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Synthesis of ketopyranosyl glycosides and determination of their anomeric configuration on the basis of the three-bond carbon–proton couplings

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Abstract—Anomeric pairs of ketopyranosyl glycosides with various substituents at C_α, C_β and C_γ were synthesized from the corresponding thioglycosides, and the influence of the C_α–C_β–C_γ–H_γ torsion angle and substituent effects on the three-bond carbon–proton couplings was studied. The cis coupling constants range from 1 to 2 Hz. The trans couplings are generally as small as 2.3–2.6 Hz; however, for compounds bearing an unsubstituted γ-carbon, a relatively large trans coupling was measured (4.8 Hz). An *S*-ethyl group at the β-position increases the cis coupling (up to 3.2 Hz) compared to the corresponding O-glycosides.

Keywords: Glycosylation; Ketopyranosyl glycosides; Anomeric pairs; Anomeric configuration; Karplus relationship; Three-bond carbon–proton coupling constant

1. Introduction

Determination of the anomeric configuration of saccharides by NMR methods typically relies on measurements of $^3J_{H,H}$ or $^1J_{C,H}$ couplings for the anomeric protons. These data are, obviously, unavailable for sugars bearing a quaternary anomeric carbon. Related substances are ketoses or ulosonic acids such as *N*-acetyl neuraminic acid and KDO. An alternative approach utilizes of the Karplus-type dependence[1,2] of three-bond carbon–proton couplings ($^3J_{C,H}$) on the torsion angle between C_α and H_γ in a C_α–C_β–C_γ–H_γ fragment, where C_γ is the adjacent carbon to the quaternary anomeric C_β. In practice, this method is expected to provide sufficient results only if H_γ is in an *axial* position.

A Karplus equation derived from a study of rigid hydrocarbons[3] predicts $^3J_{C,H}$ values ranging from 2.0 (60°) to 9.4 Hz (180°). In carbohydrates most experimental and theoretical studies apply to C–X–C–H arrays of bonded atoms (X = O, S, N) typically found in interglycosidic linkages.[4] C–C–C–H arrays were investigated, mostly in studies of CH_2OH conformations at position 6 of aldohexopyranosyl rings.[5–7] It is known, however, that substituent effects may have a quite dramatic influence on these couplings. Theoretical calculations[8–10] and experimental studies[10–12] indicated that positive and negative contributions from the oxygen substituents can be as high as 5.0 Hz. Substituent electronegativities evidently play a role and, very often, contributions from nonbonded interactions can be dominant.[13] The latter influence bond angles and bond orders and that is why the effect of a particular substituent is very much dependent also on the site of attachment along the coupling path (α, β or γ).[11,13,14] In

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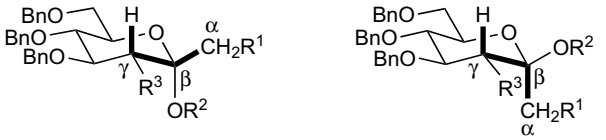
addition, the orientation of the electronegative substituent with respect to the coupled proton has a significant influence on the $^3J_{C,H}$ values. Theoretical calculations, in agreement with experimental data, have shown that, for example, $^3J_{C6,H4}$ is ~2.5 Hz smaller in aldohexopyranoses when the endocyclic oxygen (O5) is *anti*, rather than *gauche* to H4 (2.5–3.5 vs 0.5–1.5 Hz, respectively).[10]

The data published on the C_α–C_β–C_γ–H_γ torsion angle dependence of vicinal carbon–proton couplings in ketopyranosyl anomeric pairs[15–24] can be divided in two groups. In the case of KDO or sialic derivatives, these couplings show significant differences for the α- and β-anomers. Small couplings were recorded for the β-anomers ($^3J_{C1,H3ax} \sim 1$ Hz, *synclinal* arrangement), whereas remarkably larger ones for the α-anomers ($^3J_{C1,H3ax} \sim 6$ Hz, *antiperiplanar* arrangement).[15–20]

Consequently, the anomeric configuration of KDO or sialic acid derivatives could be unambiguously determined on the basis of the values of $^3J_{C1,H3ax}$. Similarly, for ketosyl-azides, -amides, -bromides[21] or C-ketosides,[25] distinct $^3J_{C\alpha,H\gamma ax}$ couplings could be observed depending on the orientation of C_α. At the same time, the sporadic data published for the anomeric pairs of ketopyranosyl-O-glycosides, other than KDO or sialic acids, do not show significant differences for the α- and β-anomers, the vicinal carbon–proton couplings are small with only ~1 Hz differences reported for the *syn* and *anti* orientations of C_α and H_γ.[22–24]

In connection with our previous studies on the sulfonic acid mimics of sialyl Lewis X saccharides,[26–28] we prepared hept-2-uloside sulfonic acid mimics (having structure **A**, $R^1 = SO_3Et$, R^2 = mono- or disaccharides, R^3 = OBn, Fig. 1), which were identified as α-glycosides on the basis of the small values of the three-bond couplings between C_α and H_γ. The stereochemistry of the anomeric centre of other ketosides[29–32] prepared only in one of the anomeric forms was also characterized by the small $^3J_{C\alpha,H\gamma ax}$ couplings. The literature data[22–24] reported small coupling constants for both of the anomers thus suggesting that structural assignments based on a single coupling constant may be dubious or unreliable. Therefore, we decided to synthesize anomeric pairs of ketopyranosyl glycosides of the type **A** and **B** (Fig. 1) with various substituents at C_α, C_β and C_γ, to test the applicability of the $^3J_{C,H}$ values for the determination of anomeric configuration.



A **B**

R^1: H, COOEt, SO_3Et, $SO_3^-Na^+$
R^2: Me, (glucosyl unit)
R^3: OBn, (H)

Figure 1. General structure of the investigated ketopyranosyl glycoside anomeric pairs.

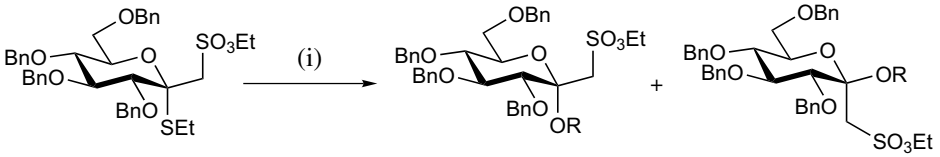
2. Results and discussion

To study the influence of the β-substituent on the C_α–H_γ couplings in the case of 1-deoxy-1-ethoxysulfonylheptulosides, several anomeric pairs of glycosides were synthesized from thioglycoside **1**.[26] First, methyl and benzyl glycosides **2a**,**b** and **3a**,**b** were prepared under conditions that afforded ~1:1 mixtures of the α- and β-anomers (Scheme 1).

For the synthesis of the ketosyl disaccharides (Scheme 2) methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **4**[33] and *p*-methoxyphenyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside **5** were used as acceptors. (Compound **5** was prepared by the hydrogenolysis of the appropriate benzylidene acetal[34] using a $LiAlH_4$–$AlCl_3$ reagent mixture). Glycosylation of **4** with thioglycoside donor **1** in the presence of the NIS–TfOH promoter furnished a mixture of disaccharides **6a** and **6b** in a 3:1 ratio, and an elimination product (**7**) from the donor was also isolated in a 17% yield. Similarly, glycosylation of **5** with donor **1** resulted in a mixture of anomeric pairs **8a** and **8b**, together with the elimination product **7**.

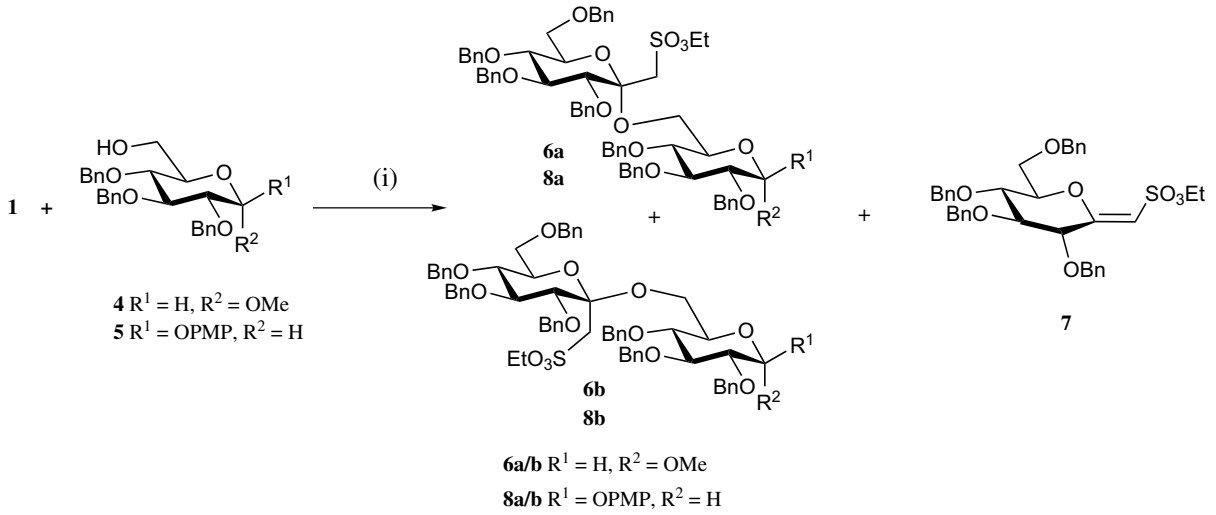
To study the effect of charged groups linked to the α-carbon, sulfonic esters **2a** and **2b** were converted into sodium sulfonates **9a** and **9b**, respectively, by means of nucleophilic substitution with NaI (Scheme 3).

α-Thioglycoside **12** was prepared from **10**[35] in two steps involving nucleophilic addition of the ethyl meth-

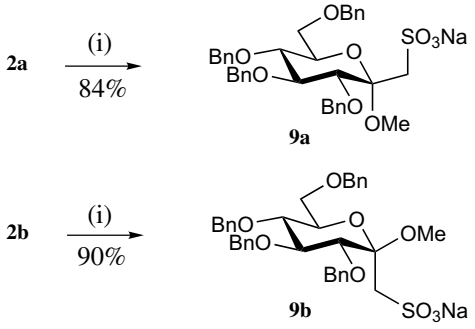


1 **2a** R = Me **2b**
3a R = Bn **3b**

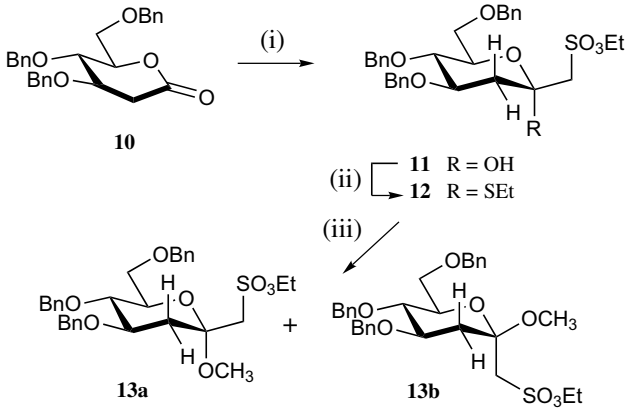
Scheme 1. Reagents and conditions: (i) for **2a/b**: dry MeOH (15 equiv), NIS (1.2 equiv), TfOH (0.4 equiv), CH_2Cl_2, 3 Å MS, −50 °C, 40 min, 35% of **2a**, 47% of **2b**; (i) for **3a/b**: BnOH (15 equiv), NIS (1.2 equiv), TfOH (0.4 equiv), CH_2Cl_2, 4 Å MS, −50 °C, 20 min, then −50 to − 20 °C, 30 min, 64% of **3a**, 21% of **3b**.



Scheme 2. Reagents and conditions: (i) for **6a/b**: 2 equiv of **4**, NIS (1.2 equiv), TfOH (0.8 equiv), CH_2Cl_2, 4 Å MS, −60 °C, 25 min, 37% of **6a**, 13% of **6b**, 17% of **7**; (i) for **8a/b**: 2 equiv of **5**, NIS (1.2 equiv), TfOH (0.8 equiv), CH_2Cl_2, 4 Å MS, −50 °C, 25 min, 30% of **8a**, 9% of **8b**, 32% of **7**.



Scheme 3. Reagents and conditions: (i) NaI (1.1 equiv), acetone, 3 h, reflux.



Scheme 4. Reagents and conditions: (i) $(i\text{-Pr})_2NH$ (1.5 equiv), *n*-BuLi (1.5 equiv), CH_3SO_3Et (1.5 equiv), −60 °C to rt, 3 h, 55%; (ii) EtSH (1.5 equiv), $BF_3{\cdot}Et_2O$ (2.5 equiv), CH_2Cl_2, −20 °C, 1.5 h, 74%, (iii) dry MeOH (15 equiv), NIS (1.6 equiv), TfOH (0.3 equiv), CH_2Cl_2, 3 Å MS, −50 °C, 20 min, 57% of **13a**, 20% of **13b**.

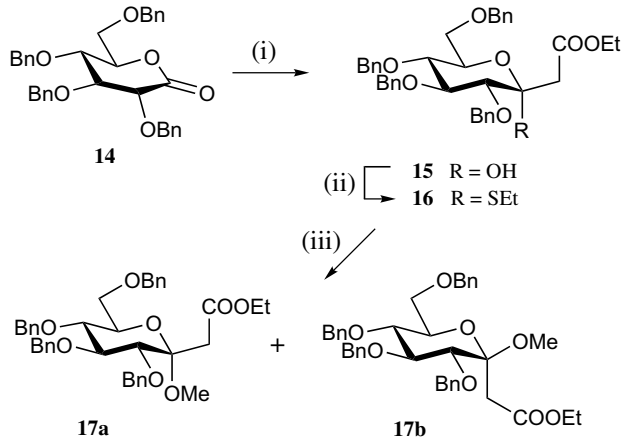
anesulfonate anion into the lactone carbonyl of **10** followed by $BF_3{\cdot}Et_2O$-promoted reaction of **11** with ethanethiol (Scheme 4). Compound **12** was subsequently converted into an anomeric mixture of methyl glycosides **13a** and **13b**, which were suitable for studying the influence of the lack of a substituent at γ-position on the three-bond couplings.

In addition to the 1-deoxy-1-sulfonatoheptuloside derivatives, compounds carrying other substituents at the α-carbon were also synthesized. Nucleophilic addition of the carbanion generated from ethyl acetate to aldonolactone **14** gave ethyl 2-deoxy-3-octulosonate **15**[36,37] as the α-anomer (Scheme 5). The reaction of the latter with ethanethiol in the presence of $BF_3{\cdot}Et_2O$ resulted in α-thioglycoside **16**, from which methyl glycoside (**17a/b**) was prepared in form of an anomeric mixture in the usual manner. These methyl glycosides were synthesized recently in a different way by Sharma et al.[24] by means of radical reactions on the corresponding 1-deoxyenolester.

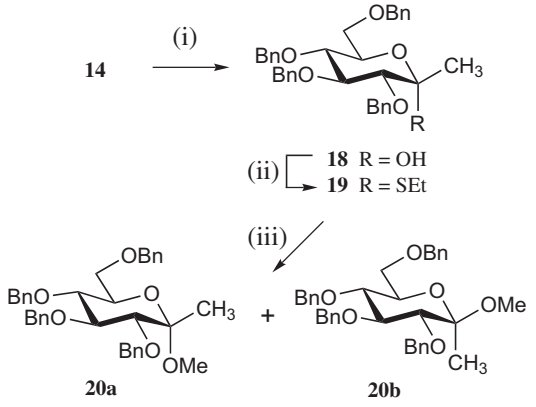
The synthesis of derivatives having an unsubstituted α-carbon started from **14**, which was converted into **18**[38] using Grignard reaction at −10 °C (Scheme 6). Ikegami and co-workers reported the exclusive formation of methyl α-glycoside **20a**[31] directly from **18**, using TMSOTf catalyst. In our hands, this reaction worked also with stereoselectivity as high as 95%, therefore the β-anomer could not be isolated this way. Fortunately, the usual reaction sequence via thioglycoside **19** led to the formation of both methyl glycosides **20a** and **20b**, albeit in low yields.

The structures of the synthesized compounds were determined by NMR. For **1**, **2a**, **3a** and **12**, the anomeric configuration was confirmed by X-ray diffraction measurements. Representative examples of the ^{1}H-coupled ^{13}C NMR spectra are shown in Figure 2.

The three-bond coupling constants between C_α and H_γ for glycosides **2a**,**b**, **3a**,**b**, **6a**,**b**, **8a**,**b**, **9a**,**b**, **13a**,**b**, **17a**,**b**,[24] and **20a**,**b** are collected in Table 1.



Scheme 5. Reagents and conditions: (i) $(i\text{-Pr})_2NH$ (1.5 equiv), *n*-BuLi (1.5 equiv), EtOAc (1.5 equiv), THF, −60 °C to rt, 1 h, 66%; (ii) EtSH (1.5 equiv), $BF_3{\cdot}Et_2O$ (2.5 equiv), CH_2Cl_2, 0 °C, overnight, 63%; (iii) dry MeOH (15 equiv), NIS (1.2 equiv), TfOH (0.4 equiv), CH_2Cl_2, 3 Å MS, −50 °C, 25 min, 22% of **17a**, 31% of **17b**.



Scheme 6. Reagents and conditions: (i) CH_3MgI (1.3 equiv), dry Et_2O, −10 °C, 15 min, 84%; (ii) EtSH (1.5 equiv), $BF_3{\cdot}Et_2O$ (2.5 equiv), CH_2Cl_2, 0 °C, 4.5 h, 30%; (iii) dry MeOH (15 equiv), NIS (1.2 equiv), TfOH (0.4 equiv), CH_2Cl_2, 3 Å MS, −50 °C, 20 min, 25% of **20a**, 18% of **20b**.

Comparing the values for the anomeric pairs we find that, in agreement with our previous data,[26–28] these couplings tend to be small: ≈1 Hz and ≈2.5 Hz, respectively, for the *syn* and *anti* relationship between the coupled nuclei (C_α and H_γ). This trend is quite consistent for derivatives carrying an electron withdrawing substituent (such as SO_3Et: **2a/2b**, **3a/3b**, **6a/6b**; SO_3^-: **9a/9b**; COOEt: **17a/17b**) attached to the α-carbon and oxygen substituents at both of the β- and γ-carbon. However, the coupling constant for compound **8a** is surprisingly high (∼2 Hz). At the same time, the size of the group attached to the β-carbon does not seem to play a role because very similar couplings are observed in monosaccharides (**2a**,**b**, **3a**,**b**), and in the respective disaccharides (**6a/b**) or trisaccharides[26–28] (i.e., when the substituent of the β-carbon is a diglycosyl unit), as well.

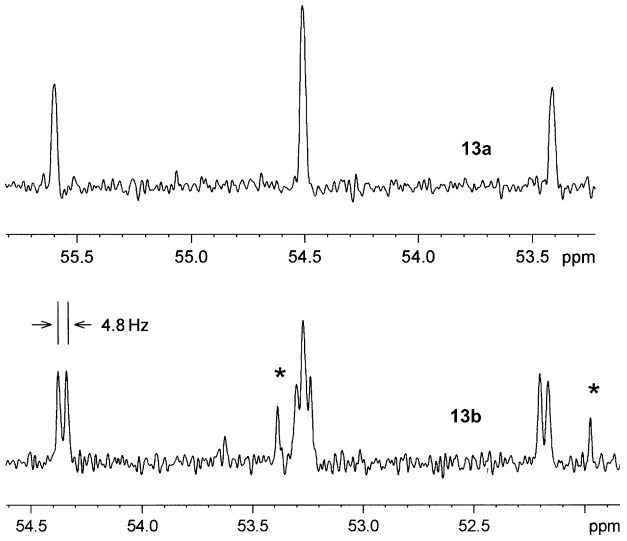


Figure 2. ^1H-coupled ^{13}C NMR spectra of compounds **13a** and **13b**, showing the triplet of the α-carbon. Additional splitting arises from coupling to the γ-proton. Asterisks identify peaks from a minor impurity.

Table 1. Three-bond carbon–proton couplings, and chemical shifts of the anomeric carbons for the anomeric pairs of O-glycosides

Compound	$^3J_{C\alpha,H\gamma}$ (Hz)	δ C_β (ppm)
2a[a]	∼1 cis	99.00
2b	2.4 trans	101.00
3a[a]	⩽1 cis	95.73
3b	2.3 trans	100.22
6a	⩽1 cis	99.10
6b	2.5 trans	100.80
8a	∼2 cis	99.09
8b	n.a.	100.48
9a	⩽1 cis	100.79
9b	2.4 trans	101.30
13a	⩽1 cis	97.78
13b	4.8 trans	98.12
17a	∼1 cis	101.10
17b	2.6 trans	101.50
20a	1.8 cis	100.20
20b	2.6 trans	102.00

[a] Structures have been verified by X-ray measurements.

For compounds bearing unsubstituted α- (**20a**[31] and **20b**) or γ-carbons (**13a**,**b**) and oxygen at the β position, the cis-coupling is similarly small [e.g., <1 Hz for **13a**, and slightly larger (1.8 Hz) for **20a**]. The magnitude of the trans-coupling is, however, different, depending on the position of the substituent. We measured a relatively large coupling (4.8 Hz) with an electronegative group (SO_3Et) at the α position (**13b**) and a significantly smaller one (2.6 Hz) in a γ-substituted (with OBn) trans-derivative (**20b**). This is a manifestation of the influence of the position of the substituent along the coupling path.[2,10,11,14] Furthermore, this example shows that the substituent effect is also dependent on the relative spatial disposition of the coupled nuclei (α substitution exerting

a significant effect on the trans coupling and a negligible one on the cis coupling); this may be due to nonbonded/steric interactions between the substituents.[1] The effect of the relative disposition of the oxygen at the β-carbon was shown to be significant even when the torsion angle between the coupled nuclei is the same.[10]

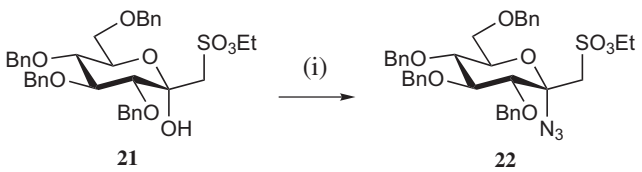
Inspection of the chemical shifts of the anomeric carbons (C_β) for the anomeric O-glycoside pairs (Table 1) indicates weak correlation between these shifts and the anomeric configuration; the shifts for β-glycosides are usually smaller than for their α-counterparts. The difference is, however, on the order of 1 ppm or less (except for **3a** vs **3b**); therefore, this correlation has very limited diagnostic value.

Because of our interest in the 1-sulfonylheptulose derivatives, the three-bond coupling constants between C_α and H_γ for thioglycosides **1** and **12**, for the anomeric OH-derivatives **11** and **21**[26] and also for glycosyl azide **22** (prepared from **21** using trimethylsilyl azide in the presence of a Lewis acid, Scheme 7) were measured.

These compounds could be synthesized only as α-anomers, the stereochemistry of the anomeric centre for **1** and **12** was also determined by X-ray measurements (an ORTEP view of compound **12** is shown in Fig. 3). The three-bond coupling constants between C_α and H_γ for compounds **1**, **11**, **12**, **21** and **22** are collected in Table 2.

It is seen that an *S*-ethyl group at the β position increases the cis coupling in the α-substituted derivatives irrespective of whether the γ-carbon bears an electronegative group or not (**1** and **12**, respectively). Because the effects of OH- or azido groups are only moderate, the cis coupling constants range from 1.7 to 2.2 Hz in **11**, **21** and **22**, compared to the usual ~1 Hz values of the *O*-alkyl derivatives. The effect of the same group on the trans coupling could not be tested because of the lack of compounds with an opposite (i.e., β-) anomeric configuration.

On the basis of these results, it should be concluded that application of three-bond carbon–proton couplings for assigning the anomeric configurations of sugars with quaternary anomeric carbon centres requires caution. When both anomers of a particular derivative are available it is likely that of the two measured $^3J_{C,H}$'s the larger one indicates trans arrangement of the coupled nuclei. Structural assignments based on a single coupling constant or from data measured on derivatives



21 22

Scheme 7. Reagents and conditions: (i) Me_3SiN_3 (1.2 equiv), $BF_3{\cdot}Et_2O$ (2 equiv), CH_2Cl_2, rt, 3 h, 78%.

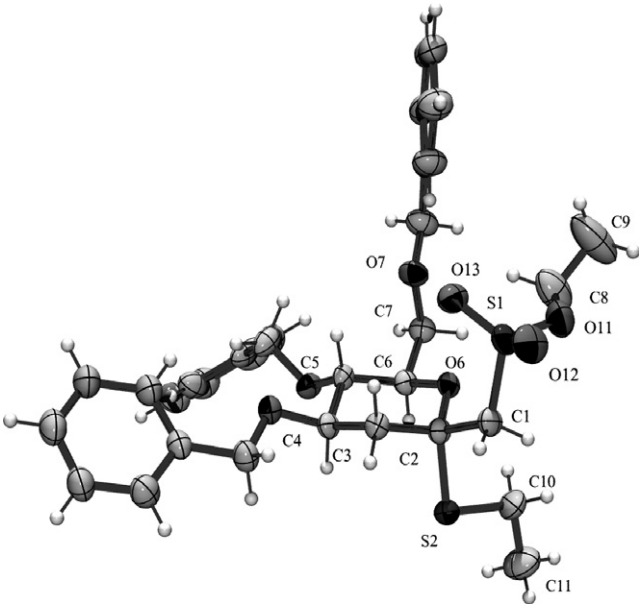


Figure 3. ORTEP view of compound **12.**

Table 2. Three-bond carbon–proton couplings, and chemical shifts of the anomeric carbons of the α-glycosides

Compound	$^3J_{C\alpha,H\gamma}$ (Hz)	δ C_β (ppm)
1[a]	2.7	89.70
11	2.2	94.86
12[a]	3.2	84.48
21	2.1	95.73
22	1.7	92.92

[a] Structures have been verified by X-ray measurements.

with different substituents and/or different substitution patterns along the coupling path are, however, unreliable and, therefore, discouraged. In such cases it is recommended to seek independent structural evidence such as NOEs, chemical shifts or X-ray determination.

3. Experimental

Optical rotations were measured at room temperature with a Perkin–Elmer 241 automatic polarimeter. Melting points were determined on a Cole-Palmer hot-stage apparatus and are uncorrected. TLC was performed on Kieselgel 60 F_{254} (Merck) with detection by charring with 50% aqueous sulfuric acid. Column chromatography was performed on Silica Gel 60 (E. Merck, 0.063–0.200 mm). The organic solutions were dried over $MgSO_4$ and concentrated in vacuo. The ^1H (200, 360 and 500 MHz) and ^{13}C NMR (50, 90 and 125 MHz) spectra were recorded with Bruker AC-200, AM-360 and DRX-500 Avance spectrometers in $CDCl_3$ solutions and in CD_3OD (for **9a/b**). Chemical shifts are referenced to Me_4Si (0.00 ppm for ^1H) or to the residual solvent

signals (77.00 ppm or 49.05 ppm for ^{13}C). The $^{13}C/^{1}H$ long-range coupling constants were measured from ^{1}H-coupled ^{13}C NMR spectra at 125 MHz.

X-ray diffraction data were collected at 293 (1) K, Enraf Nonius MACH3 diffractometer, Mo Kα radiation $\lambda = 0.71073$ Å. The structure was solved using the SIR-92 software[39] and refined on F^2 using SHELX-97 program,[40] publication material was prepared with the WINGX-97 suite.[41] Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 621975–621978. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk). MALDI-TOF MS analyses of the compounds were carried out in the positive reflectron mode using a BIFLEX III mass spectrometer (Bruker, Germany) equipped with delayed-ion extraction. The 2,4,6-trihidroxy-acetophenone (THAP) matrix solution was saturated THAP solution in MeCN.

3.1. General method A for the formation of methyl glycosides (2a/b, 13a/b, 17a/b, 20a/b)

To a solution of thioglycoside donor (1 mmol) in CH_2Cl_2 (10 mL/g) were added successively 3 Å molecular sieves (1–1.5 g/g) and dry MeOH (610 μL, 15 equiv), and the mixture was stirred at rt for 3 h. The mixture was then cooled to −50 °C and a solution of 1.2 equiv of NIS and 0.4 equiv of TfOH in dry THF was added. The mixture was kept at −50 °C until the TLC showed complete conversion of the donor (20–30 min). The reaction was quenched by addition of 139 μL (2 equiv) of Et_3N. Insoluble materials were removed by filtration, the filtrate was diluted with CH_2Cl_2, extracted three times with water, dried and evaporated. The residue was then purified by column chromatography.

3.2. General method B for the cleavage of sulfonic esters by sodium-iodide (9a, 9b)

To a solution of protected ethoxysulfonyl-derivative (1 mmol) in acetone (20 mL/g), 1.2 equiv (1.2 mmol) of NaI was added, and the solution was heated at reflux for 2 days. The mixture was evaporated, the crude yellow residue was purified by column chromatography using CH_2Cl_2–methanol (85:15).

3.3. General method C for the formation of thioglycosides (12, 16, 19)

To a solution of compound **11**, **15** or **18** in dry CH_2Cl_2 (10 mL/g) ethanethiol (1.5 equiv) was added, and the mixture was cooled before $BF_3{\cdot}Et_2O$ (2.5 equiv) was added. When TLC showed complete conversion of the starting material, the solution was diluted with dichloromethane, extracted with water until neutral and the organic layer was dried and evaporated. The crude residue was purified by column chromatography.

3.4. Methyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-gluco-hept-2-ulopyranoside (2a) and methyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-β-D-gluco-hept-2-ulopyranoside (2b)

Donor **1**[26] (1.00 g, 1.41 mmol) was converted by method **A** to give a mixture of **2a** and **2b**. The anomers were separated by column chromatography using CH_2Cl_2–acetone (98:2). Compound **2a** was isolated as white crystals (330 mg, 35%): mp 88 °C (ethyl-acetate–*n*-hexane); $[\alpha]_D$ +35.3 (*c* 0.3, $CHCl_3$); $R_f = 0.57$ (*n*-hexane–EtOAc, 6:4); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.27 (m, 20H, Ph), 5.03 (d, 1H, $J = 11.0$ Hz, CH_2Ph), 4.94 (s, 2H, CH_2Ph), 4.88 (d, 1H, $J = 10.5$ Hz, CH_2Ph), 4.84 (d, 1H, $J = 11.0$ Hz, CH_2Ph), 4.65 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.63 (d, 1H, $J = 10.5$ Hz, CH_2Ph), 4.56 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.32–4.00 (m, 4H), 3.85–3.66 (m, 4H), 3.58 (s, 2H), 3.29 (s, 3H, OCH_3), 1.26 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR (50 MHz, CD_3OD): δ 138.5, 138.2, 138.1, 138.0 (4C-quat. Ph), 128.4–127.5 (20C, Ph), 99.1 (C-2), 83.2, 79.8, 78.1 (C-3, C-4, C-5), 75.6, 75.5, 75.2, 73.4 (4CH_2Ph), 73.1 (C-6), 68.7, 67.6 ($SO_3CH_2CH_3$, C-7), 50.5 (C-1), 48.0 (OCH_3), 15.2 ($SO_3CH_2CH_3$). Anal. Calcd for $C_{38}H_{44}O_9S$: C, 67.43; H, 6.55. Found: C, 67.52; H, 6.46. Compound **2b** was isolated as a syrup (445 mg, 47%): $[\alpha]_D$ +40.6 (*c* 0.3, $CHCl_3$); $R_f = 0.74$ (*n*-hexane–EtOAc, 6:4); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.21 (m, 20H, Ph), 4.89 (d, 1H, $J = 11.2$ Hz, CH_2Ph), 4.89–4.62 (m, 6H, CH_2Ph), 4.53 (d, 1H, $J = 12$ Hz, CH_2Ph), 4.31 (q, 2H, $J = 7.0$ Hz, $SO_3CH_2CH_3$), 4.12–4.02 (m, 2H), 3.91–3.69 (m, 5H), 3.63 (d, 1H, $J = 15.0$ Hz, H-1b), 3.46 (s, 3H, OCH_3), 1.40 (t, 3H, $J = 7.0$ Hz, $SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, CD_3OD): δ 138.3, 138.2 (2×), 137.6 (4C-quat. Ph), 128.4–127.5 (20C, Ph), 100.2 (C-2), 83.0, 78.6, 77.0 (C-3, C-4, C-5) 74.2, 74.0 (2CH_2Ph), 73.8 (C-6), 73.3 (CH_2Ph), 68.6, 66.8 ($SO_3CH_2CH_3$, C-7), 51.2 (C-1), 48.8 (OCH_3), 15.1 ($SO_3CH_2CH_3$). Anal. Calcd for $C_{38}H_{44}O_9S$: C, 67.43; H, 6.55. Found: C, 67.49; H, 6.49.

3.5. Benzyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-gluco-hept-2-ulopyranoside (3a) and benzyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-β-D-gluco-hept-2-ulopyranoside (3b)

To a solution of **1** (750 mg 1.06 mmol) in dry CH_2Cl_2 (10 mL) BnOH (1.65 mL, 15.9 mmol, 15 equiv) was added, then the reaction was carried out and worked up according to method **A** to give a mixture of **3a** and

3b. The anomers were separated by column chromatography using *n*-hexane–EtOAc (7:3). Compound **3a** was isolated as white crystals (510 mg, 66%): mp 108–110 °C (ethyl acetate–*n*-hexane); $[\alpha]_D$ +54.2 (*c* 0.2, $CHCl_3$); $R_f = 0.35$ (*n*-hexane–EtOAc, 7:3); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.15 (m, 25H, Ph), 5.06 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.9 (s, 3H, CH_2Ph), 4.85 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.67–4.51 (m, 5H, CH_2Ph), 4.30 (d, 1H, $J = 9.5$ Hz), 4.26–4.11 (m, 3H), 3.82–3.67 (m, 4H), 3.63 (d, 1H, $J = 15.5$ Hz, H-2a), 3.55 (d, 1H, $J = 15.5$ Hz, H-2b), 1.22 (t, 3H, $J = 7.0$ Hz, $SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, CD_3OD): δ 138.5, 138.3, 138.0, 137.4 (4C-quat. Ph), 128.6–26.8 (25C, Ph), 99.6 (C-2), 83.0, 80.0, 78.2 (C-3, C-4, C-5), 75.4, 75.1 (2×), 73.3 (4CH_2Ph), 73.3 (C-6), 68.7, 67.5 (C-7, $SO_3CH_2CH_3$), 62.4 (CH_2Ph-aglycon), 51.7 (C-1), 15.1 ($SO_3CH_2CH_3$). Anal. Calcd for $C_{44}H_{48}O_9S$: C, 70.19; H, 6.43. Found: C, 70.11; H, 6.51. Compound **3b** was isolated as a syrup (166 mg, 22%): $[\alpha]_D$ +22.7 (*c* 0.2, $CHCl_3$); $R_f = 0.39$ (*n*-hexane–EtOAc, 7:3); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48–7.13 (m, 25H, Ph) 4.84–4.75 (m, 5H, CH_2Ph), 4.72 (s, 1H, CH_2Ph), 4.69 (d, 1H, $J = 10.8$ Hz, CH_2Ph), 4.61 (d, 1H, $J = 10.8$ Hz, CH_2Ph), 4.60 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.50 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.27–3.49 (m, 10H), 1.19 (t, 3H, $J = 7.0$ Hz, $SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, CD_3OD): δ 138.3, 138.2, 138.1, 137.8, 137.6 (5 C-quat. Ph), 128.4–127.2 (25C, Ph), 100.2 (C-2), 83.2, 79.2, 76.8 (C-3, C-4, C-5), 74.6 (CH_2Ph), 73.8 (C-6), 73.7, 73.5, 73.4, 72.1 (4CH_2Ph), 68.6, 66.8 ($SO_3CH_2CH_3$, C-7), 63.2 (CH_2Ph-aglycon), 51.4 (C-1), 14.9 ($SO_3CH_2CH_3$). Anal. Calcd for $C_{44}H_{48}O_9S$: C, 70.19; H, 6.43. Found: C, 70.27; H, 6.35.

3.6. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-gluco-hept-2-ulopyranosyl)-α-D-glucopyranoside (6a) and methyl 2,3,4-tri-*O*-benzyl-6-*O*-(3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-β-D-gluco-hept-2-ulopyranosyl)-α-D-glucopyranoside (6b) and 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-ethoxysulfonyl-α-D-gluco-hept-1-enitol (7)

To a solution of **1** (375 mg, 0.50 mmol, 1 equiv) and **4**[33] (465 mg, 1.00 mmol, 2 equiv) in dry CH_2Cl_2 (15 mL) were added 4 Å molecular sieves (1.0–1.5 g) and the mixture was stirred overnight. Then it was cooled to −50 °C and a solution of 1.2 equiv of NIS and 0.4 equiv of TfOH in dry THF was added. The mixture was kept at −50 °C until the TLC showed the complete conversion of the donor compound (**1h**). The reaction was quenched by addition of 70 μL (2 equiv) of Et_3N. Insoluble materials were removed by filtration, the filtrate was diluted with CH_2Cl_2, extracted three times with water, dried and evaporated. The residue was then purified by chromatography. First, the mixture of **6a** and **6b** were separated from **7** using CH_2Cl_2–acetone (98:2), then **6a** and **6b** were separated using *n*-hexane–EtOAc (8:2). Compound **6a**[27] (272 mg, 49%): $[\alpha]_D$ +58.7 (*c* 0.5, $CHCl_3$), lit.[27] +55.4 (*c* 3.6, $CHCl_3$); $R_f = 0.48$ (CH_2Cl_2–acetone, 98:2) and 0.24 (*n*-hexane–EtOAc 8:2). Anal. Calcd for $C_{65}H_{72}O_{14}S$: C, 70.38; H, 6.54. Found: C, 70.46; H, 6.46. Compound **6b** (94 mg, 17%): $[\alpha]_D$ +20.9 (*c* 0.7, $CHCl_3$); $R_f = 0.48$ (CH_2Cl_2–acetone, 98:2) and 0.30 (*n*-hexane–EtOAc, 8:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.14 (m, 35H, Ph), 4.97 (d, 1H, $J = 11.0$ Hz, CH_2Ph), 4.96 (d, 1H, $J = 10.9$ Hz, CH_2Ph), 4.92–4.85 (m, 4H, CH_2Ph), 4.78 (d, 1H, $J = 11.0$ Hz, CH_2Ph), 4.77 (d, 1H, $J = 10.2$ Hz, CH_2Ph), 4.74 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.72 (d, 1H, $J = 10.8$ Hz, CH_2Ph), 4.59 (d, 1H, $J = 12.2$ Hz, CH_2Ph), 4.55 (d, 1H, $J = 10.7$ Hz, CH_2Ph), 4.53 (d, 1H, $J = 12.1$ Hz, CH_2Ph), 4.49 (d, 1H, $J = 3.5$ Hz), 4.36 (d, 1H, $J = 12.15$ Hz, CH_2Ph), 4.23 (q, 2H, $J = 7.1$ Hz, $SO_3CH_2CH_3$), 4.16–4.09 (m, 1H), 4.01–3.95 (m, 3H), 3.89–3.82 (m, 5H), 3.76–3.73 (m, 2H), 3.65 (t, 1H, $J = 8.0$ Hz), 3.57 (d, 1H, $J = 15.3$ Hz, H-1b′), 3.49 (dd, 1H, $J = 3.5$, 9.6 Hz), 3.31 (s, 3H, OCH_3), 1.32 (t, 3H, $J = 7.1$ Hz, $SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, CD_3OD): δ 139.0, 138.9, 138.3, 138.2, 138.2, 138.0, 138.0 (7C-quat. Ph), 128.4–127.3 (35C, Ph), 100.8 (C-2′), 98.0 (C-1), 83.4, 82.1, 79.9, 78.7, 77.2, 77.1 (C-2, C-3, C-4, C-3′, C-4′, C-5′), 75.6, 74.8, 74.7, 74.7 (4CH_2Ph), 74.0 (C-5 or C-6′), 73.7, 73.3 (2×) (3CH_2Ph), 69.8 (C-5 or C-6′), 68.8 ($SO_3CH_2CH_3$), 66.4, 59.9 (C-6, C-7′), 55.0 (OCH_3), 51.3 (C-1′), 15.1 ($SO_3CH_2CH_3$). Anal. Calcd for $C_{65}H_{72}O_{14}S$: C, 70.38; H, 6.54. Found: C, 70.49; H, 6.43. Compound **7**[27] was isolated as a syrup (55 mg, 17%): $[\alpha]_D$ +67.7 (*c* 0.6, $CHCl_3$), lit.[27] +64.1 (*c* 0.23, $CHCl_3$); $R_f = 0.58$ (CH_2Cl_2–acetone, 98:2).

3.7. *p*-Methoxyphenyl 2,3,4-tri-*O*-benzyl-6-*O*-(3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-gluco-hept-2-ulopyranosyl)-β-D-glucopyranoside (8a) and *p*-methoxyphenyl 2,3,4-tri-*O*-benzyl-6-*O*-(3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-β-D-gluco-hept-2-ulopyranosyl)-β-D-glucopyranoside (8b) and 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-ethoxysulfonyl-α-D-gluco-hept-1-enitol (7)

To a solution of **1** (424 mg, 0.60 mmol, 1 equiv) and **5** (500 mg, 0.90 mmol, 1.5 equiv) in dry CH_2Cl_2 (15 mL) were added 4 Å molecular sieves (1.0–1.5 g) and the mixture was stirred overnight. Then it was cooled to −50 °C and a solution of 1.2 equiv of NIS and 0.4 equiv of TfOH in dry THF was added. The mixture was kept at −50 °C until the TLC showed the complete conversion of the donor compound (40 min). The reaction was quenched by addition of Et_3N (83 μL, 1.20 mmol, 2.00 equiv). Insoluble materials were removed by filtration, the filtrate was diluted with CH_2Cl_2, extracted three times with water, dried and evaporated. The residue was then purified by chromatography using CH_2Cl_2–acetone (98:2) to

afford the pure **7** and a mixture of **8a** and **8b** which were separated using *n*-hexane–EtOAc (7:3). Compound **8a** (214 mg, 30%): $[\alpha]_D$ +27.6 (*c* 0.1, $CHCl_3$); $R_f = 0.53$ (CH_2Cl_2–acetone, 98:2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.40–7.19 (m, 35H, Ph), 7.01, 6.68 (2m, each 2H, PMP-arom.), 5.07–4.49 (m, 14H, CH_2Ph), 4.26–3.05 (m, 17H), 3.52 (s, 3H, OCH_3), 1.14 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR (125 MHz, CD_3OD): δ 155.5, 151.3 (C-quat. PMP), 138.6, 138.4 (3×), 138.2, 138.1, 137.9 (7C-quat. Ph), 128.5–127.2 (35C, Ph.), 119.1, 114.7 (4C-arom. PMP), 103.4 (C-1), 99.1 (C-2′), 84.4, 82.9, 82.0, 80.0, 78.1, 77.8 (C-2, C-3, C-4, C-3′, C-4′, C-5′), 75.6, 75.3, 75.0 (3×), 74.9 (6 CH_2Ph), 73.5 (C-5 or C-6′), 73.0 (CH_2Ph), 72.9 (C-5 or C-6′), 68.6 ($SO_3CH_2CH_3$), 67.4, 60.2 (C-6, C-7′), 55.3 (OCH_3), 51.5 (C-1′), 15.0 ($SO_3CH_2CH_3$); MALDIMS: *m*/*z* calcd for $C_{71}H_{76}NaO_{15}S^+$ $[M+Na]^+$: 1223.48; found, 1223.48. Compound **8b** (64 mg, 9%): $[\alpha]_D$ +8.6 (*c* 0.2, $CHCl_3$); $R_f = 0.45$ (CH_2Cl_2–acetone, 98:2); ^{13}C NMR (125 MHz, CD_3OD): δ 155.0, 151.3 (2C-quat. PMP), 138.9, 138.8, 138.3, 138.3 (3×), 137.9 (7C-quat. Ph), 117.4, 114.6 (4C-arom. PMP), 101.9 (C-1), 100.5 (C-2′), 84.6, 83.2, 81.8, 78.9, 77.3, 76.6 (C-2, C-3, C-4, C-3′, C-4′, C-5′), 75.6, 74.9, 74.8 (3CH_2Ph), 74.3, 74.0 (C-5, C-6′), 73.8, 73.3, 73.1 (3CH_2Ph), 69.5 ($SO_3CH_2CH_3$), 66.6, 59.6 (C-6, C-7′), 55.6 (OCH_3), 51.5 (C-1′), 15.0 ($SO_3CH_2CH_3$); MALDI-MS: *m*/*z* calcd for $C_{71}H_{76}NaO_{15}S^+$ $[M+Na]^+$: 1223.48. Found: 1223.48. Compound **7** was isolated in a 32% yield (123 mg).

3.8. Methyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-sodium-sulfonato-α-D-gluco-hept-2-ulopyranoside (9a)

Compound **2a** (160 mg, 0.24 mol) was converted by method **B** to give compound **9a** (136 mg, 84%): R_f 0.26 (CH_2Cl_2–MeOH 92:8); ^1H NMR (200 MHz, CD_3OD): δ 7.42–7.41 (m, 20H, Ph), 5.02 (d, 1H, *J* 10.7 Hz, CH_2Ph), 4.88 (d, 1H, *J* 10.8 Hz, CH_2Ph), 4.87 (s, 2H, CH_2Ph), 4.84 (s, 2H, CH_2Ph), 4.75 (d, 1H, *J* 11.0 Hz, CH_2Ph), 4.73 (d, 1H, *J* 12.2 Hz, CH_2Ph), 4.62 (d, 1H, *J* 12.3 Hz, CH_2Ph), 4.54 (s, 1H, CH_2Ph), 4.49 (s, 1H, CH_2Ph), 3.93–4.02 (m, 1H), 3.76–3.56 (m, 3H), 3.50 (d, 1H, *J* 14.4 Hz, H-1a), 3.39 (d, 1H, *J* 14.4 Hz, H-1b), 3.27 (s, 3H, OCH_3); ^{13}C NMR (50 MHz, CD_3OD): δ 140.3, 140.2, 139.8, 139.7 (4C-quat. Ph), 129.4–128.5 (20C, Ph), 101.2 (C-2), 85.0, 81.0, 79.8 (C-3, C-4, C-5), 76.4, 76.3, 75.9, 74.6 (4CH_2Ph), 74.2 (C-6), 70.0 (C-7), 52.3 (C-1), 48.1 (OCH_3); ESIMS: *m*/*z* calcd for $C_{36}H_{39}O_9S^-$ $[M]^-$: 647.23; found, 647.21.

3.9. Methyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-sodium-sulfonato-β-D-gluco-hept-2-ulopyranoside (9b)

Compound **2b** (552 mg, 0.81 mmol) was converted by method **B** to give compound **9b** (523 mg, 96%): $[\alpha]_D$ +46.1 (*c* 0.2, $CHCl_3$); $R_f = 0.22$ (CH_2Cl_2–MeOH, 92:8); ^1H NMR (200 MHz, $CDCl_3$): δ 7.27–7.04 (m, 20H, Ph), 4.76–4.33 (m, 8H, CH_2Ph), 4.52–4.33 (m, 8H), 3.39 (s, 3H, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.3, 138.2, 138.1, 138.1 (4C-quat. Ph), 128.4–127.5 (20C, Ph), 100.8 (C-2), 83.0, 78.1, 77.4 (C-3, C-4, C-5), 74.4, 73.5, 73.1 (3CH_2Ph), 73.0 (C-6), 72.7 (CH_2Ph), 68.7 (C-7), 50.8 (C-1), 49.0 (OCH_3). Anal. Calcd for $C_{36}H_{39}NaO_9S$: C, 64.46; H, 5.86. Found: C, 64.39; H, 5.93.

3.10. 4,5,7-Tri-*O*-benzyl-1,3-dideoxy-1-ethoxysulfonyl-α-D-arabino-hept-2-ulopyranose (11)

A solution of $(i\text{-Pr})_2NH$ (2.16 mL, 1.50 mmol, 1.5 equiv) in dry THF (10 mL) was treated with 2.5 M *n*-BuLi in *n*-hexane (6.17 mL, 1.50 mmol, 1.5 equiv) at −15 °C under argon atmosphere. After 15 min the solution was cooled to −60 °C and CH_3SO_3Et (1.64 mL, 1.5 mmol, 1.5 equiv) was added. The mixture was kept at −60 °C for 15 min, and then aldonolactone derivative **10**[35] (4.45 g, 10.03 mmol) was added. The mixture was kept at −60 °C for 1 h, then it was allowed to warm up to rt, and concentrated. The residue was diluted with CH_2Cl_2 and was extracted with water until neutral, then dried and evaporated. The residue was purified by column chromatography using CH_2Cl_2–acetone (97:3) to afford **11** (3.14 g, 88%): $[\alpha]_D$ +27.9 (*c* 0.2, $CHCl_3$); $R_f = 0.46$ (CH_2Cl_2–acetone, 97:3); ^1H NMR (200 MHz, $CDCl_3$): δ 7.34–7.18 (m, 15H, Ph), 4.89 (d, 1H, $J = 10.9$ Hz, CH_2Ph), 4.67 (d, 1H, $J = 11.9$ Hz, CH_2Ph), 4.62 (s, 1H, CH_2Ph), 4.56 (d, 1H, $J = 11.1$ Hz, CH_2Ph), 4.55 (s, 1H, CH_2Ph), 4.49 (d, 1H, $J = 12.1$ Hz, CH_2Ph), 4.29 (q, 2H, $J = 7.1$ Hz, $SO_3CH_2CH_3$), 4.17–4.01 (m, 2H), 3.82–3.51 (m, 5H), 2.6–2.31 (m, 4H, SCH_2CH_3, H-2a, H-2b), 1.29 (t, 3H, $J = 7.1$ Hz, SCH_2CH_3), 1.20 (t, 3H, $J = 7.5$ Hz, $SO_3CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4(2×), 138.1 (3C-quat. Ph), 128.4–127.6 (15C, Ph), 94.9 (C-2), 77.8, 77.3 (2 skeleton C), 74.9, 73.4 (2CH_2Ph), 72.3 (skeleton C), 72.0 (CH_2Ph), 69.0 (C-6), 67.9 ($SO_3CH_2CH_2$), 58.8 (C-1), 40.0 (C-3), 15.0 ($SO_3CH_2CH_3$); MALDI-MS: *m*/*z* calcd for $C_{30}H_{36}NaO_8S^+$ $[M+Na]^+$: 579.20; found, 579.65.

3.11. Ethyl 4,5,7-tri-*O*-benzyl-1,2,3-trideoxy-1-ethoxy-sulfonyl-2-thio-α-D-arabino-hept-2-ulopyranoside (12)

Compound **11** (3.14 g, 5.64 mmol) was converted by method **C** to give **12** at −20 °C for 1.5 h. The residue was purified by column chromatography using CH_2Cl_2–acetone (98:2) to afford **12** as white crystals (2.51 g, 74%): mp 75–76 °C (EtOH); $[\alpha]_D$ +77.3 (*c* 0.4, $CHCl_3$); $R_f = 0.53$ (CH_2Cl_2–acetone, 98:2); ^1H NMR (200 MHz, $CDCl_3$): δ 7.34–7.18 (m, 15H, Ph), 4.91 (d, 1H, $J = 10.9$ Hz, CH_2Ph), 4.67 (d, 1H, $J = 11.9$ Hz, CH_2Ph), 4.62 (s, 1H, CH_2Ph), 4.56 (d, 1H,

$J = 11.1$ Hz, CH_2Ph), 4.55 (s, 1H, CH_2Ph), 4.49 (d, 1H, $J = 12.1$ Hz, CH_2Ph), 4.29 (q, 2H, $J = 7.1$ Hz, $SO_3CH_2CH_3$), 4,17–4.01 (m, 2H), 3.82–3.51 (m, 5H), 2.6–2.31 (m, 4H, SCH_2CH_3, H-2a, H- 2b), 1.29 (t, 3H, $J = 7.1$ Hz, SCH_2CH_3), 1.20 (t, 3H, $J = 7.5$ Hz, $SO_3CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.3, 138.2 (2×) (3C-quat. Ph), 128.3–127.4 (15C, Ph), 84.5 (C-2), 77.9, 77.8 (2 skeleton C), 75.0 (CH_2Ph), 73.6 (skeleton C), 73.2, 71.8 ($2CH_2Ph$), 69.2 (C-6), 67.1 ($SO_3CH_2CH_2$), 60.1 (C-1), 38.1 (C-3), 21.3 (SCH_2CH_3), 15.1, 13.9 ($SO_3CH_2CH_3$, SCH_2CH_3); MALDI-MS: m/z calcd for $C_{32}H_{40}NaO_7S_2^+$ $[M+Na]^+$: 623.21; found, 623.34.

3.12. Methyl 4,5,7-tri-*O*-benzyl-1,3-dideoxy-1-ethoxysulfonyl-α-D-arabino-hept-2-ulopyranoside (13a) and methyl 4,5,7-tri-*O*-benzyl-1,3-dideoxy-1-ethoxysulfonyl-β-D-arabino-hept-2-ulopyranoside (13b)

Thioglycoside donor **12** (300 mg, 0.50 mmol) was converted by method **A** to give a mixture of **13a** and **13b**. The anomers were separated by column chromatography using CH_2Cl_2–acetone (60:1). Compound **13a** was isolated as a syrup (162 mg, 57%): $[\alpha]_D$ +30.0 (*c* 0.2, $CHCl_3$); $R_f = 0.26$ (*n*-hexane–EtOAc, 7:3); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.32–7.17 (m, 15H, Ph), 4.90 (d, 1H, $J = 10.8$ Hz), 4.69 (d, 1H, $J = 11.4$ Hz, CH_2Ph), 4.61–4.47 (m, 4H, CH_2Ph), 4.30 (q, 2H, $J = 7.1$ Hz, $SO_3CH_2CH_3$), 4.07–3.95 (ddd, 1H, H-5), 3.78–3.50 (m, 5H), 3.36 (d, 1H, $J = 15.0$ Hz, H-1a), 3.27 (s, 3H, OCH_3), 2.81 (dd, 1H, $J = 5.0$, 13.2 Hz, H-3$_{eq}$), 1.84 (dd, 1H, $J = 11.2$, 13.2 Hz, H-3$_{ax}$), 1.36 (t, 3H, $J = 7.1$ Hz, $SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.4, 138.3, 138.1 (3C-quat. Ph), 128.3–127.5 (15C, Ph), 97.8 (C-2), 77.6, 77.4 (2 skeleton C), 74.9, 73.3 ($2CH_2Ph$), 72.4 (skeleton C), 71.7 (CH_2Ph), 68.9, 66.9 ($SO_3CH_2CH_3$, C-7) 54.6 (C-1), 48.4 (OCH_3), 38.4 (C-3), 15.1 ($SO_3CH_2CH_3$). Anal. Calcd for $C_{31}H_{38}O_8S$: C, 65.24; H, 6.71. Found: C, 65.17; H, 6.78. Compound **13b** was isolated as a syrup (58 mg, 20%): $[\alpha]_D$ +18.8 (*c* 0.2, $CHCl_3$); $R_f = 0.31$ (*n*-hexane-EtOAc, 7:3); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.19 (m, 15H, Ph), 4.93 (d, 1H, $J = 10.9$ Hz, CH_2Ph), 4.77 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.66–4.53 (m, 4H, CH_2Ph), 4.35 (q, 2H, $J = 7.1$ Hz, $SO_3CH_2CH_3$), 3.94–3.83 (m, 1H, H-5), 3.78–3.55 (m, 5H), 3.48 (d, 1H, $J = 14.6$ Hz), 3.47 (s, 3H, OCH_3), 2.80 (dd, 1H, $J = 4.7$, 13.5 Hz, H-3$_{eq}$), 2.03 (dd, 1H, $J = 10.6$, 13.5 Hz, H-3$_{ax}$), 1.43 (t, 3H, $J = 7.1$ Hz, $SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.2, 138.1 (2×) (3C-quat. Ph), 128.3–127.5 (15C, Ph), 98.1 (C-2), 77.5, 77.2, 74.9 (C-4, C-5, C-6), 74.6, 73.3, 71.2 ($3CH_2Ph$), 69.3, 67.2 ($SO_3CH_2CH_3$, C-7), 53.3 (C-1), 49.1 (OCH_3), 34.1 (C-3), 15.0 ($SO_3CH_2CH_3$). Anal. Calcd for $C_{31}H_{38}O_8S$: C, 65.24; H, 6.71. Found: C, 65.32; H, 6.63.

3.13. Ethyl 4,5,6,8-tetra-*O*-benzyl-2-deoxy-α-D-gluco-oct-3-ulopyranosonate (15)

A solution of diisopropylamine (504 μL, 3.60 mmol, 1.5 equiv) in dry THF (15 mL) was treated with 2.5 M *n*-BuLi in hexane (1.44 mL, 3.60 mmol, 1.5 equiv) at −15 °C under argon atmosphere. After 15 min the solution was cooled to −60 °C and dry ethyl acetate (0.35 mL, 3.6 mmol, 1.5 mmol) was added. The mixture was kept at −60 °C for 15 min, then compound **14** (1.29 g, 2.4 mmol, 1.0 equiv) in THF was added. The mixture was kept at −60 °C for 30 min, then it was allowed to warm up to room temperature, and concentrated. The residue was diluted with CH_2Cl_2 and was extracted with water until neutral, then dried and evaporated. The crude product was purified by column chromatography using CH_2Cl_2–acetone (97:3) to afford **15** (0.99 g, 66%): $[\alpha]_D$ −6.6 (*c* 0.2, $CHCl_3$), lit.[36] $[\alpha]_D$ −5.3; $R_f = 0.6$ (CH_2Cl_2–acetone, 95:5); The ^{1}H and ^{13}C NMR data were consistent with those reported previously.[37] Anal. Calcd for $C_{38}H_{42}O_8$: C, 72.82; H, 6.75. Found: C, 72.79; H, 6.73.

3.14. Ethyl (ethyl 4,5,6,8-tetra-*O*-benzyl-2,3-dideoxy-3-thio-α-D-gluco-oct-3-ulopyranosid)onate (16)

Compound **15** (740 mg, 1.18 mmol) was converted by method **C** at 0 °C for overnight to give **16**. Purification by column chromatography using CH_2Cl_2–acetone (98:2) afforded compound **16** (497 mg, 63%): $[\alpha]_D$ +84.0 (*c* 0.2, $CHCl_3$); $R_f = 0.62$. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21–7.34 (m, 20H, Ph), 5.00 (d, 1H, $J = 11.7$ Hz, CH_2Ph), 4.90 (d, 1H, $J = 11.7$ Hz, CH_2Ph), 4.88–4.84 (m, 3H, CH_2Ph), 4.61 (d, 1H, $J = 11.0$ Hz, CH_2Ph), 4.59 (d, 1H, $J = 12.1$ Hz, CH_2Ph), 4.50 (d, 1H, $J = 12.1$ Hz, CH_2Ph), 4.37 (d, 1H, $J = 9.4$ Hz), 4.19 (t, 1H, $J = 9.2$ Hz), 3.98–4.05 (m, 3H), 3.75 (dd, 2H, J= 11.3, 4.6 Hz, H-6a), 3.68 (dd, 1H, $J = 11.4$, 1.7 Hz, H-6b), 3.63 (t, 1H, $J = 9.6$ Hz), 3.00 (d, 1H, $J_{2a,2b} = 14.5$ Hz, H-2a), 2.96 (d, 1H, H-2b), 2.41–2.55 (m, 2H, SCH_2CH_3), 1.23 (t, 3H, $J = 7.5$ Hz, SCH_2CH_3), 1.18 (d, 3H, $J = 7.1$ Hz, $COOCH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0 ($COOEt$), 138.6 (2×), 138.5, 138.2 (4C-quat. Ph), 128.4–127.3 (20C, Ph), 89.7 (C-3), 83.9, 80.7, 78.2 (C-4, C-5, C-6), 75.5, 75.2, 75.0 ($3CH_2Ph$), 73.7 (C-7), 73.2 (CH_2Ph), 68.8 (C-8), 60.5 ($COOCH_2CH_3$), 42.8 (C-2), 19.8 (SCH_2CH_3), 14.2, 14.0 ($COOCH_2CH_3$, SCH_2CH_3). Anal. Calcd for $C_{40}H_{46}O_7S$: C, 71.61; H, 6.91. Found: C, 71.70; H, 6.82.

3.15. Ethyl (methyl 4,5,6,8-tetra-*O*-benzyl-2-deoxy-α-D-gluco-oct-3-ulopyranosid)onate (17a) and ethyl (methyl 4,5,6,8-tetra-*O*-benzyl-2-deoxy-β-D-gluco-oct-3-ulopyranosid)onate (17b)

Compound **16** (335 mg, 0.50 mmol) was converted by method **A** to give a mixture of **17a** and **17b**. The anomers

were separated by column chromatography using EtOAc–*n*-hexane (8:2). Compound **17a** was isolated as a syrup (70 mg, 22%): $[\alpha]_D$ +38.3 (*c* 0.3, $CHCl_3$), lit.[24] +35.8; $R_f = 0.250$ (*n*-hexane–EtOAc, 8:2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.19 (m, 20H, Ph), 4.98 (d, 1H, $J = 11.1$ Hz, CH_2Ph), 4.91 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.89 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.85 (d, 1H, $J = 10.6$ Hz, CH_2Ph), 4.83 (d, 1H, $J = 11.00$ Hz, CH_2Ph), 4.62 (d, 1H, $J = 5.3$ Hz, CH_2Ph), 4.59 (d, 1H, $J = 4.0$ Hz, CH_2Ph), 4.52 (d, 1H, $J = 12.1$ Hz, CH_2Ph), 4.12 (t, 1H, $J = 8.9$ Hz), 4.04–4.00 (m, 3H), 3.75 (dd, 1H, $J = 11.2$, 3.7 Hz, H-8a), 3.70–3.67 (m, 3H), 3.29 (s, 3H, OCH_3), 2.82 (d, 1H, $J = 14.0$ Hz, H-2a), 2.78 (d, 1H, $J = 14.0$ Hz, H-2b), 1.17 (t, 3H, $J = 7.13$ Hz, $COOCH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0 (COO), 138.6, 138.4, 138.3, 138.1 (4C-quat. Ph), 128.3–127.4 (20C, Ph), 100.1 (C-3), 83.3, 80.8, 78.3 (C-4, C-5, C-6), 75.5, 75.4, 75.0, 73.3 (4CH_2Ph), 72.6 (C-7), 68.6 (C-8), 60.5 ($COOCH_2CH_3$), 47.9 (OCH_3), 36.9 (C-2), 14.0 ($COOCH_2CH_3$). Anal. Calcd for $C_{39}H_{44}O_8$: C, 73.10; H, 6.90. Found: C, 72.98; H, 6.89. Compound **17b** (100 mg, 31%): $[\alpha]_D$ +41.7 (*c* 0.2, $CHCl_3$), lit.[24] −28.5; $R_f = 0.30$ (*n*-hexane–EtOAc, 8:2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.19–7.32 (m, 20H, Ph), 4.86 (d, 1H, $J = 11.2$ Hz, CH_2Ph), 4.84 (d, 1H, $J = 1.5$ Hz, CH_2Ph), 4.81 (d, 1H, $J = 1.8$ Hz, CH_2Ph), 4.77 (d, 1H, $J = 11.2$ Hz, CH_2Ph), 4.64–4.60 (m, 3H, CH_2Ph), 4.52 (d, 1H, $J = 12.1$ Hz, CH_2Ph), 4.13–4.03 (m, 2H, $COOCH_2CH_3$), 3.89 (dd, 1H, $J = 10.2$, 8.8 Hz), 3.83–3.78 (m, 3H), 3.73 (dd, 1H, $J = 8.4$, 7.4 Hz, 8-Ha), 3.70 (dd, 1H, $J = 10.8$, 1.7 Hz, H-8b), 3.43 (s, 3H, OCH_3), 2.96 (d, 1H, $J = 14.0$ Hz, H-2a), 2.81 (d, 1H, $J = 14.0$ Hz, H-2b), 1.20 (t, 3H, $J = 7.16$ Hz, $COOCH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0 (*C*OOEt), 138.4, 138.3, 138.1, 138.1 (4C-quat. Ph), 128.3–127.4 (20C, Ph), 101.6 (C-3), 83.4, 79.6, 77.5 (C-4, C-5, C-6), 74.9, 74.7, 73.5 (3CH_2Ph), 73.4 (C-7), 73.3 (*C*H_2Ph) 68.8 (C-8), 60.4 ($COOCH_2CH_3$), 48.9 (OCH_3), 37.0 (C-2), 14.1 ($COOCH_2CH_3$). Anal. Calcd for $C_{39}H_{44}O_9$: C, 73.10; H, 6.92. Found: C, 73.19; H, 6.83.

3.16. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-gluco-hept-2-ulopyranose (18)

To a stirred solution of compound **14** (2.70 g, 5.0 mmol) in dry Et_2O (30 mL) was added freshly prepared CH_3MgI in dry Et_2O (25 mL, CH_3MgI content ~1.10 g, 6.50 mmol) at −10 °C. The mixture was kept at −10 °C until the TLC showed complete conversion (15 min). The reaction was quenched by addition of 5% aqueous NH_4Cl, the mixture was diluted with CH_2Cl_2, extracted three times with water, dried and evaporated. The residue was purified by column chromatography using CH_2Cl_2–acetone (95:5) to give **18** as white crystals (1.26 g, 84%): mp 83–84 °C (ethyl-acetate–*n*-hexane), lit.[31] 92–93 °C; $[\alpha]_D$ +23.9 (*c* 0.3, $CHCl_3$); lit.[31] +24.7; $R_f = 0.55$ (CH_2Cl_2–acetone 95:5); The ^1H and ^{13}C NMR data were consistent with those reported previously.[31,38] Anal. Calcd for $C_{35}H_{38}O_6$: C, 75.79; H, 6.91. Found: C, 75.69; H, 6.93.

3.17. Ethyl 3,4,5,7-tetra-*O*-benzyl-1,2-dideoxy-2-thio-α-D-gluco-hept-2-ulopyranoside (19)

Compound **18** (555 mg, 1.00 mmol) was converted by method **C** at 0 °C for 3.5 h to give **19**, and purified by column chromatography using CH_2Cl_2–acetone (98:2). Compound **19** (180 mg, 30%): $[\alpha]_D$ +65.0 (*c* 0.2, $CHCl_3$); $R_f = 0.80$ (CH_2Cl_2–acetone, 120:2); ^1H NMR (200 MHz, CD_3Cl_3): δ 7.37–7.14 (m, 20H, Ph), 4.91 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.85 (s, 2H, CH_2Ph), 4.83 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.74 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.64 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.61 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.54 (d, 1H, $J = 11.4$ Hz, CH_2Ph), 4.47 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.12–4.06 (m, 2H), 3.73 (dd, 1H, $J = 4.4$, 11.1 Hz) 3.76–3.59 (m, 2H), 3.41 (d, 1H, $J = 9.2$ Hz, H-3), 2.58–2.40 (m, 2H, SCH_2CH_3), 1.61 (s, 3H, CH_3-1), 1.23 (t, 3H, $J = 7.5$ Hz, SCH_2CH_3); ^{13}C NMR (50 MHz, CD_3Cl_3): δ 138.8, 138.2 (3×) (4C-quat. Ph), 128.8–127.5 (20C, Ph), 89.1 (C-2), 85.8, 83.9, 78.5 (C-3, C-4, C-5), 75.6, 75.6, 74.9, 73.3 (4CH_2Ph), 72.9 (C-6), 68.9 (C-7), 27.5 (C-1), 19.8 (SCH_2CH_3), 14.4 (SCH_2CH_3). Anal. Calcd for $C_{37}H_{42}O_5S$: C, 74.22; H, 7.07. Found: C, 74.15; H, 7.14.

3.18. Methyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-α-D-gluco-hept-2-ulopyranoside (20a) and methyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-β-D-gluco-hept-2-ulopyranoside (20b)

Compound **19** (317 mg, 0.53 mmol) was converted by method **A** to give a mixture of **20a** and **20b**. The anomers were separated by column chromatography using CH_2Cl_2–acetone (60:1). Compound **20a** was isolated as a syrup (55 mg, 18%): $[\alpha]_D$ +20.3 (*c* 0.4, $CHCl_3$), lit.[31] +21.3; $R_f = 0.59$ (*n*-hexane–EtOAc 7:3); ^1H NMR: δ 7.41–7.10 (20H, Ph) 4.93 (d, 1H, $J = 11.0$ Hz, CH_2Ph), 4.91 (d, 1H, $J = 11.3$ Hz, CH_2Ph), 4.87 (d, 1H, $J = 11.1$ Hz, CH_2Ph), 4.83 (d, 1H, $J = 10.8$ Hz, CH_2Ph), 4.68 (d, 1H, $J = 12.3$ Hz, CH_2Ph), 4.63 (d, 1H, $J = 13.2$ Hz, CH_2Ph), 4.52 (d, 1H, $J = 10.82$ Hz, CH_2Ph), 4.54 (s, 1H, CH_2Ph), 4.13–4.03 (m, 1H), 3.74–3.62 (m, 4H), 3.35 (d, 2H, $J = 9.6$ Hz, H-3), 3.22 (s, 3H, OCH_3), 1.27 (s, 3H, CH_3-1); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7, 138.2, 138.2, 138.0 (4C-quat. Ph), 128.7–127.5 (20C, Ph), 100.3 (C-2), 83.8, 83.3, 78.6 (C-3, C-4, C-5), 75.6, 75.5, 74.9, 73.3 (4CH_2Ph), 71.5 (C-6 or C-7), 68.8 (C-6 or C-7), 47.9 (OCH_3), 19.9 (C-1). Anal. Calcd for $C_{36}H_{40}O_6$: C, 76.03; H, 7.09. Found: C, 76.11; H, 7.01. Compound **20b** (75 mg, 25%): $[\alpha]_D$ +9.5 (*c* 0.1, $CHCl_3$); $R_f = 0.69$ (*n*-hexane-EtOAc, 7:3); ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.14 (m, 20H, Ph), 4.91 (d, 1H, $J = 11.3$ Hz,

CH_2Ph), 4.87 (d, 1H, $J = 11.1$ Hz, CH_2Ph), 4.83 (d, 1H, $J = 10.8$ Hz, CH_2Ph), 4.69 (d, 1H, $J = 11.3$ Hz, CH_2Ph), 4.61 (d, 1H, $J = 12.2$ Hz, CH_2Ph), 4.53 (d, 1H, $J = 10.8$ Hz, CH_2Ph), 4.52 (d, 1H, $J = 12.2$ Hz, CH_2Ph), 4.11–4.04 (m, 1H, H-6), 3.71 (dd, 1H, $J = 2.8$, 10.4 Hz), 3.67–3.63 (m, 3H), 3.35 (d, 1H, $J = 9.6$ Hz, H-3), 3.22 (s, 3H, OCH_3), 1.27 (s, 3H, CH_3-1); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7 (2×), 138.4, 138.2 (4C-quat. Ph), 128.3–127.1 (20C, Ph), 102.0 (C-2), 84.0, 82.6, 78.2 (C-3, C-4, C-5), 75.5, 75.0, 74.1, 73.4 ($4CH_2Ph$), 71.7 (C-6), 69.4 (C-7), 48.6 (OCH_3), 16.7 (C-1). Anal. Calcd for $C_{36}H_{40}O_6$: C, 76.03; H, 7.09. Found: C, 76.16; H, 6.96.

3.19. Azido 3,4,5,7-tetra-*O*-benzyl-1,2-dideoxy-1-ethoxysulfonyl-α-D-gluco-hept-2-ulopyranoside (22)

To a solution of **21**[23] (800 mg 1.21 mmol) in dry CH_2Cl_2 (8 mL) Me_3SiN_3 (191 μL, 1.45 mmol, 1.2 equiv) and $BF_3{\cdot}Et_2O$ (304 μL, 2.42 mmol, 2.00 equiv) were added, and the mixture was stirred at rt for 3 h. The residue was diluted with CH_2Cl_2 and was extracted with water until neutral, then dried and evaporated. The residue was purified by column chromatography using CH_2Cl_2–acetone (97:3) to afford **22** (680 mg, 78%): $[\alpha]_D$ +67.1 (*c* 0.5); $R_f = 0.41$ (CH_2Cl_2–acetone, 97:3); ^1H NMR (200 MHz, $CDCl_3$): δ 7.39–7.14 (m, 20H, Ph), 5.03 (d, 1H, *J* 11.2 Hz, CH_2Ph), 4.98–4.73 (m, 4H, CH_2Ph), 4.64–4.47 (m, 3H, CH_2Ph), 4.30–4.12 (m, 3 H), 4.09–3.71 (m, 5H), 3.70 (d, 1H, $J = 14.0$ Hz, H-1a), 3.52 (d, 1H, $J = 14.0$ Hz, H-1b), 1.26 (t, 3H, $J = 7.1$ Hz, $SO_3OCH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.0, 137.8, 137.6 (2×) (4C-quat. Ph), 128.5–127.6 (20C, Ph), 91.4 (C-2), 83.3, 80.1, 77.3 (C-3, C-4, C-5), 75.7, 75.4, 75.1, 73.4 ($4CH_2Ph$), 74.6 (C-6), 68.2, 68.1 ($SO_3CH_2CH_3$, C-7), 53.5 (C-1), 151 ($SO_3CH_2CH_3$); IR (KBr): 3050, 2880, 2130 (N_3), 1510, 1460, 1360, 1100, 920, 740, 700 cm^{-1}; MALDI-MS: *m/z* calcd for $C_{37}H_{41}N_3NaO_8S^+$ $[M+Na]^+$: 710.25; found, 710.16.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.05.006.

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