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SULFENATE ESTERS AS GLYCOSYL ACCEPTORS: A NOVEL APPROACH TO O-GLYCOSIDES FROM THIOGLYCOSIDES AND SULFENATE ESTERS[1)]

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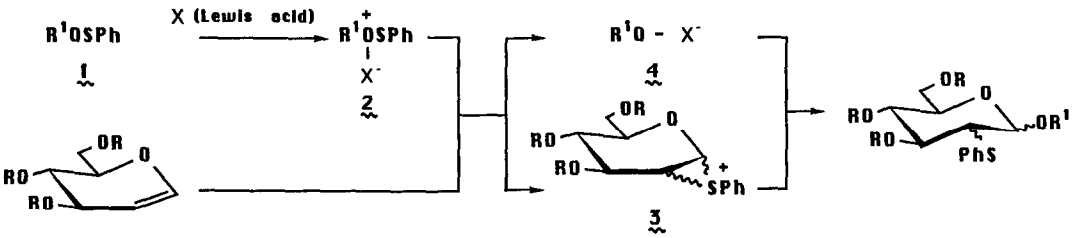
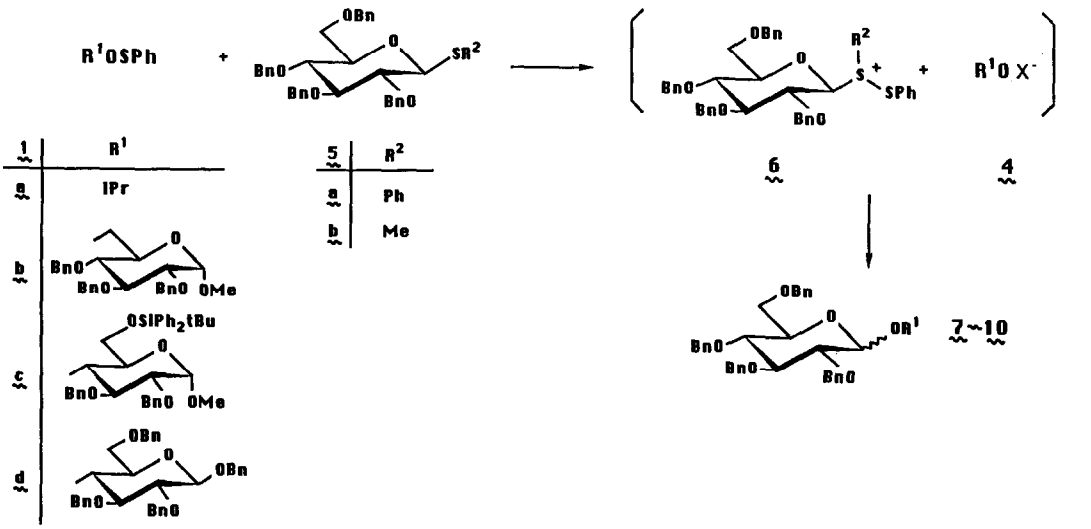
Abstract: The reactions of thioglycosides and sulfenate esters were effected in the presence of Lewis acid to give corresponding O-glycosides. The stereoselectivity was highly dependent on the solvent.

Recently we reported a conceptually novel approach to the synthesis of 2-deoxyglycosides based on the Lewis acid mediated activation of sulfenate esters **1** readily obtainable from

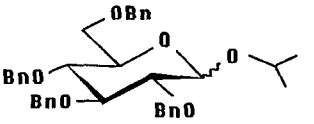


alcohols[2)]. A sulfenate ester is activated by a Lewis acid to genarate an ionic species **2** and a glycal attacks as a nucleophile on a sulfur atom of **2** giving an episulfonium ion **3**. It can be viewed that the reaction is a result of successive hard-hard (i.e. a Lewis acid and **1**) and soft-soft (i.e. **2** and a glycal) acid-base interactions. In recent years, potential utility of thioglycosides as glycosyl donors has been demonstrated in several reports[3)-11)], most of



which take advantage of the specific affinity of sulfide groups to soft electrophiles. From these facts, it was assumed that an activated form **2** of a sulfenate ester would react with a thioglycoside **5** to form a cationic intermediate **6**, which in turn reacts with a nucleophilic species **4** to give a glycosylated product.

As expected, thioglycosides **5a**[3)5)] and **5b**[12)] reacted smoothly with isopropyl benzenesulfenate **1a**[14)] in the presence of a catalytic amount of TMSOTf and the product **7** was obtained in a high yield (table 1, entry 1~6). Sulfenate esters **1b**, **1c** and **1d** derived from glucopyranosides also served satisfactorily as glycosyl acceptors to give disaccharides **8**, **9** and **10** (entry 7~12). All reactions proceeded under extremely mild conditions; less than 1h at -35°C in most of the cases. So far as 1-deoxy-1-thio-β-D-glucopyranoside **5b** was investigated as a glycosyl donor, the stereoselectivity was solvent-dependent, being α-selective in diethyl ether and β-selective in acetonitrile[15)]. The β-selectivity was higher in the sterically less hindered substrate (entry 8) and enhanced by lowering the temperature (entry 5, 6). On the contrary, the α-selectivity was higher in the more hindered substrate (entry 9) and scarecely affected by the temperature (entry 3, 4).



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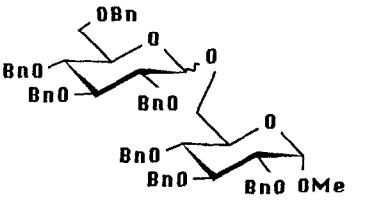

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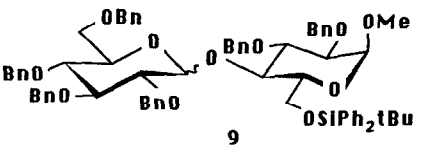

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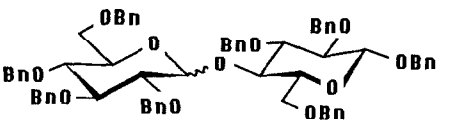

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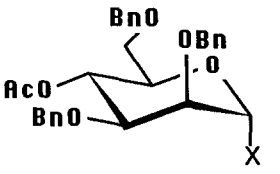
Table 1 Reactions of sulfenate esters with thioglycosides.

entry	sulfenate 1[c)]	thioglycoside 5	molar ratio 5/1/TMSOTf	solvent	temp.(°C)/time	product	yield (%)	α : β
1[a)]	a	a	1/1.3/0.1	$(ClCH_2)_2$	20/30min	7	70	44 :56[d)]
2a)	a	b	1/1.3/0.1	$(ClCH_2)_2$	0/15min	7	93	44 :56[d)]
3[a)]	a	b	1/1.3/0.1	Et_2O	0/15min	7	87	79 :21[d)]
4[a)]	a	b	1/1.3/0.1	Et_2O	-35/30min	7	90	81 :19[d)]
5[b)]	a	b	1/1.3/0.1	MeCN	0/15min	7	88	21 :79[d)]
6[b)]	a	b	1/1.3/0.1	MeCN	-35/30min	7	89	12 :88[d)]
7[a)]	b	b	1/1.3/0.1	Et_2O	-35/40min	8[17)]	65	67 :33[d)]
8[b)]	b	b	1/1.3/0.1	MeCN	-35/40min	8[17)]	90	5 :95[d)]
9[a)]	c	b	1/1.3/0.2	Et_2O	-35/20min	9[18)]	69	86 :14[e)]
10[b)]	c	b	1/1.3/0.5	MeCN	-35~20/18h	9[18)]	50	22 :78[e)]
11[a)]	d	b	1/1.5/0.4	Et_2O	-35/40min	10[19)]	74	66 :34[d)]
12[b)]	d	b	1/1.5/0.3	MeCN	-35/30min	10[19)]	68	21 :79[d)]

a) Carried out in the presence of molecular sieves 4A. b) Carried out in the presence of molecular sieves 3A. c) **1b**, **1c** and **1d** were prepared from corresponding alcohols (PhSCl, Et_3N, ether, -78°C) and used without purification. d) Determined by 400 MHz ^{1}H-NMR analysis. e) determined by individual isomer separation.

A typical glycosylation procedure was as follows (entry 8). A mixture of **5b** (59.2 mg, 104 μmol), **1b** (77.5 mg, 135 μmol), molecular sieves 4A (0.35 g) and acetonitrile (4 ml) was stirred at -35°C under dry nitrogen. TMSOTf (2 μl, 10 μmol) was added and the mixture was stirred at -35°C for 40 min. Triethylamine (60 μl) was then added and the mixtue was diluted with ethyl acetate (30 ml) and filtered through Celite. The filtrate was washed successively with aq. $NaHCO_3$ (30 ml) and brine (30 ml), dried over $MgSO_4$ and concentrated. Residue was purified by silca gel chromatography in 4:1 n-hexane-ethyl acetate to give **8** (92.6 mg, 90%; α:β=5:95), from which pure β-isomer was isolated by recrystallization from n-hexane-chloroform, m.p. 130~131.5°, $[\alpha]_D$ +18.4° (c 0.76)[16] (lit.[17] $[\alpha]_D$ +17.1° (c 0.42)).

As shown below, the present method could also be applicable to thiomannoside **11**[20]. Thus, **11** was reacted with sulfenate ester **1d** to give a 67% yield of the disaccharide **13**[21] which constitutes a structural unit of plant glycolipids (table 2, entry 1). Although the β-glycoside could not be obtained as a major product under the several conditions we attempted, a high α-selectivity was observed especially in diethyl ether.



	X
11	SMe
12	O O-C-⟨O⟩-NO_2

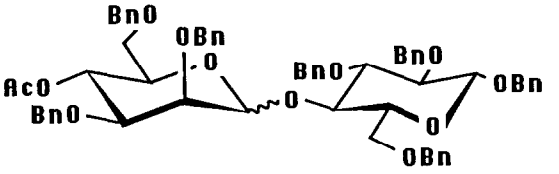


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Table 2 Reactions of sulfenate ester **1d** with thiomannoside **11**

entry[a]	catalyst	molar ratio **11**/**1d**/catalyst	solvent	temp.(°C)/time	product **13** yield(%)	α : β[b]
1	TMSOTf	1/1.2/0.4	Et_2O	-35/30min	67	92 : 8
2	TMSOTf	1/1.6/0.4	MeCN	-35/30min	65	74 : 26
3	$TrBF_4$	1/1.3/0.5	MeCN	-35/30min	44	77 : 23
4	BF_3•OEt_2	1/1.5/0.5	MeCN	-35/30min	34	75 : 25

a) Carried out in the presence of molecular sieves 4A (entry 1) or 3A (entry 2~4).
b) Determined by individual isomer separation.

In conclusion, Lewis acid catalysed reaction of sulfenate esters with thioglycosides smoothly gave glycosylated products under mild conditions.

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18) **9**α, $[\alpha]_D$ +33.6° (c 1.1), $\delta_H(CDCl_3)$ 5.728 (d, 3.9 Hz, H-1'), 4.543 (d, 3.7 Hz, H-1), $\delta_C(CDCl_3)$ 97.31 (C-1), 96.28 (C-1'); **9**β, $[\alpha]_D$ +37.2° (c 0.8), $\delta_H(CDCl_3)$, 4.752 (d, 7.8 Hz, H-1'), 4.613 (d, 3.7 Hz, H-1), $\delta_C(CDCl_3)$ 102.40 (C-1'), 98.27 (C-1).
19) **10**α, $\delta_H(CDCl_3)$ 5.671 (d, 3.7 Hz, H-1'), 4.551 (d, 7.8 Hz, H-1), $\delta_C(CDCl_3)$ 102.35 (C-1), 96.71 (C-1'); **10**β, $\delta_H(CDCl_3)$ 4.511 (d, 8.1 Hz, H-1), 4.480 (d, 7.6 Hz, H-1'), $\delta_C(CDCl_3)$ 102.51 (C-1'), 102.35 (C-1); Pure **10**β, m.p. 96-98°C, $[\alpha]_D$ +8.1° (c 0.8) was isolated by recrystallization from n-hexane-diethyl ether.
20) Prepared from p-nitrobenzoate **12**[21] by the tributylstannyl method[13]. $[\alpha]_D$ +51.1° (c 1.6), $\delta_H(CDCl_3)$ 5.397 (dd, 9.8, 9.5 Hz, H-4), 5.264 (d, 1.7 Hz, H-1), 4.161 (ddd, 9.8, 6.1, 3.2 Hz, H-5), 3.812 (dd, 3.2, 1.7 Hz, H-2), 3.773 (dd, 9.4, 3.2 Hz, H-3), 3.625 (dd, 10.7, 6.1 Hz, H-6), 3.555 (dd, 10.7, 3.2 Hz, H-6), 2.123 and 1.926 (2s, OAc and SMe), $\delta_C(CDCl_3)$ 83.38 (164.8 Hz, C-1).
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