

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

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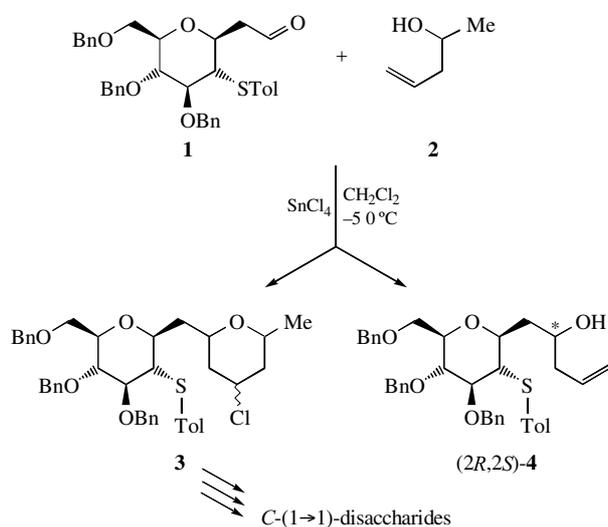
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The title reaction was observed along with cyclization in the SnCl₄-promoted reaction of 2-[3,4,6-tri-*O*-benzyl-2-deoxy-2-(*p*-tolylsulfanyl)-*D*-glucopyranosyl]ethanal with pent-4-en-2-ol and this result was interpreted in terms of anchimeric assistance 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*-glycosides² and other cyclic polyethers. An application of this cyclization to recently synthesised 2-[2-deoxy-2-arylsulfanyl-*D*-gluco(or manno)pyranosyl]ethanals³ (e.g. **1**, Scheme 1) promised to provide a convenient route to *C*-(1→1)-disaccharides.



However, we have found that the SnCl₄-promoted reaction of 2-[3,4,6-tri-*O*-benzyl-2-deoxy-2-(*p*-tolylsulfanyl)-*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 ¹H and ¹³C 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 ¹H NMR spectra (300 MHz) were assigned using the

[†] A solution of SnCl₄ (86 mg, 0.33 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (15 ml) under N₂. 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 (¹H and ¹³C 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 ¹H and ¹³C NMR spectroscopy. The composition was proved by HRMS.

COSY and homonuclear decoupling techniques. The large spin-spin coupling constants H¹-H^{2'}, H²-H^{3'}, H³-H^{4'} and H⁴-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 H¹-H^{1a} and H^{1a}-H² interactions in (2*S*)-**4** (Table 1, Figure 1) in both C₆D₆ and CDCl₃ 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_{H²H^{3a}} and ³J_{H²H^{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

[‡] (2*S*)-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. [α]_D²⁵ = –22.2° (c, 0.02, CHCl₃). ¹H NMR (300 MHz, C₆D₆) 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, H², *J* 2.1, 9.6 and 6.2 Hz), 4.26 (d, 1H, OCH₂Ph, *J* 12.1 Hz), 4.31 (d, 1H, OCH₂Ph, *J* 12.1 Hz), 4.50 (d, 1H, OCH₂Ph, *J* 11.3 Hz), 4.81 (d, 1H, OCH₂Ph, *J* 11.3 Hz), 4.91 (d, 1H, OCH₂Ph, *J* 10.4 Hz), 5.08 (br. d, 2H, H^{5a} + H^{5b}, *J* ~ 14 Hz), 5.11 (d, 1H, OCH₂Ph, *J* 10.4 Hz), 6.02 (dddd, 1H, H⁴, *J* 6.5, 7.6, 9.5 and 18.0 Hz), 6.81 (d, 2H, SC₆H₄Me, *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, SC₆H₄Me, *J* 8.0 Hz). ¹³C NMR (75.5 MHz, C₆D₆) δ: 21.13 (Me), 39.54 (CH₂), 42.81 (CH₂), 58.46 (CH), 69.69 (CH₂), 71.83 (CH), 73.66 (CH₂), 75.05 (CH₂), 76.37 (CH₂), 78.91 (CH), 80.24 (CH), 82.17 (CH), 84.94 (CH), 116.99 (=CH₂), 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 C₆D₆ signals. HRMS, *m/z*: found 625.3010; calc. for C₃₉H₄₄O₅S (MH⁺) 625.2990.

(2*R*)-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, [α]_D²⁵ = –0° (c, 0.01, CHCl₃). ¹H NMR (300 MHz, C₆D₆) 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, H², *J* 2.2, 9.3 and 7 Hz), 4.27 (d, 1H, OCH₂Ph, *J* 12.1 Hz), 4.35 (d, 1H, OCH₂Ph, *J* 12.1 Hz), 4.58 (d, 1H, OCH₂Ph, *J* 11.3 Hz), 4.86 (d, 1H, OCH₂Ph, *J* 11.3 Hz), 4.93 (d, 1H, OCH₂Ph, *J* 10.7 Hz), 5.00 (br. d, 2H, H^{5a} + H^{5b}, *J* ~ 13 Hz), 5.12 (d, 1H, OCH₂Ph, *J* 10.7 Hz), 5.80 (ddt, 1H, H⁴, *J* 9.6, 17.7 and 7 Hz), 6.80 (d, 2H, SC₆H₄Me, *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, SC₆H₄Me, *J* 8.0 Hz). ¹³C NMR (75.5 MHz, C₆D₆) δ: 21.11 (Me), 39.18 (CH₂), 42.82 (CH₂), 57.33 (CH), 68.05 (CH₂), 69.44 (CH), 73.61 (CH₂), 75.01 (CH₂), 76.29 (CH₂), 78.88 (CH), 79.05 (CH), 80.16 (CH), 85.06 (CH), 117.07 (=CH₂), 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 C₆D₆ signals. HRMS, *m/z*: found 625.2982; calc. for C₃₉H₄₄O₅S (MH⁺) 625.2990.

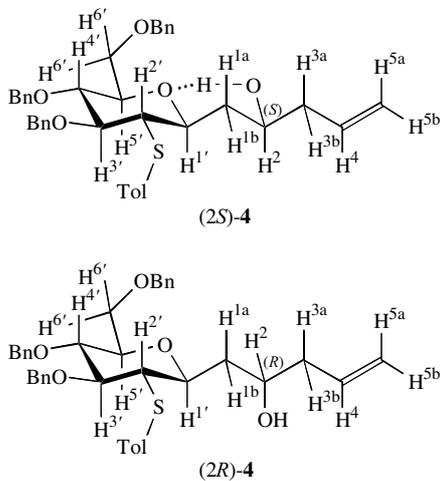
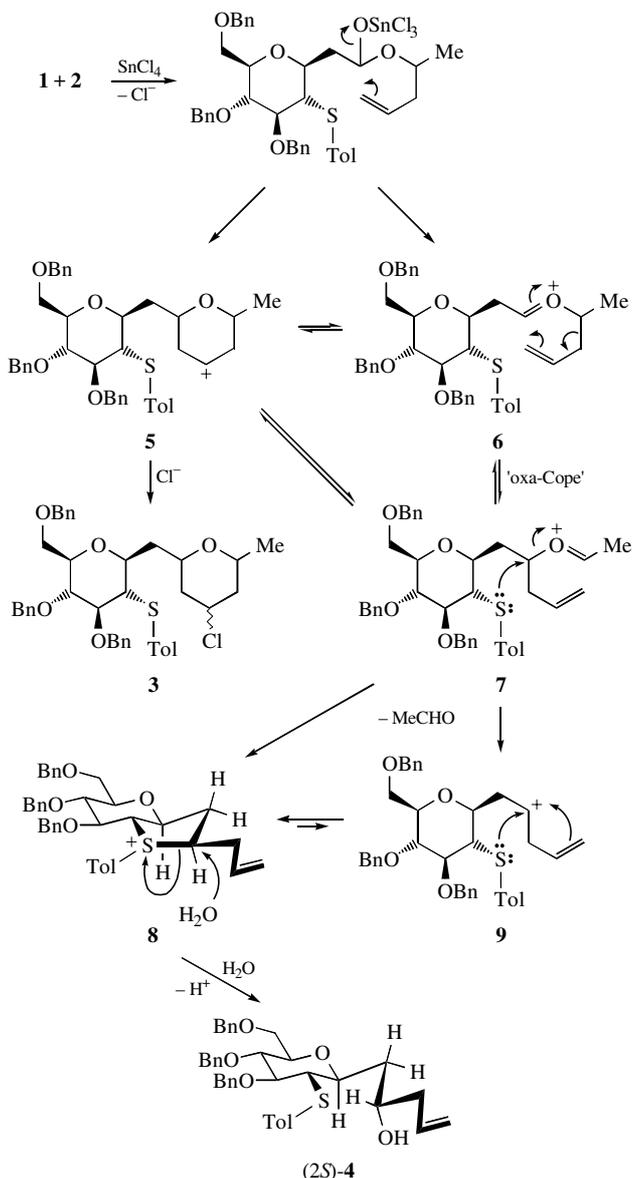
Table 1 Selected coupling constants, $^3J_{\text{HH}}/\text{Hz}$, in ^1H NMR (300 MHz) spectra of (2*S*)-**4** and (2*R*)-**4**.

$^3J_{\text{HH}}$	(2 <i>S</i>)- 4			(2 <i>R</i>)- 4		
	CDCl_3	C_6D_6	$[\text{D}_6]\text{acetone}$	CDCl_3	C_6D_6	$[\text{D}_6]\text{acetone}$
$\text{H}^1\text{-H}^{1a}$	9.9	9.6	9.5	7.4	7.7	9.5
$\text{H}^1\text{-H}^{1b}$	1.9	2.1	2.2	3.0	2.8	2.0
$\text{H}^{1a}\text{-H}^2$	9.9	9.6	7.8	2.2	2.2	2.3
$\text{H}^{1b}\text{-H}^2$	1.9	2.1	4.4	9.1	9.3	9.6
$\text{H}^2\text{-H}^{3a}$	6.1	6.2	6.0	7	7	6.5
$\text{H}^2\text{-H}^{3b}$	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 $\text{C}^1\text{C}^1\text{C}^2\text{C}^3$ 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 $[\text{D}_6]\text{acetone}$. 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 $^3J_{\text{H}^1\text{H}^2}$ and $^3J_{\text{H}^1\text{H}^2}$ have changed towards the medium values in an acetone solution of (2*S*)-**4** (Table 1). These changes are stronger for $^3J_{\text{H}^1\text{H}^2}$ and $^3J_{\text{H}^1\text{H}^2}$ than for $^3J_{\text{H}^1\text{H}^1a}$ and $^3J_{\text{H}^1\text{H}^1b}$. This indicates a larger degree of freedom for the internal rotation around the $\text{C}^1\text{-C}^2$ bond as compared with the rotation around the $\text{C}^1\text{-C}^1$ bond.

Similarly, the large values of $^3J_{\text{H}^1\text{H}^1a}$ and $^3J_{\text{H}^1\text{H}^2}$ measured for (2*R*)-**4** in an $[\text{D}_6]\text{acetone}$ solution (Table 1) attest to a predominance of the low energy zigzag conformation of the $\text{C}^1\text{C}^1\text{C}^2\text{C}^3$ 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 $^3J_{\text{H}^1\text{H}^1a}$ and $^3J_{\text{H}^1\text{H}^1b}$ 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 recently⁶ for essentially different conditions: a catalytic amount of $\text{Sn}(\text{OTf})_2$ as a Lewis acid, molecular sieves and various derivatives of 2-methylpent-4-en-2-ol at $-25\text{ }^\circ\text{C}$ 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 alkoxy-carbenium 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

**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* alkoxy-carbenium ion **7** formed either by the 'oxa-Cope' rearrangement^{1(k),6} of alkoxy-carbenium 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.⁸ 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 .

⁸ Homoallylic cation **9** can be stabilised by the participation of neighbouring double bond leading to formation of a nonclassical carbenium ion.⁷ This latter can result in various cyclization products.

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