Synthesis and bioassay of β-(1,4)-D-mannans as potential agents against Alzheimer’s disease

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Aim: Oligomannurarate 971 derived from a marine plant has shown neuroprotective effects. In this study we synthesized a series of truncated derivatives of the oligosaccharide, and investigated the effect of these derivatives against Aβ peptide toxicity in vitro.

Methods: The sulfoxide method was applied to synthesize the derivatives. SH-SYSY human neuroblastoma cells were treated with Aβ1-40 (2 µmol/L), and the cell viability was detected using a CCK8 assay.

Results: A series of β-(1,4)-D-mannosyl oligosaccharide, ranging from the disaccharide to the hexasaccharide, were synthesized. Addition of 10 µmol/L β-(1,4)-D-mannobiose 6, β-(1,4)-D-mannotriose 9 or β-(1,4)-D-mannotetraose 12 in SH-SYSY cells significantly attenuated Aβ1-40-induced toxicity. The efficacies were similar to those caused by 10 µmol/L oligomannurarate 971 or alzhemed. Other oligosaccharides including oligomaltoses and oligocelluloses were less active.

Conclusion: Synthetic homogeneous short chain β-(1,4)-D-mannans shows neuroprotective effect against Aβ peptide toxicity similar to that of heterogeneous oligomannurarate 971 and alzhemed.

Keywords: Alzheimer’s disease; Aβ peptide; oligosaccharide; β-(1,4)-D-mannan; oligomannurarate 971; alzhemed; neuroprotection; medicinal chemistry

Introduction

Alzheimer’s disease (AD) is a neurodegenerative disease with multiple etiologies. As no effective treatments have yet been developed, AD remains pandemic in the 21st century and imposes enormous social and economic burdens on patients and their families[1]. It is estimated that 5.4 million individuals in the United States suffer from the disease, with AD patients numbering as many as 30 million globally, and these numbers continue to increase[2].

AD is characterized histopathologically by senile plaques, neurofibrillary tangles, reactive astrogliosis and neuronal cell loss. The Aβ peptide, the major component of senile plaques, has been identified in numerous cases as a major causative factor in AD pathophysiology[3, 4]. The Aβ peptide has, consequently, become one of the most important targets for AD therapy.

Carbohydrate drugs are widely employed in the treatment of a number of major diseases owing to their varied bioactivities and low toxicity[5–10]. Certain types of saccharides have also been shown to demonstrate neuroprotective effects[9,10], but the limited availability of pure saccharide compounds restricts further research on their activity. However, oligomannurarate 971 is a readily available, inexpensive and potent neuroprotective drug. Derived from a marine plant, the acidic heterogeneous β-(1,4)-D-oligomannurarate 971 (Figure 1) is a potent inhibitor of neurotoxicity induced by the Aβ peptide. It is believed that 971 penetrates the blood brain barrier with the aid of the transporter GLUT1, and it exhibits better efficacy in animal models of dementia than does alzhemed (also known as AZ, an anti-AD drug targeting the HHQK subregion at the N-terminus of Aβ1-40, which failed in a late stage Phase III clinical trial)[11, 12]. Mannurarate 971 is currently undergoing Phase II clinical studies[12]. As synthetic medicinal chemists, we wondered if truncated derivatives of 971 would exhibit similar
activity. We focused specifically on β-(1,4)-D-mannans as simplified 971 analogs. To the best of our knowledge, the neuroprotective effects of β-(1,4)-D-mannans have not been reported in the literature. This may be due to the limited availability of these compounds. While it can be very difficult to synthesize pure β-(1,4)-D-mannans, an effective solution was reported recently by Crich et al.[13–17]. We followed the reported method and prepared a series of β-(1,4)-D-mannans for biological studies.

Materials and methods
Chemistry
The sulfoxide method[13–17] is one of the few approaches that can be used reliably to overcome the difficulties in controlling anomeric stereochemistry and yield the desired β-(1,4)-D-mannosyl oligosaccharide series. We have used this method to prepare the target β-(1,4)-D-mannosyl oligosaccharide series, ranging from the disaccharide to the hexasaccharide, via multistep sequences. The linear syntheses of β-mannans commenced from the sulfoxide glycoside donor 1[18], which was prepared in 6 steps from D-mannose (30% yield overall). Activation of mannose donor 1 at -78 °C with triflic anhydride (Tf₂O) in the presence of the hindered base 2,4,6-tri-tert-butyl-pyrimidine (TTBP)[17], followed by addition of benzyl alcohol, provided benzyl β-mannoside 2[19]. Removal of the benzylidene acetal of 2 under acidic conditions yielded the intermediate diol (structure not shown), which was acetylated regioselectively at the 6-OH to give mannosyl acceptor 3. Coupling of acceptor 3 with mannosyl donor 1 under Crich’s standard conditions afforded the fully protected β-(1,4)-linked mannosyl disaccharide 4 in 70% yield (Scheme 1). The β-configuration of 4 was confirmed from the assignment of the H-5 chemical shift at δ 3.09[18] in the 1H NMR spectrum. This peak appeared as a doublet of triples, which is typical and diagnostic for the β-configuration in 4,6-O-benzylidene-protected mannosides. Glycoside 4 also displayed two anomeric carbon signals at δ 101.4 and δ 99.8 with 1JCH coupling constants of 162.5 and 155 Hz, respectively, a pattern that is consistent with the presence of β-O-glycosides[20]. The anomeric stereochemistry in all subsequent coupling products was assigned by similar comparison of the H-5 chemical shift in the 1H NMR spectrum.

The preparation of β-(1,4)-linked mannosyl disaccharide 4 from β-mannoside 2 represented the first glycosylation cycle of a two-stage iterative sequence[17]. This protocol was repeated to provide the fully protected β-(1,4)-mannans 7, 10, 13, and 16. Deacetylation of the corresponding acceptor followed by global debenzylation under catalytic hydrogenation conditions furnished the corresponding β-(1,4)-D-mannans 6,

![Scheme 1](image1.png)

![Scheme 2](image2.png)
9, 12, 15, and 17 (Scheme 2).

Drugs and reagents
The β-(1,4)-D-mannosyl oligosaccharide series was synthesized in our laboratory. Oligomannurrate 971 was obtained from Mei-yu GENG’s lab at the Shanghai Institute of Materia Medica. Alzemed (AZ) was purchased from Sigma-Aldrich China and the maltose and cellulose series were purchased from J&K Chemical Ltd (Shanghai, China).

Neuroprotective effect assay against Aβ peptide toxicity
SH-SY5Y human neuroblastoma cells were purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA). These are stable cells that typically will not be differentiated by exposure to small carbohydrates. Cells were plated at 4000 cells per well in 96-well plates and cultured in Dulbecco’s modified Eagle’s medium at 37°C in 5% CO2 (v/v) in a humidified incubator. After 24 h, aged Aβ1-40 (incubated for 96 h) was added to cells in combination with various compounds at different concentrations and the cells were incubated for 48 h. The final concentration of Aβ was 2 μmol/L. Cell viability was measured in a CCK8 assay.

Statistical analysis
The data were expressed as mean±SD. The Student’s t-test was used for statistical analysis.

Results and discussion
Neuroprotective effects of oligosaccharides against Aβ peptide toxicity
The synthetic homogeneous β-(1,4)-D-mannosyl oligosaccharides were assessed for activity against Aβ peptide neurotoxicity. Control compounds included D-mannose, mannurrate 971 and AZ. Commercially available oligomaltoses, including maltobiase (M2), maltotriose (M3), maltotetraose (M4), maltopentaose (M5), maltohexaose (M6), and maltoheptaose (M7) were assessed for comparison with the synthetic compounds. Oligocelluloses, including cellobiose (C2), cellotriose (C3), cellotetraose (C4), cellopentaose (C5) and cellohexose (C6) were also assessed.

Mannurrate 971 (OD=1.31) and AZ (OD=1.37) were found to exhibit potent neuroprotective effects (Aβ model: OD=1.12, control: OD=1.42±0.02) as expected. AZ was the most potent of the compounds tested. The synthetic homogeneous β-(1,4)-D-mannosyl oligosaccharides 6 (OD=1.32), 9 (OD=1.35), 12 (OD=1.27), 15 (OD=1.22), and 17 (OD=1.24) also showed neuroprotective potency. Compounds 6 and 9 were slightly more active than 971 and were nearly as potent as AZ. This is a significant result in light of the structural simplicity of these compounds. D-mannose did not show any neuroprotective activity. Oligocelluloses and oligomaltoses were also examined to shed further light on the neuroprotective activity of oligosaccharides. Only maltoheptaose (M7) showed significant activity (OD=1.27), while the others were largely inactive (M2: OD=1.23; M3: OD=1.17; M4: OD=1.17; M5: OD=1.19; M6: OD=1.22; C2: OD=1.17; C3: OD=1.11; C4: OD=1.15; C5: OD=1.13; C6: OD=1.19) (Figure 2). The differences in activity between oligomannoses, oligomaltoses and oligocelluloses indicate that the nature of the monosaccharide unit and the configuration of the anomeric center exert significant influence over the neuroprotective potency of oligosaccharides. We believe that this preliminary finding reveals important information on the structural characteristics of oligosaccharides that exhibit neuroprotective effects. More data are required to enable a detailed analysis of structure activity relationships.

Conclusion
In this study, we applied the sulfoxide method to the preparation of a series of β-(1,4)-D-mannosyl oligosaccharides. Oligosaccharides ranging from disaccharide to hexasaccharide were synthesized in multistep sequences. The neuroprotective activity of synthetic manns was assessed and compared with that of mannose, 971, AZ and a series of commercially available oligomaltoses and oligocelluloses. Synthetic compounds β-(1,4)-D-mannobiase 6, β-(1,4)-D-mannotriose 9 and β-(1,4)-D-mannotetraose 12 showed potency similar to that of 971 (and were slightly less potent than AZ) as inhibitors of toxicity induced by the Aβ peptide. Other oligosaccharides failed to show significant neuroprotective activity. Taken together, these results demonstrate that the structure of 971 can be modified without a loss of activity. We have disclosed a new class of neuroprotective agents with potency against Aβ toxicity and gained insight that will enable development of potent agents for the treatment of Alzheimer’s disease. Further research is ongoing in our group.
Experiment

Reagents (chemicals) were purchased from Acros (Geel, Belgium) and the Shanghai Chemical Reagent Company (Shanghai, China) and were used without purification. Analytical thin-layer chromatography was performed on HSGF 254 plates (150–200 μm thickness; Yantai Huiyou Company, Yantai, Shandong, China). ^1H NMR (300 MHz or 400 MHz) spectra were recorded on Varian Mercury-300 or 400 High Performance Digital FT-NMR (Varian, Fort Collins, CO, USA) instruments using TMS as the internal standard. ^13C NMR (100 MHz) spectra were determined using a Varian Mercury-400 High Performance Digital FT-NMR. Chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). LC-MS analysis was carried out on a Thermo Finnigan LCQ Deca XP (Thermo Electron Corporation, San Jose, CA, USA) and HRMS was performed on a Finnigan MAT 95 mass spectrometer (Thermo Fisher Scientific, Waltham, Massachusetts, USA). Optical rotation values were determined using a PerkinElmer-341 (589 nm) polarimeter (PerkinElmer, Waltham, Massachusetts, USA).

General procedure for preparation of β-mannosides by the sulfoxide method

A dispersion of sulfoxide, TTBP (2.5 equiv.) and powdered molecular sieves in CH₂Cl₂ (0.1 mol/L) was cooled to -78°C for 30 min. To this mixture was added a solution of Tf₂O (1 mol/L in CH₂Cl₂, 1.1 equiv.) dropwise at -78°C. The acceptor (1.2 equiv.) was added slowly as a solution in CH₂Cl₂ (1.0 mol/L). The reaction mixture was stirred at -78°C for 1 h, then gradually warmed to -20°C while the stirring was continued. When TLC indicated complete consumption of the sulfoxide, the reaction was quenched with saturated aq. NaHCO₃. The aqueous phase was extracted thrice with EtOAc. The combined organic phases were washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography to give the title compound (6.3 g, 46%) as a colorless oil. ^1H NMR (300 MHz, CDCl₃) δ 7.44–7.21 (m, 15H, ArH), 4.99 (d, J=11.9 Hz, 2H, PhCH₂), 4.80 (d, J=12.4 Hz, 1H, PhCH₂), 4.61 (d, J=12.0 Hz, 1H, PhCH₂), 4.51–4.39 (m, 4H, 4H, PhCH₂), 4.29 (d, J=11.8 Hz, 1H, PhCH₂), 3.99–3.87 (m, 2H, H4, H2), 3.40 (ddd, J=9.6, 4.9, 3.1 Hz, 1H, H5), 3.27 (dd, J=9.4, 3.0 Hz, 1H, H3), 2.55 (s, 1H, OH), 2.12 (s, 3H, OAc). ^13C NMR (100 MHz, CDCl₃): δ=171.3, 138.4, 137.1, 128.4–127.1, 126.1, 101.7, 101.4, 99.8, 79.6, 78.6, 78.3, 75.7, 75.2, 74.1, 74.0, 73.4, 72.6, 71.7, 70.8, 68.5, 67.4, 63.5, 21.0. ESI-MS: m/z 515.3 [M+Na]^+. HRMS: calc for C₂₃H₂₁O₅Na 515.2046, found: 515.2040. [α]_D^-=−110 (c 0.5, CHCl₃).

Benzyl 2,3-di-O-benzyl-6-acetyl-4-O-(2,3-di-O-benzyl-4,6-O-benzylidene-β-D-mannopyranosyl)-β-D-mannopyranoside (4)

Coupling sulfoxide 1 with 3 under the standard sulfoxide β-mannosylation conditions afforded the title compound in 65% yield as a colorless oil. ^1H NMR (400 MHz, CDCl₃) δ 7.49–7.20 (m, 30H, ArH), 5.52 (s, 1H, PhCH₂), 5.01–4.86 (m, 3H, PhCH₂), 4.84–4.72 (m, 3H, PhCH₂), 4.68–4.55 (m, 4H, PhCH₂, H1), 4.50 (d, J=11.9Hz, 1H, PhCH₂), 4.46 (s, 1H, H1'), 4.31 (m, 2H, H6a, H6b), 4.14–4.03 (m, 2H, H4, H6a'), 3.99 (dd, J=10.4, 4.8 Hz, 1H, H6b'), 3.90 (m, 2H, H2, H2'), 3.66 (t, J=10.2 Hz, 1H, H4'), 3.58–3.49 (m, 2H, H3, H3'), 3.49–3.43 (m, 1H, H5), 3.09 (td, J=9.9, 4.9 Hz, 1H, H5'), 2.08 (s, 3H, OAc). ^13C NMR (100 MHz, CDCl₃): δ=170.8, 138.6, 138.5, 138.4, 137.6, 137.1, 128.8, 128.4–127.1, 126.1, 101.7, 101.4, 99.8, 79.6, 78.6, 78.3, 75.7, 75.2, 74.1, 74.0, 73.4, 72.6, 71.7, 70.8, 68.5, 67.4, 63.5, 21.0. ESI-MS: m/z 945.6 [M+Na]^+. HRMS: calc for C₃₈H₃₅O₁₃Na 945.3826, found: 945.3823. [α]_D^-=−58.6 (c 1, CHCl₃).

Benzyl 2,3-di-O-benzyl-6-acetyl-4-O-(2,3-di-O-benzyl-4-acetyl-β-D-mannopyranosyl)-β-D-mannopyranoside (5)

The method used to prepare 3 was employed for the synthesis of the title compound (colorless oil, 70% yield) using compound 4 as the starting material. ^1H NMR (400 MHz, CDCl₃) δ 7.30 (ddd, J=25.2, 15.9, 7.7 Hz, 25H, ArH), 5.00–4.89 (m, 2H, PhCH₂), 4.86–4.71 (m, 3H, PhCH₂), 4.56 (m, 5H, PhCH₂), 4.44 (m, 4H, H1, H1', H6a, H6b), 4.17 (m, 2H, H6a', H6b'), 4.10 (t, J=8.9 Hz, 1H, H4), 3.90 (m, 2H, H2, H2'), 3.83 (t, J=9.4 Hz, 1H, H4'), 3.62–3.53 (m, 2H, H3, H5), 3.20 (m, 1H, H3'), 3.10 (m, 1H, H5'), 2.49 (s, 1H, OH), 2.09 (s, 3H, OAc), 1.91 (s, 3H, OAc). ^13C NMR (100 MHz, CDCl₃): δ=170.1, 170.8, 138.6, 138.4, 138.2, 137.6, 137.1, 128.5–127.2, 109.9, 99.8, 81.3, 78.9, 75.0, 74.4, 74.3, 74.1, 73.9, 73.8, 73.3, 71.3, 71.2, 70.7, 66.3, 63.6, 63.4, 20.9, 20.7. ESI-MS: m/z 899.5 [M+Na]^+. HRMS: calc for C₃₈H₃₅O₁₃Na 899.3619, found: 899.3646. [α]_D^-=−87.3 (c 1, CHCl₃).

β-(1,4)-D-mannobiose (6)[21]

To a solution of compound 5 (79 mg, 0.1 mmol) in anhydrous MeOH (2.5 mL) was added powdered K₂CO₃ (13.8 mg, 0.1 mmol), and the mixture was stirred at room temperature for 1 h. When TLC showed complete consumption of 5, the mixture was filtered to remove solids and concentrated. The
residue was taken up in MeOH (5 mL), and to this solution was added Pd(OH)$_2$/C (16 mg, 20% Pd) in $\text{H}_2$. The mixture was stirred under an atmosphere of $\text{H}_2$ for 24 h. The mixture was filtered through a Celite pad and concentrated. The residue was dissolved in water and purified by Sephadex LH20 gel chromatography eluted with water. The collected fractions were lyophilized to give the title compound (18 mg, 58%) as a white amorphous solid. $^1$H NMR (400 MHz, D$_2$O) $\delta$ 5.23 (s, 0.68H), 4.96 (s, 0.32H), 4.79 (s, 1H), 4.11 (s, 1H), 4.08–3.89 (m, 5H), 3.89–3.75 (m, 3H), 3.71 (d, $J$=9.5 Hz, 1H), 3.62 (t, $J$=9.7 Hz, 1H), 3.50 (dd, $J$=19.7, 12.6 Hz, 1H). $^{13}$C NMR (100 MHz, D$_2$O): $\delta$=102.6, 102.5, 96.2, 96.0, 79.2, 78.9, 78.8, 77.2, 75.2, 74.1, 73.3, 73.0, 72.9, 72.6, 71.3, 69.1, 63.4, 62.9. ESI-MS: $m/z$ 386.6 [M+HCOO]$^-$.

HRMS: calcd for C$_{16}$H$_{31}$O$_{14}$, found: 341.1084. $[\alpha]_D^{21}=2.8$, (c 0.4, H$_2$O).

Benzyl 2,3-di-O-benzyl-4,6-O-benzylidene-β-D-mannopyranosyl-(1→4)-2,3-di-O-benzyl-6-O-acetyl-β-D-mannopyranosyl-(1→4)-2,3-di-O-benzyl-6-O-acetyl-β-D-mannopyranosyl (8)

Sulfoxide 1 was coupled with compound 5 using the standard sulfoxide β-mannosylation protocol to afford the title compound 8 in 65% yield as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62–6.96 (m, 40H), 5.51 (s, 1H), 4.99–4.90 (m, 2H), 4.84–4.68 (m, 7H), 4.65–4.48 (m, 7H), 4.44 (s, 1H), 4.33 (m, 2H), 4.14–3.92 (m, 6H), 3.91–3.82 (m, 3H), 3.61 (t, $J$=10.2 Hz, 1H), 3.56–3.43 (m, 4H), 3.26 (m, 1H), 3.07 (td, $J$=9.7, 4.9 Hz, 1H), 2.65 (t, $J$=13.0 Hz, 2H), 1.90 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$=170.8, 170.6, 138.7, 138.6, 138.5, 139.3, 139.4, 137.3, 137.5, 137.6, 128.8, 128.4–127.1, 126.1, 101.9, 101.3, 100.8, 99.3, 79.8, 79.6, 78.50, 78.2, 77.2, 75.7, 75.4, 75.2, 74.3, 74.0, 73.9, 73.3, 73.1, 72.5, 72.0, 71.4, 70.7, 68.4, 67.4, 64.3, 63.1, 20.9, 20.7. ESI-MS: $m/z$ 1329.7 [M+Na]$^+$. HRMS: calcd for C$_{37}$H$_{46}$O$_{21}$Na, found: 1329.5417. $[\alpha]_D^{21}=-66.3$, (c 1, CHCl$_3$).

Benzyl 2,3-di-O-benzyl-4,6-O-acetyl-β-D-mannopyranosyl-(1→4)-2,3-di-O-benzyl-6-O-acetyl-β-D-mannopyranosyl (11)

The method used to prepare 3 was employed for the synthesis of the title compound (colorless oil, 81% yield) using compound 7 as the starting material. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41–7.19 (m, 35H), 4.99–4.89 (m, 2H), 4.83–4.68 (m, 6H), 4.64–4.50 (m, 6H), 4.48 (s, 1H), 4.46–4.28 (m, 4H), 4.21–4.10 (m, 4H), 4.08–3.96 (m, 2H), 3.90 (m, 1H), 3.87–3.79 (m, 3H), 3.53 (m, 3H), 3.35 (dd, $J$=8.1, 4.2 Hz, 1H), 3.21 (dd, $J$=9.4, 2.6 Hz, 1H), 3.16–3.08 (m, 1H), 2.55 (s, 1H), 2.07 (s, 3H), 1.91 (s, 3H), 1.90 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$=171.2, 170.7, 170.6, 138.6, 138.5, 138.4, 138.3, 137.5, 137.0, 128.5–127.1, 101.3, 100.7, 99.8, 81.3, 79.5, 79.4, 77.2, 75.4, 75.2, 75.0, 74.4, 74.2, 74.1, 74.0, 73.9, 73.8, 73.3, 73.1, 71.7, 71.4, 71.3, 70.6, 66.2, 63.5, 63.4, 63.2, 20.9, 20.7, 20.6. ESI-MS: $m/z$ 1283.6 [M+Na]$^+$.

HRMS: calcd for C$_{40}$H$_{58}$O$_{23}$Na, found: 1283.5192. $[\alpha]_D^{21}=79.5$, (c 1, CHCl$_3$).

β-(1,4)-D-Mannotetraose (23)

The method used to prepare 9 was employed for the synthesis of the title compound (white amorphous solid, 50% yield) using compound 11 as the starting material. $^1$H NMR (400 MHz, D$_2$O) $\delta$ 5.05 (s, 0.57H), 4.79 (s, 0.43Hz), 4.62 (d, $J$=13.3 Hz, 3H), 4.00 (s, 2H), 3.94 (d, $J$=2.1 Hz, 1H), 3.89–3.83 (m, 2H), 3.80

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Benzyl 2,3-di-O-benzyl-4,6-O-benzylidene-β-D-mannopyranosyl-(1→4)-2,3-di-O-benzyl-6-O-acyetyl-β-D-mannopyranosyl (14) 

The method used to prepare 13 using the standard sulfite reducing β-mannosylation protocol to afford the title compound in 55% yield as a colorless oil.

H NMR (100 MHz, CDCl₃) δ 7.47–7.17 (m, 70H), 5.50 (s, 1H), 4.94 (dd, J = 16.4, 12.2 Hz, 2H), 4.87–4.67 (m, 2H), 3.94–3.76 (m, 12H), 3.75–3.62 (m, 1H), 3.62–3.41 (m, 2H). HRMS: m/z 2198.1068 [M+Na]⁺. [α]D = 67.3 (c 0.4, CHCl₃).

Benzyl 2,3-di-O-benzyl-4,6-O-benzylidene-β-D-mannopyranosyl-(1→4)-2,3-di-O-benzyl-6-O-acyetyl-β-D-mannopyranosyl (15) 

The method used to prepare 9 was employed for the synthesis of the title compound (white amorphous solid, 35% yield) using compound 14 as the starting material.

H NMR (400 MHz, CDCl₃) δ 7.42–7.17 (m, 55H), 4.95 (dd, J = 20.0, 12.2 Hz, 2H), 4.83–4.70 (m, 12H), 4.56 (dd, J = 31.5, 16.6, 10.2 Hz, 11H), 4.47–4.28 (m, 5H), 4.21–4.01 (m, 7H), 4.08–3.94 (m, 1H), 4.01 (dd, J = 9.1 Hz, 1H), 3.99–3.93 (m, 2H), 3.89 (dd, J = 13.4, 2.4 Hz, 2H), 3.86–3.78 (m, 4H), 3.57–3.46 (m, 5H), 3.39–3.33 (m, 1H), 3.33–3.26 (m, 2H), 3.22 (dd, J = 9.4, 2.4 Hz, 1H), 3.15–3.09 (m, 1H), 2.50 (s, 1H), 2.07 (s, 3H), 1.96–1.85 (s, 1H). HRMS: m/z 2054.8271 [M+Na]⁺. [α]D = -67.0 (c 1, CHCl₃).

β-(1,4)-D-Mannopentose (16) 

The method used to prepare 9 was employed for the synthesis of the title compound (white amorphous solid, 35% yield) using compound 16 as the starting material.

H NMR (400 MHz, CDCl₃) δ 5.08 (s, 0.60H), 4.81 (s, 0.40H), 4.71 (d, J = 6.4 Hz, 2H), 4.57 (d, J = 6.4 Hz, 2H), 4.02 (s, 3H), 3.96 (d, J = 3.1 Hz, 1H), 3.85 (dd, J = 18.0, 8.6 Hz, 7H), 3.68 (dt, J = 12.3, 10.6 Hz, 12H), 3.56 (dd, J = 14.3, 4.9 Hz, 2H), 3.45 (d, J = 9.1 Hz, 4H), 3.35 (d, J = 7.2 Hz, 1H). HRMS: calcd for C₃₀H₃₆O₃₈ Na⁺: 827.2669, found: 827.2680. [α]D = -27.0 (c 0.2, H₂O).

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Author contribution

Jing-kang SHEN and Mei-yu GENG designed research; Ru-wei JIANG, Xiao-guang DU, Xuan ZHANG, Ding-yu HU, Tao MENG, and Yue-wei CHEN performed research; Ru-wei JIANG, Yue-lei CHEN, Mei-yu GENG, and Jing-kang SHEN analyzed data; Ru-wei JIANG, Xiao-guang DU, Yue-wei CHEN, Mei-yu GENG, and Jing-kang SHEN wrote the paper.

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