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Sulfur atom configuration of sulfinyl galactofuranosides determines different reactivities in glycosylation reactions

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Abstract

Sulfinyl β-D-galactofuranosides **3(*R*,*S*)** and **9(*R*,*S*)** were used as new hexofuranosyl donors in glycosylation reactions. Activation by trifluoromethanesulfonic anhydride involved different reaction pathways depending on the stereochemistry at the sulfur atom. Experimental results underlined a more suitable reactivity of **3(*R*)** and **9(*R*)** versus **3(*S*)** and **9(*S*)**, respectively, for the synthesis of β-D-galactofuranosides. © 2000 Elsevier Science Ltd. All rights reserved.

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Since the discovery of glycosyl donor properties of sulfinyl glycosides,[1] the well known sulfoxide method was widely exploited even for the glycosylation of unreactive substrates[1,2] and for the direct synthesis of β-D-mannopyranosides.[3] Mechanistic studies have clearly underlined the formation of different intermediates[4–6] and, as a consequence of these fundamental approaches, new methods were developed in order to improve both diastereoselectivity and yield by limiting the formation of side products.[7] Nevertheless, little consideration has been directed towards the reactivity of each epimer[8] of the sulfoxide donor in glycosylation reactions. It is acknowledged that both isomers are similarly activated and so mixtures of *R* and *S* sulfinyl glycosides are generally used without previous separation.[9] Our interest in sulfinyl glycosides arose from the requirement of new *hexofuranosyl* donors for the synthesis of glycoconjugates containing such unusual residues. The aldohexosides presenting the furanose configuration are found in parasites of the *Trypanosomatid* family but are not present in mammalian cells,[10] and therefore represent interesting targets for the design of new drugs. In this context, we herein describe first evidences,

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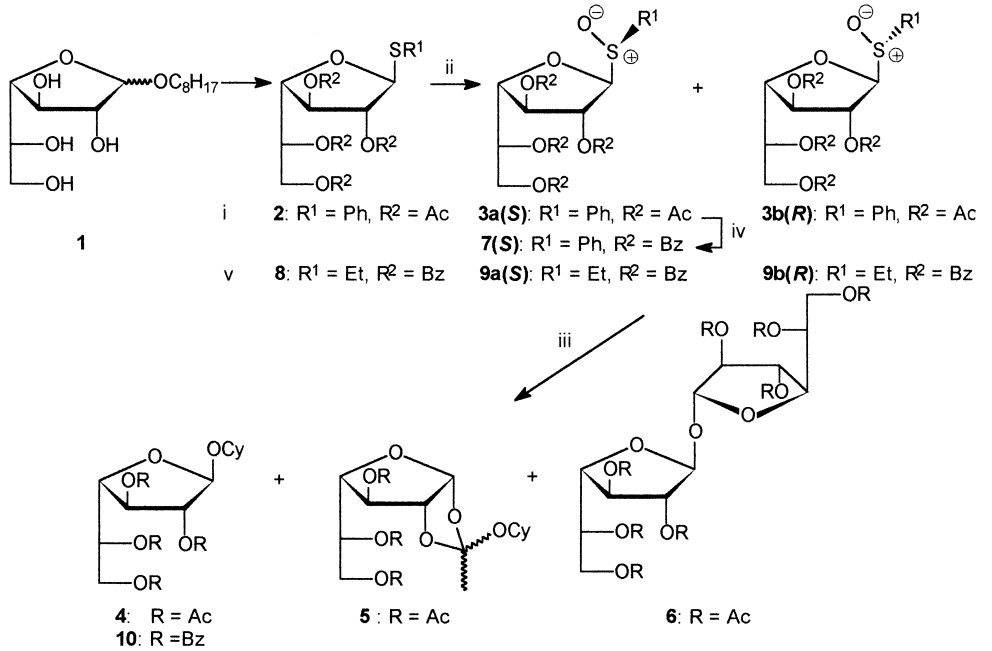
corroborated by crystal structures, that sulfinyl galactofuranosides possessing different absolute configuration at the sulfur atom, present different reactivities as glycosyl donors.

Peracetylated phenyl thiogalactofuranoside **2**, actual precursor of sulfoxides **3a,b** (Scheme 1), was prepared as described in previous papers from this laboratory.[11,12] Mild sulfoxidation of thiogalactofuranoside **2** with hydrogen peroxide and acetic acid in the presence of silica gel[13] gave a 1.7:1 mixture of both epimers in 71% yield. Structure of target **3a,b** was confirmed by NMR and HRMS.[14] Glycosylation of cyclohexanol (CyOH) as the model acceptor was then investigated under Kahne conditions.[1] Whilst, surprisingly, no reaction occurred at –78°C, the expected β-galactofuranoside **4** was obtained after only 1 min at room temperature and was isolated in 63% yield (Table 1, entry 1). Appreciable amounts of trehalose-like disaccharide **6**[15] were also obtained under slightly modified conditions (entry 2) or from couplings using pure sulfoxide **3b** (entries 3–5) which could be chromatographically separated from its epimer **3a**. In contrast, orthoester **5**[15] was mainly obtained from the major less polar sulfinyl furanoside **3a** (entries 6, 7). Consequently, our results showed that the glycosylation pathway using a sulfinyl galactofuranoside is dictated predominantly by (i) the reaction conditions, and more importantly (ii) the stereochemistry at the sulfur atom. Unfortunately, the latter could not be easily determined by X-ray analysis since neither **3a** nor **3b** could be obtained in crystalline form.[16]



Scheme 1. (i) See Ref. 12c; (ii) H_2O_2, AcOH, SiO_2: **3** (71%, **3a/3b**=1.7:1); **9**: (84%, **9a/9b**=1.7:1); (iii) CyOH, DTBMP, Tf_2O: **4–6** (see Table 1); **10** (35%); (iv) 1. NaOMe, MeOH; 2-BzCl, Py (47%); (v) 1. BzCl, Py (85%); 2. TFAA, H_2SO_4, CH_2Cl_2; EtSH, BF_3OEt_2 (75%)

Tetra-*O*-benzoyl sulfinyl galactofuranoside **7** was therefore prepared by standard protecting group manipulations starting from pure **3a**. Eventually, we were rewarded by the growth of single crystals of **7**, which sulfur atom configuration was revealed to be *S* (Fig. 1).[17]

Suitable crystals for X-ray crystallographic analysis were again obtained for ethyl sufinyl furanoside **9**, which presented the same sulfur configuration as **7(*S*)**[17] (Fig. 1). Indeed, **9** was prepared

Table 1
Reaction conditions for glycosylation of cyclohexanol (CyOH) using sulfoxide **3**

Entry	Donor (equiv.)	CyOH (equiv.)	DTBMP[a] (equiv.)	Tf_2O[b] (equiv.)	T (°C)	Time	**4** (%)	**5** (%)	**6** (%)
1	**3a,b** (2)	1	1.5	2	20	1 min	63	-	< 5%
2	**3a,b** (1)	2	2	1.1	0	4 h	44	-	24
3	**3b** (1)	2	2	1.1	20	3 min	51	-	< 5%
4	**3b** (1)	2	2	1.1	5	10 min	-	34	30
5	**3b** (1)	2	2	1.1	0	2 h	19	9	34
6	**3a** (1)	2	2	1.1	20	1 min	-	58	nd[c]
7	**3a** (1)	2	2	1.1	0	3 h	7	9	nd

[a] 2,6-di-*t*-butyl-4-methylpyridine; [b] triflic anhydride; [c] not determined.

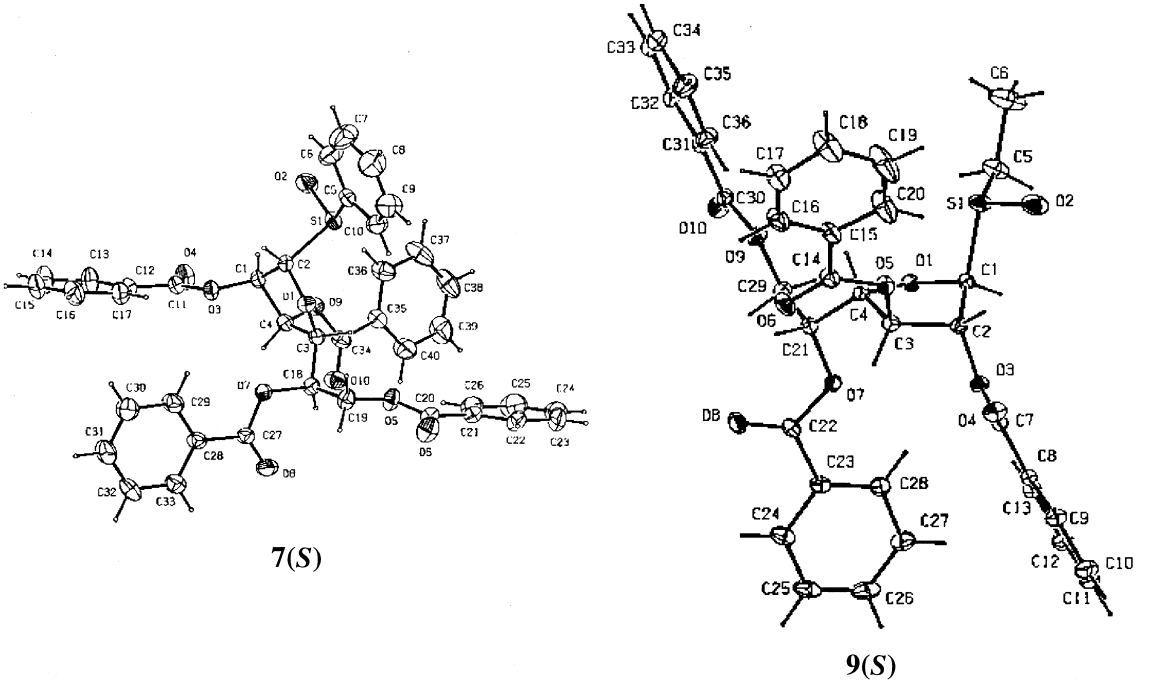


Figure 1. ORTEP plot of the crystal structures of compounds **7(*S*)** and **9(*S*)**. Thermal ellipsoids are drawn at 50% probability

from **1** by standard benzoylation followed by acetolysis using trifluoroacetic anhydride (TFAA), glycosylation of ethanethiol and mild oxidation. HRMS analysis cleanly showed the desired sulfoxidation[18] and ^{1}H NMR indicated a *R*/*S* ratio of 1.7:1, as for **3a,b**. However, while **9(*S*)** was partially crystallized out of the crude mixture, **9(*R*)** and **9(*S*)** could not be separated by chromatography. Nevertheless, treatment of 1 equiv. of **9(*R*,*S*)** (*R*/*S* = 1.7:1) with 2 equiv. of cyclohexanol under the conditions described above afforded the expected furanoside **10**. The moderate 35% yield was the result of recovering of the donor in 25% yield. It is noteworthy that the mixture of

starting sulfoxides was significantly enriched with **9(*R*)**, since the *R*/*S* ratio reached 6:1. Consequently, a marked difference in reactivity between furanosyl sulfoxide *R* and its *S* epimer was again observed in glycosylation reactions.

On the basis of previous studies,[1–7] results obtained herein could be partly rationalized. Firstly, isolation of orthoester **5** clearly indicates stabilization of a preformed anomeric cation trapped by cyclohexanol. However, isolation of the trehalose-like difuranoside **6** requires in situ formation of a glycosidic acceptor. Upon increasing temperature, the latter may be obtained by rearrangement of starting sulfoxide into anomeric sulfenate[4] which then could act either as another glycosyl donor or as a new nucleophile able to react with **3**, to afford compound **6**. Complementary mechanistic studies are currently under investigation in order to determine the discriminating factors in the stereochemical activation of both *R* and *S* sulfoxides.

Tables of atomic coordinates, bond lengths and bond angles have been deposited within the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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14. For $[C_{20}H_{24}O_{10}S+H]^+$: theoretical: 457.1168; experimental: 457.1149.
15. Structure of symmetrical difuranoside **6** and that of orthoester **5** were assigned on the basis of spectroscopic and HRMS data.
16. During the course of this work, an NMR approach for predicting absolute configuration at sulfur atom of glycopyranosyl sulfoxides was published: Buist, P. H.; Behrouzian, B.; MacIsaac, K. D.; Cassel, S.; Rollin, P.; Imberty, A.; Gautier, C.; Pérez, S.; Genix, P. *Tetrahedron: Asymmetry* **1999**, *10*, 2881–2889.
17. *Crystal data* for **7(*S*)**: $C_{40}H_{32}O_{10}S$, CH_3OH, $M = 736.76$, monoclinic, C2, $a = 28.357(5)$, $b = 11.120(4)$, $c = 12.509(3)$ Å, $\beta = 110.98(2)^\circ$, $V = 3683(2)$ Å^{-3}, $Z = 2$, $D_X = 1.329$ Mg m^{-3}. The data collection gives 4234 unique reflections from which 2880 with $I > 2.0\sigma(I)$. After Lorenz and polarization corrections the structure was solved with SIR-97, which reveals the non-hydrogen atoms of the structure and a methanol molecule. After anisotropic refinement,

many hydrogen atoms are found with a Fourier Difference. The whole structure was refined with SHELXL97 by the full-matrix least-square techniques {use of F magnitude; x, y, z, β_{ij} for S, C and O atoms, x, y, z in riding mode for H atoms; 469 variables and 2880 observations with $I > 2.0\sigma(I)$; calc. $w = 1/[\sigma^2(F_O^2)+(0.0915P)^2+0.588P]$ where $P = (F_O^2+2F_C^2)/3$} with the resulting $R = 0.487$, $R_W = 0.128$ and $S_W = 1.033$ (residual $\Delta\rho < 0.065$ eÅ^{-3}).

18. For $[C_{36}H_{32}O_{10}S+H]^+$: theoretical: 657.1794; experimental: 657.1799; *Crystal data* for **9(*S*)**: $C_{36}H_{32}O_{10}S$, CH_3OH, $M = 656.68$, orthorhombic, $P2_12_12_1$, $a = 11.058(5)$, $b = 12.035(6)$, $c = 26.839(6)$ Å, $V = 3572(3)$ Å^{-3}, $Z = 4$, $D_X = 1.221$ Mg m^{-3}. The data collection gives 4334 unique reflections from which 2203 with $I > 2.0\sigma(I)$. After Lorenz and polarization corrections the structure was solved with SIR-97 which reveals the non-hydrogen atoms of the structure and a methanol molecule. After anisotropic refinement, all the hydrogen atoms are found with a Fourier Difference. The whole structure was refined with SHELXL97 by the full-matrix least-square techniques {use of F magnitude; x, y, z, β_{ij} for S, C and O atoms, x, y, z in riding mode for H atoms; 425 variables and 4334 observations with $I > 2.0\sigma(I)$; calc $w = 1/[\sigma^2(F\sigma^2)+(0.0728P)^2+0.0940P]$ where $P = (F_O^2+2F_C^2)/3$} with the resulting $R = 0.061$, $R_W = 0.1483$ and $S_W = 0.878$ (residual $\Delta\rho < 0.32$ eÅ^{-3}).