Water-Promoted Organic Synthesis using Glyco-Organic Substrates: the Claisen Rearrangement

André Lubineau, Jacques Augé,* Nathalie Bellanger and Sylvie Caillebourdin
Laboratoire de Chimie Organique Multifonctionnelle associé au CNRS, Institut de Chimie Moléculaire d'Orsay, Université de Paris-Sud Bât 420, F-91405 Orsay Cédex, France

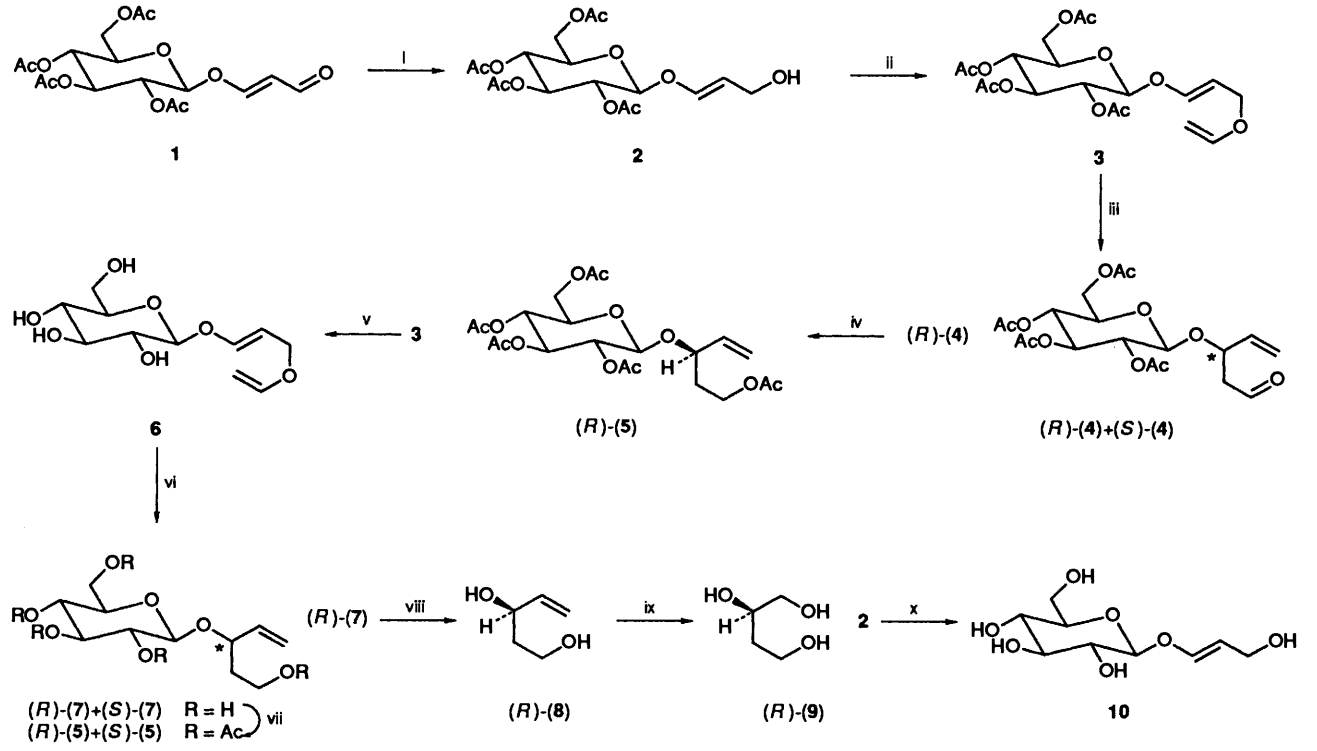
The preparation of new glyco-organic substrates, along with their enhanced reactivity in water-promoted Claisen rearrangement, are described. The chirality induced by the glucose moiety during the course of the reaction is dependent upon the α- or β-configuration of the anomeric centre. This allowed us to prepare enantiomerically pure (*R*) or (*S*) 1,3-diols **8**, with D-glucose, as the unique source of chirality.

We, and others, have already shown [1-6] that it is possible to take advantage of the hydrophobic effect to promote organic reactions in water. This effect is believed to operate in the aqueous Diels–Alder reaction,[1-6] the Mukaiyama reaction[7] and Claisen rearrangement.[8] The consequence of using water as a solvent is a huge rate enhancement of the reaction, which cannot be explained by the sole polarity of the solvent, either for the Diels–Alder reaction,[1] or the Claisen rearrangement.[9] The stereoselectivity is somewhat similar to that obtained under the application of external pressure: thus, the aqueous Diels–Alder reaction proceeds *via* a pure *endo* transition state,[2] and aldolisation in water, without any catalyst, provides the same selectivity as does the reaction carried out under 10 000 atm in dichloromethane.[7] We postulate that a kinetically controlled reaction between two hydrophobic molecules (or between the hydrophobic moieties of amphiphilic molecules), for which the volume of activation is negative, must be accelerated in water, as it is under pressure. This could be seen as a consequence of two concomitant effects. First, the hydrophobic effect tends to aggregate the two reactants in the initial state; second, the cohesive energy of water, which tends to suppress any cavity in the water structure, favours a transition state having a smaller volume than that of the initial state. In this connection, the Claisen rearrangement, which displays a negative volume of activation, is of particular interest since such a rearrangement is often one of the key steps in total synthesis.[10,11] Furthermore, the non-enzymic rearrangement of chorismate to prephenate occurs 100 times faster in water than in methanol.[12] This value is even greater than that obtained in Diels–Alder reactions (*i.e.*, 60 in the cycloaddition of cyclopentadiene with butenone[1]). The rate-accelerating effect of the Diels–Alder reaction with glyco-organic compounds in water has an entropic origin, as shown by the measurement of the activation parameters of the reaction;[13] this could be due to a decrease of the hydrophobic surface in the transition state leading to an enforced hydrophobic interaction.[5] This interaction should evidently also occur when the apolar groups belong to the same molecule, as in the Claisen rearrangement.

Here we report the preparations and the aqueous rate-enhanced Claisen rearrangement of two glyco-organic compounds (**6** and **14**), which differ only by their anomeric configuration. As for Diels–Alder reaction,[2] we chose to increase the water solubility of the reactants by grafting on the aglycone a free sugar, which could be easily removed after the aqueous reaction. The choice of glucose deserves some comment. At the early stage of our studies, it was not evident that the hydrophilic part of the molecule would not prevent the hydrophobic effect. We now know that glucose acts as a structure-making component and even enhances the hydrophobic effect.[13] Moreover, the sugar functions as a chiral template and gives highly crystalline diastereoisomers, which could be easily separated to yield pure enantiomers after enzymic hydrolysis.

Results

Preparations and Claisen Rearrangements of Glyco-organic Substrates with the β-Configuration.—The glyco-organic substrates **3** and **6** were prepared from the aldehyde **1**. This stable, crystalline compound[2] was reduced with $NaBH_4$ under neutral conditions to give the crystalline alcohol **2** (90% yield), which was then condensed with ethyl vinyl ether in the presence of a mercury(II) salt. Mercury(II) acetate did not give satisfactory results in that particular case. Since the preparation of vinyl ethers by vinyl ether exchange in the presence of Lewis acids is sometimes problematic, as emphasised in a review,[10] we advocate the use of mercury(II) oxide, a milder catalyst. Zemplen deacetylation (MeONa–MeOH) of compound **3** gave rise to the glyco-organic compound **6**. When properly conducted, the Claisen rearrangement of compound **6** in water went to completion in 4 h at 60 °C. When the reaction was carried out at neutral or slightly basic pH, compound **6** was cleaved into the alcohol **10**; the cleavage of the vinyl ether was completely obviated at pH 12. However, under basic conditions, the β-alkoxy aldehyde resulting from the Claisen rearrangement underwent a β-elimination leading to glucose. Sodium borohydride was therefore added to the reaction mixture. With 2.5 mol equiv. the reduction of the transient aldehyde was rapid enough to prevent the elimination. Finally, the Claisen rearrangement of compound **6**, at 60 °C and pH 12, gave, in 80% yield, in the presence of $NaBH_4$, a 60:40 mixture of diatereoisomers (*R*)-**7** and (*S*)-**7**, based upon ^1H NMR assignments. The Claisen rearrangement of compound **3** in toluene was investigated for comparison. At 80 °C, the rearrangement required 13 days, whereas the rearrangement of substrate **6** in water went to completion in 1 h at the same temperature. After 24 h in toluene at reflux, compound **3** afforded a 60:40 mixture of diastereoisomeric aldehydes (*R*)-**4** and (*S*)-**4** in 92% yield. Sodium borohydride reduction of the aldehydes, then acetylation of the resulting alcohols, afforded a 60:40 mixture of diastereoisomers (*R*)-**5** and (*S*)-**5**. The same mixture arose from acetylation (Ac_2O, pyridine) of the water-rearranged alcohols (*R*)-**7** and (*S*)-**7**. The major alcohol (*R*)-**5** was crystallised from a solution of (*R*)-**5** and (*S*)-**5** in diethyl ether. The crystalline, pure compound (*R*)-**5** was then deacetylated to afford pure pentaol (*R*)-**7**. Enzymic hydrolysis of compound (*R*)-**7** with β-glucosidase yielded the enantiomeri-

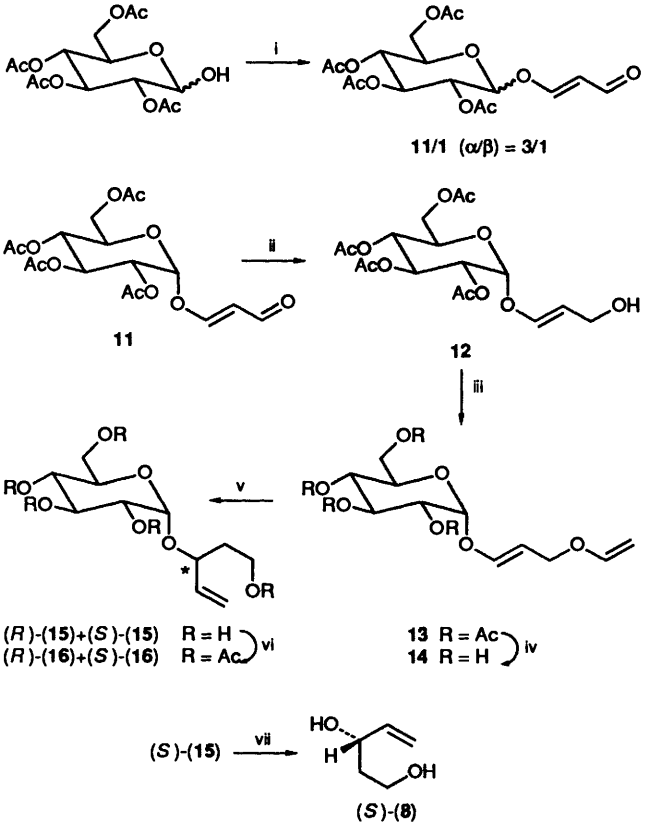


Scheme 1 *Reagents and conditions:* i, $NaBH_4$, pH 7; ii, CH_2=CHOEt, HgO; iii, toluene, 110 °C; iv, $NaBH_4$, pH 7; then Ac_2O, pyridine; v, MeONa–2MeOH; vi, NaOH, 60 °C, pH 12, $NaBH_4$; vii, Ac_2O, pyridine; viii, water, β-glucosidase; ix, O_3, Me_2S; then $NaBH_4$; x, aq. MeOH, NEt_3

cally pure diol (*R*)-**8**. The absolute configuration of the newly created asymmetric carbon atom was ascertained after ozonolysis and reduction of diol (*R*)-**8** which led to the known[14] triol (*R*)-**9** (Scheme 1).

Preparation and Claisen Rearrangement of Glyco-organic Substrates with the α-Configuration.—The glyco-organic substrates with the α-configuration were prepared from 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose[15] (as a mixture of α and β anomers in the ratio 3:1, based upon ^1H NMR spectroscopy) according to a methodology developed in our laboratory for the synthesis of α-linked derivatives of T-antigen.[16] Thus, treatment of the sodium salt of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose with tosylacrylaldehyde (prepared *in situ* from the sodium salt of malonaldehyde and tosyl chloride) in the presence of 18-crown-6 ether in tetrahydrofuran (THF) gave, at 0 °C, a mixture of the aldehydes **11** and **1** (anomeric ratio 3:1) in 81% yield. The major aldehyde **11** was reduced quantitatively to the alcohol **12** ($NaBH_4$; pH 7), then this was condensed with ethyl vinyl ether at room temperature to afford the allyl vinyl ether **13** in 74% yield. Mercury(II) acetate, as catalyst, was quite appropriate in that case. Deacetylation of compound **13** (aq. MeOH, NEt_3) gave the glyco-organic compound **14**, which was not isolated because of its sensitivity to hydrolysis. After evaporation, the reaction mixture was treated with sodium hydroxide and sodium borohydride in water (pH 12). Under these conditions, Claisen rearrangement of compound **14** proceeded in excellent yield (99%) at 60 °C within 2.5 h to give a 60:40 mixture of diastereoisomers (*S*)-**15** and (*R*)-**15**, respectively. This mixture was acetylated (Ac_2O, pyridine) and the acetates (*S*)-**16** and (*R*)-**16** were separated by crystallisation. Two successive crystallisations from diethyl ether with a small amount of hexane yielded pure compound (*S*)-**16**, which was hydrolysed in the presence of α-glucosidase to give pure alcohol (*S*)-**8** (Scheme 2), as evidenced by polarimetry.

In contrast to β-anomer **3**, the α-anomer **13** did not undergo Claisen rearrangement in toluene, even at 110 °C; at that temperature, the glucose moiety was eliminated and the starting tetraacetate was recovered.



Scheme 2 *Reagents and conditions:* i, NaH, TsOCH=CHCHO; ii, $NaBH_4$, pH 7; iii, CH_2=CHOEt, $Hg(OAc)_2$; iv, aq. MeOH, NEt_3; v, NaOH, 60 ° C, pH 12, $NaBH_4$; vi, Ac_2O, pyridine; vii, water, α-glucosidase

Discussion

The entropy-driven association of the hydrophobic parts of the glyco-organic substrates **6** and **14**, *i.e.* the hydrophobic effect, may account for the rate enhancement of their aqueous rearrangement. However, we could not eliminate the influence of the dipolar nature of the transition state, since the anomeric oxygen is an electron-donating substituent through the vinylogous anomeric effect.[17] This effect may be present in both the β- and the α-glucosides, which display similar reactivities in water.

In contrast, face selectivity for the Claisen rearrangement is strictly dependent upon the anomeric configuration of the glucosides. The facial selectivity of the β-glucosides **6** and **3** in water or in toluene is due to a preferred attack on the *re* face of the allyl vinyl ether, which leads to the major (*R*)-**7** and (*R*)-**4** diastereoisomers. To account for these results, let us consider the ground-state conformations of the β-glucoside. If we assume the vinyl ether linked to glucose lies in a plane perpendicular to the endocyclic C–O bond, as a consequence of the *exo*-anomeric effect,[2,18] then two conformers are of concern: the extended and the eclipsed ones (Fig. 1): the former prevails for steric reasons.

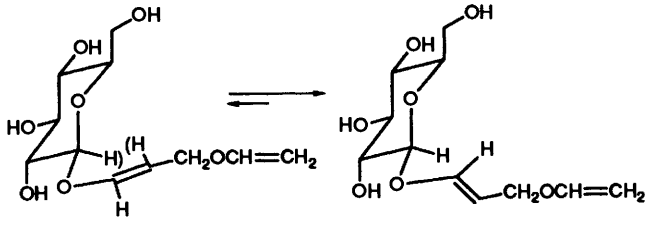


Fig. 1 Eclipsed and extended conformers of the β-glucoside **6**

Owing to the fact that, in acyclic systems, Claisen rearrangements show a well established preference for chair-like transition states, two reacting conformers, as depicted in Fig. 2, may be postulated. The preferential approach of the terminal double bond on the *re* face of the allyl vinyl ether avoids the 1,3-*syn* diaxial interaction in *si* attack.

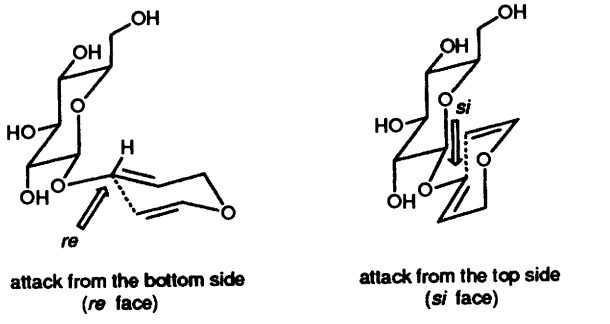


Fig. 2 Facial selectivity for the β-glucoside **6**

The reversal of face selectivity in Claisen rearrangement of the α-glucoside **14** may be rationalised in similar terms. The two reacting extended conformers of the α-glucoside **14** are depicted in Fig. 3. The preferred attack on the *si* face of the allyl vinyl ether allows us to explain the dominant formation of the diastereoisomer (*S*)-**15**. Indeed *re* approach of the terminal bond is hindered by a 1,3-*syn* diaxial interaction between the endocyclic C–O bond and the developing C–C bond.

A similar reversal of selectivity was observed in Diels–Alder reactions with butadienyl glucosides.[2,19] Hence, for both Claisen and Diels–Alder reactions, the face selectivity comes from attack on the *re* face (*si* face) of the β-glucoside (α-glucoside).

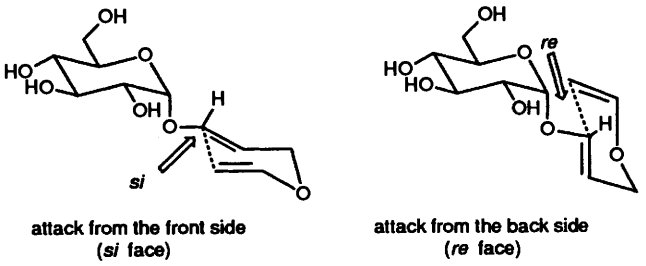


Fig. 3 Facial selectivity for the α-glucoside **14**

Conclusions.—The influence of water as solvent on the rate of the Claisen rearrangement allows us to perform the reaction at moderate temperature. This represents an enormous potential in total synthesis, in which a Claisen rearrangement is often a key step. In our model, allyl vinyl ether is linked to a sugar moiety, in order to provide water solubility. Of interest was the effect of the chirality *outside* the pericyclic arena on the outcome of the rearrangement; the advantage of the asymmetric induction by external chirality was previously emphasised.[11,20] It is worth noting that the same chiral auxiliary, *e.g.* the glucose moiety, can induce two opposite selectivities. Thus, according to the anomeric configuration of the substrates, water-promoted Claisen rearrangement affords either (*R*) or (*S*) diastereoisomers, leading to (*R*) or (*S*) enantiomerically pure diols **8**, respectively.

Experimental

General.—Solvents were distilled prior to use: toluene and dichloromethane from CaH_2; THF from Na–benzophenone; methanol from Mg–iodine. Phosphate buffers were adjusted to pH 7 with a Crison pH meter by mixing molar solutions of Na_2PO_4 and $NaHPO_4$. Enzymes were purchased from Sigma. Preparative flash column chromatographies were carried out using Merck Kieselgel 60 (230–400 mesh). Solvent compositions are quoted as v/v. M.p.s are uncorrected. Optical rotations were measured with a Roussel-Jouan electronic digital micropolarimeter. ^1H and ^{13}C NMR spectra were recorded on Bruker spectrometers (AC200 or AC250); ^1H and ^{13}C NMR spectra were reported in ppm relative to tetramethylsilane. ^{13}C NMR spectra were obtained fully decoupled and multiplicities were determined using DEPT. Coupling constants are in Hz. Elemental analyses were performed by the Service Central de Microanalyse du CNRS.

(E)-3-*Hydroxyprop*-1-*enyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucopyranoside* **2**.—Sodium borohydride (1.07 g, 28 mmol) was added dropwise to a cold solution of the aldehyde **1** (11.37 g, 28 mmol) in a mixture of ethanol–water (50 cm^3, 1:1) (phosphate buffer, pH 7). After 1 h at 0 °C, the reaction was quenched by addition of acetone (3 cm^3). After dilution with water, the reaction mixture was extracted with dichloromethane. The organic layer was washed with water, dried and evaporated. The residue was recrystallised from ethyl acetate–diethyl ether to give the *title compound* **2** (10.18 g, 90%), m.p. 133 °C; $[\alpha]_D^{20}$ −4 (*c* 1, CH_2Cl_2); δ_H($CDCl_3$; 250 MHz) 2.02, 2.05, 2.06 and 2.10 (12 H, 4 s, 4 × Ac.), 3.78 (1 H, ddd, *J* 9.5, 4.5 and 2, 5-H), 4.07 (2 H, d, *J* 7, CH=CHCH_2), 4.14 (1 H, dd, *J* 12.5 and 2, 6-H), 4.28 (1 H, dd, *J* 12.5 and 4.5, 6-H), 4.79 (1 H, d, *J* 8, 1-H), 5.11 (1 H, dd, *J* 9.5, 2-H), 5.12 (1 H, t, *J* 9.5, 4-H), 5.24 (1 H, t, *J* 9.5, 3-H), 5.35 (1 H, dt, *J* 12.5 and 7, CH=C*H*CH_2) and 6.46 (1 H, d, *J* 12.5, OC*H*=CH); δ_C($CDCl_3$; 50 MHz) 59.20 and 61.45 (2 × CH_2), 67.73, 70.50, 71.76 and 72.26 (C-2, -3, -4 and -5), 98.96 (C-1), 106.86 (OCH=*C*H) and 145.43 (O*C*H=CH) (Found: C, 50.8; H, 5.75. $C_{17}H_{24}O_{11}$ requires C, 50.50; H, 5.98%).

(E)-3-(*Vinyloxy*)*prop*-1-*enyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glu*-

copyranoside **3**.—The allylic alcohol **2** (4 g, 9.90 mmol) and red mercury(II) oxide (428 mg, 1.98 mmol) were added to ethyl vinyl ether (50 cm^3) and the mixture was stirred at 20 °C for 24 h. Careful concentration under reduced pressure and flash chromatography in hexane–ethyl acetate (3:2, v/v) at 4 °C gave the *title compound* **3** (3.18 g, 74%) along with the recovered starting compound **2** (0.8 g, 20%); compound **3** had m.p. 90–92 °C; $[\alpha]_D^{20}$ −9.5 (*c* 1, CH_2Cl_2); δ_H($CDCl_3$; 200 MHz) 3.80 (1 H, ddd, *J* 10, 5 and 2.5, 5-H), 4.03 (1 H, dd *J* 7 and 2, =C*H*H), 4.20 (5 H, m), 4.83 (1 H, d, *J* 7.8, 1-H), 5.25 (4 H, m), 6.44 (1 H, dd, *J* 14.3 and 7, OC*H*=CH_2) and 6.51 (1 H, d, *J* 12.3, OC*H*=CH); δ_C($CDCl_3$; 50 MHz) 20.38 (4 × Me), 61.55 and 64.94 (2 × CH_2), 67.81, 70.56, 71.99 and 72.35 (C-2, -3, -4 and -5), 86.98 (=CH_2), 99.11 (C-1), 104.70 (OCH=*C*H) and 146.97 and 150.99 (O*C*H=CH and O*C*H=CH_2) (Found: C, 53.05; H, 6.0. $C_{19}H_{26}O_{11}$ requires C, 53.02; H, 6.09%).

Claisen Rearrangement of Compound **3** *in Toluene*.—The allyl vinyl ether **3** (500 mg, 1.16 mmol) was dissolved in toluene (11 cm^3) and the solution was heated at 110 °C for 24 h to give, after flash chromatography [hexane–ethyl acetate (65:35)], a mixture (462 mg, 92%) of diastereoisomers (*R*)-**4** and (*S*)-**4** (60:40, ^{1}H NMR). Crystallisation from diethyl ether–hexane afforded the pure *diastereoisomer* (*R*)-**4** (205 mg, 41%), m.p. 100–102 °C; $[\alpha]_D^{20}$ −10 (*c* 1.5, CH_2Cl_2); δ_H($CDCl_3$; 250 MHz) 2.01, 2.02, 2.06 and 2.08 (12 H, 4 s, 4 × Ac), 2.53 (1 H, ddd, *J* 17.2, 4, and 1.5, C*H*HCHO), 2.86 (1 H, ddd, *J* 17.2, 9 and 2, CH*H*CHO), 3.66 (1 H, ddd, *J* 10, 5 and 2.5, 5-H), 4.09 (1 H, dd, *J* 12.5 and 2.5, 6-H), 4.22 (1 H, dd, *J* 12.5 and 5, 6-H′), 4.60 [2 H, m, 1-H and OC*H*(CH=CH_2)CH_2CHO], 4.97 (1 H, dd, *J* 9.75 and 8, 2-H), 5.05 (1 H, t, *J* 9.75, 4-H), 5.18 (1 H, d, *J* 10.2, =C*H*H), 5.20 (1 H, t, *J* 9.75, 3-H), 5.28 (1 H, d, *J* 17.5, =CH*H*), 5.92 (1 H, ddd, *J* 17.5, 10.2 and 7, C*H*=CH_2) and 9.73 (1 H, dd, *J* 2 and 1.5, CHO); δ_C($CDCl_3$; 50 MHz) 48.45 (*C*H_2CHO), 61.99 (C-6), 68.42, 71.22, 71.75 and 72.75 (C-2, -3, -4 and -5), 100.44 (C-1), 117.00 (=CH_2), 137.21 (*C*H=CH_2) 169.41, 170.23 and 170.59 (4 × Me*C*O) and 199.21 (CHO) (Found: C, 52.9; H, 6.0. $C_{19}H_{26}O_{11}$ requires C, 53.02; H, 6.09%).

Preparation of Compound (R)-**5**.—Sodium borohydride (93 mg, 2.45 mmol) was added slowly to a cold solution of the aldehyde (*R*)-**4** (1.05 g, 2.44 mmol) in ethanol–water (1:1). After being stirred for 15 min, the mixture was quenched with acetic acid, then treated with Dowex 50 resin (H^+). The filtrate was coevaporated with methanol to dryness, then acetylated with acetic anhydride (1 cm^3) in pyridine (3.3 cm^3) to afford *compound* **5** which was recrystallised from diethyl ether (0.95 g, 82%), m.p. 101–103 °C; $[\alpha]_D^{20}$ +3 (*c* 1.3, CH_2Cl_2); δ_H($CDCl_3$; 200 MHz) 3.65 (1 H, ddd, *J* 9.5, 5 and 2.5, 5-H), 4.54 (1 H, d, *J* 8, 1-H) and 5.88 (1 H, ddd, *J* 17.5, 10 and 7.5, C*H*=CH_2); δ_C($CDCl_3$; 50 MHz) 33.83 (*C*H_2CH_2OAc), 60.36 and 61.86 (2 × *C*H_2OAc), 68.29, 71.25, 71.51 and 72.68 (C-2, -3, -4 and -5), 79.95 [O*C*H_2(CH=CH_2)CH_2CH_2OAc], 100.17 (C-1), 116.37 (=CH_2) and 138.08 (*C*H=CH_2) (Found: C, 53.4; H, 6.3. $C_{21}H_{30}O_{12}$ requires C, 53.16; H, 6.37%).

(E)-3-(*Vinyloxy*)*prop*-1-*enyl* β-D-*Glucopyranoside* **6**.—Compound **3** (572 mg, 1.33 mmol) was treated with 0.5 mol dm^{-3} sodium methoxide in methanol. After 15 min at room temperature, the mixture was neutralised by addition of CG 50 resin (H^+). The filtrate was evaporated to afford *compound* **6** (330 mg, 95%), m.p. 118 °C; $[\alpha]_D^{20}$ −20 (*c* 1, EtOH); δ_H(CD_3OD; 250 MHz) 3.97 (1 H, dd, *J* 7 and 2, =C*H*H), 4.16 (2 H, d, *J* 7, CH_2OCH=CH_2), 4.20 (1 H, dd, *J* 14.5 and 2, =CH*H*), 4.58 (1 H, d, *J* 7, 1-H), 5.25 (1 H, ddd, *J* 12.5, 7.5 and 2, OCH=C*H*CH_2), 6.43 (1 H, dd, *J* 14.5 and 7, C*H*=CH_2) and 6.69 (1 H, d, *J* 12.5, OC*H*=CHCH_2); δ_C(CD_3OD; 62.5 MHz) 62.39 and 66.70 (2 × CH_2), 71.10, 74.51, 77.70 and 78.23 (C-2, -3, -4 and -5), 87.35 (=CH_2), 103.55 (C-1), 104.61 (OCH=*C*HCH_2) and 150.22 and 152.43 (O*C*H=CH and O*C*H=CH_2) (Found: C, 49.6; H, 7.0. $C_{11}H_{18}O_7$, 0.25 H_2O requires C, 49.53; H, 6.99%).

Claisen Rearrangement of Compound **6** *in Water*.—Compound **6** (262 mg, 1 mmol) was dissolved in 16 mmol dm^{-3} aq. sodium hydroxide (4.5 cm^{-3}). Sodium borohydride (94.57 mg, 2.5 mmol) was added and the mixture was heated at 60 °C for 4 h. After cooling, the mixture was quenched with 10% acetic acid, then treated with Dowex 50 resin (H^+). The filtrate was evaporated with methanol and purified by flash chromatography [dichloromethane–methanol (6:1)] to give an inseparable mixture of diastereoisomers (*R*)-**7** and (*S*)-**7** (211 mg, 80%) (60:40, ^{1}H NMR); δ_H(D_2O with acetone as internal reference at 2.09 ppm; 200 MHz) 1.73 (2 H, m, CH_2CH_2OH), 4.05 and 4.21 [0.4 H and 0.6 H respectively, td, *J* 7.7 and 7, OC*H*(CH=CH_2)CH_2CH_2OH for the (*S*)- and (*R*)-isomer, respectively], 4.38 and 4.40 [0.4 H and 0.6 H respectively, d, *J* 8 Hz, 1-H for the (*S*)- and (*R*)-isomer, respectively], 5.11 and 5.21 [0.6 H and 0.4 H respectively, d, *J* 10, =C*H*H for the (*R*)- and (*S*)-isomer, respectively], 5.20 and 5.22 [0.6 H and 0.4 H respectively, d, *J* 17.5, =CH*H* for the (*R*)- and (*S*)-isomer, respectively] and 5.62 and 5.78 [0.4 H and 0.6 H respectively, ddd, *J* 17.5, 10 and 7, C*H*=CH_2 for the (*S*)- and (*R*)-isomer, respectively]; δ_C(D_2O with acetone as internal reference at 30.5 ppm; 50 MHz) 36.53 and 37.13 [*C*H_2CH_2OH for the (*R*)- and (*S*)-isomer, respectively], 58.10 and 60.96 (2 × CH_2 for both isomers), 69.90, 73.22, 73.60 and 76.08 [C-2, -3, -4 and -5 for the (*R*)- and (*S*)-isomer, 77.19 and 80.17 [O*C*H-(CH=CH_2)CH_2CH_2OH for the (*S*)- and (*R*)-isomer, respectively], 99.15 and 101.68 [C-1 for the (*S*)- and (*R*)-isomer, respectively], 117.63 and 119.53 [=CH_2 for the (*R*)- and (*S*)-isomer, respectively] and 136.80 and 138.15 [*C*H=CH_2 for the (*S*)- and (*R*)-isomer, respectively].

Separation of Compounds (R)-**7** *and* (S)-**7**.—The mixture of diastereoisomers (*R*)-**7** and (*S*)-**7** (2.67 g, 10.1 mmol) was acetylated with acetic anhydride (20 cm^3) in pyridine (12 cm^3). After 24 h, the reaction mixture was coevaporated with toluene to give a mixture of isomers (*R*)-**5** and (*S*)-**5** (4.79 g, 100%) (60:40, ^{1}H NMR). Crystallisation from diethyl ether gave pure isomer (*R*)-**5** (2.13 g, 44%), which was deacetylated with 0.2 mol dm^{-3} sodium methoxide in methanol (10 cm^3). After 1 h, the reaction mixture was neutralised with CG 50 resin (H^+). After filtration and evaporation, pure pentaol (*R*)-**7** was obtained in quantitative yield (1.18 g); $[\alpha]_D^{20}$ −21 (*c* 1, MeOH) (Found: C, 48.2; H, 7.8. $C_{11}H_{20}O_7$·0.5 H_2O requires C, 48.35; H, 7.75%).

(R)-*Pent*-4-*ene*-1,3-*diol* **8**.—β-Glucosidase (type II from almonds) (20 mg, 112 units) was added to a solution of compound (*R*)-**7** (1 g, 3.79 mmol) in twice-distilled water (10 cm^3). After 24 h at room temperature the enzyme was precipitated in methanol, then filtered off. The filtrate was chromatographed in ethyl acetate–methanol (95:5) to afford the title diol (*R*)-**8** (377 mg, 97%); $[\alpha]_D^{20}$ −11 (*c* 1, MeOH); spectroscopic data were identical with those reported.[21]

(R)-*Butane*-1,2,4-*triol* **9**.—Compound **8** (320 mg, 3.13 mmol) was ozonolysed (O_3; 15 min; then Me_2S) at − 70 °C in methanol, then the aldehyde was reduced by addition of sodium borohydride (131 mg, 3.45 mmol) at room temperature. After quenching with acetic acid and treatment with Dowex 50 resin (H^+), evaporation of the filtrate gave the triol (*R*)-**9** (300 mg, 90%); $[\alpha]_D^{20}$ +24 (*c* 2, MeOH {lit.,[14] $[\alpha]_D^{20}$ −24.6 for the (*S*)-enantiomer}.

(E)-3-*Hydroxyprop*-1-*enyl* β-D-*Glucopyranoside* **10**.—Com-

pound **2** (404 mg, 1 mmol) was treated for 24 h with methanol–triethylamine–water (8:1:1) to give quantitatively the *title compound* **10** (236 mg), m.p. 139–141 °C; $[\alpha]_D^{20}$ −6 (*c* 1.4, MeOH); δ_H(CD_3OD; 200 MHz) 3.98 (2 H, d, *J* 7.2, CH_2OH), 4.55 (1 H, d, *J* 7.8, 1-H), 5.26 (1 H, dt, *J* 12.5 and 7.2, $CHCH_2OH$) and 6.59 (1 H, d, *J* 12.5, OCH=CH); δ_C(CD_3OD; 50 MHz) 60.13 and 62.48 (2 × CH_2), 71.21, 74.57, 77.77 and 78.26 (C-2, -3, -4 and -5), 103.50 (C-1), 108.53 (=$CHCH_2OH$) and 148.65 (OCH=CH) (Found: C, 45.9; H, 6.8. $C_9H_{16}O_7$ requires C, 45.76; H, 6.83%).

(E)-2-*Formylvinyl* 2,3,4,6-*Tetra*-O-*acetyl*-α-D-*glucopyranoside* **11**.—To a suspension of the sodium salt of malonaldehyde (1 g, 10.6 mmol) in THF (20 cm^3) were added tosyl chloride (1.33 g, 7 mmol) and 18-crown-6 ether (40 mg). After being stirred for 1 h at room temperature, the mixture was cooled at 0 °C; a solution of 2,3,4,6-tetra-*O*-acetylglucopyranose (1.7 g, 4.88 mmol) in THF (20 cm^3) was first added, and then sodium hydride (60% suspension in mineral oil; 195 mg) in several portions. After 30 min at 0 °C, the mixture was poured slowly into phosphate buffer (pH 7). After extraction and washing, the residue was rapidly chromatographed [diethyl ether–hexane (3:1)] to afford the aldehyde **1** (0.4 g, 20%) along with the *title compound* **11** (1.2 g, 61%), m.p. 118–120 °C; $[\alpha]_D^{20}$ +188 (*c* 1.2, CH_2Cl_2); δ_H($CDCl_3$; 250 MHz) 3.99 (1 H, ddd, *J* 10, 5 and 2, 5-H), 4.10 (1 H, dd, *J* 12 and 2, 6-H), 4.27 (1 H, ee, *J* 12.5 and 5, 6-H′), 5.02 (1 H, dd, *J* 10, 3.5, 2-H), 5.15 (1 H, t, *J* 10, 4-H), 5.56 (1 H, t, *J* 10, 3-H), 5.59 (1 H, d, *J* 3.5, 1-H), 5.93 (1 H, dd, *J* 13 and 8, OCH=C*H*), 7.32 (1 H, d, *J* 13, OCH=CH) and 9.43 (1 H, d, *J* 8, CHO); δ_C($CDCl_3$; 62.5 MHz) 20.53 (4 × *Me*CO), 61.17 (C-6), 67.60, 69.11, 69.33 and 69.73 (C-2, -3, -4 and -5), 96.64 (C-1), 114.56 (OCH=*C*HCHO), 165.36 (OCH=CHCHO) and 190.65 (CHO) (Found: C, 50.9; H, 5.45. $C_{17}H_{22}O_{11}$ requires C, 50.75; H, 5.51%).

(E)-3-*Hydroxyprop*-1-*enyl* 2,3,4,6-*Tetra*-O-*acetyl*-α-D-*glucopyranoside* **12**.—The procedure used in the β-series was repeated for the α-anomer; thus sodium borohydride reduction of the aldehyde **11** gave the *title compound* **12** (97%), m.p. 126–127 °C; $[\alpha]_D^{20}$ +138 (*c* 1.3, CH_2Cl_2); δ_H($CDCl_3$; 250 MHz) 2.03, 2.04, 2.08 and 2.10 (12 H, 4 s, 4 × Ac), 4.01 (1 H, ddd, *J* 10, 4.5 and 2.5, 5-H), 4.08 (2 H, d, *J* 7.5, CH=CHCH_2), 4.09 (1 H, dd, *J* 12.5 and 2.5, 6-H), 4.26 (1 H, dd, *J* 12.5 and 4.5, 6-H′), 4.94 (1 H, dd, *J* 3.5 and 10, 2-H), 5.11 (1 H, t, *J* 10, 4-H), 5.37 (1 H, d, *J* 3.5, 1-H), 5.46 (1 H, t, *J* 12.5 and 7.5, OCH=C*H*), 5.54 (1 H, t, *J* 10, 3-H) and 6.43 (1 H, d, *J* 12.5, OCH=CH); δ_H($CDCl_3$, 50 MHz) 20.60 (4 × MeCO), 59.83 and 61.48 (2 × CH_2), 67.84, 68.09, 69.78 and 70.10 (C-2, -3, -4 and -5), 94.95 (C-1), 109.33 (OCH=*C*H) and 145.12 (OCH=CH) (Found: C, 50.9; H. 6.0. $C_{17}H_{24}O_{11}$ requires C, 50.49; H, 5.98%).

(E)-3-(*Vinyloxy*)*prop*-1-*enyl* 2,3,4,6-*Tetra*-O-*acetyl*-α-D-*glucopyranoside* **13**.—Allylic alcohol **12** (1.0 g, 2.47 mmol) and mercury(II) acetate (140 mg, 0.44 mmol) were added to ethyl vinyl ether (10 cm^3) and the mixture was stirred at 20 °C for 16 h. Careful concentration under reduced pressure and flash chromatography in hexane–ethyl acetate (7:3) gave the *title compound* **13** (785 mg, 74%) along with the recovered starting compound **12** (200 mg, 20%); compound **13** showed m.p. 44–45 °C; $[\alpha]_D^{20}$ +127; δ_H($CDCl_3$; 200 MHz) 2.04, 2.05 2.08 and 2.09 (12 H, 4 s, 4 × Ac), 4.00 (1 H, ddd, *J* 10, 4 and 2, 5-H), 4.15 (6 H, m), 4.95 (1 H, dd, *J* 3.5 and 10.3, 2-H), 5.12 (1 H, t, *J* 9.5, 4-H), 5.38 (1 H, d, *J* 3.5, 1-H), 5.42 (1 H, dt, *J* 12.5, 7, OCH=C*H*CH_2), 5.54 (1 H, t, *J* 9.5, 3-H), 6.44 (1 H, dd, *J* 14.5 and 7, OCH=CH_2) and 6.47 (1 H, d, *J* 12.5, OCH=CHCH_2); δ_C($CDCl_3$; 50 MHz) 20.62 (4 × *Me*CO) 61.39 and 65.15 (2 × CH_2), 68.00, 69.78 and 70.06 (C-2, -3, -4 and -5), 87.17 (=CH_2), 95.03 (C-1), 105.22 (OCH=*C*HCH_2) and 146.32 and 151.11 (OCH=CHCH_2 and OCH_2=CH_2) (Found: C, 52.85; H, 6.1. $C_{19}H_{26}O_{11}$ requires C, 53.02; H, 6.09%).

Claisen Rearrangement of Compound **14** *in Water*.—The allyl vinyl ether **13** (692 mg, 1.61 mmol) was treated with MeOH–water–NEt_3 (8:1:1). After 16 h, the mixture was evaporated to give compound **14** contaminated with a small amount of triethylamine; δ_H(D_2O with acetone as internal reference at δ 2.09; 250 MHz) 4.02 (1 H, dd, *J* 7 and 2, =C*H*H), 4.11 (2 H, d, *J* 7.5, CH_2OCH=CH_2), 4.22 (1 H, dd, *J* 14 and 2, =CH*H*), 5.12 (1 H, d, *J* 3.5, 1-H), 5.27 (1 H, dt, *J* 12.5 and 7.5, OCH=C*H*CH_2), 6.33 (1 H, dd, *J* 14 and 7, C*H*=CH_2) and (1 H, d, *J* 12.5, OCH=$CHCH_2$); δ_C(D_2O with acetone as internal reference at δ_C 30.5; 62.5 MHz) 60.54 and 66.57 (2 × CH_2), 69.44, 71.06, 72.70 and 73.17 (C-2, -3, -4 and -5), 88.99 (=CH_2), 98.25 (C-1), 104.57 (OCH=*C*HCH_2) and 148.44 and 150.92 (OCH=CH and OCH=CH_2).

The residue was then dissolved in 16 mmol dm^{-3} aq. sodium hydroxide (14 cm^3). After addition of sodium borohydride (310 mg, 8.1 mmol), the mixture was heated at 60 °C for 2.5 h. After quenching with 10% acetic acid and treatment with Dowex 50 (H^+) cation-exchange resin, evaporation of the filtrate afforded a mixture of diastereoisomers (*S*)-**15** and (*R*)-**15** (420 mg, 99%) (60:40; ^1H NMR); δ_H(CD_3OD; 250 MHz) 5.72 (0.4 H, ddd, *J* 17.5, 10 and 7.5, C*H*=CH_2) and 5.91 (0.6 H. ddd, *J* 17.5, 10.5 and 7.5, C*H*=CH_2); δ_C(CD_3OD; 50 MHz) 38.17 and 39.10 [CH_2CH_2OH for (*S*)- and (*R*)-isomer, respectively, 96.11 and 99.82 [C-1 for the (*R*)- and (*S*)-isomer, respectively], 116.12 and 118.91 [CH=CH_2 for the (*S*)- and (*R*)-isomer, respectively] and 138.78 and 140.28 [*C*H=CH_2 for the (*R*)- and (*S*)-isomer respectively].

Separation of Compounds (S)-**15** *and* (R)-**15**.—The mixture of diastereoisomers (*S*)-**15** and (*R*)-**15** (420 mg, 1.60 mmol) was acetylated with acetic anhydride (4 cm^3) in pyridine (3 cm^3). After 24 h at room temperature, the reaction mixture was evaporated to dryness to afford quantitatively a 60:40 mixture of diastereoisomers (*S*)-**16** and (*R*)-**16**. Two successive crystallisations from diethyl ether with a small portion of hexane gave pure *compound* (S)-**16** (145 mg, 20%), m.p. 131–132 °C; $[\alpha]_D^{20}$ +116 (*c* 1, CH_2Cl_2); δ_H($CDCl_3$; 250 MHz) 1.9 (2 H, m, CH_2CH_2OAc), 2.02, 2.03, 2.04, 2.09 and 2.10 (15 H, 5 s, 5 × Ac), 4.87 (1 H, dd, *J* 10.5 and 3.5, 2-H), 5.06 (1 H, t, *J* 10, 4-H), 5.16 (1 H, d, *J* 3.5, 1-H), 5.48 (1 H, t, *J* 10, 3-H) and 5.86 (1 H, ddd, *J* 17.5, 10 and 7.5, C*H*=CH_2); δ_C($CDCl_3$; 62.5 MHz) 33.93 (CH_2CH_2OAc), 60.30 and 61.57 (2 × CH_2OAc), 67.40, 68.44, 70.05 and 70.85 (C-2, -3, -4 and -5), 78.81 [OCH(CH=CH_2)CH_2CH_2OAc], 96.38 (C-1), 117.13 (=CH_2) and 137.73 (*C*H=CH_2) (Found: C, 53.2; H, 6.3. $C_{21}H_{30}O_2$ requires C, 53.16; H, 6.37%).

The crystalline compound (*S*)-**16** (144 mg, 0.3 mmol) was deacetylated with 0.2 mol dm^{-3} sodium methoxide in methanol (3.5 cm^3). After 30 min, the reaction mixture was neutralised with Dowex 50 resin (H^+). Evaporation of the filtrate gave pure *compound* (S)-**15** (77 mg, 97%); $[\alpha]_D^{20}$ +132 (*c* 0.3, MeOH); δ_H(CD_3OD; 250 MHz) 1.82 (2 H, m, CH_2CH_2OH), 4.95 (1 H, d, *J* 3.5, 1-H), 5.11 (1 H, d, *J* 10.5, =C*H*H), 5.26 (1 H, d, *J* 17.5, =CH*H*) and 5.91 (1 H, ddd, *J* 17.5, 10.5 and 7.5, C*H*=CH_2); δ_C(CD_3OD; 62.5 MHz) 38.31 (CH_2CH_2OH), 59.35 and 62.25 (2 × CH_2OH), 71.50, 71.76, 73.62 and 75.08 (C-2, -3, -4 and -5), 79.19 [OCH(CH=CH_2)CH_2CH_2OH], 99.97 (C-1), 116.12 (CH=*C*H_2) and 140.44 (*C*H=CH_2) (Found: C, 49.1; H, 7.85. $C_{11}H_{20}O_7$·0.25 H_2O requires C, 49, 16; H, 7.69%).

(S)-*Pent*-4-*ene*-1,3-*diol* **8**.—α-Glucosidase (13 mg, 174 units) (type IV from brewers' yeast) was added to a solution of the glucoside (*S*)-**15** (77 mg, 0.29 mmol) in twice distilled water (2 cm^3). After 2 days at room temperature the enzyme was

precipitated in methanol, then filtered off. Flash chromatography in ethyl acetate–methanol (95:5) gave diol (*S*)-**8** (21 mg, 71%) $[\alpha]_D^{20}$ +11 (*c* 1, MeOH); spectroscopic data were identical with those reported.[21]

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