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Synthesis of Macrolide−Saccharide Hybrids by Ring-Closing Metathesis of Precursors Derived from Glycitols and Benzoic Acids

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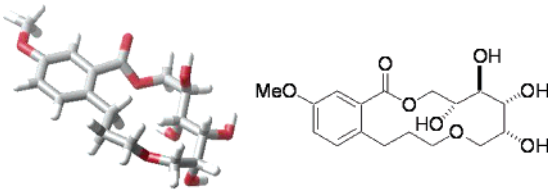
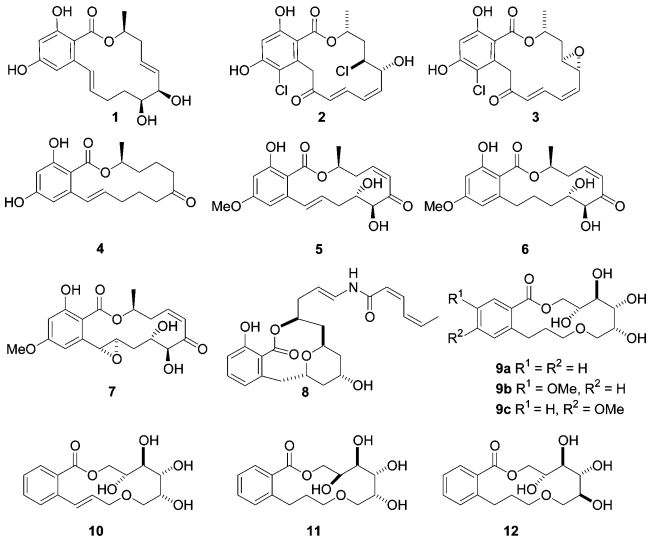


The benzomacrolactone structural motif is a privileged or evolutionarily selected scaffold that codes properties required for binding to proteins and novel analogues thereof may provide a source of new bioactive compounds. Saccharides are also privileged structures, with (amino)sugars, iminosugars, and sugar amino acids being applied as scaffolds for the development of nonpeptidal peptidomimetics. The syntheses of novel polyhydroxylated oxamacrolides, structural analogues of natural polyketide derived macrolides, are described herein, providing a basis for their development as scaffolds. The syntheses were carried out from benzoic acids and appropriately protected D-mannitol or D-sorbitol (D-glucitol). Ring-closing metathesis was applied in the macrocyclization step with high *E*-alkene selectivities being observed. X-ray crystal structures, for two polyhydroxylated derivatives, show that the macrocyclic rings display similar conformations. In addition, intermolecular hydrogen-bonding networks are observed in the lattices.

Introduction

The naturally occurring resorcylic acid lactones (e.g., **1**−**7**, Chart 1) have been of interest to chemists because of their biological properties.[1] Aigialomycin D **1** is cytotoxic and inhibits the malaria parasite;[2] its cytotoxicity has recently been attributed to its inhibition of the kinases CDK and GSK-3.[3] Pochonin C[4]

CHART 1. Structures of 1−12



2 and radicicol **3**[5] are both ATPase inhibitors, whereas zearalenone **4** is an agonist for mammalian estrogen receptors.[6] (5*Z*)-7-Oxozeaenol[7] **5** inhibits the kinase TAK-1, whereas LL-783,277[8] **6** is a potent inhibitor of MEK. Hypothemycin **7** inhibits the proliferative response, modulates the production of cytokines during T cell activation,[9] and inhibits the ras signal transduction pathway. Salicylic acid derived lactones such as salicylihalamides, apicularens (e.g., **8**), and lobatamides are also of interest for their biological properties.[10] These diverse biological effects imply that the benzomacrolactone structural motif is a privileged scaffold[11] or is an evolutionarily selected scaffold that codes properties required for binding to proteins.[12] Novel analogues of such macrolides may provide a source of new lead compounds or tools for chemical biology. Polyhydroxylated sugar derivatives are also privileged structures,[13] with (amino)sugars, iminosugars, and sugar amino acids having been applied as scaffolds for the development of bioactive compounds, including nonpeptidal peptidomimetics.[14] Herein we describe a synthesis of novel polyhydroxylated oxamacrolides

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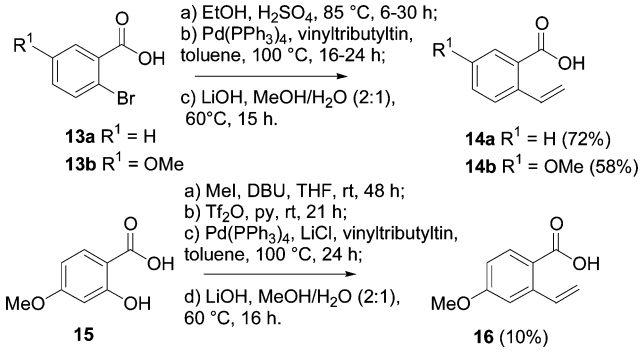
SCHEME 1. Synthesis of Benzoic Acid Precursors



9−**12** from benzoic acids and D-mannitol or D-sorbitol (D-glucitol). These new compounds can be considered hybrids or novel structural analogues of natural polyketide derived macrolides and saccharides and the work forms a basis for their investigation as novel scaffolds for bioactive compound discovery.

Our approach combined the Mitsunobu esterification and ring-closing metathesis which has been successful for synthesis of a range of resorcylic acid and salicylic acid natural products.[15] The synthesis of **9** and **10** was carried out from D-mannitol and **11** and **12** from D-sorbitol. The benzoic acid precursors **14a** and **14b** were prepared first (Scheme 1). Esterification of **13a** and **13b**, followed by a Stille coupling reaction[16] and subsequent ester hydrolysis, gave **14a**[17] and **14b**,[18] respectively. The esterification of 4-methoxysalicylic acid **15** was carried out under basic conditions, and subsequent reaction with triflic anhydride afforded an aryl triflate derivative (90%, two steps). The exchange of the triflate group of **15** to a vinyl group according to Nicolaou's variant of the traditional Stille reaction,[19] which was carried out in THF in the presence of LiCl, proceeded in ∼10% yield. An improvement to this reaction was observed when the reaction was carried out in toluene instead (27%), and subsequent hydrolysis of the resulting vinyl derivative using LiOH gave **16**. The reaction was found to occur slowly, and there was starting material remaining after a few days. According to Casado et al.,[20] the use of LiCl increases the rate of the oxidative addition step but it can also slow down the reaction in certain conditions which could explain the low yield. The tin residues, which were present in the product from the Stille reactions, were removed by chromatography[21] using a KF/silica (1:9, w/w) packed column with dichloromethane as eluent. Because of the basicity of the KF−silica column, some hydrolysis of the ester to give the benzoic acid also occurred.

The carbohydrate precursors were prepared as outlined in Scheme 2. The allyl ether **19** was obtained after monoallylation of diol **18**[22] using sodium hydride (1.4 equiv) and allyl bromide (1.1 equiv); a small amount of the di-*O*-allylated product was also observed. A similar reaction sequence beginning from D-sorbitol gave a 1:1 mixture of **20** and **21**.[23] The MOM derivative **22** was synthesized from D-mannitol **17** in four steps: regioselective pivaloylation (60%) of the two primary hydroxyl groups of **17** was followed by introduction of the MOM protecting groups, removal of the pivaloyl groups was achieved using sodium methoxide in methanol[24] at 40 °C, and subsequent monoallylation gave **22**. In the pivaloylation reaction some of the 1,2,6-tri-*O*-pivaloylated product was also obtained.

The benzoic acid and carbohydrate derived precursors were then converted to oxamacrolides (Schemes 3 and 4). The Mitsunobu coupling reaction of benzoic acids **14a**, **14b**, and **16** with allyl ether **19**, promoted by triphenylphosphine in the presence of DIAD, gave **23a**, **23b**, and **23c**, respectively. The lower yields of **23b** and **23c** were due to increased difficulty in their chromatographic separation from the byproducts of the reaction. Ring-closing metathesis[25] using the Grubbs' generation II catalyst in the presence of 2,6-dichloro-1,4-benzoquinone[26] gave the macrocyclic structures in good to excellent yield (62−92%) with only the *E*-alkene[27] being obtained in each case. Ring-closing metathesis carried out in the absence of the 2,6-dichloro-1,4-benzoquinone led only to the isolation of low yields of mixtures (∼30%) of the *E*- and *Z*-alkene containing macrocycles, and a major side reaction was the isomerization of the allyl alkene group to give acyclic vinyl ethers, which can occur for allyl derivatives at high temperature, high dilution, and forced high turnovers. [26] Catalytic hydrogenation of **23a**−**c**, carried out using the H-Cube hydrogenation flow reaction system, gave the polyhydroxylated oxamacrolides **9a**−**c** (Scheme 3).[28] The lower yield of **9c** (47%) was due to losses on chromatographic purification. The structure assigned to **9b** was confirmed by the determination of its X-ray crystal structure.

The Mitsunobu reaction of **14a** and **22** followed by ring-closing metathesis, carried out in the presence of Ti(*i*-OPr)$_4$, gave **25**, and subsequent removal of the MOM groups under acidic conditions enabled isolation of the polyhydroxylated oxamacrolide **10** containing the *E*-alkene (Scheme 4). The ring-closing metathesis provided a single stereoisomer in the macrocyclization reaction, albeit in lower isolated yield than for benzylated precursors. The metathesis catalyst, in the absence of Ti(*i*-OPr)$_4$, is most likely coordinating with the multiple oxygens of the MOM groups and leads to formation of complexes which do not go on to cyclize. In the presence of Ti(*i*-OPr)$_4$, used to counteract the retarding effect of the oxygen atoms,[29] ring closing metathesis takes place and **25** was isolated in 28% yield for the reaction carried out in dichloromethane,

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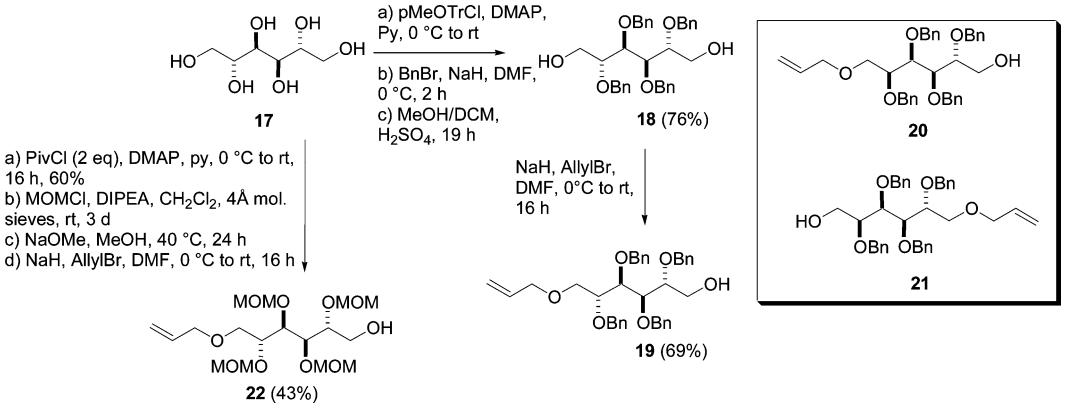
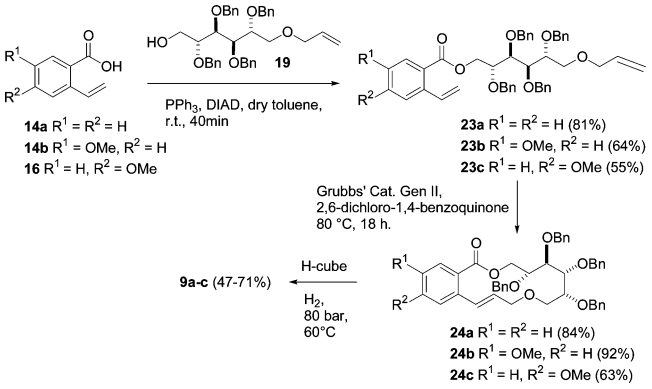
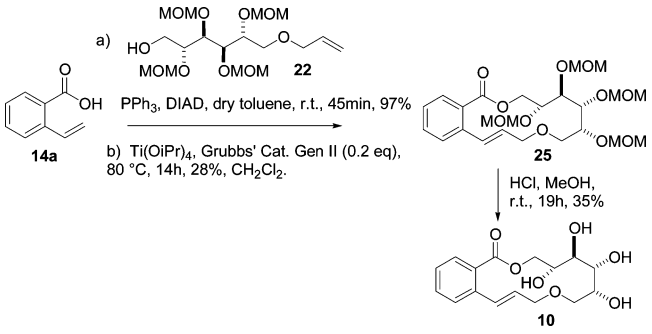
SCHEME 2. Synthesis of Carbohydrate Precursors



SCHEME 3. Synthesis of Polyhydroxylated Oxamacrolides 9a−c



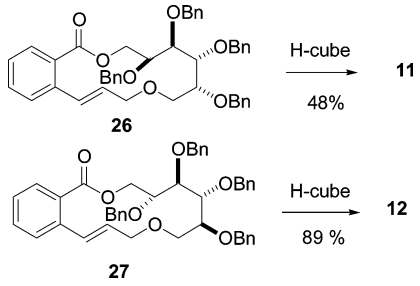
SCHEME 4. Synthesis of Polyhydroxylated Oxamacrolide 10



with an equal proportion of the starting material also being recovered. The conversion to the ring closed product was higher (~60%) when the reaction was carried out at 80 °C in toluene. In addition, the yield of **10** after removal of the MOM protecting groups (35%) was low due to difficulty in chromatographic separation of the product from unidentified byproducts.

The Mitsunobu reaction followed by ring-closing metathesis (not shown) of the D-sorbitol derivatives **20** and **21** gave a mixture of macrolactones **26** and **27**, and these were separated by column chromatography. Subsequent removal of the benzyl groups of **26** and **27** with concomitant reduction of the alkene groups gave the macrolactones **11** and **12**, respectively (Scheme 5). The structural assignment was confirmed by the determination of the X-ray crystal structure of **12**. The lower yield obtained in the hydrogenolysis of **26** is explained by the low solubility of the product **11**, which led to its precipitation and

SCHEME 5. Synthesis of Polyhydroxylated Oxamacrolides 11 and 12



consequent clogging of the hydrogenation flow reactor and was thus more difficult to isolate.

The conformation of **9b** and **12,** in the X-ray crystal structures, was also studied. The lactone group atoms and the C-3 to C-7 backbone carbon atoms (Figure 1) of **9b** and **12** were superimposed using Macromodel 8.5. This showed that the atoms of the benzene ring and C-1 to C-7 chain in these two structures adopted closely related conformations in the solid state. Consequently, the C-4, C-5, and C-6 hydroxyl groups are similarly oriented in **9b** and **12**; the 4-OH and 5-OH groups are axial and the 6-OH group is equatorial; the 7-OH group is axial for **9a** and equatorial for **12**. The stereochemical configuration of the 7-OH group, different for **9b** and **12**, thus does not lead to a change in the conformation of the C-1 to C-7 chain. However, there was not a similar conformation for the C-9 to C-12 chain of the two structures. The vicinal $^1H-^1H$ coupling constants (Table 1, MeOD) for protons of the C-3 to C-7 chain and corresponding dihedral angles measured from the crystal structures of **9b** and **12** correlate with that predicted by the Karplus relationship to a degree which indicates that the orientations of the C-4 to C-7 OH groups in solution do not deviate largely from that in the solid state. The vicinal $^1H-^1H$ coupling constants for **9a** and **9c** agree well with **9b**, indicating these analogues have the same conformations. The vicinal $^1H-^1H$ coupling constants for **10** indicate that a minor distortion of the macrocyclic ring is brought about by having the alkene group in the ring, although no major difference in conformation of these derivatives is apparent from this analysis (Table 1). It is worth noting that the macrocyclic hydroxyl groups form part of extensive hydrogen-bonding networks in the crystal lattices of **9a** and **12** (not shown herein).[30]

In summary, the syntheses of novel polyhydroxylated oxamacrolides, inspired by recent natural product and carbohydrate research, are described from simple precursors. Conformational

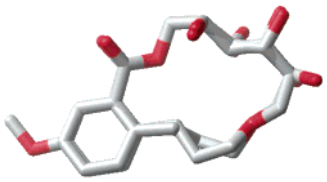
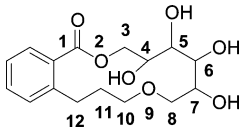


FIGURE 1. Superimposition of the X-ray crystal structures of **9b** and **12**. The hydrogen atoms are not shown.

TABLE 1. Selected ^{1}H-^{1}H Vicinal Coupling Constants (Hz) for Oxamacrolides[a]



	9a	9b	9c	10	12
$J_{3a,4}$	2.1 (68)	2.2	2.1	1.8	2.4 (62)
$J_{3b,4}$	4.7 (51)	4.8	4.6	3.2	4.6 (58)
$J_{4,5}$	7.8 (167)	7.7	7.8	9.0	7.8 (177)
$J_{5,6}$	3.2 (66)	3.2	3.6	2.3	1.2 (67)
$J_{6,7}$	3.2 (68)	3.2	2.8	2.3	8.6 (161)
$J_{7,8a}$	7.1 (49)	7.0	7.1	n.d	6.1 (49)
$J_{7,8b}$	n.d. (68)	n.d.	n.d	2.9	2.6 (69)

[a] Dihedral angles (deg) measured using Macromodel 8.5 from the X-ray crystal structures of **9a** and **12** are provided in parentheses.

analysis indicates the macrolides adopt structures in the solid state which are similar to that in solution. A preliminary screening of the hydroxylated products against a panel of 45 kinases has shown that they are not potent inhibitors of kinases, and suggests that structures based on a resorcyclic acid or salicylic acid, as suggested by one reviewer, might be required for potent compounds. The synthesis of salicylic acid analogues is currently being investigated as are efforts to apply saccharide−macrolide scaffolds to the identification of novel lead compounds or provision of tools for biological research, and the outcomes of this research will be reported in due course.

Experimental Section

(4*R*,5*R*,6*R*,7*R*)-Tetrakis(benzyloxy)-3,4,5,6,7,8,10-heptahydro-(11*E*)-1H-2,9-benzodioxacyclotetradecin-1-one (24a). To a degassed solution of **23a** (384 mg, 0.54 mmol) and 2,6-dichloro-1,4-benzoquinone (38 mg, 0.22 mmol) in dry toluene (269 mL, 2 mM solution of **23a**) was added Grubbs'catalyst II generation (43 mg, 0.05 mmol) under N_2. The reaction mixture was heated and stirred at 80 °C for 18 h. The solution was then filtered through silica and washed with diethyl ether, and the solvent was removed. The residue was purified by chromatography (9:1 cyclohexane−EtOAc) to give **24a** (311 mg, 84%, colorless oil): R_f 0.48 (4:1 cyclohexane−EtOAc); $[\alpha]^{20}_D$ −11 (*c* 0.545, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, 1H, *J* 5.8 Hz), 7.47−7.04 (m, 24H), 6.08 (d, 1H, *J* 13.9 Hz), 5.00 (m, 1H), 4.86 (d, 1H, *J* 10.4 Hz), 4.72 (m, 3H), 4.47 (m, 3H), 4.38−4.03 (m, 5H), 4.03 (d, 1H, *J* 7.3 Hz), 3.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 168.4 (C═O), 139.1, 138.2, 138.1, 137.9, 137.5 (each s), 132.1, 131.9, 131.2 (each s), 129.5 (s), 128.4, 128.3, 128.2, 128.13, 128.10, 127.9, 127.8, 127.7, 127.4, 127.3, 127.2 (each d), 82.9, 78.9, 77.4, 77.3, 75.5, 74.6, 71.8, 71.3, 69.6, 68.7, 61.0 (each t); IR (film, $CHCl_3$) ν_{max} 3062, 3029, 2917, 2865, 2358, 2341, 1712, 1598, 1454, 1392, 1373, 1288, 1261, 1027, 908, 809, 744, 698 cm^{-1}; ES-HRMS found 707.2980, $C_{44}H_{44}O_7Na$ requires 707.2985 $[M + Na]^+$.

(4*R*,5*R*,6*R*,7*R*)-Tetrakis(benzyloxy)-3,4,5,6,7,8,10,11,12-nonahydro-1*H*-2,9-benzdioxacyclotetradecin-1-one (9a). Catalytic hydrogenation of a solution of **24a** in ethanol (152 mg in 9 mL, 0.22 mmol, 25 mM) in EtOH over 5% Pd−C using a H-cube flow reactor (pressure = 80 bar, temperature = 60 °C, flow rate = 1 mL/min) followed by removal of excess ethanol under reduced pressure and subsequent purification of the residue by chromatography (19:1, CH_2Cl_2−MeOH) gave **9a** as a colorless oil (51 mg, 71%): R_f 0.48 (9:1, CH_2Cl_2−MeOH)); $[\alpha]^{20}_D$ −21 (*c* 0.94, $CHCl_3$); ^{1}H NMR (600 MHz, CD_3OD) δ 7.81 (d, 1H, *J* 7.8 Hz), 7.49 (t, 1H, *J* 7.5 Hz), 7.39 (d, 1H, *J* 7.8 Hz), 7.30 (t, 1H, *J* 7.6 Hz), 4.66 (dd, 1H, *J* 11.4, 2.2 Hz), 4.49 (dd, 1H, *J* 7.7, 3.3 Hz), 4.46 (dd, 1H, *J* 11.4, 4.8 Hz), 4.13 (m, 1H), 4.04 (t, 1H, *J* 3.0 Hz), 3.93 (m, 1H), 3.71 (dd, 1H, *J* 9.4, 7.0 Hz), 3.57 (m, 3H), 3.21 (dt, 1H, *J* 14.5, 8.3 Hz), 3.10 (m, 1H), 1.90 (m, 2H); ^{13}C NMR (400 MHz, CD_3OD) δ 170.9 (C═O), 143.5 (s), 133.1 (d), 132.1 (s), 131.9, 131.3, 127.0, 74.1 (each d), 72.8 (t), 72.6 (d), 71.8 (t), 71.7 (d), 71.0 (d), 67.3 (t), 33.0 (t), 32.2 (t); IR (film, CH_3OH) ν_{max} 3386, 2921, 2871, 2360, 2341, 1704, 1600, 1446, 1371, 1284, 1263, 1132, 1076, 860, 750 cm^{-1}; ES-HRMS found 349.1259, $C_{16}H_{22}O_7Na$ requires 349.1263 $[M + Na]^+$.

(4*R*,5*R*,6*R*,7*R*)-Tetrahydroxy-3,4,5,6,7,8,10-heptahydro-(11*E*)-1*H*-2,9-benzodioxacyclotetradecin-1-one (10). To a solution of (4*R*,5*R*,6*R*,7*R*)-tetrakis(methoxymethoxy)-3,4,5,6,7,8,10-heptahydro-(11*E*)-1*H*-2,9-benzodioxacyclotetradecin-1-one (53 mg, 0.11 mmol) in MeOH (10.6 mL, 0.01 M solution of the precursor) was added at room temperature concd HCl (1.05 mL). The reaction mixture was stirred at that temperature for 19 h, the solvent then removed, and the residue purified by chromatography (19:1, CH_2Cl_2−MeOH) to afford the title compound **10** as a colorless oil (12 mg, 35%): R_f 0.39 (9:1, CH_2Cl_2−MeOH); $[\alpha]^{20}_D$ −23 (*c* 0.61, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.85 (dd, 1H, *J* 8.1, 1.3 Hz), 7.61 (dd, 1H, *J* 7.9, 1.1 Hz), 7.50 (ddd, 1H, *J* 15.2, 1.4, 0.5 Hz), 7.48 (dt, 1H, *J* 15.3, 1.9 Hz), 7.33 (td, 1H, *J* 7.6, 1.2 Hz), 6.23 (ddd, 1H, *J* 16.0, 4.3, 4.0 Hz), 4.77 (dd, 1H, *J* 9.0, 2.3 Hz), 4.60 (dd, 1H, *J* 11.5, 1.8 Hz), 4.51 (dd, 1H, *J* 11.5, 3.2 Hz), 4.29 (dq, 1H, *J* 14.5, 1.9 Hz), 4.20 (ddd, 1H, *J* 14.5, 4.5, 2.0 Hz), 4.13 (m, 1H), 4.11 (t, 1H, *J* 2.3 Hz), 3.87 (m, 2H), 3.66 (dd, 1H, *J* 10.5, 2.9 Hz); ^{13}C NMR (CD_3OD) δ 170.5 (C═O), 139.1 (s), 133.3 (s), 132.3 (d), 131.2 (d), 130.8 (d), 129.6 (d), 128.3 (d), 128.0 (d), 75.7 (d), 73.2 (t), 71.7 (d), 71.5 (t), 71.2 (d), 70.8 (d), 67.8 (t); IR (film, CH_3OH) ν_{max} 3342, 2915, 2861, 2362, 2329, 1702, 1598, 1477, 1448, 1371, 1292, 1268, 1176, 1133, 1079, 1045, 966, 929, 836, 742, 561 cm^{-1}; ES-HRMS found 323.1145, $C_{16}H_{19}O_7$ requires 323.1131 $[M - H]^-$.

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Supporting Information Available: Full experimental procedures, ^{1}H and ^{13}C NMR spectra, NMR assignments, X-ray structures, and crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) The networks of hydrogen bonding can be viewed using the crystallographic information files (see the Supporting Information). For selected publications where hydrogen bonding networks have been of interest, see (a) Jeffrey, G. A.; Saenger, W. *Hydrogen bonding in biological structures;* Springer-Verlag: Berlin, 1991. (b) Murphy, P. V.; Mueller-Bunz, H.; Velasco-Torrijos, T. *Carbohydr. Res.* **2005**, *340*, 1437.