β-Selective C-Mannosylation of Electron-Rich Phenols

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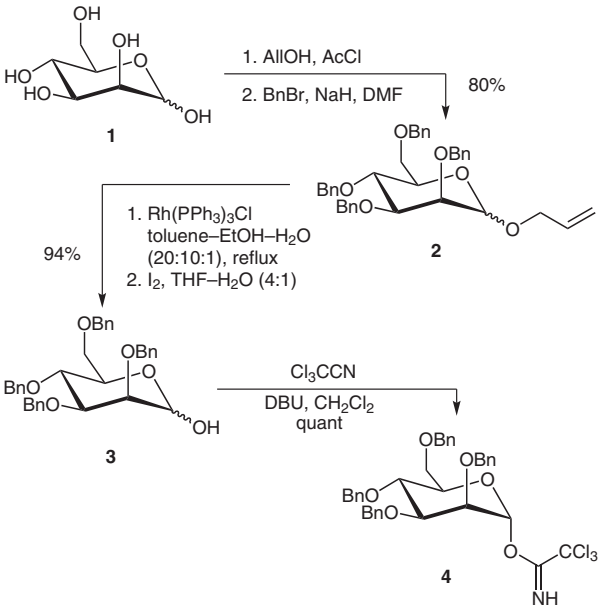
Abstract: The reaction of tetra-*O*-benzylmannosyl trichloroacetimidate with electron-rich phenols in the presence of TMSOTf surprisingly leads to the exclusive formation of aryl β-*C*-glycosides while a preference for the α-anomer could be observed with other Lewis acids such as $ZnCl_2$.

Key words: glycosylation, phenols, *C*-glycosides, Lewis acids, anomers

Due to the cooperation between the anomeric effect and steric hindrance or neighboring group participation, the synthesis of β-*O*-mannosides remains a challenging task that has attracted considerable attention.[1] Most notably, indirect methods, for example, via intramolecular aglycone delivery[2–4] or via inversion of configuration at C-2, for example, by intramolecular S_N2 reaction have been developed.[1,5] Successful direct syntheses either use Königs–Knorr type reactions[6] or dehydrative mannosylation,[7,8] but they are often limited to certain types of glycosyl acceptors. While the preference for α-*O*-mannoside formation is notorious, the C-mannosylation of electron-rich phenols using tetra-*O*-benzylmannosyl trichloroacetimidate surprisingly produced pure β-*C*-mannosides when trimethylsilyl trifluoromethanesulfonate was used as the activating agent. *C*-Glycosides are inherently inert against degradation by acid or hydrolytic enzymes and have frequently been employed as metabolically stable mimetics for *O*-glycosides. *C*-Glycosides with an aromatic or heteroaromatic aglycone have been isolated from natural sources and some of these compounds have been found to exhibit potent antibacterial and antiproliferative activity.[9] A prominent and useful method for their preparation is the *ortho*-C-glycosylation of electron-rich phenols,[10–16] which has been suggested to proceed in a stepwise fashion through intermediate formation of the *O*-glycoside followed by a Fries-type O/C-rearrangement induced by the Lewis acidic reaction conditions.[13,17,18] In addition to the high regioselectivity, a high β-selectivity is typically observed in the *gluco* and *galacto* series.[10,16,19]

In an attempt to prepare aryl *C*-mannosides as precursors for metabolically stable trisaccharide mimetics, several mannosyl donors were prepared and tested in the *ortho*-mannosylation of phenols. The trichloroacetimidates introduced by Schmidt[20] exhibited a favorable reactivity and permitted the C-glycosylation under relatively mild conditions in combination with TMSOTf as the promoter.[19,21] The O/C-rearrangement appears to be sensitive to the electronic properties of the protecting groups since tetra-*O*-acetyl-α-mannosyl trichloroacetimidate gave only the *O*-glycoside[22] while the tetra-*O*-benzyl derivative **4** smoothly yielded the desired *C*-glycosides.[19] Glycosyl donor **4** was prepared from D-mannose in five steps according to known procedures[23–27] in 75% overall yield (Scheme 1).



Scheme 1 Synthesis of 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl trichloroacetimidate (**4**) from D-mannose

The reaction of **4** with 2-naphthol (**5**) and TMSOTf furnished a single product in 63% yield, which could be identified as the *C*-mannoside **6** (Scheme 2). Since the determination of the configuration at the anomeric center in *O*-mannosides can not be based on the vicinal coupling constant of H-1, a NOESY NMR experiment was performed to elucidate the relative configuration.

As expected for the β-anomer, there were NOE interactions between H-1, H-3, and H-5 of about the same intensity as the H-1/H-2 interaction.[28] This result had to be verified for other *C*-mannosides. Therefore, mannosyl donor **4** was coupled with different electron-rich phenols under identical conditions to furnish the corresponding *C*-glycosides (Table 1). In every case, only a single product was obtained. The NOESY spectra of the products showed the same H-1/H-3/H-5 triaxial arrangement found

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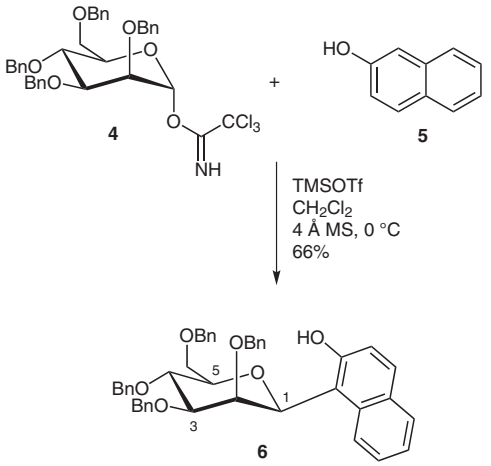
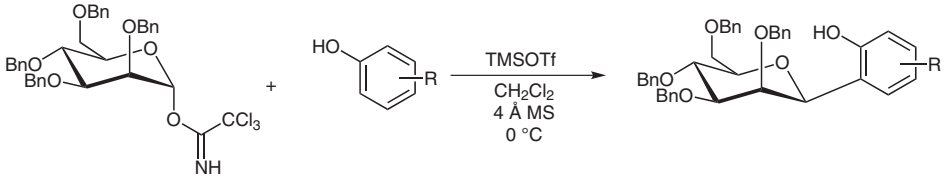


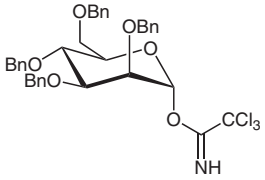
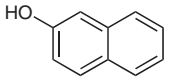
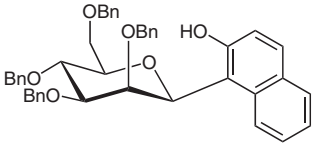
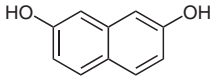
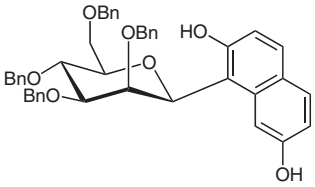
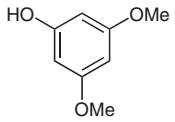
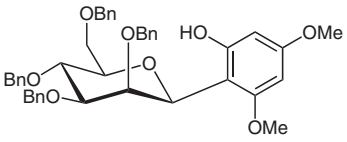
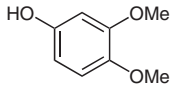
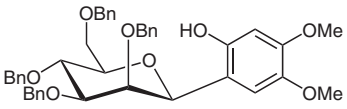
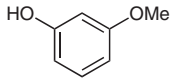
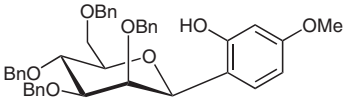
Scheme 2 Selective β-C-glycosylation of 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl trichloroacetimidate (**4**)

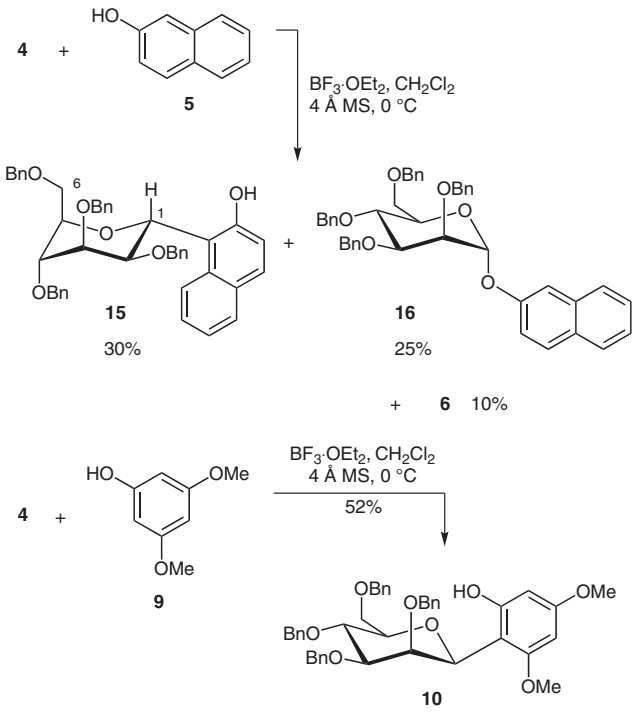
for glycoside **6**. Thus, mannose surprisingly behaves similar to glucose[19] and galactose[16] with respect to the stereochemical preference in this type of C-glycosylation.

With a reliable protocol for a β-selective *ortho*-C-mannosylation in hand, we sought for an α-selective counterpart. By applying conditions, which gave poor anomeric selectivities in other C-glycosylations to the mannosylation of 2-naphthol (**5**),[10] $BF_3{\cdot}OEt_2$ was found to produce a mixture of the α-*O*-mannoside (25%) and the β-*C*-mannoside **6** (10%) along with 30% of the α-*C*-mannoside **15**. The latter compound exhibited an unusual coupling pattern in its ^1H NMR spectrum, which can be attributed to an inversion of the ring conformation.[29] Presumably, the steric repulsion of the aryl substituent with H-3 and H-5 in the $^4C_1$ conformation accounts for this behavior. In agreement with an inverted ring conformation, the NOESY spectrum of **15** showed a remarkably strong NOE contact between H-1 and H-6a. When applied to 3,5-dimethoxyphenol (**9**), the $BF_3{\cdot}OEt_2$-catalyzed mannosylation led, however, exclusively to the β-*C*-mannoside **10** (Scheme 3).

Table 1 Synthesis of Aryl β-*C*-Mannosides

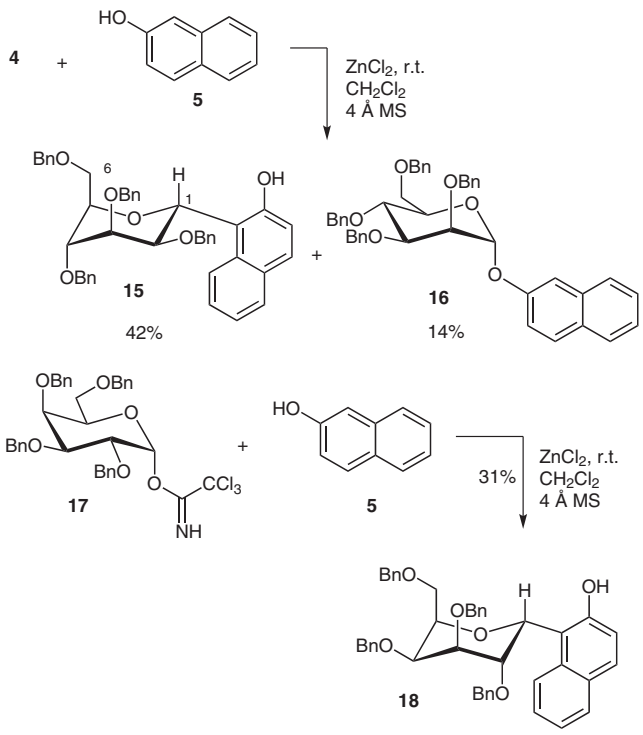


Donor	Acceptor	Product	Yield (%)
 **4**	 **5**	 **6**	66
4	 **7**	 **8**	53
4	 **9**	 **10**	57
4	 **11**	 **12**	49
4	 **13**	 **14**	45



Scheme 3 C-Mannosylations with $BF_3{\cdot}OEt_2$

Further screening of Lewis acids for the C-mannosylation of 2-naphthol (**5**) and optimization of the conditions showed the highest α-selectivity for $ZnCl_2$ (Scheme 4), which gave **15** in 42% isolated yield. To prove that this phenomenon is not only limited to mannosylation of naphthols, the same reaction was applied to the benzylated galactosyl donor **17**.[27] α-*C*-Galactoside **18** was formed in 31% yield showing the same ring inversion as **15** (Scheme 4).



Scheme 4 α-C-glycosylation with $ZnCl_2$

In summary, C-glycosylation of various electron-rich phenols with 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl trichloroacetimidate (**4**) using TMSOTf as the promoter gave exclusively the corresponding β-*C*-mannosides. The reaction of 2-naphthol (**5**) with donor **4** in the presence of $BF_3{\cdot}OEt_2$ or $ZnCl_2$ mainly furnished the corresponding α-*C*-mannoside **15**, which showed an inversion of the pyranose ring. The latter promoter also permits the preparation of α-*C*-galactosides.

The trichloroacetimidates **4** and **17** were prepared according to known procedures.[15–18] Moisture sensitive reactions were carried out under argon atmosphere in dried glassware sealed by rubber septa. Unless otherwise specified, chemicals were obtained from commercial suppliers and used without further purification. CH_2Cl_2 was dried over CaH_2 and distilled under argon atmosphere prior to use. Flash chromatography was performed on silica gel 60 (0.035–0.070 mm, Acros). Chromatography solvents (cyclohexane, EtOAc) were distilled prior to use. For analytical TLC, Merck glass plates (60 F_{254}) were used. Visualization was accomplished by UV (254 nm) and sugar reagent (1 M ethanolic H_2SO_4/0.2% ethanolic 3-methoxyphenol solution, 1:1).[30] ^1H and ^{13}C NMR spectra were recorded on a Bruker AV 400 or DRX 500 in $CDCl_3$ or CD_3OD using the residual solvent peak as internal reference ($CDCl_3$, $\delta_H = 7.26$, $\delta_C = 77.16$, CD_3OD, $\delta_H = 3.31$, $\delta_C = 49.0$). Optical rotations were measured at r.t. on a Krüss P8000 polarimeter at 589 nm. IR spectra were recorded on a ThermoNicolet Avatar 370 FT-IR spectrometer. FAB mass spectrometry was carried out on with a VG70S (Xe-FAB ionization) with *m*-nitrobenzyl alcohol as matrix. For exact mass determination (FAB-HRMS), PEG 300 or PEG 600 was used as the internal standard.

β-*C*-Arylmannosides from Trichloroacetimidate 4 with TMSOTf as Promoter; General Procedure

A mixture of 2,3,4,6-tetra-*O*-benzylmannopyranosyl trichloroacetimidate (**4**), phenol, and activated 4 Å molecular sieves (1 g) in anhyd CH_2Cl_2 (8 mL) was stirred at 0 °C for 20 min under argon to remove traces of H_2O from the reactants. Then, TMSOTf in anhyd CH_2Cl_2 (2 mL) was added and the mixture was stirred until TLC-monitoring showed no further progress. The reaction was quenched by the addition of sat. aq $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by flash chromatography (cyclohexane–EtOAc) (Table 1).

1-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-mannopyranosyl)naphthalen-2-ol (6)

The title compound was prepared according to the general procedure from **4** (54.2 mg, 79.1 μmol, 1 equiv), 2-naphthol (**5**; 13.4 mg, 95.7 μmol, 1.2 equiv), and TMSOTf (17.6 mg, 79.1 μmol, 1 equiv) within a reaction time of 3 h. Purification by flash chromatography (cyclohexane–EtOAc, 10:1) afforded **6** as a colorless oil (35 mg, 52.5 μmol, 66%); $[\alpha]_D^{20}$ +45.1 (c = 1.0, $CHCl_3$); R_f = 0.40 (cyclohexane–EtOAc, 10:1).

IR (film): 3345, 3029, 3866, 1622, 1453, 1406, 1228, 1102, 1026, 735, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.14 (s, 1 H, OH), 7.76 (d, $^3J_{5,6}$ = 8.0 Hz, 1 H, H-5), 7.70 (d, $^3J_{3,4}$ = 8.9 Hz, 1 H, H-4), 7.45–7.19 (m, 18 H, H-7, H-6, H-8, Ph-H), 7.14 (d, $^3J_{3,4}$ = 8.9 Hz, 1 H, H-3), 7.11–7.02 (m, 3 H, Ph-H), 6.97 (br d, ^3J = 6.6 Hz, 2 H, Ph-H), 5.39 (br s, 1 H, H-1′) 4.95 (d, ^2J = 10.8 Hz, 1 H, CH_{2a}Ph), 4.72 (d,

^2J = 11.7 Hz, 1 H, CH_{2a}Ph), 4.69 (d, ^2J = 11.7 Hz, 1 H, CH_{2b}Ph), 4.68 (d, ^2J = 12.2 Hz, 1 H, CH_{2a}Ph), 4.58 (d, ^2J = 10.8 Hz, 1 H, CH_{2b}Ph) 4.54 (d, ^2J = 12.2 Hz, 1 H, CH_{2b}Ph), 4.40 (d, ^2J = 11.6 Hz, 1 H, CH_{2a}Ph), 4.28 (pseudo t, $^3J_{3',4'} \approx {}^3J_{4',5'} \approx$ 9.5 Hz, 1 H, H-4′), 4.22 (d, ^2J = 11.6 Hz, 1 H, CH_{2b}Ph), 4.12 (d, $^3J_{2',3'}$ = 2.7 Hz, 1 H, H-2′), 3.86 (dd, $^3J_{3',4'}$ = 9.5 Hz, $^3J_{2',3'}$ = 2.7 Hz, 1 H, H-3′), 3.84–3.78 (m, 2 H, H-6a′, H-6b′), 3.70–3.64 (m, 1 H, H-5′).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 156.0 (C-2), 138.5, 138.3, 138.2, 138.0 (C-1″), 131.1 (C-8a), 130.2 (C-4), 129.2 (C-5), 128.6, 128.6, 128.5, 128.2, 128.0, 127.8, 127.7, 127.3 (20 CH Ph), 126.8 (C-8), 122.6 (C-6), 121.8 (C-4a), 120.4 (C-3), 120.3 (C-7), 111.5 (C-1), 84.0 (C-3′), 79.9 (C-5′), 79.1 (C-1′), 76.4 (C-2′), 75.5 (*C*H_2Ph), 74.9 (*C*H_2Ph), 74.3 (C-4′), 73.6 (*C*H_2Ph), 72.4 (*C*H_2Ph), 68.6 (C-6′).

FAB-MS: *m*/*z* (%) = 666.5 (33, $[M]^+$), 181.1 (100, matrix).

FAB-HRMS: *m*/*z* calcd for $[C_{44}H_{42}O_6]^+$: 666.2981; found: 666.3008.

1-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-mannopyranosyl)naphthalene-2,7-diol (8)

The title compound was prepared according to the general procedure from **4** (134.0 mg, 0.196 mmol, 1.0 equiv), 2,7-dihydroxynaphthalene (**7**; 84.1 mg, 0.525 mmol, 2.5 equiv), and TMSOTf (52 mg, 0.234 mmol, 1.2 equiv) within a reaction time of 2.5 h. Purification by flash chromatography (cyclohexane–EtOAc, 4:1) afforded **8** as a colorless oil (70.2 mg, 103 µmol, 53%); $[\alpha]_D^{23}$ +68.1 (*c* = 1, $CDCl_3$); R_f = 0.24 (cyclohexane–EtOAc, 4:1).

IR (film): 3372, 3247, 2869, 1693, 1453, 1218, 1109, 834, 751 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.65 (d, $^3J_{5,6}$ = 8.8 Hz, 1 H, H-5), 7.64 (d, $^3J_{3,4}$ = 8.9 Hz, 1 H, H-4), 7.41–7.20 (m, 15 H, Ph-H), 7.13–7.03 (m, 4 H, H-8, 3 Ph-H), 6.93 (d, *J* = 8.7, 3 H, H-6, 2 Ph-H), 6.88 (d, $^3J_{3,4}$ = 8.8 Hz, 1 H, H-3), 5.42 (br s, 1 H, H-1′), 4.89 (d, ^2J = 11.0 Hz, 1 H, CH_{2a}Ph), 4.66 (s, 2 H, CH_2Ph), 4.63 (d, ^2J = 12.1 Hz, 1 H, CH_{2a}Ph), 4.58 (d, ^2J = 11.0 Hz, 1 H, CH_{2b}Ph), 4.51 (d, ^2J = 12.1 Hz, 1 H, CH_{2b}Ph), 4.27 (d, ^2J = 11.3 Hz, 1 H, CH_{2a}Ph), 4.23 (m, 2 H, H-2′, H-4′), 4.11 (d, ^2J = 11.3, 1 H, CH_{2b}Ph), 3.95 (dd, $^3J_{3',4'}$ = 9.5 Hz, $^3J_{2',3'}$ = 2.9 Hz, 1 H, H-3′), 3.83 (dd, $^2J_{6a',6b'}$ = 10.7 Hz, $^3J_{5,6a}$ = 3.4 Hz, 1 H, H-6a′), 3.77 (dd, $^2J_{6a',6b'}$ = 10.7 Hz, $^3J_{5',6b'}$ = 2.1 Hz, 1 H, H-6b′), 3.66 (ddd, $^3J_{4',5'}$ = 9.8 Hz, $^3J_{5',6a'}$ = 3.2 Hz, $^3J_{5',6b'}$ = 2.4 Hz, 1 H, H-5′).

^{13}C NMR (100.6 MHz, CD_3OD): δ = 158.1 (C-7), 157.7 (C-2), 140.7, 140.6, 140.3, 140.1 (C-1″), 135.1 (C-8a), 132.3, 138.6 (C-4, C-5), 130.3, 130.2, 130.1, 130.0, 129.8, 129.7, 129.6, 129.5 (20 CH Ph), 129.2 (C-8), 125.8 (C-4a), 118.2 (C-3), 116.5 (C-6), 112.8 (C-1), 85.9 (C-3′), 81.5 (C-5′), 80.9 (C-1′), 78.0 (C-2′). 77.0, 76.6 (*C*H_2Ph), 76.2 (C-4′), 75.2, 74.1 (*C*H_2Ph), 70.5 (C-6′).

FAB-MS: *m*/*z* (%) = 683.5 (8, $[M + H]^+$), 181.1 (100, matrix).

FAB-HRMS: *m*/*z* calcd for $[C_{44}H_{42}O_7 + H]^+$: 683.3003; found: 683.3002.

2-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-mannopyranosyl)-3,5-dimethoxyphenol (10)[31]

The title compound was prepared according to the general procedure from **4** (95.2 mg, 0.139 mmol, 1.0 equiv), 3,5-dimethoxyphenol (**9**; 23.6 mg, 0.153 mmol, 1.1 equiv), and TMSOTf (38 mg, 0.17 mmol, 1.2 equiv) within a reaction time of 1.5 h. Purification by flash chromatography (cyclohexane–EtOAc, 15:1) afforded **10** as a colorless oil (53.2 mg, 79 µmol, 57%); $[\alpha]_D^{26}$ +19.6 (*c* = 1, $CHCl_3$); R_f = 0.24 (cyclohexane–EtOAc, 15:1).

IR (film): 3346, 2864, 1529, 1453, 1359, 1211, 1106, 736, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (s, 1 H, OH), 7.37–7.12 (m, 20 H, Ph-H), 6.11 (d, $^4J_{4,6}$ = 2.4 Hz, 1 H, H-6), 5.93 (d, $^4J_{4,6}$ = 2.4 Hz, 1 H, H-4), 4.93 (br s, 1 H, H-1′), 4.91 (d, ^2J = 10.9 Hz, 1 H, CH_{2a}Ph), 4.68 (s, 2 H, CH_2Ph), 4.63 (d, ^2J = 12.3 Hz, 1 H, CH_{2a}Ph), 4.57–4.50 (m, 3 H, CH_2Ph), 4.45 (d, ^2J = 11.8 Hz, 1 H, CH_{2b}Ph), 4.15 (pseudo t, $^3J_{3,4,5}$ = 9.7 Hz, 1 H, H-4′), 3.94 (pd, $^3J_{2,3}$ = 1.9 Hz, 1 H, H-2′), 3.78 (s, 3 H, OCH_3), 3.75–3.69 (m, 3 H, H-3′, H-6a′, H-6b′), 3.67 (s, 3 H, OCH_3), 3.54 (ddd, $^3J_{4,5}$ = 9.7 Hz, $^3J_{5,6a}$ = 3.4 Hz, $^3J_{5,6b}$ = 2.2 Hz, 1 H, H-5′).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.9 (C-5), 158.9 (C-1), 157.0 (C-3), 138.5, 138.4, 138.3, 138.2 (C-1″), 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.4, 127.2 (20 CH Ph), 103.2 (C-2), 94.4 (C-6), 90.2 (C-4), 84.0 (C-3′), 79.5 (C-5′), 76.7 (C-1′), 76.0 (C-2′), 75.3, 74.5 (2 *C*H_2Ph), 74.3 (C-4′), 73.4, 72.2 (2 *C*H_2Ph), 68.6 (C-6′), 55.4, 55.3 (OCH_3).

FAB-MS: *m*/*z* (%) = 677.2 (25, $[M + H]^+$), 195.0 (43), 181.1 (100, matrix).

FAB-HRMS: *m*/*z* calcd for $[C_{42}H_{44}O_8 + H]^+$: 677.3109; found: 677.3129.

2-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-mannopyranosyl)-4,5-dimethoxyphenol (12)[31]

The title compound was prepared according to the general procedure from **4** (150.1 mg, 0.219 mmol, 1.1 equiv), 3,4-dimethoxyphenol (**11**; 30.8 mg, 0.200 mmol, 1.1 equiv), and TMSOTf (56.3mg, 0.253 mmol, 1.2 equiv) within a reaction time of 2 h. Purification by flash chromatography (cyclohexane–EtOAc, 3:1) afforded **12** as a colorless oil (66.0 mg, 98 µmol, 49%); $[\alpha]_D^{26}$ +10.1 (*c* = 1, $CHCl_3$); R_f = 0.20 (cyclohexane–EtOAc, 3:1).

IR (film): 3385, 3029, 2864, 1631, 1518, 1453, 1202, 1117, 737, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (s, 1 H, OH), 7.40–7.10 (m, 20 H, Ph-H), 6.49 (s, 1 H, H-3), 6.34 (s, 1 H, H-6), 4.92 (d, ^2J = 10.8 Hz, 1 H, CH_{2a}Ph), 4.75–4.68 (m, 2 H, CH_2Ph), 4.66–4.62 (m, 2 H, CH_2Ph), 4.58 (d, ^2J = 10.8 Hz, 1 H, CH_{2b}Ph), 4.56–4.48 (m, 2 H, CH_2Ph), 4.47 (br s, 1 H, H-1′), 4.18 (pseudo t, $^3J_{3,4} \approx {}^3J_{3,5} \approx$ 9.6 Hz, 1 H, H-4′), 3.96 (d, $^3J_{2,3}$ = 1.8 Hz, 1 H, H-2′), 3.87 (s, 3 H, OCH_3), 3.79–3.71 (m, 3 H, H-3′, H-6a′, H-6b′), 3.75 (s, 3 H, OCH_3), 3.59–3.53 (m, 1 H, H-5′).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 151.5 (C-1), 150.1, 142.2 (C-4, C-5), 138.6, 138.5, 138.1 (4 C-1″), 128.8, 128.7, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.8 (20 CH Ph), 112.9 (C-2), 111.6 (C-3), 102.2 (C-6), 84.5 (C-3′), 82.6 (C-1′), 79.1 (C-5′), 78.0 (C-2′), 75.4, 74.9 (*C*H_2Ph), 74.6 (C-4′), 73.8, 72.6 (*C*H_2Ph), 69.0 (C-6′), 57.0, 56.2 (OCH_3).

FAB-MS: *m*/*z* (%) = 676.2 (92 $[M]^+$), 195.0 (47), 181.1 (100, matrix).

FAB-HRMS: *m*/*z* calcd for $C_{42}H_{44}O_8$: 676.3036; found: 676.3014.

2-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-mannopyranosyl)-5-methoxyphenol (14)

The title compound was prepared according to the general procedure from **4** (150.1 mg, 0.219 mmol, 1.1 equiv), 3-methoxyphenol (**13**) (24.8 mg, 0.200 mmol, 1.0 equiv), and TMSOTf (56.3 mg, 0.253 mmol, 1.2 equiv) within a reaction time of 2.5 h. Purification by flash chromatography (cyclohexane–EtOAc, 6:1) afforded **14** as a colorless oil (57.7 mg, 89 µmol, 45%); $[\alpha]_D^{23}$ –1.3 (*c* = 1, $CDCl_3$); R_f = 0.18 (cyclohexane–EtOAc, 5:1).

IR (film): 3355, 3029, 2866, 1596, 1511, 1453, 1149, 1107, 1038, 737, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (s, 1 H, OH), 7.37–7.14 (m, 20 H, Ph-H), 6.78 (d, $^3J_{3,4}$ = 8.5 Hz, 1 H, H-3), 6.47 (d, $^4J_{4,6}$ = 2.5 Hz, 1 H, H-6), 6.36 (dd, $^3J_{3,4}$ = 8.5 Hz, $^4J_{4,6}$ = 2.5 Hz, 1 H, H-4), 4.91 (d, ^2J = 10.8 Hz, 1 H, CH_{2a}Ph), 4.69 (m, 2 H, CH_2Ph), 4.65 (d, ^2J = 12.3 Hz, 1 H, CH_{2a}Ph), 4.61 (d, ^2J = 11.5 Hz, 1 H, CH_{2a}Ph), 4.58 (d, ^2J = 10.8 Hz, 1 H, CH_{2b}Ph), 4.53 (d, ^2J = 12.3 Hz, 1 H,

CH_{2b}Ph), 4.51 (br s, 1 H, H-1′), 4.48 (d, ^2J = 11.5 Hz, 1 H, CH_{2b}Ph), 4.16 (pseudo t, $^3J_{3,4} \approx {}^3J_{3,5} \approx$ 9.5 Hz, 1 H, H-4′), 3.96 (pseudo d, $^3J_{2,3}$ = 1.7 Hz, 1 H, H-2′), 3.79 (s, 3 H, OCH_3), 3.77 (m, 2 H, H-6′), 3.73 (dd, $^3J_{3,4}$ = 9.5 Hz, $^3J_{2,3}$ = 2.6 Hz, 1 H, H-3′), 3.55 (ddd, $^3J_{4,5}$ = 9.5 Hz, $^3J_{5,6a}$ = 3.6 Hz, $^3J_{5,6b}$ = 2.3 Hz, 1 H, H-5′).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 161.0 (C-5), 158.3 (C-1), 138.6, 138.5, 138.2 (4 C-1″), 128.8 (C-3), 128.7, 128.6, 128.4, 128.1, 128.0, 127.9, 127.8, (20 CH Ph), 115.2 (C-2), 106.0 (C-4), 102.8 (C-6), 84.4 (C-3′), 82.7 (C-1′), 79.9 (C-5′), 78.6 (C-2′), 75.7, 75.0 (*C*H_2Ph), 74.6 (C-4′), 73.8, 72.5 (*C*H_2Ph), 69.0 (C-6′), 55.6 (OCH_3).

FAB-MS: *m*/*z* (%) = 646.4 (15, $[M]^+$), 181.1 (100, matrix).

FAB-HRMS: *m*/*z* calcd for $[C_{41}H_{42}O_7]^+$: 646.2931; found: 646.2934.

C-Arylmannosides from Trichloroacetimidate 4 with BF_3·OEt_2 as Promoter; 1-(2′,3′,4′,6′-Tetra-*O*-benzyl-α-D-mannopyranosyl)naphthalen-2-ol (15)

A mixture of 2,3,4,6-tetra-*O*-benzylmannopyranosyl trichloroacetimidate (**4**; 51.3 mg, 75 μmol, 1 equiv), 2-naphthol (**5**; 13.0 mg, 90 μmol, 1.2 equiv), and dried 4 Å molecular sieves (1 g) in anhyd CH_2Cl_2 (4 mL) was stirred at 0 °C for 20 h under argon. Then, BF_3·OEt_2 (27.9 μL, 31.5 mg, 222 μmol, 3 equiv) in anhyd CH_2Cl_2 (1 mL) was added and the mixture was stirred for 3 h. The reaction was quenched with sat. aq $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (cyclohexane–EtOAc, 4:1) afforded **15** as a colorless oil (14.8 mg, 22 μmol, 30%); $[\alpha]_D^{26}$ –22.9 (*c* = 1.0, $CHCl_3$); R_f = 0.45 (cyclohexane–EtOAc, 9:1).

IR (film): 3373, 2360, 1658, 1629, 1495, 1453, 1091, 1070, 1028 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.77 (s, 1 H, OH), 7.94 (d, $^3J_{7,8}$ = 8.6 Hz, 1 H, H-8), 7.77 (d, $^3J_{5,6}$ = 8.3 Hz, 1 H, H-5), 7.75 (d, $^3J_{3,4}$ = 8.8 Hz, 1 H, H-4), 7.41 (m, 1 H, H-7), 7.37–7.20 (m, 15 H, Ph-H), 7.32 (m, 1 H, H-6), 7.16 (d, $^3J_{3,4}$ = 8.8 Hz, 1 H, H-3), 7.11 (app d, ^3J = 7.4 Hz, 1 H, Ph-H), 7.06 (t, ^2J = 7.4 Hz, 2 H, Ph-H), 6.60 (d, ^2J = 7.3 Hz, 2 H, Ph-H), 5.91 (d, $^3J_{1,2}$ = 10.1 Hz, 1 H, H-1′), 4.79 (d, ^2J = 12.2 Hz, 1 H, CH_2Ph), 4.62–4.49 (m, 4 H, CH_2Ph), 4.43 (m, 2 H, CH_2Ph, H-5′), 4.27 (dd, $^3J_{1,2}$ = 10.1 Hz, $^3J_{2,3}$ = 2.6 Hz, 1 H, H-2′), 4.19–4.10 (m, 1 H, H-6a′), 3.94 (br s, 1 H, H-3′), 3.84 (d, ^2J = 11.3 Hz, 1 H, CH_2Ph), 3.79–3.72 (m, 2 H, H-6b′, H-4′), 3.67 (d, ^2J = 11.3 Hz, 1 H, CH_2Ph).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 155.2 (C-2), 138.5, 138.2, 137.8 (4 C-1″), 133.3 (C-8a), 130.3 (C-4), 128.7 (C-4a), 128.6, 128.5 (5 CH Ph), 128.3 (C-5), 128.0, 127.8, 127.7, 127.4 (15 CH Ph), 126.4 (C-7), 123.2 (C-8), 123.0 (C-6), 119.3 (C-3), 115.1 (C-1), 76.3 (C-5′), 75.2 (C-2′), 75.1 (C-4′), 75.0 (C-3′), 73.8, 73.2, 73.0, 71.7 (*C*H_2Ph), 67.9 (C-1′), 66.9 (C-6′).

FAB-MS: *m*/*z* (%) = 666.4 (17, $[M]^+$), 181.1 (100, matrix).

FAB-HRMS: *m*/*z* calcd for $C_{44}H_{42}O_6$: 666.2981; found: 666.3008.

2-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-mannopyranosyl)-3,5-dimethoxyphenol (10)

A mixture of **4** (128.1 mg 187 μmol, 1 equiv), 3,5-dimethoxyphenol (**9**; 31.7 mg, 206 μmol, 1.2 equiv), and dried 4 Å molecular sieves (1.5 g) in anhyd CH_2Cl_2 (3 mL) was stirred at 0 °C for 20 h under argon. Then, BF_3·OEt_2 (52.0 μL, 58.7 mg, 414 μmol, 2.2 equiv) in anhyd CH_2Cl_2 (1 mL) was added and the mixture was stirred for 2 h. The reaction was quenched with sat. aq $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (cyclohexane–EtOAc, 4:1) afforded **10** as a colorless oil (74 mg, 98 μmol, 52%).

α-*C*-Arylglycosides from Trichloroacetimidates with $ZnCl_2$ as Promoter; 1-(2′,3′,4′,6′-Tetra-*O*-benzyl-α-D-mannopyranosyl)naphthalen-2-ol (15)

A mixture of **4** (260.0 mg 380 μmol, 1 equiv), 2-naphthol (**5**; 65.1 mg, 460 μmol, 1.2 equiv), $ZnCl_2$ (110.3 mg, 760 μmol, 2 equiv), and dried 4 Å molecular sieves (1.5 g) in anhyd CH_2Cl_2 (4 mL) was stirred at r.t. under argon for 2 h. The mixture was quenched with sat. aq $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (cyclohexane–EtOAc, 20:1) afforded **15** as a colorless oil (107.1 mg, 160 μmol, 42%).

1-(2′,3′,4′,6′-Tetra-*O*-benzyl-α-D-galactopyranosyl)naphthalen-2-ol (18)

A mixture of 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl trichloroacetimidate (**17**; 106 mg, 0.154 mmol, 1 equiv), 2-naphthol (**5**; 28.3 mg, 0.196 mmol, 1.2 equiv), $ZnCl_2$ (52.0 mg, 0.381 mmol, 2.2 equiv), and 4 Å dried molecular sieves (1 g) in anhyd CH_2Cl_2 (4 mL) was stirred at r.t. under argon for 1.5 h. The reaction was quenched by the addition of sat. aq $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (cyclohexane–EtOAc, 20:1) afforded **18** as a colorless oil (32.3 mg, 48.2 mmol; 31%); $[\alpha]_D^{23}$ +24.4 (*c* = 0.71, $CDCl_3$); R_f = 0.38 (cyclohexane–EtOAc, 12:1).

IR (film): 3332, 3029, 2924, 1622, 1453, 1226, 1085, 820, 737, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.14 (s, 1 H, OH), 7.77 (m_c, 1 H, H-5), 7.73–7.70 (m, 1 H, H-4), 7.46–7.07 (m, 22 H, H-3, H-6, H-7, H-8, 18 Ph-H), 6.85–6.80 (m, 2 H, Ph-H), 5.94 (br s, 1 H, H-1′), 4.74 (d, ^2J = 12.2 Hz, 1 H, CH_{2a}Ph), 4.73–4.66 (m, 1 H, H-5′), 4.63 (d, ^2J = 11.8 Hz, 1 H, CH_{2a}Ph), 4.60–4.51 (m, 4 H, CH_2Ph), 4.38 (dd, $^2J_{6a,6b}$ = 12.1 Hz, $^3J_{5,6a}$ = 8.9 Hz, 1 H, H-6a′), 4.27 (dd, ^3J = 6.6, 2.8 Hz, 1 H, H-4′), 4.03 (d, ^2J = 11.8 Hz, 1 H, CH_{2b}Ph), 3.94–3.89 (m, 2 H, H-6b′, CH_2Ph), 3.88–3.84 (m, 1 H, H-3′), 3.77 (pseudo d, $^3J_{2,3}$ = 3.3, 1 H, H-2′).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 156.5 (C-2), 138.6, 138.4, 137.7 (4 C-1″), 131.6 (C-8a), 130.2 (C-4), 129.3 (C-5), 128.9, 128.8, 128.7, 128.5, 128.4, 128.2, 128.1, 128.9, 127.9, 127.8 (20 CH-phenyl, C-4a), 126.9 (C-8), 122.8 (C-6), 121.0 (C-7), 120.3 (C-3), 111.5 (C-1), 77.6 (C-2′), 76.7 (C-5′), 75.1 (C-3′), 73.9, 73.8 (*C*H_2Ph), 73.4 (C-4′), 73.2, 72.1 (*C*H_2Ph), 69.5 (C-1′), 64.8 (C-6′).

FAB-MS: *m*/*z* (%) = 666.4 (19, $[M]^+$), 181.1 (100, matrix).

FAB-HRMS: *m*/*z* calcd for $[C_{44}H_{42}O_6]^+$: 666.2981; found: 666.2999.

Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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