An unexpected allyl-transfer reaction under conditions of Lewis acid-promoted cyclization of homoallylic alcohols with aldehydes

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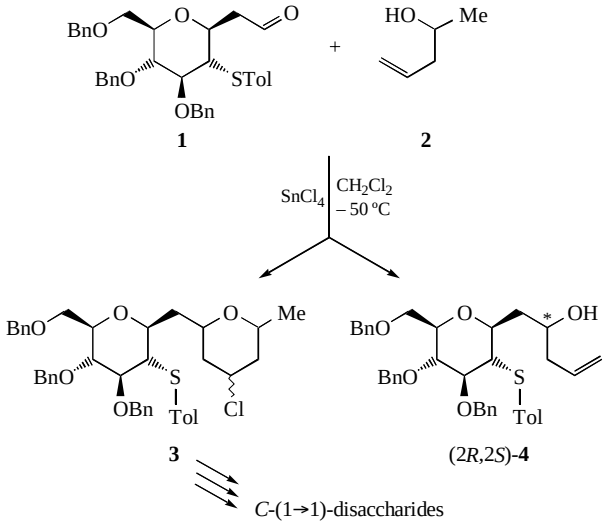
The title reaction was observed along with cyclization in the $SnCl_4$-promoted reaction of 2-[3,4,6-tri-*O*-benzyl-2-deoxy-2-(*p*-tolylsulfanyl)-β-D-glucopyranosyl]ethanal with pent-4-en-2-ol and this result was interpreted in terms of anchimeric assistance by sulfur to the unusual fragmentation of an intermediate alkoxycarbenium ion.

The Lewis acid-promoted cyclization of homoallylic alcohols with aldehydes or their acetals was suggested for the preparation of 2,6-disubstituted tetrahydropyran derivatives,[1,2] potential precursors of *C*-glycosides[2] and other cyclic polyethers. An application of this cyclization to recently synthesised 2-[2-deoxy-2-arylsulfanyl-β-D-gluco(or manno)pyranosyl]ethanals[3] (*e.g.* **1**, Scheme 1) promised to provide a convenient route to *C*-(1→1)-disaccharides.



Scheme 1

However, we have found that the $SnCl_4$-promoted reaction of 2-[3,4,6-tri-*O*-benzyl-2-deoxy-2-(*p*-tolylsulfanyl)-β-D-glucopyranosyl]ethanal[3(c)] **1** with pent-4-en-2-ol **2** under standard conditions[2,†] did not lead to the anticipated smooth formation of compound **3** (Scheme 1), but a complicated mixture of many products was formed. A flash-chromatographic separation of this mixture afforded two new homoallylic alcohols (2*S*)-**4** and (2*R*)-**4** as the major isolated products (33% and 13%, respectively).

A single set of signals was observed in ^{1}H and ^{13}C NMR spectra for each of compounds (2*S*)-**4** and (2*R*)-**4**, thus proving that these are individual diastereomers.[‡] The signals in well-resolved ^{1}H NMR spectra (300 MHz) were assigned using the COSY and homonuclear decoupling techniques. The large spin–spin coupling constants $H^{1'}$–$H^{2'}$, $H^{2'}$–$H^{3'}$, $H^{3'}$–$H^{4'}$ and $H^{4'}$–$H^{5'}$ proved the *trans*-diaxial orientation of these pairs of protons and, consequently, the equatorial position of all substituents (Figure 1).

More interestingly, large coupling constants were also observed for the $H^{1'}$–H^{1a} and H^{1a}–H^2 interactions in (2*S*)-**4** (Table 1, Figure 1) in both C_6D_6 and $CDCl_3$ indicating a predominantly antiperiplanar orientation of these pairs of protons [compare to the corresponding couplings in (2*R*)-**4** and to the medium size of $^3J_{H^2H^{3a}}$ and $^3J_{H^2H^{3b}}$, Table 1]. This fact points to the strong predominance of a certain conformation for the side chain of the molecule. Only the (*S*)-configuration of the new chiral

† A solution of $SnCl_4$ (86 mg, 0.33 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a stirred cold (–50 °C) solution of pent-4-en-2-ol (25 mg, 0.29 mmol) and aldehyde **1**[3] (140 mg, 0.24 mmol) in CH_2Cl_2 (15 ml) under N_2. The mixture was stirred for 28 h at room temperature and quenched at 0 °C by the dropwise addition of cold 1 M HCl (5 ml). The standard extraction procedure and evaporation gave a colourless oil, which was separated by flash chromatography (silica gel, hexane:ether = = 4:1) affording 60 mg of a complex mixture of cyclization products (^{1}H and ^{13}C NMR data) in addition to 50 mg (33%) of (2*S*)-**4** and 20 mg (13%) of (2*R*)-**4**. The purity of (2*S*)-**4** and (2*R*)-**4** (not less than 95%) was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The composition was proved by HRMS.

‡ *(2S)-1-[3,4,6-tri-O-benzyl-2-deoxy-2-(p-tolylsulfanyl)-β-D-glucopyranosyl]pent-4-en-2-ol* (2*S*)-**4**: white crystals, mp 113–114 °C. $[\alpha]_D^{25}$ = –22.2° (*c*, 0.02, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6) δ: 1.53 (dt, 1H, H^{1a}, *J* 14.4 and 9.6 Hz), 1.98 (s, 3H, MeAr), 2.25 (br. ddd, 1H, H^{3b}, *J* 6.1, 7.6 and 13.8 Hz), 2.42 (br. dt, 1H, H^{3a}, *J* 13.8 and 6.3 Hz), 2.59 (dt, 1H, H^{1b}, *J* 14.4 and 2.1 Hz), 2.97 (t, 1H, $H^{2'}$, *J* 10.4 Hz), 3.30 (ddd, 1H, $H^{5'}$, *J* 2.1, 5.5 and 9.3 Hz), 3.42 (ddd, 1H, $H^{1'}$, *J* 2.1, 9.6 and 10.4 Hz), 3.45 (br. t, 2H, $H^{3'}$ + $H^{4'}$, *J* ~ 10 Hz), 3.52 (m, 2H, $H^{6'}$), 3.70 (br. s, 1H, OH), 4.02 (ddt, 1H, H^2, *J* 2.1, 9.6 and 6.2 Hz), 4.26 (d, 1H, OCH_2Ph, *J* 12.1 Hz), 4.31 (d, 1H, OCH_2Ph, *J* 12.1 Hz), 4.50 (d, 1H, OCH_2Ph, *J* 11.3 Hz), 4.81 (d, 1H, OCH_2Ph, *J* 11.3 Hz), 4.91 (d, 1H, OCH_2Ph, *J* 10.4 Hz), 5.08 (br. d, 2H, H^{5a} + H^{5b}, *J* ~ 14 Hz), 5.11 (d, 1H, OCH_2Ph, *J* 10.4 Hz), 6.02 (dddd, 1H, H^4, *J* 6.5, 7.6, 9.5 and 18.0 Hz), 6.81 (d, 2H, SC_6H_4Me, *J* 8.0 Hz), 7.03–7.24 (m, 11H, Ar), 7.28 (d, 2H, Ar, *J* 7.1 Hz), 7.41 (d, 2H, Ar, *J* 6.9 Hz), 7.47 (d, 2H, SC_6H_4Me, *J* 8.0 Hz). ^{13}C NMR (75.5 MHz, C_6D_6) δ: 21.13 (Me), 39.54 (CH_2), 42.81 (CH_2), 58.46 (CH), 69.69 (CH_2), 71.83 (CH), 73.66 (CH_2), 75.05 (CH_2), 76.37 (CH_2), 78.91 (CH), 80.24 (CH), 82.17 (CH), 84.94 (CH), 116.99 (=CH_2), 127.85 (CH_{Ar}), 127.92 (CH_{Ar}), 128.25 (CH_{Ar}), 128.52 (CH_{Ar}), 128.60 (CH_{Ar}), 128.68 (CH_{Ar}), 130.13 (CH_{Ar}), 132.42 (C_{Ar}), 132.77 (CH_{Ar}), 135.84 (=CH–), 137.34 (C_{Ar}), 138.64 (C_{Ar}), 138.97 (C_{Ar}), 139.27 (C_{Ar}); some CH_{Ar} signals overlapped with C_6D_6 signals. HRMS, *m/z*: found 625.3010; calc. for $C_{39}H_{44}O_5S$ (MH^+) 625.2990.

(2R)-1-[3,4,6-tri-O-benzyl-2-deoxy-2-(p-tolylsulfanyl)-β-D-glucopyranosyl]pent-4-en-2-ol (2*R*)-**4**: colourless oil, $[\alpha]_D^{25}$ = ~0° (*c*, 0.01, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6) δ: 1.81 (ddd, 1H, H^{1a}, *J* 2.2, 7.7 and 14.6 Hz), 1.98 (s, 3H, MeAr), 2.05 (br. dt, 1H, H^{3b}, *J* 14 and 7 Hz), 2.17 (br. dt, 1H, H^{3a}, *J* 14 and 7 Hz), 2.33 (ddd, 1H, H^{1b}, *J* 2.8, 9.3 and 14.6 Hz), 2.60 (br. s, 1H, OH), 3.12 (t, 1H, $H^{2'}$, *J* 10.7 Hz), 3.25 (dt, 1H, $H^{5'}$, *J* 9.8 and 3.0 Hz), 3.49 (dd, 1H, $H^{3'}$, *J* 8.7 and 10.7 Hz), 3.56 (d, 2H, $H^{6'}$, *J* 3.0 Hz), 3.70 (br. t, 2H, $H^{1'}$ + $H^{4'}$, *J* ~ 9.2 Hz), 3.93 (ddt, 1H, H^2, *J* 2.2, 9.3 and 7 Hz), 4.27 (d, 1H, OCH_2Ph, *J* 12.1 Hz), 4.35 (d, 1H, OCH_2Ph, *J* 12.1 Hz), 4.58 (d, 1H, OCH_2Ph, *J* 11.3 Hz), 4.86 (d, 1H, OCH_2Ph, *J* 11.3 Hz), 4.93 (d, 1H, OCH_2Ph, *J* 10.7 Hz), 5.00 (br. d, 2H, H^{5a} + H^{5b}, *J* ~ 13 Hz), 5.12 (d, 1H, OCH_2Ph, *J* 10.7 Hz), 5.80 (ddt, 1H, H^4, *J* 9.6, 17.7 and 7 Hz), 6.80 (d, 2H, SC_6H_4Me, *J* 8.0 Hz), 7.02–7.30 (m, 13H, Ar), 7.43 (br. d, 2H, Ar, *J* 7.7 Hz), 7.50 (d, 2H, SC_6H_4Me, *J* 8.0 Hz). ^{13}C NMR (75.5 MHz, C_6D_6) δ: 21.11 (Me), 39.18 (CH_2), 42.82 (CH_2), 57.33 (CH), 68.05 (CH_2), 69.44 (CH), 73.61 (CH_2), 75.01 (CH_2), 76.29 (CH_2), 78.88 (CH), 79.05 (CH), 80.16 (CH), 85.06 (CH), 117.07 (=CH_2), 127.84 (CH_{Ar}), 128.23 (CH_{Ar}), 128.49 (CH_{Ar}), 128.57 (CH_{Ar}), 128.63 (CH_{Ar}), 130.09 (CH_{Ar}), 132.51 (C_{Ar}), 132.83 (CH_{Ar}), 135.74 (=CH–), 137.21 (C_{Ar}), 138.80 (C_{Ar}), 139.23 (C_{Ar}), 139.42 (C_{Ar}); some CH_{Ar} signals overlapped with C_6D_6 signals. HRMS, *m/z*: found 625.2982; calc. for $C_{39}H_{44}O_5S$ (MH^+) 625.2990.

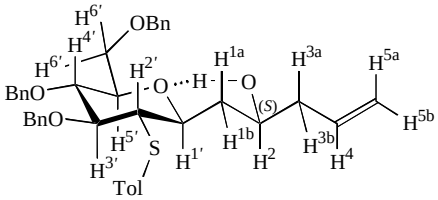
Table 1 Selected coupling constants, $^3J_{HH}$/Hz, in ^{1}H NMR (300 MHz) spectra of (2*S*)-**4** and (2*R*)-**4**.

$^3J_{HH}$	(2*S*)-**4**			(2*R*)-**4**		
	$CDCl_3$	C_6D_6	[$^2H_6$]acetone	$CDCl_3$	C_6D_6	[$^2H_6$]acetone
$H^{1'}$–H^{1a}	9.9	9.6	9.5	7.4	7.7	9.5
$H^{1'}$–H^{1b}	1.9	2.1	2.2	3.0	2.8	2.0
H^{1a}–H^2	9.9	9.6	7.8	2.2	2.2	2.3
H^{1b}–H^2	1.9	2.1	4.4	9.1	9.3	9.6
H^2–H^{3a}	6.1	6.2	6.0	7	7	6.5
H^2–H^{3b}	6.3	6.1	6.3	7	7	6.5

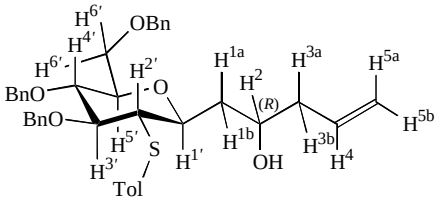
centre can enable the molecule to adopt the lowest energy conformation with a relaxed zigzag shape of the $C^{1'}C^1C^2C^3$ side chain and a stabilising intramolecular hydrogen bond (Figure 1). The downfield shift of the OH signal in C_6D_6 for (2*S*)-**4** (3.7 ppm) as compared to that for (2*R*)-**4** (2.6 ppm) is an indication of such a hydrogen bond.[4] This interpretation is also supported by a measurement in [$^2H_6$]acetone. Being a strong hydrogen-bond acceptor, acetone is capable of breaking the intramolecular hydrogen bond. This decreases the relative stability of the conformation depicted in Figure 1 and increases the population of other possible conformations (*cf.* ref. 5). As a result, the observed averaged coupling constants $^3J_{H^{1a}H^2}$ and $^3J_{H^{1b}H^2}$ have changed towards the medium values in an acetone solution of (2*S*)-**4** (Table 1). These changes are stronger for $^3J_{H^{1a}H^2}$ and $^3J_{H^{1b}H^2}$ than for $^3J_{H^{1'}H^{1a}}$ and $^3J_{H^{1'}H^{1b}}$. This indicates a larger degree of freedom for the internal rotation around the C^1–C^2 bond as compared with the rotation around the $C^{1'}$–C^1 bond.

Similarly, the large values of $^3J_{H^{1'}H^{1a}}$ and $^3J_{H^{1b}H^2}$ measured for (2*R*)-**4** in an [$^2H_6$]acetone solution (Table 1) attest to a predominance of the low energy zigzag conformation of the $C^{1'}C^1C^2C^3$ side chain (Figure 1). The possibility of intramolecular hydrogen bonding in C_6D_6 and $CDCl_3$ solutions makes alternative unstable conformations less unfavourable and changes $^3J_{H^{1'}H^{1a}}$ and $^3J_{H^{1'}H^{1b}}$ towards medium values.

The transfer of an allyl moiety from a homoallylic alcohol to an aldehyde has never been observed in Lewis acid-promoted cyclizations.[1,2] However, this interesting type of transfer was described recently[6] for essentially different conditions: a catalytic amount of $Sn(OTf)_2$ as a Lewis acid, molecular sieves and various derivatives of 2-methylpent-4-en-2-ol at –25 °C or at room temperature were used for allylation of aldehydes. Due to an additional 2-methyl group in the homoallylic alcohol, the reaction could proceed *via* a stable tertiary alkoxycarbenium ion, and emission of acetone appeared to be the driving force of the process.[6] Tin(II) triflate was unable to stabilise the intermediate cation(s) by providing a nucleophile for addition or a base for proton removal. Contrary to that, in this work we used a 40% excess of tin(IV) chloride providing the abundance of nucleophilic chloride anions. Therefore, we anticipated the

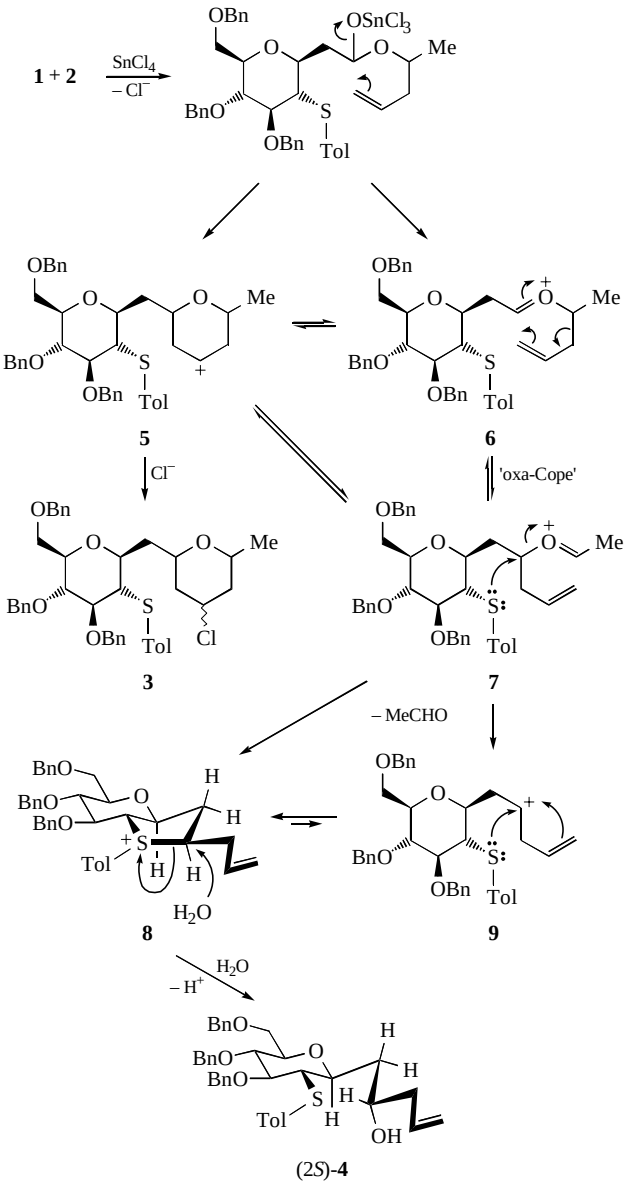


(2*S*)-**4**



(2*R*)-**4**

Figure 1



Scheme 2

transformation of intermediate cyclic cation **5** into the cyclization product **3** (Scheme 2, *cf.* refs. 1,2). The unexpected formation of allyl-transfer products **4** can be explained by the alternative reaction pathway depicted in Scheme 2. The act of allyl transfer can occur *via* alkoxycarbenium ion **7** formed either by the 'oxa-Cope' rearrangement[1(*k*),6] of alkoxycarbenium ion **6** or by its cyclization into cation **5** followed by ring opening. The anchimeric assistance by sulfur must play a crucial role in the ejection of acetaldehyde, transforming **7** into stable bicyclic sulfonium ion **8**. It is reasonable to assume that the randomly oriented allyl group in **8** is able to adopt eventually the more stable pseudo-equatorial position due to the reversible breaking of the C–S bond with the formation of cation **9** or a corresponding chloride.§ The last step of transformations occurred during a standard treatment of the reaction mixture. The predominant formation of (2*S*)-**4** diastereomer should be expected as a result of a rear-side nucleophilic displacement by water of the C–S bond (Scheme 2). In order to prove this mechanism unambiguously, we are currently exploring the possibility of using nucleophiles other than H_2O.

§ Homoallylic cation **9** can be stabilised by the participation of neighbouring double bond leading to formation of a nonclassic carbenium ion.[7] This latter can result in various cyclization products.

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