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# Expeditious synthesis of monosulfated thio-linked disaccharides

**José A. Calvo-Asín,[a] Francisco G. Calvo-Flores,[a] Juan M. Exposito-López,[b] Fernando Hernández-Mateo,[a] Juan J. García-López,[b] Joaquín Isac-García,[a] Francisco Santoyo-González*,[a] and Antonio Vargas-Berenguel[b]**

[a] *Instituto de Biotecnología, Facultad de Ciencias, Universidad de Granada, E-18071 Granada, Spain*
[b] *Area de Química Orgánica, Facultad de Ciencias Experimentales, Universidad de Almería, E-04120 Almería, Spain*

**1-Thio-sugars react with cyclic sulfate sugars to give monosulfated thio-linked disaccharides regioselectively in one step; the methodology has the advantages of the easy access and stability of the reagents and the simplicity of the procedure.**

The synthesis of sugar hetereoanalogues as potential inhibitors has received great attention in recent years. Most of the research in this area is concerned with the resistance of the natural compound to hydrolytic conditions and with the enhancement of its reactivity towards enzymes. Much of the activity has focused on the synthesis of di- and oligo-saccharide heteroanalogues in which the interglycosidic oxygen or the ring oxygen atom has been replaced. The synthesis of analogues with a carbon, selenium, nitrogen or sulfur atom in the interglycosidic linkage has been described.[1] Construction of the interthioglycosidic bond of these last thio derivatives has been performed following two general strategies: (a) $S_N2$ displacement[2] of a leaving group in one sugar moiety by a 1-thioglycose or the displacement of a glycosyl halide by a sugar thiolate and (b) Lewis acid-catalysed condensation between a glycosyl acceptor containing an SH group and a suitable glycosyl donor.[2m,3] Furthermore, a new approach based on the stereoselective Michael addition of 1-thio-sugars to the α,β-conjugated system of levoglucosenone and 1,2-dideoxy-1-nitro-D-arabinohex-1-enitol has been recently described[4] for the synthesis of thiodisaccharides. On the other hand, sulfated oligosaccharides such as glycosaminoglycans, selectin binding structures such as fucoidan repeating units, 3′-$SO_3$-Lewis$^X$ and 3′-$SO_3$-Lewis$^a$, and sulfoglycolipids play important roles in biological recognition processes. Therefore, much attention has been focused on the chemical synthesis of these oligosaccharides.[5] Methods of sulfation are mostly limited to blocked structures having one or two hydroxy groups available for sulfation. Sulfation has been generally accomplished using sulfur trioxide complexes with pyridine or trimethylamine[6] and, recently, selective sulfation has also been reported using the stannylating agents dibutyltin oxide and bis(tributyltin) oxide.[7] The sulfate group has also been introduced by displacement of the trifluoromethanesulfonate anion with tetrabutylammonium hydrogen sulfate.[8]

We have recently reported the nucleophilic opening of cyclic sulfate sugars with sulfur and selenium nucleophiles such as thioacetate, thiocyanate and selenocyanate anions leading to β-acetylthio or β-thiocyanato sulfates.[9] The good results obtained prompted us to apply the same strategy using 1-thio-sugars as the nucleophile and allowing them to react with cyclic sulfate sugars in order to obtain monosulfated sulfur linked thiodisaccharides in one step. The thiols selected for this study were 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose **1**,[10] -galactopyranose **2**[10] and 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranose **3**.[11] The cyclic sulfates methyl 2,3-di-*O*-benzoyl-α-D-glucopyranoside 4,6-cyclic sulfate **4**, methyl 2,6-di-*O*-acetyl-α-D-galactopyranosyl 3,4-*O*-cyclic sulfate **5** and methyl 2,6-di-*O*-acetyl-β-D-galactopyranosyl 3,4-*O*-cyclic sulfate **6** were readily accessible by sulfation of the diol function in the corresponding sugars following the procedure described by Gao and Sharpless.[12] Construction of the interglycosidic thio linkages was easily performed by reaction of the cyclic sulfates with the thiols in the presence of caesium carbonate. The reactions of the 4,6-cyclic sulfate **4** with the thiols **1**–**3** gave the 4-*O*-sulfo-β-(1,6)-*S*-thiodisaccharide caesium salts **7**–**9** in 52–89% yields (see Table 1). As expected in these cases opening of the cyclic sulfates takes place at the least sterically hindered 6-position. We then turned our attention to the stereochemical outcome of the ring opening of the 3,4-cyclic sulfates **5** and **6**. Treatment of **5** with thiols **1**–**3** in the reaction conditions described above gave exclusively the 3-*O*-sulfo-β-(1,4)-*S*-thiodisaccharide caesium salts **10**–**12** (61–73% yield) (see Table 1) by attack of the thiolate on C-4 of the methyl α-glycoside **5**. On the other hand, the nucleophilic attack of the same thiols **1**–**3** on the corresponding methyl β-glycoside **6** was also highly regioselective leading to the 4-*O*-sulfo-β-(1,3)-*S*-thiodisaccharide caesium salts **13** and **14** in 46–87% yield (see Table 1). In these reactions the formation of a small quantity of a minor product was observed by TLC corresponding probably to the 3-*O*-sulfo-β-(1,4)-*S*-thiodisaccharides but isolation of these products by column chromatography was not possible in any case. These results show that the attack of the nucleophile at the C-3 position is hindered when an axial methoxy group is present at C-1. However regioselective reaction at C-3 is observed when the anomeric methoxy group is in an equatorial position.[13] Regioselective ring opening of 2,3- and 3,4-cyclic sulfate sugars with lithium azide has been described by van der Klein *et al.*[14]

In summary, this new approach constitutes a highly stereoselective methodology for the introduction of a sulfur bridge between two sugar units by reaction of thio- and cyclic sulfate sugars. These cyclic sulfates are easily prepared and show good stability when compared with other activated monosaccharides used for the construction of a sulfur bond between two sugars such as trifluoromethanesulfonate sugars. In addition, the procedure allows selective access to monosulfated thiodisaccharides and has the advantage of simplicity.

## Experimental

### Methyl 2,3-di-*O*-benzoyl-α-D-glucopyranosyl 4,6-*O*-cyclic sulfate 4†

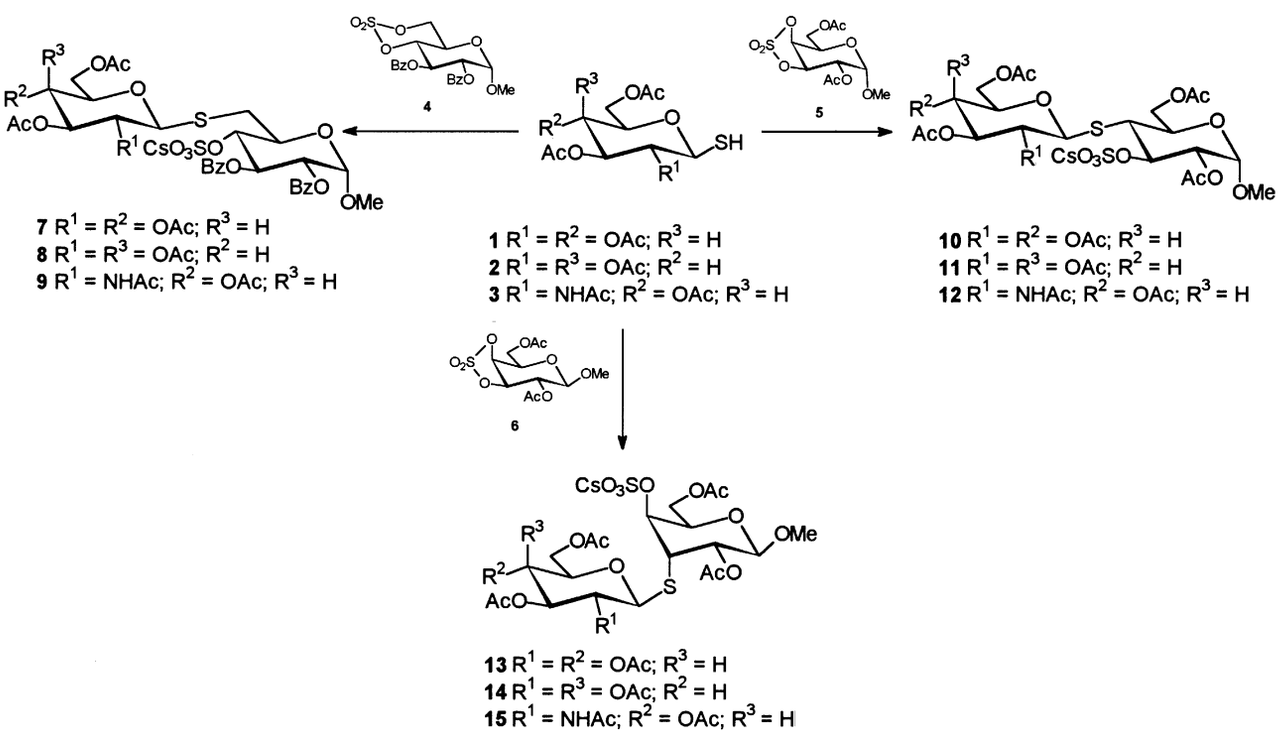
This compound was prepared starting from methyl 2,3-di-*O*-benzoyl-α-D-glucopyranoside[15] following the procedure of Gao

† Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for all new substances. $[\alpha]_D$ Values are given in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. *J* Values are given in Hz.

**Table 1** Selected physical data for compounds **7**–**15**

| Thiol | Cyclic sulfate | Product (%) | mp (°C) | $[\alpha]_D$[a] (*c* 1, methanol) | Selected NMR signals[b] |
|---|---|---|---|---|---|
| **1** | **4** | **7** (52) | 150–152 | +61 | $\delta_H$ 5.18 (d, 1 H, *J* 10.2, H-1′), 5.15 (d, 1 H, *J* 3.7, H-1), 4.46 (t, 1 H, *J* 9.6, H-4), 3.58 (dd, 1 H, *J* 14.9 and 1.4, H-6), 2.93 (dd, 1 H, *J* 14.9 and 9.7, H-6) $\delta_C$ 97.2 (C-1), 85.3 (C-1′), 33.3 (C-6) |
| **2** | **4** | **8** (89) | 163–164 | +88 | $\delta_H$ 5.16–5.09 (m, H-1,1′), 4.50 (t, 1 H, *J* 9.6, H-4), 3.50 (dd, 1 H, *J* 14.9 and 1.7, H-6), 2.95 (dd, 1 H, *J* 14.9 and 9.6, H-6) $\delta_C$ 97.2 (C-1), 85.9 (C-1′), 33.3 (C-6) |
| **3** | **4** | **9** (68) | 183–184 | +71 | $\delta_H$ 5.13–5.08 (m, H-1,1′), 4.67 (t, 1 H, *J* 9.5, H-4), 3.58 (dd, 1 H, *J* 14.0 and 2.1, H-6), 2.98 (dd, 1 H, *J* 14.0 and 8.0, H-6) $\delta_C$ 97.3 (C-1), 86.2 (C-1′), 33.1 (C-6) |
| **1** | **5** | **10** (73) | 155–157 | +12 | $\delta_H$ 5.13 (d, 1 H, *J* 10.1, H-1′), 4.76 (d, 1 H, *J* 3.7, H-1), 4.75 (t, 1 H, *J* 9.7, H-3), 3.04 (t, 1 H, *J* 10.6, H-4) $\delta_C$ 98.2 (C-1), 82.6 (C-1′), 47.3 (C-4) |
| **2** | **5** | **11** (61) | 153–154 | +17 | $\delta_H$ 5.12 (d, 1 H, *J* 9.5, H-1′), 4.80 (t, 1 H, *J* 9.6, H-3), 4.76 (d, 1 H, *J* 3.6, H-1), 3.00 (t, 1 H, *J* 10.7, H-4) $\delta_C$ 98.3 (C-1), 92.8 (C-1′), 47.3 (C-4) |
| **3** | **5** | **12** (64) | 165–167 | +7 | $\delta_H$ 5.09 (t, 1 H, *J* 9.5, H-3′), 4.74 (d, 1 H, *J* 3.4, H-1), 4.70 (dd, 1 H, *J* 10.3 and 9.9, H-3), 4.40 (br d, 1 H, *J* 11.8, H-6), 2.89 (t, 1 H, *J* 10.8, H-4) $\delta_C$ 97.0 (C-1), 79.8 (C-1′), 45.6 (C-4) |
| **1** | **6** | **13** (46) | 145–147 | −41 | $\delta_H$ 4.86 (d, 1 H, *J* 10.0, H-1′), 4.67 (d, 1 H, *J* 2.8, H-4), 4.44 (d, 1 H, *J* 8.5, H-1), 4.33–4.16 (m, H-3) $\delta_C$ 100.3 (C-1), 83.7 (C-1′), 46.6 (C-3) |
| **2** | **6** | **14** (65) | 128–130 | +99 | $\delta_H$ 4.84 (d, 1 H, *J* 9.8, H-1′), 4.50 (dd, 1 H, *J* 3.2 and 1.2, H-4), 4.42 (d, 1 H, *J* 8.3, H-1), 4.35–4.09 (m, H-3) $\delta_C$ 100.4 (C-1), 84.9 (C-1′), 47.4 (C-3) |
| **3** | **6** | **15** (87) | 171–174 | −47 | $\delta_H$ 5.07 (d, 1 H, *J* 10.2, H-1′), 4.83 (br s, 1 H, H-4), 4.53 (d, 1 H, *J* 8.0, H-1), 3.08 (br s, 1 H, H-3) $\delta_C$ 99.8 (C-1), 84.5 (C-1′), 45.5 (C-3) |

[a] In units of $10^{-1}$ deg cm$^2$ g$^{-1}$. [b] *J* Values in Hz.




and Sharpless[12] in 68% yield, mp 150–152 °C; $[\alpha]_D$ +145 (*c* 1, chloroform); $\delta_H$($CDCl_3$, 300 MHz) 8.00–7.90 and 7.48–7.32 (2 m, 10 H, 2 $C_6H_5$), 6.09 (t, 1 H, *J* 9.8, H-3), 5.23 (d, 1 H, *J* 3.7, H-1), 5.17 (dd, 1 H, *J* 9.9 and 3.7, H-2), 4.67 (t, 1 H, *J* 10.0, H-4), 4.74 (t, 1 H, *J* 10.8, H-6), 4.61 (dd, 1 H, *J* 10.5 and 5.1, H-6′), 4.41 (td, 1 H, *J* 10.6 and 5.1, H-5) and 3.47 (s, 3 H, MeO); $\delta_C$($CDCl_3$, 75 MHz) 165.7, 165.2 (2 CO), 133.8, 133.7, 130.1, 130.0, 128.6, 128.5 (2 $C_6H_5$), 98.0 (C-1), 81.5 (C-4), 72.2 (C-6), 71.7, 67.7, 60.8 (C-2, -3, -5) and 56.4 (MeO).

**Methyl 2,6-di-*O*-acetyl-α-D-galactopyranosyl 3,4-*O*-cyclic sulfate 5†**

Compound **5** was prepared starting from methyl 2,6-di-*O*-acetyl-α-D-galactopyranoside[16] following the procedure of Gao and Sharpless[12] in 97% yield, mp 128–130 °C; $[\alpha]_D$ +143 (*c* 1, chloroform); $\delta_H$($CDCl_3$, 300 MHz) 5.26 (dd, 1 H, *J* 8.8 and 3.6, H-2), 5.19 (dd, 1 H, *J* 5.1 and 1.5, H-4), 5.09 (dd, 1 H, *J* 8.8 and 5.1, H-3), 5.07 (d, 1 H, *J* 3.6, H-1), 4.39–4.23 (m, 3 H, H-5, -6, -6′), 3.41 (s, 3 H, MeO) and 2.16, 2.12 (2 s, 6 H, 2 MeCO);

$\delta_C$($CDCl_3$, 75.5 MHz) 96.6 (C-1), 80.6, 79.2, 69.3, 64.1 (C-2, -3, -4, -5), 61.8 (C-6), 56.2 (MeO) and 20.7 (*Me*CO).

### Methyl 2,6-di-*O*-acetyl-β-D-galactopyranosyl 3,4-*O*-cyclic sulfate 6†

Compound **6** was prepared starting from methyl 2,6-di-*O*-acetyl-β-D-galactopyranoside[17] following the procedure of Gao and Sharpless[12] in 90% yield, mp 125–126 °C (decomp.); $[\alpha]_D$ +9 (*c* 1, chloroform); $\delta_H$($CDCl_3$, 300 MHz) 5.32 (dd, 1 H, *J* 7.6 and 7.5, H-2), 5.12 (dd, 1 H, *J* 5.6 and 1.8, H-4), 4.98 (dd, 1 H, *J* 7.4 and 5.6, H-3), 4.45 (d, 1 H, *J* 7.7, H-1), 4.44 (dd, 1 H, *J* 11.4 and 6.7, H-6), 4.61 (dd, 1 H, *J* 11.4 and 6.4, H-6′), 4.11 (td, 1 H, *J* 6.5 and 1.8, H-5), 3.51 (s, 3 H, MeO) and 2.14, 2.12 (2 s, 6 H, 2 MeCO); $\delta_C$($CDCl_3$, 75.5 MHz) 170.4, 168.2 (2 CO), 100.5 (C-1), 82.1, 78.3, 70.0, 69.7 (C-2, -3, -4, -5), 61.7 (C-6), 56.9 (MeO) and 20.7 (*Me*CO).

### Typical procedure for synthesis of thio disaccharides 7–15†

To a solution of thiol **1**–**3** (1.2 mmol) and cyclic sulfate **4**–**6** (1.0 mmol) in dry DMF (4 ml) was added caesium carbonate (1.2 mmol). The reaction mixture was stirred at room temp. Completion of the reaction was monitored by TLC (diethyl ether and chloroform–methanol 7:1). Water (10 ml) was added and the solution was concentrated by lyophilization. The syrupy residue obtained was dissolved in water (5 ml) and lyophilization was again performed to give a white solid which was purified by column chromatography using chloroform–methanol 5:1.

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