Facile and Enantiospecific Syntheses of Goniotriol Analogues

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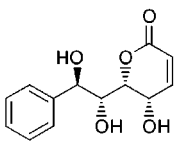
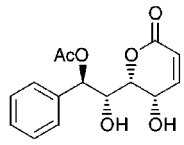
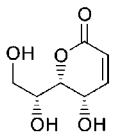
Bioactive styryl lactones[1] (+)-goniofufurone,[2] (+)-7-*epi*-goniofufurone,[3] (+)-goniobutenolide A,[4] (−)-goniobutenolide B,[4] (+)-goniopypyrone,[2] (+)-altholactone (syn: goniothalenol),[5] (+)-goniotriol (**1**),[6] and (+)-7-acetylgoniotriol (**2**)[2] have been isolated from the ethanolic extracts of the stem bark of *Goniothalamus giganteus* Hook f., Thomas (Annonaceae). As part of our ongoing program in the syntheses of heavily oxygenated lactones[7] as potential antitumor agents from sugars, we recently disclosed, from D-*glycero*-D-*gulo*-heptono-γ-lactone, first syntheses[8] (except for altholactone) of these novel styryl lactones which were found to possess marginal to significant cytotoxicities against several human tumors. Synthetic achievements on styryl lactones from other research groups have subsequently been reported.[9−13] We are also interested in the mechanism of the antitumor action of goniotriol (**1**), and its dephenyl analogues **3**−**5** are required for such investigation. As an extension of our previous synthetic endeavor, we now describe enantiospecific syntheses of **3**−**5** from commercially available D-*glycero*-D-*gulo*-heptono-γ-lactone (**6**) (D-glucoheptono-γ-lactone).



(+)-Goniotriol **1**



(+)-7-Acetylgoniotriol **2**



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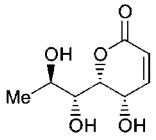

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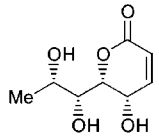

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We have recently reported that the aldehyde **7** could be obtained from D-*glycero*-D-*gulo*-heptono-γ-lactone (**6**) in three steps with 24% overall yield (Scheme 1).[8a] Reduction of the carbonyl functionalities in **7** with sodium borohydride in ethanol afforded the desired tetraol **8** whereas conducting the hydride reduction in methanol furnished the methyl ester **9** instead. Oxidative glycol cleavage[14] of the vicinal diol moiety in **8** followed by the *Z*-selective[8a,15] Wittig alkenation of the resultant aldehyde **10** produced exclusively enoate (*Z*)-**11** in 85% yield. The *E*-isomer could not be detected by TLC or by ^{1}H NMR spectroscopy. Lactonization of (*Z*)-**11** induced by DBU in dry THF under reflux smoothly gave pyrone **12** as colorless needles in 91% yield. The chemical shifts at δ 6.24 and 6.88 with 9.7 Hz coupling constant for the two vinylic protons in the ^{1}H NMR spectrum of **12** were in accord with the pyrone structure.[16] Hydrolysis of acetonide **12** by aqueous acetic acid generated the target

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(13) Syntheses of (+)-goniotriol and (+)-7-acetylgoniotriol: (a) Yang Z. C.; Zhou W. S. *Chin. Chem. Lett.* **1996**, *7*, 319. (b) see ref 9g, ref 9j, and ref 12e.

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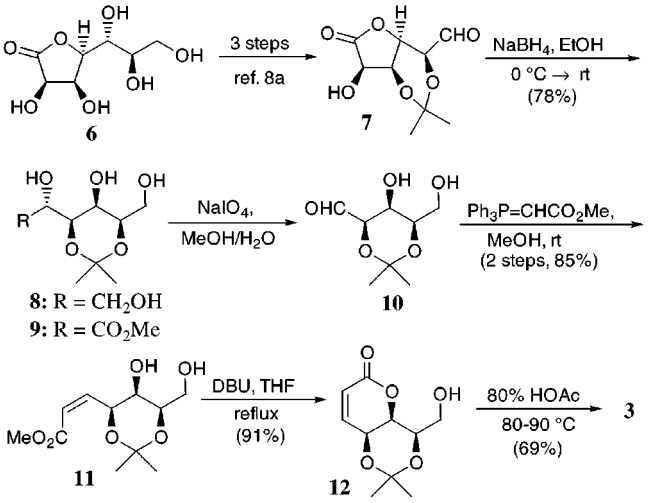
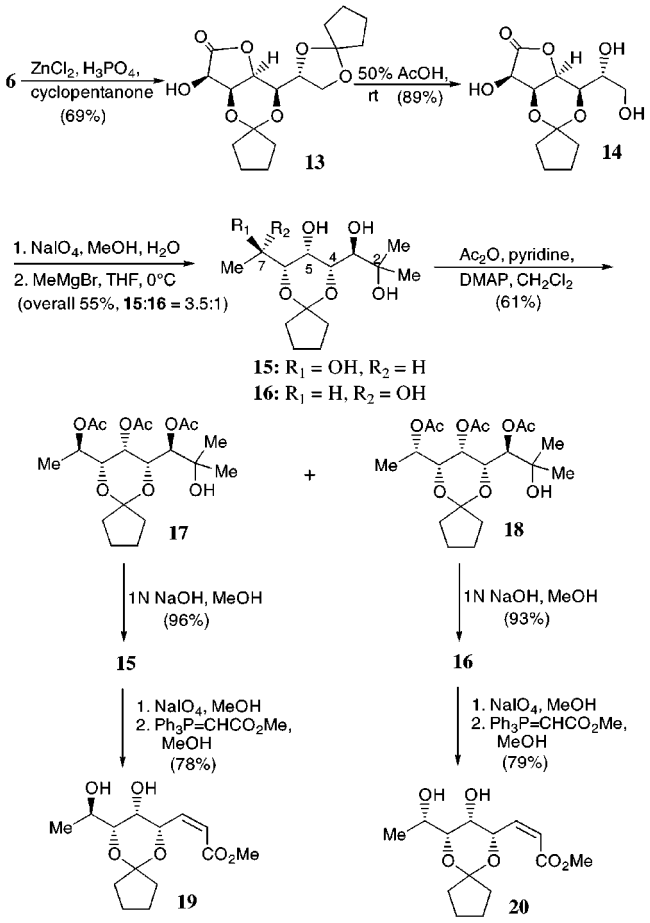
Scheme 1



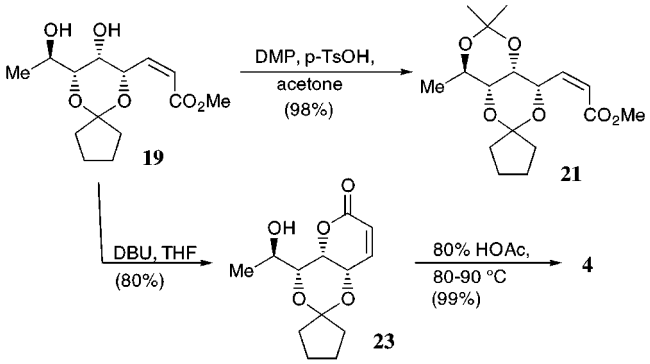
dephenyl goniotriol **3** in 69% yield as an oil. The pyrone moiety in **3** did not rearrange to the thermodynamic butenolide structure which was evident from the ^{1}H NMR spectral data. The continued existence of the two resonances at δ 6.29 and 7.24 (J = 9.7 Hz) for the two vinylic protons is characteristic of the pyrone structure **3**. Thus, dephenyl goniotriol **3** was prepared from D-*glycero*-D-*gulo*-heptono-γ-lactone (**6**) in eight steps with an overall yield of 10%.

For the syntheses of analogues **4** and **5**, the phenyl moiety in the parent goniotriol (**1**) is replaced by a methyl group. This could be readily achieved by the Grignard addition of MeMgBr to aldehyde **7**. However, we encountered an isolation problem during aqueous workup because the adduct was highly water soluble. The solubility problem was solved by changing the acetonide protecting group in **7** to a more hydrophobic cyclopentylidene blocking group. Thus lactone **6** was acetalized with cyclopentanone to furnish diacetal **13** which underwent acid-catalyzed hydrolysis selectively at the terminal acetal to give triol **14** in good yields (Scheme 2). Oxidative glycol cleavage of the vicinal diol in **14** gave the corresponding aldehyde which, without purification, reacted with an excess of methylmagnesium bromide at 0 °C to give an inseparable mixture of diastereomeric alcohols **15** and **16** in 55% yield with a ratio of 3.5 to 1, respectively. We chose these experimental conditions because both alcohols were required for the syntheses of different target molecules. Nevertheless, our earlier work[8g] on the syntheses of styryl lactones indicated that the preparation of either alcohol with high stereoselectivity should be feasible. The stereochemistry at C-7 of **15** and **16** was determined at a later stage. Separation of **15** and **16** was realized after derivatization to their corresponding acetates. Thus the mixture of alcohols **15** and **16** was acetylated to give triacetates **17** and **18**, respectively, readily separable by silica gel chromatography. Pure alcohols **15** and **16** were then regenerated from the respective acetates by alkaline hydrolysis in excellent yields. The alcohol **15** was used for the synthesis of **4**, and alcohol **16** was the intermediate for the construction of **5**. Oxidative cleavage of the vicinal diol in **15** using sodium metaperiodate followed by Wittig

Scheme 2



Scheme 3



alkenation with $Ph_3P{=}CHCO_2Me$ in dry methanol furnished enoate (*Z*)-**19** as the sole product. Likewise, reactions of tetraol **16** afforded exclusively the enoate (*Z*)-**20** without incident. It is noteworthy that the *E*-isomer could not be detected by TLC or by ^{1}H NMR spectroscopy.

The stereochemistry of the new stereogenic centers at C-7 of **15** and **16** were assigned by converting diols **19** and **20** into their corresponding acetonides **21** and **22** with 2,2-dimethoxypropane (DMP) in acetone (Schemes 3 and 4), followed by examination of their ^{13}C NMR spectra. Acetonide **21** with the quaternary ketal carbon resonating at δ_c 101.1 and the two methyl carbons at δ_c 24.3 and 24.8 was assigned as the *anti*-acetonide whereas acetonide **22**, displaying a resonance of the quaternary carbon at δ_c 98.5 and the two methyl carbons at δ_c 19.2 and 29.7, was assigned as the *syn*-acetonide. On the basis of the [^{13}C]acetonide analysis, the quaternary acetal

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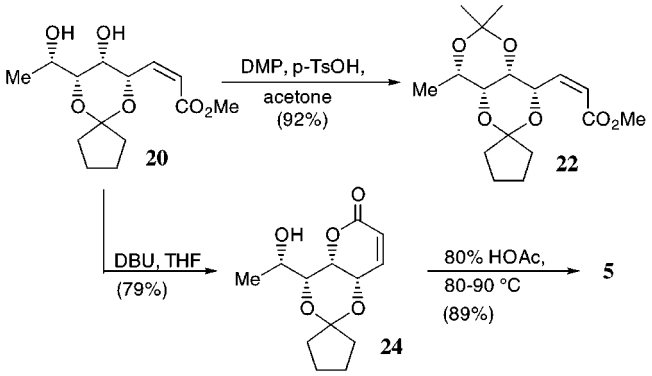
Scheme 4



chemical shifts for *anti*-acetonides average at 100.4 ppm while those for the *syn*-acetonides average at 98.5 ppm; the chemical shifts for two methyl carbons in *anti*-acetonide are in the region of 25 ppm whereas those for the two methyl groups in *syn*-acetonides are ca. 20 and 30 ppm.[17]

Coversion of the hydroxy-esters **19** and **20** into the target lactones proceeded without incident. Thus, **19** and **20** were induced to lactonize by a catalytic amount of DBU in boiling THF, furnishing crystalline styryl-2-pyrones **23** and **24**, respectively, in good yields. Hydrolysis of the cyclopentylidene protecting group in **23** and **24** with aqueous acetic acid afforded goniotriol analogues **4** and **5**, respectively. In conclusion, goniotriol analogues **4** and **5** were synthesized from D-*glycero*-D-*gulo*-heptono-γ-lactone (**6**) in nine steps and in overall yields of 12% and 10%, respectively.

Experimental Section[8a]

2,4-*O*-Isopropylidene-L-glucitol (8). Aldehyde **7**[8a] (864 mg, 4.0 mmol) was dissolved in EtOH (50 mL) and the solution cooled to 0 °C. $NaBH_4$ (230 mg, 6.06 mmol) was then added portionwise. The mixture was allowed to stir at room temperature for 18 h. Acetic acid was added slowly until neutralization as shown by pH paper. Concentration of the mixture gave a pad of white solid which was taken up with $CHCl_3$ (100 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography (20% MeOH in $CHCl_3$) gave tetraol **8** as colorless needles (700 mg, 78%), mp 165−167 °C (MeOH); R_f 0.21 (20% MeOH in $CHCl_3$); $[\alpha]^{24}_D$ −16.7 (*c* 1.0, MeOH); IR ($CHCl_3$) 3400 cm^{-1}; ^1H NMR (D_2O, DOH at δ 4.80), 1.42 (s, 3H), 1.50 (s, 3H), 3.59 (dd, 1H, J = 6.2, 12.5), 3.67−3.81 (m, 5H), 3.92 (dd, 1H, J = 1.4, 8.5), 4.10 (ddd, 1H, J = 1.4, 5.0, 6.4); ^{13}C NMR (D_2O, dioxane as internal reference at δ 67.4) 19.4, 29.2, 62.6, 63.0, 63.5, 70.2, 72.8, 74.2, 101.0; *m*/*z* (CI) 223 (MH^+, 15), 165 (100). Anal. Calcd for $C_9H_{18}O_6$: C, 48.64; H, 8.16. Found: C, 48.52; H, 8.22.

2,4-*O*-Isopropylidene-D-xylose (10). Sodium metaperiodate (750 mg, 3.51 mmol) was added in one portion to a stirred solution of the tetraol **8** (750 mg, 3.37 mmol) in MeOH (40 mL) and H_2O (4 mL) at room temperature. After being stirred at room temperature for 2 h, the mixture was filtered through a thin pad of silica gel topped with Celite. Evaporation of the solvent from the filtrate under reduced pressure gave the crude aldehyde **10**. This aldehyde was not purified further and used immediately for the next step.

(*Z*)-Methyl 4,6-*O*-Isopropylidene-D-*xylo*-hept-2-enonate (11). Methoxycarbonylmethylenetriphenylphosphorane (1.35 g, 4.05 mmol) was added in one portion to a stirred solution of the aldehyde **10** in anhydrous MeOH (30 mL) at room temperature. After being stirred at room temperature for 2 h, the solution was concentrated under reduced pressure. Purification of the residue by flash column chromatography (75% EtOAc in hexane) gave enoate **11** as colorless needles (705 mg, 85%), mp 158−159 °C; R_f 0.43 (EtOAc) $[\alpha]^{25}_D$ +132.5 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 1711, 3350 cm^{-1}; ^1H NMR ($CDCl_3$) 1.49 (s, 3H), 1.54 (s, 3H), 2.06 (m, 1H), 2.67 (d, 1H, J = 11.0), 3.73 (s, 3H), 3.69−3.88 (m, 3H), 4.07 (br t, 1H, J = 5.9), 5.51 (dt, 1H, J = 1.4, 6.8), 5.94 (dd, 1H, J = 1.4, 11.7), 6.30 (dd, 1H, J = 6.8, 11.7); ^{13}C NMR ($CDCl_3$) 19.2, 29.7, 51.4, 63.3, 66.8, 70.7, 72.8, 99.8, 120.2, 147.3, 166.2; *m*/*z* (CI) 247 (MH^+, 6), 189 (63), 157 (100). Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.47; H, 7.29.

(*Z*)-4,6-*O*-Isopropylidene-D-*xylo*-hept-2-enono-δ-lactone (12). To a solution of the ester **11** (47.4 mg, 0.193 mmol) in THF (10 mL) was added a catalytic amount of diazabicyclo-[5.4.0]undec-7-ene (DBU). The mixture was refluxed for 13 h, cooled to room temperature, filtered through a pad of silica gel, and washed with EtOAc (50 mL). Concentration of the filtrate followed by flash chromatography (EtOAc) gave lactone **12** (57.6 mg, 91%) as colorless needles, mp 149−151 °C; R_f 0.28 (EtOAc); $[\alpha]^{25}_D$ +70.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1708, 1722, 3331, 3497 cm^{-1}; ^1H NMR ($CDCl_3$) 1.45 (s, 3H), 1.55 (s, 3H), 2.13 (m, 1H), 3.88−3.96 (m, 2H), 4.15−4.22 (m, 2H), 4.38 (dd, 1H, J = 2.1, 6.1), 6.24 (d, 1H, J = 9.7), 6.88 (dd, 1H, J = 6.1, 9.7); ^{13}C NMR ($CDCl_3$) 18.9, 29.2, 60.0, 61.0, 70.1, 70.3, 99.5, 125.0, 140.9, 163.1; *m*/*z* (CI) 215 (MH^+, 30), 157 (99), 97 (100). Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.17; H, 6.58.

D-*xylo*-Hept-2-enono-δ-lactone (3). A solution of the acetonated lactone **12** (179.1 mg, 0.837 mmol) in 80% aqueous acetic acid (10 mL) was stirred at 80−90 °C for 5 h. The solvents were removed in vacuo to give a syrup which was purified by flash chromatography (11% MeOH in EtOAc) to give the dephenyl goniotriol **3** (100.4 mg, 69%) as a colorless oil; R_f 0.30 (11% MeOH in EtOAc); $[\alpha]^{25}_D$ +132.1 (*c* 1.1, EtOH); IR (MeOH) 1632, 1716, 3450 cm^{-1}; ^1H NMR (CD_3OD) 3.91 (dd, 1H, J = 4.8, 11.6), 3.99 (dd, 1H, J = 4.0, 11.6), 4.22 (dt, 1H, J = 4.4, 7.2), 4.48 (dd, 1H, J = 2.8, 5.8), 4.58 (dd, 1H, J = 2.8, 7.2), 6.29 (d, 1H, J = 9.7), 7.24 (dd, 1H, J = 5.8, 9.7); ^{13}C NMR (d_6-acetone) 61.6, 63.2, 72.4, 82.0, 123.0, 146.4, 165.1; *m*/*z* (EI) 175 (M^+ + 1, 42), 157 (78), 113 (100). Anal. Calcd for $C_7H_{10}O_5$: C, 48.28; H, 5.79. Found: C, 47.98; H, 5.91.

3,5:6,7-Di-*O*-cyclopentylidene-D-*glycero*-D-*gulo*-heptono-γ-lactone (13). To a stirred suspension of D-*glycero*-D-*gulo*-heptono-γ-lactone (**6**) (40 g, 0.192 mol) in cyclopentanone (300 mL) were added anhydrous zinc chloride (26 g, 0.192 mol) and phosphoric acid (85%, 1 mL) at room temperature. The mixture was stirred at room temperature for 24 h and then its pH adjusted with aqueous ammonia (sp gr 0.88) to 8−9. The white inorganic solid was filtered off through a pad of Celite, and EtOAc (500 mL) and H_2O (100 mL) were added to the filtrate. The aqueous phase was separated and extracted with EtOAc (3 × 150 mL), and the combined organic extracts were concentrated. The crude syrup was crystallized and recrystallized from $CHCl_3$−hexane to give the diacetal **13** (45 g, 69%) as colorless needles; mp 147−149 °C ($CHCl_3$−hexane); R_f 0.31 (50% EtOAc in hexane); $[\alpha]^{22}_D$ −59.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1778, 3450 cm^{-1}; ^1H NMR ($CDCl_3$) 1.63−1.93 (m, 16H), 2.83 (d, 1H, J = 10.0), 3.75 (dd, 1H, J = 2.0, 8.6), 3.91 (dd, 1H, J = 3.8, 8.9), 4.00 (dd, 1H, J = 6.2, 8.9), 4.28 (ddd, 1H, J = 3.8, 6.2, 8.6), 4.34 (t, 1H, J = 2.0), 4.49 (dd, 1H, J = 4.1, 10.0), 4.55 (dd, 1H, J = 2.0, 4.1); ^{13}C NMR ($CDCl_3$) 22.2, 23.3, 23.8, 24.1, 30.9, 36.0, 36.7, 39.4, 66.9, 69.0, 69.2, 71.0, 71.7, 72.6, 110.3, 119.6, 174.5; *m*/*z* (EI) 340 (M^+, 7), 311 (100). Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.95; H, 7.16.

3,5-*O*-Cyclopentylidene-D-*glycero*-D-*gulo*-heptono-γ-lactone (14). A solution of diacetal **13** (15.3 g, 45.0 mmol) in 50% aqueous acetic acid (300 mL) was stirred at room temperature for 4 h. The solvents were removed under reduced pressure to give a yellow syrup. The syrup was crystallized from EtOAc (ca. 800 mL) to give triol **14** (11.0 g, 89%) as colorless needles; mp 175−177 °C (EtOAc); R_f 0.36 (20% MeOH in $CHCl_3$); $[\alpha]^{21}_D$ −55.0 (*c* 1.1, MeOH); IR ($CHCl_3$) 1776, 3450 cm^{-1}; ^1H NMR (CD_3OD) 1.87−2.20 (m, 8H), 3.78 (dd, 1H, J = 4.7, 11.4), 3.92 (dd, 1H, J = 2.4, 11.4), 3.98 (ddd, 1H, J = 2.4, 4.7, 9.0), 4.17 (dd, 1H, J = 1.8, 9.0), 4.64 (t, 1H, J = 1.8), 4.79 (dd, 1H, J = 2.0, 4.1), 4.82 (d, 1H, J = 4.1); ^{13}C NMR (CD_3OD) 23.2, 25.1, 31.5, 40.3, 63.9, 70.5, 70.8 (× 2), 71.7, 72.6, 111.3, 177.9; *m*/*z* (EI) 274 (M^+, 7),

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245 (100). Anal. Calcd for $C_{12}H_{18}O_7$: C, 53.65; H, 7.37. Found: C, 53.47; H, 7.29.

Tetraol 15. To a solution of the triacetate **17** (704.5 mg, 1.69 mmol) in MeOH (25 mL) was added a solution of NaOH (1 M, 3 mL) at room temperature. The mixture was stirred at room temperature for 1 h, and the solvent was concentrated to give a pad of solid. The residue was dissolved in MeOH and adsorbed onto silica gel (1.5 g) which was followed by flash chromatography (10% MeOH in $CHCl_3$) to give the tetraol **15** (473.7 mg, 96%) as colorless plates; mp 160−162 °C (EtOAc); R_f 0.40 (10% MeOH in $CHCl_3$); $[\alpha]^{21}_D$ +1.8 (*c* 1.1, MeOH); IR ($CHCl_3$) 3400 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) 1.20 (s, 3H), 1.23, (d, 3H, *J* = 6.4), 1.24 (s, 3H), 1.60−2.04 (m, 8H), 3.44 (d, 1H, *J* = 7.9), 3.62 (d, 1H, *J* = 8.9), 3.79 (d, 1H, *J* = 8.9), 3.91 (quintet, 1H, *J* = 6.5), 3.99 (br s, 1H); ^{13}C NMR ($CDCl_3$ + CD_3OD) 19.1, 22.1, 23.9, 25.0, 30.5, 39.5, 62.0, 65.5, 72.7, 73.1, 75.3, 78.3, 110.8; *m*/*z* (EI) 291 (MH^+, 6), 255 (58), 189 (100). Anal. Calcd for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03. Found: C, 57.90; H, 9.10.

Tetraol 16. Similar deprotection of the triacetate **18** (33.1 mg, 0.080 mmol) as in the preparation of **15** gave, after flash chromatography (9% MeOH in $CHCl_3$), the tetraol **16** (21.4 mg, 93%) as colorless needles; mp 131−132 °C (EtOAc); R_f 0.40 (10% MeOH in $CHCl_3$); $[\alpha]^{21}_D$ +17.4 (*c* 0.7, MeOH); IR ($CHCl_3$) 3450 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) 1.21 (s, 3H), 1.22 (d, 3H, *J* = 6.5), 1.26 (s, 3H), 1.64−1.98 (m, 8H), 3.49 (dd, 1H, *J* = 1.3, 7.1), 3.60 (d, 1H, *J* = 8.5), 3.78 (br s, 1H), 3.82 (dd, 1H, *J* = 1.3, 8.5), 4.00 (quintet, 1H, *J* = 6.5); ^{13}C NMR (CD_3OD) 18.2, 23.3, 25.1, 25.9, 31.5, 40.7, 64.6, 68.6, 73.9, 74.5, 76.6, 80.7, 112.2; *m*/*z* (EI) 290 (M^+, 1), 261 (4), 85 (100). Anal. Calcd for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03. Found: C, 57.65; H, 9.03.

Triacetate 17 and Triacetate 18. To a stirred solution of triol **14** (11.0 g, 42.0 mmol) in MeOH (300 mL) was added a solution of sodium metaperiodate (10.0 g, 46.8 mmol) in H_2O (30 mL). The mixture was stirred at room temperature for 1 h, filtered through a pad of silica gel topped with Celite and washed with MeOH (100 mL). Concentration of the filtrate gave the crude aldehyde (9.6 g) as a foam. This compound was pumped dried and directly used in the Grignard reaction. To a stirred solution of the aldehyde (9.6 g) in dry THF (250 mL) at 0 °C under nitrogen was added slowly a solution of methylmagnesium bromide (3.0 M in Et_2O, 100 mL). The mixture was stirred at 0 °C for 1 h and quenched with water, and the solvent was removed under reduced pressure. The residue was flash chromatographed (EtOAc:CH_2Cl_2:MeOH, 8:8:1) to give an inseparable mixture of diastereomeric tetraols **15** and **16** (6.41 g, 55%). To a solution of the inseparable tetraols **15** and **16** (6.41 g, 22.1 mmol) in CH_2Cl_2 (150 mL) were added pyridine (30 mL), acetic anhydride (15 mL), and a catalytic amount of DMAP at room temperature. The mixture was allowed to stir at room temperature for 72 h and poured into a saturated solution of NH_4Cl (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (45% Et_2O in hexane) of the filtrate afforded first triacetate **17** (4.37 g, 47.5%) as a colorless oil and then triacetate **18** (1.47 g, 13.9%) as colorless needles.

Data for triacetate **17**: R_f 0.37 (60% Et_2O in hexane); $[\alpha]^{21}_D$ −5.1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1744, 3550 cm^{-1}; ^1H NMR ($CDCl_3$) 1.13 (s, 3H), 1.21 (d, 3H, *J* = 6.2), 1.22 (s, 3H), 1.66−2.10 (m, 8H), 1.98 (s, 3H), 2.01 (s, 3H), 2.05 (s, 3H), 3.08 (s, 1H), 3.77 (dd, 1H, *J* = 1.6, 9.0), 4.20 (dd, 1H, *J* = 1.7, 9.9), 4.74 (doublet of quintet, 1H, *J* = 6.2, 9.0), 4.93 (d, 1H, *J* = 9.9), 5.06 (dd, 1H, *J* = 1.6, 1.7); ^{13}C NMR ($CDCl_3$) 16.7, 20.6, 20.8, 21.0, 22.2, 24.0, 25.7, 26.2, 30.5, 39.6, 61.7, 67.1, 72.2, 72.5, 72.6, 75.1, 111.1, 169.8, 169.9, 170.5; *m*/*z* (EI) 374 (M^+ − 42, 5), 43 (100). Anal. Calcd for $C_{20}H_{32}O_9$: C, 57.68; H, 7.74. Found: C, 57.61; H, 7.71.

Data for triacetate **18**: mp 151−153 °C (Et_2O−hexane); R_f 0.29 (60% Et_2O in hexane); $[\alpha]^{22}_D$ −3.9 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1739, 3509 cm^{-1}; ^1H NMR ($CDCl_3$) 1.11 (s, 3H), 1.19 (s, 3H), 1.20 (d, 3H, *J* = 6.6), 1.57−1.98 (m, 8H), 1.99 (s, 3H), 2.00 (s, 3H), 2.11 (s, 3H), 3.09 (br s, 1H), 3.78 (dd, 1H, *J* = 1.1, 8.7), 4.15 (dd, 1H, *J* = 1.5, 9.9), 4.83 (doublet of quintet, 1H, *J* = 6.0, 8.7), 4.87 (d, 1H, *J* = 9.9), 4.93 (br s, 1H); ^{13}C NMR ($CDCl_3$) 15.3, 20.4 (×3), 21.8, 23.6, 25.6, 25.8, 30.0, 39.2, 62.6, 68.6, 71.6, 72.5 (×3), 74.9, 110.7, 169.4, 170.2; *m*/*z* (EI) 374 (M^+ − 42, 5), 43 (100). Anal. Calcd for $C_{20}H_{32}O_9$: C, 57.68; H, 7.74. Found: C, 57.67; H, 7.84.

(*Z*)-Methyl 4,6-*O*-Cyclopentylidene-2,3,8-trideoxy-D-*gluco*-oct-2-enonate (19). To a stirred solution of the tetraol **15** (143.6 mg, 0.437 mmol) in MeOH (25 mL) was added a solution of sodium metaperiodate (127 mg, 0.594 mmol) in H_2O (2 mL) at room temperture. The mixture was stirred at room temperature for 1 h and filtered through a pad of Celite and washed with MeOH (10 mL). Concentration of the filtrate under reduced pressure gave the crude aldehyde which was used for the Wittig reaction. To the stirred solution of the crude aldehyde in anhydrous MeOH (25 mL) was added methoxycarbonylmethylenetriphenylphosphorane (200 mg, 0.581 mmol) in one portion, and the mixture was stirred for 1 h. The solvent was removed in vacuo followed by flash chromatography (50% EtOAc in hexane) to give the enonate **19** (97.1 mg, 78%) as colorless needles; mp 150−152 °C (EtOAc−hexane); R_f 0.32 (50% EtOAc in hexane); IR ($CHCl_3$) 1650, 1715, 3366 cm^{-1}; $[\alpha]^{22}_D$ +71.4 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.28 (d, 3H, *J* = 6.4), 1.66−1.76 (m, 4H), 1.91−1.98 (m, 4H), 2.35 (br s, 1H), 3.12 (br d, 1H, *J* = 8.5), 3.60 (dd, 1H, *J* = 1.4, 6.2), 3.72 (s, 3H), 3.98 (m, 2H), 5.49 (dt, 1H, *J* = 1.4, 7.1), 5.93 (dd, 1H, *J* = 1.5, 11.8), 6.35 (dd, 1H, *J* = 7.1, 11.8); ^{13}C NMR ($CDCl_3$) 18.9, 22.3, 24.1, 30.8, 39.8, 51.2, 65.2, 66.2, 71.9, 77.2, 111.0, 119.8, 147.2, 166.1; *m*/*z* (EI) 287 (MH^+, 2), 257 (2), 85 (100). Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.74. Found: C, 58.79; H, 7.69.

(*Z*)-Methyl 4,6-*O*-Cyclopentylidene-2,3,8-trideoxy-L-*ido*-oct-2-enonate (20). Following the procedure as for the preparation of enonate **19**, tetraol **16** (477.9 mg, 1.65 mmol) gave, after flash chromatography (50% EtOAc in hexane), enonate **20** (424.5 mg, 79%) as a white solid; mp 67−69 °C; R_f 0.26 (50% EtOAc in hexane); IR ($CHCl_3$) 1650, 1714, 3450 cm^{-1}; $[\alpha]^{22}_D$ +63.8 (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.19 (d, 3H, *J* = 6.4), 1.60−1.72 (m, 4H), 1.90−1.97 (m, 4H), 2.66 (br s, 1H), 2.86 (d, 1H, *J* = 10.9), 3.55, (dd, 1H, *J* = 1.1, 6.9), 3.70 (s, 3H), 3.73 (br d, 1H, *J* = 10.9), 3.95 (quintet, 1H, *J* = 6.4), 5.34 (dt, 1H, *J* = 1.4, 6.9), 5.91 (dd, 1H, *J* = 1.4, 11.7), 6.29 (dd, 1H, *J* = 6.9, 11.7); ^{13}C NMR ($CDCl_3$) 17.3, 22.5, 24.4, 31.0, 40.1, 51.4, 66.8, 67.5, 72.3, 78.4, 111.6, 120.1, 147.3, 166.1; *m*/*z* (EI) 287 (MH^+, 48), 203 (100). Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.74. Found: C, 58.72; H, 7.81.

(*Z*)-Methyl 4,6-*O*-Cyclopentylidene-5,7-*O*-isopropylidene-2,3,8-trideoxy-D-*gluco*-oct-2-enonate (21). To a solution of the diol **19** (40.5 mg, 0.142 mmol) in anhydrous acetone (10 mL) was added 2,2-dimethoxypropane (0.8 mL) and *p*-toluenesulfonic acid (2.5 mg) at room temperature. The mixture was stirred at room temperature for 1 h and neutralized with Et_3N. The mixture was then filtered through a pad of silica gel topped with Celite. Concentration of the filtrate followed by flash chromatography (13% Et_2O in hexane) gave acetonide **21** (41.0 mg, 89%) as colorless needles; mp 88−90 °C; R_f 0.44 (14% Et_2O in hexane); IR ($CHCl_3$) 1650, 1714; $[\alpha]^{22}_D$ +116.7 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.21 (s, 3H), 1.28 (d, 3H, *J* = 6.3), 1.42 (s, 3H), 1.62−2.02 (m, 8H), 3.73 (s, 3H), 3.71−3.78 (m, 2H), 3.82 (t, 1H, *J* = 2.5), 5.53 (ddd, 1H, *J* = 1.6, 2.8, 7.0), 5.89 (dd, 1H, *J* = 1.6, 11.6), 6.36 (dd, 1H, *J* = 7.0, 11.6); ^{13}C NMR ($CDCl_3$) 19.7, 22.4, 23.8, 24.3, 24.8, 30.9, 40.0, 51.2, 62.8, 68.9, 69.1, 75.5, 101.1, 109.6, 119.1, 147.7, 166.2; *m*/*z* (EI) 327 (MH^+, 7), 311 (4), 127 (100). Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.77; H, 8.13.

(*Z*)-Methyl 4,6-*O*-Cyclopentylidene-5,7-*O*-isopropylidene-2,3,8-trideoxy-L-*ido*-oct-2-enonate (22). Similar isopropylidenation of diol **20** (101.8 mg, 0.356 mmol) as in the preparation of **21** gave, after flash chromatography (14% Et_2O in hexane), the acetonide **22** (106.8 mg, 92%) as a white solid; mp 154−155 °C (Et_2O−hexane); R_f 0.26 (14% Et_2O in hexane); IR ($CHCl_3$) 1650, 1710; $[\alpha]^{22}_D$ +117.9 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.19 (d, 3H, *J* = 6.5), 1.34 (s, 3H), 1.41 (s, 3H), 1.58−2.05 (m, 8H), 3.44 (t, 1H, *J* = 1.5), 3.70 (s, 3H), 3.86 (t, 1H *J* = 1.6), 4.01 (dq, 1H, *J* = 1.6, 6.4), 5.42 (dt, 1H, *J* = 1.5, 7.4), 5.86 (dd, 1H, *J* = 1.2, 11.8), 6.37 (dd, 1H, *J* = 7.4, 11.8); ^{13}C NMR ($CDCl_3$) 16.2, 19.2, 22.3, 24.2, 29.7, 30.7, 39.8, 51.3, 65.8, 66.4, 67.0, 70.2, 98.5, 110.3, 119.4, 147.8, 166.3; *m*/*z* (EI) 326 (M^+, 2), 311 (14), 167 (100). Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.74; H, 7.83.

4,6-*O*-Cyclopentylidene-2,3,8-trideoxy-D-*gluco*-oct-2-enono-δ-lactone (23). A solution of the diol **19** (196.4 mg, 687

mmol) and DBU (2 drops) was stirred in THF (50 mL) at 70 °C (bath temperature) for 15 h under nitrogen. The mixture was filtered through a pad of silica gel topped with Celite. Concentration of the filtrate followed by flash chromatography (67% EtOAc in hexane) afforded lactone **23** (139.3 mg, 80%) as colorless needles; mp 140−142 °C (Et_2O−hexane); R_f 0.29 (60% EtOAc in hexane); IR ($CHCl_3$) 1738, 3342 cm^{-1}; $[\alpha]^{22}_D$ +93.3 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.27 (d, 3H, *J* = 6.3), 1.61−1.98 (m, 8H), 2.69 (br s, 1H), 3.59 (dd, 1H, *J* = 1.9, 8.6), 4.20 (m, 1H), 4.26 (dd, 1H, *J* = 2.1, 6.0), 4.43 (t, 1H, *J* = 1.9), 5.21 (dd, 1H, *J* = 0.8, 9.7), 5.88 (dd, 1H, *J* = 6.0, 9.7); ^{13}C NMR ($CDCl_3$) 20.0, 22.3, 24.2, 30.5, 39.7, 61.7, 64.6, 69.7, 75.7, 111.0, 125.0, 140.8, 163.4; *m*/*z* (EI) 254 (M^+, 2), 225 (16), 97 (100). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.41; H, 7.14.

4,6-*O*-Cyclopentylidene-2,3,8-trideoxy-L-*ido*-oct-2-enono-*δ*-lactone (24). Similar cyclization of the diol ester **20** (166 mg, 0.580 mmol) under conditions as described for the preparation of lactone **23** gave, after flash chromatography (75% EtOAc in hexane), lactone **24** (119.4 mg, 84%) as a white solid; mp 128−130 °C; R_f 0.19 (60% EtOAc in hexane); IR ($CHCl_3$) 1716, 3527 cm^{-1}; $[\alpha]^{22}_D$ +77.2 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.23 (d, 3H, *J* = 6.3), 1.63−1.98 (m, 8H), 2.63 (br s, 1H), 3.62 (dd, 1H, *J* = 1.8, 8.1), 4.16 (dd, 1H, 1.8, 2.0), 4.20 (m, 1H), 4.25 (dd, 1H, *J* = 2.1, 6.0), 6.22 (d, 1H, *J* = 9.8), 6.88 (dd, 1H, *J* = 6.0, 9.8); ^{13}C NMR ($CDCl_3$) 16.8, 22.4, 24.3, 30.6, 39.9, 61.4, 66.1, 70.2, 76.7, 111.4, 125.1, 140.5, 162.6; *m*/*z* (EI) 255 (MH^+, 10), 225 (25), 97 (100). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.26; H, 7.16.

2,3,8-Trideoxy-D-*gluco*-oct-2-enono-*δ*-lactone (4). A solution of the lactone **23** (107.0 mg, 0.421 mmol) in 80% aqueous acetic acid (10 mL) was stirred at 80−90 °C for 2 h. The solvents were removed in vacuo to give a syrup which was purified by flash chromatography (9% MeOH in EtOAc) to give the triol **4** (78.2 mg, 99%) as colorless needles; mp 110−112 °C (EtOAc); R_f 0.30 (9% MeOH in EtOAc); IR (KBr) 1631, 1719, 3450; $[\alpha]^{24}_D$ +118.1 (*c* 0.7, EtOH); ^1H NMR (d_6-acetone + D_2O) 1.22 (d, 3H, *J* = 6.1), 3.76 (dd, 1H, *J* = 3.8, 7.4), 3.89 (m, 1H), 4.41 (dd, 1H, *J* = 2.8, 5.8), 4.51 (dd, 1H, *J* = 2.8, 3.8), 6.02 (d, 1H, *J* = 9.7), 7.03 (dd, 1H, *J* = 5.8, 9.7); ^{13}C NMR (d_6-acetone) 20.1, 63.2, 67.2, 76.6, 80.1, 123.1, 146.1, 165.0; *m*/*z* (EI) 189 (MH^+, 8), 171 (11), 97 (100). Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 51.11; H, 6.60.

2,3,8-Trideoxy-L-*ido*-oct-2-enono-*δ*-lactone (5). Similar hydrolysis of cyclopentalidene acetal **24** (121.7 mg, 0.479 mmol) as for the preparation of **4** gave, after flash chromatography (9% MeOH in EtOAc), triol-lactone **5** (80.0 mg, 89%) as a colorless oil; R_f 0.34 (9% MeOH in EtOAc); IR (MeOH) 1633, 1720, 3450; $[\alpha]^{24}_D$ +130.4 (*c* 1.1, EtOH); ^1H NMR (CD_3OD) 1.48 (d, 3H, *J* = 6.4), 3.99 (dd, 1H, *J* = 2.0, 8.1), 4.24 (dq, 1H, *J* = 2.0, 6.4), 4.52 (dd, 1H, *J* = 2.5, 6.0), 4.60 (dd, 1H, *J* = 2.5, 8.1), 6.30 (d, 1H, *J* = 9.5), 7.26 (dd, 1H, *J* = 6.0, 9.5); ^{13}C NMR (d_6-acetone) 20.4, 61.7, 67.7, 75.0, 82.8, 123.5, 146.1, 164.3; *m*/*z* (EI) 189 ($M^+ + 1$, 42), 171 (78), 97 (100). Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 50.79; H, 6.68.

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