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. 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, 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.

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 and 4, 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 (Bu₄NHSO₄) affording a mixture of 8 and 9, respectively, whose separation has been accomplished by column chromatography. Subsequently, their p-methoxybenzylolation gave the acetal-containing substrates 10 and 12. Catalytic hydrogenolysis of 10 was let to go to
completion, furnishing the mono-deprotected 11. The NAP group of 12 could be selectively cleaved, as well, to give 13 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-(Naphthyl)methylation of the single free hydroxyl group of the $3,4\text{-}O$-Isopropylidene-$6\text{-}O$-(methoxydimethyl)methyl-$\beta$-$D$-galactopyranosyl-(1→6)-1,2:3,4-di-$O$-isopropylidene-$\alpha$-$D$-galactopyranose $22^{17}$ afforded $23$ from which, after mild acidic hydrolysis of the mixed acetal group followed by $p$-methoxybenzylolation 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 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 monodeprotected 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 measurements and its single peak in the mass spectrum (m/z: 951.30), as a mixture of mono-debenzylated derivatives of 29 (m/z calcld 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. 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 hydroganoanalysis, 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 F254 (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 MgSO₄, and concentrated in vacuum. The ¹H (360, 400 and 500 MHz) and ¹³C 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 Me₄Si (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-$\beta$-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°C; $[\alpha]_D^{25}$ -8.51 (c 0.67, CHCl$_3$). $^1$H NMR (360 MHz, CDCl$_3$): $\delta$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$_3$): $\delta$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)-$\beta$-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°C; $[\alpha]_D^{25}$ -25.65 (c 0.46, CHCl$_3$). $^1$H NMR (360 MHz, CDCl$_3$): $\delta$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$_3$): $\delta$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-$\beta$-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°C; $[\alpha]_D^{25}$ -8.3 (c 0.53, CHCl$_3$). $^1$H NMR (360 MHz, CDCl$_3$): $\delta$H 7.76-7.00 (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$_3$): $\delta$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 °C; [α]D25 +10.71 (c 0.42, CHCl3). 1H NMR (360 MHz, CDCl3): δ_H 7.33-6.81 (18H, m, arom.), 5.03-4.57 (7H, m, 3 x CH2, H-1), 3.88-3.84 (1H, m), 3.77 (3H, s, OCH3). Anal. Calcd for C38H35O8 (586.66): C, 71.82; H, 6.57. MALDI-TOF m/z calcd for [M+Na]+: 609.66, Found: 609.43.

**Methyl 4,6-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) Bu4N-NHSO4 (2.8 g, 8.2 mmol), 5% aq. NaOH (200 mL) and 2-(bromomethyl)naphthalene (20.8 g, 94 mmol, 1.4 equiv) 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 and 9.

(8) White needles, yield: 6.55 g (23%), mp. 199-201°C, [α]D25 +71.73 (c 0.19, CHCl3), (lit. 15 [α]D25 +69.9); Rf 0.28 (n-hexane/EtOAc 6:4). 1H NMR (500 MHz, CDCl3): δ_H 7.78-7.35 (12H, m, arom.), 5.52 (1H, s, Hac), 5.07-4.92 (2H, 2d, NAP-CH2), 4.73 (1H, d, 3_J1,2 = 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, OCH3). Anal. Calcd for C24H26O6 (422.47): C, 71.07; H, 6.20. Found: C, 71.29; H, 6.17.

(9) White needles, yield: 14.49 g (51%). [α]D25 +9.85 (c 0.13, CHCl3), mp = 165-166 °C, Rf 0.43 (n-hexane/EtOAc 6:4). 1H NMR (500 MHz, CDCl3): δ_H 7.77-7.29 (12H, m, arom.), 5.46 (1H, s, Hac), 4.91-4.78 (2H, 2d, NAP-CH2), 4.57 (1H, d, 3_J1,2 = 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, OCH3). Anal. Calcd for C24H26O6 (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, [α]D25 +45.04, (c 0.13, CHCl3). 1H NMR (500 MHz, CDCl3): δ_H 7.80-6.81 (16H, m, arom.), 5.54 (1H, s, Hac), 5.06-4.96 (2H, 2d, NAP-CH2), 4.78-4.63 (2H, dd, PMB-CH2), 4.56 (1H, d, 3_J1,2 = 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-OCH₃, 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, OCH₃). ¹³C NMR (125.7 MHz, CDCl₃): δ_C 152.5-152.2 (arom.), 119.9 (C-ac), 109.7 (C-1), 82.1, 79.2, 77.8, 67.8 (2 x CH₂), 65.0 (C-6), 56.2 (2 x OCH₃). Anal. Calcd for C₁₃H₂₃O₃ (542.62): C, 73.04; H, 6.32. Found: C, 72.89; H, 6.32.

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, [α]D +38. ¹H NMR (360 MHz, CDCl₃): δ_H 7.50-6.87 (9H, m, arom.), 5.51 (1H, s, H-ac), 4.72-4.61 (2H, dd, PMB-CH₂), 4.56 (1H, d, 3_J₁₂ = 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-OCH₃), 3.69 (1H, t, J = 10.1 Hz), 3.51-3.42 (2H, m), 3.36 (3H, s, OCH₃), 2.72 (1H, bs, OH). ¹³C NMR (90 MHz, CDCl₃): 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-CH₂), 68.9 (C-6), 55.3, 55.2 (2 x OCH₃). Anal. Calcd for C₂₂H₂₆O₇ (542.44): 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, [α]D +49.19 (c 0.62, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ_H 7.81-6.80 (16H, m, arom.), 5.52 (1H, s, H-ac), 4.99-4.78 (4H, m, NAP-CH₂, PMB-CH₂), 4.59 (1H, d, 3_J₁₂ = 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-OCH₃), 3.66 (1H, t, J = 10.0 Hz), 3.59-3.55 (2H, m), 3.39 (3H, s, OCH₃). ¹³C NMR (125.7 MHz, CDCl₃): 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 CH₂), 68.9 (C-6), 55.2, 55.1 (2 x OCH₃). Anal. Calcd for C₃₃H₄₃O₇ (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 hydrogenolyzed as described for the synthesis of compound 11 to obtain 13 as white crystals (92 mg, 78%). mp =168-169°C, [α]D +78.53 (c 0.11, CHCl₃), (lit. 16: mp = 174-175 °C, [α]D +45). ¹H NMR (360 MHz, CDCl₃): δ_H 7.51-6.83 (9H, m, arom.), 5.56 (1H, s, H-ac), 4.89-4.70 (2H, 2d, PMB-CH₂), 4.78 (1H, d, 3_J₁₂ = 3.8 Hz, H-1), 4.31-4.27 (1H, m), 3.86-3.64 (4H, m), 3.78 (3H, s, PMB-OCH₃), 3.62 (1H, t, J = 9.1 Hz), 3.44 (3H, s, OCH₃), 2.39 (1H, d, J = 7.2 Hz, OH). ¹³C NMR (90 MHz, CDCl₃): 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-CH₂), 69.0 (C-6), 55.3, 55.2 (2 x OCH₃). Anal. Calcd for C₂₂H₂₆O₇ (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, Rf 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) [α]D +77.31 (c 0.12, CHCl3), Rf 0.62 (DCM/ EtOAc 96:4), mp 89-90°C. 1H NMR (500 MHz, CDCl3): δH 7.84-6.82 (16H, m, arom.), 5.45 (1H, s, Hac), 4.98-4.86 (2H, 2d, Nap-CH2), 4.83-4.62 (2H, 2d, PMB-CH2), 4.72 (1H, d, 3J1,2 = 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-OCH3), 3.48 (1H, s), 3.34 (3H, s, OCH3). 13C NMR (125.7 MHz, CDCl3): δC 159.2-113.6 (arom.), 100.9 (Cac), 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 CH2), 69.2 (C-6), 55.3, 55.1 (2 x OCH3). Anal. Caled for C33H34O7 (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) [α]D +62.60 (c 0.12, CHCl3), Rf 0.66 (DCM/ EtOAc 96:4), mp 101-103°C. 1H NMR (500 MHz, CDCl3): δH 7.79-6.83 (16H, m, arom.), 5.44 (1H, s, Hac), 5.02-4.67 (4H, 4d, Nap-CH2, PMB-CH2), 4.77 (1H, d, 3J1,2 = 3.5 Hz, H-1), 4.15 (1H, dd, 3J6a,6b = 1.5 Hz, 2J6a,6b = 12.5 Hz, H-6a), 4.12 (1H, d, H-4), 4.10 (1H, dd, 3J2,3 = 10.0 Hz, H-2), 3.98 (1H, dd, 3J3,4 = 3.5 Hz, H-3), 3.95 (1H, dd, 3J5,6b = 1.5 Hz, H-6b), 3.75 (3H, s, PMB-OCH3), 3.52 (1H, s, H-5), 3.37 (3H, s, OCH3). 13C NMR (125.7 MHz, CDCl3): δC 159.1-113.6 (arom.), 100.9 (Cac), 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 CH2), 69.2 (C-6), 55.4, 55.1 (2 x OCH3). Anal. Caled for C33H34O7 (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). [α]D +60.20 (c 0.50, CHCl3), mp 92-95°C. 1H NMR (360 MHz, CDCl3): δH 7.50-6.85 (9H, m, arom.), 5.54 (1H, s, Hac), 4.74 (1H, d, 3J1,2 = 4.0 Hz, H-1), 4.74-4.57 (2H, 2d, PMB-CH2), 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, OCH3). 13C NMR (90 MHz, CDCl3): δC 159.3-113.8 (arom.), 101.1 (Cac), 98.9 (C-1), 76.3, 76.0 68.4, 62.2 (C-2, C-3, C-4, C-5), 72.9 (PMB-CH2), 69.3 (C-6), 55.5, 55.2 (2 x OCH3). Anal. Caled for C22H26O7 (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). [α]D +176.87 (c 0.15, CHCl3), mp 175-176°C. 1H NMR (360 MHz, CDCl3): δH 7.53-6.84 (9H, m, arom.), 5.45 (1H, s, Hac), 4.94 (1H, d, 3J1,2 = 3.6 Hz, H-1), 4.69-4.62 (2H, 2d, PMB-CH2), 4.25 (1H, dd, 3J5,6a = 1.5 Hz, 2J6a,6b = 12.4 Hz, H-6a), 4.21-4.17 (2H, m, H-2, H-4), 4.02 (1H, dd, 3J5,6b = 1.5 Hz, H-6b),
To a stirred solution of Methyl 2-(2-naphthyl)methyl-2-(3,4-methoxybenzyl)-1,2:3,4-di-O-β-D-galactopyranoside (21), 1,2:3,4-di-O-α-D-galactopyranose (23). To a stirred solution of compound 20 (50 mg, 0.15 mmol) in pyridine (1 mL) Ac₂O (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%). [α]D²⁵ +15.31 (c 0.11, MeOH). ¹H NMR (500 MHz, CDCl₃): δ 7.54-6.84 (9H, arom.), 5.47 (1H, s, Hα), 5.31 (1H, dd, ³J₂₃ = 10.5 Hz, H-2), 5.06 (1H, d, ³J₁₂ = 3.4 Hz, H-1), 4.67-4.59 (2H, 2d, PMB-CH₂), 4.24 (1H, d, ²J₆₆₈ = 12.4 Hz, H-6a), 4.16 (1H, d, ³J₃₄ = 3.2 Hz, H-4), 4.01 (1H, d, H-6b), 3.96 (1H, dd, H-3), 3.79 (3H, s, PMB-OCH₃), 3.38 (3H, s, OCH₃), 2.10 (3H, s, CH₃). ¹³C NMR (125.7 MHz, CDCl₃): δ 170.2 (CO), 159.2-113.7 (arom.), 101.0 (C₁), 78.7, 73.6, 71.9, 71.3, 70.7, 70.4, 67.3 (skeleton carbons), 73.3 (¹⁰¹NAP-CH₂), 69.2, 60.1 (C-6, C-6'), 48.5 (MIP-OCH₃), 27.6, 26.3, 26.0, 25.9, 24.9, 24.3, 24.2 (6 x CH₃). Anal. Calcd for C₃₆H₅₀O₁₂ (674.77): C, 64.08; H, 7.47. Found: C, 64.17; H, 7.44.

3,4-O-Isopropylidene-2-O-(2-naphthyl)methyl-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. NaHCO₃ and water, dried, filtered and evaporated. Purification by column chromatography resulted in compound 24 as white crystals (0.67 g, 73%). [α]D²⁵ +1.59 (c 0.16, CHCl₃). mp:154-156°C. ¹H NMR (360 MHz, CDCl₃): δH 7.88-7.43 (7H, arom.), 7.91-7.42 (2H, m, NAP-CH₂), 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, OCH₃), 1.55, 1.46, 1.35, 1.34, 1.33, 1.32, 1.29, 1.20 (24H, 8 x s, 8 x CH₃). ¹³C NMR (90 MHz, CDCl₃): δC 136.0-125.5 (arom.), 109.6, 109.2, 108.5 (3 x Cα), 103.7, 96.3 (C-1, C-1'), 100.0 (MIP-Cα), 78.7, 73.6, 71.9, 71.3, 70.7, 70.4, 67.3 (skeleton carbons), 73.3 (¹⁰¹NAP-CH₂), 69.2, 60.1 (C-6, C-6'), 48.5 (MIP-OCH₃), 27.6, 26.3, 26.0, 25.9, 24.9, 24.3, 24.2 (6 x CH₃). Anal. Calcd for C₃₆H₅₀O₁₂ (674.77): C, 64.08; H, 7.47. Found: C, 64.17; H, 7.44.
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 CH₃). ¹³C NMR (90 MHz, CDCl₃): δC 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-CH₂), 68.9 (C-6), 62.4 (C-6’), 27.6, 26.3, 26.0, 25.9, 24.9, 24.3 (8 x CH₃). Anal. Calcd for C₃₂H₄₂O₁₁ (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). [α]D⁺²⁵ +0.46 (c 0.19, CHCl₃). ¹H NMR (360 MHz, CDCl₃): δH 7.88-6.84 (11H, arom.), 5.59 (1H, d, J = 5.1 Hz, H-1), 5.06-5.00 (2H, m, NAP-CH₂), 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, OCH₃), 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 CH₃). ¹³C NMR (90 MHz, CDCl₃): δC 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 CH₂), 68.5, 67.9 (C-6, C-6’), 55.1 (OCH₃), 27.6, 26.3, 26.0, 25.9, 24.9, 24.3 (6 x CH₃). Anal. Calcd for C₄₀H₅₀O₁₂ (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 hydrogenolyzed as described for the synthesis of compound 11 to obtain 26 as a syrup (441 mg, 71%). (Column chromatography: DCM/acetone 9:1). [α]D⁺²⁵ +0.51 (c 0.16, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δH 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, OCH₃), 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 CH₃). ¹³C NMR (125.7 MHz, CDCl₃): δC 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-CH₂), 69.1, 68.9 (C-6, C-6’), 55.1 (OCH₃), 28.0, 26.2, 25.9, 25.8, 24.8 (6 x CH₃). Anal. Calcd for C₂₉H₁₄O₁₂ (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-β-D-galactopyranosyl-2,3,6-tri-O-benzyl-β-D-glucopyranoside (28). Compound 27 (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). [α]D⁺²⁵ +1.54 (c 0.13, CHCl₃). ¹H NMR (360 MHz, CDCl₃): δH 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). ¹³C NMR (90 MHz, CDCl₃): δC 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 CH₂), 68.3, 68.1 (C-6, C-6’), 55.5, 55.2 (2 x OCH₃). Anal. Calcd for C₇₃H₇₄O₁₃ (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)-β-D-galactopyranosyl-2,3,6-tri-O-benzyl-β-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$_f$ 0.045). $^1$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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References and Notes

13. This observation is in good correlation with the results of Spencer et al. (see Ref. 6). They assumed, that substitution of the aromatic ring could have an adverse steric effect that would interfere with the planar geometry required for effective binding and thus reduce its affinity for the metal surface. However, the Spencer group investigated only the selective hydrogenolysis of NAP in the presence of benzyl ethers, esters or carbamates (See Ref 6-8).