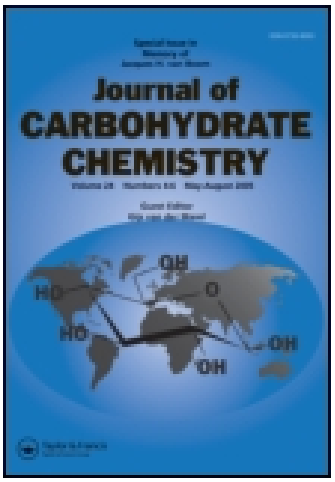

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Sven Kramer , Birte Nolting , Andrej-Jakob Ott & Christian Vogel

[a] Department of Chemistry, Division of Organic Chemistry , University of Rostock , Buchbinderstraße 9, 18051 Rostock, Germany E-mail:

[b] Department of Chemistry, Division of Organic Chemistry , University of Rostock , Buchbinderstraße 9, 18051 Rostock, Germany E-mail:

[c] Department of Chemistry, Division of Organic Chemistry , University of Rostock , Buchbinderstraße 9, 18051 Rostock, Germany E-mail:

[d] Department of Chemistry, Division of Organic Chemistry , University of Rostock , Buchbinderstraße 9, 18051 Rostock, Germany E-mail:

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SYNTHESIS OF HOMOGALACTURONAN FRAGMENTS[1]

Sven Kramer, Birte Nolting, Andrej-Jakob Ott, and Christian Vogel*

University of Rostock, Department of Chemistry, Division of Organic Chemistry,
Buchbinderstraße 9, 18051 Rostock, Germany,
christian.vogel@chemie.uni-rostock.de

Dedicated with Great Appreciation to Professor Klaus Peseke on the Occasion of his 60th Birthday

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ABSTRACT

Glycosylation of the D-galacturonic acid ester derivatives **15** and **17**, which are prepared directly from D-galacturonic acid, with the thioglycosides **28** and **32**, derived from the same sugar, provides α(1→4)-linked dimers. The formation of the glycosidic linkage between the galacturonic acid moieties is best achieved by iodonium di-*sym*-collidine perchlorate promotion. Thus, the 4'-*O*-*p*-methoxybenzyl dimer **38** can be obtained in 64% yield. Partial deprotection of the 4'-*O*-position provided the glycosyl acceptor **36**, which was coupled with the donor **32** to yield the α(1''→4')-linked trimer **39** (48%). Approximately 8% of the β(1''→4')-coupled isomer was observed in the ^{13}C NMR spectrum of the reaction mixture.

INTRODUCTION

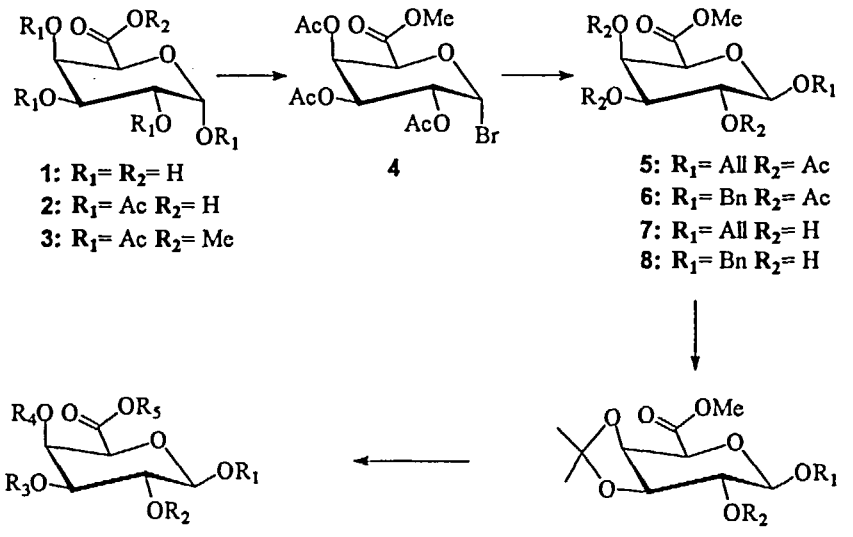
In continuation of our efforts towards the synthesis of pectin fragments, we investigated α(1→4)-coupling reactions using D-galacturonic acid derivatives by application of

thioglycosides as glycosyl donors. When we had nearly finished our investigations,[2] some French colleagues published an analogous synthesis strategy to achieve the selective preparation of α(1→4)-linked oligomers of protected methyl D-galacturonate. However, when we compared our results with the results as reported by D. Anker et al.[3] we found significant differences in the experimental details. That is why we decided to publish our own results here.

RESULTS AND DISCUSSION

For the preparation of galacturonic acid derivatives suitable as glycosyl acceptors, it is possible to proceed directly from commercially available D-galacturonic acid. This seems to be advantageous in comparison to an approach involving D-galactose-derived intermediates, because the crucial oxidation step can be avoided. As reported previously,[4] crystalline D-galacturonic acid (**1**) was transformed into its tetra-*O*-acetyl derivative **2**. In order to insure the highest reactivity from the acceptors, the partially benzylated derivatives of galacturonic acid were produced by the following optimized approach (Scheme 1). The Helferich glycosylation with galactopyranosyluronate bromide **4**[5] led to the allyl (**5**) and benzyl (**6**) glycosides in 98% and 78% yield, respectively. Cleavage of the acetyl groups of **5** and **6** was achieved with methanolic 1% hydrochloric acid in 90% yield. The products **7** and **8** were treated with acetone/2,2-dimethoxypropane/*p*-toluenesulfonic acid to give **9** and **10** in nearly 95% yield.[6] The benzylation of **9** and **10** with benzyl 2,2,2-trichloroacetimidate and a catalytic amount of trifluoromethanesulfonic acid[7] provided the fully protected derivatives **11** and **12** in 76% and 85% yield, respectively. The isopropylidene groups of **11** and **12** were removed within one hour with 90% trifluoroacetic acid in acetic acid at room temperature.[8] Crystallization and chromatographic purification of the mother liquor resulted in **13** and **14** in 78% and 80% yield, respectively. Generally it is to be noted, that in all reactions with esters of galacturonic acid in basic medium there is a high tendency for β-elimination.[9] Therefore, most protection and deprotection operations must be performed under acidic conditions. One of the exceptions was the regioselective benzylation of **13** and **14** via 3,4-*O*-butylstannyl intermediates.[8] The desired glycosyl acceptors **15** and **17** were obtained in 58% and 68% yield, respectively.

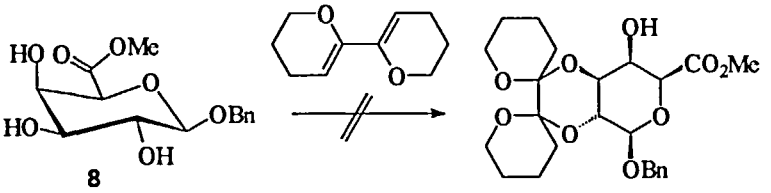
However, this reaction was connected with a partial formation of benzyl esters **16** (25%) or **18** (23%) which can also be used as suitable acceptors in glycosylation reactions.[8]



Scheme 1

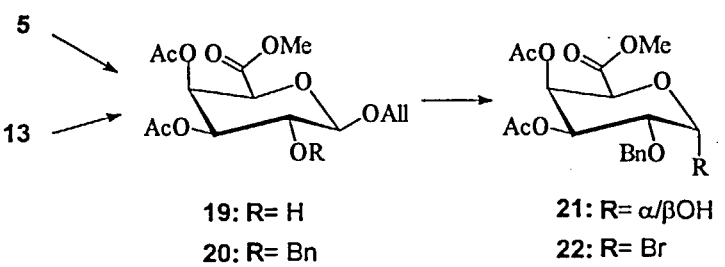
In this context we also tested the procedures of S. V. Ley and coworkers[10] and T. Ziegler[11] to prepare a 4-*O*-unprotected *galacto*-configured derivative (Scheme 2); unfortunately without success. No traces of the desired tetrahydrobipyran derivative could be detected.

In order to compare the potency of glycosyl bromides with thioglycosides in the glycosylation reaction, we synthesized the methyl galactopyranosyluronate bromide **22** (Scheme 3). After acetylation (acetic anhydride/pyridine, 88%) of **13** the glycosidic allyl group of **20** was removed with the aid of sodium acetate/palladium(II)chloride[12] to yield **21** (78%).[13]



Scheme 2

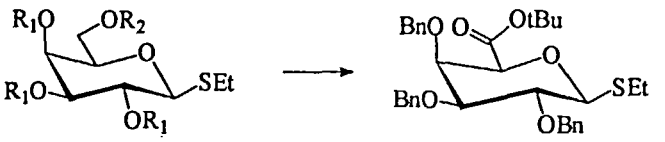
An alternative route to **21** started from compound **5** using an enzyme-catalyzed regioselective deacetylation step.[14] We could optimize the workup procedure at the end of the enzymatic process by using pure ethanol as organic solvent during the reaction. So, the 2-*O*-unprotected derivative **19** was obtained on preparative scale in 95% yield. After acid-catalyzed benzylation (**20**, 62%) and deallylation **21** was obtained with an overall yield of 46% based on **5**. Finally, the desired methylgalactopyranosyluronate bromide **22** was synthesized by treatment of **21** with *N*-bromomethylene-*N*,*N*-dimethylammonium bromide[15] in 90% yield.



Scheme 3

Presently, we not found a suitable approach to prepare a thioglycoside of a galacturonic acid ester starting directly from galacturonic acid.[2] Consequently, the synthetic route to **28** (Scheme 4) first requires tritylation and subsequent benzylation of the thiogalactoside **23**. The two-step procedure yielded 75% of **25**. During detritylation,[16] besides the main product **27**, the 6-*O*-formyl derivative **26** was sometimes observed. In this case, the whole reaction mixture was treated with sodium borohydride in order to remove the formyl group. The formation of the side-product **26** has no influence on the total yield of **27** (75%). The modified Corey oxidation[17] of compound **27** by treatment with pyridinium

dichromate/acetic anhydride in the presence of *tert*-butyl alcohol[18] resulted in formation of the *tert*-butyl(thiogalactosid)uronate **28** in 56% yield.



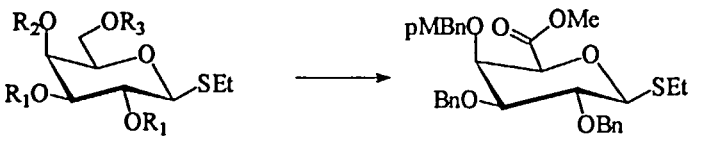
23: $R_1 = R_2 = H$
24: $R_1 = H$ $R_2 = Tr$
25: $R_1 = Bn$ $R_2 = Tr$
26: $R_1 = Bn$ $R_2 = CHO$
27: $R_1 = Bn$ $R_2 = H$

28

Scheme 4

On the other hand, for a stepwise buildup of galacturonic acid oligomers we need the option of selective deprotection of the 4-*O*-position of a glycosyl donor. The *p*-methoxybenzyl group accomplishes the dual role either as temporary protecting group[19] or as reactivity increasing group.[20] Treatment of **23** with *p*-methoxybenzaldehyde dimethylacetal and *p*-toluenesulfonic acid[21] at 40 °C under vacuum (40 mbar) provided the *p*-methoxybenzylidene acetal **29** in excellent yield (88%, Scheme 5). Benzylation of **29** in the presence of sodium hydride yielded the dibenzyl derivative **30** (82%). Reductive opening of the 4,6-*p*-methoxybenzylidene ring in **30** was performed by treatment with sodium cyanoborohydride and carefully purified trimethylchlorosilane[18,22] to give exclusively the 4-*p*-methoxybenzyl ether **31** (92%).

The critical point in this approach is the oxidation of the C-6 primary hydroxyl group in the presence of a thioglycoside functionality. In our experience, the stepwise procedure of Garegg et al.[23] achieves the best results. Thus, the Pfitzner - Moffat oxidation of **31** led to the corresponding aldehyde which was, after separation of precipitated *N,N'*-dicyclohexylurea, further oxidized in the presence of methanol and pyridinium dichromate. After this two-step procedure, the isolated yield of the desired methyl(thiogalactosid)uronate **32** amounted to 39%. Although we are not satisfied with this result, compared with the the three-step variant of Anker et al.[3] via *tert*-butyl ester, a problematic deesterification under acidic conditions and methylation (total yield 48%), our approach seems to be able to compete.

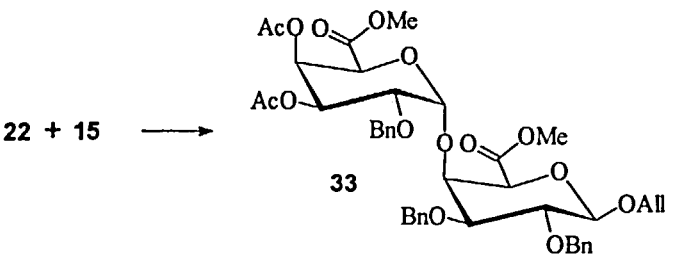


23: R_1= R_2= R_3= H
29: R_1= H R_2, R_3= >CHC_6H_4-*p*-OMe
30: R_1= Bn R_2, R_3= >CHC_6H_4-*p*-OMe
31: R_1= Bn R_2= *p*MBn R_3 = H

32

Scheme 5

Silver triflate/silver carbonate promoted glycosylation[24] of glycosyl acceptor **15** with methyl(galactopyranosyluronate)bromide **22** provided the disaccharide **33** in 35% yield based on **15** (Scheme 6).



33

Scheme 6

The NMR data secure the α-glycosidic linkage between the two galacturonic acid residues. Thus, the vicinal coupling constant value $J_{1',2'}$ = 3.7 Hz in the ^{1}H NMR spectrum and the resonance of C-1' at δ 99.36 in ^{13}C NMR spectrum of **33** indicate clearly the stereochemistry at the anomeric center. Additionally, NOE experiments revealed correlations between H-2↔H-5', H-2↔H-3' and H-1'↔H-4 leading to the conjecture that in a favored conformation the pyranose rings of both galacturonic acid moieties are stacked one on top of the other, similarly to a sandwich structure (Figure 1).

The first thioglycoside we tested as a glycosyl donor was the *tert*-butyl ester derivative **28** (Scheme 7). The reaction of a slight excess of **28** with acceptor **17** using *N*-iodosuccinimide/silver triflate promotion[25] at -20 °C with rigorous exclusion of moisture, resulted in disaccharide **34** in 42% yield based on **17**. In contrast to the results of Anker et

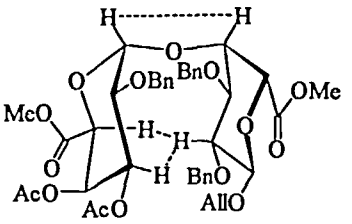
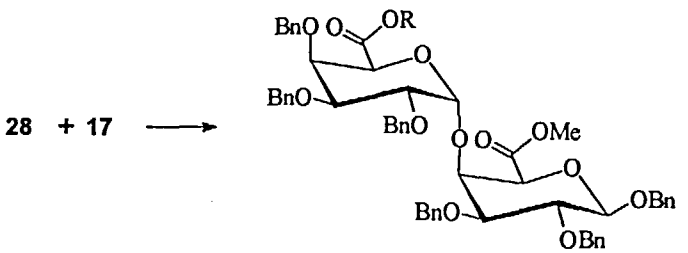


Fig. 1 Correlations between H-2 ↔H-5', H-2↔H-3' and H-1'↔H-4 in NOE experiments.

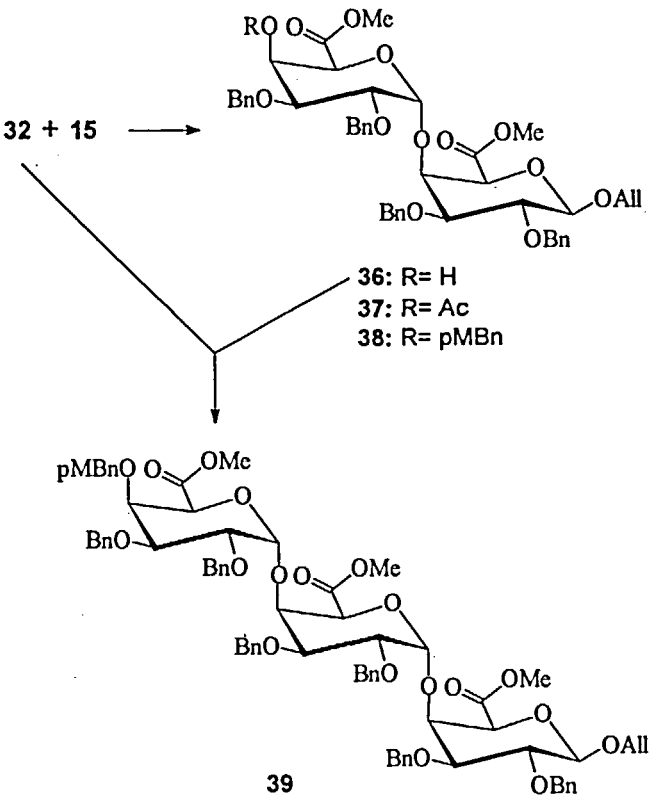
al.[3] who applied comparable conditions, the *tert*-butyl ester was not stable under the glycosylation reaction conditions. A mild esterification with diazomethane resulted quantitatively in the fully protected disaccharide **35**. The analytical data for **35** fully agree with the proposed structure. Thus, in the ^{1}H NMR spectrum of **35** a one-proton doublet at δ 5.28 with a small coupling constant $J_{1',2'}$ = 3.2 Hz and in the ^{13}C NMR spectrum the signal for C-1' at δ 99.47 established the newly formed glycosidic linkage to be α.

Next, we used the *p*-methoxybenzyl derivative **32** as glycosyl donor and compound **15** as acceptor (Scheme 8). Not quite surprisingly, under the glycosylation conditions described above, the *p*-methoxybenzyl protective group proved not to be stable[26] and the disaccharide **36** with a free hydroxyl group in the C-4'-position was isolated in only 25% yield. Compound **36** showed all the expected spectral properties. Characteristic signals in the ^{1}H NMR spectrum appeared at δ 5.21 (d, 1 H, $J_{1',2'}$ = 3.3 Hz, H-1') and at δ 4.38 (m, 1 H, H-4') and in the ^{13}C NMR spectrum at δ 99.55 for C-1'. Beside the disappearance of the signal of the *p*-methoxy group, acetylation of the 4'-OH group of **36**



34: R= H
35: R= Me

Scheme 7



Scheme 8

resulted in the expected downfield shift of the H-4' signal [δ 5.77 (dd, 1H, $J_{4',5'}$ = 1.6 Hz) in compound **37**].

In order to manage the lability of the *p*-methoxybenzyl function, we checked different promotors. The best result was obtained with an iodonium di-*sym*-collidine perchlorate,[27] freshly prepared after a specification of Lemieux et al.[28] Now, the glycosylation of **15** with a slight excess of **32** provided the disaccharide **38** in 64% isolated yield based on **15** (Scheme 8). All analytical data are in accordance with proposed structure **38**. Traces of a β-linked disaccharide could not be detected.

For a stepwise buildup of homogalacturonan fragments, the *p*-methoxybenzyl group in **38** was removed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[29] yielding the compound **36** in 88%, whereas cerium ammonium nitrate[30] in this case gave only poor results. The physical data of **36**, prepared via **38**, were identical with those obtained by glycosylation of **15** with **32** under *N*-iodosuccinimide/silver triflate promotion.

Finally, the coupling of **32** with **36** was performed in the presence of iodonium di-*sym*-collidine perchlorate in such a way that after three and six hours additional amounts of glycosyl donor and promotor were added in order to ultimately reach a ratio between **32** and **36** of 2:1 (Scheme 8). After standard workup and purification by HPLC, the trisaccharide **39** was isolated in 48 % yield related to **36**.

The ^{1}H and ^{13}C NMR spectra of **39** confirm the assigned structure. Thus, the stereochemistry of the glycosidic linkages between the galacturonic acid residues was assigned based on the small coupling constants $J_{1',2'} = 3.0$ Hz and $J_{1'',2''} = 3.3$ Hz in the ^{1}H NMR spectrum of H-1' and H-1'',respectively. In the ^{13}C NMR spectrum, the signals for C-1' and C-1'' of the α-linked product appeare in the anomeric region at δ 98.97 and 99.44, respectively. In the crude reaction mixture 8% of the β-linked isomer was detected. Signals of anomeric carbon atoms of two β-glycosidic bonds and one α-glycosidic bond were observed in ^{13}C NMR spectra at δ 102.5, 102.88 (C-1, C-1'') and 99,86 (C-1'), respectively.

In conclusion, a synthetic route to the α(1→4)-linked D-galacturonic acid dimer **38** (64%) and the trimer **39** (48%) is described, providing the option for a stepwise buildup of homogalacturonans. It seems noteworthy that the monosaccharide glycosyl acceptors **15-18** were obtained from free D-galacturonic acid in a few efficient steps (average yield in each step was 89%, most intermediates were crystalline). Unfortunately, a supply of the thioglycoside from galacturonic acid, which served as glycosyl donor, still requires the crucial C-6 hydroxyl group oxidation step of suitable galactose precursors.

EXPERIMENTAL

General methods. Melting points were determined with a Boetius micro apparatus BHMK 05 (Rapido, Dresden) and are uncorrected. Optical rotations were measured for solutions in a 1-dm cell with an automatic polarimeter "Polar L-μP" (IBZ). NMR spectra were recorded with Bruker AC-250 or ARX-300 spectrometers, at 250 MHz or 300 MHz for ^{1}H, and 62.9 MHz or 75.5 MHz for ^{13}C, respectively. Chemical shifts are given relative to the signal of internal tetramethylsilane (δ = 0). First order chemical shifts and coupling constants were obtained from one-dimensional spectra, and assignment of

proton resonances was based on COSY experiments. Thin-layer chromatography (TLC) on precoated plates of silica gel (Merck, Silica Gel 60, F_{254}, 0.25 mm) was performed with the following solvent systems (v/v): (A) 3:1, (B) 2:1, (C) 1:1, (D) 1:2, (E) 1:3 heptane-ethyl acetate, (F) ethyl acetate, (G) 2:1 toluene-ethyl acetate, (H) 6:1, (I) 10:1 chloroform-methanol, and (J) 4:2:2:1 toluene-ethyl acetate-ethanol-acetic acid. The spots were made visible by spraying with methanolic 10% H_2SO_4 solution and charring them for 3-5 min with a heat gun. Detection of benzyl derivatives was effected by UV fluorescence. Preparative flash chromatography and HPLC was performed by elution from columns of slurry-packed Silica Gel 60 (Merck, 40-63 μm) and Nucleosil 100-7 (Knauer, 7.0 μm), respectively, with the above solvent systems. All solvents and reagents were purified and dried according to standard procedures.[31] After classical work up of the reaction mixtures, the organic layers as a rule, were dried over $MgSO_4$, and then concentrated under reduced pressure (rotary evaporator).

Methyl 1,2,3,4-tetra-*O*-acetyl-α-D-galactopyranosiduronate (3). The large scale variant: To a suspension of 1,2,3,4-tetra-*O*-acetyl-α-D-galactopyranuronic acid[4] (20.0 g, 55.2 mmol) in water (40 mL) was added $NaHCO_3$ (5.1 g, 60.0 mmol) with stirring. After the end of gas evolvement, to the clear solution tetra-*n*-butylammonium bromide (19.3 g, 60.0 mmol), methyl iodide (4.5 mL, 71.0 mmol), and dichloromethane (100 mL) were added, and the suspension was stirred vigorously overnight at ambient temperature (TLC solvent G). Then, the phases were separated, and the aqueous phase was extracted with chloroform (3 x 30 mL). The combined organic phases were washed with water (20 mL), dried, and concentrated. Under slight warming the residue was dissolved in ethyl acetate (150 mL), and then cooled to -5 °C, whereupon the ammonium salts precipitated. After filtration, the solids were washed with -5 °C cold ethyl acetate (2 x 5 mL), and filtrate and washings were concentrated to dryness. Crystallization from diethyl ether gave the desired product **3** (16.9 g, 82%).

The small scale variant: 1,2,3,4-Tetra-*O*-acetyl-α-D-galactopyranuronic acid (7.25 g, 20.0 mmol) was dissolved in a minimum of chloroform and treated with an ethereal diazomethane solution. When the reaction was complete, indicated by a persisting yellow color of the solution, the excess diazomethane was destroyed with acetic acid. The solution was then diluted with heptane (200 mL), washed with sat aq $NaHCO_3$ (2 x 60 mL)

and ice-water (2 x 60 mL), dried, and concentrated. The product **3** (7.15 g, 95%) is sufficiently pure for the next step. For analytical data see lit.[32] and references cited.

Methyl 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyluronate bromide (4). To a stirred solution of **3** (18.37 g, 48.8 mmol), acetic anhydride (6 mL), acetic acid (23.5 mL), acetyl bromide (32.8 mL, 439.2 mmol) in dry chloroform (49 mL) was added dropwise a solution of water (7.74 mL, 430 mmol) in acetic acid (26.5 mL) at 0 °C. After an additional 15 min the chilling was terminated and the mixture stirred for 3 h at ambient temperature (TLC solvent B). Then, the solution was poured into ice-water (600 mL), the aqueous layer was extracted with chloroform (3 x 150 mL), the combined organic phases were washed successively with ice-water (300 mL), cold sat aq $NaHCO_3$ (2 x 300 mL), ice-water (2 x 300 mL), dried, and concentrated. The product **4** (18.5 g, 96%) was used in the next step without further purification. For analytical data see lit.[5] and references cited.

Methyl (allyl 2,3,4-tri-*O*-acetyl-β-D-galactopyranosid)uronate (5). A suspension of galactopyranosyluronate bromide **4** (18.5 g, 46.6 mmol), mercuric cyanide (5.88 g, 23.3 mmol), mercuric bromide (865 mg, 2.4 mmol), and molecular sieves (3Å, 5.0 g) in dry allyl alcohol (100 mL) was stirred overnight at ambient temperature (TLC solvent C). The mixture was concentrated, diluted with chloroform (200 mL), and filtered. The filtrate was washed with aq 10% potassium bromide (3 x 50 mL) and water (2 x 50 mL), dried, and concentrated. Crystallization from ethyl acetate-heptane gives **5** (14.9 g, 98%): mp 98-99 °C. The analytical data of **5** were fully consistent with those of the product obtained by an alternative synthetic route described in lit.[6]

Methyl (benzyl 2,3,4-tri-*O*-acetyl-β-D-galactopyranosid)uronate (6). A suspension of **4** (7.95 g, 20 mmol), mercuric cyanide (2.52 g, 10.0 mmol), mercuric bromide (360 mg, 1.0 mmol), benzyl alcohol (6.18 mL, 60.0 mmol), and molecular sieves (3Å, 3.0 g) in dry acetonitrile (12 mL) was stirred overnight at ambient temperature (TLC solvent C). The reaction mixture was filtered and concentrated. The residue was diluted with heptane-chloroform (2:1, 200 mL), washed with aq 10% potassium bromide (3 x 50 mL) and water (2 x 50 mL), dried, and concentrated. Crystallization from ethyl acetate-heptane or ethyl ether gave **6** (6.67 g, 78%): mp 108-110 °C. For further analytical data see lit.[6] and references cited.

Methyl (allyl β-D-galactopyranosid)uronate (7).[6] To methanolic 1% hydrochloric acid [prepared by adding of acetyl chloride (7.3 mL) to ice-cold dry methanol (360

mL)] was added compound **5** (3.74 g, 10 mmol) with stirring and the mixture kept for 24 h at ambient temperature (TLC solvent H). The solution was made neutral by addition of $PbCO_3 \cdot Pb(OH)_2$ (30 g). After stirring for 2 h, the lead salts were centrifuged off, washed with methanol, and the filtrate and washings were combined and concentrated. The residue was applied to a column of silica gel (eluent solvent I) to give **7** (2.22 g, 90%) as colorless crystals: mp 151-153 °C (from methanol-ethyl acetate); $[\alpha]_D^{22}$ -62.9° (*c* 1.0, acetone); ^{1}H NMR (DMSO-d_6) δ 3.33 (t, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 3.41 (dd, 1H, $J_{3,4}$ = 3.1 Hz, H-3), 3.66 (s, 3H, OCH_3), 3.93 (d, 1H, $J_{4,5}$ = 1.8 Hz, H-5), 4.15 (m, 1H, $CH_2CH{=}CH_2$), 4.22 (m, 2H, $J_{1,2}$ = 7.2 Hz, H-1, H-4), 4.42 (m, 1H, $CH_2CH{=}CH_2$), 5.14, 5.30 (2 x m, 2H, $CH_2CH{=}CH_2$), 5.89 (m, 1H, $CH_2CH{=}CH_2$); ^{13}C NMR (DMSO-d_6) δ 51.60 (OCH_3), 73.44 (CH_2-$CH{=}CH_2$), 69.67, 69.71, 72.43, 73.80 (C-2, C-3, C-4, C-5), 102.21 (C-1), 117.38 ($CH_2CH{=}CH_2$), 133.96 ($CH_2CH{=}CH_2$), 168.94 (C-6).

Anal. Calcd for $C_{10}H_{16}O_7$ (248.23): C, 48.39; H, 6.50. Found: C, 48.65; H, 6.70.

Methyl (benzyl β-D-galactopyranosid)uronate (8). Compound **6** (4.22 g, 10 mmol) was deacetylated as described for the synthesis of **7** to furnish **8** (2.77 g, 93%): mp 166 °C (from ethyl acetate-heptane). For further analytical data see lit.[6]

Methyl (allyl 3,4-*O*-isopropylidene-β-D-galactopyranosid)uronate (9). To a suspension of **7** (2.46 g, 10.0 mmol) in dry acetone (80 mL) and 2,2-dimethoxypropane (20 mL) was added *p*-toluenesulfonic acid monohydrate (400 mg), and the mixture was stirred for 24 h at ambient temperature (TLC solvent I). The mixture was then passed through a layer of alkaline alumina (2 x 3 cm), the solvent evaporated, and the residue was crystallized from ethyl acetate-heptane to give **9** (2.65 g, 92%) as colorless crystals: mp 96-97 °C (from heptane/ethyl acetate); $[\alpha]_D^{24}$ -26.7° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.33, 1.50 [2s, 6H, $C(CH_3)_2$], 2.49 (d, 1H, $J_{HO\text{-}2}$ = 2.4 Hz, OH-2), 3.82 (s, 3H, OCH_3), 3.64 (m, 1H, H-2), 4.10 (m, 1H, $CH_2CH{=}CH_2$), 4.12 (dd, 1H, $J_{3,4}$ = 5.2 Hz, H-3), 4.24 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 4.40 (dd, 1H, $J_{4,5}$ = 2.5 Hz, H-4), 4.42 (m, 1H, $CH_2CH{=}CH_2$), 4.38 (d, 1H, H-5), 5.21, 5.29 (2m, 2H, $CH_2CH{=}CH_2$), 5.91 (m, 1H, $CH_2CH{=}CH_2$); ^{13}C NMR ($CDCl_3$) δ 26.27, 27.90 [$C(CH_3)_2$], 52.49 (OCH_3), 70.18 ($CH_2CH{=}CH_2$), 72.36 (C-5), 72.96 (C-2), 73.77 (C-4), 78.45 (C-5), 100.97 (C-1), 110.69 [$C(CH_3)_2$], 118.28 ($CH_2CH{=}CH_2$), 133.45 ($CH_2CH{=}CH_2$), 167.41 (C-6).

Anal. Calcd for $C_{13}O_{20}H_7$ (288.30): C, 54.16; H, 6.99. Found: C, 54.08; H, 6.91.

Methyl (benzyl 3,4-*O*-isopropylidene-β-D-galactopyranosid)uronate (10). Processing of compound **8** (2.98 g, 10 mmol) as described above yielded **10** (3.25 g, 96%): mp 119 °C (from ethyl acetate-heptane). For further analytical data see lit.[6]

Methyl (allyl 2-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranosid)uronate (11). A solution of compound **9** (9.8 g, 34.0 mmol) and benzyl 2,2,2-trichloroacetimidate (7.61 mL, 40.8 mmol) in dry dichloromethane (40 mL) and dry heptane (110 mL) was treated with a catalytic amount of trifluoromethanesulfonic acid (50 μL). The mixture was stirred for 15 h at room temperature (TLC solvent B). The dark brown solution was passed through a layer of alkaline alumina, and the light yellow colored eluate concentrated. The residue was applied to a column of silica gel (eluent solvent A) to give syrupy **11** (9.77 g, 76%): $[\alpha]_D^{24}$ +8.6° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.31, 1.35 [2s, 2 x 3H, $C(CH_3)_2$], 3.49 (dd, 1H, $J_{2,3}$ = 6.7 Hz, H-2), 3.81 (s, 3H, OCH_3), 4.12 (m, 1H, $CH_2CH=CH_2$), 4.21 (dd, 1H, $J_{3,4}$ = 5.8 Hz, H-3), 4.34 (d, 1H, H-5), 4.40 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1), 4.43 (dd, 1H, $J_{4,5}$ = 2.4 Hz, H-4), 4.44 (m, 1H, $CH_2CH=CH_2$), 4.77, 4.82 (2 x d, 2H, $CH_2C_6H_5$), 5.19, 5.32 (2 x m, 2H, $CH_2CH=CH_2$), 5.93 (m, 1H, $CH_2CH=CH_2$), 7.20-7.40 (m, 5H, $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 26.26, 27.46 [$C(CH_3)_2$], 52.40 (OCH_3), 70.02 ($CH_2C_6H_5$), 73.56 ($CH_2CH=CH_2$), 72.07, 73.88, 78.50, 78.60 (C-2, C-3, C-4, C-5), 101.70 (C-1), 110.43 [$C(CH_3)_2$], 117.41 ($CH_2CH=CH_2$), 127.55, 128.13, 138.10 ($CH_2C_6H_5$), 133.86 ($CH_2CH=CH_2$), 167.66 (C-6).

Anal. Calcd for $C_{20}H_{26}O_7$ (378.42): C, 63.48; H, 6.93. Found: C, 63.24; H 6.75.

Methyl (benzyl 2-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranosid)uronate (12). Compound **10** (10.1 g, 34 mmol) was benzylated as described for the synthesis of **11** from **9** to yield syrupy **12** (12.3 g, 85%): $[\alpha]_D^{24}$ -9.9° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.34, 1.39 [2 x s, 2 x 3H, $C(CH_3)_2$], 3.62 (dd, 1H, $J_{2,3}$ = 7.3 Hz, H-2), 3.81 (s, 3H, OCH_3), 4.44 (dd, 1H, $J_{3,4}$ = 5.5 Hz, H-3), 4.50 (dd, 1H, $J_{4,5}$ = 2.7 Hz, H-4), 4.56-4.77 (4H, 2 x $CH_2C_6H_5$), 4.65 (d, 1H, H-5), 5.02 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 7.24-7.41 (m, 10H, 2 x $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 26.71, 28.25 [$C(CH_3)_2$], 52.85 (OCH_3), 68.22, 70.54, 72.85, 74.19 (C-2, C-3, C-4, C-5), 71.84, 75.97 (2 x $CH_2C_6H_5$), 97.05 (C-1), 110.12 [$C(CH_3)_2$], 128.18, 128.26, 128.37, 128.75, 128.86, 137.30, 138.39 (2 x $CH_2C_6H_5$), 169.01 (C-6).

Anal. Calcd for $C_{24}H_{28}O_7$ (428.48): C, 67.28; H, 6.59. Found: C, 67.04; H 6.41.

Methyl (allyl 2-*O*-benzyl-β-D-galactopyranosid)uronate (13). A solution of compound **11** (9.75 g, 25.8 mmol) in acetic acid (104 mL) and 90% aq trifluoroacetic acid (26 mL) was kept for 1 h at ambient temperature (TLC solvent D), diluted with toluene (200 mL), and concentrated. Traces of acetic acid and trifluoroacetic acid were removed by evaporation with repeating addition of toluene-heptane-ethanol (5:1:1, v/v; 4 x 200 mL). Crystallization (ethyl acetate-heptane) and chromatographic purification of the mother liquor on silica gel (eluent solvent D) yielded **13** (6.95 g, 80%): mp 64-65 °C (from ethyl acetate-heptane); $[\alpha]_D^{21}$ -10.5° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 3.50 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 3.59 (dd, 1H, $J_{3,4}$ = 3.4 Hz, H-3), 3.75 (s, 3H, OCH_3), 4.06 (m, 1H, H-5), 4.10 (m, 1H, $CH_2CH=CH_2$), 4.13 (dd, 1H, $J_{4,5}$ = 1.3 Hz, H-4), 4.36 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 4.42 (m, 1H, $CH_2CH=CH_2$), 4.67, 4.88 (2 x d, 2H, $CH_2C_6H_5$), 5.15, 5.28 (2 x m, 2H, $CH_2CH=CH_2$), 5.90 (m, 1H, $CH_2CH=CH_2$), 7.18-7.36 (m, 10H, 2 x $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 51.99 (OCH_3), 70.05, 74.60 ($CH_2CH=CH_2$, $CH_2C_6H_5$), 69.65 (C-4), 72.37 (C-3), 73.84 (C-5), 78.55 (C-2), 102.11 (C-1), 117.03 ($CH_2CH=CH_2$), 127.41, 127.82, 128.00, 138.34 ($CH_2C_6H_5$), 133.56 ($CH_2CH=CH_2$) 168.71 (C-6).

Anal. Calcd for $C_{24}H_{28}O_7$ (338.36): C, 60.35; H, 6.55. Found: C, 59.81; H 6.30.

Methyl (benzyl 2-*O*-benzyl-β-D-galactopyranosid)uronate (14). Processing of compound **12** (1.80 g, 4.2 mmol) as described above yielded **14** (1.27 g, 78%): mp 146 °C (from ethyl acetate-heptane); $[\alpha]_D^{25}$ -31.5° (*c* 1.0, chloroform); ^{1}H NMR (CH_3OD, $CDCl_3$) δ 3.60 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 3.65 (dd, 1H, $J_{3,4}$ = 3.1 Hz, H-3), 3.83 (s, 3H, OCH_3), 4.10 (d, 1H, H-5), 4.26 (dd, 1H, $J_{4,5}$ = 1.5 Hz, H-4), 4.47 (d, 1H, $J_{1,2}$ = 6.7 Hz, H-1), 4.67, 4.94, 5.04 (4 x d, 4H, 2 x $CH_2C_6H_5$), 7.23-7.42 (m, 10H, 2 x $CH_2C_6H_5$).

Anal. Calcd for $C_{21}H_{24}O_7$ (388.42): C, 64.94; H, 6.23. Found: C, 64.56; H 6.17.

Methyl (15) and benzyl (allyl 2,3-di-*O*-benzyl-β-D-galactopyranosid)uronate (16). Compound **13** (3.37 g, 10 mmol), di-*n*-butyltin oxide (2.99 g, 12 mmol) and toluene (120 mL) were heated under reflux for 2 h, whereas the water formed during the reaction was removed by 4 Å molecular sieves (especially for small quantities, it is advantageous to place the molecular sieve in a Mini-Soxhlet extractor). Then, the temperature was reduced to 60 °C, tetra-*n*-butylammonium bromide (4.43 g, 12 mmol) and benzyl bromide (2.97 mL, 25 mmol) were added, and the mixture was kept for 2 h at 60 °C and for an additional 2 h at 85° C (TLC solvent C). After cooling to room temperature, methanol was added

(25 mL), and the mixture was concentrated. The residue was dissolved in ethyl acetate (30 mL), silica gel was added, and the suspension was concentrated again. The substrate loaded on silica gel was processed by column chromatography (eluent ethyl acetate gradient 0% → 50% in heptane v/v) to give pure **15** (2.57 g, 58%; TLC, R_f 0.43, solvent C) and **16** (1.27 g, 25%; TLC solvent C R_f 0.70).

Compound **15** had mp 111 °C (from ethyl acetate-heptane); $[\alpha]_D^{22}$ -4.68° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 2.53 (m, 1H, 4-OH), 3.55 (dd, 1H, $J_{3,4}$ = 3.5 Hz, H-3), 3.71 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 3.82 (s, 3H, OCH_3), 4.04 (m, 1H, H-5), 4.13 (m, 1H, $CH_2CH=CH_2$), 4.31 (m, 1H, H-4), 4.41 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 4.48 (m, 1H, $CH_2CH=CH_2$), 4.73, 4.92 (2 x d, 2H, $CH_2C_6H_5$), 4.73 (s, 2H, $CH_2C_6H_5$), 5.19, 5.33 (2 x m, 2H, $CH_2CH=CH_2$), 5.95 (m, 1H, $CH_2CH=CH_2$), 7.23-7.40 (m, 10H, 2 x $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 52.53 (OCH_3), 70.26, 72.57, 75.21 (2 x $CH_2C_6H_5$, $CH_2CH=CH_2$), 68.00 (C-4), 73.67 (C-5), 78.29 (C-2), 79.80 (C-3), 102.32 (C-1), 117.41 ($CH_2CH=CH_2$), 127.68, 127.88, 128.00, 128.16, 128.31, 128.52, 137.59, 138.43 (2 x $CH_2C_6H_5$), 133.88 ($OCH_2CH=CH_2$), 168.41 (C-6).

Anal. Calcd for $C_{24}H_{28}O_7$ (428.48): C, 67.28; H, 6.59. Found: C, 67.17; H, 6.62.

Compound **16** had mp 100 °C (from ethyl acetate-heptane); $[\alpha]_D^{21}$ -7.2° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 2.54 (m, 1H, 4-OH), 3.55 (dd, 1H, $J_{3,4}$ = 3.5 Hz, H-3), 3.73 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 4.06 (d, 1H, H-5), 4.15 (m, 1H, $CH_2CH=CH_2$), 4.32 (m, 1H, H-4), 4.42 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 4.48 (m, 1H, $CH_2CH=CH_2$), 4.73, 4.92 (2 x d, 2H, $CH_2C_6H_5$), 4.73 (s, 2H, $CH_2C_6H_5$), 5.19, 5.32 (2 x m, 2H, $CH_2CH=CH_2$), 5.26 (d, 2H, $CH_2C_6H_5$), 5.95 (m, 1H, $CH_2CH=CH_2$), 7.23-7.41 (m, 15H, 3 x $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 67.14, 70.28, 72.63, 75.22 (3 x $CH_2C_6H_5$, $CH_2CH=CH_2$), 67.97 (C-4), 73.60 (C-5), 78.33 (C-2), 79.91 (C-3), 102.36 (C-1), 117.39 ($CH_2CH=CH_2$), 127.69, 127.86, 127.98, 128.17, 128.31, 128.40, 128.50, 128.57, 135.39, 137.66, 138.43 (3 x $CH_2C_6H_5$), 133.94 ($CH_2CH=CH_2$), 167.62 (C-6).

Anal. Calcd for $C_{30}H_{32}O_7$ (504.58): C, 71.41; H, 6.39. Found: C, 71.47; H, 6.49.

Methyl (17) and benzyl (benzyl 2,3-di-*O*-benzyl-β-D-galactopyranosid) uronate (18). The same procedure as above was used for the benzylation of the 3-OH group of compound **14** (337 mg, 1.0 mmol) to give pure **17** (325 mg, 68%; TLC solvent D R_f 0.49) and **18** (1.27 mg, 23%; TLC solvent D R_f 0.64).

Compound **17** had mp 92-94 °C (from ethyl acetate-heptane); $[\alpha]_D^{21}$ -29.8° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 2.57 (m, 1H, 4-OH), 3.55 (dd, 1H, $J_{3,4}$ = 3.3 Hz, H-3), 3.76 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 3.84 (s, 3H, OCH_3), 4.05 (d, 1H, H-5), 4.32 (m, 1H, H-4), 4.47 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 4.68, 4.73, 4.91, 5.04 (4 x d, 4H, 2 x $CH_2C_6H_5$), 4.72 (s, 2H, $CH_2C_6H_5$), 7.20-7.42 (m, 15H, 3 x $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 52.60 (OCH_3), 71.08, 72.57, 75.23 (3 x $CH_2C_6H_5$), 68.01 (C-4), 73.71 (C-5), 78.28 (C-2), 79.83 (C-3), 102.16 (C-1), 127.67, 127.80, 127.91, 128.01, 128.15, 128.30, 128.40, 128.54, 137.24, 137.57, 138.37 (3 x $CH_2C_6H_5$), 168.47 (C-6).

Anal. Calcd for $C_{28}H_{30}O_7$ (478.54): C, 70.28; H, 6.32. Found: C, 69.61; H, 6.55.

Compound **18** had mp 122-125 °C (from ethyl acetate-heptane); $[\alpha]_D^{21}$ -26.6° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 2.57 (m, 1H, 4-OH), 3.55 (dd, 1H, $J_{3,4}$ = 3.4 Hz, H-3), 3.78 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 4.07 (m, 1H, H-5), 4.33 (m, 1H, H-4), 4.47 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.68, 4.73, 4.92, 5.04, 5.27, 5.30 (6 x d, 4H, 3 x $CH_2C_6H_5$), 4.72 (s, 2H, $CH_2C_6H_5$), 7.26-7.42 (m, 20H, 4 x $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 67.11, 70.99, 72.55, 75.15 (4 x $CH_2C_6H_5$), 67.90 (C-4), 73.58 (C-5), 78.26 (C-2), 79.88 (C-3), 102.1 (C-1), 127.60, 127.72, 127.81, 127.93, 127.96, 128.09, 128.23, 128.28, 128.33, 128.36, 128.45, 128.54, 135.33, 137.19, 137.57, 138.31 (4 x $CH_2C_6H_5$), 167.61 (C-6).

Anal. Calcd for $C_{34}H_{34}O_7$ (554.64): C, 73.63; H, 6.18. Found: C, 73.36; H 6.21.

Methyl (allyl 3,4-di-*O*-acetyl-2-*O*-benzyl-β-D-galactopyranosid)uronate (20). A. *via* **13**. To a stirred solution of **13** (1.10 g, 3.2 mmol) in dry pyridine (3.1 mL) was added acetic anhydride (1.8 mL) at 0°C. After 5 h at room temperature (TLC solvent B), the mixture was diluted with heptane-chloroform (2:1 v/v, 60 mL), and the organic layer was successively washed with ice-water (30 mL), cold aq 1% hydrochloric acid (2 x 30 mL), ice-water (30 mL), ice-cold aq $NaHCO_3$ (2 x 30 mL), ice-water (30 mL), dried, and concentrated. The syrupy product **20** (1.18 g, 88%) was used without further purification for the next step. An analytical sample of **20** was obtained by column chromatography (eluent solvent A) as a syrup: $[\alpha]_D^{25}$ +56.7° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.94, 2.05 (2 x s, 2 x 3H, $OCOCH_3$), 3.69 (dd, 1H, $J_{2,3}$ = 10.3 Hz, H-2), 3.73 (s, 3H, OCH_3), 4.24 (d, 1H, H-5), 4.17, 4.50 (2 x m, 2 x 1H, $CH_2CH{=}CH_2$), 4.52 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 4.63, 4.88 (2 x d, 2 x 1H, $CH_2C_6H_5$), 5.01 (dd, 1H, $J_{3,4}$ = 3.4 Hz, H-3), 5.21, 5.34 (2 x m, 2 x 1H, $CH_2CH{=}CH_2$), 5.64 (dd, 1H, $J_{4,5}$ = 1.2 Hz, H-4), 5.94 (m, 1H,

$CH_2CH=CH_2$), 7.21-7.35 (m, 5H, $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 20.53, 20.57 (2 x $OCOCH_3$), 52.58 (OCH_3), 70.62, 74.81 ($CH_2C_6H_5$, $CH_2CH=CH_2$), 68.78 (C-4), 71.82 (C-3), 72.27 (C-5), 75.93 (C-2), 102.48 (C-1), 117.77 ($CH_2CH=CH_2$), 127.67, 127.81, 128.24, 138.21 ($CH_2C_6H_5$), 133.56 ($OCH_2CH=CH_2$), 166.79 (C-6), 169.73, 169.87 ($OCOCH_3$).

Anal. Calcd for $C_{21}H_{26}O_9$ (422.43): C, 59.71; H, 6.20. Found: C, 59.61; H, 6.22.

B. Starting from **5** *via* **19**. To a solution of **5** (6.65 g, 17.76 mmol) in ethanol (50 mL) were added buffer (KH_2PO_4/Na_2HPO_4 pH = 7.0; 500 mL) and 860 mg Acylase I (from hog kidney, Fluka Kat.-Nr. 01821, 860 mg). The suspension was stirred for 5 h at 25 °C (TLC solvent C), and then ethanol was concentrated *in vacuo*. After freeze drying of the aqueous solution, the residue was suspended in heptane-ethyl acetate (1:1 v/v) and passed through a layer of silica gel (5 x 10 cm). The eluate was concentrated, and the residue was crystallized from ethyl acetate-heptane to give methyl (allyl 3,4-di-*O*-acetyl-β-D-galactopyranosid)uronate (**19**, 5.58 g, 95%), mp 132-135 °C; $[\alpha]_D^{20}$ +32.8° (*c* 1.0, chloroform); ^1H NMR ($CDCl_3$) δ 2.03, 2.06 (2s, 2 x 3H, 2 x $OCOCH_3$), 2.48 (d, 1H, $J_{HO,2}$ = 2.6 Hz, OH-2), 3.73 (s, 3H, OCH_3), 3.86 (m, 1H, H-2), 4.16 (m, 1H, $CH_2CH=CH_2$), 4.28 (d, 1H, H-5), 4.40 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.47 (m, 1H, $CH_2CH=CH_2$), 4.97 (dd, 1H, $J_{3,4}$ = 3.6 Hz, H-3), 5.23, 5.32 (2m, 2H, $CH_2CH=CH_2$), 5.66 (dd, 1H, $J_{4,5}$ = 1.2 Hz, H-4), 5.93 (m, 1H, $CH_2CH=CH_2$); ^{13}C NMR ($CDCl_3$) δ 20.50, 20.68 (2 x $OCOCH_3$), 52.66 (OCH_3), 70.60 ($CH_2CH=CH_2$), 68.49 (C-2), 68.71 (C-5), 72.10, 72.53 (C-3, C-4,), 101.73 (C-1), 118.60 ($CH_2CH=CH_2$), 133.25 ($CH_2CH=CH_2$), 166.70 (C-6), 169.76, 170.23 (2 x $OCOCH_3$).

Anal. Calcd for $C_{14}H_{20}O_9$ (332.31): C, 50.60; H, 6.07. Found: C, 50.64; H 6.00.

A solution of compound **19** (5.25 g, 15.8 mmol) and benzyl 2,2,2-trichloroacetimidate (5.8 mL, 31.0 mmol) in dry dichloromethane (40 mL) and dry heptane (50 mL) was treated with a catalytic amount of trifluoromethanesulfonic acid (260 µL). The mixture was stirred for 1.5 h at room temperature (TLC solvent B). The slight brown solution was passed through a layer of alkaline alumina, the eluate concentrated, and the residue was applied to a column of silica gel (eluent solvent A) to give syrupy **20** (4.14 g, 62%). The analytical data of **20**, prepared via **5** and **19**, were fully consistent with those of the product obtained by acetylation of **13**.

Methyl 3,4-di-*O*-acetyl-2-*O*-benzyl-α/β-D-galactopyranosiduronate (21). To a stirred solution of **20** (2.03 g, 4.8 mmol) in acetic acid (160 mL) and water (8 mL) were added sodium acetate (4.34 g) and palladium(II) chloride (3.4 g, 19.2 mmol). After stirring for 3 h at 40 °C (TLC solvent C), the reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in heptane-chloroform (2:1 v/v, 100 mL), the organic layer was washed with water (3 x 50 mL), dried, and concentrated. The crude product was purified by column chromatography (eluate solvent C) to yield **21** (1.43 g, 78%); ^{1}H NMR ($CDCl_3$) δ 1.94β, 1.97α, 2.03α/β (3 x s, $OCOCH_3$), 3.61 (dd, $J_{2,3}$ = 10.1 Hz, H-2β), 3.69α, 3.71β (2s, 2 x OCH_3), 3.86 (dd, $J_{2,3}$ = 10.4 Hz, H-2α), 4.28 (d, H-5β), 4.78 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1β), 4.82 (d, H-5α) 4.58-4.71, 4.89 ($CH_2C_6H_5$α/β), 5.00 (dd, $J_{3,4}$ = 3.4 Hz, H-3β), 5.37 (dd, $J_{3,4}$ = 3.4 Hz, H-3α), 5.42 (d, $J_{1,2}$ = 3.4 Hz, H-1α), 5.63 (dd, $J_{4,5}$ = 1.2 Hz, H-4β), 5.71 (dd, $J_{4,5}$ = 1.2 Hz, H-4α), 7.20-7.38 (m, $CH_2C_6H_5$α/β).

Anal. Calcd for $C_{18}H_{22}O_9$ (382.37): C, 56.54; H, 5.80. Found: C, 56.27; H, 6.08.

Methyl 3,4-di-*O*-acetyl-2-*O*-benzyl-α-D-galactopyranosyluronate bromide (22). To a solution of **21** (683 mg, 1.78 mmol) in dry dichloromethane (10 mL) *N*-bromomethylene-*N,N*-dimethylammonium bromide (Vilsmeyer bromide, 581 mg, 2.68 mmol) and *sym*-collidine (400 μL, 3.0 mmol) were added. The red brown reaction solution was kept for 6 h at ambient temperature (TLC solvent C), diluted with a mixture of heptane (180 mL) and chloroform (80 mL) , and washed with ice-water (2 x 50 mL), cold aq 1% hydrochloric acid (3 x 50 mL), ice-water (50 mL), cold sat aq $NaHCO_3$ (2 x 50 mL), ice-water (50 mL), dried, and concentrated. The chromatographically pure syrup **22** (713 mg, 90%) was used without further purification for the next step and only characterized by ^{1}H NMR ($CDCl_3$) δ 1.99, 2.05 (2s, 2 x $OCOCH_3$), 3.73 (s, 3H, OCH_3), 3.82 (dd, 1H, $J_{2,3}$ = 10.3 Hz, H-2), 4.65 (s, 2H, $CH_2C_6H_5$), 4.85 (d, 1H, H-5), 5.36 (dd, 1H, $J_{3,4}$ = 3.4 Hz, H-3), 5.76 (dd, 1H, $J_{4,5}$ = 1.7 Hz, H-4), 6.45 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 7.26 - 7.40 (m, 5H, $CH_2C_6H_5$).

Ethyl 1-thio-β-D-galactopyranoside (23). To a stirred mixture of 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose[33] (19.52 g, 50 mmol; the β-anomeric compound is essential), ethyl mercaptan (4.07 mL, 55 mmol) and molecular sieves (4Å, 2g) in dry dichloromethane (175 mL) was added a solution of boron trifluoride diethyl etherate (21.7

mL, 175 mmol) in dichloromethane (35 mL) at 0 °C.[34] After an additional 10 min the chilling was terminated and the mixture was stirred for 3 h at ambient temperature (TLC solvent C), filtered through a bed of Celite, and diluted with chloroform (20 mL) and heptane (460 mL). The organic layer was then washed with sat aq $NaHCO_3$ (3 x 200 mL), water (3 x 200 mL), dried, and concentrated. The residue was dried for a few hours under high vacuum to yield ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (19.21 g, 98%), sufficiently pure for the next step. Recrystallization from ethyl acetate-heptane gave an analytical sample, mp 74 °C, $[\alpha]_D^{24}$ -9.3 ° (*c* 1.0, chloroform); lit.[35] mp 74.5-75 °C, $[\alpha]_D$ -8.5° (*c* 2.3, chloroform). To ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galacto-pyranoside (19.6 g, 50 mmol) in dry methanol (40 mL) was added 1 M sodium methoxide (1 mL), and the solution was kept for 1 h at ambient temperature (TLC solvent H). The mixture was then neutralized by addition of DOWEX 50 W X 8 [H^+], filtered, and concentrated. After drying under high vacuum, the desired compound **23** was used without further purification. An analytical sample was obtained by crystallization from ethanol-ethyl acetate, mp 122 °C; $[\alpha]_D^{24}$ -22.7° (*c* 1.0, water); lit.[35] mp 122-122.5 °C, $[\alpha]_D$ -23.5° (*c* 1.1, water).

Ethyl 6-*O*-trityl-1-thio-β-D-galactopyranoside (24). To a stirred solution of **23** (11.2 g, 50.0 mmol) in dry pyridine (80 mL) was added chlorotriphenylmethane (16.7 g, 60.0 mmol) at room temperature. Stirring was continued for 12 h (TLC solvent D), then methanol (2 mL) was added. After 30 min, the mixture was concentrated, and the residue dissolved in chloroform (300 mL). The organic layer was washed successively with ice-water (100 mL), cold aq 15% $NaHSO_4$ (3 x 100 mL), ice-water (100 mL), cold sat aq $NaHCO_3$ (2 x 100 mL), ice-water (100 mL), dried, and after adding of silica gel (30 g) concentrated. Purification by column chromatography (solvent D) furnished **24** (19.1 g, 82%): mp 80-84 °C (from ethyl acetate-heptane); $[\alpha]_D^{22}$ -19.3° (*c* 1.0, chloroform); ^1H NMR (CH_3OD, $CDCl_3$) δ 1.30 (t, 3H, SCH_2CH_3), 2.72 (m, 2H, SCH_2CH_3), 3.31 (m, 1H, H-6), 3.43 (m, 1H, H-5), 3.51 (m, 2H, H-3, H-6), 3.63 (dd, 1H, H-2), 3.98 (d, 1H, H-4), 4.28 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 7.16-7.48 (m, 15H, 3 x C_6H_5); ^{13}C NMR ($CDCl_3$) δ 15.35 (SCH_2CH_3), 24.34 (SCH_2CH_3), 62.96 (C-6), 69.44 (C-4), 70.42 (C-2), 74.90 (C-5), 77.60 (C-3), 85.91 (C-1), 86.99 [$C(C_6H_5)_3$], 127.14, 127.90, 128.68, 143.74 (C_6H_5).

Anal. Calcd for $C_{27}H_{30}O_5S$ (466.59): C, 69.50; H, 6.48; S, 6.87. Found: C, 69.30; H, 6.63; S, 6.62.

Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-1-thio-β-D-galactopyranoside (25). To a stirred solution of **24** (18.7 g, 40 mmol) in dry *N,N*-dimethylformamide (150 mL) was slowly added sodium hydride (5.4 g, 180 mmol; 80% suspension in paraffin) at 0 °C. After 30 min, benzyl bromide 21.4 mL, 180 mmol) was added dropwise, in order that the temperature does not rise above 15 °C. After stirring for 3 h (TLC solvent B), methanol (5 mL) was added, and, after 30 min, the reaction mixture was diluted with chloroform (200 mL) and heptane (400 mL). The organic layer was washed successively with ice-water (200 mL), cold aq 15% $NaHSO_4$ (4 x 100 mL), ice-water (100 mL), cold sat aq $NaHCO_3$ (2 x 100 mL), ice-water (100 mL), dried, and concentrated. The crude material was purified by column chromatography (ethyl acetate gradient 0%→10% in heptane) to yield syrupy **25** (27.2 g, 92%): $[\alpha]_D^{22}$ -1.15° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, SCH_2CH_3), 2.75 (d, 2H, SCH_2CH_3), 3.26, (m, 1H, H-6), 3.35 (m, 1H, H-5), 3.54 (m, 2H, H-3, H-6'), 3.82 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 3.93 (d, 1H, $J_{4,5}$ = 2.4 Hz, H-4), 4.4 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 4.50-4.93 (6H, 3 x $CH_2C_6H_5$), 7.15-7.45 (m, 30H, 3 x C_6H_5, 3 x $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 15.00 (SCH_2CH_3), 24.53 (SCH_2CH_3), 62.78 (C-6), 72.89, 74.25, 75.75 (3 x $CH_2C_6H_5$), 74.16 (C-4), 77.57 (C-5), 78.50 (C-2), 84.14 (C-3), 85.06 (C-1), 86.96 [$C(C_6H_5)_3$], 127.08, 127.25, 127.62, 127.67, 127.73, 127.86, 128.05, 128.32, 128.43, 128.48, 128.67, 138.38, 138.53, 138.79, 143.94 (3 x C_6H_5, 3 x $CH_2C_6H_5$).

Anal. Calcd for $C_{48}H_{48}O_5S$ (736.97): C, 78.23; H, 6.56; S, 4.35; Found: C, 77.99; H, 6.60; S, 4.20.

Ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (27). To a stirred solution of **25** (5.53 g, 7.5 mmol) in diethyl ether (11 mL) were added 85% formic acid (5 mL) and water (2 mL). Stirring was continued for 3 h at ambient temperature, then the reaction mixture was heated under reflux for 2 h. When the reaction was complete (TLC solvent C), the mixture was kept for 12 h at -15 °C. Precipitated crystals (triphenylmethanol) were separated by filtration. The filtrate was diluted with chloroform (50 mL) and heptane (100 mL), the organic layer was washed with ice-water (50 mL), cold sat aq $NaHCO_3$ (3 x 50 mL), ice-water (50 mL), dried, and concentrated. The residue was crystallized from ethyl acetate-heptane to give **27** (2.78 g, 75%): mp 100-102 °C; $[\alpha]_D^{21}$ -32.4° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, SCH_2CH_3), 2.75 (d, 2H,

SCH_2CH$_3$), 3.41, 3.50 (2m, 2H, H-6, H-6'), 3.58 (dd, 1H, $J_{3,4}$ = 2.7 Hz, H-3), 3.77 (m, 1H, H-5), 3.85 (m, 2H, H-2, H-4), 4.43 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 4.62-5.00 (m, 6H, 3 x CH_2C$_6$H$_5$), 7.26-7.42 (m, 15H, 3 x CH$_2$C$_6$$H_5$); ^{13}C NMR ($CDCl_3$) δ 15.16 (SCH$_2$$CH_3$), 24.88 (S$CH_2CH_3$), 62.22 (C-6), 73.12, 74.18, 75.80 (3 x CH_2C$_6$H$_5$), 73.25 (C-4), 78.55 (C-2), 78.74 (C-5), 84.23 (C-3), 85.50 (C-1), 127.65, 127.78, 127.90, 128.35, 128.38, 128.41, 128.44, 128.52, 138.31, 138.40 (3 x CH$_2$$C_6H_5$).

Anal. Calcd for $C_{29}H_{34}O_5S$ (494.65): C, 70.42; H, 6.93; S, 6.48. Found: C, 70.18; H, 6.69; S, 6.46.

During detritylation described above a spot appeared sometimes with TLC (solvent B R_f 0.43), which is related to ethyl 2,3,4-tri-*O*-benzyl-6-*O*-formyl-1-thio-β-D-galacto-pyranoside (**26**): ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, SCH$_2$$CH_3$), 2.73 (d, 2H, S$CH_2CH_3$), 3.56 (2m, 2H, H-3, H-5), 3.85 (m, 2H, H-2, H-4), 4.12, 4.31 (2m, 2H, H-6, H-6'),4.42 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 4.62-5.02 (6H, 3 x CH_2C$_6$H$_5$), 7.25-7.42 (m, 15H, 3 x CH$_2$C$_6$$H_5$), 7.93 (s, 1H, CH=O). In this case, the reaction mixture was concentrated directly after heating with formic acid. Then, the dry residue was dissolved in a minimum of methanol and sodium borohydride (380 mg, 10 mmol) was added. After 10 min (TLC solvent B), the reaction mixture was neutralized with 10% acetic acid in toluene, and concentrated. The residue was dissolved in chloroform (50 mL) and heptane (100 mL), the organic layer was washed with ice-water (50 mL), cold sat aq $NaHCO_3$ (3 x 50 mL), ice-water (50 mL), dried, and concentrated to give compound **27** (more or less the same yield as above).

***tert*-Butyl (ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-galactopyranosid)uronate (28).** To a solution of compound **27** (3.96 g, 8.0 mmol) in dry dichloromethane (100 mL) were added acetic anhydride (7.6 mL, 80 mmol), *tert*-butyl alcohol (15 mL, 160 mmol) and pyridinium dichromate (6.1 g, 16.0 mmol), and the mixture was stirred for 6 h at ambient temperature (TLC solvent C). The mixture was then passed through a layer of silica gel (3 x 5 cm) using ethyl acetate as eluent to remove the main part of chromium salts. The eluate was concentrated, and the residue purified by column chromatography (eluent solvent B) to give **28** (2.54 g, 56%) as a colorless foam: $[\alpha]_D^{21}$ +2.8° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, SCH$_2$$CH_3$), 1.47 [s, 9H, C(CH$_3$)$_3$], 2.80 (d, 2H, S$CH_2CH_3$), 3.62 (dd, 1H, $J_{3,4}$ = 3.1 Hz, H-3), 3.90 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 3.93 (d,

1H, H-5), 4.31 (dd, 1H, $J_{4,5}$ = 1.2 Hz, H-4), 4.43 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 4.63-5.10 (m, 6H, 3 x $CH_2C_6H_5$), 7.23-7.43 (m, 15H, 3 x $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 15.22 (SCH_2CH_3), 24.48 (SCH_2CH_3), 27.98 [$C(CH_3)_3$], 72.65, 74.54, 75.64 (3 x $CH_2C_6H_5$), 75.74 (C-4), 77.36 (C-5), 77.73 (C-2), 82.24 [$C(CH_3)_3$], 83.54 (C-3), 84.88 (C-1), 127.24, 127.47, 127.52, 127.62, 127.64, 127.98, 128.22, 128.34, 128.37, 138.15, 138.18, 138.46 (3 x $CH_2C_6H_5$), 166.81 (C=O).

Anal. Calcd for $C_{33}H_{40}O_6S$ (564.74): C, 70.19; H, 7.14; S, 5.68. Found: C, 69.99; H, 7.27; S, 6.00.

Ethyl 4,6-*O*-*p*-methoxybenzylidene-1-thio-β-D-galactopyranoside (29). A solution of **23** (11.2 g, 50 mmol), *p*-methoxybenzaldehyde dimethyl acetal (10.2 mL, 60 mmol) and *p*-toluenesulfonic acid monohydrate (750 mg) in dry *N*,*N*-dimethylformamide (50 mL) was placed in a distilling flask of a rotary evaporator, and kept for 2 h at 40 °C under vacuum (40 mbar). When the reaction was complete (TLC solvent E), the mixture was diluted with chloroform (300 mL). The organic layer was washed with cold sat aq $NaHCO_3$ (2 x 100 mL), ice-water (100 mL), dried, and concentrated. The residue was purified by column chromatography (solvent E) to yield **29** (15.1 g, 88%): $[\alpha]_D^{21}$ -67.6° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H, SCH_2CH_3), 2.78 (m, 2H, SCH_2CH_3), 3.47 (m, 1H, H-5), 3.74 (m, 1H, H-3) 3.79 (s, 3H, $H_3COC_6H_4CH$), 3.82 (m, 1H, H-2), 3.98 (dd, 1H, H-6'), 4.20 (dd, 1H, H-4), 4.29 (dd, 1H, H-6), 4.33 (d, 1H, $J_{1,2}$ = 9.3 Hz, H-1), 5.48 (s, 1H, $H_3COC_6H_4CH$), 6.88, 7.40 (2m, 4H, $H_3COC_6H_4CH$); ^{13}C NMR ($CDCl_3$) δ 15.14 (SCH_2CH_3), 23.34 (SCH_2CH_3), 55.20 ($H_3COC_6H_4CH$), 69.16 (C-6), 69.55 (C-2), 69.93 (C-5), 73.73 (C-3), 75.58 (C-4), 85.18 (C-1), 101.17 ($H_3COC_6H_4CH$), 113.53, 127.67, 130.22, 160.14 ($H_3COC_6H_4CH$).

Anal. Calcd for $C_{16}H_{22}O_6S$ (342.41): C, 56.12; H, 6.48; S, 9.35. Found: C, 55.89; H, 6.34; S, 9.24.

Ethyl 2,3-di-*O*-benzyl-4,6-*O*-*p*-methoxybenzylidene-1-thio-β-D-galactopyranoside (30). For the synthesis of compound **30**, the preceding reaction mixture was, after TLC control (compound **29**: solvent E R_f 0.22), diluted with dry *N*,*N*-dimethylformamide (70 mL), and 80 % sodium hydride (4.8 g, 160.0 mmol) was added in small portions at 0 °C. The solution was kept for 45 min at that temperature, and then benzyl bromide (19 mL, 160.0 mmol) was added dropwise. When the reaction was complete (TLC solvent C),

it was terminated by addition of methanol (4 mL), and after stirring for further 30 min, the mixture was diluted with heptane (600 mL) and chloroform (300 mL). The organic layer was washed with ice-water (2 x 200 mL), cold aq 1% hydrochloric acid (2 x 300 mL), ice-water (3 x 300 mL), dried, and concentrated. The residue was purified by column chromatography (solvent C) to give **30** (21.4 g, 82%): mp 135-140 °C (from ethyl acetate-heptane); $[\alpha]_D^{21}$ -2.2° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.34 (t, 3H, SCH_2CH_3), 2.80 (m, 2H, SCH_2CH_3), 3.33 (m, 1H, H-5), 3.57 (dd, 1H, $J_{3,4}$ = 2.7 Hz, H-3) 3.81 (s, 3H, $H_3COC_6H_4CH$), 3.88 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 3.94 (dd, 1H, H-6'), 4.14 (d, 1H, H-4), 4.29 (dd, 1H, H-6), 4.43 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.74 (s, 2H, $CH_2C_6H_5$), 4.83, 4.90 (2d, 2H, $CH_2C_6H_5$), 5.43 (s, 1H, $H_3COC_6H_4CH$), 6.90, 7.24-7.50 (2m, 14H, $CH_2C_6H_5$, $CH_3OC_6H_4CH$); ^{13}C NMR ($CDCl_3$) δ 15.08 (SCH_2CH_3), 23.80 (SCH_2CH_3), 55.32 ($H_3COC_6H_4CH$), 69.40 (C-6), 69.82 (C-5), 71.75, 75.67 (2 x $CH_2C_6H_5$), 73.95 (C-4), 76.97 (C-2), 81.24, (C-3), 84.47 (C-1), 101.35 ($H_3COC_6H_4CH$), 113.60, 127.66, 127.70, 127.75, 127.83, 128.26, 128.34, 130.67, 138.38, 138.50, 160.19 (2 x $CH_2C_6H_5$, $H_3COC_6H_4CH$).

Anal. Calcd for $C_{30}H_{34}O_6S$ (522.66): C, 68.94; H, 6.56; S, 6.12. Found: C, 68.66; H, 6.66; S, 5.91.

Ethyl 2,3-di-*O*-benzyl-4-*O*-*p*-methoxybenzyl-1-thio-β-D-galactopyranoside (31). To solution of sodium cyanoborohydride (5.65 g, 90 mmol) in dry acetontrile (100 mL) was added carefully dried **30** (7.84 g, 15 mmol), and then dropwise a solution of chlorotrimethylsilane in dry acetonitrile [45 mL, 90 mmol; prepared by adding molecular sieves (3 Å, 9.0 g) to a solution of chlorotrimethylsilane (15.2 mL, 120 mmol) in dry acetonitrile (total volume 60 mL), which was stirred for 15 min under vigorously exclusion of moisture] during 30 min at 0 °C. After additional 15 min at that temperature, the reaction mixture was stirred at room temperature overnight (TLC solvent C), and then neutralized with sat aq $NaHCO_3$ (caution, strong foam up). The phases were separated, the aqueous phase was extracted with chloroform (2 x 100 mL), and the combined organic phases concentrated. The oily residue was dissolved in heptane (400 mL) and chloroform (200 mL) whereupon a yellow colored aq layer was formed which was separated. Then, the organic layer was washed with water (3 x 200 mL), dried, and concentrated. The residue was crystallized from ethyl acetate-heptane to give **31** (7.2 g, 92%): mp 93 °C;

$[\alpha]_D^{21}$ -29.6° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, SCH_2CH_3), 2.74 (m, 2H, SCH_2CH_3), 3.39 (m, 1H, H-5), 3.47 (m, 1H, H-6), 3.55 (dd, 1H, $J_{3,4}$ = 2.7 Hz, H-3) 3.75 (m, 1H, H-6'), 3.79 (s, 3H, $H_3COC_6H_4CH_2$),3.82 (d, 1H, H-4), 3.83 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 4.42 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.56-4.94 (6H, 2 x $CH_2C_6H_5$, $H_3COC_6H_4CH_2$), 6.86, 7.21-7.42 (2m, 14H, 2 x $CH_2C_6H_5$, $H_3COC_6H_4CH_2$); ^{13}C NMR ($CDCl_3$) δ 15.12 (SCH_2CH_3), 24.85 (SCH_2CH_3), 55.28 ($H_3COC_6H_4CH_2$), 62.26 (C-6) 73.12, 73.69, 75.74 (2 x $CH_2C_6H_5$, $H_3COC_6H_4CH_2$), 72.78 (C-4), 78.60, 78.74, (C-2, C-5), 84.28 (C-3), 85.51 (C-1), 113.86, 127.61, 127.72, 127.74 128.31, 128.35, 128.48, 129.98, 130.45, 138.36, 159.42 (2 x $CH_2C_6H_5$, $H_3COC_6H_4CH_2$).

Anal. Calcd for $C_{30}H_{36}O_6S$ (524.67): C, 68.67; H, 6.92; S, 6.10. Found: C, 68.45; H, 7.00; S, 6.10.

Methyl (ethyl 2,3-di-*O*-benzyl-4-*O*-*p*-methoxybenzyl-1-thio-β-D-galacto-pyranosid)uronate (32). To a solution of **31** (2.1 g, 4.0 mmol) in dry dimethyl sulfoxide (40 mL) dry pyridine (320 μL, 4.0 mmol), trifluoroacetic acid (158 μl, 2.0 mmol) and *N,N'*-dicyclohexylcarbodiimide (2.88 g, 14 mmol) were added, and the mixture was stirred for 24 h at room temperature (TLC sovent C). Then, a solution of oxalic acid (2.0 g) in methanol (40 mL) was added, and stirring was continued for 30 min. The precipitated *N,N'*-dicyclohexylurea was filtered off, and the filtrate was diluted with heptane (200 mL) and chloroform (100 mL). The organic layer was washed with aq sat $NaHCO_3$ (3 x 100 mL), water (2 x 100 mL), dried, and concentrated. The crude dry aldehyde was used in the next step without further characterization, dissolved in a mixture of dry *N,N*-dimethyl-formamide and dry methanol (970 μL), and kept for 30 min at 0 °C. Then, pyridinium dichromate (9 g) was added, and the reaction mixture was stirred at room temperature in the dark. After 24 h (TLC solvent C), the reaction mixture was poured into a layer of ethyl acetate (30 mL) over a bed of silica gel (2 x 5 cm), whereupon chromium salts precipitated. After elution with ethyl acetate, the eluate was concentrated, and the residue dissolved in heptane (200 mL) and chloroform (100 mL). The organic layer was washed with water (5 x 100 mL), dried and concentrated. The crude material was purified by column chromatography (solvent B) to yield **32** (906 mg, 39%): mp 77-80 °C (from diethyl ether-heptane); $[\alpha]_D^{21}$ -4.2° (*c* 0.75, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, SCH_2CH_3), 2.77 (m, 2H, SCH_2CH_3), 3.59 (dd, 1H, $J_{3,4}$ = 2.8 Hz, H-3), 3.67 (s, 3H,

OCH_3), 3.78 (s, 3H, $H_3COC_6H_4CH_2$), 3.86 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 4.01 (d, 1H, H-5), 4.27 (dd, 1H, $J_{4,5}$ = 1.3 Hz, H-4), 4.42 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.53-4,94 (6H, 2 x $CH_2C_6H_5$, $H_3COC_6H_4CH_2$), 6.82, 7.20 (2m, 4H, $H_3COC_6H_4CH_2$), 7.27-7,42 (m, 10H, 2 x $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 14.98 (SCH_2CH_3), 24.93 (SCH_2CH_3), 52.33 (OCH_3), 55.28 ($H_3COC_6H_4CH_2$), 72.84, 73.94, 75.78 (2 x $CH_2C_6H_5$, $H_3COC_6H_4CH_2$), 74.59 (C-4), 77.40 (C-5), 77.86 (C-2), 83.42 (C-3), 85.23 (C-1), 113.58, 127.58, 127.76, 128.32, 128.38, 128.47, 129.72, 130.42, 138.09, 138.21, 159.22 (2 x $CH_2C_6H_5$, $H_3COC_6H_4CH_2$), 168.64 (C-6).

Anal. Calcd for $C_{31}H_{36}O_7S$ (552.68): C, 67.37; H, 6.57; S, 5.80. Found: C, 67.34; H, 6.51; S, 5.88.

Methyl (methyl 3,4-di-*O*-acetyl-2-*O*-benzyl-α-D-galactopyranosyluronate)-(1→4)-(allyl 2,3-di-*O*-benzyl-β-D-galactopyranosid)uronate (33). To a solution of **22** (485 mg, 1.1 mmol) and **15** (440 mg, 1.03 mmol) in dry dichloromethane (25 mL) were added silver carbonate (303 mg, 1.1 mmol) and silver trifluoromethanesulfonate (283 mg, 1.1 mmol), and the reaction mixture was stirred at room temperature in the dark. After 12 h (TLC solvent C), the silver salts were filtered off, washed with dichloromethane, and combined filtrate and washings were concentrated. The residue was processed by HPLC (solvent B) to give syrupy **33** (286 mg, 35% related to **15**): $[\alpha]_D^{23}$ +74.8° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.92, 1.96 (2s, 2 x 3H, $OCOCH_3$), 3.41 (s, 3H, OCH_3), 3.42 (dd, 1H, $J_{3,4}$ = 3.0 Hz, H-3), 3.67 (s, 3H, OCH_3'), 3.75 (dd, 1H, $J_{2,3}$ = 10.1 Hz, H-2), 3.88 (dd, 1H, $J_{2',3'}$ = 10.8 Hz, H-2'), 3.93 (d, 1H, H-5), 4.15 (m, 1H, $CH_2CH=CH_2$), 4.38 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 4.48 (dd, 1H, $J_{4,5}$ = 0.7 Hz, H-4), 4.49 (m, 1H, $CH_2CH=CH_2$), 4.51-4.99 (m, 6H, 3 x $CH_2C_6H_5$), 5.10 (d, 1H, H-5'), 5.19, 5.33 (2m, 2H, $CH_2CH=CH_2$), 5.28 (d, 1H, $J_{1',2'}$ = 3.7 Hz, H-1'), 5.31 (dd, 1H, $J_{3',4'}$ = 3.3 Hz, H-3'), 5.69 (dd, 1H, $J_{4',5'}$ = 1.7 Hz, H-4'), 5.95 (m, 1H, $CH_2CH=CH_2$), 7.16-7.40 (m, 15H, 3 x $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 20.45, 20.76 (2 x $OCOCH_3$), 52.11 (OCH_3), 52.96 (OCH_3'), 69.20 (C-3', C-5'), 69.86, (C-4'), 70.34, 72.35, 72.66, 75.12 (3 x $CH_2C_6H_5$, $CH_2CH=CH_2$), 71.95 (C-2'), 73.43 (C-5), 75.77 (C-4), 77.87 (C-2), 79.47 (C-3), 99.36 (C-1'), 102.90 (C-1), 117.34 ($CH_2CH=CH_2$), 127.39, 127.52, 127.59, 127.65, 127.74, 127.9, 128.24, 128.31, 128.37, 128.43 137.83, 138.07, 138.32 (3 x $CH_2C_6H_5$), 133.99 ($CH_2CH=CH_2$), 168.05, 168.24 (C-6, C-6'), 169.67, 169.70 (2 x $OCOCH_3$).

Anal. Calcd for $C_{42}H_{48}O_{15}$ (792.83): C, 63.63; H, 6.10. Found: C, 63.36, H, 5.82.

Methyl (methyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranosyluronate)-(1→4)-(benzyl 2,3-di-*O*-benzyl-β-D-galactopyranosid)uronate (35). To a stirred suspension of **28** (305 mg, 540 μmol), **17** (215 mg, 450 μmol), and molecular sieves (4Å, 500 mg) in dry dichloromethane (20 mL) were added *N*-iodosuccinimide (149 mg, 660 μmol) and silver trifluoromethanesulfonate (116 mg, 450 μmol) at -20 °C. After 15 min at that temperature, chilling was terminated, and stirring was continued for 3 h at room temperature. When compound **28** was no longer detectable by TLC (solvent C), the reaction mixture was filtered through a bed of Celite and diluted with chloroform (50 mL). The organic layer was washed with cold aq sat sodium thiosulfate (3 x 20 mL), ice-water (2 x 20 mL), dried, and concentrated. The residue was purified by column chromatography (heptane gradient 35%→0% in ethyl acetate) to give methyl (2,3,4-tri-*O*-benzyl-α-D-galactopyranosyluronic acid)-(1→4)-(benzyl 2,3-di-*O*-benzyl-β-D-galactopyranosid)uronate (**34**, 178 mg) which was dissolved in chloroform (10 mL) and treated with an ethereal diazomethane solution. When the reaction was complete, indicated by a persisting yellow color of the solution, the excess diazomethane was destroyed with acetic acid. The solution was then diluted with heptane (60 mL) and chloroform (20 mL), washed with sat aq $NaHCO_3$ (2 x 50 mL) and ice-water (2 x 50 mL), dried, and concentrated to give analytically pure **35** (178 mg, 42% related to **17**): $[\alpha]_D^{24}$ +57.8° (*c* 1.0, chloroform); ^1H NMR ($CDCl_3$) δ 3.42 (s, 3H, OCH_3), 3.47 (dd, 1H, $J_{3,4}$ = 3.0 Hz, H-3), 3.58 (s, 3H, OCH_3'), 3.77 (dd, 1H, $J_{2,3}$ = 10.3 Hz, H-2), 3.97 (d, 1H, H-5), 4.08 (dd, 1H, $J_{3',4'}$ = 2.3 Hz, H-3'), 4.14 (dd, 1H, $J_{2',3'}$ = 10.3 Hz, H-2), 4.31 (m, 1H, H-5), 4.49 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 4.54 (m, 1H, H-4), 4.55-5.15 (12H, 6 x $CH_2C_6H_5$), 4.96 (d, 1H, $J_{4',5'}$ = 1.5 Hz, H-4'), 5.28 (d, 1H, $J_{1',2'}$ = 3.2 Hz, H-1'), 7.20-7.48 (m, 30H, 6 x $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 51.81, 52.22 (2 x OCH_3), 71.81, 71.57, 72.33, 72.83 (4 x $CH_2C_6H_5$), 72.89 (C-4'), 73.49 (C-5), 74.58 (C-2'), 74.93 (C-4), 74.99 (2 x $CH_2C_6H_5$), 76.51 (C-5'), 77.97 (C-2), 78.03 (C-3'), 79.96 (C-3), 99.47 (C-1'), 102.80 (C-1), 127.38-128,41, 137.46-138,70 (6 x $CH_2C_6H_5$), 168.10, 169.51 (C-6, C-6').

Anal. Calcd for $C_{56}H_{58}O_{13}$ (939.07): C, 71.63; H, 6.23. Found: C, 71.41; H, 6.28.

Methyl (methyl 2,3-di-*O*-benzyl-α-D-galactopyranosyluronate)-(1→4)-(allyl 2,3-di-*O*-benzyl-β-D-galactopyranosid)uronate (36). To a stirred suspension of **32** (210 mg, 380 μmol), **15** (129 mg, 300 μmol), and molecular sieves (4Å, 500 mg) in dry

dichloromethane (5 mL) were added *N*-iodosuccinimide (99 mg, 440 μmol) and silver trifluoromethanesulfonate (77 mg, 300 μmol) at -70 °C. The mixture was maintained at that temperature for a further 15 min, and then allowed to warm-up to 5 °C. After 1 h (TLC solvent C), the suspension was filtered through a bed of Celite, and the filtrate was diluted with heptane (60 mL) and chloroform (25 mL). The organic layer was washed with cold aq sat sodium thiosulfate (3 x 30 mL), ice-water (2 x 30 mL), dried, and concentrated. The residue was purified by column chromatography (solvent C) to give syrupy **36** (60 mg, 25%): $[\alpha]_D^{24}$ +55.6° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 1H, 4'-OH), 3.46 (dd, 1H, $J_{3,4}$ = 2.9 Hz, H-3), 3.55, 3.57 (2s, 2 x 3H, 2 x OCH_3), 3.70 (dd, 1H, $J_{2,3}$ = 10.2 Hz, H-2), 3.85 (dd, 1H, $J_{3',4'}$ = 3.6 Hz, H-3'), 3.95 (d, 1H, H-5), 4.00 (dd, 1H, $J_{2',3'}$ = 9.9 Hz, H-2'), 4.19 (m, 1H, $CH_2CH=CH_2$), 4.38 (m, 1H, H-4'), 4.41 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 4.49 (dd, 1H, $J_{4,5}$ = 1.1 Hz, H-4), 4.53 (m, 1H, $CH_2CH=CH_2$), 4.57-4.99 (m, 8H, 4 x $CH_2C_6H_5$), 4.96 (d, 1H, H-5'), 5.21 (d, 1H, $J_{1',2'}$ = 3.3 Hz, H-1'), 5.23, 5.38 (2m, 2H, $CH_2CH=CH_2$), 6.0 (m, 1H, $CH_2CH=CH_2$), 7.2-7.44 (m, 20H, 4 x $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 52.10, 52.28 (2 x OCH_3), 68.46 (C-4'), 70.60 (C-5'), 70.57, 72.42, 72.54, 72.99 (4 x $CH_2C_6H_5$), 73.54 (C-5), 74.1 (C-2'), 75.01 ($CH_2CH=CH_2$), 75.62 (C-3'), 76.99 (C-4), 77.75 (C-2), 79.85 (C-3), 99.55 (C-1'), 102.93 (C-1), 117.51 ($CH_2CH=CH_2$), 127.42, 127.52, 127.66, 127.89, 128.28, 128.35, 128.50, 137.92, 137.95, 138.38, 138.42 (4 x $CH_2C_6H_5$), 134.02 ($CH_2CH=CH_2$), 168.11, 168.44 (C-6, C-6').

Anal. Calcd for $C_{45}H_{50}O_{13}$ (798.88): C, 67.66; H 6.31. Found: C, 67.53; H, 6.28.

Methyl (methyl 4-*O*-acetyl-2,3-di-*O*-benzyl-α-D-galactopyranosyluronate)-(1→4)-(allyl 2,3-di-*O*-benzyl-β-D-galactopyranosid)uronate (37). Compound **36** (60 mg, 75 mmol) was dissolved in a mixture of dry pyridine (1.6 mL) and acetic anhydride (950 μL) and kept for 24 h at ambient temperature (TLC solvent C). The mixture was then diluted with heptane (50 mL) and chloroform (25 mL), the organic layer was washed with cold aq 1% hydrochloric acid (30 mL), ice-water (2 x 30 mL), cold aq sat $NaHCO_3$ (2 x 30 mL), ice-water (30 mL), dried and concentrated to give analytically pure **37** (62 mg, 98%): $[\alpha]_D^{24}$ +63.1° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 3H, $OCOCH_3$), 3.44 (dd, 1H, $J_{3,4}$ = 3.1 Hz, H-3), 3.47, 3.52 (2s, 2 x 3H, 2 x OCH_3), 3.67 (dd, 1H, $J_{2,3}$ = 9.9 Hz, H-2), 3.80 (dd, 1H, $J_{2',3'}$ = 10.1 Hz, H-2'), 3.93 (s, 1H, H-5), 4.03 (dd, 1H, $J_{3',4'}$ = 3.3 Hz, H-3'), 4.17 (m, 1H, $CH_2CH=CH_2$), 4.39 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.45 (m, 1H,

H-4), 4.46-4.98 (m, 9H, $CH_2CH=CH_2$, 4 x $CH_2C_6H_5$), 5.03 (d, 1H, H-5'), 5.19 (d, 1H, $J_{1',2'}$ = 3.3 Hz, H-1'), 5.22, 5.36 (2m, 2H, $CH_2CH=CH_2$), 5.77 (dd, 1H, $J_{4',5'}$ = 1.6 Hz, H-4'), 5.99 (m, 1H, $CH_2CH=CH_2$), 7.21-7.40 (m, 20H, 4 x $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 20.65 ($OCOCH_3$), 52.08, 52.25 (2 x OCH_3), 68.90 (C-4'), 69.71 (C-5'), 70.53, 71.92, 72.54, 72.97 (4 x $CH_2C_6H_5$), 73.55 (C-5), 73.96 (C-2'), 74.93 ($CH_2CH=CH_2$), 75.71 (C-3'), 75.95 (C-4), 77.62 (C-2), 79.64 (C-3), 99.99 (C-1'), 102.89 (C-1), 117.45 ($CH_2CH=CH_2$), 127.38, 127.44, 127.54, 127.67, 127.92, 128.05, 128.12, 128.25, 128.30, 128.36, 137.84, 137.99, 138.30, 138.48 (4 x $CH_2C_6H_5$), 133.98 ($CH_2CH=CH_2$), 168.06, 168.50 (C-6, C-6'), 169.84 ($OCOCH_3$).

Anal. Calcd for $C_{47}H_{52}O_{14}$ (840.92): C, 67.13; H, 6.23. Found: C, 66.89; H, 6.05.

Methyl (methyl 2,3-di-*O*-benzyl-4-*O*-*p*-methoxybenzyl-α-D-galactopyranosyluronate)-(1→4)-(allyl 2,3-di-*O*-benzyl-β-D-galactopyranosid)uronate (38). To a solution of **32** (230 mg, 420 μmol) and **15** (150 mg, 350 μmol) in dry dichloromethane (1.5 mL) and dry diethyl ether (7.5 mL) were added molecular sieves (4Å, 500 mg), and the suspension was stirred for 20 min at 0 °C. After adding of iodonium di-*sym*-collidine perchlorate (355 mg, 750 μmol), the suspension was stirred for 40 min at 0 °C, and then for 3 h at room temperature (TLC solvent C). Removal of molecular sieves gave a red-brown filtrate which was diluted with heptane (60 mL) and chloroform (30 mL). The organic layer was washed with cold aq sat sodium thiosulfate/$NaHCO_3$ (1:1 v/v, 3 x 30 mL, until the organic layer is colorless), ice-water (30 mL), cold aq 1% hydrochloric acid (2 x 30 mL), ice-water (30 mL), cold aq sat $NaHCO_3$ (3 x 30 mL), ice-water (2 x 30 mL), dried, and concentrated. The residue was purified by column chromatography (solvent C) to give syrupy **38** (205 mg, 64%): $[\alpha]_D^{24}$ +66.3° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 3.40, 3.53 (2s, 6H, 2 x OCH_3), 3.44 (dd, 1H, $J_{3,4}$ = 3.1 Hz, H-3), 3.70 (dd, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 3.77 (s, 3H, $H_3COC_6H_4CH_2$), 3.94 (d, 1H, H-5), 4.03 (dd, 1H, $J_{3',4'}$ = 2.5 Hz, H-3'), 4.09 (dd, 1H, $J_{2',3'}$ = 10.4 Hz, H-2'), 4.20 (m, 1H, $CH_2CH=CH_2$), 4.27 (m, 1H, H-4'), 4.41 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 4.49 (m, 1H, H-4), 4.53 (m, 1H, $CH_2CH=CH_2$), 4.53-4.97 (10H, 4 x $CH_2C_6H_5$, $H_3COC_6H_4CH_2$), 4.92 (m, 1H, H-5'), 5.23 (d, 1H, $J_{1',2'}$ = 3.1 Hz, H-1'), 5.23, 5.37 (2m, 2H, $CH_2CH=CH_2$), 6.0 (m, 1H, $CH_2CH=CH_2$), 6.78, 7.12, 7.21-7.42 (3m, 24H, 4 x $CH_2C_6H_5$, $H_3COC_6H_4CH_2$); ^{13}C NMR ($CDCl_3$) δ 51.82, 52.23 (2 x OCH_3), 55.27 ($H_3COC_6H_4CH_2$), 70.55, 72.36, 72.81, 72.96, 74.17, 75.08 (4 x

$CH_2C_6H_5$, $H_3COC_6H_4CH_2$, $CH_2CH{=}CH_2$), 71.36 (C-5'), 73.54 (C-5), 74.87 (C-2'), 75.22 (C-4), 76.07 (C-4'), 77.97 (C-2), 78.14 (C-3'), 79.90 (C-3), 99.62 (C-1'), 102.91 (C-1), 117.45 ($CH_2CH{=}CH_2$), 113.51, 127.36-130.77, 138.04-138.69, 159.07 (4 x $CH_2C_6H_5$, $H_3COC_6H_4CH_2$), 134.09 ($CH_2CH{=}CH_2$), 168.10, 169.56 (C-6, C-6').

Anal. Calcd for $C_{53}H_{58}O_{14}$ (919.04): C, 69.27; H, 6.36. Found: C, 68.98; H, 6.20.

Removal of the *p*-methoxybenzyl group from 38. To a solution of **38** (195 mg, 212 μmol) in dichloromethane-water (20:1 v/v, 5 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (53 mg, 233 μmol) and the mixture was stirred for 4 h at room temperature (TLC solvent C). The reaction mixture was then diluted with heptane (50 mL) and chloroform (20 mL) and washed with cold aq sat sodium thiosulfate/$NaHCO_3$ (1:1 v/v, 3 x 30 mL) until the organic layer was colorless. After washing with water, drying and concentration, the obtained residue was purified by column chromatography (sovent B) to give **36** (150 mg, 88%). The physical parameters of **36**, prepared via **38**, were fully consistent with those obtained by glycosylation of **15** with **32** under *N*-iodosuccinimide-silver trifluoromethanesulfonate promotion.

Methyl (methyl 2,3-di-*O*-benzyl-4-*O*-*p*-methoxybenzyl-α-D-galactopyranosyluronate)-(1→4)-(methyl 2,3-di-*O*-benzyl-α-D-galactopyranosyluronate)-(1→4)-(allyl 2,3-di-*O*-benzyl-β-D-galactopyranosid)uronate (39). To a solution of **32** (220 mg, 395 μmol) and **36** (263 mg, 330 μmol) in dry dichloromethane (3 mL) and dry diethyl ether (15 mL) were added molecular sieves (4Å, 500 mg), and the suspension was stirred for 20 min at 0 °C. Then, iodonium di-*sym*-collidine perchlorate (280 mg, 595 μmol) was added and the suspension was stirred for 1 h at that temperature. After stirring for 2.5 h at room temperature (TLC solvent C), a further portion of **32** (75 mg, 130 μmol) and iodonium di-*sym*-collidine perchlorate (60 mg, 130 μmol) were added. After 3.5 h, this addition was repeated. After 4 h, the reaction mixture was worked-up exactly as described for the preparation of **38**. Purification by HPLC (solvent C) gave **39** (175 mg, 48%) as a colorless foam: $[\alpha]_D^{25}$ +66.0° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 3.30, 3.32, 3.67 (3 s, 9H, 3 x OCH_3), 3.40 (dd, 1H, $J_{3,4}$ = 2.9 Hz, H-3), 3.63 (dd, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 3.74 (dd, 1H, $J_{3'',4''}$ = 2.7 Hz, H-3''), 3.76 (s, 3H, $H_3COC_6H_4CH_2$), 3.89 (dd, 1H, $J_{2',3'}$ = 10.4 Hz, H-2'), 3.92 (d, 1H, H-5), 3.94 (dd, 1H, $J_{3',4'}$ = 2.2 Hz, H-3'), 3.99 (dd, 1H, $J_{2'',3''}$ = 10.3 Hz, H-2''), 4.17 (m, 1H, $CH_2CH{=}CH_2$), 4.19 (m, 1H, H-4''), 4.37 (d, 1H, $J_{1,2}$ =

7.6 Hz, H-1), 4.47 (m, 1H, H-4'), 4.51 (m, 1H, H-4''), 4.53 (m, 1H, $CH_2CH=CH_2$), 4.40-4.93 (14H, 6 x $CH_2C_6H_5$, $H_3COC_6H_4CH_2$, $CH_2CH=CH_2$), 4.71 (m, 1H, H-5'), 4.84 (m, 1H, H-5''), 5.04 (d, 1H, $J_{1'',2''}$ = 3.3 Hz, H-1''), 5.21 (d, 1H, $J_{1',2'}$ = 3.0 Hz, H-1'), 5.22, 5.35 (2 x m, 2H, $CH_2CH=CH_2$), 5.98 (m, 1H, $CH_2CH=CH_2$), 6.76, 7.07, 7.17-7.45 (3 x m, 34H, 6 x $CH_2C_6H_5$, $H_3COC_6H_4CH_2$); ^{13}C NMR ($CDCl_3$) δ 51.68, 52.27 (3 x OCH_3), 55.18 ($H_3COC_6H_4CH_2$), 70.45, 72.15, 72.28, 72.86, 73.18, 74.07, 74.88 (6 x $CH_2C_6H_5$, $H_3COC_6H_4CH_2$, $CH_2CH=CH_2$), 70.96 (C-5''), 71.65 (C-5'), 72.71 (C-2'), 73.43 (C-5), 74.24 (C-2''), 74.76 (C-4), 76.11 (C-4''), 76.50 (C-4'), 76.77 (C-3'), 77.65 (C-2), 78.64 (C-3''), 79.19 (C-3), 98.97 (C-1'), 99.44 (C-1''), 102.83 (C-1), 117.34 ($CH_2CH=CH_2$), 113.39, 127.17-130.72, 137.94-158.93 (6 x $CH_2C_6H_5$, $H_3COC_6H_4CH_2$), 133.99 ($CH_2CH=CH_2$), 168.11, 168.78, 169.34 (C-6, C-6', C-6'').

Anal. Cald for $C_{60}H_{80}O_{20}$ (1121.28): C, 64.27; H, 7.19. Found: C, 64.16; H, 7.13.

The β(1''→4')-coupled Isomer: ^{1}H NMR ($CDCl_3$) δ 4.39 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 5.26 (d, 1H, $J_{1',2'}$ = 3.0 Hz, H-1'), 4.69 (d, 1H, $J_{1'',2''}$= 7.6 Hz, H-1''); ^{13}C NMR ($CDCl_3$) δ 99.86 (C-1'), 102.05, 102.88 (C-1, C-1'').

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