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Regio- and stereoselective introduction of ether-linked carboxylic side chains into carbohydrates by conjugate addition reactions

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Abstract

By intermolecular conjugate addition a number of derivatives were obtained in which various carbohydrates ether-linked to β-hydroxy butyric acid represent the central structural elements. Their structures were assigned and a rationalisation for the regio- and stereoselective results proposed. © 1998 Elsevier Science Ltd. All rights reserved

Keywords: Conjugate addition; Carbohydrate ethers; Hydroxy carboxylates

1. Introduction

Many biologically active carbohydrates carry negative charges under physiological conditions which define their interactions in biological processes. The sources of the anionic character are usually phosphates, sulfates or carboxyl groups, which commonly occur in the form of uronic acids, pyruvate ketals, lactate ethers or as special carbohydrates such as sialic acids. As has been shown in some cases rather simply the location of the anionic part is important for the biological activity and not the specific structure of the charge-carrying carbohydrate moiety. Thus, the sialic acid in Lewis structures could be replaced by a carboxymethyl group without loss of biological activity [1]. Therefore, methods for the regioselective introduction of carboxyl groups with defined stereochemistry are of interest for the preparation of structurally simple and biologically active carbohydrate derivatives.

2. Results and discussion

In order to use the chiral information of carbohydrate components we chose the conjugate addition of an *O*-nucleophile to an unsaturated ester. This type of reaction is mainly used in natural product synthesis for the formation of tetrahydropyrans by intramolecular addition; however, there are also some reports on intermolecular addition reactions [2–8]. Although the formation of seven-membered cyclic ethers via intramolecular conjugate addition to unsaturated esters was reported [9], attempts to achieve a 7-*endo*-trig ring

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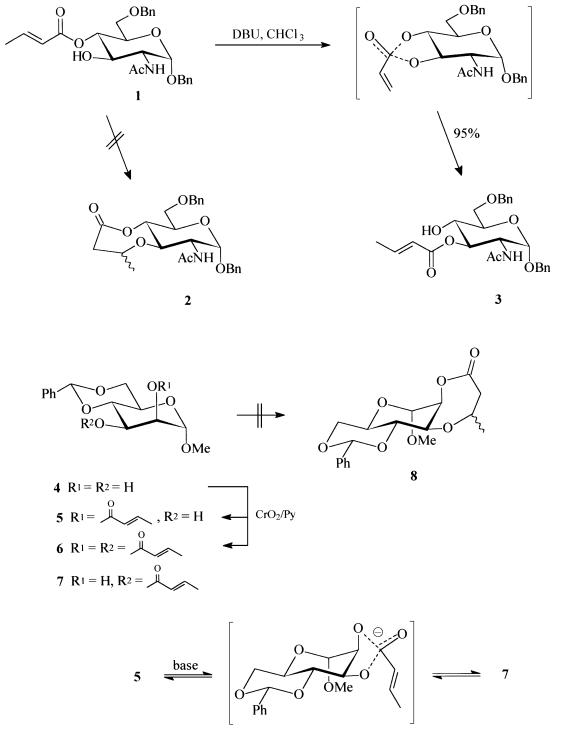
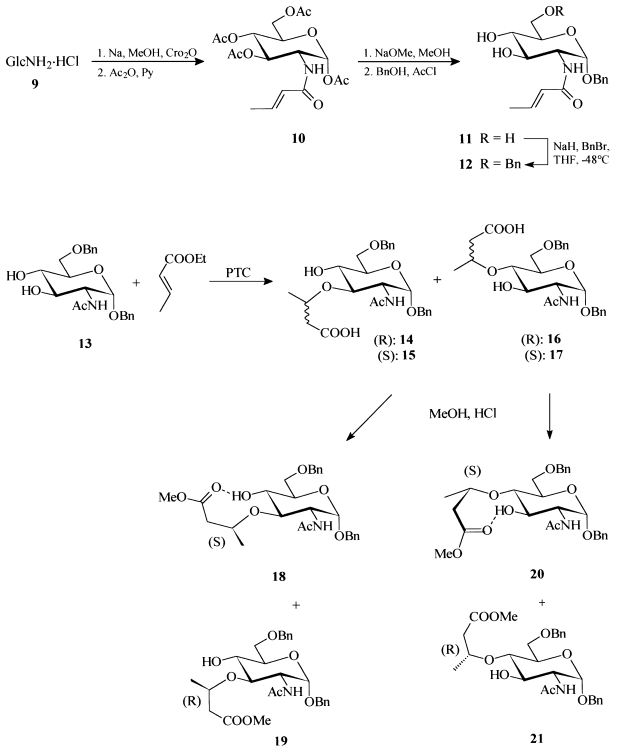
closure [10,11] in the glucosamine crotyl ester derivative **1** to give the homomuramic acid derivative **2**, only led to the formation of the regioisomer **3**, as the product of an ester migration from one equatorial hydroxy group to another [12]. By reaction of the benzylidene mannoside **4** with 1.2 eqiv of crotonic acid anhydride in pyridine, the 2-monoester **5** (24%) and the bis-acylated product **6** (33%) were obtained. By reaction of **5** with base, again a facile migration of the acyl groups was observed to give the regioisomeric 3-monoester **7**. Depending on the reaction conditions different amounts of migration product were formed. Reaction of **5** in THF with $KOBu^t$, for instance, lead to 39% of the migration product **7**, whereas the reaction in dichloromethane with DBU gave 56% of **7**; however, in no case could the desired addition product **8** be formed.



In an attempt to achieve an intramolecular reaction and to prevent an ester migration the amides **11** and **12** were synthesized and reacted with different bases. Starting with glucosamine hydrochloride **9** the free amine was prepared, *N*-acylated with crotonic acid anhydride and further peracetylated to give compound **10** in 91% yield. After deacetylation of **10**, Fischer glycosylation followed by selective benzylation with benzyl bromide at −48 °C in THF gave **11** (24%) and **12** (32%), respectively. Both compounds were treated in different solvents with several bases but in no case could products of an intramolecular conjugate addition reaction be observed. On the other hand, the intermolecular reaction of **13** with crotonic acid ethyl ester under phase transfer conditions gave the 3-ester derivative **15** in an almost stereoselective fashion as the main product together with small amounts of the isomeric 4-esters **16** and **17** [12].



The intermolecular addition reaction of **13** to crotonic acid ethylester was dependent on the solvent and the catalyst. In all cases the addition via the 3-OH group was favoured (Table 1). With tetrabutylammonium hydrogensulfate ($TBAHSO_4$) the reaction was fastest in dichloromethane, to give **15** as single diastereomer and the diasteromeric mixture of **16** and **17** in 91% overall yield. In diethylether the reaction was much slower and yielded only products of the 3-OH addition with **15** as predominant diasteromer (ratio of (*S*) and (*R*) 11:1) in 49% overall yield. In toluene there was no reaction at room temperature, but under reflux the diastereomeric mixtures of the addition products at the 3-OH and the 4-OH position were obtained in 83% overall yield. By use of benzyl triethylammonium chloride ($BnEt_3NCl$) as catalyst in toluene the reaction was further slowed down but led to a regioselective addition at C-3 to give exclusively the diastereomeric mixture of **14** and **15**.

All products were subsequently treated with MeOH/HCl to give the corresponding methyl

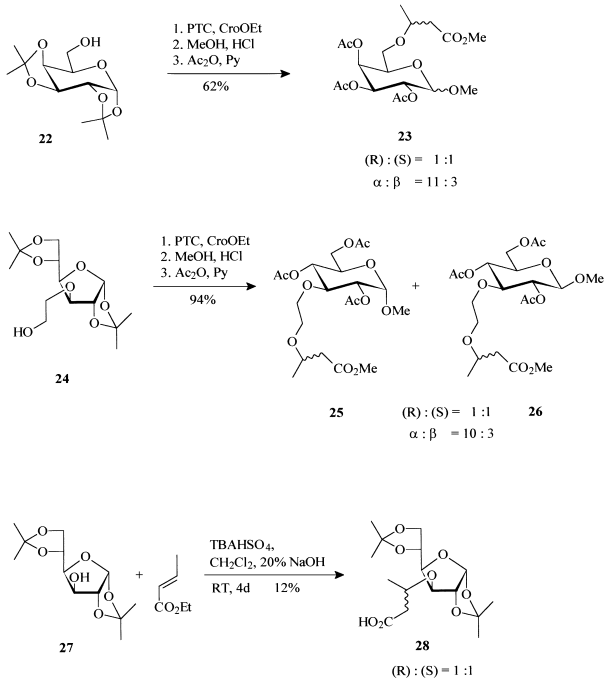
Table 1
Addition reaction of **13**:reaction conditions, yields and (*S*):(*R*) ratios

Reaction conditions	Addition to 3-OH		Addition to 4-OH		Overall yield (%)
	Yield (%)	(*S*):(*R*) ratio	Yield (%)	(*S*):(*R*) ratio	
CH_2Cl_2, $TBAHSO_4$, r.t., 2d	76	1:0	15	1:1	91
Et_2O, $TBAHSO_4$, r.t., 5d	49	11:1	—		49
Toluene, $TBAHSO_4$, refl., 6h	63	1:1	20	1:1	83
Toluene, $BnEt_3NCl$, refl., 16h	80	1:1	—		80

esters **18**–**21**. These allowed determination of the novel stereocentres due to formation of intramolecular hydrogen bridges in case of the (*S*)-configuration in the side chain. In the ^1H NMR spectrum a doublet at rather low field (5.20 ppm for **19** and 5.06 ppm for **20**) disappeared upon addition of D_2O or MeOD which indicated an intramolecular hydrogen bridge between the carbonyl group of the ester and the 4-OH proton of the sugar. This nine-membered hydrogen bridged ring formed in $CDCl_3$ solution and allowed the determination of the absolute configuration of the new stereocentre in the side chain by NOE experiments. In the case of the (*R*)-configuration no hydrogen bridges could be observed [12]. For further investigations of the regio- and stereoselectivity of this conjugate addition the optimum phase transfer conditions (dichloromethane, $TBAHSO_4$) were tested with a number of other carbohydrate derivatives. Free acids were difficult to isolate and thus directly transformed into the corresponding methyl esters by treatment with MeOH/HCl. This simultaneously led to the formation of methyl glycosides, and finally the free hydroxy groups were acetylated.

For sugars with free primary hydroxy groups at different distances to the next chiral centre (**22** and **24** [13]) no stereoselectivity was found. The ratio of diastereomers **23** and **25**/**26** was 1:1 as determined by ^1H NMR, using the relative ratio of integrals of the characteristic doublets for the methyl group in the side chain at 1.15–1.19 ppm, since in no case their separation could be achieved. The reaction of a single secondary hydroxy group with an adjacent chiral centre such as in **27** was expected to give better stereoselectivity; however, due to the lower reactivity the reaction was slow, and again **28** was obtained as a 1:1 mixture of diastereomers in poor yield.

These results indicated that participation of another hydrogen may be the reason for the observed stereoselectivity in the formation of **15**. As depicted in Fig. 1 the approach of the unsaturated ester to compound **13** can be assumed to be guided by a hydrogen bridge formed either via the 4-OH group (model A, Fig. 1) or the amide proton (model B, Fig. 1) of **13** and the ester carbonyl oxygen. In model A both reactions show roughly the same steric requirements. In contrast, due to steric hindrance of the (*R*)-product model B favours the formation of the (*S*)-derivative. In ether, however, this steric influence seems to be less important, in contrast to the reaction in dichloromethane in which no (*R*)-configured product was found. The other diastereomer was also formed in minor amounts but at higher temperatures (e.g. in toluene under reflux) no stereoselectivity was found at all.



By reaction of the gluco compound **29**, again with the *trans*-diequatorial hydoxyl groups and a rigid pyranose ring, the regioselectivity was about

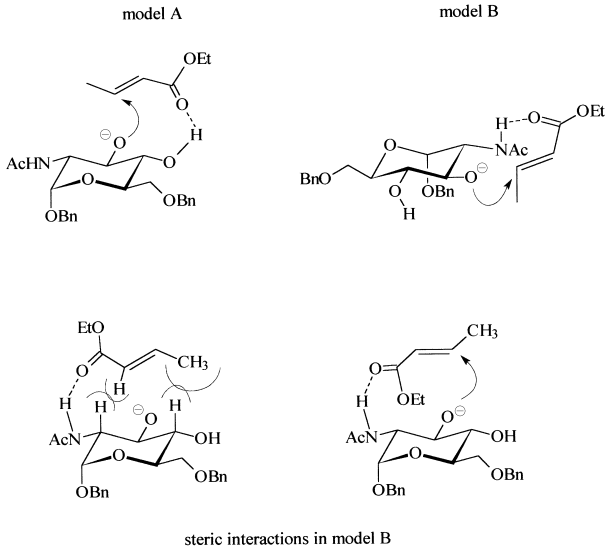
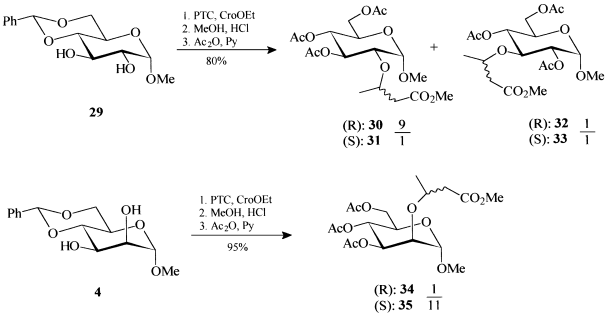


Fig. 1.

4.5:1 in favour of the more reactive 2-position (overall 56%). The diastereomeric ratio at the 2-position (**30** and **31**) was 9:1, but at the 3-position no stereoselection was found (**32**:**33** = 1:1). In the corresponding reaction of the manno-configured compound **4** only the diastereomers **34** and **35** were formed, resulting from the exclusive reaction of the 2-OH group. The reaction proceeded in good yields (95%) and with high stereoselection (11:1), favouring the (*S*)-configured product. As shown in Fig. 2 a prearrangement including hydrogen bonds may guide the approach of the reactants in the reaction of **29** or **4**, respectively, with the unsaturated ester. The configurations in the side chains in **30** and **35** were assigned by NOESY experiments. The observed NO-effects are shown in Fig. 3 (only relevant protons and substituents are drawn).



In summary, the conjugate addition under phase transfer conditions provides a useful method for the introduction of ether linked carboxylic side chains to carbohydrates. The reaction proceeds

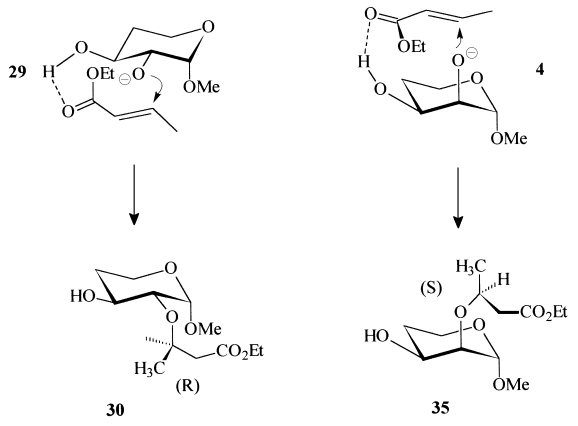


Fig. 2.

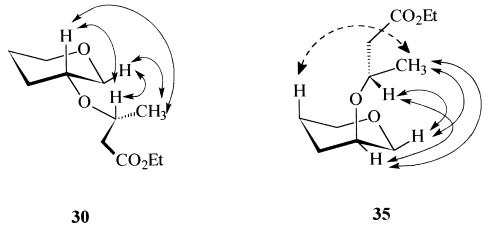


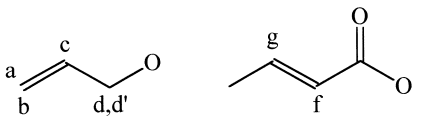
Fig. 3.

with good to excellent regio- and stereoselectivity for several carbohydrate diol components.

3. Experimental

General methods.—^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX 400 at 400 and 100.67 MHz, respectively, with $SiMe_4$ as internal standard. Chemical shifts are given in ppm downfield from $SiMe_4$ and *J* values in Hz. NMR assignments were made using standard ^{1}H,^{1}H-COSY experiments. ^{1}H NMR chemical shifts of overlapping signals were obtained from the centre of the cross-peaks in the ^{1}H,^{1}H COSY spectra. Melting points were taken using an Olympus polarising microscope and are uncorrected. TLC was carried out on silica gel 60 F_{254} (Merck) on aluminium foil with detection by charring with H_2SO_4. Preparative column chromatography was performed on silica gel (230–400 mesh, 0.040–0.063 mm, Merck) using the flash technique. Optical rotations were measured at ~20 °C using a Perkin-Elmer Model 241 polarimeter and a 1 dm cuvette. Evaporations were carried out at less than 45 °C under diminished pressure.

The protons in the allyl and crotyl groups were named as shown:



Methyl 4,6-O-*benzylidene-2*-O-*crotyl*-α-D-*mannopyranoside* (**5**) *and methyl 4,6*-O-*benzylidene-2,3-di*-O-*crotyl*-α-D-*mannopyranoside* (**6**).—Crotonic acid anhydride was added dropwise at 0 °C to a solution of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**4**, 225 mg, 0.8 mmol) in pyridine (5 mL). The solution was allowed to warm to room temperature and was stirred overnight, poured on ice-water and extracted with chloroform. The organic phase was dried ($MgSO_4$), the solvent evaporated and the two products separated by flash chromatography (3:1 toluene–ethyl acetate) to give 109 mg of **6** (33%, syrup) und 66 mg of **5** (24%, syrup). Compound **5**: $[\alpha]_D^{20}$ −3.9° (*c* 0.5, chloroform); ^{1}H NMR ($CDCl_3$): δ 7.53–7.30 (m, 5 H, Ph), 7.09 (m, 1 H, H-g), 5.96 (m, 1 H, H-f, $^4J_{f,Me}$ 2.0, $J_{f,g}$ 15.8), 5.61 (s, 1 H, PhCH), 5.27 (dd, 1 H, H-2, $J_{1,2}$ 1.5, $J_{2,3}$ 3.6), 4.72 (d, 1 H, H-1), 4.29 (dd, 1 H, H-4, $J_{3,4}$ 9.7, $J_{4,5}$ 9.7), 4.25 (dd, 1 H, H-6eq, J_{gem} 9.7, $J_{5,6eq}$ 4.1), 3.92 (dd, 1 H, H-3), 3.89–3.80 (m, 2 H, H-5 u. H-6ax), 3.40 (s, 3 H, OMe), 1.91 (m, 3 H, Me, $J_{g,Me}$ 7.1); EIMS: *m*/*z* 350 (M^+). Compound **6**: $[\alpha]_D^{20}$ −204° (*c* 4, chloroform); ^{1}H NMR ($CDCl_3$): δ 7.48–7.30 (m, 5 H, Ph), 7.07 (m, 1 H, H-g2), 6.93 (m, 1 H, H-g3), 5.95 (m, 1 H, H-f2, $^4J_{f,Me}$ 2.0, $J_{g,f}$ 15.8), 5.89 (m, 1 H, H-f3, $^4J_{f,Me}$ 2.0, $J_{g,f}$ 15.8), 5.59 (s, 1 H, PhCH), 5.50 (dd, 1 H, H-3, $J_{2,3}$ 3.6, $J_{3,4}$ 10.2), 5.41 (dd, 1 H, H-2, $J_{1,2}$ 1.5), 4.70 (d, 1 H, H-1α), 4.30 (dd, H-6eq, J_{gem} 10.2, $J_{5,6eq}$ 4.6), 4.10 (dd, 1 H, H-4, $J_{4,5}$ 9.7), 3.97 (ddd, 1 H, H-5), 3.86 (dd, 1 H, H-6ax, $J_{5,6ax}$ 10.2), 3.39 (s, 3 H, OMe), 1.92 (m, 3 H, Me-2, $J_{g,Me}$ 7.1), 1.82 (m, 3 H, Me-3, $J_{g,Me}$ 7.1); EIMS: *m*/*z* 417 (M–H).

Methyl 4,6-O-*benzylidene-3*-O-*crotyl*-α-D-*mannopyranoside* (**7**).—Method A: To a stirred solution of **5** (16 mg, 0.05 mmol) in dry THF (2 mL) potassium *tert*-butylate (10 mg, 0.08 mmol) was added and stirring continued overnight. Methanol (0.2 mL) and water (10 mL) were added and the solution extracted with dichloromethane (4×10 mL). The organic layer was dried over μgSO$_4$, the solvent evaporated and the residue purified by flash chromatography (3:1 toluene–ethyl acetate). Compound **7** was isolated as a colourless syrup (7 mg, 44%) together with 9 mg of the starting material. Method B: To a solution of **5** (25 mg, 0.07 mmol) in dichloromethane (3 mL) one drop of DBU was added and the mixture stirred overnight. The solvent was evaporated and **7** (15 mg, 61%) and the starting material (10 mg) were sparated by flash chromatography (3:1 toluene–ethyl acetate). $[\alpha]_D^{20}$ +5.5° (*c* 0.75, chloroform); ^{1}H NMR ($CDCl_3$): δ 7.50–7.30 (m, 5 H, Ph), 7.04 (m, 1 H, H-g), 5.90 (m, 1 H, H-f, $^4J_{f,Me}$ 2.0, $J_{f,g}$ 15.8), 5.56 (s, 1 H, PhCH), 5.48 (dd, 1 H, H-3, $J_{2,3}$ 3.6, $J_{3,4}$ 10.2), 4.76 (d, 1 H, H-1α, $J_{1,2}$ 1.5), 4.29 (dd, 1 H, H-6eq, J_{gem} 10.2, $J_{5,6eq}$ 4.1), 4.19 (dd, 1 H, H-2), 4.12 (dd, 1 H, H-4, $J_{4,5}$ 9.7), 3.94 (ddd, 1 H, H-5, $J_{5,6ax}$ 10.2), 3.87 (dd, 1 H, H-6ax), 3.42 (s, 3 H, OMe), 1.89 (m, 3 H, Me, $J_{g,Me}$ 7.1).

1,3,4,6-Tetra-O-*acetyl-2-crotamido-2-deoxy*-α-D-*glucopyranose* (**10**).—Glucosamine hydrochloride (29 g, 134 mmol) was added at 0 °C to a stirred solution of sodium (3 g, 130 mmol) in dry methanol (125 mL), the precipitated sodium chloride was filtered off, the residue washed twice with dry methanol (25 mL) and crotonic acid anhydride (23.7 mL, 160 mmol) was added. After standing overnight the solvent was evaporated, the residue washed thoroughly with petrolether and then peracetylated with pyridine–acetanhydride. Evaporation of the solvent yielded **10** (56.4 g, 91%) as colourless crystals. mp 79–80 °C; $[\alpha]_D^{20}$ +69.9° (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$): δ 6.84 (m, 1 H, H-g), 6.20 (d, 1 H, H-1, $J_{1,2}$ 3.6), 5.71 (m,1 H, H-f, $^4J_{f,Me}$ 1.5, $J_{f,g}$ 13.7), 5.54 (d, 1H, NH, $J_{NH,2}$ 8.7), 5.28 (dd, 1 H, H-3, $J_{2,3}$ 10.7, $J_{3,4}$ 9.7), 5.22 (dd, 1 H, H-4, $J_{4,5}$ 9.7), 4.55 (ddd, 1 H, H-2), 4.26 (dd, 1 H, H-6ax, J_{gem} 12.2, $J_{5,6ax}$ 4.1), 4.07 (dd, 1 H, H-6eq, $J_{5,6eq}$ 2.5), 4.00 (ddd, 1 H, H-5), 2.18, 2.09, 2.05, 2.03 (s, 3 H, Ac), 1.85 (m, 3 H, Me, $J_{g,Me}$ 6.6); EIMS: *m*/*z* 356 (M–Acyl$^+$).

Benzyl 2-crotamido-2-deoxy-α-D-*glucopyranoside* (**11**).—Compound **10** (8.0 g, 20 mmol) was deacetylated following the Zemplén procedure. The resulting solid was dissolved in benzyl alcohol, acetyl chloride was added (1 mL) and the solution quickly heated to reflux and kept refluxing for 30 min. After cooling, diethyl ether (200 mL) was added to the resulting black solution, the precipitate filtered off and recrystallized from ethanol–acetone to yield slightly yellowish crystals (1.7 g, 24%). mp 183–184 °C; $[\alpha]_D^{20}$ +133° (*c* 1, EtOH); ^{1}H NMR (D_2O): δ 7.60–7.45 (m, 5 H, Ph), 6.89 (m, 1 H, H-g), 6.08 (m, 1 H, H-f, $^4J_{f,Me}$ 2.0, $J_{f,g}$ 15.8), 5.06 (d, 1 H, H-1, $J_{1,2}$ 3.6), 4.89 (d, 1 H, Bn, J_{gem} 11.7), 4.67 (d, 1 H, Bn′), 4.07 (dd, 1 H, H-2, $J_{2,3}$ 10.7), 4.00–3.85 (m, 4 H, H-3, H-5, H-6ax u. H-6eq),

3.63 (dd, 1 H, H-4, $J_{3,4}$ 9.2, $J_{4,5}$ 9.2), 1.99 (m, 3 H, Me, $J_{g,Me}$ 6.6).

Benzyl 6-O-benzyl-2-crotamido-2-deoxy-α-D-glucopyranoside (**12**).—To a solution of **11** (780 mg, 2.2 mmol) in dry THF (50 mL) sodium hydride (85 mg of a 60% suspension in mineral oil, 2.2 mmol) was added at −48 °C and the mixture was stirred for 15 min. Benzyl bromide (0.26 mL, 2.2 mmol) was added dropwise and the stirring continued for 30 min. Water (0.5 mL) was added to destroy excess reagents, and the solvents were evaporated to dryness. Flash chromatograpy of the residue (gradient ethyl acetate–methanol 20:1–5:1) yielded colourless crystals of **12** (310 mg, 32%). mp 156–159 °C; $[\alpha]_D^{20}$ +36.3° (*c* 0.6, methanol); ^{1}H NMR ($CDCl_3$): δ 7.40–7.23 (m, 10 H, Ph), 6.84 (m, 1 H, H-g), 5.81 (d, 0.8H, NH, $J_{NH,2}$ 8.7), 5.77 (m, 1 H, H-f, $^4J_{f,Me}$ 1.5, $J_{f,g}$ 15.3), 4.93 (d, 1 H, H-1, $J_{1,2}$ 4.0), 4.76 (d, 1 H, 1-Bn, J_{gem} 12.2), 4.63 (d, 1 H, 6-Bn, J_{gem} 12.2), 4.59 (d, 1 H, 6-Bn′), 4.48 (d, 1 H, 1-Bn′), 4.17 (ddd, 1 H, H-2, $J_{2,3}$ 10.7), 3.81 (ddd, 1 H, H-5), 3.78–3.69 (m, 3 H, H-3, H-6ax u. H-6eq), 3.64 (ddd, 1 H, H-4, $J_{3,4}$ 9.2, $J_{4,5}$ 9.2, $J_{OH,4} < 1.0$), 3.48 (d, 0.6 H, 3-OH, $J_{OH,3}$ 5.0), 2.92 (bs, 0.8H, 4-OH), 1.85 (m, 3 H, Me, $J_{g,Me}$ 6.6).

Methyl 2,3,4-tri-O-acetyl-6-O-[(R,S)-1-carboxymethyl-isopropyl]-α,β-D-galactopyranoside (**23**).—Crotonic acid ethylester (1 mL) was added to a vigorously stirred mixture of a solution of diisopropylidene galactose **22** (40 mg, 0.15 mmol) and tetrabutylammonium hydrogensulfate (40 mg, 0.1 mmol) in dichloromethane (4 mL) and 20% sodium hydroxide solution (2 mL). After three days the mixture was diluted with dichloromethane (10 mL) and the layers were separated. The aqueous layer was extracted three times with dichloromethane (15 mL), acidified with concentrated hydrochloric acid and again extracted with dichloromethane (15 mL). The combined organic layers were dried over μgSO_4, the solvent evaporated and the residue dissolved in dry methanol (30 mL). Acetyl chloride (0.1 mL) was added and the mixture was stirred overnight. After evaporation of the solvent the resulting syrupy product was acetylated with pyridine–acetic anhydride, the solvents removed and the residue subjected to flash chromatography (toluene–ethyl acetate) to yield a colourless syrup. $[\alpha]_D^{20}$ +79° (*c* 1.5, chloroform); ^{1}H NMR ($CDCl_3$): δ 5.46 (2d, each 1 H, H-1, $J_{1,2}$ 3.6), 5.45 (m, 0.4 H, H-2b), 5.35 u. 5.34 (dd, 1 H, H-2a, $J_{2,3}$ 10.7), 5.21–5.12 (m, 2.4 H, H-3, $J_{3,4}$ 3.3), 5.04–4.96 (m, 2.4 H, H-4), 4.40 u. 4.39 (d, 0.2H, H-1b, $J_{1,2}$ 8.1), 4.22–4.04 (m, 7.2 H, H-5, H-6, H-6′), 3.94–3.76 (m, 2.4 H, CH), 3.70 u. 3.69 (s, 0.6H, $CO_2Me\beta$), 3.69 u.3.68 (s, 3H, $CO_2Me\alpha$), 3.52 u. 3.51 (s, 0.6 H, OMeβ), 3.41 u.3.40 (s, 3 H, OMeα), 2.58–2.48 (m, 2.4 H, CH_2, J_{gem} 15.3), 2.38–2.30 (m, 2.4 H, CH_2'), 2.18–1.96 (m, ca. 22H, div. Ac), 1.19 u. 1.15 (d, 3 H, $CH_3\alpha$, $J_{CH,CH3}$ 6.1), 1.15 u. 1.14 (d, 0.6 H, $CH_3\beta$, $J_{CH,CH3}$ 6.1). ^{13}C NMR ($CDCl_3$, characteristic signals): δ 101.63 (C-1β), 96.76 (C-1α), 61.34 (C-6), 55.04 (OMe), 51.15 (CO_2Me), 41.16 (CH_2). EIMS: *m*/*z* 389 ($M-CH_3O^+$). Anal. Calcd. for $C_{18}H_{28}O_{11}$ (420.4): C, 51.42; H, 6.71. Found: C, 51.24; H, 6.66.

Methyl 2,4,6-tri-O-acetyl-3-O-[2-O-{(R,S)-1-carboxymethyl-isopropyl}-ethyl]-α-D-glucopyranoside (**25**) *and methyl 2,4,6-tri-O-acetyl-3-O-[2-O-{(R,S)-1-carboxymethyl-isopropyl}-ethyl]-β-D-glucopyranoside* (**26**).—Crotonic acid ethylester (1 mL) was added to a vigorously strirred mixture of a solution of **24** [13] (50 mg, 0.16 mmol) and tetrabutylammonium hydrogensulfate (60 mg, 0.15 mmol) in dichloromethane (4 mL) and 20% sodium hydroxide solution (2 mL). After stirring overnight the mixture was diluted with dichloromethane (10 mL) and the layers were separated. The aqueous layer was extracted three times with dichloromethane (15 mL), acidified with concentrated hydrochloric acid and again extracted with dichloromethane (15 mL). The combined organic layers were dried over μgSO_4, the solvent evaporated and the residue dissolved in dry methanol (30 mL). Acetyl chloride (0.1 mL) was added and the mixture was stirred overnight. After evaporation of the solvent the resulting syrupy product was acetylated with pyridine–acetic anhydride, the solvents removed and the residue subjected to flash chromatography (toluene–ethyl acetate) to yield **25** (54 mg, 73%) and **26** (16 mg, 21%) as colourless syrups. Compound **25**: ^{1}H NMR ($CDCl_3$): δ 5.04 u. 5.01 (dd, 0.5 H, H-4, $J_{3,4}$ 9.7, $J_{4,5}$ 9.7), 4.94 u. 4.92 (dd, 0.5 H, H-1, $J_{1,2}$ 3.1), 4.86–4.78 (m, 1H, H-2), 4.25–4.17 (m, 1 H, H-6), 4.14–4.06 (m, 1 H, H-6′), 3.90–3.81 (m, 3 H, H-3, H-5 u. CH), 3.80–3.71 (m, 1 H, H-a), 3.67–3.50 (m, 2 H, H-c u. H-d), 3.49–3.42 (m, 1 H, H-b), 3.40 u. 3.39 (s, 1.5 H, OMe), 2.57 u. 2.56 (dd, 0.5 H, CH_2ax, J_{gem} 15.3, $J_{CH,CH2ax}$ 7.1), 2.36 u. 2.35 (dd, 0.5 H, CH_2eq, $J_{CH,CH2eq}$ 6.1), 2.13, 2.10 u. 2.06 (s, 3 H, Ac), 1.19 (d, 3 H, CH_3, $J_{CH,CH3}$ 6.1). Compound **26**: ^{1}H NMR ($CDCl_3$): δ 5.08 u. 5.05 (dd, 0.5 H, H-4, $J_{3,4}$ 9.7, $J_{4,5}$ 9.7), 4.98 u. 4.96 (dd, 0.5 H, H-2, $J_{1,2}$ 8.1, $J_{2,3}$ 9.7), 4.44 u. 4.43 (d, 0.5 H,

H-1b), 4.27–4.18 (m, 1 H, H-6), 4.17–4.05 (m, 3 H, H-3, H-5 u. H-6′), 3.89–3.81 (m, 1 H, CH), 3.78–3.73 (m, 1 H, H-a), 3.67–3.53 (m, 2 H, H-c u. H-d), 3.50–3.42(m, 1 H, H-b), 3.49 and 3.48 (s, 1.5 H, OMe), 2.57 and 2.55 (dd, 0.5 H, CH_2ax, J_{gem} 15.3, $J_{CH,CH2ax}$ 7.1), 2.36 and 2.35 (dd, 0.5 H, CH_2eq, $J_{CH,CH2eq}$ 6.1), 2.11, 2.09 and 2.07 (s, 3H, Ac), 1.17 (d, 3 H, CH_3, $J_{CH,CH3}$ 6.1).

3-O-[(R,S)-1-Carboxy-isopropyl]-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**28**).—Crotonic acid ethylester (1 mL) was added to a vigorously stirred mixture of diisopropylidene glucose **27** (83 mg, 0.32 mmol) and tetrabutylammonium hydrogensulfate (120 mg, 0.35 mmol) in dichloromethane (4 mL) with 20% sodium hydroxide solution (4 mL). After four days the mixture was diluted with dichloromethane (10 mL) and the layers were separated. The aqueous layer was extracted three times with dichloromethane (15 mL), acidified with concentrated hydrochloric acid and again extracted with dichloromethane (15 mL). The combined organic layers were dried over μgSO_4 and the solvent evaporated. The crude product was purified by flash chromatography (gradient toluene–ethyl acetate 1:1–ethyl acetate) to yield **28** as a colourless syrup (14 mg, 12%). ^{1}H NMR ($CDCl_3$): δ 5.74 and 5.66 (d, 1 H, H-1 and H-1′, $J_{1,2}$ 3.6), 4.59 and 4.45 (dd∼d, 1 H, H-2 and H-2′), 4.24–4.14 (m, 2 H, H-5 and H-5′), 4.07–4.00 (m, 2 H, H-4 and H-4′), 3.99–3.87 (m, 5 H, H-3, H-3′, H-6a, H-6a′ and CH), 3.82–3.73 (m, 3 H, H-6b, H-6b′ and CH′), 2.47 (dd, 1 H, CH_2ax, J_{gem} 15.0, $J_{CH,CH2ax}$ 6.6), 2.40 (dd, 1 H, CH_2ax′, J_{gem} 15.3, $J_{CH,CH2ax'}$ 7.1), 2.33 (dd, 1 H, CH_2eq, $J_{CH,CH2eq}$ 5.6), 2.27 (dd, 1 H, CH_2eq′, $J_{CH,CH2eq'}$ 5.6), 1.35, 1.29, 1.22 and 1.19 (s, 6 H, i-Prop), 1.11, 1.09, 1.06 and 1.04 (s, 3 H, CH_3, $J_{CH,CH3}$ 6.1).

Methyl 3,4,6-tri-O-acetyl-2-O-[(R)-1-carboxymethyl-isopropyl]-α-D-glucopyranoside (**30**), *methyl 3,4,6-tri-O-acetyl-2-O-[(S)-1-carboxymethyl-isopropyl]-α-D-glucopyranoside* (**31**), *methyl 2,4,6-tri-O-acetyl-3-O-[(R)-1-carboxymethyl-isopropyl]-α-D-glucopyranoside* (**32**) *and methyl 2,4,6-tri-O-acetyl-3-O-[(S)-1-carboxymethyl-isopropyl]-α-D-glucopyranoside* (**33**).—Crotonic acid ethylester (1 mL) was added to a vigorously strirred mixture of **29** (40 mg, 0.14 mmol) and tetrabutylammonium hydrogensulfate (47 mg, 0.14 mmol) in dichloromethane (4 mL) with 20% sodium hydroxide solution (2 mL). After stirring overnight the mixture was diluted with dichloromethane (10 mL) and the layers were separated. The aqueous layer was extracted three times with dichloromethane (15 mL), acidified with concentrated hydrochloric acid and again extracted with dichloromethane (15 mL). The combined organic layers were dried over μgSO_4, the solvent evaporated and the residue dissolved in dry methanol (30 mL). Acetyl chloride (0.1 mL) was added and the mixture was stirred overnight. After evaporation of the solvent the resulting syrupy product was acetylated with pyridine–acetic anhydride, the solvents removed and the residue subjected to flash chromatography (3:1 toluene–ethyl acetate). The major fraction was **30** (syrup, 33 mg, 56%) and another fraction (syrup, 14 mg, 24%) contained the stereo- and regioisomers **31**, **32**, and **33** in equal amounts (as determined by ^{1}H NMR). Compound **30**: $[\alpha]_D^{20}$ +64° (*c* 1.5, chloroform); ^{1}H NMR ($CDCl_3$): δ 5.33 (dd, 1 H, H-4, $J_{3,4}$ 9.7, $J_{4,5}$ 9.7), 4.98 (dd, 1 H, H-3, $J_{2,3}$ 9.7), 4.78 (d, 1 H, H-1, $J_{1,2}$ 3.6), 4.27 (dd, 1 H, H-6ax, J_{gem} 12.7, $J_{5,6ax}$ 5.1), 4.08 (dd, 1 H, H-6eq, $J_{5,6eq}$ 2.0), 4.05 (m, 1 H, CH), 3.95 (ddd, 1 H, H-5), 3.66 (s, 3 H, CO_2Me), 3.58 (dd, 1 H, H-2), 3.44 (s, 3 H, OMe), 2.59 (dd, 1 H, CH_2ax, J_{gem} 15.3, $J_{CH,CH2ax}$ 7.1), 2.34 (dd, 1 H, CH_2eq, $J_{CH,CH2eq}$ 5.6), 2.09, 2.06, 2.01 (each s, 3 H, Ac), 1.21 (d, 3 H, CH_3, $J_{CH,CH3}$ 6.1); EIMS: *m*/*z* 389 ($M-CH_3O^+$). Anal. Calcd for $C_{18}H_{28}O_{11}$ (420.4): C, 51.42; H, 6.71. Found: C, 51.43; H 6.91. Characteristic ^{1}H NMR ($CDCl_3$) signals of the side chain methylene groups in **31**, **32** and **33**: δ 1.25 (d, 3 H, CH_3, $J_{CH,CH3}$ 6.1), 1.17 (d, 3 H, CH_3, $J_{CH,CH3}$ 6.1), 1.13 (d, 3 H, CH_3, $J_{CH,CH3}$ 6.1).

Methyl 3,4,6-tri-O-acetyl-2-O-[(R)-1-carboxymethyl-isopropyl]-α-D-mannopyranoside (**34**) *and methyl 3,4,6-tri-O-acetyl-2-O-[(S)-1-carboxymethyl-isopropyl]-α-D-mannopyranoside* (**35**).—Crotonic acid ethylester (1 mL) was added to a vigorously strirred mixture of a solution of **4** (40 mg, 0.14 mmol) and tetrabutylammonium hydrogensulfate (39 mg, 0.1 mmol) in dichloromethane (4 mL) and 20% sodium hydroxide solution (2 mL). After stirring overnight the mixture was diluted with dichloromethane (10 mL) and the layers were separated. The aqueous layer was extracted three times with dichloromethane (15 mL), acidified with concentrated hydrochloric acid and again extracted with dichloromethane (15 mL). The combined organic layers were dried over μgSO_4, the solvent evaporated and the residue dissolved in dry methanol (30 mL). Acetyl chloride (0.1 mL) was added and the mixture was stirred overnight. After evaporation of the solvent the resulting

syrupy product was acetylated with pyridine–acetic anhydride, the solvents removed and the residue subjected to flash chromatography (3:1 toluene–ethyl acetate) to yield 56 mg of a colourless syrup (**35**, 56 mg, 95%). The product contained a small amount of the stereoisomer **34** (5% from ^{1}H NMR). Compound **35**: $[\alpha]_D^{20}$ +53.9° (*c* 2, chloroform); ^{1}H NMR ($CDCl_3$): δ 5.26 (dd, 1 H, H-4, $J_{3,4}$ 9.7, $J_{4,5}$ 0 9.7), 5.16 (dd, 1 H, H-3, $J_{2,3}$ 3.6), 4.68 (d, 1 H, H-1, $J_{1,2}$ 1.5), 4.24 (dd, 1 H, H-6ax, J_{gem} 12.2, $J_{5,6ax}$ 5.1), 4.10 (dd, 1 H, H-6eq, $J_{5,6eq}$ 2.6), 3.95 (m, 1 H, CH), 3.86 (ddd, 1 H, H-5), 3.83 (dd, 1 H, H-2), 3.70 (s, 3 H, CO_2Me), 3.39 (s, 3 H, OMe), 2.66 (dd, 1 H, CH_2ax, J_{gem} 14.7, $J_{CH,CH2ax}$ 7.6), 2.37 (dd, 1 H, CH_2eq, $J_{CH,CH2eq}$ 5.6), 2.10, 2.08, 2.02 (Je s, 3 H, Ac), 1.20 (d, 3 H, CH_3, $J_{CH,CH3}$ 6.1); EIMS: *m*/*z* 389 (M–CH_3O^+). Compound **34**: characteristic ^{1}H NMR ($CDCl_3$) signals: δ 5.12 (dd, 1 H, H-3, $J_{2,3}$ 3.6), 4.72 (d, 1 H, H-1a, $J_{1,2}$ 1.5), 1.15 (d, 3 H, CH_3, $J_{CH,CH3}$ 6.1).

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