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Preliminary communication

Iodonium ion-assisted glycosylation of alkyl (aryl) 1-thioglycosides: regulation of stereoselectivity and reactivity

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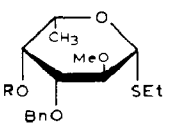
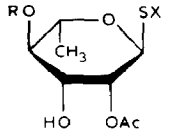
Recent studies from this laboratory revealed[1] that iodonium ion-mediated glycosylations of suitably protected alkyl 1-thioglycosides showed great promise for the synthesis of antigenic oligosaccharides[2]. In evaluating the scope of this glycosylation method, we now report a stereoselective and high-yielding approach toward the synthesis of an appropriately protected 1,2-*cis*-linked disaccharide (*i.e.*, **8**), which is a key intermediate in the preparation of the tetrasaccharide hapten 4-*O*-Me-α-L-Rha*p*-(1→4)-2-*O*-Me-α-L-Fuc*p*-(1→3)-α-L-Rha*p*-(1→2)-6-deoxytalitol[3] from the glycopeptidolipid antigen of *Mycobacterium avium* serotype 4.

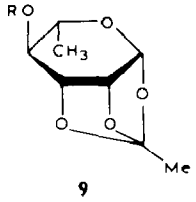
An effective route to **8** has to allow the stereoselective formation of a 1,2-*cis* linkage and extension at C-1 and C-4′ with L-talose and L-rhamnose units, respectively.



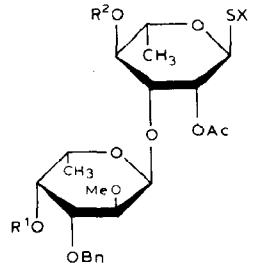
1 R = Allyl
2 R = $ClCH_2CO$
3 R = Ac



4 R = Bn, X = Et
5 R = Bz, X = Et
6 R = Bz, X = Ph
7 R = Bn, X = Ph



9



8a R^1 = Allyl, R^2 = Bn, X = Et
8b R^1 = Allyl, R^2 = Bz, X = Et
8c R^1 = $ClCH_2CO$, R^2 = Bn, X = Et
8d R^1 = $ClCH_2CO$, R^2 = Bz, X = Et
8e R^1 = Ac, R^2 = Bz, X = Et
8f R^1 = $ClCH_2CO$, R^2 = Bz, X = Ph
8g R^1 = $ClCH_2CO$, R^2 = Bn, X = Ph

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Thus, the ethyl 1-thio-L-fucopyranoside donor **1** (ref. 4) was coupled with the ethyl 1-thio-L-rhamnopyranoside acceptor **4** (ref. 2a) in the presence of 2 equiv. of iodonium dicollidine perchlorate (IDCP). Work-up and purification gave ethyl 2-*O*-acetyl-3-*O*-(4-*O*-allyl-3-*O*-benzyl-2-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzyl-1-thio-α-L-rhamnopyranoside (**8a**) (see Table I) as an α,β-mixture. However, an increase in the yield of ethyl 2-*O*-acetyl-3-*O*-(4-*O*-allyl-3-*O*-benzyl-2-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (**8b**), but not in stereoselectivity, was observed (Table I) when the acceptor **5** with BnO-4 replaced by BzO-4 was condensed with **1**. The higher yield of the latter condensation reaction may be rationalised on the basis of the following experiments. Treatment of **4** with IDCP (2 equiv.) (see footnote *a* in Table I) resulted in the rapid formation (2 min) of 4-*O*-benzyl-β-L-rhamnopyranose 1,2,3-orthoacetate (**9**, R = Bn, 45%), the ^{1}H and ^{13}C-n.m.r. data of which accorded with published data[5]. Likewise, **5** was converted, although at a lower rate, into 4-*O*-benzoyl-β-L-rhamnopyranose 1,2,3-orthoacetate (**9**, R = Bz). Therefore, the relatively slower cyclisation of **5** in **9** (R = Bz) will result in an enhanced yield of **8b**. On the other hand, the non-stereoselective outcome of both coupling reactions (Table I) may be attributed to the presence in **1** of the non-participating groups at C-2,4.

It was reasoned that replacement of the 4-*O*-allyl group by a chloroacetyl group would suppress[6] the formation of an intermediate oxycarbonium ion, thus favouring an S_N2-type reaction of the activated thioethyl group with an alcohol. However, IDCP-mediated condensation of **2** with **4** did not afford the expected product **8c** (Table I), but mainly **9** (R = Bn). Thus, the glycosylation of **4** by **2**, which is deactivated by the 4-chloroacetate group, cannot compete effectively with the IDCP-promoted internal cyclisation of **4** to give **9** (R = Bn). Indeed, glycosylation of the relatively less-active acceptor **5** with **2** gave exclusively (Table I) the 1,2-*cis* anomer ethyl 2-*O*-acetyl-4-*O*-benzoyl-3-*O*-(3-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-methyl-α-L-fucopyranosyl)-1-thio-α-L-rhamnopyranoside (**8d**), $[\alpha]_D^{25}$ −86°*, R_f 0.64 (97:3 dichloromethane–acetone). N.m.r. data ($CDCl_3$): ^{1}H, δ 5.23 (d, $J_{1,2}$ 1.3 Hz, H-1), 5.00 (d, $J_{1',2'}$ 3.7 Hz, H-1'); ^{13}C, δ 99.6 (C-1',

TABLE I

Yields and other data on the IDCP-assisted formation of the disaccharide derivatives **8a–g**

Donor	*Acceptor*	*Product*[a]	*Time (min)*	*Yield (%)*	*α,β-Ratio*[b]
1	**4**	**8a**	10	57	2:1
1	**5**	**8b**	10	80	2.5:1
2	**4**	**8c**	2	0	-
2	**5**	**8d**	20	65	1:0
3	**5**	**8e**	15	61	5:1
2	**6**	**8f**	20	80	1:0
2	**7**	**8g**	20	72	1:0

[a] Reactions conducted in 1:5 1,2-dichloroethane–ether. [b] Determined by ^{13}C-n.m.r. spectroscopy, *e.g.*, for **8b**: C-1α 99.5 p.p.m. ($J_{C-1,H-1}$ 168.5 Hz), C-1β 101.0 p.p.m. ($J_{C-1,H-1}$ 155.3 Hz).

* Values of $[\alpha]_D^{25}$ were measured for solutions (*c* 1) in $CHCl_3$. All new compounds gave satisfactory analyses.

$J_{C\text{-}1',H\text{-}1'}$ 168.5 Hz), 82.1 (C-1). The effect of the chloroacetyl group is illustrated by the condensation of the donor **3**, which has the chloroacetyl group replaced by acetyl group, with **5**, which gave a 5:1 α,β-mixture of ethyl 2-*O*-acetyl-3-*O*-(4-*O*-acetyl-3-*O*-benzyl-2-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (**8e**).

It was anticipated[7] that the formation of the required disaccharide derivative could be enhanced further, without affecting the stereoselectivity, by replacing SEt in the acceptor by SPh. Thus, condensation of **2** with the acceptor **6** gave (Table I) a high yield of phenyl 2-*O*-acetyl-4-*O*-benzoyl-3-*O*-(3-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-methyl-α-L-fucopyranosyl)-1-thio-α-L-rhamnopyranoside (**8f**), $[\alpha]_D^{25}$ −94°, R_F 0.44 (97:3 dichloromethane–acetone). N.m.r. data ($CDCl_3$: ^1H, δ 5.47 (s, H-1), 5.36 (d, $J_{1',2'}$ 3.1 Hz, H-1'); ^{13}C, δ 99.5 (C-1'; $J_{C\text{-}1',H\text{-}1'}$ 164.1 Hz), 85.8 (C-1). As expected, the IDCP-mediated conversion of **7** into **9** (R = Bz) proceeded sluggishly.

Thus, the nature of the protecting group at position 4 of ethyl thioglycosides may have a profound effect on the reactivity and stereospecificity in IDCP-assisted glycosylations. Furthermore, the pseudo-disarmed[8] ethyl thioglycosides **4** and **5**, which are readily activated by the thiophilic promoter IDCP originally devised[1a] for the chemoselective activation of armed ethyl thioglycosides (*i.e.*, **1–3**), can be transformed into the more truly-disarmed phenyl thioglycosides **6** and **7**. The latter deactivation effect was demonstrated further by the condensation of **2** with **7** to give, in sharp contrast with the result of the glycosylation of **4** (Table I), exclusively the 1,2-*cis*-linked product phenyl 2-*O*-acetyl-4-*O*-benzyl-3-*O*-(3-*O*-benzyl-4-*O*-chloroacetyl-2-*O*-methyl-α-L-fucopyranosyl)-1-thio-α-L-rhamnopyranoside (**8g**) in a good yield; $[\alpha]_D^{25}$ −118°, R_F 0.68 (97:3 dichloromethane–acetone). ^{13}C-N.m.r. data ($CDCl_3$): δ 99.5 (C-1', $J_{C\text{-}1',H\text{-}1'}$ 164.0 Hz), 85.5 (C-1).

Preliminary experiments showed that **8d,f,g** can be used to assemble the above-mentioned tetrasaccharide hapten via an *N*-iodosuccinimide–trifluoromethanesulfonic acid promoted[1b] glycosylation approach.

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