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Enantiomerically enriched [2-^{2}H]-isopentenyl alcohol from (*E*)-2-methylbut-2-ene-1,4-diol by an asymmetric retro-ene reaction

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A sample of [2-^{2}H]-isopentenyl alcohol containing 72% of the (*S*)-enantiomer has been prepared *via* pyrolysis of a C-1′ deuterated form of the 1-tetra-*O*-acetyl-β-D-glucoside of (*E*)-2-methylbut-2-ene-1,4-diol.

The retro-ene reaction of allyl acetals is a thermal sigmatropic rearrangement that leads to the formation of olefins and esters.[1,2] This reaction takes place under milder temperatures than the retro-ene reaction of allyl ethers,[3] and has been applied to the synthesis of allyl esters[4] and of chirally labelled [2-^{2}H, 2-^{3}H]-acetic acid.[5] In connection with continuing investigations of the deoxyxylulose pathway of isoprenoid biosynthesis,[6] experiments were carried out to determine whether stereospecifically labelled [2-^{2}H]-isopentenyl alcohol could be prepared by means of the retro-ene reaction.[7]†

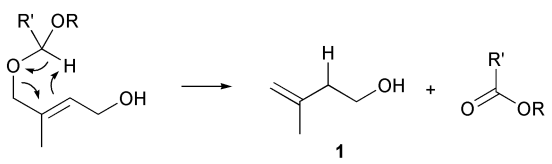
Isopentenyl alcohol (**1**) is the expected product of retro-ene pyrolysis of a 1-acetal of (*E*)-2-methylbut-2-ene-1,4-diol. A stereospecific transfer of the acetal H-atom to the 2-position of isopentenyl alcohol could be achieved, in principle, by pyrolysis of a chiral acetal such as a glycoside. In order to test this possibility, the 1-tetraacetyl-β-D-glucoside of (*E*)-2-methylbut-2-ene-1,4-diol (**2**) and its silyl derivative **4** were synthesized and subjected to pyrolysis.

Königs–Knorr coupling of acetobromoglucose (**3**) with the known silyl protected diol **4**[8] led to the silyl protected tetraacetylglucoside **5** (Fig. 1). In the presence of silver trifluoroacetate,[9] the reaction proceeded with partial desilylation, which could be avoided through the use of silver carbonate.[10] The yields of these reactions were highly variable, and never exceeded 50%. Desilylation of **5** could be cleanly effected with fluoride ion (TBAF in THF) to give the tetraacetyl glucoside **2**. Acetylation of **2** led to the pentaacetate **6**, which exhibited ^{1}H- and ^{13}C-NMR data identical to those reported in the literature for the derivative of the naturally occurring glucoside.[11]

Pyrolysis of **5** in a sealed NMR tube in d_6-benzene at 300 °C led to the loss of the signals corresponding to the starting material and the appearance of the signals of the *tert*-butyldimethylsilyl isopentenyl ether (**7**).[12] The NMR signals due to gluconolactone tetraacetate (**8**)[13] were observed only at very early points in the course of the reaction. This was found to be due to the thermal instability of gluconolactone **8**, which under the conditions of pyrolysis undergoes decomposition within 25 min to give the monounsaturated lactone **9**,[14] followed by the α-pyrone **10**.[14,15]

A specimen of **5** carrying 88% deuterium at the anomeric position was prepared by the use of [1-^{2}H]-**3**[16] in the Königs–Knorr reaction. When pyrolysis of this labelled material was carried out to 63% completion (1.5 h), product **7** was labelled with deuterium to the extent of 78%, in keeping with the presence of a deuterium isotope effect in the retro-ene reaction.[2] For determination of the stereochemical course of the rearrangement, [2-^{2}H]-**7** was desilylated and the resulting [2-^{2}H]-**1** esterified with (*R*)-acetylmandelic acid to provide ester **11**, which was submitted to ^{1}H-NMR analysis.[17,18] Inspection of the ^{1}H-NMR spectrum of **11** showed that the (*R*)-[2-^{2}H]- and the (*S*)-[2-^{2}H]-enantiomers were formed in a ratio of 28 : 72 (Fig. 2). The same result was obtained when [2-^{2}H]-**1** was prepared directly by pyrolysis of the deuterium substituted desilylated glucoside **2**.

To account for the observed asymmetric induction it is necessary to evaluate the relative stabilities of the four transition states which can be accessed from the conformers **12**–**15** (Fig. 3). In each of these the migrating deuterium atom is engaged in a kinetically favourable antiperiplanar arrangement with non-bonding electron pairs on both oxygen atoms of the acetal group. Conformers **13** and **14** are clearly destabilized with respect to **12** and **15** by the lack of an anomeric effect between the external oxygen atom and the adjacent C–O bond,[19] as well



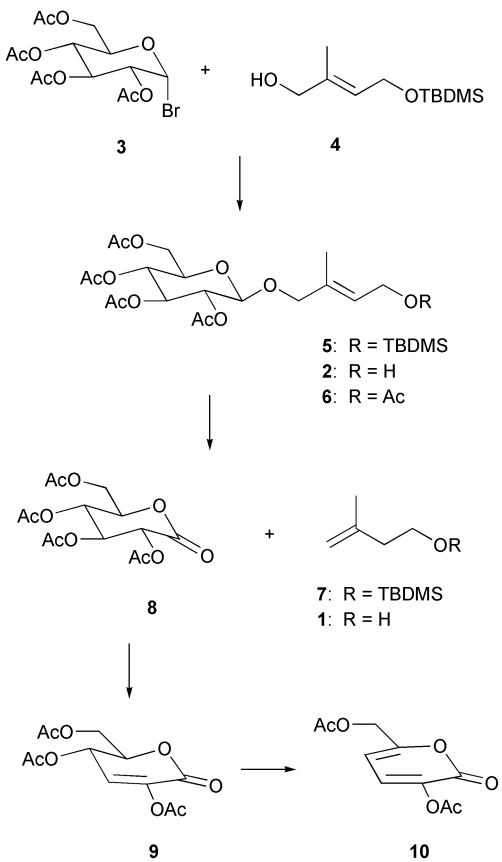


Fig. 1 Synthesis of and pyrolysis reaction of (*E*)-4-hydroxy-2-methylbut-2-enyl 1-tetra-*O*-acetyl-β-D-glucopyranoside (**2**) and its silyl derivative (**5**).

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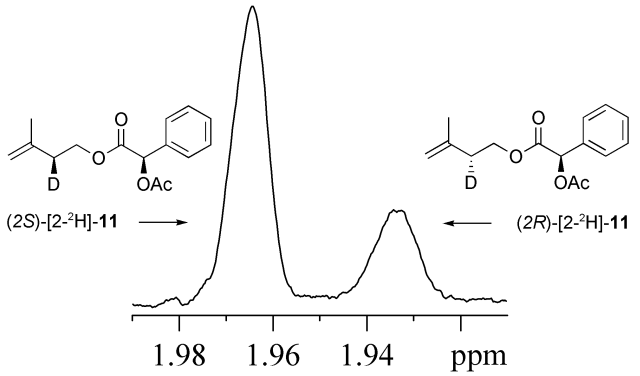

Fig. 2 600 MHz ^{1}H-NMR analysis (C_6D_6) of [2-^{2}H]-isopentenyl alcohol obtained from the pyrolysis of [1′-^{2}H]-**2**.

as by strain arising from the 1,3 repulsion between the methylene group linked to the external acetal oxygen and the C-2 acetoxy group. Thus, the main competition can be traced back to the stability and kinetic behaviour of conformers **12** and **15**. This pair displays few of the steric interactions which normally disfavour boat conformations from their chair counterparts, but it is noteworthy that the quasi-chair arrangement of **12** in moving to the transition state that gives the observed predominant (*S*)-product **16** provides better overlap between the π-orbitals of the double bond and the scissible C–O bond than in the case of the quasi-boat arrangement of **15** on its way to the (*R*)-isomer **17**.

The thermal reaction which leads from **5** to **7** shares a number of features with the last step of the deoxyxylulose pathway, in which the IspH protein catalyzes the conversion of (*E*)-2-methylbut-2-ene-1,4-diol 4-diphosphate into the universal C-5 building block isopentenyl diphosphate.[6] Both reactions involve derivatives of (*E*)-2-methylbut-2-ene-1,4-diol and it is interesting to note that the 1-β-D-glucoside of this substance has been found in nature.[11,20] The predominant stereochemical course of the retro-ene reaction matches that of the biosynthetic process, in which a new hydrogen atom is introduced into the H_{Si}- position at C-2 of the product.[21] While the cofactors of the IspH catalyzed reaction have not yet been identified, labelling studies carried out with *Zymomonas mobilis* indicate that, at least in this organism, the hydrogen atom introduced in the last reductive step stems from C-1 of glucose.[22] These striking coincidences, however, must be considered fortuitous in view of the fact that, in contrast to the thermal reaction, the biochemical process catalyzed by the IspH protein involves a branching point which leads to the parallel and independent formation of both isopentenyl and dimethylallyl diphosphates.[6]

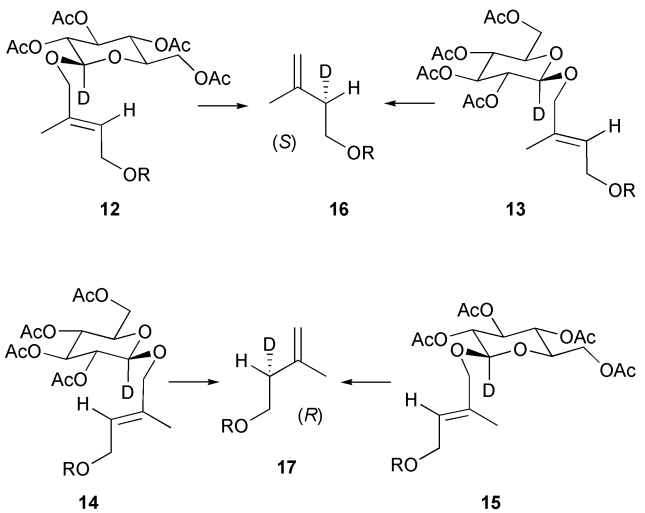

Fig. 3

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Notes and references

† Physical and spectral characterization: **2:** $[\alpha]^{23}_D$ −18.0 (*c* 0.77, acetone). TLC R_f = 0.31 (hexane–ethyl acetate 1 : 2). ^{1}H-NMR ($CDCl_3$, 600 MHz) 5.64 (br t, *J* = 6.7 Hz, 1H, C-3), 5.20 (t, *J* = 9.5 Hz, 1H, C-3′), 5.09 (t, *J* = 9.6 Hz, 1H, C-4′), 5.01 (dd, *J* = 8.1, 9.6 Hz, 1H, C-2″, 4.52 (d, *J* = 8.0 Hz, 1H, C-1′), 4.25 (dd, *J* = 4.7, 12.1 Hz, 1H, C-6′), 4.21 (m, 2H, C-4), 4.20 (d, *J* = 12.2 Hz, 1H, C-1), 4.16 (dd, *J* = 2.5, 12.2 Hz, 1H, C-6′), 4.01 (d, *J* = 12.2 Hz, 1H, C-1), 3.68 (ddd, *J* = 2.5, 4.6, 10.0, Hz, 1H, C-5′), 2.09 (s, 3H, Ac), 2.04 (s, 3H, Ac), 2.02 (s, 3H, Ac), 2.00 (s, 3H, Ac), 1.66 (s, 3H, Me). ^{13}C-NMR ($CDCl_3$, 151 MHz) 170.7 (Ac), 170.3 (Ac), 169.4 (Ac), 169.3 (Ac), 134.1 (C-2), 127.3 (C-3), 99.3 (C-1′), 74.2 (C-1), 72.9 (C-3′), 71.8 (C-5′), 71.4 (C-2′), 68.5 (C-4′), 62.0 (C-6′), 59.0 (C-4), 20.7 (Ac), 20.6 (Ac), 20.6 (Ac), 20.6 (Ac), 13.7 (2-Me).

5: $[\alpha]^{23}_D$ −28.2 (*c* 1.17, acetone). TLC R_f = 0.43 (hexane–ethyl acetate 2 : 1). ^{1}H-NMR ($CDCl_3$, 600 MHz) 5.54 (br t, *J* = 6.0 Hz, 1H, C-3), 5.18 (t, *J* = 9.5 Hz, 1H, C-3′), 5.08 (t, *J* = 9.7 Hz, 1H, C-4′), 5.01 (dd, *J* = 8.2, 9.5 Hz, 1H, C-2′), 4.49 (d, *J* = 8.0 Hz, 1H, C-1′), 4.24 (dd, *J* = 4.7, 12.2 Hz, 1H, C-6′), 4.22 (m, 2H, C-4), 4.18 (d, *J* = 12.5 Hz, 1H, C-1), 4.13 (dd, *J* = 2.0, 12.2 Hz, 1H, C-6′), 3.98 (d, *J* = 12.2 Hz, 1H, C-1), 3.65 (ddd, *J* = 2.3, 4.5, 10.0, Hz, 1H, C-5′), 2.08 (s, 3H, 6′-Ac), 2.03 (s, 3H, 2′-Ac), 2.01 (s, 3H, 4′-Ac), 1.99 (s, 3H, 3′-Ac), 1.60 (s, 3H, 2-Me), 0.89 (s, 9H, *t*-Bu), (s, 6H, SiMe). ^{13}C-NMR ($CDCl_3$, 151 MHz) 170.7 (6′-Ac), 170.3 (3′-Ac), 169.4 (4′-Ac), 169.3 (2′-Ac), 131.6 (C-2), 129.0 (C-3), 98.8 (C-1′), 74.3 (C-1), 72.9 (C-3′), 71.7 (C-5′), 71.2 (C-2′), 68.4 (C-4′), 61.9 (C-6′), 59.8 (C-1 4), 25.9 (*t*-Bu Me), 20.7 (6′-Ac), 20.6 (Ac), 20.6 (Ac), 20.6 (Ac), 18.3 (*t*-Bu C), 13.8 (2-Me), −5.2 (SiMe).

6:$[\alpha]^{23}_D$ −5.9 (*c* 0.28, acetone). TLC R_f = 0.64 (hexane–ethyl acetate 1 : 2).

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