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# Scope and limitation of the application of the (methoxydimethyl)methyl group in the synthesis of 2′-*O*-, 6′-*O*- and 2′,6′-di-*O*-(α-L-arabinofuranosyl)-β-D-galactopyranosyl-(1→6)-D-galactoses☆

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**Abstract**

For the characterisation of the anticipated epitope of an arabinogalactan, isolated from the extract of *Echinacea purpurea*, the trisaccharide α-L-Ara*f*-(1→2)-β-D-Gal*p*-(1→6)-D-Gal was synthesized. The easily available 3,4-*O*-isopropylidene-6-*O*-(methoxydimethyl)methyl-β-D-galactopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose having the OH-2′ free served as aglycone upon direct arabinosylation at the 2′ position under Helferich conditions. The formed $HgBr_2$ cleaved the acid sensitive protecting group at position 6′, but under basic conditions the desired, fully protected trisaccharide, or its symmetrical dimerization derivative linked 6′- to 6′-position via an isopropylidene bridge, could be obtained. An alternative route involved arabinosylation of a hepta-O-acetylated digalactose with free OH-2′. Two other oligosaccharides, namely, α-L-Ara*f*-(1→6)-β-D-Gal*p*-(1→6)-D-Gal and (α-L-Ara*f*)$_2$-(1→2,6)-β-D-Gal*p*-(1→6)-D-Gal were also synthesized and characterised. 

*Keywords:* *Echinacea purpurea*; Arabinogalactans; (Methoxydimethyl)methyl ethers; Oligosaccharides; Dimerization

## 1. Introduction

The medical use of the extracts of *Echinacea purpurea* is long known and the polysaccharide components of these extracts have been systematically investigated by Wagner et al. [1–3]. As a result of these studies, the polysaccharides of *Echinacea purpurea* are produced in industrial scale by cell cultures [4,5]. These polysaccharides are 4-*O*-methylglucuronoarabinoxylans [3] and arabinorhamnogalactans [3]. Most recently an arabinogalactan fraction possessing promising biological activity was isolated [6] (Scheme 1). Structure elucidation suggested that all third or fourth galactose units of the β-(1→6)-linked galactan skeleton contain either an α-L-arabinofuranosyl or an α-L-arabinofuranosyl-(1→5)-α-L-arabinofuranosyl side chain. The presence of a rather similar structural unit is supposed by Albersheim et al. [7] in the polysaccharide isolated from suspension-cultured sycamore maple (*Acer pseudoplatanus*). Three different tetrasaccharide derivatives were synthesized most recently by van Boom et al. [8] for the

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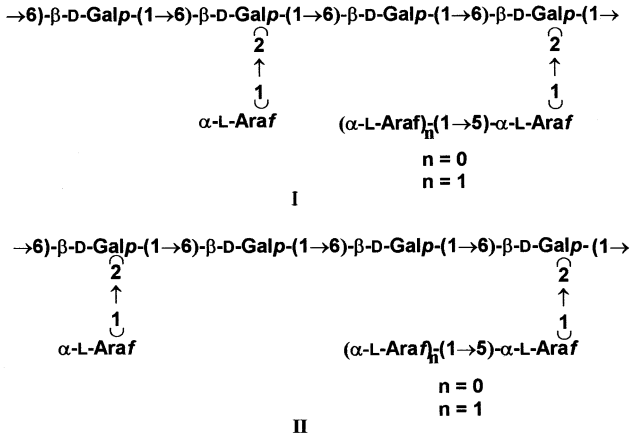


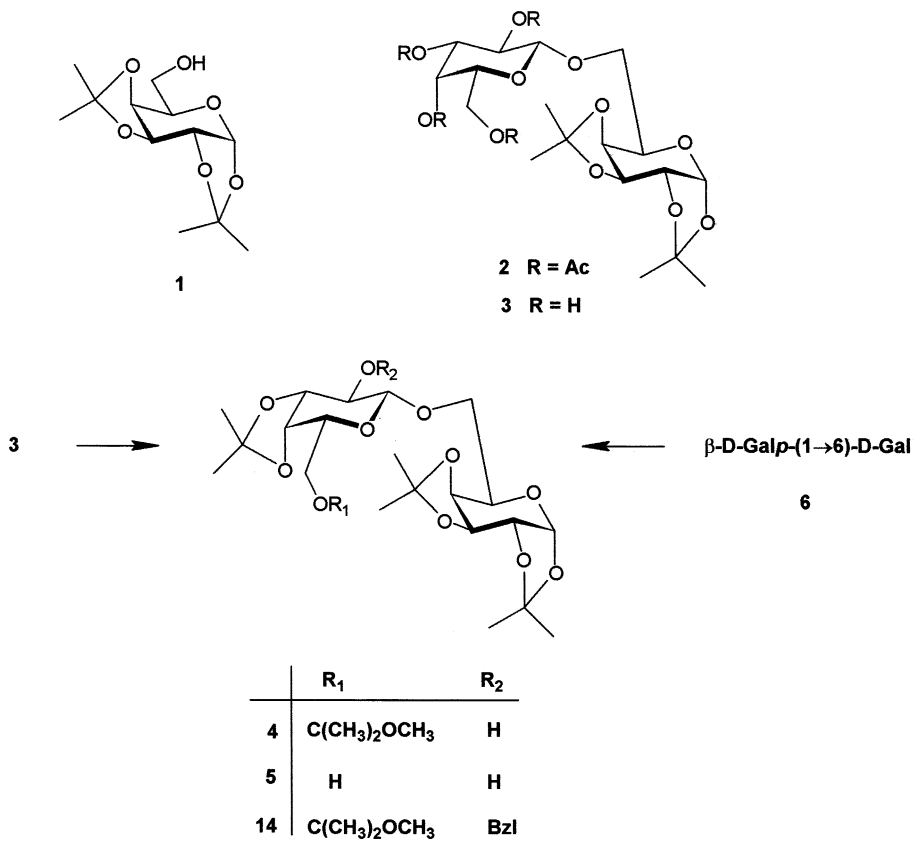

Scheme 1. Suggested structure of the arabinogalactane fraction isolated from *Echinacea purpurea*.

characterisation of several monoclonal antibodies elucidated by the epitopes of polysaccharides isolated from *Acer pseudoplatanus*.

## 2. Results and discussion

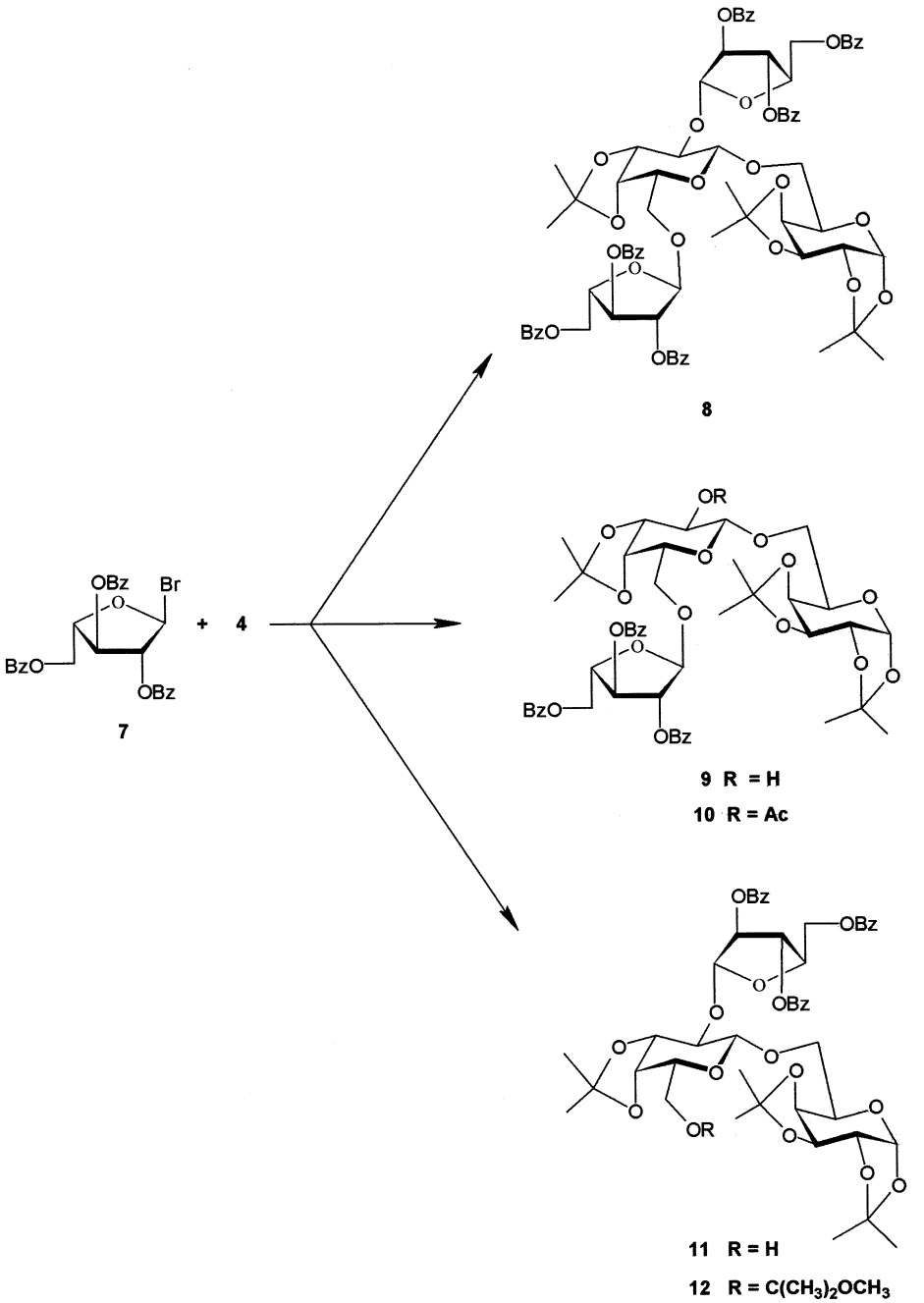
The aim of the present synthetic work was to establish a method for the preparation of well-defined parts of the next two structural units and employ these oligosaccharides to raise monoclonal antibodies. These antibodies might be suitable tools for structure elucidation of plant polysaccharides [9]. To the best of our knowledge there are only four examples in the literature [8,10–12] for the preparation of non-symmetrically 2,6-di-*O*-glycosylated β-D-galactopyranosyl derivatives. Now we report our first results obtained with some oligosaccharides having the desired minimal structural unit.

We were the first to report [13] that the reaction of alkyl β-D-galactopyranosides with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid resulted in alkyl 3,4-*O*-isopropylidene-6-*O*-(methoxydimethyl)methyl-β-D-galactopyranosides. Other authors [14–16] succesfully used this procedure for the preparation of different galactopyranoside derivatives having a free OH-2 group, and abbreviated the (methoxydimethyl)methyl group as MIP (2-methoxyisopropyl).




| | $R_1$ | $R_2$ |
|---|---|---|
| 4 | $C(CH_3)_2OCH_3$ | H |
| 5 | H | H |
| 14 | $C(CH_3)_2OCH_3$ | Bzl |

Scheme 2. Synthesis of the 6-*O*-(methoxydimethyl)methyl containing disaccharide building blocks.




Scheme 3. Arabinosylation of the 6-*O*-(methoxydimethyl)methyl containing digalactose-type aglycon under Helferich conditions.

In the knowledge of this reaction, our strategy was to galactosylate a galactopyranos(e)yl unit having free OH-6, and after deprotection of the second galactosyl unit and treatment with 2,2-dimethoxypropane, a partially protected digalactose having the OH-2′ free was expected to be obtained. This should be amenable to direct arabinosylation.

Based on the above considerations, 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose [17] (**1**) was glycosylated with α-acetobromo-D-galactose under Helferich conditions (Schemes 2 and 3) and the known 6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose [18] (**2**) was obtained. Compound **2** was deacetylated to give 6-*O*-(β-D-galactopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose [19] (**3**), and this disaccharide was treated with 50 equivalents of neat 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid. A nearly quantitative reaction yielded 6-*O*-(3,4-

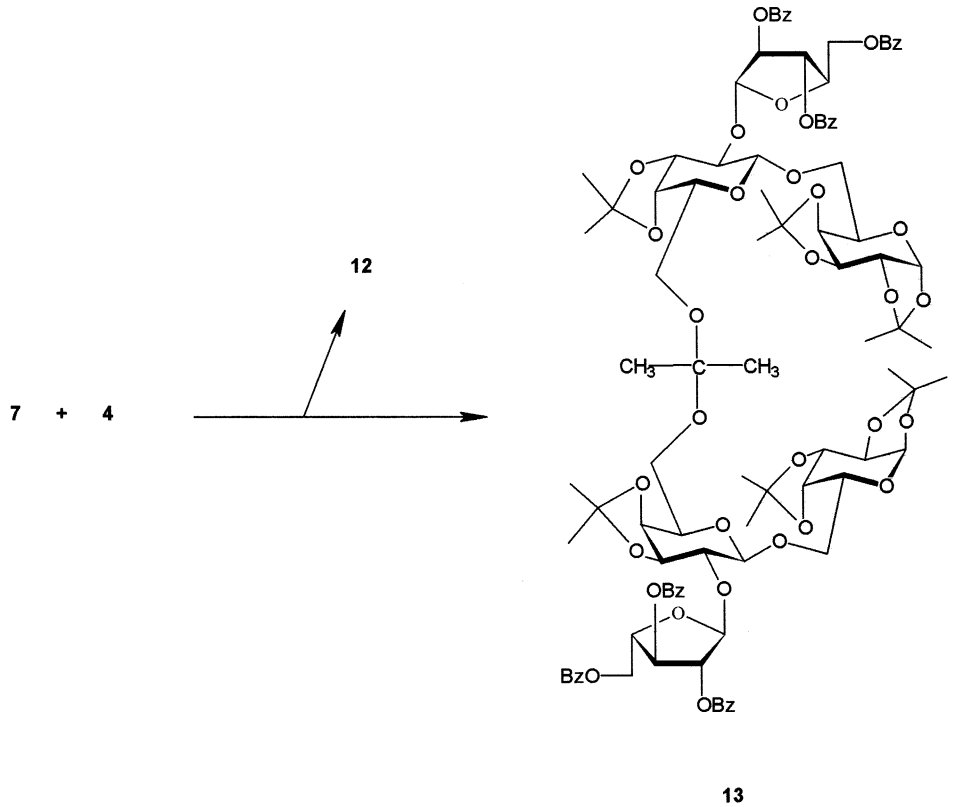
*O*-isopropylidene-6-*O*-(methoxydimethyl)-methyl-β-D-galactopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**4**). Compound **5** with 6′-OH free was formed only as a side product.

The direct treatment of β-D-galactopyranosyl-(1→6)-D-galactose (**6**) with 2,2-dimethoxypropane also resulted in compound **4**. The MIP derivatives show very easily characterisable $^1$H and $^{13}$C NMR signals: in compound **4** there were eight C-methyl signals in the $^1$H NMR spectrum between 1.50 and 1.30 ppm; the $OCH_3$ group resonated at 3.12 ppm. In the $^{13}$C NMR spectrum the quaternary acetal carbon of the (methoxydimethyl)methyl group resonated at 100.1 ppm, the C-6 showed a rather strong upfield shift at 60.26 ppm, and the $OCH_3$ signal appeared at 48.53 ppm. These signals also helped the structure elucidation of other, more complex oligosaccharide derivatives.

To synthesize the trisaccharide repeating unit of structure **I**, compound **4** seemed to be a good candidate as the aglycone. Arabinosylation of **4** with 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranosyl bromide [20] (**7**) using $Hg(CN)_2$ as promoter resulted in three chromatographically well-separable substances, but, unfortunately, none of them contained the MIP group. The fully protected compound proved to be 6-*O*-[2,6-di-*O*-(2,3,5-tri-*O*-benzoyl-α-L-arabinofuranosyl)-3,4-*O*-isopropylidene-β-D-galactopyranosyl-]-1,2:3,-4-di-*O*-isopropylidene-α-D-galactopyranose (**8**). The presence of three quaternary acetalic signals (110.24, 108.99 and 108.21 ppm), the four anomeric carbon signals (105.67, 103.73, 101.19 and 95.94 ppm), the absence of the MIP group and the glycosylation shift at the carbon C-6′ verified the structure of compound **8**. The second product in the reaction mixture proved to be the trisaccharide **9**. The three anomeric carbon signals resonated at 105.60, 103.36 and 96.14 ppm, the C-6′ was glycosylated (C-6′: 65.72 ppm), and three dioxolane-type isopropylidene groups were present (109.89, 109.35 and 108.64 ppm). Acetylation of **9** gave the monoacetyl derivative (**10**) and one proton triplet was shifted to the lower field. The acetylated OH group was assigned as OH-2′, having the triplet at 5.08 ppm, and 8.5 Hz coupling constants assignable to $J_{1',2'}$ and $J_{2',3'}$. The third (minor) component was also a trisaccharide (**11**), in which C-6′ (62.38 ppm) was free, three acetal rings were present (109.98, 109.46 and 108.74 ppm), and an arabinofuranosyl unit was anchored at C-2′. This compound was the planned trisaccharide, although without the terminal MIP substitutent: 6-*O*-[2-*O*-(2,3,-5-tri-*O*-benzoyl-α-L-arabinofuranosyl)-3,4-*O*-isopropylidene-β-D-galactopyranosyl]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**11**).

In the knowledge of the extreme acid-sensitive properties of the MIP derivatives, the formation of the above oligosaccharides (**8, 9** and **11**) can be easily explained. In the initial stage of the glycosylation reaction the OH-2′ is the only nucleophilic partner and the MIP-containing **12** (vide infra) was produced. During this reaction mercury bromide was also formed and this rather strong Lewis acid hydrolysed the acid-sensitive MIP blocking group. Then, reaction of the more nucleophilic OH-6′ resulted in the trisaccharide derivative **9**, and the excess of the glycosyl donor glycosylated it to the tetrasaccharide main product **8**. The small amount of compound **11** formed from its 6-OMIP derivative (**12**), which did not lose its MIP during the coupling reaction, but was cleaved during the work-up procedure. Similar reaction mixtures were obtained by using $Ag_2O$ or $Ag_2CO_3$ promoters.

To avoid the cleavage of the MIP group we executed the glycosylation reaction promoted by AgOTf in the presence of *sym*-collidine (2,4,6-trimethylpyridine), hoping that this strong base can prevent the hydrolysis of the acid-sensitive mixed acetalic protecting group. The reaction proceeded with an acceptable rate and two products (**12** and **13**) were formed. It was also observed that the chromatographically faster-moving component (**12**) was transformed into the slower-moving one (**13**). Although the two products showed very similar chromatographic mobility, their separation could be achieved rather easily. The $^1$H and $^{13}$C NMR spectra of the faster-moving component showed the presence of the MIP group ($\delta$: 3.2 ppm, $OCH_3$, 24 H was integrated between $\delta$: 1.18–1.62 ppm), and three benzoyl moieties were also present. The $^{13}$C NMR spectrum was more informative;




Scheme 4. Arabinosylation of the 6-*O*-(methoxydimethyl)methyl containing digalactose-type aglycon under basic conditions.

three dioxolane-type acetalic carbon signals could be assigned ($\delta$: 110.15, 109.06 and 108.31), the three anomeric carbon atoms resonated at 103.82, 101.28 and 96.04 ppm, and the quaternary acetalic carbon atom of the MIP appeared at 100.10 ppm. The O-6′ contained the -*O*-$C(CH_3)_2$-$OCH_3$ group, an upfield shift of $\sim 2$ ppm could be detected ($\delta$: 60.08 ppm) and the $OCH_3$ group resonated at 48.49 ppm. Mild acid hydrolysis of the MIP group in compound **12** resulted in **11** in a quantitative yield.

The $^1H$ and $^{13}C$ NMR spectra of the second, slower-moving compound (**13**) showed a trisaccharide character. The spectra did not contain $OCH_3$ signal(s), but there was a quaternary carbon signal at 100.5 ppm which could be an acetalic carbon resonance. The C-6′ also appeared at high field ($\delta$: 60.18 ppm), and there were 21 hydrogens in the methyl-proton region. These spectral data suggested a symmetrical isopropylidene acetal structure in which the alcoholic components were the two trisaccharide molecules; its composition can be depicted by structure **13**. Formation of symmetrical dimerization products of monosaccharides having similar structure to **13** was reported by Barresi and Hindsgaul [21] in a publication dealing with synthesis of β-mannopyranosides by intramolecular aglycone delivery. The assumed structure of **13** was verified by MALDI-TOF MS measurement giving $m/z$: 1853.9. In the spectrum of compound **13** two additional fragments appeared with $m/z$: 906.5 and 946.5; the first could be assigned to **11** and the second to the 6-*O*-isopropenyl ether of **11**. The symmetrical acetalic bond in compound **13** is more stable than the bonds of the mixed acetals (MIP) but more sensitive than the cyclic dioxolane-type isopropylidene acetals. Mild acid hydrolysis of **13** resulted in **11** with a quantitative yield. Compound **11** can be a choice as the aglycone for additional glycosylation, or even an aglycone for dimerisation into the hexasaccharide **I**.

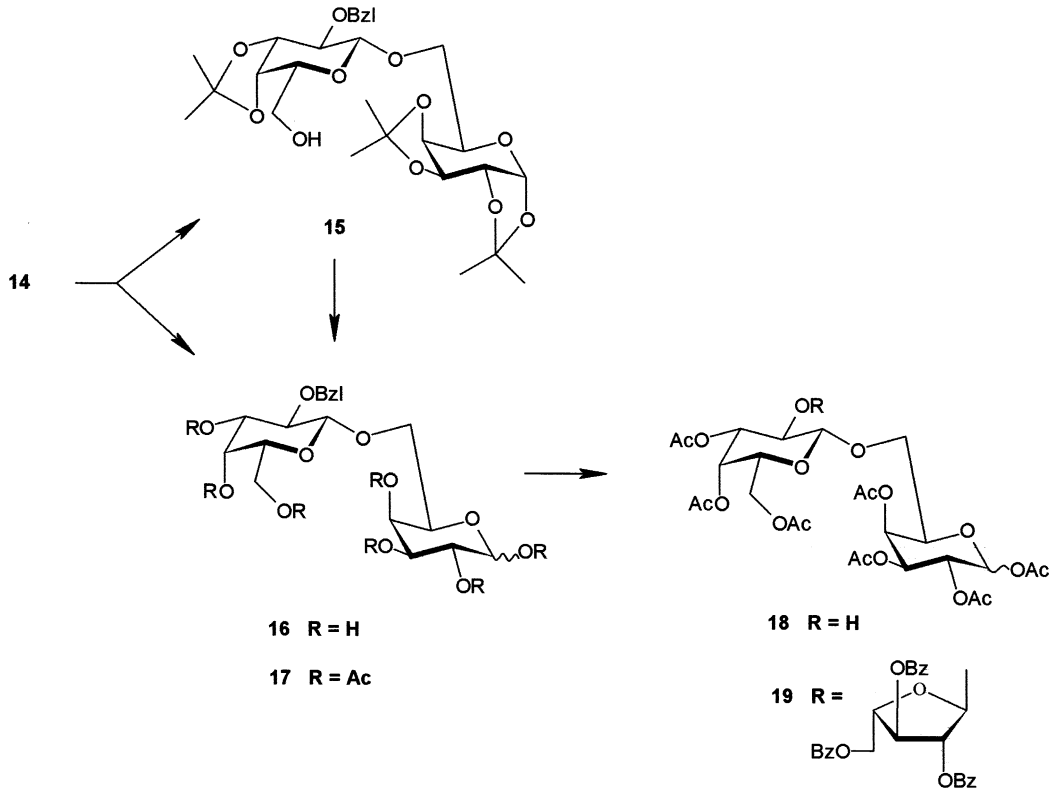
These results demonstrate that the easily available MIP derivatives can serve as aglycones in glycosylation reactions, but basic or neutral conditions are required for the coupling reactions and also for the work-up procedure.

It is known that the MIP derivatives can be successfully etherified under basic conditions [15] (Scheme 4). Benzylation of compound **4** gave the fully protected crystalline disaccharide

Table 1
$^{13}C$ NMR data for protected oligosaccharides

| | **2** | **3** | **4** | **5** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C-1 | 96.60 | 96.14 | 96.27 | 96.23 | 95.94 | 96.14 | 96.08 | 96.13 | 96.04 | 96.02 | 96.33 | 96.28 |
| C-2 | 71.06 | 70.99 | 70.73 | 70.62 | 70.64 | 70.57 | 70.49 | 70.72 | 70.77 | 70.64 | 70.69 | 70.34 |
| C-3 | 71.23 | 71.07 | 71.17 | 70.99 | 71.54 | 71.03 | 71.17 | 71.42 | 71.69 | 71.18 | 71.92 | 70.23 |
| C-4 | 70.84 | 70.31 | 70.39 | 70.33 | 69.73 | 70.26 | 70.40 | 70.19 | 69.84 | 70.40 | 70.39 | 69.30 |
| C-5 | 67.48 | 67.57 | 67.73 | 67.55 | 67.13 | 67.79 | 67.86 | 67.02 | 67.18 | 67.18 | 67.24 | 67.06 |
| C-6 | 70.03 | 68.92 | 68.72 | 68.72 | 69.41 | 69.09 | 69.34 | 68.94 | 69.19 | 69.22 | 69.12 | 68.79 |
| $C_{quat}$ | 109.80 | 109.32 | 109.90 | 110.20 | 110.24 | 109.89 | 110.28 | 109.98 | 110.15 | 110.10 | 109.60 | 109.88 |
| | 109.07 | 108.07 | 108.77 | 108.73 | 108.21 | 108.64 | 108.55 | 108.74 | 108.31 | 108.26 | 108.48 | 108.41 |
| C-1′ | 102.41 | 103.84 | 103.34 | 103.10 | 101.19 | 103.36 | 101.14 | 101.20 | 101.28 | 101.25 | 103.66 | 103.31 |
| C-2′ | 71.34 | 71.07 | 73.28 | 73.55 | 79.75 | 77.00 | 76.74 | 79.88 | 79.74 | 76.76 | 78.75 | 78.57 |
| C-3′ | 71.23 | 73.24 | 78.73 | 79.05 | 77.90 | 78.67 | 73.35 | 74.86 | 77.69 | 74.86 | 78.64 | 78.94 |
| C-4′ | 67.48 | 68.38 | 73.60 | 73.72 | 74.61 | 73.16 | 72.62 | 73.98 | 74.86 | 73.64 | 73.63 | 73.74 |
| C-5′ | 71.69 | 74.41 | 72.61 | 73.32 | 73.32 | 71.93 | 71.47 | 73.18 | 73.66 | 71.90 | 71.92 | 72.98 |
| C-6′ | 61.60 | 60.91 | 60.26 | 62.20 | 65.74 | 65.72 | 65.40 | 62.38 | 60.07 | 60.18 | 60.15 | 62.09 |
| $C'_{quat}$ | | | 109.48 | 109.44 | 108.99 | 109.35 | 109.22 | 109.46 | 109.06 | 109.03 | 109.26 | 109.22 |
| $\mathbf{C}OCH_3$ | | | 100.10 | | | | | | 100.10 | 100.50 [a] | 100.02 | |
| $OCH_3$ | | | 48.53 | | | | | | 48.49 | | 48.48 | |
| C-1″ | | | | | 105.67 | 105.60 | 105.55 | 103.90 | 103.82 | 103.82 | | |
| | | | | | 103.73 | | | | | | | |
| C-2″ | | | | | 80.97 80.34 | 80.89 | 80.96 | 80.65 | 80.44 | 80.45 | | |
| C-3″ | | | | | 77.68 77.60 | 77.91 | 77.92 | 77.68 | 77.69 | 77.66 | | |
| C-4″ | | | | | 82.78 82.50 | 82.08 | 82.11 | 82.15 | 83.30 | 82.26 | | |
| C-5″ | | | | | 63.62 64.13 | 63.57 | 63.60 | 64.08 | 64.18 | 64.16 | | |

[a] Signal of the bridge carbon atom of $-OC(CH_3)O-$

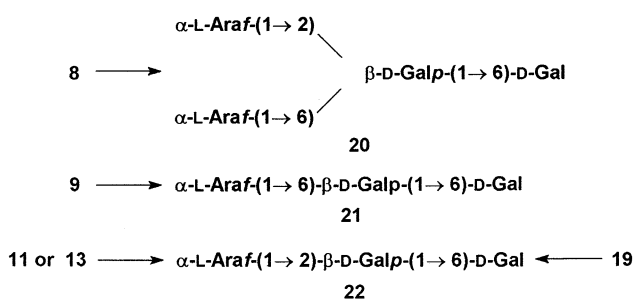



Scheme 5. Alternative route for the synthesis of the target trisaccharide.

**14** (Scheme 2). Selective hydrolysis of the MIP fgroup resulted in the crystalline 6-*O*-(2-*O* - benzyl - 3,4 - *O* - isopropylidene - β - D - galactopyranosyl) - 1,2:3,4 - di - *O* - isopropylidene-α-D-galactopyranose (**15**). Complete hydrolysis of the isopropylidene acetals either of **14** or **15** gave 6-*O*-(2-*O*-benzyl-β-D-galactopyranosyl)-D-galactose (**16**). Acetylation of **16** afforded the peracetylated derivative (**17**) from which, after hydrogenolysis, 6-*O*-(3,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-1,2,3,4-tetra-*O*-acetyl-α,β-D-galactopyranose (**18**) was obtained. Compound **18** could be arabinosylated with **7** and the persubstituted trisaccharide **19** was isolated.

For the removal of the isopropylidene groups of the oligosaccharides **8**, **9**, **11** and **13** aqueous 90% trifluoroacetic acid was used. The acyl groups were removed by Zemplén transesterification to furnish the tetrasaccharide **20** from compound **8** and the trisaccharide **21** from the protected **9**. The target trisaccharide **22** was obtained from three different protected intermediates: **11**, **13** and **19** (Scheme 5).

Detailed two-dimensional (2D) $^{1}H$ and $^{13}C$ NMR studies resulted in the pertinent spectral assignments. The $^{13}C$ NMR data of the protected derivatives are collected in Table 1. Similar measurements were done in the case of the free oligosaccharides, too. These trisaccharides, in aqueous solutions, occur as mixture of two anomers, but in the case of the branched tetrasaccharide **20**, the reducing D-galactose unit existed in four isomeric forms (α-, β-pyranose and α-, and β-furanose forms) and in the equilibrium mixture the quadruplication of some individual carbon-13 signals could be detected. Similar spectral behaviours have been reported earlier from our laboratory [22,23] (Scheme 6).




Scheme 6. Synthesis of the deprotected sugars.

## 3. Experimental

*General methods.*—Optical rotations were measured at room temperature with a Perkin–Elmer 241 automatic polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected. TLC was performed on Kieselgel 60 $F_{254}$ (E. Merck) with detection by charring with 50% of aqueous sulfuric acid. Column chromatography was performed on Silica Gel 60 (E. Merck 0.063–0.200 mm). The organic solution was dried over $MgSO_4$, and concentrated in a vacuum. The $^1H$ (200, 360 and 500 MHz) and $^{13}C$ NMR (50.3, 90.54, 125.76 MHz) spectra were recorded with Bruker WP-200 SY, Bruker AM-360 and Bruker DRX-500 spectrometers in $CDCl_3$ solutions. Internal references: TMS (0.000 ppm for $^1H$), $CDCl_3$ (77.00 ppm for $^{13}C$).

*2,3,4,6-Tetra-*O*-acetyl-β-*D*-galactopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose* (**2**).—Powdered $Hg(CN)_2$ (16.4 g, 0.065 mol) and 4 Å molecular sieves (10 g) were added to a solution of **1** (13.0 g, 0.050 mol) in 120 mL of dry $CH_3CN$, and the mixture was stirred overnight. To the mixture was added 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (24.6 g, 0.060 mol) in five portions. After 2 h the reaction was complete (TLC, 23:2 $CH_2Cl_2$–acetone, $R_f$ 0.5). The mixture was diluted with 500 mL of $CH_2Cl_2$, the inorganic salts were filtered off, and the filtrate was concentrated in vacuo. The residue was dissolved in 1000 mL of $CH_2Cl_2$, the inorganic salts were filtered off again, the filtrate was washed with aq 5% KI solution (4 × 250 mL), and water (2 × 250 mL). The organic layer was dried and evaporated. The syrupy residue was purified by column chromatography ($CH_2Cl_2$–acetone, 96:4→92:8) to yield **2** (19.0 g, 64.4%): $[\alpha]_D^{22}$ −44.2° (*c* 1.0, $CHCl_3$) lit. −44° [18]; $^1H$ NMR (500 MHz, $CDCl_3$): δ 5.51 (d, 1 H, H-1, $J_{1,2}$ 4.9 Hz), 5.39 (dd, 1 H, H-4′, $J_{3',4'}$ 3.4 Hz, $J_{4',5'}$ 1.0 Hz), 5.22 (dd, 1 H, H-2′, $J_{1',2'}$ 7.9 Hz, $J_{2',3'}$ 10.5 Hz), 5.03 (dd, 1 H, H-3′), 4.59 (2 d, 2 H, H-1′, H-3, $J_{3,4}$ 8.0 Hz), 4.30 (dd, 1 H, H-2, $J_{2,3}$ 2.5 Hz), 4.16 (m, 3 H, H-5′, H-6′a,b, $J_{gem}$ 11.1 Hz), 4.04 (dd, 1 H, H-6a, $J_{5,6a}$ 3.2 Hz, $J_{gem}$ 11.5 Hz), 3.95–3.85 (m, 2 H, H-4, H-5), 3.69 (dd, 1 H, H-6b, $J_{5,6b}$ 7.6 Hz), 2.15–1.95 (4 s, each 3 H, 4 $CH_{3acetyl}$), 1.55–1.30 (4s, each 3 H, 4 $CH_{3ip}$). Anal. Calcd for $C_{26}H_{38}O_{15}$ (590.57): C, 52.87; H, 6.48. Found: C, 52.90; H, 6.51.

*β-*D*-Galactopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose* (**3**).—To a stirred solution of **2** (16.5 g, 0.028 mol) in 200 mL of dry MeOH NaOMe (100 mg) was added (pH ~8). After 2.5 h the TLC (85:15 $CH_2Cl_2$–MeOH, $R_f$ 0.5) showed complete conversion. The solution was neutralized with Amberlite IR-120 $H^+$ ion-exchange resin, filtered and evaporated to yield **3** as a white foam (11.7 g, 98.8%): $[\alpha]_D^{22}$ −63.1° (*c* 1.0, $CHCl_3$) lit. −49.7° (*c* 2, aq 0.5 M TRIS) [19]; $^1H$ NMR (360 MHz, $CDCl_3$): δ 5.50 (d, 1 H, H-1, $J_{1,2}$ 5 Hz), 4.62 (d, 1 H, H-1′, $J_{1',2'}$ 8 Hz), 4.40–3.45 (m, 14 skeleton H), 1.45 (m, 12 H, 4 $CH_{3ip}$). Anal. Calcd for $C_{18}H_{30}O_{11}$ (422.43): C, 51.17; H, 7.16. Found: C, 51.32; H, 7.13.

*3,4-*O*-Isopropylidene-6-*O*-(methoxydimethyl)-methyl-*D*-galactopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose* (**4**) *and 3,4-*O*-isopropylidene-β-*D*-galactopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose* (**5**).—To a solution of **3** (11.5 g, 0.027 mol) in 2,2-dimethoxypropane (170 mL, 1.36 mol) was added 400 mg of *p*-toluenesulfonic acid, and the mixture was stirred overnight. By TLC (4:1 $CH_2Cl_2$–acetone; + 0.1% $Et_3N$) the starting material disappeared, compounds **4** ($R_f$ 0.54) and **5** ($R_f$ 0.25) were formed in a ratio of 4:1. After addition of $Et_3N$ (2 mL) the reaction mixture was diluted with 1 L of $CH_2Cl_2$, washed with water (3 × 400 mL), dried and evaporated. The residue was chromatographed with $CH_2Cl_2$–acetone, 9:1→8:2, containing 1% $Et_3N$ to give **4** (10.6 g, 72.5%) and **5** (2.5 g, 19.7%). The same products in similar ratio were obtained from **6** by treatment of 50 equivalents of 2,2-dimethoxy-propane and catalytic amount of *p*-toluenesulfonic acid. Compound **4**: $[\alpha]_D^{22}$ −35.6° (*c* 1.3, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 5.54 (d, 1 H, H-1, $J_{1,2}$ 5.0 Hz), 4.60 (dd, 1 H, H-3, $J_{2,3}$

2.4 Hz, $J_{3,4}$ 7.9 Hz), 4.31 (dd, 1 H, H-2), 4.28 (dd, 1 H, H-1′, $J_{1',2'}$ 8.4 Hz), 4.24 (dd, 1 H, H-4, $J_{4,5}$ 1.7 Hz), 4.16 (dd, 1 H, H-4′, $J_{3',4'}$ 5.4 Hz, $J_{4',5'}$ 2.1 Hz), 4.06 (m, 2 H, H-3′, H-$6_a$, $J_{2',3'}$ 7.8 Hz), 4.00 (m, 1 H, H-5), 3.85 (dt, 1 H, H-5′, $J_{5',6a'} = J_{5',6b'}$ 6.2 Hz), 3.75–3.69 (m, 3 H, H-$6_a$, H-6′a,b), 3.59 (dd, 1 H, H-2′), 3.25 (s, 3 H, $OCH_3$), 1.50–1.27 (8 s, each 3 H, 8 $CH_{3ip}$). Anal. Calcd for $C_{25}H_{42}O_{12}$ (534.58): C, 56.17; H, 7.91. Found: C, 56.31; H, 8.00.

Compound **5**: $[\alpha]_D^{22}$ −29.6° (*c* 1.0, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 5.48 (d, 1 H, H-1, $J_{1,2}$ 5.0 Hz), 4.55 (dd, 1 H, H-3, $J_{2,3}$ 2.4 Hz, $J_{3,4}$ 7.9 Hz), 4.26 (dd, 1 H, H-2), 4.22 (dd, 1 H, H-1′, $J_{1',2'}$ 8.0 Hz), 4.20 (dd, 1 H, H-4, $J_{4,5}$ 1.7 Hz), 4.09–3.66 (m, 8 H), 3.49 (t, 1 H, H-2′ $J_{2',3'}$ 8.0 Hz), 1.50–1.27 (m, 18 H, 6 $CH_{3ip}$). Anal. Calcd for $C_{21}H_{34}O_{11}$ (462.49): C, 54.53; H, 7.40,. Found: C, 54.31; H, 7.37.

*β-D-Galactopyranosyl-(1→6)-D-galactose* (**6**).—A solution of **4** (50 mg, 0.090 mmol) in 1 mL of 90% trifluoroacetic acid was stirred for 15 min, and concentrated at 20 °C in vacuo. Ethyl acetate (6 mL) was added to the residue, and the precipitate formed was washed three times with ethyl acetate to yield **6** (20 mg, 64%): $[\alpha]_D^{22}$ +17.3° (*c* 0.19, $H_2O$); $R_f$ 0.4 (dichloromethane: methanol: $H_2O$, 80:50:13). Anal. Calcd for $C_{12}H_{22}O_{11}$ (342.29): C, 41.10; H, 6.47. Found: C, 41.44; H, 6.48.

*2,3,5-Tri-O-benzoyl-α-L-arabinofuranosyl-(1→2)-[2,3,5-tri-O-benzoyl-α-L-arabinofuranosyl-(1→6)]-3,4-O-isopropylidene-β-D-galactopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose* (**8**), *2,3,5-tri-O-benzoyl-α-L-arabinofuranosyl-(1→6)-3,4-O-isopropylidene-β-D-galactopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose* (**9**) *and 2,3,5-tri-O-benzoyl-α-L-arabinofuranosyl-(1→2)-3,4-O-isopropylidene-β-D-galactopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose* (**11**).—To a solution of **4** (390 mg, 0.84 mmol) in 5 mL of dry $CH_3CN$ were added powdered $Hg(CN)_2$ (512 mg, 2.4 equiv) and 4 Å molecular sieves (0.5 g), the mixture was stirred for 3 h and 1.0 g (1.9 mmol) of **7** [20] was added. After 2 h the TLC (49:1 $CH_2CL_2$–acetone) showed ~50% conversion of **4**, 100 mg of $Hg(CN)_2$ was added and the mixture was kept at 50 °C for 6 h. The work-up procedure was the same as that described for compound **2**. The crude product was purified by coloumn chromatography to give **8** (280 mg, 24.7%), **9** (190 mg, 24.8%) and **11** (40 mg, 5.3%).

Compound **8**: $[\alpha]_D^{22}$ +2.7° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{73}H_{74}O_{25}$ (1351.36): C, 64.88; H, 5.51. Found: C, 64.57; H, 5.53.

Compound **9**: $[\alpha]_D^{22}$ −15.5° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{47}H_{54}O_{18}$ (906.94): C, 62.24; H, 6.00. Found: C, 62.44; H, 6.04.

Compound **11**: $[\alpha]_D^{22}$ −3.17° (*c* 0.82, $CHCl_3$). Anal. Calcd for $C_{47}H_{54}O_{18}$ (906.94): C, 62.24; H, 6.00. Found: C, 62.11; H, 5.97.

*2,3,5-Tri-O-benzoyl-α-L-arabinofuranosyl-(1→6)-2-O-acetyl-3,4-O-isopropylidene-β-D-galactopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose* (**10**).—To a solution of **9** (50 mg) in pyridine (1 mL) was treated with acetic anhydride (1 mL). The solution was evaporated with toluene to yield **10**, which was used for NMR measurements only.

*2,3,5-Tri-O-benzoyl-α-L-arabinofuranosyl-(1→2)-3,4-O-isopropylidene-6-O-(methoxydimethyl)methyl-β-D-galactopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose* (**12**) *and 2-propanone bis-[2,3,5-tri-O-benzoyl-α-L-arabinofuranosyl-(1→2)-3,4-O-isopropylidene-β-D-galactopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose]-6,6 acetale* (**13**).—Powdered 4 Å molecular sieves (1.2 g) were added to a solution of **4** (534 mg, 1.0 mmol) and **7** [20] (630 mg, 1.2 mmol) in dry $CH_2Cl_2$ (20 mL), and the mixture was stirred in dark. After 2 h, the reaction mixture was cooled to −25 °C, *sym*-collidine (0.29 mL, 2 equiv), and silver triflate (514 mg, 2 equiv) in dry toluene (4 mL) were added. After 2 h, the TLC showed complete conversion and formation of two products, $Et_3N$ (1 mL) was added, the mixture was diluted with $CH_2Cl_2$ and filtered through a pad of Celite. The

filtrate was washed with aq 10% $Na_2S_2O_3$ and water, dried and evaporated. The products were separated by column chromatography (23:2 $CH_2Cl_2$–acetone, + 1% $Et_3N$) to give **12** (280 mg, 28.6%) and **13** (430 mg, 23.1%). Compound **12**: $[\alpha]_D^{22}$ − 13.4° (*c* 0.48, $CHCl_3$); $R_f$ 0.45 (in the chromatographic eluent). Anal. Calcd for $C_{51}H_{62}O_{19}$ (979.0): C, 62.56; H, 6.38. Found: C, 62.81; H 6.33.

Compound **13**: $[\alpha]_D^{22}$ − 8.9° (*c* 0.76, $CHCl_3$); $R_f$ 0.40; MALDI-TOF MS: *m*/*z* $[M + Na]^+$ 1876.9; Anal. Calcd for $C_{97}H_{112}O_{36}$ (1853.9): C, 62.84; H, 6.08. Found: C, 63.11; H, 6.07.

*2-O-Benzyl-3,4-O-isopropylidene-6-O-(methoxydimethyl)methyl-β-D-galactopyranosyl*-(1→6)-*1,2:3,4-di-O-isopropylidene-α-D-galactopyranose* (**14**).—To a stirred solution of **4** (10.0 g, 0.018 mol) in dry *N*,*N*-dimethyl formamide (15 mL) 80% NaH (672 mg, 0.022 mol) was added at 0 °C. After 30 min benzyl bromide (2.4 mL, 0.220 mol) was added dropwise, and the mixture was stirred for 3 h. The mixture was diluted with 400 mL of $CH_2Cl_2$, washed with water until neutral, dried and evaporated. The crude product was purified by column chromatography (24:1 $CH_2Cl_2$–acetone) to yield **14** (8.2 g, 70.1%); mp 116–117 °C (MeOH); $[\alpha]_D^{22}$ − 7.09° (*c* 1.0, $CHCl_3$); $^1H$ NMR (360 MHz, $CDCl_3$): $\delta$ 7.53–7.28 (m, 5 H, Ph), 5.63 (d, 1 H, H-1, $J_{1,2}$ 5 Hz), 4.93 (dd, 2 H, $CH_2$-Ph, $J_{gem}$ 12 Hz), 4.67 (dd, 1 H, H-3, $J_{2,3}$ 8 Hz, $J_{3,4}$ 2.1 Hz), 4.44 (d, 1 H, H-1′, $J_{1',2'}$ 8 Hz), 4.38 (dd, 1 H, H-2), 4.32 (dd, 1 H, H-4, $J_{4,5}$ 1.7 Hz), 4.21–4.10 (m, 4 H, H-3′, H-4′, H-5, H-6), 3.86 (dt, 1 H, H-5′, $J_{4',5'}$ 2 Hz, $J_{5',6a'} = J_{5',6b'}$ 6 Hz), 3.77 (m, 3 H, H-6, H-6′ab), 3.43 (dd, 1 H, H-2′, $J_{2',3'}$ 6 Hz), 3.28 (s, 3 H, $OCH_3$), 1.61–1.32 (4 s, each 3 H, 4 $CH_{3ip.}$). Anal. Calcd for $C_{32}H_{48}O_{12}$ (624,73): C, 61.52; H, 7.74. Found: C, 61.37; H, 7.72.

*2-O-Benzyl-3,4-O-isopropylidene-β-D-galactopyranosyl*-(1→6)-*1,2:3,4-di-O-isopropylidene-α-D-galactopyranose* (**15**).—To a solution of **14** (3.0g, 4.8 mmol) in 50 mL of $CH_2Cl_2$, 2 mL of 96% acetic acid and two drops of water were added, and the solution was heated at reflux temperature for 3 h. The mixture was diluted with $CH_2Cl_2$, washed with aq $NaHCO_3$ and water, dried and evaporated. The solid residue (2.7 g) was crystallized from *c*-hexane to yield **15** (2.4 g, 90.1%); mp 128–129 °C; $R_f$ 0.45 (17:3 $CH_2Cl_2$–acetone); $[\alpha]_D^{22}$ − 2.6° (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_{28}H_{40}O_{11}$ (552.62): C, 60.85; H, 7.29. Found: C, 61.01; H, 7.27.

*3,4,6-Tri-O-acetyl-2-O-benzyl-β-D-galactopyranosyl*-(1→6)-*1,2,3,4-tetra-O-acetyl-α,β-D-galactopyranose* (**17**).—To a stirred solution of **14** (300 mg, 0.48 mmol) in 30 mL of $CH_2Cl_2$, 3 mL of trifluoroacetic acid and one drop of water were added. After 16 h triethylamine was added, and the mixture was evaporated to give **16** ($R_f$ 0.53, 8:5:1 $CH_2Cl_2$–acetone–water) which was acetylated without purification in a mixture of 5 mL of pyridine and 5 mL of acetic anhydride to give **17**. The crude product was purified by column chromatography (93:7 $CH_2Cl_2$–acetone, $R_f$ 0.40) to yield **17** (230 mg, 74.5% for two steps); $[\alpha]_D^{22}$ + 25.2° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{26}H_{42}O_{18}$ (642.61): C, 48.59; H, 6.58. Found: C, 48.81; H, 6.61.

*3,4,6-Tri-O-acetyl-β-D-galactopyranosyl*-(1→6)-*1,2,3,4-tetra-O-acetyl-α,β-D-galactopyranose* (**18**).—Palladium on activated carbon (30 mg) was added to a solution of **17** (300 mg) in ethyl acetate (3 mL) and the mixture was stirred under $H_2$. After 4 h the mixture was diluted with ethyl acetate, filtered through a layer of Celite, and evaporated to yield **18** (260 mg), which was used for further conversion without purification.

*2,3,5-Tri-O-benzoyl-α-L-arabinofuranosyl*-(1→2)-*3,4,6-tri-O-acetyl-β-D-galactopyranosyl*-(1→6)-*1,2,3,4-tetra-O-acetyl-α,β-D-galactopyranose* (**19**).—A mixture of **18** (130 mg, 0.200 mmol), powdered $Hg(CN)_2$ (110 mg, 2.2 equivalents), and 4 Å molecular sieves (500 mg) in dry $CH_3CN$ (3 mL) was stirred for 30 min., compound **7** (200 mg, 0.380 mmol) in 1 mL of dry $CH_3CN$ was added and the mixture was stirred overnight. The work-up procedure was the same as that described for compound **2**. The residue was purified by column chromatography

(93:7 $CH_2Cl_2$–acetone, $R_f$ 0.55) to yield **19** (152 mg, 70.1%), which was characterized after deprotection.

α-L-*Arabinofuranosyl*-(1→2)-*[α-L-arabinofuranosyl* - (1→6)*]* - *β* - D - *galactopyranosyl*-(1→6)-D-*galactose* (**20**).—To a solution of **8** (370 mg, 0.270 mmol) in dry MeOH (10 mL) a catalytic amount of NaOMe was added and was stirred overnight. The solution was neutralized with Amberlite IR-120 $H^+$ ion-exchange resin, filtered and evaporated. The residue was treated with aq 90% trifluoroacetic acid for 15 min, the product was precipitated by addition of diethyl ether, filtered, and washed twice with diethyl ether to yield **20** (120 mg, 73.3% for two steps); $[\alpha]_D^{22}$ −26.38 (*c* 0.29, $H_2O$); $^{13}C$ NMR (90 MHz) *δ* 108.79 (C-$1''_{1''\rightarrow 2''}$), 108.49 (C-$1''_{1''\rightarrow 6''}$), 103.75, 102.53 (C-1′), 97.32, 96.96 (C-1β), 93.13, 92.93 (C-1α), 70.06 (C-6α), 69.95 (C-6β), 67.87 (C-6′), 61.95, 61.75 (2 × C-5″). Anal. Calcd for $C_{22}H_{38}O_{19}$ (606.52): C, 43.56; H, 6.31. Found: C, 43.81; H, 6.33.

α-L-*Arabinofuranosyl*-(1→6)-*β*-D-*galactopyranosyl*-(1→6)-D-*galactose* (**21**).—Compound **21** was prepared from **9** by the same method as described for **20**. Compound **21**: $[\alpha]_D^{22}$ −13.6 (*c* 0.35, $H_2O$); $^{13}C$ NMR (90 MHz) *δ* 108.54 (C-1″), 103.80 (C-1′), 97.05 (C-1β), 92.96 (C-1α), 84.45 (C-4″), 81.63 (C-2), 77.03 (C-3″), 74.45 (C-5β, C-5′), 73.17 (C-3β, C-3′), 72.40 (C-2′), 71.31 (C-2β), 70.13 (C-6α), 70.11 (C-4α), 69.86 (C-6β, C-3α, C-5α), 69.38 (C-4β, C-4′), 68.89 (C-2α), 67.99 (C-6′), 61.94 (C-5″). Anal. Calcd for $C_{17}H_{30}O_{15}$ (474.42): C, 43.03; H, 6.37. Found: C, 43.31; H, 6.36.

α-L-*Arabinofuranosyl*-(1→2)-*β*-D-*galactopyranosyl*-(1→6)-D-*galactose* (**22**).—To a solution of **19** (90 mg, 0.083 mmol) in dry MeOH (5 mL) NaOMe was added and the solution was stirred overnight. The solution was neutralized with Amberlite IR-120 $H^+$ ion-exchange resin, filtered and evaporated to give **22** (36 mg, 91.4%). Compound **22** was also prepared starting from **11** and from **13**, respectively, by the same method as described for **20**. Compound **22**: $[\alpha]_D^{22}$ −17.5 (*c* 0.16, $H_2O$); $^{13}C$ NMR (90 MHz): *δ* 108.81 (C-1″), 102.51 (C-1′), 97.00 (C-1β), 92.96 (C-1α), 84.80 (C-4″), 81.49 (C-2″), 77.44 (C-3″), 76.57 (C-2′), 75.66 (C-5′), 74.28 (C-5β), 73.50 (C-3β), 73.21 (C-2β), 72.37 (C-3′), 69.94 (C-4α), 69.87 (C-6α), 69.86 (C-3α), 69.74 (C-5α), 69.59 (C-6β), 69.39 (C-4β, C-4′), 68.86 (C-2α), 61.94 (C-5″), 61.48 (C-6′). Anal. Calcd for $C_{17}H_{30}O_{15}$ (474.42): C, 43.03; H, 6.37. Found: C, 43.37; H, 6.40.

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