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A concise synthesis of arabinogalactan with β-(1→6) galactopyranose backbone and α-(1→2) arabinofuranose side chains

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Abstract—Penta- and octasaccharides composed of β-(1→6)-linked galactose backbone with α-(1→2)-linked arabinose branches were synthesized through coupling of α-(1→5)-linked arabinofuranosyl disaccharide donor with a tri- and tetrasaccharide backbone at C-2, respectively.

Arabinogalactans (AGs) widely distribute in plant cell walls[1,2] and they complex with protein to form glycoprotein\proteoglycan (AGPs).[3] AGPs play important roles in cell differentiation and development, as defense systems in plants, and are involved in cell–cell interactions and elongation growth of the cell wall.[4] And many AGPs have biological activities, such as immunomodulating activity,[5] anti-complement activity;[6] reticuloendothelial system activating properties,[7] and many other activities.[8] The arabinogalactans with β-(1→6)-linked galactopyranose backbone and α-(1→2)-linked arabinofuranose side chains such as **19** and **20** may exist in *Echinacea purpurea* which have immunomodulating activity.[5] Although the presence of 2,6-branched residues in AGPs is well defined, the exact structure of these saccharides remains to be established. Especially, for elucidation of the molecular structure responsible for their biological activity, it would be necessary to synthesize 2,6-branched arabinogalactans (Scheme 1).

Until now, very few examples exist on the chemical synthesis of the arabinogalactans.[9,10] We present herein a facile synthesis of penta- and octasaccharides comprised of β-(1→6)-linked galactose backbone with α-(1→2)-linked arabinose side chains.

Retrosynthetic analysis indicated that the best way to obtain the arabinogalacto-pentasaccharide **19** and arabinogalacto-octasaccharide **20** is to prepare first the β-(1→6)-linked trisaccharide acceptor with 2′-OH and the tetrasaccharide acceptor with 2,2″-OH, and then to assemble the arabinofuranose side chains. In our synthesis, we applied benzoyl group as relatively 'permanent' group, and acetyl group as temporary group. The benzoyl and acetyl protecting groups are well differentiated by treating the protected sugars with ~3% solution of MeCOCl in $CHCl_3$–MeOH,[11] which produces dry HCl in situ, and the acetyl is removed completely. For syntheses of the tri- and tetrasaccharide backbone, four simple galactopyranose synthons **1**,[12] **2**, **3**, and **4** were prepared. Compound **2** was obtained by 6-*O*-tritylation of galactose, benzoylation, acetolysis, 1-*O*-deacetylation, and trichloroacetimidation. Compound **3** was obtained by 6-*O*-tritylation of 1,2-*O*-ethylidene-α-D-galactopyranose, benzoylation, acetolysis, 1-*O*-deacetylation, trichloroacetimidation, and coupling with 4-methoxyphenol. Compound **4** was obtained by condensation of **2** with 4-methoxyphenol. Our initial attempt was to deacetylate **3** with MeCOCl/CH_3OH/CH_2Cl_2 (1:25:25) to provide **5**. However, it was found that even when the reaction was run at room temperature for 10 h, the required 2,6-OH derivative **5** was obtained in only 40% yield together with the byproduct **6** (30%), and the reaction mixture was difficult to be separated. So, our focus turned to prepare **6** by selective 6-*O*-deacetylation under much milder acidic conditions. For this purpose, **3** was dissolved in MeCOCl/CH_3OH/CH_2Cl_2 (1:500:500), and the mixture was stirred at room temperature for 12 h, leading to acceptor **6** in excellent yield (88%), without affecting the 2-*O*-acetyl group. This seems to be a fine method to

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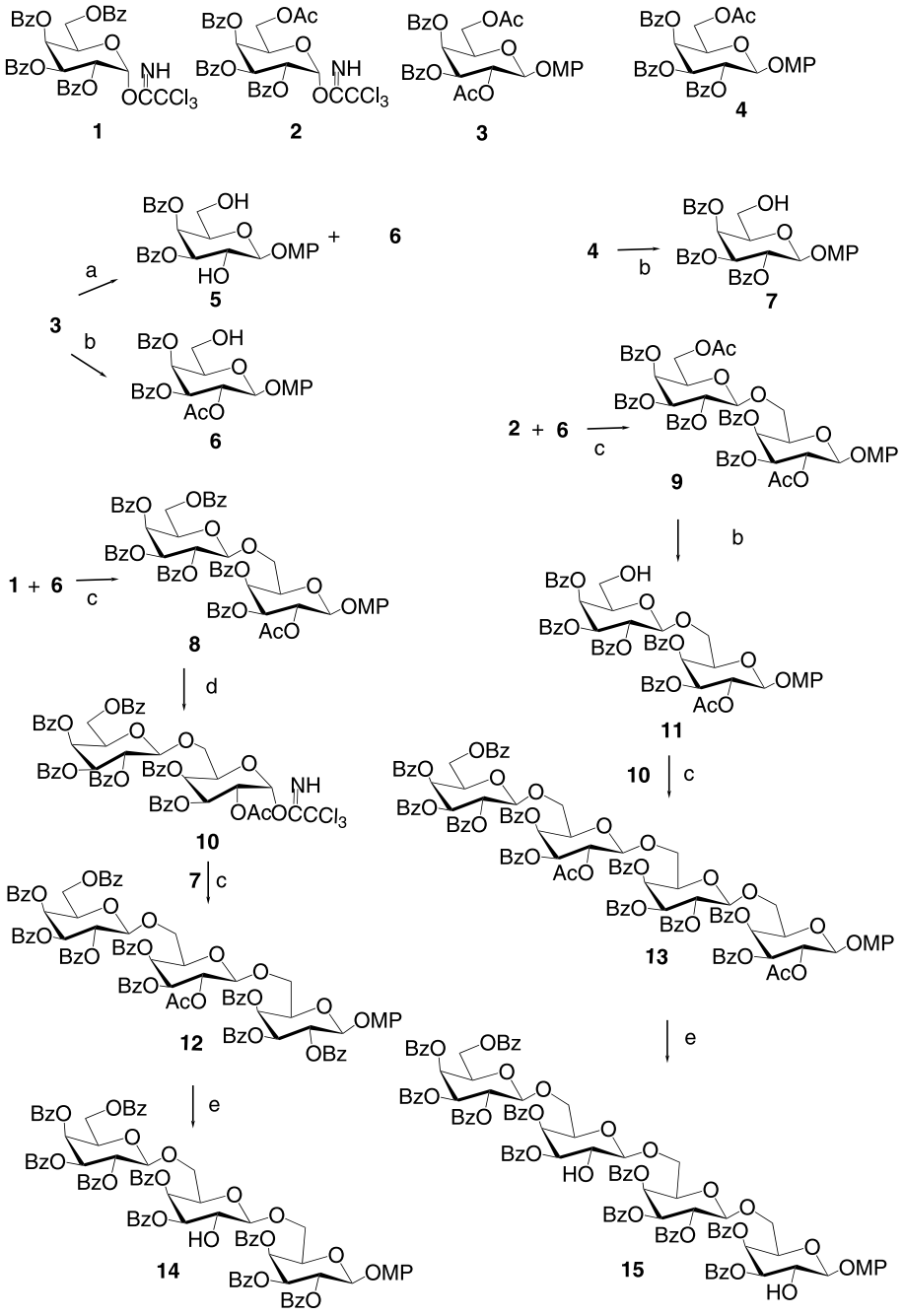
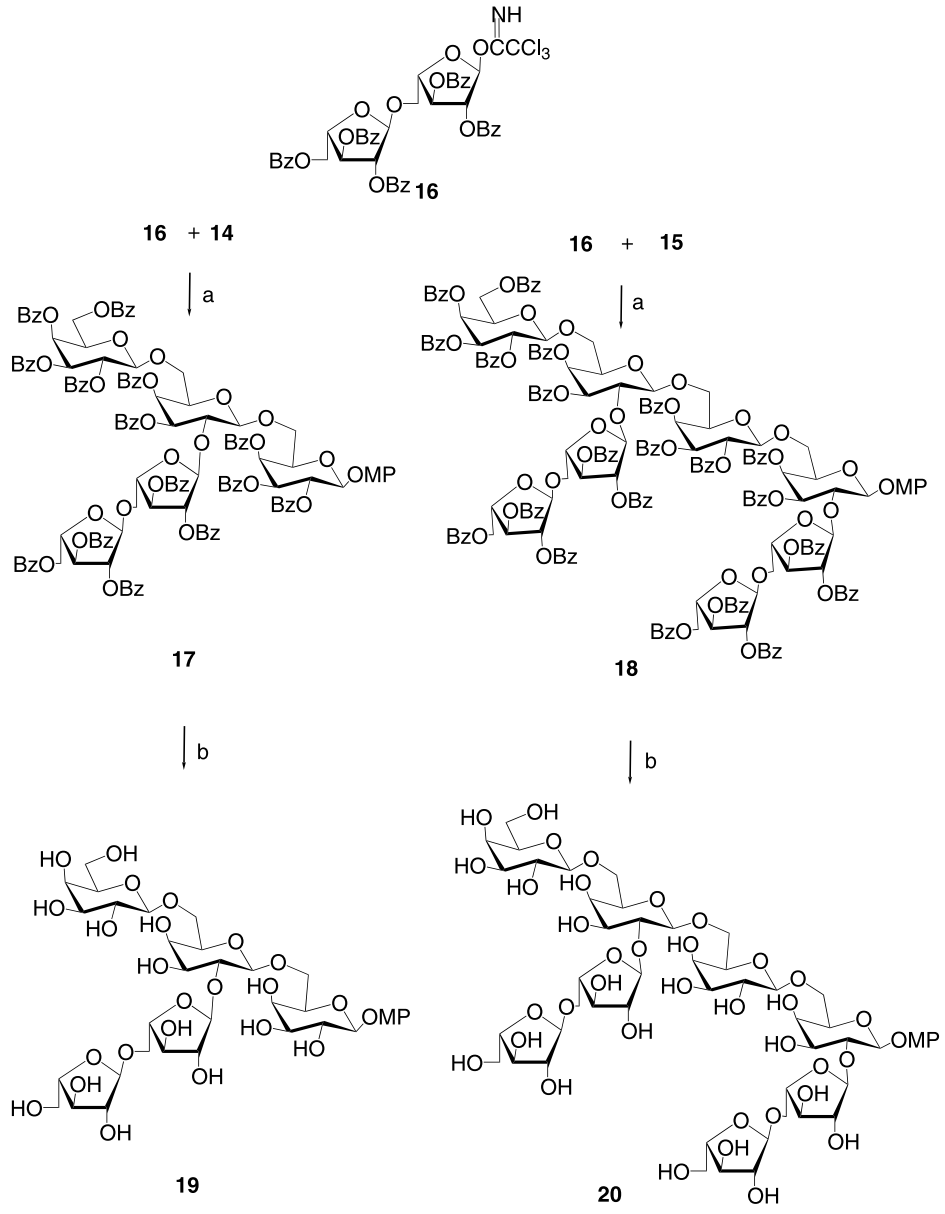


Scheme 1. *Reagents and conditions*: (a) $MeCOCl/CH_3OH/CH_2Cl_2$ (1:25:25), 10 h; (b) $MeCOCl/CH_3OH/CH_2Cl_2$ (1:500:500), 12 h, **6**, 88%; **7**, 90%; **11**, 85%; (c) TMSOTf, CH_2Cl_2, N_2, −20°C to rt, 4 h, **8**, 83%; **9**, 79%; **12**, 77%; **13**, 75%; (d) CAN, H_2O/CH_3CN, 0.5 h, then CCl_3CN, DBU, CH_2Cl_2 (dry), 10 h, **10**, 66% two steps; (e) $MeCOCl/CH_3OH/CH_2Cl_2$ (1:50:50), 48 h, **14**, 87%; **15**, 80%.

differentiate galactose primary hydroxyl acetate from the secondary one. Compound **4** was also deacetylated under the same reaction conditions to give acceptor **7**.

Condensation of the donors **1**, and **2** with the acceptor **6** in the presence of TMSOTf as catalyst afforded exclusively β-(1→6)-linked disaccharide building block **8** (83%) and **9** (79%), respectively. The disaccharide acceptor **11** with 6′-OH was obtained in a satisfactory yield (85%) by treatment of **9** with $MeCOCl/CH_3OH/CH_2Cl_2$ (1:500:500), indicating that the mild acidic conditions were also suitable for selective 6-*O*-deacetylation of disaccharides. Oxidative cleavage of 1-OMP of **8** with CAN (4.5 equiv.) in $CH_3CN–H_2O$ (4:1 v/v) followed by trichloroacetimidation with trichloroacetonitrile and DBU in dry dichloromethane gave the disaccharide donor **10** (71%).

Coupling of the disaccharide donor **10** with the monosaccharide acceptor **7** afforded the β-(1→6)-linked galactose trisaccharide **12** (77%). Similarly, the β-(1→6)-linked galactose tetrasaccharide **13** was obtained by coupling donor **10** with the disaccharide acceptor **11** in good yield (75%). Removal of the 2′-*O*-acetyl of **12** and



Scheme 2. *Reagents and conditions*: (a). TMSOTf, CH_2Cl_2, N_2, −20°C to rt, 4 h, **17**, 72%; **18**, 74%; (b). NH_3, CH_3OH, **19**, 95%; **20**, 97%.

2-*O*-, 2″-*O*-acetyl of **13** with MeCOCl/CH_3OH/CH_2Cl_2 (1:50:50) for 48 h at room temperature gave the trisaccharide acceptor **14** (87%) and tetrasaccharide acceptor **15** (80%), respectively.

The donor 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranosyl-(1→5)-2,3-di-*O*-benzoyl-α-L-arabinofuranosyl trichloroacetimidate **16** was prepared with reference to our previous report.[9b] The galacto-acceptors **14** and **15** were condensed with the arabinofuranose donor **16** to give the penta-**17** (72%) and octasaccharide **18** (74%), respectively. The fully protected arabinogalactans **17** and **18** were deprotected with a saturated solution of ammonia in MeOH (40 mL) for a week giving the target **19** (95%) and **20** (97%) (Scheme 2).

In the syntheses, through smooth reactions all compounds described here were obtained in satisfactory yields with easily accessible materials and inexpensive reagents, and were isolated and identified with ^1H, ^{13}C NMR spectra.[13]

In summary, a special strategy particularly suitable for the preparation of 2,6-branched arabinogalacto-oligosaccharides has been developed based on trichloroacetimidate donors and selective deacetylation.

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13. All the new compounds involved in the study were identified by ^{1}H or ^{13}C NMR spectrometry, and elemental analyses. Selected data for some important compounds: **8**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (d, 1H, *J* 3.2 Hz, H-4), 5.89 (d, 1H, *J* 3.2 Hz, H-4), 5.78 (dd, 1H, *J* 8.0 Hz, 10.4 Hz, H-2), 5.70 (dd, 1H, 5.53 (dd, 1H, *J* 3.2 Hz, 10.4 Hz, H-3), 5.38 (dd, 1H, *J* 3.4 Hz, 10.4 Hz, H-3), 5.03 (d, 1H, *J* 8.0 Hz, β H-1), 4.94 (d, 1H, *J* 8.0 Hz, β H-1), 4.42–4.39 (dd, 1H, *J* 5.4 Hz, 11.2 Hz, H-6), 4.27–4.18 (m, 3H, 2H-5, H-6), 4.13–4.10 (dd, 1H, *J* 4.0 Hz, 10.4 Hz, H-6), 4.01–3.98 (dd, 1H, *J* 4.0 Hz, 10.4 Hz, H-6), 3.73 (s, 3H, CH_3O), 1.99 (s, 3H, CH_3CO). **9**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99–6.83 (dd, 4H, -C_6H_4-), 5.89 (d, 1H, *J* 3.4 Hz, H-4), 5.82 (d, 1H, *J* 3.4 Hz, H-4), 5.74 (dd, 1H, *J* 8.0 Hz, 10.4 Hz, H-2), 5.70 (dd, 1H, *J* 8.0 Hz, 10.4 Hz, H-2), 5.48 (dd, 1H, *J* 3.4 Hz, 10.4 Hz, H-3), 5.39 (dd, 1H, *J* 3.4 Hz, 10.4 Hz, H-3), 5.02 (d, 1H, *J* 8.0 Hz, β H-1), 4.89 (d, 1H, *J* 8.0 Hz, β H-1), 4.23–4.21 (m, 1H, H-5), 4.10–4.06 (m, 4H, H-5, 3H-6), 3.99–3.94 (dd, 1H, *J* 4.4 Hz, 11.2 Hz, H-6), 3.73 (s, 3H, CH_3O), 2.00 (s, 3H, CH_3CO), 1.96 (s, 3H, CH_3CO). **10**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 1H, N*H*), 6.34 (d, 1H, *J* 3.2 Hz, α H-1), 5.87 (d, 1H, *J* 3.2 Hz, H-4), 5.85 (d, 1H, *J* 3.2 Hz, H-4), 5.74 (dd, 1H, *J* 8.0 Hz, 10.4 Hz, H-2), 5.55 (dd, 1H, *J* 3.2 Hz, 10.4 Hz, H-3), 5.41 (dd, 1H, *J* 3.4 Hz, 10.4 Hz, H-3), 5.15 (dd, 1H, *J* 4.0 Hz, 10.4 Hz, H-2), 5.04 (d, 1H, *J* 8.0 Hz, β H-1), 4.47–4.44 (dd, 1H, *J* 5.2 Hz, 11.2 Hz, H-6), 4.27–4.10 (m, 4H, 2H-5, 2H-6), 4.00–3.97 (dd, 1H, *J* 5.2 Hz, 10.4 Hz, H-6), 1.96 (s, 3H, CH_3CO). **11**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97 (d, 1H, *J* 3.4 Hz, H-4), 5.84–5.79 (m, 2H, H-4, H-2), 5.74 (dd, 1H, *J* 8.0 Hz, 10.4 Hz, H-2), 5.44 (dd, 1H, *J* 3.4 Hz, 10.4 Hz, H-3), 5.40 (dd, 1H, *J* 3.4 Hz, 10.4 Hz, H-3), 5.04 (d, 1H, *J* 8.0 Hz, β H-1), 4.90 (d, 1H, *J* 8.0 Hz, β H-1), 4.67–4.44 (dd, 1H, *J* 4.0 Hz, 11.2 Hz, H-6), 4.27–4.10 (m, 3H, H-5, 2H-6), 4.10–4.09 (m, 1H, H-5), 4.00–3.97 (dd, 1H, *J* 4.0 Hz, 10.4 Hz, H-6), 3.73 (s, 3H, CH_3O), 1.98 (s, 3H, CH_3CO). **12**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.99 (dd, 1H, *J* 8.0 Hz, 10.4 Hz, H-2), 5.92 (d, 1H, *J* 3.4 Hz, H-4), 5.88 (d, 1H, *J* 3.4 Hz, H-4), 5.84 (d, 1H, *J* 3.4 Hz, H-4), 5.65 (dd, 1H, *J* 8.0 Hz, 10.4 Hz, H-2), 5.60 (dd, 1H, *J* 3.4 Hz, 10.4 Hz, H-3), 5.54 (dd, 1H, *J* 3.4 Hz, 10.4 Hz, H-3), 5.44 (dd, 1H, *J* 8.0 Hz, 10.4 Hz, H-2), 5.27 (dd, 1H, *J* 3.4 Hz, 10.4 Hz, H-3), 5.22 (d, 1H, *J* 8.0 Hz, β H-1), 4.69 (d, 1H, *J* 8.0 Hz, β H-1), 4.62 (d, 1H, *J* 8.0 Hz, β H-1), 3.73 (s, 3H, CH_3O), 1.84 (s, 3H, CH_3CO). **13**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 (d, 1H, *J* 3.2 Hz, H-4), 5.86–5.85 (m, 2H, 2H-4), 5.81 (d, 1H, *J* 3.2 Hz, H-4), 5.75–5.61 (m, 3H, 3H-2), 5.52–5.49 (m, 2H, 2H-3), 5.38 (dd, 1H, *J* 3.2 Hz, 10.4 Hz, H-3), 5.32 (dd, 1H, *J* 7.8 Hz, 10.4 Hz, H-2), 5.22 (dd, 1H, *J* 3.2 Hz, 8.0 Hz, H-3), 5.00 (d, 1H, *J* 8.0 Hz, β H-1), 4.89 (d, 1H, *J* 8.0 Hz, β H-1), 4.66 (d, 1H, *J* 7.8 Hz, β H-1), 4.57 (d, 1H, *J* 8.0 Hz, β H-1), 3.73 (s, 3H, CH_3O), 1.98 (s, 3H, CH_3CO), 1.91 (s, 3H, CH_3CO). **14**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90–5.88 (m, 2H, 2H-4), 5.82 (d, 1H, *J* 3.4 Hz, H-4), 5.81 (dd, 1H, *J* 8.0 Hz, 10.4 Hz, H-2), 5.71 (dd, 1H, *J* 8.0 Hz, 10.4 Hz, H-2), 5.64 (dd, 1H, *J* 3.4 Hz, 10.4 Hz, H-3), 5.57 (dd, 1H, *J* 3.4 Hz, 10.4 Hz, H-3), 5.27 (dd, 1H, *J* 3.4 Hz, 10.4 Hz, H-3), 5.17 (d, 1H, *J* 8.0 Hz, β H-1), 4.75 (d, 1H, *J* 8.0 Hz, β H-1), 4.59 (d, 1H, *J* 8.0 Hz, β H-1), 3.73 (s, 3H, CH_3O). **15**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91–5.90 (m, 2H, 2H-4), 5.82–5.77 (m, 4H, 2H-4, 1H-2), 5.67 (dd, 1H, *J* 8.0 Hz, 10.4 Hz, H-2), 5.55–5.51 (m, 2H, 2H-3), 5.38 (dd, 1H, *J* 3.2 Hz, 10.0 Hz, H-3), 5.18 (dd, 1H, *J* 3.6 Hz, 10.0 Hz, H-3), 5.02 (d, 1H, *J* 7.8 Hz, β H-1), 4.93 (d, 1H, *J* 8.0 Hz, β H-1), 4.69 (d, 1H, *J* 8.0 Hz, β H-1), 4.37 (d, 1H, *J* 8.0 Hz, β H-1), 3.69 (s, 3H, CH_3O). **17**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.03 (d, 1H, *J* 3.2 Hz, H-4, Galp), 5.96 (dd, 1H, *J* 8.0 Hz, 10.4 Hz, H-2, Galp), 5.87 (d, 1H, *J* 3.6 Hz, H-4, Galp), 5.76 (d, 1H, *J* 3.6 Hz, H-4, Galp), 5.72 (d, 1H, *J* 4.8 Hz, H-3, Araf), 5.68 (s, 1H, H-2, Araf), 5.65 (dd, 1H, *J* 8.0 Hz, 10.4 Hz, H-2, Galp), 5.61 (d, 1H, *J* 4.8 Hz, H-3, Araf), 5.53 (s, 1H, H-2, Araf), 5.47 (s, 1H, α H-1), 5.43 (s, 1H, α H-1), 5.34 (dd, 1H, *J* 4.0 Hz, 10.4 Hz), 5.26 (d, 1H, *J* 8.0 Hz, β H-1), 4.82-4.77 (m, 2H), 4.68 (d, 1H, *J* 7.8 Hz, β H-1), 4.66–4.62 (m, 2H), 4.55 (d, 1H, *J* 8.0 Hz, β H-1), 4.39–4.24 (m, 4H), 3.61 (s, 3H, CH_3O), 3.40 (dd, 1H, *J* 3.2 Hz, 10.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 165.9, 165.3, 165.7, 165.6, 165.36, 165.3, 165.1 (Ph*C*O), 156.0, 151.3, 118.8, 114.7 (MeO*Ph*), 106.7, 106.0 (2 α C-1), 101.7, 101.2, 101.1 (3 β C-1), 82.5, 82.2, 81.3, 78.0, 73.7, 73.3, 72.4, 71.94 71.7, 71.5, 69.9, 68.4, 68.2, 68.0, 67.4, 66.8, 65.6, 63.8, 61.7, 60.5, 55.6 (some signal overlapped). Anal. calcd for $C_{133}H_{110}O_{39}$: C, 68.49; H, 4.75. Found: C, 68.33; H, 4.66. **18**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 (d, 1H, *J* 3.2 Hz), 5.85–5.84 (m, 2H), 5.65–5.55 (m, 11H, 2 α-H-1), 5.47–5.37 (m, 8H, 2 α H-1), 4.94 (d, 1H, *J* 8.0 Hz, β H-1), 4.83–4.49 (m, 8H, β H-1), 4.54–4.45 (m, 3H), 4.41 (d, 1H, *J* 8.0 Hz, β H-1), 4.32–4.14 (m, 5H, β H-1), 4.02–3.83 (m, 11H), 3.58 (s, 3H, CH_3O), 3.45–3.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 165.9, 165.7, 165.3, 165.1, 165.0, 164.9, 164.7 (Ph*C*O), 155.6, 151.5, 118.7, 114.7 (MeO*Ph*), 106.5, 106.2, 106.0, 105.9 (4 α C-1), 101.9, 101.1, 100.9, 100.9 (4β C-1). Anal. calcd for $C_{198}H_{164}O_{59}$: C, 68.19; H, 4.94. Found: C, 68.30; H, 4.81. **19**. ^{1}H NMR (400 MHz, D_2O): δ 5.27 (s, 1H, H-1), 4.99 (s, 1H, H-1), 4.75 (d, 1H, *J* 8.0

Hz, H-1), 4.54 (d, 1H, *J* 7.9 Hz, H-1), 4.39 (d, 1H, *J* 7.9 Hz, H-1); ^{13}C NMR (100 MHz, D_2O): δ 108.1, 107.0 (2 α C-1), 103.1, 103.1, 101.4 (3β C-1). Anal. calcd for $C_{35}H_{54}O_{25}$: C, 48.05; H, 6.22. Found: C, 48.19; H, 6.17. **20**. ^{1}H NMR (400 MHz, D_2O): δ 5.34 (s, 1H, H-1), 5.29 (s, 1H, H-1), 5.05 (s, 1H, H-1), 5.01 (s, 1H, H-1), 4.54 (d, 1H, *J* 8.0 Hz, H-1), 4.45 (d, 1H, *J* 7.9 Hz, H-1), 4.39 (d, 1H, *J* 7.9 Hz, H-1), 4.38 (d, 1H, *J* 8.0 Hz, H-1); ^{13}C NMR (100 MHz, D_2O): δ 154.3, 150.5, 118.3, 114.9 (MeO*Ph*), 108.5, 108.2, 107.2, 107.1 (4 α C-1), 103.2, 103.1, 102.0, 100.0 (4 β C-1), 55.6. Anal. calcd for $C_{51}H_{80}O_{38}$: C, 47.08; H, 6.20. Found: C, 47.23; H, 6.27.