.7 127.7, 127.7 (12 C, arom.), 117.4 ($CHSO_3Et$), 100.7, 99.9 (2 C, 2 C_q butanedione), 87.9 (C-1), 70.9 (C-5), 69.0 (C-4), 67.6 (C-3), 67.3 ($SO_3CH_2CH_3$), 61.9 (C-6), 48.5 (2 C, 2 OCH_3 butanedione), 27.0 (3 C, 3 CH_3, *t*Bu), 19.5 (C_q, *t*Bu), 17.8 (2 C, 2 CH_3 butanedione), 15.0 ($SO_3CH_2CH_3$) ppm. MS (MALDI-TOF): *m*/*z* = 659.3 $[M + Na]^+$. $C_{31}H_{44}O_{10}SSi$ (636.24): calcd. C 58.47, H 6.96, S 5.03; found C 58.31, H 7.13, S 5.12.

Phenyl 2-*O*-Benzyl-4,6-*O*-benzylidenethio-β-D-*ribo*-hexopyranoside-3-ulose (18): A solution of dry Me_2SO (6.10 mL, 0.086 mmol) in dry CH_2Cl_2 (70 mL) under argon was cooled to –70 °C ■■ ((<= Author: 78 in caption to Scheme 6)) ■■ and oxalyl chloride (3.75 mL, 10.5 mmol) was added dropwise. After 15 min, a solution of **3**[40] (9.0 g, 5.24 mmol) in dry CH_2Cl_2 (70 mL) was added slowly, keeping the temperature below –65 °C. After 30 min, *N*,*N*-diisopropylethylamine (DIPEA; 37.00 mL, 212 mmol) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and the solution was washed with 1 M aq. HCl (2 × 200 mL) and H_2O (200 mL). The organic layer was dried and concentrated. The crude product was purified by silica gel chromatography in 98:2 CH_2Cl_2/acetone to give **18** (7.80 g, 87 %) as white needles. $[\alpha]_D$ = –15.89 (*c* = 0.20, $CHCl_3$); R_f 0.48 (75:25 C_6H_{14}/ethyl acetate). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.58–7.27 (m, 15 H, arom.), 5.51 (s, 1 H, CH benzylidene), 4.92 (s, 1 H, CH_{2a} benzyl), 4.89 (s, 1 H, CH_{2b} benzyl), 4.57 (d, *J* = 11.0 Hz, 1 H, skeleton proton), 4.45 (dd, *J* = 10.5, 4.8 Hz, 1 H, 6-H_a), 4.21 (d, *J* = 9.9 Hz, 1 H, skeleton proton), 3.88 (d, *J* = 9.6 Hz, 1 H, skeleton proton), 3.85 (t, *J* = 10.2 Hz, 1 H, 6-H_b), 3.65 (dt, *J* = 9.8, 4.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 197.3 (C-3), 136.9, 136.4, 133.7, 131.5, 129.5, 129.2, 128.7, 128.6, 128.6, 128.4, 128.3, 126.5 (15 C, arom.), 101.8 (CH benzylidene), 89.7 (C-1), 82.1, 81.1 (2 C, skeleton carbons), 73.9 (CH_2 benzyl), 72.1 (skeleton carbon), 69.2 (C-6) ppm. $C_{26}H_{24}O_5S$ (448,13): calcd. C 69.62, H 5.39, S 7.15; found C 71.52, H 5.31, S 7.22.

Phenyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-deoxy-3-*C*-(*E*)-(ethylsulfonatomethylene)-1-thio-β-D-*ribo*-hexopyranoside (19a) and Phenyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-deoxy-3-*C*-(*Z*)-(ethylsulfonatomethylene)-1-thio-β-D-*ribo*-hexopyranoside (19b): Ethyl diethylphosphorylmethanesulfonate (857 mg, 3.293 mmol) was dissolved in abs. THF and the stirred mixture was cooled to –78 °C under argon before 2.5 M *n*-butyllithium (1.427 mL, 3.568 mmol) was added dropwise. After 30 min at this temperature **18** (1.231 g, 2.744 mmol) dissolved in abs. THF was added dropwise and the mixture was warmed up. When complete conversion of the starting material was observed (by TLC), a saturated ammonium chloride solution was added. The mixture was diluted with dichloromethane. The organic layer was washed with water three times, dried, filtered and concentrated. The crude product was purified by silica gel chromatography to give **19a** (346 mg, 24 %) and **19b** (647 mg, 44 %) ■■ ((<=Author: yields reversed in caption to Scheme 6)) ■■ .

19b: Colourless syrup, R_f = 0.61 (75:25 C_6H_{14}/ethyl acetate). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.63–7.12 (m, 15 H, arom.), 6.58 (s, 1 H, $CHSO_3Et$), 5.49 (s, 1 H, CH benzylidene), 4.67 (d, $J_{1,2}$ = 8.29 Hz, 1 H, 1-H), 4.59 (d, J_{gem} = 10.99 Hz, 1 H, CH_{2a} benzyl), 4.45 (d, J_{gem} = 10.98 Hz, 1 H, CH_{2b} benzyl), 4.26 (dd, *J* = 10.06, 4.50 Hz, 1 H, 6-H_a), 4.22–4.16 (m, 1 H, 4-H), 3.99–3.90 (m, 2 H, $SO_3CH_2CH_3$), 3.81–3.74 (m, 1 H, 2-H), 3.72–3.54 (m, 2 H, 6-H_b, 5-H), 1.08 (t, $^3J_{H,H}$ = 7.09 Hz, 3 H, $SO_3CH_2CH_3$) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 148.1 (C-3), 136.3, 136.2 (2 C, 2 C_q arom.), 132.3, 128.9, 128.4, 128.2, 128.0, 127.8, 126.4 (10 C, arom.), 122.0 ($CHSO_3Et$), 102.0 (CH benzylidene), 89.5 (C-1), 78.3 (C-2), 76.9 (C-4), 73.9 (CH_2 benzyl), 71.7 (C-5), 68.9 (C-6), 66.1 ($SO_3CH_2CH_3$), 14.6 ($SO_3CH_2CH_3$) ppm. $C_{29}H_{30}O_7S_2$ (554.14): calcd. C 62.80, H 5.45, S 11.56; found C 64.91, H 5.62, S 11.72.

19a: Colourless syrup, $[\alpha]_D$ = –62.88 (*c* = 0.26, $CHCl_3$); R_f = 0.50 (75:25 C_6H_{14}/ethyl acetate). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.52–7.22 (m, 15 H, arom.), 6.67 (dd, *J* = 2.05, 1.14 Hz, 1 H, $CHSO_3Et$), 5.61 (s, 1 H, CH benzylidene), 5.46 (d, $J_{1,2}$ = 3.11 Hz, 1 H, 1-H), 5.25–5.22 (m, 1 H, 2-H), 4.94–4.88 (m, 1 H, 4-H), 4.77 (d, J_{gem} = 10.63 Hz, 1 H, CH_{2a} benzyl), 4.71 (d, J_{gem} = 10.64 Hz, 1 H, CH_{2b} benzyl), 4.38 (dd, J_{gem} = 10.52, $J_{5,6a}$ = 4.96 Hz, 1 H, 6-H_a), 4.23–4.12 (m, 3 H, 5-H, $SO_3CH_2CH_3$), 3.73 (t, J_{gem} = 10.29, $J_{5,6b}$ = 10.29 Hz, 1 H, 6-H_b), 1.26 (t, *J* = 7.10 Hz, 3 H, $SO_3CH_2CH_3$) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 147.2 (C-3), 137.1, 136.6, 129.3, 129.2, 126.2 (10 C, arom.) 132.4 (2 C, 2 C_q arom.), 123.7 ($CHSO_3Et$), 101.7 (CH benzylidene), 83.5 (C-1), 75.1 (C-4), 74.0 (C-2), 72.8 (CH_2 benzyl), 69.9 (C-6), 67.2 ($SO_3CH_2CH_3$), 66.6 (C-5), 14.7 ($SO_3CH_2CH_3$) ppm. $C_{29}H_{30}O_7S_2$ (554.14): calcd. C 62.80, H 5.45, S 11.56; found C 63.41, H 5.39, S 11.68.

Phenyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-deoxy-3-*C*-(ethylsulfonatomethyl)-1-thio-β-D-glucopyranoside (20) and Phenyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-deoxy-3-*C*-(ethylsulfonatomethyl)-

1-thio-β-D-allopyranoside (21): Sodium borohydride (38 mg, 0.99 mmol) was added to a solution of **19a** (220 mg, 0.397 mmol) in methanol (10 mL) and CH_2Cl_2 (5 mL). After stirring for 3 h the mixture was concentrated. Methanol was added and the mixture was concentrated again. This step was repeated two more times. The residue was dissolved in CH_2Cl_2 and extracted with saturated aqueous ammonium chloride and water, dried and concentrated. The crude product was purified by column chromatography to yield **20** and **21** (153 mg, 69 %). R_f = 0.56 (7:3 C_6H_{14}/ethyl acetate).

21: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.24 (m, 15 H, arom.), 5.56 (s, 1 H, *C*H benzylidene), 4.91 (d, J_{gem} = 10.58 Hz, 1 H, CH_{2a} benzyl), 4.61 (d, $J_{1,2}$ = 9.88 Hz, 1 H, 1-H), 4.49 (d, J_{gem} = 10.58 Hz, 1 H, CH_{2b} benzyl), 4.35 (dd, J = 10.55, 4.99 Hz, 1 H, 6-H_a), 4.10–4.01 (m, 1 H, $SO_3CH_{2a}CH_3$), 3.99–3.89 (m, 1 H, $SO_3CH_{2b}CH_3$), 3.80–3.69 (m, 2 H, 4-H, 6-H_b), 3.62 (dd, $J_{1,2}$ = 9.86, $J_{2,3}$ = 5.13 Hz, 1 H, 2-H), 3.57–3.44 (m, 2 H, CH_2SO_3Et), 3.50–3.39 (m, 2 H, 5-H, 3-H), 0.97 (t, J = 7.05 Hz, 3 H, $SO_3CH_2CH_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.8, 132.8, 132.6, 129.2, 128.8, 128.3, 128.0, 126.2 (arom.), 101.7 (*C*H benzylidene), 85.8 (C-1), 76.8 (C-4),75.0 (C-2), 72.5 (CH_2 benzyl), 69.0 (C-6), 68.0 (C-5), 67.1 ($SO_3CH_2CH_3$), 44.0 (CH_2SO_3Et), 36.5 (C-3), 14.5 ($SO_3CH_2CH_3$) ppm. $C_{29}H_{32}O_7S_2$ (556.16): calcd. C 62.57, H 5.79, S 11.52; found C 63.82, H 5.59, S 11.67.

1,5-Anhydro-2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-3-*C*-(*E*)-(ethylsulfonatomethylene)-1-thio-β-D-*ribo*-hex-1-enitol (22): Raney-Ni (200 mg) in MeOH (10 mL) was added to a solution of **19** (133 mg, 0.240 mmol) in CH_2Cl_2 (2 mL). After stirring the suspension overnight under H_2, the Raney-Ni was removed by filtration and the residue was concentrated under reduced pressure. The crude product was purified by column chromatography to give **22** (34 mg, 32 %) as a colourless syrup. $[\alpha]_D$ = –44.86 (c = 0.14, $CHCl_3$); R_f 0.19 (8:2 C_6H_{14}/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.28 (m, 10 H, arom.), 6.73 (t, $J_{CH,2}$ = 1.7, $J_{CH,4}$ = 1.7 Hz, 1 H, *CH*SO_3Et), 5.59 (s, 1 H, *CH* benzylidene), 4.69 (d, J_{gem} = 11.9 Hz, 1 H, CH_{2a} benzyl), 4.61 (d, J_{gem} = 11.9 Hz, 1 H, CH_{2b} benzyl), 4.36 (dd, J_{gem} = 10.5, $J_{5,6a}$ = 4.9 Hz, 1 H, 6-H_a), 4.22 (dd, $J_{4,5}$ = 9.1, $J_{CH,4}$ = 1.8 Hz, 1 H, 4-H), 4.19–4.11 (m, 3 H, 1-H_a, $SO_3CH_2CH_3$), 4.04 (ddd, $J_{1b,2}$ = 9.7, $J_{1a,2}$ = 5.7, $J_{CH,2}$ = 1.6 Hz, 1 H, 2-H), 3.71 (t, J_{gem} = 10.3, $J_{5,6b}$ = 10.3 Hz, 1 H, 6-H_b), 3.56 (dt, $J_{5,6b}$ = 9.6, $J_{4,5}$ = 9.6, $J_{5,6a}$ = 4.8 Hz, 1 H, 5-H), 3.36 (t, J_{gem} = 10.2, $J_{1b,2}$ = 10.2 Hz, 1 H, 1-H_b), 1.27 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, $SO_3CH_2CH_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.1 (C-3), 136.9, 136.6 (2 C, 2 C_q arom.), 129.1, 128.9, 128.6, 128.2, 127.9, 126.8 (10 C, arom.), 120.2 (*CH*SO_3Et), 102.5 (*CH* benzylidene), 79.8 (C-4), 75.2 (C-2), 73.4 (C-5), 73.0 (CH_2 benzylidene), 71.6 (C-1), 69.4 (C-6), 66.2 ($SO_3CH_2CH_3$), 15.0 ($SO_3CH_2CH_3$) ppm. $C_{23}H_{26}O_7S$ (446.14): calcd. C 61.87, H 5.87, S 7.18; found C 60.73, H 5.96, S 7.20.

Supporting Information (see footnote on the first page of this article): Crystallographic data of compounds **9** and **19a**, ^{1}H and ^{13}C NMR spectra of all described compounds.

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[1] J. Kovensky, *Curr. Med. Chem.* **2009**, *16*, 2338–2344.
[2] A. Borbás, M. Csávás, L. Szilágyi, G. Májer, A. Lipták, *J. Carbohydr. Chem.* **2004**, *23*, 133–146.
[3] M. Herczeg, E. Mező, D. Eszenyi, L. Lázár, M. Csávás, I. Bereczki, S. Antus, A. Borbás, *Eur. J. Org. Chem.* **2013**, 5570–5573.
[4] L. Franchini, F. Compostella, D. Colombo, L. Panza, F. Ronchetti, *J. Org. Chem.* **2010**, *75*, 5363–5366.
[5] L. Lázár, M. Csávás, A. Borbás, Gy. Gyémánt, A. Lipták, *ARKIVOC (Gainesville, FL, U.S.)* **2004**, *7*, 196–207.
[6] M. Herczeg, L. Lázár, A. Borbás, A. Lipták, *Org. Lett.* **2009**, *11*, 2619–2622.
[7] B. Musicki, T. S. Widlanski, *J. Org. Chem.* **1990**, *55*, 4231–4233.
[8] B. Musicki, T. S. Widlanski, *Tetrahedron Lett.* **1991**, *32*, 1267–1270.
[9] P. A. Crooks, R. C. Reynolds, J. A. Maddry, A. Rathore, M. S. Akhtar, J. A. Montgomery, J. A. Secrist III, *J. Org. Chem.* **1992**, *57*, 2830–2835.
[10] A. Jeanjean, M. Gary-Bobo, P. Nirdé, S. Leiris, M. Garcia, A. Morère, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6240–6243.
[11] V. Barragan-Montero, A. Awwad, S. Combemale, P. Santa Barbara, B. Jover, J.-P. Molès, J.-L. Montero, *ChemMedChem* **2011**, *6*, 1771–1774.
[12] A. Borbás, G. Szabovik, Zs. Antal, P. Herczegh, A. Agócs, A. Lipták, *Tetrahedron Lett.* **1999**, *40*, 3639–3642.
[13] A. Borbás, G. Szabovik, Zs. Antal, K. Fehér, M. Csávás, L. Szilágyi, P. Herczegh, A. Lipták, *Tetrahedron: Asymmetry* **2000**, *11*, 549–566.
[14] Z. B. Szabó, A. Borbás, I. Bajza, A. Lipták, S. Antus, *Tetrahedron Lett.* **2008**, *49*, 1196–1198.
[15] Zs. Jakab, A. Fekete, A. Borbás, A. Lipták, S. Antus, *Tetrahedron* **2010**, *66*, 2404–2414.
[16] L. Lázár, M. Herczeg, A. Fekete, A. Borbás, A. Lipták, S. Antus, *Tetrahedron Lett.* **2010**, *51*, 6711–6714.
[17] M. Herczeg, L. Lázár, A. Mándi, A. Borbás, I. Komáromi, A. Lipták, S. Antus, *Carbohydr. Res.* **2011**, *346*, 1827–1836.
[18] L. Lázár, E. Mező, M. Herczeg, A. Lipták, S. Antus, A. Borbás, *Tetrahedron* **2012**, *68*, 7386–7399.
[19] M. Herczeg, L. Lázár, Zs. Bereczky, K. E. Kövér, I. Timári, J. Kappelmayer, A. Lipták, S. Antus, A. Borbás, *Chem. Eur. J.* **2012**, *18*, 10643–10652.
[20] M. Herczeg, E. Mező, L. Lázár, A. Fekete, K. Kövér, S. Antus, A. Borbás, *Tetrahedron* **2013**, *69*, 3149–3158.
[21] M. Herczeg, E. Mező, D. Eszenyi, S. Antus, A. Borbás, *Tetrahedron* **2014**, *70*, 2919–2927.
[22] M. Herczeg, E. Mező, S. Antus, A. Borbás, *Carbohydr. Res.* **2014**, *388*, 19–29.
[23] J. A. Bisceglia, L. R. Orelli, *Curr. Org. Chem.* **2012**, *16*, 2206–2230.
[24] A. Borbás, P. Herczegh, *Carbohydr. Res.* **2011**, *346*, 1628–1632.
[25] J. C. Carretero, M. Demillequand, L. Ghosez, *Tetrahedron* **1987**, *43*, 5125–5134.
[26] J. C. Carretero, J. Davies, J. Marchand-Brynaert, L. Ghosez, *Bull. Soc. Chim. Fr.* **1990**, *127*, 835–842.
[27] A. El Nemr, T. Tsuchiya, *Carbohydr. Res.* **2001**, *330*, 205–214.
[28] M. A. Nashed, *Carbohydr. Res.* **1978**, *60*, 200–205.
[29] a) A. C. Richardson, *Carbohydr. Res.* **1969**, *10*, 395–402; b) M. Miljkovic, M. Gligorijevic, D. Glisin, *J. Org. Chem.* **1974**, *39*, 3223–3226.
[30] P. Kovác, H. J. C. Yeh, G. L. Jung, C. P. J. Glaudemans, *J. Carbohydr. Chem.* **1986**, *5*, 497–512.
[31] a) J. Wu, D. Li, H. Wu, L. Sun, W.-M. Dai, *Tetrahedron* **2006**, *62*, 4643–4650; b) J. Wu, H. Wu, S. Weia, W.-M. Dai, *Tetrahedron Lett.* **2004**, *45*, 4401–4404.
[32] Zs. Jakab, A. Mándi, A. Borbás, A. Bényei, I. Komáromi, L. Lázár, S. Antus, A. Lipták, *Carbohydr. Res.* **2009**, *344*, 2444–2453.
[33] D. Cremer, J. A. Pople, *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358; S. Fushinobu, *Cremer–Pople Parameter Calculator*, http://www.ric.hi-ho.ne.jp/asfushi/.
[34] D. Crich, A. U. Vinod, J. Picione, D. J. Wink, *ARKIVOC (Gainesville, FL, U.S.)* **2005**, *6*, 339–344.
[35] R. Kudchadkar, R. Gonzalez, K. D. Lewis, *Expert Opin. Invest. Drugs* **2008**, *17*, 1769–1776.

[36] M. Basche, D. L. Gustafson, S. N. Holden, C. L. O'Bryant, L. Gore, S. Witta, M. K. Schultz, M. Morrow, A. Levin, B. L. Creese, M. Kangas, K. Roberts, T. Nguyen, K. Davis, R. S. Addison, J. C. Moore, S. G. Eckhardt, *Clin. Cancer Res.* **2006**, *12*, 5471–5480.
[37] a) E. C. Lourenço, M. R. Ventura, *Eur. J. Org. Chem.* **2011**, 6698–6703; b) M. Herczeg, F. Demeter, E. Mező, M. Pap, A. Borbás, *Eur. J. Org. Chem.* **2015**, 5730–5741.
[38] a) G. Hewitt, J. R. Fletcher, L. H. Koehler, C. S. Hudson, *J. Am. Chem. Soc.* **1949**, *71*, 3679–3681; b) H. M. Zuurmond, P. A. M. van der Klein, G. A. van der Marel, J. H. van Boom, *Tetrahedron* **1993**, *49*, 6501–6514.
[39] P. K. Mandal, J. S. McMurray, *J. Org. Chem.* **2007**, *72*, 6599–6601.
[40] V. Rusu, E. Sisu, I. Sisu, C. Neanu, A. Lascu, C. Csunderlik, A. Zamfir, J. P. Katalinic, *Rev. Chim.* **2002**, *53*, 848–850.
[41] D. A. Case, T. A. Darden, T. E. Cheatham III, C. L. Simmerling, J. Wang, R. E. Duke, R. Luo, M. Crowley, R. C. Walker, W. Zhang, K. M. Merz, B. Wang, S. Hayik, A. Roitberg, G. Seabra, I. Kolossváry, K. F. Wong, F. Paesani, J. Vanicek, X. Wu, S. R. Brozell, T. Steinbrecher, H. Gohlke, L. Yang, C. Tan, J. Mongan, V. Hornak, G. Cui, D. H. Mathews, M. G. Seetin, C. Sagui, V. Babin, P. A. Kollman, *AMBER 10*, University of California, San Francisco, USA, **2008**.
[42] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09*, revision B.01, Gaussian, Inc., Wallingford, CT, **2010**.
[43] W. Humphrey, A. Dalke, K. Schulten, *J. Mol. Graph.* **1996**, *14*, 33–38.

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Carbohydrate Sulfonic Acids

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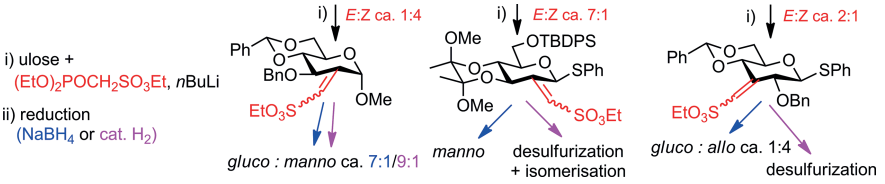
Synthesis of *C*-2- and *C*-3-Sulfonatomethyl *O*- and *S*-Glycosides by Horner–Wadsworth–Emmons Olefination



The Horner–Wadsworth–Emmons olefination has been applied to the synthesis of thioglycosides bearing a secondary sulfonatomethyl moiety as potential building blocks for the synthesis of biorelevant sulfated oligosaccharides. The configurations and conformations of the products were investigated by NMR spectroscopy, X-ray diffraction, and molecular dynamics.

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