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Note

Steric effect of a bulky 6-substituent in the I^+-promoted glycosylation with pent-4-enyl and thioethyl glycosides

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Soft electrophiles such as iodonium dicollidine perchlorate (IDCP) can activate pent-4-enyl glycosides for glycosylation [1], but α- and β-glycosides were obtained in various proportions regardless of the nature of donors or acceptors (primary or secondary hydroxyl groups). It was claimed [1b] that the initial configuration of the glycosyl donor has no influence on the resulting glycosidic linkage.

We have investigated glycosylations of 1,2:5,6-di-*O*-isopropylidene-α-D-glycofuranose (**4**), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**5**), and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**6**) variously with pent-4-enyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside derivatives in which HO-6 was protected by a benzyl (**1**), a trityl (**2**), or a *tert*-butyldimethylsilyl group (**3**) in order to assess the effect of the bulk of the 6-substituent. Table I gives the reaction conditions and results which show that the presence of a bulky 6-substituent (*a*) increases significantly the proportion of the α product (entries 1, 3, and 4); (*b*) decreases the yield when a secondary hydroxyl group is glycosylated (entries 1, 3, and 4), but the effect is less or opposite when a primary hydroxyl group is involved (entries 2 and 5–7); (*c*) lowers the increase in yield of the α product when a primary hydroxyl group is glycosylated (entries 2, 5, 6, and 9); and (*d*) gives a much better yield of the α anomer when there is a higher proportion of ether in the solvent as already noted [1a,2] (entries 6–8).

Veeneman and van Boom [3] reported on iodonium-promoted *cis*-glycosylation starting from thioethyl glycosides. Taking into account the above results, we have investigated such glycosylations with the 6-*O*-benzyl (**7**) and 6-*O*-trityl (**8**) derivatives of ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside. The results are shown in Table II which reveal the same directing effect as for the glycosylations in Table

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TABLE I

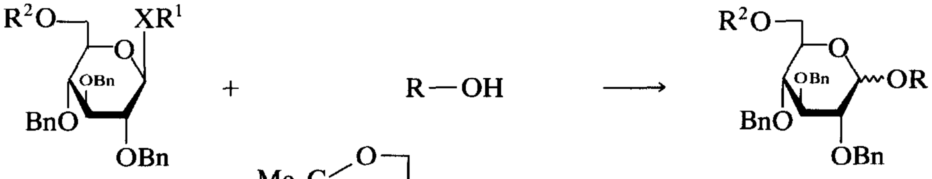
IDCP-promoted glycosylations of pent-4-enyl glycosides

Entry	Donor	Acceptor group	Product [a]	Time (h)	Solvent [b]	Yield (%) [c]	$\alpha:\beta$ Ratio [d]
1	**1**	**4**	**10**α,β	1.00	A	84	3:1
2	**1**	**5**	**11**α,β	0.50	A	80	1:1.4
3	**2**	**4**	**12**α,β	2.50	A	53	13:1
4	**3**	**4**	**13**α,β	0.40	A	56	7:1
5	**3**	**5**	**14**α,β	1.00	A	92	1.4:1
6	**2**	**5**	**15**α,β	1.25	A	91	1.9:1
7	**2**	**5**	**15**α,β	5.00	B	70	7:1
8	**2**	**5**	**15**α	12.0	C	52	1:0
9	**2**	**6**	**16**α,β	1.00	A	53	2.5:1

[a] All reactions were carried out at room temperature under nitrogen, in the presence of 4A molecular sieves: donor–acceptor–IDCP = 1:1:5:2. [b] A, CH_2ClCH_2Cl; B, 1:1.5 $CH_2ClCH_2Cl–Et_2O$; C, 1:5 $CH_2ClCH_2Cl–Et_2O$. [c] Products isolated by column chromatography or HPLC on SiO_2. [d] Determined by ^{1}H-NMR spectroscopy.

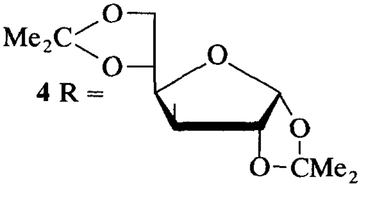
I. Glycosylation of the secondary OH group in **4** was stereospecific (entry 3) even in 1,2-dichloroethane which is known to disfavour *cis*-glycosylation as compared to ether.

Thus, the presence of a bulky 6-substituent affects the steric course of the glycosylation reaction and increases the proportion of α-glycosides even if there is some loss of yield. Since the phenomenon was observed with both pent-4-enyl and thioethyl glycosides, steric hindrance may affect the course of the reaction, possibly because of shielding of the β face of the anomeric carbocationic transition-state.



1 R^1 = pent-4-enyl, R^2 = Bn, X = O
2 R^1 = pent-4-enyl, R^2 = Tr, X = O
3 R^1 = pent-4-enyl, R^2 = $^tBuMe_2Si$, X = O
7 R^1 = Et, R^2 = Bn, X = S
8 R^1 = Et, R^2 = Tr, X = S

4 R =



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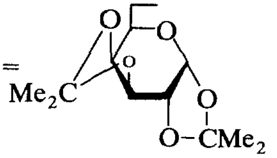

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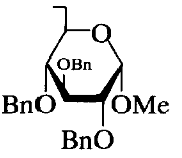

10 R = **4**, R^2 = Bn
11 R = **5**, R^2 = Bn
12 R = **4**, R^2 = Tr
13 R = **4**, R^2 = $^tBuMe_2Si$
14 R = **5**, R^2 = $^tBuMe_2Si$
15 R = **5**, R^2 = Tr
16 R = **6**, R^2 = Tr
17 R = **6**, R^2 = Bn

TABLE II

IDCP-promoted glycosylations of thioethyl glycosides

Entry	Donor	Acceptor group	Product [a]	Time (h)	Solvent [b]	Yield (%) [c]	$\alpha:\beta$ Ratio [d]
1	**7**	**6**	**17**α,β	2.30	B	68%	5.3:1
2	**8**	**6**	**16**α,β	12.0	B	48%	7.35:1
3	**8**	**4**	**12**α	10.0	A	65%	1:0

[a] All reactions were carried out at room temperature under nitrogen, in the presence of 4A molecular sieves: donor–acceptor–IDCP = 1:0.9:2, 1:0.9:4, 1:0.9:10; added in small portions until no further reaction occurred. [b] A, CH_2ClCH_2Cl; B, 1:5 CH_2ClCH_2Cl–Et_2O. [c] Products isolated by column chromatography or HPLC on SiO_2. [d] Determined by ^{1}H-NMR spectroscopy.

EXPERIMENTAL

General methods.—All solvents were dried. The glycosylation reactions were conducted under N_2, and monitored by TLC on Silica Gel 60 (Riedel-de-Haën, 37332), using 7:3 hexane–EtOAc and detection by charring with H_2SO_4. Flash column chromatography was performed on Silica Gel 60 (Merck, 70–230 mesh). HPLC was performed on a Merck apparatus with refractive index detection, a home-packed column of SiO_2 (10 μm), and elution with 9:1 hexane–EtOAc at 3 mL/min. The ^{1}H- and ^{13}C-NMR spectra were recorded for solutions in $CDCl_3$ or $(CD_3)_2CO$ (internal Me_4Si) with a Bruker AC200 or AM400 spectrometer.

Compounds **1–8** were prepared by standard methods (benzylation [4], silylation [5], thioglycosidation [3b]). The pent-4-enyl β-glycosides were obtained by Koenigs–Knorr synthesis with the glycosyl bromides in the presence of silver carbonate.

Glycosylation reactions.—To a solution of donor (0.10 mmol) and acceptor (0.15 mmol) in 1,2-dichloroethane (1 mL) were added freshly powdered 4A molecular

TABLE III

NMR data [a] for **10**α to **17**β (δ in ppm, J in Hz)

	10α	**10**β	**11**α	**11**β	**12**α	**12**β	**13**α	**13**β
H-1	5.88	6.00	5.44	5.49	5.88	5.82	5.88	5.75
$J_{1,2}$	3.50	3.67	5.01	4.94	3.51	3.82	3.56	3.83
H-1′	5.25	4.45	4.93	4.44	5.36	4.53	5.21	4.45
$J_{1',2'}$	3.53	7.76	3.85	7.50	3.46	7.76	3.51	7.82
C-1	105.13	105.23	96.22	96.31	104.34 *	104.07 *	104.30 *	104.10 *
C-1′	97.96	101.45	96.97	104.28	97.03 *	99.71 *	97.12 *	99.92 *

	14α	**14**β	**15**α	**15**β	**16**α	**16**β	**17**α	**17**β
H-1	5.52	5.57	5.51	5.59	4.55	4.68	4.54	4.60
$J_{1,2}$	5.03	5.00	4.98	5.01	3.49	3.40	3.54	3.21
H-1′	5.00	4.44	5.12	4.51	5.08	4.35	4.96	4.34
$J_{1',2'}$	3.45	7.75	3.67	7.22	3.53	7.35	3.49	7.72
C-1	95.43 *	95.49 *	96.26	96.35	97.83	98.18	97.81	97.94
C-1′	95.67 *	102.92 *	96.26	104.19	96.93	103.74	97.12	103.69

[a] Obtained for solutions in $CDCl_3$ or $(CD_3)_2CO$ *.

sieves, and the mixture was stirred under N_2 for 30 min. Iodonium dicollidine perchlorate (IDCP, 0.2 mmol) was then added, and the reaction was monitored by TLC. At completion, the solution was diluted with CH_2Cl_2, filtered, and washed successively with aq sodium thiosulfate and water, dried, and concentrated. Column chromatography or HPLC of the residue afforded an α,β-mixture of the disaccharide derivatives.

The FAB-mass spectra of the disaccharides derivatives **11**–**17** each contained pseudomolecular ions $(M + Cs)^+$ at m/z $(M + 132.9)^+$ and some for $(M - H)^+$. $PhCH_2^+$ (m/z 90.8) was the base peak except for tritylated products for which it was Tr^+ (m/z 243.1): **11** $(M + Cs)^+$ 915.4 (8%), **12** $(M + Cs)^+$ 1067.6 (9%), **13** $(M + Cs)^+$ 939 (13%), $(M - H)^+$ 805.1 (2%), **14** $(M + Cs)^+$ 939 (10%), $(M - H)^+$ 805.1 (1%), **15** $(M + Cs)^+$ 1067.6 (8%), **16** $(M + Cs)^+$ 1270.9 (2.1%), **17** $(M + Cs)^+$ 1118.9 (1.6%). The NMR data are given in Table III.

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