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An olefin cross metathesis approach to C-disaccharide analogs of the α-D-arabinofuranosyl-(1→5)-α-D-arabinofuranoside motif found in the mycobacterial cell wall

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Abstract—Reported is the synthesis of a C-disaccharide analog of the α-D-Ara*f*-(1→5)-α-D-Ara*f* motif present in the cell wall of mycobacteria, including the human pathogen *Mycobacterium tuberculosis*. The key step is an olefin cross metathesis reaction that proceeds in excellent yield and which can be carried out on mmol scale.

Ethambutol (**1**, Fig. 1) is a front-line antibiotic used to treat tuberculosis (TB).[1] Like some of the other anti-TB drugs, ethambutol acts by inhibiting the biosynthesis of the mycobacterial cell wall.[2] In particular, **1** inhibits the arabinosyltransferases[3] involved in the assembly of the mycolyl-arabinogalactan (mAG) complex, the major structural motif of the cell wall.[4] Recent concern[5] about the resurgence of TB and the emergence of drug resistant strains of *Mycobacterium tuberculosis* has led to interest in the identification of new drugs that can be used to treat this disease.[6] Novel arabinosyltransferase inhibitors have received special attention and work in this area has involved both the synthesis of libraries of ethambutol analogs,[7] and the preparation of mimics of various structural motifs in the arabinan portion of the mAG complex.[8] The arabinan moiety of this glycoconjugate consists of approximately 70 D-arabinofuranose (D-Ara*f*) residues attached via α-(1→5), α-(1→3) and β-(1→2) linkages, with the α-(1→5)-linked motif (**2**) predominating.[4]

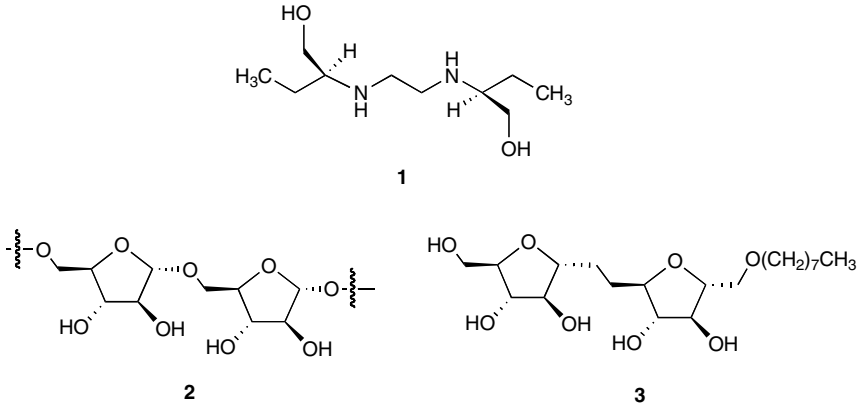

Figure 1. Structures of ethambutol (**1**), the α-D-Ara*f*-(1→5)-α-D-Ara*f* motif present in the cell wall of mycobacteria (**2**) and the C-disaccharide analog of **2** synthesized in this letter (**3**).

Keywords: C-Glycoside; Olefin metathesis; Mycobacteria; Arabinosyltransferase; Cell wall; Inhibitors.
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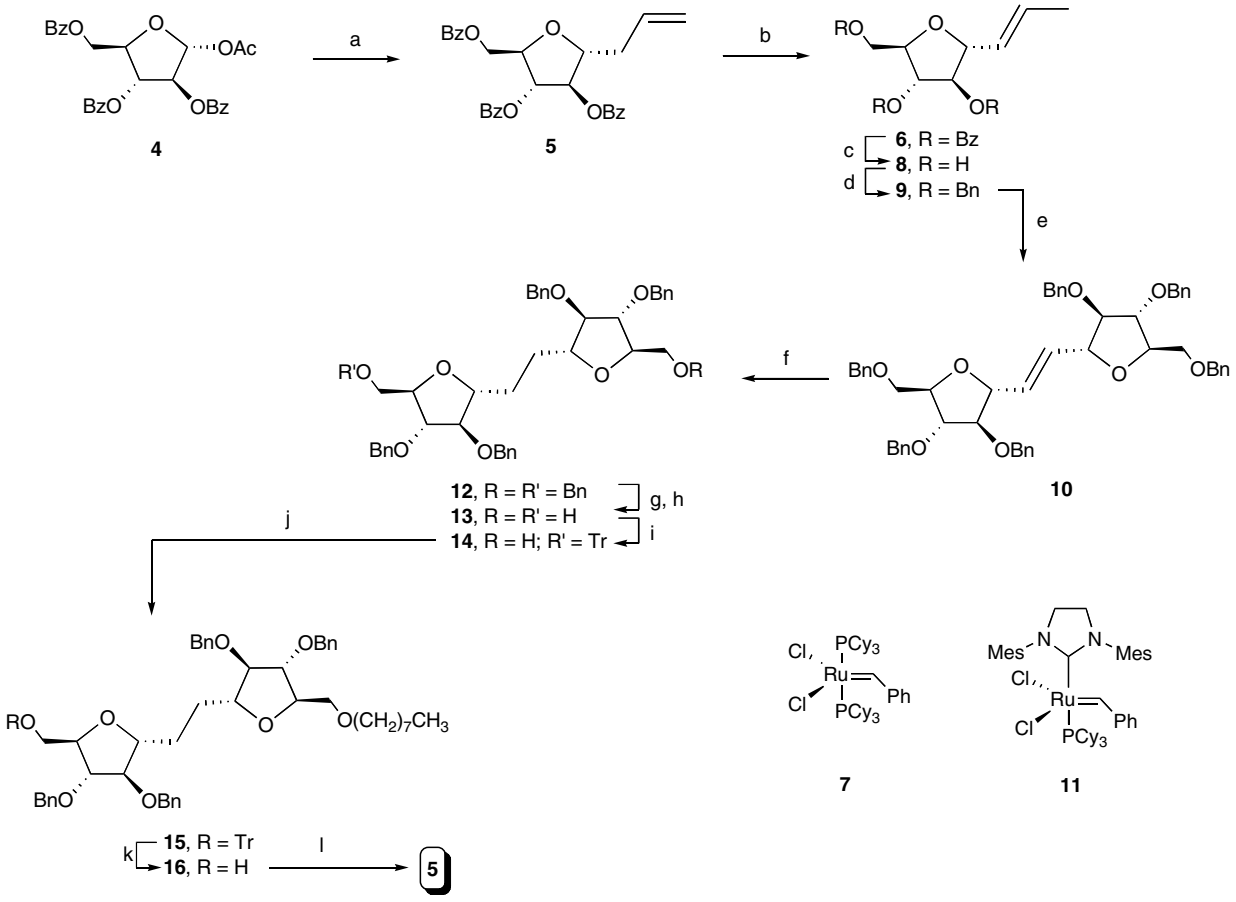
C-Glycoside oligosaccharide analogs have been of long-standing interest as synthetic targets.[9] The attraction of these compounds stems from the belief that C-glycosides are better potential drug candidates because, compared to their O-glycoside parents, they are not only more stable to acid, but also to glycosidases and thus will have better biological half-lives. In the interest of developing C-glycoside based arabinosyltransferase inhibitors, several groups have reported the synthesis of C-glycoside analogs of the α-D-Ara*f*-(1→5)-α-D-Ara*f* disaccharide motif (**2**) in which the C–C bond between the monosaccharide residues was formed either by a nitroaldol reaction,[10] a Wittig olefination,[11] or an acetylide addition to monosaccharide lactone.[12] Very recently, Prandi and coworkers synthesized a novel C-glycoside–azasugar conjugate and tested its ability to inhibit mycobacterial growth.[13] We describe here an alternate route to a C-glycoside analog (**3**) of the α-D-Ara*f*-(1→5)-α-D-Ara*f* disaccharide motif found in the mAG complex. In the method reported here, the key step is an olefin cross metathesis[14] dimerization of a D-arabinofuranose derived alkene.

The synthesis of **3** began from anomeric acetate **4** (Scheme 1), which was prepared as previously reported.[15] Treatment of **4** with allyltrimethylsilane and boron trifluoride etherate in acetonitrile at 0 °C afforded allyl C-glycoside **5**[16] in 90% yield as a 10:1 α:β mixture that could be separated by chromatography. The double bond was then isomerized in 91% yield upon stirring a solution of **5** in toluene with $Ph(CH_3CN)_2Cl_2$ at 40 °C. As expected, the *trans* alkene **6**[17] was the major product (coupling between the olefinic hydrogens = 15.8 Hz) and only traces of the corresponding *cis* alkene could be seen in the ^1H NMR spectrum.

With **6** in hand, attempts were made to dimerize this material using the first-generation Grubbs' catalyst (**7**[18]). However, with this catalyst only unreacted **6** was isolated and the decision was made to replace the benzoate ester protecting groups with benzyl ethers. Thus, treatment of **6** with sodium methoxide afforded **8**,[19] which was then alkylated upon treatment with benzyl bromide and sodium hydride to give **9**[20] (69% over two steps). Dimerization of **9** with **7** gave only small amounts (~10% yield) of the desired product **10**. However, the use of the second-generation Grubbs' catalyst (**11**[21]) in dichloromethane at reflux[22] provided a nearly quantitative (96%) yield of **10**.[23] That the dimerization had occurred was evident from the mass spectrum, which showed a peak for the sodium adduct of **10** at $m/z = 855.3870$. In the ^1H and ^{13}C NMR spectra



Scheme 1. Reagents and conditions: (a) $CH_2{=}CHCH_2Si(CH_3)_3$, BF_3–OEt_2, CH_3CN, 0 °C, 18 h, 90%; (b) $Pd(CH_3CN)_2Cl_2$ (5 mol %), toluene, 40 °C, 24 h, 91%; (c) $NaOCH_3$, CH_3OH, rt, 2 h, 92%; (d) BnBr, NaH, DMF, rt, 19 h, 75%; (e) **11** (10 mol %), CH_2Cl_2, reflux, 18 h, 96%; (f) H_2, $(Ph_3P)_3RhCl$, toluene, 35 °C, 18 h, 81%; (g) Ac_2O, HOAc, H_2SO_4, 0 °C, 30 min; (h) $NaOCH_3$, CH_3OH, rt, 10 h, 68% from **12**; (i) TrCl, pyridine, rt, 12 h, 60%; (j) $CH_3(CH_2)_7I$, NaH, DMF, rt, 1 h, 92%; (k) *p*-TsOH, CH_2Cl_2, CH_3OH, rt, 2 h, 89%; (l) H_2, Pd/C, CH_2Cl_2, CH_3OH, rt, 16 h, 86%.

of **10**, the symmetry of the molecule was apparent. For example, only eight peaks were present for the ring and benzylic carbons in the ^{13}C spectrum and only a single olefinic hydrogen resonance was present in the ^{1}H NMR spectrum. Further support for the success of the reaction was the absence of a peak corresponding to the allylic methyl group in **9**. This reaction could be carried out on a 1.2 mmol scale, which bodes well for the use of this approach in the synthesis of additional analogs based on this C-disaccharide scaffold.

Having successfully achieved the key C–C bond forming reaction, the remainder of the steps in the sequence were straightforward. First, hydrogenation of the alkene moiety in **10** was achieved upon reaction with Wilkinson's catalyst and hydrogen gas at 35 °C in toluene, which afforded the expected product **12**[24] in 81% yield. Conversion of **12** into diol **13**[25] was accomplished first by acetolysis[26] of the benzyl ethers protecting the primary hydroxyl groups (acetic anhydride/acetic acid/H_2SO_4 at 0 °C) and then cleavage of the resulting diacetate with sodium methoxide (68% yield over two steps). Monoprotection of **13** was achieved by reaction with chlorotriphenylmethane in pyridine and the corresponding trityl ether **14**[27] was isolated in 60% yield. Alkylation of **14** with octyl iodide and sodium hydride gave a 92% yield of **15**,[28] which was then partially deprotected by acid hydrolysis of the trityl ether. Alcohol **16**[29] was obtained in an 89% yield. Conversion of **16** into the target compound **3**[30] was carried out in 86% yield upon treatment with hydrogen gas and 5% Pd/C in a 5:1 mixture of methanol and dichloromethane.

In summary, we describe here the synthesis of a C-disaccharide analog of the α-D-Ara*f*-(1→5)-α-D-Ara*f* motif present in the mycobacterial mAG complex. The key step in the synthesis is an olefin cross metathesis reaction that proceeds in excellent yield and which can be carried out on mmol scale. This route should therefore be amenable to the preparation of large amounts of intermediates that are needed to synthesize additional analogs of this motif, for example, through parallel synthesis. Such analogs are potential inhibitors of mycobacterial arabinosyltransferases and, in turn, are candidates for novel anti-TB drugs.

Acknowledgment

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References and notes

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16. Data for **5**: Syrup; $[\alpha]_D$ +14.8 (*c* 1.0, $CHCl_3$); R_f 0.42 (6:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, δ_H) 8.02–8.11 (m, 6H), 7.31–7.58 (m, 9H), 5.86–6.03 (m, 1H), 5.69 (t, 1H, $J = 2.4$ Hz), 5.57 (t, 1H, $J = 2.4$ Hz), 5.15–5.27 (m, 2H), 4.65–4.79 (m, 2H), 4.56–4.61 (m, 1H), 4.42–4.49 (m, 1H), 2.65 (t, 2H, $J = 8.5$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ_C) 166.07, 165.43, 165.42, 133.42, 133.33, 133.09, 132.93, 129.65, 129.63, 129.02, 128.95, 128.48, 128.47, 128.46, 128.39, 128.38, 128.37, 128.20, 128.19, 128.18, 128.09, 128.08, 118.09, 82.77, 81.17, 80.90, 79.65, 64.02, 36.83; HR-ESI-MS calcd for $[C_{29}H_{26}O_7]Na^+$ 830.4351, found: 830.4354.
17. Data for **6**: Syrup; $[\alpha]_D$ +17.1 (*c* 1.0, $CHCl_3$); R_f 0.40 (6:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, δ_H) 8.04–8.11 (m 6H), 7.34–7.57 (m, 9H), 5.92 (dq, 1H, $J = 15.8$, 6.5 Hz), 5.75 (dd, 1H, $J = 15.8$, 8.2 Hz), 5.69 (t, 1H, $J = 2.5$ Hz), 5.59 (t, 1H, $J = 2.5$ Hz), 4.69–4.81 (m, 3H), 4.57–4.63 (m, 1H), 1.76 (d, 3H, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ_C) 166.13, 165.52, 165.48, 133.41, 133.35, 132.96, 130.14, 129.97, 129.69, 129.66 (2C), 129.51 (2C), 129.09 (2C), 129.03, 128.41, 128.39, 128.26, 128.22, 128.13, 127.19, 126.47, 83.89, 81.56, 81.14, 79.21, 64.33, 17.71.

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19. Data for **8**: Syrup; $[\alpha]_D$ +3.6 (*c* 1.0, CH_3OH); R_f 0.27 (10:1 CH_2Cl_2/CH_3OH); ^1H NMR (D_2O, 400 MHz, δ_H) 5.80 (dq, 1H, $J = 15.2$, 6.3 Hz), 5.44 (dd, 1H, $J = 15.2$, 8.2 Hz), 4.04–4.08 (m, 1H), 3.94–3.99 (m, 1H), 3.78–3.82 (m, 2H), 3.57–3.68 (m, 2H), 1.65 (d, 3H, $J = 6.3$ Hz); ^{13}C NMR (D_2O, 100 MHz, δ_C) 133.46, 128.09, 83.15, 82.10, 80.33, 76.33, 61.63, 17.47; HR-ESI-MS calcd for $[C_8H_{14}O_4]Na^+$ 197.0784, found 197.0783.
20. Data for **9**: Syrup; $[\alpha]_D$ +2.5 (*c* 1.1, $CHCl_3$); R_f 0.48 (6:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz, δ_H) 7.22–7.35 (m, 15H), 5.80 (dq, 1H, $J = 15.2$, 6.2 Hz), 5.65 (dd, 1H, $J = 15.2$, 8.0 Hz), 4.51–4.59 (m, 6H), 4.35–4.40 (m, 1H), 4.15–4.22 (m, 1H), 4.06–4.11 (m, 1H), 3.89–3.94 (m, 1H), 3.55–3.61 (m, 2H), 1.71 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ_C) 138.11, 137.93, 137.86, 129.70 (4C), 129.67 (2C), 128.33 (2C), 128.28 (3C), 127.72 (2C), 127.65 (3C), 127.52, 88.13, 84.84, 83.19, 80.90, 73.31, 71.97, 71.89, 70.29, 18.29; HR-ESI-MS calcd for $[C_{29}H_{32}O_4]Na^+$ 467.2193, found 467.2190.
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22. Olefin metathesis procedure: Catalyst **11** (97 mg, 10 mol %) was added, in a dry box, to a solution of **9** (530 mg, 1.2 mmol) in dry CH_2Cl_2 (15 mL). The flask was removed from the dry box and the solution was heated at reflux under argon for 18 h, before being cooled and concentrated under vacuum. Column chromatography (4:1 hexanes/EtOAc) of the resulting residue gave **10** (461 mg, 96%).
23. Data for **10**: Syrup; $[\alpha]_D$ +0.3 (*c* 1.0, $CHCl_3$); R_f 0.29 (3:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz, δ_H) 7.24–7.32 (m, 30H), 5.89 (br s, 2H), 4.44–4.55 (m, 14H), 4.20 (dd, 2H, $J = 4.8$ Hz, 10.1 Hz), 4.06–4.08 (m, 2H), 3.92 (dd, 2H, $J = 1.2$ Hz, 5.0 Hz), 3.56 (d, 4H, $J = 5.4$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ_C) 138.15 (2C), 137.92 (2C), 137.77 (2C), 130.77 (2C), 128.38 (4C), 128.34 (4C), 128.32 (4C), 127.73 (6C), 127.70 (4C), 127.65 (4C), 127.57 (4C), 88.28 (2C), 84.82 (2C), 82.22 (2C), 81.25 (2C), 73.36 (2C), 72.10 (2C), 71.87 (2C), 70.25 (2C); HR-ESI-MS calcd for $[C_{54}H_{56}O_8]Na^+$ 855.3867, found 855.3870.
24. Data for **12**: Syrup; $[\alpha]_D$ +13.3 (*c* 1.0, $CHCl_3$); R_f 0.29 (3:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz, δ_H) 7.18–7.33 (m, 30H), 4.44–4.54 (m, 12H), 4.18 (dd, 2H, $J = 3.9$ Hz, 5.8 Hz), 4.00–4.05 (m, 4H), 3.78–3.82 (m, 2H), 3.50–3.61 (m, 4H), 1.50–1.90 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ_C) 138.16 (2C), 137.91 (2C), 137.87 (2C), 128.30 (6C), 128.26 (4C), 128.05 (4C), 127.69 (4C), 127.63 (4C), 127.62 (4C), 127.49 (4C), 88.34 (2C), 85.94 (2C), 82.52 (2C), 81.73 (2C), 73.82 (2C), 72.26 (2C), 72.23 (2C), 70.80 (2C), 29.76 (2C); HR-ESI-MS calcd for $[C_{54}H_{58}O_8]Na^+$ 857.4024, found 857.4020.
25. Data for **13**: Syrup; $[\alpha]_D$ +17.1 (*c* 1.1, $CHCl_3$); R_f 0.21 (1:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz, δ_H) 7.23–7.46 (m 20H), 4.45–4.52 (m, 8H), 3.96–4.10 (m, 6H), 3.80–3.82 (m, 2H), 3.64–3.67 (m, 4H), 2.39 (broad s, 2H), 1.47–1.82 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ_C) 137.65 (2C), 137.57 (2C), 128.42 (4C), 128.41 (4C), 127.83 (2C), 127.80 (2C), 127.69 (4C), 127.64 (4C), 87.32 (2C), 84.44 (2C), 82.67 (2C), 82.13 (2C), 72.02 (2C), 71.69 (2C), 62.73 (2C), 28.98 (2C); HR-ESI-MS calcd for $[C_{40}H_{46}O_8]Na^+$ 677.3085, found 877.3081.
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27. Data for **14**: Syrup; $[\alpha]_D$ +28.9 (*c* 1.0, $CHCl_3$); R_f 0.14 (6:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz, δ_H) 7.16–7.46 (m, 35H), 4.40–4.52 (m, 8H), 4.16–4.22 (m, 1H), 3.97–4.10 (m, 6H), 3.77–3.84 (m, 2H), 3.65–3.68 (m, 2H), 3.17–3.30 (m, 2H) 1.45–1.82 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ_C) 143.95 (3C), 137.89, 137.73 (2C), 137.63, 128.74 (4C), 128.47 (4C), 128.44 (4C), 128.38 (4C), 128.35 (4C), 127.78 (2C), 127.77, 127.73 (2C), 127.72 (2C), 127.68, 127.67, 127.66, 127.65 (2C), 126.97, 126.96, 126.95, 88.05, 87.35, 87.30, 86.74, 85.31, 85.32, 84.52, 82.61, 82.42, 81.83, 81.70, 77.20, 72.09, 71.78, 64.32, 62.86, 29.16.
28. Data for **15**: Syrup; $[\alpha]_D$ +16.4 (*c* 0.9, $CHCl_3$); R_f 0.35 (10:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz, δ_H) 7.21–7.45 (m, 35H), 4.39–4.59 (m, 8H), 4.17–4.20 (m, 1H), 4.11–4.15 (m, 1H), 4.05–4.08 (m, 1H), 3.91–4.00 (m, 3H), 3.76–3.80 (m, 2H), 3.39–3.54 (m, 4H), 3.18–3.29 (m, 2H), 1.25–1.63 (m, 16H), 0.87 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ_C) 143.97 (2C), 143.93, 138.07, 138.00, 137.94 (2C), 128.75 (5C), 128.37 (5C), 127.77 (5C), 127.69 (5C), 127.66 (4C), 127.64, 127.63 (3C) 127.62, 127.61, 126.94 (2C), 126.93 (2C), 126.94, 88.44, 88.43, 88.00, 87.99, 86.72, 86.73, 85.65, 85.46, 82.26, 82.25, 81.63, 81.13, 71.81, 71.74, 70.95, 64.34, 33.52, 33.50, 31.83, 30.27, 29.43, 29.26, 26.13, 22.65, 14.09; HR-ESI-MS calcd for $[C_{67}H_{76}O_8]Na^+$ 1031.5432, found 1031.5429.
29. Data for **16**: Syrup; $[\alpha]_D$ +26.3 (*c* 0.8, $CHCl_3$); R_f 0.41 (2:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz, δ_H) 7.25–7.35 (m, 20H), 4.49–4.60 (m, 8H), 4.12–4.19 (m, 1H), 4.02–4.10 (m, 1H), 3.93–4.00 (m, 4H), 3.75–3.82 (m, 2H), 3.66–3.71 (m, 2H), 3.42–3.55 (m, 4H), 2.04 (s, 1H), 1.23–1.68 (m, 16H), 0.87 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ_C) 137.98, 137.90, 137.68, 137.60, 128.71 (3C), 128.48 (2C), 128.46 (3C), 128.38 (2C), 127.87 (3C), 127.78 (2C), 127.73 (3C), 127.68 (2C), 87.95, 87.31, 85.56, 84.48, 82.72, 82.63, 82.20, 81.13, 73.30, 72.08, 71.81, 71.71, 72.61, 70.93, 62.82, 32.89, 31.79, 29.62, 29.39, 29.26, 26.77, 26.11, 22.64, 14.08.
30. Data for **3**: Syrup; $[\alpha]_D$ +46.0 (*c* 0.9, CH_3OH); R_f 0.17 (8:1 CH_2Cl_2/CH_3OH); ^1H NMR (D_2O, 400 MHz, δ_H) 3.44–3.95 (m, 14H), 1.51–1.57 (m, 6H), 1.20–1.22 (m, 10H), 0.79 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (D_2O, 100 MHz, δ_C) 85.51, 82.50, 82.16, 81.41, 80.69, 80.70, 78.08, 77.21, 72.05, 70.99, 61.62, 32.01, 32.00, 29.53, 29.44, 29.38, 28.79, 26.05, 22.80, 14.12; HR-ESI-MS calcd for $[C_{20}H_{38}O_8]Na^+$ 429.2459, found 429.2457.