Monosaccharidic mimetics of the sialyl Lewis^X tetrasaccharide based on 2,7-dihydroxynaphthalene

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Dedicated to Professor Rainer Beckert on the occasion of his 60th birthday

Abstract

A potential monosaccharidic mimetic of the sialyl Lewis^X tetrasaccharide (sLe^X) was identified based on an *in silico* docking study using the crystal structure of an E-selectin-sLe^X complex. The chemical synthesis of the mimetic in an ortho-selective C-glycosylation is described. This compound and two close analogues were evaluated in a cell-based selectin binding assay where none of the tested mimetics showed an IC_{50} below 1mM. This result can be explained by an unexpected $^1C_4$ conformation of the mannosyl residue which precludes the required binding of the Ca^{2+}-ion in E-selectin.

Keywords: Carbohydrates, phenols, C-glycosides, cell adhesion, molecular modelling

Introduction

Oligosaccharides are known to play an important role in cell recognition processes and in the communication between cells in higher organisms.[1] A prominent example is the recruitment of leucocytes during the inflammatory cascade, which is initiated by the interaction between selectins and their cognate oligosaccharide ligands such as sialyl Lewis^X (sLe^X**, 1**) (Fig.1).[2] Undesired interactions caused by overexpression or dysregulation have been associated with various diseases e.g. asthma,[3] psoriasis,[4] reperfusion syndrome[1b] or the metastasis of tumors.[5] Therefore, some effort has been put into the development of selectin ligands[6] and their mimetics[7] as potential therapeutics.

Previous studies have shown that the three hydroxyl groups of the L-fucose[8] and the carboxylic acid moiety of the sialic acid[9] are essential for binding of sialyl Lewis^X (**1**) towards the selectins. However, the L-fucose portion has been successfully substituted by other monosaccharides with similar configuration such as D-arabinose,[6a,6b] L-galactose [7e,10] or D-mannose as demonstrated by Kogan's functional mannosyl mimetic **2**.[7b,7c] Furthermore, the (*S*)-cyclohexyl lactic acid moiety successfully employed by Ernst and Thoma e.g. in compound **3** turned out to be a privileged mimetic for the sialic acid portion.[7d,11] A potential general drawback of oligosaccharidic therapeutics is their instability against acidic hydrolysis and their degradation by glycosidases. For instance, O-fucosidic bonds are typical targets for ubiquitous fucosidases.[12] An approach to overcome the metabolic lability of O-glycosidic bonds can be the use of C-glycosidic mimetics,[7c,10] the synthesis of which can be effected along various routes.[13] Here, we report on the preparation and biological evaluation of potential sLe^X analogues based on a mannosylated 2,7-dihydroxynaphthalene scaffold.

Results and Discussion

Virtual docking experiments using the crystal structure of the E-selectin/sLe^X complex and mimetics composed of various aromatic and heteroaromatic core structures in combination with (*S*)-cyclohexyl lactic acid and D-mannose revealed a good fit of compound **4** containing an α-C-mannosylated 2,7-dihydroxynaphthalene (Figure 1, Figure 2).

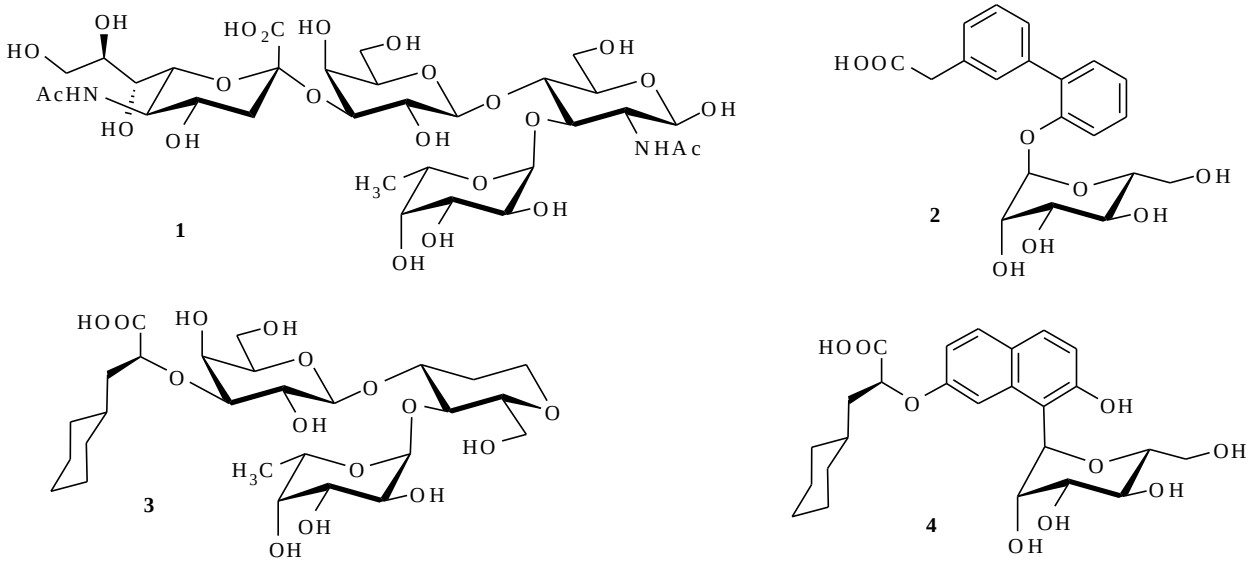


Figure 1. Sialyl Lewis^X and mimetic **4** identified by virtual docking.

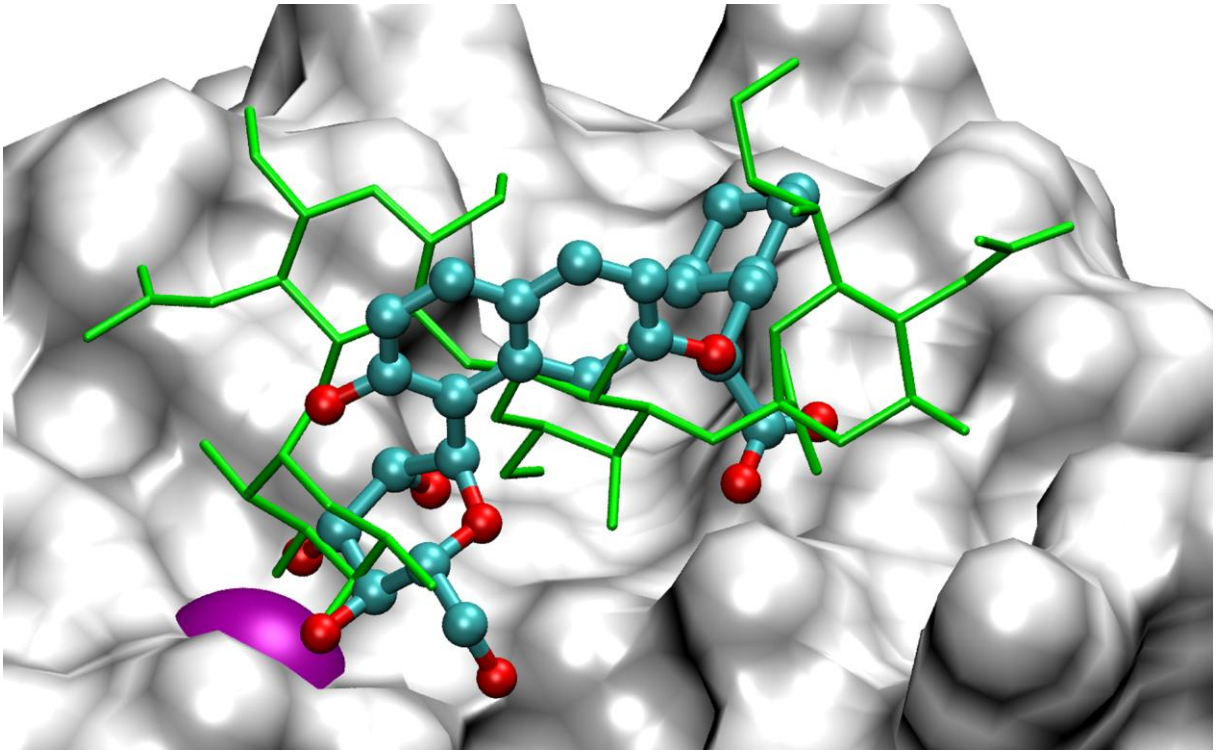
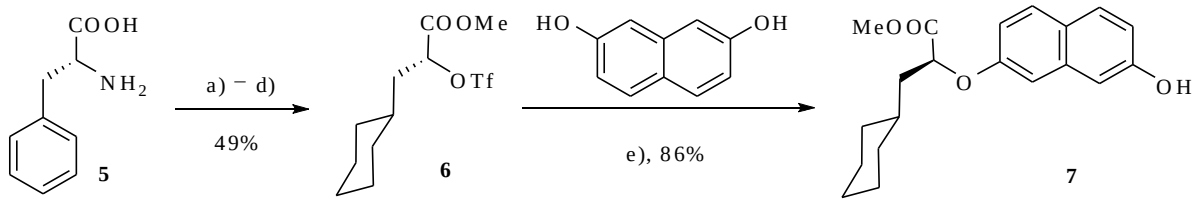


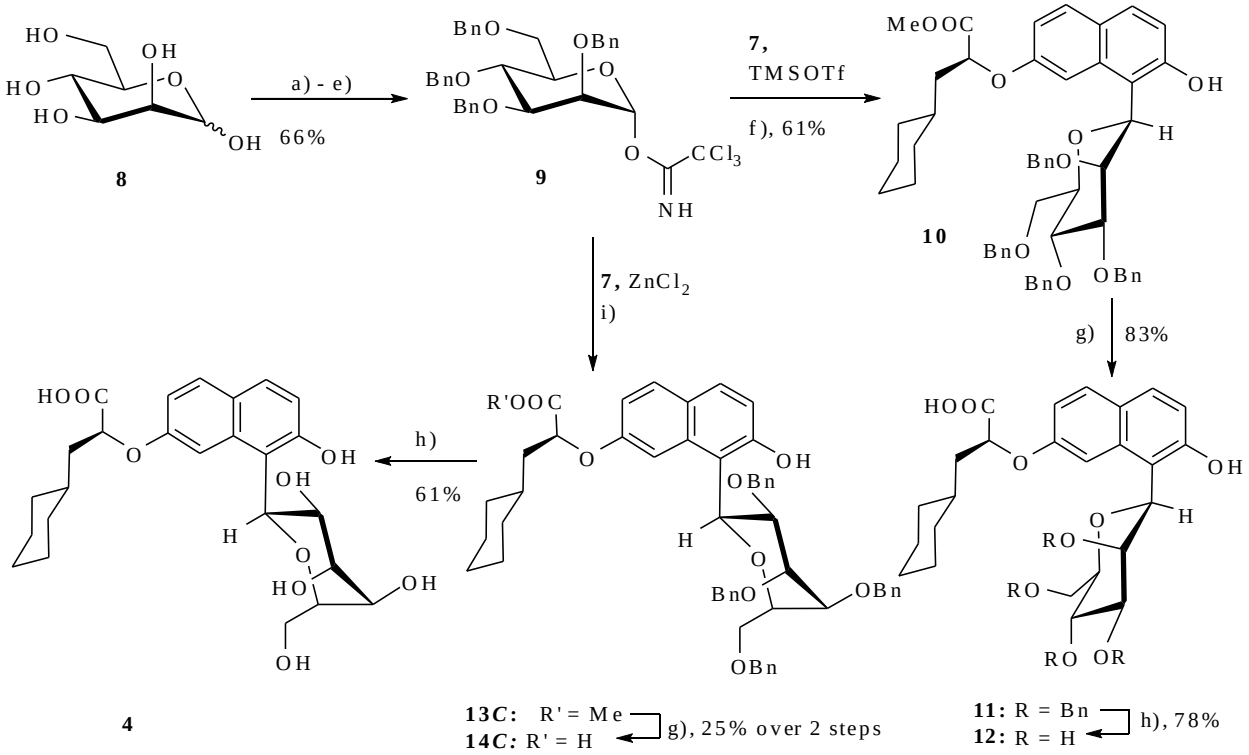
Figure 2. Docking of sialyl Lewis^X (green) and mimetic **4** to E-selectin. The Ca^{2+}-ion bound by the protein is highlighted in purple.

The key step for the synthesis of **4** was a direct C-glycosylation of an electron rich phenol using a mannosyl trichloracetimidate as a reactive glycosyl donor.[14] Reactions of this kind are suggested to proceed in a stepwise fashion and usually yield a single regioisomer in high stereoselectivity.[13b,14-15] The triflate of (*S*)-cyclohexyl lactic acid (**6**) was prepared from D-phenylalanine in four steps with 49% overall yield.[16] Its reaction with an excess of 2,7-dihydroxynaphthalene in the presence of K_2CO_3 gave the desired phenol ether **7** in 86% yield (Scheme 1).



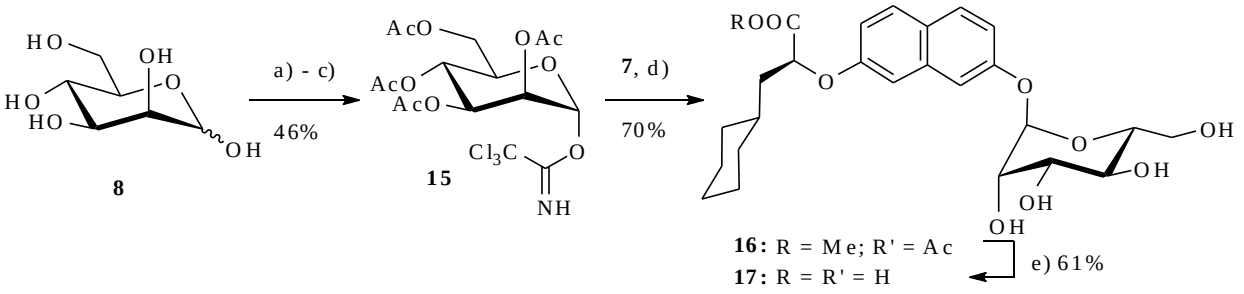
Scheme 1. Synthesis of the glycosyl acceptor **7**. Reagents and conditions: (a) $NaNO_2$, 1.25 M H_2SO_4; (b) MeOH, DOWEX-50WX8 (H^+); (c) Rh-Al_2O_3, H_2, THF/H_2O; (d) Tf_2O, 2,6-lutidine, DCM; (e) K_2CO_3, CH_3CN.

Glycosyl donor **9** could be synthesized in five steps from D-mannose in 66% overall yield.[17] The direct glycosylation of **9** to the acceptor **7** in the presence of TMSOTf gave the C-glycoside **10** in 61% yield but unfortunately with the undesired β-configuration at the anomeric center.[18] Hydrolysis of the methyl ester and cleavage of the benzyl ethers gave the corresponding β-configured mimetic **12** in 65% yield (Scheme 2).



Scheme 2. Synthesis of β-*C*-mannoside **12** and α-*C*-mannoside **4**. Reagents and conditions: a) All-OH, AcCl; b) NaH, BnBr, DMF, 0 °C; c) $(Ph_3P)_3RhCl$, toluene/EtOH/H_2O, reflux; d) I_2, THF/H_2O; e) Cl_3CCN, DBU, DCM; f) **7**, TMSOTf, DCM, MS 4 Å, 0 °C; g) 1,4-dioxane /MeOH/4*N* NaOH; h) H_2 (10 bar) $Pd(OH)_2/C$; i) **7**, $ZnCl_2$, DCM, MS 4 Å, rt.

It has been demonstrated with other phenolic acceptors that α-C-mannosides can be obtained if $ZnCl_2$ is used as the promoter.[18] However, these conditions only gave a 2:1 mixture of the α-C-glycoside **13*C*** and the α-O-glycoside **13*O***. The products could be separated after ester hydrolysis giving the acid **14*C*** in 25% over two steps. Unfortunately, the mannosyl residue in **14*C*** was found to adopt the $^1C_4$ conformation[18] which also prevailed after hydrogenolysis of the benzyl ethers to yield the α-configured mimetic **4**, albeit in an unfavorable conformation (Scheme 2).



Scheme 3. Synthesis of α-O-mannoside **17**. Reagents and conditions: a) Ac_2O, pyridine; b) $H_2NCH_2CH_2NH_2$, THF; c) Cl_3CCN, DBU, DCM d) TMSOTf, DCM, MS 4Å; e) 1,4-dioxane /MeOH/4*N* NaOH.

For comparison of its biological activity with the two C-mannosides, glycoside **17** was synthesized from the acetylated mannosyl trichloroacetimidate **15** which has a strong preference for α-O-glycosylation. Donor **15** was obtained from D-mannose in three steps[19] and reacted with phenol **7** in the presence of TMSOTf to give the α-configured O-glycoside **16** in 70% yield. After removal of the acetyl groups and alkaline hydrolysis of the methyl ester, the O-glycosidic mimetic **17** was obtained in 61% yield (Scheme 3). As expected, the mannose in this compound adopts the $^4C_1$ conformation while the distance between carboxylate and the carbohydrate is larger than in the C-glycosides **4** and **12**.

The three mimetics **4**, **12** and **17** were evaluated for their selectin inhibition in a cell-based assay, based on binding of soluble P- or E-selectin-Immunoglobulin chimera to selectin ligand-bearing murine Th1 cells or neutrophils. However, no inhibition exceeding 50% could be observed up to concentrations of 1 mM.

Assuming that the mannosyl residue in **4** adopts a $^1C_4$ conformation in solution we performed docking calculations in order to test whether **4** could fit favorably into the binding pocket of E-selectin in this conformation. None of the 100 best poses showed a twofold coordination of the calcium and the binding energy score was lower than for **4** with the mannosyl residue in a $^4C_1$ conformation. This result might explain why the compound did not show the expected inhibition in the biological test. DFT calculations (B3LYP/SOLV, 6-31G**) predict the $^4C_1$ conformer of a simplified model of **4** to be 1.7 kJ·mol^{-1} more stable in the gas phase while the $^1C_4$ conformer is more stable in solution by 11.5 kJ·mol^{-1}, see supporting information.

Conclusions

Three potential monosaccharidic mimetics of the sialyl Lewis^X tetrasaccharide based on 2,7-dihydroxynaphthalene have been prepared and evaluated for their selectin-inhibitory activity. While mimetic **4** compared favorably with other tested mimetics in an *in silico* screening, none of the compounds showed a significant biological activity in a cytometric assay up to concentrations of 1 mM. The reason for this may be the unexpected preference of the mannosyl

residue in **4** for the $^1C_4$ conformation, in which the spatial arrangement of the hydroxyl groups in positions 2, 3, and 4 precludes the required binding of the Ca^{2+}-ion in E-selectin.

Experimental Section

General. 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 were used without further purification. CH_2Cl_2 and acetonitrile were dried over CaH_2 and distilled under argon atmosphere prior to use. $ZnCl_2$ was dried at 130 °C in vacuo. 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 silica gel aluminium sheets (60 F_{254}) were used. Visualisation was accomplished by UV (254 nm) and sugar reagent[20] (1 M ethanolic H_2SO_4/0.2% ethanolic 3-methoxyphenol solution 1:1). Purification of products was accomplished by flash chromatography on silica gel and the purified compounds showed a single spot in analytical TLC.
^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300, AV 400 or DRX 500 in $CDCl_3$ or methanol-d_4 using the residual solvent peak as internal reference ($CDCl_3$, δ_H = 7.26, δ_C = 77.16, methanol-d_4, δ_H = 3.31, δ_C = 49.0). Optical rotations were measured at room temperature on a Krüss P8000 polarimeter at 589 nm or on a Perkin Elmer 241 polarimeter at 546 and 578 nm; the optical rotation at 589 nm was extrapolated using the Drude equation. IR spectra were recorded on a ThermoNicolet Avatar 370 FT-IR spectrometer. FAB mass spectrometry was carried out on with VG70S (Xe-FAB ionisation) with *m*-nitrobenzyl alcohol as the matrix. For exact mass determination (FAB-HRMS), PEG 300 or PEG 600 was used as internal standard. ESI mass spectrometry was carried out on an Agilent 1200 LC/MSD Trap XCT. The samples were dissolved in acetonitrile (c ≈ 0.1 g/l) and injected via an Agilent 1200 HPLC with an Ascentis Express C8 (30 x 2.1 mm, 2.7 µm particle size) column (acetonitrile/water 80:20, Flow: 0.5 ml/min). Exact mass determination (ESI-HRMS) was carried out on a Q-ToF-Ultima 3-Instrument with a Lock Spray-interface. NaI/CsI clusters were used as an external reference.

Docking

The program Glide 4.5[21] was used for the docking of a small, manually designed, library of potential sLe^X mimetics. The setup of the receptor was performed using the protein preparation wizard of the Maestro program[22] based on the X-ray structure of E-selectin complexed with sLe^X (pdb code 1G1T).[23] The ligands were built and optimized using Maestro. The grid defining the binding site was positioned using the sLe^X ligand as center and had a dimension of 31 Å x 29 Å x 29 Å. The docking was performed in GlideScore SP4.5 mode using default parameters. The 10 best poses were stored for each ligand and manually inspected.

Cellular assay for determination of inhibitory potency for E- and P-selectin

Inhibition of binding of E- and P-selectin to its natural ligands on either T cells or neutrophils was tested by cytometry as described.[24] In short, CD4+ T cells were isolated from mice, activated under Th1 conditions and incubated with soluble E- or P-selectin-IgG chimera in absence or presence of the compounds. Cell-bound selectin was stained with fluorescently labeled anti-human IgG antibody as secondary reagent in HBSS containing Ca^{2+} and Mg^{2+} and quantified in a fluorescence-activated cell sorter (FACS). Alternatively, neutrophils were stained in whole blood after erythrocyte lysis as above and identified by anti GR-1 antibody.

(*S*)-3-Cyclohexyl-2-(7-hydroxynaphthalen-2-yloxy)-propionic acid methyl ester (7)

A solution of **6** (1.68 g, 5.28 mmol) in dry acetonitrile (8 mL) was added to a mixture of 2,7-dihydroxynaphthalene (4.20 g, 26.2 mmol) and K_2CO_3 (1.80 g) in dry acetonitrile (17 mL) under argon atmosphere. The mixture was stirred for 1.5 h at room temperature and partitioned between CH_2Cl_2 (70 mL) and H_2O (40 mL). The organic layer was washed twice with H_2O (10 mL each) and once with saturated aq $NaHCO_3$ (20 mL). Drying over Na_2SO_4 and removal of the solvent in vacuo furnished a crude residue which was purified by flash chromatography (cyclohexane/EtOAc 5:1) to give **7** as a colorless solid (1.49 g, 4.54 mmol, 86%). Mp 88–90 °C, $[\alpha]_D^{25} = -13.6$ (c = 1, $CDCl_3$), R_f = 0.23 (cyclohexane/EtOAc 5:1), IR (NaCl, ν_{max}, cm^{-1}): 3416, 2923, 2850, 1736, 1634, 1515, 1447, 1203, 1159, 831. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.67 (d, $^3J_{H\text{-}3,H\text{-}4}$ = 8.9 Hz, 1 H, H-4), 7.65 (d, $^3J_{H\text{-}5,H\text{-}6}$ = 8.7 Hz, 1 H H-5), 7.03 (dd, $^3J_{H\text{-}3,H\text{-}4}$ = 8.9 Hz, $^4J_{H\text{-}1,H\text{-}3}$ = 2.6 Hz, 1 H, H-3), 7.01 (d, $^4J_{H\text{-}6,H\text{-}8}$ = 2.5 Hz, 1 H, 8), 6.95 (dd, $^3J_{H\text{-}5,H\text{-}6}$ = 8.7 Hz, $^4J_{H\text{-}6,H\text{-}8}$ = 2.5 Hz, 1 H, H-6), 6.89 (d, $^4J_{H\text{-}1,H\text{-}3}$ = 2.6 Hz, 1 H, H-1), 4.83 (dd, ^3J = 9.4 Hz, ^3J = 4.1 Hz, 1 H, C*H*COOMe), 3.75 (s, 3 H, OCH_3), 2.02–1.93 (m, 1 H, CH_{2a}CHCOOMe), 1.83–1.58 (m, 7 H, CH_{2b}CHCOOMe, CH, 5 CH_2), 1.31–1.13 (m, 3 H, CH_2), 1.08–0.91 (m, 2 H, CH_2). ^{13}C NMR (100.6 MHz $CDCl_3$): δ_C 173.5 (COOH), 156.9, 154.5 (C-2, C-7), 136.1 (C-8a), 129.9, 129.8 (C-4, C-5), 125.1 (C-4a) 116.6, 116.1, 109.2, 106.7 (C-1, C-3, C-6, C-8), 75.0 (*C*HCOOMe), 52.7 (OCH_3), 20.7 (*C*H_2CHCOOMe), 34.3 (CH), 34.1, 32.8, 26.7, 26.5, 26.3 (CH_2). ESI-MS: *m/z* = 351.1 (100) $[M+Na]^+$, 329.1 (20) $[M+H]^+$; ESI-HRMS: *m/z* calcd for $[C_{20}H_{24}O_4+Na]^+$: 351.1567, found 351.1574.

(2*S*)-3-Cyclohexyl-2-[2-hydroxy-1-(2,3,4,6-tetra-*O*-benzyl-β-D-mannpyranosyl)naphthalen-7-yloxy]propionic acid methyl ester (10)

A mixture of **9** (577 mg, 0.84 mmol), **7** (291 mg 0.89 mmol) and activated molecular sieves (4 Å, 2.00 g) in dry CH_2Cl_2 (10 mL) was stirred at 0 °C for 20 min under argon atmosphere to remove traces of water from the reactants. Then, TMSOTf (155 µL, 190 mg, 0.86 mmol) in dry CH_2Cl_2 (2 mL) was added and the mixture was stirred for 2.5 h. The reaction was quenched by addition of saturated aq $NaHCO_3$ (20 mL). The organic layer was separated and the aq phase extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (cyclohexane/EtOAc, 15:1) to give **10** (435 mg, 0.51 mmol, 61%) as colorless oil. $[\alpha]_D^{25}$ = +62.3

(c = 1, $CHCl_3$), R_f = 0.35 (cyclohexane/EtOAc 10:1). ^{1}H NMR, COSY, NOESY (500 MHz, $CDCl_3$): δ_H 9.15 (s, 1 H, OH), 7.68 (d, $^3J_{H\text{-}5,H\text{-}6}$ = 8.9 Hz, 1 H, H-5), 7.63 (d, ^3J = 8.9 Hz, 1 H, H-4), 7.41–7.24 (m, 13 H, H–Ph), 7.19 (dd, ^3J = 7.3 Hz, ^4J = 1.9 Hz, 2 H, H-Ph), 7.08–6.95 (m, 5 H, H-3, H-6, 3 H–Ph), 6.91 (d, ^3J = 7.1 Hz, 2 H, H–Ph), 6.81 (d, $^4J_{H\text{-}6,H\text{-}8}$ = 1.8 Hz, 1 H, H-8), 5.32 (pseudo s, 1 H, H-1‘), 4.92 (d, ^2J = 10.8 Hz, 1 H, (C-4‘)–O–CH_2Ph), 4.82 (d, ^2J = 11.8 Hz, 1 H, (C-3‘)–O–CH_2Ph). 4.80–4.74 (m, 2 H, (C-3‘)–O–CH_2Ph, C*H*COOMe), 4.67 (d, ^2J = 12.2 Hz, 1 H, (C-6‘)–O–CH_2Ph), 4.57 (d, ^2J = 10.9 Hz, 1 H, (C-4‘)–O–CH_2Ph), 4.54 (d, ^2J = 12.2 Hz, 1 H, (C-6‘)–O–CH_2Ph), 4.43 (d, ^2J = 11.8 Hz, 1 H, (C-2‘)–O–CH_2Ph), 4.28 (m, 2 H, H-4‘, (C-2‘)–O–CH_2Ph), 4.13 (d, $^3J_{H\text{-}2',H\text{-}3'}$ = 2.6 Hz, 1 H, H-2‘), 3.98 (dd, $^3J_{H\text{-}3',H\text{-}4'}$ = 9.5 Hz, $^3J_{H\text{-}2',H\text{-}3'}$ = 2.6 Hz, 1 H, H-3‘), 3.83 (dd, ^2J = 10.7 Hz, $^3J_{H\text{-}5',H\text{-}6a'}$ = 3.5 Hz, 1 H, H-6a‘), 3.80 (dd, ^2J = 10.7 Hz, $^3J_{H\text{-}5',H\text{-}6b'}$ = 2.1 Hz, 1 H, H-6b‘), 3.75–3.68 (m, 1 H, H-5‘), 3.56 (s, 3 H, OCH_3), 2.01–1.94 (m, 1 H, CH_2CHCOOH), 1.85–1.57 (m, 7 H, 1 CH_2CHCOOH, CH, 5 CH_2), 1.33–1.12 (m, 3 H, CH_2), 1.09–0.93 (m, 2 H, CH_2). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ_C 173.6 (COOH), 157.0 (C-7), 156.9 (C-2), 139.0, 138.8, 138.5, 138.2 (*C-1‘‘‘*), 132.4 (C-8a), 131.1 (C-5), 130.0 (C-4), 128.8, 128.7, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5 (20 CH Ph), 124.5 (C-4a), 118.5 (C-3), 114.6 (C-6), 111.3 (C-1), 102.1 (C-8), 84.6 (C-3‘), 80.1 (C-5‘), 79.5 (C-1‘); 75.9, 75.8, 75.6 (*C*HCOOMe, C-2‘, (C-4‘)-O-*C*H_2Ph), 74.9 ((C-2‘)-O-*C*H_2Ph), 74.6 (C-4‘), 73.8 ((C-6‘)-O-*C*H_2Ph); 72.6 ((C-3‘)-O-*C*H_2Ph), 68.8 (C-6‘); 52.6 (COO*C*H_3), 40.5 (*C*H_2CHCOOMe), 34.2 (CH), 34.0, 32.9, 26.7, 26.5, 26.4 (CH_2). ESI-MS: *m/z* (%) = 873.5 (100) $[M+Na]^+$, ESI-HRMS: *m/z* calcd for $[C_{54}H_{58}O_9+Na]^+$: 873.3973, found: 873.3975.

(2*S*)-3-Cyclohexyl-2-[2-hydroxy-1-(2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranosyl) naphthalen-7-yloxy]propionic acid (11)

Methyl ester **10** (327 mg, 0.39 mmol) was stirred in a mixture of 1,4-dioxane (10 mL), methanol (3.5 mL) and 4 N NaOH (1 mL) for 3 h at room temperature. The reaction was quenched by adding 2 N HCl (10 mL) and H_2O (30 mL) and the mixture was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude residue was purified by flash chromatography (cyclohexane/EtOAc 3:1) to give **11** (272 mg, 0.32 mmol, 83%) as colorless oil. $[\alpha]^{26}_D$ = +75.9 (c = 1, $CHCl_3$), R_f = 0.18 (cyclohexane/EtOAc 3:1), IR (NaCl, ν_{max}, cm^{-1}): 3340, 3031, 2922, 1724, 1624, 1454, 1212, 1098, 1027, 736. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ_H 9.13 (s, 1 H, OH), 7.66 (d, $^3J_{H\text{-}5.H\text{-}6}$ = 8.9 Hz, 1 H, H-5), 7.61 (d, $^3J_{H\text{-}3,H\text{-}4}$ = 8.9 Hz, 1 H, H-4), 7.42–7.24 (m, 13 H, H–Ph), 7.21 (dd, ^3J = 7.3 Hz, ^3J = 2.1 Hz, 2 H, H–Ph), 7.07–6.99 (m, 4 H, H-3, 3 H–Ph), 6.96 (dd, $^3J_{H\text{-}5,H\text{-}6}$ = 8.9 Hz, $^4J_{H\text{-}6,H\text{-}8}$ = 2.3 Hz, 1 H, H-6), 6.92 (m, 2 H, H-Ph), 6.71 (d, $^4J_{H\text{-}6,H\text{-}8}$ = 2.3 Hz, 1 H, H-8), 5.26 (pseudo s, 1 H, H-1‘), 4.94 (d, ^2J = 10.9 Hz, 1 H, CH_2Ph), 4.75 (s, 2 H, CH_2Ph), 4.70 (dd, ^3J = 9.2 Hz, ^3J = 4.4 Hz, 1 H, C*H*COOH), 4.67 (d, ^2J = 12.2 Hz, 1 H, CH_2Ph), 4.58 (d, ^2J = 10.9 Hz, 1 H, CH_2Ph), 4.54 (d, ^2J = 12.2 Hz, 1 H, CH_2Ph), 4.40 (d, ^2J = 11.7 Hz, 1 H, CH_2Ph), 4.28 (d, ^2J = 11.7 Hz, 1 H, CH_2Ph), 4.27 (pseudo t, J_{app} = 9.4 Hz, 1 H, H-4‘) 4.10 (d, $^3J_{H\text{-}2',H\text{-}3'}$ = 2.8 Hz, 1 H, H-2‘), 3.88 (dd, $^3J_{H\text{-}3',H\text{-}4'}$ = 9.4 Hz, $^3J_{H\text{-}2'H\text{-}3'}$ = 2.8 Hz, 1 H, H-3‘), 3.83 (dd, ^2J = 10.7 Hz, $^3J_{H\text{-}5',H\text{-}6a'}$ = 3.5 Hz, 1 H, H-6a‘), 3.79 (dd, ^2J = 10.7 Hz, $^3J_{H\text{-}5',H\text{-}6b'}$ = 2.2 Hz, 1 H, H-6b‘), 3.68 (m, 1 H,

H-5‘), 2.01–1.90 (m, 1 H, C*H*$_2$CHCOOH), 1.84–1.55 (m, 7H, C*H*$_2$CHCOOH, CH, 5 CH$_2$), 1.32–1.11 (m, 3 H, CH$_2$), 1.07–0.85 (m, 2 H, CH$_2$). ^{13}C NMR, HSQC, HMBC (100.6 MHz, CDCl$_3$): δ_C 174.0 (COOH), 157.1 (C-7), 156.6 (C-2), 139.1, 138.7, 138.5, 138.2 (C-1‘‘‘), 132.3 (C-8a), 131.3 (C-5), 130.2 (C-4), 128.9, 128.8, 128.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.5, (CH Ph), 124.7 (C-4a), 118.7 (C-3), 114.6 (C-6), 111.3 (C-1), 102.3 (C-8), 84.1 (C-3‘), 80.2 (C-5‘), 79.5 (C-1‘), 75.8, 75.6, 75.1 (*C*HCOOH, C-2’, CH$_2$Ph), 74.9 (CH$_2$Ph), 74.8 (C-4‘), 73.8 (CH$_2$Ph), 72.2 (CH$_2$Ph), 68.9 (C-6‘), 40.3 (*C*H$_2$CHCOOH), 34.3, 34.0, 32.8, 27.3, 26.5, 26.4 (CH, 5 CH$_2$). FAB-MS: *m/z* (%) = 836.2 (15) [M]$^+$, 181.1 (100) [matrix], FAB-HRMS: *m/z* calcd for [$C_{53}H_{56}O_9$]$^+$: 836.3957, found: 836.3924; *m/z* calcd for [$C_{53}H_{56}O_9$+H]$^+$: 837.3997, found: 837.3983.

(2*S*)-3-Cyclohexyl-2-[2-hydroxy-1-(β-D-mannopyranosyl)naphthalen-7-yloxy]propionic acid (12)

A mixture of **11** (159 mg, 0.19 mmol) and Pd(OH)$_2$ on charcoal (15 mg, 20 wt% Pd) and methanol (5 mL) was degassed in an autoclave under N_2 and flushed with H_2 (10 bar). The mixture was stirred for 2 days under H_2 (10 bar) at room temperature. The catalyst was removed by filtering through Celite and the solvent was removed in vacuo. The crude residue was purified by flash chromatography (EtOAc/EtOH 9:1) to give **12** as colorless amorphous solid (70 mg, 0.15 mmol, 78%). $[\alpha]^{26}_D$ = +45.8 (c = 1, MeOH), R_f = 0.10 (EtOAc/EtOH 9:1). IR (KBr, ν_{max}, cm^{-1}): 3387, 2923, 1727, 1625, 1522, 1451, 1227, 1074, 834, 782. ^{1}H NMR, COSY, NOESY (400 MHz, CD$_3$OD): δ_H 7.67 (d, $^3J_{H\text{-}5,H\text{-}6}$ = 8.9 Hz, 1 H, H-5), 7.62 (d, $^3J_{H\text{-}3,H\text{-}4}$ = 8.9 Hz, 1 H, H-4), 7.15 (pseudo s, 1 H, H-8), 6.99 (dd, $^3J_{H\text{-}5,H\text{-}6}$ = 8.9 Hz, $^4J_{H\text{-}6,H\text{-}8}$ = 2.3 Hz, 1 H, H-6), 6.92 (d, $^3J_{H\text{-}3,H\text{-}4}$ = 8.8 Hz, 1 H, H-3), 5.50 (pseudo s, 1 H, H-1‘), 4.83 (dd, ^3J = 9.2 Hz, ^3J = 3.9 Hz, 1 H, C*H*COOH), 4.12 (d, $^3J_{H\text{-}2',H\text{-}3'}$ = 2.0 Hz, 1 H, H-2‘), 3.98 (dd, ^2J = 12.1 Hz, $^3J_{H\text{-}5',H\text{-}6a'}$ = 2.2 Hz, 1 H, H-6a‘), 3.88 (m, 3 H, H-3‘, H-4‘, H-6b‘), 3.53 (m, 1 H, H-5‘), 2.00–1.66 (m, 8 H, C*H*$_2$CHCOOH, CH, 5 CH$_2$), 1.39–0.97 (m, 5 H, CH$_2$). ^{13}C NMR, HSQC, HMBC (101 MHz, CD$_3$OD): δ_C 178.8 (COOH), 158.9 (C-7), 157.8 (C-2), 135.1 (C-8a), 132.1 (C-5), 131.2 (C-4), 126.6 (C-4a), 118.9 (C-3), 117.1 (C-6), 114.4 (C-1), 104.9 (C-8), 84.1 (C-5’), 81.3 (C-1’), 77.5 (*C*HCOOH), 77.0 (C-3’), 74.1 (C-2’), 69.2 (C-4’), 63.6 (C-6’), 42.4 (*C*H$_2$CHCOOH), 36.7, 35.9, 34.6, 28.4, 28.3, 28.1 (CH, 5 CH$_2$). FAB-MS: *m/z* (%) = 515.2 (100) [M+K]$^+$, 499.2 (59) [M+Na]$^+$, 476.2 (31) [M]$^+$, FAB-HRMS: *m/z* calcd for [$C_{25}H_{32}O_9$]$^+$: 476.2046, found: 476.2061; calcd for *m/z* [$C_{25}H_{32}O_9$+H]: 477.2119, found: 477.2115.

(2*S*)-3-Cyclohexyl-2-[2-hydroxy-1-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl) naphthalen-7-yloxy]propionic acid methyl ester (13*C*) and (2*S*)-3-Cyclohexyl-2-[2-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyloxy)naphthalen-7-yloxy]-propionic acid methyl ester (13*O*)

A mixture of **9** (320 mg, 0.50 mmol), **7** (174 mg, 0.53 mmol) and molecular sieves 4 Å (1.00 g) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 20 min under argon atmosphere to remove traces of water from the reactants. Dried $ZnCl_2$ (206 mg, 1.52 mmol) was added and the

mixture was stirred for 2 h at room temperature. The reaction was quenched by addition of saturated aq $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude residue was purified by flash chromatography (cyclohexane/EtOAc 12:1) to give a 2:1 mixture (^{1}H NMR) of **13*C*** (A) and **13*O*** (B) (222 mg total, 0.26 mmol, combined yield 52%) as colorless oil. R_f (both compounds) = 0.20 (cyclohexane/EtOAc 12:1), ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ_H 8.83 (s, 1 H^A, OH^A), 7.69–7.63 (m, 2 H^A, H-4^A, H-5^A, 2 H^B, H-4^A, H-5^A), 7.47–6.91 (m, 21 H^A, H-3^A,H-6^A, H-8^A, 18 H-Ph^A, 24 H^B, H-1^B, H-3^B, H-6^B, H-8^B, 20 H-Ph^B), 6.57 (d, ^3J = 7.4 Hz, 2 H^A, 2 H-Ph^A), 5.82 (d, $^3J_{H\text{-}1,H\text{-}2}$ = 10.1 Hz, 1 H^A, H-1'^{A}), 5.76 (d, $^3J_{H\text{-}1,H\text{-}2}$ = 1.9 Hz, 1 H^B, H-1'^{B}), 4.91 (d, ^2J = 10.7 Hz, 1 H^B, CH_2Ph), 4.87–4.78 (m, 2 H^A, C*H*COOMe^A, CH_2Ph^A, 1 H^B, C*H*COOMe^B), 4.74 (d, ^2J = 11.7 Hz, 1 H^B, CH_2Ph^B), 4.70 (d, ^2J = 11.7 Hz, 1 H^B, CH_2Ph^B), 4.69–4.62 (m, 1 H^A, CH_2Ph^A, 3 H^B, CH_2Ph^B), 4.60 (d, ^2J = 12.2 Hz, 1 H^A, CH_2Ph^A), 4.56 (d, ^2J = 12.0 Hz, 1 H^A, CH_2Ph^A), 4.53 (d, ^2J = 9.5 Hz, 1 H^B, CH_2Ph^B), 4.50–4.42 (m, 2 H^A, CH_2Ph^A, 1 H^B, CH_2Ph^B), 4.41 (pseuso t, $^3J \approx 6.7$ Hz, 1 H^A, H-5'^{A}), 4.23 (dd, $^3J_{H\text{-}1',H\text{-}2'}$ = 10.1 Hz, $^3J_{H\text{-}2',H\text{-}3'}$ = 2.8 Hz, 1 H^A, H-2'^{A}), 4.20–4.13 (m, 2 H^B, H-3'^{B}, H-4'^{B}), 4.07 (dd, ^2J = 10.3 Hz, $^3J_{H\text{-}5',H\text{-}6a'}$ = 7.2 Hz, 1 H^A, H-6a'^{A}), 4.03–4.00 (m, 1 H^B, H-2^B), 3.98 (pseudo t, J_{app} = 3.0 Hz, 1 H^A, H-3'^{A}), 3.95–3.86 (m, 2 H^A, CH_2Ph^A, H-6b'^{A}, 1 H^B, H-5'^{B}), 3.80 (m, 1 H^A, H-4'^{A}, 1 H^B, H-6a'^{B}), 3.73 (s, 3 H^B, $OCH_3{}^B$), 3.70-3.62 (m, 1 H^A, CH_2Ph^A, 1 H^B, H-6b'^{B}), 3.54 (s, 3 H^A, $OCH_3{}^A$), 1.97 (ddd, ^3J = 14.5 Hz, ^3J = 9,4 Hz, ^3J = 5.4 Hz, 1 H^B, CH_2CHCOOMe^B), 1.93–1.84 (m, 1 H^A, CH_2CHCOOMe^A), 1.83–1.55 (m, 7 H^A, CH_2CHCOOMe^A, CH^A, $CH_2{}^A$, 7 H^B, CH_2CHCOOMe^B, CH^B, 5 $CH_2{}^B$), 1.33–0.79 (m, 5 H^A, $CH_2{}^A$, 5 H^B, $CH_2{}^B$).

(2*S*)-3-Cyclohexyl-2-[2-hydroxy-1-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl) naphthalen-7-yloxy]propionic acid (14*C*) and (2*S*)-3-cyclohexyl-2-[2-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyloxy)naphthalen-7-yloxy]-propionic acid (14*O*)

The mixture (2:1) of **13*C*** and **13*O*** (150 mg total, 0.18 mmol) was dissolved in a mixture of 1,4-dioxane (5 mL), methanol (1.8 mL) and 4 N aq NaOH (0.5 mL) and stirred for 3 h at room temperature. The reaction was quenched with 2 N HCl (10 mL) and H_2O (30 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude residue was purified by flash chromatography (cyclohexane/EtOAc 3:1) to give **14*C*** and **14*O*** (combined yield 138 mg, 0.16 mmol, 93%). The separation yielded a mixture of **14*C*** and **14*O*** (29 mg, 34 µmol, 19%) along with the pure components:

14*C* (72 mg, 83 µmol, 49%), colorless oil. $[\alpha]^{28}{}_D$ = −57.6 (c = 1, $CHCl_3$), R_f = 0.16 (cyclohexane/EtOAc 3:1), IR (NaCl, ν_{max}, cm^{-1}): 3354, 3029, 2923, 1726, 1623, 1453, 1211, 1093, 750, 698. ^{1}H NMR, COSY, NOESY (500 MHz, $CDCl_3$): δ_H 8.86 (s, 1 H, OH), 7.68 (pseudo d, ^3J = 8.9 Hz, 2 H, H-4, H-5), 7.41–7.31 (4 H, H 8, 3 H–Ph), 7.30–7.20 (m, 12 H, H–Ph), 7.13 (t, ^3J = 7.2 Hz, 1 H, H–Ph), 7.07 (m, 3 H, H 3, 2 H–Ph), 7.02 (dd, $^3J_{H\text{-}5,H\text{-}6}$ = 8.9 Hz, $^4J_{H\text{-}6,H\text{-}8}$ = 2.0 Hz, 1 H, H-6), 6.59 (d, ^3J = 7.2 Hz, 2 H, H–Ph), 5.85 (d, $^3J_{H\text{-}1',H\text{-}2'}$ = 10.1 Hz, 1 H, H-1'), 4.79 (d, ^2J =12.4 Hz, 1 H, CH_2Ph), 4.74 (dd, ^3J = 8.5 Hz, ^3J = 4.1 Hz, 1 H, C*H*COOH),

4.65–4.56 (m, 2 H, C*H*$_2$Ph), 4.54–4.43 (m, 3 H, C*H*$_2$Ph), 4.39 (pseudo t, J_{app} = 6.6 Hz, 1 H, H-5'), 4.23 (dd, $^3J_{H\text{-}1',H\text{-}2'}$ = 10.1 Hz, $^3J_{H\text{-}2',H\text{-}3'}$ = 2.4 Hz, 1 H, H-2'), 4.08–4.01 (m, 1 H, H-6a'), 3.95 (pseudo s, 1 H, H-3'), 3.92–3.82 (m, 2 H, H-6b', C*H*$_2$Ph), 3.78 (pseudo d, J_{app} = 3.6 Hz, 1 H, H-4'), 3.66 (d, ^2J = 11.1 Hz, 1 H, C*H*$_2$Ph), 1.95–1.87 (m, 1 H, C*H*$_2$CHCOOH), 1.71 (m, 2 H, C*H*$_2$CHCOOH, CH$_2$ ^{c}Hex), 1.62 (m, 5 H, CH, 4 CH$_2$), 1.34–1.05 (m, 3 H, CH$_2$), 0.92 (m, 1 H, CH$_2$), 0.78 (m, 1 H, CH$_2$). ^{13}C NMR, DEPT, HSQC, HMBC (126 MHz, $CDCl_3$): δ_C 176.2 (COOH), 156.1, 156.0 (C-2, C-7), 138.7, 138.4, 138.0 (4 C-1'''), 134.6 (C-8a), 130.4, 130.1 (C-4, C-5), 128.9, 128.7, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6 (20 CH Ph), 124.9 (C-4a), 118.0 (C-3), 115.2 (C-6), 114.4 (C-1), 105.2 (C-8), 76.3 (C-5'), 75.8 (C-2'), 75.1 (C-4'), 74.6 (*C*HCOOH), 74.2 (C-3'), 73.6, 73.3, 73.1, 71.9 (CH$_2$Ph), 68.3 (C-1'), 67.3 (C-6'), 40.1 (*C*H$_2$CHCOOH), 33.9 (CH, CH$_2$), 32.5, 26.6, 26.4, 26.3 (CH$_2$). FAB-MS: *m/z* = 836.5 (15) $[M]^+$, 181.1 (100) [matrix] FAB-HRMS: *m/z* calcd for $[C_{53}H_{56}O_9+H]^+$: 837.3997, found. 837.3975.

14*O* (37 mg, 43 µmol, 25%), colorless oil. $[\alpha]^{28}_D$ = +68.5 (c = 1, $CHCl_3$), R_f = 0.10 (cyclohexane/EtOAc 3:1), IR (NaCl, ν_{max}, cm^{-1}): 3441, 3029, 2922, 1733, 1633, 1453, 1208, 1095, 1027, 749, 697. ^{1}H NMR, COSY, NOESY (400 MHz, $CDCl_3$): δ_H 7.70 (d, $^3J_{H\text{-}5,H\text{-}6}$ = 8.9 Hz, 1 H, H-5), 7.67 (d, ^3J = 8.9 Hz, 1 H, H-4), 7.48–7.17 (m, 21 H, H-1, H-Ph), 7.10 (dd, $^3J_{H\text{-}5,H\text{-}6}$ = 8.9 Hz, $^4J_{H\text{-}6,H\text{-}8}$ = 2.4 Hz, 1 H, H-6), 7.08–7.01 (m, 2 H, H-8, H-3), 5.78 (d, $^3J_{H\text{-}1',H\text{-}2'}$ = 1.5 Hz, 1 H, H-1'), 4.94 (d, ^2J = 10.7 Hz, 1 H, CH$_2$Ph), 4.88 (dd, ^3J = 9.4 Hz, ^3J = 3.9 Hz, 1 H, C*H*COOH), 4.84 (m, 2 H, CH$_2$Ph), 4.77 (d, ^2J = 11.8 Hz, 1 H, CH$_2$Ph), 4.73 (d, ^2J = 11.8 Hz, 1 H, CH$_2$Ph), 4.65 (d, ^2J = 12.0 Hz, 1 H, CH$_2$Ph), 4.56 (d, ^2J = 10.7 Hz, 1 H, CH$_2$Ph), 4.42 (d, ^2J = 12.0 Hz, 1 H, CH$_2$Ph), 4.26–4.16 (m, 2 H, H-4', H-3'), 4.04 (m, 1 H, H-2'), 3.92 (m, 1 H, H-5'), 3.82 (dd, ^2J = 10.8 Hz, $^3J_{H\text{-}5',H\text{-}6a'}$ = 4.1 Hz, 1 H, H-6a'), 3.69 (dd, ^2J = 10.8 Hz, $^3J_{H\text{-}5',H\text{-}6b'}$ = 1.3 Hz, 1 H, H-6b'), 2.10–1.97 (m, 1 H, C*H*$_2$CHCOOH), 1.91–1.62 (m, 7 H, C*H*$_2$CHCOOH, CH, 5 CH$_2$), 1.38–0.92 (m, 5 H, CH$_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 176.6 (COOH), 156.6 (C-7), 155.0 (C-2), 138.8, 138.7, 138.5 (4 C-1'''), 135.8 (C-8a), 129.8 (C-5), 129.5 (C-4), 128.8, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8 (20 CH Ph), 125.9 (C-4a), 117.1 (C-6, C-3), 110.4 (C-1), 107.9 (C-8), 96.6 (C-1'), 80.3 (C-3'), 75.5 (C*H*$_2$Ph), 75.0 (C-4'), 74.9 (C-2'), 74.6 (*C*HCOOH), 73.5, 73.1 (C*H*$_2$Ph), 72.8 (C-5'), 72.7 (C*H*$_2$Ph), 69.1 (C-6'), 40.4 (*C*H$_2$CHCOOH), 34.3 (CH), 34.0, 32.7, 26.7, 26.5, 26.3 (CH$_2$). ESI-MS: *m/z* (%) = 854.6 (100) $[M+NH_4]^+$, ESI-HRMS: *m/z* calcd for $[C_{53}H_{56}O_9+Na]^+$: 859.3817, found: 859.3797.

(2*S*)-3-Cyclohexyl-2-[2-hydroxy-1-(α-D-mannopyranosyl)naphthalen-7-yloxy]propionic acid (4)

A mixture of **14*C*** (52 mg, 62 µmol) and $Pd(OH)_2$ on charcoal (4 mg, 20 wt% Pd) in MeOH (2 mL) was degassed in an autoclave under N_2 and then flushed with H_2 (10 bar). The mixture was stirred under H_2 (10 bar) at room temperature. The catalyst was removed by filtration through Celite and the solvent was removed in vacuo. The crude residue was purified by flash chromatography (EtOAc/EtOH 9:1) to give **4** (18 mg, 38 µmol, 61%) as a colorless oil. $[\alpha]^{25}_D$ = +16.9 (c = 0.16, MeOH), R_f = 0.11 (EtOAc/EtOH 9:1). IR (ATR, ν_{max}, cm^{-1}): 3339, 2921, 2850, 1726, 1624, 1522, 1450, 1226, 1137, 1073, 833, 783. ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.65 (m_c,

J_{app} = 9.5 Hz, 3 H, H-4, H-5, H-8), 6.99 (dd, $^3J_{H-5,H-6}$ = 8.9 Hz, $^4J_{H-6,H-8}$ = 2.3 Hz, 1 H, H-6), 6.96 (d, $^3J_{H-3,H-4}$ = 8.8 Hz, 1 H, H-3), 5.73 (d, $^3J_{H-1',H-2'}$ = 9.2 Hz, 1 H, H-1'), 4.91 (m, 1 H, C*H*COOH), 4.55 (dd, $^3J_{H-1',H-2'}$ = 9.2 Hz, $^3J_{H-2',H-3'}$ = 3.4 Hz, 1 H, H-2'), 4.33 (dd, ^2J = 12.3 Hz, $^3J_{H-5',H-6a'}$ = 7.7 Hz, 1 H, H-6a'), 4.16 (pseudo t, J_{app} = 4.0 Hz, 1 H, H-3'), 3.98 (dd, $^3J_{H-3',H-4'}$ = 4.6 Hz, $^3J_{H-4',H5'}$ = 2.4 Hz, 1 H, H-4'), 3.95 (m, 1 H, H-5'), 3.78 (dd, ^2J = 12.3 Hz, $^3J_{H-5', H-6b'}$ = 3.7 Hz, 1 H, H-6b'), 1.99–1.66 (m, 8 H, 2 C*H*$_2$CHCOOH, CH, 5 CH$_2$), 1.38–1.23 (m, 5 H, CH$_2$). ^{13}C NMR, HSQC (100.6 MHz, CD_3OD) δ_C 178.9 (COOH), 158.4 (C-7), 156.8 (C-2), 136.9 (C-8a), 131.4, 131.3 (C-4, C-5), 126.8 (C-4a), 118.0 (C-3), 117.1 (C-1), 116.9 (C-6), 107.3 (C-8), 82.0 (C-5'), 77.3 (*C*HCOOH), 72.9 (C-3') 71.3 (C-4'), 70.6 (C-1'), 69.2 (C-2'), 61.5 (C-6'), 42.2 (*C*H$_2$CHCOOH), 36.0, 35.5, 34.4, 31.2, 27.9, 27.8 (CH, 5 CH$_2$). FAB-MS: *m/z* (%) = 515.1 (44) $[M+K]^+$, 499.1 (86) $[M+Na]^+$, 476.1 (17) $[M]^+$,176 (100) [matrix], FAB-HRMS: *m/z* calcd for $[C_{25}H_{32}O_9]^+$: 476.2046, found: 476.2041; *m/z* calcd for $[C_{25}H_{32}O_9+H]^+$: 477.2125, found: 477.2116.

(2*S*)-3-Cyclohexyl-2-[2-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)naphthalen-7-yloxy]-propionic acid methyl ester(16)

A mixture of **7** (192 mg, 0.58 mmol), **15** (270 mg, 0.55 mmol) and molecular sieves 4 Å (1.00 g) in dry CH_2Cl_2 (10 mL) is stirred at 0 °C for 20 min under argon atmosphere to remove traces of water from the reactants. TMSOTf (20 µL, 24.6 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) was added and the mixture was stirred for 2 h at 0 °C. The reaction was quenched by addition of saturated aq $NaHCO_3$ (30 mL) and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude residue was purified by flash chromatography (cyclohexane/EtOAc 2:1) to give **16** (252 mg, 0.38 mmol, 70%) as colorless oil. $[\alpha]^{22}_D$ = +60.1 (c = 1, $CHCl_3$), R_f = 0.13 (cyclohexane/EtOAc 4:1), IR (ATR, ν_{max}, cm^{-1}): 2923, 2851, 1749, 1631, 1514, 1437, 1370, 1208, 1129 1036, 835, 755. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.70 (d, J_{app} = 8.9 Hz, 2 H, H-4, H-5), 7.33 (d, $^4J_{H-6,H-8}$ = 2.4 Hz, 1 H, H-8), 7.12–7.08 (m, 2 H, H-3, H-6), 6.92 (d, $^4J_{H-1,H-2}$ = 2.4 Hz, 1 H, H-1), 5.66 (d, $^3J_{H-1',H-2'}$ = 1.8 Hz, 1 H, H-1'), 5.60 (dd, $^3J_{H-3',H-4'}$ = 10.0 Hz, $^3J_{H-2',H-3'}$ = 3.5 Hz, 1 H, H-3'), 5.49 (dd, $^3J_{H-2',H-3'}$ = 3.5 Hz, $^3J_{H-1'-H-2'}$ = 1.8 Hz, 1 H, H-2'), 5.39 (t,$^3J_{H-3',H-4',H-5'}$ = 10.0 Hz, 1 H, H-4'), 4.80 (dd, ^3J = 9.5 Hz, ^3J = 4.0 Hz, 1 H, C*H*COOMe), 4.31 (dd, ^2J = 12.2 Hz, $^3J_{H-5',H-6a'}$ = 5.3 Hz, 1 H, H-6a'), 4.16–4.08 (m, 1 H, H-5'), 4.05 (dd, ^2J = 12.2 Hz, $^3J_{H-5',H-6b'}$ = 2.2 Hz, 1 H, H-6b'), 3.75 (s, 3 H, OCH_3), 2.22 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 2.00-1.93 (m, 1 H, C*H*$_2$CHCOOMe) 1.95 (s, 3 H, CH_3), 1.82–1.56 (m, 7 H, C*H*$_2$CHCOOMe, CH, 5 CH$_2$), 1.30–0.90 (m, 5 H, CH$_2$). ^{13}C NMR, HSQC (101 MHz, $CDCl_3$): δ_C 173.0 (*C*OOMe), 170.9, 170.3, 170.2, 170.1 (CH_3*C*=O), 157.0, 154.3 (C-2, C-7), 135.7 (C-8a), 129.8 (C-4, C-5), 126.1 (C-4a), 117.9, 116.7 (C-3, C-6), 110.5, 107.5 (C-1, C-8), 96.2 (C-1'), 75.1 (*C*HCOOMe), 69.8 (C-2'), 69.7 (C-5'), 69.3 (C-3'), 66.4 (C-4'), 62.5 (C-6'), 52.7 (COO*C*H$_3$), 40.6 (*C*H$_2$CHCOOMe), 34.3, 34.1, 32.8, 26.7, 26.5, 26.3 (CH, 5 CH$_2$), 21.2, 2x 21.0, 20.9 (*C*H$_3$C=O).

ESI-MS: *m/z* (%) = 681.4 (100) $[M+Na]^+$, ESI-HRMS: *m/z* calcd for $[C_{34}H_{42}O_{13}+Na]^+$: 681.2518, found: 681.2519.

(2*S*)-3-Cyclohexyl-2-[2-(α-D-mannopyranosyloxy)naphthalen-7-yloxy]-propionic acid (17)
A mixture of **16** (57 mg, 86 µmol) in 1,4-dioxane (10 mL), MeOH (3.6 mL) and 4 N NaOH (1 mL) was stirred 16 h at room temperature. The reaction was quenched with 2 N HCl, the solvent was removed in vacuo and the residue was coevaporated three times with methanol in vacuo. The crude residue was purified by flash chromatography (EtOAc/EtOH 9:1) to give **17** (25 mg, 53 µmol, 61%) as colorless oil. R_f = 0.09 (EtOAc/EtOH 9:1). ^{1}H NMR, COSY (500 MHz, CD_3OD): δ_H 7.69 (d, J_{app} = 8.9 Hz, 2 H, H-4, H-5), 7.42 (d, $^4J_{H\text{-}1,H\text{-}3}$ = 2.1 Hz, 1 H, H-1), 7.09 (dd, $^3J_{H\text{-}3,H\text{-}4}$ = 8.9 Hz, $^4J_{H\text{-}1,H\text{-}3}$ = 2.1 Hz, 1 H, H-3), 7.04 (m, 2 H, H-6, H-8), 5.61 (d, $^3J_{H\text{-}1'H\text{-}2'}$ = 1.5 Hz, 1 H, H-1‘), 4.80 (dd, ^3J = 9.3 Hz, ^3J = 3.6 Hz, 1 H, C*H*COOH), 4.05 (dd, $^3J_{H\text{-}2',H\text{-}3'}$ = 3.3 Hz, $^3J_{H\text{-}1',H\text{-}2'}$ = 1.5 Hz, 1 H, H-2‘), 3.95 (dd, $^3J_{H\text{-}3',H\text{-}4'}$ = 9.4 Hz, $^3J_{H\text{-}2',H\text{-}3'}$ = 3.3 Hz, 1 H, H-3‘), 3.80–3.71 (m, 3 H, H-4‘, H-6‘), 3.64 (ddd, $^3J_{H\text{-}4',H\text{-}5'}$ = 9.7 Hz, $^3J_{H\text{-}5',H\text{-}6a'}$ = 4.9 Hz, $^3J_{H\text{-}5',H\text{-}6b'}$ = 2.7 Hz, 1 H, H-5‘), 1.92 (ddd, ^2J = 14.3 Hz, ^3J = 9.3 Hz, ^3J = 5.3 Hz, 1 H, CH_2CHCOOH), 1.76 (m, 6 H, CH_2CHCOOH, 5 ^{c}Hex), 1.36–1.15 (m, 4 H, ^{c}Hex), 1.01 (m, 2 H, ^{c}Hex). ^{13}C NMR, HSQC, HMBC (126 MHz, CD_3OD): δ_C 177.2 (COOH), 158.1 (C-7), 156.3 (C-2), 137.1 (C-8a), 130.2 (C-4, C-5), 126.8 (C-4a), 118.1 (C-6), 117.7 (C-3), 111.2 (C-1), 108.1 (C-8), 100.1 (C-1’), 76.2 (*C*HCOOH), 75.4 (C-5’), 72.5 (C-3’), 72.0 (C-2’), 68.4 (C-4’), 62.7 (C-6’), 41.6 (*C*H_2CHCOOH), 35.5 (CH), 35.0, 33.6, 27.6, 27.4, 27.2 (CH_2). ESI-MS: *m/z* (%) = 494.2 (100) $[M+NH_4]^+$, ESI-HRMS: *m/z* calcd for $[C_{25}H_{32}O_9+Na]^+$: 499.1939, found: 499.1957.

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