

## Mercury Iodide as a Catalyst in Oligosaccharide Synthesis

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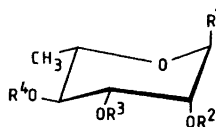
The disaccharide 4-*O*- $\alpha$ -D-mannopyranosyl- $\alpha$ -L-rhamnopyranose and the trisaccharide 2-*O*- $\alpha$ -D-galactopyranosyl-4-*O*- $\beta$ -D-mannopyranosyl- $\alpha$ -L-rhamnopyranose determinants, which are analogs of the repeating unit of *Salmonella* serogroup A, B and D, have been synthesized using mercury(II) iodide as a catalyst in the glycosylation reaction. The reducing end of the di- and the trisaccharide was substituted with a linking arm for covalent attachment to a protein carrier. Reaction of 8-ethoxycarbonyloct-1-yl 2,3-di-*O*-benzoyl- $\alpha$ -L-rhamnopyranoside with acetobromomannose in the presence of mercury(II) iodide gave, after deprotection, the disaccharide in 49 % yield. The trisaccharide was prepared by a block synthesis in which 6-*O*-acetyl-4-*O*-allyl-2-*O*-(6-*O*-acetyl-2-*O*-allyl-3,4-di-*O*-benzoyl- $\alpha$ -D-galactopyranosyl)-3-*O*-benzyl- $\alpha$ -D-mannopyranosyl bromide (21) and 8-methoxycarbonyloct-1-yl 2,3-*O*-cyclohexylidene- $\alpha$ -L-rhamnopyranoside were condensed in the presence of mercury(II) iodide. These conditions gave the trisaccharide (26) in 26 % yield. The disaccharide 21 was prepared by mercury(II) iodide catalyzed condensation of the protected galactopyranosyl bromide (15) and 4-*O*-allyl-1,6-anhydro-3-*O*-benzyl- $\beta$ -D-mannopyranose followed by acetolysis and reaction with titanium tetrabromide.

Mercury(II) salts have found wide application as catalysts for promotion of glycosidic bond formation.<sup>1</sup> Thus mercury(II) cyanide and mercury(II) bromide are generally used in glycosylation with glycosyl halides of medium reactivity, mainly producing  $\alpha$ -linked glycosides.<sup>1</sup> In reaction of less reactive glycosyl halides silver salts have been advantageously used as catalysts. The silver salts are very active catalysts and decomposition products are often observed on prolonged reaction times.<sup>1</sup> In the present paper

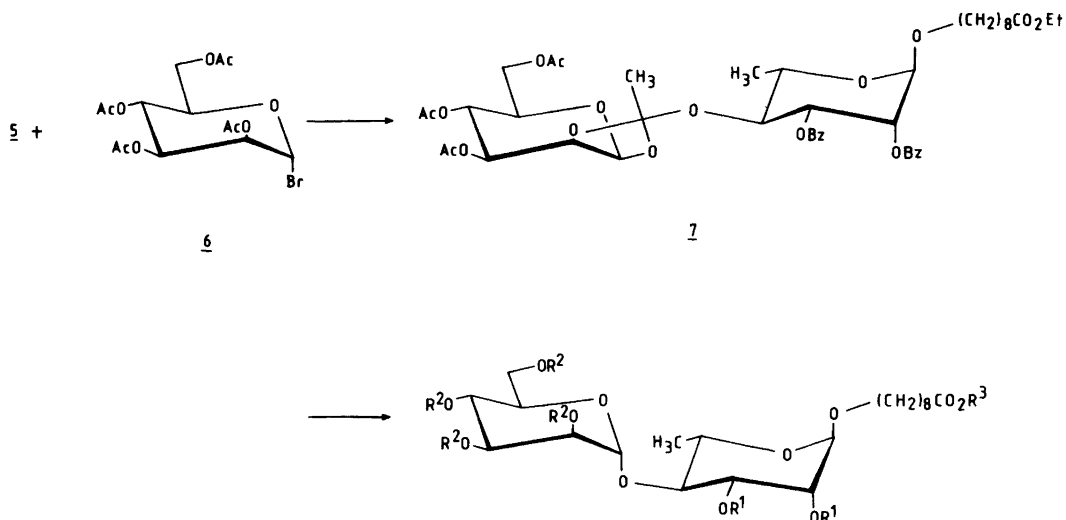
mercury(II) iodide is introduced as a new catalyst of medium activity for glycosidation reactions. Based on the ion pair equilibration theory by Lemieux *et al.*<sup>2</sup> mercury(II) iodide may be an alternative catalyst to mercury(II) bromide in the formation of  $\alpha$ -linked glycosides, the latter extensively used by Paulsen and Kolár.<sup>3</sup> The nucleophilicity of the iodide ion, the soft character and the solubility of mercury(II) iodide in unpolar solvents like chloroform and dichloromethane as well as the reactivity of the intermediate  $\beta$ -glycosyl iodide-mercury(II) iodide ion-pair complex all seem to favour selective  $\alpha$ -glycosylation.

### RESULTS AND DISCUSSION

In this investigation attempts were made to synthesize oligosaccharides related to *Salmonella* antigens. The selectively protected  $\alpha$ -L-rhamnopyranoside (5) was prepared from 1,2,3 tri-*O*-



- 1  $R^1=OBz$ ;  $R^2=R^3=Bz$ ;  $R^4=H$
- 2  $R^1=OBz$ ;  $R^2=R^3=Bz$ ;  $R^4=ClH_2CCO$
- 3  $R^1=Br$ ;  $R^2=R^3=Bz$ ;  $R^4=ClH_2CCO$
- 4  $R^1=-O-(CH_2)_8CO_2Et$ ;  $R^2=R^3=Bz$ ;  $R^4=ClH_2CCO$
- 5  $R^1=-O-(CH_2)_8CO_2Et$ ;  $R^2=R^3=Bz$ ;  $R^4=H$
- 22  $R^1=Br$ ;  $R^2=R^3=R^4=Bz$
- 23  $R^1=-O-(CH_2)_8CO_2Et$ ;  $R^2=R^3=R^4=Bz$
- 24  $R^1=-O-(CH_2)_8CO_2Me$ ;  $R^2=R^3=R^4=H$
- 25  $R^1=-O-(CH_2)_8CO_2Me$ ;  $R^2$ ,  $R^3=cyclohexylidene$ ;  $R^4=H$



8  $R^1 = \text{Bz}$ ;  $R^2 = \text{Ac}$ ;  $R^3 = \text{Et}$

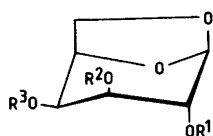
9  $R^1 = R^2 = \text{H}$ ;  $R^3 = \text{Me}$

benzoyl- $\alpha$ -L-rhamnopyranose (*1*), by the method developed by Garegg and Norberg.<sup>4</sup> The rhamnose derivative (*1*) was chloroacetylated and transformed into the rhamnopyranosyl bromide (*3*) which, in turn, was reacted with 8-ethoxycarbonyloctan-1-ol in the presence of mercury(II) cyanide to give *4*. Selective removal of the chloroacetyl group with thiourea gave *5* in an overall yield of 52 % from *1*. Reaction of *5* with acetobromomannose (*6*) in the presence of mercury(II) iodide led almost exclusively to the formation of the orthoester (*7*) which was isolated in 86 % yield. Rearrangement of the orthoester with boron trifluoride etherate gave the  $\alpha$ -linked disaccharide (*8*) in 49 % yield overall from *5*. Finally, deacylation of *8* afforded the disaccharide (*9*). From these results it appears that mercury(II) iodide was not a strong enough Lewis acid to rearrange the orthoester to the glycoside at room temperature.

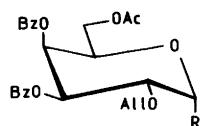
Synthesis of the trisaccharide 8-methoxycarbonyloct-1-yl 2- $O$ - $\alpha$ -D-galactopyranosyl-4- $O$ - $\alpha$ -D-mannopyranosyl- $\alpha$ -L-rhamnopyranoside, a moiety of the repeating unit of *Salmonella* lipopolysaccharides, was attempted in order to investigate the use of mercury(II) iodide as a catalyst in glycosylation with halides having inactive 2- $O$ -substituents. 1,6-Anhydro-3,4- $O$ -isopropylidene- $\beta$ -D-galactopyranose (*10*) was reacted with allyl bromide and sodium hydride to give 82 % of *11*.

Removal of the isopropylidene group gave 92 % of *12* which was quantitatively benzoylated. Acetolysis of *13* gave *14* (90 % yield), transformed into the crystalline bromide (*15*) in 83 % yield. This bromide was used for mercury(II) iodide promoted condensation with 4- $O$ -allyl-1,6-anhydro-3- $O$ -benzyl- $\beta$ -D-mannopyranose (*18*), obtained in 72 % yield from 1,6-anhydro-2,3- $O$ -endo-benzylidene- $\beta$ -D-mannopyranose<sup>5</sup> (*16*) by allylation and selective cleavage of the benzylidene group with lithium aluminium hydride-aluminium trichloride according to Lip-tak *et al.*<sup>6</sup>

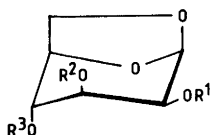
Condensation of *15* and *18* gave 60 % yield of the disaccharide (*19*); only one anomer was observed in the crude product. The 1,6-anhydro ring of *19* was opened by acetolysis in the presence of trifluoroacetic acid and the product (*20*) was transformed to the unstable bromide (*21*) on treatment with titanium tetrabromide according to Paulsen and Jansen.<sup>7</sup> In this reaction some removal of the benzyl group was observed when traces of hydrogen bromide were present. Condensation of *21* with 8-methoxycarbonyloct-1-yl 2,3- $O$ -cyclohexylidene- $\alpha$ -L-rhamnopyranoside (*25*) was carried out in the presence of mercury(II) iodide. The cyclohexylidene derivative was considered more suitable than the benzoyl derivative (*5*) for this reaction due to the higher reactivity. Hence, *25* was prepared in four



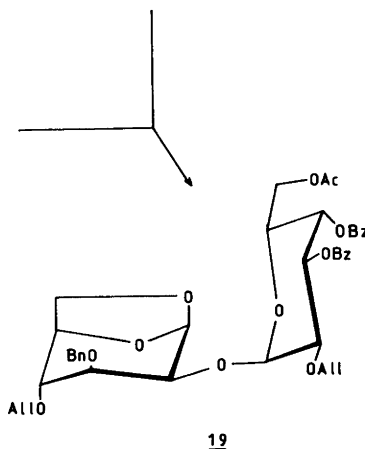
- 10  $R^1=H$ ;  $R^2, R^3$ =isopropylidene  
 11  $R^1=All$ ;  $R^2, R^3$ =isopropylidene  
 12  $R^1=All$ ;  $R^2=R^3=H$   
 13  $R^1=All$ ;  $R^2=R^3=Bz$



- 14  $R^1=OAc$   
 15  $R^1=Br$



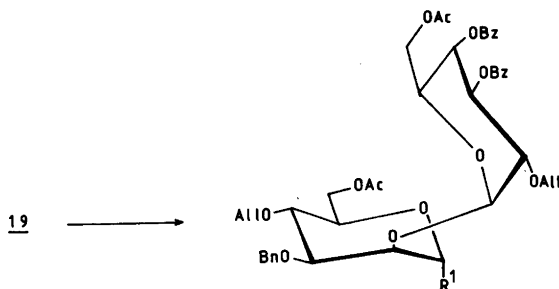
- 16  $R^1, R^2$ =*endo*-benzylidene;  $R^3=H$   
 17  $R^1, R^2$ =*endo*-benzylidene;  $R^3=All$   
 18  $R^1=H$ ;  $R^2=Bn$ ;  $R^3=All$



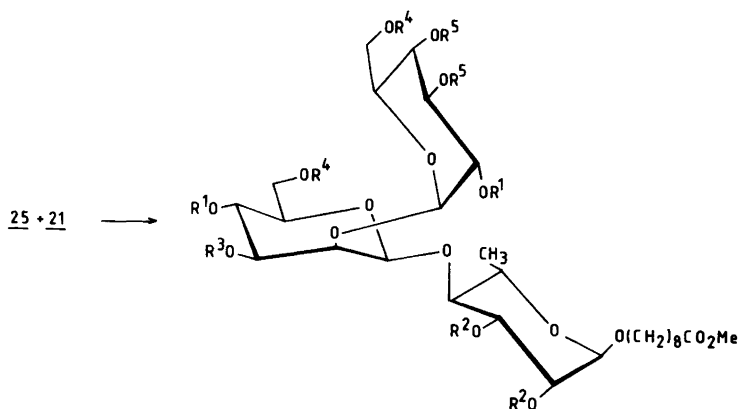
steps from tri-*O*-benzoyl- $\alpha$ -L-rhamnopyranosyl-bromide (22) in an overall yield of 92 %. The condensation of 21 with 25 gave unexpectedly the trisaccharide (26) in 26 % yield overall from 19. The exclusive formation in this case of a  $\beta$ -linkage was ascribed to sterically conditioned suppression of the intermediate  $\beta$ -ion pair concentration through the proximity of the galactopyranosyl residue to the  $\beta$ -site of the anomeric center of the mannose unit. Such proximity

problems could be interpreted on the basis of the well documented orientational effect of the exo-anomeric energy. In fact, this might be a general way to obtain oligosaccharides containing 2-*O*- $\alpha$ -D-glycosylated  $\beta$ -D-mannopyranoside or 2-*O*- $\alpha$ -L-glycosylated  $\beta$ -L-rhamnopyranoside moieties.

The allyl group of 26 was removed by the method of Gigg and Gent<sup>8</sup> and the cyclohexylidene group subsequently hydrolyzed. Acetylation gave 27 in 56 % overall yield, followed by



- 20  $R^1=Ac$   
 21  $R^1=Br$



26  $R^1 = \text{All}$ ,  $R^2 = \text{cyclohexylidene}$ ;  $R^3 = \text{Bn}$ ;

$R^4 = \text{Ac}$ ;  $R^5 = \text{Bz}$

27  $R^1 = R^2 = R^4 = \text{Ac}$ ;  $R^3 = \text{Bn}$ ;  $R^5 = \text{Bz}$

28  $R^1 = R^2 = R^4 = \text{Ac}$ ;  $R^3 = \text{H}$ ;  $R^5 = \text{Bz}$

29  $R^1 = R^2 = R^3 = R^4 = R^5 = \text{H}$

debenzylation to 28 which was deacylated to give overall 71 % of 29. This trisaccharide constitutes an isomer of the repeating main-chain trisaccharide common to *Salmonella* antigens of serogroups A, B and D.

## EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 141 polarimeter. NMR spectra were obtained on Bruker WH-90 and HX-270 NMR instruments. The spectra of protected compound were measured in  $\text{CDCl}_3$  and non-protected products in  $\text{D}_2\text{O}$ . Acetone ( $\delta$  2.12) was used as internal reference for  $^1\text{H}$  NMR spectra and dioxane (67.4 ppm) for  $^{13}\text{C}$  NMR spectra in  $\text{D}_2\text{O}$ . Microanalyses were performed by NOVO microanalytical laboratory.

*1,2,3-Tri-O-benzoyl-4-O-chloroacetyl- $\alpha$ -L-rhamnopyranose* (2). *1,2,3-Tri-O-benzoyl- $\alpha$ -L-rhamnopyranose*<sup>9</sup> (1) (10 g, 21 mmol) was dissolved in acetonitrile (75 ml) and pyridine (3.34 ml, 43 mmol) and cooled to 0 °C. Chloroacetyl chloride (3.34 ml, 42 mmol) dissolved in acetonitrile (10 ml) was added dropwise over a period of 15 min. The mixture was stirred for 2 h at 20 °C and evaporated three times with toluene (30 ml). The residue was dissolved in dichloromethane (40 ml) and washed with saturated sodium hydrogencarbonate (50 ml) and water (50 ml). The organic phase was dried, filtered

through carbon and evaporated. It was redissolved in ethyl acetate (30 ml) and filtered through silica gel. Evaporation at 1 mm Hg and 40 °C left 11.3 g (97 %) of rather unstable 2.  $^1\text{H}$  NMR:  $\delta$  6.48 (H-1); 5.78 (H-2); 5.85 (H-3); 5.54 (H-4); 4.24 (H-5); 1.38 (H-6).  $J_{12}$  1.5 Hz;  $J_{34}$  9.8;  $J_{45}$  9.8;  $J_{56}$  6.4.

*8-Ethoxycarbonyloct-1-yl 2,3-di-O-benzoyl- $\alpha$ -L-rhamnopyranoside* (5). Compound (2) (11.3 g, 20.5 mmol) was dissolved in dichloromethane (20 ml) and cooled to 0 °C. Hydrogen bromide in acetic acid (35 %, 20 ml) was added and the mixture was stirred at 0 °C for 2 h. The solution was evaporated and dissolved in dichloromethane (50 ml). Successive washing with ice water (100 ml), cold saturated aqueous sodium hydrogencarbonate (50 ml) and ice water (50 ml), followed by drying for 40 min gave chromatographically pure *2,3-di-O-benzoyl-4-O-chloroacetyl- $\alpha$ -L-rhamnopyranosyl bromide* (3).  $^1\text{H}$  NMR:  $\delta$  6.45 (H-1); 5.79 (H-2); 6.01 (H-3); 5.51 (H-4); 4.30 (H-5); 1.39 (H-6).  $J_{12}$  2.0 Hz;  $J_{23}$  3.5;  $J_{34}$  10.3;  $J_{45}$  10.3;  $J_{56}$  6.0.

The solution was dried over molecular sieves (4 Å, 3 g) for 2 h under nitrogen and added to a solution of 8-ethoxycarbonyloctan-1-ol (4.2 g, 20.8 mmol) in dichloromethane (20 ml) which had been stirred under nitrogen with mercury(II) cyanide (6 g, 23.8 mmol) and molecular sieves (4 Å, 5 g) for 2 h. The mixture was stirred for 18 h and filtered. The residue was washed with dichloromethane (20 ml) and the filtrate was washed with water (50 ml), saturated sodium hydrogencarbonate solution (50 ml) and water

(50 ml). Drying, filtration through carbon and evaporation gave 4 (12.1 g) as a syrup.  $^1\text{H NMR}$  showed 90 % conversion to the glycoside. The product was dissolved in acetonitrile (50 ml) and water (9 ml) followed by addition of thiourea (2.58 g, 34 mmol). The mixture was stirred for 2 d and evaporated. The residue was extracted with chloroform (75 ml) and filtered. The filtrate was washed twice with saturated sodium hydrogen-carbonate solution (50 ml) and water. The organic phase was dried, filtered through carbon and evaporated. Separation on a silica gel column (ethyl acetate-pentane: 1:2.8) gave 6.03 g (52 % overall from 1) of 5.  $[\alpha]_{\text{D}}^{20} + 24^\circ$  (c 1.9,  $\text{CHCl}_3$ ). Analysis for  $\text{C}_{31}\text{H}_{40}\text{O}_9$ : C, H.  $^1\text{H NMR}$ :  $\delta$  4.89 (H-1); 5.56 (H-2); 5.49 (H-3); 3.88 (H-4); 3.88 (H-5); 1.44 (H-6).  $J_{12}$  1.4 Hz;  $J_{56}$  6.0.

**8-Ethoxycarbonyloct-1-yl 2,3-di-O-benzoyl-4-O-(2,3,4,6-tetra-O-acetyl- $\alpha$ -D-mannopyranosyl)- $\alpha$ -L-rhamnopyranoside (6).** Compound (5) (1.6 g, 2.9 mmol) was dissolved in chloroform (5 ml) and stirred overnight with red mercury(II) iodide (2.3 g, 5 mmol) and molecular sieves (4 $\text{\AA}$ , 6 g) under nitrogen. 2,3,4,6-Tetra-O-acetyl- $\alpha$ -D-mannopyranosyl bromide (6) (1.8 g, 4.4 mmol), dissolved in chloroform (10 ml) and dried overnight over molecular sieves (4 $\text{\AA}$ , 2g), was added and the mixture was stirred under nitrogen at 20 °C for 7 d. The mixture was filtered and the residue was washed with chloroform. The filtrate was washed 3 times with aqueous potassium iodide (75 ml), saturated sodium hydrogencarbonate solution (50 ml) and water (50 ml). The organic phase was dried, filtered and evaporated followed by separation on a silica gel column (ethyl acetate-pentane: 4:5). This gave the intermediate orthoester (7) (2.2 g, 86 %) containing 10 % of the disaccharide (8) according to a  $^1\text{H NMR}$  spectrum. The orthoester (7) (530 mg) was dissolved in dichloromethane-chloroform: 1:1 and stirred with powdered 4 $\text{\AA}$  molecular sieves for 4 h and boron trifluoride etherate (2 drops) was added. The mixture was stirred for 4 d. Filtration and evaporation gave a syrup, which was purified on a silica gel column to give 300 mg of 8 (49 % yield overall).  $[\alpha]_{\text{D}}^{20} + 65.5^\circ$  (c 2.8,  $\text{CHCl}_3$ ). Analysis for  $\text{C}_{45}\text{H}_{58}\text{O}_{18}$ : C, H.  $^1\text{H NMR}$ :  $\delta$  5.03 (H-1.1); 5.17-5.27 (H-2.1, H-3.1, H-4.1); 3.82 (H-5.1) 3.68 (H-6.1); 3.49 (H-6'.1); 4.87 (H-1.2); 5.55 (H-2.2); 5.70 (H-3.2); 3.94 (H-4.2); 4.03 (H-5.2); 1.46 (H-6.2).  $J_{12.1}$  1.1 Hz;  $J_{56.1}$  3.4;  $J_{66'.1}$  10.0;  $J_{12.2}$  1.7;  $J_{23.2}$  3.3;  $J_{34.2}$  9.0;  $J_{45.2}$  9.0;  $J_{56.2}$  5.9.

**8-Methoxycarbonyloct-1-yl 4-O-( $\alpha$ -D-mannopyranosyl)- $\alpha$ -L-rhamnopyranoside (9).** The disaccharide (8) (500 mg, 0.564 mmol) was dissolved in sodium methoxide (0.05 M, 50 ml) and the mixture was stirred for 16 h at room temperature.

Sodium ions were removed by stirring for 2 h with ion exchange resin (Amberlite IRC 50). Evaporation gave a syrup which was separated on a silica gel column (methanol-ethyl acetate: 1:3). Fractions containing the title compound were evaporated giving 213 mg (76 %) of 9.  $[\alpha]_{\text{D}}^{20} - 1.3^\circ$  (c 0.4, MeOH).  $^1\text{H NMR}$ :  $\delta$  4.87 (H-1.1); 3.87 (H-2.1); 3.66 (H-3.1); 3.62 (H-4.1); 3.82 (H-5.1); 3.75 (H-6.1); 3.68 (H-6'.1); 4.66 (H-1.2); 3.81 (H-2.2); 3.80 (H-3.2); 3.43 (H-4.2); 3.60 (H-5.2); 1.20 (H-6.2).  $J_{12.1}$  1.5 Hz;  $J_{23.1}$  2.8;  $J_{34.1}$  9.4;  $J_{45.1}$  9.4;  $J_{56.1}$  2.6;  $J_{66'.1}$  5.2;  $J_{66'.1}$  12.2;  $J_{12.2}$  1.1;  $J_{23.2}$  2.8;  $J_{34.2}$  9.4;  $J_{45.2}$  9.4;  $J_{56.2}$  6.0  $^{13}\text{C NMR}$ : 102.4 ppm (C-1.1); 71.3 (C-2.1); 71.5 (C-3.1); 68.4 (C-4.1); 74.0 (C-5.1); 61.7 (C-6.1); 100.5 (C-1.2); 71.5 (C-2.2); 70.3 (C-3.2); 82.4 (C-4.2); 67.7 (C-5.2); 17.8 (C-6.2).  $J_{\text{CH1.1}}$  167 Hz;  $J_{\text{CH1.2}}$  166.

**2-O-Allyl-1,6-anhydro-3,4-O-isopropylidene- $\beta$ -D-galactopyranose (11).** 1,6-Anhydro-3,4-O-isopropylidene- $\beta$ -D-galactopyranose (10) (25 g, 124 mmol) was dissolved in dry *N,N'*-dimethyl formamide (185 ml) and allyl bromide (15 ml, 175 mmol) was added. Sodium hydride (8.9 g, 185 mmol, 50 % oil-suspension) was washed several times with light petroleum and added in small portions over a period of 45 min at 20 °C with stirring and cooling. The mixture was stirred at 0 °C for 70 min and methanol (10 ml) was added dropwise. After 10 min the mixture was partitioned between dichloromethane (500 ml) and water (500 ml) and filtered through celite, the organic phase was separated and washed twice with water (500 ml). Drying, filtration and evaporation at 1 mmHg and 60 °C gave a syrup which crystallized on cooling. The material was recrystallized from ethanol (150 ml) and water (125 ml). Filtration and washing with water (25 ml) gave, upon drying *in vacuo* over potassium hydroxide, 19.5 g of 11  $[\alpha]_{\text{D}}^{22} - 60^\circ$  (c 0.8,  $\text{CHCl}_3$ ), mp 56.5-57.5 °C,  $^1\text{H NMR}$ :  $\delta$  5.38 (H-1); 3.50 (H-2); 4.36 (H-3); 4.51 (H-4); 4.17 (H-5); 4.05 (H-6); 3.54 (H-6').  $J_{15}$  1.0 Hz;  $J_{23}$  1.5;  $J_{34}$  6.3;  $J_{66'}$  7.5. Analysis for  $\text{C}_{12}\text{H}_{18}\text{O}_5$ : C, H. Processing of the mother liquors gave an additional 5.1 g of 11 bringing the total yield to 82 %.

**2-O-Allyl-1,6-anhydro- $\beta$ -D-galactopyranose (12).** The anhydro compound (11) (4.06 g, 20 mmol) was dissolved in 75 % aqueous acetic acid (80 ml) and stirred for 4 d at 40 °C. The mixture was evaporated, dissolved in water (40 ml) and extracted twice with chloroform (20 ml). The aqueous phase was evaporated at 1 mmHg, 50 °C and the product crystallized from diethyl ether (20 ml)-pentane (20 ml). Filtration at 0 °C gave, after drying *in vacuo*, 3.11 g (92 %) of 12,  $[\alpha]_{\text{D}}^{22} - 34^\circ$  (c 0.3,  $\text{CHCl}_3$ ), mp. 55.0-57.0 °C. Analysis for  $\text{C}_7\text{H}_{14}\text{O}_5$ : C, H.  $^1\text{H NMR}$ :  $\delta$  5.42 (H-1); 3.54

(H-2); 3.94 (H-3); 3.96 (H-4); 4.41 (H-5); 4.16 (H-6); 3.60 (H-6');  $J_{12}$  1.3 Hz;  $J_{15}$  1.3;  $J_{23}$  0.7;  $J_{34}$  0.5;  $J_{45}$  4.5;  $J_{56}$  0;  $J_{56'}$  4.7;  $J_{66'}$  7.0.

**2-O-Allyl-1,6-anhydro-3,4-di-O-benzoyl- $\beta$ -D-galactopyranose (13).** Compound (12) (3.59 g, 17.8 mmol) was stirred in pyridine (25 ml) and cooled to 0 °C. Benzoyl chloride (6.19 ml, 53.4 mmol) was added over a period of 45 min at this temperature. The suspension was stirred overnight at 5 °C and water (3 ml) was added. The mixture was diluted with dichloromethane (75 ml) and extracted successively with water (50 ml), cold hydrochloric acid (4 M, 150 ml and 50 ml), saturated sodium hydrogen carbonate solution (50 ml), and water (50 ml). The organic phase was dried, filtered through carbon and evaporated at 1 mm Hg and 50 °C to give 7.39 g (100 %) of (13).  $[\alpha]_D^{25}$   $-70^\circ$  (c 1.5, CHCl<sub>3</sub>). <sup>1</sup>H NMR:  $\delta$  5.50 (H-1); 3.61 (H-2); 5.60 (H-3); 5.63 (H-4); 4.68 (H-5); 4.55 (H-6); 3.83 (H-6').  $J_{12}$  1.3 Hz;  $J_{15}$  1.5;  $J_{23}$  1.3;  $J_{45}$  4.8;  $J_{56}$  0;  $J_{56'}$  4.8;  $J_{66'}$  12.3.

**1,6-Di-O-acetyl-2-O-allyl-3,4-di-O-benzoyl- $\alpha$ -D-galactopyranose (14).** Compound (13) (30.2 g, 32 mmol) was dissolved in acetic anhydride (80 ml, 800 mmol) and cooled to 0 °C with stirring. Sulfuric acid (20 drops) was added and the mixture was stirred for 20 min at 0 °C, and then poured onto crushed ice (200 ml) and ethanol (100 ml). After stirring for 2 h the crystalline product was isolated by filtration followed by washing three times with water (30 ml). Drying over potassium hydroxide *in vacuo* gave 34.03 g (90 %) of 14.  $[\alpha]_D^{22}$   $+142^\circ$  (c 0.3, CHCl<sub>3</sub>) m.p. 141–146 °C. Analysis for C<sub>27</sub>H<sub>28</sub>O<sub>10</sub>: C, H. <sup>1</sup>H NMR:  $\delta$  6.50 (H-1); 4.13 (H-2); 5.60 (H-3); 5.85 (H-4); 4.46 (H-5); 4.14 (H-6); 4.14 (H-6').  $J_{12}$  3.9 Hz;  $J_{23}$  10.5;  $J_{34}$  3.3;  $J_{45}$  0.9;  $J_{56}$  6.2;  $J_{56'}$  6.2.

**6-O-Acetyl-2-O-allyl-3,4-di-O-benzoyl- $\alpha$ -D-galactopyranosyl bromide (15).** The acetate (14) (18.5 g, 33 mmol) was dissolved in dichloromethane (50 ml) and cooled to 0 °C. Hydrogen bromide in acetic acid (35 %, 50 ml) was added and the mixture was stirred for 50 min and then concentrated at 35 °C. The residue was crystallized from diethyl ether (150 ml) and light petroleum (250 ml) giving 16.5 g (83 %) of 15 as a fine powder m.p. 90–95 °C. <sup>1</sup>H NMR:  $\delta$  6.67 (H-1); 4.03 (H-2); 5.67 (H-3); 5.89 (H-4); 4.69 (H-5); 4.31 (H-6); 4.29 (H-6').  $J_{12}$  4.1 Hz;  $J_{23}$  10.5;  $J_{34}$  3.1;  $J_{45}$  1.3;  $J_{56}$  6.0;  $J_{56'}$  6.0.

**4-O-Allyl-1,6-anhydro-2,3-O-endo-benzylidene- $\beta$ -D-mannopyranose (17).** 1,6-Anhydro-2,3-O-endo-benzylidene- $\beta$ -D-mannopyranose (16) (2.5 g 10 mmol) was dissolved in dry *N,N'*-dimethyl formamide (15 ml) and allyl bromide (1.20 ml, 14 mmol) was added with stirring. Sodium hydride (720 mg, 15 mmol, 50 % oil

suspension) was washed several times with pentane and added in portions at 20 °C to the stirred solution over a period of 40 min. The mixture was stirred for 1 h at 20 °C and excess of reactants were decomposed by addition of methanol (1 ml). The reaction mixture was diluted with dichloromethane (100 ml) and washed three times with water (100 ml). Drying, filtration and evaporation gave 2.91 g (100 %) of 17. Crystallization from pentane gave m.p. 48–50 °C,  $[\alpha]_D^{22}$   $-15^\circ$  (c 0.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR:  $\delta$  5.47 (H-1) 3.73 (H-2); 4.23 (H-3); 4.23 (H-4); 4.64 (H-5); 3.82 (H-6); 3.96 (H-6').  $J_{12}$  1.0 Hz;  $J_{15}$  1.5;  $J_{56}$  1.2;  $J_{56'}$  5.6;  $J_{66'}$  5.8. Analysis for C<sub>16</sub>H<sub>18</sub>O<sub>5</sub>: C, H.

**4-O-Allyl-1,6-anhydro-3-O-benzyl- $\beta$ -D-mannopyranose (18).** Compound (17) (3.00 g, 10 mmol) was dissolved in dry dichloromethane (30 ml) and cooled to 0 °C with stirring under a nitrogen atmosphere. Lithium aluminium hydride (433 mg, 11.4 mmol) was added and a solution of aluminium chloride (1.53 g, 11.4 mmol) in dry diethyl ether (30 ml) was added dropwise over a period of 10 min. The mixture was stirred for 30 min and excess of reagent was destroyed by addition of ethyl acetate (12 ml) at 0 °C. After 40 min at 0 °C water (4 ml) was added and stirring was continued for 20 min. The organic phase was separated and the solid residue was extracted twice with diethyl ether (50 ml). The combined organic extracts were washed twice with water (25 ml) and evaporated. The residue was redissolved in dichloromethane (30 ml), dried, filtered and evaporated leaving 2.86 g of a clear syrup. Purification on a silica gel column (ethyl acetate–pentane: 23:17) gave 2.17 g (72 %) of 18,  $[\alpha]_D^{23}$   $-66^\circ$  (c 0.6, CHCl<sub>3</sub>). <sup>1</sup>H NMR:  $\delta$  5.31 (H-1); 3.67 (H-2); 3.74 (H-3); 3.45 (H-4); 4.50 (H-5); 4.10 (H-6); 3.70 (H-6').  $J_{12}$  1.5 Hz;  $J_{15}$  1.0;  $J_{34}$  1.0;  $J_{45}$  0.5;  $J_{56}$  0.7;  $J_{56'}$  6.0;  $J_{66'}$  6.9. Analysis for C<sub>16</sub>H<sub>20</sub>O<sub>5</sub>: C, H.

**4-O-Allyl-2-O-(6-O-acetyl-2-O-allyl-3,4-di-O-benzoyl- $\alpha$ -D-galactopyranosyl)-1,6-anhydro-3-O-benzyl- $\beta$ -D-mannopyranose (19).** Compound (18) (5.95 g, 20 mmol), red mercury(II) iodide (13.6 g, 30 mmol), molecular sieves (4Å, 15 g) and dichloromethane (40 ml) were stirred for 18 h under a nitrogen atmosphere and 15 (16.5 g, 30 mmol) in dry dichloromethane (20 ml) was added dropwise at 20 °C. The mixture was stirred for 48 h and filtered through celite. The residue was washed with dichloromethane (100 ml) and the filtrate was washed three times with aqueous potassium iodide (75 ml, 10 %) and with water (75 ml). After drying, filtration through carbon and evaporation 18.2 g of syrup was isolated. Purification on a silica gel column (ethyl acetate–pentane: 3:4) gave 8.9 g (60 %) of 19  $[\alpha]_D^{22}$   $+73.3^\circ$  (c 0.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR:  $\delta$  5.29 (H-1.1); 4.11

(H-2.1); 5.77 (H-3.1); 5.85 (H-4.1); 4.74 ((H-5.1); 4.18 (H-6.1); 4.25 (H-6'.1); 5.14 (H-1.2); 3.76 (H-2.2); 3.89 (H-3.2); 3.47 (H-4.2); 4.50 (H-5.2); 4.36 (H-6.2); 3.78 (H-6'.2).  $J_{12.1}$  3.5 Hz;  $J_{23.1}$  12.0;  $J_{34.1}$  2.8;  $J_{45.1}$  0.0;  $J_{56.1}$  7.6;  $J_{56'.1}$  5.0;  $J_{66'.1}$  11.2;  $J_{12.2}$  0.0;  $J_{23.2}$  4.8;  $J_{34.2}$  0.0;  $J_{45.2}$  0.0;  $J_{56.2}$  0.0;  $J_{56'.2}$  5.0;  $J_{66'.2}$  7.0.

**1,6-Di-O-acetyl-4-O-allyl-2-O-(6-O-acetyl-2-O-allyl-3,4-di-O-benzoyl- $\alpha$ -D-galactopyranosyl)-3-O-benzyl- $\alpha$ -D-mannopyranose (20).** Compound (19) (6.2 g, 8.33 mmol) was dissolved in acetic anhydride (75 ml) and trifluoroacetic acid (10 ml) was added. The mixture was stirred for 2 h at 20 °C and evaporated three times with toluene (25 ml) at 40 °C, 10 mm Hg and then at 40 °C, 1 mm Hg. This gave 7.09 g of a syrup which according to a  $^1\text{H}$  NMR spectrum contained mainly the title compound. A small amount (115 mg) was purified on a silica gel plate (ethyl acetate-pentane: 1:1) to give 91 mg of 19,  $[\alpha]_{\text{D}}^{20} +135^\circ$  (c 2.2,  $\text{CHCl}_3$ ). Analysis for  $\text{C}_{45}\text{H}_{50}\text{O}_{16}$ : C, H.  $^1\text{H}$  NMR:  $\delta$  5.47 (H-1.1); 4.05 (H-2.1); 5.64 (H-3.1); 5.84 (H-4.1); 4.54 (H-5.1); 4.22 (H-6.1); 4.14 (H-6'.1); 6.23 (H-1.2); 4.33 (H-2.2); 3.88 (H-3.2); 3.99 (H-4.2); 3.84 (H-5.2); 4.0-4.1 (H-6.2-H-6'.2).  $J_{12.1}$  4.8 Hz;  $J_{23.1}$  10.8;  $J_{34.1}$  3.2;  $J_{45.1}$  1.0;  $J_{56.1}$  5.8;  $J_{56'.1}$  6.8;  $J_{66'.1}$  11.0;  $J_{12.2}$  2.4;  $J_{23.2}$  2.8;  $J_{34.2}$  9.3;  $J_{45.2}$  9.6;  $J_{56.2}$  3;  $J_{56'.2}$  3.

**6-O-Acetyl-4-O-allyl-2-O-(6-O-acetyl-2-O-allyl-3,4-di-O-benzoyl- $\alpha$ -D-galactopyranosyl)-3-O-benzyl- $\alpha$ -D-mannopyranosyl bromide (21).** Compound (20) (6.98 g, 8.0 mmol) was stirred with titanium tetrabromide (5 g, 14 mmol), dry dichloromethane (50 ml) and dry ethyl acetate (7.5 ml) for 5 h at 20 °C. Acetonitrile (65 ml) and anhydrous sodium acetate (10.4 g) were added and the mixture was stirred until the color had disappeared (5-10 min). Toluene (75 ml) was added and the mixture was stirred for 10 min at 10 °C and filtered. The filtrate was evaporated and the residue extracted with toluene (30 ml). Filtration through celite and evaporation at 1 mm Hg gave 8.0 g of a syrup containing 21 as the main component.  $^1\text{H}$  NMR:  $\delta$  6.63 (H-1.1); 5.80 (H-4.2); 5.55 (H-3.2); 5.00-5.36 (H-1.1 and terminal allyl protons), 4.70 (benzyl- $\text{CH}_2$ -protons); 3.75-4.54 (H-2.1-H-6'.1, H-2.2, H-5.2-H-6'.2 and aliphatic allyl protons); 2.06 (acetyl protons). The unstable bromide was used directly in the next step.

**8-Ethoxycarbonyloct-1-yl 2,3,4-tri-O-benzoyl- $\alpha$ -L-rhamnopyranoside (23).** 8-Ethoxycarbonyloctan-1-ol (40.5 g, 200 mmol) was dissolved in dry dichloromethane (250 ml) and stirred with drierite (15 g), molecular sieves (15 g, 4 Å) and mercury(II) cyanide (50.4 g, 200 mmol) for 8 h under a nitrogen atmosphere. A suspension of 2,3,4-tri-O-benzoyl- $\alpha$ -L-rhamnopyranosyl bro-

mid (22)<sup>9</sup> (108 g, 200 mmol) in dichloromethane (200 ml), dried over molecular sieves (4 Å), was added in portions with stirring over a period of 1 h at 20 °C. The mixture was stirred for 3 d. The solid material was removed by filtration through celite and the filtrate was washed twice with aqueous potassium iodide (200 ml), twice with saturated sodium hydrogen carbonate solution (200 ml), and with water (200 ml). Drying, filtration and evaporation at 1 mmHg, 50 °C left 131.7 g (99.5 %) of a syrup.  $^1\text{H}$  NMR:  $\delta$  4.96 (H-1); 5.54 (H-2); 5.83 (H-3); 5.54 (H-4); 4.17 (H-5); 1.38 (H-6).  $J_{12}$  1.3 Hz;  $J_{23}$  3.3;  $J_{34}$  9.8;  $J_{45}$  9.8;  $J_{56}$  6.0.

**8-Methoxycarbonyloct-1-yl  $\alpha$ -L-rhamnopyranoside (24).** The glycoside (23) (131.5 g, 199 mmol) was dissolved in methanolic sodium methoxide (500 ml, 0.2 M) and stirred at 20 °C for 2 h. Sodium ions were removed by stirring with ion exchange resin (Amberlite IRC-50, 10 g) for 1.5 h. The filtrate was concentrated *in vacuo* and dissolved in water (150 ml). The aqueous phase was extracted twice with pentane-toluene (5:1, 100 ml) and then twice with toluene (100 and 50 ml). Repeated evaporation at 1 mmHg of the toluene phase left 73.3 g of chromatographically pure 24 containing a small amount of toluene.  $^1\text{H}$  NMR data were identical to those reported<sup>10</sup> and showed no other impurities.

**8-Methoxycarbonyloct-1-yl 2,3-O-cyclohexylidene- $\alpha$ -L-rhamnopyranoside (25).** The glycoside (24) (72.3 g) was dissolved in dry acetonitrile (350 ml) and cooled to 0 °C with stirring. *p*-Toluenesulfonic acid (700 mg) and 1-ethoxycyclohexane (52.5 ml, 2 eqv) were added over 2 min and the stirring was continued for 10 min at 0-5 °C with cooling. The mixture was neutralized with pyridine (0.80 ml) and extracted twice with pentane (400 ml). The acetonitrile phase was filtered through charcoal and evaporated *in vacuo* giving 78.7 g of 25 (total yield of 92 % from 22). An analytical sample gave  $[\alpha]_{\text{D}}^{23} -19^\circ$  (c 1.2,  $\text{CHCl}_3$ ). Analysis for  $\text{C}_{22}\text{H}_{38}\text{O}_7$ : C, H.  $^1\text{H}$  NMR:  $\delta$  4.87 (H-1); 4.05 (H-2); 4.01 (H-3); 3.33 (H-4); 3.61 (H-5); 1.27 (H-6).  $J_{12}$  0 Hz;  $J_{45}$  9.0;  $J_{56}$  6.4.

**8-Methoxycarbonyloct-1-yl 4-O-(6-O-acetyl-4-O-allyl-2-O-(6-O-acetyl-2-O-allyl-3,4-di-O-benzoyl- $\alpha$ -D-galactopyranosyl)-3-O-benzyl- $\beta$ -D-mannopyranosyl)-2,3-O-cyclohexylidene- $\alpha$ -L-rhamnopyranoside (26).** The glycoside (25) (3.1 g, 7.3 mmol) was dissolved in chloroform (75 ml) and stirred with mercury(II) iodide (4 g, 8.8 mmol) and molecular sieves (4 Å, 20 g) under an atmosphere of nitrogen for 6 h. The bromide (21) (prepared from 20 (6.97 g, 8 mmol)) dissolved in dry chloroform was added dropwise over a period of 2 h at 20 °C. The mixture was stirred for 4 d at

20 °C and then filtered through celite. The residue was washed with chloroform (75 ml) and the filtrate was washed twice with aqueous potassium iodide solution (40 ml, 10 %), with saturated sodium hydrogencarbonate solution (50 ml) and with water (50 ml). The chloroform phase was dried, filtered and evaporated. The residue was acetylated in toluene (25 ml) with acetic anhydride (2 ml) and pyridine (4 ml) for 20 h at 20 °C. Filtration and evaporation left 9.58 g of syrup which was separated on a silica gel column (ethyl acetate–pentane 3:7) giving 2.29 g of 26 (26 %).  $[\alpha]_D^{25} + 70^\circ$  (c 1.0, CHCl<sub>3</sub>). Analysis for C<sub>65</sub>H<sub>84</sub>O<sub>21</sub>: C, H. <sup>1</sup>H NMR: δ 5.64 (H-1.1); 3.99 (H-2.1); 5.66 (H-3.1); 5.81 (H-4.1); 4.93 (H-5.1) 4.1–4.2 (H-6.1–H6'.1); 4.98 (H-1.2); 3.42 (H-2.2); 3.58 (H-3.2); 3.83 (H-4.2); 3.40 (H-5.2); 4.49 (H-6.2); 5.02 (H-1.3); 4.08 (H-2.3); 4.10 (H-3.3); 3.66 (H-4.3); 3.70 (H-5.3); 1.38 (H-6.3).  $J_{12.1}$  3.5 Hz;  $J_{23.1}$  9.9;  $J_{34.1}$  3.5;  $J_{45.1}$  1.0;  $J_{56.1}$  5.9;  $J_{56'.1}$  6.8;  $J_{12.2}$  0.0;  $J_{23.2}$  1.9;  $J_{34.2}$  9.6;  $J_{45.2}$  9.6;  $J_{56.2}$  2.7;  $J_{56'.2}$  5.9;  $J_{66'.2}$  11.7;  $J_{12.3}$  0.0;  $J_{34.3}$  9.4;  $J_{45.3}$  9.6;  $J_{56.3}$  6.0.

**8-Methoxycarbonyloct-1-yl 2,3-di-O-acetyl-4-O-(3-O-benzoyl-4,6-di-O-acetyl-2-O-(2,6-di-O-acetyl-3,4-di-O-benzoyl-α-D-galactopyranosyl)-β-D-mannopyranosyl)-α-L-rhamnopyranoside (27).** The compound (26) (260 mg, 0.214 mmol) was dissolved in toluene (7 ml) and ethanol (3 ml), water (1 ml) and 1,8-diaza-[2.2.2]-biscyclooctane (25 mg) was added. The mixture was heated to reflux temperature and tris (triphenyl phosphine) rhodium chloride (100 mg, 0.054 mmol) was added with stirring. The mixture was stirred for 12 h at reflux temperature, filtered through celite and evaporated. The residue was dissolved in aqueous acetone (90 %, 6 ml) and red mercury(II) oxide (120 mg, 0.55 mmol) was added. A solution of mercury(II) chloride (120 mg, 0.44 mmol) in aqueous acetone (90 %, 2.5 ml) was added over a period of 3 min and the mixture was stirred for 7 min. The mixture was evaporated and the residue was partitioned between diethyl ether (30 ml) and aqueous potassium iodide (10 %, 15 ml). The organic phase was washed twice with aqueous potassium iodide (10 ml), dried, filtered and evaporated to give 233 mg of a syrup containing one major product according to TLC (ethyl acetate–pentane 1:2). The product was dissolved in aqueous acetic acid (80 %, 13 ml) and heated to 50 °C for 2 d. Filtration through celite and evaporation with toluene gave a clear syrup (260 mg) which was dissolved in pyridine (5 ml) and acetylated by stirring with acetic anhydride (2 ml) for 20 h at 20 °C. The mixture was evaporated twice with toluene and the residue was purified on a silica gel plate (ethyl acetate–pentane: 1:1) to give 140 mg (56 %) of

27.  $[\alpha]_D^{23} + 61^\circ$  (c 0.5 CHCl<sub>3</sub>). Analysis for C<sub>61</sub>H<sub>76</sub>O<sub>25</sub>: C, H. <sup>1</sup>H NMR: δ 5.60 (H-1.1); 5.42 (H-2.1); 5.78 (H-3.1); 5.88 (H-4.1); 4.86 (H-5.1); 4.20 (H-6.1); 4.13 (H-6'.1); 4.56 (H-1.2); 3.98 (H-2.2); 3.42 (H-3.2); 5.33 (H-4.2); 3.54 (H-5.2); 4.29 (H-6.2); 4.14 (H-6'.2); 4.68 (H-1.3); 5.22 (H-2.3); 5.23 (H-3.3); 3.71 (H-4.3); 3.82 (H-5.3); 1.45 (H-6.3).  $J_{12.1}$  3.7 Hz;  $J_{23.1}$  10.8;  $J_{34.1}$  3.5;  $J_{45.1}$  1.0;  $J_{56.1}$  6.8;  $J_{56'.1}$  5.9;  $J_{66'.1}$  11.8;  $J_{12.2}$  0;  $J_{23.2}$  2.2;  $J_{34.2}$  9.4;  $J_{45.2}$  9.6;  $J_{56.2}$  3.0;  $J_{56'.2}$  5.9;  $J_{66'.2}$  12.2;  $J_{12.3}$  0;  $J_{34.3}$  9.6;  $J_{45.3}$  9.6;  $J_{56.3}$  6.0.

**8-Methoxycarbonyloct-1-yl 4-O-(2-O-α-D-galactopyranosyl)-β-D-mannopyranosyl)-α-L-rhamnopyranoside (29).** Compound (27) (125 mg, 0.10 mmol) was hydrogenated in methanol (50 ml) and acetic acid (10 ml) with palladium on charcoal (5 %, 200 mg) under hydrogen pressure (1400 psi) for 20 h at 20 °C. The mixture was filtered through celite and evaporated twice with chloroform giving 110 mg of 28. This product (95 mg) was dissolved in methanolic sodium methoxide (0.1 M, 15 ml) and the mixture was stirred for 12 h. After neutralization with ion exchange resin (Amberlite IRC-50) and filtration the mixture was evaporated and the residue was purified on silicagel (ethyl acetate–methanol–water: 6:3:1) to give 38 mg (71 %) of 29.  $[\alpha]_D^{23} + 0.2^\circ$  (c 3.0, H<sub>2</sub>O). <sup>1</sup>H NMR: δ 5.18 (H-1.1); 3.74 (H-2.1); 3.82 (H-3.1); 3.88 (H-4.1); 4.16 (H-5.1); 3.55–3.61 (H-6.1–H-6'.1); 4.81 (H-1.2); 4.12 (H-2.2); 3.61 (H-3.2); 3.53 (H-4.2); 3.26 (H-5.2); 3.82 (H-6.2); 3.65 (H-6'.2); 4.65 (H-1.3); 3.77 (H-2.3); 3.81 (H-3.3); 3.53 (H-4.3); 3.59 (H-5.3); 1.55 (H-6.3).  $J_{12.1}$  3.9 Hz;  $J_{23.1}$  9.8;  $J_{34.1}$  3.0;  $J_{45.1}$  1.2;  $J_{56.1}$  6.3;  $J_{56'.1}$  6.3;  $J_{12.2}$  0;  $J_{23.2}$  3.0;  $J_{34.2}$  9.5;  $J_{45.2}$  9.8;  $J_{56.2}$  2.5;  $J_{56'.2}$  6.3;  $J_{66'.2}$  12.2;  $J_{12.3}$  0;  $J_{34.3}$  9.8;  $J_{45.3}$  9.8;  $J_{56.3}$  6.0. <sup>13</sup>C NMR: 101.1 ppm (C-1.1); 69.1 (C-2.1); 70.4 (C-3.1); 70.2 (C-4.1); 71.5 (C-5.1); 62.2 (C-6.1); 101.9 (C-1.2); 78.1 (C-2.2); 77.7 (C-3.2); 71.9 (C-4.2); 75.4 (C-5.2); 61.8 (C-6.2); 100.9 (C-1.3); 71.7 (C-2.3); 70.6 (C-3.3); 81.2 (C-4.3); 68.5 (C-5.3); 18.2 (C-6.3).  $J_{\text{C}1\text{H}1.1}$  171 Hz;  $J_{\text{C}1\text{H}1.2}$  158;  $J_{\text{C}1\text{H}1.3}$  169.

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