Selective removal of the (2-naphthyl)methyl protecting group in the presence of *p*-methoxybenzyl group by catalytic hydrogenation

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Dedicated to Prof. Ferenc Fülöp on the occasion of his 60th birthday

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Abstract

Selective cleavage of the (2-naphthyl)methyl (NAP) group in the presence of *p*-methoxybenzyl (PMB), benzyl and benzylidene groups was achieved by catalytic hydrogenation with a series of monosaccharides. At a disaccharide level, the PMB group was stable upon hydrogenolysis of the NAP, however, partial cleavage of benzyl ether functions was observed.

Keywords: Carbohydrates, orthogonal protecting groups, benzyl type protecting groups, selective removal, catalytic hydrogenation

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Introduction

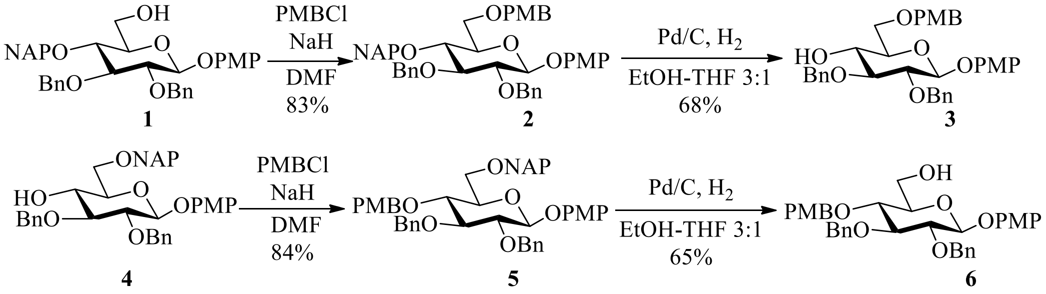
In carbohydrate chemistry, the benzyl-type ethers are the most frequently used protecting groups, since they are removable upon mild catalytic hydrogenation, and, due to their different reactivities, adoptable in orthogonal protecting strategies.[1] The *p*-methoxybenzyl (PMB) ether can be cleaved selectively by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone)[2] or CAN (cerium(IV) ammonium nitrate)[3,4] leaving most of the protecting groups intact, therefore, it became one of the most popular tools for temporary hydroxyl protection. However, the PMB group has the disadvantage of extreme acid-sensitivity. The 2-(naphthyl)methyl (NAP) group,[5,6] being removable by either catalytic hydrogenation[6-8] or DDQ[9] in the presence of benzyl ether and, unlike its *p*-methoxybenzyl counterpart, being stable under acidic conditions, seems to be a remarkably useful protecting group for polyhydroxy systems.

Recently, Spencer et al. have demonstrated a sequential deprotection strategy for sugars based upon the PMB, NAP and benzyl groups, applying CAN as a selective reagent to cleave PMB in the presence of the NAP-ether.[4] This set of benzyl-type protecting groups would be more useful, if orthogonal deprotection of NAP would be carried out in the presence of PMB. Investigating the relative stability of benzyl, *p*-methoxybenzyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl,[10,11] diphenylmethyl, 9-fluorenyl and *p*-chlorobenzyl ethers to catalytic hydrogenation in competitive reactions, we have found that splitting of the substituted benzyl ethers such as PMB did not start until the removal of the extended aromatic system became complete.[12,13]

To explore the utility of this observation, a series of mono- and disaccharides carrying NAP and PMB groups were prepared and subjected to catalytic hydrogenation.

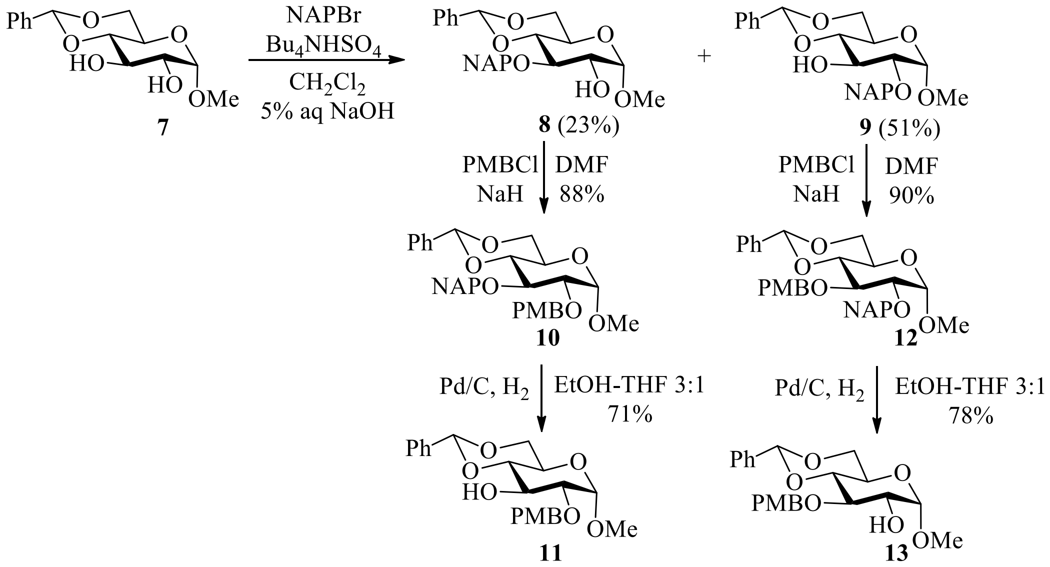
Results and Discussion

Fully protected glucoside derivatives **2** and **5** carrying benzyl, *p*-methoxybenzyl and 2-(naphthyl)methyl protecting groups were prepared by conventional alkylation, starting from **1**[14] and **4**,[14] respectively. Tlc monitoring of the Pd/C-catalyzed hydrogenolysis of **2** showed formation of a single product until the conversion reached at 80-90%; prolongation of the reaction time led to the formation of some polar side products. Therefore, the reaction mixture was worked up at 90% completion, and compound **3**, selectively deprotected at position 4, could be isolated with 68% yield. Similarly, the NAP group could be removed from primary hydroxyl group of **5** in the presence of PMB and benzyl ethers, to yield **6** (Scheme 1).



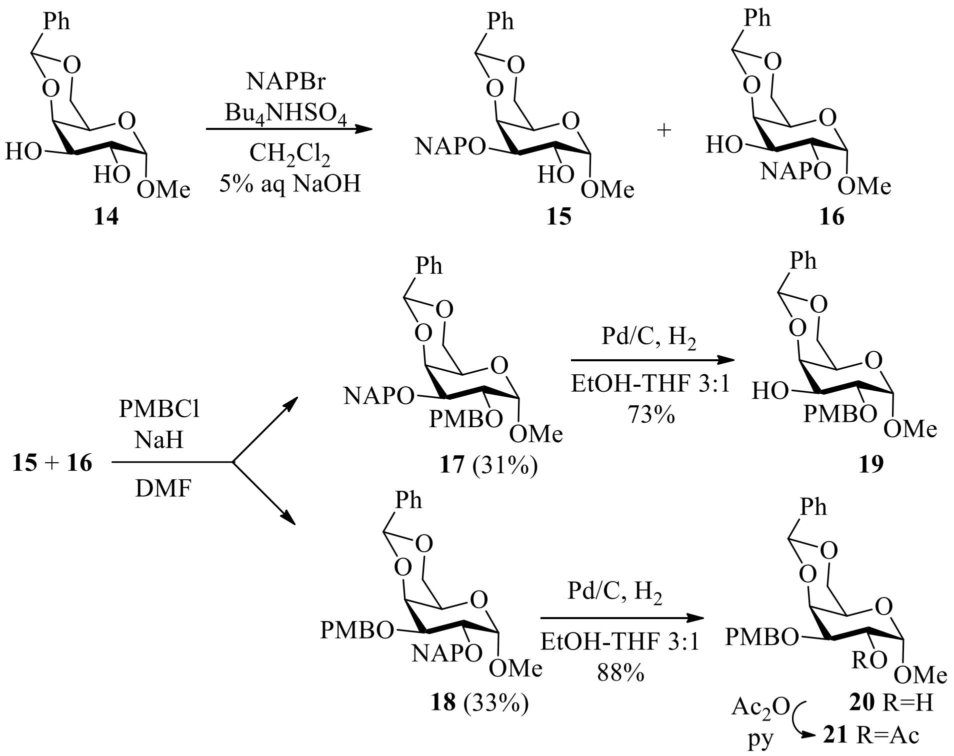
Scheme 1. Removal of the (2-naphthyl)methyl group in the presence of the *p*-methoxybenzyl PMB and benzyl groups by catalytic hydrogenation.

Compound **7** was alkylated with (2-naphthyl)methyl bromide in the presence of phase transfer catalyst (Bu_4NHSO_4) affording a mixture of **8**[15] and **9**, respectively, whose separation has been accomplished by column chromatography. Subsequently, their *p*-methyoxybenzylation gave the acetal-containing substrates **10** and **12**. Catalytic hydrogenolysis of **10** was let to go to completion, furnishing the mono-deprotected **11**.[16] The NAP group of **12** could be selectively cleaved, as well, to give **13**[16] in high yield (Scheme 2).



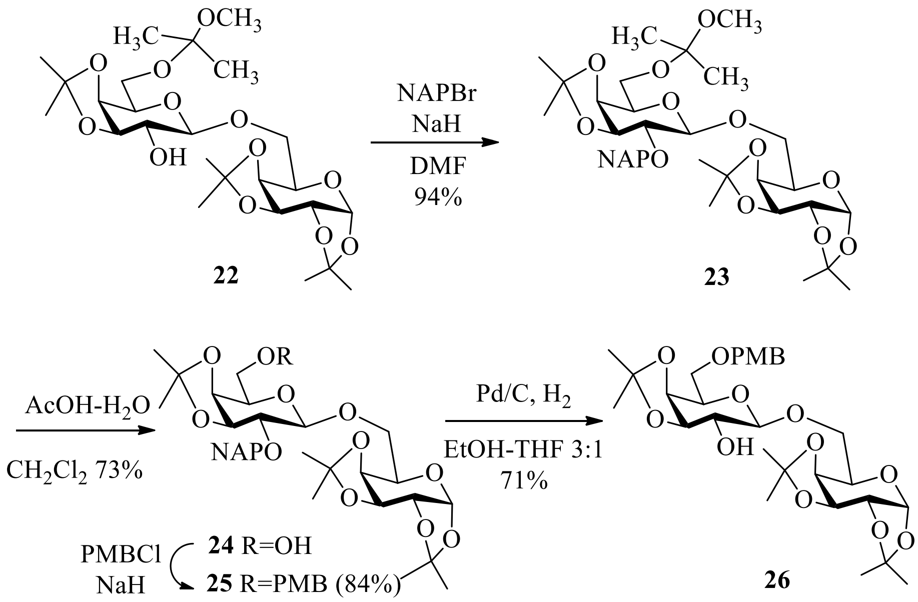
Scheme 2. Removal of the (2-naphthyl)methyl group in the presence of the *p*-methoxybenzyl and benzylidene groups.

Starting from the galactopyranoside derivative **14**, the synthesis of **17** and **18** was achieved by an analogous manner (**14→15→17**; **14→16→18**), but the regioisomers formed in the phase transfer alkylation could only be separated after the introduction of the PMB group. The NAP group of **17** and **18** could be cleanly removed in the presence of the PMB and benzylidene functions to result in **19** and **20** in high yields, respectively. Compounds **17**-**20** were identified after the synthesis and structural elucidation of the acetylated derivative **21** (Scheme 3).



Scheme 3. Removal of the (2-naphthyl)methyl group in the presence of the *p*-methoxybenzyl and benzylidene groups.

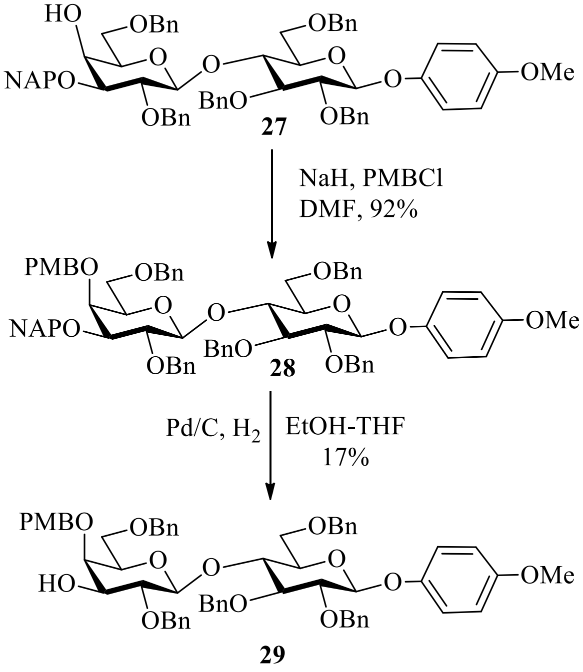
Orthogonal deprotection of the NAP group was studied at a disaccharide level, too. 2-(Napthyl)methylation of the single free hydroxyl group of the 3,4-*O*-Isopropylidene-6-*O*-(methoxydimethyl)methyl-β-D-galactopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **22**[17] afforded **23** from which, after mild acidic hydrolysis of the mixed acetal group followed by *p*-methoxybenzylation compound **25** could be obtained. Upon catalytic hydrogenation, the NAP group could be cleaved selectively form the secondary hydroxyl group to give **26** in high yield (Scheme 4).



Scheme 4. Removal of the (2-naphthyl)methyl group in the presence of isopropylidene groups by catalytic hydrogenation.

Treatment of the known lactoside **27**[18] with *p*-methoxybenzyl chloride as a reagent furnished **28**, as another disaccharide substrate, suitable for studying the selective removal of NAP in the presence of PMB and multiple benzyl ethers. Catalytic hydrogenolysis of **28** clearly demonstrated the limitation of the method, since the monodeproteced **29** could be isolated in rather low yield (Scheme 5). A side product formed in this transformation was also isolated in a similar amount; it could be identified, by NMR measurments and its single peak in the mass spectrum (m/z: 951.30), as a mixture of mono-debenzylated derivatives of **29** (m/z calcd for $[M+Na]^+$: 951.40).

The higher hydrogenolytic stability of the *p*-methoxybenzyl ether in comparison to the benzyl can be explained by steric effect of the methoxy substituent which inhibits the effective binding of the aromatic ring to the catalyst surface.[6] This phenomenon was utilized for selective hydrogenation of phenolic benzyl ether or ester in the presence of phenolic PMB ether using a Pd/C-pyridine combination as a catalyst.[19,20]



Scheme 5. Removal of the (2-naphthyl)methyl group in the presence of benzyl groups by catalytic hydrogenation.

Conclusions

The (2-naphthyl)methyl (NAP) protecting group could be selectively removed by catalytic hydrogenation from primary and secondary hydroxyl groups in the presence of the *p*-methoxybenzyl (PMB), benzylidene and multiple benzyl functions in the case of monosaccharides. At a disaccharide level, the *p*-methoxybenzyl (PMB) group proved to be stable toward catalytic hydroganolysis, however, partial cleavage of benzyl ether functions was also observed.

Experimental Section

General. Optical rotations were measured at room temperature with a Perkin-Elmer 241 automatic polarimeter. TLC was performed on Kieselgel 60 F_{254} (Merck) with detection by immersing into 5% ethanolic sulfuric acid soln followed by heating. Column chromatography was performed on Silica gel 60 (Merck 0.063-0.200 mm). Organic solutions were dried over $MgSO_4$, and concentrated in vacuum. The ^1H (360, 400 and 500 MHz) and ^{13}C NMR (90.54, 100.28 and 125.76 MHz) spectra were recorded with Bruker DRX-360, Bruker DRX-400 and Bruker DRX-500 spectrometers. Chemical shifts are referenced to Me_4Si (0.00 ppm for ^1H) or to the residual solvent signals ($CDCl_3$: 77.00 ppm for ^{13}C). MALDI-TOF MS analyses of the compounds were carried out in the positive reflectron mode using a BIFLEX III mass spectrometer (Bruker, Germany) equipped with delayed-ion extraction. The matrix solution was a satd 2,4,6-trihydroxy-acetophenone (THAP) solution in MeCN. A Vario MICRO CUBE instrument was used for elemental analyses.

***p*-Methoxyphenyl 2,3-di-*O*-benzyl-6-*O*-(*p*-methoxybenzyl)-4-*O*-(2-naphthyl)methyl-β-D-glucopyranoside (2).** Compound **1**[14] (694 mg, 1.14 mmol) was dissolved in DMF (10 ml) then 60% NaH (69 mg, 1.5 equiv) was added at 0°C and it was stirred for 30 min. *p*-Methoxybenzyl chloride (0.15 mL, 1.3 equiv) was added to the reaction mixture and stirred for further 15 min at 0°C and 1h at room temperature. The mixture was evaporated, diluted with DCM, washed with water (4x), dried, filtered and evaporated. The crude product was purified by column chromatography (DCM/acetone 95:5) to yield **2** as white needles (654 mg, 83%). mp = 83-85 ºC; $[\alpha]_D^{25}$ -8.51 (*c* 0.67, $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$): δ_H 7.81- 6.68 (25H, m, arom.), 5.07-4.44 (9H, m, 4 x CH_2, H-1), 3.81-3.67 (5H, m), 3.75 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.59-3.58 (1H, m). ^{13}C NMR (90 MHz, $CDCl_3$): δ_C 159.1-113.6 (arom.), 102.7 (C-1), 84.6, 82.0, 77.6 (C-2, C-3, C-4, C-5), 75.7, 74.9, 73.1 (4 x CH_2), 68.4 (C-6), 55.5, 55.1 (2 x OCH_3). Anal. Calcd for $C_{46}H_{46}O_8$ (726.85): C, 76.01; H,6.38. Found: C, 76.24; H,6. 36.

***p*-Methoxyphenyl 2,3-di-*O*-benzyl-6-*O*-(*p*-methoxybenzyl)-β-D-glucopyranoside (3).** To a solution of compound **2** (218 mg, 0.03 mol) in a mixture of EtOH and THF (3:1, 20 mL) Pd on carbon (30 mg) was added and the mixture was stirred in hydrogen atmosphere until TLC showed 90% conversion (6h). It was then filtered through a layer of Celite and concentrated. The crude product was purified by column chromatography (DCM/EtOAc 96:4) to yield compound **3** as white needles (120 mg, 68%). mp = 73-74 ºC; $[\alpha]_D^{25}$ -25.65 (*c* 0.46, $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$): δ_H 7.32-6.79 (18H, m, arom.), 5.06-4.74 (5H, m, 2 x CH_2, H-1), 4.47, 4.51 (2H, 2d, J_{gem} = 10.5 Hz, CH_2), 3.78 (3H, s, OCH_3), 3.76 (4H, s, OCH_3, skeleton H), 3.70-3.62 (3H, m), 3.54-3.49 (2H, m), 2.65 (1H, s, OH). ^{13}C NMR (90 MHz, $CDCl_3$): δ_C 159.2-113.7 (arom.), 102.7 (C-1), 83.9, 81.4, 74.2, 71.4 (C-2, C-3, C-4, C-5), 75.3, 74.8, 73.2 (3 x CH_2), 69.8 (C-6), 55.5, 55.2 (2 x OCH_3). Anal. Calcd for $C_{35}H_{38}O_8$ (586.26): C, 71.65; H, 6.53. Found: C, 71.50; H, 6.55. MALDI-TOF m/z calcd for $[M+Na]^+$: 609.66, Found: 609.41.

***p*-Methoxyphenyl 2,3-di-*O*-benzyl-4-*O*-(*p*-methoxybenzyl)-6-*O*-(2-naphthyl)methyl-β-D-glucopyranoside (5).** Compound **4**[14] (519 g, 0.86 mmol) was treated with *p*-methoxybenzyl chloride (113 µL, 1.2 equiv) as described for the synthesis of compound **2** to yield compound **5** as a white powder (533 mg, 84%). (Column chromatography: DCM/acetone 95:5). mp = 91-93 ºC; $[\alpha]_D^{25}$ -8.3 (*c* 0.53, $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$): δ_H 7.76-6.70 (25H, m, arom.), 5.04-4.71 (9H, m, 4 x CH_2, H-1), 3.83-3.59 (6H, m), 3.72 (3H, s, OCH_3), 3.70 (3H, s, OCH_3). ^{13}C NMR (90 MHz, $CDCl_3$): δ_C 159.2-113.6 (arom.), 102.6 (C-1), 84.6, 82.0, 77.3, 75.0 (C-2, C-3, C-4, C-5), 75.7, 74.9, 74.6, 73.4 (4 x CH_2), 68.7 (C-6), 55.5, 55.1 (2 x OCH_3). Anal. Calcd for $C_{46}H_{46}O_8$ (726.85): C, 76.01; H, 6.38. Found: C, 75.78; H, 6.41.

***p*-Methoxyphenyl 2,3-di-*O*-benzyl-4-*O*-(*p*-methoxybenzyl)-β-D-glucopyranoside (6).** Compound **5** (218 mg, 1.05 mmol) was hydrogenolysed as described for the synthesis of compound **3** to obtain **6** as white powder (132 mg, 65%). (Column chromatography: DCM/EtOAc 96:4). mp = 110-111 ºC; $[\alpha]_D^{25}$ -10.71 (*c* 0.42, $CHCl_3$). ^{1}H NMR (360 MHz, $CDCl_3$): δ_H 7.33-6.81 (18H, m, arom.), 5.03-4.57 (7H, m, 3 x CH_2, H-1), 3.88-3.84 (1H, m), 3.77 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.72-3.41 (5H, m), 2.15 (1H, s, OH). ^{13}C NMR (90 MHz, $CDCl_3$): δ_C 159.3-113.8 (arom.), 102.4 (C-1), 84.4, 82.0, 77.1, 75.2 (C-2, C-3, C-4, C-5), 75.6, 75.0, 74.7 (3 x CH_2), 61.9 (C-6), 55.6, 55.2 (2 x OCH_3). Anal. Calcd for $C_{35}H_{38}O_8$ (586.26): C, 71.65; H, 6.53. Found: C, 71.82; H, 6.57. MALDI-TOF m/z calcd for $[M+Na]^+$: 609.66, Found: 609.43.

Methyl 4,6-*O*-benzylidene-3-*O*-(2-naphthyl)methyl-α-D-glucopyranoside (8) and **methyl 4,6-*O*-benzylidene-2-*O*-(2-naphthyl)methyl-α-D-glucopyranoside (9).** To a stirred solution of **7** (19.00 g, 67 mmol) in DCM (500 mL) Bu_4NHSO_4 (2.8 g, 8.2 mmol), 5% aq. NaOH (200 mL) and 2-(bromomethyl)naphthalene (20.8 g, 94 mmol, 1.4 eqiuv) were added, then it was stirred for 24 hours at reflux temperature. The organic layer was then separated, diluted with DCM, washed with water, dried, filtered and concentrated. The crude product was purified by column chromatography (*n*-hexane/EtOAc 6:4) to yield compound **8**[15] and **9**.

(8) White needles, yield: 6.55 g (23%), mp. 199-201°C, $[\alpha]_D^{25}$ +71.73 (*c* 0.19, $CHCl_3$), (lit. 15 $[\alpha]_D^{25}$ +69.9); R_f 0.28 (n-hexane/EtOAc 6:4). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.78-7.35 (12H, m, arom.), 5.52 (1H, s, H_{ac}), 5.07-4.92 (2H, 2d, NAP-CH_2), 4.73 (1H, d, $^3J_{1,2}$ = 4.0 Hz, H-1), 4.27-4.24 (1H, m), 3.85 (1H, t, *J* = 9.5 Hz), 3.81-3.78 (1H, m), 3.72-3.70 (2H, m), 3.60 (1H, t, *J* = 9.5 Hz), 3.38 (3H, s, OCH_3), 2.26 (1H, d, *J* = 8.2 Hz, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 138.37-125.0 (arom.), 101.2 (C_{ac}), 99.9 (C-1), 81.7, 78.7, 72.1, 62.4 (C-2, C-3, C-4, C-5), 74.6 (NAP-CH_2), 68.8 (C-6), 55.2 (OCH_3). Anal. Calcd for $C_{25}H_{26}O_6$ (422.47): C, 71.07; H, 6.20. Found: C, 71.29; H, 6.17.

(9) White needles, yield: 14.49 g (51%). $[\alpha]_D^{25}$ +9.85 (*c* 0.13, $CHCl_3$), mp = 165-166 °C, R_f 0.43 (n-hexane/EtOAc 6:4). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.77-7.29 (12H, m, arom.), 5.46 (1H, s, H_{ac}), 4.91-4.78 (2H, 2d, NAP-CH_2), 4.57 (1H, d, $^3J_{1,2}$ = 3.5 Hz, H-1), 4.22-4.15 (2H, m), 3.82-3.75 (1H, m), 3.62 (1H, t, *J* = 10.5 Hz), 3.48-3.43 (2H, m), 3.32 (3H, s, OCH_3), 2.88 (1H, d, *J* = 2.2 Hz, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 137.0-125.7 (arom.), 101.1 (C_{ac}), 98.5 (C-1), 81.1, 79.3, 70.1, 61.9 (C-2, C-3, C-4, C-5), 73.3 (NAP-CH_2), 68.8 (C-6), 55.2 (OCH_3). Anal. Calcd for $C_{25}H_{26}O_6$ (422.47): C, 71.07; H, 6.20. Found: C, 71.14; H, 6.22. MALDI-TOF m/z calcd for $[M+Na]^+$: 445.46, Found: 445.21.

Methyl 4,6-*O*-benzylidene-2-*O*-(*p*-methoxybenzyl)-3-*O*-(2-naphthyl)methyl-α-D-glucopyranoside (10). Compound **8** (1.78 g, 9.59 mmol) was treated with *p*-methoxybenzyl chloride (0.69 mL, 1.2 equiv) as described for the synthesis of compound **2** to yield compound **10** as white crystals (2.37 g, 88%). (Column chromatography: DCM/EtOAc 97:3) mp = 94-95 °C, $[\alpha]_D^{25}$ +45.04, (*c* 0.13, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.80-6.81 (16H, m, arom.), 5.54 (1H, s, H_{ac}), 5.06-4.96 (2H, 2d, NAP-CH_2), 4.78-4.63 (2H, dd, PMB-CH_2), 4.56 (1H, d, $^3J_{1,2}$ = 3.5 Hz, H-1), 4.26-4.23 (1H, m), 4.07 (1H, t, *J* = 9.0 Hz), 3.85-3.79 (1H, m), 3.73 (3H, s, PMB-OCH$_3$), 3.69 (1H, t, *J* = 10.0 Hz), 3.61 (1H, t, *J* = 9.0 Hz), 3.56-3.54 (1H, m), 3.37 (3H, s, OCH$_3$). ^{13}C NMR (125.7 MHz, CDCl$_3$): δ_C 159.3-113.8 (arom.), 101.9 (C$_{ac}$), 99.2 (C-1), 82.1, 78.9, 78.5, 62.3 (C-2, C-3, C-4, C-5), 75.2, 73.2 (2 x CH$_2$), 69.0 (C-6), 55.2, 55.1 (2 x OCH$_3$). Anal. Calcd for $C_{33}H_{34}O_7$ (542.62): C, 73.04; H, 6.32. Found: C, 73.22; H, 6.35.

Methyl 4,6-*O*-benzylidene-2-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside (11). To a solution of compound **10** (160 mg, 0.23 mmol) in a mixture of EtOH and THF (3:1, 20 mL) Pd on carbon (30 mg) was added and the mixture was stirred in hydrogen atmosphere until TLC showed complete conversion (6h). It was then filtered through a layer of Celite and evaporated. The crude product was purified by column chromatography (DCM/acetone 96:4) to yield compound **11** as white crystals (84 mg, 71%). mp = 98-100 °C, $[\alpha]_D^{25}$ +78.71 (*c* 0.16, CHCl$_3$), (lit. 16: mp = 102 °C, $[\alpha]_D$ +38). ^{1}H NMR (360 MHz, CDCl$_3$): δ_H 7.50-6.87 (9H, m, arom.), 5.51 (1H, s, H$_{ac}$), 4.72-4.61 (2H, dd, PMB-CH$_2$), 4.56 (1H, d, $^3J_{1,2}$ = 3.6 Hz, H-1), 4.27-4.23 (1H, m), 4.12 (1H, t, *J* = 9.3 Hz), 3.83-3.76 (1H, m), 3.79 (3H, s, PMB-OCH$_3$), 3.69 (1H, t, *J* = 10.1 Hz), 3.51-3.42 (2H, m), 3.36 (3H, s, OCH$_3$), 2.72 (1H, bs, OH). ^{13}C NMR (90 MHz, CDCl$_3$): δ_C 159.5-113.9 (arom.), 101.8 (C$_{ac}$), 98.6 (C-1), 81.2, 79.1 70.1, 61.9 (C-2, C-3, C-4, C-5), 72.9 (PMB-CH$_2$), 68.9 (C-6), 55.3, 55.2 (2 x OCH$_3$). Anal. Calcd for $C_{22}H_{26}O_7$ (402.44): C, 65.66; H, 6.51; O. Found: C, 65.54; H, 6.49.

Methyl 4,6-*O*-benzylidene-3-*O*-(*p*-methoxybenzyl)-2-*O*-(2-naphthyl)methyl-α-D-glucopyranoside (12). Compound **9** (4.05 g, 9.56 mmol) was treated with *p*-methoxybenzyl chloride as described for the synthesis of compound **2** to give **12** as white crystals (4.56 g, 90%). mp = 96-98°C, $[\alpha]_D^{25}$ -49.19 (*c* 0.62, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 7.81-6.80 (16H, m, arom.), 5.52 (1H, s, H$_{ac}$), 4.99-4.78 (4H, m, NAP-CH$_2$, PMB-CH$_2$), 4.59 (1H, d, $^3J_{1,2}$ = 3.5 Hz, H-1), 4.25-4.22 (1H, m), 4.06 (1H, t, *J* = 9.5 Hz), 3.84-3.78 (1H, m), 3.74 (3H, s, PMB-OCH$_3$), 3.66 (1H, t, *J* = 10.0 Hz), 3.59-3.55 (2H, m), 3.39 (3H, s, OCH$_3$). ^{13}C NMR (125.7 MHz, CDCl$_3$): δ_C 159.1-113.6 (arom.), 101.1 (C$_{ac}$), 99.1 (C-1), 82.1, 78.9, 78.5, 62.3 (C-2, C-3, C-4, C-5), 74.2, 73.7 (2 x CH$_2$), 68.9 (C-6), 55.2, 55.1 (2 x OCH$_3$). Anal. Calcd for $C_{33}H_{34}O_7$ (542.62): C, 73.04; H, 6.32. Found: C, 72.89; H, 6.30.

Methyl 4,6-*O*-benzylidene-3-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside (13). Compound **12** (160 mg, 0.23 mmol) was hydrogenolysed as described for the synthesis of compound **11** to obtain **13** as white crystals (92 mg, 78%). mp =168-169°C, $[\alpha]_D^{25}$ +78.53 (*c* 0.11, CHCl$_3$), (lit. 16: mp = 174-175 °C, $[\alpha]_D$ +45). ^{1}H NMR (360 MHz, CDCl$_3$): δ_H 7.51-6.83 (9H, m, arom.), 5.56 (1H, s, H$_{ac}$), 4.89-4.70 (2H, 2d, PMB-CH$_2$), 4.78 (1H, d, $^3J_{1,2}$ = 3.8 Hz, H-1), 4.31-4.27 (1H, m), 3.86-3.64 (4H, m), 3.78 (3H, s, PMB-OCH$_3$), 3.62 (1H, t, *J* = 9.1 Hz), 3.44 (3H, s, OCH$_3$), 2.39 (1H, d, *J* = 7.2 Hz, OH). ^{13}C NMR (90 MHz, CDCl$_3$): δ_C 159.2-113.7 (arom.), 101.2 (C$_{ac}$), 99.8 (C-1), 81.9, 78.3, 72.3, 62.5 (C-2, C-3, C-4, C-5), 74.4 (PMB-CH$_2$), 69.0 (C-6), 55.3, 55.2 (2 x OCH$_3$). Anal. Calcd for $C_{22}H_{26}O_7$ (402.44): C, 65.66; H, 6.51. Found: C, 65.71; H, 6.55.

Methyl 4,6-*O*-benzylidene-2-*O*-(*p*-methoxybenzyl)-3-*O*-(2-naphthyl)methyl-α-D-galactopyranoside (17) and **methyl 4,6-*O*-benzylidene-3-*O*-(*p*-methoxybenzyl)-2-*O*-(2-naphthyl)methyl-α-D-galactopyranoside (18).** Compound **14** (840 mg, 3 mmol) was treated with 2-(bromomethyl)naphthalene as described for the synthesis of compound **8** and **9** to give the unseparated, purified mixture of compound **15** and **16** (993 mg, 79%). (Column chromatography: toluene: acetone 75:25, R$_f$ 0.40 and 0.35.)

Purified mixture of compound **15** and **16** (736 mg, 1.8 mmol) was treated with *p*-methoxybenzyl chloride as described for the synthesis of compound **2** to yield **17** as white crystals (501 mg, 31% over two steps) and **18** as white crystals (535 mg, 33% over two steps). (Column chromatography: DCM/Ac 93:7).

(17) $[\alpha]_D^{25}$ +77.31 (*c* 0.12, $CHCl_3$), R$_f$ 0.62 (DCM/EtOAc 96:4), mp 89-90°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.84-6.82 (16H, m, arom.), 5.45 (1H, s, H$_{ac}$), 4.98-4.86 (2H, 2d, NAP-CH$_2$), 4.83-4.62 (2H, 2d, PMB-CH$_2$), 4.72 (1H, d, $^3J_{1,2}$ = 3.5 Hz, H-1), 4.16-4.13 (2H, m), 4.07 (1H, dd, *J* = 3.5 Hz, *J* = 10.0 Hz), 3.99 (1H, dd, *J* = 3.5 Hz, *J* = 10.0 Hz), 3.91 (1H, dd, *J* = 1.5 Hz, *J* = 11.5 Hz), 3.75 (3H, s, PMB-OCH$_3$), 3.48 (1H, s), 3.34 (3H, s, OCH$_3$). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 159.2-113.6 (arom.), 100.9 (C$_{ac}$), 99.4 (C-1), 75.8, 75.0, 74.8, 62.3 (C-2, C-3, C-4, C-5), 73.3, 72.2 (2 x CH$_2$), 69.2 (C-6), 55.3, 55.1 (2 x OCH$_3$). Anal. Calcd for $C_{33}H_{34}O_7$ (542.62): C, 73.04; H, 6.32. Found: C, 73.14; H, 6.33. MALDI-TOF m/z calcd for $[M+Na]^+$: 565.61, Found: 565.49.

(18) $[\alpha]_D^{25}$ +62.60 (*c* 0.12, $CHCl_3$), R$_f$ 0.66 (DCM/EtOAc 96:4), mp 101-103°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.79-6.83 (16H, m, arom.), 5.44 (1H, s, H$_{ac}$), 5.02-4.67 (4H, 4d, NAP-CH$_2$, PMB-CH$_2$), 4.77 (1H, d, $^3J_{1,2}$ = 3.5 Hz, H-1), 4.15 (1H, dd, $^3J_{5,6a}$ = 1.5 Hz, $^2J_{6a,6b}$ = 12.5 Hz, H-6a), 4.12 (1H, d, H-4), 4.10 (1H, dd, $^3J_{2,3}$ = 10.0 Hz, H-2), 3.98 (1H, dd, $^3J_{3,4}$ = 3.5 Hz, H-3), 3.95 (1H, dd, $^3J_{5,6b}$ = 1.5 Hz, H-6b), 3.75 (3H, s, PMB-OCH$_3$), 3.52 (1H, s, H-5), 3.37 (3H, s, OCH$_3$). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 159.1-113.6 (arom.), 100.9 (C$_{ac}$), 99.4 (C-1), 75.6, 75.3, 74.6, 62.4 (C-2, C-3, C-4, C-5), 73.7, 71.6 (2 x CH$_2$), 69.2 (C-6), 55.4, 55.1 (2 x OCH$_3$). Anal. Calcd for $C_{33}H_{34}O_7$ (542.62): C, 73.04; H, 6.32. Found: C, 72.90; H, 6.34. MALDI-TOF m/z calcd for $[M+Na]^+$: 565.61, Found: 565.48.

Methyl 4,6-*O*-benzylidene-2-*O*-(*p*-methoxybenzyl)-α-D-galactopyranoside (19). Compound **17** (160 mg, 0.3 mmol) was hydrogenolysed as described for the synthesis of compound **11** to obtain **19** as white crystals (96 mg, 80%). (Column chromatography: DCM/Ac 93:7). $[\alpha]_D^{25}$ + 60.20 (*c* 0.50, $CHCl_3$), mp. 92-95 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ_H 7.50-6.85 (9H, m, arom.), 5.54 (1H, s, H$_{ac}$), 4.74 (1H, d, $^3J_{1,2}$ = 4.0 Hz, H-1), 4.74-4.57 (2H, 2d, PMB-CH$_2$), 4.26-4.21 (2H, m), 4.13-4.08 (1H, m), 4.05 (1H, dd, *J* = 1.4 Hz, *J* = 12.5 Hz), 3.82-3.79 (4H, m), 3.65 (1H, s), 3.36 (3H, s, OCH$_3$), 2.44 (1H, s, OH). ^{13}C NMR (90 MHz, $CDCl_3$): δ_C 159.3-113.8 (arom.), 101.1 (C$_{ac}$), 98.9 (C-1), 76.3, 76.0 68.4, 62.2 (C-2, C-3, C-4, C-5), 72.9 (PMB-CH$_2$), 69.3 (C-6), 55.5, 55.2 (2 x OCH$_3$). Anal. Calcd for $C_{22}H_{26}O_7$ (402.44): C, 65.66; H, 6.51. Found: C, 65.90; H, 6.50. MALDI-TOF m/z calcd for $[M+Na]^+$: 425.43, Found: 425.42.

Methyl 4,6-*O*-benzylidene-3-*O*-(*p*-methoxybenzyl)-α-D-galactopyranoside (20). Compound **18** (160 mg, 0.3 mmol) was hydrogenolysed as described for the synthesis of **11** to obtain **20** as white crystals (105 mg, 88%). (Column chromatography: DCM/Ac 93:7). $[\alpha]_D^{25}$ +176.87 (*c* 0.15, $CHCl_3$), mp. 175-176°C. ^{1}H NMR (360 MHz, $CDCl_3$): δ_H 7.53-6.84 (9H, m, arom.), 5.45 (1H, s, H$_{ac}$), 4.94 (1H, d, $^3J_{1,2}$ = 3.6 Hz, H-1), 4.69-4.62 (2H, 2d, PMB-CH$_2$), 4.25 (1H, dd, $^3J_{5,6a}$ = 1.5 Hz, $^2J_{6a,6b}$ = 12.4 Hz, H-6a), 4.21-4.17 (2H, m, H-2, H-4), 4.02 (1H, dd, $^3J_{5,6b}$ = 1.5 Hz, H-6b), 3.79 (3H, s, PMB-OCH$_3$), 3.77 (1H, dd, $^3J_{2,3}$ = 10.0 Hz, H-3), 3.60 (1H, s, H-5), 3.44 (3H, s, OCH$_3$), 2.30 (1H, s, OH). ^{13}C NMR (90 MHz, CDCl$_3$): δ_C 159.3-113.8 (arom.), 100.9 (C$_{ac}$), 99.9 (C-1), 76.1, 73.5, 67.8, 62.7 (C-2, C-3, C-4, C-5), 71.0 (PMB-CH$_2$), 69.4 (C-6), 55.5, 55.2 (2 x OCH$_3$). Anal. Calcd for $C_{22}H_{26}O_7$ (402.44): C, 65.66; H, 6.51. Found: C, 65.49; H, 6.49. MALDI-TOF m/z calcd for [M+Na]$^+$: 425.43, Found: 425.43.

Methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(*p*-methoxybenzyl)-α-D-galactopyranoside (21). To a stirred solution of compound **20** (50 mg, 0.15 mmol) in pyridine (1 mL) Ac$_2$O (0.2 mL) was added. When the TLC showed complete conversion, the solvent was evaporated, co-evaporated twice with toluene and the residue was purified by column chromatography (DCM/acetone 95:5) to yield **21** as a syrup (51 mg, 92%). $[\alpha]_D^{25}$ +15.31 (*c* 0.11, MeOH). ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 7.54-6.84 (9H, m, arom.), 5.47 (1H, s, H$_{ac}$), 5.31 (1H, dd, $^3J_{2,3}$ = 10.5 Hz, H-2), 5.06 (1H, d, $^3J_{1,2}$ = 3.4 Hz, H-1), 4.67-4.59 (2H, 2d, PMB-CH$_2$), 4.24 (1H, d, $^2J_{6a,6b}$ = 12.4 Hz, H-6a), 4.16 (1H, d, $^3J_{3,4}$ = 3.2 Hz, H-4), 4.01 (1H, d, H-6b), 3.96 (1H, dd, H-3), 3.79 (3H, s, PMB-OCH$_3$), 3.59 (1H, s, H-5), 3.38 (3H, s, OCH$_3$), 2.10 (3H, s, CH$_3$). ^{13}C NMR (125.7 MHz, CDCl$_3$): δ_C 170.2 (CO), 159.2-113.7 (arom.), 101.0 (C$_{ac}$), 97.9 (C-1), 74.3, 73.1, 70.1, 62.4 (C-2, C-3, C-4, C-5), 71.5 (PMB-CH$_2$), 69.2 (C-6), 55.4, 55.2 (2 x OCH$_3$), 21.0 (CH$_3$). Anal. Calcd for $C_{24}H_{28}O_8$ (444.47): C, 64.85; H, 6.35. Found: C, 64.71; H, 6.37.

3,4-*O*-Isopropylidene-6-*O*-(methoxydimethyl)methyl-2-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (23). To a stirred solution of compound **22**^{17} (1.3 g, 2.4 mmol) in DMF (10 mL) 60% NaH (150 mg, 2 equiv) was added at 0°C. After 30 min 2-(bromomethyl)naphthalene (540 mg, 1.3 equiv) was added to the reaction mixture. When TLC (DCM/acetone 75:25 + 1% Et$_3$N) showed complete conversion, it was diluted with methanol and evaporated. Usual work-up procedure resulted in compound **23** as a syrup (1.55 g, 94%). $[\alpha]_D^{25}$ +0.63 (*c* 0.53, CHCl$_3$). ^{1}H NMR (360 MHz, CDCl$_3$): δ_H 7.91-7.42 (7H, arom.), 5.60 (1H, d, *J* = 5.1 Hz, H-1), 5.07-5.00 (2H, m, NAP-CH$_2$), 4.61-4.59 (1H, m), 4.40 (1H, d, *J* = 8.1 Hz, H-1'), 4.35-4.33 (1H, m), 4.26-4.24 (1H, m), 4.17-4.11 (4H, m), 3.82-3.65 (4H, m), 3.45-3.40 (1H, m), 3.21 (3H, s, OCH$_3$), 1.55, 1.46, 1.35, 1.34, 1.33, 1.32, 1.29, 1.20 (24H, 8 x s, 8 x CH$_3$). ^{13}C NMR (90 MHz, CDCl$_3$): δ_C 136.0-125.5 (arom.), 109.6, 109.2, 108.5 (3 x C$_{ac}$), 103.7, 96.3 (C-1, C-1'), 100.0 (MIP-C$_{ac}$), 78.7, 73.6, 71.9, 71.3, 70.7, 70.4, 67.3 (skeleton carbons), 73.3 (^{NAP}-CH$_2$), 69.2, 60.1 (C-6, C-6'), 48.5 (MIP-OCH$_3$), 27.6, 26.3, 26.0, 25.9, 24.9, 24.3, 24.2 (6 x CH$_3$). Anal. Calcd for $C_{36}H_{50}O_{12}$ (674.77): C, 64.08; H, 7.47. Found: C, 64.17; H, 7.44.

3,4-*O*-Isopropylidene-2-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (24). Compound **23** (1.038 g, 1.5 mmol) was dissolved in DCM (25 mL) and 96% AcOH (1mL) and 1 drop of water were added and it was stirred for 3h at reflux temperature. After complete conversion of the starting material it was diluted with DCM (60 mL), washed with satd. aq. NaHCO$_3$ and water, dried, filtered and evaporated. Purification by column chromatography resulted in compound **24** as white crystals (0.67 g, 73%). $[\alpha]_D^{25}$ +1.59 (*c* 0.16, CHCl$_3$). mp:154-156°C. ^{1}H NMR (360 MHz, CDCl$_3$): δ_H 7.88-7.43 (7H, arom.), 5.59 (1H, d, *J* = 5.1 Hz, H-1), 5.04-5.00 (2H, m, NAP-CH$_2$), 4.64-4.61 (1H, dd), 4.42 (1H, d, *J* =

8.1 Hz, H-1'), 4.35-4.29 (2H, m), 4.21-4.07 (4H, m), 3.95-3.90 (1H, m), 3.83-3.76 (3H, m),3.15-3.12 (1H, m), 3.53 (1H, s, OH), 1.56, 1.49, 1.34, 1.30, 1.21 (18H, 5 x s, 6 x CH_3). ^{13}C NMR (90 MHz, $CDCl_3$): δ_C 135.8-125.8 (arom.), 110.1, 109.4, 108.6 (3 x C_{ac}), 103.4, 96.4 (C-1, C-1'), 79.0, 78.6, 73.9, 73.0, 71.1, 70.7, 70.4, 67.1 (skeleton carbons), 73.3 (NAP-CH_2), 68.9 (C-6), 62.4 (C-6'), 27.6, 26.3, 26.0, 25.9, 24.9, 24.3 (8 x CH_3). Anal. Calcd for $C_{32}H_{42}O_{11}$ (602.67): C, 63.77; H, 7.02. Found: C, 63.97; H, 7.03.

3,4-*O*-Isopropylidene-6-*O*-(*p*-methoxybenzyl)-2-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (25). Compound **24** (380 mg, 0.63 mmol) was treated with *p*-methoxybenzyl chloride as described for the synthesis of compound **2** to yield **25** as a syrup (382 mg, 84%). (Column chromatography *n*-hexane/acetone 75:25). $[\alpha]_D^{25}$ +0.46 (*c* 0.19, $CHCl_3$). ^{1}H NMR (360 MHz, $CDCl_3$): δ_H 7.88-6.84 (11H, arom.), 5.59 (1H, d, *J* = 5.1 Hz, H-1), 5.06-5.00 (2H, m, NAP-CH_2), 4.59-4.47 (3H, m), 4.40 (1H, d, *J* = 8.0 Hz, H-1'), 4.14-4.10 (6H, m), 3.89-3.85 (1H, m), 3.77 (3H, s, OCH_3), 3.75-3.70 (3H, m), 3.40-3.38 (1H, m), 1.55, 1.44, 1.32, 1.30, 1.29, 1.17 (18H, 6 x s, 6 x CH_3). ^{13}C NMR (90 MHz, $CDCl_3$): δ_C 159.1-113.6 (arom.), 109.7, 109.3, 108.7 (3 x C_{ac}), 103.7, 96.3 (C-1, C-1'), 78.6, 78.5, 73.6, 71.9, 71.3, 70.6, 70.3, 67.4 (skeleton carbons), 73.2, 73.1 (2 x CH_2), 68.5, 67.9 (C-6, C-6'), 55.1 (OCH_3), 27.6, 26.3, 26.0, 25.9, 24.9, 24.3 (6 x CH_3). Anal. Calcd for $C_{40}H_{50}O_{12}$ (722.82): C, 66.47; H, 6.97. Found: C, 66.24; H, 6.99.

3,4-*O*-Isopropylidene-6-*O*-(*p*-methoxybenzyl)-β-D-galactopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (26). Compound **25** (700 mg, 1.05 mmol) was hydrogenolysed as described for the synthesis of compound **11** to obtain **26** as a syrup (441 mg, 71%). (Column chromatography: DCM/acetone 9:1). $[\alpha]_D^{25}$ +0.51 (*c* 0.16, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.27-6.86 (4H, arom.), 5.53 (1H, d, *J* = 5.5 Hz, H-1), 4.59-4.47 (3H, m), 4.31-4.20 (3H, m), 4.14-4.12 (1H, m), 4.07-4.02 (3H, m), 4.00-3.91 (1H, m), 3.79 (3H, s, OCH_3), 3.78-3.72 (3H, m), 3.58-3.55 (1H, m), 3.20 (1H, s, OH), 1.52, 1.50, 1.43, 1.33, 1.31, 1.20 (18H, 6 x s, 6 x CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 159.1, 129.9, 129.2, 113.4 (arom.), 109.8, 109.3, 108.6 (3 x C_{ac}), 103.3, 96.1 (C-1, C-1'), 78.7, 73.5, 73.2, 72.5, 71.1, 70.6, 70.3, 67.8 (skeleton carbons), 73.1 (PMB-CH_2), 69.1, 68.9 (C-6, C-6'), 55.1 (OCH_3), 28.0, 26.2, 25.9, 25.8, 24.8 (6 x CH_3). Anal. Calcd for $C_{29}H_{42}O_{12}$ (582.64): C, 59.78; H, 7.27. Found: C, 59.88; H, 7.30.

***p*-Methoxyphenyl 2,6-di-*O*-benzyl-4-*O*-(p-methoxybenzyl)-3-*O*-(2-naphthyl)methyl-ß-D-galactopyranosyl-2,3,6-tri-*O*-benzyl-ß-D-glucopyranoside (28).** Compound **27**[18] (234 mg, 0.23 mmol) was treated with *p*-methoxybenzyl chloride as described for the synthesis of compound **2** to yield **28** as a syrup (234 mg, 92%). (Column chromatography: *n*-hexane/EtOAc 8:2). $[\alpha]_D^{25}$ +1.54 (*c* 0.13, $CHCl_3$). ^{1}H NMR (360 MHz, $CDCl_3$): δ_H 7.77-6.76 (40H, arom.), 5.07-4.75 (10H, m), 4.56-4.23 (6H, m), 3.99-3.94 (2H, m), 3.80-3.37 (16H, m). ^{13}C NMR (90 MHz, $CDCl_3$): δ_C 158.9-113.5 (arom.), 102.8, 102.7 (C-1, C-1'), 82.9, 82.4, 81.5, 79.9, 76.7, 75.3, 72.9 (skeleton carbons), 75.4, 75.1, 74.2, 73.7, 72.4 (7 x CH_2), 68.3, 68.1 (C-6, C-6'), 55.5, 55.2 (2 x OCH_3). Anal. Calcd for $C_{73}H_{74}O_{13}$ (1159.36): C, 75.63; H, 6.43. Found: C, 75.76; H, 6.41. MALDI-TOF m/z calcd for $[M+Na]^+$: 1181.50, Found: 1181.77.

***p*-Methoxyphenyl 2,6-di-*O*-benzyl-4-*O*-(p-methoxybenzyl)-ß-D-galactopyranosyl-2,3,6-tri-*O*-benzyl-ß-D-glucopyranoside (29).** Compound **28** (110 mg, 0.01 mmol) was hydrogenolysed as described for the synthesis of compound **3** to obtain **29** as a syrup (16 mg, 17%). (Column chromatography: DCM/acetone 97:3, R_f 045). ^{1}H NMR (360 MHz, $CDCl_3$): δ_H 7.31-6.77 (33H, arom.), 5.06-4.27 (14H, m), 4.01-3.39 (19H, m). ^{13}C NMR (90 MHz, $CDCl_3$): δ_C 159.2-113.7 (arom.), 102.7 (C-1, C-1'), 82.9, 81.5, 80.7, 76.6, 75.5, 75.3, 74.0, 73.2 (skeleton carbons), 75.4, 75.1, 75.0, 74.7, 73.3, 73.1 (6 x CH_2), 68.3, 67.9 (C-6, C-6'), 55.6, 55.2 (2 x OCH_3). Anal. Calcd for $C_{62}H_{66}O_{13}$ (1019.18): C, 73.06; H, 6.53. Found: C, 73.16; H, 6.50. MALDI-TOF m/z calcd for $[M+Na]^+$: 1041.44, Found: 1041.39.

Another chromatographically uniform product with lower mobility (DCM/acetone 97:3, R_f 0.21) was also isolated (13 mg). MALDI-TOF m/z calcd. for $[M+Na]^+$ of mono-debenzylated derivative of **29**: 951.40, found: 951.30. The NMR spectra showed a mixture of isomers possessing the PMB group.

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